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REVIEW ARTICLE

A Review on Synthesis, Reactions and Biological Properties of Seven Member Heterocyclic Compounds: Azepine, Azepane, Azepinone

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Abstract: Seven membered heterocyclic Azepine and its derivatives have great pharmacological and therapeutic implications. In this review, the literature of the last fifty years has been exploited for the synthesis, reaction, and biological properties of these seven-member heterocyclic compounds. Most of the mechanisms involved the ring expansion of either five or six-membered compounds using various methods such as thermally, photo-chemically, and microwave irradiation. The systematically designed schemes involve the synthesis of different derivatives of azepine, azepinone, azepane, *etc.,* using similar moieties by various researchers. However, there is much work yet to be done in the biological section, as it is not explored and reported in the literature; therefore, N-containing seven-membered heterocycles still have much scope for the researchers.


Harvinder S. Sohal

Keywords: Azepine, azepane, azepinone, benzazepine, dibenzazepinone, thiazipine.

1. INTRODUCTION

Heterocyclic compounds keep on pulling the consideration of medicinal chemists due to their assorted scope of natural properties. The heterocyclic science managed unlimited assets of novel biologically active compounds, as about 67% of the healing plant contains a heterocyclic ring. These compounds have also many applications in different industries, such as information storage, antioxidants, solvents, reprography, cosmetics, plastics, and vulcanization accelerators [1-3]. Notably, some of the heterocyclic compounds are the most necessary and usual constituent of living cells and play a significant role in biochemical processes. Different heterocyclic compounds with the most favorable physical, chemical, and biological properties are constructed with a broad range of combinations of carbon, hydrogen, and hetero-atoms such as O, N, and S. Therefore, various new techniques have been introduced for the preparation of heterocyclic compounds. Other than the traditional methodology (conventional heating) [4], many new techniques (ultrasound irradiation [3b], *etc*.) have been continuously introduced by the researchers to obtain complex heterocyclic compounds that are rich in biological activities. Among which the most exclusive and biologically active framework is N-containing heterocyclic compounds such as pyrrole [5] (Anti-cancer, Anticoccidial, Antifungal, Antibacterial, Anti-mycobacterial), pyrrolidine [6] (Anti-microbial, Antifungal), imidazole (Antifungal [7, 8], Antibacterial [7, 8], Anti-tuberculosis [8], Antilishmanial [8, 9]), thiazole (Anti-convulsant [10], Anti-HIV [11]) as five-membered, pyridines [12], piperidine (Antimicrobial [13], Anti-tuberculosis [14]) pyrimidine [15] (Anti-folates, Anti-HIV), piperazine [16] (Anti-depressant and anxiolytic, Antialzheimer) as six-membered heterocyclic compounds.

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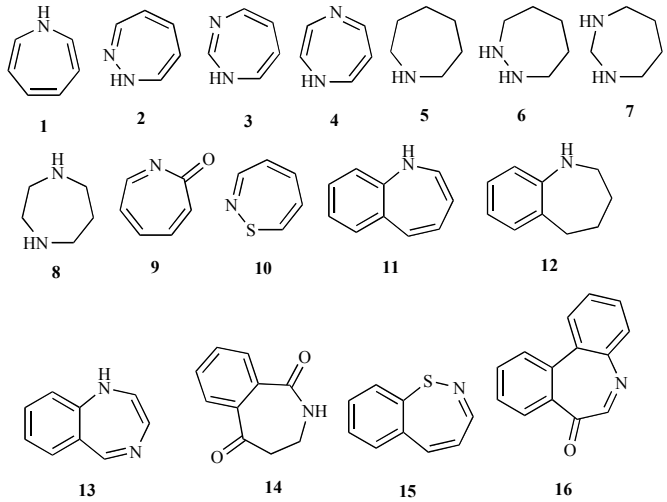
From the literature survey, it was observed that there is no such report present, which can describe the present scenario going on in the synthesis and biological application of N-containing seven-membered heterocyclic compounds, although many reviews are reported till now [17]. So, this encouraged us to write a report from 1966 to date. Seven membered Nitrogen-containing heterocyclics exist as Azepines **1**, 1,2-diazepine **2**, 1,3-diazepine **3**, 1,4-diazepine **4**, azepane **5**, 1,2-diazepane **6**, 1,3-diazepane **7**, 1,4-diazepane **8**, azepinone **9**, thiazipine **10**, benzazepine **11**, benzazepane **12**, 1,4-Benzodiazepine **13**, benzoazepinedione **14**, benzothiazipine **15** and dibenzazepinone **16** (Scheme **1**).



Scheme 1. Seven membered Nitrogen-containing heterocyclics.

Azepines correspond to a vital class of seven-member heterocycles present in bioactive molecules and natural products [18]. A chemical compound with Azepine moiety has discovered use in the scope of territories, most unmistakably as medications for the treatment of heart disease [19], neuropsychiatric disorders [20], as

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well as in the look of novel structures for the treatment of cancer and tumor [21, 22]. The scope of the present study is to provide all the information regarding synthesis and applications of azepine and their related derivatives in a single publication so that researchers can easily interpret gaps in the present studies, and this study also provides an idea of some reactant/ named reactions used in future drug discoveries. In this study, we observe that researchers around the world have prepared a number of azepine derivatives by substitution of different groups on the ring. Substituted azepine and azepane derivatives are notable as bioactive natural products and also pharmaceutically relevant compounds [23]. Some of the highly active and commercially available drugs **17-36** are given in Table **1**.

2. REVIEW OF LITERATURE

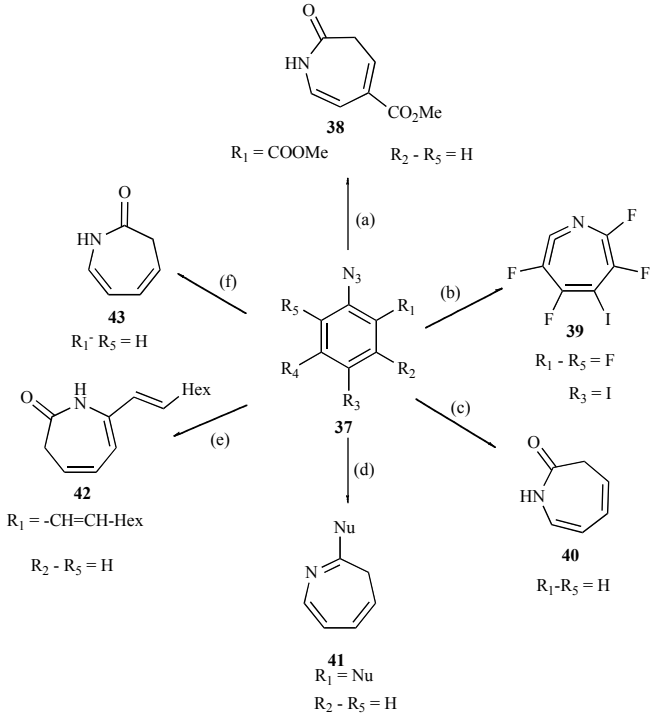
2.1. Synthesis of Azepines and its Derivatives

In due course of time, various methods have been adopted to synthesize the seven-membered heterocyclic compounds. In this review, an effort has been made to conclude all the similar moieties, such as substituted aryl azides, N-substituted phthalimide, substituted indoles, *etc., that* have been used by different researchers for the synthesis of various derivatives of Azepines, in a single scheme along with their significant activities.

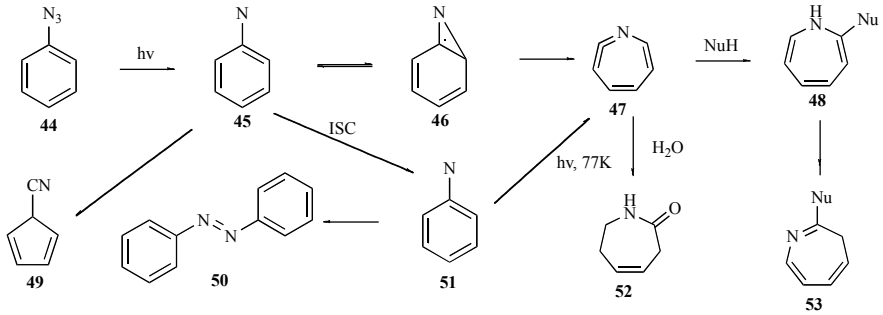
2.1.1. Synthesis of Azepine Derivatives from Azides.

By photolysis of aryl azide **37**, many substituted azepine **39 & 41** and azepinones **38, 40, 42 & 43** are obtained by the rearrangement, and ring expansion of aryl nitrenes **37** under varied reaction conditions (Scheme **2a**) and mechanism of the same have been described in the (Scheme **2b**) It came out from the literature survey that most of the products were synthesized either under the photochemical conditions or at different thermal conditions. Lamara *et al*. [44, 45] and some other researchers synthesized substituted Azepine **38** at room temperature (298K). Wenk and Sander [46, 47] in the year 2002 did a similar reaction at very low temperature (3K) to get a product yield **39** of 60-75% under aqueous conditions. However, maximum yield (75%) is obtained by Farhan at 298K temperature by applying continuous flow photolysis on aryl azides [45].

Many reactive intermediates were formed by the photolysis [47,51- 56] of aryl azide **44**. In which the primary molecule was singlet aryl nitrene [48] **45,** which is in resonance with **46**. The

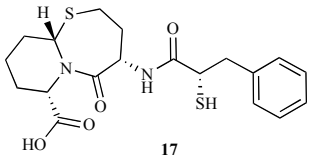
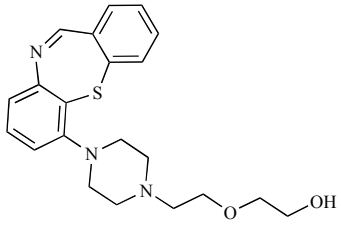
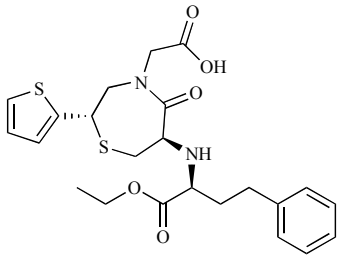
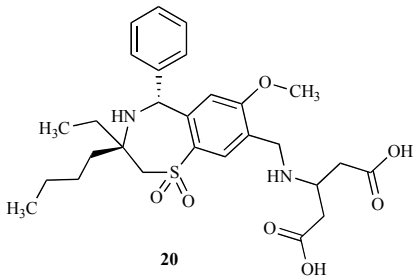
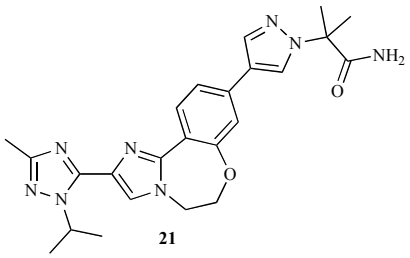
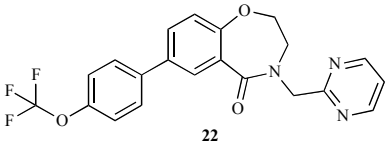
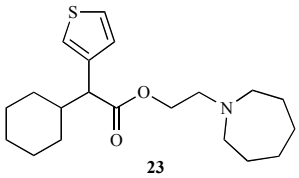


Scheme 2a. Synthesis of Azepines and Azepinone from substituted aromatic azides. Reagents: a)THF/H_2O(4:3), hν, 25°C , 30 min, flow photoreactor; [44, 45] b) (i) 320 nm, Ar, 3K (ii) 254 nm, Ar or Ne , 25°C; [46, 47] c) hv, H_2O; [35] d) hν, NuH; [48, 49] e) hν, >345 nm , H_2O, MeCN, 25°C, 3h; [47, 50] f) THF/H_2O(4:3), hν , 25°C , 30 min[51].

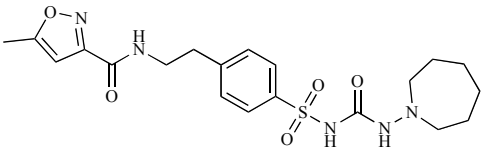
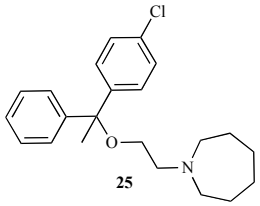
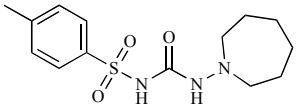
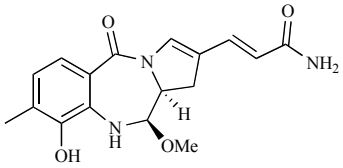
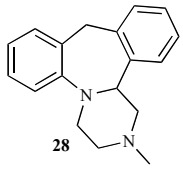
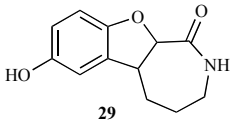
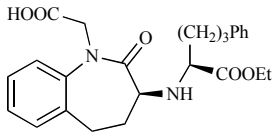
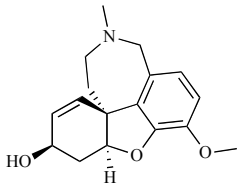
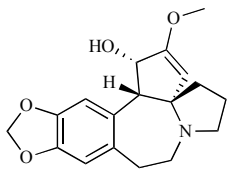


Scheme 2b. Mechanism of azepine synthesis *via* ring expansion of aryl azide.

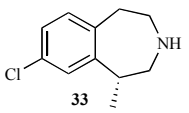
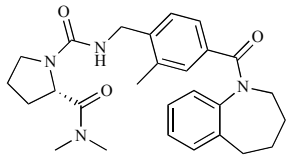
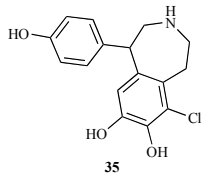
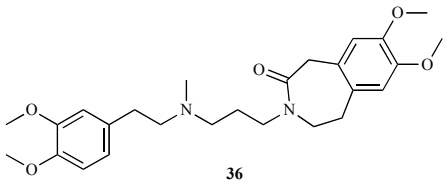
Table 1. Commercially available drugs contain azepine derivatives.

S.No.	Drug Common Name	Structure	Pharmacological properties.	References
1	Omapatrilat	 **17**	Hypertension	[24]
2	Quetiapine	 **18**	Major depressive disorder.	[25]
3	Temocapril	 **19**	Hypertension and Congestive heart failure, Diabetic Nephropathy, and Improvement of prognosis for coronary artery diseases	[26]
4	GSK-2330672	 **20**	Treatment of Diabetes Mellitus,	[27]
5	Taselisib	 **21**	Breast Cancer, Ovarian Cancer, Solid Neoplasm, and HER2/Neu Negative, among others.	[28]
6	Eleclazine	 **22**	Heart Disease.	[29]
7	Cetiedel	 **23**	Anti-sicking agent.	[30]

(Table 1) contd….

S.No.	Drug Common Name	Structure	Pharmacological properties.	References
8	Glisoxepide	 **24**	Anti-diabetic	[31]
9	Setastine	 **25**	Anti- allergic.	[32]
10	Tolazamide	 **26**	Type -2 diabetes.	[33]
11	Anthramycin	 **27**	Anti-tumor	[34]
12	Mianserin	 **28**	Anti-depressant	[35]
13	CID755673	 **29**	Protein kinase D inhibitor	[36]
14	Benzazepril	 **30**	High blood pressure	[37]
15	Galantamine	 **31**	Alzheimer's disease	[38]
16	Cephalotaxine	 **32**	Antitumor agent	[39]

(Table 1) contd….

S.No.	Drug Common Name	Structure	Pharmacological properties.	References
17	Lorcaserin	 **33**	Treatment of obesity	[40]
18	Fedovapagon	 **34**	Antidiuretic	[41]
19	Fenoldopam	 **35**	D1-like receptor agonist	[42]
20	Zatebradine	 **36**	Cardioprotective drugs	[43]

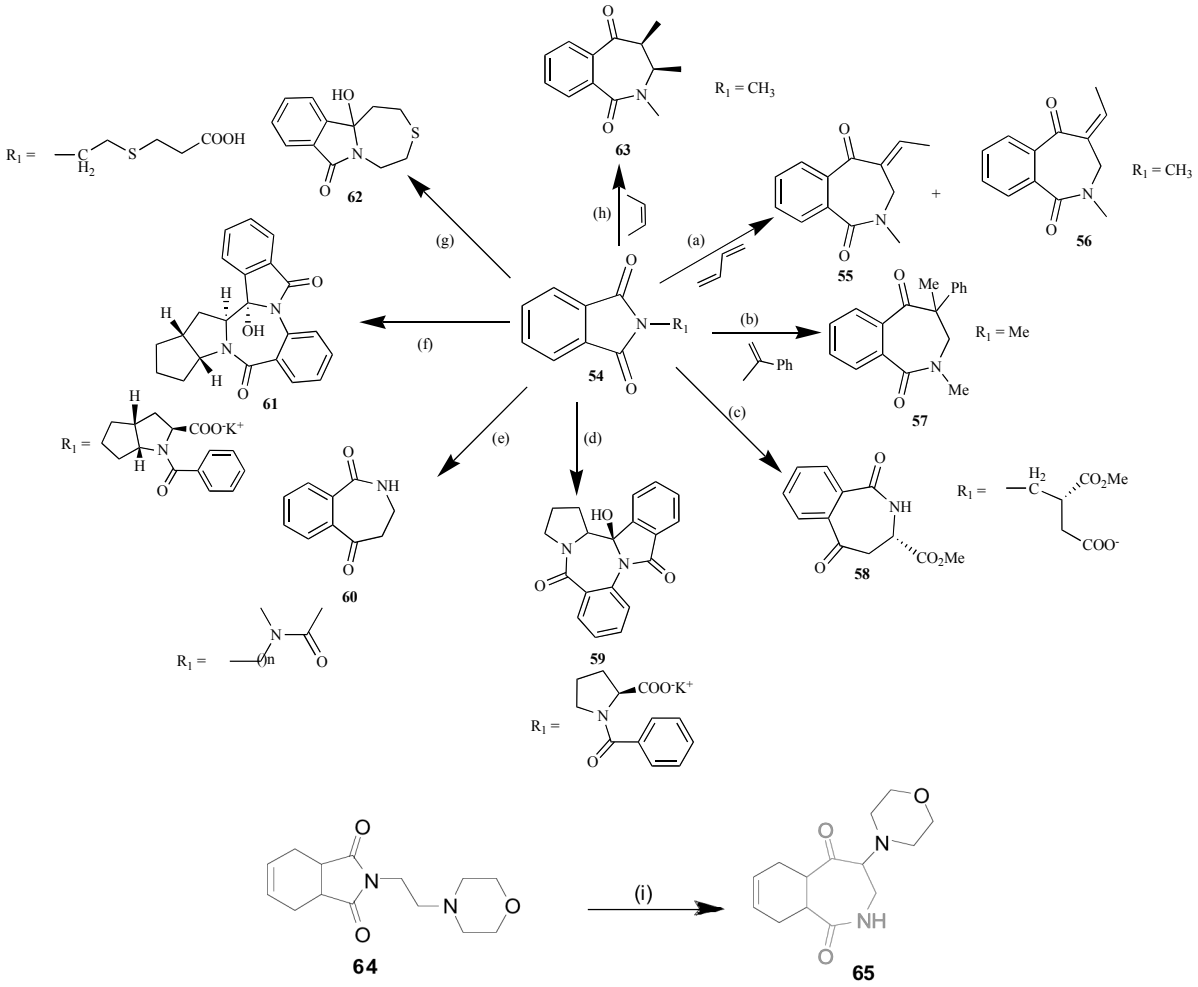
triplet nitrene **51** undergoes intersystem crossing and result in the formation of a dimerized product **50**. By the ring expansion of benzazirine yield didehydroazepine **37,** which upon treatment with nucleophile gives a number of highly strained azepine derivatives depending upon the type of nucleophile used in the reaction **48 & 53**. The treatment of didehydroazepine **47** with water yields 3H-Azepenones **52 [**57, 58]. However, in fewer cases, the ring contraction of singlet aryl nitrene **35** can also take place to provide cyanocyclopentadienes **49 [**54, 59].

2.1.2. Synthesis of Benzazepindiones and its Homologous from Substituted Indole

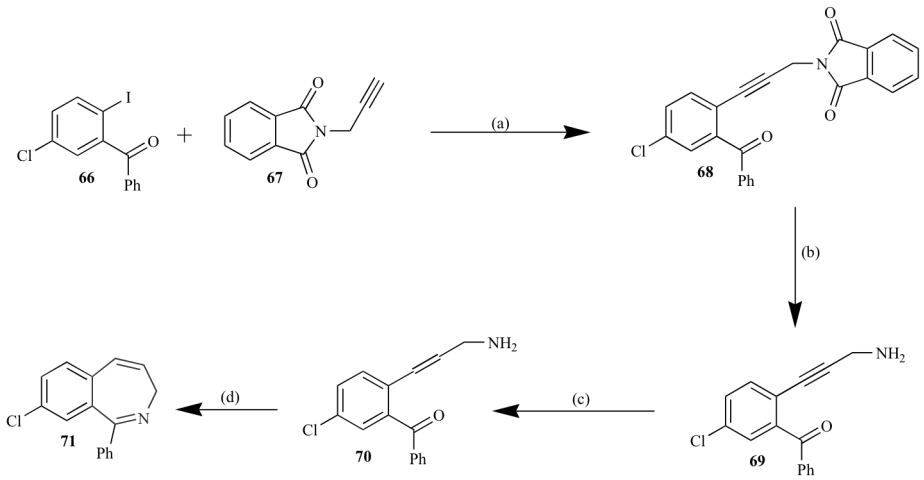
Substituted Benzazepinedione and its homologous were prepared either by the ring expansion of 5-membered heterocyclic ring of 1H-isoindole-1,3(2H)-dione **54** or by the cyclization under variable photochemical irradiation reaction conditions (Scheme **3**). Mazzocchi and co-workers [61] synthesize substituted benzazepinediones **55-57** by the $[\pi^2+\sigma^2]$ photocycloaddition of 1-substituted, 1,2-disubstituted, and 1,1-disubstituted alkenes with substituted 1*H*-isoindole-1,3(2*H*)-dione in MeCN to give a maximum yield [59,60] of 93%. Axel *et al.* [62] and Machida *et al.* [68] photochemically synthesized substituted benzazepinone **58 & 60** from compound **54** under the mild reaction condition. In acetone substituted 1*H*-isoindole-1,3(2*H*)-dione **undergoes** intramolecular cyclization to form the substituted benzdiazepanones **59** and tetrahydro-[1,4]thiazipine **62** derivative in about 70% yield [62-69, 70]. The product formed shows high stereoselectivity and diastereoselectivity [62-69]. Griesbeck *et al.* [67] and find a new protocol for the synthesis of [1,4]pyrrolobenzodiazepine **61** in MeCN using compound **54** in 86% yield. In 1983, Bryant [72] and his co-workers worked on the synthesis of benzazepine **65** by intramolecular cyclization and photo-chemically ring-opening of substituted 1H-isoindole-1,3(2H)-dione in **64** MeCN to give 74% yield.

Roche Synthesis [73] is one of the most effective methods for the synthesis of benzazepine derivatives (Scheme **4**). When (5-chloro-2-iodophenyl)(phenyl)methanone **66** couples with 2-(prop-2-yn-1-yl)isoindoline-1,3-dione **67** under basic condition using Palladium as a catalyst it gives 2-(3-(2-benzoyl-4-chlorophenyl)-prop-2-yn-1-yl)isoindoline-1,3-dione **68** as an intermediate product followed by the removal of phthaloyl protecting group to give free primary amine *i.e.,* (2-(3-aminoprop-1-yn-1-yl)-5-chlorophenyl)-(phenyl)methanone **69** which is further hydrogenated to give (2-(3-aminoprop-1-en-1-yl)-5-chlorophenyl)(phenyl)methanone **70** followed by ring cyclization to give the desired 8-chloro-1-phenyl-3H-benzo[c]azepine **71** in 92% yield.

Mingo [74], with his co-workers, worked on the synthesis of tricyclic Skelton, which proved to be a drug for ovarian cancer [85]. The chiral Pd-catalyzed azepin-indolone **73** was synthesized in 98% yield by the reaction of NSO_2Py-protected (S)-tryptophan methyl ester **72** under the desired reaction conditions at very high temperature *i.e.*, 383K. Wei [75], along with co-workers, worked on the $ZnBr_2$ Catalyzed [5+2] annulations of substituted indoles **72** with N-tosyl-4-ethyl-2,3-dihydropyrrole. The product formed by the reaction of $ZnBr_2$-catalyzed indole with N-tosyl-4-ethyl-2,3-dihydropyrrole, the intermediate undergoes decarboxylation on reaction with NaCl in wet DMSO at 403K, and the final product was formed in 50% yield by the intramolecular cyclization after removal of N-tosyl group by Na/naphthalene. (-)-aurantioclavine *i.e.,* 6-isobutyl-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole **74 & 75** is an azepino-indole-type alkaloid which was isolated from Penicillium aurantiovirens in 1998 [76]. Yamada *et al.* [77] worked on the synthesis of this alkaloid by Pictet–Spengler cyclization. The reaction of protected 5-hydroxytryptamine **72** and enal lead to the formation of iminium ion, which was further attacked by the adjacent ring to give the desired azepine as a triflate derivative to avoid ring opening. In the final step, deprotection and deoxygenation gave the desired azepino-indole-type alkaloid, *i.e.,* (-)-aurantioclavine **76** in 80% yield. Qu *et al.* [78] synthesized azepino-indole derivative *via* a two-step reaction pathway. Initially, indole **72** is transformed

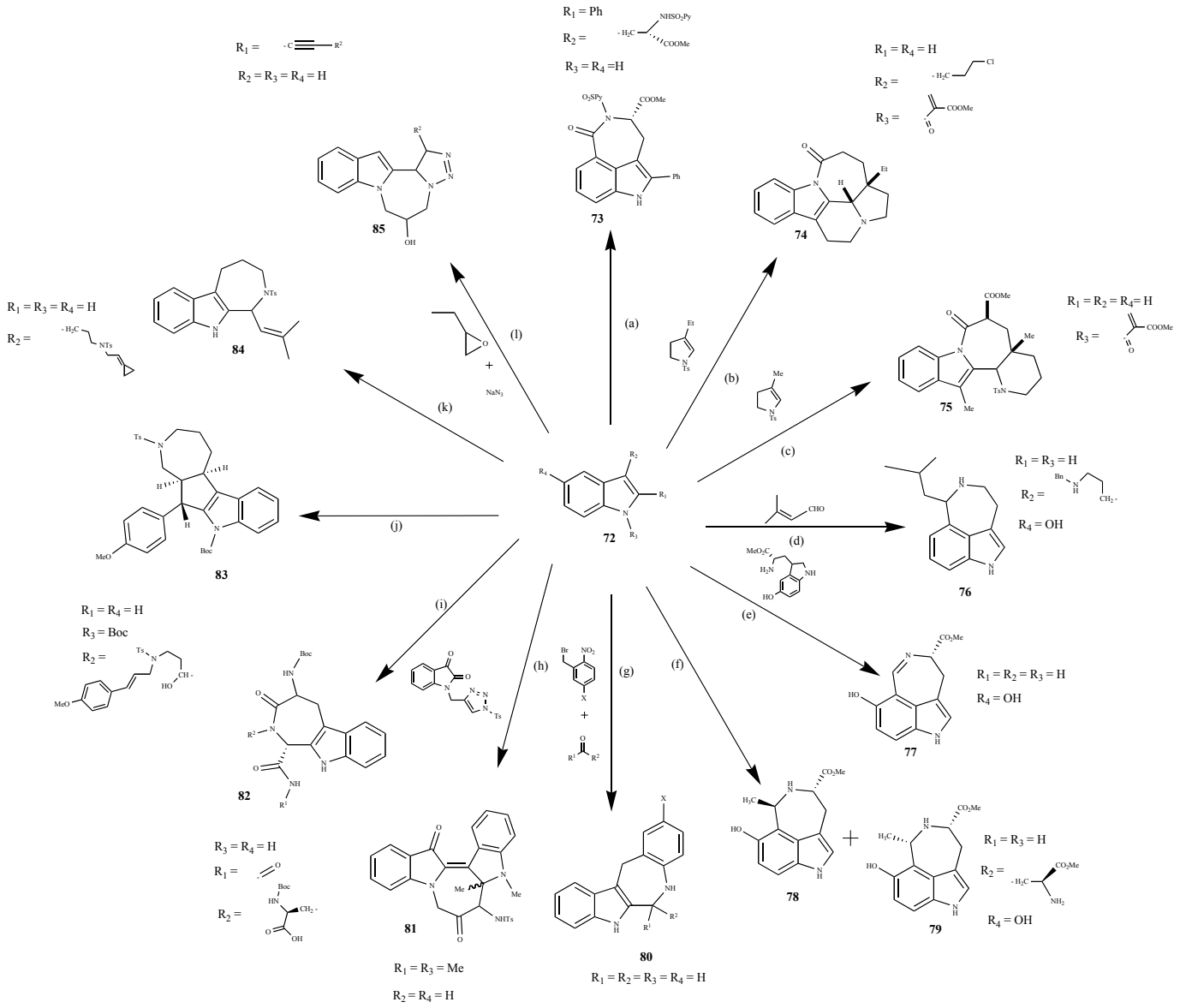


Scheme 3. Synthesis of benzazepinedione and its derivatives by intramolecular cyclization of substituted 1H-isoindole-1,3(2H)-dione. Reagents: a) hν, MeCN; [59, 60] b) hν, MeOH; [60, 61] c) hν, ^{3}Sens; [62, 63] d) hν, acetone/H_2O >98%de/ >86% ee; [64-67] e) hν/acetone, n=4; [68, 69] f) hν, acetone/H_2O,>98% de; [63, 67] g) hν, acetone/H_2O; [63, 70] h) hν, MeCN; [71] i) hν, MeCN, HgI/Lamp [72].



Scheme 4. Synthesis of benzazepine derivative *via* Roche synthesis. Reagents: a) $PdCl_2$, Ph_3P, CuI, Et_2NH; b) $MeNH_2$; c) 10% Pd/C, $BaSO_4$, H_2 [73].

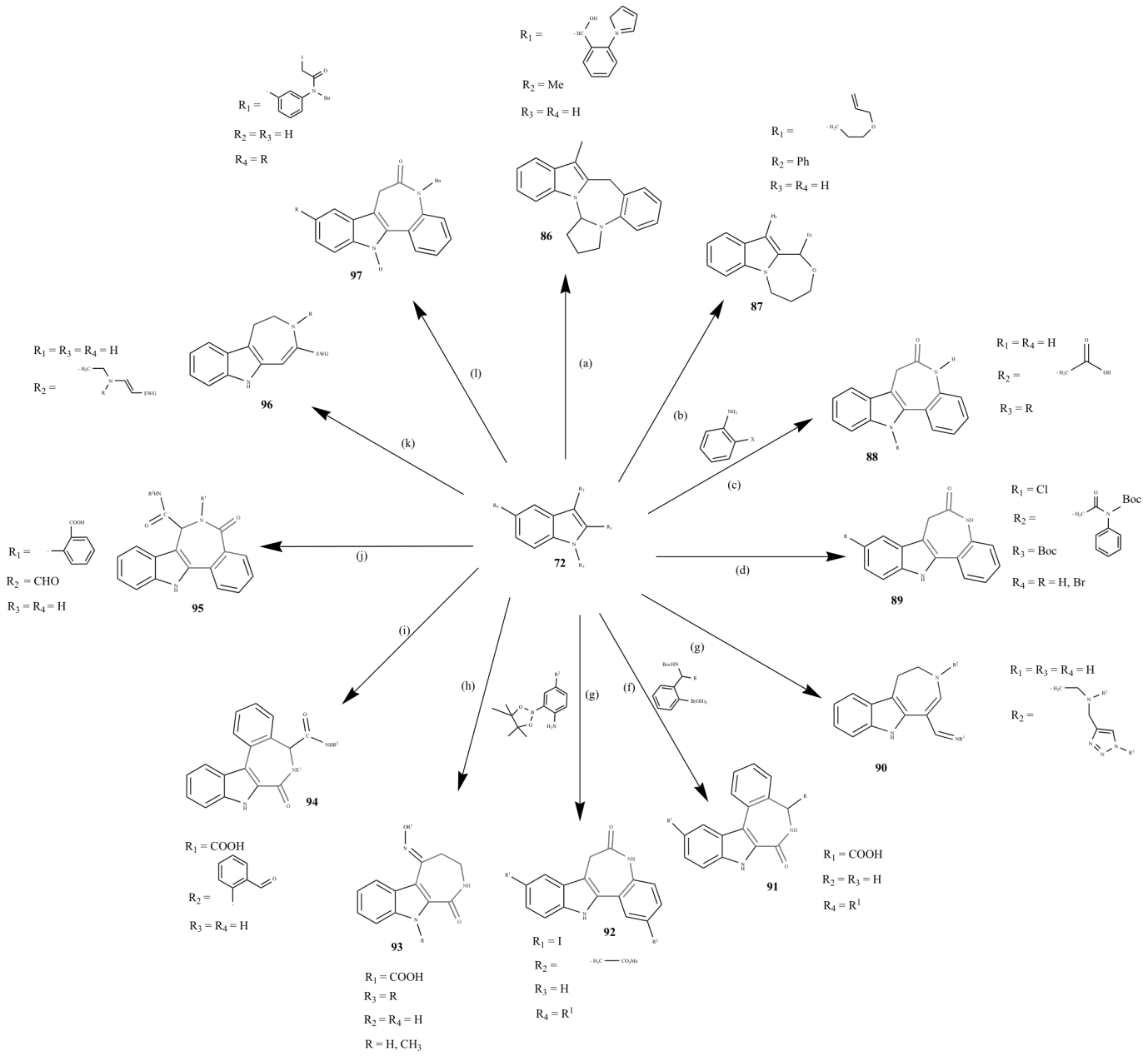
into an indole carbaldehyde, which under basic conditions, reacts with tryptophan derivative to give azepino-indole. The latter is converted to the (S)-methyl 7-hydroxy-3,4-dihydro-1H-azepino[5,4,3-cd]indole-4-carboxylate *i.e.*, fargesin core **77** in three reaction steps. The core of fargesin is a natural product extracted from Evodia fargesii. Abe and Yamada [79] worked on the synthesis of Hyrtioreticulin C and D **78 & 79** by reacting 5-hydroxytryptophan **72** with ethanal under basic conditions. Sharma *et al.* [80] synthesized 6,6,10-trimethyl-5,6,7,12-tetrahydrobenzo [6,7]azepino[3,4-b]indole **80** by reacting indole **72** with 2-



Scheme 5. Synthesis of azepino-indole derivative. Reagents: a) $Pd(OAc)_2$ (10 mol%), $Mo(CO)_5$ (0.33 equiv) AgOAc (1.5 equiv) BQ (2 equiv) CD_3COOD (6 equiv), 1,4-dioxane, 110 °C, 4h;[74] b) (i) $ZnBr_2$ (10 mol%), 4A MS, DCM (12.5 ml), 35°C, 84h; (ii) NaCl, DMSO-H_2O, 130°C, 1.5h; (iii) Na/Naphthalene, DME, -78°C, 10 min, Cs_2CO_3, NaI, CH_3CN, 65°C, 4h; [75] c) $ZnBr_2$ (10 mol%), 4A MS, DCM (12.5 ml), 25°C, 48h; [76] d) (i) Et_3N, MeOH, rt 5h, (ii) Tf_2O, Et_3N, DCM, 0 °C, 30min, (iii) Pd-C, H_2, MeOH, rt; [77] e) DABCO, TFE, reflux, 24h; [78] f) DIEE, MeOH, reflux, 6h; [79] g) (i) Na_2CO_3, acetone, H_2O, 70 °C, 36h, Fe, HCl, EtOH, 100°C, 1.5h (ii) TFA (2%) in DCM, rt, 30min to 30h; [80] h) 5 mol%, $Rh_2(Oct)_4$, DCE, 80 °C, 8h; [81] i) CNR_1, NH_2R_2, MeOH, 70 °C; [82] j) (i) TFA (8 equiv), DCM, 0°C, (ii) $B(C_6H_5)$ (20mol%), DCM, 4A MS; [83] k) $[RhCl(PPh_3)_3]$ 5mol%, toluene, 110-120°C; [84] l) Cs_2CO_3, DMSO, 120 °C, MW, 90min [85].

nitrobenzylbromide. The substrate formed is then treated with ketone or aldehyde to form the desired product. Kahar [81] and his team worked on the reaction of 1,2-dimethyl indole **72** with triazole under the desired reaction conditions, which results in semipinacol rearrangement/1,3-dipolar cycloaddition to give octahydroazepino diindole **81** in 88% yield as diastereoisomers. A three-component Ugi reaction, *i.e.*, aminindoloazepinone derivatives **82**, was reported by Jida *et al.* [82] under the optimized reaction conditions. The acid-promoted [83] cyclization reaction produced azepino-fused cyclopenta[b]indole derivative **83**. Zhang *et al.* [84] synthesized azepinoindole derivative **84** by the rhodium(I)-catalyzed cycloisomerization of nitrogentethered indole-alkylidenecyclopropanes **72**. Gillmore *et al.* [85] worked on the synthesis of indolo(triazolo)-1,4-diazepine derivatives **85** by a microwave-heated involving N-alkylation of indole **(72)** with epichlorohydrin, followed by ring-opening of the epoxide ring with azide, which further undergoes intramolecular azide-alkyne 1,3-dipolar cycloaddition reactions [86] (Scheme **5**).

In continuation of the above work, Liu *et al.* [87] worked on the synthesis of indolodiazepines **86** *via* 7-cyclization cascades or [1,5] hydrogen shifts. (3-methyl-1H-indol-2-yl)(2-(pyrrolidin-1-yl)phenyl)-methanol was reacted with $BF_3.Et_2O$ at 373K, 10-methyl-2,3,9,15a-tetrahydro-1H-benzo[4,5]pyrrolo[2',1':2,3] [1,3]diazepino [1,7-a]indole **(86)** was formed in 92% yield. Lombardo [88], along with his team, worked on the synthesis of Iridium catalyzed 1-ethyl-11-phenyl-1,3,4,5-tetrahydro-[1,4]oxazepino[4,3-a]indole **87** from



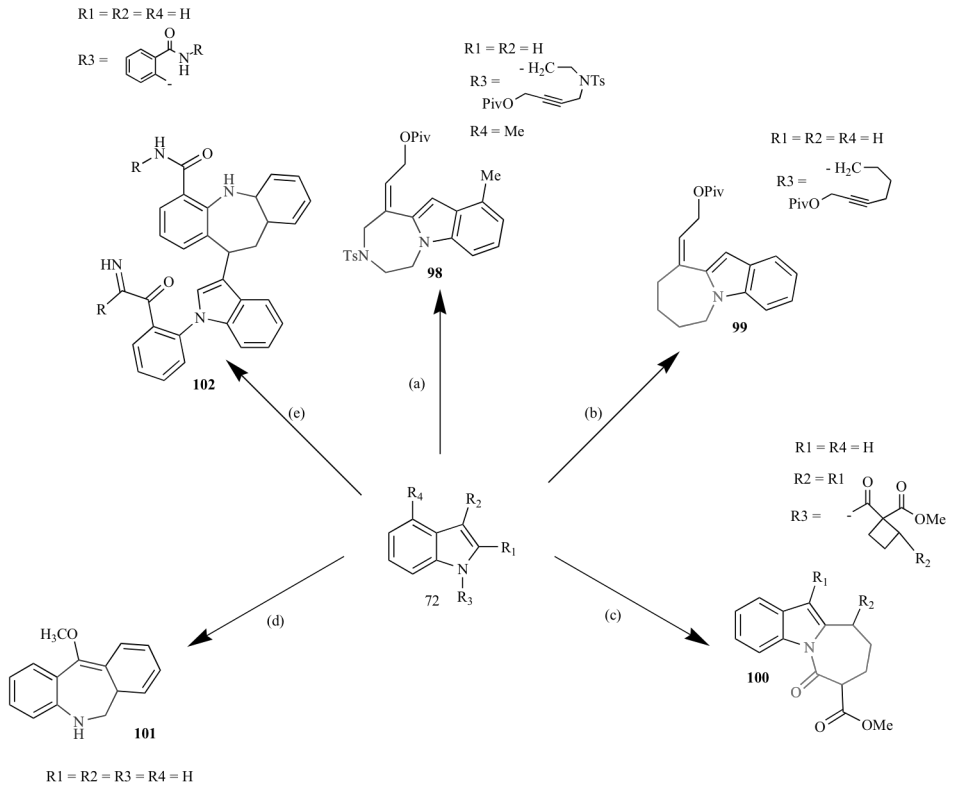
Scheme 6. Synthesis of indolodiazepines *via* cyclization. Reagents: a) $BF_3.Et_2O$ (10mol%), toluene, 353K, 10min; [87] b) $[IrH_2(THF)_2(PPh_2Me)_2]PF_6$ (1mol%), $Bi(OTf)_3$ (1mol%), THF, rt; [88] c) (i) DCC in DCM (ii) Heck reaction, $Pd(OAc)_2$, PPh_3; [89] d) *hv*, Ar, Acetone, Pyridine, (ii) $Mg(ClO_4)_2$, CH_3CN, 60ºC, 3h, (iii) K_2CO_3, MEOH-H_2O (3:1) reflux, 15h; [89] e) Rh catalyzed; [94] f) (i) Cat. H_2SO_4, EtOH, reflux, 16h, KOH, I_2, DMF, rt, 45 min, $PhSO_2Cl$, NaH, THF, rt, 16h, (ii) $Pd(PPh_3)_4$, Na_2CO_3, toluene-EtOH (1:1), reflux, 20 h, (iii) TFA, DCM, rt, 16h, Na/EtOH, reflux, 20h; [95] g) $Pd(OAc)_2$, dppf, CuCl, Cs_2CO_3, DMF, 353K; [96] h) beta-alanine ethyl ester, EDCl, DMAP, DCM, (ii) $MeSO_3H$, P_2O_5, 353K, (iii)$NaOR^1$, $BF_3.OEt_2$, pyridine, THF; [97] i) R^1NH_2 + R^2NC, MeOH, 323K; j) R^1NH_2 + R^2NC, MeOH, 323K; [98] k) N-Bromosuccinimide, Br^+; [99] l) Bu_3SnH, AIBN, toluene, relflux [100].

2-(3-(allyloxy)propyl)-3-phenyl-1H-indole **72** at room temperature in 75% yield. The reactant **72** undergoes an isomerization/protonation series by a Prins-type oxocarbenium intermediate, with successive C–C bond formation to give oxepane-fused indole **87**. The synthesis of paullone *i.e.*, 7,12-dihydroindolo[3,2-d][1]benzazepin-6(5H)-one **88** from *o*-halo anilides of indole by heck coupling reaction is the second most general procedure [89-92]. Zarraga *et al.* [90] designed a straightforward Heck coupling reaction for the synthesis of oxepane-fused indole **88** from *o*-Bromo and *o*-Iodo anilides and 3-indolylacetic acid **72** in a solution of DCC in DCM by a Pd-catalyzed intramolecular coupling. Li *et al.* [93] described an effective route for the synthesis of paullone and kenpaullone **89** derivatives in very high yields by photoinduced intramolecular cross-coupling reactions of (2-chloro-1H-indole-3-yl)-N-arylacetamides **72** in acetone at room temperature. Zhang *et al.* [94] were successful in synthesizing azepino[4,5-b]indoles **90** by Rh(II)-catalyzed intramolecular [3+2] cycloaddition and C-H functionalization of indolyltriazoles **72**. Suzuki coupling [95] proved to be another efficient method for the synthesis of 5-alkylindolobenzazepin-7-ones **91**. This reaction involves the coupling between appropriate R-alkylbenzylamino, *o*-boronic acids and the 3-iodoindole-2-carboxylates followed by cyclization to form the

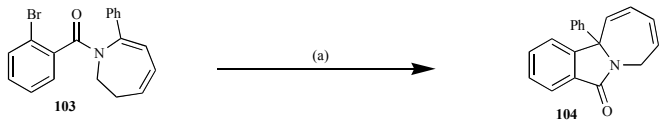
desired lactam. 3-iodoindole-2-carboxylates **92** are synthesized from indole 2-carboxylate **72**, which is first converted into the ethyl esters, and then in the presence of KOH, ethyl esters react with iodine in DMF followed by protection of indole nitrogen with a benzenesulfonyl group. The product formed is coupled with the benzylboronic acids, and then the benzyl amino group is deprotected with TFA in DCM. Soto *et al.* [96] used one-step Suzuki Miyaura cross-coupling of *o*-aminoarylboronic acid with methyl 2-iodoindoleacetate **72** followed by intramolecular amide formation for the synthesis of 7,12-dihydrobenzo[2,3]azepino[4,5-b]indol-6(5H)-one **92**. White *et al.* [97] gave a three steps reaction for the synthesis of indoloazepinones **93**. In the first step, indole-2-carboxylic acid **72** is coupled with *β*-alanine ethyl ester using EDCI coupling reagent to form a cyclized precursor of indoloazepinone. In the next step, using methanesulfonic acid-phosphorous pentoxide, indoloazepinone is gained from cyclodehydration of a cyclized precursor. The last step involves adding a Lewis acid catalyst ($BF_3.OEt_2$) to give the desired indoloazepinones derivatives **93**. Beaumont *et al.* [98] described the intramolecular four-component reaction approach for the synthesis of indoloazepinones **94 & 95**. Kumar *et al.* [99] reported a one-pot reaction cascade indole-fused azepine ring **96** *via* intramolecular cyclization of starting substrate **72**. Bremner *et al.* [100] describe the synthesis of indoloazpines derivatives **97** *via* the free-radical cyclization of N-benzyliodoacetamide in the presence of Bu_3SnH and AIBN to afford N-benzylated paullone derivative **26** (Scheme **6**).

In resemblance to the above scheme, Yang *et al.* [101] worked on the gold-catalyzed synthesis of azepine-indole ring (Scheme **7**). The substrate with the 4-methyl group on the indole ring **72** is converted to a seven-membered azepine ring **98 & 99** under the optimized reaction condition. Prasad *et al.* [102] synthesized azepino[1,2-a]indole **100** *via* intramolecular ring-opening cyclization of cyclobutanes **72**. Indole [103] undergo a substitution reaction with bromobenzene followed by ring cyclization under the optimized reaction condition to form the 11-methoxy-6,6a-dihydro-5H-dibenzo[b,e]azepine **101**. Kotipalli *et al.* [104] Synthesized 10-(1-(2-(2-iminoacetyl)phenyl)-1H-indol-3-yl)-5,10,11,11a-tetrahydro-4aH-dibenzo[b,f]azepine-6-carboxamide derivative **102** by the ring expansion of substituted indole **72** under acidic condition in DCM at room temperature.

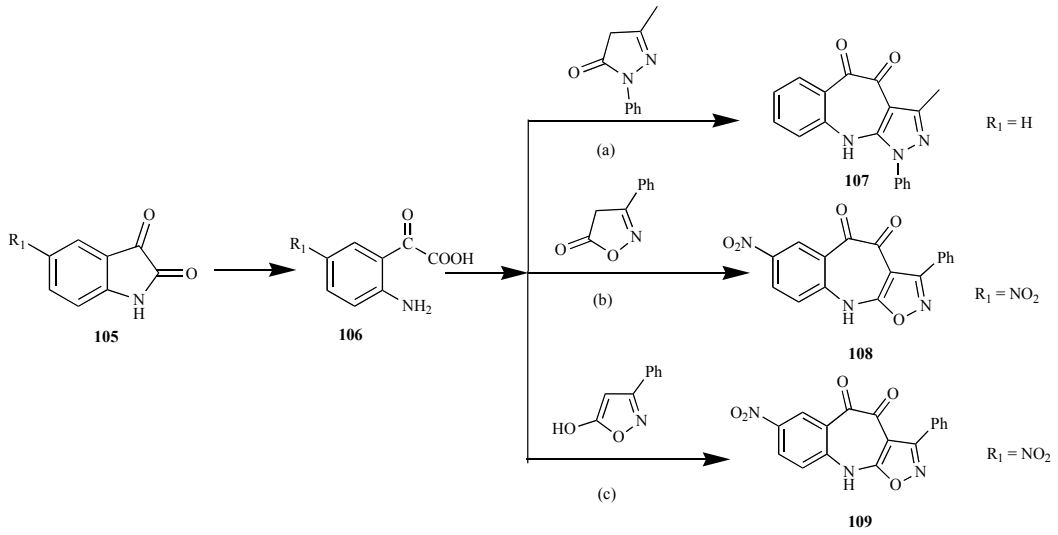
Zhu, *et al.* [105a] were successful in the synthesis of 11a-phenyl-7,11a-dihydro-5H-azepino[2,1-a]isoindol-5-one **104**. 11a-phenyl-7,11a-dihydro-5H-azepino[2,1-a]isoindol-5-one **103** was obtained by the intermolecular cross-coupling reaction between α-carbon of tertiary enamide and the bromobenzene moiety of compound **103** at 80°C under the appropriate reaction conditions to give the fused tricyclic azepine ring in 92% yield (Scheme **8**).



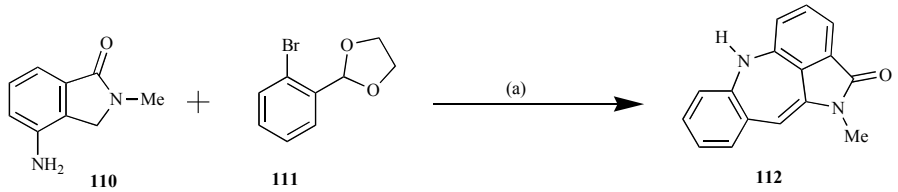
Scheme 7. Synthesis of Indole derivatives. Reagents: a) [Au(*n*-BuPAd$_2$)(CH$_3$CN)][SbF$_6$] (2.5 mol%), DCE, H_2O (1.0 equiv), 353K, 3h;[101] b) [Au(*n*-BuPAd$_2$)(CH$_3$CN)][SbF$_6$] (2.5 mol%), DCE, H_2O (1.0 equiv), 353K, 3h;[101] c) Sc(OTf)$_3$ (10 mol%), DCM, rt, 1h;[102] d) (i) ArBr, DBTL, (ii) P_2O_5.CH_3SO_3H (1: 10), (iii) NaOH/MeOH, reflux, 24h; [103] e) $BF_3.OEt_2$, DCM, rt, [104].



Scheme 8. Synthesis of 11a-phenyl-7,11a-dihydro-5H-azepino[2,1-a]isoindol-5-one by intramolecular cross coupling reaction. Reagents: Pd(dba)$_2$ (5 mol%), PPh$_3$ (10 mol%), PivOH (30 mol%), Cs_2CO_3 (1.5 equiv), Mesitylene, 80°C. 12h [105a].



Scheme 9. Reaction of substituted 1H-indole-2,3-dione. Reagents: a) hν, THF, 48h; b) hν, THF, 48h; c) hν [105b].



Scheme 10. Synthesis of 1-methyl-1H-benzo[6,7]azepino[4,3,2-cd]isoindol-2(6H)-one. Reagents: a) (i) $Pd(OAc)_2$, S-Phos, Cs_2CO_3, toluene, MW, 150ºC, 20 min; (ii) *p*-TsOH, EtOH/H_2O, rt, 10 min, then K_2CO_3, EtOH, reflux, 12h [106].

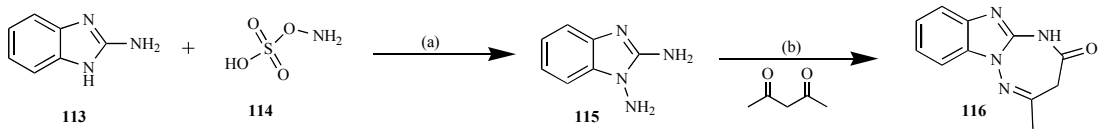
Isatin **105** is another key reactant used by Sharma and his co-workers [105b] for the synthesis of various substituted benzazepinediones **107-109** under photolytic conditions (Scheme **9**). Synthesis of compound **107-109** from isatin took place by the condensation of isatic acid **106** intermediates with isoxazolone and pyrazolone to form different substituted benazepines as a major product in low yield of about 30-40%.

Song *et al.* [106] synthesized 1-methyl-1H-benzo[6,7]azepino-[4,3,2-cd]isoindol-2(6H)-one **112** by the reaction of 4-amino-2-methylisoindolin-1-one **110** and 2-(2-bromophenyl)-1,3-dioxolane **111** under microwave irradiation to form the product in low yield (Scheme **10**).

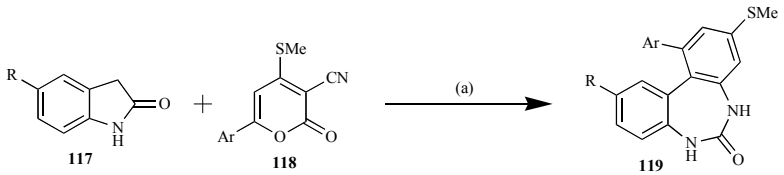
Bakri *et al.* [107] proposed a straight pathway for the synthesis of 2-methyl-3H-benzo[4,5]imidazo[1,2-b][1,2,4]triazepin-4(5H)-one **116** by the condensation of 1H-benzo[d]imidazol-2-amine **115** with ethyl acetoacetate in a solvent-free system at 453K. The compound **115** was prepared by the reaction of 1H-benzo[d]imidazol-2-amine **113** with (aminooxy)sulfonic acid **114** under the basic condition (Scheme **11**).

Kumar *et al.* [108, 109] in 2003 observed that indolin-2-ones **117** undergo conjugate addition with 2H-pyran-2-one-3-carbonitriles **118** under optimized reaction condition in a strongly basic medium to produce dibenzo[d,f]diazepinones **119** as in final compound in good to excellent yield (Scheme **12**).

Isatin derived enals are the key reactant used by Gao *et al.* [110] for the synthesis of spirocyclic oxindole-benzofuroazepinones **122** by NHC-catalysed [3+4] annulation of enal **120** and azadienes **121**, which possess a wide range of biological activities against cancer cells (Scheme **13**). In this reaction, Isatin-derived enals **120** reacts with aurone-derived azadienes **121** to form the desired product, *i.e.,* spirocyclic oxindole-benzofuroazepinones **122** at room temperature in an acceptable amount.



Scheme 11. Synthesis of 2-methyl-3H-benzo[4,5]imidazo[1,2-b][1,2,4]triazepin-4(5H)-one from 1H-benzo[d]imidazol-2-amine. Reagents: (i) KOH; (ii) 453K, 2h [107].



Scheme 12. Synthesis of substituted dibenzidiazepinones. Reagents: a) *t*-BuOK, *t-Bu*OH, Δ [108, 109].

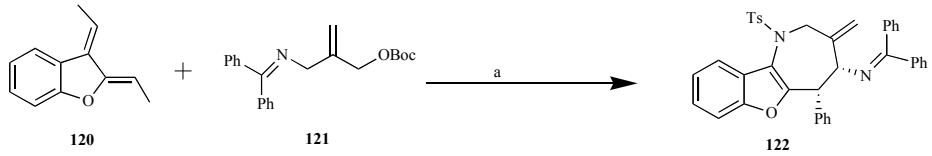
Isatin derived enals **123** are the key reactant used by Gao *et al.* [111] for the synthesis of spirocyclic oxindole-benzofuroazepinones **125** by NHC-catalysed [3+4] annulation of enal and azadienes, which possess anti-cancer properties. In this reaction, Isatin-derived enals **123** react with Aurone-Derived Azadienes **124** to form the desired product **125** (Scheme **14**).

Kim *et al.* [112] gave Rh-catalysed synthetic route for the synthesis of a tricyclic moiety, *i.e.,* azepinoindles **128**, which possess a wide range of biological properties. At 80°C, diazoindolin-2-imines **126** undergo [4+3] cycloaddition with 1,3-dienes **127** to form substituted azepinoindoles *i.e.,* 10-methyl-2-phenyl-1-tosyl-1,2,5,10-tetrahydroazepino[2,3-b]indole **128** as major product (Scheme **15**).

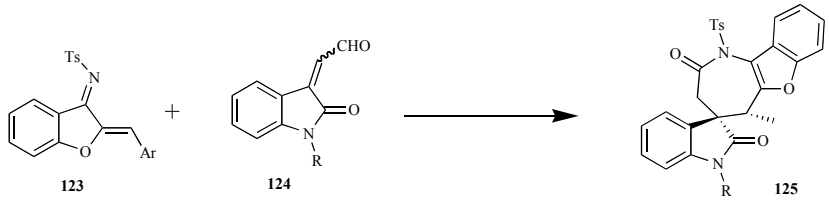
2.1.3. Synthesis of Benzazepine and its Derivatives from Aryl Halides

Substituted aryl halides were taken as a key reactant for the synthesis of various azepine derivatives under various reaction conditions (Scheme **16**). In 2012, Ciofi [113] and his co-workers worked on the synthesis of Ti-/Cu catalyzed benzdiazepinone **130** derivative in methylamine from substituted aryl halides **129** to give a yield of about 60%. Yang [110], along with his co-workers, was successful in synthesizing substituted benzazepinone **131**. The aryl halides **129** were cyclized by the Cu-catalyzed intramolecular N-arylation, to get the desired product *i.e.,* benzazepinone **131** [114, 115]. Ma *et al.* [116] and his co-workers in 2009 synthesize the copper-catalyzed benzodiazepinones **132-133** derivatives in 64% yield obtained by the reaction of o-benzylamines and amino acids. By heating, the reactant at 363K, undergo C–N coupling and intramolecular dehydration Amidation by reacting it with DMAP, DMF, and CuI as a base to give the target product [117]. Ohta [118] and his co-workers in 2008, uses N-methyl-2-ethynylaniline **60** as a key reactant to synthesize Cu catalyzed indole-fused benzo-1,4-diazepines **134** under microwave irradiation. The product was formed in 88% yield using HCHO, dioxane, and sodium methoxide as a base [119]. 2-chloro nitrobenzoic acid **129** is another key reactant used by Wang and his co-workers for the synthesis of Cu catalyzed benzodiazepine-2,5-diones derivative **135**. 2-chloro nitrobenzoic acid **129** undergo a number of steps to form the targeted compound, *i.e.*, ring cyclization, esterification, Friedel Craft acylation, Ulmn Reaction, and Friedel Craft alkylation in CH_3OH, DCC, DMAP, methylamine, potassium carbonate and using triethylamine as a base [120, 121]. Aryl iodides **129** with amine as a functional group on the second position were utilized as a coupling reagent for the synthesis of benzo[b]thiophene derivative connected with diazepinone ring [73] **136**. The product was obtained after 72 hours of cross-coupling with 2-iodoaniline **129**. Lu [123], with his team in 2010, uses the chiral reactant **129** to synthesize the product in 46-97% enantiomeric excess. Pyrrolo[2,1-c][1,4]-benzodiazepine-5,11-diones **137** was afforded in very high yield by the coupling of methylamine with aryl halides **129**. In 2018, Casnati [124] was successful in synthesizing the Pd catalyzed Azepine derivative at a very high temperature (378K) in a very high yield. Pd catalyzed Azepine derivative **138** and was prepared by reacting to the 1-iodo-2-isopropoxybenzene norbornene and *o*-bromoaniline **129** in PPh_3 and using Cesium carbonate as a base in DMF. Ma.*et al.* [125] reported the synthesis of benzazepinone **139** by the intramolecular rearrangement of amino acid derivative **129** at 363K.

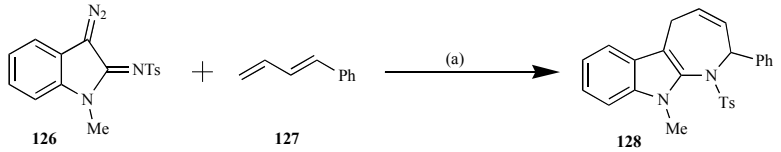
In continuation of the above framework starting with aryl halides, Guastavino, along with his co-workers [128] in 2011, synthesized benzazepinone **141** derivatives by photochemical irradiation in reflux (scheme **17**). The starting material **140** was reacted with pinacolone enolate anion, which undergoes the SN^1 mechanism in Liquid ammonia. The reaction was carried out in DMSO, AcOH, and NH_4OH to get a yield of about 88%. Lucas [128] and his co-workers in 2013, photo-chemically synthesize the benzazepine derivative **142** in very low yield by the ring cyclization. In 2019, Kaper, with his co-workers [129] synthesized titanium catalyzed Azepine derivative **143-145** using 4-(2-bromophenyl)-1-butene derivative **140** with N-methylaniline in toluene, $Pd(dba)_3$ at 413K to give the target product in very high yield, *i.e.,* 93%. Li *et al.* in 2011, developed a protocol for the syntheisis of lennoxamine **146**. The compound **140** was coupled with 1-alkyne derivative using a copper catalyst in DMF to form the intermediate, which is further converted to the desired product **146** by the procedure given by Cossy and coworkers [130]. Evano and his co-workers in 2008 [129,115], used the starting material to synthesize the Cu- catalyzed heterocyclic compound **147** in very low to average yield in CH_3CN.



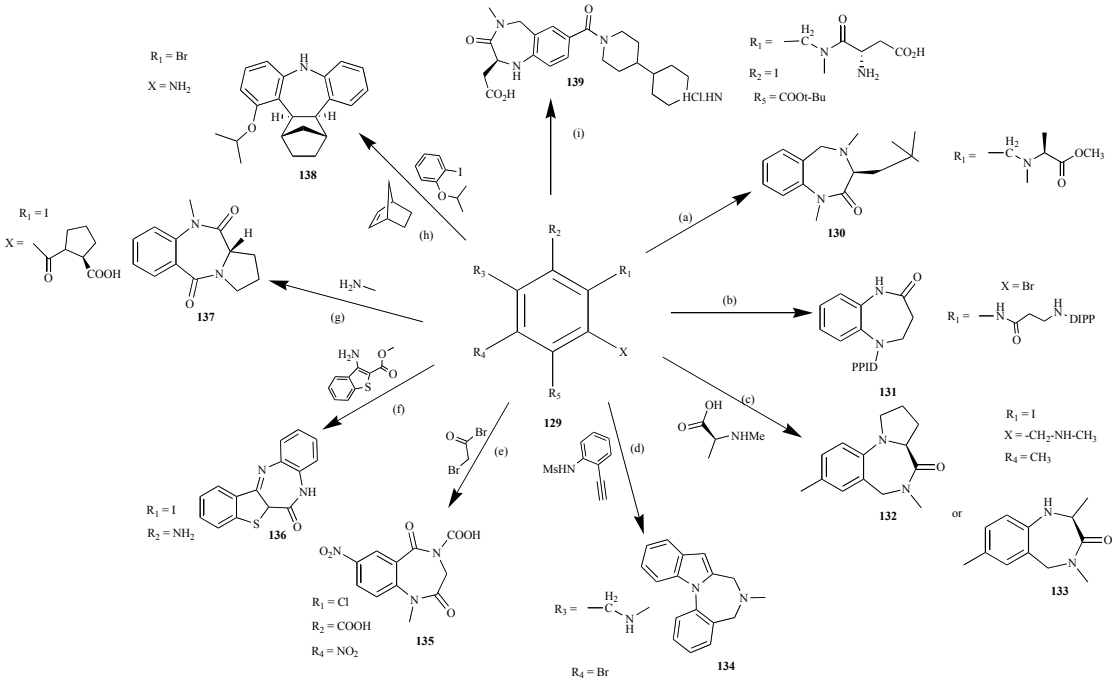
Scheme 13. Synthesis of Pd-catalyzed fused azepine by [4+3] cycloaddition. Reagents: $Pd_2(dba)_3$ (1.5mol%), L1 (6mol%), toluene, 25°C [110].



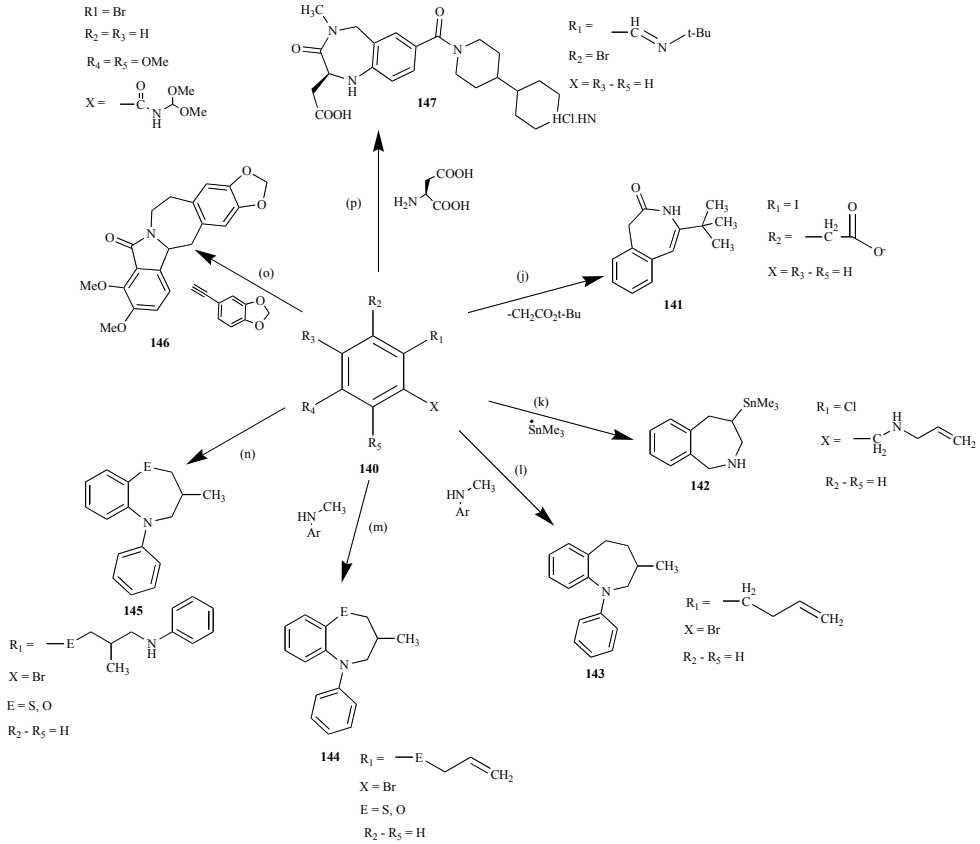
Scheme 14. Synthesis of spirocyclic oxindole-benzofuroazepinones by NHC catalyzed.



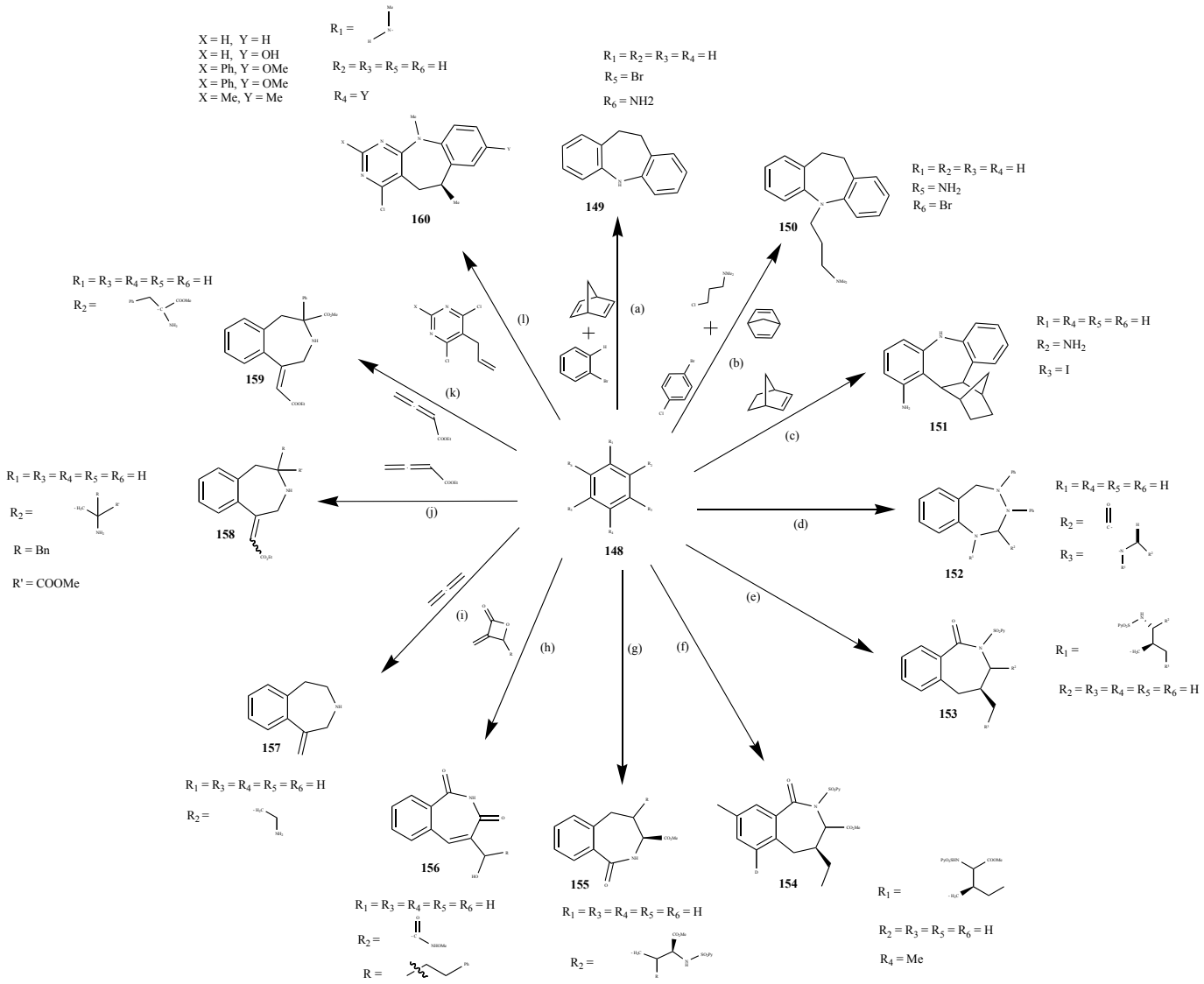
Scheme 15. One pot synthesis of Azepinoindoles *via* Rh-Catalyzed Aza-[4 + 3] Cycloaddition Reaction of 3-Diazoindolin-2-imines with 1,3-Dienes. Reagents: $Rh_2(OPiv)_4$ (1.0 mol%), PhCl, 80°C, 1h [112].



Scheme 16. Synthesis of various Cu/Pd catalyzed azepine derivatives starting with substituted aryl halides. Reagents: a) cat. $Ti(OiPr)_4$, cat. CuI, CH_3NH_2;[113] b) CuI, K_2CO_3 , toluene, 110°C;[110, 114, 115] c) 10mol% CuI,Cs_2CO_3, DMF, 90°C, DPPA, 0-5°C;[116,117] d) $(HCHO)_n$, CuI (2.5 mol%), dioxane then, Me-ONa;[118,119] e) (i) CH_3OH, DCC, DMAP (ii) CH_3-NH_2, Cu, K_2CO_3, DMF, (iii) Et_3N, DCM, (iv) CH_3-NH_2, Et_3N, DCM;[120,121] f) CuI, Cs_2CO_3,L-proline, dioxane,heat, 72h; [122] g) Cu_2O, L-proline (0.2 eq.), Cs_2CO_3, DMSO, 80°C , 1N HCl;[123] h) $Pd(OAc)_2$, PPh_3 , Cs_2CO_3, DMF,105°C, 24h;[124] i) CuI,K_2CO_3. DMF, 90°C, > 67% [125, 115, 126].



Scheme 17. Synthesis of various azepine derivatives starting with substituted aryl halides (Part 2 of scheme) Reagents: j) (i) DMSO , hν (ii) NH_4OAc , HOAc, 120 min , reflux; [126, 127] k) hν , $NH_3(l)$; [128] l) (i) 10 mol% I, toluene , 140°C, 24h (ii) 2.5 mol% $Pd_2(dba)_3$, 7 mol% RuPhos, NaO*t*-Bu, toluene, 110°C,24h ;[129] m) (i) 20 mol% I, toluene 160°C, 48h, (ii) 2.5 mol% $Pd_2(dba)_3$, 7 mol% RuPhos, NaOtBu, toluene, 110°C, 24h; [129] n) (i) 2.5 mol% $Pd_2(dba)_3$, 7 mol% RuPhos, NaOtBu (ii) toluene , 110°C, 24h; [129] o) 0.1 eq. CuI; [117, 130] p) CuI, *n*-Bu_4NOH, CH_3CN, reflux, 55% [131, 115].

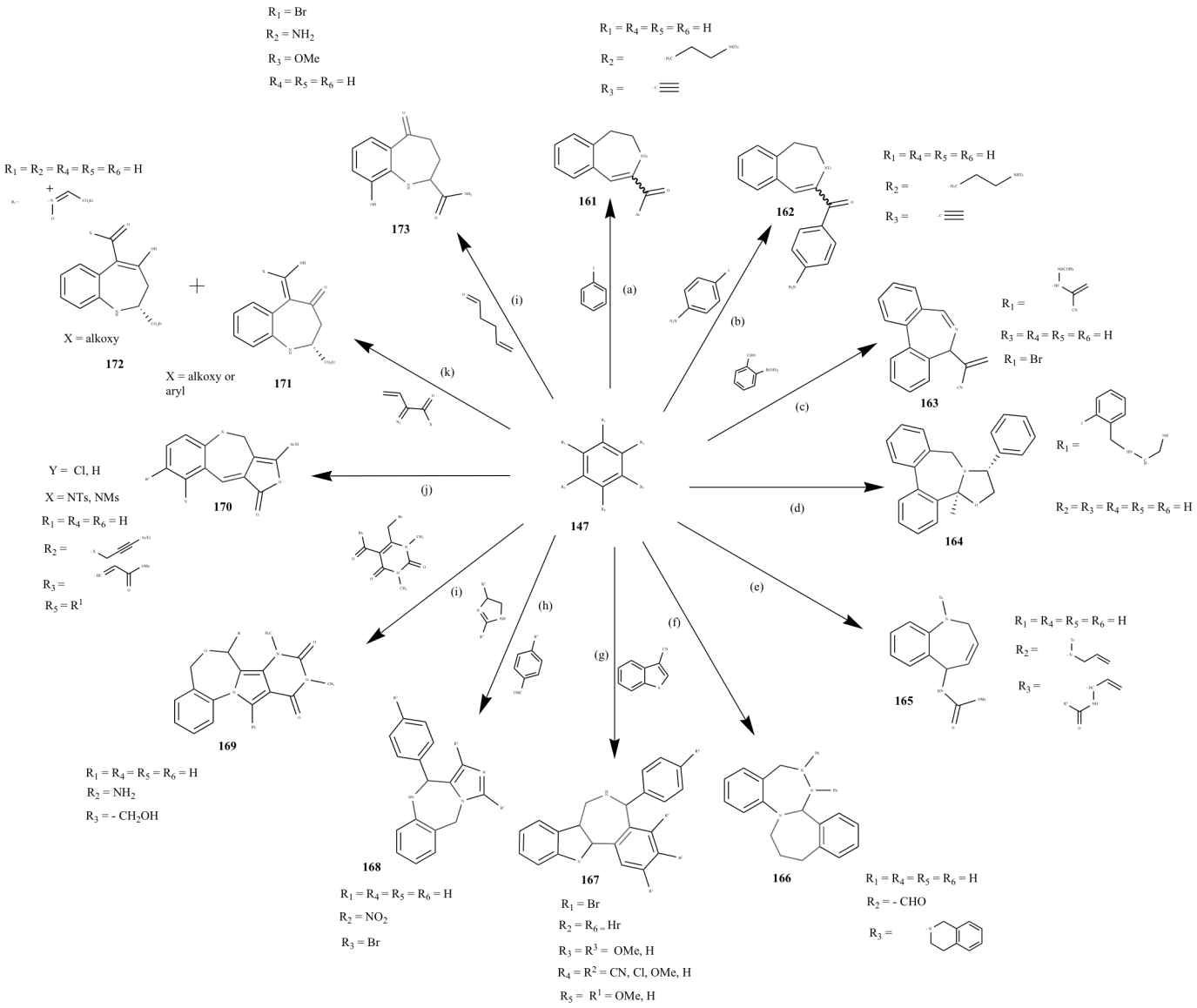


Scheme 18. Synthesis of benzazepine derivatives. Reagents: a) (i) $Pd(OAc)_2$, PPh_3, KI, Cs_2CO_3, DMF, 105°C; (ii) 130°C, 24h;[132] b) (i) 5% $Pd(OAc)_2$, 12.5% PPh_3, 50% KI, Cs_2CO_3, DMF, 105°C, 46h, 130°C, 24h; (ii) Mg, MeOH, 50°C, 1.5h.[132] c) $Pd(OAc)_2/PPh_3$, KI, Cs_2CO_3, DMF, 25h, 105°C;[132] d) HFIP;[133] e) $Pd(OAc)_2$ (10 mol%), $Mo(CO)_6$ (33 mol%), AgOAc (1.5 equiv), BQ (2.0equiv), 1.4-doixane (0.25 M), 110°C, 18h;[134] f) $Pd(OAc)_2$ (10 mol%), $Mo(CO)_6$ (33 mol%), AgOAc (1.5 equiv), BQ (2.0equiv), 1.4-doixane (0.25 M); [134] g) (i) CO, M-cat (ii) mild conditions; [134] h) $[Os(p\text{-cymene})Cl_2]_2$,CsOAc (0.5 equiv), DCE, rt, 24h; [135] i) Pd $(OAc)_2$ (6 mol%), BQ, AcOH, 80°C;[136] j) Pd $(OAc)_2$ (6 mol%), BQ, AcOH, 80°C;[136] k) Pd $(OAc)_2$ (6 mol%), BQ, AcOH, 80°C; [136] l) (i) $(Me_2CH)_2Net$; (ii) CH_3SO_3H [137].

Researchers around the world show interest in the synthesis of substituted benzazepine and its homologous under different reaction conditions from the suitability of substituted aromatic systems (Scheme **18**). Casnati *et al.* [132] worked on the synthesis of Pd-catalyzed EWG substituted 5H-dibenzo[b,f]azepines **149, 150 & 151** in the mixture of a solution of PPh_3, KI, Cs_2CO_3, DMF at different temperature range. *o*-bromoanilines **148**, norbornadiene, and aryl bromides were subjected to mild reaction conditions to give 10,11-dihydro-5H-dibenzo[b,f]azepine **149**. Using the same conditions, when 2-bromoaniline **148**, norbornadiene, and 4-bromochlorobenzene were reacted, they produce 3-chloro-5H-dibenzo[b,f]azepine in 65% yield, which was further hydrogenated to give 3-chloro-10,11-dihydro-5H-dibenzo[b,f]azepine followed by alkylation of 3-chloro-N, N-dimethylpropan-1-amine to afford the synthesis of 3-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-N, N-dimethylpropan-1-amine **150** as a final product in high yield. Similarly, When Pd-catalyzed norbornene and 2-iodoaniline **148** react under the same condition, the halogen exchange reaction took place, which leads to the formation of (IR, 4S, 4As, 13bS)-2,3,4,4a,9,13b-hexahydro-1H-1,4-methanotribenzo[b,d,f]azepin-5-amine **151** in moderate yield. HFIP [133] was reported as another versatile solvent used for amination, esterification, and hydride transfer alkylation to afford the synthesis of benzotriazepines **152**. Mingo [134], along with his team, were successful in the synthesis of benzazepinone and its homologous **153, 154 & 155** by benzyl substituted aliphatic amine **148** using the same Pd as a catalyst under the mild reaction condition in medium yield. Yang *et al.* [135] synthesized benzazepinedione derivatives **156** by [4+2] annulations of substituted 3-methyleneoxetan-2-one and N-methoxybenzamides **148** using Osmium (II) as a catalyst and DCE as a solvent at room temperature. Rodriguez [136], with his team, worked on the synthesis of substituted benzazepane **157, 158 & 159**

by the reaction of allenes with substituted benzyl amines **148**. In 2015, Lina *et al.* [137] worked on the acid-catalyzed synthesis of (S)-4-chloro-6,11-dimethyl-6,11-dihydro-5H-benzo[b]pyrimido[5,4-f]azepine **160** using N-methylaniline **148** and a dichloropyrimidine followed by intramolecular alkylation reaction under basic conditions.

In continuation of the above work, Albano *et al.* [138] paid their attention to the synthesis of dihydrobenzoazepine derivatives. They were successful in the synthesis of (2,3-dihydro-1H-benzo[d]-azepin-4-yl)arylmethanones **161** using Pd (II) as a catalyst. The iodoarenes were made to react with N-(2-ethynylphenethyl)-4-methylbenzenesulfonamide at 110°C, for 6h to obtain (2,3-dihydro-1H-benzo[d]azepin-4-yl)arylmethanones in average yield. Similarly, 1-iodo-4-nitrobenzene reacts with N-(2-ethynylphenethyl)-4-methylbenzenesulfonamide **148** under the same reaction condition to obtain aminobenzazepine derivative **162**. Bhowmik *et al.* [139] obtained 5H-dibenz[c,e]azepine **163** in more than 95% yield by the Suzuki cross-coupling reaction. 2-formylphenylboronic acid undergoes cross-coupling reaction with N-(1-(2-bromophenyl)-2-cyanoallyl)benzamide **148** at 80°C in a mixture of dioxane and Na_2CO_3 to give N-(2-cyano-1-(20-formyl-[1,10-biphenyl]-2-yl)allyl)benzamide as an intermediate product which further undergoes intramolecular cyclization by an imine formation to give 5H-dibenz[c,e]azepine **163** in 95% yield. (4S,7R)-4b-methyl-7-phenyl-4b,6,7,9-tetrahydrodibenzo[c,e]oxazolo[3,2-a]azepine **164** was synthesized in 40% yield by Suzuki intramolecular cross-coupling reaction of N-(2-iodobenzyl)-1-phenylpropan-1-amine **148** under the desired reaction condition [140]. Chwastek *et al.* [141] worked

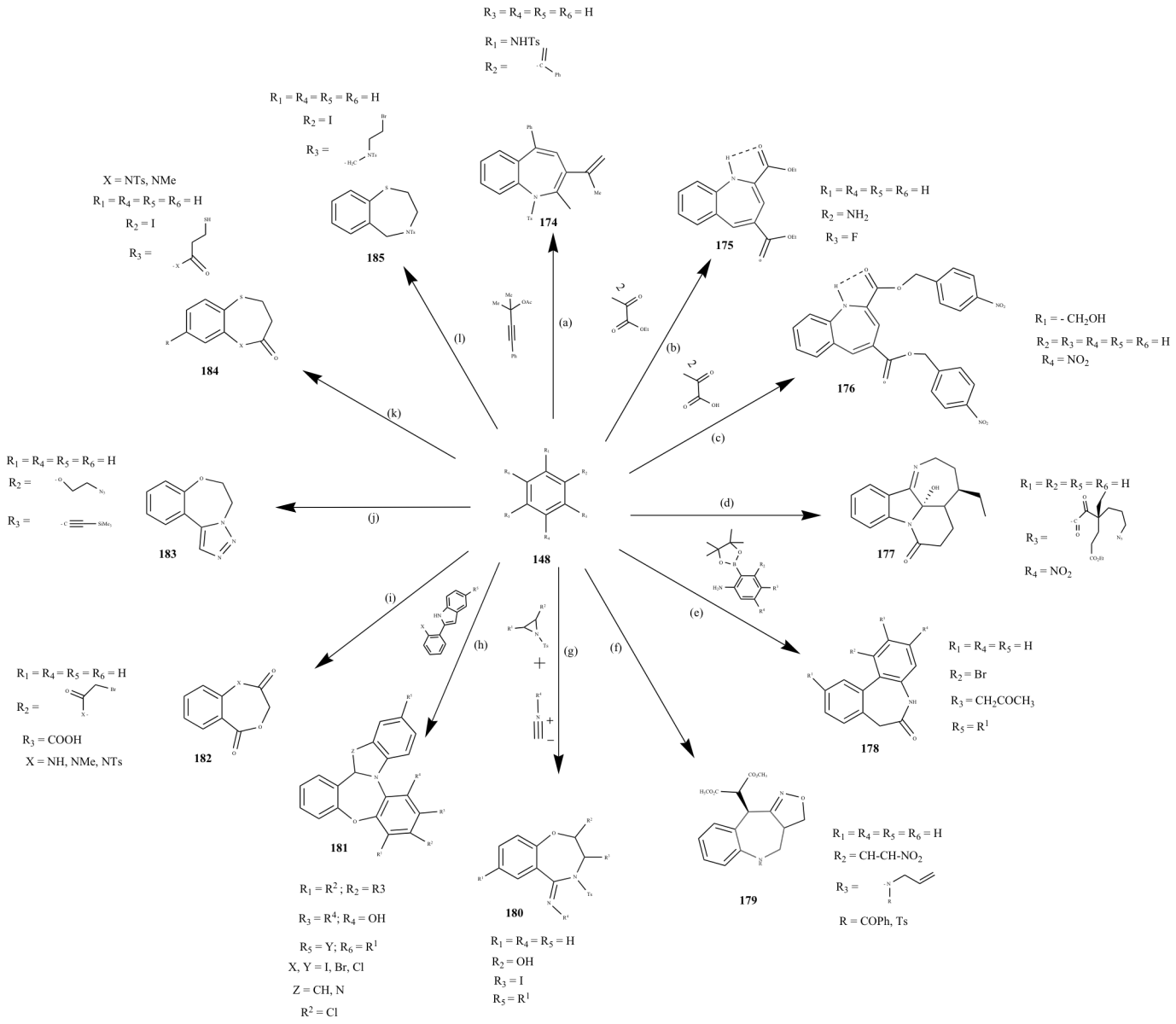


Scheme 19. Synthesis of fused azepine derivative by cross-coupling reaction. Reagents: a) CO, 110°C, 0.4 mol% $PdCl_2(PPh_3)_2$; [138] b) CO, 110°C, 0.4 mol% $PdCl_2(PPh_3)_2$; [138] c) (i) $Pd(PPh_3)_4$ (5 mol%), aq. Na_2CO_3, dioxane, 80°C, 2h, (ii) HCl/EtOH, (1:3), 80°C, 2h;[139] d) 2-acetylphenylboronic acid, PhMe:H_2:EtOH, $Pd(PPh_3)_4$, aq. K_2CO_3, Δ, 24h, silica gel, $CHCl_3$, rt, 15h;[140] e) Grubbs II cat. (5 mol%), DCE, 50°C;[141] f) HFIP, rt, 30min;[142] g) (i) $Pd(OAc)_2$, K_2CO_3, DCH-18-C-6, DMF, 140°C, BH_3.THF, reflux; (ii) 4-$R^4C_6H_4CHO$, CH_2Cl_2, rt, THF, reflux;[143] h) (i) NaH, DMF, 30min, rt, Pd/C, H_2, 2h; (ii) *p*-TSA, toluene , 125°C, 18h;[144] i) (i) MW, Et_3N, EtOH; (ii) RCHO, TFA, $CHCl_3$, reflux, 3h;[145] j) $PdCl_2$ (10 mol%), $CuCl_2.H_2O$ (2.0 equiv), THF, 50°C, 7h;[146] k) X mol% catalyst, DCE, rt, 2h;[147] l) (i) $Zn(CN)_2$, EtOH:AcOH, (3:1), 80°C, 7h; (ii) $Pd(OAc)_2$, KOAc, TPP, 1,4-dioxane, 100°C, 12h; (iii) O_3, DCM, -78°C, rt, 12h; (iv) 1N.NaOH, 30% H_2O_2, EtOH, 1h, 0°C; (v) $AlCl_3$, Me_2N.HCl, DCM, 60°C, 1h[148].

on the ring-closing mechanism of methyl (1-(2-(N-allyl-4-methylphenylsulfonamido)phenyl)allyl)carbamate **148** derivatives under the suitable condition to give methyl (1-tosyl-2,5-dihydro-1H-benzo[b]azepin-5-yl)carbamate **165** derivatives in medium yield. Shen *et al*. [142] synthesize 5,6-diphenyl-5,6,7,13,14,15-hexahydro-4bH-benzo[e]benzo[3,4]azepino[2,1-c][1,2,4]triazepine **166** via hydride transfer reaction. David *et al.* [143] gave a novel route for the synthesis of benz[c]benzothiopheno[2,3-e]azepine derivatives **167** in low to medium yield. Benzo[b]thiophene-3-carbonitrile were reacted with bromobenzene **148** derivative by Heck coupling using $Pd(OAc)_2$, K_2CO_3, DCH-18-C-6, DMF, BH_3, THF as reagents at 140°C to give amine derivative which further on reaction with benzaldehyde give the desired azepine derivative **167** in medium yield. The imidazoles on reaction with 1-bromo-2-nitrobenzene undergo N-arylation by reducing the nitro group to amine in DMF solvent at room temperature to give the product by elimination reaction, which further on reacting with benzaldehyde give fused azepine derivatives **168** in good to excellent yield using *p*-toluenesulfonic acid as catalyst [144]. Lee *et al*. [145] were successful in the synthesis of benzoxazepines derivatives **169** by microwave irradiation in two steps. In the first step, bromo ketones were reacted with an aromatic amine **148** under the basic condition to give the intermediate product, which further reacted with an aldehyde in chloroform to give the desired benzoxazepines derivatives in the other step. Karuppasamy and co-workers [146], after spending much time, were successful in the synthesis of 9-chloro-1H-benzo[b]furo[3,4-e]azepin-1-ones derivatives **170** under the appropriate reaction conditions *via* Pd (II) catalyzed intramolecular cyclization. Pagar *et al.* [147] synthesized Benzo[b]azepine Derivatives **171 & 172** in very high yield, *i.e.,* 96% by gold-catalyzed diazo decomposition of isoxazolidine in DCE (dichloroethane) at room temperature. Marepu *et al*. [148] synthesized 9-hydroxy-5-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepine-2-carboxamide **173** in a number of step. The reaction proceeds by the condensation of pent-4-enal and 2-bromo-6-methoxyaniline, followed by multiple steps to give the desired azepine in a 66% yield (Scheme **19**).

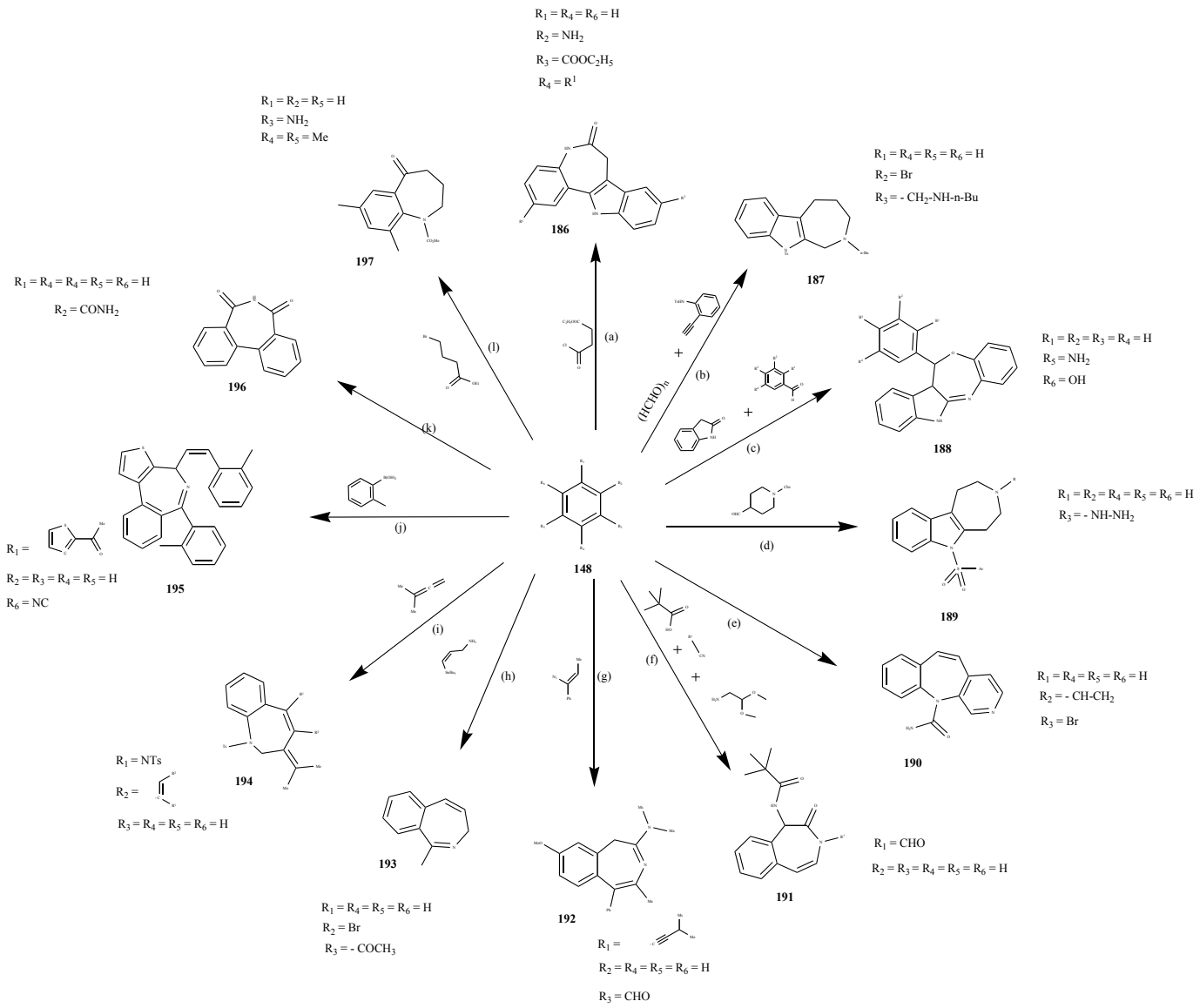
Qiao *et al.* [149] in 2019 were successful in the synthesis of 2-methyl-5-phenyl-3-(prop-1-en-2-yl)-1-tosyl-1H-benzo[b]azepine **174** by intermolecular cycloaddition reaction of Pd-catalyzed (3-methylbut-1-yn-1-yl)benzene and 4-methyl-N-(2-(1-phenylvinyl)-phenyl) benzenesulfonamide **148** in DMF at 100°C. Ramig and his co-workers [150] discovered the reaction for the synthesis of 1H-benzazepine **175 & 176** by the reaction of ethyl pyruvate with 2-fluoroaniline **148** and using *p*-toluenesulfonic acid as a catalyst in xylene under reflux conditions. The 1H-benzazepine **175 & 176** bearing the diester group was obtained as a product that was stabilized by hydrogen bonding. Xu *et al.* [151] after his continuous efforts synthesized (4R,4a1S)-4-ethyl-4a1-hydroxy-2,3,4,4a,5,6-hexahydro azepino[4,3,2-hi]benzo[b]indolizin-7(4a1H)-one **177** by Beckmann rearrangement [152]. The diketones were converted to product by reduction followed by oxidation and cyclization at room temperature to give a moderate yield. Synthesis of substituted dibenzoazepinones **178** was reported by Deb [153] and his team by microwave irradiation. The reaction of 2-aminophenyl boronates and 2-(2-bromophenyl)acetic acid esters **148** in DME and Cs_2CO_3 lead to the synthesis of substituted dibenzoazepinones **178** by one-pot Suzuki-Miyaura coupling reaction. Rohlmann *et al.* [154] reported the one-pot synthesis of isoxazoline-fused benzazepines **179**. The reaction of β-nitrostyrene derivatives with dimethyl malonate proceeds by the Michael addition between dimethyl malonate and nitro olefin in xylene at 10°C undergo addition of DMAP and BOC_2O to give the desired azepine derivative **179** in a maximum of 60% yield. Ji *et al.* [155] were successful in the synthesis of substituted 1,4-benzoxazepines **180** in medium to high yield by ring-opening of aziridine with substituted 2-iodophenol followed by insertion of isocyanide using Pd (II) as a catalyst, Cs_2CO_3, and toluene under refluxing condition for 24h. Sang *et al.* [156] successfully reported 2-(2-halophenyl)-1H-indoles **181** by Ullmann–Smiles cyclization process. The 2-halophenols were reacted with 2-(2-halophenyl)-1H-indoles undergo copper-catalyzed cyclization to get the product **181** in high yield. Liu *et al.* [157] reported the one-pot conversion of bromocarboxylic acids into 1,4-benzoxazepinones or -diones **182** using Ag as a catalyst under mild reaction conditions. Ellison *et al.* [158] successfully synthesized 5,6-dihydro-benzo[f][1,2,3]triazolo[1,5-d][1,4]oxazepine **183** by microwave irradiation. ((2-(2-azidoethoxy)phenyl)ethynyl)trimethylsilane undergoes intramolecular 1,3-dipolar cycloaddition under the desired condition to furnish compound **183** as a product in medium yield. X. B and co-workers [159] worked on the synthesis of 1,5-benzothiazepines **184** by intramolecular C-S coupling reaction of Ni(0) catalyzed aryl iodides. 1,4-benzothiazepine **185** is synthesized by the intramolecular C-S coupling reaction of Pd-catalyzed aryl iodides under optimized reaction conditions in a 50% yield [160] (Scheme **20**).

Benzazepine derivatives also exhibit various biological properties and also attract researchers for its synthesis (Scheme **21**). The Kunick, Link, and Schultz [161-163] gave a synthetic route for the synthesis of Indole-fused azepines and it's homologous in multi-step reaction. The reaction proceeds when ethyl succinyl chloride reacts with anthranilic acid ethyl esters in pyridine/toluene to give amide, which further undergoes Dickmann condensation using KH as a catalyst to obtain benzazepine derivatives as a product. Further, the product undergoes heating to give 3,4-dihydro-1H- [1]-benzazepine-2,5-diones in DMSO, and in the final step, the ring is cyclized upon addition of conc. H_2SO_4 to obtain benzazepinone derivatives **186** as a final product. Ohta *et al.* [164] worked on the one-pot synthesis of 2-butyl-10-tosyl-1,2,3,4,5,10-hexahydroazepino[3,4-b]indole **187** by microwave irradiation using three-component coupling by mannich-type coupling reaction. Aldehydes, secondary amines, and 2-ethynylanilines undergo a coupling reaction at 170°C in the desired solvent to give the product in 88% yield. Singh and co-workers [165] were successful in the synthesis of indole-fused heteroazepines **188** *via* a one-pot three-component reaction. In this reaction, aromatic aldehydes, 2-amino phenol, and 2-oxindole undergo acid-catalyzed reaction in MeOH under reflux to get indole-fused benzooxazepines **188**. Synthesis of tricyclic azepinoindole **189** by the multi-step reaction was reported by Liu *et al.* [166] by taking an equimolar amount of N-Cbz-piperidine-4-carbaldehyde and phenylhydrazine in acetic acid. The Pd-catalyzed substituted 2-chloroanilines and 2-bromostyrene undergo ring cyclization [167] in 1,4-dioxane under reflux using tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] as a catalyst, 2-dicyclohexylphosphino-20-(N,N-dimethylamino)biphenyl (DavePhos), and NaO*t*-Bu to afford the synthesis of substituted dibenzazepine derivatives **190** in low to moderate yields. Wang *et al.* [168] synthesized a fused seven-membered heterocyclic ring by the four-component system. At room temperature, in methanol benzaldehyde, isocyanide moiety, pivalic acid, and trimethoxymethane react, an intermediate is formed, which is cyclized by HCl in dioxane to give the substituted benzazepinone **191** in medium yield. Wu *et al.* [169] portrayed the synthesis of gold-catalyzed benzazepine derivative **192** in 36% yield by [4+3] cycloaddition of (Z)-



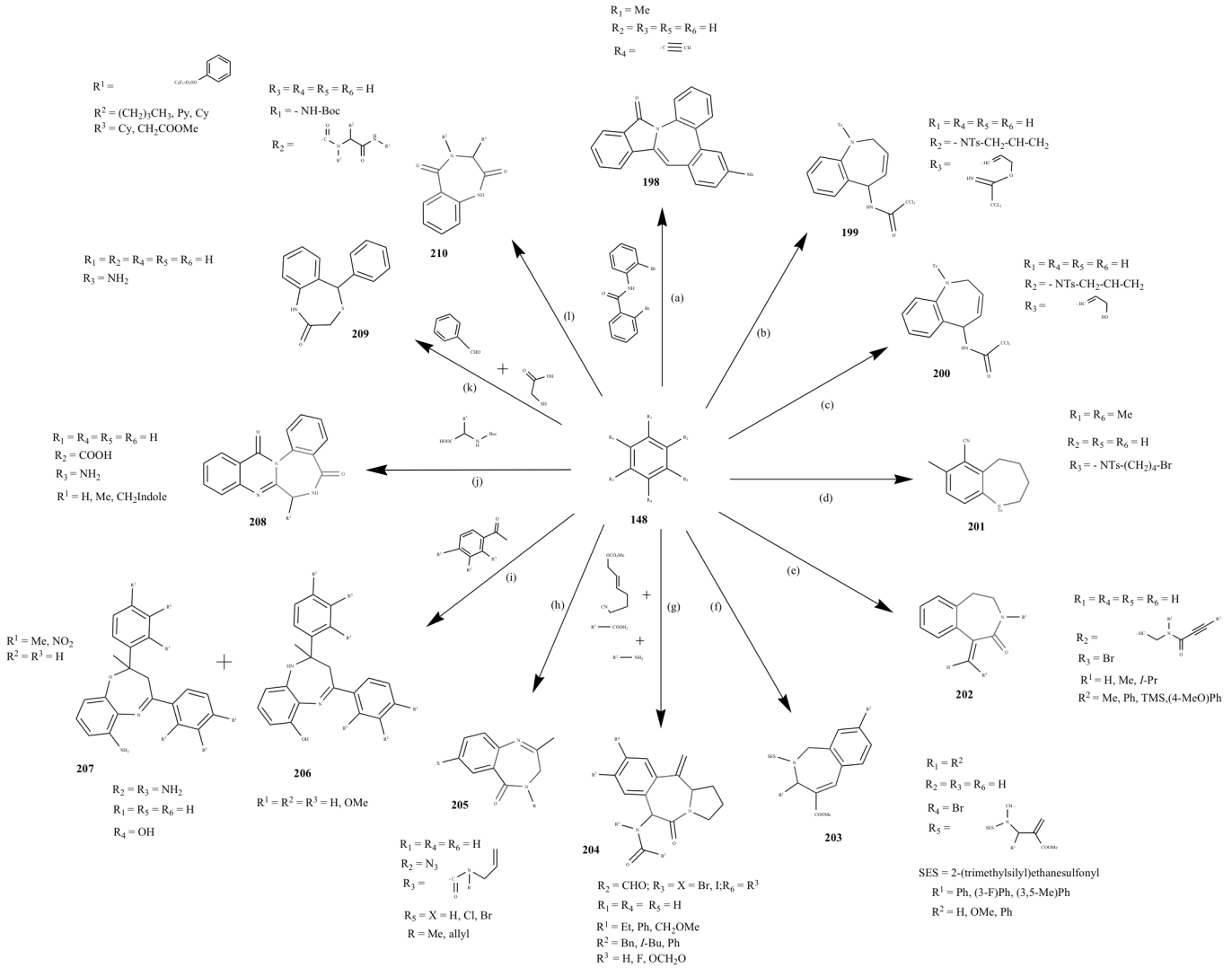
Scheme 20. Synthesis of various benzazepine derivatives. Reagents: a) $Pd(OAc)_2$ (10 mol%), $Yb(OTf)_3$ (10 mol%), $Cu(OAc)_2.H_2O$ (2.5equiv), DMF, 100°C, 12h; [149] b) *p*TsOH, xylene, reflux; [150] c) DCC, DMAP, p-TsOH; [150] d) (i) Pd/C, H_2, EtOH, rt, 3h; (ii) KOH, O_2 then Me_2S; [151, 152] e) (i) $Pd(PPh_3)$, Cs_2CO_3, 125°C, DME, MW, 30min; (ii) KO*t*-Bu, 0°C, 10 min; [153] f) (i) dimethyl malonate, chiral catalyst (10 mol%), *o*-xylene, 10°C; (ii) DMAP (20 mol%), Boc_2O (2.5 equiv), *o*-xylene, 90°C; [154] g) $Pd(PPh_3)_2Cl_2$ (5 mol%), Cs_2CO_3, toluene, reflux 24h; [155] h) CuI (2 mol%), dbm (2 mol%), K_3PO_4, DMF, 120°C, 12h; [156] i) (i) K_2CO_3, CH_3CN or DMSO, 30 min; (ii) $AgBF_4$, 80°C, 3-8h;[157] j) CsF, DMF, µW, 180°C, 30min; [158] k) Zn, $NiCl_2$ (50 mol%), ethyl crotonate, pyridine, rt, 3-5h; [159] l) $PdCl_2$(dppf) (10 mol%), dppf (5 mol%), $Na_2S_2O_3.5H_2O$, Cs_2CO_3, *n*-Bu_4NBr, CH_3CN:H_2O (20:1), 150°C, 8h [160].

(1-azidoprop-1-en-1-yl)benzene with 2-(3-methoxyphenyl)-N,N-dimethylethynamine using DCE as a solvent at 60°C. Wu *et al.* [170] reported the synthesis of Pd-catalyzed benzazepine derivatives **193** by a cross-coupling reaction. The 1-(2-bromophenyl)ethanone under cross-coupling reaction with (Z)-3-(tributylstannyl)prop-2-en-1-amine in refluxing with toluene to give allylic amine, which further cyclized to give benzazepine in 86% yield. Wu *et al.* [171] worked on the synthesis of benzazepine **194** by reacting orthovinylanilinic substrates with 3-methylbuta-1,2-diene followed by intermolecular cyclization under the optimized reaction condition. Yao *et al.* [172] afford the synthesis of (Z)-4-(2-methylstyryl)-6-(o-tolyl)-4H-benzo[c]thieno[3,2-e]azepine **195** in 83% yield by the intermolecular cross-coupling reaction of 2-(2-acetylthiophen-3-yl)benzonitrile with *o*-tolylboronic acid under the required condition. Benzamide [173] undergo intramolecular cross-coupling reaction to synthesized Pd-catalyzed 5H-dibenzo[a,c][7]annulene-5,7(6H)-dione **196** in 28% yield. Vaid *et al.* **174** in 2014 achieved the synthesis of benzo[b]azepine-1-carboxylate derivative **197** by the multistep reaction of 2,4-dimethylaniline **148** with ethyl 4-bromobutanoate. In the first step, the compound **148** is reacted with ethyl 4-bromobutanoate in toluene solution to form the intermediate, which further undergoes carbamoylation followed by hydrolysis to form the corresponding acid, which further undergoes intramolecular friedal craft acylation followed by ring-closing to form the desired azepine derivative **197.**



Scheme 21. Synthesis of fused azepine derivatives. Reagents: a) (i) pyridine/ toluene, Δ; (ii) 80°C, N_2, KH, DMF/toluene; (iii)DMSO/H_2O, 150°C, N_2; (iv) AcOH, NaOAc, rt; (iv) H_2SO_4, AcOH, 70°C;[161-163] b) CuI (2.5 mol%), dioxane, MeONa (6 equiv), MW, 170°C, 20 min; [164] c) conc. HCl, MeOH, reflux, 18h; [165] d) (i) AcOH; (ii) $ArSO_2Cl$, NaH, DMF; (iii) HBr/HOAc (iv) R'COR", $NaBH(OAc)_3$; [166] e) (i) 2-chloroaniline derivatives, $Pd_2(dba)_3$, DavePhos, NaO*t*-Bu, 1,4-dioxane, 115°C; (ii) NaOCN, HOAc, 65°C, 2h; (iii) BBr_3, DCM, 0°C to rt, 24h; [167] f) (i) rt, 15h, CH_3OH; (ii)HCl, Dioxane; [168] g) JohnPhos, $Au(MeCN)SbF_6$ (3mol%), DCE (0.3M); Ar, 60°C, 2.5h; [169] h) $Pd(PPh_3)_4$, toluene, reflux; [170] i) $Pd(OAc)_2$ (10 mol), $Cu(OAc)_2$ (2.5 equiv); [171] j) $Pd(TFA)_2$, L_1, MsOH, DMF, air, 24h, 100°C; [172] k) $Pd(OAc)_2$ (5mol%), $Na_2S_2O_8$ (2equiv), TFA, 130°C, 6h; [173] l) (i) Et_3N, toluene, 95-100°C; (ii) Na_2CO_3, $ClCO_2Me$, toluene; (iii) MeOH, NaOH, H_2O, 55-60°C, workup, conc, HCl; (iv) $SOCl_2$, DMF, CH_2Cl_2, 0-5°C, (v) $AlCl_3$, DCM, 35°C, workup crystallization [174].

Microwave irradiation proves to be a very efficient method for the synthesis of fused benzazepine to enhance their yield and to reduce reaction time (Scheme **22**). Saini *et al.* [175] worked on the one-pot synthesis of 6-methyl-14H-dibenzo[4,5:6,7]azepino[2,1-a]isoindol-14-one **198**. Phenylacetylene and 2-bromo-N-(2-bromophenyl)benzamide were reacted in the presence of K_2CO_3 (2 equiv.), CuI (30 mol %) in DMF (4 mL) at 130°C for 1hr followed by addition of PPh_3 (10 mol%) and $Pd(OAc)_2$ (5 mol %) to give the product **199** in 76% yield. In 2016, Salaheddin *et al.* [176] worked on the synthesis of 2,2,2-trichloro-N-(1-tosyl-2,5-dihydro-1H-benzo[b]azepin-5-yl)acetamide **199 & 200** by the intramolecular cyclization of (E)-N-allyl-N-(2-(3-hydroxypropyl-1-en-1-yl)phenyl)-4-methylbenzenesulfonamide **148** under the required reaction condition. Lautens and co-workers [177] also worked on the synthesis of benzonitriles **201** from aryl bromides **148** with O- and N-containing alkyl side chains *via* microwave irradiation in the presence of $Pd(OAc)_2$, triphenylphosphine (PPh_3), norbornene, Cs_2CO_3, $Zn(CN)_2$, in DME at 150°C. N-(2-bromophenethyl)but-2-ynamide and it is homologous [178] undergo microwave irradiation in the presence of HCOONa, $Pd(PPh_3)_4$, DMF/H_2O at 110°C to get (Z)-1-ethylidene-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one **202** and its derivatives as a product in good to excellent yield. Lamaty and co-workers [179] synthesized benzazepines derivatives **203** by an intramolecular Heck reaction of 2-(trimethylsilyl)-ethane sulfonyl (SES)-protected β-amino esters **148** in the presence of $Pd(OAc)_2$, K_2CO_3 in PEG at 100°C for 30 min. Riva and co-



Scheme 22. Synthesis of fused benzazepine derivative *via* Microwave irradiation. Reagents: a) (i) $Cu(OAc)_2$, H_2O, K_2CO_3, DMF, 130°C, 1h; (ii) $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), 130°C, 2h; [175] b) (i) Cl_3CCN, DBU, DCM, rt, 2h; (ii) 160°C, K_2CO_3, *p*-xylene, 24h; (iii) Grubbs II (5 mol%), 60°C, 18h;[176] c) (i) Cl_3CCN, DBU, DCM, rt, 2h; (ii) 160°C, K_2CO_3, *p*-xylene, 24h; (iii) Grubbs II (5 mol%), 60°C, 18h;[176] d) $Pd(OAc)_2$, PPh_3, Cs_2CO_3, norbornane, $Zn(CN)_2$, DME, MW, 150°C, 66 min;[177] e) $Pd(PPh_3)_4$, HCOONa, DMF/H_2O, MW, 110°C, 15min;[178] f) $Pd(OAc)_2$, K_2CO_3, PEO, 3400, MW, 100°C, 30 min;[179] g) (i) Ugi, CF_3CH_2OH/EtOH, 45°C; (ii) $Pd(PPh_3)_4$, DPPE, CH_3CN, 60°C; (iii) Heck, $Pd(PPh_3)_4$, DPPE, Cs_2CO_3, DMF, MW, 120°C, 60 min;[180] h) DMF, MW, 80°C, 5 min;[181] i) MW, 80W, 2-5 min, CH_3COOH or *p*-TsA;[182] j) $P(OPh)_3$, pyridine, MW, 230°C, 20 min;[183] k) Water, MW, , 110°C, 7-10min;[184] l) TFA, MeOH, MW, 150°C, 20 min[185].

workers [180] proposed a new reaction pathway for the synthesis of a tricyclic moiety, *i.e.,* fused benzazepinone **204** by the Heck process. It is a multi-component reaction between the amine, acid, benzaldehyde, and (E)-6-isocyanohex-2-en-1-yl methyl carbonate under the required reaction condition to give the tricyclic moiety, which resembles the structure of cephalotaxus alkaloids. Santagada *et al.* [181] were successful in the synthesis of 2-methyl-1,4-benzodiazepin-5-ones **205** by microwave irradiation in 52-97% yield. Substituted azides undergo intramolecular cycloaddition reaction in DMF at 80°C. Stephanatou *et al.* [182] proposed the synthesis of 6-hydroxybenzodiazepines and 6-aminobenzoxazepines **206 & 207**. The 2,3-diaminophenol and substituted acetophenones undergo microwave-assisted condensation reaction in acetic acid or para toluene sulfonic acid at 80W for 2-5 min. Liu *et al.* [183] worked on the reaction of N-Boc protected amino acids with 2-aminobenzoic acid **148** under the microwave irradiation in pyridine at 230°C to give quinazolino benzodiazepine moiety *i.e.,* 6,7-dihydrobenzo[6,7][1,4] diazepino[2,1-b]quinazoline-5,13-dione **208**, which are present in various alkaloids, *i.e.,* (±)-sclerotigenin, (±)-circumdatin F and (±)-asperlicin C. Tu and co-workers [184] proposed the reaction of benzaldehyde, mercaptoacetic acid and an aromatic amine in the aqueous condition under microwave irradiation to give benzo[e][1,4]thiazepin-2-ones **209** as a product at 110°C. The seven-membered heterocyclic ring is synthesized by the reaction of an organic compound bearing protected amino group and an amide **148** by intramolecular cyclization followed by deprotection at 150°C to give biaryl-substituted 1,4-benzodiazepine-2,5-diones **210** in maximum 97% yield [185].

An *et al.* [186] were successful in the synthesis of 4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine **213** *via* [1,5] hydride transfer reaction. The 2-(pyrrolidin-1-yl)benzaldehyde **211** undergoes condensation reaction with 1-

benzyl-2-phenylhydrazine to get the iminium ion as an intermediate **212**, which further undergoes intramolecular cyclization by [1,5] hydride transfer to get the desired tricyclic azepine **213** in good amount (Scheme **23**).

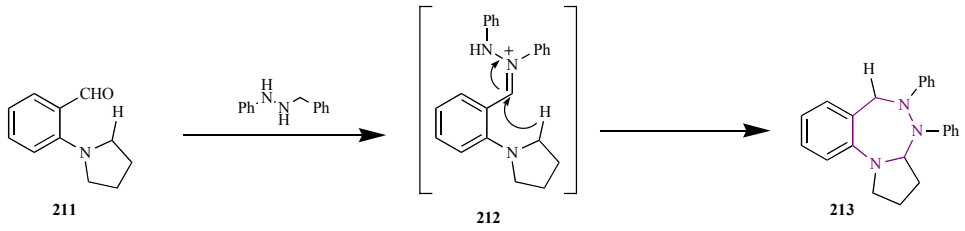
In 2020, Hu and co-workers [187a] successfully synthesized Tribenzo[b,d,f]azepines **216**. The 2-aminobenzoic **214** acid undergoes ring cyclization with 9H-fluorene **215** followed by oxidation in DMF at 145°C using $Pd(OAc)_2$ as a catalyst to give the N-aryl substituted Tribenzo [b, d, f] azepines **216** in moderate to high yield (Scheme **24**).

Yu *et al.* [187b] in 2020, designed a reaction path for the synthesis of substituted dibenzoazepinone **219** (Scheme **25**). The *o*-halo substituted benzaldehydes **217** undergoes [4+3] cycloaddition reaction with N-tosylhydrazones **218** using Pd as a catalyst along with dppb in 1,4-dioxane at 100°C to give the bioactive product **219** in good yield.

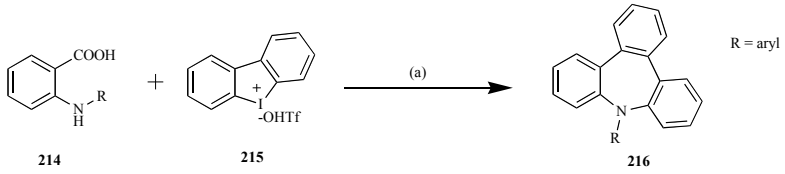
Prasad *et al.* [187c] in 2020, reported a new method for the synthesis of tetracyclic moiety **223, 225** in excellent yield (Scheme **26**). The compound **220** undergoes a coupling reaction with 3,4-dimethoxyphenylacetonitrile **221a** and methyl 3,4-dimethoxyphenylacetate **222b** in TMSCN to form an intermediate compound **222** & **224**, which further undergoes base-catalyzed ring cyclization to form the desired azepine **223** & **225** in maximum yield.

2.1.4. Synthesis of Dibenzoazepin Derivative from Biaryl Compounds

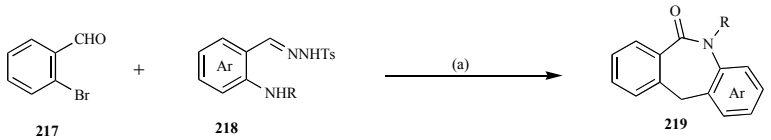
Other than azepines, it's benzo and dibenzo derivatives are also the very interesting site of research for many researchers (Scheme **27**). In 2015, Luan *et al.* [188] had synthesized Pd-catalysed imine containing dibenzo-[b,d]azepines **227** by oxidative annulations of *o*-aryl aniline **226** with alkynes. The product was obtained by employing $Cu(OAc)_2$ as an oxidant with DMSO at 393K for 5h. In



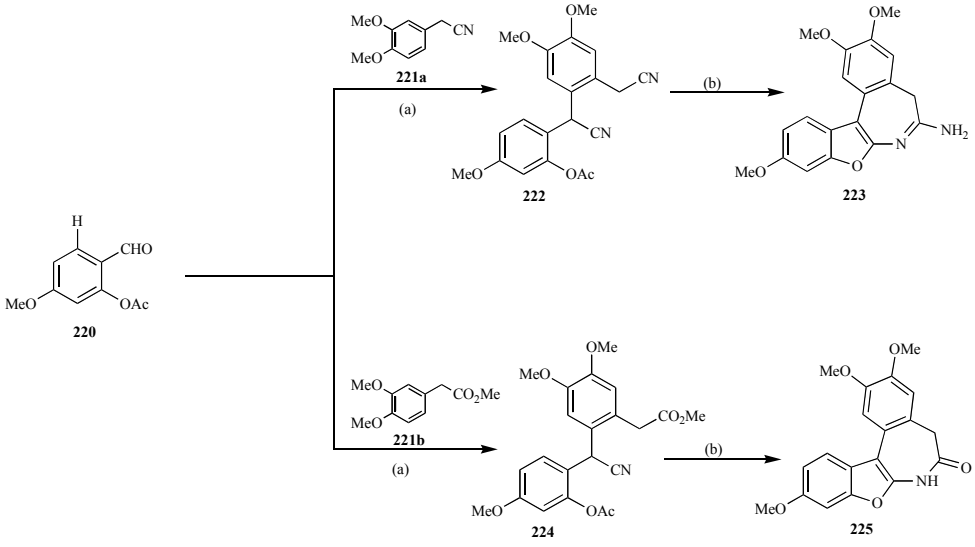
Scheme 23. Synthesis of triazepine by [1,H] hydride transfer.



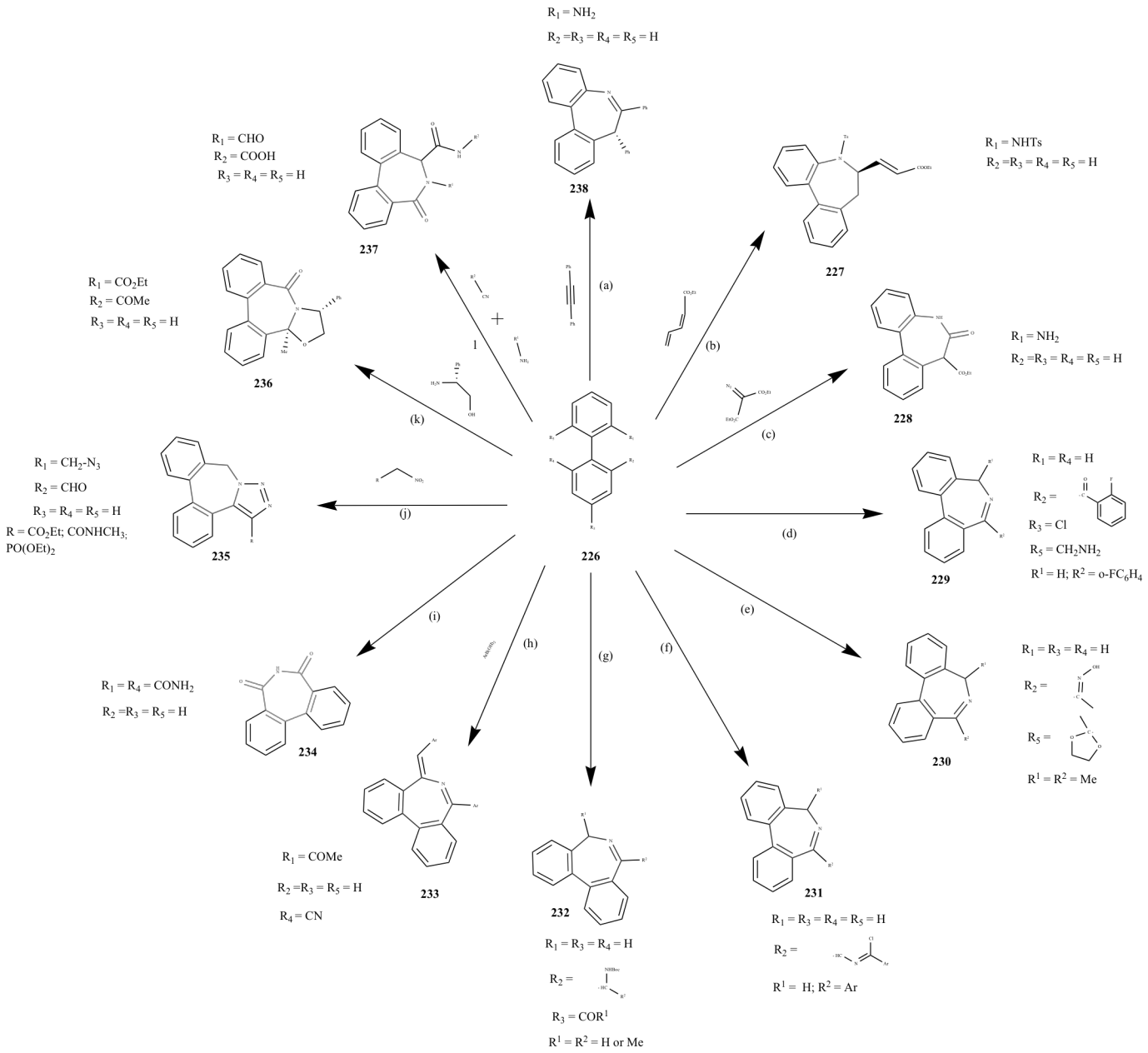
Scheme 24. Synthesis of Tribenzo [b, d, f] azepines. Reagents: a) $Pd(OAc)_2$ (10 mmol%), K_2CO_3 (2.0 equiv), DMF, 145°C [187].



Scheme 25. Synthesis of substituted dibenzoazepinone. Reagents: a) $Pd(OAc)_2$ (5 mol%), dppb (7.5 mol%), K_2CO_3 (3equiv), 1,4-dioxane (0.1 M), 100°C.



Scheme 26. Synthesis of indole fused azepine derivatives. Reagents: a) TMSCN (1.5equiv), BF_3-OEt_2 (2 equiv), rt, 8h-10h; b) Et_3N (2 equiv), MeOH, rt, 10h-15h.



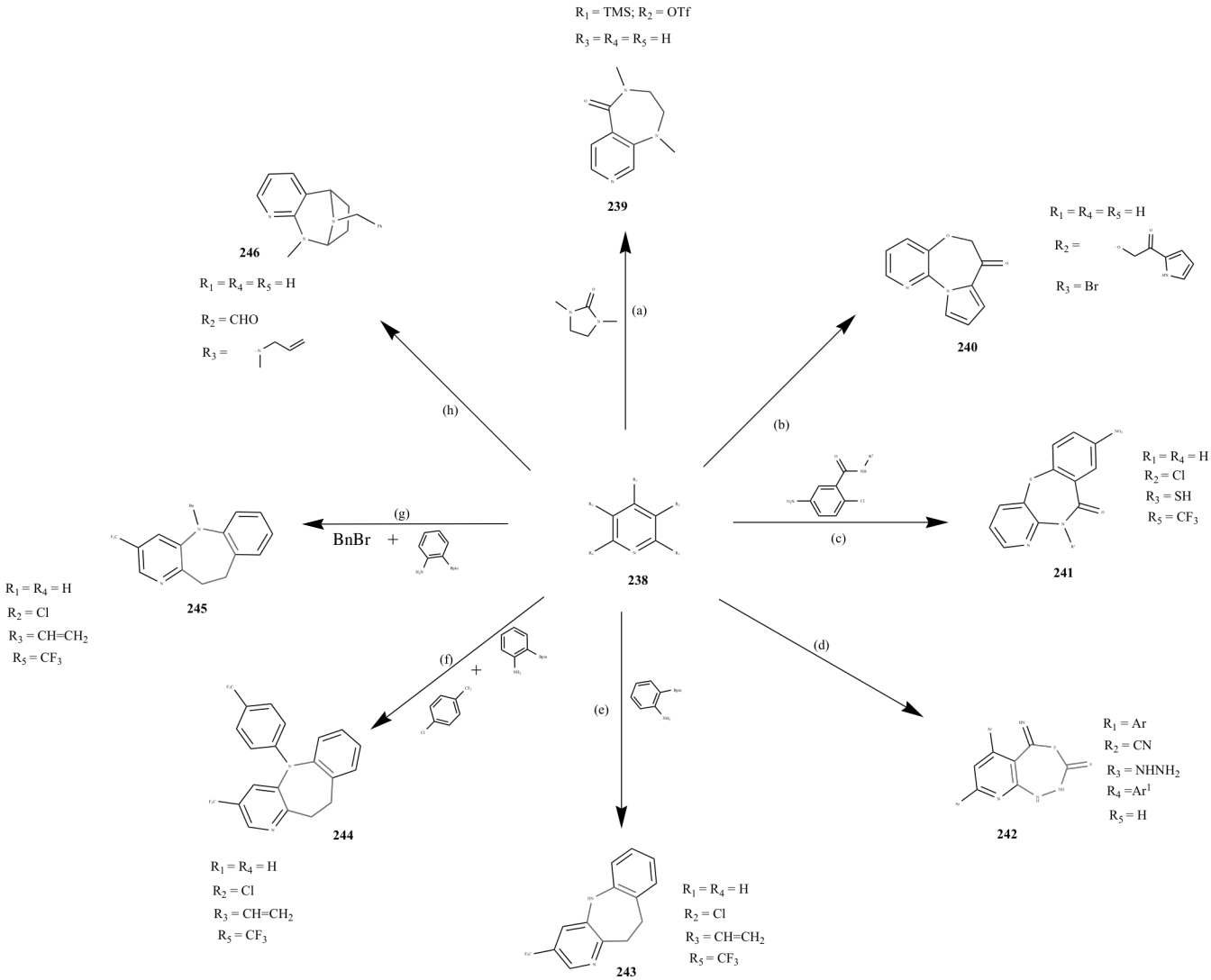
Scheme 27. Synthesis of dibenzoazepine derivatives. Reagents: a) $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (2.1equiv), DMSO, 393K, 5h; [188] b) $Pd(TFA)_2$ (5mol%), $Cu(OAc)_2$ (2.1 equiv), MeCN, 393K, 36h; [189] c) $[RhCp^*Cl_2]_2$ (2.5 mol%), $AgSbF_6$ (10mol%), AcOH (2.5 equiv), EtOH, 333K; [190] d) CNBr, NH_3; [191] e) Na, 1-pentanol; [192] f) BuOK, THF; [193] g) TFA, HCl/Et_2O; [194, 195] h) $Pd(TFA)_2$ (6mol%), L_1 (12mol%), MsOH (2mmol), DMF (2mol%), air, 373K, 24h; [196] i) $Pd(OAc)_2$ (5mol%), $Na_2S_2O_3$ (2equiv), TFA, 403K, 6h; [173] j) L-proline (1.0 equiv), BHT (5 mol%), CH_3CN, 310K, 24h, 4A MS; [197] k) toluene, reflux, de>95%; [198] l) CF_3CH_2OH, Na_2SO_4,MW, 383K, 50min [199].

2007, Luan [189], with his co-workers, developed a new synthetic route for the synthesis of Pd-catalysed diastereoselective dibenzo[b,d]azepines **228** from N-tosyl *o*-aryl aniline **226** and 1,3-dienes using $Cu(OAc)_2$ as an oxidant and MeCN as a solvent. In 2016, Huang and co-workers [190] synthesized azepinone **229** derivatives in a very high yield from *o*-aryl aniline **226**. The reaction proceeds at 60°C using EtOH as a solvent, AcOH as an additive, a mixture of $AgSbF_6$ and $[RhCp^*Cl_2]_2$ as the catalyst. Gschwend and Boyer [191] synthesize 9-chloro-7-(o-fluorophenyl)-5H-dibenz[c,e]azepine **230** from (4-chloro-2'-((dimethylamino)methyl)-[1,1'-biphenyl]-2-yl)(2-fluorophenyl)methanone **226** using CNBr a highly toxic and volatile solvent followed by subsequent cyclization in the ethanolic ammonia. Weitzberg [192] synthesize 5,7-dimethyl-5H-dibenzo[c,e]azepine **231** followed by cyclization or reduction of (E)-1-(2'-(2-methyl-1,3-dioxolan-2-yl)-[1,1'-biphenyl]-2-yl)ethanone oxime **226** using Na in solution of pentanol. Cullen *et al.* [193] synthesized 7-argio-5H-dibenzo[c,e]azepine **232** from (E)-N-([1,1'-biphenyl]-2-ylmethyl)argoncarbimidoyl chloride **226** using THF solvent. This reaction proceeds by intramolecular cyclization of nitrile ylides. France [194] and Yang [195] carried out the reaction for the synthesis of 5H-dibenzo[c,e]azepine **233** by intramolecular cyclization of Boc protected arylbridged aminoketones **226**. A Pd-catalyzed reaction took place between [1,1′-biphenyl]-2-carbonitriles **226** and aryl boronic acid [196] to form the product *i.e.,* (Z)-7-argio-5-(2-argiovinyl)-5H-dibenzo[c,e]azepine **234** at 373K in maximum 90% yield. Kondapalli *et al.* [173] synthesized

Pd-catalyzed 5H-dibenzo[c,e]azepine-5,7(6H)-dione **235** in a very high yield of about 95% by the ring cyclization of [1,1'-biphenyl]-2,2'-dicarboxamide **226** at 403K. Vasiliev [197] developed another synthetic route for the synthesis of triazolodibenzoazepines and its homologous **236** in medium yield at low temperatures. At 37°C, triazolodibenzoazepines **236** was synthesized from 2'-(azidomethyl)-[1,1'-biphenyl]-2-carbaldehyde **226** under the optimized reaction condition. Postikova *et al.* [198] describe a novel route for the synthesis of seven-membered heterocyclic dibenzazepinone derivatives. Dibenzazepinone derivatives **237** were prepared by the Meyers' lactamization reaction of a 2-amino-2-phenylethanol with biphenyl ketoester **226** in a very high yield of about 95% and show high diastereomeric selectivity. Under microwave irradiation, [199] dibenzo-[c,e]azepinones **238** in excellent diastereoselectivities are synthesized from four-component system using suitable 2'-formyl-[1,1'-biphenyl]-2-carboxylic acid **226**. The above product form shows resemblance with g-secretase inhibitor LY411575.

2.1.5. Synthesis of Fused Azepine Ring from Pyridine/ Nitrogen-containing Six-membered Ring

Substituted pyridine is another key reactant used by various authors to synthesize benzazepine derivatives under various reaction conditions (Scheme **28**). Goetz [200] used pyridine derivative *i.e.,* 4-(trimethylsilyl)pyridin-3-yl trifluoromethanesulfonate **238** under controlled reaction condition for the synthesis of pyrido[4,3-*e*][1,4]diazepin-5-one **239** derivative with the addition of 1,3-dimethylimidazolidin-2-one. Huang *et al.* [201] proposed the synthesis of pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazepin-7(6H)-one **240** from 2-(2-iodophenoxy)-1-(1H-pyrrol-2-yl)ethanones **238** by intramolecular Ullmann N-arylation process using Copper iodide, L-proline, K_2CO_3 and DMSO at 80°C. Smiles rearrangement [202] proves to be an effective method for the synthesis of substituted pyridobenzothiazepines **241** in medium to high yield by the reaction of N-substituted nitrobenzamides with 3-chloro-5-(trifluoromethyl) pyridine-2-thiol **238** under the basic condition in DMSO or DMF. Salem *et al.* [203] worked on the reaction of 2-



Scheme 28. Synthesis of pyridine fused azepine ring. Reagents: a) CsF, MeCN;[200] b) CuI (2 mol%), L-proline (20 mol%); K_2CO_3, DMSO, 80°C, 1-6h;[201] c) KOH, DMF, or DMSO, 150°C, 4h;[202] d) CS_2, KOH, EtOH, reflux, 10h; [203] e) (i) $[Rh(cod)Cl]_2$ (2.5 mol%), K_2CO_3 (3 equiv), dioxane/H_2O (10:1), 110°C, 1h; (ii) $Pd(OAc)_2$ (5 mol%), XPhos (10 mol%), NaO^tBu (3 equiv), dioxane, 110°C, 16h; [204] f) $[Rh(cod)Cl]_2$ (2.5 mol%), Pd-G1-RuPhos (5 mol%), XPhos (5 mol%), KOH (3 equiv), dioxane/H_2O (10:1), 110°C, 16h; [204] g) $[Rh(cod)Cl]_2$ (2.5 mol%), Pd-G1-RuPhos (5 mol%), XPhos (5 mol%), KOH (3 equiv), dioxane/H_2O (10:1), 110°C, 16h; [204] h) $BnNH_2$ 5% TsOH, toluene, 111°C [205].

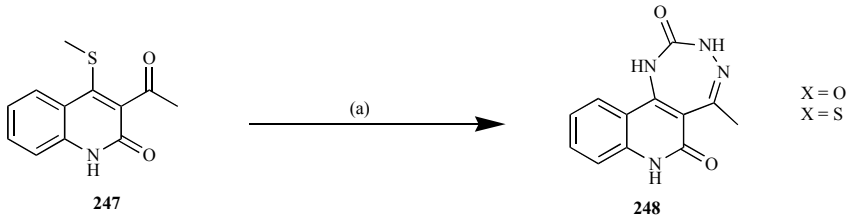
hydrazinonicotinonitrile **238** under the basic condition with carbon disulphide in reflux to form an unexpected product, *i.e.,* 1,2-Dihydropyrido[2,3-*e*][1,3,4]thiadiazepine-3(5*H*)-thione **242**, which possess a wide range of antibacterial property. Lam *et al.* [204] proposed the reaction of 3-chloro-5-(trifluoromethyl)-2-vinylpyridine **238** with substituted amino benzyl derivative to yield 2-(2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethyl)aniline as an intermediate in 91% yield using K_2CO_3 as the base and $[Rh(cod)Cl]_2$ as the catalyst. The intermediate further undergoes intramolecular C-N bond formation to give 3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine **243** as a product in 95% yield. Similarly, the C-N bond formation took place by the three-component system to give 3-substituted (trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido [2,3-f]azepine **244 & 245** in medium yield under the same reaction condition. Zhang *et al.* [205] synthesized 10-benzyl-9-methyl-6,7,8,9-tetrahydro-5H-5,8-epiminopyrido[2,3-b]azepine **246** by the Imino ene-type cyclization of 2-(allyl(methyl)amino)nicotinaldehyde **238** under the optimized reaction condition.

Hassan and co-workers [206] were successful in the synthesis of quinolines derivatives **248,** which possess a range of biological properties. The derivatives were prepared by the reaction of hydrazinecarbamide derivative with 3-acetyl-4-(methylthio)quinolin-2(1*H*)-one **247** using DMF as a solvent in reflux for 6h (Scheme **29**).

Ibrahim and co-workers [207] developed a synthetic route for the synthesis of 1,3,4-benzotriazepin-5-one derivatives **250,** and these derivatives show significant anti-tumor activity [208]. The unsubstituted 2-amino-1,3,4-benzotriazepin-5-one **250** was synthesized by the reaction of 1H-benzo[d][1,3]oxazine-2,4-dione **249** with hydrazinecarboximidamide, in an excellent yield of 82% (Scheme **30**).

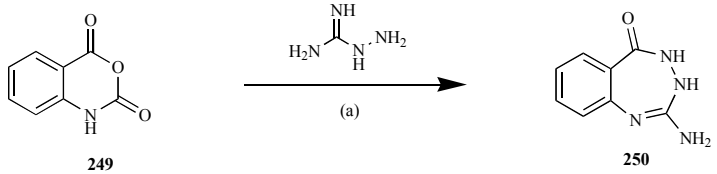
At room temperature, when the ruthenium carbine **251** is reacted with cyclopropylethylene in DCM, the substituted ruthenium complex *i.e.,*cyclopropyl-substituted pyridoazepine, **252** is formed as an orange solid with a medium yield of 65% and when the product **252** formed is reacted with tetrafluoroboric acid diethyl ether complex in DCM the dimer of ruthenium complex **253** is formed, and when pyridoazepine **252**, is treated with tetrafluoroboric acid water complex in carbon monoxide, it results in dissociation of pyrido[1,2-α]azepine unit **254** and protonation of the ring take place. The yield [209] thus obtained was about 65-84% (Scheme **31**).

Kroc and his team [210], give the synthetic route for the synthesis of substituted bicyclic benz[b]azepin-4-ones and its homologous



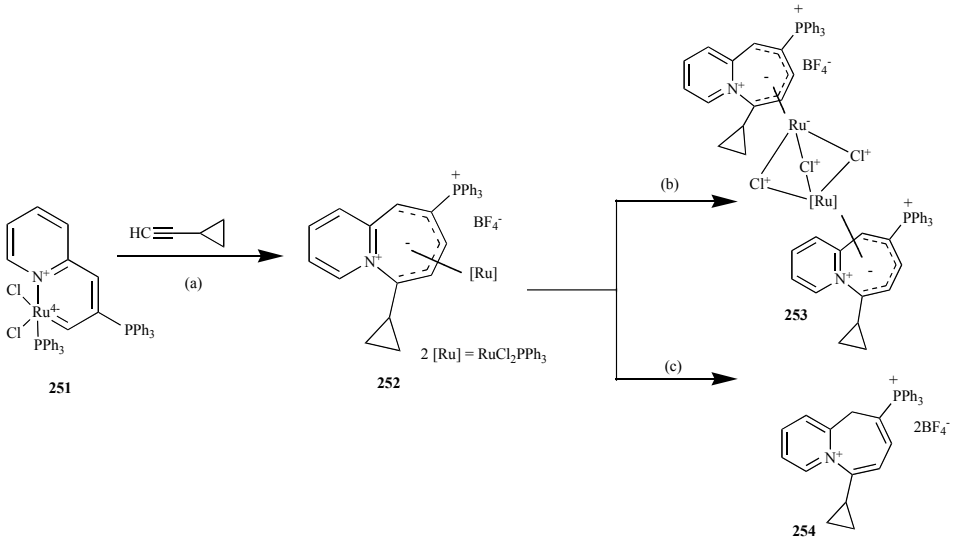
247 **248**

Scheme 29. Synthesis of Quinolines derivatives. Reagents: $NH_2NHCXNH_2$, DMF, reflux, 6h [206].



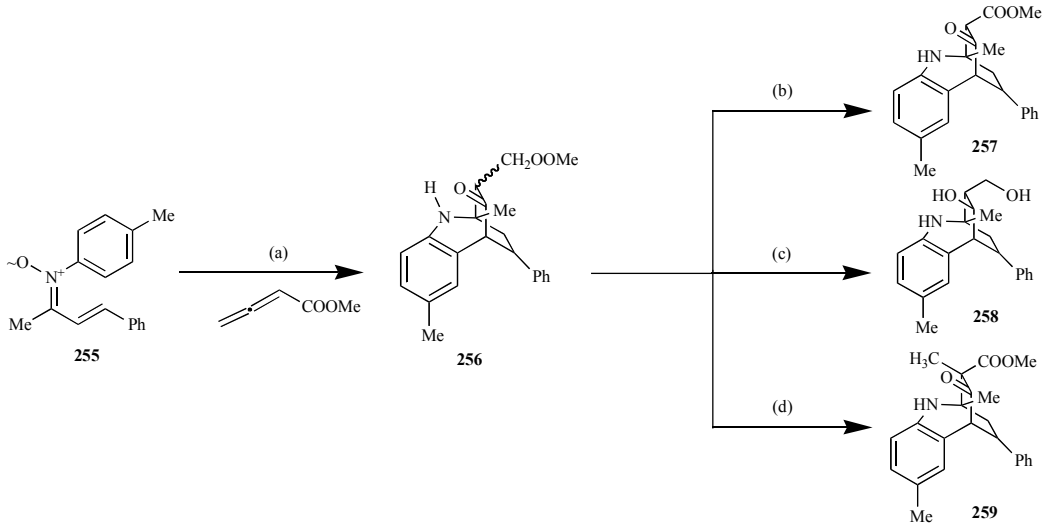
249 **250**

Scheme 30. Synthesis of 1,3,4-benzotriazepin-5-one derivative. Reagents: AcOH, reflux, 4h [207].



251 **252** **253** **254**

Scheme 31. Formation of azepine derivative from ruthenium complex. Reagents: a) rt, CH_2Cl_2, 30 min; b) $HBF_4.Et_2O$, CH_2Cl_2/C_6H_6 rt, 5h; c) $HBF_4.H_2O$, CO, CH_2Cl_2, rt, 2h [209].



Scheme 32. Synthesis of substituted bicyclic benz[b]azepin-4-ones and its derivatives using nitrones and allenes. Reagents: a)DABCO (5mol%), toluene, 60°C , 3h; b) MeOH, 1h, 25°C; c) $LiAlH_4$, THF, 80°C; d) MeI (2equiv), 18-crown-6, K_2CO_3, MeCN, DMF, 25°C [210].

257-259 in moderate to high yield using nitrones **255** and allenes at a different temperature range in a different solvent system using a Squaramide as a catalyst (Scheme **32**). At 60°C, bicyclic tetrahydrobenz[b]azepin-4-ones **256** were prepared in toluene, and the same product **257** is formed in methanol at 25°C. On further reduction with lithium aluminum hydride, it forms homologous of bicyclic benz[b]azepin-4-ones **258** at 80°C. The bicyclic benz[b]azepin-4-ones homologous **259** were prepared at 25°C in DMF, MeCN, MeI (2equiv), 18-crown-6, and K_2CO_3.

2.1.6. Synthesis of Azepine Derivatives from Allenes via Intermolecular Cycloaddition

Dai *et al.* [211] worked on the synthesis of azepine derivatives **261-264** under suitable reaction conditions (Scheme **33**). The reaction proceeds by [4+3] cycloaddition of aldimine ester with allenoates **260** at room temperature to obtain the 1,3-dihydro-2H-azepine-2,2,4-tricarboxylates **261** in very high yield. Similarly, when the same reaction proceeds at 60°C with a naphthalene ring in place of the benzene ring, 2,3-dihydro-1Hazepine- 2,4,6-tricarboxylate **262** obtained in 68% yield. In the presence of a catalyst, the same reaction undergoes cyclization and give 2,3-dihydrochromeno[4,3-b]azepin-6(1H)-ones **263**, and it's homologous as a product in medium to high yield. He *et al.* [212] used the diazo compound for the synthesis of Cu- catalyzed substituted 3-azabicyclo[5.2.0] **264**. Diazo compounds bearing different ester groups such as benzyl, ethyl, methyl, or active allyl group are reacted with 1,n-allenynes under the optimized reaction conditions to form the product in good yield

Benzo[b]naphtho[1,2d]Azepine and its derivatives **266-270** by Intramolecular Radical Tandem Cyclization of Alkyl Bromide-Tethered Alkylidenecyclopropanes **265** thermally in a different solvent system (Scheme **34**) gives moderate to high yield reported by Jiang and his co-workers [213]. Benzo[b]naphtho[1,2d]Azepine **266** at a high temperature with $NiBr_2$ (DME), 1,10-phenZn, DMF, N_2 give 80% yield. However, a mixture of products **267-270** is obtained when the same reactant **257** is treated with different solvents at a very high temperature to produce moderate to low yield. The further oxidation of Benzo[b]naphtho[1,2-d]Azepine **266** form an epoxide ring **270** at very low temperature, and the yield obtained is very high.

Hu and his co-workers [214] describe a synthetic route for the synthesis of substituted seven-membered heterocyclic dibenzooxaazepine **272, 273, 275, 277, 278** and dibenzodiazepine **274** rings. Substituted Dibenzoazepine and its derivatives **272-278** were prepared by the ring cyclization of 1-isocyano-2-phenoxybenzene **271** with phenyliodide, O-benzoyl hydroxylamine and 4-iodobenzaldehydein maximum of 92% yield catalyzed by $Pd(OAc)_2/PPh_3$ in Cs_2CO_3 as a base in DMF, Toluene and methanol at 100°C (Scheme **35**).

2.1.7. Synthesis of Substituted Pyridobenzazepine from Stilbenes

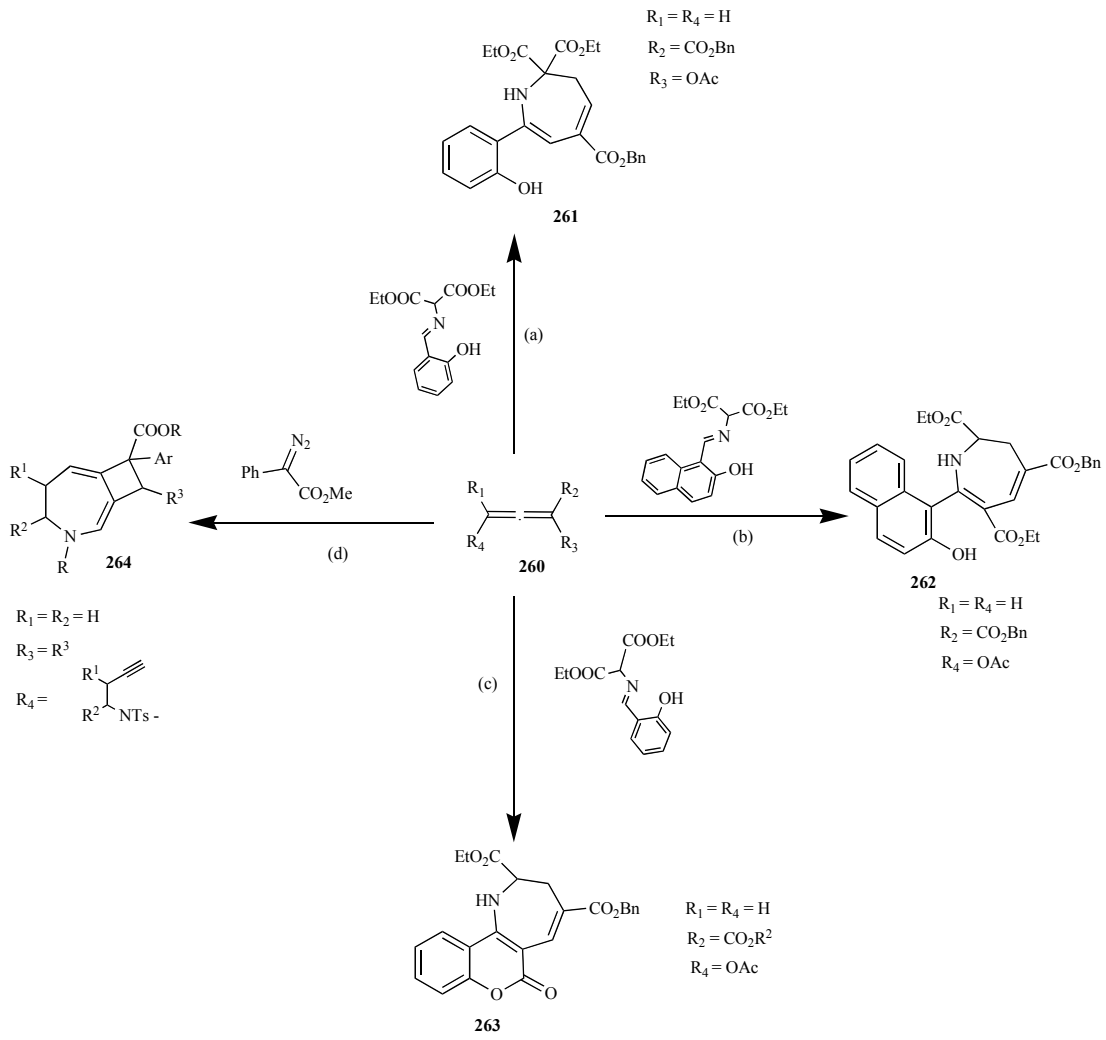
Nina Bozinovic and her team [215] gave the Pd-catalysed synthetic route for the synthesis of the tricyclic moiety, *i.e.*, substituted pyridobenzazepine **280-282,** which possess a wide range of *in vitro* antimicrobial and antifungal properties. At 100°C, substituted stilbenes **279** undergo ring expansion followed by ring closure to form substituted pyridobenzazepine **280-282** as a major product catalyzed by $Pd(OAc)_2$ and NaO*t*-Bu as a base in toluene to give a high yield of approx 83% (Scheme **36**).

2.1.8. Synthesis of Substituted Dibenzoazepinone from 2-Amino Chalcones

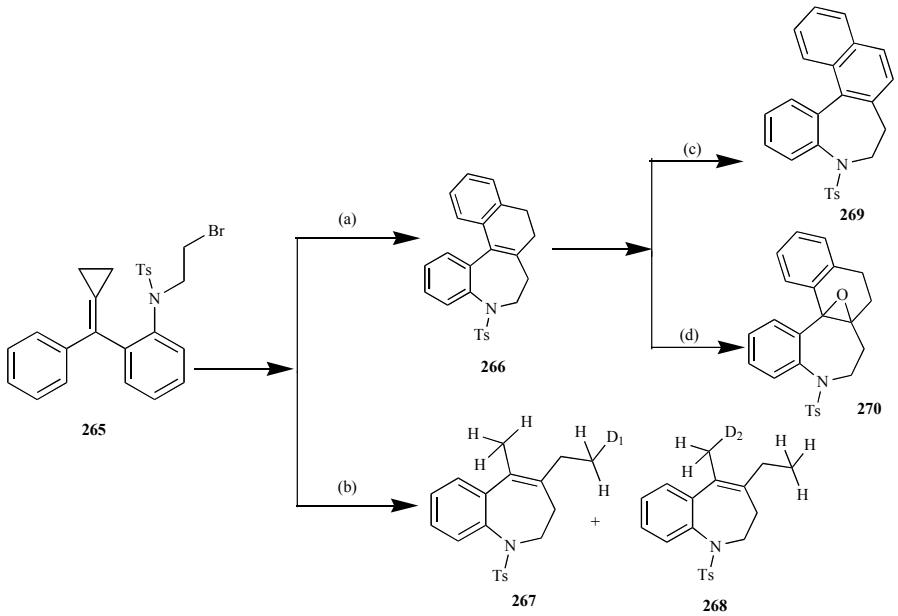
Dobrowolski [216] and his co-workers synthesized substituted benzazepinone **284-286 & 288** derivatives from substituted 2-aminochalcones **283 & 287** at different temperature ranges to give low to high yield. The 1,4-bis(2-aminophenyl)butane-1,4-dione **283** in acidic conditions give rise to the formation of doubly cyclised 7-phenyl-7,13-dihydro-8H-benzo[6,7]azepino[3,2-c]quinolin-8-ones **284** in propylphosphonic anhydride solution in 50% DMF (T3P®)[a] in very low yield. 2-aminochalcones **283, 287** were reacted with 2-oxindole, benzaldehyde, and acetone to form the substituted benzazepinone **284-286, 288** derivatives (Scheme **37**) in DMF and NaOH as a solvent with a wide range of anti-cancer properties to give low to high yield.

2.1.9. Synthesis of Azepin and Azepane from Alkynes via Intramolecular Cycloaddition

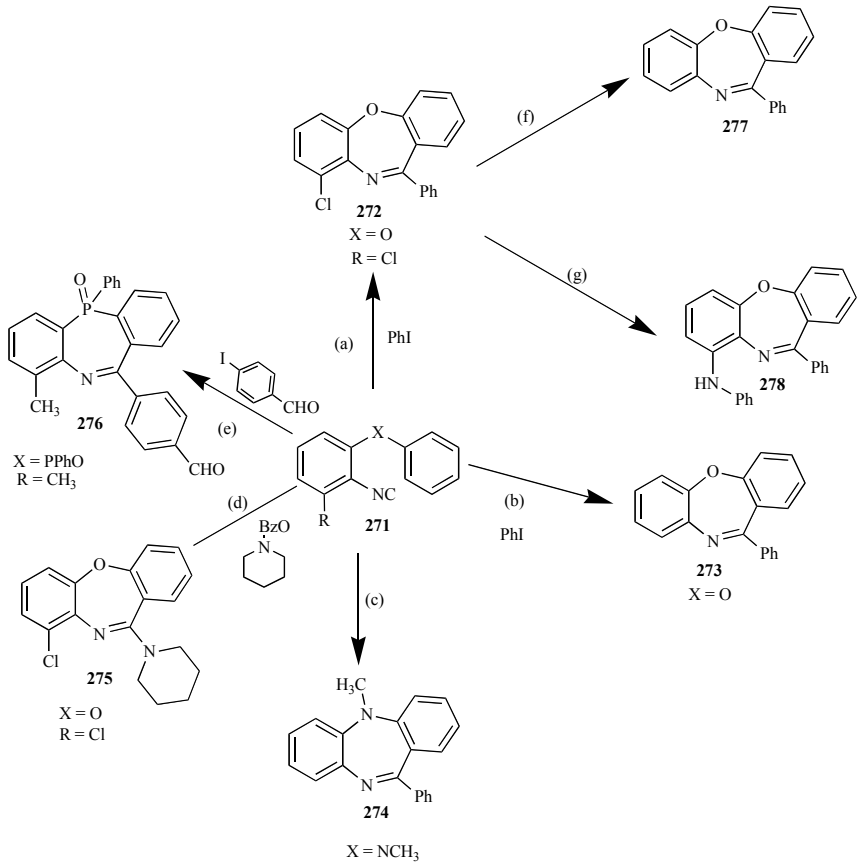
A number of scientists all over the world have been continuously working on the synthesis of azepine and its derivatives **290-295** from alkynes under varied reaction conditions. From the literature survey, it was clear that all the reactions were performed at a very high temperature to get a maximum yield of 99%. Han *et al.*



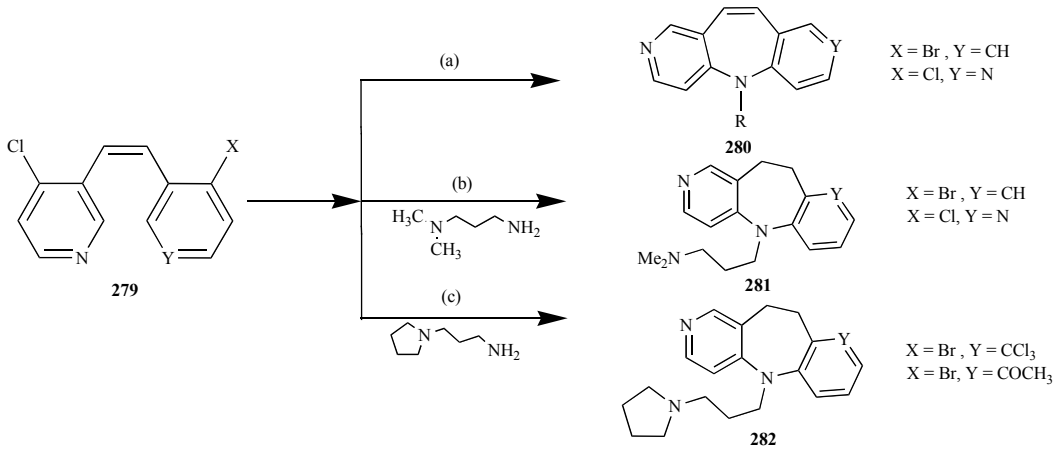
Scheme 33. Synthesis of azepine derivatives by [4+3] and [2+2] cycloaddition. Reagents: a) PPh_3 (20 mol%), $CHCl_3$, rt, 2h; [211] b) PPh_3 (20 mol%), $CHCl_3$, 25°C, 6h; [211] c) PPh_3 (20 mol%),Cs_2CO_3 (1.2equiv), D_2O (5.0 equiv), $CHCl_3$, 60°C; [211] d) DCM (0.4mmol) (1.0ml) $Cu(PPh_3)_3Br$ (10mol%), rt, 2h [212].



Scheme 34. Synthesis of azepine derivatives *via* ring cyclization.Reagents:a)$NiBr_2$ (DME) (10 mol%) , 1,10-phen(10mol%), Zn(2.0 equiv), DMF, N_2, 80°C, 70%; b) $NiBr_2$(DME)(10 mol%), 1, 10-phen (10mol%), Zn(2.0 equiv), DMSO-d_6, N_2, 120°C, 43%; c) DDQ (2.0 equiv), PhCl, 80°C,50%; d) m-CPBA (2.0 equiv) , CH_2Cl_2 , 0°C, 84% [213].



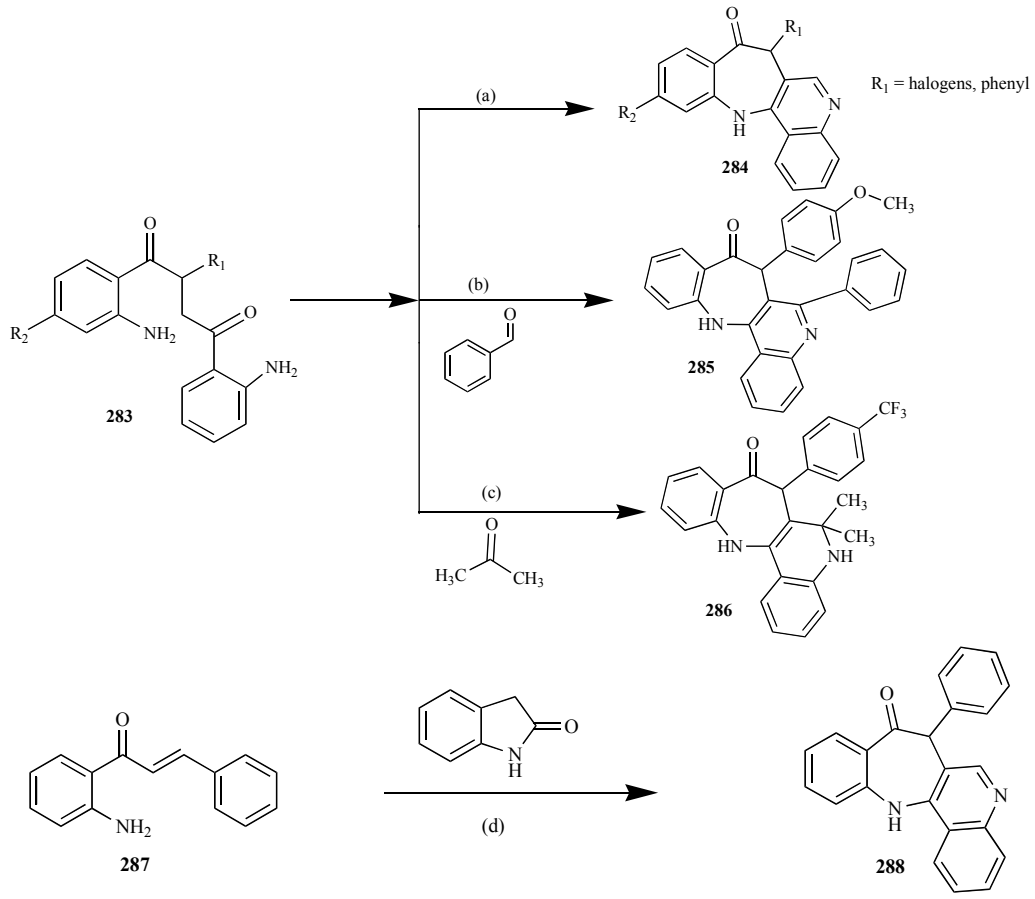
Scheme 35. Synthesis of substituted dibenzoazepine ring. Reagents: a)$Pd(OAc)_2$ (10mol%), PPh_3 (20mol%), PivOH (1.5 equiv), Cs_2CO_3 (0.6 equiv) , DMF/DMSO, 80°C, Ar; b) $Pd(OAc)_2$ (10mol%), PPh_3 (20mol%), PivOH (1.5 equiv), Cs_2CO_3 (0.6 equiv) , DMF/DMSO, 80°C, Ar; c) $Pd(OAc)_2$ (10mol%), PPh_3 (20mol%), PivOH (1.5 equiv), Cs_2CO_3 (0.6 equiv) , DMF/DMSO, 80°C, Ar; d) $Pd(OAc)_2$, PPh_3, toluene, 100°C, e) not mentioned; f) $Pd(OAc)_2$,JohnPhos, HCOONa, MeOH, g) Pd(dba), ^{t}BuXPhos, $PhNH_2$, 89% [214].



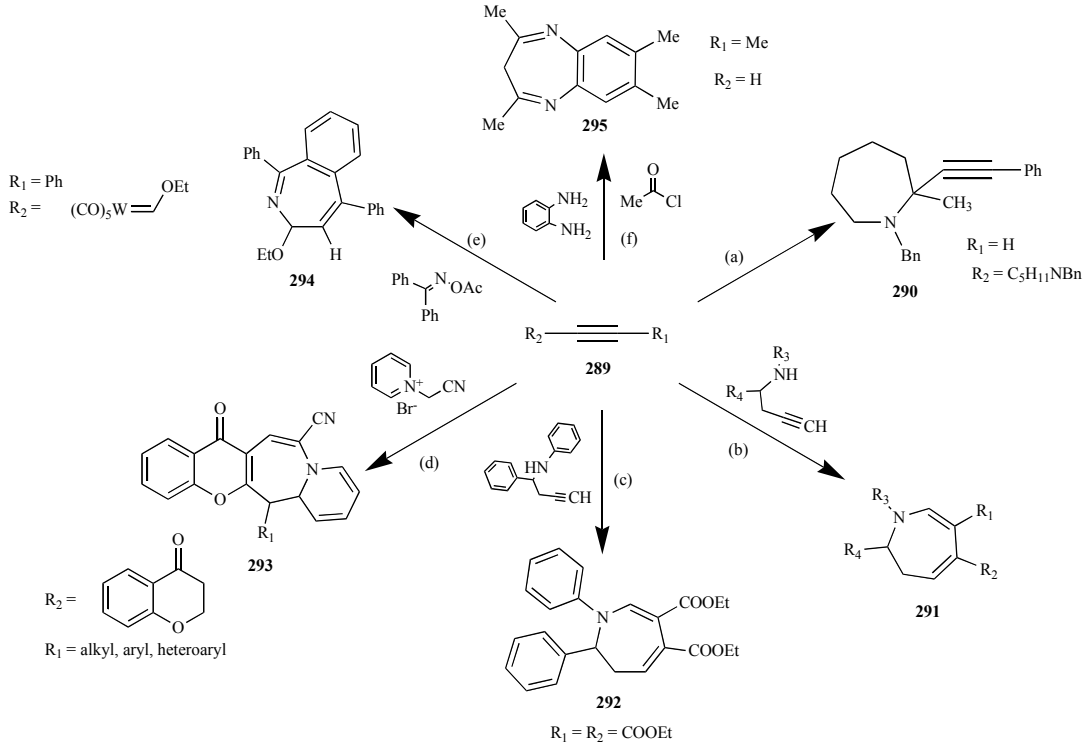
Scheme 36. Synthesis of substituted pyridobenzazepine from stilbenes by Pd catalyst. Reagents: a)$Pd(OAc)_2$ (5 mol%), JohnPhos (10 mol%), RNH_2, NaO*t*-Bu, PhMe, 100°C; b) $Pd(OAc)_2$ (5 mol%), JohnPhos (10 mol%), amine(3 equiv); c) $Pd(OAc)_2$ (5 mol%), JohnPhos (10 mol%), amine(3 equiv)[215].

[217, 218] in 2009, work on the synthesis of substituted benzazepine **290** from alkynes **289** using phenylacetylene and dioxane as a solvent at a very high temperature of 378K to get the maximum yield of 90%. Li *et al.* [219] in 2019, synthesize gold-catalyzed Azepines **291 & 292** in a maximum of 99% yield by [5+2] cycloaddition reaction at very high temperature (423K) using DMF as a solvent (Scheme **38**). Under basic conditions, azepine **293** derivatives were prepared in a 93% yield [220]. Photochemically, a very low yield (9%) was obtained with Hg in acetonitrile (CH_3CN) at low pressure [221].

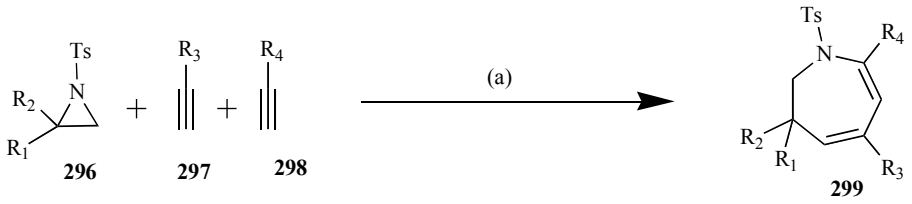
Li and co-workers [222], In 2014, described another synthetic route for the synthesis of substituted N-tosyl-azepine ring **299** by [3+2+2] cycloaddition reaction. Under mild oxidizing agents, N-substituted 1-tosylaziridines **296** undergo [3+2+2] cycloaddition reaction with alkynes **297 & 298** to give substituted N-tosyl-azepine ring **299** in excellent yield (Scheme **39**).



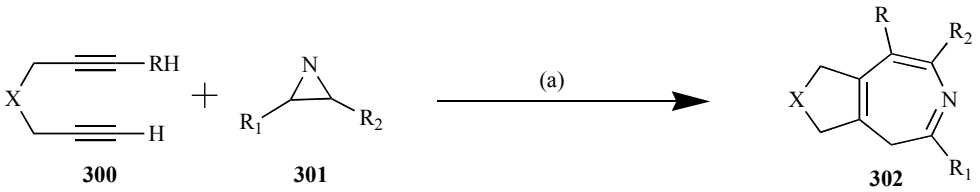
Scheme 37. Synthesis of substituted benzazepinone derivative. Reagents: a) T_3P in 50% DMF, 80°C, 24h. d) (i) NaOH, DMSO, air. (ii) T_3P in 50% DMF [216].



Scheme 38. Synthesis of Azepine and its derivatives from alkynes. Reagents: a) phenylacetylene, CuBr 5 mol%, dioxane, 100°C, MW, 0.5h; [217, 218] b) 5mol%, Ph_3PAuCl, DMF, 150°CAr; [219] c) 0.6mol%, Ph_3PAuCl, DMF, 150°C, 24h, Ar;[219] d) Et_3N, DCM, rt; [220] e) hν/CH_3CN , low-pressure, Hg; [220] f) 2% $PdCl_2(PPh_3)_2$, 4% CuI, (1.05 eq) NEt_3, THF, 1h, rt, CH_3COOH, 3d, 90°C (oil bath) or 1 h, 120°C (MW) [221].



Scheme 39. Synthesis of substituted N-tosyl-azepine ring. Reagents: a) 15 mol% $HSbF_6$, DCM, 40°C [222].



Scheme 40. Synthesis of fused azepine derivative by [3+2+2] cycloaddition reaction between diynes and 2H-azirines. Reagents: a) [$Cp^*Ru(COD)Cl$] (10 mol%), DCE, rt, 20h [223].

Similarly, Li and co-workers [223] were successful in the synthesis of fused azepine **302** derivatives by a similar type of [3+2+2] cycloaddition reaction. The Rh-catalyzed diynes **300** and 2H-azirines **301** undergo [3+2+2] cycloaddition reaction under the mild reaction condition to afford the synthesis of fused azepine ring **302** (Scheme **40**).

After spending a long time in research, Liu and co-workers [224] were successful in the synthesis of 3,4-fused bicyclic azepine derivative **305** in medium to high yield. The reaction proceeds by the [3+2+2] cycloaddition of 2-(1-alkynyl)-2-alken-1-ones **303** with 1,3,5-triazines **304** using $(p\text{-Tol})_3PAuNTf_2$ as a catalyst in DCM at room temperature (Scheme **41**).

Feng *et al.* [225] and Singh *et al.* [226b] worked on the reaction of substituted vinyl aziridines **306** with substituted alkynes **307**, which undergo [5+2] cycloaddition reaction to give the substituted azepine **308** and its homologous under the optimized reaction condition (Scheme **42**).

Hu and co-workers [227] were successful in the synthesis of Substituted azepine derivative **311** by [5+2] cycloaddition. The 2-(2-Aminoethyl)oxiranes **309** undergo [5+2] cycloaddition with substituted alkynes **310** followed by the opening of epoxide C-O bond, annulations and dehydroxylation to give the desired substituted azepine derivative **311** in medium yield (Scheme **43**).

Campillo *et al.* [228] worked on the synthesis of azepine derivative **314** *via* [5+2] cycloaddition. The cyclopropylmethanimine **312** undergoes [5+2] cycloaddition with alkynes **313**, followed by the ring-opening of cyclopropyl skeleton under the desired condition to give the product **314** in good yield (Scheme **44**).

Zhou *et al.* [229a] reported the synthesis of dihydroazepines **317** and it's homologous by [5+2] cycloaddition. The substituted acetylene **315** undergo [5+2] cycloaddition with N-tosylpyrrole derivative **316** under the controlled reaction condition followed by the ring-opening of pyrrole to give the desired product in low to moderate yield (Scheme **45**).

Ajarul *et al.* in 2020, [229b] reported a new reaction pathway for the synthesis of benzazepinone derivatives **319** *via* intramolecular ring cycloaddition. The compound **318** undergoes intramolecular cycloaddition reaction in toluene under reflux to afford the bioactive molecule **319** in maximum yield (Scheme **46**).

2.1.10. Synthesis of Azepin Derivative from Alkenes via Intramolecular and Intermolecular Cycloaddition

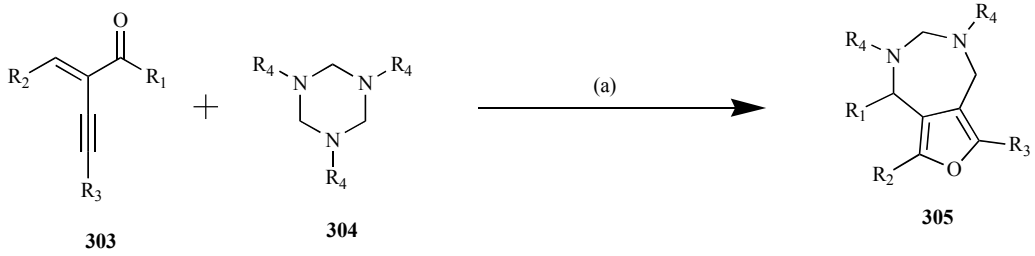
Feng *et al.* [230] synthesize bicyclic fused azepine derivative **322** in very high yield *via* hetero-[5+2] intramolecular cycloaddition. The vinyl aziridines bearing alkene terminal **320** undergo hetero-[5+2] intramolecular cycloaddition under the mild reaction condition to form the Rh catalyzed intermediate **321,** which was further converted to desired product **322** in moderate to high yield. The product obtained shows high region-stereoselectivity (Scheme **47**).

Zhu *et al.* [231] describe a novel one-pot route for the synthesis of N-tosyl substituted azepine derivative **324** *via* intermolecular Aza-[4+3] cycloaddition reaction. The Vinyl Aziridines **323** and Dienes undergo intermolecular Aza-[4+3] cycloaddition reaction using $[(Rh(NBD)Cl)_2]$ as a catalyst in DCM at 0°C to give the desired product in moderate to high yield (Scheme **48**).

Zhu [231] and Motornov [232] *et al.* worked on the synthesis of Substituted N-substitutedPerfluoroalkyl-Azepines **326-333** by microwave heating. Several Rh(II) catalyzed seven-membered N-heterocyclic ring was formed by aza [4+3]-annulation of substituted dienes and N-perfluoroalkyl-1,2,3-triazoles **325** in moderate to high yield by microwave heating at 130°C for only about 5-10 min using 1,2-dichloroethane (DCE) as a solvent (Scheme **49**).

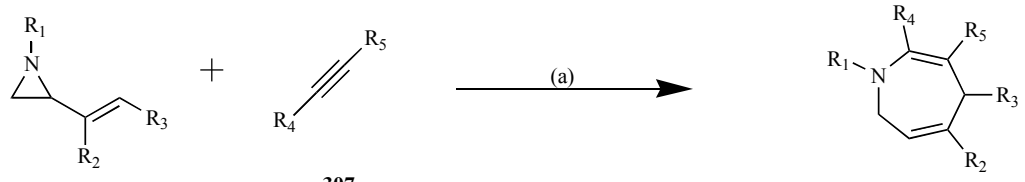
Schultz *et al.* [233] and Tian *et al.* [234] synthesized Rh-Catalyzed fused azepine derivatives. 4-(((2E,4E)-hexa-2,4-dien-1-yloxy)methyl)-1-tosyl-1H-1,2,3-triazole **334** underwent Rh-catalysed aza-cope rearrangement taking chloroform as a solvent at 60°C for 16h to give (6R,8aS)-6-methyl-5-tosyl-3,5,6,8a-tetrahydro-1H-furo[3,4-c]azepine **335** as a product in 73% yield (Scheme **50**).

Shang *et al.* [235], in 2014, worked on the synthesis of substituted 6-phenyl-1-tosyl-2,5-dihydro-1H-azepine **337-339** *via* microwave heating or thermally at high temperature. Many Rh-catalyzed Seven-Membered N-heterocyclic azepines were formed by the [4+3] cycloaddition of 4-phenyl-1-tosyl-1H-1,2,3-triazole **336** with dienes followed by ring-opening of triazole using DCE as a solvent (Scheme **51**).



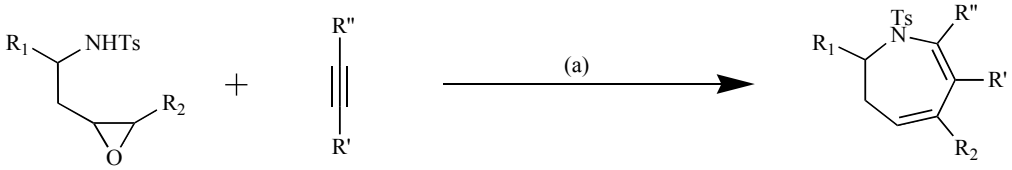
303 **304** **305**

Scheme 41. Synthesis of gold-catalyzed 3,4-fused bicyclic azepine derivative by [3+2+2] cycloaddition reaction. Reagents: a) (*p*-Tol)$_3$PAuNTf$_2$(5 mol%), DCM, rt [224].



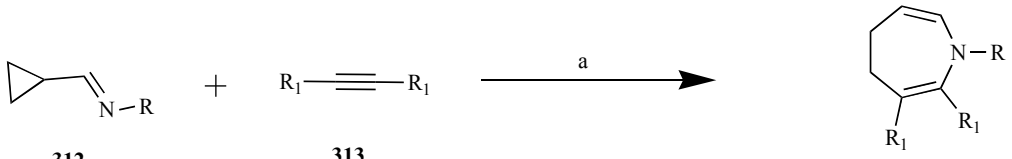
306 **307** **308**

Scheme 42. Synthesis of azepine derivative by [5+2] cycloaddition of vinyl aziridines with alkynes. Reagents: a) BF_3OEt_2 (1.2 equiv), DCM, rt, metal free [225, 226].



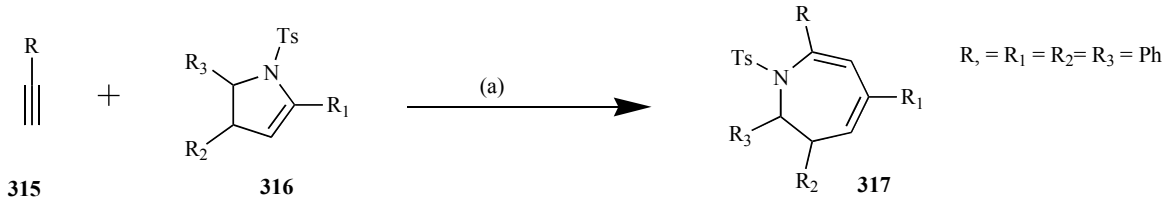
309 **310** **311**

Scheme 43. Synthesis of Substituted azepine derivative by [5+2] cycloaddition of 2-(2-Aminoethyl)oxiranes with Alkynes. Reagents: a) $FeCl_3$ (10 mol%), $BF_3.OEt_2$ (1 equiv), DCM, rt, 10min [227].



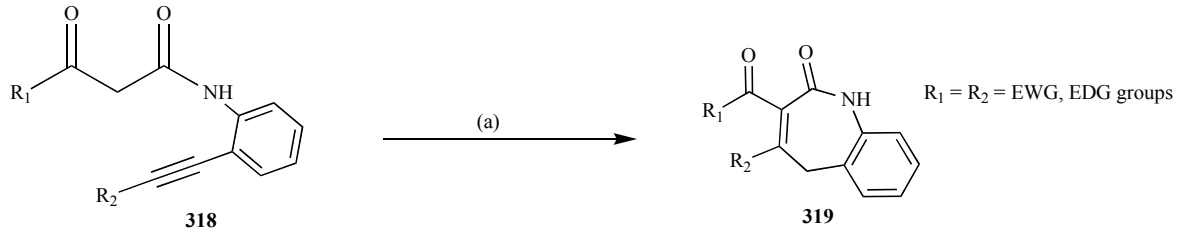
312 **313** **314**

Scheme 44. Synthesis of azepine derivative *via* [5+2] cycloaddition of imine and alkynes. Reagents: $[Rh(CO)_2Cl]_2$ [228].



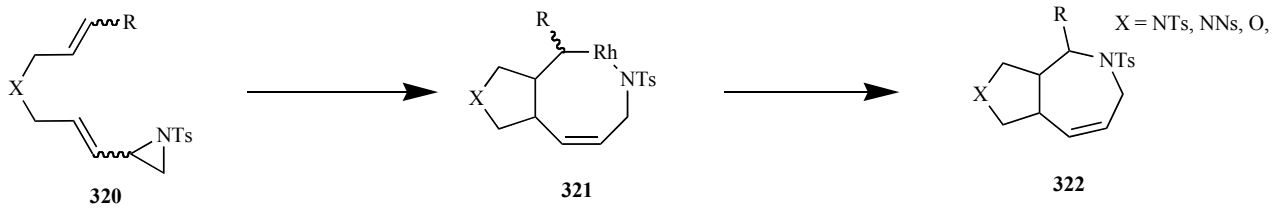
315 **316** **317**

Scheme 45. Synthesis of 1-tosyl-2,3-dihydro-1H-azepine *via* [5+2] cycloaddition. Reagents: a) $FeCl_3$ (4 mol%), BF_3Et_2O (40 mol%), CH_2ClCH_2Cl, 80^{o}C, Ar, 24h [229].

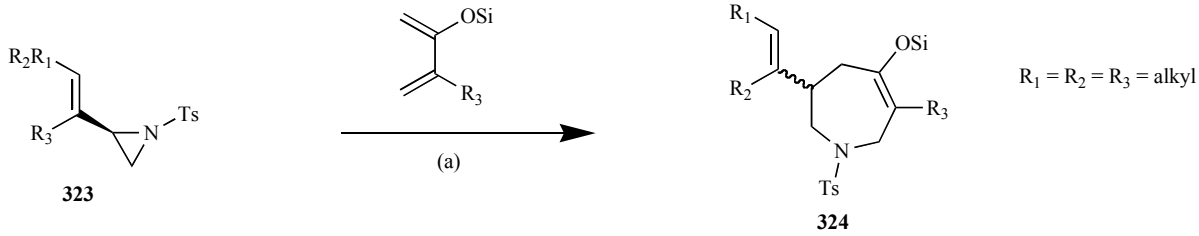


318 **319**

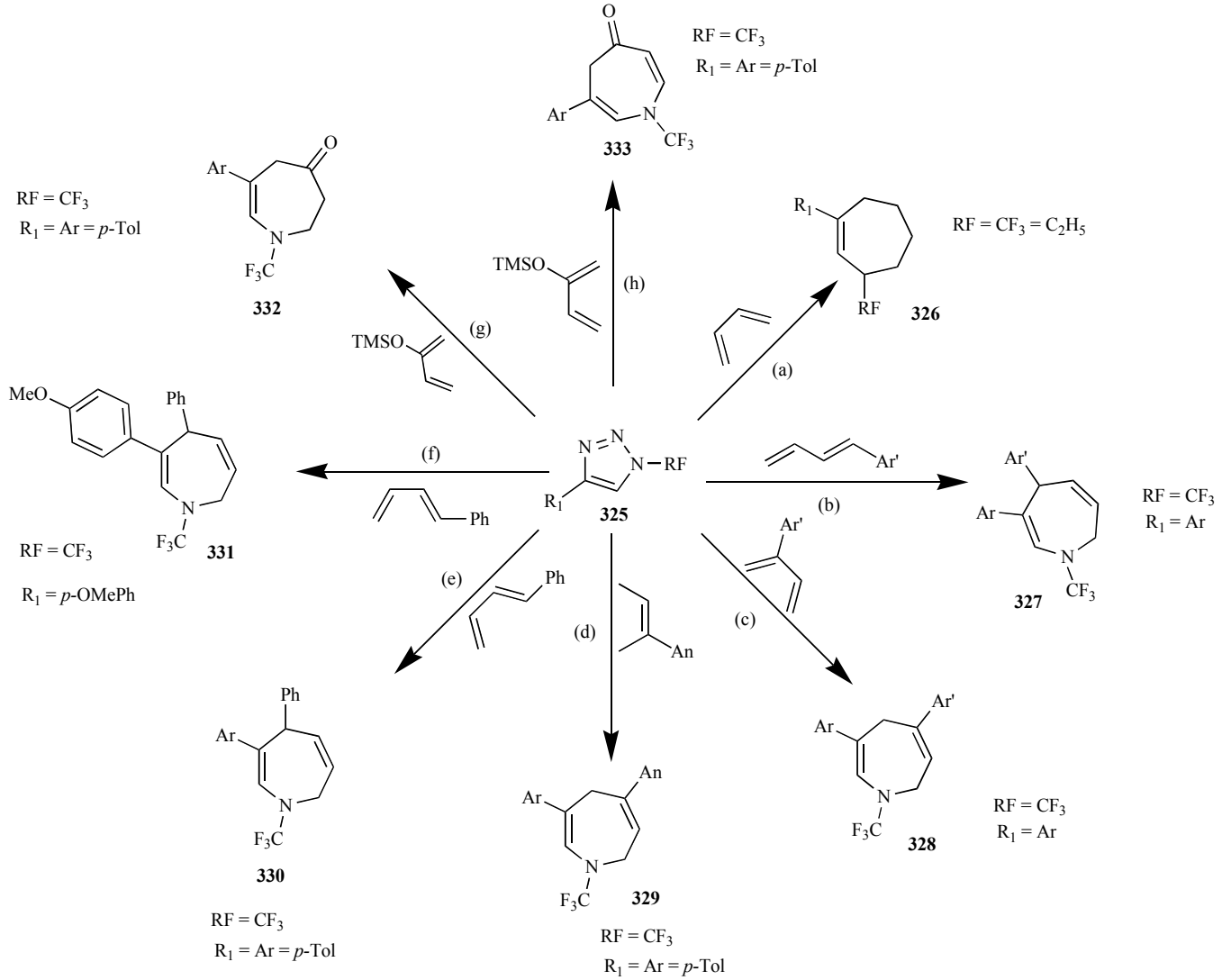
Scheme 46. Synthesis of Benzazepinone derivatives *via* intramolecular cycloaddition. Reagents: a) $ZnCl_2$, (20 mol%), toluene, reflux, 3-8h.



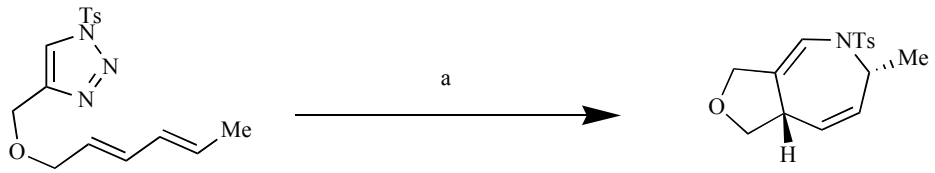
Scheme 47. Synthesis of bicyclic fused azepine derivative *via* hetero-[5+2] cycloaddition.



Scheme 48. Synthesis of azepine derivative *via* [4+3] cycloaddition. Reagents: a) [(Rh(NBD)Cl)$_2$] (5 mol%), $AgClO_4$ (10 mol%), DCE/0^{o}C [231].

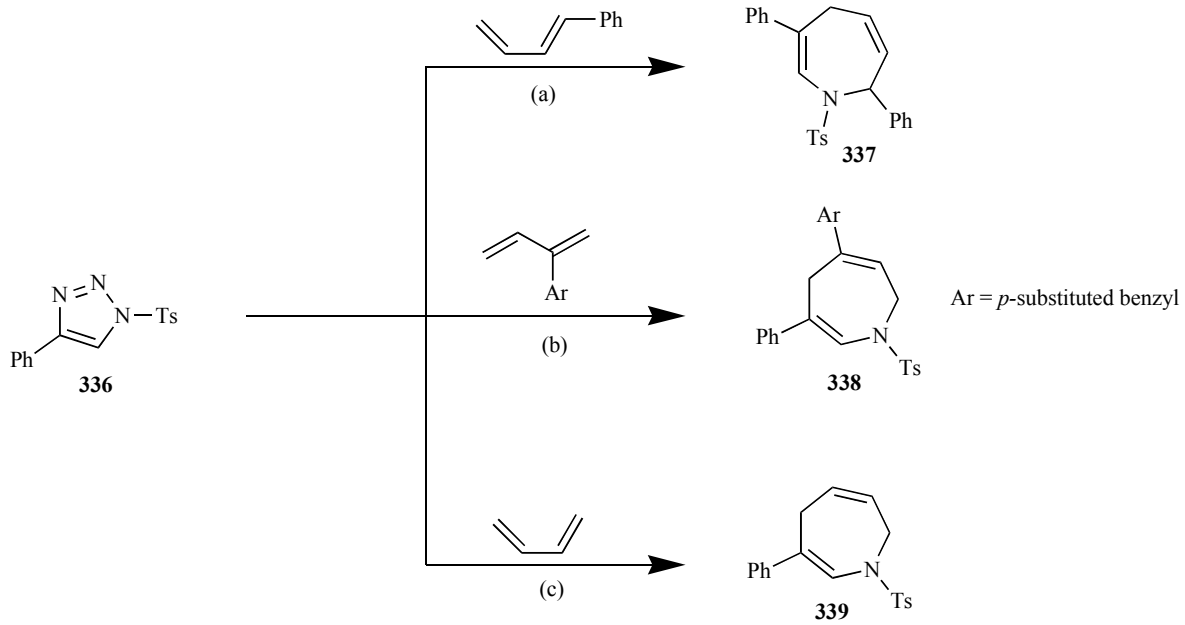


Scheme 49. Synthesis of Substituted N-Perfluoroalkyl-Azepines. Reagents: a) $Rh_2(Oct)_4$ (2 mol%), MW, 130^{o}C, 5-60 min; b) Rh, -N_2, aza-cope; c) Rh, -N_2, aza-cope; d) $Rh_2(Oct)_4$ (2 mol%)MW, 130^{o}C; e) $Rh_2(Oct)_4$ (2 mol%); f) Rh_2 $(Oct)_4$ (0.5 mol%, 14 mg), DCE (18 ml), MW, 130^{o}C, 7min; g) (i) Rh_2 $(Oct)_4$ (2 mol%), MW, 130^{o}C, 5 min (ii) HCl/ H_2O; h) (i) Rh_2 $(Oct)_4$ (2 mol%), MW, 130^{o}C, 5 min (ii) $Pd(OAc)_2$, MeCN. rt, [232].

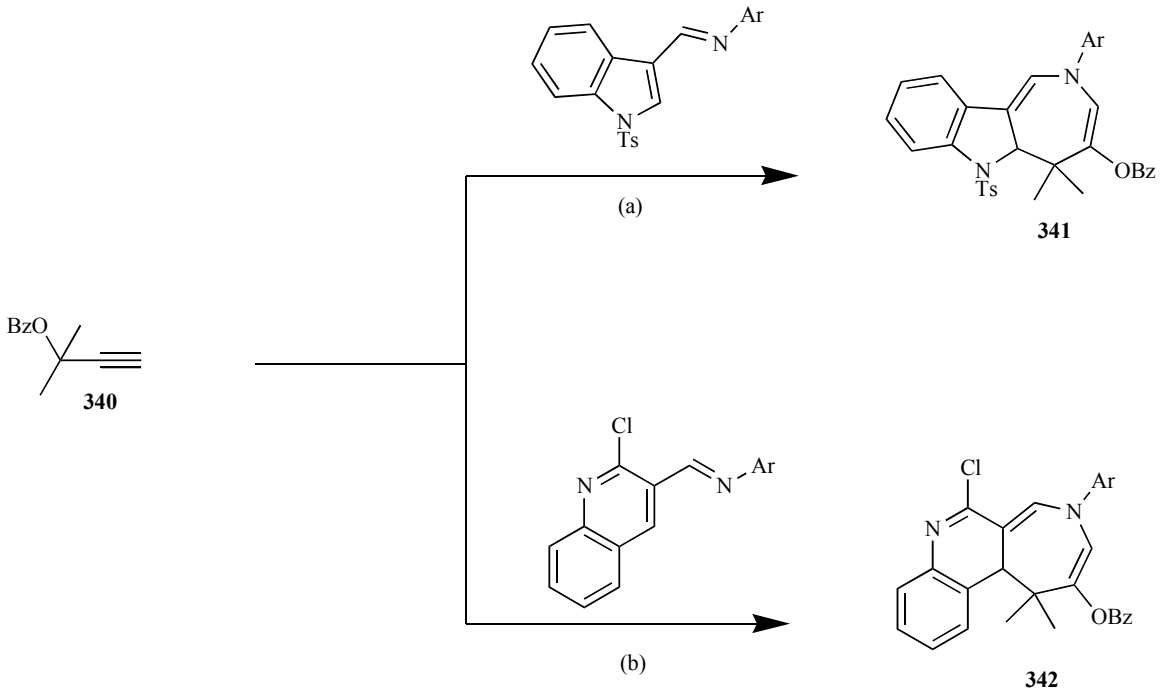


334 **335**

Scheme 50. Synthesis of Rh-catalyzed fused azepine derivatives. Reagents: a) $[Rh_2(Adc)_4]$ (1 mol%), $CHCl_3$, 60°C, 16h[233,234].



Scheme 51. [4+3] cycloaddition of triazoles with dienes. Reagents: a) $[Rh_2(oct)_4]$ (1 mol%), 1,2-DCE, 120°C, 12h; b) $[Rh_2(oct)_4]$ (0.002 mmol%) in DCE (1.0Ml) at 120°C, A Å M.S., MW, 5-10min; c) $[Rh_2(oct)_4]$ (0.002 mmol%) in DCE (1.0Ml) at 140°C, 12h; or $[Rh_2(oct)_4]$ (0.002 mmol%) in DCE (1.0Ml) at 120°C, A Å M.S., MW, 5-10min [235].



Scheme 52. Synthesis of gold-catalyzed fused azepine ring *via* [4+3] cycloaddition. Reagents: a) DCE, 60°C; b) CH_2Cl_2, rt, [236].

Shapiro with co-workers [236] was successful in the synthesis of tricyclic azepines *via* [4+3] cycloaddition of 2-methylbut-3-yn-2-yl benzoate **340** with (E)-N-((1-tosyl-1H-indol-3-yl)methylene)-argonamine using DCE as a solvent at 60^{o}C to get the indole azepine derivative **341** in moderate yield or with (E)-N-((2-chloroquinolin-3-yl)methylene)argonamine in DCM at room temperature to get the tricyclic azepine **342** in excellent yield (Scheme **52**).

Liu *et al*. [237a] proposed a reaction pathway for the synthesis of 1-benzyl-4,4,5,5-tetramethyl-4,5-dihydro-1H-azepine-3,6-diyl dibenzoate **345** using benzyl azide. The 2-methylbut-3-yn-2-yl benzoate **343** undergoes cycloaddition reaction with (azidomethyl)benzene **344** using $AuCl_3$ as a catalyst in DCM followed by reduction with $NaBH_4$ gave the desired 1-benzyl-4,4,5,5-tetramethyl-4,5-dihydro-1H-azepine-3,6-diyl dibenzoate **345** in low yield (Scheme **53**).

Pan *et al.* in 2020, [237b] worked on the new technique for the metal-free decarboxylative cycloaddition (Scheme **54**). The N-arylacrylamides **346** undergoes [3+2] or [5+2] cycloaddition reaction with vinyl acids **347**, which results in the formation of benzo[b]azepin-2-ones derivatives **348** in DMSO and using $(NH_4)_2S_2O_8$ as an oxidant at 50^{o}C as a final product in acceptable yield.

2.1.11. Synthesis of Azepine Derivative from Miscellaneous Reactants

1-benzyl-4,4,5,5-tetramethyl-4,5-dihydro-1H-azepine-3,6-diyl-dibenzoate **349** undergoes hydrogenation reaction in a mixture of NaOH and MeOH/THF at room temperature to give the dione product *i.e.,* 1-benzyl-4,4,5,5-tetramethylazepane-3,6-dione **350** in 80% yield [237] (Scheme **55**).

Substituted indolin-2-one is an another key reactant used by Zhan *et al.* [238] for the synthesis of Sphiro indole fused azepine derivative **352 & 353** (Scheme **56**). The (Z)-methyl 3-bromo-2-(1-methyl-2-oxoindolin-3-ylidene)propanoate **351** undergoes [4+3] cycloaddition with ethyl (2-(chloromethyl)phenyl)carbamate or with ethyl (3-(chloromethyl)naphthalen-2-yl)carbamate using (4-$FC_6H_4)_3P$ as a catalyst in excess of Cs_2CO_3 give 1-ethyl 3-methyl 1'-methyl-2'-oxospiro[benzo[b]azepine-4,3'-indoline]-1,3(5H)-dicarboxylate **352** and 1'-ethyl 3'-methyl 1-methyl-2-oxospiro[indoline-3,4'-naphtho[2,3-b]azepine]-1',3'(5'H)-dicarboxylate **353**, respectively.

Insuasty [239] developed a new method for the synthesis of a fused 1,4-benzodiazepine derivatives. pyrimidine-4,5,6-triamine **354** underwent microwave radiation for 2-5 min for the synthesis of 6-(benzo[d][1,3]dioxol-5-yl)-8-phenyl-8,9-dihydro-7H-pyrimido[4,5-b][1,4]diazepin-4-amine **355** and 8-(benzo[d][1,3]dioxol-5-yl)-6-phenyl-8,9-dihydro-7H-pyrimido[4,5-b][1,4]diazepin-4-amine **356** in DMF at 150^{o}C. It is a single-step reaction which leads to the formation of 1 C-C bond and 3 C-N bond to give the desired azepine derivative (Scheme **57**).

Acosta *et al*. [240] were successful in the synthesis of (R)-4-chloro-6,11-dimethyl-6,11-dihydro-5H-benzo[b]pyrimido[5,4-f]azepine **360**, and it's homologous *via* intramolecular Friedel–Crafts alkylation. The substituted 5-allyl-4,6-dichloropyrimidine **357** and substituted N-methylaniline **358** undergoes intramolecular Friedel–Crafts alkylation to give the substrate **359**, which further undergoes intramolecular cyclization to give the desired product **360** in different yield (Scheme **58**).

Acosta *et al*. [240] in 2015 synthesized a tricyclic moiety *i.e.,* (R)-4-chloro-6,11-dimethyl-6,11-dihydro-5H-benzo[b]pyrimido[5,4-f]azepine **362** and (R)-4-chloro-6-methyl-5,6,10,11-tetrahydro-pyrimido[5',4':6,7] azepino[3,2,1-hi]indole **363** derivatives by the ring cyclization of substituted 5-allyl-6-chloro-N-methyl-N-phenylpyrimidin-4-amine **361** under the appropriate reaction condition (Scheme **59**).

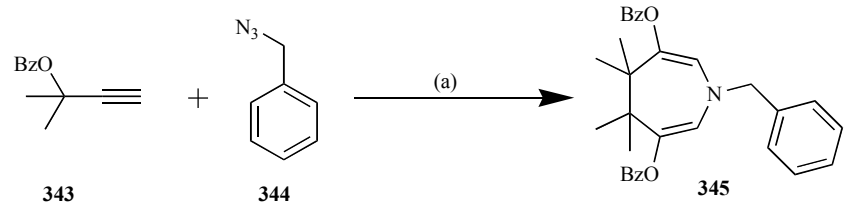
Mingo *et al.* [134] also synthesized substituted benzazepinone derivatives *via* intramolecular cyclization reaction (Scheme **60**). The Pd-catalyzed valine-glycine dipeptide **364** reacts under the optimized reaction condition to give the corresponding seven-membered N-heterocyclic product, *i.e.,* benzazepinone derivative **365** in 78% yield with high *trans*-diastereoselectivity.

(E)-4-((7-amino-3-mercapto-5-(piperidin-1-yl)-2H-1,2,4-triazepin-6-yl)diazenyl)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one **368** and (E)-7-amino-6-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)diazenyl)-5-(piperidin-1-yl)-1,4-thiazepin-3(2H)-one **369** are synthesized by the diazo-coupling of 4-amino-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one **366** in ethanolic sodium acetate solution with malononitrile at very low temperature *i.e.,* 0-5^{o}C, which is then reacted with piperidine under reflux condition in ethanol to give the corresponding 1:1 acyclic enaminonitrile *i.e.,* (Z)-3-amino-2-((E)-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)diazenyl)-3-(piperidin-1-yl)acrylonitrile **367**. The solution of enaminonitrile **367** was stirredin DMF with CS_2 and NaOH solution to give the formation of its sodium salt, which further ungerdo methylation with $(CH_3)_2SO_4$ to get methyl mercaptan derivative. The compound formed followed by the further addition of hydrazine hydrate to the cyano group in enaminonitrile derivative **367** followed by cyclization and elimination to give the desired azepine derivative *i.e.,* E)-4-((7-amino-3-mercapto-5-(piperidin-1-yl)-2H-1,2,4-triazepin-6-yl)diazenyl)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one **368**. Similarly the reaction of enaminonitrile derivative **367** with 2-mercaptoacetic acid in refluxing pyridine give 1,4-thiazepinone derivative *i.e.,* (E)-7-amino-6-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)diazenyl)-5-(piperidin-1-yl)-1,4-thiazepin-3(2H)-one **369 [**241**]**. (Scheme **61**).

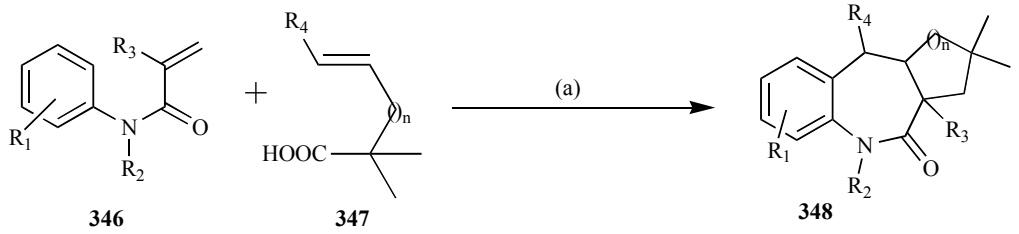
Many researchers work on the synthesis of methyl 2,2,7,7-tetramethylazepane-1-carboxylate from N-chlorolactam **370** at different temperature ranges and in different basic conditions. Winter and her co-workers successfully describe the reaction of N-chlorolactams **370** to form the target product **372**. According to her, at -78^{o}C N-chlorolactams **370**, were irradiated photochemically at 254nm in DCM to give the intermediate product carbamoyl chloride **371**which was then reacted with base (K_2CO_3 or Et_3N) in MeOH to give the product methyl 2,2,7,7-tetramethylazepane-1-carboxylate **372** in very low yield (Scheme **62**). The intermediate product was isolated by chromatography [242].

Winter and her co-workers [242] successfully synthesize 2-methoxy-7,7-dipropyl-4,5,6,7-tetrahydro-1,3-oxazepine **374** from 1-chloro-3,3-dipropylpiperidin-2-one **373** by ring expansion of N-chlorolactams (Scheme **63**). N-chlorolactams were irradiated photochemically at -78^{o}C in basic condition at 254nm in MeOH to give seven membered N-chlorolactams **374** in moderate yield.

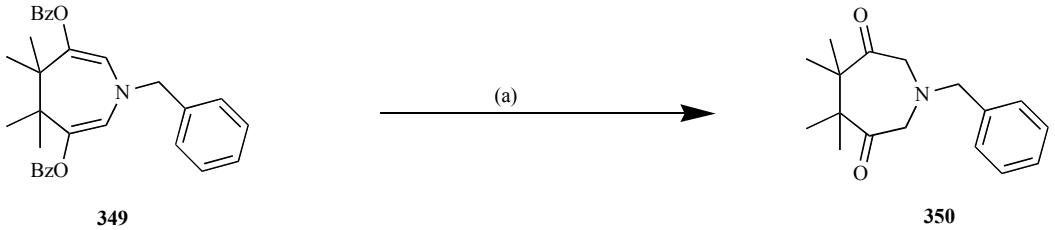
Winter and her co-workers [242] also work on the synthesis of a racemic mixture of substituted azepan-2-one. (2R)-2,6-dimethylcyclohexanone **375** was taken as the starting material for the synthesis of a racemic mixture of substituted azepan-2-one **377 & 378**. The ring expansion takes place according to Beckmann rearrangement. (2R)-2,6-dimethylcyclohexanone **375** was reacted with $NH_2OH.HCl$, the intermediate (1E,2R)-N-hydroxy-2,6-dimethylcyclohexanimine **376**, is formed, which undergo acid hy-



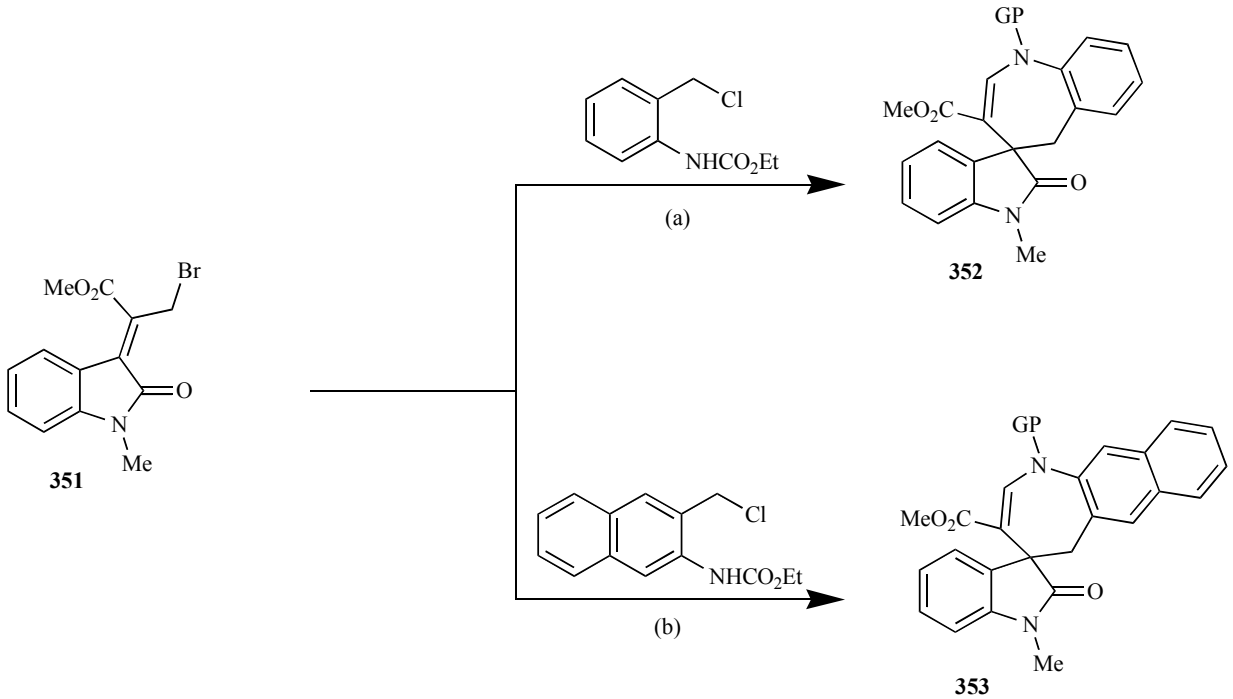
Scheme 53. Synthesis of of 1-benzyl-4,4,5,5-tetramethyl-4,5-dihydro-1H-azepine-3,6-diyl dibenzoate *via* cycloaddition. Reagents: a) $AuCl_3$, DCM, $BaBH_4$, 4Å MS [237].



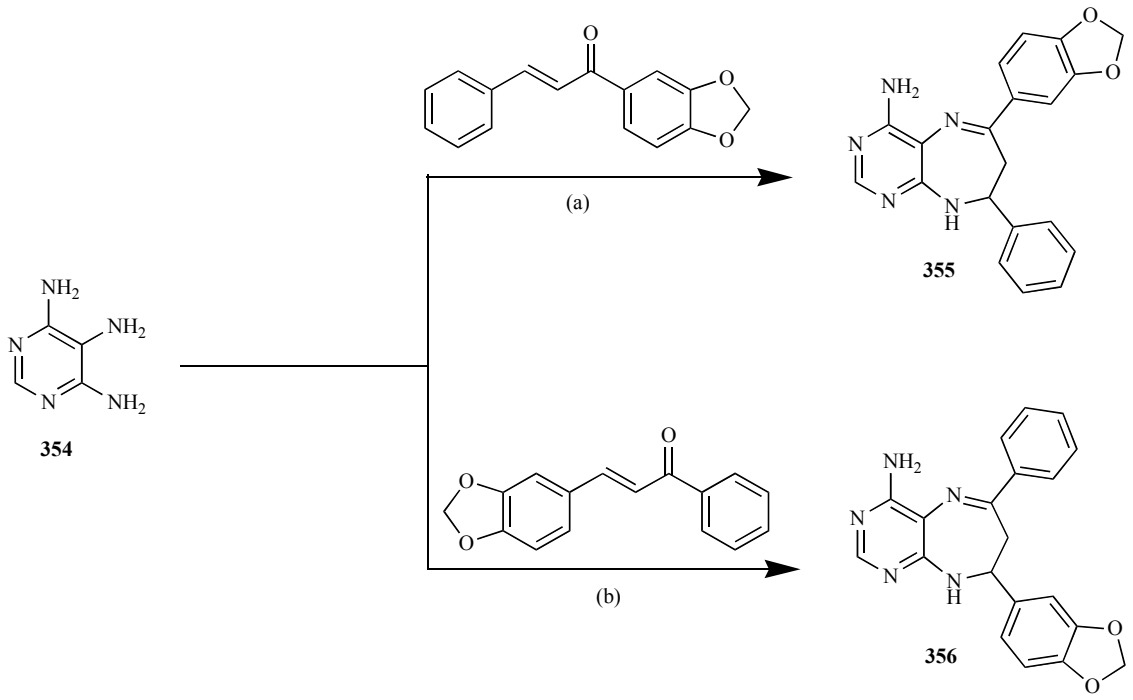
Scheme 54. Synthesis of benzo[b]azepin-2-ones derivatives *via* [3+2] or [5+2] cycloaddition reaction. Reagents: a) $(NH_4)_2S_2O_8$, DMSO, 50°C, Ar.



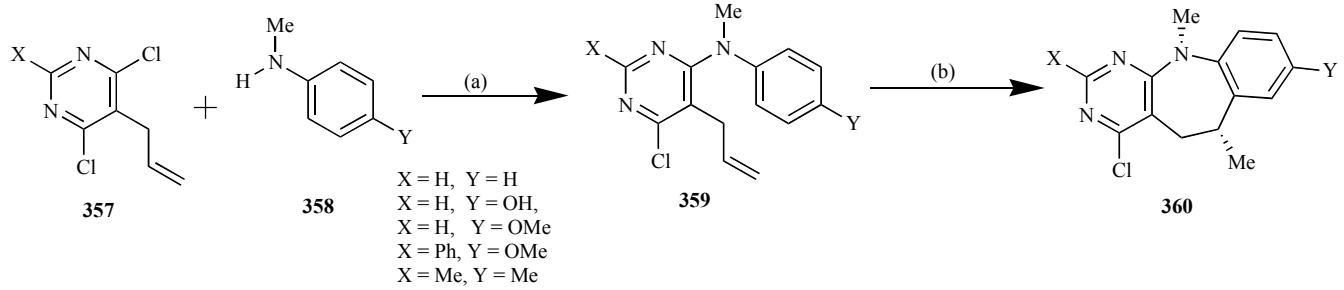
Scheme 55. Hydrolyzation of 1-benzyl-4,4,5,5-tetramethyl-4,5-dihydro-1H-azepine-3,6-diyl dibenzoate. Reagengts: 1M NaOH (6.0 equiv), MeOH/THF = 2/1, rt [237].



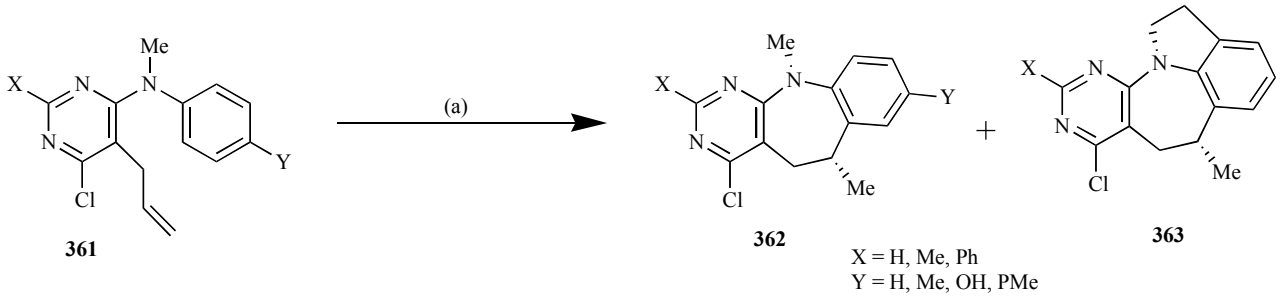
Scheme 56. Synthesis of indolin-2-one fused azepine derivatives *via* [4+3] cycloaddition. Reagents: a) $(4\text{-}FC_6H_4)_3P$, Cs_2CO_3, 4 Å MS, $PhCF_3$, 50°C, 12h; b) $(4\text{-}FC_6H_4)_3P$, Cs_2CO_3, 4 Å MS, $PhCF_3$, 50°C, 12h [238].



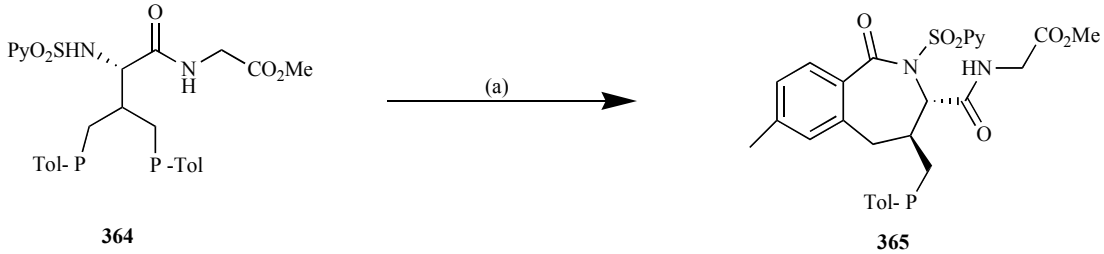
Scheme 57. Synthesis of 1,4-benzodiazepine derivative by microwave irradiation. Reagents: a) DMF, MW, 150°C, 2-5 min; b) DMF, MW, 150°C, 2-5 min [239].



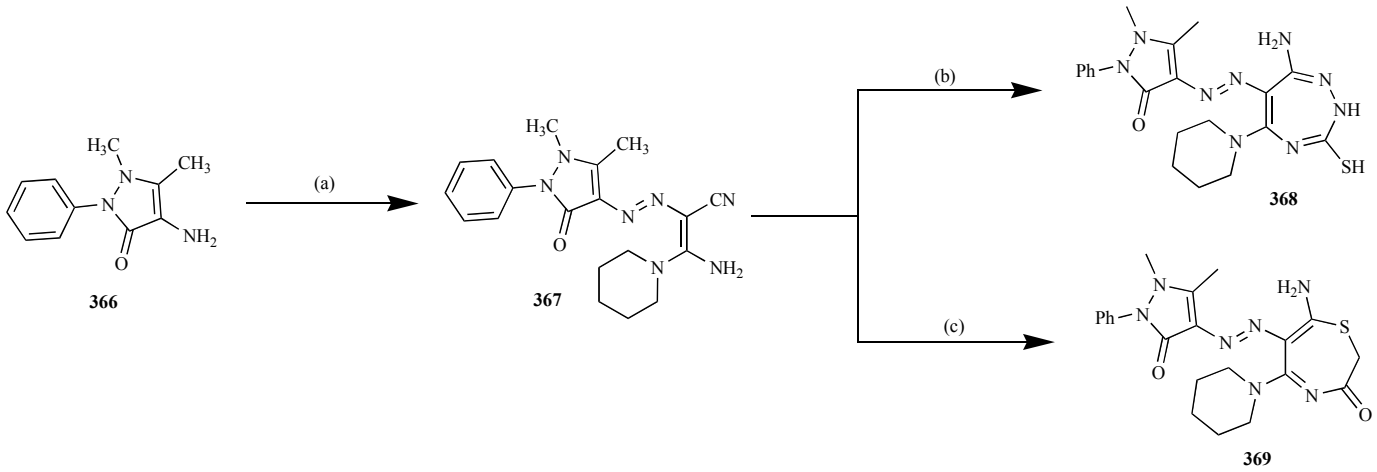
Scheme 58. Synthesis of dihydro-5H-benzo[b]pyrimido[5,4-f]azepine and it's homologous *via* intramolecular Friedel–Crafts alkylation. Reagents: a) $(Me_2CH)_2NEt$; b) CH_2SO_3H[240].



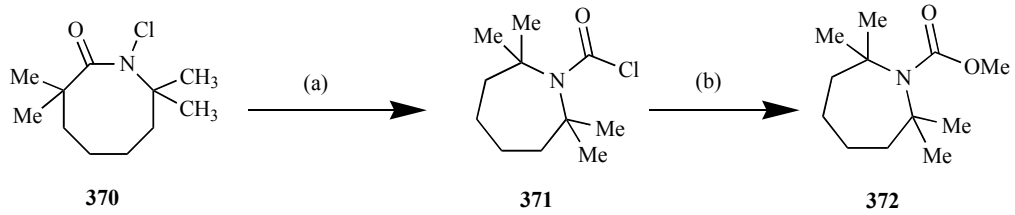
Scheme 59. Synthesis of azepine derivatives by ring cyclization. Reagents: a) CF_3SO_3H [240].



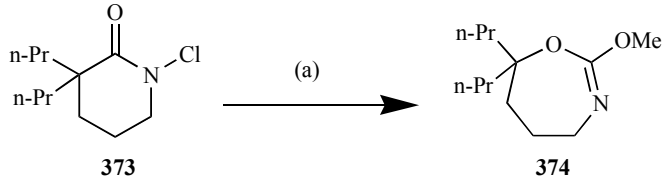
Scheme 60. Synthesis of substituted benzazepinone derivative *via* intramolecular cyclization. Reagents: a) $Pd(OAc)_2$ (10 mol%), $Mo(CO)_6$ (33 mol%), AgOAc (1.50 equiv), BQ (2.00 equiv), 1,4-Dioxane (0.25 M), 110°C, 18h [134].



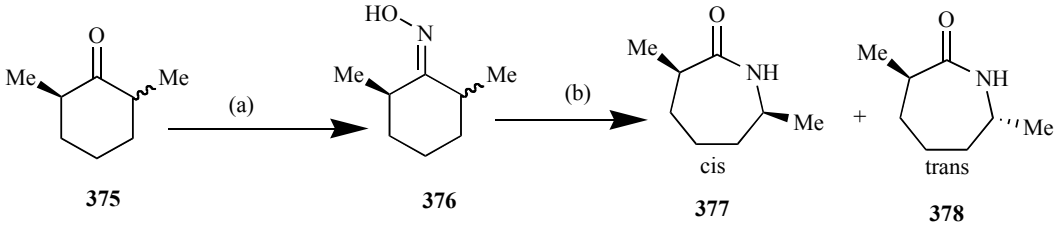
Scheme 61. Synthetic route for the synthesis of azepine derivative. reagents: a) (i) HCl, $NaNO_2$, H_2O, 0-5°C; (ii) malononitrile, EtOH/AcONa/H_2O, cooled, 30 min, overnight cooled; (iii) Secondary amine, EtOH, reflux; (iv) [1,5] H migration; b) (i) CS_2/DMF, NaOH, rt; (ii) $(CH_3)_2SO_4$, 5-10°C, or dil HCl; (iii) $NH_2NH_2.H_2O$, EtOH, TEA; c) 2-mercaptoacetic acid, pyridine, reflux [241].



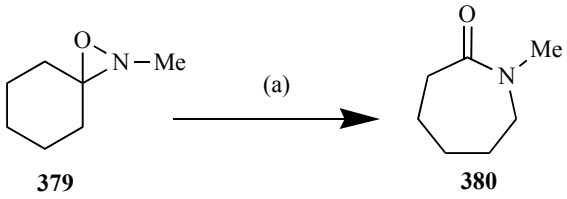
Scheme 62. Synthesis of methyl 2,2,7,7-tetramethylazepane-1-carboxylate from N-chlorolactams. a) h*v*, 254nm, -78°C, DCM,b) MeOH, base [242].



Scheme 63. Synthesis of substitutedoxazepine from 1-chloro-3,3-dipropylpiperidin-2-one. Reagents: a) h*v*, 254nm, -78°C, MeOH, base [242].



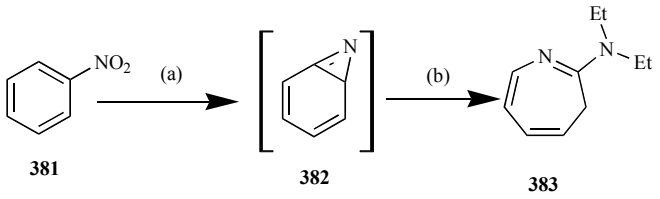
Scheme 64. Synthesis of substituted azepan-2-one. Reagents: a)$NH_2OH.HCl$, MeOH/H_2O, Na_2CO_3; b) TsCl, NaOH, H_2O, dioxane, 50% [242].



Scheme 65. Synthesis of 1-methylazepan-2-one from 2-methyl-1-oxa-2-azaspiro[2.5]octane. Reagents: a) h*v* or heat [243-245].

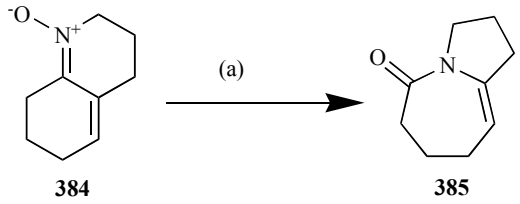
drolysis to give the racemic mixture of 3,7-dimethylazepan-2-one **377 & 378** in 99% yield (Scheme **64**).

Gritsan and her co-workers [243-245] were successful in the synthesis of 1-methylazepan-2-one **380**. 1-methylazepan-2-one **380** was obtained by the ring expansion of oxaziridines **379** by thermally or photo-chemically (Scheme **65**). The oxaziridines **379** undergo ring expansion because the three-membered heterocyclic ring is highly unstable due to ring strain, so it undergoes ring rearrangement to form the stable seven-membered heterocyclic ring, *i.e.*, of 1-methylazepan-2-one **380**.



Scheme 66. Synthesis of 2-diethylamino-3H-azepine from nitrobenzene. Reagents: a) $P(OEt)_3$, 145°C, 50 min, h*v*;b) Et_2NH[246-249].

Nitrobenzene **381** undergo reductive cyclization at a very high temperature, *i.e.*, at 418K, to give substituted 3H-azepine in very low yield [246-249]. By photolysis of nitrobenzene **381** with diethyl amine in excess of triethylphosphite, 2-diethylamino-3H-azepine **383** was obtained as a product (Scheme **66**). This reaction took place by the ring expansion of intermediate **382** to give the final product 3H-azepine.



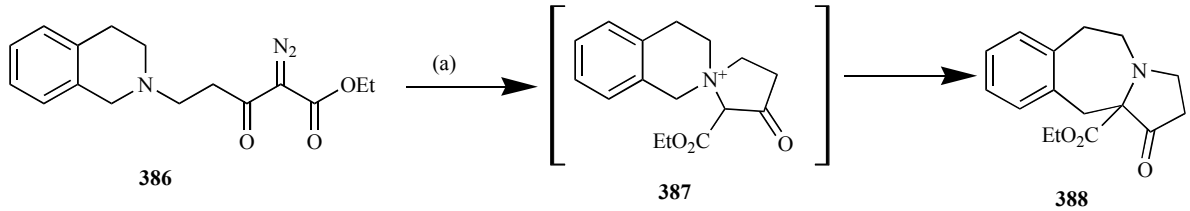
Scheme 67. Ring expansion of bicyclic lactam to bicyclic azepinones. Reagents: a) h*v*, 2h [250].

The bicyclic lactams **384** when undergo ring rearrangement and ring expansion under photochemical conditions (Scheme **67**) to form the stable bicyclic ring **385**. Two six-membered rings rearrange themselves to form a stable seven-membered 2,3,7,8-tetrahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one **385** as a major product [250].

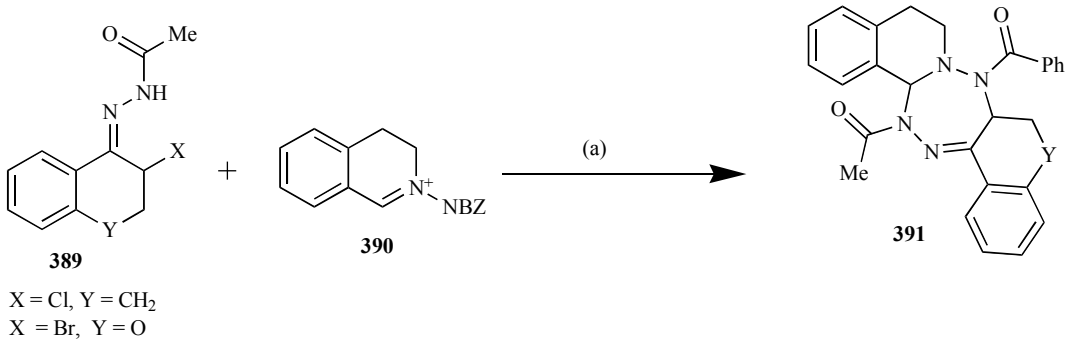
Padwa *et al.* [251], after much research, synthesized a seven-membered heterocyclic organic compound **388** in average yield by ammonium-ylide shift **387** (Scheme **68**). In the presence of copper(II) acetylacetonate ($Cu(acac)_2$), the ethyl 1-oxo-2,3,6,11-tetrahydro-1H-pyrrolo[2,1-b][3]benzazepine-11a(5H)-carboxylate **388** is formed in 73% yield when the starting substrate **386** undergo ring rearrangement in refluxing toluene. This reaction is slow, and it took a long period of time to complete in the presence of rhodium acetate.

Hu *et al.* [252] described another synthetic route for synthesizing biologically active 1,2,4,5-tetrazepine derivatives **391**. These derivatives were prepared in medium yield by the [4+3] cycloaddition of C, N-cyclic azomethine imine ylides **390**, and 1,2-diaza-1,3-dienes **389** using K_2CO_3 and THF as a solvent (Scheme **69**).

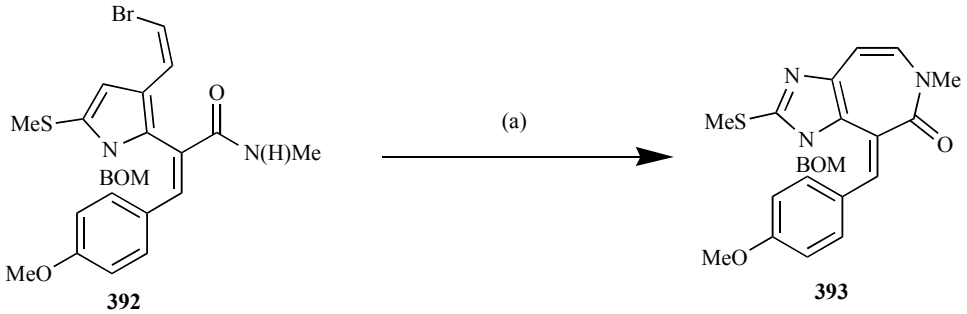
Nodwell and his co-workers [253] work on the synthesis of imidazoazepine **393**, which shows an antimitotic activity. The starting substrate **392** undergoes an intramolecular cross-coupling reaction between N-methylamide and vinyl bromide under buchwald's condition (Scheme **70**).



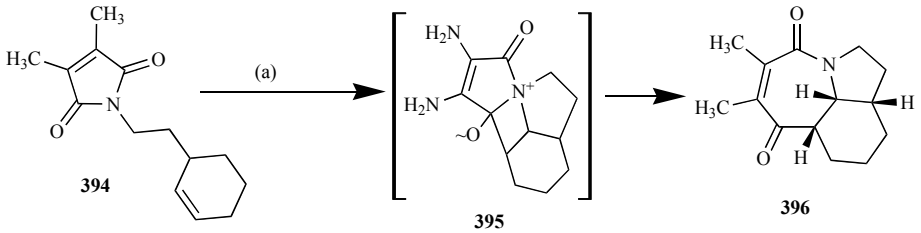
Scheme 68. Synthesis of 5-7fused heterocyclic ring. Reagents: a) $Cu(acac)_2$, toluene ,reflux [251].



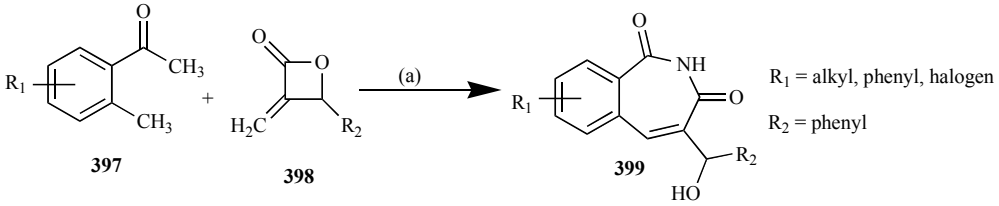
Scheme 69. Synthesis of 1,2,4,5-tetrazepine derivatives by [4+3] cycloaddition. Reagents: a) K_2CO_3 (2 equiv), THF, 25°C [252].



Scheme 70. Synthesis of imidazoazepine. Reagents: a) CuI 1eq, Cs_2CO_3 2 eq, THF, rt [253].



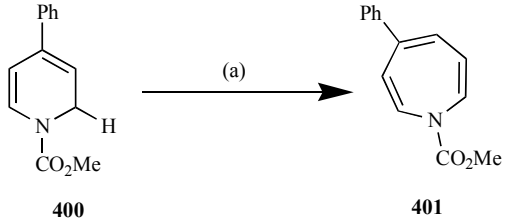
Scheme 71. Synthesis of tricyclic octahydroazepino[3,2,1-hi]indole-4,7-dione. Reagents: a) h*v*,MeCN, Pyrax [254, 255].



Scheme 72. Synthesis of 1Hbenzo[c]azepine-1,3(2H)-diones. Reagents: a)[Cp*$RhCl_2$]$_2$(2.5mol%), CsOAc (1equiv) , DCE, rt, 24h [256].

Paterno-buchi reaction proves to be very efficient for the rearrangement of substituted 1H-pyrrole-2,5-dione **394** to give tricyclic octahydroazepino[3,2,1-hi]indole-4,7-dione **396** in 90% yield (Scheme **71**). The intermediate **395** formed in this rearrangement is present in many alkaloids, such as stenine, neotuberostemonine, and tuberostemonine. These alkaloids are present in the roots of the plant, which are used as remedies for human cough and in domestic animals as antihelminthic [254, 255].

After the continuous efforts made by Bian and her co-workers [256], they were successful in the synthesis of Rh(II) catalyzed seven-membered heterocyclic ring, *i.e.*, 1H-benzo[c]azepine-1,3(2H)-diones **399** in very high yield (Scheme **72**). At room temperature, the substituted N-methoxybenzamides **397** react with 3-methylideneoxetan-2-one **398** in an equivalent amount of DCE and CsOAc. The Rh (II) catalyzed [4+3] annulated 1H-benzo[c]azepine-1,3(2H)-dione **399** is obtained in 88% yield by *via* the tandem β-Helimination /C–H activation /cyclization process.



Scheme 73. Synthesis of substituted azepine. Reagents: a)$Ph_3C^+ClO_4^-$ (1.0equiv), MeCN, rt, 30 min, $TMSCNH_2$ (2.4equiv), rt, 1h[257].

Stockerl and his co-workers [257] successfully work on the synthesis of substituted Azepine **401** in medium yield (Scheme **73**). When 4-phenyl dihydropyridine **400** undergo ring expansion to form methyl 4-phenyl-1H-azepine-1-carboxylatecarboxylate **401** in 58% yield using acetonitrile and Trimethylsilyldiazomethane as an organic solvent at room temperature.

Zubenko with his co-workers [258] in 2019 worked on the synthesis of dihydroazepines **408, 411** starting with the substituted 2,3dihydropyridine **402** by first performing the alkylation of the ring **403** followed by the hydroxylation of the ring **404** to reduce the double bond between the carbon and nitrogen **405**, in the next step oxidation of hydroxyl group with simultaneous ring-opening, followed by the ring expansion by using a suitable base (Scheme **74**). Further modification can be done like acyl rearrangement accordingly.

In 2018, Pan and his co-workers [259] synthesized imidazo[4,5-d]Azepine **415** in a multi-step mechanism, starting with histamine dihydrochloride **412**. Initially, histamine dihydrochloride **412** was brominated after the protection of the amine group **413** followed by the Knoevenagel condensation to add cinnamic acids on the amine group **414**, after the deprotection and finally the cyclization to get the target compound **415** with the removal of HBr. A detailed account of the reagents used is mentioned in Scheme **75**.

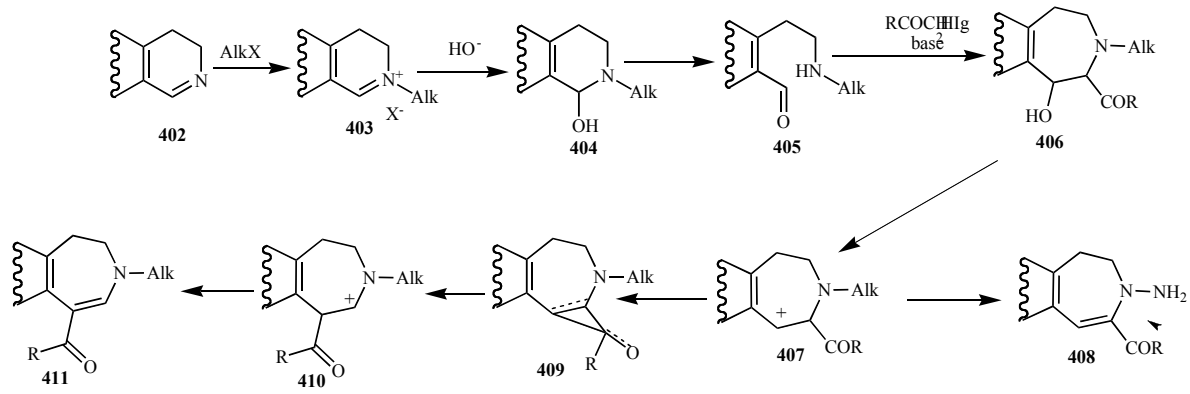
Triazolodiazepium salts **420** were obtained by the condensation of alkyl 2-amino-2-thioxoacetates **416** with 2-hydroxyethylhydrazine to obtain 2Z)-2-amino-2-(2-hydroxyethylhydrazono)acetates **417** as an intermediate, which was further reacted with N-protected β-amino propanoyl chloride to give the [1,2,4]triazoleas as intermediates **418** followed by intramolecular substitution of hydroxyl and the pendant amino group gave the intermediate **419** which further undergoes ring-cyclization to give the final product, *i.e.,* [1,4]-diazepine ring **420** in very poor yield [260] (Scheme **76)**.

In 2007, Wlodarczyk and co-workers [261] synthesise 7-substituted-2,3,4,5-tetrahydro-1,4-diazepin-5-ones **423** (Scheme **77**). Substituted β-ketoesters **421** with ethylenediamine **422** undergoes condensation reaction in xylene at 135^{o}C lead to the synthesis 7-substituted-2,3,4,5-tetrahydro-1,4-diazepin-5-ones **423**.

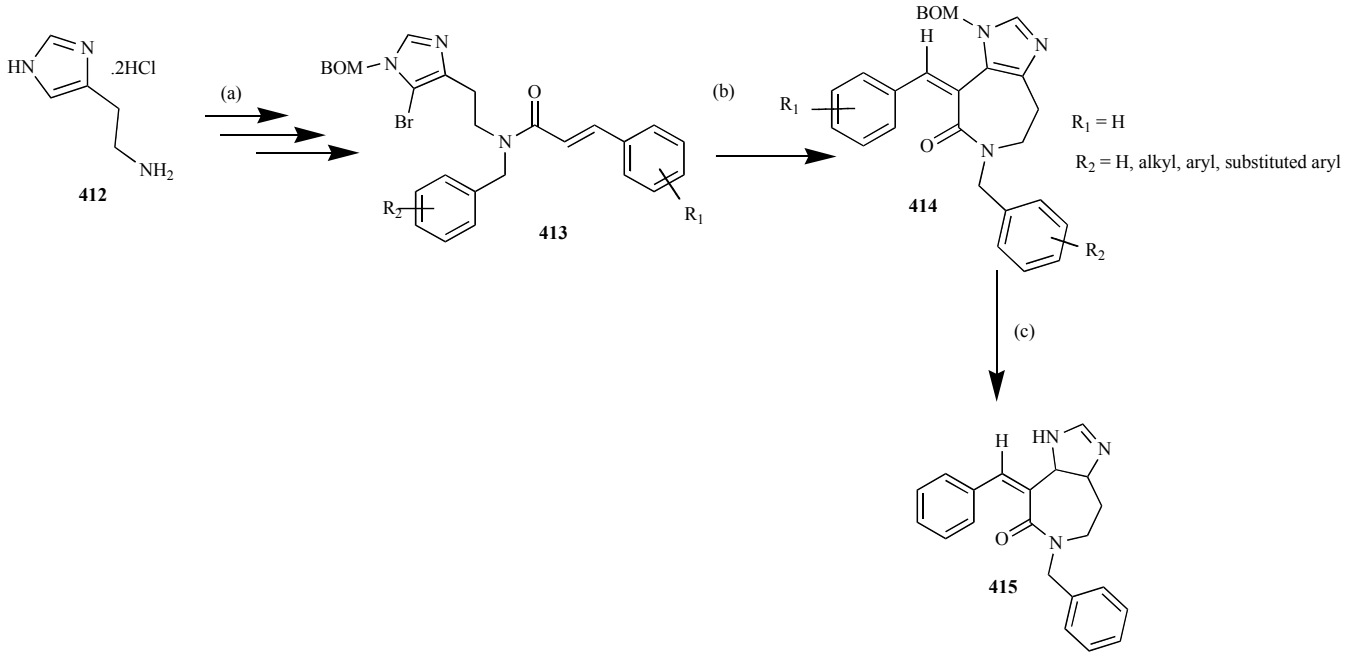
N-substituted dibenzo[b,e]azepine-6,11-diones **426** was synthesized by two-step reaction (Scheme **78**). In the first step, anthracene-9,10-dione **424** was reacted with sodium azide in sulphuric acid to give 5H-dibenzo[b,e]azepine-6,11-dione **425** *via* Schmidt rearrangement. The product formed further undergo alkylation to get the N-substituted dibenzo[b,e]azepine-6,11-diones **426** in moderate to excellent yield [262].

Gini & Mancheno [263] were successful in the synthesis of N-substituted dibenzoazepine **428**. The N-substituted 9,10-dihydroacridine **427** undergoes ring-expansion under the optimized reaction condition to get the desired N-substituted dibenzoazepine **428** in medium yield (Scheme **79**).

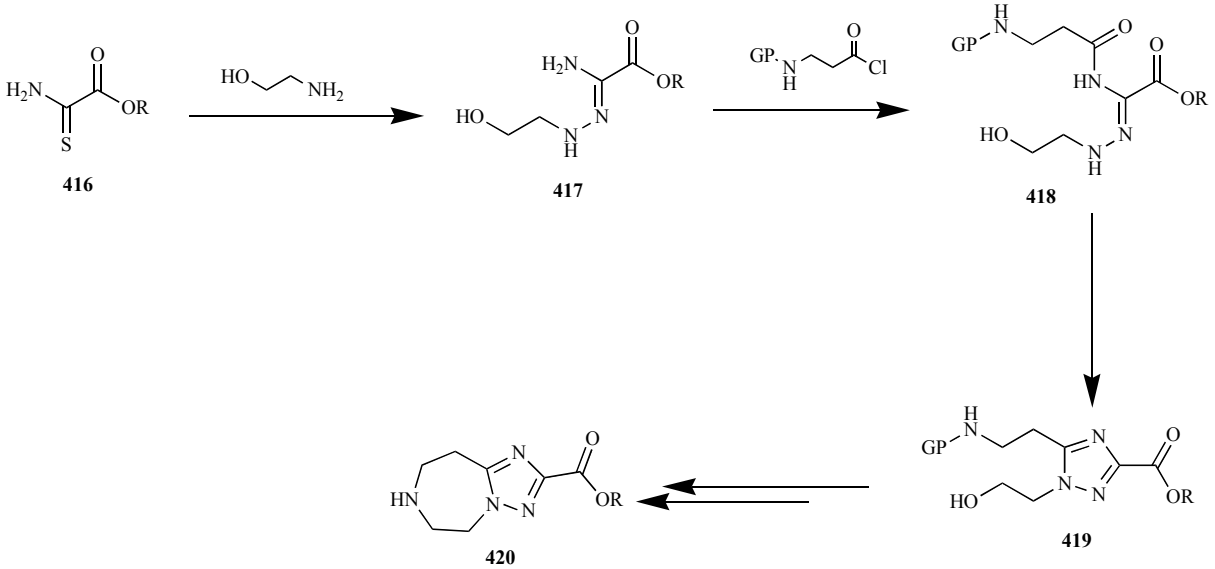
Mahmoud and El-Azm [264] worked on the synthesis [1,3,4]thiadiazepine-5,6(5*H*,11*H*)-dione **430**, which possess a wide range of antimicrobial properties. The ethyl 6-nitro-2-oxo-2H-chromene-3-carboxylate **429** undergo cycloaddition reaction with hydrazine carbothioamide to give fused azepine ring **430** as a product which contains coumarin core structure (Scheme **80**).



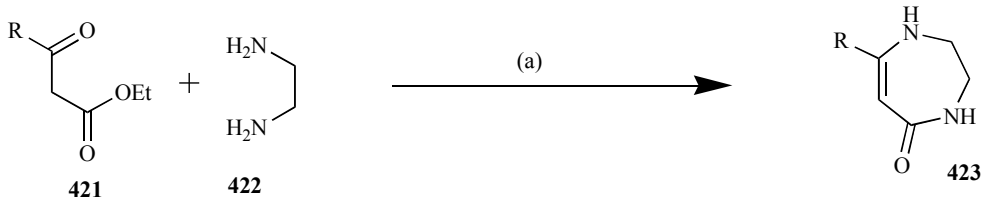
Scheme 74. Synthesis of dihydroazepines starting with 2,3dihydropyridine.



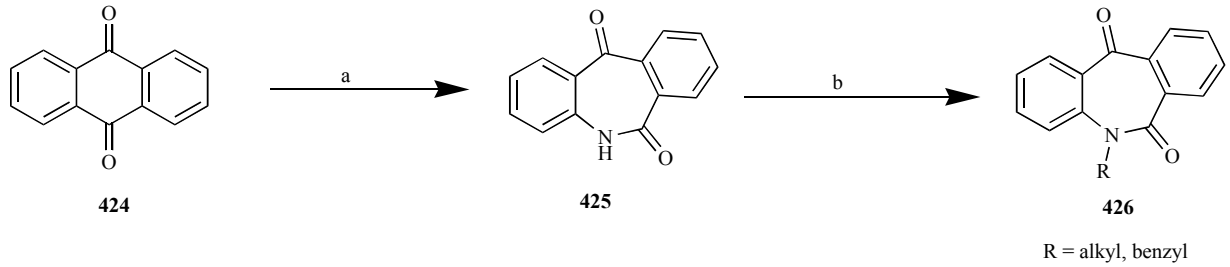
Scheme 75. Synthesis of imidazo[4,5-d]Azepine. Reagents: a) (i) BOC_2, 4N NaOH, dioxane/ H_2O (2:1), rt, 2h , 95%; (ii) B=NBS, THF, rt, 5h, 92%; (iii)BOMCl, Et_3N, THF, rt, overnight, 82h; (iv) CH_2Cl, rt, 4h, 93%; (v) EDCl, DMAP, CH_2Cl, rt, 30h; (vi)NaH, DMF, rt, overnight , 76-92% (over 2-steps); b) $Pd(PPh_3)_4$, Methyl dicyclohexylamine, DMF, 120°C, 20h, 50-65%; c) $AlCl_3$, CH_2Cl_2, rt, 1h [259].



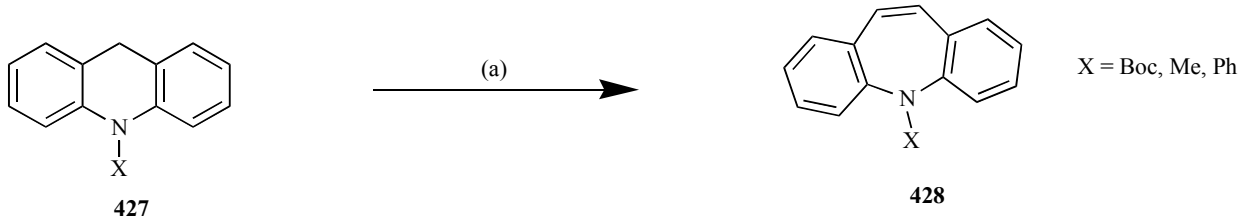
Scheme 76. Synthesis of Triazolodiazepium salts by [3+2] cycloaddition.



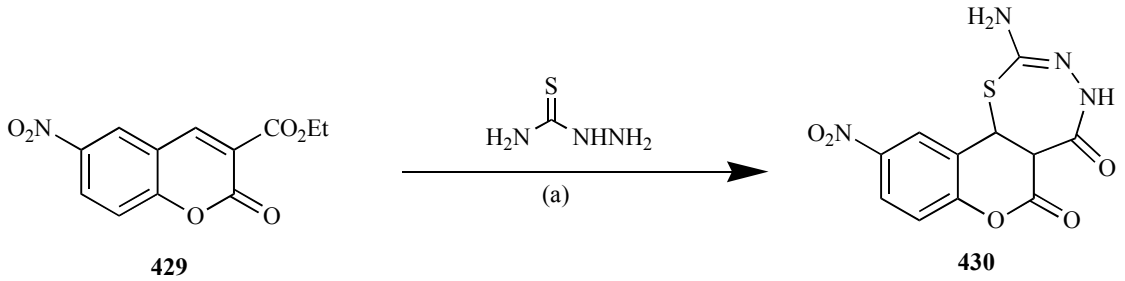
Scheme 77. Synthesis of 7-substituted-2,3,4,5-tetrahydro-1,4-diazepin-5-ones by microwave irradiation. Reagents: a) Xylene, MW, 135°C, 10 min [261].



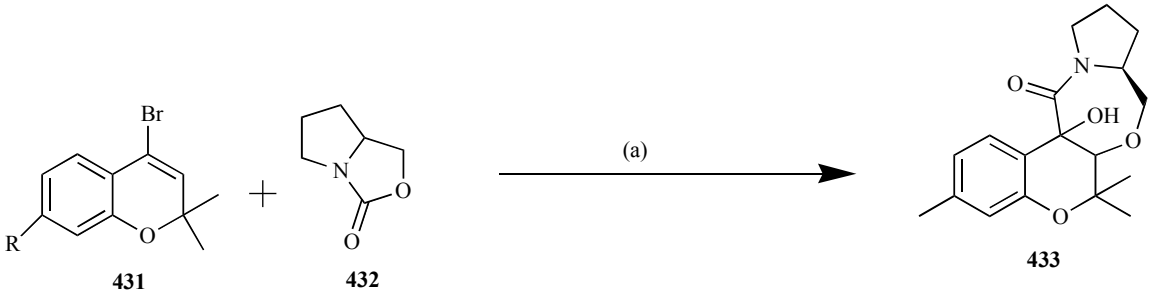
Scheme 78. Synthesis of N-substituted dibenzo[b,e]azepine-6,11-diones. Reagents: a) H_2SO_4, NaN_3; b) R-Br[262].



Scheme 79. Synthesis of N-substituted dibenzoazepine. Reagents: a) $Cu(OTf)_2$ (10 mol%), 2,2'-bypyridine (30 mol%), $TMSCHN_2$ (2.4 equiv), $(PhCO_2)_2$ (1.2 equiv), MeCN (2.0 ml), rt, 18h [263].



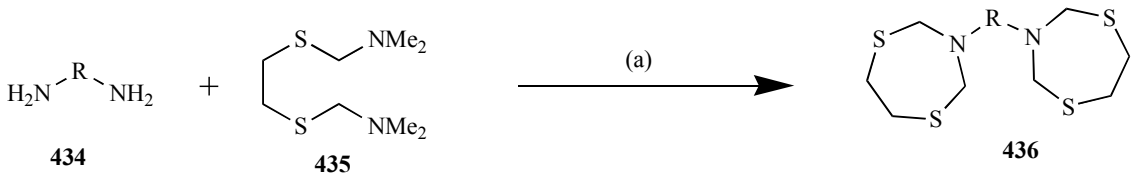
Scheme 80. Synthesis of 1,3,4]thiadiazepine-5,6(5*H*,11*H*)-dione. Reagents: a) *n*-Bu-OH, reflux, 6h [264].



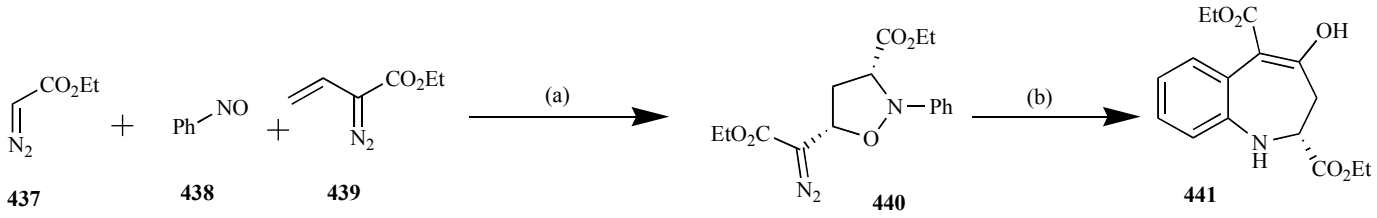
Scheme 81. One-pot cascade synthesis of fused oxazepinones. Reagents: a) (i) *n*-BuLi, THF, -78°C, 5-10 min (ii) -78 °C-rt, 2h, (iii) H_2O_2, 0 °C, 15 min, 15-20% [265].

Singh and his co-workers [265] worked on the synthesis of chiral chroman-fused oxazepinones **433** at very low temperature, *i.e.*, -78°C. l-proline-derived oxazolone **431** and 4-bromochroman **432** reacted under the desired condition to form chiral chroman-fused oxazepinones **433**, in very low yield, *i.e.,* 15-20% (Scheme **81**).

Rakhimova [266a], after doing lots of research, has successfully synthesized seven-membered heterocyclic organic compounds **436** by heterocyclization of hetero and carbon-chain, which possess a wide range of antifungal activities. This reaction proceeds by the heterocyclization of hetero and carbon-chain dithiahexanediamine **434** with α,ω-diamines **435** to give bis(1,5,3-dithiazepan-3-yl)alkanes **436** in good yields (Scheme **82**).



Scheme 82. Synthesis of *N*-substituted bis-1,5,3-dithiazepanes derivatives. Reagents: a) $SmCl_3.6H_2O$, $CHCl_3$, EtOH, rt, 3h [266a].



Scheme 83. Synthesis of (R)-diethyl 4-hydroxy-2,3-dihydro-1H-benzo[b]azepine-2,5-dicarboxylate by gold catalysed. Reagents: a) 5 mol% [IPrAuCl]/$AgSbF_6$, DCE, RT, 6h; b) 10 mol% [IPrAuCl]/$AgSbF_6$, RT, 6h [147].

In 2015, after the continuous efforts made by Paga *et al.* [147] were successful in the synthesis of Au-catalyzed in (R)-diethyl 4-hydroxy-2,3-dihydro-1H-benzo[b]azepine-2,5-dicarboxylate **441** in moderate yield. At room temperature, ethyl 2-diazobut-3-enoate **439**, nitrosobenzene **438**, and ethyl 2-diazoacetate **437** underwent cycloaddition reaction in the reaction mixture of [IPrAuCl]/$AgSbF_6$, DCE to obtain the required azepine **441** in 68% yield (Scheme **83**).

Tolkunov and his team [266b] worked on the synthesis of 1,2-benzodiazepine derivatives **443**. 3-aminoquinazolinone **442** is reacted with a heterocyclic aldehyde to give 1,2-benzodiazepine derivatives **443** using Dioxane-HCl as a catalyst at 75°C (Scheme **84**).

In 2017, Ren *et al.* [267] worked on the synthesis of tricyclic azepine moiety **446** by Rh-catalyzed [4+3] cycloaddition. 4-diazoisochroman-3-imines **444** undergo [4+3] cycloaddition with 2,3-Dimethylbuta-1,3-diene **445** to give the corresponding products in relatively lower yields (30-55%) under the required reaction condition (Scheme **85**).

Shenje *et al.* [268] gave a one-pot cascade route for the synthesis of substituted azepino[1,2-a]indole **448** in a very high yield. Substituted methyl 1-(1H-indole-1-carbonyl)cyclobutane-carboxylate **447** underwent ring-opening cyclization in DCM at room temperature to afford substituted azepino[1,2-a]indole **448** in 94% yield (Scheme **86**).

Gerard *et al*. [269] synthesized fused oxazepane ring **450** by the Lewis acid-mediated epoxide ring opening followed by ring-closing of the starting substrate **449** in DCM at room temperature. The reaction continues for 2 hours (Scheme **87**).

Cosford *et al.* [270] worked on the Ugifour-component system to synthesize fused 1,3-oxazepanones and –thiazepanones **455** derivatives. The coupling reaction of ammonia **452**, carboxylic acid **451,** isonitriles **454,** and aldehyde **453** give the synthesis of fused 1,3-oxazepanones and –thiazepanones **455** in medium yield. Oxazepanone inhibits a range of cancer cell lines with no adverse effect observed for healthy cells (Scheme **88**).

Keto-alcohols **456** undergo intramolecular reductive etherification process to give differentially substituted 1,4-oxazepanes **457** mostly in high yields with diastereoselectivities under the required reaction condition [271] (Scheme **89**).

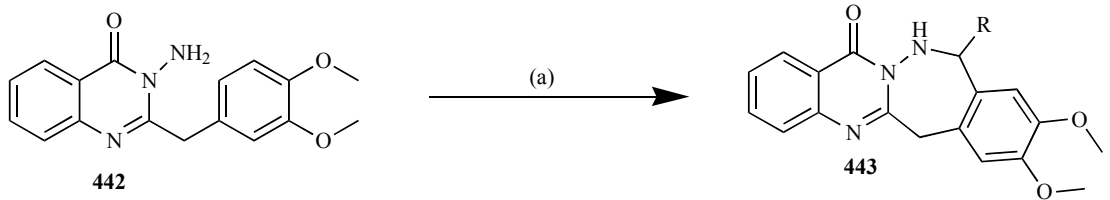
1-(3-methoxy-2,2-dimethyl-2H-benzo[b][1,4]thiazin-4(3H)-yl)-2-phenylethanone **458** proves to be a very good reactant for the synthesis of 6,6-dimethyl-5a,6-dihydrobenzo[d]benzo[4,5]thiazolo-[3,2-a]azepin-12(11H)-one **459** in moderate yield (Scheme **90**). The reaction proceeds by the Lewis acid-catalyzed ring contraction, followed by the Friedel–Crafts-type cyclization to get the desired product [272, 273].

Ouchakour [274] proposed a three-step reaction pathway for the synthesis of 2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine **463**. In the first step 1,2-dihydronaphthalene **460** is converted to (1R,2S)-1,2,3,4-tetrahydronaphthalene-1,2-diol **461** using OsO_4 (2 mol%)/*t*-BuOH as an oxidizing agent in acetone at 0°C. The diol is further subjected to C-C bond cleavage to form an unstable diformyl intermediate **462** in $NaIO_4$, THF, H_2O, 20°C. The intermediate undergoes double reductive amination with 2,2,2-trifluoroethylamine hydrochloride followed by ring-closing to give benzo[c]azepine derivative **463** as a product in moderate yield in the presence of $NaHCO_3$ and $NaBH_3CN$ in CH_2Cl_2 at room temperature (Scheme **91**).

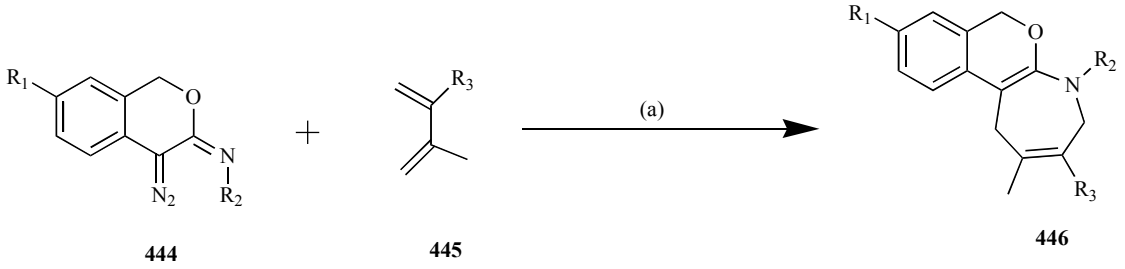
Ouchakour [274] proposed a three-step reaction pathway for the synthesis 3-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-benzo[d] azepine **467**. In the first step 1,4-dihydronaphthalene **464** is converted into (2R,3S)-1,2,3,4-tetrahydronaphthalene-2,3-diol **465** using OsO_4 (2 mol%)/*t*-BuOH as an oxidizing agent in acetone at 0°C. The diol is further subjected to C-C bond cleavage to form an unstable diformyl intermediate **466** in $NaIO_4$, THF, H_2O, 20°C. The intermediate undergoes double reductive amination with 2,2,2-trifluoroethylamine hydrochloride followed by ring-closing to give benzo[d]azepine derivative **467** as a product in 45% yield in the presence of $NaHCO_3$ and $NaBH_3CN$ in CH_2Cl_2 at room temperature (Scheme **92**).

Batanero and Barba [275] worked on the synthesis of (Z)-7-(2-argiohydrazono)-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one **470** starting with phenanthrene-9,10-dione **468** and aryldiazonium salts **469**, using *N*-methylformamide as a solvent. The desired azepine **470** is formed in a very high yield (Scheme **93**).

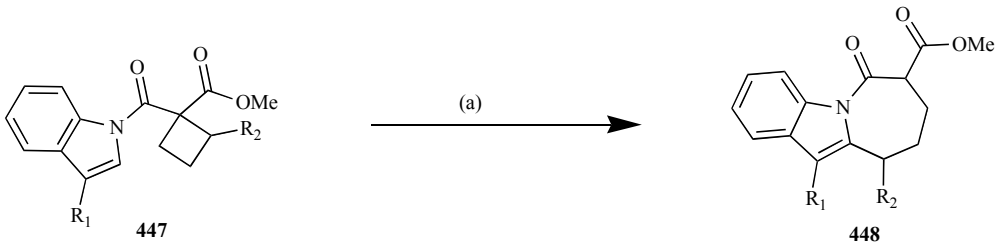
Truong *et al.* [276] gave a one-pot route for the synthesis of benzazepanones **472**. The desired benzazepanones **472** was obtained by the intramolecular [4+3] cycloaddition of aryl imines with cyclopropenes **471** at 0°C - rt followed by the ring expansion of the compound formed by cycloaddition to get the desired benzazepanones derivative (Scheme **94**).



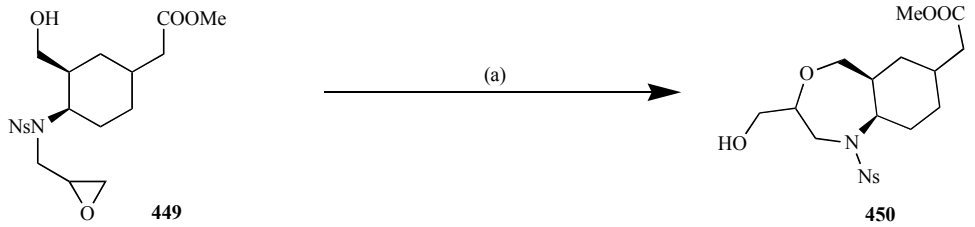
Scheme 84. Synthesis of 1,2-benzodiazepine derivatives. Reagents: a) RCHO, DIoxane-HCl, 75°C, 3h [266b].



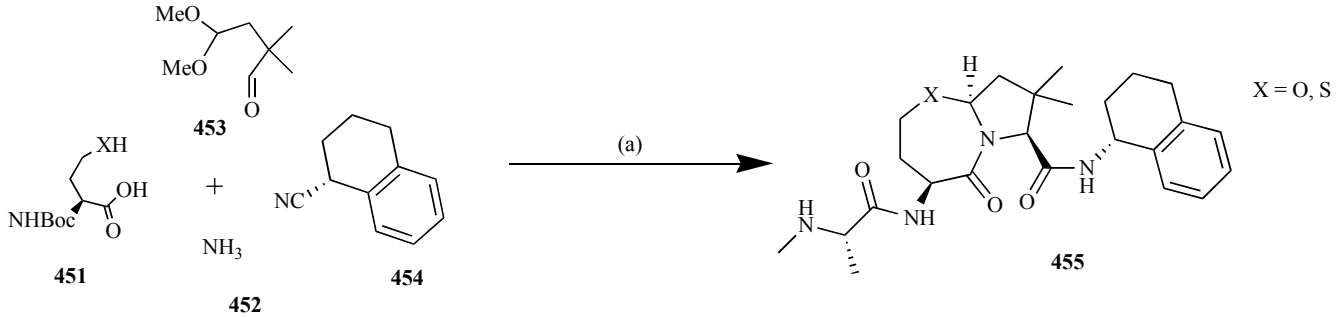
Scheme 85. Synthesis of Reagents tricyclic moiety azepine derivative by [4+3] cycloaddition of dienes and 4-diazoisochroman-3-imines. Reagents: $Rh_2(Oct)_4$ (1 mol %), DCE (1 mL), room temperature, N_2, 3 h [267].



Scheme 86. Synthesis of azepino[1,2-a]indole by intramolecular ring opening cyclization of cyclobutanes. Reagents: $Sc(OTf_3)$ (10 mol%), DCM, rt [268].

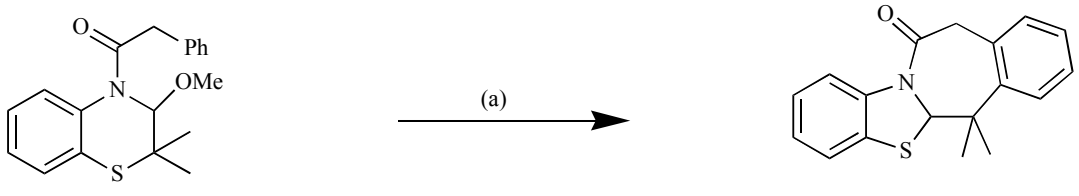


Scheme 87. Synthesis of oxazepane ring by ring-opening/ring-closing of epoxide ring. Reagents: $BF_3.OEt_2$, CH_2Cl_2, rt, 2h [269].



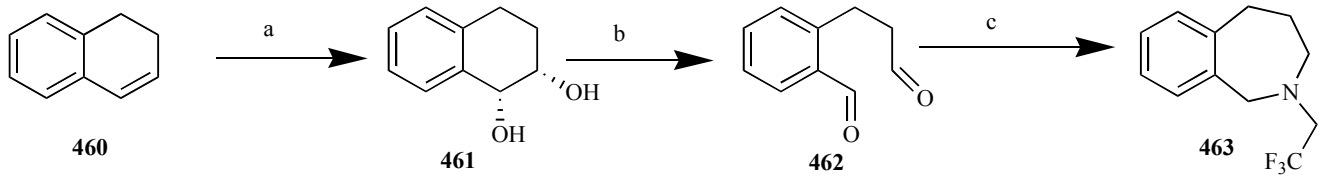
Scheme 88. Synthesis of fused 1,3-oxazepanones and –thiazepanones *via* coupling reaction. Reagents: a) (i) 80°C, µW, 20min; (ii) TFA (8equiv), CH_2Cl_2, 32°C; (iii)Boc-N-Me-Ala-OH, HOBT, EDC, NMM, THF; (iv) TFA (8equiv), CH_2Cl_2, 23 °C [270].

Scheme 89. Synthesis of substituted 1,4-oxazepanes. Reagents: a) TMSOTf, Et_3SiH [271].



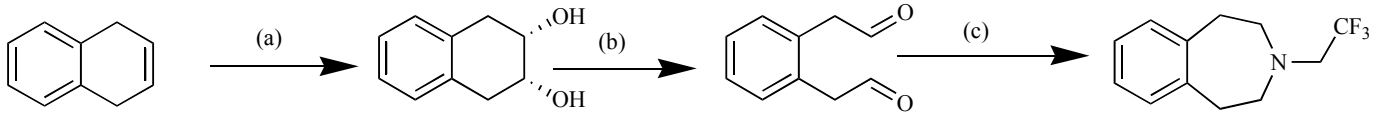
458 **459**

Scheme 90. Synthesis of 6,6-dimethyl-5a,6-dihydrobenzo[d]benzo[4,5]thiazolo[3,2-a]azepin-12(11H)-one. Reagents: a) $AlCl_3$, CH_2CL_2, 0°C-rt [272, 273].



460 **461** **462** **463**

Scheme 91. Synthesis of benzazepine bearing trifluoromethyl group. Reagents: a) OsO_4 (2 mol%)/*t*-BuOH, NMO, acetone, 0°C, 3h; b)$NaIO_4$, THF, H_2O, 20°C, 30 min; c) $CF_3CH_2NH_2HCl$, $NaHCO_3$, $NaBH_3CN$, AcOH, CH_2Cl_2 20°C, 3h [274].



464 **465** **466** **467**

Scheme 92. Synthesis of 3-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine. Reagents: a) OsO_4 (2 mol%)/*t*-BuOH, NMO, acetone, 0°C, 3h; b)$NaIO_4$, THF, H_2O, 20°C, 30 min; c) $CF_3CH_2NH_2HCl$, $NaHCO_3$, $NaBH_3CN$, AcOH, CH_2Cl_2 20°C, 3h [274].

Wang and co-workers [277] worked on the synthesis of ethyl 4-(4-nitrophenyl)-1-tosyl-5-vinyl-2,3-dihydro-1H-benzo[b]azepine-3-carboxylate **(475)** *via* [4+3] cycloaddition. The 1-tosyl-4-vinyl-1H-benzo[d][1,3]oxazin-2(4H)-one **(473)** undergoes [4+3] cycloaddition with Baylis–Hillman acetates **(474)** using $Pd(PPh_3)_4$ as a catalyst in DCM to give ethyl 4-(4-nitrophenyl)-1-tosyl-5-vinyl-2,3-dihydro-1H-benzo[b]azepine-3-carboxylate **(475)** as a product in 46% yield (Scheme **95)**.

Bosque *et al.* [278] successfully worked on the synthesis of (2R,7R)-2-methyl-7-(3-methylbut-2-en-1-yl)azepane **478**. The desired azepane derivative is synthesized by the aza-Cope rearrangement of an iminium ion **476** followed by reductive amination of intermediate **477** to form the seven-membered ring, *i.e.,* (2R,7R)-2-methyl-7-(3-methylbut-2-en-1-yl)azepane **478** in very poor yield (Scheme **96**).

Thiel and Deska [279] in 2013, working on the synthesis (3R, 7R)-1-benzyl-7-(hydroxymethyl)azepan-3-ol **480** by the ring-expansion of trifluoroacetate derivative of ((2R,6S)-1-benzyl-6-(hydroxymethyl) piperidin-2-yl)methyl acetate **479**, which further undergo hydroxylation to give the desired azepane **480** in very low yield (Scheme **97**).

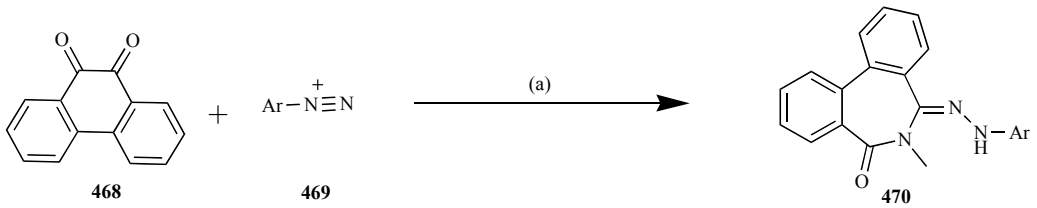
Nirmala *et al.* [280] worked on the synthesis of N-Substituted caprolactams **482**. They were synthesized by the reaction of carboxylic acid or alcohol **481** with 1,8-diazabicycloundecane(DBU) and carbonyl diimidazole (CDI). In this reaction, an intermediate is formed by the attack of DBU, which acts as a nucleophile on an N-acylimidazole, the intermediate formed undergo ring opening to give the product in good yield (Scheme **98**).

Acharya *et al.* [281] worked on the synthesis of (4aS,7R,8S)-8-ethyl-3,4,7,8-tetrahydro-4a,7-epoxy[1,2]oxazino[2,3-a]azepin-9(2H)-one **486** *via* intramolecular [4+3] cycloaddition of 2-bromo-N-(3-(furan-2-yl)propoxy)butanamide **485**. 2-furanpropanol **483** are reacted under the optimized condition to get O-(3-(furan-2-yl)propyl)hydroxyl amine **484** which further undergo acylation with 2-bromo-2-propanoyl bromide to get 2-bromo-N-(3-(furan-2-yl)propoxy)butanamide **485** which further undergoes intramolecular [4+3] cycloaddotion in basic condition at 0°C to get the product (Scheme **99**).

3. REACTIONS OF AZEPINS AND ITS DERIVATIVES

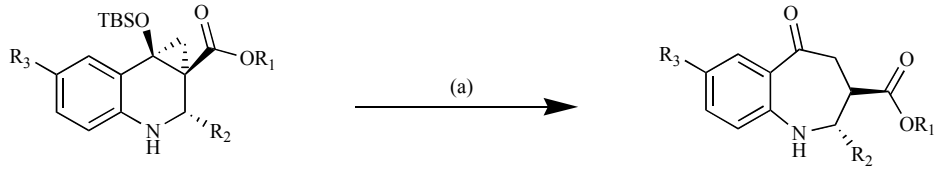
Other than synthesis, researchers also explored the reactions of Azepins with various other heterocyclic moieties. These derivatives are further explored for their biological properties. However, only a little work is done till now, and the researchers have not reached any conclusion regarding its biological applications. Few of the reactions are discussed below.

Many substituted 5H-dibenz[b,f]Azepine derivatives **488-493** have been prepared from 5H-dibenzo[b,f]Azepine **487** by different researchers all over the world under varied reaction conditions at different temperature in moderate to high yield (Scheme **100**). 5H-dibenz[b,f]Azepine possesses a wide range of pharmacological property, *i.e.*, antibacterial and antifungal. At room temperature, Kumar [282] synthesized 3-chloro-1-(5H-dibenzo[b,f]azepin-5-yl)propan-1-one **488** by N-acylation of 5H-dibenz[b,f]azepine **487** with 3-chloro propionyl chloride using triethylamine (Et_3N) as a base in 85% yield. In 2010, Rao [283] worked on the reaction of 5H-dibenz[b,f]Azepine **487** with triphosgene to obtain 5H-dibenzo(b,f)azepine-5-carbonyl chloride **489** in a high yield of 90%. When 5H-dibenzo(b,f)azepine-5-carbonyl chloride **487** and hydrazine hydrate was stirred in ethanol for approximately 1 hour, 5H-Dirbenzo (b,f) azepine-5-acid hydrazide **491** was obtained in 75% yield [283]. The 5H-Dirbenzo (b,f) azepine-5-acid hydrazide **487**was heated with oxazolones to obtain in absolute alcohol for 15-16h at 65-70°C to get the desired product [283] *i.e.*, 5H-dibenzo(b,f)azepine-5-{4substituted-benzylidine-2-methylimidazo-



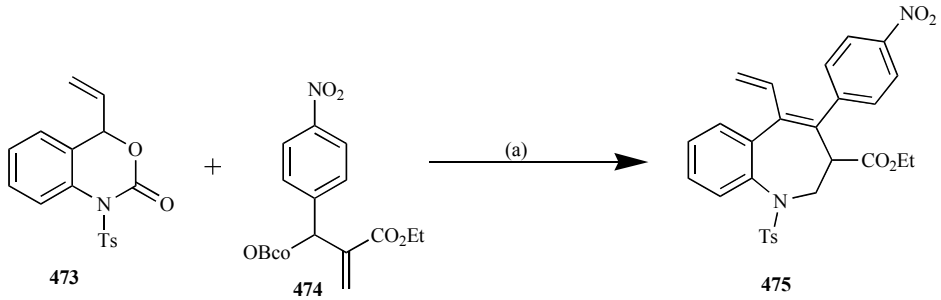
468 **469** **470**

Scheme 93. Synthesis of (Z)-7-(2-argiohydrazono)-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one. Reagents : a) MeNHCHO, $BuNClO_4$ [275].



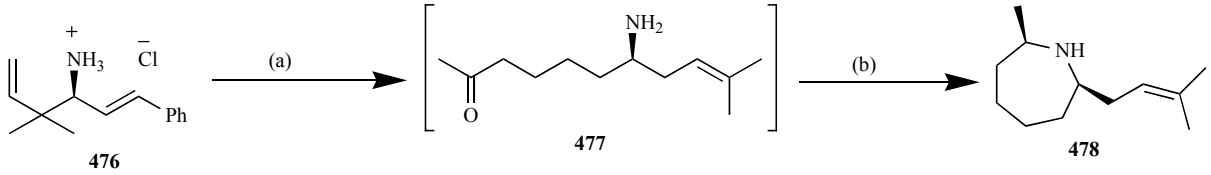
471 **472**

Scheme 94. Synthesis of benzazepanones by [4+3] cycloaddition. Reagent: a) TBAF (1.2equiv), 0°C – rt, 2h[276].



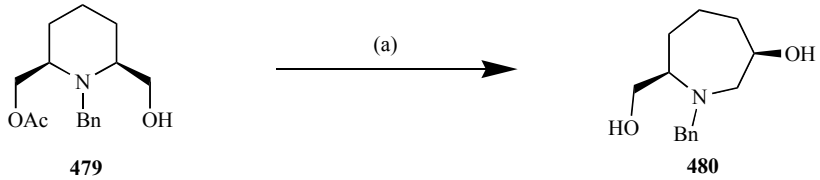
473 **474** **475**

Scheme 95. Synthesis of ethyl 4-(4-nitrophenyl)-1-tosyl-5-vinyl-2,3-dihydro-1H-benzo[b]azepine-3-carboxylate (3) *via* [4+3] cycloaddition. Reagents: $Pd(PPh_3)_4$ (5 mol%), PPh_3 (30 mol%), DCM, rt [277].



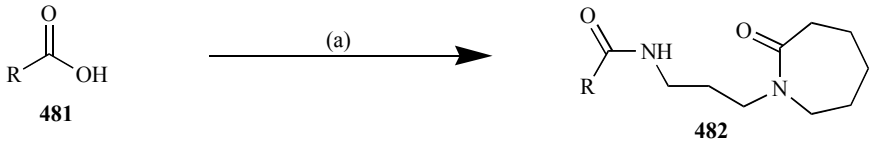
476 **477** **478**

Scheme 96. Synthesis of azepane derivative. Reagents: a) 6-oxo-heptanal, DCM, 40°C, 12h; b) $NaCNBH_3$, er 86:14 [287].



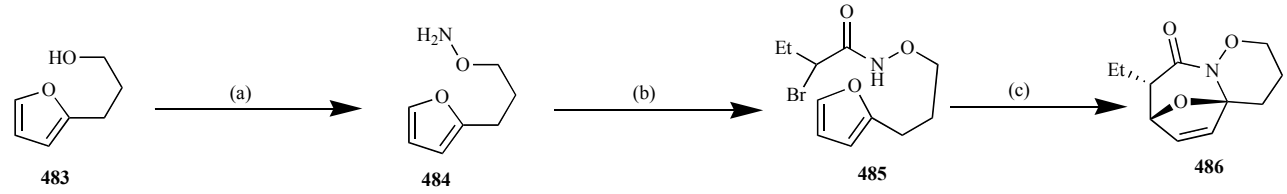
479 **480**

Scheme 97. Synthesis of (3R,7R)-1-benzyl-7-(hydroxymethyl)azepan-3-ol by ring expansion. Reagents: TFFA, Et_3N, THF, Δ, EtOH, NaOH, 0°C [279].



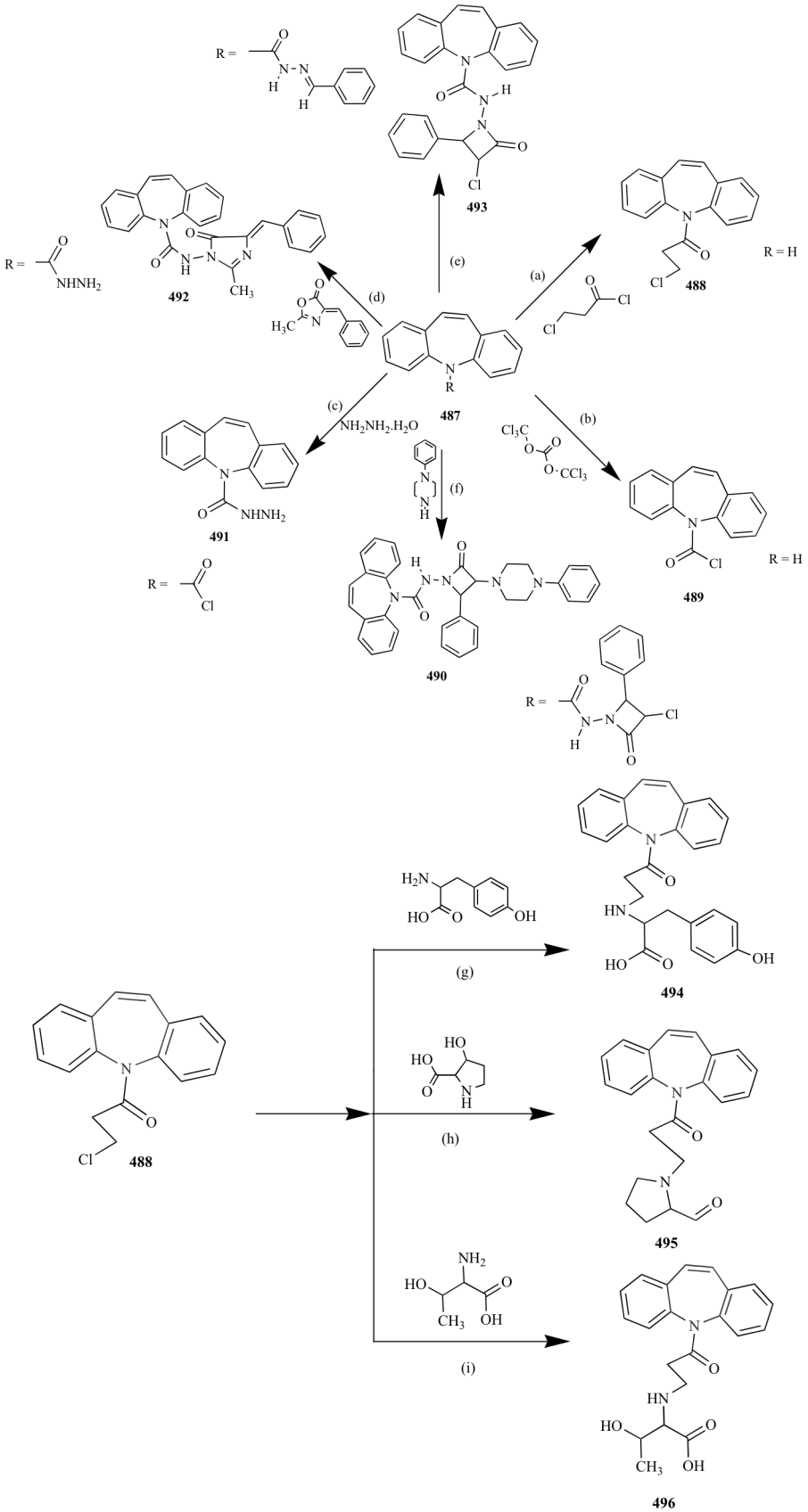
481 **482**

Scheme 98. Synthesis of N-Substituted caprolactams. Reagents: CDI (1.2equiv), DBU (1.2equiv), THF, rt [280].

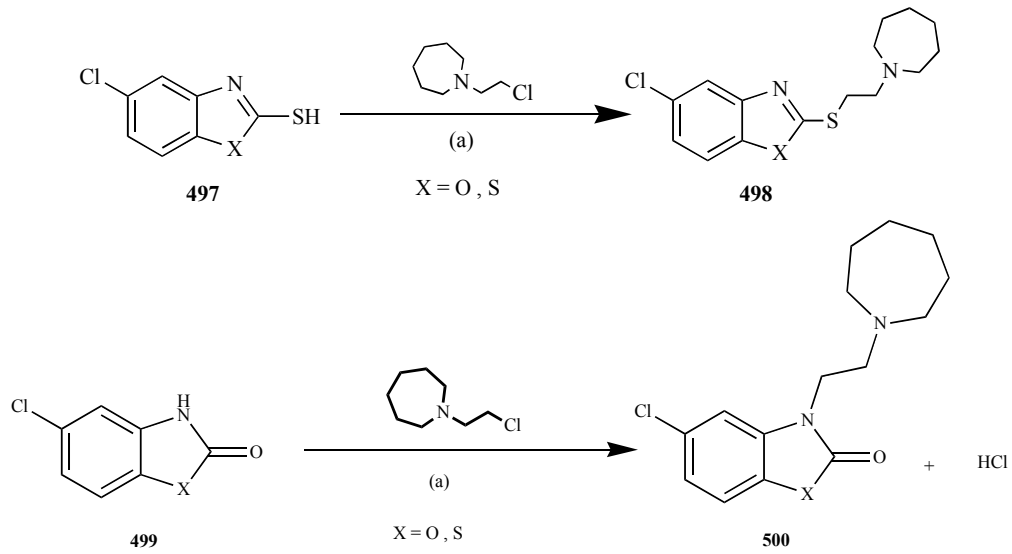


483 **484** **485** **486**

Scheme 99. Synthesis of fused azepine derivative *via* [4+3] cycloaddition. Reagents: a) (i) N-hydroxtphthalimide, Ph_3P, DEAD; (ii) $NH_2NH_2.H_2O$; c) Et_3N, CF_3CH_2OH, 0°C [281].



Scheme 100. Reaction of substituted 5H-dibenz[b,f]Azepineto form its derivatives. Reagents: a)triethylamine, C_6H_6, rt, 60h; [282] b) triphosgene, toluene; [283] c) absolute ethanol; [283] d) absolute alcohol , reflux, 16h, 492K; [283] e) CAC, triethylamine, 0ºC, 12-24h; [283] f) (i) 40% NaOH,Reflux in methanol, extract in toluene , (ii) DMF, K_2CO_3; [283] (g) Methanol , K_2CO_3, Reflux, 8h; [283] (h) Methanol , K_2CO_3, Reflux, 8h; [282] i) Methanol , K_2CO_3, Reflux, 8h [282].



Scheme 101. The reaction of 1-(2-chloroethyl)azepane with 5-chlorobenzthiazole and 5-chlorobenzoxazole. Reagents: a) DMF, K_2CO_3, 60°C, 3h [284].

le-5-one}-carboxamides **492** in a maximum of 95%yield. The coupling of 3-chloro-1-(5H-dibenzo[b,f]azepin-5-yl)propan-1-one **488** to amino acid derivative gives the desired amino acid analogues [282] **494-496.**

Romeo and his co-workers [284] work on the reaction of 1-(2-chloroethyl)hexahydro-1H-azepine hydrochloride with 5-chlorobenzthiazole **497** and 5-chlorobenzoxazole **499** in DMF in the presence of K_2CO_3 at 60 °C for three hours, which undergo nucleophilic substitution reaction to get the desired product **498, 500.** This reaction involves the two-step mechanism; in the first step, the intermediate bromoalkylbenzoxazoles and bromoalkylbenzothiazolesis formed when 5-chlorobenzthiazole **497** and 5-chlorobenzoxazole **499** is reacted with dibromoalkanes in the presence of K_2CO_3 at room temperature in acetone. The second step involves the formation of our desired product when the nucleophilic substitution reaction between the intermediate formed and 1-(2-chloroethyl)hexahydro-1H-azepine hydrochloride **497** took place in DMF in the presence of K_2CO_3 at 60°C for 3 hours (Scheme **101**).

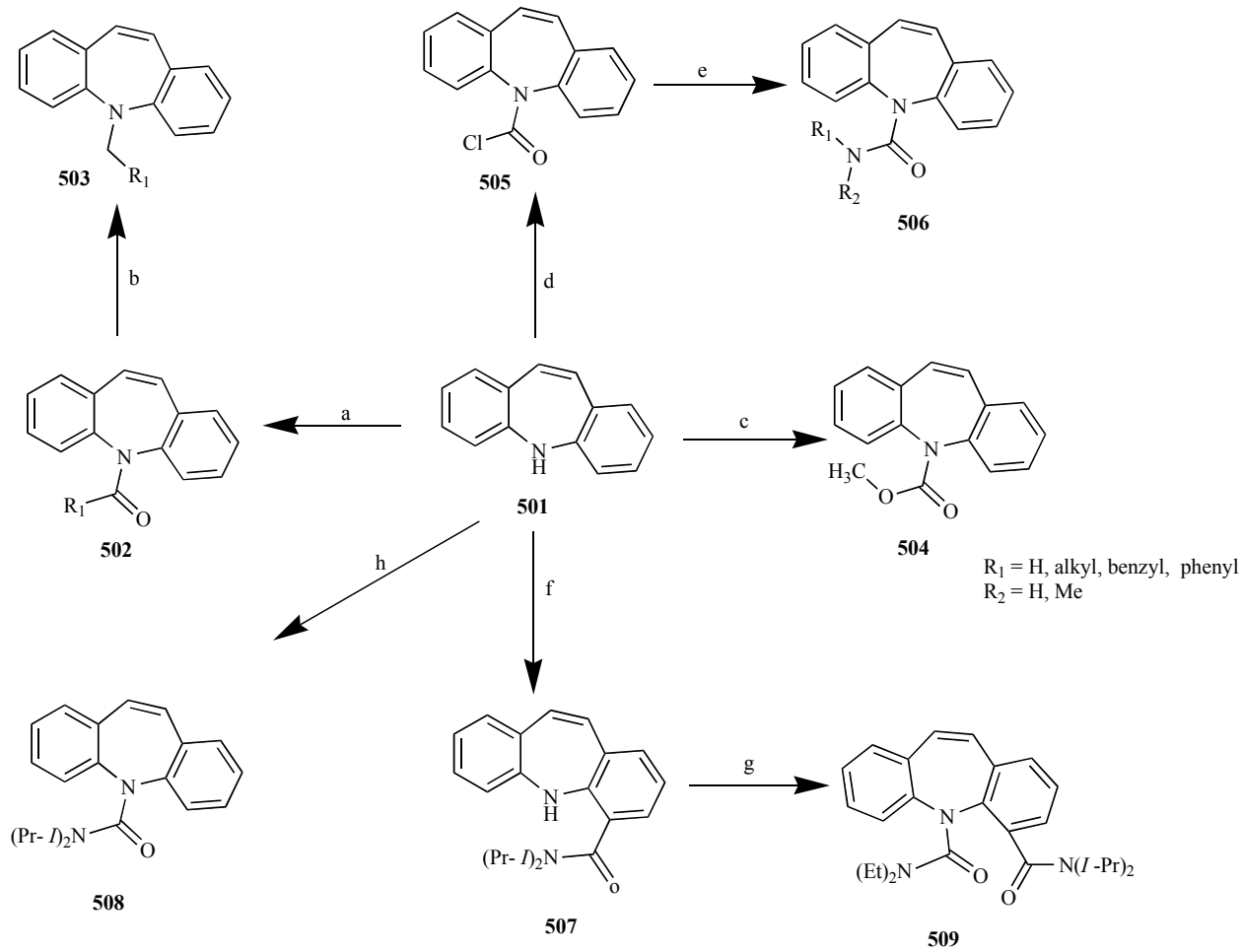
5H-dibenzo[b,f]azepine **501** is another key reactant used by Tian *et al.* [285] for the preparation of various N-substituted 5H-dibenzo[b,f]azepine **502-509** at different temperature range to give the product in low to high yield (Scheme **102**). 5H-dibenzo[b,f]azepine. 5H-dibenzo[b,f]azepine **501** reacts with anhydride or acyl chloride at room temperature to give the desired amide, *i.e.*, substituted 1-(5H-dibenzo[b,f]azepin-5-yl)ethanone **502** in medium yield. Further, the amide undergoes reduction with Lithium aluminum hydride (LAH) in THF at room temperature to give the amine, *i.e.*, 5-ethyl-5H-dibenzo[b,f]azepine **503** in very low yield. Further, the derivatives are prepared by the reaction of 5H-dibenzo[b,f]azepine either with chloroformates at 90-110°C for 3h to give methyl 5H-dibenzo[b,f]azepine-5-carboxylate **506** or react with diisopropylcarbamoyl chloride, toluene in reflux to give urea derivative **508**. The dibenz[b,f]azepine-5-carbonyl chloride **505** derivate are synthesized by the reaction of 5H-dibenzo[b,f]azepine with triphosgene in DCM at room temperature which further reacts with a primary or secondary amine in DCM to give the urea derivative **504** in good yield. The 5H-dibenzo[b,f]azepine reacts with diisopropylcarbamoyl chloride in the presence of LDA to give 4-substituted dibenz[b,f]azepine derivative **507** which further reacts with diethylamine in DCM give urea derivative **509** in 76% yield.

2-hydroxy-5H-dibenzo[b,f]azepine-5-carboxamide was prepared in three-step by Tian and co-workers (Scheme **103**). In the first step, 5H-dibenzo[b,f]azepine **510** undergoes oxidation with Fremy's salt to give 2H-dibenzo[b,f]azepin-2-one **511**, which is further reduced by sodium dithionite to give 5H-dibenzo[b,f]azepin-2-ol **512** as an intermediate product in medium yield. The 5H-dibenzo[b,f]azepin-2-ol **512** is further reacted with sodium isocyanate to give an intermediate, followed by selective hydrolysis by sodium hydrogen carbonate to give 2-hydroxy-5H-dibenzo[b,f]azepine-5-carboxamide **513** as a final product [285].

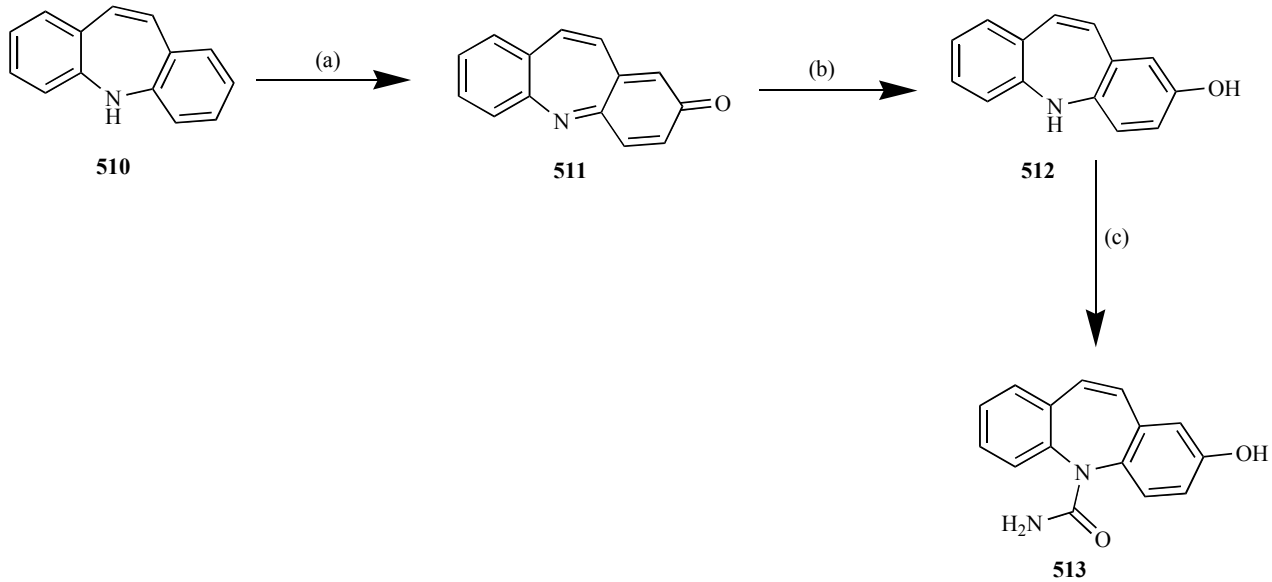
Tian and co-workers also worked on the synthesis of 10-amino-5H-dibenzo[b,f]azepine-5-carboxamide **518** and its derivative (Scheme **104**). 5H-dibenzo[b,f]azepine-5-carboxamide **514** undergoes epoxidation reaction with suitable reagents to get 1aH-dibenzo[b,f]oxireno[2,3-d]azepine-6(10bH)-carboxamide **515**. The epoxide ring is hydrogenated using Palladium as a catalyst under basic condition to give 10-hydroxy-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide **516** which is further oxidized to 10-oxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide **517** which further undergoes amination to give 10-amino-5H-dibenzo[b,f]azepine-5-carboxamide **518** and its derivative as a main product [285].

Batra *et al.* [139] worked on the synthesis of fused azepine derivative. 5-(1-isocyanovinyl)-5H-dibenzo[c,e]azepine **519** is reduced with $NaBH_3CN$ in a mixture of glacial AcOH/EtOH (1:9) at room temperature to give 5-(1-isocyanovinyl)-6,7-dihydro-5H-dibenzo[c,e] azepine **520**, which further react with allyl bromide in the presence of K_2CO_3, DMF at room temperature to form intermediate **521** which is further cyclized in DCM to give the desired target compound, *i.e.,* 7,9-dihydro-4bH-dibenzo[c,e]pyrrolo[1,2-a]azepine-5-carbonitrile **522** in medium yield (Scheme **105**).

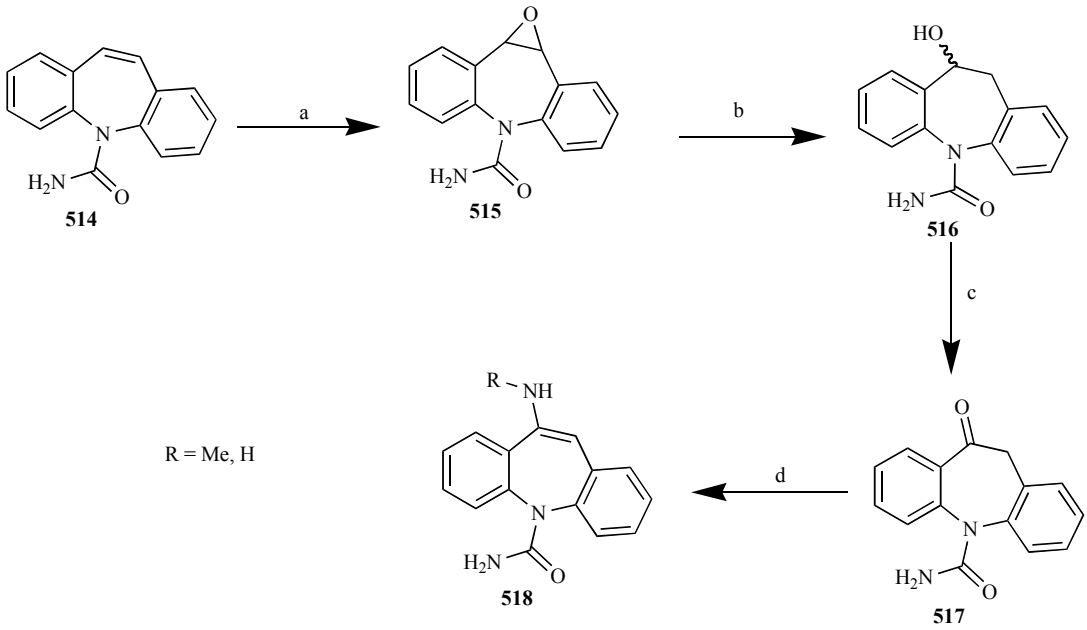
Zhang *et al.* [205] in 2014 derived a novel route for the synthesis of substitutedpyrido[2,3-b]azepine derivatives **524** in 88% yield by ring-opening of aza-bridged azepines **523**. N,N,9-trimethyl-6,7,8,9-tetrahydro-5H-5,8-epiminopyrido[2,3-b]azepine-10-carboxamide **523** underwent CN^2 bond cleavage of aza-bridged azepines in AcOH at room temperature for 30 min to afford aromatic fused azepines **524** (Scheme **106**).



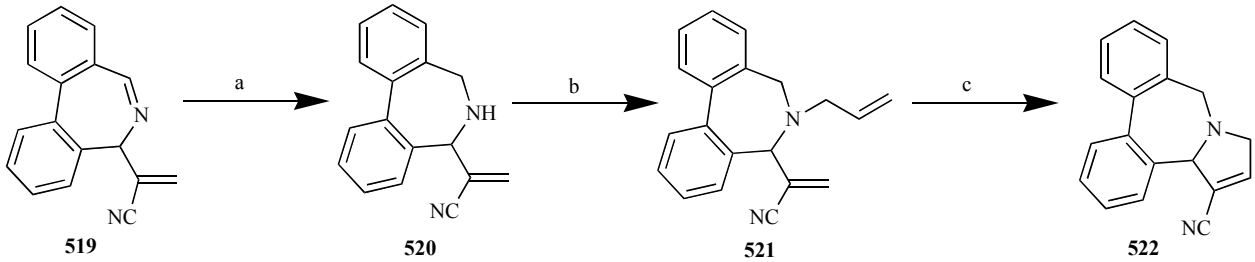
Scheme 102. Preparation of 5H-dibenzo[b,f]azepine derivative. Reagents: a) anhydride or acyl chloride, rt to 100°C, 3h; b) Lithium aluminum hydride (LAH), THF, rt, 1h; c) chloroformates, 90-110°C, 3h; d) triphosgene, DCM, 0°C to rt; e) R_1R_2NH, rt to 110°C, DCM or toluene, 1-4h; f) LDA, diisopropylcarbamoyl chloride, THF; g) triphosgene, diethylamine, DCM; h) diisopropylcarbamoyl chloride, toluene, reflux [285].



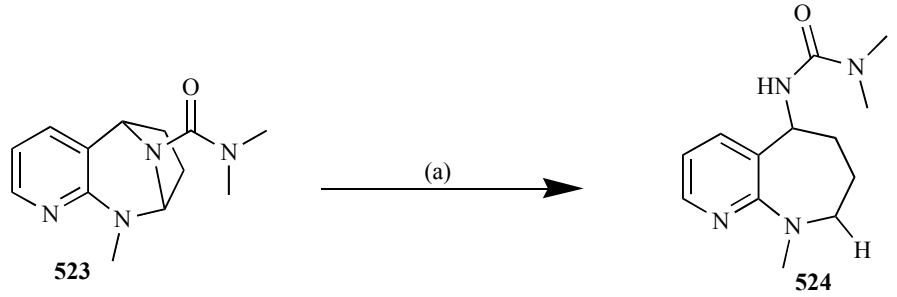
Scheme 103. Synthesis of 2-hydroxy-5H-dibenzo[b,f]azepine-5-carboxamide. Reagents: a) $(KSO_3)_2NO$, Na_2HPO_4, H_2O/acetone, rt, 3h; b) $Na_2S_2O_4$, rt; c) NaOCN, HOAc, 70°C, 2h: $NaHCO_3$, H_2O/MeOH, 0°C, 30min [285].



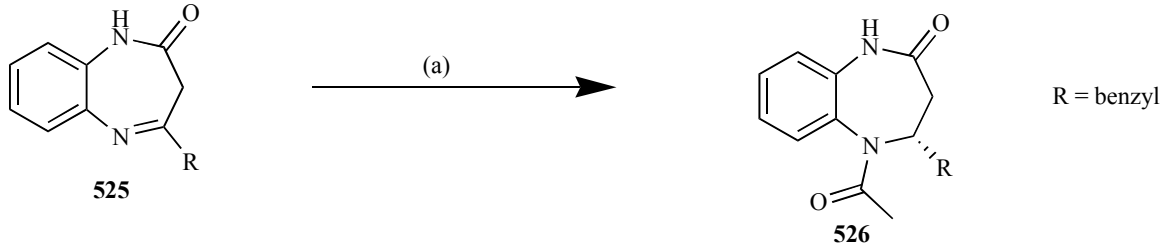
Scheme 104. Synthesis of 10-amino-5H-dibenzo[b,f]azepine-5-carboxamide derivatives. Reagents: a) HOOAc, $KMnO_4/Al_2O_3$, DCM, rt, rh; b) H_2, Pd/C, $N(Et)_3$, MeOH-H_2O, 2h; c) $K_2Cr_2O_7$, CH_3CO_3H; d) RHN_2, $Ti(OiPr)_4$, EtOH [285].



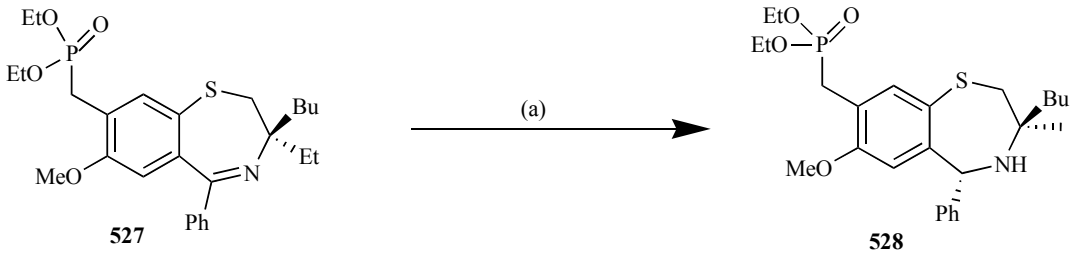
Scheme 105. Preparation of azepine derivative. Reagents: a) $NaBH_3CN$, glacial AcOH/EtOH (1:9), rt, 1.5h; b) allyl bromide, K_2CO_3, DMF, rt, 1.5h; c) Grubbs II, DCM, 40°C, 6h [139].



Scheme 106. Synthesis of substituted pyrido[2,3-b]azepines by C-N^2 bond cleavage. Reagents: $NaBD_3CN$, AcOH, rt, 30 min [205].



Scheme 107. Synthesis of substituted benzodiazepinones. Reagents: a) (i) 2.0 mol% *(R,R)*-1e, 50 atm H_2, DCM, 40°C; (ii) acetyl chloride, pyridine, DMF [286].



527 **528**

Scheme 108. Synthesis of Dihydrobenzothiazepine derivative. Reagents: a) Ir(COD)BArF (2.5 mol%), Taniaphos (5 mol%), H_2 (30 bar), 25°C, 2h, *de* 80 [287].

In 2017, Yang and co-workers [286] worked on the asymmetric hydrogenation of 4-substituted 1Hbenzo[b][1,4]diazepin-2(3H)-ones **525** to give substituted benzodiazepinones **526** in medium to high yield using DCM as a solvent. The reaction proceeds at 40°C (Scheme **107**).

After the continous efforts made by Cowan *et al.* [287] they were successful in the synthesis of diethyl (((3R,5R)-3-butyl-7-methoxy-3-methyl-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]thiazepin-8-yl)methyl) phosphonate **528** (Scheme **108**). (R)-diethyl ((3-butyl-3-ethyl-7-methoxy-5-phenyl-2,3-dihydrobenzo[f][1,4]thiazepin-8-yl)methyl) phosphonate **527** undergo an iridium-catalyzed asymmetric hydrogenation followed by two step cyclocondensation reaction under the required reaction condition at 25°C to obtain a very high yield of product.

Many researchers work on the synthesis of tetrahydrobenz[1,4]oxazepines **530** from 2,3-dihydrobenzo[*f*][1,4]oxazepines **529** in different reaction conditions and at different temperature range. Banfi *et al.* [288] successfully describe the reaction of dihydrobenzo[*f*][1,4]oxazepines **529** to form the desired product **530** at room temperature (Scheme **109**).

Sharif *et al.* [176] worked on the synthesis of N-(4-(5-(dimethylamino)-2,3,4,5-tetrahydro-1H-benzo[b]azepine-1-carbonyl)phenyl)-2-methyl benzamide **534** by a three-step reaction mechanism (Scheme **110**). In the first step 2,2,2-trichloro-N-(1-tosyl-2,5-dihydro-1H-benzo[b]azepin-5-yl)acetamide **531**, the amino group is protected followed by the removal of trichloroacyl group under basic condition, taking methanol as a solvent give tert-butyl (1-tosyl-2,5-dihydro-1H-benzo[b]azepin-5-yl)carbamate **532**, in the next step compound **532** undergoes Pd-catalysed hydrogenation at 60°C followed by de-tosylation under mild reaction condition give tert-butyl (2,3,4,5-tetrahydro-1H-benzo[b]azepin-5-yl)carbamate **533** in 88% yield which is further reacted with 1H-benzo[b]azepine ring nitrogen, followed by the removal of the Boc-protecting group, and then the product undergo reductive amination with formaldehyde to give the desired N-(4-(5-(dimethylamino)-2,3,4,5-tetrahydro-1H-benzo[b]azepine-1-carbonyl) phenyl)-2-methylbenzamide **534**.

Dragan *et al.* [289] was successful in the synthesis of 4,5,6,7,9,9a,10,11,12,12a-decahydrocyclopenta[c][1,4]diazepino[6,7,1-ij]quinoline **539** which is used for the treatment of schizophrenia (Scheme **111**). The reaction proceeds *via* the condensation of formaldehyde **537**, cyclopentanone **535**, and benzodiazepine **536** in the presence of iodine and hydrogen iodide lead to the formation of fused quinolinium ion **538,** which further undergo iridium-catalyzed asymmetric hydrogenation to afford the product **539**, after removal of the protecting group.

Dinda *et al.* [289] confirmed the structure of benzazepinedione **542** by oxidation and acetylation (Scheme **112**). The benzazepinedione **540** was acetylated with acetic anhydride-pyridine to give methyl 5-acetoxy-1-oxo-2,5-dihydro-1H-benzo[c]azepine-3-carboxylate **541**, and the same on oxidation with MnO_2 at room temperature give methyl 1,5-dioxo-2,5-dihydro-1H-benzo[c]azepine-3-carboxylate **542**.

An attempt was made by Dinda *et al.* [289] to reduce the olefinic bond of benzazepinone ring **543 & 545**. On reduction of methyl 4-methyl-1,5-dioxo-2,5-dihydro-1H-benzo[c]azepine-3-carboxylate **545** with Palladium catalysed surface in methanol at room temprature give triply reduced methyl 4-methyl-1-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepine-3-carboxylate **544** in moderate yield *i.e.,* 75% yield. On hydrogenation of methyl 5-hydroxy-4-methyl-1-oxo-2,5-dihydro-1H-benzo[c]azepine-3-carboxylate **545** with the same reaction condition give methyl 4-methyl-1-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepine-3-carboxylate **544** (Scheme **113**).

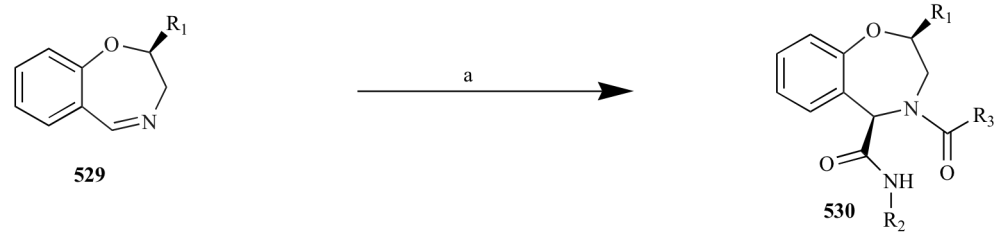
Dai [211] described the reaction for the ring cyclization of azepine derivatives (Scheme **114**). The hydroxyl group at the carbon of aldimine **261** activates the carbonyl group, followed by the stabilization of azemethine ylide **546** by an intramolecular hydrogen bond. The reaction proceeds at 60°C in chloroform in the presence of Cs_2CO_3.

Quintero and co-workers [290] in 2019, gave the synthetic route for the synthesis of substituted dihydro-5H-benzo[b]pyrimido[5,4-f]azepin-4-amine **549** using 4-chloro-6,11-dimethyl-6,11-dihydro-5H-benzo[b]pyrimido[5,4-f]azepine **547** by nucleophilic substitution reaction. The 4-chloro-6,11-dimethyl-6,11-dihydro-5H-benzo[b]pyrimido[5,4-f]azepine **547** reacts with hydrazine hydrate undergoes nucleophilic substitution reaction to form the intermediate, *i.e.,* 4-hydrazinyl-6,11-dimethyl-6,11-dihydro-5H-benzo[b]pyrimido[5,4-f]azepine **548** which further undergoes an acid-catalyzed condensation reaction with 4-chlorobenzaldehyde to get the target product **537** (Scheme **115**).

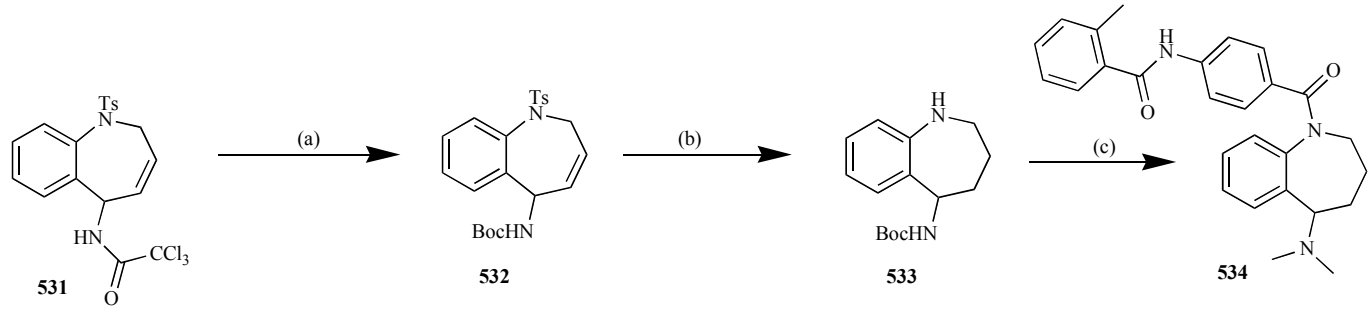
M. *et al.* [134] successfully worked on the reductive removal of N-SO_2Py group (Scheme **116**). The removal of N-SO_2Py group of Benzazepinone **550** proceeds under the mild condition to give the N-unprotected bicyclic lactams **551** in medium yield.

Shen *et al.* [291] were successful in the synthesis of 2-isocyano-6a,7,8,9,10,11-hexahydro-5H-benzo[4,5][1,3]oxazino[3,2-a]azepine **553** *via* intramolecular ring cyclization/[1,5]-hydride transfer. HFIP proves to be a very versatile solvent for hydride transfer. The 4-isocyano-2-(pyrrolidin-1-yl)benzaldehyde **552** undergoes intramolecular ring cyclization/[1,5]-hydride transfer at 120°C to get the desired product in very poor yield (Scheme **117**).

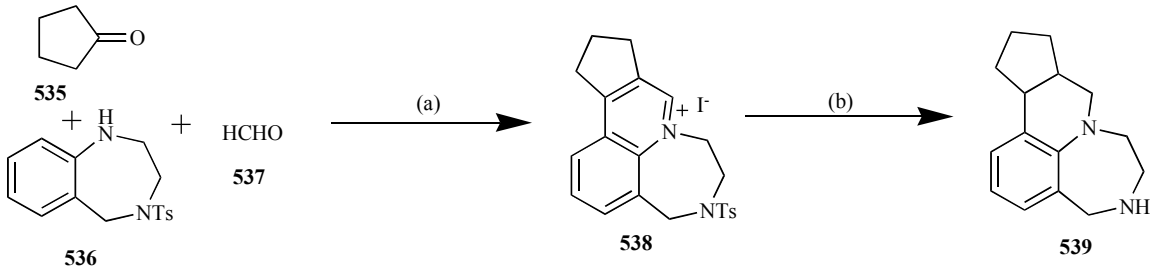
The N-tosyl protected azepinone **125** is further deprotected to give the desired product in sufficient yield (Scheme **118**). The N-tosyl group is removed in approx 20 min by Na/naphthalene in DME at -78°C to give the deprotected azepinone *i.e., (*3'R,5R)-1'-benzyl-5-phenyl-3,5-dihydrospiro[benzofuro[3,2-b]azepine-4,3'-in-



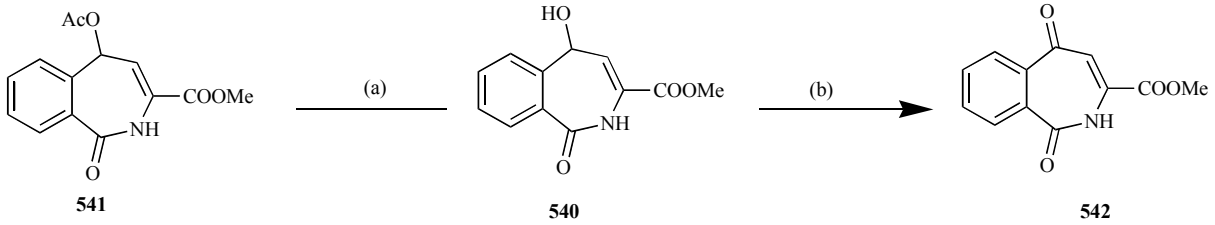
Scheme 109. Synthesis of tetrahydrobenz[1,4]oxazepines derivatives. Reagents: a) i) R_2-NC, R_3-COOH, MeOH, rt, 48h [288].



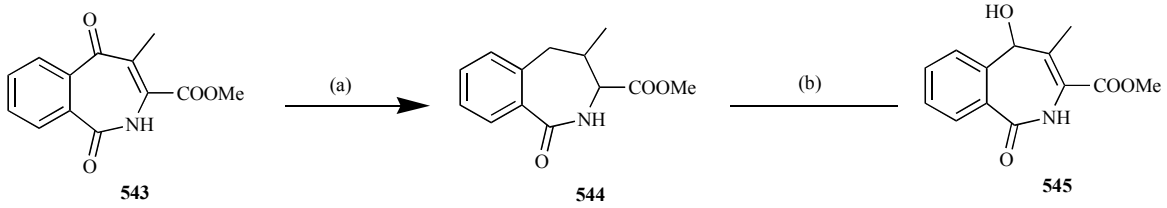
Scheme 110. Synthesis of azepine derivative. Reagents: a) (i) 2 M NaOH, MeOH, 60°C, 18h; (ii) Boc_2O, rt, 24h; b) (i) H_2,Pd/C, EtOAc, 60°C, 17h; (ii)Mg, MeOH, Δ, 4h [176].



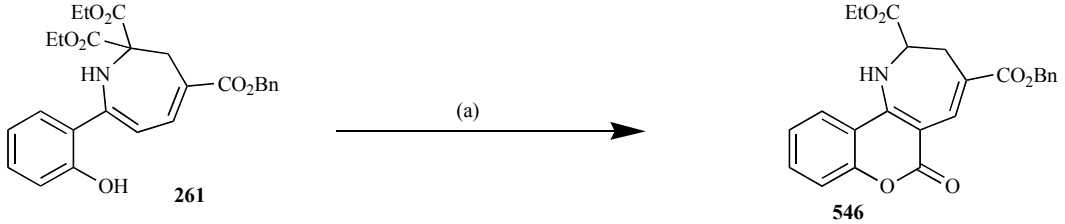
Scheme 111. Synthesis of seven-membered quinoline derivative. Reagents: a) HI, I_2, MeOH, 30°C; b) H_2 250psi, $[Ir(COD)Cl]_2$ (0.0075 equiv), (S)-Morphos, (*t*-Bu)$_3$P, 2,6-Dt-BP, 50 °C, 20h, 1:1 DCE/MeOH, *er* 94:6; c) HCl, AcOH, 115°C, recryst. 95% EtOH, MTBE, *ee* 99.9% [289].



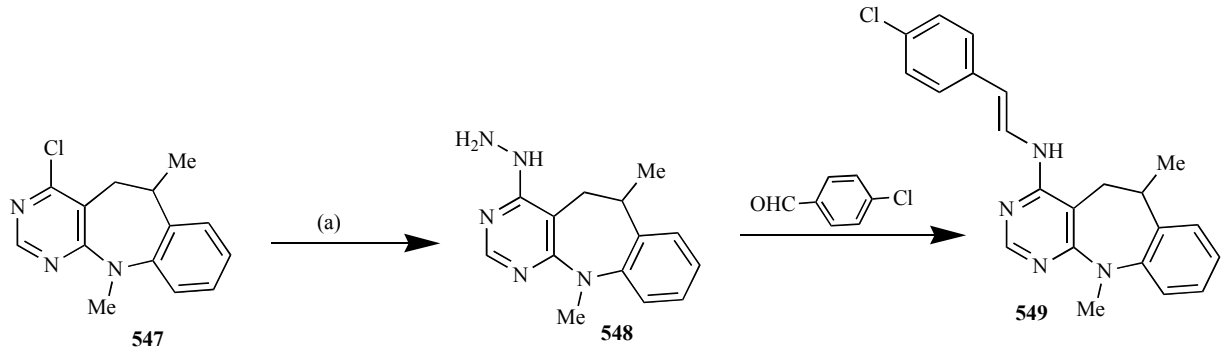
Scheme 112. Acetylation and Oxidation of benzazepinedione. Reagents: a) Ac_2OPy; b) active MnO_2 [289].



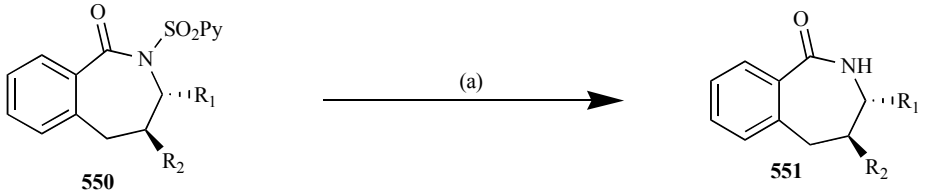
Scheme 113. Reduction of benzazepinones. Reagent: a)H_2/Pd-C (10%), MeOH, rt; b) H_2/Pd-C (10%), MeOH, rt [289].



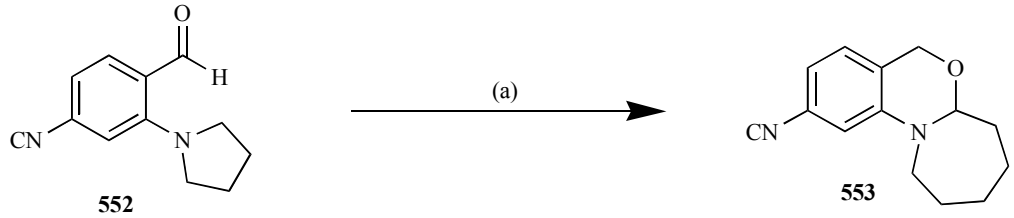
Scheme 114. Ring cyclization of azepine derivative. Reagents: a) Cs_2CO_3 (1.2equiv), $CHCL_3$, 60°C [211].



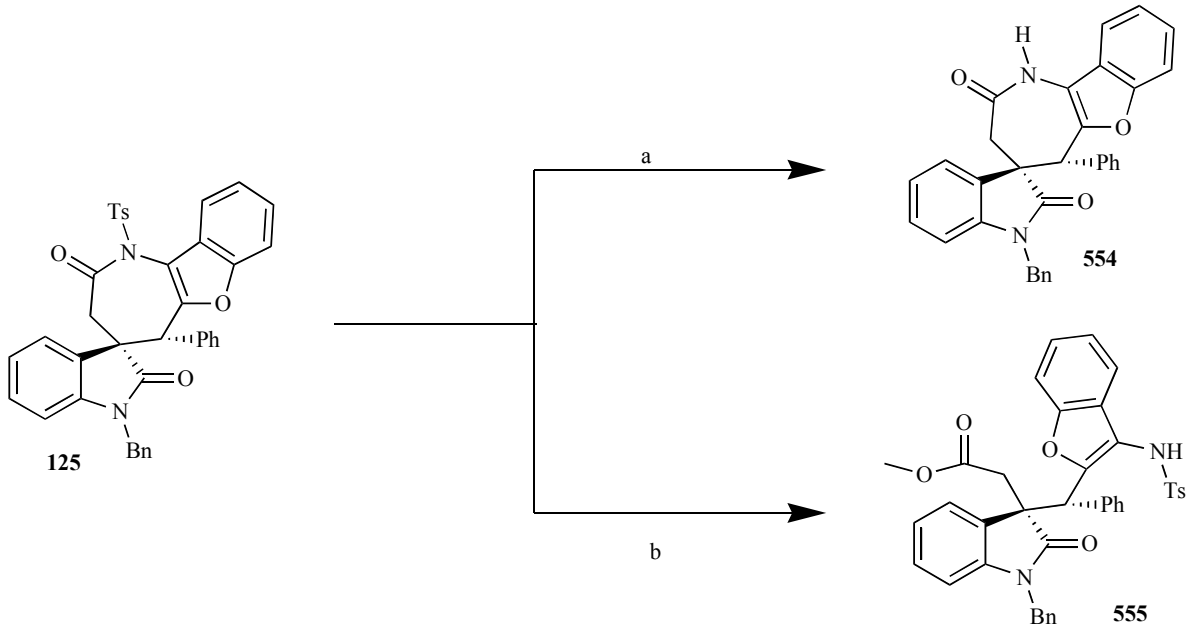
Scheme 115. Preparation of dihydro-5H-benzo[b]pyrimido[5,4-f]azepin-4-amine. Reagents: a) $N_2H_4.H_2O$ [290].



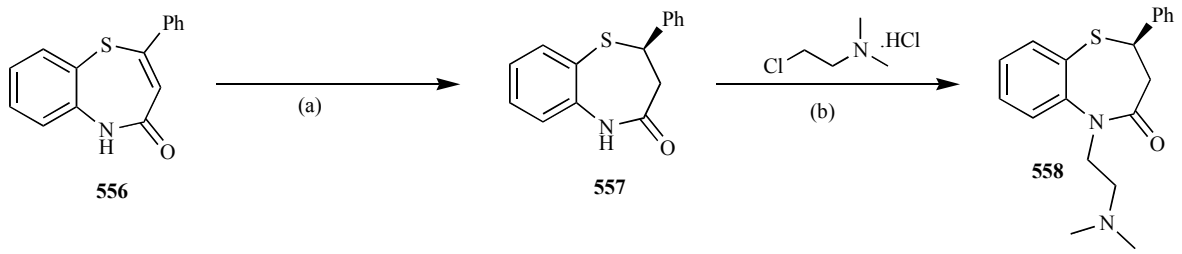
Scheme 116. Removal of N- SO_2Py group of Benzazepinone. Reagents: a) Zn, THF/NH_4Cl, 60°C [134].



Scheme 117. Synthesis of 2-isocyano-6a,7,8,9,10,11-hexahydro-5H-benzo[4,5][1,3]oxazino[3,2-a]azepine *via* intramolecular ring cyclization/[1,5]-hydride transfer. Reagents: a) HFIP, 120°C, 24h [291].



Scheme 118. Reaction of N-tosyl protected azepinone. Reagent: a) Na/naphthalene, -78°C, DME, 20min; b) Mg, CH_3OH, sonication, rt, 3h [111].



556 557 558

Scheme 119. Reaction of 2-phenylbenzo[b][1,4]thiazepin-4(5H)-one. Reagents: a) $Rh(NBD)_2BF_4$/Zhaophos, S/C = 100, DCM (6mL), H_2 (70 bar), 45 ^{O}C, 70h; b) K_2CO_3, H_2O/EA.

doline]-2,2'(1H)-dione **554** as a product in 71% yield, with >20:1 dr and 95% ee [111]. The ring-opening reaction took place when the same reactant is reacted with ethanol and give ester as a product **555.**

Yin *et al.* in 2020, [292] proposed a new pathway for the reaction of 2-phenylbenzo[b][1,4]thiazepin-4(5H)-one **556**. The compound **556** undergoes reduction using Rh complex as a catalyst in DCM at 45^{o}C for 70h under 70 bar hydrogen pressure to give the product **557**, which further undergoes reaction with 2-chloro-N,N-dimethylethanamine hydrochloride to give N-substituted product **558** in 99% yield with 99% *ee* which acts as an antidepressant drug (Scheme **119**).

CONCLUSION

This study contains critical analysis in a very confined manner to cover-up the maximum reported work for sustainable and efficient synthesis. However, only a few researchers have worked on the biological properties of these derivatives, leaving a broad work area to explore and exploit the biological potential. This study will resolve many problems of different researchers by providing interesting findings such as the substituted aryl halides have been exploited more for their synthesis, giving a clue about the best-suited starting moiety to work on with. It has also been observed that some of the named reactions such as Roche, Synthesis, Pictet–Spengler cyclization, semipinacol rearrangement, Suzuki coupling, Heck coupling, Beckmann rearrangement, Suzuki-Miyaura coupling reaction, Michael addition, Ullmann–Smiles cyclization process, *etc.,* have been used for the synthesis seven-membered heterocyclic compounds. Moreover, all the schemes are also discussed and drawn in a very conclusive manner to understand the similarity in the different work that has been done by the different researchers to find out the possible gaps in the studies. So this review will provide enough information for the researchers to fill the gap in the existing studies.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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