New protocol for Biginelli reaction-a practical synthesis of Monastrol

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Dedicated to Dr. A. V. Rama Rao on his 70th birthday April 2, 2005
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Abstract
A simple, efficient, and cost-effective method has been developed for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by a one-pot three component cyclocondensation reaction of 1,3 dicarbonyl compound, aldehyde, and urea using benzyltriethylammonium chloride as the catalyst, under solvent-free conditions: the scope of this protocol is utilized for the synthesis of mitotic Kinesin EG5 inhibitor monastrol.

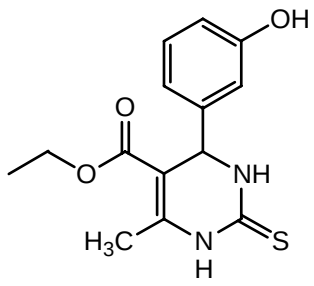
Keywords: Mitotic, monastrol, Biginelli reaction, benzyltriethylammonium chloride, multicomponent reaction, dihydropyrimidin-2(1*H*)-ones

Introduction

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry for various reasons.[1] In times where a premium is put on speed, diversity, and efficiency in the drug discovery process,[2] MCR strategies offer significant advantages over conventional linear-type syntheses. MCR condensations involve three or more compounds reacting in a single event, but consecutively to form a new product, which contains the essential parts of all the starting materials. The search and discovery for new MCR's on one hand,[3] and the full exploitation of already known multicomponent reactions on the other hand, is therefore of considerable current interest. One such MCR that belongs in the latter category is the venerable Biginelli dihydropyrimidine synthesis. In 1893, Italian chemist Pietro Biginelli reported on the acid-catalyzed cyclocondensation reaction of an aldehyde, a β-ketoester, and urea (or thiourea), a procedure known as the Biginelli reaction,[4] is receiving increased attention. More than a century ago, Biginelli intuitively anticipated the synthetic potential of multicomponent reactions by combining in a single flask the reactants of two different reactions having one

component in common.[5] The result of the three-component reaction was a new product that was correctly characterized as a substituted 3,4-dihydropyrimidine-2(1*H*)-one (DHPM).

Over the past decade, dhydropyrimidin-2(1*H*)-ones and their derivatives have attracted considerable attention in organic and medicinal chemistry as the dihydropyrimidine scaffold displays a fascinating array of pharmacological and therapeutic properties.[6] They have emerged as integral backbones of several calcium channel blockers, antihypersentive agents, α-1a-antagonists, and neuropeptide Y (NPY) antagonists.[7] Moreover, several alkaloids containing the dihydropyrimidine core unit have been isolated from marine sources, which also exhibit interesting biological properties. Most notably, among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors. The scope of this pharmacophore has been further increased by the identification of the 4-(3-hydroxyphenyl)-2-thione derivative (±)-**4i** called monastrol,[8] as a novel cell-permeable lead molecule for the development of new anticancer drugs (Figure 1). Monastrol (±)-**4i** has been identified as a compound that specifically affects cell-division (mitosis) by a new mechanism which does not involve tubulin targeting. It has been established that the activity of (±)-**4i** consists of the specific and reversible inhibition of the motility of the mitotic kinesin Eg5, a motor protein required for spindle bipolarity.



Monastrol

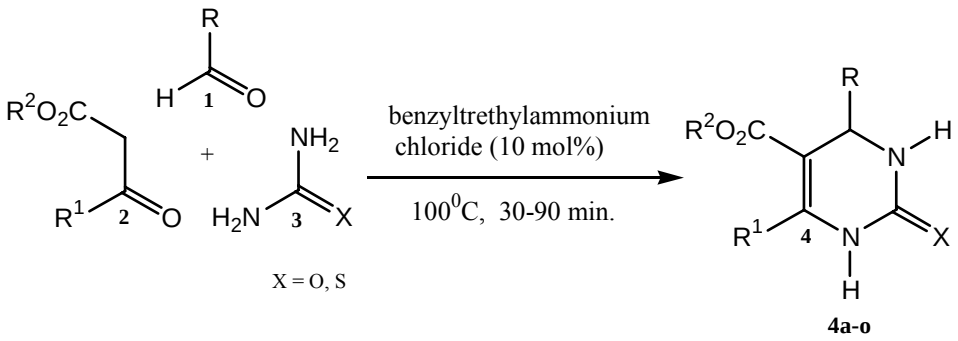
Figure 1

Results and Discussions

The original Biginelli protocol for the preparation of the DHMPs consisted of heating a mixture of the three components (aldehyde **1**, β-keto-ester **2**, and urea **3**) in ethanol containing a catalytic amount of HCl.[6] This procedure leads in one step-one pot to the desired DMPM. The major drawback associated with this protocol is the low yields, particularly for substituted aromatic and aliphatic aldehydes.[9] This has led to the development of multi-step synthetic strategies[10] involving combinations of Lewis acids and transition metal salts, e.g. $BF_3.OEt_2$, polyphosphate esters, and reagents like $InCl_3$, $Mn(OAc)_3$, trimethylsilyltriflate, $LaCl_3.7H_2O$, $CeCl_3.7H_2O$, $LiClO_4$, $Yb(OTf)_3$, clays, etc. However, many of these methods involve expensive reagents, long reaction times, strongly acidic conditions, and stoichiometric amount of catalysts, and difficult to

handle especially on a large scale. Therefore, the discovery of a new and an inexpensive catalyst for the preparation of dihydropyrimidin-2-(1*H*)-ones under neutral and mild conditions is of prime importance.

For the increasing environmental and economical concerns in recent years, it is now essential for chemists to search environmentally benign catalytic reactions as many as possible. Here we wish to report the use of a new catalytic agent, trialkylammonium halide benzyltriethylammonium chloride (TEBA) in the Biginelli's reaction under solvent-free conditions (Equation 1). Benzyltriethylammonium chloride (TEBA) is one of many commonly used phase transfer catalysts in organic synthesis[11] in general and in particular in the formation of carbenes in heterogeneous systems.[12]



Scheme 1

This method not only preserved the simplicity of Biginelli's one-pot condensation but also remarkably improved the yields (>85%) of dihydropyrimidinones in shorter reaction times (30-90 min) as against the longer reaction times required for other catalysts after the addition of a low catalyst concentration. The procedure gives the products in good yields and avoids problems associated with solvent use (cost, handling, safety and pollution). Decreased reaction times are also realized because of the increased reactivity of the reactant in the solid state and the fact that the other reaction product, water, evaporates at the reaction temperature of 100°C. In order to improve the yields, we performed reactions using different quantities of reagents. The best results were obtained with a 0.1:1:1:1.5 ratio of TEBA, aldehyde, 1,3-dicarbonyl compound and urea or thiourea. Higher amounts of TEBA did not improve the result to a greater extent. After completion of the reaction, as indicated by TLC, the reaction mixture was poured onto crushed ice from which the dihydropyrimidinones were isolated by filtration and recrystallized. The crude products obtained are of high purity (>95% by ^{1}H NMR). Another important aspect of this procedure is the survival of a variety of functional groups such as NO_2, Cl, OH, OCH_3, and a conjugated C=C double bond under the reaction conditions.

Table 1. TEBA-catalysed (10 mol%) synthesis of Dihydropyrimidinones under solvent-free conditions

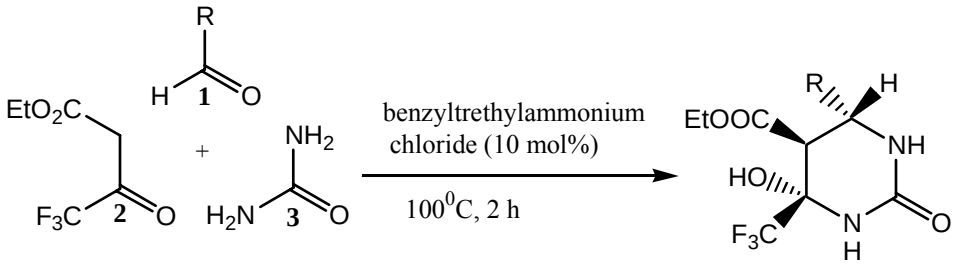
Entry	R	R^1	R^2	X	Time (min)	Product (**4**)[a]	Yield (%)[b]	Ref.
1	Ph	CH_3	CH_3	O	30	**4a**	90	10a
2	4-(OCH_3)-C_6H_4	CH_3	C_2H_5	O	40	**4b**	95	10b
3	4-$(NCH_3)_2$-C_6H_4	CH_3	CH_3	O	65	**4c**	88	10f
4	4-$(NCH_3)_2$-C_6H_4	CH_3	CH_3	S	90	**4d**	86	10f
5	2,4-$(OCH_3)_2$-C_6H_3	CH_3	CH_3	O	30	**4e**	95	10f
6	2,4-$(OCH_3)_2$-C_6H_3	CH_3	CH_3	O	30	**4e**	90[c]	10f
7	2,4-$(Cl)_2$-C_6H_3	CH_3	CH_3	O	75	**4f**	90	10f
8	3,4-$(OCH_3)_2$-C_6H_3	C_2H_5	C_2H_5	O	45	**4g**	91	10f
9	3,4-$(OCH_3)_2$-C_6H_3	CH_3	$C(CH_3)_3$	S	45	**4h**	95	10f
10	3-(OH)-C_6H_4	CH_3	C_2H_5	S	60	**4i**	90	13
11	C_6H_5-CH=CH	CH_3	C_2H_5	O	55	**4j**	88	10f
12	CH_3CH_2CH	CH_3	C_2H_5	O	90	**4k**	83	15
13	$(CH_3)_2CH$	CH_3	C_2H_5	O	70	**4l**	80	15
14	3,4,5-$(OCH_3)_3$-C_6H_2	CH_3	$C(CH_3)_3$	O	45	**4m**	95	10f
15		CH_3	$C(CH_3)_3$	O	30	**4n**	93	10f
16	2-(NO_2)-C_6H_4	CH_3	C_2H_5	O	90	**4o**	82	14

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy. [b]Isolated and unoptimized yields.[c]5 mol% catalyst was used.

To study the generality of this process, several examples were studied and are summarized in Table 1. Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency. A variety of substituted aromatic, aliphatic, and heterocyclic aldehydes carrying either electron donating or – withdrawing substituents afforded high yields of products in high purity. Acid sensitive aldehydes such as furfural worked well without the formation of any side products. Thiourea has been used with similar success to provide the corresponding dihydropyrimidine-(*2H*)-thiones, which are also of much interest with regard to the biological activity (eg., monastrol **4i**, 90%).[8] By using traditional conditions ethanol/HCl turned out to be not compatible with the thiourea obtained **4i** in much lower yield (17%).[13] Thus, variations in all three components have been accommodated very comfortably. However, under the present reaction conditions β-ketoaldehydes do not produce the corresponding

dihydropyrimidinones; instead they lead to multiple products whose identities are yet to be established.

It is interesting to note that when ethyl trifluoroacetoacetate is used as the 1,3-dicarbonyl compound in this synthesis, the hexahydropyrimidine (Scheme 2), considered to be an intermediate in the Biginelli reaction, was isolated in good yields (65-70%).

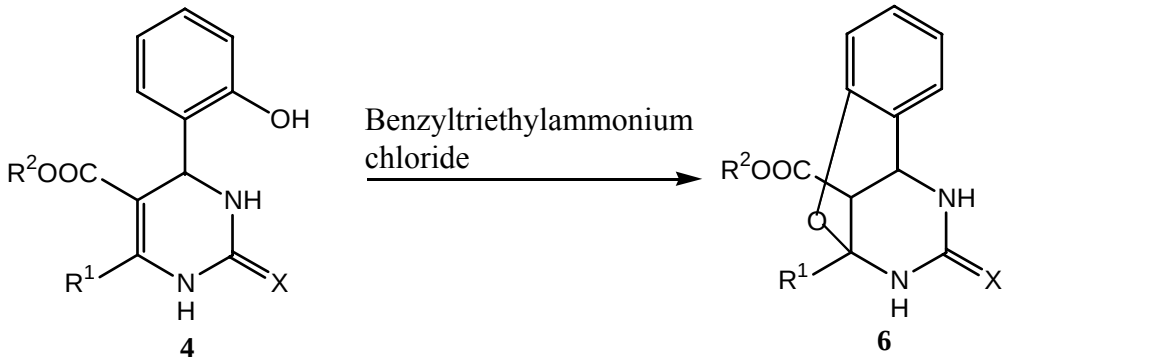


5a: R = C_6H_5
5b: R =4-(OCH_3)-C_6H_4

Scheme 2

This confirms the earlier report by Kappe *et al*.[14] that in the ^{1}H NMR spectrum of **5b** the doublets at δ 3.12 and 4.81 with a coupling constant of 11.0Hz are assignable to the 4-H and 5-H protons, which are *trans* to each other. The isolation and characterization of this intermediate (**5b**) for the first time assumes significance in terms of confirming the mechanism of the reaction. It may be presumed that the OH group at C-6 may be *cis* to 5-H, thereby the elimination of water requires drastic conditions.

During the course of our studies, we have observed that the products derived from the condensation reactions involving 2-hydroxybenzaldehyde showed NMR spectra inconsistent with the expected DHPM structure **4**. However, the product isolated from the reaction was diazatricyclo compound **6b**, which was confirmed by IR, NMR and mass spectroscopy. The production of compounds **6a-b** (60-65% yield) can be explained by the isomerization reaction of the DHPM's **4** which were initially formed (Scheme 3).



a: $R^1 = CH_3$; $R^2 = C_2H_5$; X = O

b: $R^1 = CH_3$; $R^2 = C_2H_5$; X = S

Scheme 3. The isomerization of DHPMs to diazatricyclic compounds.

In summary, we have developed an economically and environmentally friendly procedure for the synthesis of dihydropyrimidinones with high yields and short reaction times, which involves the use of inexpensive catalyst benzyltriethylammonium chloride under solvent-free conditions. Furthermore, the present procedure is readily amenable to parallel synthesis and the generation of combinatorial DHPMs libraries.

Experimental Section

General Procedures. Reagents and solvents were of analytical grade or were purified by standard procedures prior to use, and petroleum ether refers to bp 60-80°C. Evaporation of solvents was performed at reduced pressure, using a Buchi rotary evaporator. ^{1}H NMR spectra were recorded on Varian FT-200MHz (Gemini) in $CDCl_3$. Chemicals shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were recorded under electron impact at 70eV on Finnigan Mat 1020B mass spectrometer. Melting points were recorded on Buchi 535 and are uncorrected. Column chromatography was performed on silica gel (60-120 mesh) supplied by Acme Chemical Co. (India). Thin-layer chromatography was performed on Merck 60 F-254 silicagel gel plates.

General experimental procedures

Representative procedure for 5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dyhydropyrimidine-2(1*H*)-one (4b). A mixture containing the 4-methoxybenzaldehyde (1.36g, 10 mmol), methyl acetoacetate (1.16g, 10 mmol), urea (0.9g, 15 mmol) and benzytriethylammonium chloride (228mg, 10 mol%) was heated at 100°C for the appropriate time as mentioned in Table 1. After completion of the reaction, as indicated by TLC, the reaction mixture was poured onto crushed ice (30g) and stirred for 5-10min. The solid separated was

filtered under suction (water aspirator), washed with ice-cold water (50 mL), and then recrystallized from hot ethanol to afford pure product (2.62 g, 95%).

This procedure was followed for the preparation of all the dihydropyrimidinones and thiones listed in Table 1.

Spectral section

The known compounds have been identified by comparison of spectral data and mp with those reported. The mp, spectral, and analytical data of the new compounds have been presented below in order of their entries.

4a. Reference 10a

4b. Reference 10b.

4c-4h. Reference 10f.

4i. mp 185-187°C; IR (KBr): 3300, 3180, 2900-2600, 1680, 1651, 1570 cm^{-1};
^1H NMR (300 MHz, DMSO-d_6, TMS): δ 1.10 (t, *J* = 7.5Hz, 3H), 2.36 (s, 3H), 4.08 (q, *J* = 7.5Hz, 2H), 5.22 (d, *J* = 3.5Hz, 1H), 6.64-6.78 (m, 3H), 7.02-7.15 (m, 1H), 8.90 (s, 1H, OH), 9.18 (br s, N1-H), 9.82 (br s, N3-H).
^{13}C NMR δ 174.1, 165.3, 157.1, 144.4, 144.0, 129.0, 117.4, 113.6, 101.4, 111.0, 59.5, 54.7, 17.4, 13.8.
EIMS: m/z (%) 292 (M^+, 80), 263 (45), 219 (41), 199 (100), 171(35).
Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58. Found: C, 57.43, H, 5.55, N, 9.42.

4j. Reference 10f.

4k-4l. Reference 15.

4m-4o. Reference 10f.

5b. mp 98-100°C; IR (KBr): 3420, 3105, 3045, 1600, 1520 cm^{-1};
^1H NMR: (300 MHz, DMSO-d_6, TMS): δ 0.90 (t, *J* = 7.5Hz, 3H), 3.12 (d, 1H, *J* = 11.0Hz), 3.82 (s, 3H), 3.92-4.03 (m, 2H), 4.81(d, 1H, J = 11.0Hz), 5.35 (br s, 1H, NH), 5.58 (s, 1H, OH), 5.90 (br s, 1H, NH), 6.82-6.93 (m, 2H), 7.21-7.36 (m, 2H).
^{13}C NMR δ 167.0, 159.1, 153.8, 129.8, 128.6, 113.2, 111.8, 102.7, 95.5, 60.0, 54.6, 52.8, 50.2, 23.4, 13.3. EIMS: m/z (%) 362 (M^+).
Anal. Calcd for $C_{15}H_{17}F_3N_2O_5$: C, 49.71; H, 4.70; N, 7.74. Found: C, 49.85, H, 4.63, N, 7.76.

6a. mp 200-202°C; IR (KBr): 3220, 3085, 1745, 1690 cm^{-1};
^1H NMR: (300 MHz, DMSO-d_6, TMS): δ 9.83 (br s, N1-H), 9.12 (br s, N1-H), 7.28-6.62 (m, 4H), 4.53 (d, *J*=2.1Hz, 1H), 4.15 (q, *J*=7.0Hz, 2H), 3.28 (d, *J*=2.1Hz, 1H), 1.78 (s, 3H), 1.22 (t, *J*= 7.0Hz, 3H). ^{13}C NMR δ 168.5, 155.2, 150.5, 129.5, 128.6, 125.3, 121.0, 116.5, 83.5, 61.0, 48.0, 44.2, 23.9, 14.3. EIMS: m/z (%) 276 (M^+, 62), 247 (81), 229 (97), 203 (71), 183 (100).
Anal. Calcd for $C_{14}H_{16}O_4N_2$: C, 60.84; H, 5.84; N, 10.14. Found: C, 60.78, H, 5.90, N, 10.16.

6b. mp 203-205°C; IR (KBr): 3365, 3175, 3085, 1745, 1590, 1565 cm^{-1};
^1H NMR: (300 MHz, DMSO-d_6, TMS): δ 9.75 (br s, N1-H), 9.22 (br s, N1-H), 7.21-6.88 (m, 4H), 4.57 (d, *J*=2.2Hz, 1H), 4.15 (q, *J*=7.0Hz, 2H), 3.32 (d, *J*=2.2Hz, 1H), 1.76 (s, 3H), 1.22 (t,

J= 7.0Hz, 3H). ^{13}C NMR δ 175.5, 167.7, 150.5, 129.8, 128.6, 123.5, 121.0, 116.5, 82.5, 60.8, 48.2, 42.4, 23.6, 14.2. EIMS: m/z (%) 292 (M^+, 100), 263 (67), 219 (51), 199 (71).
Anal. Calcd for $C_{14}H_{16}O_3N_2S$: C, 57.49; H, 5.52; N, 9.59. Found: C, 57.65, H, 5.61, N, 9.43.

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