*S. Afr. J. Chem.*, 2012, **65**, 1–4,
<http://journals.sabinet.co.za/sajchem/>.

# An Efficient and Convenient Protocol for the Synthesis of Optically Active 1,2,4-Triazolo-[3,4-*b*]-[1,3,4]-Thiadiazole, 1,3,4-Oxadiazole and 1,3,4-Thiadiazole Derivatives having L-Amino Acid Moieties

**Naser Foroughifar[a,*], Sattar Ebrahimi[b], Akbar Mobinikhaldei[c] and Reza Mozafari[c]**

[a]*Faculty of Chemistry, North Tehran Branch, Islamic Azad University, Tehran, Iran.*
[b]*Department of Chemistry, Malayer Branch, Islamic Azad University, Malayer Iran.*
[c]*Department of Chemistry, Arak University, Arak 38156-8-8349, Iran.*

Received 28 April 2011, revised 12 September 2011, accepted 2 December. 2011.

ABSTRACT

**A series of novel bis triazolothiadiazole, 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives attached to L-amino acid moieties were synthesized in good yields using a simple and practical method. The structure of all synthesized compounds was confirmed by IR, $^1$H NMR, $^{13}$C NMR spectroscopy and elemental analysis.**

KEYWORDS

**Amino acid, triazolothiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, phosphorus oxychloride, triazole.**

## 1. Introduction

Over the past decades, the considerable interest has been focused on the chemistry of five-membered heterocyclic rings due to their unique biological importance. The [1,2,4]-triazolo-[3,4-*b*]-[1,3,4]-thiadiazole derivatives, prepared by combination of the bio-labile [1,2,4]-triazole and [1,3,4]-thiadiazole ring, may exert antifungal, antibacterial, antiviral, analgesic and plant growth regulatory effects.[1] A literature survey revealed that preparation of these compounds has been extensively studied and the most convenient procedure for the synthesis of [1,2,4]-triazolo-[3,4-*b*]-[1,3,4]-thiadiazole derivatives is based on the reaction of 5-substituted 4-amino-(4*H*)-1,2,4-triazole-3-thioles with carboxylic acids.[2–5]

The replacement of acid and ester groups in medicinal chemistry is a known approach in the search for compounds with improved pharmacokinetic characterization. In particular, 1,3,4-oxadiazole and 1,3,4-thiadiazole rings have been of interest for many medicinal chemists over the past few years, because of their antimitotic,[6] antimicrobial,[7] anti-inflammatory,[8] anti-convulsant[9] and antitubercular[10] activities.

On the basis of these reports and also as a continuation of our research program on the synthesis of heterocyclic compounds containing 1,2,4-triazole and optically active compounds,[11–15] we wish to report the synthesis of some new 3,6-disubstituted 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles, 1,3,4-oxadiazole and 1,3,4-thiadiazole rings containing a L-amino acid moiety, with the hope to improve their biological activities, because chirality is a main factor of the bioactive molecules and recognition phenomena associated with these molecules.

## 2. Experimental

### 2.1. General

The purity of compounds confirmed with thin layer chromatography (TLC) using EtOH/n-hexane (1:1 v/v) as an eluent. IR spectra were performed on a galaxy series FT-IR 5000 spectrophotometer using KBr discs. $^1$H NMR spectra were recorded on a Brucker spectrophotometer (300 MHz) in DMSO-$d_6$ using TMS as an internal standard. Elemental analyses were performed on a Vario EL III elemental analyzer. Specific rotations were measured by using a Perkin Elmer 341 polarimeter.

*To whom correspondence should be addressed. E-mail: n_forougifar@yahoo.com

### 2.2. General Procedure for Preparation of Compounds 3a–e

A mixture of triazole **1** (2 mmol), compounds **2a–e**[(16a–16b)] (1 mmol) in $POCl_3$ (7 mL) was refluxed for 16 h. The reaction mixture was slowly poured into crashed ice with stirring and neutralized with solid potassium carbonate. The mixture was allowed to stand overnight and the solid separated out was filtered and washed with cold water. The compound so obtained was dried and recrystallized from an appropriate solvent to give the pure products **3a–e**.

Compound **3a**

Yield 73 % (recrystallized from DMF); m.p. 230–231 °C; IR (KBr cm$^{-1}$): 3030 (aromatic CH stretch.), 2928 (aliphatic CH stretch.), 1784, 1722 (C=O), 1596 (C=N); $\delta_H$ (300 MHz, DMSO-$d_6$): 5.27 (4H, s, 2N-$CH_2$), 5.46 (4H, s, 2O$CH_2$), 6.93–7.02 (6H, m, $H_{arom}$), 7.25 (4H, br, $H_{arom}$), 8.38 (2H, s, $H_{arom}$), $\delta_C$ (75 MHz, DMSO-$d_6$: 38.4, 59.5, 115.3, 118.7, 122.0, 130.0, 137.4, 144.1, 155.2, 158.0, 165.8, 166.0. (Found: C, 54.38; H, 2.78; N, 19.62; S, 8.89 %. Calcd. for $C_{32}H_{20}N_{10}O_6S_2$: C, 54.54; H, 2.86; N, 19.88; S, 9.10 %).

Compound **3b**

Yield 84 % (recrystallized from DMF:EtOH (1:2)); $[\alpha]_D^{22} = -15$ (c = 0.02, DMSO); m.p. 208–210 °C; IR (KBr cm$^{-1}$): 3097 (aromatic CH stretch.), 2920 (aliphatic CH stretch.), 1782, 1726 (C=O), 1601 (C=N); $\delta_H$ (300 MHz, DMSO-$d_6$): 1.91 (6H, d, 2$CH_3$, *J* 6.5 Hz) 5.45 (4H, s, 2O$CH_2$), 5.95 (2H, q, 2N-CH, *J* 6.7 Hz), 6.93–7.06 (6H, m, $H_{arom.}$), 7.26–7.30 (4H, m, $H_{arom.}$), 8.34 (2H, s, $H_{arom.}$), $\delta_C$ (75 MHz, DMSO-$d_6$): 17.0, 47.27, 60.0, 115.4, 118.7, 122.0, 130.0, 137.3, 144.2,

155.2, 158.0, 167.7, 170.4.; (Found: C, 55.51; H, 3.24; N, 18.99; S, 8.51 % Calcd. for $C_{34}H_{24}N_{10}O_6S_2$: C, 55.73; H, 3.30; N, 19.12; S, 8.75 %).

Compound **3c**

Yield 71 % (recrystallized from DMF); $[\alpha]_D^{22}$ = –45 (c = 0.02, DMSO); m.p. 213–215 °C; IR (KBr $cm^{-1}$): 3055 (aromatic CH stretch.), 2930 (aliphatic CH stretch.), 1776, 1712 (C=O), 1605 (C=N); $\delta_H$ (300 MHz, DMSO-$d_6$): 3.72 (4H, br, 2Ph-$CH_2$) 5.49 (4H, s, 2$OCH_2$), 6.11 (2H, br, 2N-CH), 6.93–7.04 (6H, m, $H_{arom.}$), 7.15–7.24 (16H, m, $H_{arom.}$), 8.25 (2H, s, $H_{arom.}$), $\delta_C$ (75 MHz, DMSO-$d_6$): 36.1, 39.1, 53.9, 59.6, 115.4, 119.0, 122.0, 127.7, 129.0, 129.4, 130.0, 135.9, 136.7, 144.1, 155.2, 158.0, 165.5, 168.4.; (Found: C, 62.15; H, 3.51; N, 15.55; S, 7.06 % Calcd. for $C_{46}H_{32}N_{10}O_6S_2$: C, 62.43; H, 3.64; N, 15.83; S, 7.2 5 %).

Compound **3d**

Yield 62 % (recrystallized from DMF:EtOH (1:3)); $[\alpha]_D^{22}$ = –40 (c = 0.02, DMSO); m.p. 2170–171 °C; IR (KBr $cm^{-1}$): 3050 (aromatic CH stretch.), 2922 (aliphatic CH stretch.), 1778, 1716 (C=O), 1597 (C=N); $\delta_H$ (300 MHz, DMSO-$d_6$): 0.96–1.02 (12H, br, 4$CH_3$), 2.94 (2H, br, 2CH,), 5.31 (2H, d, 2N-CH, *J* 6.1 Hz), 5.50 (4H, s, 2$OCH_2$), 6.98–7.07 (6H, m, $H_{arom.}$), 7.29 (4H, br, $H_{arom.}$), 8.37 (2H, s, $H_{arom.}$), $\delta_C$ (75 MHz, DMSO-$d_6$): 19.4, 19.9, 29.7, 58.3, 59.5, 115.4, 119.0, 122.0, 130.0, 137.1, 144.0, 155.6, 158.0, 166.1, 167.6.; (Found: C, 57.59; H, 4.02; N, 17.65; S, 8.01 % Calcd. for $C_{38}H_{32}N_{10}O_6S_2$: C, 57.86; H, 4.09; N, 17.76; S, 8.13 %).

Compound **3e**

Yield 65 % (recrystallized from DMF:EtOH (1:3)); $[\alpha]_D^{22}$ = –25 (c = 0.02, DMSO); m.p. 158–160 °C; IR (KBr $cm^{-1}$): 3040 (aromatic CH stretch.), 2930 (aliphatic CH stretch.), 1774, 1724 (C=O), 1585 (C=N); $\delta_H$ (300 MHz, DMSO-$d_6$): 0.93 (12H, d, 4$CH_3$, *J* 4.6 Hz ), 1.61 (2H, br, 2CH), 2.13 (2H, br, 2CH), 2.46 (2H, br, 2CH), 5.48 (4H, s, 2$OCH_2$), 5.83 (2H, br, 2N-CH), 6.92–7.05 (6H, m, $H_{arom.}$), 7.27 (4H, br, $H_{arom.}$), 8.38 (2H, s, $H_{arom.}$), $\delta_C$ (75 MHz, DMSO-$d_6$): 21.7, 23.0, 24.8, 50.1, 60.0, 115.4, 119.1, 122.0, 130.0, 137.1, 144.1, 155.2, 158.0, 166.0, 169.4.; (Found: C, 58.74; H, 4.39; N, 17.03; S, 7.64. % Calcd. for $C_{40}H_{36}N_{10}O_6S_2$: C, 58.81; H, 4.44; N, 17.15; S, 7.85 %).

2.1.2. *General Procedure for Synthesis of Compounds* **7a–b**

A solution of diacyl hydrazides **6a–b**[13] (5 mmol) and $H_2SO_4$ (5 mL) was stirred at room temperature for 24 h. After completion of the reaction, the mixture was slowly added into crashed ice (150 g) with stirring and neutralized with concentrated ammonia. The mixture was allowed to stand overnight; the obtained precipitate was filtered and washed with cold water (200 mL). The product so obtained was dried and recrystallized from EtOH/$H_2O$ to give the pure compound.

Compound **7a**

Yield 53 % (recrystallized from $CHCl_3$:EtOH (1:2)); m.p. 223–224 °C; IR (KBr $cm^{-1}$): 3066 (aromatic CH stretch.), 2960 (aliphatic CH stretch.), 1778 (C=O), 1712 (C=O), 1600 (C=N), 1560, 1450 (C=C); $\delta_H$ (300 MHz, DMSO-$d_6$): 5.04 (4H, s, 2N-$CH_2$), 7.87–7.95 (8H, m, $H_{arom}$); $\delta_C$ (75 MHz, DMSO-$d_6$): 32.7, 124.0, 131.8, 135.4, 162.9, 167.2.; (Found: C, 61.58; H, 3.21; N, 14.65 % Calcd. for $C_{20}H_{12}N_4O_5$: C, 61.86; H, 3.11; N, 14.43 %).

Compound **7b**

Yield 57 % (recrystallized from EtOH); $[\alpha]_D^{22}$ = –18 (c = 0.02, DMSO); m.p. 195–197 °C; IR (KBr $cm^{-}$): 3060 (aromatic CH stretch.), 2930 (aliphatic CH stretch.), 1776 (C=O), 1716 (C=O), 1605 (C=N), 1550, 1465 (C=C); $\delta_H$ (300 MHz, DMSO-$d_6$): 1.86 (3H, d, $CH_3$, *J* 5.4 Hz), 5.83 (2H, q, 2N-CH, *J* 5.5 Hz), 7.86–7.95 (8H, m, $H_{arom.}$); $\delta_C$ (75 MHz, DMSO-$d_6$): 15.5, 48.0, 123.8, 131.7, 135.4, 164.3, 168.4.; Found: C, 63.28; H, 3.68; N, 13.62 % Calcd. for $C_{22}H_{16}N_4O_5$: C, 63.46; H, 3.87; N, 13.46 %).

### 2.3. General Procedure for Synthesis of 1,3,4-Thiadiazoles 9a–b

A solution of thiosemicarbazide **8a–b** (5 mmol) and $H_2SO_4$ (5 mL) was stirred at room temperature for 8 h. After the reaction was completed, the mixture was slowly added into crashed ice (150 g) with stirring and neutralized with concentrated ammonia. The mixture was allowed to stand overnight; the obtained precipitate was filtered and washed with cold water (200 mL). The product was air dried and recrystallized to give the pure compound.

Compound **9a**

Yield 64 % (recrystallized from DMF:EtOH (1:3)); m.p. > 320 °C; IR (KBr $cm^{-1}$): 3292, 3196 ($NH_2$), 3030 (aromatic CH stretch.), 2928 (aliphatic CH stretch.), 1776 (C=O), 1710 (C=O), 1612 (C=N); $\delta_H$ (300 MHz, DMSO-$d_6$): 4.93 (2H, s, N-$CH_2$), 7.19 (2H, s, $NH_2$, $D_2O$ exchange), 7.89 (2H, d, *J* 2.3 Hz $H_{arom.}$), 7.91 (2H, d, *J* 2.4 Hz $H_{arom.}$); $\delta_C$ (75 MHz, DMSO-$d_6$): 36.7, 123.8, 131.8, 135.2, 152.9, 167.6, 170.1; (Found: C, 50.71; H, 3.08; N, 21.41; S, 12.23 %; Calcd. for $C_{11}H_8N_4O_2S$: C, 50.76; H, 3.10; N, 21.53; S, 12.32 %.

Compound **9b**

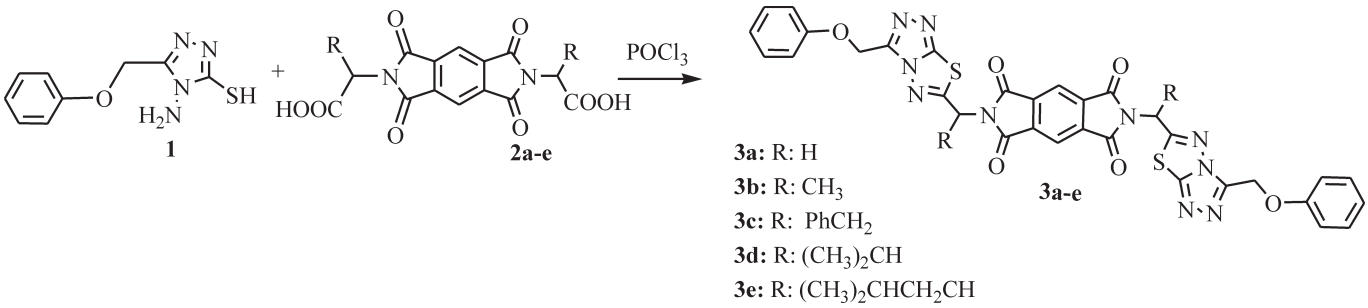
Yield 60 % (recrystallized from EtOH); $[\alpha]_D^{22}$ = –30 (c = 0.02, DMSO); m.p. > 320 °C; IR (KBr $cm^{-1}$): 3285, 3196 ($NH_2$), 3065 (aromatic CH stretch.), 2934 (aliphatic CH stretch.), 1778 (C=O), 1716 (C=O), 1618 (C=N); $\delta_H$ (300 MHz, DMSO-$d_6$): 1.94 (3H, d, $CH_3$, *J* 6.2 Hz), 5.83 (2H, q, 2N-CH, *J* 6.3 Hz), 7.23 (2H, s, $NH_2$, $D_2O$ exchange), 7.87–7.92 (4H, m, $H_{arom.}$); $\delta_C$ (75 MHz, DMSO-$d_6$): 117.5, 52.4, 124.1, 132.0, 135.1, 152.8, 167.6, 172.0; (Found: C, 52.44; H, 3.64; N, 20.35; S, 11.62 % Calcd. for $C_{12}H_{10}N_4O_2S$: C, 52.54; H, 3.67; N, 20.43; S, 11.69 %).

## 3. Results and Discussion

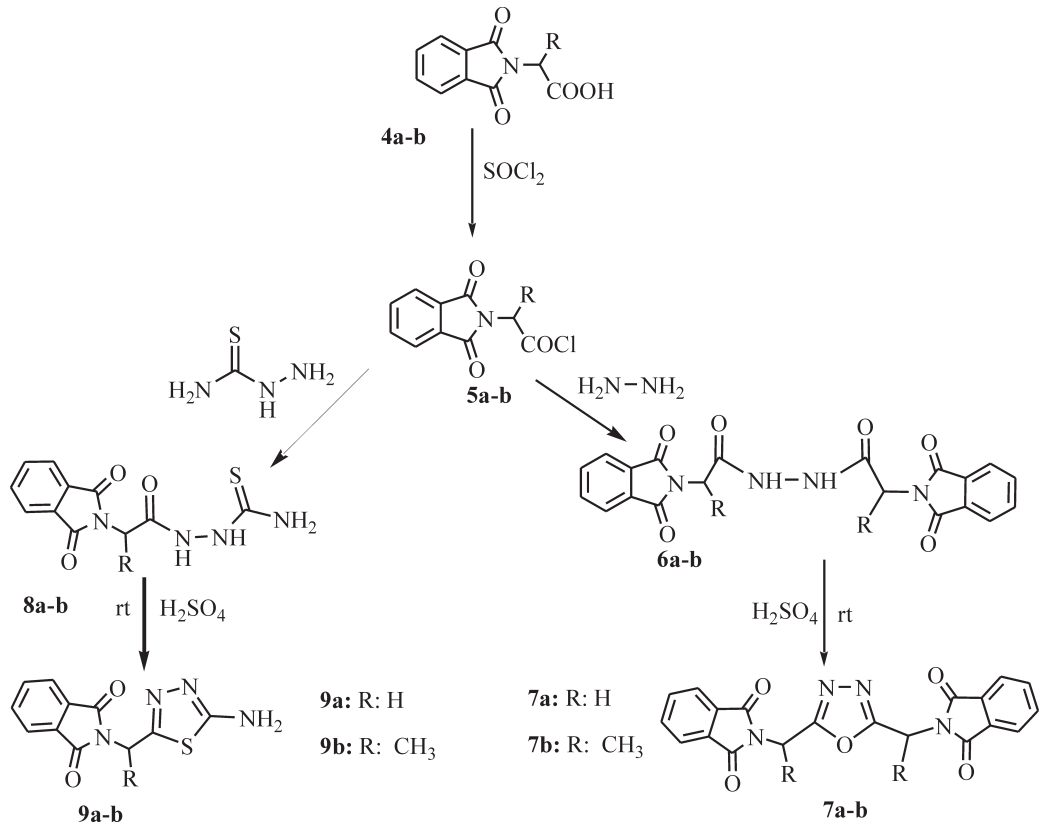
This paper describes the synthesis of some five-membered heterocyclic systems containing three heteroatoms. Firstly, 2-[6-(2-hydroxy-2oxoalkyl)1,3-,5,7-tetraoxo-5,7-dihydropyrolo [3,4,*f*] isoindol-2-(1*H*, 3*H*)-yl]acetic acid **2a–e**[16a,16b] and N-phethaloyl-L-amino acids **4a–b**[17a–17b] were chosen as starting materials. 5-Substituted 4-amino-(4*H*)-1,2,4-triazole-3-thiole **1** was prepared by heating phenoxy acetic acid with one equivalent of carbonothioic dihydrazide in an oil bath at 170 °C. The resultant triazole **1** was further converted to 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazoles **3a–e** through a one pot reaction by condensation with compounds **2a–e** (Scheme 1). Phosphorus oxychloride works best for this condensation, which activates the carboxyl group of the amino acids by converting it to the acid chloride (*in situ*). The acid chloride has an increased electrophilicity which enhances the addition of amino-triazole to it.

The infrared spectrum of the triazole **1** shows two absorption bands, at 2730 $cm^{-1}$ and 3203–3317 $cm^{-1}$ due to SH and $NH_2$ groups, which are absent in the IR spectra of the triazolo thiadiazoles **3a–e**. Similarly the $^1H$ NMR spectrum of compound **1** shows two characteristic absorptions (broad singlets at $\delta$ 5.68, and 12.95 ppm) attributed to the $NH_2$ and SH groups, respectively. These groups both disappear upon formation of the corresponding triazolothiadiazoles.

1,3,4-Oxadiazoles **7a–b** and 1,3,4-thiadiazoles **9a–b** were syn-




**Scheme 1**
Synthesis of compounds **3a–e**




**Scheme 2**
Synthesis of compounds **7a–b** and **9a–b.**

thesized through a three steps pathway. N-Phetaloyl-L-amino acids **4a–b**, (Gly, Ala) were converted to the corresponding acyl chlorides **5a–b**,[17c] using $SOCl_2$ activation. The reaction of acyl chlorides with hydrazine or hydrazinecarbothioamide in N,N-dimethyl acetamide (DMAc) for 2 hours at room temperature afforded the corresponding semicarbazides **6a–b**[13] or thiosemicarbazides **8a–b** in reasonable yields. Then diacyl hydrazides **6a–b** and compounds **8a–b** were cyclized to 2,5-disubstituted 1,3,4-oxadiazoles **7a–b** and 2,5-disubstituted 1,3,4-thiadiazoles **9a–b**, respectively (Scheme 2). The driving force for formation of these compounds from **6a–b** and **8a–b** is the formation of an aromatic ring. However, the yield of these products is relatively low, which may be due to low nucleophilic reactivity of the hydrazide group.

## 4. Conclusion

In conclusion, we have described a simple and efficient synthetic method for preparation of triazolothiadiazoles, 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives. In addition to the efficiency and simplicity provided, this protocol is associated with good yields of cyclization and simple purification for these products.

## References

1 (a) G.L. Almajan, S.F. Barbuceanu, G. Bancescu, I. Saramet, G. Saramet and C. Draghici, *Eur. J. Med. Chem.* 2010, **45**, 6139–6146. (b) M.A. Azam, B. Suresh, S. S. Kalsi, A. and A. Shinesh, *S. Afr. J. Chem.*, 2010, **63**, 114–122. (c) B. Guessas, A. A. Othman and Z. Khiati, *S. Afr. J. Chem.*, 2007, **60**, 20–24.

2 R.J. Singha and D.K. Singh, *S. Afr. J. Chem.*, 2009, 62, 105–108.

3 S.M. El-Khawass and N.S. Habib, H. Fu, *J. Heterocycl. Chem.*, 1989, **26**, 177–181.

4 D. Li, D. Long and H. Fu, *Synthetic Commun.* 2005, **35**, 2495–2500.

5 K.S. Bhat, D.J. Prasad, B. Poojary and B.S. Holla, *Phosphorus, Sulfur Silicon Relat. Elem.* 2004, **179**, 1595–1603.

6 K.M. Lokanatha Rai and N. Linganna, *Farmaco* 2000, **55,** 389–392.

7 A.S. Shawali, M.A. Abdallah and M.E.M. Zayed, *Eur. J. Med. Chem.* 2009, **44**, 2106–2112.

8 H. Kumar, S.A. Javed, S.A. Khan and M. Amir, *Eur. J. Med. Chem.* 2008, **43**, 2688–2698.

9 V. Jatav, P. Mishra, S. Kashaw and J.P. Stables, *Eur. J. Med. Chem.* 2008, **43**, 1945–1954.

10 S. Talath and A.K. Gadad, *Eur. J. Med. Chem.* 2006, **41**, 918–924.

11 N. Foroughifar, A. Mobinikhaledi, S. Ebrahimi, M.A. Bodaghi Fard and H. Moghanian, *J. Chin. Chem. Soc.* 2009, **56**, 1043–1047.

12 N. Foroughifar, A. Mobinikhaledi, S. Ebrahimi and M. Khanpour, *Eur. J. Chem.* 2010, **1**, 33–36.

13 N. Foroughifar, A. Mobinikhaledi and S. Ebrahimi, *Turk. J. Chem.* 2010, **34**, 603–611.

14 N. Foroughifar, A. Mobinikhaledi and S. Ebrahimi, *Synthetic Commun.* 2010, **40**, 2421–2428.

15 S. Ebrahimi, *Eur. J. Chem.* 2010, **4**, 322–324.

16 (a) S. Mallakpour and M.H. Shahmohammadi, *J. Appl. Polym. Sci.,* 2004, **92**, 951–959. (b) Kh. Faghihi and M. Hajibeygi, *Chinese J. Polym. Sci.* 2010, **28**, 517–525.

17 (a) E. Hoffmann and H. Schiff-Shenmav, *J. Org. Chem*. 1962, **27**, 4686–4688. (b) Kh. Faghihi, *J. Sci. I.A.U.* (JSIAU) 2007, **17**, 2–6. (c) A. Hajipour, S. Mallakpour and G. Imanzadeh, *Indian. J. Chem.,* 2001, **40B**, 250–251.