J. Iran. Chem. Soc., Vol. 7, No. 3, September 2010, pp. 752-758.

JOURNAL OF THE
Iranian
Chemical Society

Efficient and Green Protocol for the Synthesis of Thioamides in $C_6(mim)_2Cl_2$ as a Dicationic Ionic Liquid

A.R. Khosropour*, J. Noei and A. Mirjafari
Catalyst Division, Department of Chemistry, Faculty of Science, University of Isfahan, Isfahan 81746-73441, Iran

(Received 22 May 2009, Accepted 9 November 2009)

A simple, efficient, facile and eco-friendly process for the synthesis of thioamides from nitriles using 1,6-bis(3-methylimidazolium-1-yl)hexane chloride [$C_6(mim)_2Cl_2$] as a dicationic ionic liquid (DIL) was developed. The ionic liquid was easily separated from the reaction mixture and was recycled at least four times without any loss of its activity.

Keywords: Thioamides, Nitriles, Dicationic ionic liquid, Ammonium sulfide, Green chemistry, $C_6(mim)_2Cl_2$

INTRODUCTION

The increasing demand for clean and efficient chemical synthesis is especially important from both economical and environmental points of view [1]. Recently, ionic liquids (ILs) have attracted considerable interest as environmentally benign reaction media in synthetic chemistry [2]. Numerous chemical reactions can take place in ILs [3]. Although ionic liquids were initially introduced as an alternative green reaction medium, today they have gone far beyond it, exhibiting significant role in controlling reactions as catalysts [4-6]. So, the development and application of so-called ‘‘task-specific’’ ionic liquids are highly desirable. Polyvalent ionic liquids are a new class of ionic liquids which have not yet been studied extensively [7]. In this paper, we describe the use of 1,6-bis(3-methylimidazolium-1-yl)hexane chloride [$C_6(mim)_2Cl_2$] as a dicationic ionic liquid for the synthesis of thioamides.

Thioamides and their derivatives have received considerable attention due to their prsence as useful synthon in organic chemistry, for instance, synthesis of a variety of hetrocycles such as thiazoline or thiazole derivatives [8,9], mesoionic rhodanine [10], betaines [11] and other heterocyclic compounds [12,13]. Owing to their versatile properties, thioamides are used in rubber vulcanization as boosters or as inhibitors of metal corrosion [14]. In addition, thioamides such as 6-mercapto-purine show antitumor activity of their own [15]. More recently, a platinum-pyridine thione complex has been patented for clinical use in cancer treatment [16]. Fungicidal activity has also been reported for these compounds [17]. Thus, the direct synthesis of thioamides is of prime importance. Consequently, various methods have been developed for the thioamide synthesis using a variety of reagents under diverse reaction conditions [18,19]. However, these classical methods often involve harsh reaction conditions and the yields are typically low. Some modifications have been made in two general ways: (i) the thionation of amides with electrophilic reagents [20-22] and (ii) the reaction of nucleophilic thionating reagent with amides or nitriles [23,24] However, most of these procedures suffer from drawbacks such as long reaction times, low yields, harsh reaction conditions, tedious work-up and the use of environmentally toxic reagent or media.

Recently, Kaboudin *et al*., demonstrated a process for the synthesis of thioamides which was limited in that only

*Corresponding author. E-mail: khosropour@chem.ui.ac.ir

carbocyclics tolerated [25]. More recently, Williams *et al*. reported another procedure for the synthesis of these compounds through the two-step reaction with azides in the presence of dithiobenzoic acid/Et_3N [26]. The latter strategy seems to be more flexible but harsh reaction conditions to completion and narrow scope/purification of the desired products are limitations of this protocol. On the other hand, high toxicity of the reagent, and non-recyclability of the catalyst or solvent make the method objectionable, especially from the standpoint of green chemistry. Very recently, Lukyanov *et al*. used O,O-diethyl dithiophosphate, in concentrated HCl for direct conversion of nitriles to their primary thioamides. However, the corresponding products were obtained in moderate yields (39-85%) after long reaction times (8-100 h) [27].

Consequently, due to the beneficial biological and synthetic properties of certain molecules containing the thioamide moiety, a short selective and low-cost protocol for their synthesis is clearly in order.

EXPERIMENTAL

All compounds were identified by comparison of their spectral data and physical properties with those of the authentic samples. ^{1}N NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer at 500.1 and 125.7 MHz, respectively using $CDCl_3$ as the solvent. Chemical shifts (δ) are given in ppm relative to TMS. Coupling constants are given in Hz. IR spectra were recorded on Mattson 1000 IR spectrometer using KBr pellets. Nitriles and ammonium sulfide were purchased from Merck chemical company. $C_6(mim)_2Cl_2$ was prepared according to the procedures reported in the literature [7]. TLC was performed on silica gel on precoated silica gel plates (Merck 60 F254, 0.25 mm).

Typical Procedure for the Synthesis of Primary Thioamides in $C_6(mim)_2Cl_2$

To a mixture of nitrile (1 mmol) in $C_6(mim)_2Cl_2$ (1.1 mmol), ammonium sulfide (1.2 mmol) was added. The resulting mixture was stirred at 70 ºC for the appropriate time as shown in Table 2. After the completion of the reaction, as indicated by TLC, the mixture quenched immediately with cold water to afford a precipitate of the thioamide. This was collected by suction filtration and recrystallised from ethanol where appropriate.

Typical Procedure for the One-Pot Synthesis of Secondary and Tertiary Thioamides in $C_6(mim)_2Cl_2$

To a mixture of nitrile (1 mmol) in $C_6(mim)_2Cl_2$ (1.1 mmol), ammonium sulfide (1.2 mmol) was added. The resulting mixture was stirred at 70 ºC for the appropriate time shown in Table 2. After the completion of the reaction, as indicated by TLC, amine (5 mmol) was added to the reaction and stirred at 70 ºC for 10 min to 5 h (Table 3). Then the reaction took place, was quenched with ice-water (10 ml) and stirred at room temperature for 10 min. The above mixture was extracted with ethyl acetate (3 × 5 ml) and the organic layers were combined. When the residue was dried and concentrated *in vacuo*, it was chromatographied on silica gel (*n*-heptane/ethyl acetate as eluent) to afford the pure products in 70-95% yields.

Recycling of Ionic Liquid $C_6(mim)_2Cl_2$

The residual ionic liquid was washed with Et_2O (3 × 10 ml) to remove any organic impurity and dried at 80 °C. Under this procedure, $C_6(mim)_2Cl_2$ could be reused for four runs without any loss of its activity.

Spectroscopic Data

Compound 2a. pale yellow solid, m.p.: 113-114 °C. δ_H 7.40 (t, *J* = 7.1, 2H), 7.51 (t, *J* = 8.13, 1H), 7.87 (d, *J* = 8.16, 2H), 9.50 (s, 1H), 9.88 (s, 1H).

Compound 2b. yellow solid, m.p.: 207-210 °C. δ_H 7.44 (t, *J* = 7.5, 1H), 7.94 (d, *J* = 8.6, 2H), 8.29 (s, 1H), 9.57 (s, 2H), 9.99 (s, 2H). ν_{max} (cm^{-1}) 3286, 3178, 3114, 1627.

Compound 2c. pale yellow solid, m.p.: 107-108 °C. δ_H 7.36-7.46 (m, 4H), 9.69 (s, 1H), 10.17 (s, 1H).

Compound 2d. pale yellow solid, m.p.: 112-115 °C. δ_H 7.45 (t, *J* = 8.3, 1H), 7.57 (d, *J* = 7.4, 1H), 7.82 (d, *J* = 8.3, 1H), 7.89 (s, 1H), 9.63 (s, 1H), 10.04 (s, 1H).

Compound 2e. pale yellow solid, m.p.: 126-129 °C. δ_H 7.49 (d, *J* = 8.9, 2H), 7.9 (d, *J* = 7.9, 2H), 9.57 (s, 1H), 9.97 (s, 1H).

Compound 2f. pale yellow solid, m.p.: 83-85 °C. δ_H 7.46-7.53 (m, 2H), 7.72 (s, 1H), 9.81 (s, 1H), 10.32 (s, 1H).

Compound 2g. yellow solid, m.p.: 120-123 °C. δ_H 7.39 (t, *J* = 8, 1H), 7.70 (d, *J* = 8.5, 1H), 7.86 (d, *J* = 6.4, 1H), 8.03 (s, 1H), 9.62 (s, 1H), 10.03 (s, 1H). δ_C 121.5, 126.6, 130.2, 130.4, 134.0, 141.8, 198.6.

Compound 2h. pale yellow solid, m.p.: 139-142 °C. δ_H 7.63 (d, *J* = 9.3, 2H), 7.83 (d, *J* = 9.3, 2H), 9.58 (s, 1H), 9.96 (s, 1H).

Compound 2i. pale yellow solid, m.p.: 144-146 °C. δ_H 7.04 (m, 2H), 7.57 (m, 2H), 9.31 (s, 1H), 9.70 (s, 1H). δ_C 115.1, 130.3, 136.2, 163.1, 198.9.

Compound 2j. yellow solid, m.p.: 114-115 °C. δ_H 7.55 (t, *J* = 7.5, 1H), 8.05 (d, *J* = 7.5, 1H), 8.15 (d, *J* = 7.5, 1H), 8.45 (s, 1H), 9.66 (s, 1H), 10.05 (s, 1H). δ_C 122.6, 125.9, 130.1, 133.5, 141.1, 143.7, 197.4.

Compound 2k. pale yellow solid, m.p.: 146-148 °C. δ_H 3.8 (s, 3H), 6.95 (d, *J* = 9.7, 2H), 7.95 (d, *J* = 8.9, 2H), 9.33 (s, 1H), 9.66 (s, 1H). δ_C 55.8, 113.3, 129.8, 131.6, 162.2, 198.9.

Compound 2l. yellow solid, m.p.: 170-172 °C. δ_H 5.18 (s, 2H), 7.03 (d, *J* = 9.7, 2H), 7.33-7.47 (m, 5H), 7.94 (d, *J* = 8.1, 2H), 9.34 (s, 1H), 9.67 (s, 1H).

Compound 2m. pale yellow solid, m.p.: 205-207 °C. δ_H 7.49 (s, 2H), 8.44 (s, 2H), 9.59 (s, 1H), 10.01 (s, 1H). δ_C 125.8, 131.2, 132.7, 135.4, 201.1. ν_{max} (cm^{-1}) 3339, 3243, 3039, 1678. (Found: C, 51.89; H, 4.51; N, 20.43; S, 23.67%. $C_6H_6N_2S$ requires: C, 52.15; H, 4.38; N, 20.27; S, 23.20%).

Compound 2o. pale yellow solid, m.p.: 134-137 °C. δ_H 7.59 (m, 1H), 7.97 (m, 1H), 8.55 (m, 2H), 9.95 (s, 1H), 10.18 (s, 1H). δ_C 124.9, 126.6, 137.7, 147.9, 152.1, 195.0.

Compound 2p. yellow solid, m.p.: 103-105 °C. δ_H 6.93 (t, *J* = 4.4, 1H), 7.48 (d, *J* = 3.2, 1H), 7.56 (d, *J* = 4.8, 1H), 9.25 (s, 1H), 9.48 (s, 1H). δ_C 134.6, 141.9, 152.7, 165.2, 189. ν_{max} (cm^{-1}) 3329, 3275, 3157, 1624. (Found: C, 46.96; H, 4.10; N, 11.17; S, 25.67%. C_5H_5NOS requires: C, 42.22; H, 3.96; N, 11.01; S, 25.22%).

Compound 2q. pale yellow solid, m.p.: 232-235 °C. δ_H 6.8 (s, 2H), 7.53 (s, 1H), 8.26 (s, 1H), 8.32 (s, 1H), 11.64 (s, 2H). δ_C 141.9, 152.7.18, 175.1, 189.0. ν_{max} (cm^{-1}) 3436, 3329, 3232, 2931, 1640. (Found: C, 33.61; H, 4.04; N, 39.56; S, 22.79%. $C_4H_6N_4S$ requires: C, 33.79; H, 4.25; N, 39.40; S, 22.55%).

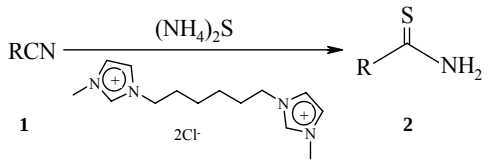
Compound 2r. pale yellow solid, m.p.: 154-156 °C. δ_H 5.14 (s, 1H), 7.24-7.41 (m, 10H), 8.27 (s, 1H), 9.07 (s, 1H).

RESULTS AND DISCUSSION

To expand our work to design new synthetic methodologies [28,29], specially in ionic liquids [30,31], we developed a simple, green and efficient procedure for direct synthesis of primary thiamides from various nitriles using $C_6(mim)_2Cl_2$ [7] as a dicationic ionic liquid (Scheme 1).

In an initial study, to examine the activity of different ionic liquids, 4-chlorobenzonitrile was caused to react with ammonium sulfide in the presence of each ionic liquid separately. As shown in Table 1, $C_6(mim)_2Cl_2$ is the most effective in terms of yield of the corresponding thioamide (97%) while in the presence of other ionic liquids the product was obtained in 15-85% yields.

Interestingly, no reaction was observed in the absence of ionic liquids. Consequently, we focused our attention only on the reaction in $C_6(mim)_2Cl_2$ as a dicationic ionic liquid. Using



Scheme 1. Synthesis of primary thioamides from nitriles in the dicationic ionic liquid

Table 1. Ionic Liquid Effect on the Thionation of 4-Chlorobenonitrile with Ammonium Sulfide[a]

Entry	Ionic liquid	Yield (%)[b]
1	[bmim][c]OTf	32
2	[bmim]BF_4	25
3	[bmim]PF_6	41
4	[bmim]Cl	89
5	[bmim]Br	85
6	[Hmim]HSO_4[d]	15
7	$PYR_{1n4}TFSI$[e]	51
8	$C_6(mim)_2Cl_2$	97

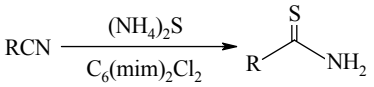
[a]After 5 min. [b]Isolated yields. [c]1-Buthyl-3-methylimidazolium. [d]1-Methylimidazolium hydrogen sulfate. [e]N-butyl-N-methyl-pyrrolidinium bis(trifluoromethanesulfonyl)imide.

these optimal conditions, we evaluated the scope of this method for transformation of various nitriles to their thoamides. The experimental results are summarized in Table 2.

The experimental procedure for this reaction is very simple and requires no organic solvent or inert atmosphere. The reaction took place by stirring an aromatic or aliphatic nitrile with ammonium sulfide in the presence of $C_6(mim)_2Cl_2$ at 70 ºC. All the products were characterized by IR and NMR spectroscopic data.

A broad range of aromatic or heterocyclic nitriles bearing electron donating or electron withdrawing substitutents underwent this reaction to produce thioamides in high to excellent yields. Interestingly, we found that in the case of 1,3-dicyanobenzene, dithioamidation occurred under the same reaction conditions (Table 2, compound **2b**). Moreover,

Table 2. Thionation of Nitriles with Ammonium Sulfide in $C_6(mim)_2Cl_2$



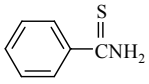
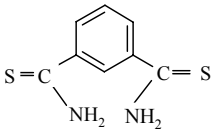
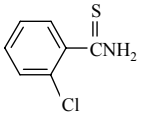
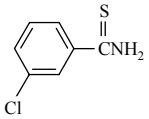
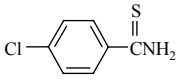
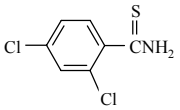
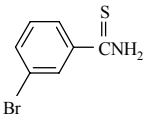
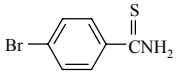
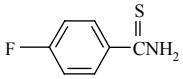
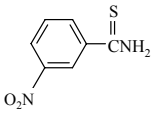
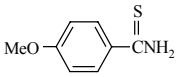
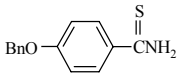
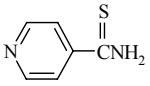
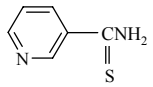
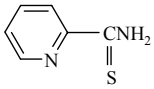
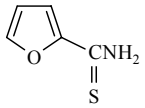
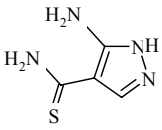
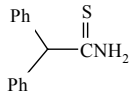
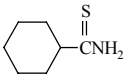
	Product	Yield (%)[a]	Time (min)
a		95	7
b		89	20
c		93	6
d		94	3
e		97	5

Table 2. Continued

f		95	5
g		96	5
h		93	4
i		92	6
j		94	6
k		89	50
l		95	50
m		98	4
n		95	10
o		90	10
p		97	5
q		86	45
r		90	35
s		94	15

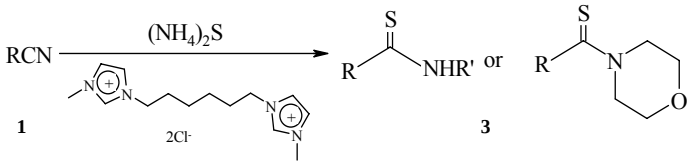
[a]Isolated yield.

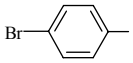
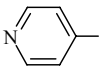
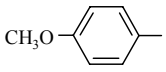
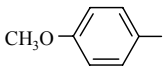
various functionalities such as ether, halide or nitro, survived under the said reaction conditions. On the other hand, heterocyclic (Table 2, compounds **1m-1q**) or aliphatic nitriles (Table 2, compounds **1r** and **1s**), which normally would produce poor yields in the reported methods [16,17], gave the corresponding thioamides in excellent yields at short reaction times (4-45 min).

Furthermore, in order to demonstrate the efficiency and the applicability of the suggested method, we started the reaction of nitriles and ammonium sulfide with different amines in $C_6(mim)_2Cl_2$ which gave the desired thioamides in high to excellent yields (Table 3**, 3a-j**). This method can also be considered as an efficient and novel protocol for the synthesis of secondary and tertiary thioamides from nitriles through a one-pot procedure with clearly short reaction times (Table 3).

To the best of our knowledge, this is the first attempt for the synthesis of thioamides in ionic liquids. In general, the reactions were clean and no side products were detected. The use of $C_6(mim)_2Cl_2$ as a new catalytic media in this transformation exhibited rate enhancements, high yields and

Table 3. Synthesis of Secondary and Tertiary Thioamides with Nitriles in $C_6(mim)_2Cl_2$



	R	Amine	Yield (%)[a]	Time (min)
a		CH_3NH_2	95	15
b		CH_3NH_2	92	10
c		CH_3NH_2	95	10
d		CH_3NH_2	91	10
e		CH_3NH_2	90	10
f		CH_3NH_2	89	15
g		CH_3NH_2	94	10
h		$CH_2CH_3NH_2$	93	90
l		$CH_2CH_3NH_2$	80	120
j		$CH_2CH_3NH_2$	90	60
k		Morpholine	70	300

short reactions times.

We also examined the reusability of the IL with 3-cyanopyridine as a substrate. We found that when the reaction occurred, after washing the reaction mixture with ethyl acetate and drying it at 80 °C, $C_6(mim)_2Cl_2$ could be reused for at least four runs without any loss of its activity (Table 4).

Although the mechanistic details of the reaction are not yet known exactly, a plausible rationalization may be advanced to explain the product formation (Fig. 1). Presumably, the interaction between the IL and nitrile group (Fig. 1, **A**) and then its conversion to the intermediate **B** and finally proton transfer can form the product.

Table 4. Recycling of $C_6(mim)_2Cl_2$ in the Reaction of 3-Cyanopyridine with Ammonium Sulfite[a]

Cycle	Yield (%)[b]
1	95
2	94
3	95
4	93

[a]After 10 min. [b]Isolated yield.

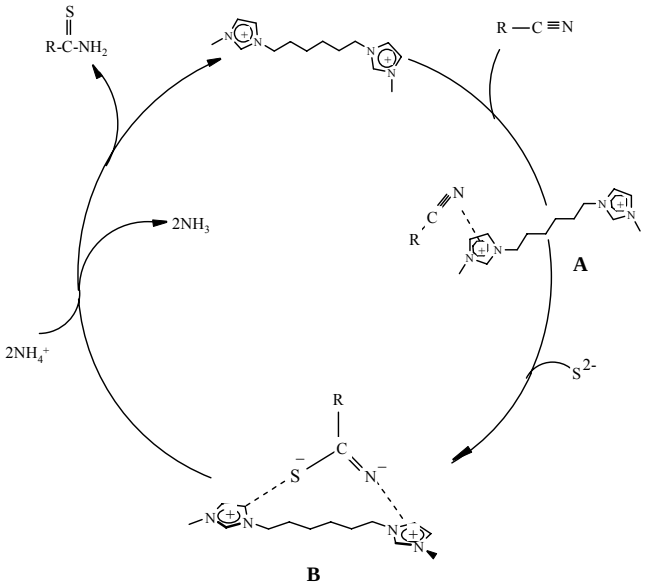


Fig. 1

In conclusion, we have described an efficient and eco-friendly method for the transformation of nitriles to their thioamides in $C_6(mim)_2Cl_2$ as a dicationic ionic liquid in high to excellent yields. This ionic liquid is a low-cost and recyclable medium. Reduced reaction time, no need for toxic solvents and simple experimental work-up make this a green, facile and superior method for the synthesis of thioamides.

ACKNOWLEDGEMENTS

We are thankful to both the 'Center of Excellence of Chemistry (Catalysis and Fuel Cell)' and the Research Council of University of Isfahan for the partial support of this work.

REFERENCES

[1] K. Tanaka, Solvent Free Organic Synthesis, Wiley-VCH, Weinheim, 2003.

[2] N.V. Plechkova, K.R. Seddon, Chem. Soc. Rev. 37 (2008) 123.

[3] P. Wasserscheid, T. Welton, Ionic Liquids in Synthesis, Wiley-VCH, Weinheim, 2008.

[4] M. Lombardo, F. Pasi, C. Trombini, K.R. Seddon, W.R. Pitner, Green Chem. 9 (2007) 321.

[5] Z.F. Zhang, E. Xie, W.J. Li, S.Q. Hu, J.L. Song, T. Jiang, B.X. Han, Angew. Chem. Int. Ed. 47 (2008) 1127.

[6] T.L. Greaves, C.J. Drummond, Chem. Rev. 108 (2008) 206.

[7] Q. Liu, F. Rantwijk, R.A. Sheldon, J. Chem. Technol. Biotechnol. 81 (2006) 401.

[8] P. Wipf, S. Venkatraman, J. Org. Chem. 61 (1996) 8004.

[9] O.A. Attanasi, S. Berretta, L.D. Crescentini, G. Favi, P. Filippone, G. Giorgi, S. Lillini, F. Mantellini, Tetrahedron Lett. 48 (2007) 2449.

[10] S.P. McManus, K.Y. Lee, C.U. Pittman, J. Org. Chem. 39 (1974) 3041.

[11] A. Padwa, L.S. Beall, T.M. Heidelbaugh, L. Bing, S.M. Sheehan, J. Org. Chem. 65 (2000) 2684.

[12] T.S. Jagodziñski, Chem. Rev. 103 (2003) 197.

[13] H. Prokopcová, C.O. Kappe, J. Org. Chem. 72 (2007) 4440.

[14] K.A. Petrov, L.N. Andreev, Usp. Khim. 38 (1969) 41.
[15] A. Bitton, Inflamm. Bowel Dis. 11 (2005) 513.
[16] E.S. Raper, Coord. Chem. Rev. 153 (1996) 199.
[17] S. Sinha, A.K. Srivastava, C.M. Tripathi, O.P. Pandey, S.K. Sengupta, Bioinorg. Chem. Appl. (2007) 87918.
[18] K.B. Wiberg, J. Am. Chem. Soc. 75 (1953) 3961.
[19] S.A. Benner, Tetrahedron Lett. 22 (1981) 1851.
[20] D. Brillon, Sulfur Rep. 12 (1992) 297.
[21] K. Hartke, H.D. Gerber, J. Prakt. Chem. 338 (1996) 763.
[22] M.P. Cava, M.I. Levinson, Tetrahedron 41 (1985) 5061.
[23] A.B. Charette, M. Grenon, J. Org. Chem. 68 (2003) 5792.
[24] M.C. Bagley, K. Chapaneri, C. Glover, E.A. Merritt, Synlett. (2004) 2615.
[25] B. Kaboudin, D. Elhamifar, Synthesis (2006) 224.
[26] R.V. Kolakowski, N. Shangguan, L.J. Williams, Tetrahedron Lett. 47 (2006) 1163.
[27] S.M. Lukyanov, I.V. Bliznets, S.V. Shorshnev, ARKIVOC 4 (2009) 21.
[28] A.R. Khosropour, M.M. Khodaei, M. Beygzadeh, Heteroatom. Chem. 18 (2007) 684.
[29] A.R. Khosropour, Ultrason. Sonochem. 15 (2008) 659.
[30] A.R. Khosropour, Can. J. Chem. 86 (2008) 264.
[31] J. Noei, A.R. Khosropour, Tetrahedron Lett. 49 (2008) 6969.