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Ionic liquid promoted efficient synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones

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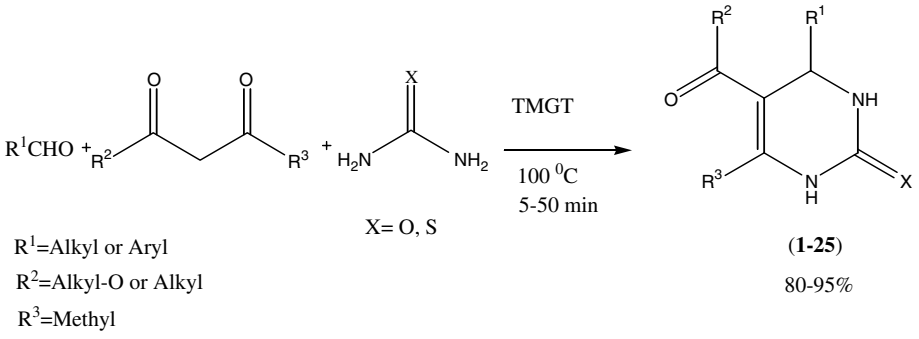

3,4-Dihydropyrimidin-2-(1*H*)-ones have been synthesized in very short time with excellent yields in the presence of 1,1,3,3-tetramethylguanidinium trifluoroacetate as a room temperature ionic liquid under solvent free conditions at 100 °C.

KEY WORDS: 1,1,3,3-tetrametylguanidinium trifluoroacetate; Biginelli reaction; dihydropyrimidinones; ionic liquid; one-pot condensation reaction.

1. Introduction

Ionic liquids (ILs) are emerging as effective promoters and solvents for green chemical reaction. Over the past few years, a variety of catalytic reactions have been successfully conducted using ILs as solvents. Many interesting results have been obtained which demonstrate advantages of using ILs are alternative for organic solvents. Especially, one of the most important advantages of ILs is the behavior of solvophobic interactions that generate an internal pressure which promote the association of the reagents in a solvent cavity during the activation process and showed an acceleration of the multi-component reactions (MCRs) in comparison to conventional solvents [1–4].

Dihydropyrimidinones (DHPMs) and their derivatives are an important class of compounds in the field of pharmaceuticals and exhibit a wide spectrum of biological activities [4–6]. Owing to the versatile biological activity of these compounds introduction of an alternative synthetic methodology is of prime importance. Very recently, we reported NH_4Cl as a catalyst for this transformation under solvent free conditions [7]. Despite NH_4Cl is very cheap reagent and product yields were relatively good, but the reaction times necessary for these yields were relatively long (3 h).

Recently guanidine-based ILs was synthesized [8]. Herein, we wish to report the utilization of 1,1,3,3-tetrmethylguanidinium trifluoroacetate (TMGT), as a very efficient promoter for the multi-component Biginelli's reaction. TMGT not only preserved the simplicity of Biginelli's reaction, but also remarkably by improved the yields of products of dihydropyrimidinones (> 80%) in shorter reaction times (5–50 min) in comparison of NH_4Cl (Scheme 1).

2. Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a Finnigan-Mat 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively. NMR spectra were obtained on solutions in DMSO-d_6.

A mixture of 4-nitrobenzaldehyde (0.151 g, 1 mmol), ethyl acetoacetate (0.13 g, 1 mmol), urea (0.18 g,

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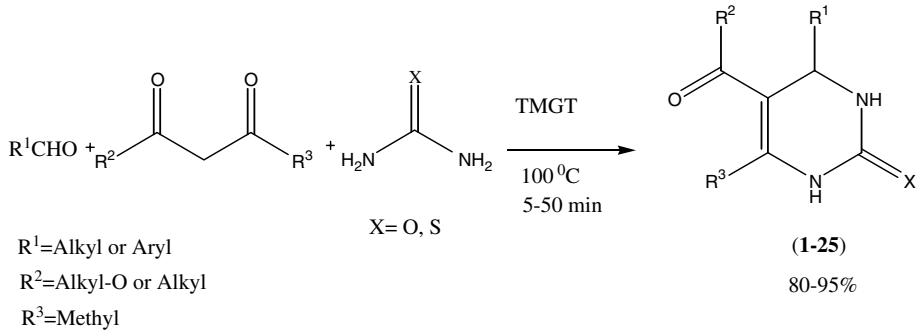

Scheme 1.

3 mmol) and 1,1,3,3-tetrmethylguanidinium trifluoroacetate (0.08 g, 0.4 mmol) was heated with stirring at 100 °C for 20 min. After cooling, the reaction mixture was washed with cold water (2 × 50 mL) and residue crystallized from water and ethanol to afford the pure product **11** (0.284 g, 0.93 mmol, 93%).

2.1. 5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**11**, $C_{14}H_{15}N_3O_5$)

Mp 203–204 ° C; IR (KBr):ν_{max} = 3215, 1731, 1707, 1641, 1495 and 1327 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.07 (t, ^3J 6.8 Hz, CH_3), 2.26 (s, CH_3), 3.97 (q, ^3J 5.4 Hz, OCH_2), 5.27 (1*H*, s, CH), 7.50 (d, ^3J 7.3 Hz, $C_6H_4NO_2$), 7.87 (s, NH), 8.20 (d, ^3J 7.2 Hz, $C_6H_4NO_2$), 9.33 (s, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.5, 18.3, 54.2, 59.8, 98.7, 124.2, 128.1, 147.2, 149.8, 152.2, 152.5, 165.5 ppm; MS: *m*/*z*(%) = 305 (M^+, 25), 276 (92), 260 (20), 183 (100).

All the products are known compounds (except 23 and 24), which were characterized by IR and ^1H NMR spectral data and their mp's compared with literature reports.

2.2. 5-Methoxycarbonyl-6-methyl-4-(phenyl)-3,4-dihydropyrimidin-2(1H)-thione (**23**, $C_{13}H_{14}N_2O_2S$)

Mp 228–229 °C(dec); IR (KBr):ν_{max} = 3340, 1662, 1600, 1566 cm^{-1} ; ^1H NMR (DMSO-d_6): δ = 2.30 (s, CH_3), 3.55 (s, OCH_3), 5.18 (s,C_6H_5–CH), 7.21–7.37 (m, C_6H_5), 9.68 (s, NH), 10.37 (s, NH) ppm; ^{13}C NMR (DMSO-d_6):δ = 17.7, 51.6, 54.4, 100.9, 126.8, 128.2, 129.1, 143.8, 145.8, 166.1, 174.7 ppm; MS: *m*/*z*(%) 262 (M^+, 75), 247 (50), 203 (50), 185(100).

5-Methoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-thione, (**24**, $C_{14}H_{16}N_2O_3S$)

Mp 185–186 °C; IR (KBr):$\nu_{max=3320}$, 1660, 1602, 1550 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.29 (s, CH_3), 3.54 (s, OCH_3), 3.72 (3H, s, OCH_3), 5.1 (s, CH), 6.88 (d, ^3J 8.4 Hz, CH_3O–C_6H_4), 7.13 (d, ^3J, 8.4 Hz, CH_3O–C_6H_4), 9.63 (s, NH), 10.33 (s, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 17.6, 51.5, 53.8, 55.5, 101.1, 114.4, 128.0, 135.9, 145.5, 159.2, 166.1, 174.5 ppm; MS: *m*/*z*(%) = 292 (M^+, 75), 277 (63), 233 (27), 185 (100).

3. Results and discussion

The successful results of TMGT catalyzed Biginelli's reaction are given in table 1. The procedure gives the products in excellent yields and avoids problems associated with solvent use (handling, safety and pollution). Decreased reaction times are also realized because of the solvophobic interaction behavior of TMGT that generates an internal pressure, which promote the association of the reagents in solvent cavity.

In a typical experiment, TMGT (0.4 mmol), aldehyde (1 mmol), β-dicarbonyl compound (1 mmol) and urea (3 mmol) were successively charged into a screw-capped vial containing a magnetic stirring bar. Then the reaction proceeded at 100 °C for 5–50 min during which time a solid product gradually formed. After the completion of reaction (TLC), the resulting solid product washed with cold water filtered and dried to afford the product.

We studied the influence of the amount of TMGT and temperature on the reaction times and yields. The best results were obtained with 0.4:1:1:3 ratio of TMGT, benzaldehyde, ethylacetoacetate and urea after 30 min at 100 °C.

To explore the scope and limitations of this reaction, we extended the procedure to various aromatic aldehydes carrying either electron-releasing or electron-withdrawing substituents in the *ortho, meta*, and *para* positions. We found that the reaction proceeds very efficiently in with all of that. Another advantage of this procedure is its efficiency for the high yield synthesis dihydropyrimidinones from aliphatic aldehydes, which normally show poor yields in Biginelli reaction [9].

Conclusion

We have developed an efficient and environmentally friendly method for the synthesis of dihydropyrimidinones in excellent yield with in short reaction times using 1,1,3,3-tetramethylguanidinium trifluoroacetate as a reaction media as well as promoters.

Table 1
1,1,3,3-Tetramethylguanidinium trifluoroacetate catalyzed syntheses of 3,4-dihydropyrimidin-2(1*H*)-ones under solvent-free conditions at 100 °C

DHMP	R_1	R_2	R_3	X	Yield of TMGT (%)[a] time (min)	Yield of NH_4Cl (%)[a] after 3 h	Mp(°C)	
							Found	Reported
1	C_6H_5	OEt	Me	O	95(20)	90	200–201	201–203[b]
2	2-Me–C_6H_4	OEt	Me	O	93(30)	81	207–208	208–210[c]
3	2-OMe–C_6H_4	OEt	Me	O	95(10)	–	255–259	259–260[d]
4	3-Cl–C_6H_4	OEt	Me	O	95(10)	–	190–192	190–193[e]
5	3-OMe–C_6H_6	OEt	Me	O	86(10)	–	206–207	207–208[f]
6	3-NO_2–C_6H_4	OEt	Me	O	95(5)	80	225–227	226–228[g]
7	4-OMe–C_6H_4	OEt	Me	O	87(15)	84	198–199	199–201[b]
8	4-Me–C_6H_4	OEt	Me	O	93(30)	–	169–170	170[h]
9	4-Cl–C_6H_4	OEt	Me	O	95(10)	83	207–209	210–212[b]
10	4-Br–C_6H_4	OEt	Me	O	91(10)	–	197–198	197[h]
11	4-NO_2–C_6H_4	OEt	Me	O	93(20)	–	203–204	205–207[i]
12	CH_3	OEt	Me	O	91(40)	42	185–188	189–190[j]
13	C_3H_7	OEt	Me	O	80(50)	78	155–157	153–155[k]
14	C_6H_5	OMe	Me	O	90(30)	92	210–211	207–210[b]
15	4-NO_2–C_6H_4	OMe	Me	O	92(40)	79	237–239	235–237[b]
16	4-OMe–C_6H_4	OMe	Me	O	89(35)	90	190–191	191–193[b]
17	C_6H_5	Me	Me	O	91(40)	79	230–234	233–236[b]
18	4-NO_2–C_6H_4	Me	Me	O	90(40)	83	229 (dec)	230 (dec)[b]
19	4-OMe–C_6H_4	Me	Me	O	91(30)	86	175–178	178–180[b]
20	C_6H_5	OEt	Me	S	88(30)	88	204–206	205–207[c]
21	4-NO_2–C_6H_4	OEt	Me	S	91(30)	–	107–108	109–111[c]
22	4-OMe–C_6H_4	OEt	Me	S	92(50)	86	136–138	140[l]
23	C_6H_5	OMe	Me	S	88(50)	–	228–229 (dec)	–
24	4-OMe–C_6H_4	OMe	Me	S	82(40)	–	185–186	–
25	C_6H_5	Me	Me	S	84(50)	–	216–219	220–222[f]

[a] Isolated yield.
[b] Ref [10]. [c] Ref [11]. [d] Ref [12]. [e] Ref [13]. [f] Ref [14]. [g] Ref [9]. [h] Ref [15]. [i] Ref [7]. [j] Ref [16]. [k] Ref [17]. [l] Ref [18].

Acknowledgments

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