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Organic Chemistry

Elixir Org. Chem. 49 (2012) 10038-10041

ISSN: 2229-712X

Chile saltpeter catalyzed one-pot synthesis of 3,4-dihydro-2(1*H*)-pyrimidinones and –thiones

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ARTICLE INFO

Article history:

Received: 21 May 2012;

Received in revised form:

10 August 2012;

Accepted: 17 August 2012;

Keywords

Three-component,
Biginelli reaction,
Dihydropyrimidin-2(1*H)*-one,
Monastrol,
Chile saltpeter,
$NaNO_3$.

ABSTRACT

A simple, efficient and cost-effective method has been developed for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones by a one-pot three component cyclocondensation reaction of ethyl aceteoacetate, aromatic aldehydes, and urea/thiourea using sodium nitrate as catalyst. The significant advantages of the present protocol are simplicity, high yields, no chromatographic separation, eco-friendliness and recoverability of the catalyst.

Introduction

Several dihydropyrimidinones (DHPMs) and their derivatives exhibit a broad spectrum of biological activities such as anti-viral, anti-tumor, antibacterial antifungal as well as anti-inflammatory actions[1-4] and antioxidative properties[5]. More recently, appropriately functionalized DHPMs have emerged as orally active antihypertensive agents[6-8] and as α1a adrenoceptor-selective antagonists[9]. A very recent highlight in this context has been the identification of the structurally rather simple DHPM Monastrol (figure 1) as a mitotic kinesin Eg5 motor protein inhibitor and potential new lead for the development of anticancer drugs[10]. Apart from synthetic DHPM derivatives, several marine natural products with interesting biological activities containing the dihydropyrimidine-5- carboxylate core have recently been isolated[11]. Most notably among these are the batzelladine alkaloids A and B which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy[12].

The original Biginelli protocol for the preparation of the DHMPs consisted of heating a mixture of an aromatic aldehyde, ethyl acetoacetate and urea in ethanol containing a catalytic amount of HCl[13]. Unfortunately this method led to low to moderate yields of the desired DHPMs particularly when substituted aromatic or aliphatic aldehydes and thiourea were employed[1a, 14-19]. This has led to the recent disclosure of several improved reaction protocols for the synthesis of DHPMs, either by modification of the classical one-pot Biginelli approach itself[20], or by the development of novel, but more complex multistep strategies[21]. In addition, several combinatorial approaches towards DHPMs have been advanced[22], using *e.g.* solid phase[22a, b] or fluorous phase[22c, d] reaction conditions.

Experimental section and characterization data

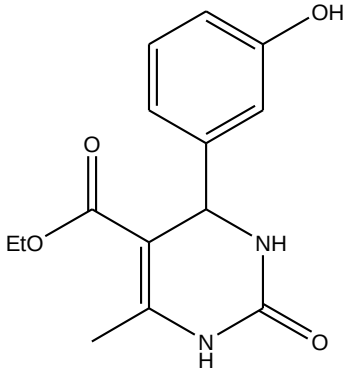
All products were characterized by mp, IR, ^{1}H and ^{13}CNMR. Melting points were measured using a fine control Electro thermal capillary apparatus and are uncorrected. ^{1}H and ^{13}CNMR spectra were recorded on a BRUKER AVANCE DPX spectrometer at 250 and 75 MHz respectively. NMR spectra were obtained on solutions in DMSO-d_6. Chemical shifts are reported in parts of million (δ.ppm) relative to TMS (δ.0.0) as internal standard and coupling constant (*J*) is reported in hertz (Hz). IR spectra were obtained as potassium bromide (KBr) pellets with a Shimadzu FT IR 8201 PC spectrometer. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254, was used to monitor the progress of reactions.

General procedure for synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones (4a–q)

A solution of ethylacetoacetate (2.5 mmol), aromatic aldehyde (2.5 mmol) and urea (3.4 mmol) in CH_3CN (5 ml) was heated under reflux in the presence of $NaNO_3$ (10 mol %) for 3 hours. The progress of the reaction was monitored by TLC. After the completion of the reaction, the obtained mixture was poured into ice-cold water; the formed0 solid was filtered and recrystallized from hot ethanol to afford the pure products.

Physical and spectral data for selected compounds

5-Ethoxycarbonyl-6-methyl-4-(3-hydroxyphenyl)-3,4-dihydropyrimidin-2-(1H)-one (4d)



4d

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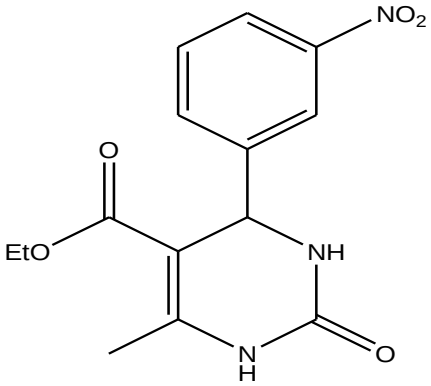
Reaction was carried out for 3 h. Yield: 94%. mp 164-166 ºC (lit 26: 163-166°C). IR (KBr) [cm^{-1}]: 3513, 3341, 3237, 3116, 1723, 1675, 1633, 1599, 1452, 1296, 1218, 1089, 1026, 872, 775, 701.^{1}H NMR (250 MHz, DMSO-d_6) 1.11 (t, 3H, *J* 7.0 Hz), 2.22 (s, 3H), 3.98 (q, 2H, *J* 7.0 Hz), 5.04 (s, 1H), 6.64-7.09 (m, 4H), 7.64 (s, 1H, NH), 9.15 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) d 14.2, 17.6, 52.9, 59.2, 100.1, 113.2, 114.9, 116.7, 129.4, 147.0, 148.5, 152.2, 157.3, 165.

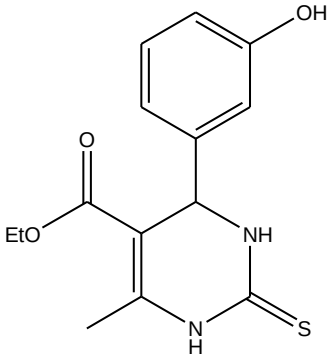
5-Ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2-(1H)-one (4e)



4e

Reaction was carried out for 3 h. Yield: 93%. mp 225-227 ºC (lit 27: 225-227°C). IR (KBr) [cm^{-1}]: 3326, 3090, 2963, 1706, 1686, 1626, 1523, 1456, 1345.1, 1310, 1266, 1221, 1086, 900, 816, 794, 739, 685. ^{1}H NMR (250 MHz, DMSO-d_6) d 1.08 (t, 3H, *J* 6.9 Hz), 2.26 (s, 3H), 3.98 (q, 2H, *J* 6.9 Hz), 5.29 (s, 1H), 7.64-8.10 (m, 4H), 8.90 (s, 1H, NH), 9.37 (s, 1H, NH). ^{13}C NMR (62.5 MHz, DMSO-d_6) d 14.0, 17.9, 53.6, 59.4, 98.4, 121.2, 122.3, 130.0, 133.0, 147.0, 147.8, 149.3, 151.9, 165.0.

5-Ethoxycarbonyl-6-methyl-4-(3-hydroxyphenyl)-3,4-dihydropyrimidin-2-(1H)-thione (4p)



4p

Reaction was carried out for 3 h. Yield: 90%. mp 184-187 ºC (lit 28 : 182–183°C). IR (KBr) [cm^{-1}]: 3299, 3180, 2984, 1663, 1573, 1474, 1445, 1370, 1282, 1188, 1153, 1113, 1024, 788, 752, 700.^{1}H NMR (250 MHz, DMSO-d_6) d 1.14 (t, 3H, *J* 7.1 Hz), 2.30 (s, 3H), 4.04 (q, 2H, *J* 7.1 Hz), 5.11 (d, 1H, *J* 3.7 Hz), 6.65-6.69 (m, 3H), 7.10-7.18 (m, 1H), 9.46 (s, 1H, OH), 9.62 (br s, 1H, NH), 10.31 (br s, 1H, NH). ^{13}C NMR (62.5 MHz, DMSO-d_6) d 14.1, 17.2, 53.9, 59.6, 100.8, 113.2, 114.6, 117.0, 129.5, 144.8, 144.9, 157.5, 165.2, 174.2.

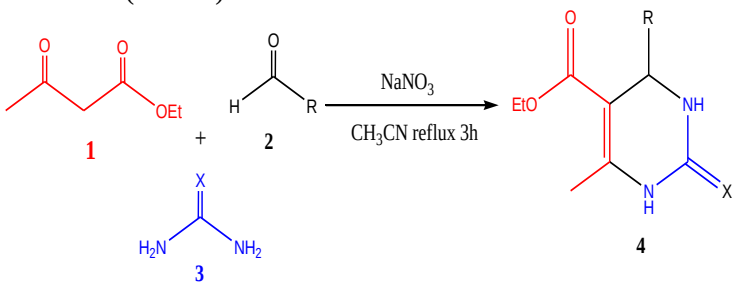
Results and discussion

The intense activity in the field of dihydropyrimidinone chemistry during the past decade from both academic and industrial laboratories, and the search for novel catalysts, which show atom efficiency and environmental friendliness, have prompted us to report herein a new and eco-friendly catalyst ($NaNO_3$) for the preparation of dihydropyrimidin-2-(1*H*)-ones/thiones in good to excellent yields under mild conditions.

To optimize the reaction conditions, some experimentation with respect to the molar ratio of reactants, the reaction temperature/time, and the nature of the solvent were carried out. A set of conditions that consistently produced good to excellent yields of dihydropyrimidone 4a utilized a 1:1:1.36 ratio of ethyl acetoacetate, benzaldehyde, and urea/thiourea in a one-pot condensation employing refluxing CH_3CN as solvent, which had previously been employed successfully in the Biginelli condensation[23] and $NaNO_3$ (10 mol%) as a reaction mediator (Table 1).

Reaction conditions: a solution of benzaldehyde 2a (2.5 mmol), ethyl acetoacetate (2.5 mmol), urea 3a (3.4 mmol), and a catalyst in a solvent (5 ml) was stirred at reflux for 3h. [b]Isolated yield.

Prompted by the success of $NaNO_3$ as catalyst, the optimized protocol was expanded to a variety of benzlaldehyde derivatives (Table 2).



Scheme 1.General synthetic scheme of the obtained products from Biginelli reaction

As demonstrated in table 2, the structural variation in the aldehydes employed in the reaction has no effect neither on the course nor on the yield of the reaction. Furthermore, this catalyst also worked well even with acid-sensitive aldehydes such as 4l and 4m without leading to the formation of any side products.

The scope of the reaction was further expanded when the reaction was carried out successfully using thiourea to provide the corresponding dihydropyrimidin-2(1*H*)-thiones (4o–4q). These thiones are also of much interest with regard to biological activity. One of the well-known examples of dihydropyrimidin-2-(1*H*)-thiones is the Monastrol (4p, fig.1) which could be synthesized in one step using 3-hydroxybenzaldehyde, thiourea, ethyl acetoacetate and $NaNO_3$, under the above mentioned reaction conditions, in 90% yield.

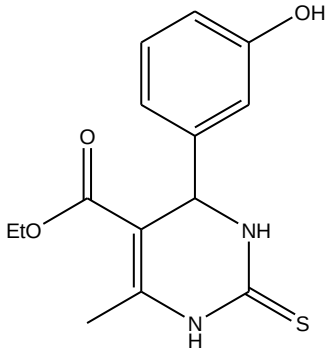


Figure 1: **Monastrol (4p)**

In general, this three component reaction proceeded smoothly and rapidly to give the corresponding dihydropyrimidinones/thiones in the presence of catalytic amount of $NaNO_3$ (Scheme 1) in high yields (Table 2). All

products were known and were identified by comparing their physical or spectral data with those of authentic samples.

For comparison purposes, the traditional Biginelli conditions described by Folkers *et al.*[25] (EtOH/HCl, reflux)[1] also provided dihydropyrimidines 4a-q (yields are not shown). For all cases investigated, the $NaNO_3/CH_3CN$ method produced significantly higher yields (35-45% on average) than the classical Biginelli method.

In summary, we have devised a simple, smooth and efficient protocol for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives using $NaNO_3$ as catalyst via one-pot three-component condensation reaction of ethyl acetoacetate, benzaldehyde derivatives and urea/ thiourea in excellent yields. The advantages offered by this catalyst ($NaNO_3$) versus known ones are (i) inexpensive; (ii) recoverable; (iii) and eco-friendly. The significant features of this protocol are good yields; no need chromatographic separation and applicable to the broad range of substrates which make this procedure a useful and attractive process for the synthesis of such important class of heterocyclic compounds.

Acknowledgements

We gratefully acknowledge the MESRES (Ministère de l'Enseignement Supérieur et de la Recherche Scientifique) for Financial support.

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Table 1. Screening Catalysts and optimization of reaction conditions[a]

Entry	Catalyst (mol %)	Solvent	Yield (%)
1	20	Neat	80
2	20	CH_3CN	94
3	10	CH_3CN	98

Reaction conditions: a solution of benzaldehyde 2a (2.5 mmol), ethyl acetoacetate (2.5 mmol), urea 3a (3.4 mmol), and a catalyst in a solvent (5 ml) was stirred at reflux for 3h. [b]Isolated yield.

Table 2: $NaNO_3$-Mediated Synthesis of DHPMs 4[a]

Entry	DHPM[a]	R/X	Yield(%)[b]
1	4a	C_6H_5-/O	98
2	4b	4-Cl-C_6H_4-/O	94
3	4c	4-OH-C_6H_4-/O	96
4	4d	3-OH-C_6H_4-/O	94
4	4e	3-NO_2-C_6H_4/O	93
5	4f	4-NO_2-C_6H_4-/O	96
6	4g	4-Br-C_6H_4-/O	81
7	4h	2-OMe-C_6H_4-/O	95
8	4i	4-OMe-C_6H_4-/O	90
9	4j	2-Me-C_6H_4-/O	94
10	4k	4-Me-C_6H_4-O	89
11	4l	2-Furyl-/O	93
12	4m	2-thienyl-/O	91
13	4n	C_6H_6-/S	88
14	4o	4-NO_2-C_6H_4-/S	90
15	4p	3-OH- C_6H_4-/S	90
16	4q	4-OMe-C_6H_4-/S	84

These products have been previously reported [23,24]

Isolated yields: new reaction conditions: $NaNO_3$ (10mol%) in CH_3CN (5ml), reflux 3h.