Solvent-free synthesis of novel benzodiazepine derivatives by a three-component base-catalysed reaction of isatoic anhydride, a primary amine and chloroacetyl chloride

Mohsen Khalilpour Seydey[a*], Zahra Rezaei[b] and Seyed Saied Homami[a]

[a]*Department of Applied Chemistry, Faculty of Science, Islamic Azad University, South Tehran Branch, Tehran, Iran*
[b]*Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 14176, Iran*

Heating isatoic anhydride with a series of primary amines at 150 °C under solvent-free conditions yielded 2-amino-*N*-alkylbenzamides which, in the same pot, reacted readily with chloroacetyl chloride in the presence of poly(dimethylaminoethyl acrylamide)-modified magnetic nanoparticles (MNP@PDMA), a base catalyst, to give 4-alkyl-1,4-benzodiazepine-2,5-diones in good yields without formation of by-products.

Keywords: 4-alkyl-1,4-benzodiazepine-2,5-diones, 2-amino-*N*-alkylbenzamides, isatoic anhydride, chloroacetyl chloride, MNP@PDMA

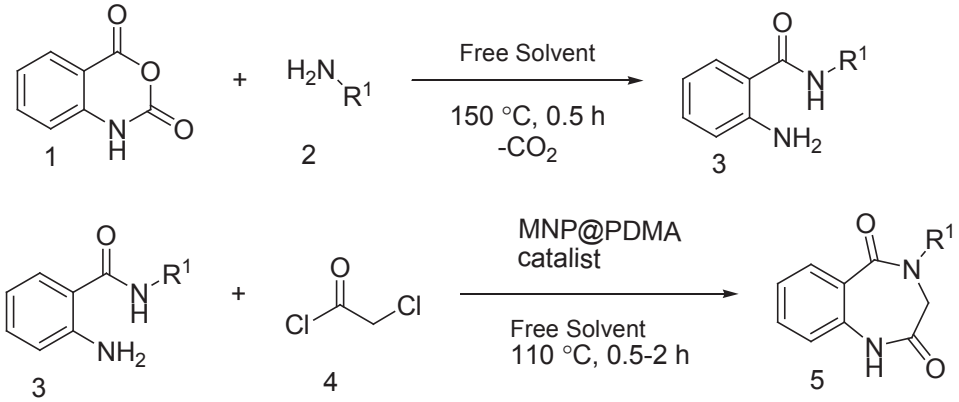
Heterocyclic compounds containing one or more nitrogen atoms in their ring have much importance in pharmaceutical research.[1] The benzodiazepines, especially 1,4-benzodiazepine-2,5-diones, represent significant scaffolds in medicinal chemistry.[2] In spite of their popular properties as psychoactive drugs, which function as anti-anxiety and anti-convulsants,[3] they display other biological properties acting as anti-cancer agents,[4,5] antagonists of cholecystokinin receptors (CCK)[6] and of the platelet glycoprotein IIb–IIIa[7] that mimics the arginine–glycine–aspartic acid (RGD) peptide sequence[8] and agonist of melanocortin receptors.[9]

There are several synthetic methods for this scaffold, many of them multicomponent reactions (MCRs)[10].[11-13] Synthetic organic chemists are attracted to the use of MCRs for the synthesis of complex scaffolds because they offer efficient use of energy, hazard reduction, waste minimisation, and the use of renewable resources.[14] Recently, magnetic nanoparticles (MNPs) acting as support for catalysts have attracted considerable attention in organic synthesis.[15,16] Great stability, easy synthesis and functionalisation methods and high surface area are a number of advantages of magnetic nanoparticles.[17,18] A number of researches focused on modification of silica based surfaces. For example, Zohreh *et al.* introduced in 2014[19] magnetic iron oxide nanoparticles surface-modified by polyamides (MNP@PDMA) as a catalyst.

We now present a green synthesis of various derivatives of 4-alkyl-1,4-benzodiazepine-2,5-diones **5** using a sequential one-pot three-component reaction of isatoic anhydride **1**, an amine **2** and chloroacetyl chloride **4**, in which 2-amino-*N*-alkylbenzamides derivatives **3** are produced *in situ* by the reaction of **1** and **2**, followed by reaction of intermediate **3** with compounds **4** to give the title compounds **5** (Scheme 1). Poly (dimethylaminoethyl acrylamide) (PDMA) modified magnetic nanoparticles were used as a convenient base catalyst for an efficient one-pot synthesis.

Results and discussion

The reaction of isatoic anhydride and reaction with amines has been explained in detail elsewhere.[20,21] Clearly, the nucleophilic attack of amine on the isatoic anhydride yields an amide with concurrent elimination of CO_2.[21] As is known, isatoic anhydride undergoes ring opening upon heating with various amines to produce 2-amino-*N*-alkylbenzamides. Moreover, benzamides can easily react with chloroacetyl chloride as potential precursors for nucleophilic attack. Initially, to obtain the best reaction conditions, the reaction of isatoic anhydride (1 mmol) and benzylamine (1 mmol) was selected as a model reaction and starting materials were allowed to react at 150 °C under solvent-free conditions for 30 minutes. After the completion of reaction (checked by TLC), chloroacetyl chloride (1 mmol) was added to the reaction mixture, which continued at the same temperature in the presence of MNP@PDMA as base catalyst, and after 0.5–2 h, the reaction was completed. The great advantage of MNP@PDMA catalyst is the large number of nitrogen atoms in the polymer structure which induces strong basic properties to the catalyst. Other than MNP@PDMA as catalyst, all compounds in the reaction mixture were completely dissolved in ethanol,



Scheme 1

* Correspondent. E-mail: kpsmohsen@gmail.com

and thus the catalyst was easily removed from the mixture by simple filtration for 10 min. In the next step, the crude product was purified by column chromatography on silica gel using petroleum ether and ethyl acetate (4:1) as eluent. The product was obtained in 85% yield. Seven other amines reacted readily under these optimal conditions to give similar products, as revealed by their spectral data. The results are shown in Table 1. As can be seen, arylamines **5d** and **5f** reacted more slowly and gave lower yields than alkylamines.

We then investigated the mechanism of the reaction. According to the literature,[22] the first step in the modified Neimentowski synthesis of a quinazolinone involves condensation of an amine group with the keto function of the original amide. To confirm our mechanism of reaction, the structure of the product was characterised by its ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectrum, a signal due to the NH group was observed at δ 7.9–8.1 ppm. In the ^{13}C NMR spectrum, the presence of two signals at δ 167.6 and 176.4 ppm attributed to two amide carbonyl groups provided further evidence for the formation of a 1,4 benzodiazepine-2,5-dione instead of a quinazolinone.

A possible explanation for the formation of a 1,4-benzodaizepine-2,5-dione is based on S_N2 nucleophilic substitution. The first step is the formation of a 2-amino-*N*-alkylbenzamide **3** from the reaction of isatoic anhydride **1** and an amine **2**. Then chloroacetyl chloride **4** is added to **3** in the presence of base catalyst. This chloroacatylates **3** by nucleophilic attack of the Cole group by the aromatic amine. A cyclisation reaction is followed by an elimination of the other chloro group to afford compound **5**. In the absence of catalyst, condensation is the main reaction which leads to quinazolinone as the product.[22] This proves the necessity of using MNP@PDMA for obtaining 1,4-benzodiazepine-2,5-diones. The most important feature of the catalyst is its selectivity in the formation of 1,4-benzodiazepine-2,5-diones which might be due to the strong basic nature of the catalyst. It is known that the thermodynamically more stable quinazolinone with a six membered ring is the main product when no catalyst is used. Using the base catalyst MNP@PDMA strongly activates the nitrogen of amide for a nucleophilic attack. Therefore the attack occurs on the C-Cl bond, while the activated nucleophile prefers the more electrophilic carbon in the mentioned bond. As mentioned above, it was observed that arylamines reacted more slowly and gave a lower yield than alkylamines. This is due to the ability of the nitrogen atom of arylamines to participate in resonance with the aromatic ring, which decreases the nucleophilic reactivity of their amino groups.

Conclusion

In conclusion, we have developed a facile heterogeneous base catalyst for a simple and highly efficient green protocol for the synthesis of potential pharmaceutically active 1,4-benzodiazepine-2,5-diones derivatives. The advantages of this work are its green procedure, simple workup and good yields, which make it one of the most convenient methods for the synthesis of this class of heterocycles.

Experimental

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. NMR spectra were obtained on a Bruker FT-500 spectrometer (^{1}H NMR at 500 Hz, ^{13}C NMR at 125 Hz) in $CDCl_3$ using TMS as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz. The IR spectra were obtained in the range of 400–4000 cm^{-1} on a Shimadzu FTIR-8400S spectrophotometer. All reagents and solvents were obtained from Merck or Aldrich and used without any purification. Silica gel 60 (0.040-0.063 mm) was used for column chromatography. The elemental analyses were performed for C, H, N using an Elementar Vario EL III element analyser. TLC was performed using silica gel 60/Kieselguhr F254 precoated on aluminum sheets (thickness 0.2 mm) (Merck). Visualisation of spots on TLC plates was accomplished with UV light.

Table 1 Yields/reaction times for the preparation of 4-alkyl-3,4-dihydro-1*H*-benzo[e][1,4]diazepine- 2,5-diones **5a–h** from a variety of amines R^1NH_2 (Scheme 1)

Entry	R^1NH_2	Product	Time/ h	Yield/%[a]
1	Benzylamine	**5a**	1	86
2	Furfurylamine	**5b**	1.5	85
3	2-Cholorobenzylamine	**5c**	1.5	78
4	Aniline	**5d**	2	72
5	4-Methoxibenzylamine	**5e**	1	81
6	4-Methoxianiline	**5f**	2	68
7	2-(2,4-Dimethoxyphenyl) ethanamine	**5g**	1.5	80
8	Propylamine	**5h**	1.5	84

[a] Isolated yield.

Synthesis of 4-alkyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-diones **5a-h***; general procedure*

A mixture of isatoic anhydride (1 mmol) and an amine (1 mmol) was heated at 150 °C under solvent-free conditions for 30 min. Then chloroacetyl chloride (1 mmol) and a catalytic amount of MNP@PDMA[19] (15 mol%) was added to the reaction mixture, and heating was continued at 110 °C. After 0.5–2 h the reaction was complete (checked by TLC). The crude products were purified by column chromatography on silica gel using petroleum ether and ethyl acetate (4:1) as eluent. The pure products **5a-h** were obtained in 68–86% yield. (The reaction time required for the formation of each product and the yield obtained are listed in Table 1.) All the products, which were novel, were recrystallised in EtOH, their IR and ^{1}H and ^{13}C NMR recorded and their elemental analyses determined.

*4-Benzyl-3,4-dihydro-1*H*-benzo*[e]*[1,4]diazepine-2,5-dione* (**5a**): White powder; m.p. 118–122 °C (EtOH); IR (KBr): 3335 (NH), 1698 (C=O), 1650 (C=O) cm^{-1}; ^{1}H NMR: δ 4.43 (s, 2H, C3H), 5.03 (s, 2 H, NCH_2), 6.80 (m, 1 H, C9H), 6.99–7.05 (m, 2 H, C2′H, C6′H), 7.17–7.19 (m, 3 H, C3′H, C4′H ,C5′H), 7.26–7.27 (m, 1 H, C7H), 7.36 (m, 1 H, C8H), 7.98 (s, 1H, NH, Amid), 8.21 (m, 1 H, C6H); ^{13}C NMR: δ 48.5, 56.5, 116.4, 117.9, 119.1, 126.7, 126.9, 128.2, 132.2, 133.9, 138.2, 145.8, 167.6, 176.4. Anal. calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52; found: C, 72.30; H, 5.40; N, 10.68%.

*4-(Furan-2-ylmethyl)-3,4-dihydro-1*H*-benzo*[e]*[1,4]diazepine-2,5-dione* (**5b**): White needles; m.p. 115–118 °C (EtOH); IR (KBR): 3366 (NH), 1695 (C=O), 1625 (C=O) cm^{-1}; ^{1}H NMR: δ 4.37(s, 2H, C3H), 5.17 (s, 2 H, NCH_2), 6.28–6.29 (m, 2 H, furan), 6.71 (dd, *J* = 7.6, 0.9 Hz, 1 H, C9H), 6.92 (dt, *J* = 7.6, 0.9 Hz, 1 H, C7H), 7.30 (dd, *J* = 3.0, 1.0 Hz, 1 H, furan), 7.34 (dt, *J* = 7.6, 1.4 Hz, 1 H, C8H), 8.01(s, 1H, NH, Amid), 8.21 (dd, *J* = 7.6, 1.4 Hz, 1 H, C6H); ^{13}C NMR: δ 42.1, 57.8, 108.1, 110.2, 118.2, 118.9, 119.6, 133.5, 134.1, 141.6, 144.6, 151.4, 167.2, 173.2. Anal. calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93; found: C, 65.72; H, 4.78; N, 11.00%.

*4-(2-Chlorobenzyl)-3,4-dihydro-1*H*-benzo*[e]*[1,4]diazepine-2,5-dione* (**5c**): White needles; m.p. 128–131 °C (EtOH); IR (KBR): 3338 (NH), 1697 (C=O), 1622 (C=O) cm^{-1}; ^{1}H NMR: δ 4.37 (s, 2 H, C3H), 5.26 (s, 2 H, NCH_2), 6.76 (dd, *J* = 8.2, 1.0 Hz, 1 H, C9H), 6.95 (ddd, *J* = 8.2, 6.5, 1.1 Hz, 1 H, C5′H), 7.05 (t, *J* = 7.0 Hz, 1 H, C7H), 7.14–7.17 (m, 2 H, C4′H, C6′H), 7.34 (dd, *J* = 6.5, 3.0 Hz, 1 H, C3′H), 7.38 (ddd, *J* = 8.2, 7.0, 1.5 Hz, 1 H, C8H), 7.95 (s, 1H, NH, Amid), 8.20 (dd, *J* = 7.0, 1.5 Hz, 1 H, C6H); ^{13}C NMR: δ 47.3, 58.0, 118.4, 119.1, 119.9, 126.6, 127.0, 127.9, 129.4, 132.9, 133.5, 134.3, 135.1, 144.8, 167.6, 173.5. Anal. calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31; found: C, 63.82; H, 4.28; N, 9.18%.

*4-Phenyl-3,4-dihydro-1*H*-benzo*[e]*[1,4]diazepine-2,5-dione* (**5d**): White needles; m.p. 133–136 °C (EtOH); IR (KBR): 3470 (NH), 1691

(C=O), 1645 (C=O) cm^{-1}; ^1H NMR: δ 4.53 (s, 2 H, C3H), 5.13 (d, *J* = 15.7 Hz, 1 H, NCH_2), 6.77 (d, *J* = 8.1 Hz, 1 H, C9H), 6.89 (t, *J* = 7.5 Hz, 1 H, C7H), 6.98–7.00 (m, 1 H, C4′H), 7.06–7.11 (m, 2 H, C2′H, C6′H), 7.29–7.39 (m, 3 H, C8H, C3′H, C5′H), 8.11 (d, *J* = 7.5 Hz, 1 H, C6H); ^{13}C NMR: δ 61.2, 118.1, 119.0, 119.6, 126.5, 126.8, 127.7, 129.2, 132.6, 133.2, 134.2, 134.9, 144.7, 167.5, 173.7. Anal. calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10; found: C, 71.60; H, 4.93; N, 10.96%.

*4-(4-Methoxybenzyl)-3,4-dihydro-1*H-*benzo[*e*][1,4]diazepine-2,5-dione* (**5e**): White powder; m.p. 120–122 °C (EtOH); IR (KBr): 3329 (NH), 1694 (C=O), 1649 (C=O) cm^{-1}; ^1H NMR: δ 3.76 (s, 3 H, OCH3), 4.43 (s, 2 H, C3H), 5.14 (s, 2H, NCH_2), 6.71 (d, *J* = 7.3 Hz, 1 H, C9H), 6.81 (d, *J* = 8.6 Hz, 2 H, C3′H, C5′H), 6.90 (t, *J* = 7.3 Hz, 1H, C7H), 7.32 (dt, *J* = 7.3, 1.5 Hz, 1 H, C8H), 7.36 (d, *J* = 8.6 Hz, 2 H, C2′H, C6′H), 7.90 (s, 1H, NH, Amid), 8.19 (dd, *J* = 7.3, 1.5 Hz, 1 H, C6H); ^{13}C NMR: δ 48.7, 55.1, 60.9, 113.5, 118.3, 118.8, 119.3, 129.8, 130.2, 133.2, 134.0, 144.3, 158.5, 167.7, 173.1. Anal. calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45; found: C, 68.75; H, 5.36; N, 9.35%.

*4-(4-Methoxyphenyl)-3,4-dihydro-1*H-*benzo[*e*][1,4]diazepine-2,5-dione* (**5f**): White needles; m.p. 128–133 °C (EtOH); IR (KBR); 3320 (NH), 1698 (C=O), 1647 (C=O) cm^{-1}; ^1H NMR: δ 3.77 (s, 3 H, OCH_3), 4.42 (s, 2 H, C3H), 5.12 (s, 2 H, NCH_2), 6.70 (d, *J* = 8.1 Hz, 1 H, C9H), 6.82 (d, *J* = 8.5 Hz, 2 H, C3′H, C5′H), 6.91 (t, *J* = 7.6 Hz, 1 H, C7H), 7.31–7.34 (m, 3 H, C8H, C2′H, C6′H), 7.94 (s, 1H, NH, Amid), 8.20 (dd, *J* = 7.6, 1.4 Hz, 1 H, C6H); ^{13}C NMR: δ 24.4, 48.7, 55.1, 57.7, 113.6, 114.1, 118.4, 118.8, 119.4, 129.4, 130.2, 133.4, 134.0, 144.5, 158.5, 167.8, 173.0. Anal. calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92; found: C, 68.18; H, 5.18; N, 10.04%.

*4-(3,5-Dimethoxyphenethyl)-3,4-dihydro-1*H-*benzo[*e*][1,4] diazepine-2,5-dione* (**5g**): White powder; m.p. 133–135 °C (EtOH); IR (KBr): 3377 (NH), 1688(C=O), 1640 (C=O) cm^{-1}; ^1H NMR: δ 2.87 (t, *J* = 7.8 Hz, 2 H, $NCH_2\boldsymbol{CH_2}$), 3.85 (s, 6 H, OCH_3), 4.13 (t, *J* = 7.8 Hz, 2 H, $N\boldsymbol{CH_2}CH_2$), 4.47 (s, 2 H, C3H), 6.72–6.80 (m, 4 H, C9H, C2′H, C4′H, C6′H), 6.90 (t, *J* = 7.5 Hz, 1 H, C7H), 7.32 (t, *J* = 7.5 Hz, 1 H, C8H), 7.96 (s, 1H, NH, Amid), 8.12 (d, *J* = 7.5 Hz, 1 H, C6H); ^{13}C NMR: δ 34.1, 48.2, 55.7, 55.8, 57.8, 112.1, 118.8, 119.5, 120.7, 132.4, 133.1, 134.0, 144.4, 147.4, 148.6, 168.1, 173.2. Anal. calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23; found: C, 66.90; H, 5.78; N, 8.38%.

*4-Propyl-3,4-dihydro-1*H-*benzo[*e*][1,4]diazepine-2,5-dione* (**5h**): White needles; m.p. 114–116 °C (EtOH); IR (KBR): 3367 (NH), 1687 (C=O), 1634 (C=O) cm^{-1}; ^1H NMR: δ 0.78 (t, *J*=7.5 Hz, 3H, CH_3), 1.60 (m, 2H, CH_2), 3.87 (t, *J*=8.9 Hz, 2H, NCH), 4.52(s, 2H, C3H), 6.70 (dd, *J*=8.1, 1.2 Hz, 1H, C9H), 6.89 (t, *J*=8.2 Hz, 1H,C7H), 7.32 (t, *J*=8.45 Hz, 1H, C8H), 8.13 (s, 1H, NH, Amid), 8.35 (dd, *J*=8.4, 1.2 Hz, 1H, C6H); ^{13}C NMR: δ 11.3, 21.4, 48.0, 57.7, 118.4, 118.8, 119.4, 126.5, 133.2, 133.9, 144.4, 163.2, 169.1. Anal. calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84; found: C, 66.18; H, 6.56; N, 12.78%.

Support of this investigation by a grant from the Islamic Azad University Tehran South Branch is gratefully acknowledged.

Received 26 December 2015; accepted 30 April 2015
Paper 1403107 doi: 10.3184/174751915X14304939994023
Published online: 08 May 2015

References

1 O. Sharma, R. K. Singla and B. Shrivastava, *Indo Glob. J. Pharm. Sci.,* 2012, **2**, 142.
2 L. Costantino and D. Barlocco, *Curr. Med. Chem.,* 2006, **13**, 65.
3 U. Rudolph and H. Möhler, *Curr. Opin. Pharmacol.,* 2006, **6**, 18.
4 H. K. Koblish, S. Zhao, C. F. Franks, R. R. Donatelli, R. M. Tominovich, L. V. LaFrance, K. A. Leonard, J. M. Gushue, D. J. Parks and R. R. Calvo, *Mol. Cancer. Ther.,* 2006, **5**, 160.
5 D. J. Parks, L. V. LaFrance, R. R. Calvo, K. L. Milkiewicz, J. Jose Marugan, P. Raboisson, C. Schubert, H. K. Koblish, S. Zhao and C. F. Franks, *Bioorg. Med. Chem. Lett.,* 2006, **16**, 3310.
6 A. Ursini, A. M. Capelli, R. A. Carr, P. Cassara, M. Corsi, O. Curcuruto, G. Curotto, M. Dal Cin, S. Davalli and D. Donati, *J. Med. Chem.,* 2000, **43**, 3596.
7 B. K. Blackburn, A. Lee, M. Baier, B. Kohl, A. G. Olivero, R. Matamoros, K. D. Robarge and R. S. McDowell, *J. Med. Chem.,* 1997, **40**, 717.
8 R. S. McDowell, B. K. Blackburn, T. R. Gadek, L. R. McGee, T. Rawson, M. E. Reynolds, K. D. Robarge, T. C. Somers and E. D. Thorsett, *J. Am. Chem. Soc.,* 1994, **116**, 5077.
9 C. G. Joseph, K. R. Wilson, M. S. Wood, N. B. Sorenson, D. V. Phan, Z. Xiang, R. M. Witek and C. Haskell-Luevano, *J. Med. Chem.,* 2008, **51**, 1423.
10 A. Domling, *Chem. Rev.,* 2006, **106**, 17.
11 S. Gunawan, M. Ayaz, F. De Moliner, B. Frett, C. Kaiser, N. Patrick, Z. Xu and C. Hulme, *Tetrahedron,* 2012, **68**, 5606.
12 J. R. Donald, R. R. Wood and S. F. Martin, *ACS Combi. Sci.,* 2012, *14*, 135.
13 M. Mahdavi, M. Asadi, M. Saeedi, Z. Rezaei, H. Moghbel, A. Foroumadi and A. Shafiee, *Synlett.,* 2012, **23**, 2521.
14 P. T. Anastas and J. C. Warner, *Green chemistry: theory and practice*. Oxford University Press: 2000.
15 R. N. Baig, and R. S. Varma, *Chem., Commun.,* 2013**, 49**, 752.
16 J. Y. Kim, J. T. Kim, E. A. Song, Y. K. Min and H. O. Hamaguchi, *Macromolecules,* 2008, **41**, 2886.
17 D. K. Yi, S. S. Lee and J. Y. Ying, *Chem. Mater.,* 2006**, 18**, 2459.
18 P. D. Stevens, J. Fan, H. M. Gardimalla, M. Yen and Y. Gao, *Org. Lett.,* 2005**, 7**, 2085.
19 N. Zohreh, S. H. Hosseini, A. Pourjavadi and C. Bennett, *RSC Adv.,* 2014**, 4**, 50047.
20 G. M. Coppola, *Synthesis.,* 1980, 505.
21 R. H. Clark and E. Wagner, *J. Org. Chem.,* 1944**, 9**, 55.
22 P. Wiklund and J. Bergman, *Curr. Org. Synth.,* 2006**, 3**, 379.