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Iranian Chemical Communication
Original Research Article
Payame Noor University http://icc.journals.pnu.ac.ir

One-pot synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines using homogeneous catalyst under solvent-free conditions

Asadollah Farhadi*, Mohammad Ali Takassi, Lila Hejazi

Petroleum University of Technology, Faculty of Science, Ahwaz, Iran, 61981-44471

Received: 26 December 2015, Accepted: 9 April 2016, Published: 9 April 2016

Abstract

Synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidine derivative was reported via P. Biginelli three-component condensation reaction. This work reports on the preparation of 2-oxo-1,2,3,4-tetrahydropyrimidines using the NaF as catalyst. One-pot condensation reactions were carried out for various aryl aldehydes, ethyl acetoacetate, acetyl acetone and urea under solvent-free conditions at 100 °C and afforded the target molecules in good to excellent yields. Furthermore, this reaction was examined in various solvents such as EtOH, CH_3CN, H_2O andis DMSO. Compared with classical Biginelli reaction conditions, this method has the advantage of high yields of product and shorter reaction times. Since this catalyst is very soluble in the water, however separation of this catalyst is very comfortable. At the same conditions, the time three-component condensation reaction for acetylacetone reactant is shorter then ethyl acetoacetate reactant and the yields of two groups are close together. However, according to the experimental data, we have proposed the suitable mechanism for this reaction.

Keywords: Solvent-free; NaF; catalyst; 2-oxo-1,2,3,4-tetrahydropyrimidines; Biginelli reaction; mechanism.

Introduction

The chemistry of hydropyrimidiens has developed since 1893 [1]; when the first compound of this type was reported by P. Biginelli. Several effective catalytic and non-catalytic

*Corresponding author: Asadollah Farhadi
Tel: +98 (61) 35551321, Fax: +98 (61) 35551321
E-mail: farhadichem@put.ac.ir

strategies were proposed to produce Biginelli-type products [2-4]. The suggested catalysts used in these approaches are often expensive, harmful and ineffective in the absence of acidic additives.

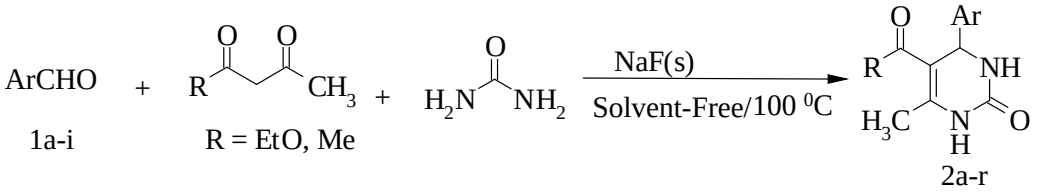
Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry for various reasons [5]. Regarding the above statement it is worth mentioning that MCR that belongs to the latter category is the venerable Biginelli dihydropyrimidine synthesis. This method has been reported on the acid-catalyzed cyclocondensation reaction of an aldehyde, a β-ketoester, and urea (or thiourea), a procedure known as the Biginelli reaction [1], is receiving increased attention. In recent decades, many improved procedures for synthesis of Biginelli compounds have been reported [6-8]. Many of these procedures require a large excess of reagents, long reaction times and drastic reaction conditions. Furthermore, they do not consider to the adverse effects of solvents and catalysts on the environment [9,10].

These compounds exhibit broad range of therapeutic and pharmacological properties, namely anticancer, antihypertensive, antiviral, and antifungal. 2-Oxo-1,2,3,4-tetrahydropyrimidines derivatives which are found as core units in many marine alkaloids, have been found to be potent HIV gp-120CD_4 inhibitors [11-17].

Dehydrogenation of 2-oxo-1,2,3,4-tetrahydropyrimidines is an important method for the preparation of pyrimidine derivatives. Because pyrimidine cores with extended π-systems have interesting fluorescence properties and similar compounds are useful in the development of advanced electronic and photonic materials [16].

In this context, we present the practical method for synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidine depicted in scheme 1.

Reactions with such reagents and catalysts often have the advantages such as ease of set-up and operation, mild reaction conditions and increased yield.



Scheme 1. One-pot synthesis of some 2-oxo-1,2,3,4-tetrahydropyrimidines

Results and discussion

In a model reaction, the reaction of equivalent amounts of benzaldehyde 1a, ethyl acetoacetate (EAA) and urea in the presence of catalytic amount of the sodium fluoride catalyst was studied (Scheme 1). The effect of different factors including solvents, reaction temperature, amount of catalyst and reaction time was examined. The results have been summarized in Table 1.

The reaction was studied in different solvents such as EtOH, CH_3CN, H_2O and DMSO. In the presence of solvents, reaction was sluggish and the lower yields were observed.

However, ethyl acetoacetate (EAA, 2 mmol), aldehyde (2 mmol) and urea (2 mmol) were mixed with sodium fluoride (0.1 mmol) and heated at 100°C under solvent-free conditions for two hours. This condition reaction has the best yield and lower reaction time.

Table 1. Synthesis of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-carboxylate **2a** in various conditions

Entry	**Solvent**	**Catalyst**	**EAA:NaF (mmol)**	**T (°C)**	**Time (h)[a]**	**Yield (%)[b]**
1	EtOH	NaF	2:0.2	reflux	2	80
2	EtOH	NaF	2:0.05	reflux	2	55
3	EtOH	NaF	2:0.1	reflux	2	80
4	EtOH	NaF	2:0.1	r.t.	20	40

5	EtOH	NaF	2:0.1	60	6	60
6	EtOH	NaF	2:0.1	140	2	85
7	CH_3CN	NaF	2:0.1	reflux	2	65
8	DMSO	NaF	2:0.1	100	4	46
9	H_2O	NaF	2:0.1	reflux	2	23
10	solvent-free	NaF	2:0.1	100	2	85
11	solvent-free	NaF	2:0.1	50	3	30
12	solvent-free	NaF	2:0.1	r.t.	4	25
13	solvent-free	NaF	2:0.1	140	2	85

[a]Times are given after maximum progression of reaction. [b] Isolated yield.

Having established the reaction conditions, various 2-oxo-1,2,3,4-tetrahydropyrimidines were synthesized in excellent yields through the reaction of different aldehydes, ethyl acetoacetate or acetylacetone and urea. The results have been summarized in Table 2.

Table 2. Scope and yields of the NaF-catalyzed synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines

Comp.	**R**	**Ar**	**Time (min)**	**Yield (%)[a]**	**Observed m.p.**	**Reported m.p.**	**Ref.**
2a	EtO	C_6H_5-	120	90	204-206	204-206	[8]
2b	EtO	4-$MeOC_6H_4$-	100	85	203-205	201-205	[8]
2c	EtO	3-$MeOC_6H_4$-	80	90	209-211	207-209	[8]
2d	EtO	2-$MeOC_6H_4$-	60	85	262-263	262-263	[8]

2e	EtO	4-ClC_6H_4-	100	80	213-215	210-212	[17]
2f	EtO	3-ClC_6H_4-	15	95	197-198	197-198	[8]
2g	EtO	2-ClC_6H_4-	60	75	218-219	218-219	[8]
2h	EtO	4-$NO_2C_6H_4$-	120	70	207-208	207-208	[8]
2i	EtO	4-$NO_2C_6H_4$-	120	75	226-228	226-227	[8]
2j	Me	C_6H_5-	90	80	232-236	228-230	[18]
2k	Me	4-$MeOC_6H_4$-	90	85	169-170	170-172	[19]
2l	Me	3-$MeOC_6H_4$-	90	90	225-227	226-228	[18]
2m	Me	2-$MeOC_6H_4$-	45	85	250-252	250-252	[18]
2n	Me	4-ClC_6H_4-	90	75	220-221	223-224	[20]
2o	Me	3-ClC_6H_4-	45	90	282-284	285-287	[18]
2p	Me	2-ClC_6H_4-	45	70	263-265	262-264	[18]
2q	Me	4-$NO_2C_6H_4$-	90	70	228 (dec.)	229-230	[18]
2r	Me	3-$NO_2C_6H_4$-	90	75	286-288	286-288	[18]

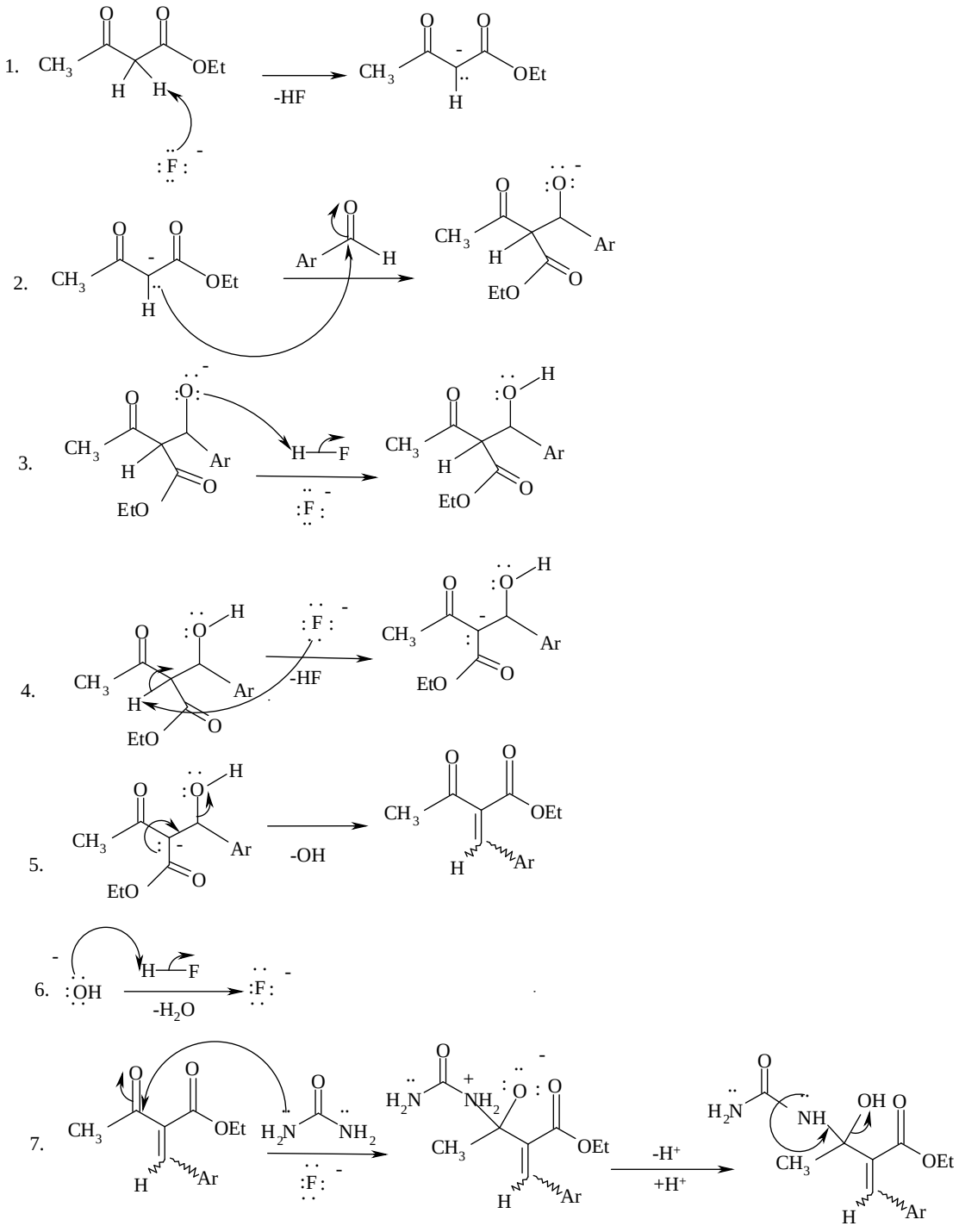
[a]Isolated yield

Mechanism

The time of reaction and the yield of product for ethyl acetoacetate and acetylacetone are different. Therefore, we believe these differences are due to resonance and steric hindrance. However, we believe that in the beginning 1, 3-diketone converts to anion form (step 1). In the next step it was attached to the functional group of aldehyde (step 2). An acid base reaction occurred in step 3. At steps 4 and 5, benzylidene compound was generated by condensation reaction. At the final steps, this compound was reacted to

urea or thiourea to produce the 2-oxo-1,2,3,4-tetrahydropyrimidine.

According to the data reported in table 2, one can propose the following mechanism.



Scheme 2. Proposed conceivable mechanism for this method

Experimental

Materials and instrumentation

All of the substrates and reagents were purchased from Merk and Sigma Aldrich. Melting points were determined on an IA9200 apparatus and are uncorrected. IR spectra were recorded from KBr discs on a Shimadzu apparatus IR 435. ^{1}H NMR spectra were recorded using a Bruker 300 MHz instrument. They are reported as follows: chemical shifts, multiplicity, coupling constants *J* (Hz), number of protons, and assignment. Mass spectra were obtained on a Platform II spectrometer from Micromass; EI mode at 70 eV. UV spectra (in CH_3CN) were taken with a Shimadzu UV-160 spectrometer.

General procedure for synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines

A mixture of aldehyde (**1a-i**, 2 mmol), 1,3-dicarbonyl compound (2 mmol), urea (2 mmol) and NaF (0.1 mmol) under solvent-free condition was heated in a round bottom flask with the magnetic stirring and dipped in preheated oil bath at 100 °C (bath temperature). The contests were stirring to complete the reaction. TLC monitoring of the reaction using *n*-hexane/ethyl acetate (4:1) as eluent was followed until total disappearance of the 1,3-dicarbonyl compounds was observed. The results are reported in table 2. After cooling to room temperature, the mixture was stirred with cold water (10 mL) for 30 minutes and then the white and yellow precipitate was filtered. The crude product was recrystallized from EtOH.

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidinine-5-carboxylate (2b)

White solid; M.p. 203-205^{o}C; UV/vis (CH_3CN), λ_{max} (log ε_{max}): 274 nm (3.47), 230 (3.75); IR (KBr), ν, cm^{-1}: 1725 ($CO_2C_2H_5$), 1700 (2-CO), 1650 (C=C); ^{1}H NMR (DMSO-d_6), δ 1.10 (t, *J* = 7.08 Hz, 3H, OCH_2CH_3), 2.23 (s, 3H, CCH_3), 3.71 (s, 3H, OCH_3), 3.97 (q, *J* = 7.07 Hz, 2H, OCH_2CH_3), 5.09 (d, *J* = 2.9 Hz, 1H, CCHNH), 6.87 (d, *J* = 8.5 Hz, 2H, Ar), 7.14 (d, *J* = 8.5 Hz, 2H, Ar), 7.66 (s, 1H, NH), 9.15 (s, 1H, NH).

Ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2h)

Yellow solid; M.p. 207-208^{o}C; UV/vis (CH_3CN), λ_{max} (log ε_{max}): 264 nm (3.31), 225 (3.17); IR (KBr), ν, cm^{-1}:

1725 ($CO_2C_2H_5$), 1700 (2-CO), 1640 (C=C); ^{1}H NMR (DMSO-d_6), δ 1.09 (t, *J* = 6.90 Hz, 3H, OCH_2CH_3), 2.26 (s, 3H, CCH_3), 3.98 (q, *J* = 7.20 Hz, 2H, OCH_2CH_3), 5.27 (d, 1H, *J* = 3.30 Hz, CC*H*NH), 7.49–7.52 (m, 2H, Ar), 7.89 (s, 1H, N*H*), 8.20–8.23 (m, 2H, Ar), 9.36 (s, 1H, N*H*).

Conclusion

An efficient and mild methodology has been developed for the synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidine. The reaction was carried out as one pot three-component reaction. In this reaction ethyl acetoacetate or acetylacetone was reacted with aryl aldehyde, and urea under solvent-free condition using NaF catalyst. NaF catalyst when compared to other catalysts (*n*-BuLi, $Co(NO_3)_2.6H_2O/K_2S_2O_8$, Copper(II) Sulfamate, nano ZrO_2, ….) is inexpensive and commercially available. The other advantages of this method are high isolated yield, easily remove of catalyst and high purity of products.

Acknowledgments

We would like to acknowledge the Petroleum University of Technology's Research council for their financial support.

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