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Phenols Catalyzed Biginelli Reactions: A Self Catalyzed Monastrol Protocol

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A simple and efficient approach towards one step synthesis of various dihydropyrimidones and thiones (Biginelli reaction) was developed by using phenols as catalysts. The multicomponent reaction was conducted between aromatic aldehydes, active methylenes and urea (or thiourea) in an appropriate solvent. This seems to be a first example, where weak acids such as phenols have been employed with success.

Keywords: 3,4-Dihydropyrimidones, Phenols, Biginelli reaction, One pot reaction.

INTRODUCTION

Dihydropyrimidones (DHPM) and their derivatives occupy an important place in medicinal and synthetic organic chemistry due to their wide range of biological activities, *e.g.* SQ 32926 [1] which act as calcium channel blockers. Low molecular weight natural products like batzelladine A and B are used to inhibit the binding of HIV gp-120 to CD4 cells [2]. It offers a new insight towards the development of AIDS therapy. Different antiproliferative effects of monastrol on cancer cell lines were recently reported [3].

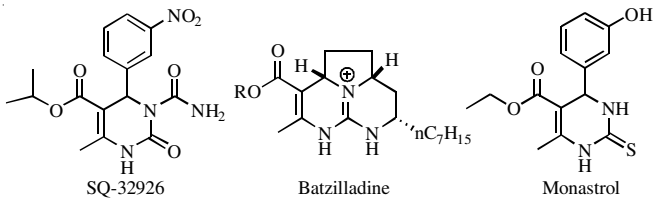
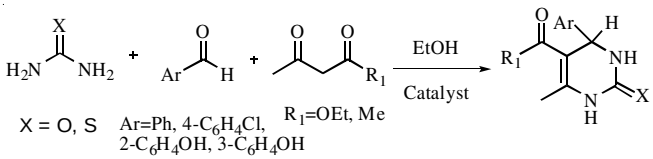


Fig. 1. Some bioactive dihydropyrimidone derivatives

Pyrimidines and their various derivatives have been prepared through the famous Biginelli reaction from aldehydes, 1,3-diketones and urea (thiourea or amidines), *etc*. in a multicomponent reaction (MCR) (**Scheme-I**) [4].

Biginelli reaction has been carried out under a great variety of reaction conditions; aprotic solvents such as tetrahydrofuran [5], dioxane [6] or acetonitrile [7] have been successfully applied in addition to common solvents such as methanol or ethanol. When condensation is carried out between an aromatic aldehyde and urea, it results in an insoluble bisureide derivative *i.e.* $ArCH(NHCONH_2)_2$ [8]. This might not react further when ethanol is used as a solvent. In some reactions, acetic acid was used as a solvent in order to overcome this difficulty [9]. Biginelli condensation in H_2O [10] and ionic liquids [11] have also been reported. Condensation, without using a solvent has been reported recently by using that components which were either adsorbed on an inorganic support or by using suitable catalyst [12].



Scheme-I: General procedure for Biginelli three components condensation reaction

The Biginelli condensation is also strongly dependant upon the acidic catalyst present in the reaction medium [13]. Strong Brønsted acids such as conc. hydrochloric acid or sulphuric acid have been employed [14]. But a variety of Lewis acids are used now a days, such as $BF_3{\cdot}OEt_2$ and CuCl [5], $LaCl_3$ [15], $FeCl_3$ [16], $NiCl_2$ [17], $Yb(OTf)_3$ [18], $InCl_3$ [19], $InBr_3$ [20], $BiCl_3$ [7], $LiClO_4$ [21], $Mn(OAc)_3$ [22], or $ZrCl_4$ [23]. Solid acid catalysts such as acidic clay [24], a zeolite [25] or amber material have also found their use [26]. In addition, amidosulphonic acid has also been utilized as a catalyst [27].

It is also possible for Biginelli condensation to activate the process by strong heating rather than to carryout the

reaction at room temperature with a slow rate. In addition to traditional heating methods, microwave heating for some of the catalyst systems mentioned above has been used to shorten reaction times up to a significant extent [28].

It has been useful to use an excess of the CH-acidic carbonyl or urea components with regard to their molar ratio rather than an excess of an aldehyde. By using MeOH or EtOH as a solvent, dihydropyrimidones products are usually sparingly soluble at room temperature; work-up in most cases simply involves the isolation of product by filtration. A review article has concisely covered various aspects of this reaction [29].

Our continuous interest in Biginelli reaction has led us to explore diverse catalysts and conditions of the reaction and these include: metal acetate [30], alcohols [31], amino acids [32], carboxylic acids [33] and aromatic and heteroaromatic acids [34]. Now we would like to report our success with phenols as catalysts in these reactions.

EXPERIMENTAL

All the chemicals and reagents used in the present study were commercially available. These were purified by usual methods of distillation (for liquids) and crystallization from appropriate solvents (for solids). Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer spectrum BX 1 and NMR on a Brucker 400 MHz spectrometer using tetramethylsilane as an internal reference. The instrument used for Low-resolution electron impact mass spectra was Finningan MAT 311 with MASPEC data system. All the products of the reactions were compared with the authentic samples prepared by the literature methods and were found to be identical in all respects [m.p., mixed m.p., FTIR or other spectra].

General procedure for the preparation of 3,4-dihdropyrimidin-2(1H)-ones or thiones: A mixture of 0.025 mol of urea or thiourea, 0.025 mol of an arylaldehyde, 0.025 mol of ethyl acetoacetate or acetylacetone, 10 mL ethanol and 3 drops of a liquid or 2-3 mg of solid phenol was heated under reflux for 6-24 h and the reaction mixture was then cooled to 0 °C and the product was filtered, washed with water, dried and recrystallized from a suitable solvent. The progress of the reaction was monitored by TLC using ethyl acetate and *n*-hexane (1:2) as eluent.

Reactions with phenols as catalyst (1-3)

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-carboxylate (1, Table-1): FT-IR (KBr, ν_{max}, cm^{-1}): 3175 (N-H); 2923 (C=C-H); 1723 (ester); 1699 (C=O); 1465 (CH_2); 1376 (CH_3). ^{1}H NMR (MeOH): δ 1. 13 (t, 3H *J* = 7.2 Hz), δ 2.33 (s, 3H), δ 3.30 (s, 1H, NH), δ 4.03 (q, 2H *J* = 7.2 Hz), δ 4.86 (s, 1H, NH), δ 5.30 (s, 1H), δ 7.25 (m, 5H). EIMS, *m/z* (%): 259.9 (18 %) [M^+], 230.9 (42 %), 182.9 (97 %), 154.9 (31 %), 137 (22 %), 110 (8 %), 76.9 (17 %).

Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (2, Table-2): FT-IR (KBr, ν_{max}, cm^{-1}): 3245 (N-H); 2923 (C=C-H); 1722 (ester); 1700 (C=O); 1460 (CH_2); 1376 (CH_3); 780 (C-Cl). ^{1}H NMR (MeOH): δ 1. 14 (t, 3H *J* = 7.2 Hz), δ 2.32 (s, 3H), δ 3.30 (s, 1H, NH), δ 4.04 (q, 2H *J* = 6.4 Hz), δ 4.86 (s, 1H, NH), δ 5.297 (s, 1H), δ 7.27 (m, 4H). EIMS, *m/z* (%): 293.9 (21 %) [M^+], 264.9 (72 %), 220.9 (58 %), 182.9 (96 %), 154.9 (60 %), 137 (45 %), 110.0 (25 %).

5-Acyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (3, Table-3): FT-IR (KBr, ν_{max}, cm^{-1}): 3252 (N-H); 2922 (C=C-H); 1722 (ester); 1699 (C=O); 1461 (CH_2); 1377 (CH_3); ^{1}H NMR (MeOH): δ 2. 13 (s, 3H), δ 2.36 (s, 3H), δ 3.30 (s, 1H, NH), δ 4.85 (s, 1H, NH), δ 5.40 (s, 1H), δ 7.31 (m, 5H), EIMS, *m/z* (%): 228.9 (50 %) [M^+], 186.9 (29 %), 153 (95 %), 76.9 (19 %), 68.0 (14 %).

Reactions without an added catalyst (self catalyzed) (4-7)

Ethyl 4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4, Table-4): Yield: 4.89 g (71 %), white crystals, m.p. 165 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3300 cm^{-1} (Ar-OH); 3247 (N-H); 2916 (C=C-H); 1719 (ester); 1701 (C=O); 1460 (CH_2); 1376 (CH_3).

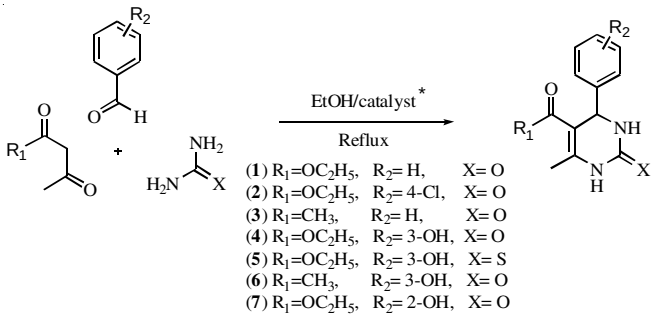
Ethyl 4-(3-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5, Table-4): Yield: 6.27 g (86 %), white powder, m.p. 195 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3321 cm^{-1} (Ar-OH); 3254 (N-H); 2910 (C=C-H); 1728 (ester); 1697 (C=O); 1464 (CH_2); 1375 (CH_3).

5-Acetyl-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (6, Table-4): Yield: 1.90 g (31 %), white crystals, m.p. 199 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3296 (Ar-OH); 3239 (N-H); 2915 (C=C-H); 1710 (C=O); 1372 (CH_3).

Ethyl 4-(2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7, Table-4): Yield: 4.21 g (61 %), white powder, m.p. 140 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3303 (Ar-OH); 3256 (N-H); 2914 (C=C-H); 1735 (ester); 1700 (C=O); 1456 (CH_2); 1367 (CH_3).

RESULTS AND DISCUSSION

Beside a number of catalysts, Biginelli reaction has also been successfully conducted under various acidic conditions [29,33,34]. Phenols, being aromatic in nature are weakly acidic and as such these could also be effective catalysts for the synthesis of dihydropyrimidones. Literature revealed that these have, as yet, not been tried in Biginelli reactions.



(**1**) R_1=OC_2H_5, R_2= H, X= O
(**2**) R_1=OC_2H_5, R_2= 4-Cl, X= O
(**3**) R_1=CH_3, R_2= H, X= O
(**4**) R_1=OC_2H_5, R_2= 3-OH, X= O
(**5**) R_1=OC_2H_5, R_2= 3-OH, X= S
(**6**) R_1=CH_3, R_2= 3-OH, X= O
(**7**) R_1=OC_2H_5, R_2= 2-OH, X= O

*For compounds **4**,**5**,**6** and **7**, no added catalyst were used.

Scheme-II: Phenols catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones

A reaction of an aldehyde, an active methylene compound and urea was conducted in ethanol in the presence of phenol as catalyst (**Scheme-II**, Tables 1-3). Good to excellent yields of the products **1-3** were obtained. Having successful results with phenol, other substituted phenols and naphthols were tried and also found to be equally effective (Tables 1-3). This led us

TABLE-1
EFFECT OF DIFFERENT PHENOL CATALYST FOR THE FORMATION OF **1**

Entry	Phenols	Time (h)	Yield (%)	m.p. (°C)**
01	Hydrochloric acid*	1	68	203
02	α-Naphthol	6	58	197
03	β-Naphthol	24	49	200
04	2-Ethyl phenol	12	57	204
05	4-Ethyl phenol	6	33	203
06	2-Nitro phenol	24	49	202
07	4-Nitro phenol	24	45	201
08	Resorcinol	6	36	202
09	Phenol	12	47	203
10	Guiacol	24	45	200
11	4-Hydroxyazobenzene	7	28	210
12	2,7-Dihydroxynaphthalene	6	30	202
13	1,3-Dihydroxynaphthalene	6	45	202
14	3,5-Dimethoxyphenol	7	37	186

*Model reaction; **Lit. m.p. = 200-202 [Ref. 35]

TABLE-2
EFFECT OF DIFFERENT PHENOL CATALYSTS FOR THE FORMATION OF **2**

Entry	Phenols	Time (h)	Yield (%)	m.p. (°C)*
01	α-Naphthol	5	71	195
02	β-Naphthol	5	86	195
03	2-Ethyl phenol	6	31	199
04	4-Ethyl phenol	6	61	174
05	2-Nitro phenol	10	78	200
06	4-Nitro phenol	10	64	180
07	Resorcinol	5	50	190
08	Phenol	6	28	178
09	Guiacol	6	77	190
10	4-Hydroxyazobenzene	5	67	189
11	2,7-Dihydroxynaphthalene	6	50	195
12	1,3-Dihydroxynaphthalene	6	58	190
13	3,5-Dimethoxyphenol	10	75	180

*Lit. m.p. = 210-212 [Ref. 35]

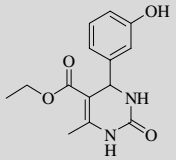
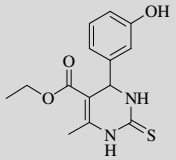
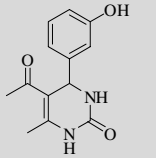
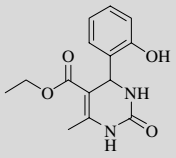
TABLE-3
EFFECT OF DIFFERENT PHENOL CATALYSTS FOR THE FORMATION OF **3**

Entry	Phenols	Time (h)	Yield (%)	m.p. (°C)*
01	α-Naphthol	12	75	227
02	α-Naphthol	12	60	230
03	2-Ethyl phenol	10	73	228
04	4-Ethyl phenol	16	61	227
05	2-Nitro phenol	15	84	225
06	4-Nitro phenol	15	78	227
07	Resorcinol	10	27	210
08	Phenol	15	67	228
09	Guiacol	16	77	225
10	4-Hydroxyazobenzene	15	80	225
11	2,7-Dihydroxynaphthalene	15	66	227
12	1,3-Dihydroxynaphthalene	10	73	227
13	3,5-Dimethoxyphenol	10	69	224

*Lit. m.p. = 212-215 [Ref. 36]

to further experiments where the aldehydes used carries a phenolic functionality (hydroxybenzaldehydes). Here no added phenol was used since the aldehyde acted as an auto-catalyst and, as expected; good to excellent yields of the products **4-7** (Table-4) were obtained. The mass spectra, ^{1}H NMR and

TABLE-4
SELF CATALYZED SYNTHESIS OF DIHYDROPYRIMIDONES

Product No.	Biginelli products	Time (h)	Yield (%)	m.p. (°C) Found	m.p. (°C) Reported
4		4	71	165	163-165
5		4	86	195	185-187
6		4	31	199	184-187
7		4.5	61	140	134

IR data were compatible with the expected products and the melting points were also in agreement with those reported in the literature.

Phenols catalyzed reactions: Further, to study the effect of various phenols as efficient catalysts, as a test, we have used the reactions of benzaldehyde and 4-chlorobenzaldehyde with ethyl acetoacetate and urea leading to the formation of **1** and **2** respectively (Tables 1 and 2) and of benzaldehyde with acetylacetone and urea to afford **3** (Table-3). It can be safely concluded that these phenols are good catalysts for a general Biginelli reaction (Table-5). The experimental yields were not optimized; however these may be further improved by extending reaction time and efficient isolation procedures. Some of the product might have remained soluble and could precipitate out on standing for a longer time period (2-3 days).

TABLE-5
PRODUCTS **1-3** YIELDS WITH DIFFERENT PHENOLS AS CATALYS*

No.	Phenols	Products (Yield %)		
		1	**2**	**3**
1	α-Naphthol	58	71	75
2	β-Naphthol	49	86	60
3	2-Ethyl phenol	57	31	73
4	4-Ethyl phenol	33	61	61
5	2-Nitro phenol	49	78	84
6	4-Nitro phenol	45	64	78
7	Resorcinol	36	50	27
8	Phenol	47	28	67
9	Guiacol	45	77	77
10	4-Hydroxyazobenzene	28	67	80
11	2,7-Dihydroxynaphthalene	30	50	66
12	1,3-Dihydroxynaphthalene	45	58	73
13	3,5-Dimethoxyphenol	37	75	69

*From Tables 1-3

Self catalyzed reactions: If we compare the results of phenols catalyzed products with results reported in the literature for Biginelli reactions mediated by HCl catalysts. The yield in most of the phenols catalyzed reaction was comparable to or higher than the yields obtained by using HCl as catalyst as listed in Table-1. However, all the phenol catalysts required longer reaction times as compare to other strong acids.

Conclusion

From the various experiments performed to prepare Biginelli compounds, it was discovered that not only the phenols are efficient catalysts for these reactions but also for reactions with hydroxybenzaldehydes (such as for monastrol formation) no added catalyst is needed (self catalysis) and ethanol works well as a solvent. The reaction time of 12 to 15 h was sufficient to give up to 86 % yield. In these reactions naphthols and nitro phenols gave better results. In addition to better yields and catalytic activity, the present methodology involves ease of workup, environment friendly procedure and survival of different functional groups throughout the reaction period.

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