

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

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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, CH₃CN, H₂O and 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 than 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 hydroxyrimidines has developed since 1893 [1]; when the first compound of this type was reported by P. Biginelli. Several effective catalytic and non-catalytic 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

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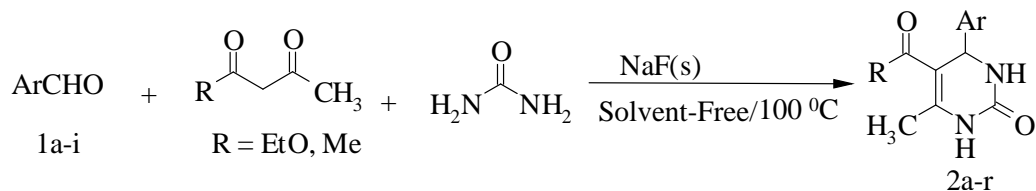
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drastic reaction conditions. Furthermore, they do not consider to the adverse effects of solvents and catalysts on the environment [9,10].

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-120CD₄ inhibitors [11-17].

Dehydrogenation of 2-oxo-1,2,3,4-tetrahydropyrimidines is an important



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.

method for the preparation of pyrimidine derivatives. Because pyrimidine cores with extended - 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.

The reaction was studied in different solvents such as EtOH, CH₃CN, H₂O 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 ₃ CN	NaF	2:0.1	reflux	2	65
8	DMSO	NaF	2:0.1	100	4	46
9	H ₂ O	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

^aTimes are given after maximum progression of reaction. ^bIsolated 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 ₆ H ₅ -	120	90	204-206	204-206	[8]
2b	EtO	4-MeOC ₆ H ₄ -	100	85	203-205	201-205	[8]
2c	EtO	3-MeOC ₆ H ₄ -	80	90	209-211	207-209	[8]
2d	EtO	2-MeOC ₆ H ₄ -	60	85	262-263	262-263	[8]
2e	EtO	4-ClC ₆ H ₄ -	100	80	213-215	210-212	[17]
2f	EtO	3-ClC ₆ H ₄ -	15	95	197-198	197-198	[8]
2g	EtO	2-ClC ₆ H ₄ -	60	75	218-219	218-219	[8]
2h	EtO	4-NO ₂ C ₆ H ₄ -	120	70	207-208	207-208	[8]
2i	EtO	4-NO ₂ C ₆ H ₄ -	120	75	226-228	226-227	[8]

2j	Me	C ₆ H ₅ -	90	80	232-236	228-230	[18]
2k	Me	4-MeOC ₆ H ₄ -	90	85	169-170	170-172	[19]
2l	Me	3-MeOC ₆ H ₄ -	90	90	225-227	226-228	[18]
2m	Me	2-MeOC ₆ H ₄ -	45	85	250-252	250-252	[18]
2n	Me	4-ClC ₆ H ₄ -	90	75	220-221	223-224	[20]
2o	Me	3-ClC ₆ H ₄ -	45	90	282-284	285-287	[18]
2p	Me	2-ClC ₆ H ₄ -	45	70	263-265	262-264	[18]
2q	Me	4-NO ₂ C ₆ H ₄ -	90	70	228 (dec.)	229-230	[18]
2r	Me	3-NO ₂ C ₆ H ₄ -	90	75	286-288	286-288	[18]

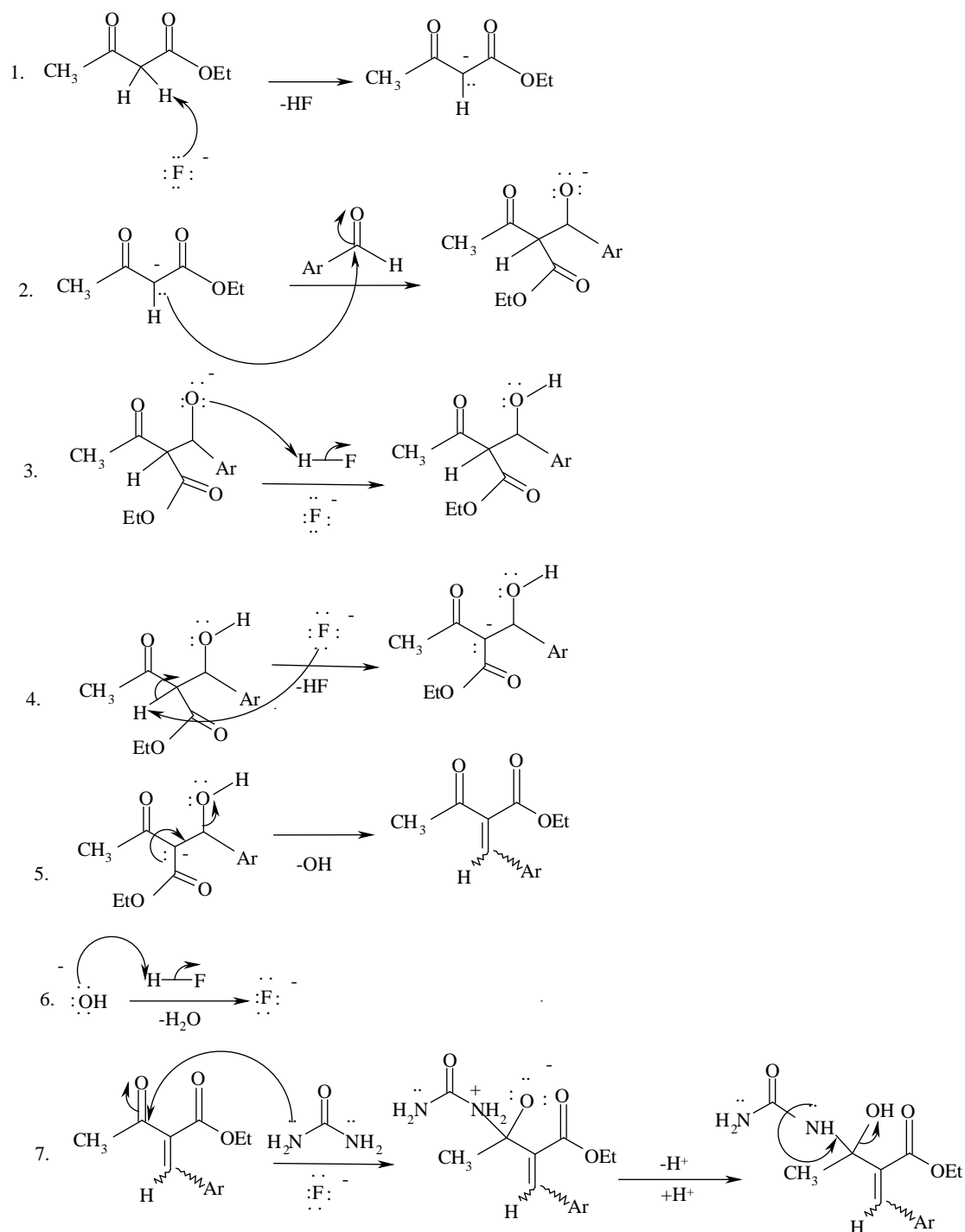
^aIsolated yield

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 Merck 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. ^1H 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 CH₃CN) 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 contents 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-tetrahydropyrimidine-5-carboxylate (**2b**)

White solid; M.p. 203-205°C; UV/vis (CH₃CN), λ_{\max} (log ϵ_{\max}): 274 nm (3.47), 230 (3.75); IR (KBr), ν , cm⁻¹: 1725 (CO₂C₂H₅), 1700 (2-CO), 1650 (C=C); ¹H NMR (DMSO-d₆), 1.10 (t, J = 7.08 Hz, 3H, OCH₂CH₃), 2.23 (s, 3H, CCH₃), 3.71 (s, 3H, OCH₃), 3.97 (q, J = 7.07 Hz, 2H, OCH₂CH₃), 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°C; UV/vis (CH₃CN), λ_{\max} (log ϵ_{\max}): 264 nm (3.31), 225 (3.17); IR (KBr), ν , cm⁻¹: 1725 (CO₂C₂H₅), 1700 (2-CO), 1640 (C=C); ¹H NMR (DMSO-d₆), 1.09 (t, J = 6.90 Hz, 3H, OCH₂CH₃), 2.26 (s, 3H, CCH₃), 3.98 (q, J = 7.20 Hz, 2H, OCH₂CH₃), 5.27 (d, 1H, J = 3.30 Hz, CCHNH), 7.49–7.52 (m, 2H, Ar), 7.89 (s, 1H, NH), 8.20–8.23 (m, 2H, Ar), 9.36 (s, 1H, NH).

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(NO₃)₂·6H₂O/K₂S₂O₈, Copper(II) Sulfamate, nano ZrO₂, ...) is inexpensive and commercially available. The other advantages of this method are high isolated yield, easily remove of catalyst and high purity of products.

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