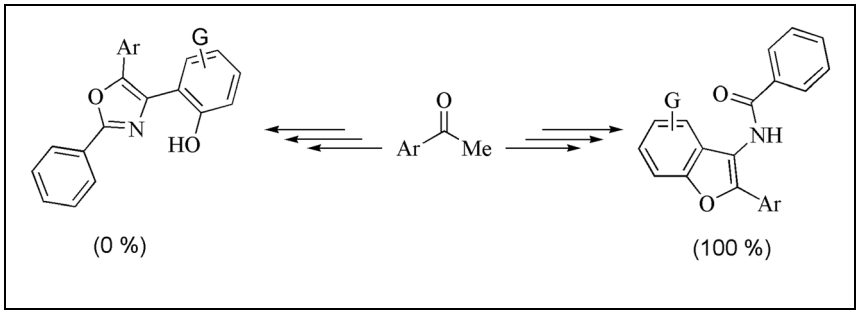
Fatemeh Hashemi,[a] Bahador Karami,[a,b]* and Saeed Khodabakhshi[a]

[a]Department of Chemistry, Gachsaran Branch, Islamic Azad University, Gachsaran, Iran
[b]Department of Chemistry, Yasouj University, Yasouj 75918-74831, Iran
*E-mail: karami@mail.yu.ac.ir

Additional Supporting Information may be found in the online version of this article.
Received November 2, 2012
DOI 10.1002/jhet.1961
Published online 4 November 2013 in Wiley Online Library (wileyonlinelibrary.com).



A solvent-free and synthetic pathway to novel benzofuran derivatives, starting from oxidation of phenyl ketones to arylglyoxals in three steps was developed. The molybdate sulfuric acid catalyzed the reaction of arylglyoxals with benzamide and phenols to afford 2-aryl-3-benzamidobenzofurans in high yield. The structures of the synthesized compounds were assigned on the basis of elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR spectral data. The present methodology offers several advantages such as non-hazardous reaction condition, simple operation, and work-up procedure.

J. Heterocyclic Chem., **51**, 322 (2014).

INTRODUCTION

Benzofurans are present in various biologically active molecules [1] possessing anti-bacterial [2], anti-fungal [3], anti-inflammatory [4], anti-depressant [5], anti-convulsant [6], and so forth. For example, *Benzbromaron* is a uricosuric agent used in the treatment of gout [7], cloridarol is a vasodilator [8], oxetorone is an antimigraine agent [9], and amiodarone is an antiarrhythmic agent [10] used for various types of cardiac dysrhythmias, both ventricular and atrial (Fig. 1).

The methods for synthesis of benzofuranes have been reviewed by Kadieva and Oganesyan in 1997 [11]. The traditional methods for the synthesis of benzofurans are the preparation via *O*-alkylation of salicylaldehyde with chloroacetic acid followed by dehydration of the resulting ether [12] and via Perkin rearrangement in which a coumarin is reacted with a hydroxide [13–15]. Recently, new strategies were employed for synthesis of this benzoheterocycle such as Claisen rearrangement and ring-closing metathesis [16], condensation of benzil with phenols and aryl ethers mediated by $SnCl_2$ [17], reaction of phenols, arylglyoxal monohydrates, and *para* toluenesulfonamide [18].

To the best of our knowledge, there is no report on the synthesis of 2-aryl-3-amido benzofurans via three-component reaction of arylglyoxals, benzamide, and phenols in literature. Therefore, we describe here a three-step synthesis of novel class of 2-aryl-3-benzamidobenzofurans by employing green reaction conditions.

RESULTS AND DISCUSSION

Considering the aforementioned background and our programmatic interest on the heterocyclic synthesis [19–21], and catalyzed organic reactions [22–25], we found that arylglyoxals **2**, which in turn are obtained by selenium dioxide oxidation of the corresponding phenyl ketones **1**, can participate in a one-pot and three-component reaction with benzamide (**3**) and phenols **4** in the presence of molybdate sulfuric acid (MSA) under solvent-free conditions yielding novel benzofurans **5** (Scheme 1). It is interesting to note that these reactions showed regiospecificity toward benzofurans **5** because it was obtained as the only isomer via heterocyclization reaction of intermediate 2; and therefore, the oxazoles **6** were not formed. It should be also noted that the intermediate 1 was *in situ* generated, and the intermediate 2 was not isolable during the reaction as previous report in literature [26] for aldehydes instead of arylglyoxals.

In order to optimize the reaction conditions for the synthesis of compounds **5**, the reaction of phenylglyoxal (**2a**), benzamide (**3**), and β-naphthol (**4a**) was selected as a model (Scheme 2). We found that in the absence of the catalyst, the reaction did not complete, even at long reaction times in high temperatures. Through screening, we found that this reaction was completed with MSA (10 mol%) under solvent-free conditions at 120°C.

To test the generality of the reaction, this thermal and solvent-free procedure was employed for similar substrates in the presence of MSA. The results have been shown in

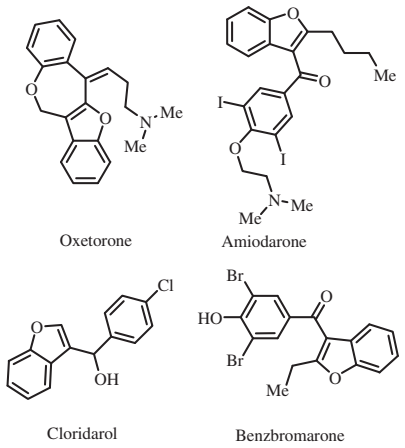
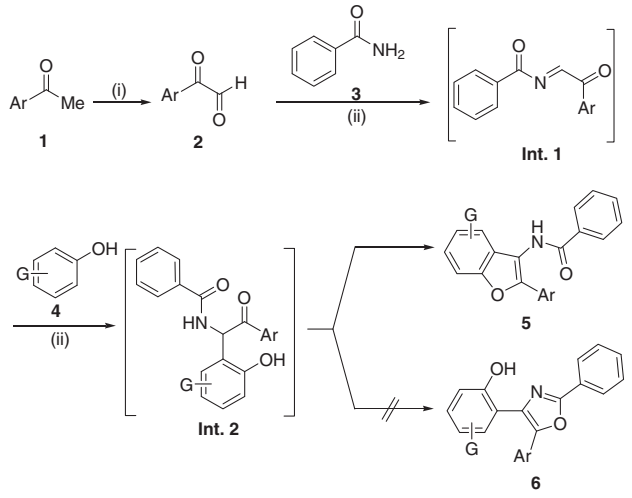


Figure 1. Benzofuran derivatives as drug.

Scheme 1. Regiospecific formation of new benzofurans.



Scheme 2. A model for the optimization of reaction conditions.

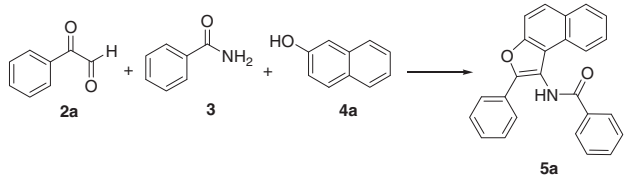


Table 1. In regard of thin layer chromatography experiments during the reaction progresses, we found that only one regioisomer has been formed. The regiospecificity of these reactions was proved by NMR and IR spectroscopy. As a representative sample, the ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of **5e** exhibited a sharp singlet identified as a methyl ($\delta = 3.74$) protons. The signals ($\delta = 8.25$–6.99) corresponded to the aromatic protons. The protons of NH groups also appeared as a singlet at $\delta = 10.77$ (Fig. 2). The proton decoupled ^{13}C NMR spectrum of **5e** also showed 24 distinct resonances in agreement with the proposed structure. As can be seen in Figure 2, the appearance of the signal for carbonyl of amide group at 166.63 ppm can prove that the compounds **5e** have been formed. Another evidence for the formation of regioisomer **5e** is the appearance of one peak in the infrared for secondary amide at 3200 cm^{-1}.

The nature of Ar groups showed no significant effect on the yield or reaction rate. Minimizing catalyst loss and avoidance of organic solvents during chemical reactions require a fundamental understanding of green chemistry factors. These concepts may be useful in the improvement of organic syntheses and environmental and economic problems. The advantages of solvent-free procedures include cost savings, reduced energy consumption, decreased reaction times, and a considerable reduction in reactor size and, therefore, capital investment. These attributes have inspired a substantial research effort directed toward the development of solvent-free reactions [27,28]. Solid acid catalysts are interesting alternatives for the common liquid acids because of their simple handling and isolation of the reaction products and reagent [29,30]. A practical test of the recyclability of the MSA was also examined for the model reaction, and this catalyst was reused for three cycles during which a little appreciable loss was observed in the catalytic activities.

Table 1

Synthesis of benzofuran derivatives using MSA at 120°C under solvent-free conditions.

Entry	Ar	Phenol	Product	Yield[a] (%)	Mp (°C)
5a	C_6H_5	2-Naphthol		80	230–232
5b	4-MeO-C_6H_4	2-Naphthol		75	239–241
5c	4-Br-C_6H_4	2-Naphthol		85	286–288
5d	4-Cl-C_6H_4	2-Naphthol		80	270–272
5e	3-MeO-C_6H_4	2-Naphthol		85	198–200
5f	2-Naphthyl	2-Naphthol		75	220–222
5g	C_6H_5	1,2,3-$(OH)_3$ C_6H_3		85	248–250
5h	4-Cl-C_6H_4	1,2-$(OH)_2$ C_6H_4		75	225–227

MSA, molybdate sulfuric acid.
[a]Isolated yield.

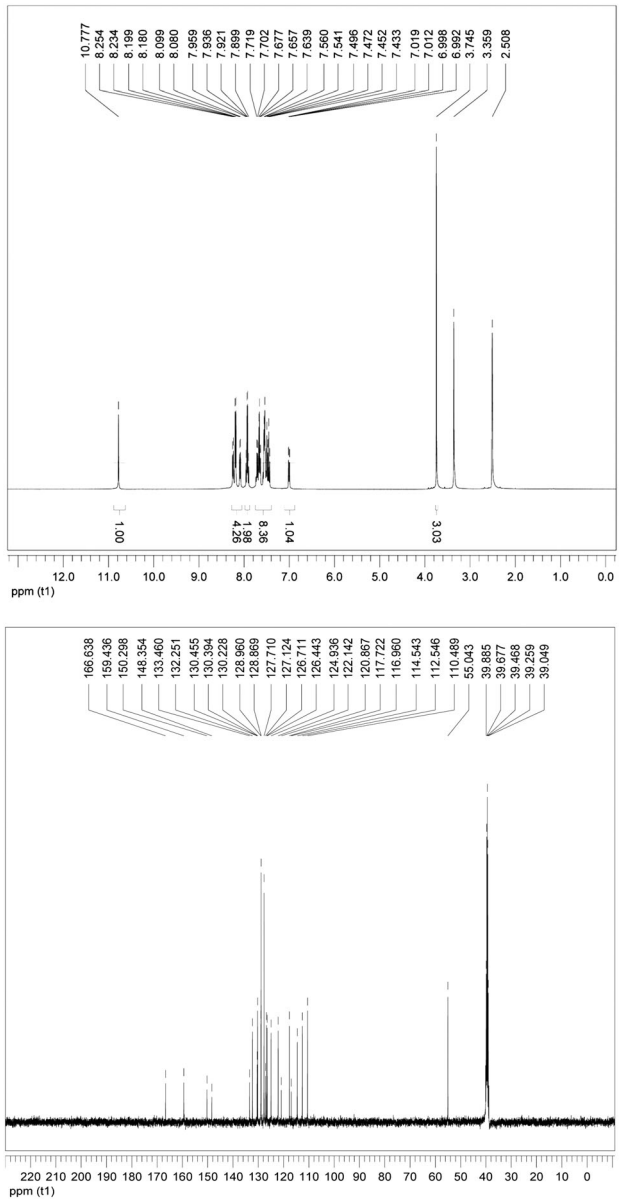


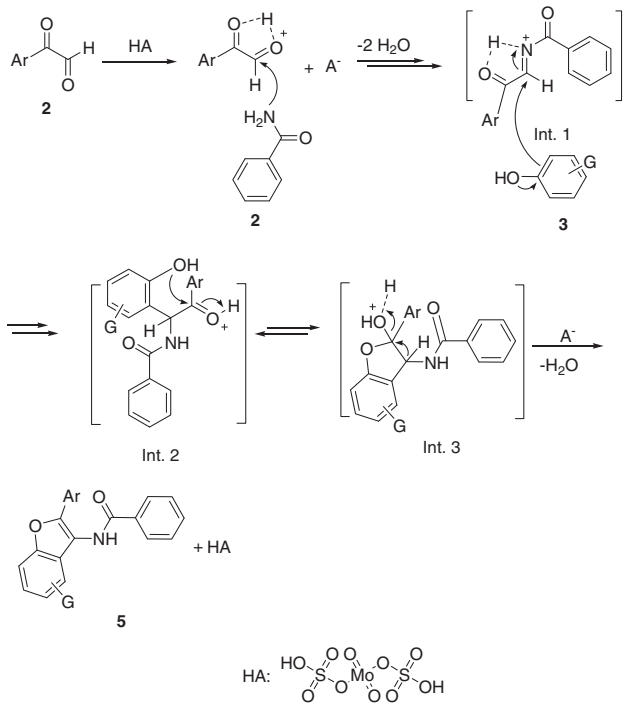
Figure 2. The NMR spectra for compound **5e**.

On the basis of the general mechanistic pathway for the formation of compounds **5**, Scheme 3 shows a reasonable mechanism. The reaction is thought to take place in three steps. It is reasonable to assume that the initial event involves the generation of intermediate 1 via condensation of the amide and arylglyoxal. In the next step, intramolecular cyclization of intermediate 2 gives intermediate 3 followed by dehydration to form corresponding product **5**.

EXPERIMENTAL

Arylgloxals were synthesized in accord with report by Riley and Gray [31]. Molybdate sulfuric acid was prepared in accord with our previous literature [32]. All chemicals were purchased from Merck and Aldrich. The reactions were monitored by TLC (silica gel 60 F_{254}, hexane/EtOAc). IR spectra were recorded on a FT-IR JASCO-680, and the NMR spectra were obtained on a Bruker-Instrument DPX-400 MHz Avance III model. The Vario EL CHNS at the Isfahan Industrial University was used for elemental analysis.

Scheme 3. Suggested mechanism for the formation of benzofuran **5** using molybdate sulfuric acid (MSA).



General procedure for the synthesis of benzofurans 5. A mixture of arylglyoxal (1 mmol), benzamide (1 mmol), and MSA (0.1 mmol) was stirred and heated at 120°C in a preheated oil bath for 30 min. Then the phenolic substrate was added, and the mixture was stirred for an appropriate time (120–240 min). After completion of the reaction as indicated by TLC (EtOAc/hexan, 1:2), the reaction mixture was dissolved in hot EtOH, and the catalyst was separated by filtration. The solvent was evaporated and the products **5** were purified by recrystallization in EtOH.

1-Benzamido-2-phenylnaphtho[2,1-b]furan (5a). IR (KBr) *v*: 3160, 3110, 2089, 1640, 1485, 1260, 1040, 800, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): 10.78 (s, 1H), 8.26 (d, 1H, $J = 7.6$), 8.21 (d, 2H, $J = 7.2$ Hz), 8.09 (d, 1H, $J = 8.0$ Hz), 7.90–8.04 (m, 4H), 7.74–7.65 (m, 3H), 7.53, 7.57 (2d, 4H, $J = 8.0$, 7.6 Hz), 7.43 (t, 1H, $J = 7.6$ Hz); ^{13}C NMR (DMSO-d_6, 100 MHz): 167.21, 150.86, 149.10, 134.07, 132.72, 130.92, 129.83, 129.54, 129.47, 129.38, 129.25, 128.27, 127.66, 127.18, 126.87, 125.84, 125.41, 122.67, 121.40, 117.26, 113.05; *Anal.* Calcd. for $C_{25}H_{17}NO_2$: C, 82.63; H, 4.72; N, 3.85. Found: C, 82.90; H, 4.65; N, 3.77.

1-Benzamido-2-(4-methoxyphenyl)naphtho[2,1-b]furan (5b). IR (KBr) *v*: 3165, 3110, 2950, 1640, 1510, 1475, 1260, 1040, 800, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): 10.70 (s,1H), 8.22, 8.24 (2d, 3H, $J = 8.0$, 6.8 Hz), 8.07 (d, 1H, $J = 8.0$ Hz), 7.89 (t, 4H, $J = 8.4$ Hz), 7.74–7.64 (m, 3H), 7.56–7.50 (m, 2H), 3.81 (s, 3H), 7.11

(d, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): 167.20, 160.10, 150.46, 149.46, 134.11, 132.66, 130.89, 129.40, 129.35, 128.25, 127.58, 127.45, 126.99, 126.20, 125.28, 122.65, 122.36, 121.54, 115.61, 115.05, 112.95, 55.77; *Anal*. Calcd. for $C_{26}H_{19}NO_3$: C, 79.37; H, 4.87; N, 3.56. Found: C, 79.51; H, 4.80; N, 3.45.

1-Benzamido-2-(4-bromophenyl)naphtho[2,1-b]furan (5c). IR (KBr) *v*: 3200, 1650, 1490, 1395, 1270, 1090, 800, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): 10.78 (s, 1H), 8.22 (d, 1H, J = 8.4 Hz), 8.17 (d, 2H, J = 7.6 Hz), 8.09 (d, 1H, J = 8.0 Hz), 7.96 (d, 1H, J = 8.8 Hz), 7.91–7.87 (m, 3H), 7.76 (dd, 2H, J = 6.8, 2.0 Hz), 7.72 (d, 1H, J = 7.1 Hz), 7.66 (t, 2H, J = 7.6 Hz), 7.57–7.53 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): 167.10, 151.00, 148.13, 133.90, 132.79, 132.59, 130.93, 129.51, 129.39, 128.94, 128.28, 127.68, 127.58, 127.29, 127.25, 125.53, 122.65, 122.48, 121.24, 117.67, 113.03; *Anal*. Calcd. for $C_{25}H_{16}BrNO_2$: C, 67.89; H, 3.65; N, 3.17. Found: C, 68.01; H, 3.48; N, 3.02.

1-Benzamido-2-(4-chlorophenyl)naphtho[2,1-b]furan (5d). IR (KBr) *v*: 3205, 1640, 1485, 1395, 1280, 1090, 800, 710, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): 10.78 (s, 1H), 8.22 (d, 1H, J = 7.6 Hz), 8.17 (d, 2H, J = 8.0 Hz), 8.09 (d, 1H, J = 7.8 Hz), 7.97–7.89 (m, 4H), 7.74–7.61 (m, 5H), 7.58–7.51 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): 166.63, 150.47, 147.50, 133.43, 133.25, 132.26, 130.41, 129.19, 129.00, 128.87, 128.11, 127.78, 127.08, 126.94, 126.77, 126.70, 125.00, 122.13, 120.72, 117.25, 112.52; *Anal*. Calcd. for $C_{25}H_{16}ClNO_2$: C, 75.47; H, 4.05; N, 3.52. Found: C, 75.55; H, 3.95; N, 3.31.

1-Benzamido-2-(3-methoxyphenyl)naphtho[2,1-b]furan (5e). IR (KBr) *v*: 3200, 20100, 1650, 1509, 1390, 1250, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): 10.77 (s, 1H), 8.24 (d, 1H, J = 8.0 Hz), 8.19 (d, 2H, J = 7.6 Hz), 8.09 (d, 1H, J = 7.6 Hz), 7.94, 7.91 (2d, 2H, J = 9.2, 8.8 Hz), 7.71–7.63 (m, 3H), 7.56–7.43 (m, 5H), 7.00 (dd, 1H, J = 8.2, 2.4 Hz), 3.74 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): 166.63, 159.43, 150.29, 148.35, 133.45, 132.25, 130.45, 130.39, 130.22, 128.96, 128.86, 127.71, 127.123, 126.711, 126.44, 124.93, 122.14, 120.86, 117.72, 116.95, 114.54, 112.54, 110.488, 55.043; *Anal*. Calcd. for $C_{26}H_{19}NO_3$: C, 79.37; H, 4.87; N, 3.56. Found: C, 79.48; H, 4.70; N, 3.50.

1-Benzamido-2-(2-naphthyl)naphtho[2,1-b]furan (5f). IR (KBr) *v*: 3190, 2200, 1650, 1500, 1395, 1010, 790; ^{1}H NMR (DMSO-d_6, 400 MHz): 10.86 (s, 1H), 8.28 (d, 1H, J = 7.6 Hz), 8.21 (d, 2H, J = 7.6 Hz), 8.11–7.93 (m, 8H), 7.75–7.68 (m, 3H), 7.59–7.52 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz): 166.84, 161.36, 150.54, 148.56, 133.64, 132.80, 132.55, 132.23, 130.43, 128.98, 128.90, 128.61, 128.28, 127.74, 127.66, 127.14, 126.98, 126.94, 126.740, 126.54, 124.97, 124.56, 122.67, 122.23, 120.97, 117.25, 112.53; *Anal*. Calcd. for $C_{29}H_{19}NO_2$: C, 84.24; H, 4.63; N, 3.39. Found: C, 84.49; H, 4.48; N, 3.31.

6,7-Dihydroxy-2-phenyl-3-benzamidobenzofuran (5g). ^{1}H NMR (DMSO-d_6, 400 MHz): 10.81 (s, 1H), 9.26 (s, 1H), 8.99 (s, 1H), 7.93,7.98 (2d, 2H, J = 8, 7.6 Hz), 7.44–7.61 (m, 8H), 6.48 (d, 1H, J = 8.4 Hz), 6.28 (d, 1H, J = 8.4 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz): 166.82, 146.84, 166.74, 146.84, 144.76, 135.66, 134.31, 133.73, 133.62, 131.82, 129.15, 128.69, 128.61, 128.54, 128.19, 127.93, 119.57, 114.25, 107.35; IR (KBr) *v*: 3520–3100, 1620, 1521, 1470, 1285, 710, 690, 668; *Anal*. Calcd. for $C_{21}H_{15}NO_4$: C, 73.03; H, 4.38; N, 4.06. Found: C, 73.15; H, 4.32; N, 3.95.

7-Hydroxy-2-phenyl-3-benzamidobenzofuran (5h). IR (KBr) *v*: 3410–3200, 3050–3000, 1668–1615, 1540–1498, 1100–1098, 740–689; ^{1}H NMR (DMSO-d_6, 400 MHz): 10.74 (s, 1H), 9.31 (d, 1H, J = 8 Hz), 8.00–8.02 (m, 2H), 7.90–7.95 (m, 3H), 7.48–7.72 (m, 6H), 6.97 (d, 2H, J = 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): 166.56, 166.48, 138.78, 133.61, 132.81, 132.37, 131.32, 130.46, 130.03, 129.38, 128.89, 128.03, 126.03, 122.12, 120.01; *Anal*. Calcd. for $C_{21}H_{14}ClNO_3$: C, 69.33; H, 3.88; N, 3.85. Found: C, 69.55; H, 3.71; N, 3.70.

CONCLUSION

In summary, the reaction between arylglyoxals, phenols, and benzamide in the presence of molybdate sulfuric acid provides a simple one-pot entry for the synthesis of novel 2-aryl-3-benzamidobenzofurans of potential synthetic and pharmaceutical interest. The use of a green and recyclable catalyst (MSA) under solvent-free conditions, high yield of pure products, and a simple workup procedure make the present method a valid contribution in accord with green chemistry principles. It is worthwhile to note that the presence of transformable functionalities in the products makes them potentially valuable for further synthetic manipulations.

Acknowledgments. Partial financial support from the Islamic Azad University, Gachsaran Branch is gratefully acknowledged.

REFERENCES AND NOTES

[1] Viti, G.; Giannotti, D.; Nannicini, R.; Ricci, R.; Pestellini, V., J Heterocycl Chem 1991, 28, 379.

[2] Kirilmis, C.; Ahmedzade, M.; Suleyman, S.; Koca, M.; Kizirgil, A. Eur J Med Chem 2008, 43, 300.

[3] Aslam, S. N. ; Stevenson, P. C. ; Phythian, S. J.; Veitch, N. C.; Hall, D. R. Tetrahedron 2006, 62, 4214.

[4] Mane, B. Y.; Agasimundin, Y. S.; Shivkumar, B.; Shinde, D. B. J Chil Chem Soc 2009, 54, 77.

[5] Malik, W. U.; Mahesh,V. K.; Raishighani, M. Indian J Chem 1971, 9, 655.

[6] Dauzonne, D.; Gillardin, J. M.; Lepage, F.; Pointet, R.; Risse, S.; Lamotte, G.; Demerseman, P. Eur J Med Chem 1995, 30, 53.

[7] Kuzmits, R.; Bresnik, W.; Muller, M. M. Fortschr Med 1979, 97, 2057.

[8] Mossuti, E.; Nigro, P.; Diene, G.; Petralito, A. Minerva Med 1976, 67, 1394.

[9] Massiou, H. Rev Neurol 2000, 156, 79.

[10] Punnam, S. R.; Goyal, S. K.; Kotaru, V. P.; Pachika, A. R.; Abela, G. S.; Thakur, R. K.; Cardiovasc Hematol Disord Drug Targets 2010, 10, 73.

[11] Kadieva, M. G.; Oganesyan, E. T. Chem Heterocyl Compd 1997, 33, 1245.

[12] Burgstahler, A. W.; Worden, L. R. Org Synth 1966, 5, 251

[13] Perkin, W. H. J Chem Soc 1870, 23, 368.

[14] Perkin, W. H. J Chem Soc 1871, 24, 37.

[15] Bowden, K.; Battah, S. J Chem Soc Perkin Trans 1998, 2, 1603.

[16] Tsai, T.-W.; Wang, E.-C.; Li, S.-R.; Chen, Y.-H.; Lin, Y.-L.; Wang, Y.-F.; Huang, K.-S. J Chin Chem Soc 2004, 51, 1307.

[17] Morrison, B. J.; Musgrave, O. C. Tetrahedron 2002, 58, 4255.

[18] Chen, C. X.; Liu, L.; Yang, D.-P.; Wang, D.; Chen, Y.-J. Synlett 2005, 13, 2047.

[19] Karami, B.; Khodabakhshi, S.; Eskandari, K. Tetrahedron Lett 2012, 53, 1445.
[20] Khodabakhshi, S.; Karami, B. Catal Sci Technol 2012, 2, 1940.
[21] Karami, B.; Eskandari, K.; Khodabakhshi, S. Arkivoc 2012, (ix), 7684.
[22] Karami, B.; Ghashghaee, V.; Khodabakhshi, S. Catal Commun 2012, 20, 71.
[23] Karami, B.; Farahi, M.; Khodabakhshi, S. Helv Chim Acta 2012, 95, 455.
[24] Karami, B.; Rooydel, R.; Khodabakhshi, S. Acta Chim Slov 2012, 59, 183.
[25] Karami, B.; Hoseini, S. J.; Eskandari, K.; Ghasemi, A.; Nasrabadi, H. Catal Sci Technol 2012, 2, 331.
[26] Hajipour, A. R.; Ghayeb, Y.; Sheikhan, N.; Ruoho, A. E.; Tetrahedron Lett 2009, 50, 5649.
[27] Nasr-Esfahani, M.; Karami, B.; Behzadi, M. J Heterocycl Chem 2009, 46, 1183.
[28] Rostami-Charati, F.; Hossaini, Z.; Khalilzadeh, M. A.; Jafaryan, H. J Heterocyclic Chem 2012, 49, 217.
[29] Nasr-Esfahani, M.; Karami, B.; Montazerozohori, M.; Abdi, K. J Heterocycl Chem. 2008, 45, 1183.
[30] Rostamizadeh, S.; Amirahmadi, A.; Shadjou, N.; Amani, A. M. J Heterocycl Chem 2012, 49, 111.
[31] Riley H. A.; Gray, A. R. Org Synth Coll 1935, 15, 67.
[32] Karami, B.; Khodabakhshi, S.; Nikrooz, M. Polycyclic Aromat Compd 2011, 31, 97.