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DABCO AS A MILD AND EFFICIENT CATALYST FOR THE SYNTHESIS OF TETRAHYDROPYRIMIDINES

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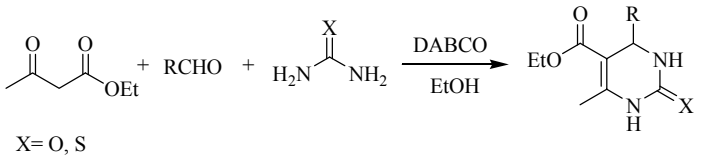
Tetrahydropyrimidine derivatives have been synthesized in good to high yields through an efficient and one-pot condensation reaction of aldehydes, ethyl acetoacetate and urea (thiourea) using 1,4-diazabicyclo[2.2.2]octane (DABCO) as an inexpensive, eco-friendly, high reactive, easy to handle and non-toxic base catalyst in ethanol under reflux conditions. Compared with the classical Biginelli reaction conditions, this new procedure has the advantage of high yields and short reaction times.



INTRODUCTION

Multicomponent reactions (MCRs) have received considerable attention and are known as some of the most important reactions in organic and medicinal chemistry.[1] A MCR is a domino process, in which three or more different molecules are reacted together in a single process to produce a new product without the isolation of the intermediates, where all or most of the atoms contribute to the structure of new product. The Biginelli reaction[3] is one of the most useful examples of MCRs, which have gained increasing importance in organic synthesis and medicinal chemistry due to their capacity for preparation of multifunctionalized compounds including tetrahydropyrimidines, their thiones analogs and other related heterocyclic compounds.

By the Biginelli condensation many tetrahydropyrimidines have been synthesized to exhibit a wide range of pharmacological activities such as calcium channel modulation,[3] anticancer,[4] antiviral,[5] antibacterial and antifungal activity.[6] Moreover, several alkaloids containing the pyrimidine core unit have been isolated from marine sources, which also exhibit interesting biological activities.[7]

Recently, special interest has been focused on Biginelli reaction and several synthetic procedures have been reported for preparation of tetrahydropyrimidines. For these reasons there is a variety of suitable reaction conditions, traditionally with strong Brönsted acid, but recently, several other methods indicate the use of lanthanide compounds,[8] Lewis acids such as LiBr,[9] NH_4Cl,[10] $NiCl_2.6H_2O$,[11] $CuCl_2.2H_2O$,[12] $CeCl_3.7H_2O$,[13] $Mn(OAc)_3.2H_2O$,[14] $ZrCl_4$,[15] $InCl_3$,[16] $ZnCl_2$,[17] $LiClO_4$,[18] $Zn(OTf)_2$,[19] $Al(HSO_4)_3$,[20] can overcome the drawback of the classical Biginelli reaction.

1,4-Diazabicyclo[2.2.2]octane (DABCO) is known as an inexpensive, eco-friendly, high reactive, easy to handle and non-toxic base catalyst for various organic transformations,[21] affording the corresponding products in good to excellent yields with high selectivity.

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RESULTS AND DISCUSSION

In connection with our ongoing work on multi-component reactions (MCRs)[22] and synthesis of pyrimidines,[23-25] we wish to report a facile and rapid one-pot three component procedure for the preparation of tetrahydropyrimidines with 1,4-diazabicyclo[2.2.2]octane (DABCO) as a non-toxic, inexpensive and easily available reagent, under reflux conditions (Scheme 1).

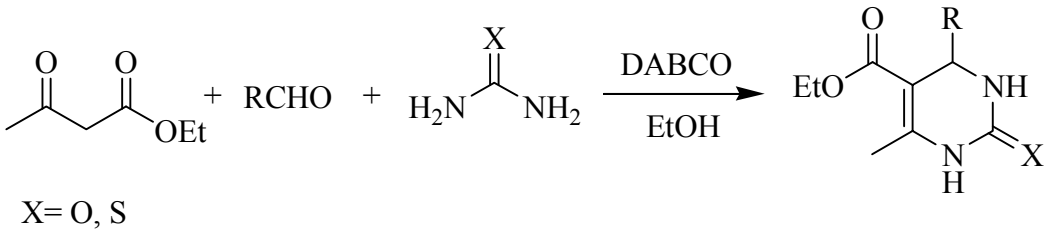
For the primarily study, under environmentally benign conditions, first we chose benzaldehyde and ethyl acetoacetate as a simple model for the reaction with urea and the influence of amount of DABCO on the yield of corresponding DHPM, discovered by a simple optimization study (Table 1).

We selected the ethanol after the examination of the same reaction under the similar conditions using different solvents including dichloro-methane, ethanol, tetrahydrofuran, acetonitrile, toluene and 1,4-dioxane (Table 1). The desired product was obtained in 48%, 92%, 73%, 84%, 66% and 85% yields, respectively. Ethanol was thus found to be the solvent of choice.

To explore the generality of the reaction, we extended our study using DABCO as a catalyst under reflux condition with different aromatic aldehydes to prepare a series of tetrahydropyrimidines (Table 2). Various aromatic aldehydes bearing electron-withdrawing groups (such as nitro, halide), electron-releasing groups (such as methyl, methoxy) show equal ease towards the product formation in good to high yields.

Encouraged by the successful condensation of aldehydes, ethyl acetoacetate and urea under reflux condition, we further studied the reaction of aldehydes, and ethyl acetoacetate with thiourea under similar conditions. It was found that the corresponding tetrahydropyrimidines could also be obtained in good to high yields without any difficulty (Table 2). This environmentally benign and clean synthetic procedure offers some advantages, such as high yields, short reaction times and easy workup, which is comparable to previously reported methods.[8-20]

Biginelli reaction is a typically acid-catalysed reaction. However, it is known that DABCO, a basic catalyst, may catalyze the reaction of a carbonyl group with a nucleophile.[34] The first step of this reaction involves the condensation of ethyl acetoacetate and aldehyde to give **3**, which followed by nucleophilic attack of urea or thiourea on intermediate **4** to give **5**, which after cyclization and loss of one molecule of water produce tetrahydropyrimidine **6**. DABCO probably facilitates this reaction by formation of enol form **2**, or making OH group as a good leaving group as shown in Scheme 2.



X= O, S

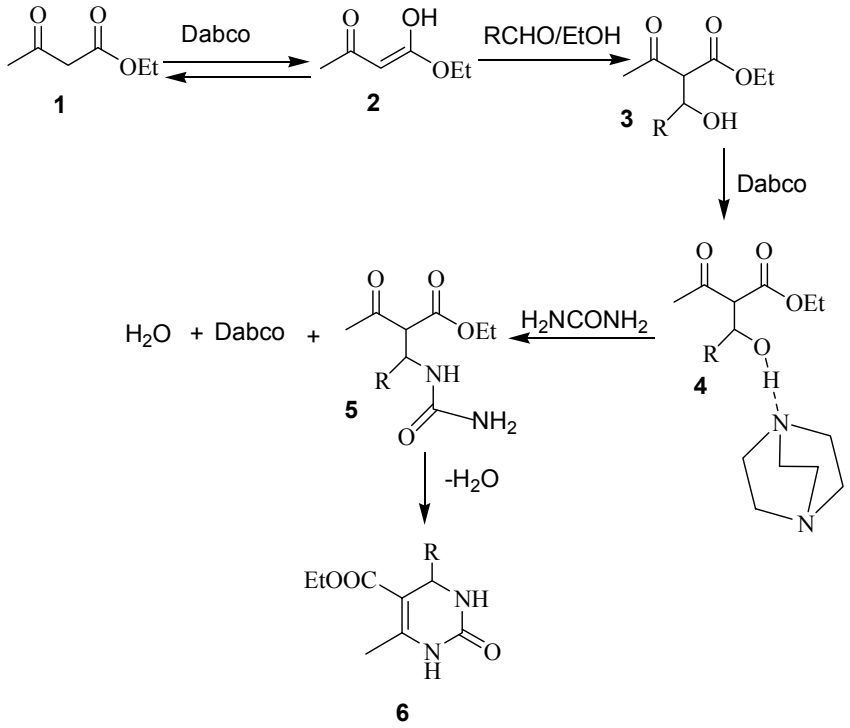
Scheme 1 – The synthetic pathway for synthesis of tetrahydropyrimidines in the presence of DABCO.

Table 1

Optimization of Biginelli reaction conditions in the presence of DABCO

Entry	Solvent	DABCO (mol%)	Time (min)	Yield (%)[a]
1	CH_2Cl_2	10	4	48
2	C_2H_5OH	10	120	92
3	THF	10	120	73
4	CH_3CN	10	120	84
5	Toluene	10	6	66
6	1,4-dioxane	10	120	85
7	C_2H_5OH	5	15	86
8	C_2H_5OH	20	15	88

[a] Isolated yields



Scheme 2 – The possible mechanism for synthesis of tetrahydropyrimidines in the presence of DABCO as a catalyst.

Table 2

Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones derivatives using DABCO as a catalyst

Entry	R	X	Time/min	Yield/%[a]	Mp (°C)	
					Found	Reported [lit.]
1	4-$MeOC_6H_4$	O	15	91	248-250	247-248 [26]
2	C_6H_5	O	10	92	200-202	202-204 [27]
3	4-$N(Me)_2C_6H_4$	O	20	82	258-260	255-257 [28]
4	2-ClC_6H_4	O	15	86	217-219	215-217 [27]
5	4-$NO_2C_6H_4$	O	15	82	206-207	205-207 [26]
6	4-$MeOC_6H_4$	S	15	85	153-154	154-155 [29]
7	C_6H_5	S	15	87	205-206	206-207 [30]
8	3-$NO_2C_6H_4$	S	20	75	201-202	203-205 [31]
9	4-$NO_2C_6H_4$	S	20	79	190-192	193-194[25]
10	4-furyl	S	25	74	228-229	-
11	4-CH_3 C_6H_4	S	25	83	183-185	186-187 [30]
12	4-ClC_6H_4	S	15	88	190-191	188 [32]
13	4-BrC_6H_4	S	20	89	190-193	191-192[25]
14	3-BrC_6H_4	S	25	77	140-142	171[32]
15	4-$MeOC_6H_4$	S	25	85	149-151	140 [33]
16	4-$N(Me)_2C_6H_4$	S	30	81	208-210	197-198 [30]

[a] Isolated yields

All products were characterized by NMR and IR spectra as well as their elemental analysis data. In the ^{1}H-NMR spectra of these compounds the two different broad signals at low field were assigned to the resonance of two NHs protons of the pyrimidine ring. This was supported by IR spectra, which included signals in he region 3220-3245 cm^{-1}.

EXPERIMENTAL

NMR spectra were recorded on a Brucker 300 MHz spectrometer. IR spectra were performed on a Galaxy FT-IR 5000 spectrophotometer. All products were characterized by a comparison of their spectral (IR, ^{1}H NMR, and elemental analysis) data or by comparison of their physical and spectroscopic data with those reported in the literature. Microanalyses were performed by the Elemental Analyzer (Elemental, Vario EL III). Melting points were measured by using capillary tubes on an electro thermal digital apparatus and are uncorrected. The progress of reactions was monitored by TLC using n-hexane/EtOAc as an eluent.

General procedure for preparation of tetrahydropyrimidines

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea or thiourea (1.2 mmol), and DABCO (0.1 mmol) in ehanol (5 mL) was stirred under reflux conditions for appropriate time according to Table 2. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the mixture was filtered, and the precipitate was washed with H_2O-EtOH (1:1, 10mL) and air dried. The crude product was purified by recrystallization from EtOH.

Selected Spectra:

Ethyl 4-phenyl-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate (entry 2): IR (KBr) (ν_{max}): 3245 , 3120, 2980, 1730, 1710, 1649 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H: 1.14 (3H, t, *J* 7.1 Hz, CH_3), 2.32 (3H, s, CH_3), 4.03 (2H, q, *J* 7.2 Hz, CH_2), 5.36 (1H, s, H-4), 7.29 (5H, m, aromatic, CH), 7.79 (1H, s, NH) and 8.50 ppm (1H, s, NH). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.54; H, 6.45; N, 10.86.

Ethyl 4-(4-nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahy-dropyrimidine-5-carboxylate (entry 5): IR (KBr) (ν_{max}): 3230, 3120, 1730, 1710, 1650 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H: 1.06 (3H, t, *J* 6.9 Hz, CH_3), 2.26 (3H, s, CH_3), 4.04 (2H, q, *J* 7.0 Hz, CH_2), 5.28 (1H, s, H-4), 7.88 (4H, m, aromatic, CH), 7.88 **(**1H, s, NH) and 9.37 ppm (1H, s, NH). Anal. Calcd for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.76. Found: C, 55.21; H, 4.74; N, 13.51.

Ethyl 4-phenyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate (entry 7): IR (KBr) (ν_{max}): 3340,3180, 3100, 2990, 1676 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H: 1.12 (3H, t, *J* 7.03 Hz, CH_3), 2.30 (3H, s, CH_3), 4.00 (2H, q, *J* 7.2 Hz, CH_2), 5.30 (1H, s, H-4), 7.50 (5H, m, aromatic, CH), 9.60 (1H, s, NH) and 10.30 ppm (1H, s, NH). Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.61; H, 6.03; N, 10.31.

Ethyl 4-(furan-2yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate (entry 10): IR (KBr) (ν_{max}): 3200, 1670, 1560 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H:1.13 (3H, t, *J* 7.02 Hz, CH_3), 2.27 (3H, s, CH_3), 4.03 (2H, q, *J* 7.1 Hz, CH_2), 5.21 (1H, s, H-4), 6.14-6.38 (3H, m, aromatic, CH), 9.66 (1H, s, NH) and 10.41 ppm (1H, s, NH). Anal. Calcd for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52. Found: C, 53.87; H, 5.20; N, 10.72.

Ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (entry 16): IR (KBr) (ν_{max}): 3320, 3160, 3100, 2920, 1720 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H:1.19 (3H, t, *J* 7.03 Hz, CH_3), 2.31 (3H, s, CH_3), 2.89 (6H, s, $2CH_3$) 4.10 (2H, q, *J* 7.2 Hz, CH_2), 5.20 (1H, s, H-4), 6.90 (4H, m, aromatic, CH), 7.20 (1H, s, NH) and 7.90 ppm (1H, s, NH). Anal. Calcd for $C_{16}H_{21}N_3O_2S$: C, 60.16; H, 6.63; N, 13.16. Found: C, 60.35; H, 6.50; N, 13.01.

CONCLUSIONS

In conclusion, DABCO was found to be a mild and effective catalyst for the formation of tetrahydropyrimidines with excellent yields. The uses of this inexpensive and easily available catalyst under reflux conditions make this protocol practical and economically attractive. The simple workup procedure, mild reaction conditions, selectivity and very good yields make our methodology a valid contribution to the existing processes in the field of pyrimidine derivatives synthesis.

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