



Original Research Article

Facile ionic liquid-mediated, multi component synthesis of dihydro-1*H*-furo[2,3-*c*]pyrazoles

Venkata Swamy Tangeti

Dr. S.R.K. Government Arts College (Pondicherry University), Yanam, U.T of Puducherry, India

ARTICLE INFORMATION

Received: 2 August 2018

Received in revised: 5 September 2018

Accepted: 5 October 2018

Available online: 14 November 2018

DOI: [10.22034/ajgc.2018.142927.1090](https://doi.org/10.22034/ajgc.2018.142927.1090)

KEYWORDS

Ionic liquid

Multi component reaction (MCR)

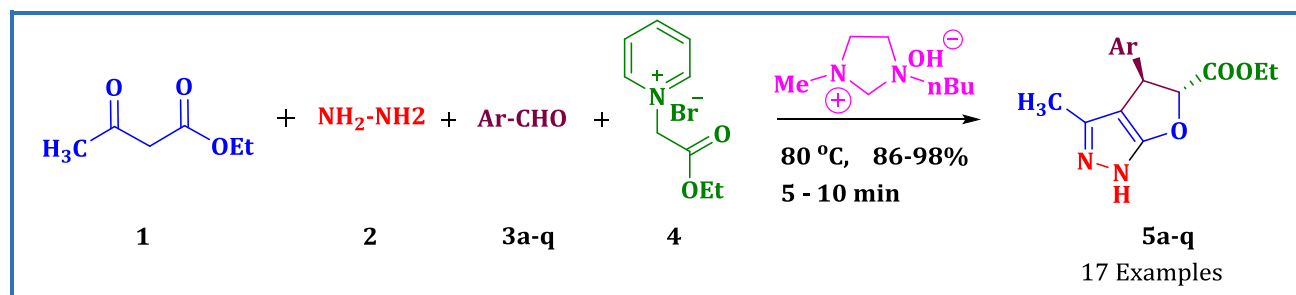
Dihydrofuro[1,2*b*]pyrazole

Green synthesis

ABSTRACT

A facile, convenient, efficient, and high-yielding diastereoselective synthesis of a novel dihydro-1*H*-furo[2,3-*c*]pyrazole fused by a one-pot four-component reaction of β -keto ester, hydrazine, aromatic aldehyde and pyridinium salt in the presence of [bmIm]OH ionic liquid medium has been provided with excellent yields. Three new bonds (two C-C and one C-O), and two stereo centres are generated in a single operation. Low cost, short reaction time, excellent yield, operational simplicity, and more importantly the purification of the compounds by a non-chromatographic method make this process very significant for academic research and practical applications.

Graphical Abstract



Introduction

Multicomponent reactions (MCRs) [1–5] have gained prominence as a synthetic tools for producing the structurally complex molecular entities with attractive biological features through the establishment and cleavage of numerous carbon–carbon and carbon–heteroatom bonds in one pot [6, 7]. It is becoming increasingly important both in academia and in industry to design less toxic and more environmentally friendly MCRs [8–15].

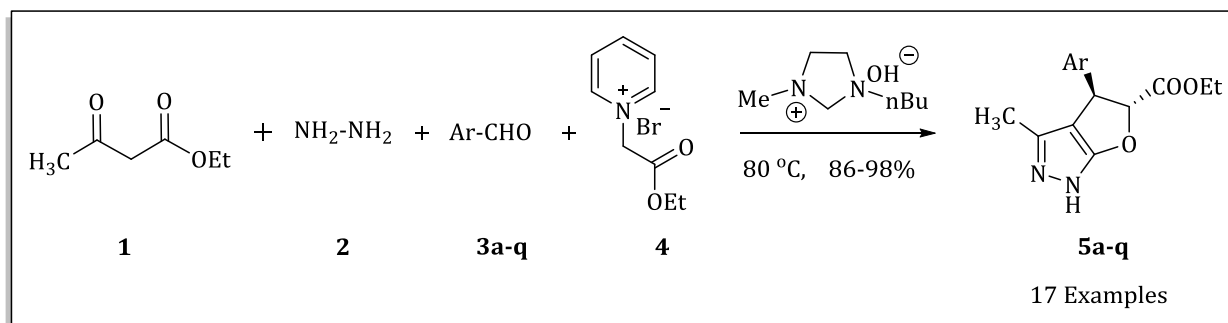
Owing to these green credentials, ionic liquids have attracted a great deal of attention as environmentally benign reaction media, catalysts and reagents, besides they have many other applications. In particular, the basic ionic liquid 1-butyl-3-methylimidazolium hydroxide ([BMIm]OH) has attracted widespread interest in organic synthesis [16]. The development of multicomponent reactions in ionic liquids, although relatively unexplored is of great interest. For more than a decade our laboratory has been actively engaged in the synthesis, characterization and biological evolution of oxygen heterocycles [17–21].

As a part of our continuous efforts towards the development of new synthetic methods for important heterocyclic compounds, we have recently developed a novel methodology for the synthesis of dihydro-1*H*-furo[2,3-*c*]pyrazoles by a one-pot four-component reaction of β -keto ester, hydrazine, aromatic aldehyde and pyridinium salt in the presence of tri ethyl amine under microwave mediated conditions. In this method, the yields of the reactions are from moderate to high (70–80%). Many of the therapeutically useful compounds such as phenylbutazone, oxyphenbutazone, celecoxib belonging to pyrazoles exhibit anti-inflammatory, anti-pyritic, and analgesic properties [22–24]. Sheng-Chu Kuo and co-workers have reported that furo pyrazole molecules are anti-leukemia agents [25]. Recently, we have developed a new methodology for the synthesis of dihydro-1*H*-furo[2,3-*c*]pyrazoles under microwave mediated condition. But the yields of the reaction are poor. In this sense, we contemplated to synthesize dihydro-1*H*-furo[2,3-*c*]pyrazoles by employing ionic liquid medium conditions for improving the yields of the reactions with operational simplicity.

Herein, we report an efficient and ecofriendly four-component reaction protocol in ionic liquid medium for the facile diastereo selective synthesis of novel fused dihydro-1*H*-furo[2,3-*c*]pyrazole by a one-pot four-component reaction of β -keto ester, hydrazine, aromatic aldehyde and pyridinium salt in the presence of in [bmIm]OH ionic liquid medium.

Experimental

Materials and methods



Scheme 1. Ionic liquid mediated synthesis of substituted furo-pyrazole

The progression of all the reactions was monitored by TLC using hexanes (60-80 °C boiling mixture)/ethyl acetate mixture as eluent. Column chromatography was carried on silica gel (100-200 mesh SRL chemicals) using increasing percentage of ethyl acetate in hexanes. ¹H NMR spectra (400 MHz), ¹³C NMR (100 MHz) and DEPT spectra were recorded for (CDCl₃ + CCl₄) solutions on a Bruker 400 spectrometer with tetramethylsilane (TMS) as internal standard; *J*-values were in Hz. IR spectra and were recorded as KBr pellets on a Nicolet 6700 spectrometer. UV spectra were recorded using Hitachi ratio-beam spectrometer. Melting points were recorded using open-ended capillary tubes on VEEGO VMP-DS instrument. High resolution mass spectra were recorded on a waters micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Organic solvents were distilled and dried before use. The ionic liquid [bmIm]OH was prepared according to the procedure described in literature [15].

General procedure for synthesis of furo pyrazoles (5a-q)

Rac-(4*R*,5*R*)-ethyl 3-methyl 4-phenyl-4,5-dihydro-1*H*-furo[2,3-*c*]pyrazole-5-carboxylate 5a

Ionic liquid 1-butyl-3-methyl imidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.153), benzaldehyde **3a** (172 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and, then, the resulting mixture was stirred for 5 min at 80 °C. After completion of the reaction (confirm by TLC), cold water was added to the reaction mixture and stirred for 10 min to get solid compound which was filtered. Afterwards, the filtrate was removed, then the obtained solid was washed with 1N HCl and dried under vacuum to get pure product. Aqueous layer was evaporated under reduced pressure at 90 °C to obtain pure ionic liquid. Finally, the products were recrystallized from EtOH light yellow colour solid, yield 394 mg (89%), mp 123.4 °C, IR (KBr) (ν_{max} /cm⁻¹): 3205, 3085, 2981, 2690, 2639, 1644, 1491, 1404, 1370, 1338, 1215, 1179, 1119, 1086, 1026, 998, 965, 883, 842, 769, 742, and 692. ¹H NMR (400 MHz, CDCl₃): δ 12.27 (s, 1H), 7.22–7.30 (m, 5H),

5.29 (d, $J = 4.6$ Hz, 1H), 5.16 (d, $J = 4.6$ Hz, 1H), 4.16 (q, $J = 6.6$ Hz, 2H), 1.91 (s, 3H), 0.95 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 191.4 (C=O), 161.4 (C), 142.17 (C), 138.1 (C), 126.7 (CH), 124.6 (CH), 123.3 (CH), 109.4 (C), 88.0 (CH), 62.7 (CH₂), 44.2 (CH), 26.7 (CH₃), 14.2 (CH₃); HRMS (ESI, m/z) 295.1053 calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3$ (M+Na) found 295.1051. Analysis calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3$: C, 66.16; H, 5.92; N, 10.29; Found C, 66.14; H, 5.90; N, 10.27.

Rac-(4R,5R)-ethyl 4-(4-chlorophenyl)-3-methyl-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5b

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.163), 4-chlorobenzaldehyde **3b** (214 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Light yellow colour solid, yield 383 mg (82%), mp 126.4 °C, IR (KBr) (ν_{max} / cm^{-1}): 3205, 3085, 2981, 2690, 2639, 1743, 1644, 1491, 1404, 1370, 1338, 1215, 1179, 1119, 1086, 1026, 998, 883, 742, and 692. ^1H NMR (400 MHz, CDCl_3): δ 12.29 (s, 1H), 7.36 (d, $J = 7.9$ Hz, 2H), 7.16 (d, $J = 7.9$ Hz, 2H), 5.29 (d, $J = 4.6$ Hz, 1H), 5.16 (d, $J = 4.6$ Hz, 1H), 4.12 (q, $J = 6.6$ Hz, 2H), 1.91 (s, 3H), 0.93 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 191.5 (C=O), 161.2 (C), 142.1 (C), 138.1 (C), 131.3 (C), 126.76 (CH), 124.6 (CH), 109.4 (C), 88.0 (CH), 62.7 (CH₂), 44.2 (CH), 26.7 (CH₃), 14.2 (CH₃). HRMS (ESI, m/z) 329.7340 calcd for $\text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}_3$ (M+Na) found 329.7339. Analysis calcd for $\text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}_3$: C, 58.73; H, 4.93; N, 9.13; Found C, 58.71; H, 4.92; N, 9.11.

Rac-(4S,5R)-ethyl 4-(2-chlorophenyl)-3-methyl-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5c

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.163), 2-chlorobenzaldehyde **3c** (214 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Light yellow colour solid, yield 337 mg (72%), mp 141.3 °C. IR (KBr) (ν_{max} / cm^{-1}): 3200, 3084, 2980, 2693, 2631, 1649, 1490, 1403, 1370, 1330, 1222, 1166, 1119, 1086, 1026, 993, 961, 880, 846, 769, 741, and 692. ^1H NMR (400 MHz, CDCl_3): δ 12.24 (s, 1H), 7.30–7.22 (m, 4H), 5.29 (d, $J = 4.6$ Hz, 1H), 5.16 (d, $J = 4.6$ Hz, 1H), 4.16 (q, $J = 6.6$ Hz, 2H), 1.91 (s, 3H), 0.95 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 190.1 (C=O), 161.7 (C), 142.1 (C), 138.2 (C), 131.3 (CH), 129.7 (CH), 126.7 (CH), 124.1 (CH), 121.6 (C), 109.4 (C), 88.1 (CH), 62.8 (CH₂), 44.3 (CH), 26.7 (CH₃), 14.7 (CH₃). HRMS (ESI, m/z) 329.7340 calcd for $\text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}_3$ (M+Na) found 329.7339. Analysis calcd for $\text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}_3$: C, 58.73; H, 4.93; N, 9.13; Found C, 58.71; H, 4.92; N, 9.11.

Rac-(4S,5R)-ethyl 4-(2,6-dichlorophenyl)-3-methyl-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5d

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.163), 2,6-dichlorobenzaldehyde **3c** (214 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Light yellow colour solid, yield 369 mg (71%), 151.1 °C. IR (KBr) (ν_{\max} / cm^{-1}): 3218, 3062, 2974, 2690, 2644, 1738, 1645, 1490, 1408, 1360, 1331, 1211, 1184, 1120, 1081, 1020, 985, 879, 755, and 693. ^1H NMR (400 MHz, CDCl_3): δ 12.27 (s, 1H), 7.30–7.22 (m, 3H), 5.29 (d, J = 4.6 Hz, 1H), 5.16 (d, J = 4.6 Hz, 1H), 4.12 (q, J = 6.6 Hz, 2H), 1.91 (s, 3H), 0.93 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 192.1 (C=O), 161.3 (C), 142.1 (C), 138.1 (C), 134.7 (C), 127.6 (C), 126.7 (CH), 109.4 (C), 88.0 (CH), 62.7 (CH₂), 44.2 (CH), 26.7 (CH₃), 14.2 (CH₃). HRMS (ESI, m/z) 363.0279 calcd for $\text{C}_{15}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_3$ (M+Na) found 363.0277. Analysis calcd for $\text{C}_{15}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_3$: C, 52.80; H, 4.14; N, 8.21; Found C, 52.79; H, 4.13; N, 8.20.

Rac-(4S,5R)-ethyl 3-methyl 4-(2,4,6-trichlorophenyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5e

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.163), 2,4,6-trichlorobenzaldehyde **3c** (214 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Light yellow colour solid, yield 417 mg (73%), mp 128.6 °C, IR (KBr) (ν_{\max} / cm^{-1}): 3221, 3065, 2975, 1640, 1485, 1400, 1370, 1331, 1232, 1191, 1122, 1086, 1026, 977, and 961. ^1H NMR (400 MHz, CDCl_3): δ 12.24 (s, 1H), 7.54 (s, 2H), 5.28 (d, J = 4.6 Hz, 1H), 5.15 (d, J = 4.6 Hz, 1H), 4.16 (q, J = 6.6 Hz, 2H), 1.91 (s, 3H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 191.6 (C=O), 161.4 (C), 142.2 (C), 138.0 (C), 134.7 (C), 130.0 (C), 126.7 (CH), 109.8 (C), 88.2 (CH), 62.7 (CH₂), 44.2 (CH), 26.8 (CH₃), 14.3 (CH₃). HRMS (ESI, m/z) 396.9889 calcd for $\text{C}_{15}\text{H}_{13}\text{Cl}_3\text{N}_2\text{O}_3$ (M+Na) found 396.9884. Analysis calcd for $\text{C}_{15}\text{H}_{13}\text{Cl}_3\text{N}_2\text{O}_3$: C, 47.96; H, 3.49; N, 7.46; Found C, 47.94; H, 3.48; N, 7.44.

Rac-(4R,5R)-ethyl 4-(4-bromophenyl)-3-methyl-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5f

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethylacetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.163), 4-bromobenzaldehyde **3f** (283 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Light yellow colour solid,

yield 283 mg (78%), mp 131.4 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3203, 3081, 2980, 2683, 2637, 1740, 1639, 1493, 1400, 1373, 1343, 1211, 1180, 1121, 1078, 1021, 995, 881, 740, and 689. ^1H NMR (400 MHz, CDCl_3): δ 12.28 (s, 1H), 7.25 (d, $J = 7.9$ Hz, 2H), 7.06 (d, $J = 7.9$ Hz, 2H), 5.29 (d, $J = 4.6$ Hz, 1H), 5.16 (d, $J = 4.6$ Hz, 1H), 4.12 (q, $J = 6.6$ Hz, 2H), 1.91 (s, 3H), 0.95 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 191.7 (C=O), 161.3 (C), 142.3 (C), 138.0 (C), 131.3 (C), 126.7 (CH), 124.6 (CH), 109.4 (C), 88.0 (CH), 62.7 (CH_2), 44.2 (CH), 26.7 (CH_3), 14.2 (CH_3). HRMS (ESI, m/z) 373.0164 calcd for $\text{C}_{15}\text{H}_{15}\text{BrN}_2\text{O}_3$ (M+Na) found 373.0162. Analysis calcd for $\text{C}_{15}\text{H}_{15}\text{BrN}_2\text{O}_3$; C, 51.30; H, 4.31; N, 7.98; Found C, 51.30; H, 4.31; N, 7.98.

Rac-(4R,5R)-ethyl 3-methyl 4-p-tolyl-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5g

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.153), 4-methyl benzaldehyde **3g** (183 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Light yellow colour solid, Yield 350 mg (80%), mp 129.5 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3214, 3074, 3003, 2968, 2689, 2634, 1738, 1644, 1481, 1412, 1372, 1345, 1215, 1185, 1120, 1085, 1002, 997, 868, 732, and 678. ^1H NMR (400 MHz, CDCl_3): δ 12.27 (s, 1H), 7.25 (d, $J = 7.9$ Hz, 2H), 7.05 (d, $J = 7.9$ Hz, 2H), 5.28 (d, $J = 4.6$ Hz, 1H), 5.15 (d, $J = 4.6$ Hz, 1H), 4.16 (q, $J = 6.6$ Hz, 2H), 2.25 (s, 3H), 1.91 (s, 3H), 0.95 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 191.7 (C=O), 161.4 (C), 142.1 (C), 138.0 (C), 126.7 (C), 124.6 (CH), 123.3 (CH), 109.4 (C), 88.0 (CH), 62.1 (CH_2), 44.2 (CH), 26.7 (CH_3), 21.1 (CH_3), 14.2 (CH_3). HRMS (ESI, m/z) 309.1215 calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3$ (M+Na) found 309.1214. Analysis calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3$; C, 67.12; H, 6.34; N, 9.78; Found C, 67.10; H, 6.33; N, 9.76.

Rac-(4R,5R)-ethyl 4-(2,4-dimethylphenyl)-3-methyl-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5h

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.163), 2,4-dimethylbenzaldehyde **3h** (205 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Light yellow colour solid, yield 330 mg (72%), mp 125.1 °C. IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3214, 3074, 3003, 2968, 2689, 2634, 1738, 1644, 1481, 1412, 1372, 1345, 1215, 1185, 1120, 1085, 1002, 997, 868, 732, and 678. ^1H NMR (400 MHz, CDCl_3): δ 12.38 (s, 1H), 7.05 (d, $J = 7.9$ Hz, 2H), 6.75 (s, 1H), 5.29 (d, $J = 4.6$ Hz, 1H), 5.16 (d, $J = 4.6$ Hz, 1H), 4.16 (q, $J = 6.6$ Hz, 2H), 2.38 (s, 3H), 2.26 (s, 3H), 1.91 (s, 3H), 0.95 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 191.6 (C=O), 161.3 (C), 142.1 (C), 138.0 (C), 128.4 (C), 126.7 (C),

124.6 (CH), 123.3 (CH), 121.4 (CH), 109.4 (C), 88.1 (CH), 62.7 (CH₂), 44.3 (CH), 26.4 (CH₃), 21.3 (CH₃), 21.1 (CH₃), 14.2 (CH₃). HRMS (ESI, m/z) 323.1372 calcd for C₁₇H₂₀N₂O₃ (M+Na) found 323.1370. Analysis calcd for C₁₇H₂₀N₂O₃: C, 67.98; H, 6.71; N, 9.33; Found C, 67.95; H, 6.70; N, 9.32.

Rac-(4R,5R)-ethyl 4-(4-(dimethylamino)phenyl)-3-methyl-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5i

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.163), 4-(dimethylamino) benzaldehyde **3i** (228 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Yellow colour solid, yield 361 mg (75%), mp 132.4 °C, IR (KBr) (ν_{\max} / cm⁻¹): 3201, 3022, 2951, 2698, 2655, 1640, 1484, 1399, 1373, 1344, 1205, 1170, 1119, 1086, 1032, 991, 964, 885, and 842. ¹H NMR (400 MHz, CDCl₃): δ 12.24 (s, 1H), 7.15 (d, J = 7.9 Hz, 2H), 6.75 (d, J = 7.9 Hz, 2H), 5.29 (d, J = 4.6 Hz, 1H), 5.16 (d, J = 4.6 Hz, 1H), 4.16 (q, J = 6.6 Hz, 2H), 3.16 (s, 6H), 1.91 (s, 3H), 0.95 (t, J = 7.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 191.1 (C=O), 162.7 (C), 148.4 (C), 138.0 (C), 132.1 (C), 126.7 (CH), 114.6 (CH), 109.4 (C), 88.0 (CH), 62.8 (CH₂), 44.2 (CH), 41.7 (CH₃), 26.7 (CH₃), 14.2 (CH₃). HRMS (ESI, m/z) 338.1481 calcd for C₁₇H₂₁N₃O₃ (M+Na) found 338.1479. Analysis calcd for C₁₇H₂₁N₃O₃: C, 64.74; H, 6.71; N, 13.32; Found C, 64.72; H, 6.70; N, 13.30.

Rac-(4R,5R)-ethyl 4-(4-hydroxyphenyl)-3-methyl-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5j

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.163), 4-hydroxybenzaldehyde **3j** (186 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Light yellow colour solid, yield 330 mg (75%), mp 138.1 °C, IR (KBr) (ν_{\max} / cm⁻¹): 3236, 3201, 3065, 2969, 2678, 2631, 1728, 1642, 1490, 1409, 1372, 1344, 1211, 1179, 1120, 1081, 1035, 985, 878, 755, and 685. ¹H NMR (400 MHz, CDCl₃): δ 12.29 (s, 1H), 9.09 (s, 1H), 7.35 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 5.29 (d, J = 4.6 Hz, 1H), 5.15 (d, J = 4.6 Hz, 1H), 4.16 (q, J = 6.6 Hz, 2H), 1.91 (s, 3H), 0.95 (t, J = 7.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 191.7 (C=O), 162.7 (C), 158.1 (C), 138.0 (C), 132.1 (C), 126.7 (CH), 114.6 (CH), 109.4 (C), 88 (CH), 62.7 (CH₂), 44.2 (CH), 26.7 (CH₃), 14.2 (CH₃). HRMS (ESI, m/z) 311.1008 calcd for C₁₅H₁₆N₂O₄ (M+Na) found 311.1005. Analysis calcd for C₁₅H₁₆N₂O₄: C, 62.49; H, 5.59; N, 9.72; Found C, 62.48; H, 5.58; N, 9.71.

Rac-(4R,5R)-ethyl 4-(4-methoxyphenyl)-3-methyl-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5k

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.163), 4-methoxybenzaldehyde **3k** (208 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Light yellow colour solid, yield 351 mg (76%), mp 134.2 °C. IR (KBr) (ν_{\max} / cm^{-1}): 3203, 3079, 2977, 2686, 2631, 1732, 1645, 1495, 1406, 1372, 1342, 1211, 1183, 1125, 1076, 1028, 991, 886, 744, and 680. ^1H NMR (400 MHz, CDCl_3): δ 12.06 (s, 1H), 7.47 (d, $J = 8.4$ Hz, 2H), 6.95 (d, $J = 6.2$ Hz, 2H), 5.37 (d, $J = 4.4$ Hz, 1H), 5.13 (d, $J = 4.4$ Hz, 1H), 4.16 (q, $J = 6.6$ Hz, 2H), 3.83 (s, 3H), 1.91 (s, 3H), 0.95 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 191.3 (C=O), 161.3 (C), 158.1 (C), 142.1 (C), 138.1 (C), 126.7 (CH), 114.6 (CH), 109.4 (C), 88.0 (CH), 62.7 (CH_2), 54.2 (CH_3), 44.2 (CH), 26.7 (CH_3), 14.2 (CH_3). HRMS (ESI, m/z) 302.1267 calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_4$ (M+Na) found 302.1266. Analysis calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_4$; C, 63.56; H, 6.00; N, 9.27; Found C, 63.54; H, 5.99; N, 9.26.

Rac-(4R,5R)-ethyl 4-(3,4-dimethoxyphenyl)-3-methyl-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate **5l**

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.153), 3,4-dimethoxybenzaldehyde **3l** (253 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Light yellow colour solid, yield 391 mg (77%), mp 141.1 °C, IR (KBr) (ν_{\max} / cm^{-1}): 3211, 3068, 2972, 2681, 2634, 1734, 1640, 1492, 1401, 1368, 1341, 1212, 1181, 1121, 1079, 1021, 990, 881, 745, and 689. ^1H NMR (400 MHz, CDCl_3): δ 12.26 (s, 1H), 7.05 (d, $J = 7.9$ Hz, 2H), 6.75 (s, 1H), 5.29 (d, $J = 4.6$ Hz, 1H), 5.16 (d, $J = 4.6$ Hz, 1H), 4.16 (q, $J = 6.6$ Hz, 2H), 3.63 (s, 3H), 3.55 (s, 3H), 1.92 (t, $J = 7.4$ Hz, 3H), 0.95 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 191.3 (C=O), 162.7 (C), 147.3 (C), 144.0 (C), 138.2 (C), 134.6 (C), 121.0 (CH), 116.7 (CH), 114.6 (CH), 113.4 (C), 88.0 (CH), 62.7 (CH_2), 55.1 (OCH_3), 54.7 (OCH_3), 44.2 (CH), 26.7 (CH_3), 14.2 (CH_3). HRMS (ESI, m/z) 332.1372 calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_5$ (M+Na) found 332.1370. Analysis calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_5$; C, 61.44; H, 6.07; N, 8.43; Found C, 61.42; H, 6.06; N, 8.42.

Rac-(4R,5R)-ethyl 3-methyl-4-(4-nitrophenyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate **5m**

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.153), 4-nitrobenzaldehyde **3m** (231 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Yellow colour solid, yield 349 mg (72%), mp 129.2 °C. IR (KBr) (ν_{\max} / cm^{-1}): 3208, 3088, 2984, 2680, 2631, 1748, 1638, 1300,

1491, 1409, 1370, 1341, 1221, 1167, 1128, 1068, 1020, 992, 880, 745, and 682. ^1H NMR (400 MHz, CDCl_3): δ 12.87 (s, 1H), 8.30 (d, $J = 8.4$ Hz, 2H), 7.54 (d, $J = 8.4$ Hz, 2H), 5.29 (d, $J = 4.64$ Hz, 1H), 5.16 (d, $J = 6.6$ Hz, 1H), 4.12 (q, $J = 6.6$ Hz, 2H), 1.91 (s, 3H), 0.95 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 191.3 (C=O), 161.3 (C), 144.4 (C), 141.3 (C), 138.8 (C), 126.7 (CH), 123.30 (CH), 114.4 (CH), 109.4 (C), 88.0 (CH), 62.4 (CH_2), 44.3 (CH), 26.7 (CH_3), 14.2 (CH_3). HRMS (ESI, m/z) 340.0909 calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_5$ (M+Na) found 340.0906. Analysis calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_5$; C, 56.78; H, 4.76; N, 13.24; Found C, 56.77; H, 4.74; N, 13.22.

Rac-(4R,5R)-ethyl 3-methyl-4-(3-nitrophenyl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5n

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.153), 3-nitrobenzaldehyde **3n** (231 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Yellow colour solid, yield 394 mg (78%), mp 133.5 °C. IR (KBr) (ν_{max} / cm^{-1}): 3208, 3088, 2984, 2680, 2631, 1748, 1638, 1300, 1491, 1409, 1370, 1341, 1221, 1167, 1128, 1068, 1020, 992, 880, 745, and 682. ^1H NMR (400 MHz, CDCl_3): δ 12.24 (s, 1H), 7.33–7.22 (m, 4H), 5.29 (d, $J = 4.6$ Hz, 1H), 5.16 (d, $J = 4.6$ Hz, 1H), 4.16 (q, $J = 6.6$ Hz, 2H), 1.91 (s, 3H), 0.95 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 191.4 (C=O), 161.3 (C), 144.4 (C), 141.3 (C), 138.8 (C), 128.3 (CH), 126.7 (CH), 123.3 (CH), 114.4 (CH), 109.4 (C), 88.1 (CH), 62.3 (CH_2), 44.3 (CH), 26.8 (CH_3), 14.2 (CH_3) ppm; HRMS (ESI, m/z) 340.0909 calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_5$ (M+Na) found 340.0906. Analysis calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_5$; C, 56.78; H, 4.76; N, 13.24; Found C, 56.77; H, 4.74; N, 13.22.

Rac-(4R,5R)-ethyl 4-(furan-2-yl)-3-methyl-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5o

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.153), furan-2-carbaldehyde **3o** (146 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Yield 325 mg (81%), mp 135.1 °C. IR (KBr) (ν_{max} / cm^{-1}): 3203, 3081, 2980, 2683, 2637, 1740, 1639, 1493, 1400, 1373, 1343, 1211, 1180, 1121, 1078, 1021, 995, 881, 740, and 689. ^1H NMR (400 MHz, CDCl_3): δ 12.29 (s, 1H), 7.29 (d, $J = 6.6$ Hz, 1H), 6.86 (t, $J = 6.6$ Hz, 1H), 6.29 (d, $J = 6.6$ Hz, 1H), 5.29 (d, $J = 4.6$ Hz, 1H), 5.15 (d, $J = 4.6$ Hz, 1H), 4.12 (q, $J = 6.6$ Hz, 2H), 1.91 (s, 3H), 0.95 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 192.1 (C=O), 161.4 (C), 158.1 (C), 142.1 (CH), 138.0 (C), 114.6 (C), 111.7 (CH), 109.4 (CH), 88.0 (CH), 62.7 (CH_2), 44.2 (CH), 26.7 (CH_3), 14.2 (CH_3). HRMS (ESI, m/z) 285.0851 calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_4$

(M+Na) found 285.0850. Analysis calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68; Found C, 59.53; H, 5.36; N, 10.67.

Rac-(4R,5R)-ethyl 3-methyl 4-(thiophen-2-yl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5p

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.153), thiophene-2-carbaldehyde **3p** (171 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Light yellow colour solid, yield 329 mg (78%), mp 136.6 °C. IR (KBr) (ν_{\max} / cm^{-1}): 3213, 3082, 2978, 2679, 2641, 1741, 1645, 1499, 1404, 1370, 1341, 1210, 1185, 1123, 1074, 1023, 992, 884, 742, and 693. 1H NMR (400 MHz, $CDCl_3$): δ 12.67 (s, 1H), 7.31–7.21 (m, 3H), 5.29 (d, $J = 4.6$ Hz, 1H), 5.15 (d, $J = 4.6$ Hz, 1H), 4.16 (q, $J = 6.6$ Hz, 2H), 1.92 (s, 3H), 0.95 (t, 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2 (C=O), 161.4 (C), 144.1 (C), 138.0 (C), 128.6 (CH), 126.7 (CH), 124.2 (CH), 109.4 (C), 88.0 (CH), 62.7 (CH_2), 44.2 (CH), 26.7 (CH_3), 14.2 (CH_3). HRMS (ESI, m/z) 301.3166 calcd for $C_{13}H_{14}N_2O_3S$ (M+Na) found 301.3163. Analysis calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06; S, 11.52; Found C, 56.09; H, 5.06; N, 10.04; S, 11.51.

Rac-(4R,5R)-ethyl 3-methyl 4-(pyridin-3-yl)-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5q

Ionic liquid I-butyl-3-methylimidazolium hydroxide [bmIm]OH (76 mg, 15 mol%) was added to a mixture of ethyl acetoacetate **1** (211 mg, 0.153 mmol), hydrazine **2** (81 mg, 0.153), pyridine 3-carbaldehyde **3q** (163 mg, 0.153 mmol), and 1-(2-ethoxy-2-oxoethyl) pyridinium salt **4** (272 mg, 0.153 mmol) and resulting mixture was stirred for 5 min at 80 °C. Light yellow colour solid, yield 315 mg (84%), mp 141.8 °C. IR (KBr) (ν_{\max} / cm^{-1}): 3210, 3054, 2965, 2696, 2642, 1721, 1634, 1490, 1398, 1354, 1340, 1211, 1168, 1121, 1098, 1011, 998, and 878. 1H NMR (400 MHz, $CDCl_3$): δ 12.26 (s, 1H), 8.29 (d, $J = 10.6$ Hz, 1H), 8.16 (s, 1H), 7.30–7.22 (m, 2H), 5.29 (d, $J = 4.6$ Hz, 1H), 5.15 (d, $J = 4.6$ Hz, 1H), 4.12 (q, $J = 6.6$ Hz, 2H), 1.91 (s, 3H), 0.93 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.4 (C=O), 162.7 (C), 148.1 (CH), 146.7 (CH), 138.1 (C), 133.0 (CH), 132.1 (C), 126.7 (CH), 109.4 (C), 88.0 (CH), 62.7 (CH_2), 44.2 (CH), 26.7 (CH_3), 14.2 (CH_3). HRMS (ESI, m/z) 296.1011 calcd for $C_{14}H_{15}N_3O_3$ (M+Na) found 296.1009. Analysis calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38; Found; C, 61.51; H, 5.52; N, 15.37.

Results and discussion

As a part of our continuous effort towards developing a new synthetic method for the important heterocyclic compounds **5a–q**.

We report an efficient and ecofriendly four-component reaction protocol in ionic liquid medium at room temperature for the facile chemo and region selective synthesis of highly substituted furopyrazole derivatives from β -Keto ester, benzaldehyde, hydrazine hydride and pyridinium salt. The reactions were completed within 10–15 min and the pure products were isolated in high yields simply by the filtration. The synthetic route is facile, convergent, and allows easy placement of a variety of substituents around the periphery of the heterocyclic ring system (Scheme 1).

Initially, the synthesis of compound **8a** was selected as a model reaction to optimize the reaction conditions with different base catalysts (Table 1). The reaction was carried out by heating a mixture of ethyl acetoacetate **1** (0.153 mmol), hydrazine **2** (0.153 mmol), benzaldehyde **3a** (0.153 mmol), 1-(2-ethoxy-2-oxoethyl) and pyridinium salt **4** (0.153 mmol) in the presence of various amount of 1-methyl-3-butylimidazolium hydroxide [bmim]OH in water at different temperatures. As it can be delineated from Table 2, within a very short time the best yield was achieved in the presence of 15 mol% of catalyst at 90 °C (Table 2, Entry 7). No side product was observed in any reaction. The structure of the compound was fully characterized by ¹H and ¹³C NMR, MS and IR spectra and the elemental analysis. In the ¹H NMR spectra, the two protons at 2,3-position of dihydrofuran ring display two doublets at 5.29 and 5.15 ppm with the vicinal coupling constant $J = 4.6$ Hz and 4.6 Hz, respectively. It has been documented that in cis-2,3-dihydrofuran the vicinal coupling constant of the two methine protons appears at $J = 7, 10$ Hz, while in trans-2,3-dihydrofuran vicinal coupling constant appears at $J = 4, 7$ Hz. Thus, it can be concluded that thermodynamically stable trans isomer of 2,3-dihydrofuran derivatives were formed. Furthermore, according to what has been stated before, it was confirmed from the analysis of the NOESY spectrum of the compound. The mass spectrum shows a sharp distinguishable peak of compound **5a** at 295.1053 [M+Na]⁺.

Ionic liquids such as [bmIm]Br, and [bmIm]BF₄, [bmim]AlCl₄, [bmim]PF₆, [omIm]PF₆, [bmim]SbF₆ were used for the synthesis of furopyrazole derivatives by the same protocol and they were not efficient for providing better yields.

Furthermore, the same reaction model in the presence of 15 mol% catalyst was carried out at different solvents to assess the effect of the solvent on the reaction. As shown in Table 2, the yield of the reaction under aqueous conditions was greater and the reaction time was generally shorter than that of the other methods. Products which were obtained by simple filtration were followed by crystallization from ethanol, and thus hazardous chemicals were totally avoided. The structure of the products (**5a–q**) was confirmed after being compared to the literature..

A plausible mechanism for the synthesis of the furopyrazole in the presence of [bmIm]OH, BH may proceed as depicted in Scheme 2. In the first step, pyrazolone **A** and aldehyde **3** gave Knoevenagel condensation adduct **B**, which acted as a Michael acceptor. The adduct **B** immediately

undergoes Michael type addition with pyridinium salt to generate the open chain intermediate **C**. The intermediate **C** undergoes intramolecular O-cyclization to give the compound **5a** with elimination of pyridine. In this step, ionic liquid [bmim]OH increases the nucleophilicity carbonyl oxygen which leads to facilitate the intramolecular cyclization of intermediate **C**.

Table 1. Effect of base and solvent

Entry	Base	Solvent	Time (min)	Yield
1	[BMIm]Br	EtOH	30	15
2	[BMIm]BF ₄	EtOH	30	12
3	[BMim]AlCl ₄	EtOH	30	24
4	[Bmim]PF ₆	EtOH	30	19
5	[Bmim]SbF ₆	EtOH	30	21
6	[BMIm]OH	EtOH	30	33
7	[BMIm]OH	Water	30	38
8	[BMIm]OH	Water	30	58
9	[BMIm]OH	Water	30	53
10	[BMIm]OH	Water	10	94
11	pyridine	Water	30	62
12	Et ₃ N	Water	30	63
13	DBU	Water	60	71

Table 2. Synthesis of compound **6a** in the presence of various amount of [bmim]OH at different temperatures

Entry	Catalyst (mol%)	T (°C)	Time/min	Yield%
1	None	110	120	20
2	5	70	30	58
3	10	70	20	73
4	15	70	15	81
5	5	90	15	72
6	10	90	10	86
7	15	90	5	97
8	20	90	10	92
9	5	110	15	78
10	10	110	10	89

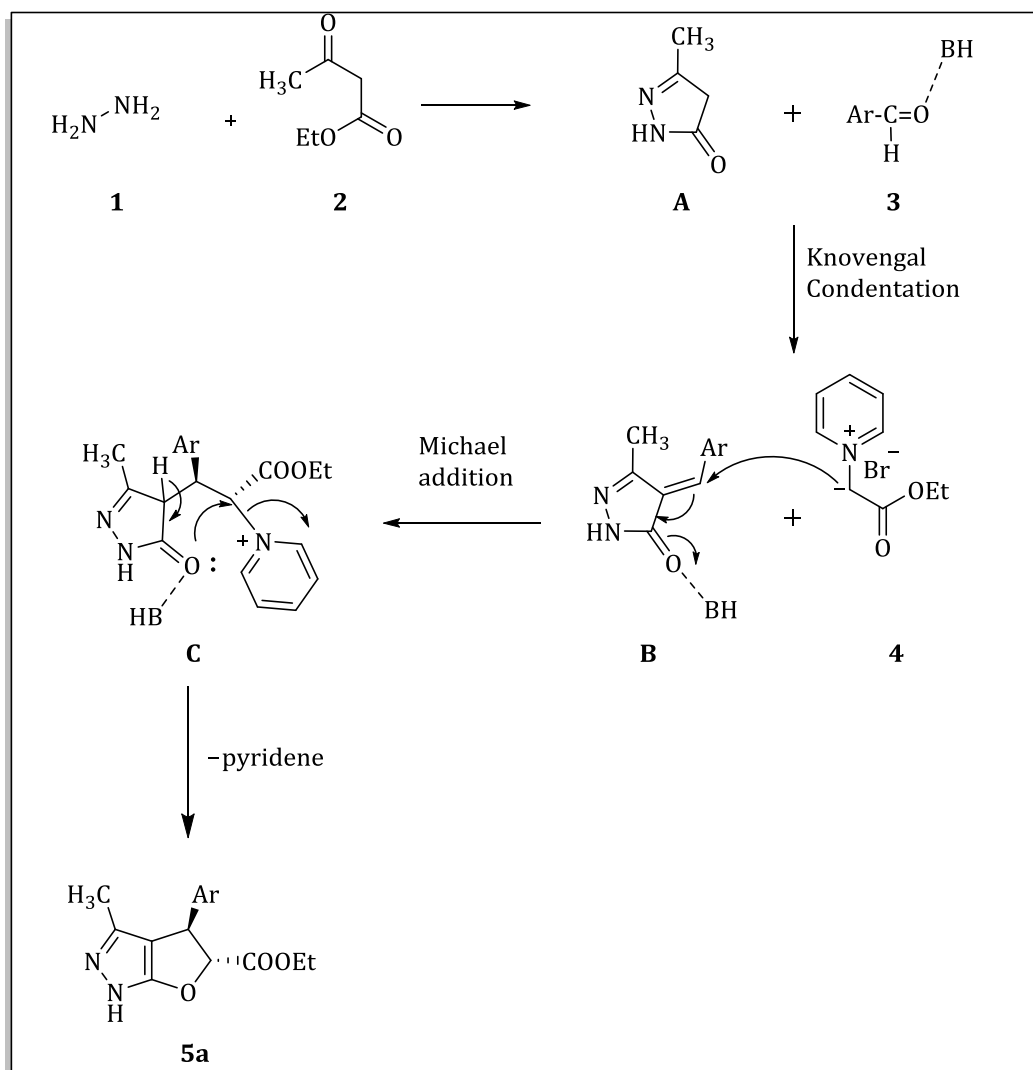
11

15

110

10

90



Scheme 2. Plausible mechanism for the formation of **8** in ionic liquid medium

In this simple experimentally process, three new bonds and two stereo centre are generated in a single operation such that all reactants are efficiently utilized. To evaluate the generality of this model reaction, we prepared a range of furo pyrazole derivatives under the optimized reaction conditions. In all cases, the aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully under ionic liquid mediated conditions and gave the expected products in excellent yields and short reaction times. As observed, no obvious

electronic effects were found. This is due to the fact that, the substituent groups were observed in the aldehyde, and the products were obtained in high yields (Table 3).

In this process, three new bonds (two C–C and one C–O), and two stereo centre are generated in a single operation with all reactants efficiently utilized. Moreover, the methylamine and nitro substituents in the 2- and 3-positions of the pyrone ring are reactive entities, making these compounds good candidates as precursors for further synthetic transformations. Further studies on the extension of the scope of anticancer activity of derivatives of furo pyrazoles are currently underway in our laboratory.

Table 3. Multi-component synthesis of dihydro furo pyrazoles (**5a–q**)

Entry	Compound	Ar	Yield (%) ^a
1	5a	C ₆ H ₅	89
2	5b	<i>p</i> -ClC ₆ H ₄	82
3	5c	<i>o</i> -ClC ₆ H ₄	72
4	5d	2, 6-Cl ₂ C ₆ H ₃	71
5	5e	2, 4, 6- Cl ₃ C ₆ H ₂	73
6	5f	<i>p</i> -BrC ₆ H ₄	78
7	5g	<i>p</i> -MeC ₆ H ₄	80
8	5h	2, 4- (CH ₃) ₂ C ₆ H ₃	72
9	5i	<i>p</i> -N(CH ₃) ₂ C ₆ H ₄	75
10	5j	<i>p</i> -(OH)C ₆ H ₄	75
11	5k	<i>p</i> -(OMe)C ₆ H ₄	76
12	5l	3,4- (OMe) ₂ C ₆ H ₃	77
13	5m	<i>P</i> -(NO ₂)C ₆ H ₄	72
14	5n	<i>m</i> -(NO ₂)C ₆ H ₄	78
15	5o	Furyl	81
16	5p	Thiophenyl	78
17	5q	3-Pyridyl	84

Conclusion

In this research study, we improved the yield of the one-pot multicomponent condensation of the substituted β -keto ester, hydrazine, aromatic aldehyde, and pyridinium salt under ionic liquid [bmIm]OH mediated conditions. The short reaction times, excellent yield, low cost, operational

simplicity and more importantly the purification of compounds by a non-chromatographic method make this process very significant for academic research and practical applications.

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How to cite this manuscript: Venkata Swamy Tangeti. Facile ionic liquid-mediated, multi component synthesis of dihydro-1H-furo[2,3-c]pyrazoles. *Asian Journal of Green Chemistry*, 3(3) 2019, 306-321. DOI: [10.22034/ajgc.2018.142927.1090](https://doi.org/10.22034/ajgc.2018.142927.1090)