2-Hydroxyethylammonium acetate as a reusable and cost-effective ionic liquid for the efficient synthesis of bis(pyrazolyl)methanes and 2-pyrazolyl-1-nitroalkanes

Sara Sobhani, Razieh Nasseri, and Moones Honarmand

Abstract: A new and convenient method for the synthesis of bis(pyrazolyl)methanes by one-pot tandem Knoevenagel–Michael reaction of 3-methyl-1-phenyl-5-pyrazolone with aryl, heteroaryl, or alkyl aldehydes in the presence of 2-hydroxyethylammonium acetate (2-HEAA) as a task-specific ionic liquid is described. This method was also successfully applied for the synthesis of 2-pyrazolyl-1-nitroalkanes by Michael addition of 3-methyl-1-phenyl-5-pyrazolone with β-nitrostyrenes in short reaction times. The present protocol offers several advantages such as using a reusable and cost-effective ionic liquid, an environmentally benign reaction media, being amenable to scale-up and good to high yields of the products.

Key words: bis(pyrazolyl)methane, ionic liquid, aldehydes, β-nitrostyrene.

Résumé : On a développé une méthode nouvelle et simple de synthèse des bis(pyrazolyl)méthanes par une réaction monotope en tandem de Knoevenagel–Michael de la 3-méthyl-1-phényl-5-pyrazolone avec des aldéhydes d'aryles, d'hétéroaryles ou d'alkyles, en présence d'acétate de 2-hydroxyéthylammonium (acétate de 2-HEA) dans un liquide ionique spécifique pour cette réaction. On a appliqué cette méthode avec succès pour la synthèse de 2-pyrazolyl-1-nitroalcanes par le biais d'une addition de Michael de la 3-méthyl-1-phényl-5-pyrazolone sur le β-nitrostyrène avec un très court temps de réaction. Le présent protocole offre plusieurs avantages, tel l'usage d'un liquide ionique réutilisable et efficace, un milieu réactionnel écologique et la possibilité de pouvoir être amené à produit des grandes quantités de produits avec des rendements allant de bons à élevés.

Mots-clés : bis(pyrazolyl)méthane, liquide ionique, aldéhydes, β-nitrostyrène.

[Traduit par la Rédaction]

Introduction

Pyrazoles are an important class of bioactive drug targets in the pharmaceutical industry, as they are the core structure of numerous biologically active compounds.[1–3] Among the pyrazole derivatives, the synthesis of pyrazolone derivatives has attracted much attention from organic chemists because of their various biological activities, such as antitumor[4,5] and selective COX-2 inhibitory.[6] Pyrazolone derivatives are also used as cytokine inhibitors,[7] human telomerase inhibitors,[8] therapeutics for kinase-mediated inflamatory disorders,[9] and dyes.[10,11] For example, 2,4-dihydro-3*H*-pyrazol-3-one derivatives, including 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s, are being used as anti-inflammatory, antipyretic, gastric secretion stimulatory antidepressant, antibacterial, and antifilarial agents.[12–16] Moreover, the corresponding 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ol)s are applied as fungicides, pesticides, insecticides, dyestuffs, and chelating and extracting reagents for different metal ions.[17–20] The conventional chemical approach to 4,4′-(arylmethylene) bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s involves the successive Knoevenagel synthesis of the corresponding arylidene-pyrazolones and its base-promoted Michael reaction.[17,18,21] One-pot tandem Knoevenagel–Michael reaction of aldehydes with 2 equiv of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one, which was performed under a variety of reaction conditions, is another approach for achieving these important scaffolds.[22–33] Even though, 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s could be synthesized by these methods, most of the methods suffer from limitations such as low yields, long reaction time, application of hazardous solvents, tedious work-up procedures and noncompliance with green chemistry protocols. On the other hand, a literature survey indicates that the methods for the synthesis of 4-substituted pyrazolones are mainly focused on the condensation reaction of 3-methyl-1-phenyl-5-pyrazolone with aldehydes.[22–33] It also shows that Michael addition of pyrazolone with Michael acceptors such as β-nitrostyrene as possibly the strongest and particularly versatile Michael acceptors has been less explored.[34,35] Therefore, it is necessary to develop an efficient and convenient method for the synthesis of 4-substituted pyrazolones such as bis(pyrazolyl)methanes and 2-pyrazolyl-1-nitroalkanes.

Received 14 April 2012. Accepted 17 July 2012. Published at www.nrcresearchpress.com/cjc on 19 September 2012.

S. Sobhani, R. Nasseri, and M. Honarmand. Department of Chemistry, College of Sciences, Birjand University, Birjand 414, Iran.

Corresponding author: Sara Sobhani (e-mail: ssobhani@birjand.ac.ir, sobhanisara@yahoo.com).

In recent years, room-temperature ionic liquids have received considerable attention as an alternative green reaction medium for numerous organic reactions because of their favorable properties, such as good solvating capability, wide liquid range, negligible vapor pressure, tunable polarity, high thermal stability, and ease of recyclability.[36,37] Ionic liquids, as catalysts, have also played a significant role in controlling these reactions.[38–40] The major concern in using ionic liquids as reaction media in industrial processes is the cost of the ionic liquid, which would be directly dependent on the price of the cations and anions that are used for their production.[41] The currently popular ionic liquids incorporate expensive cations, such as alkyl methyl imidazolium or dialkyl imidazolium, and expensive anions, such as tetrafluoroborate or hexafluorophosphate. Thus, introduction of cost-effective ionic liquids as reaction media should be a priority.

Having this point in mind, and as part of our continued interest in the development of new methods for the synthesis of pyrazolone derivatives,[30,31] herein, we wish to report a new method for environmentally benign synthesis of bis(pyrazolyl)methanes and 2-pyrazolyl-1-nitroalkanes in the presence of 2-hydroxyethylammonium acetate (2-HEAA)[42–44] as a cost-effective and reusable ionic liquid at room temperature.

Results and discussion

At first, to find the best solvent, the reaction of benzaldehyde (1 equiv) with 3-methyl-1-phenyl-5-pyrazolone (**1**, 2 equiv) was studied in EtOH, H_2O, CH_3CN, CH_2Cl_2, petroleum ether, and toluene in the presence of 2-HEAA (5 mol %) at room temperature (Table 1, entries 1–6). The results revealed that EtOH was the best solvent for this reaction (Table 1, entry 1). Low yield of the product was obtained in the absence of any solvent (Table 1, entry 7).

In the next step, to show the generality of this method, the reaction of different types of aldehydes with **1** in the presence of 2-HEAA (5 mol %) in EtOH at room temperature was investigated (Scheme 1). The results of these studies are summarized in Table 2.

As shown in Table 2, substituted benzaldehyde with electron-donating and electron-withdrawing groups underwent one-pot tandem Knoevenagel–Michael reaction with 2 equiv of **1** and gave the corresponding products in 74%–95% yields (entries 1–6). Both formyl groups in terphthaldehyde reacted with **1** to produce the desired product in 85% yield (Table 2, entry 7). The reaction of naphthalene-2-carbaldehyde as a polynuclear aromatic aldehyde gave the corresponding product in 40 min (Table 2, entry 8). Acid-sensitive aldehydes, such as thiophene-2-carbaldehyde, underwent smooth reactions without any decomposition or polymerization (Table 2, entry 9). This method is also applicable for the synthesis of bis(pyrazolyl)methanes (**2j** and **2k**) from the reaction of **1** with aliphatic aldehydes (Table 2, entries 10 and 11).

It was observed that the ionic liquid was reusable at least 15 times in multiple sequential condensations by the addition of new samples of benzaldehyde and **1** to the reaction mixture. This protocol was also easily amenable to scale-up. For example, the condensation of benzaldehyde with **1** in a semi scale-up procedure (20 times) was carried out successfully and produced the desired product in 85% yield.

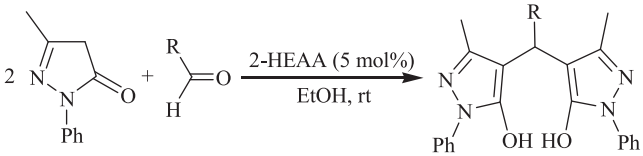
It is important to note that the reports for the condensation reaction of aldehydes with **1** in ionic liquid are rare in the literature.[45,46] In these reports, 4-[(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-phenyl-methyl]-5-methyl-2-phenyl-1,2-dihydropyrazol-3-ones (Fig. 1) were obtained instead of bis(pyrazolyl)methanes (**2**). Therefore, the present method is the first protocol for the synthesis of bis(pyrazolyl)methanes in the presence of an ionic liquid.

Table 1. Reaction of 3-methyl-1-phenyl-5-pyrazolone (**1**) with benzaldehyde under different reaction conditions.

Entry	Catalyst	Solvent	Time (min)	Yield (%)[a]
1	Ionic liquid	EtOH	15	90
2	Ionic liquid	H_2O	15	30
3	Ionic liquid	CH_3CN	60	70
4	Ionic liquid	CH_2Cl_2	60	65
5	Ionic liquid	Petroleum ether	60	60
6	Ionic liquid	Toluene	60	65
7	Ionic liquid	—	30	30

[a]Isolated yield; reaction conditions: benzaldehyde (1 mmol), 3-methyl-1-phenyl-5-pyrazolone (**1**, 2 mmol), catalyst (5 mol%), room temperature.

Scheme 1.



1 **2a-k**

R = aryl, alkyl, heteroaryl

To show the catalytic effect of 2-HEAA on the synthesis of bis(pyrazolyl)methanes **2**, the coupling reaction between benzaldehyde and **1** in the absence of ionic liquid at room temperature was considered. This reaction led to the formation of the desired product (**2a**) in low yield (40%) after 20 h (Table 3, entry 1). A similar reaction in the presence of $[CH_3CH_2NH_3^+][AcO^-]$ proceeded with a longer reaction time compared with 2-HEAA and produced the desired product in 81% yield (Table 3, entries 2 and 3). These results showed the role of the hydroxyl group of 2-HEAA in imparting the catalytic property and indicates that 2-HEAA can act as a functionalized or task-specific ionic liquid in this method. We have also found that lengthening of the alkyl chain in $[HO(CH_2)_nNH_3^+][AcO^-]$ has no influence on the efficiency of the ionic liquid (Table 3, entries 4 and 5).

We also suggest a plausible mechanism for the reaction of **1** and aldehydes in the presence of 2-HEAA (Scheme 2). The process represents a typical tandem reaction in which aldehydes first condensed with **1** to form the Knoevegel product followed by Michael addition with **1** to produce bis(pyrazolyl)methanes **2**. In this reaction, two spontaneous interactions between NH_3^+ and the OH of 2-HEAA with the carbonyl groups of aldehydes and the methylene group of **1** took place. These interactions activated the reactants and facilitated formation of the product.

Successful application of 2-HEAA as a reusable ionic liquid for the one-pot synthesis of bis(pyrazolyl)methanes encouraged us to study the applicability of this method for the synthesis of 2-pyrazolyl-1-nitroalkanes by the reaction of 3-

Table 2. Synthesis of bis(pyrazolyl)methanes **2a**–**2k** catalyzed by 2-hydroxyethylammonium acetate (2-HEAA).

Entry (Ref.)	Aldehyde	Product	Time (min)	Yield (%)[a]
1 (27)	3-Methylbenzaldehyde	**2a**	15	91
2 (30, 33)	4-Chlorobenzaldehyde	**2b**	15	92
3 (30)	4-Bromobenzaldehyde	**2c**	12	93
4 (30)	4-Nitrobenzaldehyde	**2d**	5	95
5 (27)	4-Cyanobenzaldehyde	**2e**	5	95
6 (30)	4-Hydroxybenzaldehyde	**2f**	30	74
7 (27)	Terephthaldehyde[b]	**2g**	40	85
8 (30)	Naphthalene-2-carbaldehyde	**2h**	40	81
9 (30)	Thiephene-2-carbaldehyde	**2i**	40	85
10 (30)	Isobutyraldehyde	**2j**	30	92
11 (30)	*n*-Butyraldehyde	**2k**	15	83

[a]Isolated yield; reaction conditions: 2-HEAA (5 mol %), EtOH, room temperature.
[b]Reaction conditions: terephthaldehyde (1 mmol), and 3-methyl-1-phenyl-5-pyrazolone (**1**, 4 mmol), 2-HEAA (5 mol %), EtOH (4 mL), room temperature.

Fig. 1. 4-[(5-Hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-phenylmethyl]-5-methyl-2-phenyl-1,2-dihydropyrazol-3-ones.

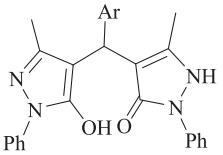


Table 3. The coupling reaction of benzaldehyde and 3-methyl-1-phenyl-5-pyrazolone (**1**) in the presence of different $[X(CH_2)_nNH_3^+][AcO^-]$.

Entry	$[X(CH_2)_nNH_3^+][AcO^-]$	Time	Yield (%)[a]
1	—	20 h	40
2	$n = 2$, X = H	1 h	81
3	$n = 2$, X = OH	20 min	90
4	$n = 3$, X = OH	20 min	90
5	$n = 5$, X = OH	15 min	92

[a]Isolated yield. Reaction conditions: benzaldehyde (1 mmol), 3-methyl-1-phenyl-5-pyrazolone (**1**, 2 mmol), ionic liquid (5 mol %), EtOH (4 mL), room temperature.

methyl-1-phenyl-5-pyrazolone with β-nitrostyrene (Scheme 3 and Table 4). As indicated in Table 4, Michael addition of 3-methyl-1-phenyl-5-pyrazolone with β-nitrostyrenes bearing electron-withdrawing or electron-releasing groups proceeded well to afford the corresponding 2-pyrazolyl-1-nitroalkanes in 83%–95% yields.

Conclusions

In conclusion, we have successfully developed a new and simple protocol for the synthesis of bis(pyrazolyl)methanes via a one-pot tandem Knoevenagel–Michael reaction in the presence of 2-HEAA as a task-specific ionic liquid. This simple procedure allows a series of bis(pyrazolyl)methanes to be synthesized in good to high yields from the reaction of aryl, heteroaryl, or alkyl aldehydes and 3-methyl-1-phenyl-5-pyrazolone at room temperature. The method was also applicable for the synthesis of 2-pyrazolyl-1-nitroalkanes via Michael addition reaction of 3-methyl-1-phenyl-5-pyrazolone with β-nitrostyrene in short reaction times. The present protocol offers several advantages such as using a reusable and cost-effective ionic liquid, an environmentally benign reaction media, being amenable to scale-up, and good to high yields of the products.

Experimental section

General procedures and materials

Chemicals were purchased from the Merck and Fluka Chemical Companies. Melting points were determined by a Buchi 510 apparatus and are uncorrected. IR spectra were run on a PerkinElmer 780 instrument. NMR spectra were recorded on a Bruker Avance DPX-250, 400, or 500. Mass spectra were recorded on a Shimadzu GC–MS QP5050A spectrometer operating at an ionization potential of 70 eV. Conductivities were measured by an Istek 915PDC apparatus at 25 °C. The electrochemical measurements were performed by a Solartron Electrochemical Interface model 1287 at 25 °C. The purity of the products and the progress of the reactions were accomplished by TLC on silica gel polygram SILG/UV_{254} plates. Elemental analysis for C, H, and N were obtained by using an Elementar Vario EL III.

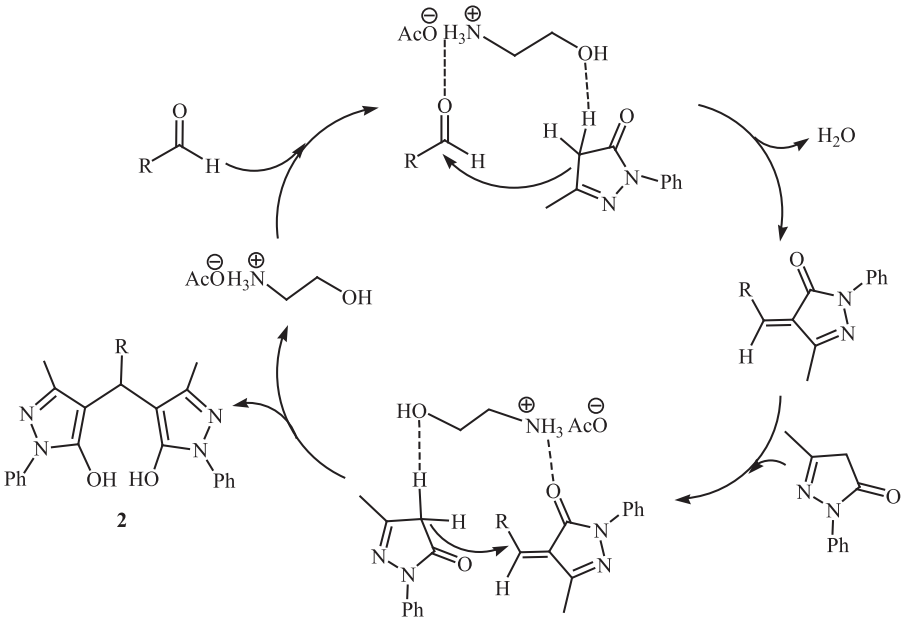
A typical procedure for the synthesis of 2-HEAA

2-HEAA was prepared according to a previously reported procedure.[43] A solution of acetic acid (50 mmol, 3.00 g) in EtOH (1.5 mL) was added dropwise to a stirring solution of 2-aminoethanol (50 mmol, 3.05 g) in EtOH (1.5 mL) at room temperature within 1 h. The resultant solution was stirred at room temperature for another 20 h. EtOH was removed in vacuo, and the oil residue was dried in vacuo at 50 °C for 48 h to give 2-HEAA as a yellow viscous liquid (pH 7.96 at 25 °C, bp 191 °C, density = 1.11 g cm^{-3} at 25 °C, electrochemical stability between –0.6 and 0.7 V, relative viscosity = 9390.6 at 25 °C, conductivity = 263.3 μs cm^{-1}).

General procedure for the synthesis of bis(pyrazolyl) methanes (2)

2-HEAA (5 mol%) was added to a mixture of aldehyde (1 mmol) and **1** (2 mmol) in EtOH (4 mL) at room temperature. The mixture was stirred at room temperature for the

Scheme 2.



Scheme 3.

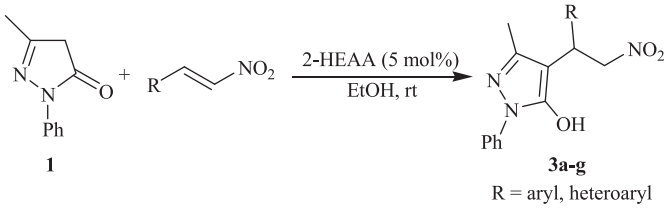


Table 4. Synthesis of 2-pyrazolyl-1-nitroalkanes **3a**–**3g** catalyzed by 2-hydroxyethylammonium acetate (2-HEAA).

Entry (Ref.)	R	Product	Time (min)	Yield (%)[a]
1 (35)	C_6H_5	**3a**	10	83
2 (34)	2-$CH_3OC_6H_4$	**3b**	8	91
3	4-$CH_3C_6H_4$	**3c**	8	84
4	4-ClC_6H_4	**3d**	5	95
5	4-$NO_2C_6H_4$	**3e**	5	95
6	4-BrC_6H_4	**3f**	8	95
7	2-Thienyl	**3g**	10	88

[a]Isolated yield. Reaction conditions: 3-methyl-1-phenyl-5-pyrazolone (**1**, 1 mmol), β-nitrostyrene (1 mmol), 2-HEAA (5 mol %), EtOH (4 mL), room temperature.

appropriate time (Table 2). After evaporation of the solvent, water (10 mL) was added to the reaction mixture and the resulting solid was filtered and washed three times with H_2O (5 mL). The pure product (**2**) was obtained from this solid by recrystallization in EtOH.

4,4′-[(3-Methylphenyl)methylene]bis(3-methyl-1-phenyl-pyrazol-5-ol) (2a)

White solid; yield: 91%, 0.41 g; mp 193–194 °C. IR (ν_{max}, cm^{-1}): 3023 (O–H). ^1H NMR (400 MHz, DMSO-d_6) δ_H: 2.25 (3H, s, CH_3), 2.31 (6H, s, CH_3), 4.91 (1H, s, CH), 6.98 (1H, d, $^3J_{HH}$ = 7.6 Hz, Ar), 7.06 (1H, s, Ar), 7.07 (1H, d, $^3J_{HH}$ = 6.8 Hz, Ar), 7.16 (1H, t, $^3J_{HH}$ = 7.2 Hz, Ar), 7.25 (2H, t, $^3J_{HH}$ = 7.2 Hz, Ar), 7.44 (4H, t, $^3J_{HH}$ = 7.6 Hz, Ar), 7.71 (4H, d, $^3J_{HH}$ = 7.6 Hz, Ar), 13.98 (2H, br s, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 12.1, 21.7, 33.6, 121.0, 124.8, 126.0, 127.1, 128.2, 128.5, 129.4, 137.5, 142.7, 146.7. MS *m/z* (%): 276 (28.4), 174 (21).

4,4′-[(4-Chlorophenyl)methylene]bis(3-methyl-1-phenyl-pyrazol-5-ol) (2b)

White solid; yield: 92%, 0.43 g; mp 212–214 °C. IR (ν_{max}, cm^{-1}): 3044 (O–H). ^1H NMR (500 MHz, DMSO-d_6) δ_H: 2.32 (6H, s, CH_3), 4.97 (1H, s, CH), 7.26 (4H, d, $^3J_{HH}$ = 8.2 Hz, Ar), 7.34 (2H, d, $^3J_{HH}$ = 8.0 Hz, Ar), 7.44 (4H, t, $^3J_{HH}$ = 7.14 Hz, Ar), 7.71 (4H, d, $^3J_{HH}$ = 7.6 Hz, Ar), 12.40 (1H, br s, OH), 13.87 (1H, br s, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 33.4, 40.1, 121.4, 126.4, 128.9, 129.8, 130.0, 131.4, 142.0, 147.1. MS *m/z* (%) 296 (6.3), 174 (14.0).

4,4′-[(4-Bromophenyl)methylene]bis(3-methyl-1-phenyl-pyrazol-5-ol) (2c)

White solid; yield: 93%, 0.48 g; mp 215–216 °C. ^1H NMR (400 MHz, DMSO-d_6) δ_H: 2.32 (6H, s, CH_3), 4.95 (1H, s, CH), 7.19 (2H, d, $^3J_{HH}$ = 8.0 Hz, Ar), 7.23–7.26 (2H, m, Ar), 7.42–7.48 (6H, m, Ar), 7.69 (4H, d, $^3J_{HH}$ = 7.6 Hz, Ar), 12.52 (1H, br s), 13.87 (2H, br s, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 12.1, 33.0, 119.5, 121.0, 126.1, 129.34, 130.0, 131.4, 142.1, 146.7.

4,4′-[(4-Nitrophenyl)methylene]bis(3-methyl-1-phenyl-pyrazol-5-ol) (2d)

Yellow solid; yield: 95%, 0.46 g; mp 229–231 °C. IR (ν_{max}, cm^{-1}): 3056 (O–H). ^1H NMR (500 MHz, DMSO-d_6) δ_H: 2.35 (6H, s, CH_3), 5.13 (1H, s, CH), 7.25–7.27 (2H, m, Ar), 7.44 (4 H, t, $^3J_{HH}$ = 7.0 Hz, Ar), 7.52 (2H, d, $^3J_{HH}$ = 8.1 Hz, Ar), 7.71 (4H, d, $^3J_{HH}$ = 7.6 Hz, Ar), 8.17 (2H, d, $^3J_{HH}$ = 8.2 Hz, Ar), 13.86 (2H, br s, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 34.1, 56.9, 121.5, 124.2, 126.6, 129.5, 129.8, 146.8, 147.2, 151.2. MS *m/z* (%): 307 (9.2), 174 (18.3).

4,4′-[(4-Cyanophenyl)methylene]bis(3-methyl-1-phenyl-pyrazol-5-ol) (2e)

White solid; yield: 95%, 0.44 g; mp 210–212 °C. IR (ν_{max}, cm^{-1}): 3090 (O–H). ^1H NMR (500 MHz, DMSO-d_6) δ_H: 2.33 (6H, s, CH_3), 5.07 (1H, s, CH), 7.25 (2H, t, $^3J_{HH}$ = 7.3 Hz, Ar), 7.42–7.46 (6H, m, Ar), 7.40 (4H, d, $^3J_{HH}$ = 7.8 Hz, Ar), 7.76 (2H, d, $^3J_{HH}$ = 8.3 Hz, Ar), 13.89 (2H, br s, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 18.5, 32.4, 114.8, 120.5, 125.5, 128.1, 128.9, 132.3, 137.4, 146.2, 155.5.

4,4′-[(4-Hydroxyphenyl)methylene]bis(3-methyl-1-phenyl-pyrazol-5-ol) (2f)

Yellow solid; yield: 74%, 0.33 g; mp 150–151 °C. IR (ν_{max}, cm^{-1}): 3420 (O–H). ^1H NMR (500 MHz, DMSO-d_6) δ_H: 2.31 (6H, s, CH_3), 4.86 (1H, s, CH), 6.67 (2H, d, $^3J_{HH}$ = 8.02 Hz, Ar), 7.06 (2H, d, $^3J_{HH}$ = 8.5 Hz, Ar), 7.24 (2H, t, $^3J_{HH}$ = 7.0 Hz, Ar), 7.44 (4H, t, $^3J_{HH}$ = 8.0 Hz, Ar), 7.72 (4H, d, $^3J_{HH}$ = 8.0 Hz, Ar), 9.16 (1H, br s, OH), 12.40 (1H, br s, OH), 13.95 (1H, br s, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 12.5, 33.2, 115.7, 121.4, 126.4, 128.9, 129.8, 133.2, 143.6, 147.0, 156.4. MS *m/z* (%): 279 (30.2), 174 (91.4).

1,4-Diphenylene-4,4′-(methylene)bis(3-methyl-1-phenyl-pyrazol-5-ol) (2g)

Yellow solid; yield: 85%, 0.67 g; mp 194–196 °C. ^1H NMR (500 MHz, DMSO-d_6) δ_H: 2.29 (12H, s, CH_3), 5.05 (2H, s, CH), 7.17 (4H, s, Ar), 7.22 (4H, t, $^3J_{HH}$ = 7.1 Hz, Ar), 7.41 (8H, t, $^3J_{HH}$ = 7.8 Hz, Ar), 7.69 (8H, d, $^3J_{HH}$ = 8.0 Hz, Ar), 12.41 (2H, br s, OH), 14.11 (2H, s, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 12.5, 33.7, 121.5, 127.8, 129.7, 140.9, 147.0, 155.0.

4,4′-[(2-Naphthyl)methylene]bis(3-methyl-1-phenyl-pyrazol-5-ol) (2h)

Pale yellow solid; yield: 81%, 0.39 g; mp (dec.) 194 °C. IR (ν_{max}, cm^{-1}): 3055 (O–H). ^1H NMR (400 MHz, DMSO-d_6) δ_H: 2.49 (6H, s, CH_3), 5.29 (1H, s, CH), 7.35 (2H, t, $^3J_{HH}$ = 7.2 Hz, Ar), 7.42 (1H, d, $^3J_{HH}$ = 8.4 Hz, Ar), 7.45–7.48 (2H, m, Ar), 7.50 (4H, t, $^3J_{HH}$ = 7.6 Hz, Ar), 7.73 (4H, d, $^3J_{HH}$ = 7.6 Hz, Ar), 7.76 (1H, s, Ar), 7.84–7.88 (3H, m, Ar). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 11.4, 33.1, 105.5, 122.3, 125.5, 126.1, 126.5, 126.7, 127.5, 127.8, 128.3, 128.4, 129.6, 132.2, 133.3, 135.9, 139.1, 146.5.

4,4′-[(2-Thienyl)methylene]bis(3-methyl-1-phenyl-pyrazol-5-ol) (2i)

White solid; yield: 85%, 0.37 g; mp 190–192 °C. IR (ν_{max}, cm^{-1}): 3420 (O–H). ^1H NMR (500 MHz, DMSO-d_6) δ_H: 2.38 (6H, s, CH_3), 5.11 (1H, s, CH), 6.90 (2H, d, $^3J_{HH}$ = 8.5 Hz, Ar), 7.09–7.48 (7H, m, Ar), 7.77–7.85 (4H, m, Ar), 13.56 (2H, br s, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 12.5, 33.2, 121.3, 125.0, 125.1, 128.2, 128.6, 131.5, 131.9, 134.2, 139.8, 144.3, 154.9. MS *m/z* (%): 268 (100), 174 (71).

4,4′-[(isoPropyl)methylene]bis(3-methyl-1-phenyl-pyrazol-5-ol) (2j)

White solid; yield: 92%, 0.37 g; mp 210–212 °C. IR (ν_{max}, cm^{-1}): 3428 (O–H). ^1H NMR (500 MHz, DMSO-d_6) δ_H: 0.84 (6H, d, $^3J_{HH}$ = 7.9 Hz, CH_3), 2.21 (6H, s, CH_3), 2.55–2.69 (1H, m, CH), 2.97–3.08 (1H, m, CH), 7.25–7.28 (2H, m, Ar), 7.40–7.48 (4H, m, Ar), 7.71–7.43 (4H, m, Ar), 11.93 (1H, br s, OH), 13.64 (1H, br s, OH). MS *m/z* (%): 228 (21), 174 (33).

4,4′-[(n-Buthyl)methylene]bis(3-methyl-1-phenyl-pyrazol-5-ol) (2k)

White solid; yield: 83%, 0.34 g; mp 125–127 °C. IR (ν_{max}, cm^{-1}): 3420 (O–H). ^1H NMR (400 MHz, DMSO-d_6) δ_H: 0.85 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.16–1.19 (2H, m, CH_2), 1.27–1.32 (2H, m, CH_2), 1.92–1.96 (2H, m, CH_2), 2.92 (6H, s, CH_3), 3.53 (1H, t, $^3J_{HH}$ = 8.0 Hz, CH), 4.00 (2H, br s, OH), 7.33 (2H, t, $^3J_{HH}$ = 7.2 Hz, Ar), 7.49 (4H, t, $^3J_{HH}$ = 8.0 Hz, Ar), 7.68 (4H, d, $^3J_{HH}$ = 8.0 Hz, Ar). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 10.9, 14.3, 22.4, 28.28, 30.0, 31.7, 106.4, 122.6, 127.9, 129.7, 135.0, 145.7, 158.6. MS *m/z* (%): 243 (23.3), 174 (100).

General procedure for the synthesis of 2-pyrazolyl-1-nitroalkanes (3)

2-HEAA (5 mol %) was added to a mixture of β-nitrostyrene (1 mmol) and **1** (1 mmol) in EtOH (4 mL) at room temperature. The mixture was stirred at room temperature for the appropriate time (Table 4). After evaporation of the solvent, water (10 mL) was added to the reaction mixture, and the resulting solid was filtered and washed three times with H_2O (5 mL). The pure product (**3**) was obtained from this solid by recrystallization in EtOH.

3-Methyl-4-[2-nitro-1-(phenylethyl)ethyl]-1-phenyl-5-pyrazolone (3a)

White solid; yield: 83%, 0.32 g; mp 89–90 °C. IR (ν_{max}, cm^{-1}): 2901 (O–H). ^1H NMR (400 MHz, DMSO-d_6) δ_H: 2.51 (3H, s, CH_3), 4.58 (1H, t, $^3J_{HH}$ = 8.0 Hz, CH), 5.31 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 7.6 Hz, CH_2), 5.37 (1H, dd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 6.8 Hz, CH_2), 7.20 (1H, d, $^3J_{HH}$ = 7.2 Hz, Ar), 7.25 (1H, d, $^3J_{HH}$ = 7.2 Hz, Ar), 7.33 (2H, t, $^3J_{HH}$ = 7.6 Hz, Ar), 7.44 (2H, t, $^3J_{HH}$ = 8.0 Hz, Ar), 7.50 (2H, t, $^3J_{HH}$ = 7.6 Hz, Ar), 7.71 (2H, d, $^3J_{HH}$ = 8.0 Hz, Ar), 11.23 (1H, br s, OH).

3-Methyl-4-[2-nitro-1-(2-methoxyphenyl)ethyl]-1-phenyl-5-pyrazolone (3b)

White solid; yield: 91%, 0.32 g; mp 147–149 °C. IR (ν_{max}, cm^{-1}): 2955 (O–H). ^1H NMR (400 MHz, DMSO-d_6) δ_H: 2.16 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 4.95 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 6.8 Hz, CH), 5.15 (1H, dd, $^3J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 6.6 Hz, CH_2), 5.36 (1H, dd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 6.6 Hz, CH_2), 6.91 (1H, t, $^3J_{HH}$ = 7.6 Hz, Ar), 7.01 (1H, d, $^3J_{HH}$ = 8.4 Hz, Ar), 7.19 (1H, t, $^3J_{HH}$ = 7.6 Hz, Ar), 7.24 (1H, t, $^3J_{HH}$ = 8.0 Hz, Ar), 7.43 (2H, t, $^3J_{HH}$ = 8.0 Hz, Ar), 7.51 (1H, d, $^3J_{HH}$ = 7.2 Hz, Ar), 7.70 (2H, d, $^3J_{HH}$ = 8.6 Hz, Ar). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 11.7, 32.1, 56.0, 57.9, 76.1, 102.4, 111.3, 119.1, 120.7, 124.9, 127.5, 128.5, 128.6, 129.3, 137.8, 148.3, 156.5. MS *m/z* (%): 353 (3.6), 173 (30.8), 77 (100), 91 (64.8). Anal. calcd for $C_{19}H_{19}N_3O_4$ (353.14) (%): C 64.58, H 5.42, N, 11.89; found: C 64.64, H 5.48, N 11.91.

3-Methyl-4-[2-nitro-1-(4-methylphenyl)ethyl]-1-phenyl-5-pyrazolone (3c)

White solid; yield: 84%, 0.28 g; mp 80–81 °C. IR (ν_{max}, cm^{-1}): 2994 (O–H). ^1H NMR (400 MHz, $CDCl_3$) δ_H: 1.93

(3H, s, CH_3), 2.31 (3H, s, CH_3), 4.42 (1H, t, $^3J_{HH}$ = 8.0 Hz, CH), 4.81 (1H, dd, $^3J_{HH}$ = 12.8 Hz, $^3J_{HH}$ = 6.8 Hz, CH_2), 5.20 (1H, dd, $^3J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 9.6 Hz, CH_2), 7.06 (3H, d, $^3J_{HH}$ = 8.0 Hz, Ar), 7.13 (2H, t, $^3J_{HH}$ = 7.2 Hz, Ar), 7.20 (2H, d, $^3J_{HH}$ = 8.0 Hz, Ar), 7.30 (2H, d, $^3J_{HH}$ = 8 Hz, Ar), 10.9 (1H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 10.6, 21.0, 39.3, 76.8, 103.4, 120.7, 125.6, 127.4, 128.8, 129.5, 135.6, 136.2, 136.5, 137.1, 146.9. MS *m/z* (%): 337 (3.6), 118 (100), 42 (30.0); Anal. calcd for $C_{19}H_{19}N_3O_3$ (337.14) (%): C 67.64, H 5.68, N 12.46; found: C 67.54, H 5.71, N 12.39.

3-Methyl-4-[2-nitro-1-(4-chlorophenyl)ethyl]-1-phenyl-5-pyrazolone (3d)

White solid; yield: 95%, 0.34 g; mp 155–156 °C. IR (ν_{max}, cm^{-1}): 2900 (O–H). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.91 (3H, s, CH_3), 4.39 (1H, t, $^3J_{HH}$ = 7.6 Hz, CH), 4.78 (1H, dd, $^3J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 6.8 Hz, CH_2), 5.12 (1H, dd, $^3J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 8.8 Hz, CH_2), 7.12 (1H, d, $^3J_{HH}$ = 8.0 Hz, Ar), 7.15 (3H, t, $^3J_{HH}$ = 6.8 Hz, Ar), 7.17–7.28 (5H, m, Ar), 11.10 (1H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 10.5, 14.2, 39.0, 76.5, 120.9, 126.3, 128.9, 129.0, 129.1, 129.3, 133.3, 136.9, 137.7, 146.7. MS *m/z* (%): 358 (3.3), 360 (1.1), 139 (3.3), 141 (1.1), 42 (CNO, 100). Anal. calcd for $C_{18}H_{16}ClN_3O_3$ (357.09) (%): C 60.42, H 4.51, N 11.74; found: C 60.51, H 4.55, N 11.81.

3-Methyl-4-[2-nitro-1-(4-nitrophenyl)ethyl]-1-phenyl-5-pyrazolone (3e)

White solid; yield: 94%, 0.34 g; mp 176–180 °C. IR (ν_{max}, cm^{-1}): 2832 (O–H). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.24 (3H, s, CH_3), 4.65 (1H, t, $^3J_{HH}$ = 7.2 Hz, CH), 5.08 (1H, dd, $^3J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 7.2 Hz, CH_2), 5.41 (1H, dd, $^3J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 8.8 Hz, CH_2), 7.22 (1H, t, $^3J_{HH}$ = 7.2 Hz, Ar), 7.38 (2H, t, $^3J_{HH}$ = 7.6 Hz, Ar), 7.55 (2H, d, $^3J_{HH}$ = 7.6 Hz, Ar), 7.7 (2H, d, $^3J_{HH}$ = 8.8 Hz, Ar), 8.2 (2H, d, $^3J_{HH}$ = 8.4 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 11.3, 39.7, 75.9, 120.0, 124.2, 124.4, 126.2, 128.8, 129.0, 129.3, 136.0, 146.2, 147.3, 148.4. MS *m/z*: 368 (1.2), 149 (2.9), 42 (100). Anal. calcd for $C_{18}H_{16}N_4O_5$ (368.11) (%): C 58.69, H 4.38, N 15.21; found: C 58.71, H 4.44, N 15.11.

3-Methyl-4-[2-nitro-1-(4-bromophenyl)ethyl]-1-phenyl-5-pyrazolone (3f)

White solid; yield: 95%, 0.38 g; mp 169–170 °C. IR (ν_{max}, cm^{-1}): 2703 (O–H). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.18 (3H, s, CH_3), 4.62 (1H, dd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 6.8 Hz, CH), 5.36 (2H, dd, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 6.8 Hz, CH_2), 7.22 (2H,d, $^3J_{HH}$ = 8.0 Hz, Ar), 7.45 (3H, t, $^3J_{HH}$ = 6.8 Hz, Ar), 7.53 (2H, d, $^3J_{HH}$ = 8.0 Hz, Ar), 7.70 (2H, d, $^3J_{HH}$ = 7.6 Hz, Ar), 11.33 (1H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 11.4, 38.6, 76.8, 103.2, 119.2, 120.7, 125.3, 129.4, 130.4, 131.9, 137.4, 139.9, 148.1. MS *m/z*: 401 (2.0), 403 (1.6), 226 (2.1), 228 (2.3), 173 (77.6), 76 (100). Anal. calcd for $C_{18}H_{16}BrN_3O_3$ (401.04) (%): C 53.75, H 4.01, N 10.45; found: C 53.85, H 4.21, N 10.38.

3-Methyl-4-[2-nitro-1-(thiophen-2-yl)ethyl]-1-phenyl-5-pyrazolone (3g)

White solid; yield: 88%, 0.29 g; mp 124–125 °C. IR (ν_{max}, cm^{-1}): 2802 (O–H). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.13 (3H, s, CH_3), 4.91 (1H, t, $^3J_{HH}$ = 8.0 Hz, CH), 5.32 (2H, dd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 6.8 Hz, CH_2), 6.97 (1H, dd, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 3.6 Hz, Ar), 7.11 (1H, d, $^3J_{HH}$ = 6.8 Hz, Ar), 7.22 (1H, t, $^3J_{HH}$ = 7.2 Hz, Ar), 7.39 (1H, d, $^3J_{HH}$ = 5.2 Hz, Ar), 7.45 (2H, t, $^3J_{HH}$ = 8.0 Hz, Ar), 7.71 (2H, d, $^3J_{HH}$ = 8.2 Hz, Ar), 11.35 (1H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 11.1, 34.3, 77.3, 103.8, 119.0, 121.2, 125.4, 127.4, 129.4, 137.3, 143.0, 148.2, 162.4. Anal. calcd for $C_{16}H_{15}N_3O_3$ S (329.08) (%): C 58.34, H 4.59, N 12.76; found: C 58.25, H 4.50, N 12.69.

Acknowledgments

We are thankful to Birjand University Research Council for their support of this work.

References

(1) McDonald, E.; Jones, K.; Brough, P. A.; Drysdale, M. J.; Workman, P. *Curr. Top. Med. Chem.* **2006**, *6* (11), 1193. doi:10.2174/156802606777812086.

(2) Elguero, J. In *Comprehensive Heterocyclic Chemistry II;* Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5.

(3) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. Pyrazoles as Drugs: Facts and Fantasies. In *Targets in Heterocyclic Systems;* Attanasi, O. A.; Spinelli, D., Eds.; Italian Society of Chemistry: Roma, 2002; Vol. 6, pp 52–98.

(4) Park, H.-J.; Lee, K.; Park, S.-J.; Ahn, B.; Lee, J.-C.; Cho, H. Y.; Lee, K.-I. *Bioorg. Med. Chem. Lett.* **2005**, *15* (13), 3307. doi:10.1016/j.bmcl.2005.03.082.

(5) Clark, M. P.; Laughlin, S. K.; Laufersweiler, M. J.; Bookland, R. G.; Brugel, T. A.; Golebiowski, A.; Sabat, M. P.; Townes, J. A.; Vanrens, J. C.; Djung, J. F.; Natchus, M. G.; De, B.; Hsieh, L. C.; Xu, S. C.; Walter, R. L.; Mekel, M. J.; Heitmeyer, S. A.; Brown, K. K.; Juergens, K.; Taiwo, Y. O.; Janusz, J. M. *J. Med. Chem.* **2004**, *47* (11), 2724. doi:10.1021/jm049968m.

(6) Cho, I. H.; Noh, J. Y.; Park, S. W.; Ryu, H. C.; Lim, J. W.; Kim, J. H.; Chae, M. Y.; Kim, D. H.; Jung, H. S.; Park, H. J.; Kim, Y. H.; Min, I. K. US Patent 2,004,002, 2004; p 532.

(7) Clark, M. P.; Laughlin, S. K.; Golebiowski, A.; Brugel, T. A.; Sabat, M. WO Patent 2005047, 2005; p 287.

(8) Kakiuchi, Y.; Sasaki, N.; Satoh-Masuoka, M.; Murofushi, H.; Murakami-Murofushi, K. *Biochem. Biophys. Res. Commun.* **2004**, *320* (4), 1351. doi:10.1016/j.bbrc.2004.06.094.

(9) Clark, M. P.; Bookland, R. G. *Expert Opin. Ther. Pat.* **2005**, *15* (11), 1617. doi:10.1517/13543776.15.11.1617.

(10) Ishida, M. WO Patent 2006212, 2006.

(11) Speckbacher, M.; Braun, H.-J. WO Patent 2006012, 2006; p 934.

(12) Sugiura, S.; Ohno, S.; Ohtani, O.; Izumi, K.; Kitamikado, T.; Asai, H.; Kato, K.; Hori, M.; Fujimura, H. *J. Med. Chem.* **1977**, *20* (1), 80. doi:10.1021/jm00211a016.

(13) Behr, L. C.; Fusco, R.; Jarboe, C. H. In *The Chemistry of Heterocyclic Compounds, Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings;* Weissberger, A., Ed.; Interscience Publishers: New York, 1967.

(14) Rosiere, C. E.; Grossman, M. I. *Science* **1951**, *113* (2945), 651. doi:10.1126/science.113.2945.651.

(15) Bailey, D. M.; Hansen, P. E.; Hlavac, A. G.; Baizman, E. R.; Pearl, J.; Defelice, A. F.; Feigenson, M. E. *J. Med. Chem.* **1985**, *28* (2), 256. doi:10.1021/jm00380a020.

(16) Mahajan, R. N.; Havaldar, F. H.; Fernandes, P. S. *J. Indian Chem. Soc.* **1991**, *68* (4), 245.

(17) Singh, D.; Singh, D. *J. Indian Chem. Soc.* **1991**, *68* (3), 165.
(18) Londershausen, M. *Pestic. Sci.* **1996**, *48* (4), 269. doi:10.1002/(SICI)1096-9063(199612)48:4<269::AID-PS478>3.0.CO;2-B.
(19) Lube, H. A. *The Chemistry of Synthetic Dyes and Pigments;* American Chemical Society: Washington, DC, 1970.
(20) Garnovskii, A. D.; Uraev, A. I.; Minkin, V. I. *ARKIVOC* **2004**, *2004* (iii), 29.
(21) Singh, D.; Singh, D. *J. Chem. Eng. Data* **1984**, *29* (3), 355. doi:10.1021/je00037a040.
(22) Pavlov, P. T.; Goleneva, A. F.; Lesnov, A. E.; Prokhorova, T. S. *Pharm. Chem. J.* **1998**, *32* (7), 370. doi:10.1007/BF02645994.
(23) Buzykin, B. I.; Lonshchakova, T. I. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1971**, *20* (10), 2224. doi:10.1007/BF00851295.
(24) Wang, W.; Wang, S.-X.; Qin, X.-Y.; Li, J.-T. *Synth. Commun.* **2005**, *35* (9), 1263. doi:10.1081/SCC-200054854.
(25) Elinson, M. N.; Dorofeev, A. S.; Nasybullin, R. F.; Nikishin, G. I. *Synthesis* **2008**, *2008* (12), 1933. doi:10.1055/s-2008-1067079.
(26) Sujatha, K.; Shanthi, G.; Selvam, N. P.; Manoharan, S.; Perumal, P. T.; Rajendran, M. *Bioorg. Med. Chem. Lett.* **2009**, *19* (15), 4501. doi:10.1016/j.bmcl.2009.02.113.
(27) Niknam, K.; Saberi, D.; Sadegheyan, M.; Deris, A. *Tetrahedron Lett.* **2010**, *51* (4), 692. doi:10.1016/j.tetlet.2009.11.114.
(28) Hasaninejad, A.; Shekouhy, M.; Zare, A.; Hoseini Ghattali, S. M. S.; Golzar, N. *J. Iran. Chem. Soc.* **2011**, *8* (2), 411.
(29) Niknam, K.; Mirzaee, S. *Synth. Commun.* **2011**, *41* (16), 2403. doi:10.1080/00397911.2010.502999.
(30) Sobhani, S.; Hasaninejad, A.-R.; Maleki, M. F.; Parizi, Z. P. *Synth. Commun.* **2012**, *42* (15), 2245. doi:10.1080/00397911.2011.555589.
(31) Sobhani, S.; Safaei, E.; Hasaninejad, A. R.; Rezazadeh, S. *J. Organomet. Chem.* **2009**, *694* (18), 3027. doi:10.1016/j.jorganchem.2009.05.004.
(32) Hasaninejad, A. R.; Zare, A.; Shekouhy, M.; Golzar, N. *Org. Prep. Proced. Int.* **2011**, *43* (1), 131. doi:10.1080/00304948.2010.526827.
(33) Mosaddegh, E.; Hassankhani, A.; Baghizadeh, A. *J. Chil. Chem. Soc.* **2010**, *55* (4), 419. doi:10.4067/S0717-97072010000400001.
(34) Mustafa, A.; Fleifel, A. M.; Ali, M. I.; Hassan, N. M. *Justus Liebigs Ann. Chem.* **1970**, *739* (1), 75. doi:10.1002/jlac.19707390111.
(35) Perkalin, V. V.; Sopava, A. S. *Uch. Zap. Leninger. Gos. Ped. Inst.* **1959**, *160*, 45.
(36) Welton, T. *Chem. Rev.* **1999**, *99* (8), 2071. doi:10.1021/cr980032t.
(37) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39* (21), 3772.
(38) Mi, X.; Luo, S.; Cheng, J. P. *J. Org. Chem.* **2005**, *70* (6), 2338. doi:10.1021/jo048391d.
(39) Hangarge, R. V.; Jarikote, D. V.; Shingare, M. S. *Green Chem.* **2002**, *4* (3), 266. doi:10.1039/b111634g.
(40) Singh, V.; Kaur, S.; Sapehiyia, V.; Singh, J.; Kad, G. L. *Catal. Commun.* **2005**, *6* (1), 57. doi:10.1016/j.catcom.2004.10.011.
(41) Wasserscheid, P.; Welton, T. *Ionic Liquid in Synthesis;* Wiley-VCH: Weinheim, 2004.
(42) Zhang, S. J.; Yuan, X. L.; Chen, Y. H.; Zhang, Y. Q. Chin. Patent 10069408.5, 2005.
(43) Yue, C.; Mao, A.; Wei, Y.; Lü, M. *Catal. Commun.* **2008**, *9* (7), 1571. doi:10.1016/j.catcom.2008.01.002.
(44) Shaterian, H. R.; Honarmand, M. *Synth. Commun.* **2011**, *41* (23), 3573. doi:10.1080/00397911.2010.519594.
(45) Zang, H.; Su, Q.; Mo, Y.; Cheng, B. *Ultrason. Sonochem.* **2011**, *18* (1), 68. doi:10.1016/j.ultsonch.2010.08.001.
(46) Zang, H.; Su, Q.; Guo, S.; Mo, Y.; Cheng, B. *Chin. J. Chem.* **2011**, *29* (10), 2202. doi:10.1002/cjoc.201180381.