Synthesis of 3-hydroxy-2*H*-iminolactones and 3-hydroxy-2*H*-pyrrol-2-ones from reaction between isocyanides and methyl 2-acetylacetoacetate

Nourallah Hazeri, Malek Taher Maghsoodlou,* Sayyed Mostafa Habibi-Khorassani, and Ghasem Marandi

Department of Chemistry, The University of Sistan and Balouchestan, P. O. Box 98135-674, Zahedan, Iran
E-mail: mt_maghsoodlou@yahoo.com

Abstract
A one pot synthesis of new lactam derivatives is reported from reactions between alkyl or aryl isocyanides and methyl 2-acetylacetoacetate in good yields.

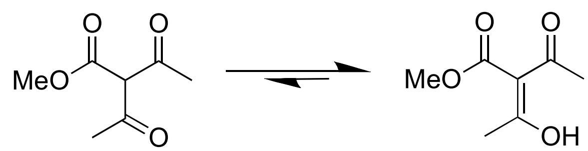
Keywords: Methyl 2-acetylacetoacetate, isocyanides, 3-hydroxy-2*H*-iminolactones, 3-hydroxy-2*H*-pyrrol-2-ones

Introduction

Five-membered rings such as furan and pyrrole have many useful synthetic applications in drug structures.[1-13] Using the isocyanide carbon atom for synthesis of many cyclic systems in a formal [1+4] cycloaddition reaction is an elegant approach to systems which are inaccessible by other methods.[14-16] In recent years, syntheses of iminolactones have been reported by many research groups.[17-30] Recently we reported another route involving two-component reactions between isocyanides and *N*,*N'*-dimethylbarbituric acid for the preparation of enaminones.[31-34] Herein, we report the synthesis of new iminolactones **3** from the reaction between alkyl or aryl isocyanides **2** and methyl 2-acetylacetoacetate **1**, as a two-component reaction and conversion of **3** into **4** under thermal conditions.

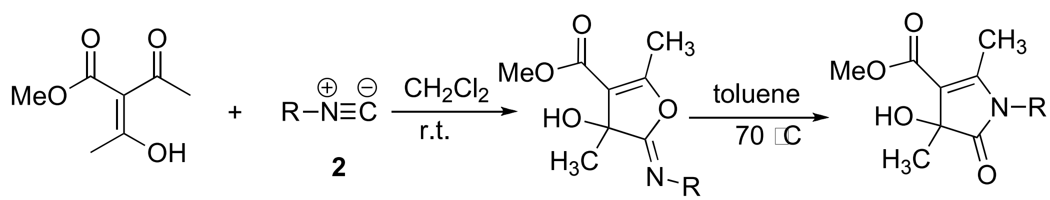
Result and Discussion

Isocyanides react readily with most multiple bonds to give three, four or five-membered cycloadducts derived from 1:1, 1:2, 2:1 substrate-isocyanide interactions.[8-10] Cycloadditon reactions of this type are unique to isocyanides. The reaction of isocyanides with carbon-carbon double bonds tends to occur in a stepwise manner and is involves a zwitterionic intermediate the ultimate fate of which appears to be dictated by the nature of the original double bond substrate. In the present work, methyl 2-acetylacetoacetate **1a**, which is completely enolized in the liquid phase (Scheme 1), reacted with isocyanides **2** *via* insertion into the carbon-carbon double bond of an electron-deficient hetero-1,3-diene (**1b**) to afford iminolactone derivatives **3** in high yields. Heating the iminolactone **3** in toluene at 70 °C gave the pyrrole derivatives **4** as new lactam derivatives (see Scheme 2). A proposed mechanism is shown in Scheme 3.



1a **1b**

Scheme 1



1b **2** **3** **4**

3, **4**	R	Yield (%) of **3** and **4**	
a	*t*-butyl	85	90
b	$EtOOCCH_2$	80	87
c	Cyclohexyl	87	92
d	$PhCH_2$	75	85

Scheme 2

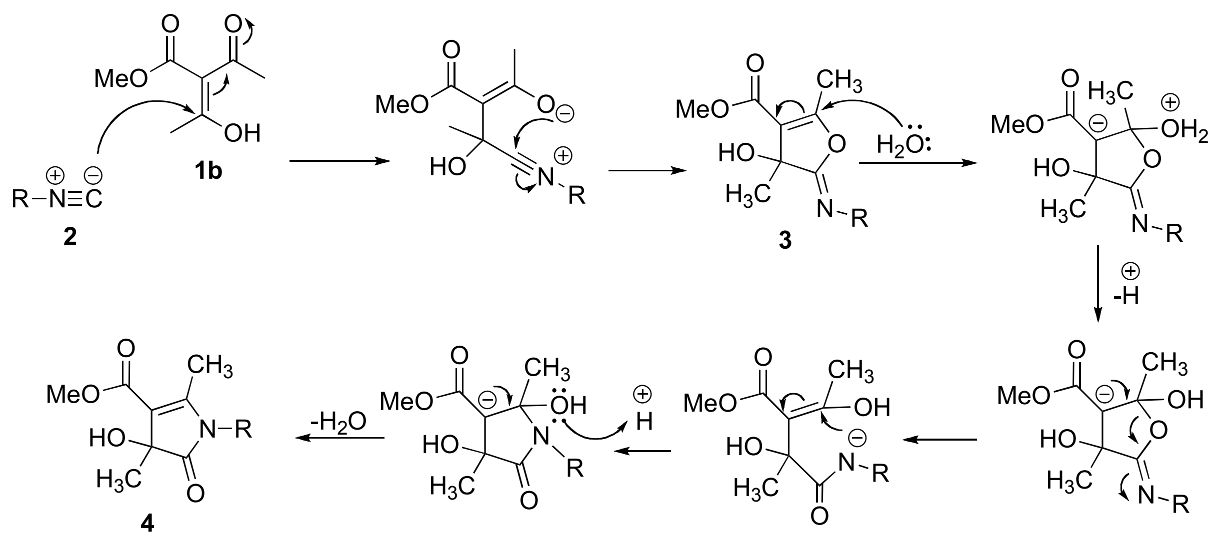
The structures of **3** and **4** were deduced from their elemental analyses, IR, ^1H and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values, any initial fragmentation involving the loss of the ester moieties. The ^1H and ^{13}C NMR data for compounds **3** and **4** are given in the experimental part.

The ^1H NMR spectrum of compound **3a** exhibited four singlets arising from *t*-butyl (δ 1.32), two methyl groups (δ 1.65 and 2.35), and a methoxy group (δ 3.78) respectively, and the proton of the OH group resonated at δ 3.37. The ^{13}C NMR spectrum of compound **3a** showed ten distinct resonances according to the iminobutyrolactone structure. The IR spectrum of compound

3a displayed strong and appropriate absorption bands in the carbonyl and imine region (1723 and 1653 cm^{-1}) respectively (see experimental section for data for **3b-d**).

The ^{1}H NMR spectrum of compound **4a** showed four sharp singlets arising from the three methyls of *t*-butyl (δ 1.36), two methyl groups (δ 1.63 and 1.84), and a methoxy group (δ 3.62) respectively, and the proton of the OH group exhibited a broad peak at δ 5.71. The ^{13}C NMR spectrum of compound **4a** exhibited ten distinct resonances compatible with the lactam structure.

The IR spectrum of compound **4a** had absorption bands at 1695 cm^{-1} (carbonyl) consistent with the proposed structure (see experimental section for **4b-d**). In spite of very similar of ^{13}C chemical shifts for imine groups and amidic carbon in compounds **3** and **4**, the IR spectra are different. Hence, this difference may be considered as a good evidence for the transformation of iminolactones **3** to lactams **4**.



Scheme 3

In conclusion, we have prepared novel 3-hydroxy-2*H*-iminolactones and 3-hydroxy-2*H*-pyrrol-2-ones *via* one-pot reactions between isocyanides and methyl 2-acetylacetoacetate. The present reaction is performed under neutral conditions and starting materials and reagent can be reacted without any prior activation.

Experimental Section

General Procedures. Melting points were taken on an Electrothermal 9100 apparatus and IR spectra were measured on a Shimadzu IR-460 spectrometer. The ^{1}H and ^{13}C NMR spectra were obtained using a BRUKER DRX-500 AVANCE instrument with $CDCl_3$ as a solvent at 500.1 and 125.8 MHz respectively. In addition, the mass spectra were recorded on a Finnigan-Matt

8430 mass spectrometer operating at an ionization potential of 70 eV and elemental analyses for C, H and N were taken using a Heraeus CHN-O-rapid analyzer. Isocyanides and methyl 2-acetylacetoacetate were purchased from Fluka, and used without further purifications.

General procedure for preparation of 3 (exemplified by 3a)

To a magnetically stirred solution of methyl 2-acetylacetoacetate (1 mmol) in 10 mL of dry CH_2Cl_2 was added dropwise a mixture of *t*-butyl isocyanide (1 mmol) in CH_2Cl_2 (3 mL) at room temperature over 5 min. After one week at room temperature, solvent was removed under reduced pressure and the solid residue washed with cold diethyl ether (2×3 mL) to obtain **3a** as gray crystals, yield (85%), mp 85-88 °C, IR (KBr) (ν_{max}, cm^{-1}): 1653 (C=N), 1723 (C=O), 3230 (OH). ^1H NMR (500.1 MHz, $CDCl_3$): δ_H 1.32 (9H, s, C*Me*$_3$), 1.65 (3H, s, CH_3), 2.35 (3H, s, C=C-CH_3), 3.37 (1H, br s, OH), 3.78 (3H, s, OMe). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 14.4 (C=C-*C*H_3), 26.8 (CH_3), 27.9 (C*Me*$_3$), 51.2 (OCH_3), 54.7 (*C*Me_3), 75.8 (C-OH), 111.7 (O-C=*C*), 157.6 (O-*C*=C), 164.4 (N=C-O), 165.1 (C=O). MS (*m/z*, %): 242 (M^++1, 2), 224 (8), 193 (5), 178 (100), 136 (73), 124 (33). Anal. Calcd for $C_{12}H_{19}NO_4$ (241.13): C, 59.73; H, 7.94; N, 5.81% Found: C, 59.64; H, 7.93; N, 5.74%

3b. Gray crystals, yield (80%), mp. 102-105 °C, IR (KBr) (ν_{max}, cm^{-1}): 1658 (C=N), 1720 and 1724 (C=O), 3227 (OH). ^1H NMR (500.1 MHz, $CDCl_3$): δ_H 1.23 (3H, t, *J*=6.8 Hz, OCH_2*Me*), 1.73 (3H, s, CH_3), 2.21 (3H, s, C=C-CH_3), 3.41 (1H, br s, OH), 3.73 (3H, s, OMe), 3.83 (2H, q, *J*=6.8 Hz, OC*H*$_2$Me), 3.96 (2H, s, NCH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 13.0 (C=C-*C*H_3), 20.0 (CH_2*Me*), 29.1 (CH_3), 50.4 (NCH_2), 51.2 (OCH_3), 60.4 (OCH_2), 75.5 (C-OH), 108.6 (O-C=*C*), 159.8 (O-*C*=C), 160.9 (N=C-O), 166.5 and 168.6 (2 C=O). MS (*m/z*, %): 271 (M^+, 3), 256 (8), 244 (47), 242 (95), 226 (100), 212 (5). Anal. Calcd for $C_{12}H_{17}NO_6$ (271.11): C, 53.13; H, 6.32; N, 5.16% Found: C, 53.25; H, 6.35; N, 5.21%

3c. Pale white crystal, yield (87%), mp. 115-117 °C, IR (KBr) (ν_{max}, cm^{-1}): 1670 (C=N), 1732 (C=O), 3179 (OH). ^1H NMR (500.1 MHz, $CDCl_3$): δ_H 1.22-1.98 (10H, m, 5 CH_2), 1.75 (3H, s, CH_3), 2.15 (3H, s, C=C-CH_3), 3.73 (1H, m, NCH), 3.84 (3H, s, OMe), 4.21 (1H, br s, OH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 13.6 (C=C-*C*H_3), 24.4 (2 CH_2), 25.3 (CH_3), 25.8 (CH_2), 32.9 (2 CH_2), 50.5 (OCH_3), 55.6 (NCH), 74.7 (C-OH), 112.0 (O-C=*C*), 160.9 (O-*C*=C), 163.8 and 164.4 (C=O and N=C-O). MS (*m/z*, %): 269 (M^++2, 10), 268 (M^++1, 57), 267 (M^+, 59), 252 (80), 236 (17), 220 (38), 125 (58), 83 (79). Anal. Calcd for $C_{14}H_{21}NO_4$ (267.15): C, 62.90; H, 7.92; N, 5.24% Found: C, 63.05; H, 7.92; N, 5.30%

3d. White crystal, yield (75%), mp. 92-95 °C, IR (KBr) (ν_{max}, cm^{-1}): 1667 (C=N), 1726 (C=O), 3211 (OH). ^1H NMR (500.1 MHz, $CDCl_3$): δ_H 1.71 (3 H, s, CH_3), 2.12 (3 H, s, C=C-CH_3), 3.73 (1 H, br s, OH), 3.67 (1 H, s, OMe), 4.51 (2 H, m, NC*H*$_2$Ph), 7.45 (5 H, m, Ar*H*). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 13.6 (C=C-*C*H_3), 23.5 (CH_3), 43.5 (NCH_2), 51.7 (OCH_3), 81.3 (C-OH), 112.1 (O-C=*C*), 127.0, 127.6, 128.3 and 128.7 (6 C_{arom}), 161.3 (O-*C*=C), 162.8 and 169.3 (C=O and N=C-O). MS (*m/z*, %): 275 (M^+, 4), 260 (5), 244 (38), 227 (75), 198 (95), 169 (100). Anal. Calcd for $C_{15}H_{17}NO_4$ (275.16): C, 65.44; H, 6.22; N, 5.09% Found: C, 65.54; H, 6.23; N, 5.16%

General procedure for preparation of 4 (exemplified by 4a)

3a was heated in 15 mL of toluene at 70 °C for a week then the solvent was removed under reduced pressure and the solid residue was washed with cold diethyl ether (2×3 mL) and the product **4a** was obtained as gray crystals, yield (90%), mp. 125-128 °C, IR (KBr) (ν_{max}, cm^{-1}): 3365 (OH), 1716 and 1695 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.36 (9H, s, C*Me*$_3$), 1.63 (3H, s, CH_3), 1.84 (3H, s, C=C-CH_3), 3.62 (3H, s, OMe), 5.71 (1H, br s, OH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 11.0 (C=C-*C*H_3), 22.1 (CH_3), 28.99 (C*Me*$_3$), 52.0 (OCH_3), 56.7 (*C*Me_3), 91.5 (C-OH), 141.9 and 143.3 (*C*=*C*), 164.0 (O=C-N), 168.9 (C=O). MS (*m/z*, %): 241 (M$^+$, 7), 226 (65), 210 (13), 169 (100), 138 (78), 111 (14), 57 (97). Anal. Calcd for $C_{12}H_{19}NO_4$ (241.13): C, 59.73; H, 7.94; N, 5.81% Found: C, 59.78; H, 7.87; N, 5.86%

4b. Pale white crystals, yield (87%), mp. 117-119 °C, IR (KBr) (ν_{max}, cm^{-1}): 3352 (OH), 1713 and 1695 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.20 (3H, t, *J*=7.0 Hz, OCH_2*Me*), 1.78 (3H, s, CH_3), 2.43 (3H, s, C=C-CH_3), 3.17 (1H, br s, OH), 3.81 (3H, s, OMe), 3.86 (2H, s, NCH_2), 4.18 (2H, q, *J*=7.0 Hz, OC*H*$_2$Me). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 10.7 (C=C-*C*H_3), 20.0 (CH_2*Me*), 23.3 and 24.4 (2 CH_3), 51.5 (OCH_3), 61.3 (OCH_2), 80.87 (NCH_2), 88.3 (C-OH), 142.2 and 142.9 (*C*=*C*), 163.2 (O=C-N), 169.0 and 171.8 (2 C=O). MS (*m/z*, %): 270 (M$^+$-1, 5), 268 (100), 226 (3), 224 (67), 198 (2), 154 (3). Anal. Calcd for $C_{12}H_{17}NO_6$ (271.11): C, 53.13; H, 6.32; N, 5.16% Found: C, 53.18; H, 6.40; N, 5.12%

4c. White crystals, yield (92%), mp. 134-137 °C, IR (KBr) (ν_{max}, cm^{-1}): 3350 (OH), 1718 and 1694 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.20-2.13 (10H, m, 5 CH_2), 1.75 (3H, s, CH_3), 2.18 (3H, s, C=C-CH_3), 3.40 (1H, m, NCH), 3.85 (3H, s, OMe), 6.08 (1H, br s, OH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 10.8 (C=C-*C*H_3), 23.7 (CH_2), 25.2 (CH_2), 26.3 (2 CH_2), 30.0 (2 CH_2), 51.9 (OCH_3), 52.3 (NCH), 89.2 (C-OH), 140.4 and 144.9 (*C*=*C*), 163.9 and 167.3 (O=C-N and C=O). MS (*m/z*, %): 268 (M$^+$+1, 8), 267 (M$^+$, 23), 252 (63), 223 (25), 186 (100), 169 (93), 137 (73), 98 (95), 83 (15). Anal. Calcd for $C_{14}H_{21}NO_4$ (267.15): C, 62.90; H, 7.92; N, 5.24% Found: C, 63.15; H, 7.80; N, 5.27%

4d. White crystals, yield (85%), mp. 167-170 °C, IR (KBr) (ν_{max}, cm^{-1}): 3338 (OH), 1716 and 1698 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.88 (3H, s, CH_3), 2.01 (3H, s, C=C-CH_3), 3.69 (1H, s, OMe), 3.82 (1H, br s, OH), 4.45 (2H, m, NC*H*$_2$Ph), 7.32 (5H, m, Ar*H*). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 14.1 (C=C-*C*H_3), 22.9 (CH_3), 43.1 (NCH_2), 48.0 (OCH_3), 84.1 (C-OH), 126.9, 127.00, 128.6 and 136.5 (6 C_{arom}), 137.8 and 136.5 (*C*=*C*), 169.3 and 171.8 (O=C-N and C=O). MS (*m/z*, %): 275 (M$^+$, 1), 244 (5), 228 (10), 226 (100), 214 (13), 142 (18). Anal. Calcd for $C_{15}H_{17}NO_4$ (275.16): C, 65.44; H, 6.22; N, 5.09% Found: C, 65.32; H, 6.18; N, 5.12%

Acknowledgements

We gratefully acknowledge financial support from the Research Council of the University of Sistan & Balouchestan.

References

1. Sternberg, E. D.; Dolphin, D.; Brückner, C. *Tetrahedron* **1998**, *54*, 4151.
2. Melvin, M. S.; Tomlinson, J. T.; Saluta, G. R.; Kucera, G. L.; Lindquist, N.; Manderville, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 6333.
3. Fürstner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3582.
4. Joule, J. A.; Mills, K. *Heterocyclic Chemistry at a Glance*, Blackwell: Oxford, 2007.
5. Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433.
6. Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.
7. Patil, N. T.; Yamamoto, Y. *ARKIVOC* **2007**, (*x)*, 121.
8. Larionov, O. V.; Meijere, A. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 5664.
9. D'Alessio, R.; Margiotti, A.; Carlini, O.; Colotta, F.; Ferrari, M.; Gnocchi, P.; Isetta, A. M.; Mongelli, N.; Motta, P.; Rossi, A.; Rossi, M.; Tibolla, M.; Vanotti, E. *J. Med. Chem.* **2000**, *43*, 2557.
10. Tobisu, M.; Yamaguchi, S.; Chatani, N. *Org. Lett.* **2007**, 9 (*17*), 3351.
11. O'Hagen, D. *Nat. Prod. Rep.* **2000**, *17*, 435.
12. Sato, A.; McNulty, L.; Cox, K.; Kim, S.; Scott, A.; Daniell, K.; Summerville, K.; Price, C.; Hudson, S.; Kiakos, K.; Hartley, J. A.; Asao, T.; Lee, M. *J. Med. Chem.* **2005**, *48*, 3903.
13. Kaki, H.; Onozawa, C.; Sato, M.; Arai, K.; Osada, H. *J. Med. Chem.* **1997**, *40*, 391.
14. I. Ugi, *Angew. Chem.*, *Int. Ed. Engl.* **1982**, *21*, 810.
15. Walborsky, H. M.; Periasamy, M. P. In Patai, S.; Rappoport, Z., Ed., *The Chemistry of Functional Groups*, Supplement C, John Wiley: New York, 1983, Chap. 20, pp 835-887.
16. Marcaccini, S.; Torroba, T. *Org. Prep. Proc. Intl.* **1993**, *25*, 141.
17. Villemin, D.; Liao, L. *Synth. Commun.* **2003**, *33*, 1757.
18. Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899.
19. Nair, V.; Vinod, A. U.; Somarajan-Nair, J.; Sreekanth, A. R.; Rath, N. P. *Tetrahedron Lett.* **2000**, *41*, 6675.
20. Yoshida, Y.; Fukushima, H.; Morishita, T.; Ohshita, J.; Kunai, A. *Tetrahedron* **2007**, *63*, 4793.
21. Yavari, I.; Djahaniani, H. *Tetrahedron Lett.* **2005**, *46*, 7491.
22. Xiong, T.; Zhang, Q.; Zhang, Z.; Liu, Q. *J. Org. Chem.* **2007**, *72*, 8005.
23. Szakonyi, Z.; Hetényi, A.; Fülöp, F. *ARKIVOC* **2008**, (*iii)*, 33.
24. Yavari, I.; Shaabani, A.; Maghsoodlou, M. T. *Monatsh. Chem.* **1997**, *128*, 697.
25. Maghsoodlou, M. T.; Hazeri, N.; Habibi-khorassani, S. M.; Marandi G.; Nassiri, M. *J. Heterocycl. Chem.* **2006**, *43*, 481.
26. Maghsoodlou, M. T.; Hazeri, N.; Habibi-khorassani, S. M.; Heydari, R.; Marandi G.; Nassiri, M. *Synth. Commun.* **2005**, *35*, 2569.
27. Maghsoodlou, M. T.; Hazeri, N.; Habibi-khorassani, S. M.; Marandi G.; Nassiri, M. *Synth. Commun.* **2005**, *35*, 2771.

28. Hazeri, N.; Maghsoodlou, M. T.; Habibi-khorassani, S. M.; Marandi, G.; Khandan-Barani, K.; Ziyaadini, M.; Aminkhani, A. *ARKIVOC* **2007**, (*i*), 173.
29. Hazeri, N.; Maghsoodlou, M. T.; Habibi-khorassani, S. M.; Ziyaadini, M.; Marandi, G.; Khandan-Barani, K.; Bijanzadeh, H. R. *ARKIVOC* **2007**, *(xiii)*, 34.
30. Yavari, I.; Mokhtarporyani-Sanandaj, A.; Moradi, L.; Mirzaei, A. *Tetrahedron* **2008**, *64*, 5221.
31. Yavari, I.; Hazeri, N.; Maghsoodlou, M. T.; Moradi, A. *J. Chem. Res.* **2001**, 272.
32. Maghsoodlou, M. T.; Hazeri, N.; Habibi-khorassani, S. M.; Solimani, V.; Marandi, G.; Razmjoo, Z. *J. Chem. Res.* **2008**, 198.
33. Yavari, I.; Hazeri, N.; Maghsoodlou, M. T.; Zabarjad-Shiraz, N. *Monatsh. Chem.* **2001**, *132*, 683.
34. Maghsoodlou, M. T.; Yavari, I.; Nassiri, F.; Djahaniani, H.; Razmjoo, Z. *Monatsh. Chem.* **2003**, *134*, 1585.