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Ionic liquid promoted efficient and rapid one-pot synthesis of pyran annulated heterocyclic systems

Ahmad Shaabani*, Sima Samadi, Zahra Badri, and Abbas Rahmati

Department of Chemistry, Shahid Beheshti University, P.O. Box 19396-4716, Tehran, Iran

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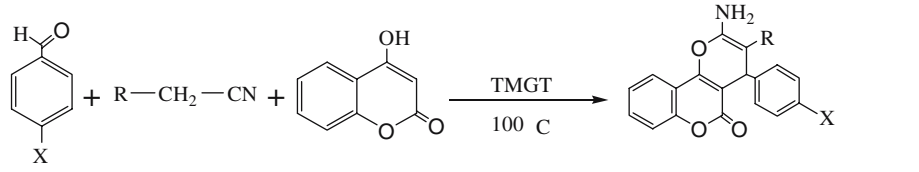


4a-4d X= H, NO_2, OCH_3
60-82 % R= CN, COOEt

X= H, NO_2, OCH_3 R= CN, COOEt

1,1,3,3-*N*,*N*,*N*′,*N*′-Tetramethylguanidinium trifluoroacetate as an ionic liquid, efficiently promotes one-pot, three-component condensation of aldehydes, alkyl nitriles and α-hydroxy or α-amino activated C–H acid to afford the corresponding pyran annulated heterocyclic systems. Ionic liquid can be recycled for subsequent reactions without any appreciable loss of efficiency.

KEY WORDS: ionic liquid; three-component reaction; pyran annulated heterocyclic systems; 4-hydroxycoumarin; 4-hydroxy-6-methylpyrone; 1,3-dimethylbarbituric acid; 1,1,3,3-*N*,*N*,*N*′,*N*′-tetramethylguanidinium trifluoroacetate.

1. Introduction

Pyrano[2,3-*d*]-, pyrido[2,3-*d*]pyrimidines and pyrano[3,2-*c*]benzopyran have attracted much attention owing to their biological activities [1]. A number of methods have been reported for the synthesis of these compounds in the presence of organic bases like piperidine or pyridine in an organic solvents i.e. ethanol, methanol and pyridine. However, most of these rely on multi-step reactions and complex synthetic pathways, long reaction times and yields are low [2–13].

Recently, the one-pot synthesis of pyran annulated heterocyclic systems from condensation of 4-hydroxycoumarin [14] or 4-hydroxy-6-methylpyrone [14] or 1,3-dimethylbarbituric acid [15] with relatively expensive reagent such as dimethyl acetylenedicarboxylate and isocyanide has been reported in toxic benzene under reflux conditions. In addition, a new method based on multi-component reaction strategy using microwave heating in the solid state has been presented [16], but requires special instrument.

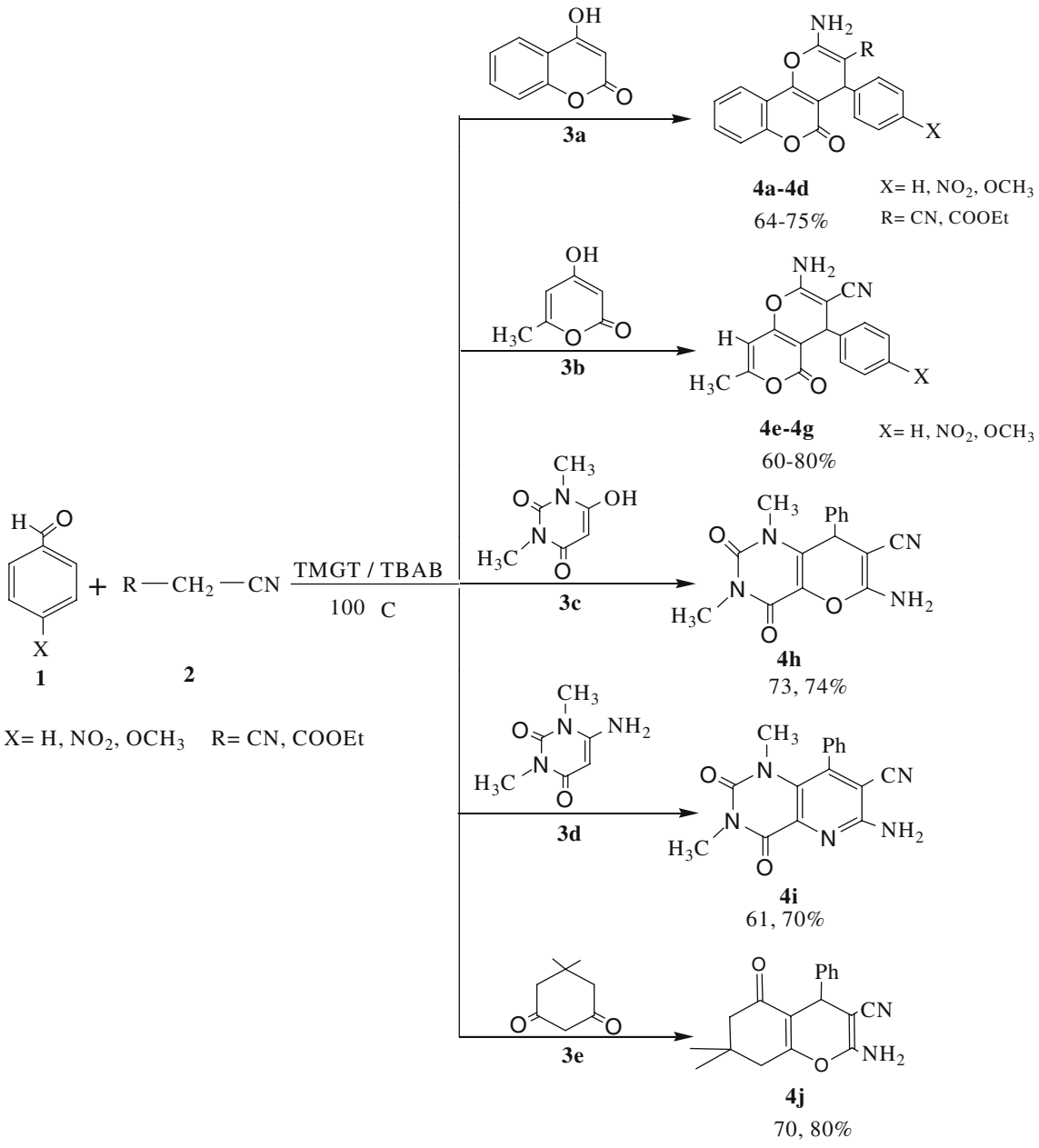
During the course of our studies towards the development of new routes to the synthesis of highly substituted hetrocycles [17–19], we wish to report here a simple and efficient method for the synthesis of pyran annulated heterocyclic systems **4a--4j** by a three component condensation of an aldehyde **1**, an alkyl nitrile **2** and a α-hydroxy or an α-amino activated C–H acid such as 4-hydroxycoumarin **3a** or 4-hydroxy-6-methylpyrone **3b** or 1,3-dimethylbarbituric acid **3c** or 1,3-dimethyl-6-amino uracil **3d** and dimedone **3e** in the presence of 1,1,3,3-*N*,*N*,*N*′,*N*′-tetramethylguanidinium trifluoroacetate (TMGT) as an ionic liquid, which does not require any other reagent or organic solvent (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. ^{1}H 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. All the products are known compounds (except **4b**, **4c** and **4d**), which were characterized by IR, ^{1}H NMR and mass spectral data and their mp's compared with literature reports.

A mixture of malononitrile (0.066 g, 1 mmol), benzaldehyde (0.106 g, 1 mmol) and 4-hydroxycoumarin (0.162 g, 1 mmol) and TMGT (0.025 g, 0.1 mmol) was

* To whom correspondence should be addressed.
E-mail: a-shaabani@cc.sbu.ac.ir



Scheme 1.

heated with stirring at 100 °C for 60 min. After cooling, the reaction mixture was washed with cold water (25 mL) and residue crystallized from Et_2O or acetone to afford the pure product to yield 0.248 g of **4a** as yellow crystals (79%).

2.1. 2-Amino-4-(phenyl)-3-cyano-4H,5H-pyrano[3,2-c][1]benzopyran-5-one (**4a**, $C_{19}H_{12}N_2O_3$)

Yellow crystals (0.248 g, 79%); mp 245–247 °C; IR (KBr): $\nu_{max} = 3370$ (NH_2), 2190 (CN), 1701 (C = O) cm^{-1}; ^1H NMR (Acetone-d_6, TMS): $\delta = 4.56$ (s, CH), 6.66 (br s, NH_2), 7.25–8.00 (m, arom. 9H) ppm; MS: m/z (%) = 316 (M^+, 15), 249 (100), 221 (21), 163 (15), 121 (28), 92 (69).

2.2. 2-Amino-4-(4-nitropheny)-3-cyano-4H,5H-pyrano[3,2-c][1]benzopyran-5-one (**4b**, $C_{19}H_{11}N_3O_5$)

Yellow crystals (0.292 g, 81%); mp 250–252 °C; IR (KBr): $\nu_{max} = 3275$ (NH_2), 2180 (CN), 1703 (C = O); ^1H NMR (DMSO-d_6, TMS): $\delta = 4.67$ (s, CH), 7.45–8.19 (m, arom. 8H, and NH_2,2H) ppm; ^{13}C NMR (DMSO-d_6, TMS): $\delta = 37.24$, 57.17, 103.24, 113.35, 117.09, 119.38,

123.03, 124.19, 125.20, 129.64, 133.63, 147.04, 151.23, 152.72, 154.40, 158.49, 160.03 ppm; MS: m/z (%) = 362 (M^+, 47), 345 (15), 296 (40), 278 (100), 248 (83), 92 (85).

2.3. 2-Amino-4-(4-methoxypheny)-3-cyano-4H,5H-pyrano[3,2-c][1]benzopyran-5-one (**4c**, $C_{20}H_{14}N_2O_4$)

Yellow crystals (0.243 g, 70%); mp 247–249 °C; IR (KBr): ν_{max} = 3365 (NH_2), 2185 (CN), 1702 (C = O); ^{1}H NMR (DMSO-d_6, TMS): δ = 3.72 (s, OCH_3), 4.40 (s, CH), 6.87–7.90 (m, arom. 8H and NH_2,2H) ppm; ^{13}C NMR (DMSO-d_6, TMS): δ = 36.66, 55.54, 58.66, 104.74, 113.46, 114.32, 117.02, 119.77, 122.92, 125.13, 129.23, 133.33, 135.86, 152.55, 153.56, 158.37, 158.79, 160.00 ppm; MS: m/z (%) = 346 (M^+, 10), 280 (100), 249 (80), 184 (59), 162 (25), 120 (30).

2.4. 2-Amino-4-(4-nitropheny)-3-acethyl-4H,5H-pyrano[3,2-c][1]benzopyran-5-one (**4d**, $C_{21}H_{16}N_2O_7$)

Yellow crystals (0.346 g, 82%); mp 238–240 °C; IR (KBr): ν_{max} = 3430 (NH_2), 1714 (C = O); ^{1}H NMR ($CDCl_3$, TMS): δ = 1.16 (t, ^{3}J 7.11 Hz, CH_3), 4.08 (q, ^{3}J 7.11 Hz, CH_2), 5.03 (s, CH), 6.56 (br s, NH_2), 7.33–8.13 (m, arom. 8H) ppm; ^{13}C NMR ($CDCl_3$, TMS): δ = 14.19, 35.76, 60.25, 106.42, 113.11, 117.02, 122.35, 123.37, 124.33, 124.56, 129.54, 132.75, 146.70, 151.74, 152.71, 153.64, 158.00, 160.55, 168.22 ppm; MS: m/z (%) = 408 (M^+, 2), 335 (25), 286 (100), 240 (90), 121 (40), 92 (25).

2.5. 2-Amino-4-(phenyl)-3-cyano-4H,5H-pyrano[4,3-b][1]pyran-3-methyl-5-one (**4e**, $C_{16}H_{12}N_2O_3$)

Yellow crystals (0.215 g, 77%); mp 223–225 °C; IR (KBr): ν_{max} = 3300 (NH_2), 2190 (CN), 1706 (C = O); ^{1}H NMR (Acetone-d_6, TMS): δ = 2.25 (s, CH_3), 4.38 (s, CH), 6.17 (s, C = CH), 6.40 (br s, NH_2), 7.23–7.32 (m, arom. 5H) ppm; MS: m/z (%) = 281 (M + 1, 52), 280 (M^+, 50), 203 (100), 171(10), 102 (38), 43 (52).

2.6. 2-Amino-4-(4-methoxypheny)-3-cyano-4H,5H-pyrano[4,3-b][1]pyran-3-methyl-5-one (**4f**, $C_{17}H_{14}N_2O_4$)

Yellow crystals (0.233 g, 75%); mp 200–202 °C; IR (KBr): ν_{max} = 3320 (NH_2), 2275 (CN), 1700 (C = O); ^{1}H NMR (DMSO-d_6, TMS): δ = 2.21 (s, CH_3), 3.72 (s, OCH_3), 4.22 (s, CH), 6.26 (s, C = CH), 6.84–7.16 (m, arom. 5H and NH_2, 2H) ppm; MS: m/z (%) = 310 (M^+, 75), 279 (10), 243 (90), 203 (90), 145 (55), 117 (30), 43 (100).

2.7. 2-Amino-4-(4-nitrophenyl)-3-cyano-4H,5H-pyrano[4,3-b][1]pyran-3-methyl-5-one (**4g**, $C_{16}H_{11}N_3O_5$)

Yellow crystals (0.230 g, 71%); mp 211–213 °C; IR (KBr): ν_{max} = 3390 (NH_2), 2190 (CN), 1701 (C = O); ^{1}H NMR (DMSO-d_6, TMS): δ = 2.23 (s, CH_3), 4.51 (s, CH), 6.32 (s, C = CH), 7.36 (br s, NH_2), 7.51 (d, 2H, ^{3}J 8.03 Hz, $C_6H_4NO_2$), 8.19 (d, 2H, ^{3}J 8.03 Hz, $C_6H_4NO_2$) ppm; MS: m/z (%) = 325 (M^+, 25), 301 (10), 273 (30), 242 (40), 203 (75), 43 (100).

2.8. 2-Amino-4-(phenyl)-3-cyano-2H-pyrano[2,3-d]pyrimidines (**4h**, $C_{16}H_{13}N_4O_3$)

White crystals (0.229 g, 74%); mp 205–207 °C; IR (KBr): ν_{max} = 3300 (NH_2), 2195 (CN), 1710 (C = O); ^{1}H NMR (DMSO-d_6, TMS): δ = 3.07 (s, CH_3), 3.36 (s, CH_3), 4.31 (s, CH), 7.24–7.34 (m, arom. 5H, and NH_2,2H) ppm; MS: m/z (%) = 311 (M^+, 23), 243 (100), 186 (33), 131 (16).

2.9. 2-Amino-4-(phenyl)-3-cyano-2H-pyrido[2,3-d]pyrimidines (**4i**, $C_{16}H_{13}N_5O_2$)

White crystals (0.213 g, 70%); mp 285–287 °C; IR (KBr): ν_{max} = 3350 (NH_2), 2195 (CN), 1710 (C = O); ^{1}H NMR (DMSO-d_6, TMS): δ = 3.06 (s, CH_3), 3.49 (s, CH_3), 7.21–7.43 (m, arom. 5H, and NH_2, 2H) ppm; MS: m/z (%) = 306 (M^+, 100), 249 (16), 222 (10), 194 (52), 165(10), 140 (28).

2.10. 2-Amino-3-cyano-7,7-dimethyl-4-phenyl-5-oxo-5,6,7,8-tetra-4H-chromene (**4j**, $C_{18}H_{17}N_2O_2$)

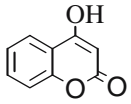
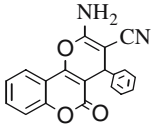
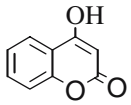
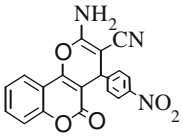
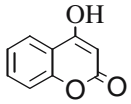
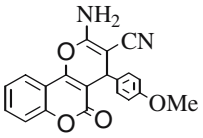
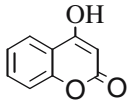
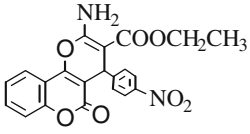
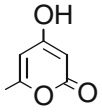
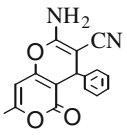
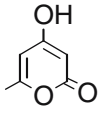
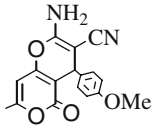
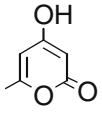
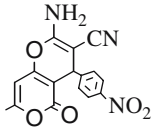
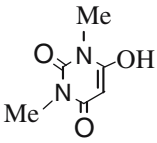
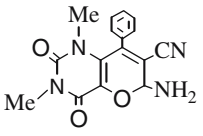
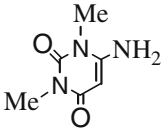
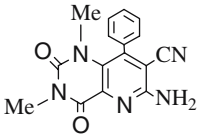
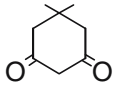
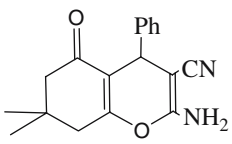
White crystals (0.233 g, 80%); mp 225–227 °C; IR (KBr): ν_{max} = 3390 (NH_2), 2190 (CN), 1675 (C = O); ^{1}H NMR ($CDCl_3$, TMS): δ = 1.04 (s, CH_3), 1.12 (s, CH_3), 2.22 (AB-q, ^{2}J 16.40, CH_AH_B,), 2.45 (s, CH_2), 4.40 (s, CH), 4.58 (br s, NH_2), 7.17–7.32 (m, arom. 5H) ppm; 293 (28), 217 (100), 161(35), 133 (25), 102 (20), 77 (25), 39 (45).

3. Results and discussion

The successful results of the synthesis of pyran annulated hetrocyclic systems in TMGT are given in table 1.

The experimental procedure is very simple. A mixture of the aldehyde (1 mmol), an alkyl nitrile (1 mmol) and a activated C-H acid (1 mmol) was added to TMGT (0.025 g) and the reaction mixture was heated with stirring at 100 °C for the period of time required to complete the reaction (TLC). The

Table 1
One-pot synthesis of pyran annulated heterocyclic system in TMGT as ionic liquid at 100 °C

Entry	Activated C–H acid	Product	TMGT Yield%[a] (Time; min)	mp (°C) Found [reported]
4a			79,72,66[b](60)12[c](60)	245–247 [273–275][2]
4b			81 (25)	250–252
4c			70 (50)	247–249
4d			82 (50)	238–240
4e			77 (50)	223–225 [236–238][11]
4f			75 (25)	200–202 [205–207][11]
4g			71 (45)	211–213 [216–218][11]
4h			74 (35)	205–207 [210–212][16]
4i			70 (50)	285–287 [308–309][16]
4j			80 (50)	225–227 [226–228][21]

[a] Isolated yield.
[b] The same catalyst was used for each of the three runs.
[c] In the absence of ionic liquid.

reaction mixture was cooled and washed with distilled water (25 mL) to remove the TMGT. The solid residue was dried and crystallized from Et_2O or acetone to yield the product.

Experiments were conducted to study the reaction of benzaldehyde, malononitrile and 4-hydroxycoumarin at 100 °C in the absence of TMGT. The yield of product was only 12% after 1 h (table 1, entry **4a**). The TMGT effects can be explained to solvophobic interactions that generate an internal pressure, which promotes the association of the reactants in a solvent cavity during the activation process and showed an acceleration of the multi-component reactions (MCRs) in comparison to conventional solvents [20].

One of the most advantages of these TMGT is its ability to be recyclable as a reaction medium. We were easily able to separate TMGT from reaction medium, with washing it with water and evaporated the solvent under vacuum, and reused it for subsequent reaction. As indicated in table 1 (Entry **4a**), no appreciable loss of efficiency with regard to reaction time and yield after two times. However it can be add fresh IL after two reuses for comparable in subsequent runs.

4. Conclusion

In summary, we have developed a one-pot three-component conversion of a α-hydroxy or an α-amino activated C–H acid compound with an aldehyde and an alkyl nitrile to pyran annulated heterocyclic systems has been carried out in TMGT. To the best our knowledge, this is the first report of a IL synthesis of pyran annulated heterocyclic systems and this new reaction conditions open an important alternation to the use of ionic solvents.

Acknowledgment

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