An Efficient One-pot Synthesis of Pyrazolone Derivatives Promoted by Acidic Ionic Liquid

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A new class of pyrazolone derivatives has been isolated in good to excellent yields from the 2∶1 condensation reaction between 3-methyl-1-phenyl-5-pyrazolone and arylaldehydes in the presence of ionic liquid [HMIM]HSO_4. The compounds were characterised by their IR, NMR spectra, MS and elemental analyses. The important features of the methodology are a wide application range of substrates, higher yields and shorter reaction time.

Keywords pyrazole, ionic liquid, 3-methyl-1-phenyl-5-pyrazolone, aldehydes

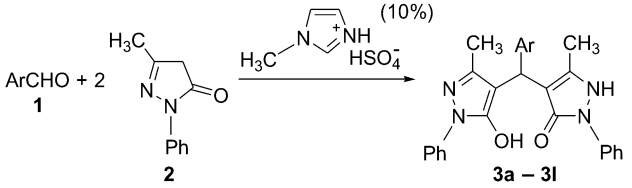
Introduction

The pyrazole moiety is one of the significant core structures in natural and unnatural heterocyclic compounds with prominent properties.[1] Among pyrazoles, 2,4-dihydro-3*H*-pyrazol-3-one derivatives are of considerable interests: some are biologically active with anti-inflammatory, antipyretic, antibacterial, gastric secretion stimulatory, antidepressant, and antifilarial activity,[2,3] others are important intermediates in organic synthesis. For instance, aryl-bis(3-methyl-1-phenyl-5-pyrazol-one-4-yl)methane forms the basis of nitro-heterocycle to the dipyrazolo diazepine derivative.[4]

The condensation of aldehydes with 3-methyl-1-phenyl-5-pyrazolone is a known used route for synthesizing 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ols). Acetic acid or piperidine,[5] sodium dodecyl sulfate,[6] ETBA[7] and CAN[8] can be used as catalysts for this transformation. The electrocatalytic procedure and solid-state condensation procedure were also applied to the preparation of 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ols).[9-12] So far, intensive work has been focused on developing efficient catalytic systems for conforming to the concept of green chemistry. Recently, Niknam *et al*. reported a reaction for the synthesis of 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ols) through the condensation of aldehydes with 3-methyl-1-phenyl-5-pyrazolone in the presence of silica-bonded *S*-sulfonic acid.[13] However, the synthesis of 4-[(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-phenyl-methyl]-5-methyl-2-phenyl-1,2-dihydro-pyrazol-3-ones **3a**—**3l** from aldehydes and 3-methyl-1-phenyl-5-pyrazolone has seldom been reported.

Ionic liquids, especially those based on the imidazolium cation, have attracted increasing interest in the context of green synthesis due to their many unique properties. For example, they have practical non-volatility, low melting point as well as good electrochemical and thermal stability. 1-Methylimidazolium hydrogen sulfate ([HMIM]HSO_4) is a Brφnted acidic ionic liquid and has been used as catalyst in organic reactions.[14,15] To the best of our knowledge, there is a lack of literature on the synthesis of 4-[(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-phenyl-methyl]-5-methyl-2-phenyl-1,2-dihydro-pyrazol-3-ones catalyzed by [HMIM]HSO_4. In continuation of our interest in the synthesis of heterocyclic compounds, we describe the synthesis of 4-[(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-phenyl-methyl]-5-methyl-2-phenyl-1,2-dihydro-pyrazol-3-ones via the reaction between 3-methyl-1-phenyl-5-pyrazolone and arylaldehydes catalyzed by ionic liquid [HMIM]HSO_4 in ethanol (Scheme 1).

Scheme 1



Experimental

All reagents were purchased from Tianjin KEMIOU Chemical Agents Co., Ltd. and liquid aldehydes were purified by distillation before use. [HMIM]HSO_4, [BMIM]Cl, [BMIM]Br, [BMIM]BF_4 and [BMIM]OAc were synthesized based on the literature.[16,17] Melting

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points were measured on an electrothermal apparatus and were uncorrected.

General procedure

To a solution of 1-phenyl-3-methyl-pyrazol-5-one (2 mmol) and [HMIM]HSO_4 (10 mol%) in 5 mL ethanol aromatic aldehyde (1 mmol) was added. The mixture was stirred at refluxing for an appropriate time. After the completion of the reaction followed by TLC and cooling the reaction mixture to room temperature, 20 mL water was added. Then the obtained product was filtered, dried and if necessary was purified by column chromatography on silica gel to afford the pure product. All the known products **3a**—**3l**, **4m** were fully characterized by IR and ^{1}H NMR spectroscopy, and melting points, which were consistent with the literature data.

Rusults and discussion

As shown in Table 1, 3-methyl-1-phenyl-5-pyrazolone was treated with benzaldehyde in the presence of 10% of [HMIM]HSO_4 in 5 mL ethanol under reflux condition to afford **3a**, which was obtained in higher yield (81%, Entry 2) in comparsion with the condition of stirring at room temperature (41%, Entry 1). To investigate the effect of [HMIM]HSO_4, the synthesis of **3a** as a model was studied with and without [HMIM]HSO_4 (Table 1, Entryies 2, 7) at the same temperature (75 ℃). Furthermore, other ionic liquids, such as [BMIM]Cl, [BMIM]Br, [BMIM]BF_4 and [BMIM]OAc, were examined as catalysts for the reaction between 3-methyl-1-phenyl-5-pyrazolone and benzaldehyde (Table 1, Entryies 3—6). The products were obtained in 72%, 66%, 69% and 68% yields, respectively. It was obvious that [HMIM]-HSO_4 was an efficient catalyst for this transformation.

Subsequently, to show the role of the ratio of the starting reactants, treatment of 4-chlorobenzaldehyde with 3-methyl-1-phenyl-5-pyrazolone (molar ratio 1∶1) was carried out. The mixture of **3b** (74%) and the 1∶1 product **4b** (22%) was obtained. However, when the ratio of the starting reactants was 1∶2, **3b** was produced as the single product. The results showed that the ratio of the starting reactants has effect on the reaction to some extent. Thus, the 1∶2 ratio of the starting reactants was chosen in the subsequent reactions.

To examine the scope and limitation of this process, we selected various arylaldehydes and conducted the reactions in order to synthesize a series of pyrazolone

Table 1 Synthesis of **3a** under different conditions

Entry	Catalyst	Catalyst loading/%	Conditions	Time/min	Yield/%
1	[HMIM]HSO_4	10	r.t., stirring	20	41
2	[HMIM]HSO_4	10	reflux at 75 ℃	20	81
3	[BMIM]Cl	10	reflux at 75 ℃	20	72
4	[BMIM]Br	10	reflux at 75 ℃	20	66
5	[BMIM]BF_4	10	reflux at 75 ℃	20	69
6	[BMIM]OAc	10	reflux at 75 ℃	20	68
7	[HMIM]HSO_4	0	reflux at 75 ℃	20	46

Table 2 The condensation of arylaldehydes with 3-methyl-1-phenyl-5-pyrazolone catalyzed by [HMIM]HSO_4 in ethanol under reflux at 75 ℃

Entry	Ar	Product **3**	Time/min	Yield/%	m.p./℃	
					Found	Report
a	C_6H_5	**3a**	20	81	167—169	169—171[18]
b	4-ClC_6H_4	**3b**	10	88	214—215	214—21[18]
c	2-ClC_6H_4	**3c**	10	83	235—238	235—237[18]
d	2,4-$(Cl)_2C_6H_3$	**3d**	10	81	226—228	228—230[18]
e	2-BrC_6H_4	**3e**	15	77	230—232	229—231[18]
f	4-$O_2NC_6H_4$	**3f**	20	90	218—220	218—220[18]
g	3-$O_2NC_6H_4$	**3g**	15	91	153—155	153—155[18]
h	2-$O_2NC_6H_4$	**3h**	5	80	219—221	221—222[18]
i	2-HOC_6H_4	**3i**	35	82	223—225	222—226[18]
j	4-HOC_6H_4	**3j**	35	85	158—159	157—159[18]
k	2-$CH_3OC_6H_4$	**3k**	25	93	210—212	210—213[18]
l	4-$CH_3OC_6H_4$	**3l**	35	87	172—173	172—173[18]
m	4-$(CH_3)_2NC_6H_4$	**4m**	17	72	193—195	194—195[12]

derivatives. The results are listed in Table 2. We found that the reactions proceeded efficiently and provided the corresponding products in good to excellent yields. The substituents (either electron-withdrawing or electron-donating groups, except *p*-dimethylamino) on the benzene ring in the arylaldehydes do not significantly affect neither the yields of the products nor the selectivities. Although the differences in the reaction times were slight, generally the electron-withdrawing (nitro groups) were superior to the electron-donating ones (hydroxyl groups and methoxy groups) in this regard. When the condensation of *p*-(dimethylamino)benzaldehyde with 3-methyl-1-phenyl-5-pyrazolone was carried out under the same conditions, the reaction mainly gave the 1∶1 product. Similar phenomenon and the reason have been described in the literatures reported by Li *et al*. and Devinder Singh.[5,10]

Conclusions

In summary, a highly efficient method for the synthesis of 4-[(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-phenyl-methyl]-5-methyl-2-phenyl-1,2-dihydro-pyrazol-3-ones through the condensation of 3-methyl-1-phenyl-5-pyrazolone with arylaldehydes under reflux conditions has been described. The present methodology offers several advantages such as short reaction times, high yields, high selectivity, and easy separation of the products.

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