[Bmim][$InCl_4$]-Catalyzed Addition of Hydrazones to β-Diketones: An Efficient Regioselective Synthesis of Pyrazoles and Pyrazole-Fused Cyclohexanones

Shirin Safaei,[a] Iraj Mohammadpoor-Baltork,*[a] Ahmad Reza Khosropour,*[a] Majid Moghadam,[a] Shahram Tangestaninejad,[a] Valiollah Mirkhani,[a] Hamid Reza Khavasi[b]

[a] Catalysis Division, Department of Chemistry, University of Isfahan, Isfahan 81746-73441, Iran
Fax +98(311)6689732; E-mail: imbaltork@sci.ui.ac.ir; E-mail: khosropour@chem.ui.ac.ir

[b] Department of Chemistry, Shahid Beheshti University, Tehran 19839-63113, Iran

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Abstract: The Lewis acidic room-temperature ionic liquid, [bmim][$InCl_4$], was found to be an efficient catalyst for the regioselective synthesis of fully substituted pyrazoles and pyrazole-fused cyclohexanones through condensation of hydrazones with symmetrical and unsymmetrical 1,3-diketones. This procedure is simple, affording the corresponding products in good to high yields.

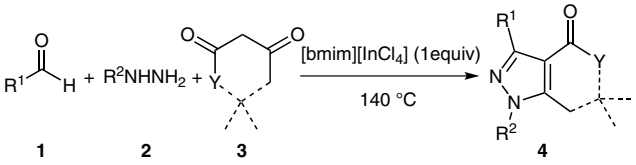
Key words: pyrazoles, arylhydrazones, Lewis acid room-temperature ionic liquid, regioselective

Substituted pyrazoles have received considerable attention in the field of synthetic organic chemistry due to their numerous applications in the pharmaceutical industry. Functionalized pyrazoles have shown antimicrobial,[1] antitumor,[2] hypoglycemic,[3]and hypolipidemic[4] activities, and act as HIV-1 reverse transcriptase inhibitors.[5] Two commercially known drugs, Celebrex[6] and Viagra,[7] have pyrazole scaffolds.

Different methods such as condensation of hydrazonoyl chlorides with acetylenic esters[8] or 1,3-diketones,[9] 1,3-dipolar cycloaddition of active dipoles to the triple bonds[10] and cyclization of 1,3-diketones with hydrazines[11] have been reported for the synthesis of these heterocyclic compounds. Low regioselectivity and consequent difficult isolation of the two regioisomers resulting from unsymmetrical diketones are the most important limitations of some of these methods.

Although much research effort has been directed towards the development of versatile protocols for the synthesis of pyrazole derivatives, there are only few reports on the regioselective formation of pyrazoles from unsymmetrical diketones.[12] Consequently, there continues to be a need to develop efficient methods for the regioselective synthesis of pyrazole derivatives.

Over the years, ionic liquids have received a great interest as reaction media and/or catalysts, as they allow more environmentally friendly processes and display unique reactivity and selectivity.[13] Numerous organic reactions promoted by ionic liquids have been reported with high selectivity.[14–18] Recently, we reported the synthesis of fully substituted pyrazoles and bispyrazoles via three-component reactions catalyzed by $Zn(OTf)_2$.[19] In continuation of our interest in developing new and efficient protocols for the preparation of heterocyclic compounds,[20] herein we report a novel one-pot and regioselective synthesis of fully substituted pyrazoles and pyrazole-fused cyclohexanones from aldehydes, arylhydrazines, and acyclic or cyclic 1,3-diketones catalyzed by [bmim][$InCl_4$] (Scheme 1).[21]



Scheme 1 Regioselective synthesis of fully substituted pyrazoles and pyrazole-fused cyclohexanones catalyzed by [bmim][$InCl_4$]

In order to investigate the effect of the catalyst on the regioselectivity, the reaction of benzaldehyde (1 mmol) and phenylhydrazine (1 mmol) with 1-phenylbutane-1,3-dione (1.2 mmol) was examined in the presence of different catalysts at 140 °C under solvent-free conditions (Table 1, entries 1–9). As shown, in the presence of Lewis acid catalysts (10 mol%), two regioisomeric products were produced with poor selectivity (Table 1, entries 1–4); whereas, the regioselectivity was improved using Lewis acidic ionic liquids (Table 1, entries 5–9). Among different Lewis acidic ionic liquids, the best selectivity was achieved with [bmim][$InCl_4$], which afforded only one regioisomer (Table 1, entry 5). It should be noted that, in the absence of the catalyst, the reaction failed to give the desired product, even after extended reaction time (10 h, Table 1, entry 1). Subsequently, the effects on the yield of the product like temperature, the amount of the catalyst, and the reaction time were examined. Increasing either the temperature or the amount of the catalyst did not improve the yield (Table 1, entries 11 and 13), while decreasing either led to reduction in yield (Table 1, entries 12 and 14). Therefore, 1 mmol of [bmim][$InCl_4$] at 140 °C under solvent-free conditions was found to be optimal.

In order ascertain the effect of [bmim] on the rgioselectivity, the model reaction was also performed with Na[$InCl_4$]

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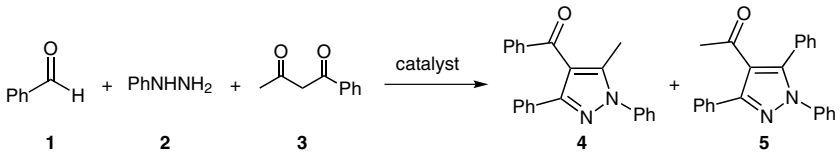
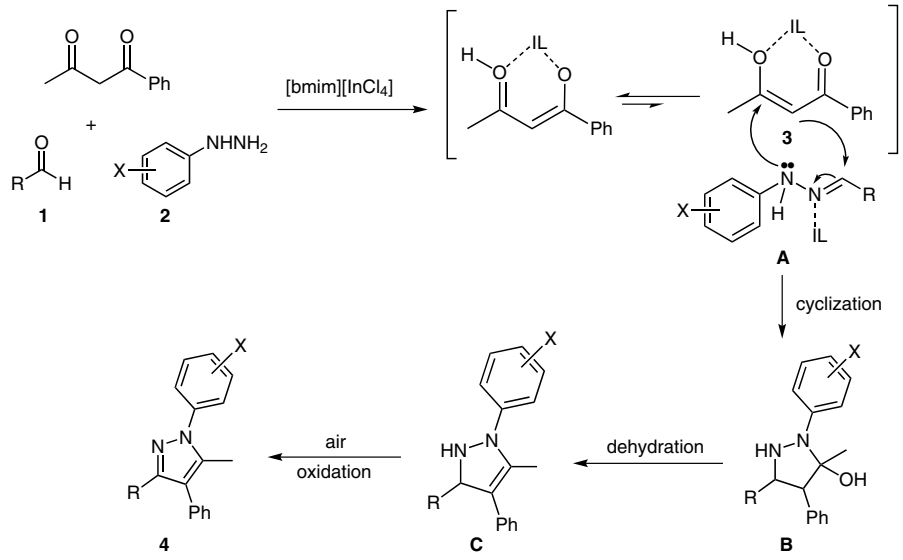
Table 1 The Effect of Reaction Parameters on the Regioselective Synthesis of **4a**[a]



Entry	Catalyst (mmol)	Time (min)	Yield (%)[b]	**4a**/**5a**
1	no catalyst	10	–	–
2	$Zn(OTf)_2$ (0.1)	60	90	80:20
3	$Bi(OTf)_3$(0.1)	60	82	55:45
4	$InCl_3{\cdot}4H_2O$ (0.1)	60	86	80:20
5	[bmim][$InCl_4$] (1)	60	85	100:0
6	[bmim][$CuCl_3$] (1)	60	78	90:10
7	[bmim][$FeCl_4$] (1)	60	60	100:0
8	[bmim][PF_6] (1)	60	15	100:0
9	[bpy][$InCl_4$] (1)	60	80	65:35
11	[bmim][$InCl_4$] (1.2)	60	86	100:0
12	[bmim][$InCl_4$] (0.85)	60	75	100:0
13[c]	[bmim][$InCl_4$] (1)	60	85	100:0
14[d]	[bmim][$InCl_4$] (1)	60	70	100:0
15	Na[$InCl_4$] (1)	60	85	80:20

[a] Reaction conditions: aldehyde (1 mmol), phenylhydrazine (1 mmol), benzoylacetone (1.2 mmol), solvent-free conditions, 140 °C.
[b] Isolated yield.
[c] Reaction was performed at 150 °C.
[d] Reaction was performed at 130 °C.

under the same reaction conditions. As can be seen, the yield is comparable to [bmim][$InCl_4$] but the regioselectivity is lower (Table 1, entry 15). According to the data in Table 1, it seems that the synergistic effect of anion and cation in [bmim][$InCl_4$] enhances the regioselctivity.



Scheme 2 Proposed mechanism for the regioselective synthesis of fully substituted pyrazoles catalyzed by [bmim][$InCl_4$]

Under the optimized conditions, aldehydes or hydrazines containing electron-withdrawing and electron-donating groups in the aromatic ring reacted smoothly with unsymmetrical 1,3-diketones such 1-phenylbutane-1,3-dione in the presence of [bmim][$InCl_4$] to afford the corresponding fully substituted pyrazoles in high yields and total regioselectivity (Table 2, entries 1–7). The symmetrical 1,3-diketone, acetylacetone, also reacted efficiently to give the desired products in high yields (Table 2, entries 8 and 9).

Table 2 Synthesis of Fully Substituted Pyrazoles and Pyrazole-Fused Cyclohexanones Catalyzed by [bmim][$InCl_4$][a]

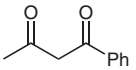
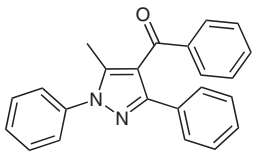
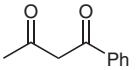
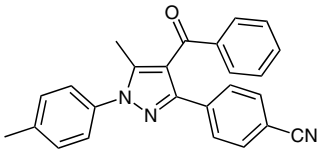
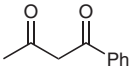
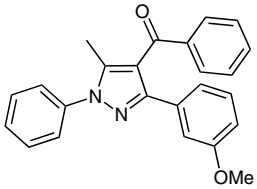
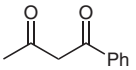
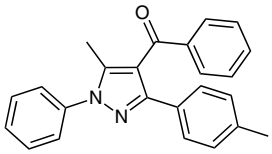
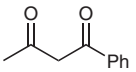
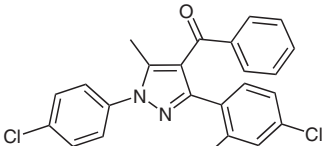
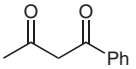
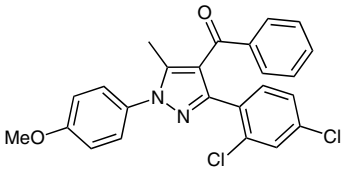
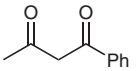
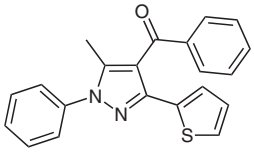
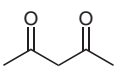
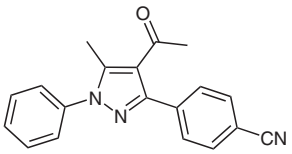
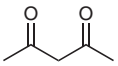
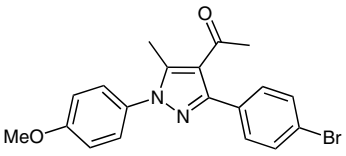
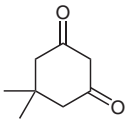
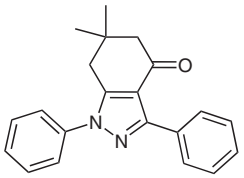
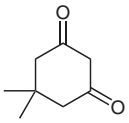
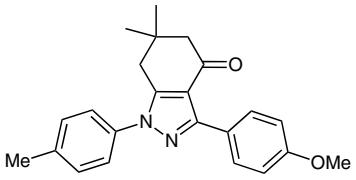
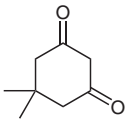
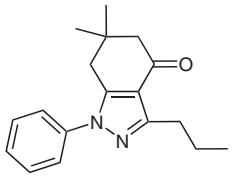
Entry[b]	R^1	R^2	1,3-Diketone	Product **4**		Time (min)	Yield (%)
1	Ph	Ph			**4a**	60	85
2	4-CNC_6H_4	4-MeC_6H_4			**4b**	70	80
3	3-$MeOC_6H_4$	Ph			**4c**	60	83
4	4-MeC_6H_4	Ph			**4d**	60	90
5	2,4-$Cl_2C_6H_3$	4-ClC_6H_4			**4e**	60	78
6	2,4-$Cl_2C_6H_3$	4-$MeOC_6H_4$			**4f**	60	82
7	2-thiophene	Ph			**4g**	60	72
8	4-CNC_6H_4	Ph			**4h**	120	68

Table 2 Synthesis of Fully Substituted Pyrazoles and Pyrazole-Fused Cyclohexanones Catalyzed by [bmim][$InCl_4$][a] (continued)

Entry[b]	R^1	R^2	1,3-Diketone	Product **4**		Time (min)	Yield (%)
9	4-BrC_6H_4	4-$MeOC_6H_4$			**4i**	90	71
10	Ph	Ph			**4j**	60	70
11	4-$MeOC_6H_4$	4-MeC_6H_4			**4k**	60	80
12	*n*-Bu	Ph			**4l**	60	61

[a] Reaction conditions: aldehyde (1 mmol), arylhydrazine(1 mmol), 1,3-diketone (1.2 mmol), catalyst (1 mmol), solvent-free conditions, 140 °C.
[b] Isolated yield.

To expand the scope of this new multicomponent reaction further and cognizant of the applications of heterocycle-fused cyclohexanone in medicinal chemistry,[22] the synthesis of pyrazole-fused cyclohexanones was also examined. The reaction of several hydrazones with dimedone in the presence of [bmim][$InCl_4$] proceeded efficiently to provide the corresponding pyrazole-fused cyclohexanones in high yields (Table 2, entries 10–12). To the best of our knowledge, there are only a few reports on the synthesis of pyrazole-fused cyclohexanones,[23] but there is no report on the regioselective synthesis of fully substituted pyrazoles and pyrazole-fused cyclohexanones through the one-pot multicomponent reaction of aldehydes and arylhydrazines with unsymmetrical diketones or dimedone. Consequently, this strategy can be considered as a useful advance in the preparation of such heterocycle libraries.

A plausible mechanism for the regioselective formation of pyrazoles is proposed in Scheme 2. The hydrazone **A** is first produced by the reaction of aldehyde with arylhydrazine, which upon reaction with the enol form of 1,3-dicarbonyl compound gives intermediate **B**. Dehydration of the intermediate **B** affords pyrazoline **C**, which upon aromatization gives the corresponding pyrazole **4**.

The structures of the products were confirmed by their IR, mass, ^1H NMR, and ^{13}C NMR spectra and elemental analysis. Furthermore, the structure of **4g** was confirmed by X-ray crystallographic analysis (Figure 1; CCDC 905447).

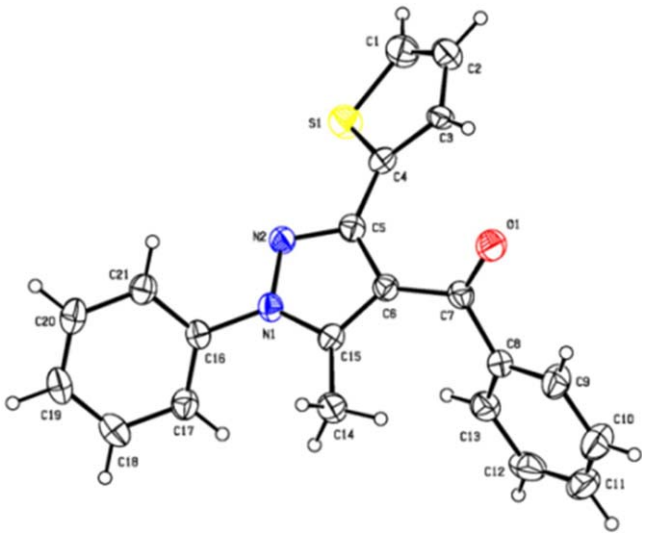


Figure 1 X-ray crystal structure of **4g**

The recyclability of the catalyst was investigated in the model reaction. After completion of the reaction, the mixture was cooled to room temperature and water was added. The crude product was filtered, and the aqueous layer was evaporated under reduced pressure. The recovered

catalyst was dried and reused at least three times without showing obvious loss of activity.

In summary, we have demonstrated a regioselective, efficient, and novel three-component synthesis of fully substituted pyrazoles and pyrazole-fused cyclohexanones in the presence of the Lewis acidic room-temperature ionic liquid, [bmim][$InCl_4$], as a reusable and green catalyst. Short reaction times, high yields of products, and operational simplicity make this method a practical and attractive process for the synthesis of pyrazole derivatives.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(21) **General Procedure for the Synthesis of Fully Substituted Pyrazoles and Pyrazole-Fused Cyclohexanones**
A mixture of aldehyde **1** (1 mmol) and arylhydrazine **2** (1 mmol) was stirred for 20 min, then 1,3-diketone **3** (1.2 mmol) and [bmim][$InCl_4$] (1 mmol) were added, and the mixture was stirred at 140 °C for the appropriate time according to Table 2. The progress of the reaction was monitored by TLC (eluent: *n*-hexane–EtOAc, 10:1). After completion of reaction, the mixture was cooled to r.t. and H_2O was added (30 mL). The mixture was filtered, and the crude residue was purified by recrystallization from EtOH to afford the pure product. If necessary, the product was purified by silica gel column chromatography (eluent: *n*-hexane–EtOAc, 12:1).
(5-Methyl-1,3-diphenyl-1*H*-pyrazol-4-yl)(phenyl)methanone (4a)
Mp 100–103 °C. IR (KBr): ν_{max} = 3059, 2925, 1725, 1643, 1498, 1252, 911, 772, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 7.12–7.14 (m, 3 H), 7.22 (t, J = 8 Hz, 2 H), 7.34–7.56 (m, 8 H), 7.71 (dd, J_1 = 8.2 Hz, J_2 = 0.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.26, 118.83, 125.56, 127.92, 127.99, 128.06, 128.61, 128.65, 129.30, 129.72, 132.44, 132.55, 138.40, 138.84, 143.27, 152.45, 192.74. MS: *m/z* (%) = 339.13 (54.12) $[M + 1]^+$, 338.13 (82.75) $[M]^+$, 261.10 (79.61), 167.07 (70.20), 148.96 (95.69), 76.63 (100), 57.08 (100). Anal. Calcd for $C_{23}H_{18}N_2O$ (338.4): C, 81.63; H, 5.36; N, 8.28. Found: C, 81.59; H, 5.46; N, 8.20.

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