This article was downloaded by: [Istanbul Universitesi Kutuphane ve Dok]
On: 05 September 2013, At: 06:04
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK


Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrp20

# An efficient synthesis of [1,3,4]thiadiazolo[2,3-c][1,2,4] triazin-4-ones

Razieh Mohebat [a], Masoumeh Tabatabaee [a] & Mohammad Ashrafi Bafghi [a]
[a] Department of Chemistry, Islamic Azad University, Yazd Branch, PO Box 89195-155, Yazd, Iran
Published online: 27 Nov 2012.

To cite this article: Razieh Mohebat, Masoumeh Tabatabaee & Mohammad Ashrafi Bafghi (2013) An efficient synthesis of [1,3,4]thiadiazolo[2,3-c][1,2,4] triazin-4-ones, Journal of Sulfur Chemistry, 34:4, 377-382, DOI: 10.1080/17415993.2012.744408

To link to this article: http://dx.doi.org/10.1080/17415993.2012.744408

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

*Journal of Sulfur Chemistry*, 2013
Vol. 34, No. 4, 377–382, http://dx.doi.org/10.1080/17415993.2012.744408

Taylor & Francis
Taylor & Francis Group

Downloaded by [Istanbul Universitesi Kutuphane ve Dok] at 06:04 05 September 2013

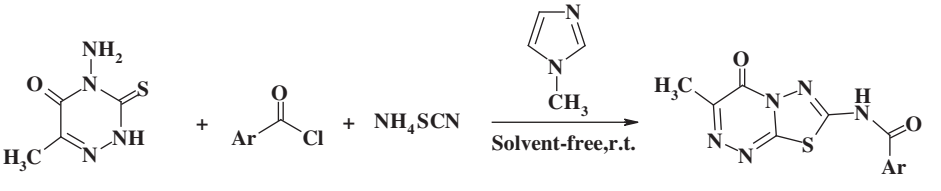
# An efficient synthesis of [1,3,4]thiadiazolo[2,3-*c*][1,2,4] triazin-4-ones

Razieh Mohebat*, Masoumeh Tabatabaee and Mohammad Ashrafi Bafghi

*Department of Chemistry, Islamic Azad University, Yazd Branch, PO Box 89195-155, Yazd, Iran*

(*Received 12 September 2012; final version received 25 October 2012*)

A three-component reaction between 4-amino-6-methyl-3-thioxo-3,4-dihydro-2*H*-[1,2,4]triazin-5-one, ammonium thiocyanate and aroyl chlorides in the presence of *N*-methylimidazole to afford the [1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-4-ones in excellent yields is described.




**Keywords:** *N*-methylimidazole; aroyl chlorides; ammonium thiocyanate; AMTTO; three-component reaction

## 1. Introduction

Triazines and their derivatives are important groups of heterocyclic compounds. They have attracted considerable interest because of their exceptional biological antitumor (*1*, *2*), anti-HIV (*3*), antiviral (*4*), antimalarial (*5*), antibacterial (*6*), antifungal (*7*), and antioxidant activities (*8*). Triazines have also found wide applications as herbicides (*9*, *10*) and pesticides (*11*) in the field of agriculture. In addition, a number of thiadiazole derivatives exhibit a broad range of biological activities due to the presence of the −NCS moiety (*12*). Bartlett *et al*. described 1,2,4-triazinones as anti-inflammatory agents with immune modulating properties (*13*). They reported that these compounds are effective not only in preventing, but also curing established arthritic disorders in rats. They also reported that these compounds effectively inhibited the carrageenan-induced paw edema, attenuated the active Arthus reaction, and demonstrated antierythema as well as antipyretic activity. Part of the anti-inflammatory effects of these compounds is most probably related to their

*Corresponding author. Email: rozitakalami@yahoo.com

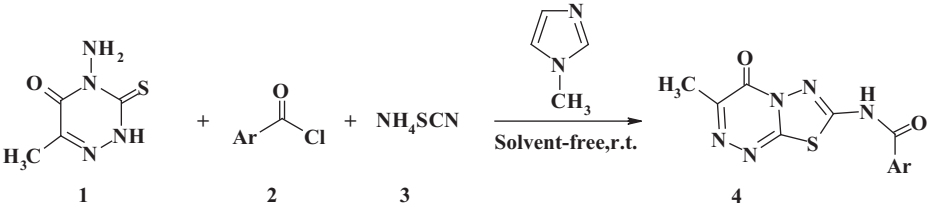
© 2013 Taylor & Francis

antioxidative activity, as well as to the inhibition of lipoxygenase metabolites (*13*). As a result, many efforts have been devoted to the development of new methodologies for efficient synthesis of 1,2,4-triazinones (*14*, *15*).

A few years ago, several substituted 4*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-4-ones were prepared by refluxing a solution of 4-amino-6-methyl-3-thioxo-3,4-dihydro-2*H*-[1,2,4]triazin-5-one (AMTTO) and aroyl chlorides with potassium thiocyanate in acetonitrile for 4 h (*16*). Unlike previously reported methods, the present method does not require toxic organic solvents and also the experimental results show that the reaction times are shorter and the yields of the products are higher under solvent-free conditions to produce the [1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-4-one derivatives. As part of an ongoing development of efficient protocols for the preparation of biologically active sulfur-containing heterocycles (*17–24*), we report here an efficient one-pot synthesis of the [1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-4-ones, employing readily available starting materials.

## 2. Results and discussion

Reaction of AMTTO **1** and aroyl chlorides **2** with ammonium thiocyanate **3** in the presence of *N*-methylimidazole affords [1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-4-one derivatives **4** in excellent yields (Scheme 1).




| 2, 4 | Ar | %Yield* |
|---|---|---|
| a | phenyl | 80 |
| b | o-$CH_3$ $C_6H_4$ | 83 |
| c | m-$CH_3$ $C_6H_4$ | 88 |
| d | p-Cl $C_6H_4$ | 88 |
| e | p-Br $C_6H_4$ | 87 |
| f | m-$NO_2$ $C_6H_4$ | 92 |

* Isolated yields

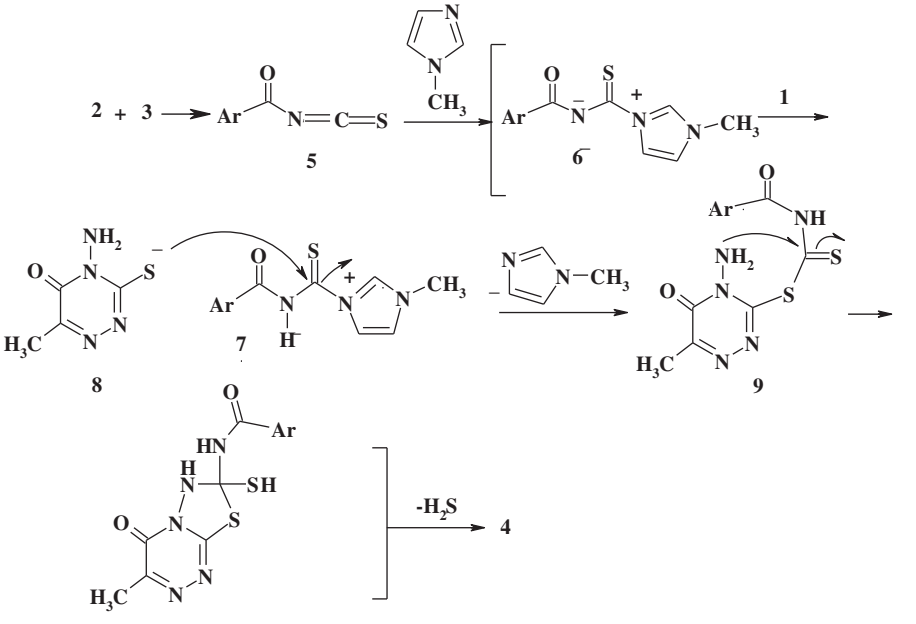
Scheme 1. Three-component reaction between AMTTO, ammonium thiocyanate and aroyl chlorides in the presence of *N*-methylimidazole.

Structures of compounds **4a**–**4f** were confirmed by IR, $^1$H NMR, $^{13}$C NMR, and mass spectral data. For example, the $^1$H NMR spectrum of **4b** shows two sharp signals ($\delta = 2.42$ and 2.45 ppm) corresponded to the protons of the methyl groups. The aromatic protons resonated between 7.35–8.04 ppm and a singlet signal was observed at $\delta = 13.75$ ppm for an NH proton which disappears after addition of a few drops of $D_2O$ to a DMSO solution of **4b**.

Downloaded by [Istanbul Universitesi Kutuphane ve Dok] at 06:04 05 September 2013

The $^{13}$C NMR spectrum of compound **4b** shows 13 distinct signals, which is consistent with the proposed structure. The mass spectrum of **4b** displayed the molecular ion peak at $m/z = 301$. The IR spectrum of compound **4b** also supported the suggested structure, and strong absorption bands were observed at 3200, 1700, and 1681 cm$^{-1}$, respectively, for the NH and carbonyl groups.

A tentative mechanism for this transformation is proposed in Scheme 2.



Scheme 2. Suggested mechanism for the formation of compound **4**.

It is conceivable that the reaction starts with the formation of aroyl thiocyanate **5**, followed by the formation of the 1:1 adducts **6** and its subsequent protonation by AMTTO to produce **7**. Then, the positively charged ion **7** is attacked by the anion of AMTTO **8**. Intermediate **9** undergoes a cyclization reaction and elimination of $H_2S$ to produce **4**.

In conclusion, the reaction AMTTO and aroyl chlorides with ammonium thiocyanate in the presence of *N*-methylimidazole led to [1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-4-one derivatives. The present procedure has advantages such as shorter reaction times and simple work-up, and affords excellent yields.

## 3. Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer at analytical laboratory of Islamic Azad University Yazd Branch. Mass spectra were recorded on an FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Compound AMTTO **1** was prepared as previously described in the literature (*25*).

Downloaded by [Istanbul Universitesi Kutuphane ve Dok] at 06:04 05 September 2013

Downloaded by [Istanbul Universitesi Kutuphane ve Dok] at 06:04 05 September 2013

### 3.1. *General procedure*

Aroyl chloride (2 mmol) was added to ammonium thiocyanate (2 mmol) in a 50 ml flask at room temperature (rt). The reaction mixture was stirred in a water bath at about 90 °C for 5 min. Then, AMTTO (2 mmol) was added at this temperature. The reaction mixture was allowed to cool to room temperature. Finally, *N*-methylimidazole (0.032 g) (10 mol%) was added via syringe. The resulting mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, 15 ml distilled water was added for more than 5 min to the reaction mixture. The resulting precipitate was collected by filtration on a Buchner funnel and washed with 10 ml of cold diethyl ether to afford the pure title compounds.

#### 3.1.1. *N-(3-methyl 4-oxo-4H-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-7-yl)benzamide* ***(4a)***

White powder; m.p. > 290 °C, IR (KBr) ($\nu_{max}$ cm$^{-1}$): 3205, 2980, 1702, 1670, 1599, 1564, 1374. Analyses: Calcd for $C_{12}H_9N_5O_2S$: C, 50.17; H, 3.16; N, 24.38%. Found: C, 50.35; H, 3.03; N, 24.50. MS (*m/z*, %): 287 ($M^+$, 5). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.44 (3H, s, $CH_3$), 7.60 (2H, t, $^3J_{HH}$ = 7.6 Hz, 2CH of $C_6H_5$), 7.72 (1H, d, $^3J_{HH}$ = 7.6 Hz, 1CH of $C_6H_5$), 8.15 (2H, d, $^3J_{HH}$ = 7.6 Hz, 2CH of $C_6H_5$), 13.75 (1H, s, NH) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 17.2 ($CH_3$), 128.3, 129.1, 130.7, and 133.06 (phenyl moiety), 147.9 (C), 151.9 (C), 153.5 (C), 161.7 and 167.3 (2C=O) ppm.

#### 3.1.2. *N-(3-methyl 4-oxo-4H-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-7-yl) 2-methylbenzamide* ***(4b)***

White powder; m.p. > 270 °C, IR (KBr) ($\nu_{max}$ cm$^{-1}$): 3200, 2975, 1700, 1681, 1600, 1566, 1375. Analyses: Calcd for $C_{13}H_{11}N_5O_2S$: C, 51.82; H, 3.68; N, 23.24%. Found: C, 51.73; H, 3.81; N, 23.15. MS (*m/z*, %): 301 ($M^+$, 10). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.42 and 2.45 (6H, 2s, $2CH_3$), 7.35–7.38 (2H, m, 2 CH of $C_6H_4CH_3$), 7.78 (1H, t, $^3J_{HH}$ = 7.6 Hz, 1CH of $C_6H_4CH_3$), 8.04 (2H, d, $^3J_{HH}$ = 7.6 Hz, 2CH of $C_6H_4CH_3$), 13.76 (1H, s, NH) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 17.4 and 21.6 ($2CH_3$), 126.9, 129.3, 130.2, 132.3, 134.9, and 138.8 (aryl moiety), 148.0 (C), 148.6 (C), 151.7 (C), 161.6 and 167.7 (2C=O) ppm.

#### 3.1.3. *N-(3-methyl 4-oxo-4H-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-7-yl) 3-methylbenzamide* ***(4c)***

White powder; m.p. > 280 °C, IR (KBr) ($\nu_{max}$ cm$^{-1}$): 3200, 2975, 1705, 1666, 1587, 1564, 1374. Analyses: Calcd for $C_{13}H_{11}N_5O_2S$: C, 51.82; H, 3.68; N, 23.24%. Found: C, 51.93; H, 3.55; N, 23.30. MS (*m/z*, %): 301 ($M^+$, 7). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.43 and 2.49 (6H, 2s, $2CH_3$), 7.48 (2H, t, $^3J_{HH}$ = 7.6 Hz, 2CH of $C_6H_4CH_3$), 7.54 (1H, d, $^3J_{HH}$ = 7.5 Hz, 1CH of $C_6H_4CH_3$), 7.91 (2H, d, $^3J_{HH}$ = 7.6 Hz, 2CH of $C_6H_4CH_3$), 7.97 (1H, s, 1CH of $C_6H_4CH_3$), 13.76 (1H, s, NH) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 17.5 and 21.7 ($2CH_3$), 126.9, 129.3, 130.2, 132.3, 134.9, and 138.8 (aryl moiety), 148.0 (C), 148.5 (C), 151.8 (C), 161.6 and 167.6 (2C=O) ppm.

#### 3.1.4. *N-(3-methyl 4-oxo-4H-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-7-yl) 4-chlorobenzamide* ***(4d)***

White powder; m.p. > 300 °C, IR (KBr) ($\nu_{max}$ cm$^{-1}$): 3250, 2965, 1705, 1666, 1587, 1551, 1374. Analyses: Calcd for $C_{12}H_8ClN_5O_2S$: C, 44.80; H, 2.51; N, 21.77%. Found: C, 44.93; H, 2.61; N,

21.59. MS (*m*/*z*, %): 321 ($M^+$, 11). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.43 (3H, s, $CH_3$), 7.83 (2H, d, $^3J_{HH}$ = 8.4 Hz, 2CH of $C_6H_4Cl$), 8.11 (2H, d, $^3J_{HH}$ = 8.4 Hz, 2CH of $C_6H_4Cl$), 13.77 (1H, s, NH) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 17.4 ($CH_3$), 128.7, 129.9, 134.1, and 139.1 (aryl moiety), 148.1 (C), 148.5 (C), 151.6 (C), 161.8 and 168.6 (2C=O) ppm.

### 3.1.5. *N-(3-methyl 4-oxo-4H-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-7-yl) 4-bromobenzamide* ***(4e)***

White powder; m.p. > 300 °C, IR (KBr) ($\nu_{max}$ cm$^{-1}$): 3250, 2980, 1707, 1665, 1589, 1556, 1376. Analyses: Calcd for $C_{12}H_8BrN_5O_2S$: C, 39.36; H, 2.20; N, 19.12%. Found: C, 39.20; H, 2.14; N, 19.26. MS (*m*/*z*, %): 366 ($M^+$, 5). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.43 (3H, s, $CH_3$), 7.93 (2H, d, $^3J_{HH}$ = 8.4 Hz, 2CH of $C_6H_4Br$), 8.06 (2H, d, $^3J_{HH}$ = 8.4 Hz, 2CH of $C_6H_4Br$), 13.76 (1H, s, NH) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 17.4 ($CH_3$), 126.7, 129.8, 132.1, and 136.1 (aryl moiety), 148.2 (C), 148.6 (C), 151.5 (C), 161.8 and 168.7 (2C=O) ppm.

### 3.1.6. *N-(3-methyl 4-oxo-4H-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-7-yl) 3-nitrobenzamide* ***(4f)***

White powder; m.p. > 310 °C, IR (KBr) ($\nu_{max}$ cm$^{-1}$): 3230, 1697, 1675, 1596, 1524, 1497, 1457, 1378. Analyses: Calcd for $C_{12}H_8N_6O_4S$: C, 43.37; H, 2.43; N, 25.29%. Found: C, 43.51; H, 2.30; N, 25.48. MS (*m*/*z*, %): 332 ($M^+$, 9). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.43 (3H, s, $CH_3$), 7.76 (2H, t, $^3J_{HH}$ = 7.6 Hz, 2CH of $C_6H_4NO_2$), 8.32 (1H, d, $^3J_{HH}$ = 8.0 Hz, 1CH of $C_6H_4NO_2$), 8.51 (2H, d, $^3J_{HH}$ = 7.6 Hz, 2CH of $C_6H_4NO_2$), 8.89 (1H, s, 1CH of $C_6H_4NO_2$), 13.76 (1H, s, NH) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 17.6 ($CH_3$), 123.2, 125.7, 130.2, 134.9, 140.0, and 148.2 (aryl moiety), 148.4 (C), 151.1 (C), 153.8 (C), 161.9 and 169.1 (2C=O) ppm.

## Acknowledgement

We gratefully acknowledge financial support from the Research Council of Islamic Azad University of Yazd of Iran.

## References

(1) El-Gendy, Z.; Morsy, J.M.; Allimony, H.A.; Abdel-Monem, A.R.; Abdel-Rahman, R.M. *Pharmazie* **2001,** *56,* 376–384.
(2) Sztanke, K.; Pasternak, K.; Sztanke, M.; Kandefer-Szerszeń, M.; Kozioł, A.E.; Dybała, I. *Bioorg. Med. Chem. Lett.* **2009,** *19,* 5095–5100.
(3) Abdel-Rahman, R.M.; Seada, M.; Fawzy, M.; el Baz, I. *Boll. Chim. Farm.* **1994,** *133,* 381–388.
(4) Rusinov, V.L.; Chupakhin, O.N.; Deev, S.L.; Shestakova, T.S.; Ulomskii, E.N.; Rusinova, L.I.; Kiselev, O.I.; Deeva, E.G. *Russ. Chem. Bull.* **2010,** *59,* 136–143.
(5) Louis, C.K.; Gurdip, S.B.; Jesse, L.; Khizar, W.; Madeleine, M.J.*J. Med. Chem.* **1976,** *19,* 845–852.
(6) Holla, B.S.; Sarojini, B.K.; Gonsalves, R. *Farmaco* **1998,** *53,* 395–398.
(7) Davidson, W.M.; Boykin, W.D. *J. Pharm. Sci.* **1978,** *65,* 737–376.
(8) Pustoshnaya, L.S.; Pustoshnyi, V.P.; Mazitova, A.K.; Khamaev, V.K.; Davydov, E.Y.; Zaikov, G.E.; Minsker, K.S. *Polym. Degrad. Stab.* **2000,** *70,* 39–41.
(9) Oettmeier, W.; Hilp, U. *J. Pestic. Sci.* **1991,** *33,* 399–409.
(10) Olmeda, C.; Deban, L.; Barrado, E.; Castrillejo, Y.; Herrero, L. *Electrochim. Acta* **1994,** *39,* 2237–2241.
(11) Kang-Chieu, L.; Bi-Jane, S.; Chuen-Hsiang, L. *J. Heterocycl. Chem.* **1992,** *29,* 97–101.
(12) Onar, M.; Omaima, M.E.; Aboulwafa, M. *J. Heterocycl. Chem.* **1986,** *23,* 1339–1341.
(13) Bartlett, R.R.; Gebert, U.; Kerekjarto, V.; Schleyerbach, R.; Thorwart, W.; Weithmann, K.U. *Drugs Exp. Clin. Res.* **1989,** *15,* 521–526.
(14) Mizutani, M.; Sanemitsu, Y. *Tetrahedron Lett.* **1985,** *26,* 1237–1240.
(15) El-Shehawy, A.A. *Tetrahedron Asymmetry* **2006,** *17,* 2617–2624.
(16) Coppo, F.T.; Fawzi, M. *J. Heterocycl. Chem.* **1997,** *34,* 1351–1354.
(17) Mohebat, R.; Mosslemin, M.H.; Dehghan-Darehshiri, A.; Hassanabadi, A. *J. Sulfur. Chem.* **2011,** *32,* 557–561.

Downloaded by [Istanbul Universitesi Kutuphane ve Dok] at 06:04 05 September 2013

(18) Ramazani, A.; Mahyari, A. *Helv. Chim. Acta* **2010,** *93,* 2203–2209.
(19) Khoobi, M.; Ramazani, A.; Foroumadi, A.R.; Hamadi, H.; Hojjati, Z.; Shafiee, A. *J. Iran. Chem. Soc.* **2011,** *8,* 1036–1042.
(20) Yavari, I.; Ramazani, A. *J. Chem. Res. (S)* **1996,** *8,* 382–383.
(21) Yavari, I.; Ramazani, A.; Yahya-Zadeh, A. *Synth. Commun.* **1996,** *26,* 4495–4499.
(22) Safaei-Ghomi, J.; Salimi, F.; Ramazani, A.; Zeinali Nasrabadi, F.; Ahmadi, Y. *J. Sulfur Chem.* **2012,** *33,* 87–92.
(23) Zareai, Z.; Khoobi, M.; Ramazani, A.; Foroumadi, A.; Souldozi, A.; Lepokura K.; Lis, T.; Shafiee, A. *Tetrahedron* **2012,** *68,* 6721–6726.
(24) Vessally, E.; Ramazani, A.; Yaaghubi, E. *Monatsh. Chem.* **2011,** *142,* 1143–1147.
(25) Dornow, A.; Enzel, H.M.; Marx, P. *Chem. Ber.* **1964,** *97,* 2173–2178.

Downloaded by [Istanbul Universitesi Kutuphane ve Dok] at 06:04 05 September 2013