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Phase Transfer Catalysis Improved Synthesis of 3,4-Dihydropyrimidinones

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ABSTRACT

Various 3,4-dihydropyrimidinones can be prepared via Biginelli reaction in aqueous media by using quaternary ammonium salts of different alkyl groups (C4 and C8) and anions (Cl^- and Br^-) as catalysts. The use of quaternary ammonium salts along with longer alkyl chains increases the yield of the Biginelli reaction; however, bromide ammonium salts are less active than the chloride ones.

Keywords: Multicomponent Reaction; Biginelli Reaction; 3,4-Dihydropyrimidinones; Phase-Transfer Catalysis; Quaternary Ammonium Salts

1. Introduction

Multicomponent reaction [1-3] is defined as the process in which three or more reactants are combined in one step. These reactions are of great interest and also of great importance in organic synthesis and medicinal chemistry because they offer direct access to complex molecules [4-10]. In this context, the Biginelli reaction, discovered by Biginelli [11], is a multi-component reaction that involves the cyclocondensation of aldehyde. *β*-ketoester and urea or thiourea lead to the formation of 3,4-dihydropyrimidinones derivatives. Dihydropyrimidinones belong to an important class of heterocyclic compounds with pharmacological and biological properties [12-17]. Despite the diversity of methodologies used for the synthesis of dihydropyrimidinones by Biginelli reaction [18-24], many of these methods suffer from harsh conditions, high reaction times and low yields, particularly in the case of substituted aromatic and aliphatic aldehydes [25-27]. Organic transformations in aqueous media without using hazardous solvents or reagents are of considerable interest. Syntheses of Biginelli products have been developed in aqueous media [28-30].

In search of inexpensive and environmentally benign catalysts, tetraalkylammonium salts were tested alternatively as catalysts for Biginelli reaction in water, which was easily available, harmless and environmentally benign solvent [31-35]. In this paper, we have reported the synthesis of dihydropyrimidinones by Biginelli reaction in aqueous sodium hydroxide under phase transfer catalysis using tetrabutylammonium bromide (TBAB) or chloride (TBAC) or methyltrioctylammonium chloride (Aliquat-336) as phase transfer agent.

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2. Experimental

All the products were characterized by IR, ^{1}H NMR spectra and ^{13}C NMR spectra. IR spectra are recorded in KBr on a Bruker Tensor 27 spectrometer in the range 400 - 4000 cm^{-1}. The ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75MHz) were obtained on a Bruker AC300 spectrometer using DMSO-d_6 or $CDCl_3$ as solvent. Melting points were taken on a Reichert-Heizbank appartus.

All the products were confirmed by comparing their melting points, ^{1}H NMR and ^{13}C NMR data with the literature data [23,36,37-39].

Representative procedure for 5-Ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**2**): A mixture of 4-hydroxybenzaldehyde (732 mg, 6 mmol), ethyl acetoacetate (780 mg, 6 mmol), urea (540 mg, 9 mmol) were mixed together followed by the addition of sodium hydroxide (240 mg, 6 mmol in 4 mL of water) and catalytic amount of PTC (250 mg of TBAC, 290 mg of TBAB, 0.9 mmol) in a 25 mL flask. After

completion, the resultant mass was poured into crushed ice and solid obtained was filtered through Buckner funnel, washed with ice-cold water, twice with petroleum-ether and air-dried over Buckner. The solid crude products were recrystalized from ethanol.

5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-opyrimidin-2(1H)-one (**1**): mp = 199˚C - 201˚C. IR: 3242, 3113, 2975, 2938, 1720, 1704, 1647, 1600 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ_H: 1.09 (t, J = 6.9 Hz, 3H), 2.25 (s, 3H), 3.98 (q, J = 6.9 Hz, 2H), 5.14 (s, 1H), 7.22 - 7.35 (m, 5H), 7.77 (b, 1H), 9.23 (b, 1H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ_C: 14.03, 17.74, 53.91, 59.16, 99.18, 126.21, 127.24, 128.36, 144.82, 148.34, 152.12, 165.29.

5-Ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**2**): mp = 226˚C - 227˚C. ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ_H: 1.10 (t, J = 6.9 Hz, 3H), 2.38 (s, 3H), 3.98 (q, J = 6.9 Hz, 2H), 5.04 (s, 1H), 6.69 (dd, J = 6.6 Hz, 2.1 Hz, 2H), 7.03 (dd, J = 6.6 Hz, 2.1 Hz, 2H), 7.60 (b, 1H), 9.09 (b, 1H), 9.33 (b, 1H). ^{13}C NMR (DMSO-d_6) δ_C: 14.052, 17,688, 53.400, 59.071, 99.736, 114.945, 127.360, 135.397, 147.689, 152.148, 156.488, 165.396. Anal. calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.79; N, 10.14. Found: C, 60.97; H, 5.68; N, 9.96.

5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**3**): mp = 202˚C - 203˚C. IR: 3226, 3100, 2929, 2835, 1710, 1652, 1614, 1581, 1510 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ_H: 1.14 (t, J = 7.2 Hz, 3H), 2.29 (s, 3H), 3.75 (s, 3H), 4.07 (q, J = 7.2 Hz, 2H), 5.3 (d, J = 2.7 Hz, 1H), 6.09 (b, 1H), 6.80 (dd, J = 6.6 Hz, 2.1 Hz, 2H), 7.20 (dd, J = 6.6 Hz, 2.1 Hz, 2H), 8.51 (b, 1H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ_C: 14.50, 18.58, 55.35, 55.58, 50.30, 101.88, 114.31, 128.13, 136.53, 146.49, 154.14, 159.53, 166.10.

5-ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (**4**): mp = 215˚C - 216˚C. IR: 3325, 3154, 1690, 1564, 1230, 1052, 874 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ_H: 1.08 (t, J = 7.02 Hz, 3H), 2.21 (s, 3H), 3.32 (s, 3H), 3.96 (q, J = 7.02 Hz, 2H), 5.09 (s, 1H), 7.02 - 7.21 (m, 4H), 7.66 (b, 1H), 9.13 (b, 1H). ^{13}C-NMR (75MHz, DMSO-d_6) δ_C: 14.21, 17.79, 20.86, 53.78, 59.13, 99.65, 126.31, 129.08, 136.43, 142.19, 148.20, 152.43, 165.53.

5-ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**5**): mp = 206˚C - 208˚C. IR: 3230, 3118, 2980, 1710, 1652, 1595, 1520 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ_H: 1.07 (t, J = 6.90 Hz, 3H), 2.26 (s, 3H), 3.97 (q, J = 6.90 Hz, 2H), 5.27 (s, 1H), 7.50 (d, J = 7.35 Hz, 2H), 7.84 (b, 1H), 8.23 (d, J = 7.35 Hz, 2H), 9.35 (b, 1H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ_C: 14.45, 18.43, 54.12, 59.78, 98.87, 124.16, 128.18, 147.20, 149.80, 152.19, 152.49, 165.54.

5-ethoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (**6**): mp = 210˚C - 213˚C. IR: 3224, 3102, 2980, 2931, 1724, 1651 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ_H: 1.10 (t, J = 6.9 Hz, 3H), 2.25 (s, 3H), 3.99 (q, J = 6.9 Hz, 2H), 5.10 (s, 1H), 7.19 - 7.42 (m, 4H), 7.81 (b, 1H), 9.25 (b, 1H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ_C: 14.25,18.72, 50.70, 53.54, 98.57, 128.10, 128.35, 131.74, 143.52, 148.90, 151.92, 165.63.

5-ethoxycarbonyl-4,6-dimethyl-3,4-dihydropyrimidin-2(1H)-one (**7**): mp = 193˚C - 195˚C. IR: 3260, 3108, 1702, 1650. ^{1}H-NMR (300 MHz, DMSO-d_6) δ_H: 1.08 (d, J = 6.60 Hz, 3H), 1.10 (t, J = 6.90 Hz, 3H), 2.17 (s, 3H), 4.03 - 4.27 (m, 3H), 7.20 (b, 1H), 9.01 (b, 1H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ_C: 14.32, 17.42, 23.61, 46.00, 59.11, 100.60, 147.36, 152.70, 165.43.

5-ethoxycarbonyl-6-methyl-4-ethyl-3,4-dihydro-pyrimidin-2(1H)-one (**8**): IR: 3248, 3120, 1709, 1658. ^{1}H-NMR (300 MHz, DMSO-d_6) δ_H: 0.78 (t, J = 7.02 Hz, 3H), 1.14 (t, J = 7.02 Hz, 3H), 1.29 - 1.41 (m, 2H), 2.13 (s, 3H), 3.98 - 4.56 (m, 3H), 7.26 (b, 1H), 8.90 (b, 1H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ_C: 9.21, 14.91, 18.39, 30.30, 51.97, 59.70, 99.37, 149.16, 153.50, 166.20.

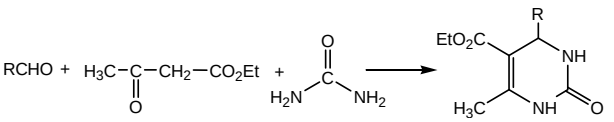
5-ethoxycarbonyl-6-methyl-4-propyl-3,4-dihydro-pyrimidin-2(1H)-one (**9**): mp = 179˚C - 181˚C. IR: 3250, 3120, 2960, 2934, 2875, 1718, 1646. ^{1}H-NMR (300 MHz, DMSO-d_6) δ_H: 0.86 (t, J = 6.90 Hz, 3H), 1.19 (t, J = 5.10 Hz, 3H), 1.26 - 1.41 (m, 4H), 2.15 (s, 3H), 4.03 - 4.11 (m, 3H), 7.33 (b, 1H), 8.94 (b, 1H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ_C: 9.70, 12.82, 15.91, 18.96, 31.40, 52.00, 60.70, 99.87, 148.80, 153.06, 166.05.

5-ethoxycarbonyl-6-methyl-4-butyl-3,4-dihydro-pyrimidin-2(1H)-one (**10**): mp = 164˚C - 166˚C. IR: 3245, 3116, 1728, 1706, 1652. ^{1}H-NMR (300 MHz, DMSO-d_6) δ_H: 0.85 (t, J = 7.20 Hz, 3H), 1.11 - 1.36 (m, 9H), 2.14 (s, 3H), 3.93 - 4.11 (m, 3H), 7.30 (b, 1H), 8.92 (b, 1H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ_C: 12.95, 14.56, 18.01, 24.06, 28.50, 33.40, 51.00, 60.72, 109.80, 140.80, 155.06, 166.01

3. Results and Discussion

We have under taken the synthesis of different derivatives of 3,4-dihydropyrimidinones by three component one-pot Biginelli condensation of an aldehyde, ethyl acetoacetate and urea (**Scheme 1**).

The reaction was carried out in aqueous sodium hydroxide in the presence of tetraalkylammonium salts as a phase transfer agent. The choice of water as solvent assisted in the maintenance of a basic pH during the course of the reaction [40]. It is seen that aldehyde, ethyl acetoacetate and urea in the presence of tetraalkylammonium salt gave the corresponding 3,4-dihydropyrimidinones in



Scheme 1. Biginelli reaction.

Moderate to good yields (**Table 1**). 3,4-dihydropyrimidinones derived from aromatic aldehyde bearing electron-donating or electron-withdrawing substituents in the *para* position were obtained in good yields. However, non aromatic aldehyde, which normally shows, extremely poor yields [41], were less reactive, providing moderate yields of Biginelli adducts (**Table 1**).

The tetraalkylammonium salts have an important role as a catalyst in the Biginelli reaction (**Table 1**). The tetralkylammonium halide catalyst is the critical actor in this reaction. Results show that the reactivity depends on the structure of quaternary ammonium salts (alkyl group and anions). Tetrabutylammonium chloride is less effective than aliquat-336. The quaternary ammonium salt with longer alkyl chain length increase the yield of Biginelli reaction (**Table 1**). In the same context, Ju *et al.* showed in their study of the rection of the conversion of butyl glycidyl ether to cyclic carbonate catalyzed by tetraalkyl ammonium salts that the catalytic activity increased with increasing alkyl chain length [42]. However, for the counter anion of the tetrabutylammonium salt catalysts, the yield of Biginelli reaction decreased in the order $Cl^- > Br^-$. Similar results were obtained previously in our study for michael reaction [43].

The proposed reaction mechanism (**Scheme 2**) includes a liquid-liquid phase transfer.

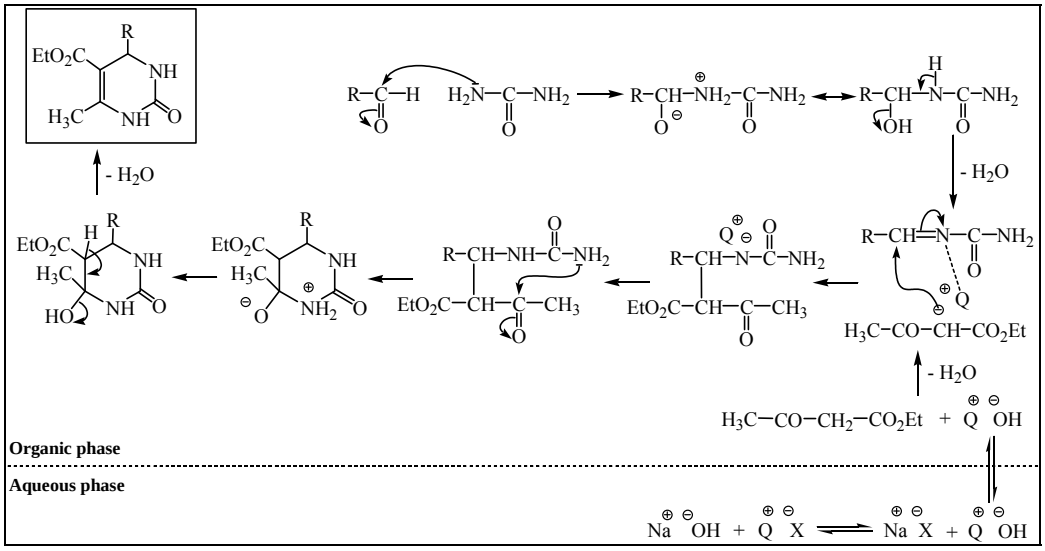
The reaction begins with the formation of an intermediate of acylimine type generated by the condensation between the aldehyde and urea in organic phase. The second intermediate is the Q^+-enolate, produced by deprotonation of the ethyl acetoacetate by the hydroxide ion. The hydroxide ion is transferred from aqueous to organic phase after ionic exchange equilibria of Na^+ with tetraalkyl ammonium cation in aqueous media. This leads to an exaltation of the basicity of hydroxide anion. In fact, the presence of quaternary ammonium salt, the active base would be Q^+, ^-OH [44,45]. Then, the Q^+-enolate reacts with the acylimine intermediate to produce the open-chain uride product. This intermediate undergoes cyclization and a dehydration to produce the desired 3,4-dihydropyrimidinone.

4. Conclusion

We have presented the synthesis of some 3,4-dihydropyrimidinones using quaternary ammonium salts in aqueous sodium hydroxide. The yield of Biginelli product increased according to the size of the cation of the quaternary ammonium salt. The use of quaternary ammonium salt leads to an exaltation of the basicity of hydroxide anion, which is transferred to organic phase

Table 1. Synthesis of 3,4-dihydropyrimidinones.

		Yield (%)		
R	Compound	TBAC	TBAB	Aliquat-336 [36]
C_6H_5	**1**	84	91	96
4HO-C_6H_4	**2**	78	85	92
4MeO-C_6H_4	**3**	82	93	95
4Me-C_6H_4	**4**	80	86	92
4NO_2-C_6H_4	**5**	76	82	90
4Cl-C_6H_4	**6**	76	86	89
CH_3	**7**	66	72	76
C_2H_5	**8**	72	83	84
C_3H_7	**9**	74	86	88
C_4H_9	**10**	74	80	86



Scheme 2. Proposed mechanism of Biginelli reaction.

where reaction occurs. The yield decreased in the order $Cl^- > Br^-$.

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