

Synthesis and Characterization of Some Novel 4-Aryloxy Substituted Pyrazoles

MUHAMMAD SHER¹, PERVAIZ ALI¹, ZAMAN ASHRAF¹, MUHAMMAD AAMIR¹, EJAZ AHMED^{2*}, AHSAN SHARIF², NADIA RIAZ¹ and SHAHID IQBAL³

¹Department of Chemistry, AllamaIqbal Open University, Islamabad-44000, Pakistan

²Institute of Chemistry, University of the Punjab, Quaid-e-Azam Campus, Lahore-54590, Pakistan

³Department of Chemistry, University of Sargodha, Sargodha 40100, Pakistan

*Corresponding author: Fax: +92 42 99231269; Tel: +92 42 99230463; E-mail: dr.ejaz.ahmed@gmail.com

Received: 6 February 2014;

Accepted: 6 May 2014;

Published online: 30 September 2014;

AJC-16155

The synthesis of some novel 4-aryloxy substituted pyrazoles was performed in two steps. The synthetic route involves the synthesis of 3-aryloxy substituted 1,3-dicarbonyl compounds (**3a-e**) in first step by the condensation of 3-chloro-pentan-2,4-dione (**1**) and substituted phenols (**2a-e**). The hydrazine monohydrate/substituted aromatic hydrazides (**4a-e**) in the second step were then treated with compounds **3a-e** to afford the target pyrazoles (**5a-e**). The interesting feature of this reaction is the isolation of the intermediate pyrazoline. The structure of this intermediate was also confirmed by the X-ray single crystal. The structures of the synthesized compounds **5a-e** were assigned on the basis of FT-IR, ¹H NMR, ¹³C NMR and mass spectroscopic data.

Keywords: Hydrazides, 4-Aryloxy pyrazoles, 5-Hydroxy-2-pyrazoline.

INTRODUCTION

Pyrazoles and their substituted analogues are important class of five membered heterocyclic systems that find extensive use in pharmaceutical and agrochemical industries¹. The growing interest in bioactive *N*-arylpyrazoles has led to an increasing demand for efficient syntheses of this class of heterocyclic compounds. Several reports have found diverse applications for *N*-arylpyrazoles in medicine such as antitumor²⁻¹², antiviral¹³, antiinflammatory¹⁴ agents, or kinase inhibitors for the treatment of type 2 diabetes, hyperlipidemia and obesity¹⁵. Moreover, these compounds have remarkable potential in nanomedicine applications against malignant gliomas¹⁶. 1-(4-Chlorophenyl)-4-hydroxy-3-substituted-1*H*-pyrazoles were reported by the U.S. National Cancer Institute (NCI) to have pronounced anticancer activity^{17,18}.

1,3-Dicarbonyl compounds are most widely used precursors for the preparation of pyrazoles. The various strategies employed for the synthesis of pyrazoles include 1,3-dipolar cycloaddition of diazo compounds onto triple bond¹⁹, cycloaddition of 6-nitroquinoline with aromatic hydrazones²⁰, biaryl coupling²¹ and addition of hydrazines to 1,3-dicarbonyl compounds and α,β -unsaturated compounds²²⁻²⁴. Among these, addition of hydrazine to 1,3-dicarbonyl compounds is the most easily accessible route for the synthesis of pyrazoles.

We report herein the two-step synthesis of 4-aryloxy substituted pyrazoles. The first step involves synthesis of 3-aryloxy

substituted 1,3-dicarbonyl compounds and their condensation in the latter step with hydrazine hydrate and substituted hydrazides to afford the target molecules. The method adopted for the synthesis of pyrazoles also employed for the synthesis of stable 5-hydroxy pyrazolines which can act as bidentate chelating agents²⁵.

EXPERIMENTAL

Melting points were recorded using a digital Gallenkamp (SANYO) model MPD.BM 3.5 apparatus and are uncorrected. ¹H and ¹³C NMR spectra were determined in CDCl₃ at 300 MHz and 75 MHz, respectively using a BrukerAMX spectrophotometer. FTIR spectra were recorded on 1310 FT-IR spectrometer with KBr pellets. All chemicals were purchased from Merck and Aldrich and were used without further purification. Mass spectra were recorded on SHIMADZU GCQP-2010 and API 4000 by ion trap system.

Synthesis of 4-aryloxy substituted pyrazoles (5a-j): The 3-aryloxy substituted pentan-2,4-diones (**3a-e**) have been synthesized according to reported procedure²⁶. The 3-chloro pentan-2,4-dione (**1**) dissolved in acetone was treated with substituted phenols (**2a-e**) in the presence of potassium carbonate to afford the compounds **3a-e**. Then 3-aryloxy pentan-2,4-dione (**3a-e**) were condensed in ethanol with hydrazine monohydrate/substituted aromatic hydrazides (**4a-e**) in equimolar ratio. The reaction mixture was refluxed for 4-8 h in the presence of catalytic amount of conc. H₂SO₄. The reaction

was monitored by thin layer chromatography. After the completion of reaction solvent was removed under reduced pressure and residue was recrystallized from 70 % ethanol to afford the pyrazoles (**5a-j**).

4-Chlorophenyl-(3,5-dimethyl-4-(*p*-tolylloxy)-1*H*-pyrazol-1-yl)-methanone (5a**):** Yellow solid (yield, 37 %), m.p. 155 °C. ¹H NMR (300 MHz, CDCl₃) δ = 7.71 (d, *J* = 7.5 Hz, 2H, ArH), 7.44 (d, *J* = 7.5 Hz, 2H, ArH), 6.97 (d, *J* = 7.5 Hz, 2H, ArH), 6.72 (d, *J* = 7.5 Hz, 2H, ArH), 2.52 (s, 3H, CH₃), 2.42 (s, 1H, CH₃), 2.32 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ: 166.3, 153.7, 141.9, 140.6, 139.7, 134.2, 132.8, 129.8, 129.2, 128.6, 125, 119.9, 21.1, 10.2, 9.1. IR (KBr, ν_{max}, cm⁻¹): 3095 (CH), 2919 (CH), 1586 (C=N), 1640 (C=O), 1567-1488 (C=C), 1070 (C-O). GC-MS (EI, 70 eV): *m/z* (%): 340 (M⁺, 37Cl, 24), 238 (M⁺, ³⁵Cl, 54), 207 (26), 164 (15), 139 (100), 111 (45), 91 (15).

4-Aminophenyl[3,5-dimethyl-4-(*p*-tolylloxy)-1*H*-pyrazol-1-yl]methanone (5b**):** Red solid (yield, 35 %), m.p. 160 °C. ¹H NMR (300 MHz, CDCl₃) δ: 7.57 (d, *J* = 7.5 Hz, 2H, ArH), 6.97 (d, *J* = 7.5 Hz, 2H, ArH), 6.76-6.67 (m, 4H, ArH), 3.82 (s, 2H, NH₂), 2.52 (s, 1H, CH₃), 2.43 (s, 3H, CH₃), 2.32 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ: 166.3, 153.7, 152.7, 141.9, 140.6, 134.2, 131.8, 128.6, 125, 122.8, 119.9, 112.3, 21.1, 10.2, 9.1. IR (KBr, ν_{max}, cm⁻¹): 3127 (CH), 2952 (CH), 1573 (C=N), 1670 (C=O), 1592-1498 (C=C), 1060 (C-O). GC-MS (EI, 70 eV): *m/z* (%): 238 (M⁺, 100), 209 (7), 119 (35), 91(30), 65 (25), 51 (10).

4-Aminophenyl[3,5-dimethyl-4-(4-nitro-phenoxy)-pyrazol-1-yl]methanone (5c**):** Light yellow oil (yield, 45 %), ¹H NMR (300 MHz, CDCl₃) δ = 8.02 (d, *J* = 7.5 Hz, 2H, ArH), 7.68 (d, *J* = 7.3 Hz, 2H, ArH), 6.76-6.67 (m, 4H, ArH), 3.82 (s, 2H, NH₂), 2.43 (s, 3H, CH₃), 2.32 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ = 178.3, 158.7, 152.7, 141.9, 140.6, 134.2, 131.8, 128.6, 125, 122.8, 119.9, 112.3, 21.1, 10.2. IR (KBr, ν_{max}, cm⁻¹) 3437 (NH), 3115 (CH), 2955 (CH), 1569 (C=N), 1595-1495 (C=C), 1070 (C-O). GC-MS (EI, 70 eV) *m/z* (%): 352 (M⁺, 52), 232 (7), 120 (100), 91 (30), 65 (25), 51 (10).

3,5-Dimethyl-4-(naphthalen-2-yloxy)-1*H*-pyrazole (5d**):** Pink solid (yield, 70 %), m.p. 120 °C. ¹H NMR (300 MHz, CDCl₃) δ = 9.20 (s, 1H, NH), 7.83-7.63 (m, 2H), 7.59 (qd, *J* = 7.5, 1.4 Hz, 2H, ArH), 7.40-7.29 (m, 3H, ArH), 2.41 (d, *J* = 11.5 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃) δ = 156.5, 136.1, 134.2, 129.8, 129.6, 127.7, 126.9, 126.6, 124.2, 117.6, 108.9, 108.6, 106.2, 9.6. IR (KBr, ν_{max}, cm⁻¹): 3160 (*sp*²CH), 2899 (*sp*³CH), 1528 (C=N), 1597-1508 (C=C), 1053 (C-O). GC-MS (EI, 70 eV) *m/z* (%): 238 (M⁺, 100), 209 (10), 155 (15), 127 (30), 115 (11), 77 (10).

3,5-Dimethyl-4-(*p*-tolylloxy)-1*H*-pyrazole (5e**):** Colorless oil (yield, 65 %), m.p. 71 °C. ¹H NMR (300 MHz, CDCl₃) δ = 9.28 (s, 1H, NH), 7 (d, *J* = 7.5 Hz, 2H, ArH), 6.76 (d, *J* = 7.5 Hz, 2H, ArH), 2.41 (s, 1H, CH₃), 2.33 (s, 3H, CH₃), 2.21 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ = 153.1, 139.6, 137.6, 135.4, 134.2, 128.9, 128.9, 120.3, 21.1, 10.1, 8.5. IR (KBr, ν_{max}, cm⁻¹): 3125 (*sp*²CH), 2935 (*sp*³CH), 1577 (C=N), 1600-1485 (C=C), 1053 (C-O). GC-MS (EI, 70 eV) *m/z* (%): 202 (M⁺, 100), 132 (7), 119 (35), 111 (9), 105 (6), 91 (30), 65 (25), 51 (10).

4-(4-Bromo-phenoxy)-3,5-dimethyl-1*H*-pyrazole (5f**):** Redish oil (yield, 40 %), ¹H NMR (300 MHz, CDCl₃) δ = 9.53 (s, 1H, NH), 7.34 (d, *J* = 7.5 Hz, 2H, ArH), 6.65 (d, *J* = 7.3 Hz, 2H, ArH), 2.43 (s, 1H, CH₃), 2.26 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ = 154.8, 144.9, 137.6, 124, 120.4, 110.4, 11.1, 9.5. IR (KBr, ν_{max}, cm⁻¹) 3115 (*sp*²CH), 2955 (*sp*³CH), 1569 (C=N), 1595-1495 (C=C), 1070 (C-O). GC-MS (EI, 70 eV): *m/z* (%): 267 (M⁺, ⁸¹Br, 49), 265 (M⁺, 79Br, 48), 156 (7), 136 (100), 111 (10), 91 (30), 65 (25), 51 (10).

3,5-Dimethyl-4-(4-nitrophenoxy)-1*H*-pyrazole (5g**):** Pink oil (yield, 58 %), ¹H-NMR (300 MHz, CDCl₃) δ = 9.33 (s, 1H, NH), 8.02 (d, *J* = 7.5 Hz, 2H, ArH), 7.08 (d, *J* = 7.3 Hz, 2H), 2.41 (s, 1H, CH₃), 2.24 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ = 155.8, 143.9, 139.6, 137.6, 134.2, 123.05, 120.4, 10.1, 8.5. IR (NaCl Cell, ν_{max}, cm⁻¹) 3115 (*sp*²CH), 2955 (*sp*³CH), 1569 (C=N), 1595 (C=C), 1070 (C-O). GC-MS (EI, 70 eV): *m/z* (%): 233 (M⁺, 100), 138 (7), 111 (10), 91 (30), 65 (25), 51 (10).

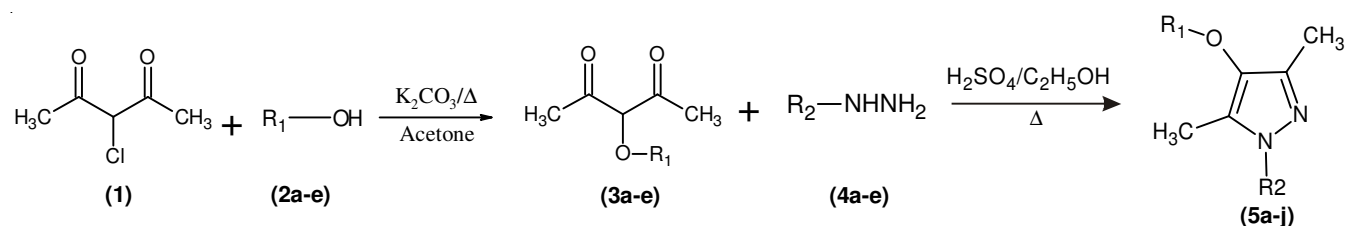
4-(4-Methoxy-phenoxy)-3,5-dimethyl-1*H*-pyrazole (5h**):** Pink oil (yield, 38 %), ¹H NMR (300 MHz, CDCl₃) δ = 9.28 (s, 1H, NH), 7 (d, *J* = 7.5 Hz, 2H, ArH), 6.70 (d, *J* = 7.5 Hz, 2H, ArH), 3.41 (s, 1H, OCH₃), 2.33 (s, 3H, CH₃), 2.21 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ = 153.1, 139.6, 137.6, 135.4, 134.2, 128.9, 120.3, 61.1, 10.1, 8.5. IR (KBr, ν_{max}, cm⁻¹): 3125 (*sp*²CH), 2935 (*sp*³CH), 1577 (C=N), 1600-1485 (C=C), 1053 (C-O). GC-MS (EI, 70 eV) *m/z* (%): 218 (M⁺, 100), 123 (7), 111 (35), 107 (6), 91 (30), 65 (25), 51 (10).

3,5-Dimethyl-4-(2,4,6-trinitro-phenoxy)-1*H*-pyrazole (5i**):** Yellow oil (yield, 40 %), ¹H NMR (300 MHz, CDCl₃) δ = 9.34 (s, 1H, NH), 8 (d, *J* = 7.5 Hz, 2H, ArH), 2.41 (s, 3H, CH₃), 2.33 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ = 152.1, 148.6, 145.6, 138.4, 128.9, 107.3, 10.1, 8.5. IR (KBr, ν_{max}, cm⁻¹): 3125 (*sp*²CH), 2935 (*sp*³CH), 1579 (C=N), 1600-1485 (C=C), 1053 (C-O). GC-MS (EI, 70 eV) *m/z* (%): 323 (M⁺, 100), 212 (30), 111 (9), 105 (6), 65 (25), 51 (10).

4-(3,4-Dimethoxy-phenoxy)-3,5-dimethyl-1*H*-pyrazole (5j**):** Pink solid (yield, 45 %), m.p. 85 °C, ¹H NMR (300 MHz, CDCl₃) δ = 9.32 (s, 1H, NH), 6.75 (d, *J* = 8.7 Hz, 1H, ArH), 6.55 (d, *J* = 2.8 Hz, 1H, ArH), 6.31 (dd, *J* = 8.7 Hz, 2.8 Hz, 1H, ArH), 3.83 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 2.41 (s, 3H, CH₃), 2.33 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ = 152.1, 148.6, 145.6, 145.7, 145.6, 122.9, 120.9, 109.3, 107.3, 56.5, 53.5, 10.1, 8.5. IR (KBr, ν_{max}, cm⁻¹): 3125 (*sp*²CH), 2935 (*sp*³CH), 1577 (C=N), 1600-1485 (C=C), 1053 (C-O). GC-MS (EI, 70 eV) *m/z* (%): 248 (M⁺, 100), 137 (30), 111 (9), 105 (6), 65 (25), 51 (10).

RESULTS AND DISCUSSION

The synthetic sequence leading to the 4-aryloxy substituted pyrazoles is outlined in **Scheme-I**. The 3-aryloxy substituted 1,3-dicarbonyl compounds (**3a-e**) were synthesized by treating 3-chloropentan-1,3-dione with substituted phenols (**2a-e**). The reaction involves nucleophilic substitution of chloro functional from compound **1** by hydroxyl group of substituted phenols (**2a-e**). The reaction was carried out according to the reported procedure²⁶. The resulting 1,3-dicarbonyl (**3a-e**) were then condensed with hydrazine/substituted hydrazides in the presence of catalytic amount of conc. H₂SO₄ to afford the target 4-aryloxy substituted pyrazoles (**5a-j**) in moderate to good yield.



Compound	R ₁	R ₂	Yield (%)	Compound	R ₁	R ₂	Yield (%)
5a			37	5f		H	40
5b			35	5g		H	58
5c			45	5h		H	46
5d		H	70	5i		H	35
5e		H	65	5j		H	45

Scheme-I: Synthesis of pyrazoles (5a-j)

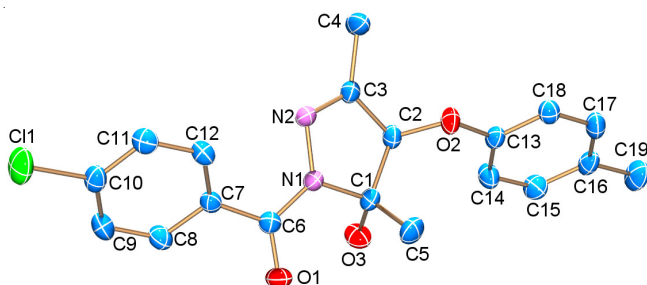


Fig. 1. ORTEP plot of 5-hydroxy-2-pyrazoline

Typically, pyrazoles (**5a-j**) are characterized by FTIR absorptions at 1560-1580 cm^{-1} for C=N linkage and disappearance of the carbonyl stretching vibrations. The two methyl groups at position 3 and 5 give characteristic signals in the range 2.24-2.46 and 2.51-2.60 in ^1H NMR spectrum respectively. The one proton singlet appeared at δ 9.28-9.52 for (NH) proton in compounds (**5d-5j**). The structure of the target pyrazoles were also confirmed by the presence of peaks in the range 150-159 ppm for C-4 in ^{13}C NMR spectrum. The characteristic signal for C-3 also appeared in the range 165-168 ppm which confirmed the formation of pyrazole ring. Mass spectra of all of the compounds showed the molecular ion peaks and the base peak were derived from the 4-substituted aryloxylation. The literature revealed that the synthesis of pyrazoles by the conden-

sation of 1,3-diketones with hydrazines proceed through the formation of 5-hydroxy-2-pyrazoline intermediate. It was also proposed that the presence of strongly electron withdrawing groups at position 5 of pyrazoline stabilize the intermediate²⁷. The present work depicted that when reaction of 1,3-diketone (**2a**) with hydrazide (**3a**) was carried in the absence of catalyst then 5-hydroxy-2-pyrazoline was stable enough can be isolated. The structure of the said compound was also confirmed by X-ray crystallography (Fig. 1).

REFERENCES

1. C. Lamberth, *Heterocycles*, **71**, 1467 (2007).
2. A.M. Farag, A.S. Mayhoub, S.E. Barakat and A.H. Bayomi, *Bioorg. Med. Chem.*, **16**, 4569 (2008).
3. B. Insuasty, A. Tigreros, F. Orozco, J. Quiroga, R. Abonia, M. Nogueras, A. Sanchez and J. Cobo, *Bioorg. Med. Chem.*, **18**, 4965 (2010).
4. A.M. Farag, A.S. Mayhoub, S.E. Barakat and A.H. Bayomi, *Bioorg. Med. Chem.*, **16**, 881 (2008).
5. J. Svete, *ARKIVOC*, 35 (2006).
6. I.M. El-Deeb and S.H. Lee, *Bioorg. Med. Chem.*, **18**, 3961 (2010).
7. D. Raffa, G. Daidone, B. Maggio, S. Cascioferro, F. Plescia and D. Schillaci, *IL Farmaco*, **59**, 215 (2004).
8. S.A.F. Rostom, *Bioorg. Med. Chem.*, **14**, 6475 (2006).
9. K.M. Cheung, T.P. Matthews, K. James, M.G. Rowlands, K.J. Boxall, S.Y. Sharp, A. Maloney, S.M. Roe, C. Prodromou, L.H. Pearl, G.W. Aherne, E. McDonald and P. Workman, *Bioorg. Med. Chem. Lett.*, **15**, 3338 (2005).

10. B.W. Dymock, X. Barril, P.A. Brough, J.E. Cansfield, A. Massey, E. McDonald, R.E. Hubbard, A. Surgenor, S.D. Roughley, P. Webb, P. Workman, L. Wright and M.J. Drysdale, *J. Med. Chem.*, **48**, 4212 (2005).
11. X. Barril, M.C. Beswick, A. Collier, M.J. Drysdale, B.W. Dymock, A. Fink, K. Grant, R. Howes, A.M. Jordan, A. Massey, A. Surgenor, J. Wayne, P. Workman and L. Wright, *Bioorg. Med. Chem. Lett.*, **16**, 2543 (2006).
12. G.M. Allan, C. Bubert, N. Vicker, A. Smith, H.J. Tutill, A. Purohit, M.J. Reed and B.V.L. Potter, *Mol. Cell. Endocrinol.*, **248**, 204 (2006).
13. A.E. Rashad, M.I. Hegab, R.E. Abdel-Megeid, J.A. Micky and F.M.E. Abdel-Megeid, *Bioorg. Med. Chem.*, **16**, 7102 (2008).
14. R.V. Ragavan, V. Vijayakumar and N.S. Kumari, *Eur. J. Med. Chem.*, **45**, 1173 (2010).
15. D. Kim, Y. Lee, Y.W. Lee, P.M. Dewang, Y.Y. Sheen, Y.W. Kim, H. Park, J. Yoo, H.S. Lee and Y. Kim, *Bioorg. Med. Chem.*, **18**, 4459 (2010).
16. M. Comes Franchini, B.F. Bonini, C.M. Camaggi, D. Gentili, A. Pession, M. Rani and E. Stocchi, *Eur. J. Med. Chem.*, **45**, 2024 (2010).
17. S.A.F. Rostom, M.A. Shalaby and M.A. El-Demellawy, *Eur. J. Med. Chem.*, **38**, 959 (2003).
18. M.S.M. Al-Saadi, S.A.F. Rostom and H.M. Faid Allah, *Saudi Pharm. J.*, **13**, 89 (2005).
19. V.K. Aggarwal, J. de Vicente and R.V. Bonnert, *J. Org. Chem.*, **68**, 5381 (2003).
20. T. Kawakami, K. Uehata and H. Suzuki, *Org. Lett.*, **2**, 413 (2000).
21. R. Olivera, R. SanMartin and E. Domínguez, *J. Org. Chem.*, **65**, 7010 (2000).
22. V. Padmavathi, K. Sharmila, A. Balaiah, A.S. Reddy and D.B. Reddy, *Synth. Commun.*, **31**, 2119 (2001).
23. K. Longhi, D.N. Moreira, M.R.B. Marzari, V.M. Floss, H.G. Bonacorso, N. Zanatta and M.A.P. Martins, *Tetrahedron Lett.*, **51**, 3193 (2010).
24. L. Pizzuti, L.A. Piovesan, A.F.C. Flores, F.H. Quina and C.M.P. Pereira, *Ultrason. Sonochem.*, **16**, 728 (2009).
25. A.B. Khudoyarov, Kh.T. Sharipov, V.G. Yusupov and N.A. Parpiev, *Koordinats. Khim.*, **13**, 1113 (1987).
26. M. Sher, Z. Ahmed, M.A. Rashid, C. Fischer, A. Spannenberg and P. Langer, *Tetrahedron*, **63**, 4929 (2007).
27. K.N. Zelenin, A.R. Tugusheva, S.I. Yakimovich, V.V. Alekseev and E.V. Zerova, *Chem. Het. Comp.*, **38**, 668 (2002).