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REVIEW ARTICLE

1,4-Dithiane-2,5-diol: A Versatile Synthon for the Synthesis of Sulfur-containing Heterocycles

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ARTICLE HISTORY

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Abstract: ***Background*:** 1,4-Dithiane-2,5-diol (1,4-DTD) is the stable dimer of *α*-mercapto acetaldehyde. This commercially available ambidentade compound is characterized as having in its chemical structure one group that acts as an electrophile and another that acts as a nucleophile, this permits its use as versatile and efficient synthon in synthetic heterocycle procedures.

***Objective*:** The aim of this review is to present synthetic applications of 1,4-DTD in heterocyclic chemistry and their applicability to the synthesis of bioactive compounds.

***Conclusion*:** Gewald reactions to obtain C-4 and C-5 unsubstituted 2-amino-thiophene derivatives; sulfa-Michael/Henry and sulfa-Michael/aldol sequences to obtain polysubstituted tetrahydrothiophenes, and other heterocyclic reactions that allow synthesizing several functionalized sulfur-containing heterocycles such as thiazolidines, oxathiazinoles and thiazoles are presented and discussed. The use of such heterocyclics in subsequent reactions allows obtaining various bioactive compounds including the antiretroviral lamivudine which is one of the examples presented in this review.

Keywords: 1,4-dithiane-2,5-diol, 2-amino-thiophene, Gewald reaction, sulfur heterocycles, sulfanyl carbonyl, tetrahydrothiophene.

1. INTRODUCTION

1,4-Dithiane-2,5-diol (1,4-DTD), the stable dimeric form of *α*-mercaptoacetaldehyde (Chart **1**), is a versatile and efficient synthon used in heterocyclic synthesis procedures [1] for obtaining functionalized amino-thiophenes [2, 3], tetrahydro-thiophenes [4,5], thiazolidine-2-thiones [6], 5,6-dihydro-1,4,2-oxathiazin-6-ols [7] and other related five- and six-membered sulfur-containing heterocycles derivatives [8,9].

It´s structure contains a bifunctional group that acts as an electrophile (-CHO) and as a nucleophile (-SH) which can be used in several kinds of reactions resulting in compounds such as serine protease [10], Metallo-β-lactamase inhibitors [11], antivirals [12, 13], antibiotics [14], phytogrowth inhibitors [15], and others with a wide range of biological properties.

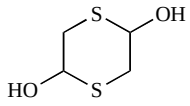

Chart 1. Chemical structure of 1,4-dithiane-2,5-diol.

The purpose of this review is to present synthetic applications of 1,4-DTD in heterocyclic chemistry, with biological applications of bioactive compounds as obtained through the use of 1,4-DTD. The focus of this review is the last 20 years, covering the period from 1997 to 2017, yet without discarding certain historical works that involve the synthesis of sulfur heterocycles.

1.1. 1,4-DTD in the Synthesis of 2-aminothiophene Derivatives

2-aminothiophene (2-AT) derivatives are a class of five-membered sulfur-containing heterocycles [16] which has been receiving great attention in the last years due to the availability of reagents, mild reaction conditions, and its great chemical versatility that allows its use as a structural motif, for synthesis of a wide range of bioactive compounds, dyes, electro- and optoelectronic device elements, and others [17, 18].

The main synthetic procedure to obtain 2-AT is the classical Gewald reaction [19] which consists of a multicomponent reaction between a ketone or aldehyde containing an α-methylene, an activated nitrile, and sulfur in the presence of a base. This reaction has been optimized in diverse synthetic methods [20-23].

Puterová and coauthors in 2010 [18] published a review which describes four versions of the Gewald reaction. In the fourth version, stable dimeric forms of *α*-sulfanylcarbonyl compounds (substituted 1,4-DTD) undergo condensation and subsequent cyclization in a one-pot procedure with α-activated acetonitrile derivatives in the presence of an amine (Chart **2**). The advantage of this fourth version of the Gewald reaction is the possibility of preparing 2-AT without substituents in position C-4 and C-5 of the thiophene ring. This allows, synthesizing new derivatives with lower LogP structure-activity relationship (SAR) studies.

Several authors have described the use of 1,4-DTD in thiophene azo dye synthesis. Generally, the initial synthetic steps apply the fourth version of the Gewald reaction, to obtain the 2-AT nucleus,

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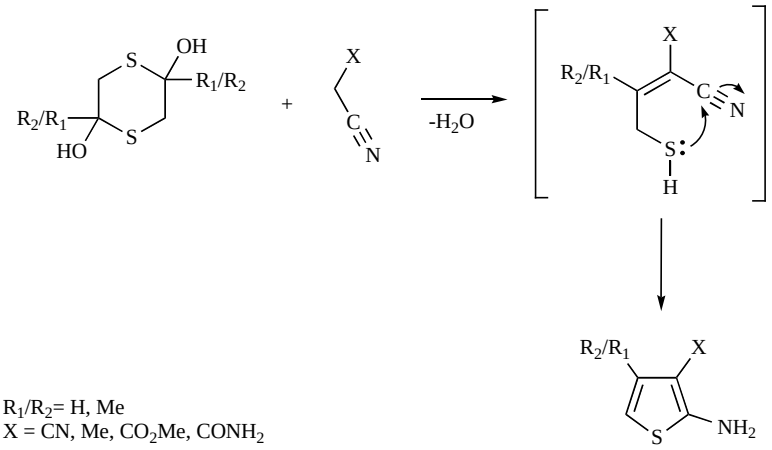
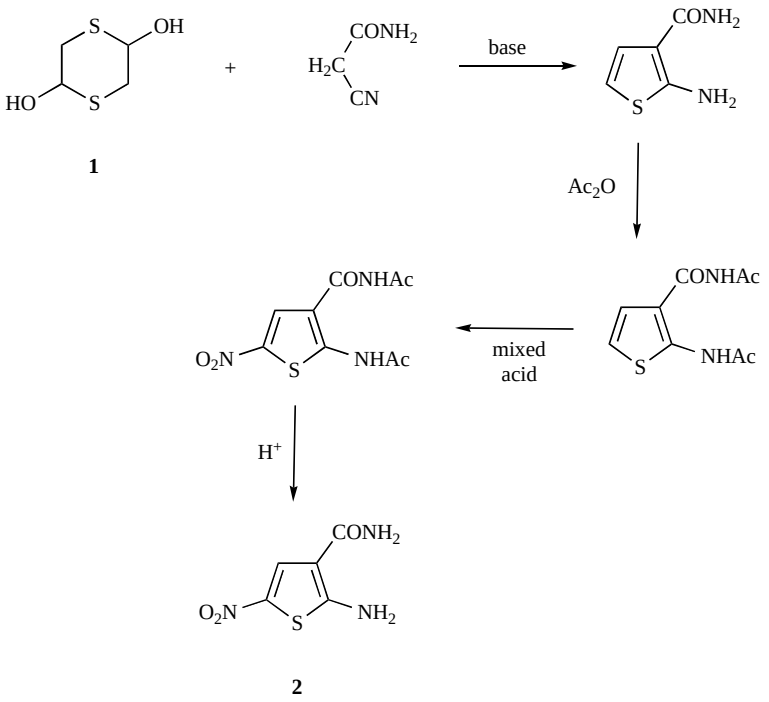
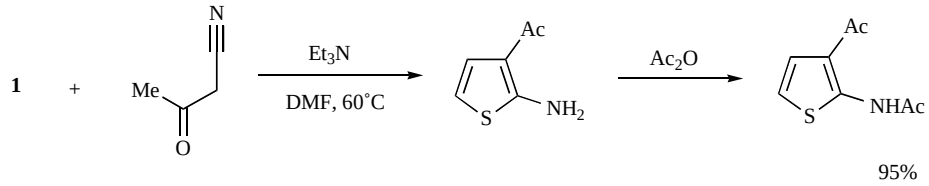


Chart 2. Fourth version of Gewald reaction.



Scheme 1. Synthesis of 2-amino-3-substituted-5-nitrothiophene.



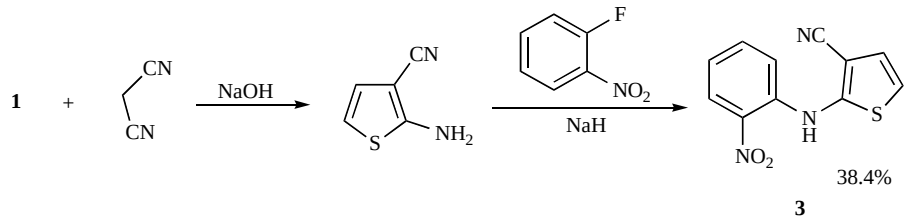
Scheme 2. Synthesis of 3-acetyl-2-aminothiophenes as building blocks for the synthesis of thiophene azo-dyes.

which was later functionalized according to the purpose of the research group.

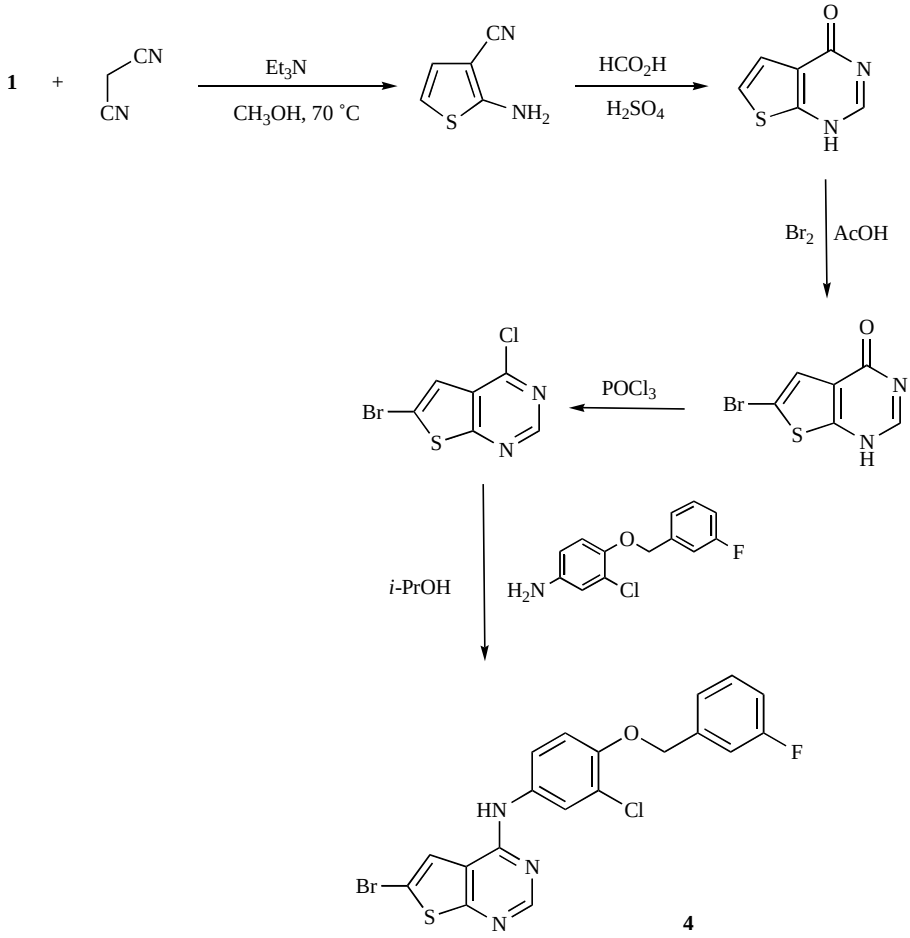
In this context, Hallas and Towns used 1,4-DTD (**1**) to obtain a series of thienylazo dyes. 1,4-DTD was used in the initial reaction with 2-cyanoacetamide in a basic medium using the Gewald reaction to obtain 2-aminothiophene-3-carboxamide. In sequence, this compound was acetylated, nitrated, and then deacetylated by hydrolysis yielding 2-amino-5-nitrothiophene-3-carboxamide (**2**) (Scheme **1**) which is a precursor for the synthesis of various thienylazo dyes [2].

The Gewald reaction can also be modified using labile cyanoacetone cyclized with α-mercaptoaldehyde dimers from 1,4-DTD, with triethylamine in DMF at 60°C to afford 3-acetyl-2-aminothiophenes, and subsequent heating with acetic anhydride to obtain acetamide. The same building block was used by Eller and Holzer [24] to obtain thiophene azo dyes (Scheme **2**).

Hallas and Choi also reported a modified Gewald reaction for the preparation of 2-aminothiophenes: In this variation, 1,4-DTD and ethanol were cooled to 10ºC. A solution of malononitrile in ethanol was added for 10 min, followed by a solution of diethy-



Scheme 3. Synthesis of 2-[(2-nitrophenyl)amino]-thiophene-3-carbonitrile (**ROY**). ROY – Represents the abbreviation of the three color polymorphous: red (**R**), orange (**O**), and yellow (**Y**).



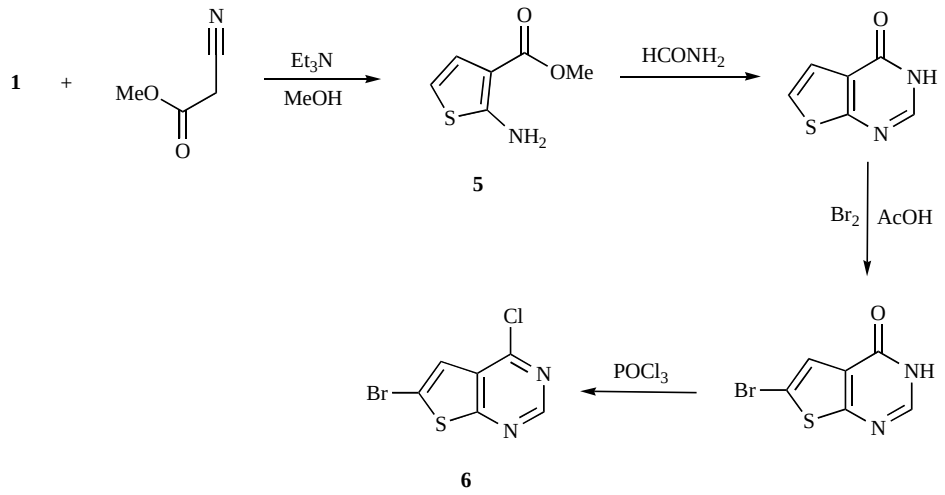
Scheme 4. Total synthesis of 6-bromo-*N*-[3-chloro-4-(3-fluorobenzyloxy)phenyl]-thieno[2,3-*d*]pyrimidin-4-amine.

lamine in ethanol which was added dropwise. The temperature was then raised to 35±5ºC and the reaction mixture was stirred for 2h. The reaction mixture was poured into water and the resulting 2-amino-3-cyanothiophene was obtained as a brown solid, at a 72% yield. This compound was used as an intermediary for the synthesis of several azo-dyes [25].

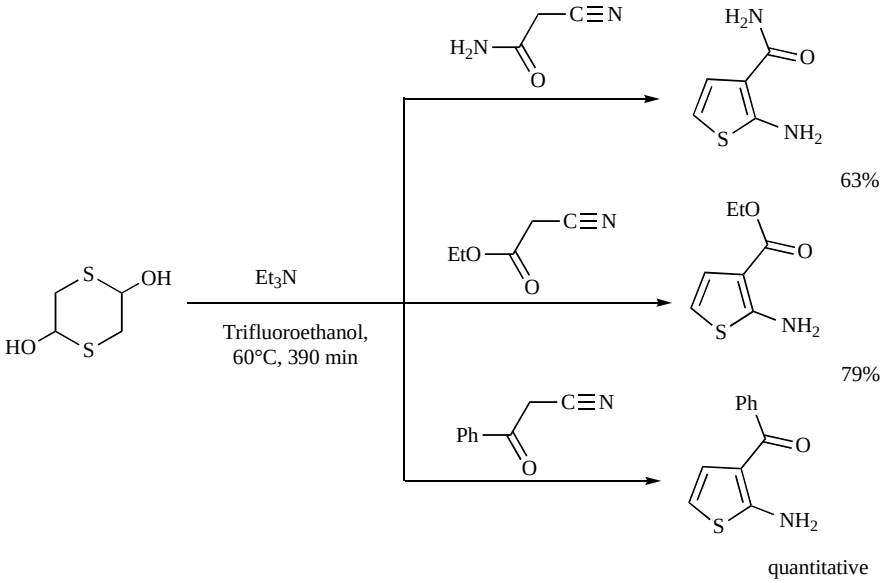
Li *et al.* [26] synthesized 2-[(2-nitrophenyl)-amino]-3-thiophenecarbonitrile (**ROY**) (**3**) in a two-step synthesis. This compound´s structures present the highest number of polymorphs described in the literature. The initials ROY, represent the first letters of the colors of crystals already obtained and characterized: red (R), orange (O), and yellow (Y). The first step was the synthesis of 2-amino-thiophene-3-carbonitrile through the Gewald reaction between malononitrile and 1,4-DTD (**1**) in a 64% yield after recrystallization in benzene. The reaction of 2-AT with 2-fluoro-1-nitrobenzene in a sodium hydride solution (NaH, 60% dispersion) in anhydrous tetrahydrofuran (THF), yielded ROY (**5**) in 38.4% yield (Scheme **3**).

A novel method of synthesis was reported by Zhan *et al*. [27] for 6-bromo-*N*-[3-chloro-4-(3-fluorobenzyloxy)phenyl]-thieno[2,3-*d*]pyrimidin-4-amine (**4**) (Scheme **4**). The synthesis begins from 1,4-DTD and malononitrile, following the Gewald reaction, aromatic ring bromination, condensation, cyclization and then a Dimroth rearrangement reaction to yield the desired compound (**4**). The reaction method demonstrates certain advantages: availability of the reagents involved, high final yield (84%), and simple procedures and purification steps for both intermediates and final products.

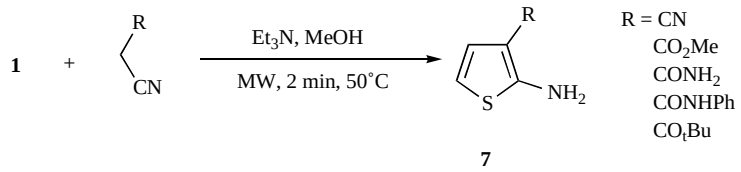
Bugge and coauthors [28] conducting a Gewald reaction using 1,4-DTD and methyl cyanoacetate in methanol containing triethylamine using the microwave and conventional heating (Scheme **5**) to obtain methyl 2-amino-thiophene-3-carboxylate (**5**), an intermediate for the synthesis of 6-bromo-4-chlorothieno[2,3-*d*]pyrimidine (**6**). This compound **6** is a key intermediate for the synthesis of the compound (**4**) described in Scheme **4**. The method involved four synthetic steps: Gewald reaction, pyrimidone formation, bromina-



Scheme 5. Reaction conditions of methyl 2-aminothiophene-3-carboxylate.



Scheme 6. Reaction conditions of ethyl 2-aminothiophene-3-carboxylate.



Scheme 7. Monosubstituted 2-AT obtained through Gewald reaction under MW.

tion, and chlorination, allowing the synthesis of **6** in an overall yield of 49% without using chromatographic procedures for purification either intermediates or final product.

To obtain 2-AT, in excellent yields, Mallia *et al.* [8] reacted 1,4-DTD, 2-cyanoacetophenone, cyanoacetamide, and ethyl cyanoacetate in 2,2,2-trifluoroethanol at 60°C and a reaction time of 390 min (Scheme **6**).

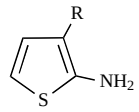
A major breakthrough for 2-AT synthesis is the advent of microwave irradiated reactions (MW), which allows increasing reaction rates in many cases to shorten the reaction times and to improve product yields [29, 30]. Many authors have now used this procedure starting from an α-mercapto aldehyde or *α*-mercapto acetone dimers and *α*-activated acetonitrile to obtain 2-AT in higher yields and with significantly shorter reaction times.

Using microwave irradiation (MW), Hesse and coauthors [3] synthesized 2-AT (**7**) by reaction of 1,4-DTD with different *α*-activated acetonitrile in only 2 min (Scheme **7**). Comparison of classical reaction condition times and reaction yields [19, 31, 32] with the methodology using microwave [3, 15] are present in Table **1**, demonstrating that MW improves yields and reduces reaction times.

Certain authors have also explored the Gewald reaction for simpler, more efficient, and environmentally friendly methods for 2-AT derivatives synthesis.

In this context, Ma *et al.* [33] developed a new *N*-methylpiperazine-functionalized polyacrylonitrile fiber to catalyze the Gewald reaction between 2-DTD and activated nitriles that afforded Gewald adducts in good to excellent yields (65–91%).

Table 1. Comparison of yields of 2-AT obtained by classical and microwave reaction conditions.

	**Microwave Conditions Yield % / [Reference]**	**Classical Conditions Yield % / [Reference]**
R = CN	60 / [3,17]	58 / [30,19]
R = CO_2Me	82 / [3,17]	55 / [30, 19]
R = $CONH_2$	78 / [3,17]	78 / [31]
R = CONHPh	87 / [3,17]	55 / [19]
R = CO_tBu	81 / [3,17]	-

Li and coauthors [34] also used four aminopyridine-functionalized polyacrylonitrile fiber ($PAN_{AP}F$) as the catalyst in Gewald reactions of 1,4-DTD and activated nitriles in different solvents to obtain the corresponding 2-AT (**8**). The best results were obtained with water as solvent and $PAN_{p\text{-}AP\text{-}3}F$ as the catalyst (92% yield) (Scheme **8**).

1.2. 1,4-DTD in Tetrahydrothiophene Synthesis

1,4-DTD has an important role in the synthesis of tetrahydrothiophene compounds. In order to generate these products, many authors explore the use of 1,4-DTD as a starting reagent using Michael and Henry reactions [4, 35, 36].

Barco *et al.* [4] reacted between 1,4-DTD and 2-nitroalkenes and 2-nitroethylacetates through one-pot sulfa-Michael/Henry reactions to obtain 4-nitro-tetrahydro-thiophene-3-ol derivatives (**9**) through intra-molecular cyclization in yields ranging between 65 and 80% (Scheme **9**).

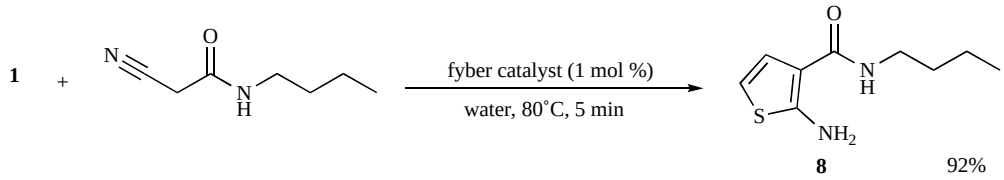
In another work by the same group, Baricordi and coauthors [35] applied 1,4-DTD as a synthon in Michael and Henry reactions for the synthesis of tetrahydrothiophenes in reactions with electrophilic acrylates and *α,β*-unsaturated carbonyl compounds. The reaction of 1,4-DTD with different *α,β*-unsaturated ketones (cyclohexenone, cyclopentenone and *β*-ionone) in CH_2Cl_2 and Et_3N (5 mol %) as catalyzer resulted in diastereomeric mixtures of 3-hydroxythiophanes in good yields (Scheme **10**).

Xu *et al.* [36] by Michael/Henry reaction used 1,4-DTD for the synthesis of diastereomeric 4-hydroxy-3-nitro-2-substituted-tetrahydrothiophenes. The authors used *trans-β*-nitrostyrenes as a starting material and tertiary amine functionalized polyacrylonitrile as a fiber catalyst. Diastereomeric mixtures were obtained in good yields (74-99%) (Scheme **11**).

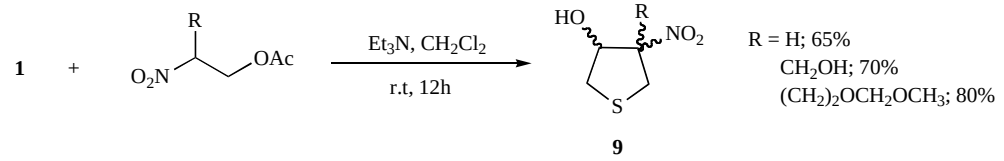
Using Knoevenagel condensation followed by sulfa-1,6-Michael and vinylogous Henry reactions, Nagaraju and coauthors [37] employed 1,4-DTD in the one-pot synthesis of isoxazole–thiolane hybrid (Scheme **12**).

In others works using the Michael/aldol reactions, Meninno *et al.* [38] synthetized 3,4,5-substituted tetrahydrothiophenes with quaternary stereocenters from sulfa-Michael/aldol reactions between 1,4-DTD and nitroalkenes (Scheme **13**).

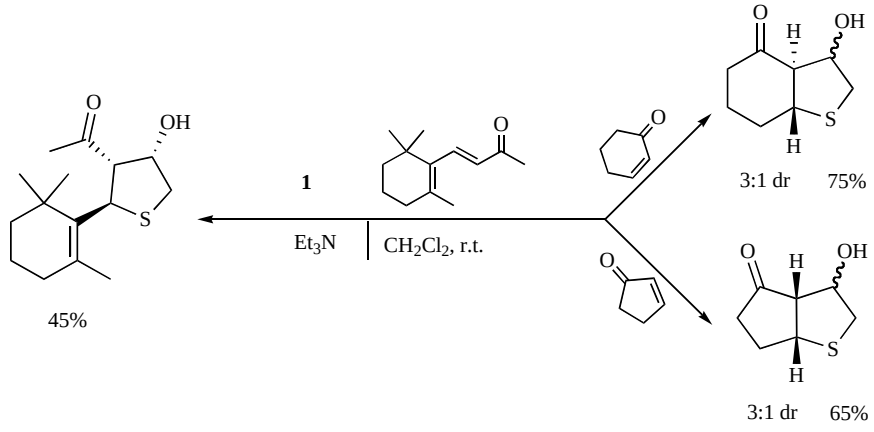
Duan *et al.* [39] described the asymmetric synthesis of tetrahydrothiophene derivatives *via* sulfa-Michael/aldol condensation reactions between 1,4-DTD and a variety of *α,β*-unsaturated ketones, catalyzed by Song's chiral oligoEG. Condensation of 1,4-DTD with chalcone derivatives provided tetrahydrothiophenes in excellent



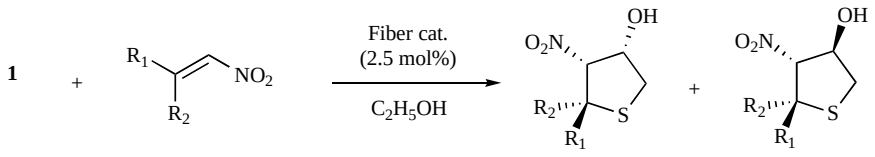
Scheme 8. Synthesis of 2-amino-3-substituted thiophene using fiber $PAN_{AP}F$ as catalyst.



Scheme 9. Synthesis of 4-nitro-tetrahydro-thiophene-3-ol derivatives through one-pot sulfa-Michael/Henry reactions.



Scheme 10. Synthesis of 3-hydroxythiophanes from 1,4-DTD.

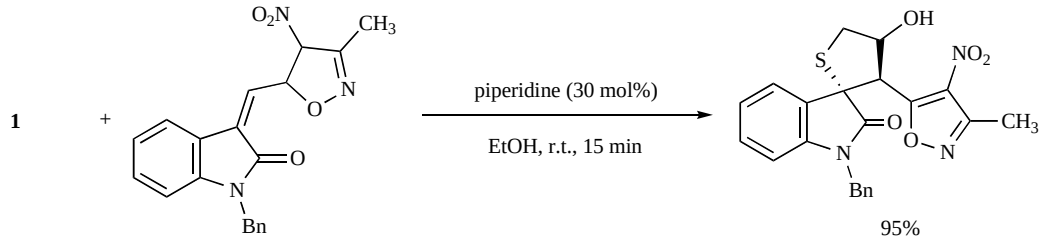


R_1,R_2= 2-OMe-Ph, H; 78, 82%
3-OMe-Ph, H; 81%
4-OMe-Ph H; 92%
4-NO_2-Ph, H; 80, 80%
3-NO_2-Ph, H; 87%

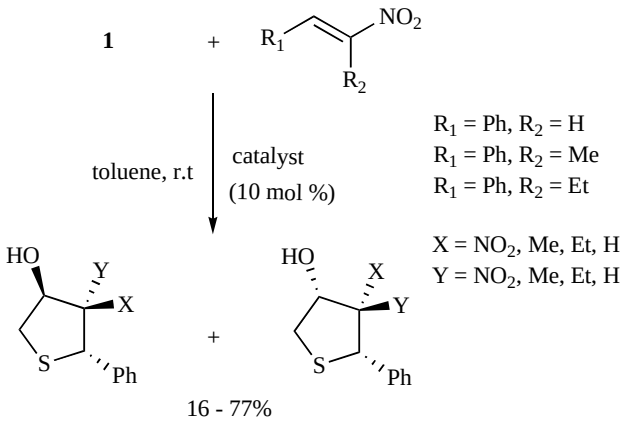
R_1,R_2= 4-F-Ph, H; 85%
2-Cl-Ph, H; 85%
4-Cl-Ph, H; 89%
4-Br-Ph, H; 82%
4-$C_2H_2NO_2$, H; 75%

R_1,R_2= 2,4-Me; H; 88%
Ph, Me; 90%
Ph, H; 93%
2-furyl, H; 85%
2-thienyl, H; 92%

Scheme 11. 3,4,5-Substituted tetrahydrothiophenes synthesized from sulfa-Michael/aldol reaction of 1,4-DTD and nitroalkenes.



Scheme 12. Synthesis of hybrid isoxazole–thiolane.



Scheme 13. Synthesis of 3-nitro-2-substituted thiophenes by reaction between 1,4-DTD and nitroalkenes.

yields (90-99%), independent of the presence of donor or withdrawing electron substituents (Scheme **14**).

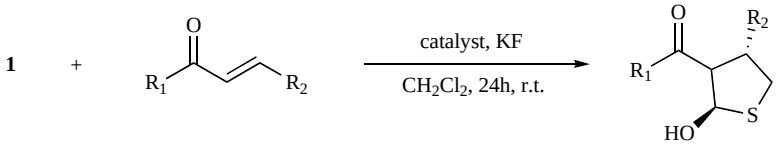
After establishing of the reaction conditions, Duan *et al.* [39] utilized the same method for synthesis of spiro tetrahydrothiophene derivatives, starting from *α,β*-unsaturated benzocyclic ketones and 1,4-DTD, with good to excellent yields (68-99%) (Scheme **15**).

Via sulfa-Michael/aldol reactions, Liang and coauthors [40] linked 1,4-DTD and chalcones to obtain spiro-tetrahydrothiophene. The final compounds were obtained in yields ranging from 15 to 94% (Scheme **16**).

Zhou and coauthors [41] synthesized spirocyclic compounds (oxindole-fused tetrahydrothiophenes) from thia-Michael/aldol reactions of 1,4-DTD and 3-alkenyloxindoles. When 1,4-DTD was used in sulfa-Michael/aldol reaction with iso-indigos the reactions afforded bis-pirooxindole tetrahydrothiophene derivatives [42]. (Scheme **17**) The compounds were obtained with good enantio- and diastereoselectivities and good yields (71-91%).

Zhao *et al.* [43] described sulfa-Michael/aldol reactions between benzylidene chroman-4-ones and 1,4-DTD to yield the corresponding spirocyclic tetrahydrothiophene chromanone derivatives. The reaction was performed in the presence of a 1 mol% organo-catalyst in toluene at 55°C for 30–96 h and provided the desired compounds in high yields (up to 99%) (Scheme **18**).

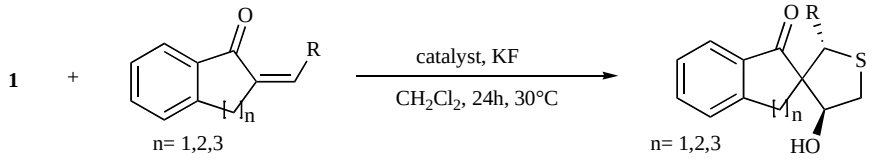
DABCO was used by Zhong *et al.* [44] in Michael-Aldol [3+2] cycloaddition reactions of 1,4-DTD with maleimides, resulting in



R_1,R_2 = Ph; 95%
Ph, *p*-Me-Ph; 97%
Ph, *p*-OMe-Ph; 99%
Ph, 3,4,5-OMe-Ph; 99%
Ph, P-F-Ph; 99%
Ph, *p*-CF_3-Ph; 93%
Ph, Furan; 90%

R_1,R_2 = *p*-Me-Ph; 91%
p-F-Ph, *m*-Me-Ph; 93%
p-F-Ph, *p*-OMe-Ph; 98%
p-OMe-Ph, *p*-Br-Ph; 99%
p-Me-Ph, *p*-Br-Ph; 99%
p-F-Ph, *p*-Br-Ph; 94%
p-OMe-Ph, Ph; 91%

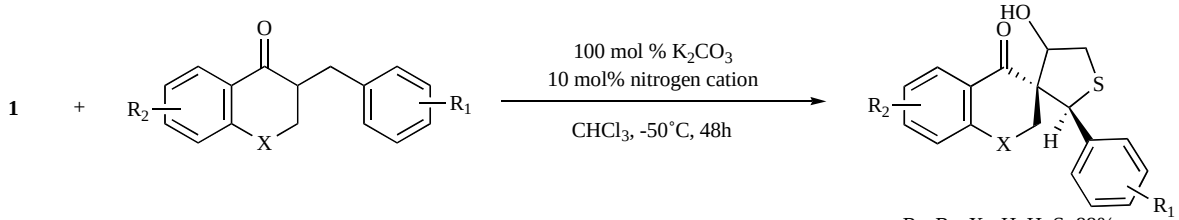
Scheme 14. Synthesis of tetrahydrothiophene derivatives *via* sulfa-Michael/aldol condensation reaction.



R= *p*-Me-Ph, n = 1; 99%
p-OMe-Ph, n = 1; 99%
p-Cl-Ph, n = 1; 99%
p-Me-Ph, n = 3; 68%
Naphtil, n = 1; 99%
Ph, n = 3; 85%

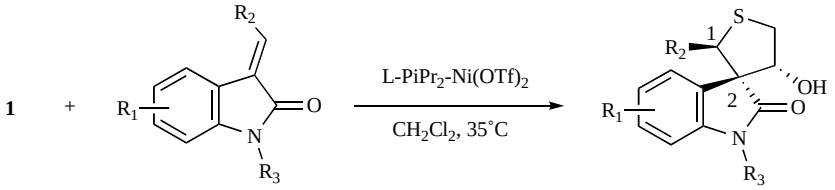
R= Ph, n = 2; 88%
Ph, n = 1; 99%
p-Me-Ph, n = 2; 83%
p-OMe-Ph, n = 2; 83%
p-F-Ph, n = 2; 92%
p-Cl-Ph, n = 2; 91%

Scheme 15. Synthesis of spiro-tetrahydrothiophene derivatives.

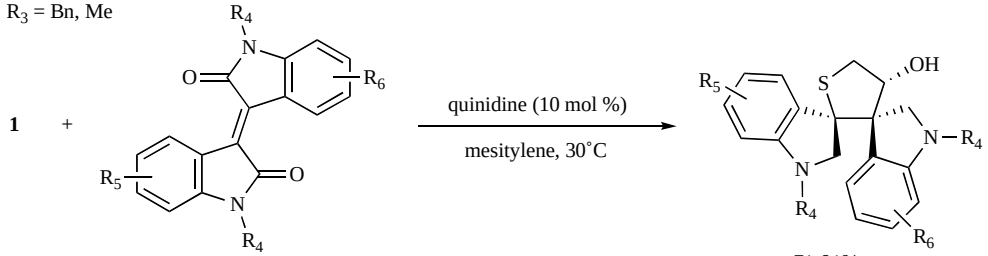


R_1, R_2, X= H, H, S; 88%
H, H, CH_2; 58%
p-F, H, S; 94%
p-Br, H, S; 93%
p-Br, H, CH_2; 63%

Scheme 16. Spirotetrahydrothiophene derivatives obtained through sulfa-Michael/aldol reactions between 1,4-DTD and chalcones.

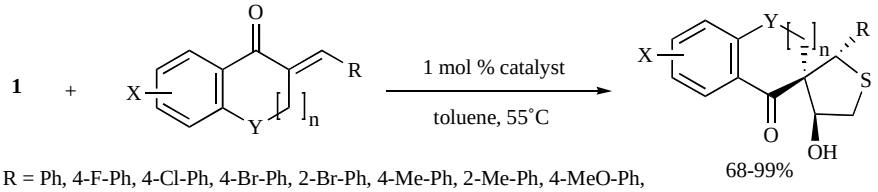


R_1 = H, 5-Me, 5-OMe, 5,7-Me_2, 5-F, 5-Cl, 5-Br, 6-Cl, 7-Br, 7-CF_3
R_2 = COOMe, COOEt, COO-*i*-Pr, COO-*t*-Bu, COOPh, COPh, Ph, 4-Me-Ph, 4-F_3C-Ph,4-Cl-Ph, 2-naphthyl, 3-thienyl, Me, *n*-decyl, COOEt
R_3 = Bn, Me



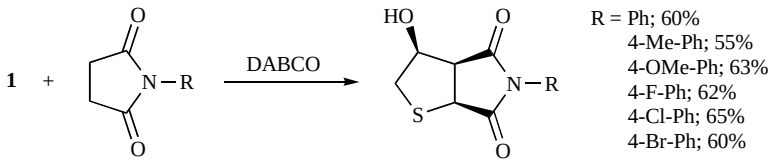
R_4 = Me, Et, *n*-Pr, Allyl, *i*-Pr, *n*-Bu, *n*-Octyl, Bn, H
R_5 = H, 5-Me, 5-Br, 6-Br, 7-F, 5-OMe, 5-Cl, 6-Cl
R_6 = H, 5'-Me, 5'-Br, 6'-Br, 7'-F, 5'-F, 5'-OMe, 5'-Cl, 6'-Cl

Scheme 17. Use of 1,4-DTD in the synthesis of oxindole-fused tetrahydrothiophenes.

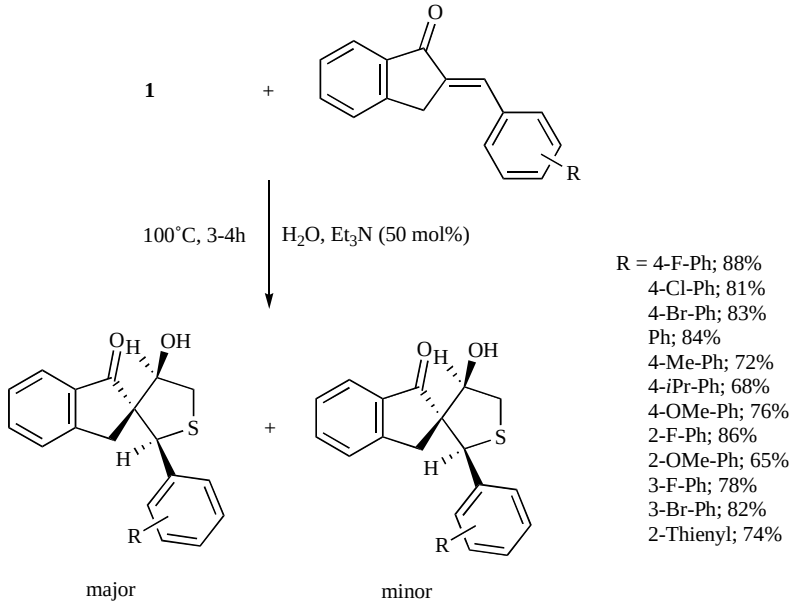


R = Ph, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph, 2-Br-Ph, 4-Me-Ph, 2-Me-Ph, 4-MeO-Ph, 4-CN-Ph, 2-NO_2-Ph, 2-furyl, 2-thienyl, 3-pyridinyl, cyclohexyl
X = H, 6-Cl, 6-OMe, 5-Cl, 6-Me
Y = O, CH_2
n = 1, 0

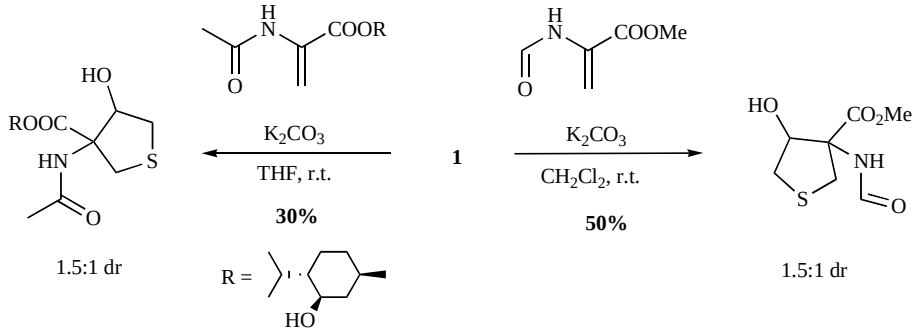
Scheme 18. Synthesis of spirocyclic tetrahydrothiophene chromanone derivatives.



Scheme 19. Synthesis of biheterocyclic tetrahydrothiophenes obtained by Michael-Aldol [3+2] cycloaddition reactions.



Scheme 20. Synthesis of spiro-thiophenes through domino reactions between 1,4-DTD and indenones.



Scheme 21. Synthesis of 3,4-di-substituted tetrahydrothiophenes from 1,4-DTD.

bicyclic heterocycles (fused tetrahydrothiophene and pyrrolidine) in yields of up to 98% (Scheme **19**).

Kumar *et al*. [45] using Michael addition methodology reacted 1,4-DTD and *(E)*-2-(aryl)-2,3-dihydro-1*H*-inden-1-ones through domino reactions in water to generate 2'-(aryl)-4'-hydroxy-4',5'-dihydro-2'*H*-spiro[indene-2,3'-thiophen]-1(3*H*)-ones with yields of 65-88% (Scheme **20**).

In another methodology, reaction between 1,4-DTD and methyl 2-formamidoacrylate and (-)-menthyl-2-acetamidoacrylate, in the presence of K_2CO_3 afforded inseparable 1.5:1 diastereomeric mixtures of 3,4-disubstituted tetrahydrothiophenes in satisfactory to low yields. Interestingly, attempts at asymmetric induction with the chiral auxiliary (-)-menthol did not promote increases in either the reaction selectivity or yield [35] (Scheme **21**).

Ling *et al*. [46] obtained tetrahydrothiophenes differently. They realized reactions between 1,4-DTD and chalcones. The trisubstituted tetrahydrothiophenes were obtained through a hydrogen-bond mediated cascade reaction (yield up to 91%) (Scheme **22**).

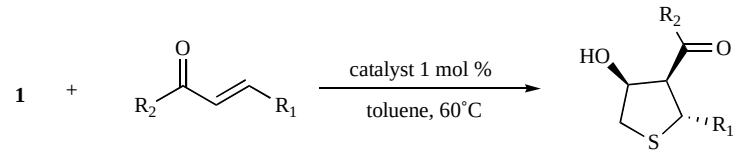
1.3. 1,4-DTD in the Synthesis of Thiophenes

The use of 1,4-DTD in the synthesis of substituted thiophenes has been performed in several ways: using nitroalkenes [5, 47], Michael addition reaction [48], cycloaddition [49-51], the use of aldehydes [1, 52], using DABCO [53], among othersc.

Kumar *et al*. [5] reported combining nitroalkenes and 1,4-DTD, using *α*-nitroketene *N*,*S*-aryl/alkylaminoacetals for synthesis of 3-nitro-*N*-aryl/alkylthiophen-2-amines in overall yields of from 82-98% (Scheme **23**).

O'Connor and coauthors [47] also reacted 1,4-DTD with nitroalkenes to obtain 3-nitro-2-substituted thiophene derivatives in yields ranging from 37 to 91% (Scheme **24**).

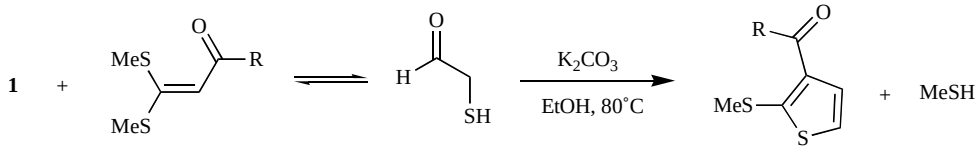
Based on the Michael addition methodology Selvi and coauthors [48] obtained 2,3-disubstituted thiophenes from 1,4-DTD and 2-aryl-3-nitrocyclopropane-1,1-dicarboxylates. Initially substituted tetrahydrothiophenes were obtained by the treatment of a cyclopropane precursor with BF_3OEt_2, followed by Michael reaction with 1,4-DTD. Oxidation with *p*-toluenesulfonic acid resulted in 2,3-



R_1,R_2= Ph, Ph; 81%
2-Me-Ph, Ph; 80%
3-Me-Ph, Ph; 91%
3-Cl-Ph , Ph; 79%
4-Me-Ph, Ph; 75%
4-F-Ph, Ph; 89%
4-Cl-Ph, Ph; 86%

R_1,R_2= Ph, 3-Br-Ph; 88%
Ph, 4-Cl-Ph; 86%
Ph, 4-Br-Ph; 71%
Ph, 4-OMe-Ph; 80%
Ph, 2-thienyl; 90%
Ph, 2-furyl; 82%
4-Br-Ph, Ph; 76%
4-OMe-Ph, Ph; 91%

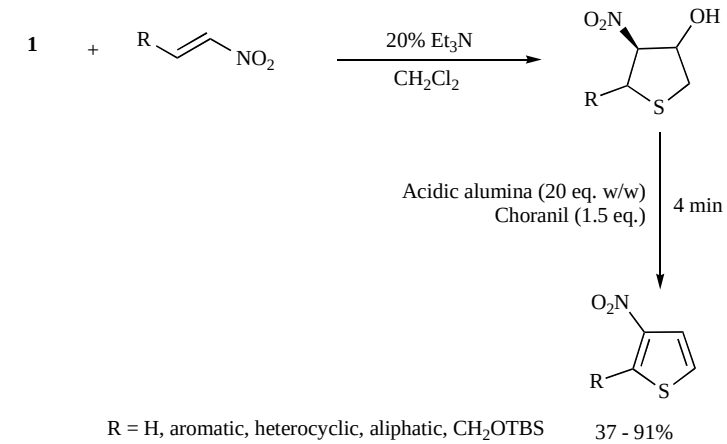
Scheme 22. Synthesis of tri-substituted tetrahydrothiophenes.



R= Ph; 60%
4-Me-Ph; 55%
4-OMe-Ph; 63%
3,4-OMe-Ph; 55%
2,4-OMe-Ph; 65%
4-F-Ph; 62%

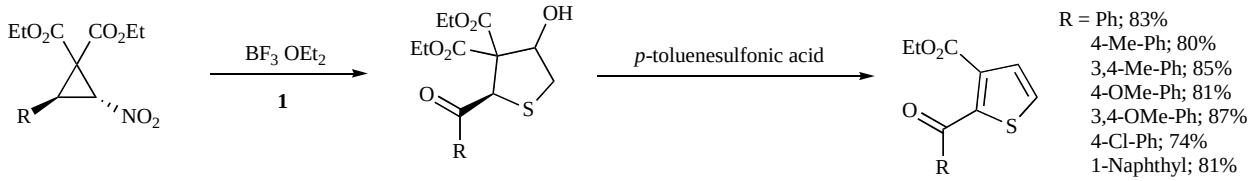
R= 4-Br-Ph; 60%
4-Cl-Ph; 65%
alfa-naphthyl; 70%
beta-naphthyl; 66%
2-pyridyl; 50%
2-thienyl; 70%

Scheme 23. Synthesis of 3-nitro-*N*-aryl/alkylthiophen-2-amines using 1,4-DTD and nitroketenes.



R = H, aromatic, heterocyclic, aliphatic, CH_2OTBS 37 - 91%

Scheme 24. Synthesis of 3-nitro-2-substituted thiophenes by reaction between 1,4-DTD and nitroalkenes.



R = Ph; 83%
4-Me-Ph; 80%
3,4-Me-Ph; 85%
4-OMe-Ph; 81%
3,4-OMe-Ph; 87%
4-Cl-Ph; 74%
1-Naphthyl; 81%

Scheme 25. Synthesis of 2,3-disubstituted thiophenes.

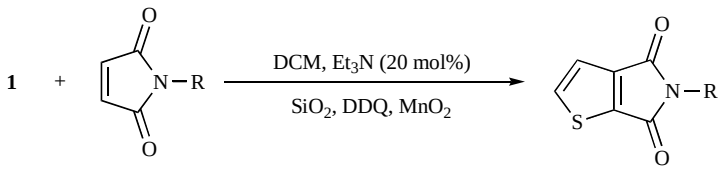
disubstituted thiophenes in yields range to 74% from 87% (Scheme **25**).

Other thiophenes resulting from cycloaddition reactions.

Shi *et al.* [49] also investigated [3+2] cycloaddition reactions to synthesize 2,3-thienoimide derivatives. They joined *N*-substituted imides and 1,4-DTD, yielding compounds in good yields (67-85%) (Scheme **26**).

Shi *et al.* [50] conducted a reaction between ynals and 1,4-DTD through [3+2] cycloaddition, leading to 3-aldehyde-2-substituted thiophenes in overall yields of 63–86% (Scheme **27**).

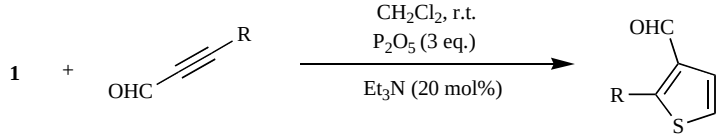
Sathishkannan and Srinivasan [51] also noted that 1,4-DTD could be used for the synthesis of tetrasubstituted thiophenes in cycloadditions [3+3] with cyclopropanes in moderate to good yield (55-82%) (Scheme **28**).



R = Ph; 85%
4-F-Ph; 82%
4-Cl-Ph; 80%
4-OMe-Ph; 76%
2-Br-Ph; 75%
2-F-Ph; 80%
2-Cl-Ph; 78%

R = 2-Me-Ph; 78%
2-OMe-Ph; 73%
3-F-Ph; 78%
2-Me, 4-Cl-Ph; 75%
alfa-naphthyl; 70%
cyclohexyl; 78%
pentyl; 67%

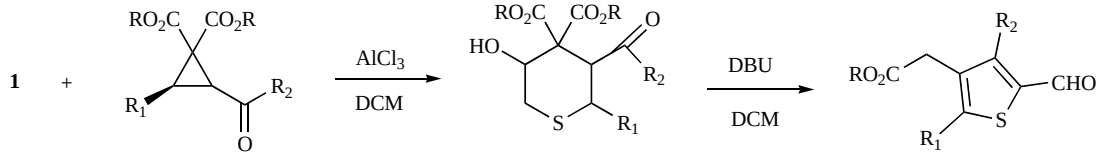
Scheme 26. 1,4-DTD in the synthesis of 2,3-thienoimide derivatives.



R = Ph; 86%
4-F-Ph; 77%
4-Cl-Ph; 76%
4-Br-Ph; 68%
4-Me-Ph; 73%
4-Ph; 70%

R = 4-OMe-Ph; 74%
4-tBu-Ph; 63%
2-Cl-Ph; 65%
2-thienyl; 67%
Butyl; 72%
Triethylsilane; 70%

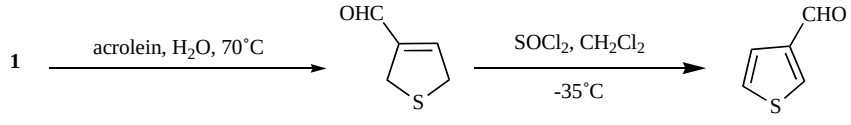
Scheme 27. Synthesis of 3-aldehyde-2-substituted thiophenes using ynals and 1,4-DTD.



R1, R2= Ph, Ph; 72%
4-Me-Ph, Ph; 74%
4-Cl-Ph, Ph; 77%
3-F-Ph, Ph; 63%
Ph, 4-Me-Ph; 68%
Ph, 4-OMe-Ph; 75%
Ph, 4-Cl-Ph; 73%

R1, R2 = 4-Cl-Ph, 4-Me-Ph;72%
4-OMe-Ph, 4-OMe-Ph; 71%
Ph, 2-thienyl; 78%
4-Cl-Ph, 2-thienyl; 82%
4-NO_2-Ph, 2-thienyl; 55%
Ph, Ph; 70%
Ph, 2-thienyl; 79%

Scheme 28. General structure of tetrasubstituted thiophenes obtained through cycloadditions [3+3].



92%

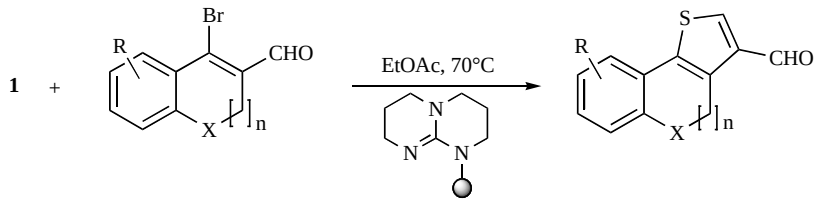
Scheme 29. Synthesis of 3-thiophene-carboxaldehyde.

Others authors have used aldehydes in their methodologies. Stuk and Huckabee [52] used an aldehyde acrolein to obtain 3-aldehyde-thiophenes. They reacted acrolein and 1,4-DTD generating 2,5-dihydro-thiophene-3-carbaldehyde. Reaction with thionyl chloride ($SOCl_2$) yielded 3-thiophenecarboxaldehyde (Scheme **29**).

Through the reaction between β-halo-α,β-unsaturated aldehydes and 1,4-DTD, Goswami *et al.* [1] synthesized polycyclic 2-formylthiophenes,. They used a variety of polymer-supported organic bases, where 1,5,7-triazabicyclo[4.4.0]dec-5-ene, bound to polystyrene, was proved to be more effective. The yields obtained varied from good to excellent (59-94%) (Scheme **30**).

An example of the use of DABCO and 1,4-DTD in thiophenes synthesis can be seen in the work of Bharathiraja and co-workers [53]. Tetra-substituted thiophenes were synthesized in good yields (46- 81%). The reactions were performed in chloroform medium at room temperature using some 1,3-enynes and 1,4-DTD (Scheme **31**).

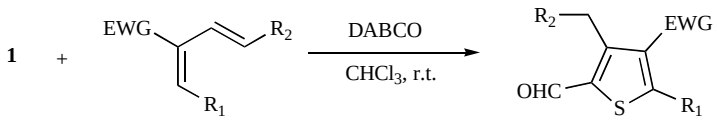
In another methodology using acetals, Kumara *et al.* [54] synthesized a series of 2-methylthio-3-aroyl thiophenes (Scheme **32**) using α-oxoketenedithioacetals as starting material and 1,4-DTD, in the presence of anhydrous potassium carbonate (K_2CO_3) in ethanol.



R, X, n = H, CH_2, 1; 89%
6-OMe, CH_2, 1; 93%
7-OMe, CH_2, 1; 87%
8-OMe, CH_2, 1; 81%
8-F, CH_2, 1; 90%

R, X, n = 6,8-OMe, CH_2, 1; 94%
6,8-Me, CH_2, 1; 87%
5-Me, CH_2, 1; 91%
H, CH_2, 2; 77%
H, O, 1; 78%
H, S, 1; 59%

Scheme 30. Synthesis of polycyclic 2-formyl thiophene.

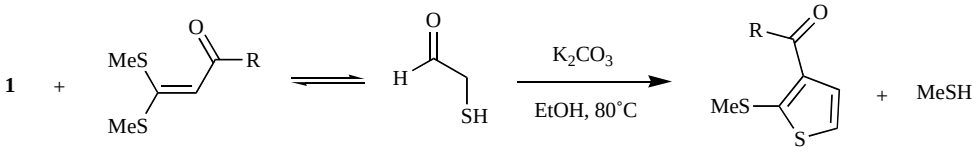


EWG = nitro, keto, ester

R_1, R_2= Ph, Ph; 71%
Ph, 4-Cl-Ph; 78%
Ph, 4-OMe-Ph; 66%
Ph,3,4-Me-Ph; 79%
Ph, 3,5-Me-Ph; 81%
Ph, alfa-naphthyl; 68%
Ph, cyclopropyl; 29%

R_1, R_2= 2-Me-Ph, Ph; 66%
3-Me-Ph, Ph; 73%
4-F-Ph, Ph; 74%
4-OMe-Ph, Ph; 69%
4-Me-Ph, Ph; 77%
alfa-naphthyl, Ph; 62%
4-Me-Ph, 3,4-Me2-Ph; 60%

Scheme 31. DABCO catalyzes reaction between 1,3-enynes and 1,4-DTD.



R= Ph; 60%
4-Me-Ph; 55%
4-OMe-Ph; 63%
3,4-OMe-Ph; 55%
2,4-OMe-Ph; 65%
4-F-Ph; 62%

R= 4-Br-Ph; 60%
4-Cl-Ph; 65%
alfa-naphthyl; 70%
beta-naphthyl; 66%
2-pyridyl; 50%
2-thienyl; 70%

Scheme 32. Synthesis of 2-methylthio-3-heteroaroyl thiophenes.

Aroyl-thiophenes were obtained in moderate to good yields (50-70%).

1.4. 1,4-DTD in the Synthesis of Other Sulfur-containing Heterocycles

1.4.1. Thiazol Derivatives

A variety of thiophene derivatives have been synthesized using 1,4-DTD as a precursor. Yet other heterocyclic rings (containing sulfur and other heteroatoms) can be synthesized using 1,4-DTD. Thiazol derivatives have been obtained by Kumar *et al*. [6] and Ciogli *et al.* [55].

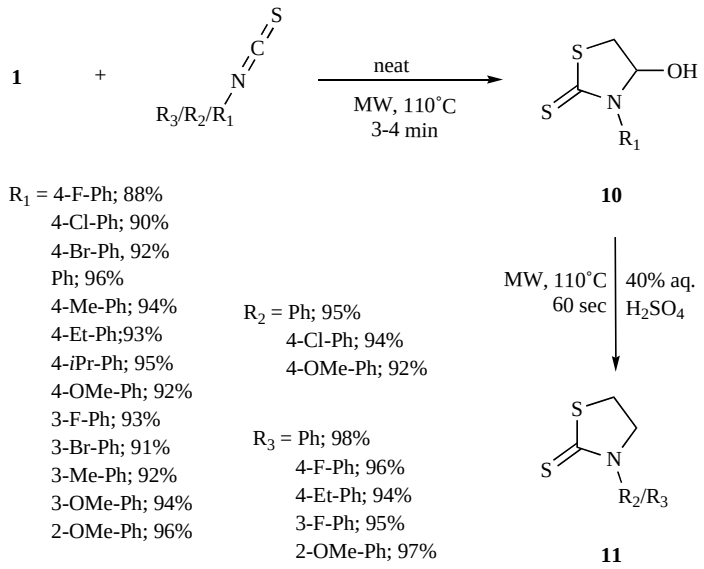
For the synthesis of 3-arylthiazolidine-2-thiones (**11**), 3-arylthiazol-2(3*H*)-one and 4-hydroxy-3-thiazolidine-2-thiones (**10**), Kumar *et al.* [6] used MW procedures under solvent and catalyst-free reactions, which yielded the desired compounds in excellent yields (88-98%) (Scheme **33**).

In the work of Ciogli *et al*. [55] the authors synthesized thiazol using MW. Synthesis of 4-hydroxy-3-arylthiazolidine-2-thione derivatives from isothiocyanate and 1,4-DTD, at 110°C, using 120 W of potency and 1 bar of pressure, for 3-4 minutes of irradiation, provided yields between 59–81% (Scheme **34**).

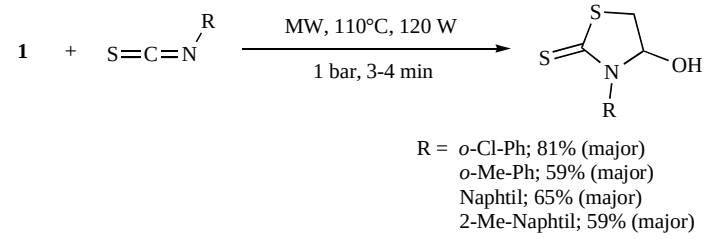
Mallia *et al.* [8] explored the synthesis of 2-substituted thiazoles *via* a blocked Gewald reaction. 1,4-DTD was reacted with several α-methine nitriles, where aromatic and ester moieties were varied. Blockage of the Gewald reactions was observed, and there was no formation of the expected 2-amino-thiophenes. The presence of an alkyl or aryl group adjacent to the nitrile, afforded 2-substituted thiazoles exclusively, which were obtained in yields ranging from 60 to 83% (Scheme **35**).

1.4.2. Six-membered Ring Heterocycles

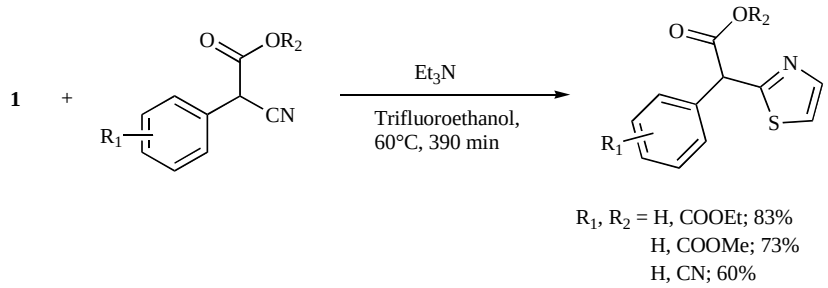
1,4-DTD is a flexible compound, able to participate in synthesis of various molecules, such as 5- and 6-membered heterocycles.



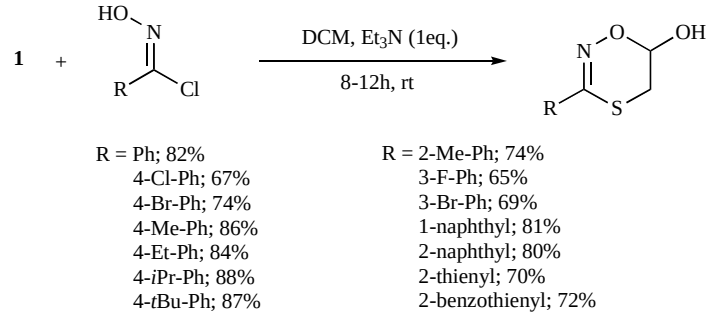
Scheme 33. Synthesis of 4-hydroxy-3-arylthiazolidine-2-thiones (**9**), and 3-arylthiazolidine-2-thiones (**10**).



Scheme 34. Synthesis of 4-hydroxy-3-arylthiazolidine-2-thiophene derivatives.



Scheme 35. Example of thiazole synthesis.

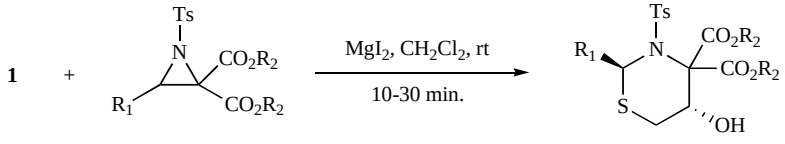


Scheme 36. Synthesis of 5,6-dihydro-1,2,4-oxathiazin-6-ols through a reaction between 1,4-DTD and hydroxyarylimidoyl chlorides.

Many authors employ 1,4-DTD to synthesize six-membered rings heterocycles: oxathiazines, thiazines, oxathianes, *etc.*

Kumar and Perumal [7] used 1,4-DTD to synthesize 3-aryl-5,6-dihydro-1,2,4-oxathiazin-6-ols. Heterocyclization using different *(E)-N*-hydroxyarylimidoyl chlorides was used in a domino reaction, affording 5,6-dihydro-1,2,4-oxathiazin-6-ols in good yields (65-88%) (Scheme **36**).

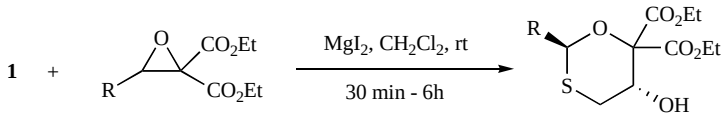
Another example of 1,4-DTD application 6-membered heterocycles rings can be seen in the synthesis of thiazines and oxathianes derivatives.



R_1, R_2 = *p*-NO_2-Ph, Et; 86%
p-CN-Ph, Et; 84%
p-F-Ph, Et; 81%
p-Cl-Ph, Et; 80%
p-Br-Ph, Et; 78%
o-Br-Ph, Et; 74%

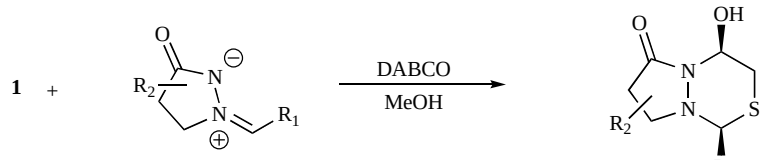
R_1, R_2 = Ph, Et; 70%
Naphtil, Et; 74%
p-Me-Ph, Et; 74%
p-NO_2, Me; 87%
p-NO_2-Ph, $_i$Pr; 83%
p-(isopropyl)-Ph, Et; 72%

Scheme 37. Synthesis of thiazines derivatives *via* [3+3] annulation.



R = Ph; 80%
p-Cl-Ph; 76%
p-NO_2-Ph; 74%
p-Me-Ph; 82%

Scheme 38. Synthesis of oxathianes *via* [3+3] annulation.



R_1, R_2= Ph, H; 93%
o-Me-Ph, H; 83%
m-Me-Ph, H; 86%
p-Me-Ph, H; 92%
o-Cl-Ph, H; 82%
m-Cl-Ph, H; 85%
p-Br-Ph, H; 87%
p-CN-Ph, H; 90%

R_1, R_2= 2-naphthyl, H; 88%
(*E*)-styryl, H; 80%
2-furyl, H; 75%
3-pyridyl, H; 96%
n-pentyl, H; 89%
Ph, 4,4-dimethyl; 86%
Ph, 5-Me; 80%
Ph, 5-Ph; 89%

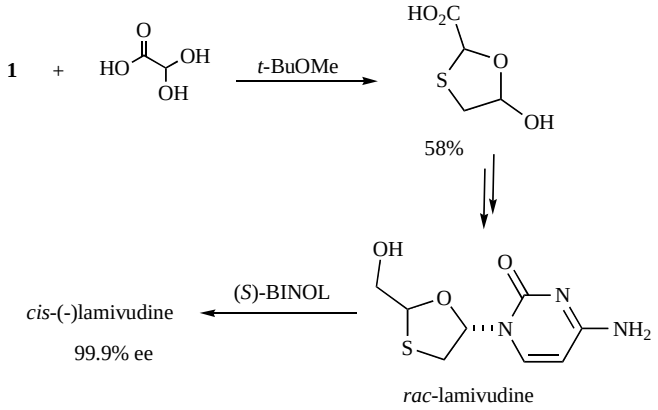
Scheme 39. Synthesis of six-membered di-nitrogen-fused heterocycles.

Varshnaya and Banerjee [56] performed synthesis of thiazines and oxathianes derivatives *via* [3+3] annulation, utilizing of *N*-tosylaziridinedicarboxylates or oxiranes and 1,4-DTD, in the presence of a Lewis acid (MgI_2) in dichloromethane, at room temperature. The products were obtained in good yields, varying from 70-87%, for the first class of reactions (Scheme **37**), and from 74-82% for the second reaction (Scheme **38**).

Application of 1,4-DTD to obtain of six-membered di-nitrogen-fused heterocycles was explored by Fang and coauthors [57]. The authors used 1,4-DTD in [3+3] cycloaddition reactions with azomethine imines, using DABCO as a catalyst to obtain six-membered di-nitrogen-fused heterocycles in excellent yields (up to 96%) and high diastereoselectivity (Scheme **39**).

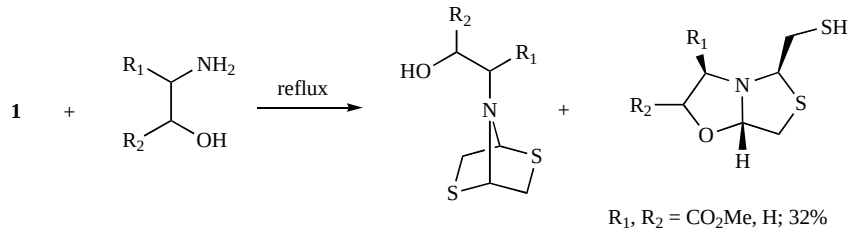
1.3. Applications of 1,4-DTD for the Synthesis of Bioactive Compounds

Lamivudine is an antiretroviral drug (used in the anti-HIV cocktail) which acts by inhibiting the synthesis of viral nucleic acids. A synthetic route for lamivudine, proposed by Jin *et al.* [13] started with the synthesis of the oxathiolane ring, which was obtained through an acetal exchange reaction between 1,4-DTD and glyoxylic acid. The steps involve followed: alcohol acetylation, esterification of the acid with (-)-*L*-menthol (for separation of the two diastereoisomers), and coupling with *bis*-TBDMS-cytosine, followed by reduction of the menthyl ester. For large scale racemate resolution, Roy *et al.* [58] proposed the use of (*S*)-BINOL as the co-crystallization agent to crystallize with the *cis*-(-)-lamivudine (Scheme **40**).

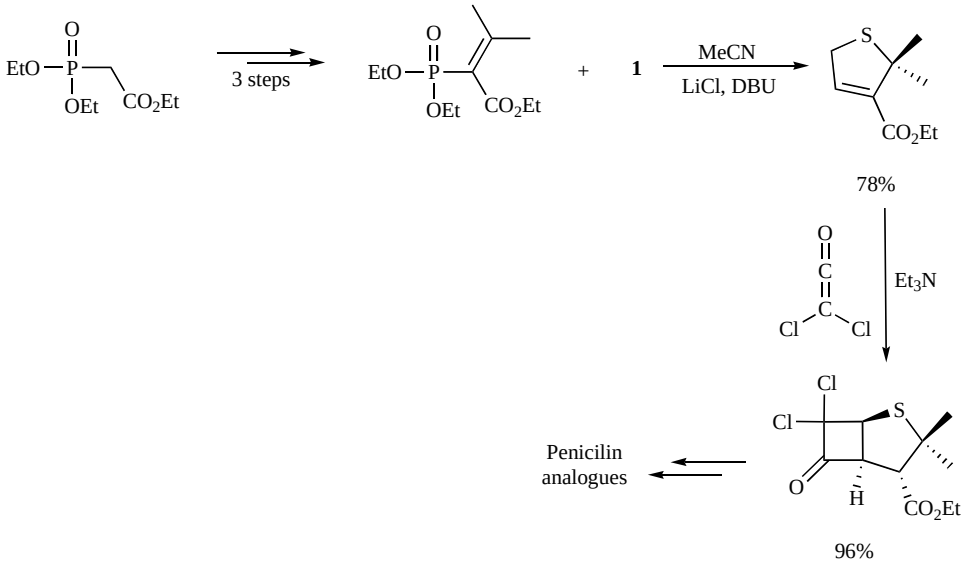


Scheme 40. Synthesis of the anti-HIV *cis*-(−)-lamivudine.

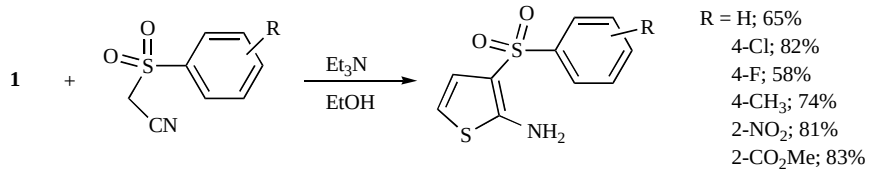
Saiz *et al.* [11] explored the synthesis of new oxazolidinylthiazolidines bicycles and/or dithioazabicycles and their activities against Metallo-*β*-lactamase NDM-1. Several reaction conditions were explored aiming at stereoselective production of the isomeric heterocycles (oxazolidinylthiazolidines and dithioazabicycles), formed during the reaction between 1,4-DTD and β-amino alcohols in one pot reactions (Scheme **41**). Among the various reaction conditions, the use of an acetate buffer at pH 5, resulted in the formation (in good yields) of only one of the heterocycles. However, it is the nature of the amino alcohol substituents (R^1 and R^2) used in the reactions, that selects which isomer will be formed. The



Scheme 41. Synthesis of oxazolidinylthiazolidines derivatives active against metallo-*β*-lactamase NDM-1.



Scheme 42. Synthesis of penicillin analogues.



Scheme 43. 2-Aminothiophene derivatives with antiviral and antitumor activities.

oxazolidinylthiazolidine 4f (with R^1 = CO_2Me and R^2 = hydrogen) was found effective against Metallo-β-lactamase NDM-1, demonstrating to be a competitive inhibitor, with a K_i value = 1.6 μM. The probable mechanism of action occurs through the formation of complexes in the active site of the enzyme between the thiol moiety and the two Zn(II) ions, the carboxylate groups interact with the Lys224 residue, providing in a strong interaction.

Ferguson *et al.* [14] developed a synthetic route using 1,4-DTD that allows for the synthesis of cyclobutanone analogues of penicillin (antibiotic). 1,4-DTD was used in the fourth step of the synthesis to obtain the dihydrothiophene nucleus through a modified Horner-Wadsworth-Emmons cyclization in 78% yield, from a procedure previously described by Martyres *et al.* [59]. The bicyclic structure used as a precursor for the synthesis of penicillin analogues was obtained at a yield of 96% by a [2+2] cycloaddition between dihydrothiophene and dichloroketene (Scheme **42**).

Stephens *et al.* [12] synthesized and evaluated the antiviral and antitumor activities of 2-amino-3-(arylsulfonyl)thiophenes. The compounds were synthesized through Gewald conditions [19] using a substituted (arylsulfonyl)acetonitrile with 1,4-DTD (Scheme **43**). Some of the 2-AT synthesized exhibited moderate activities against the cytopathic effects of HIV-1 and HIV-2 in human T-lymphocyte (CEM/0) cells. 2-amino-3-(2-nitro-phenylsulfonyl)thiophene was the most potent and selective, with an EC_{50} of 3.83 mg/mL and a CC_{50} >100mg/mL.

Inamori *et al.* [15] studied phytogrowth-inhibitory activity in 2,5-dihydroxy-1,4-dithiane and dithiane-related compounds (Chart **3**) against two plant species: *Brassica rapa L.* and *Medicago sativa*. It was observed that all of the compounds were able to inhibit the growth of the two plants, being the 2,5-diacetoxy-2,5-dimethyl-1,4-dithiane (**12**) the most active inhibiting growth at a concentration of 1.0×10^{-4} M.

Tranberg *et al.* [60] in order to provide information concerning the structure-activity relationship, and the importance of substituents at C-3, C-4 and C-5 positions for the allosteric enhancement (AE) of agonist activity at the A1 adenosine receptor, synthesized several series of 2-amino-3-aroylthiophenes. Unsubstituted C-4 and C-5 thiophene derivatives were synthesized by reaction of 1,4-DTD with aroylacetonitriles (Scheme **44**). However, none of these derivatives were active, evidence that the presence of radicals or groups at C-4, C-5 positions are essential for the AE activity.

Gütschow and Neumann [10] synthesized a series of thieno[2,3-*d*][1,3]oxazin-4-one (**13**) inhibitors of human leukocyte elastase. The first synthetic step involved the Gewald reaction using 1,4-DTD. The reaction of the Gewald adult with alkyl chloroformates was followed by reaction with a mixture of trifluoroacetic acid

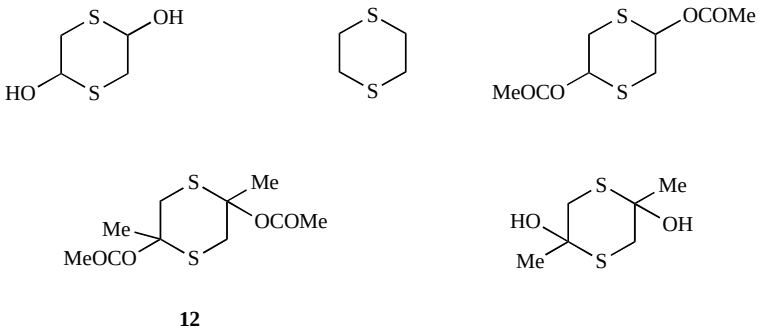


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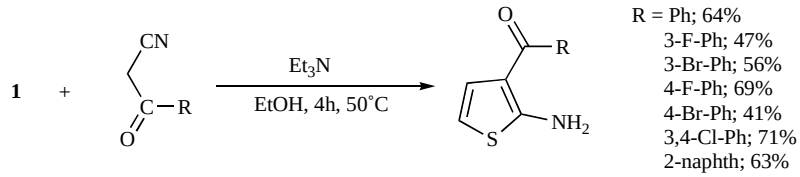
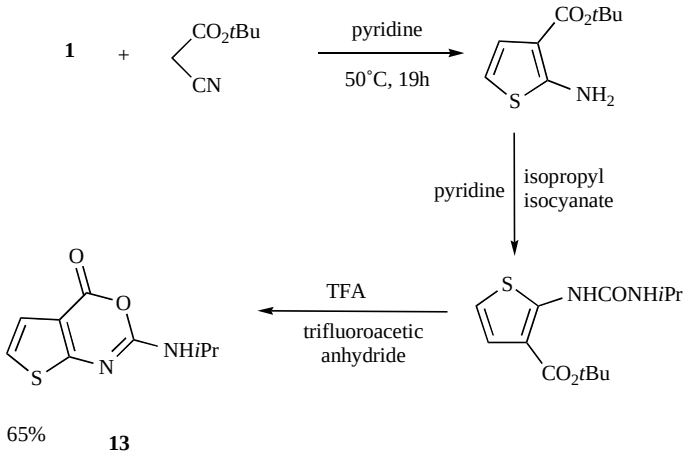
Chart 3. 1,4-Dithianes with phytogrowth-inhibitory activity.



Scheme 44. 2-amino-3-aroylthiophenes agonist allosteric enhancers at Human A1 adenosine receptors.



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Scheme 45. Synthesis of thieno[2,3-*d*][1,3]oxazin-4-one (**13**) derivatives - potent inhibitors of human leukocyte elastase.

(TFA) and trifluoroacetic anhydride and resulted in thieno[2,3-*d*][1,3]oxazin-4-ones (Scheme **45**). *In vitro* evaluation of their inhibitory activity against human leukocyte elastase indicated that the presence of ethoxy, *n*-propoxy, and ethylthio radicals at C-2 delivers the most potent leukocyte elastase inhibition activity of the series with Ki values lower than 11 nM.

CONCLUSION

In summary, we have described various reactions and chemical applications for obtaining functionalized sulfur-containing heterocycles such as 2-amino-thiophenes, thiazolidines, oxathiazinoles and thiazoles, all from the use of mercaptoacetaldehyde dimer (1,4-dithiane-2,5-diols) as a common, versatile and convenient synthon. The use of these heterocyclic compounds in subsequent chemical reactions allows synthesize various and potent bioactive compounds.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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

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