Polish J. Chem., **76**, 1419–1424 (2002)

Synthesis of Heterocycles on the Basis of Arylation Products of Unsaturated Compounds. Part 9. Dialkyl 2,6-Diamino-4-arylfuro[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylates from 2-Aryl-1,4-benzoquinones and Cyanoacetic Esters*

by M.D. Obushak, R.L. Martyak and V.S. Matiychuk**

Department of Organic Chemistry, Ivan Franko National University of Lviv, Kyryla and Mefodiya 6, 79005 Lviv, Ukraine
e-mail:obushak@in.lviv.ua

(Received March 18th, 2002; revised manuscript June 12th, 2002)

2-Aryl-1,4-benzoquinones **1a–h** (aryl = RC_6H_4, R = H, 4-Me, 3-CF_3, 4-COOH, 3-Cl, 4-Cl, 4-F, 4-NO_2) react with methyl **2a** and ethyl **2b** cyanoacetates in the presence of some bases to form dialkyl 2,6-diamino-4-arylfuro[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylates **3a–l**. Regardless of the reagents ratio benzodifuran derivatives are formed selectively. Only in reaction of 2-(4-nitrophenyl)-1,4-benzoquinone **1h** with **2b** ethyl 2-amino-5-hydroxy-4-(4-nitrophenyl)benzo[b]furan-3-carboxylate **4** is formed as minor component besides of **3l**. Starting compounds **1a–h** are prepared by arylation of the 1,4-benzoquinone with arenediazonium chlorides (Meerwein reaction).

Key words: benzoquinone, 2-aryl-1,4-benzoquinones, cyclizations, heterocycles, benzodifuran derivatives, cyanoacetic esters, arylation, Meerwein reaction

It is known that interaction of quinones with various C-nucleophiles is often not finished by 1,4-addition. In the presence of other functional groups intramolecular cyclization takes place to form condensed heterocyclic compounds [2]. However, mainly 1,4-benzoquinone and also disubstituted quinones were investigated in these reactions. Due to asymmetry of monosubstituted 1,4-benzoquinones a formation of different isomers is possible in the reactions with C-nucleophiles. Therefore, such quinones are studied considerably less in these reactions, but in published works [2–8] some contradictions which concerned their regioselectivity took place. It was reported that toluoquinone and 2-chloro-1,4-benzoquinone react with ethyl acetoacetate or ethyl benzoylacetate to form linear furo[2′,3′:4,5]benzo[b]furan isomers [3,4]. Under changed reaction conditions benzofuran derivatives (1:1 adduct) were received, moreover CH-acid added in position 5 of 2-aryl-1,4-benzoquinones [3]. Subsequently evidences were found that 1:1 adduct formed as a result of nucleophilic attack in position 6 [5]. The condensation of ethyl benzoylacetate with toluoquinone

---

* See ref. [1].
**Author for correspondence.

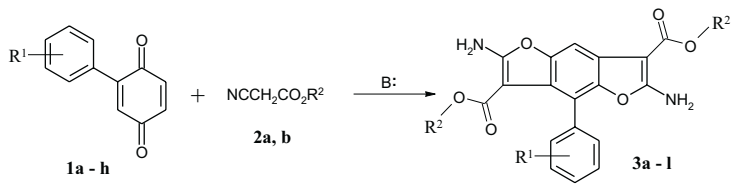
has been reported to lead to two benzofuran isomers [5,6]. However, for one of them in these works a different structure was assigned. The ratio of 1:1 and 1:2 adducts largely depends on reaction conditions [7,8]. From result obtained at analysis of interaction of 2-acetyl-1,4-benzoquinone with CH-acid, it is possible to make the conclusion that the electron-withdrawing groups in quinone ring direct nucleophilic attack to "*ortho*"-position (to position 3) [9–11]. It is necessary to stress, that at interaction of ethyl acetoacetate enol with 2-acetyl-1,4-benzoquinone in similar conditions is described as a product of intramolecular ring closure [10,11] and as uncyclized product [9]. Unsubstituted quinone reacts mainly with cyanoacetic esters to form dialkyl 2,6-diaminofuro[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylate [12,13].

In this paper interaction of 2-aryl-1,4-benzoquinones **1a–h** with cyanoacetic esters **2a**, **b** is investigated. Compounds **1a–h** are prepared by arylation of the 1,4-benzoquinone with arenediazonium chlorides [14–16].

RESULTS AND DISCUSSION

One or two molecules of CH-acids may react with quinone derivatives by the type of Michael reaction [17–20] with subsequent cyclization to derivatives of benzofuran and benzodifuran respectively. We have established that quinones **1a–h** react with cyanoacetic esters **2a**, **b** to form benzodifuran derivatives **3a–l** (Scheme 1).

Scheme 1



1: R^1=H (**a**), 4-Me (**b**), 3-CF_3 (**c**), 4-COOH (**d**), 3-Cl (**e**), 4-Cl (**f**), 4-F (**g**), 4-NO_2 (**h**);
2: R^2=Me (**a**), Et (**b**).

3	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**
R^1	H	4-Me	3-CF_3	4-Cl	4-F	H	4-Me	4-COOH	3-Cl	4-Cl	4-F	4-NO_2
R^2	Me	Me	Me	Me	Me	Et	Et	Et	Et	Et	Et	Et

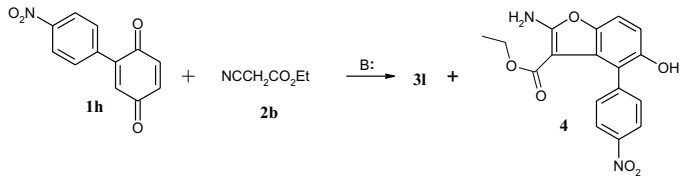
Reaction was carried out in alcohol in the presence of bases (ammonium hydroxide, piperidine, alcoholates). Arylquinones with *ortho*-substituents in aromatic ring were practically unreactive in this reaction. In those cases benzodifuran or benzofuran derivatives are not isolated in pure form.

The interesting pecularity of the reaction is that regardless of the reagents ratio benzodifuran derivatives are formed selectively. Only in the reaction of ethyl cyano-

acetate **2b** with 2-(4-nitrophenyl)-1,4-benzoquinone **1h** as a minor component – ethyl 2-amino-5-hydroxy-4-(4-nitrophenyl)benzo[b]furan-3-carboxylate **4** (Scheme 2) – is formed besides of benzodifuran **3l** (**3l:4** = 77:23).

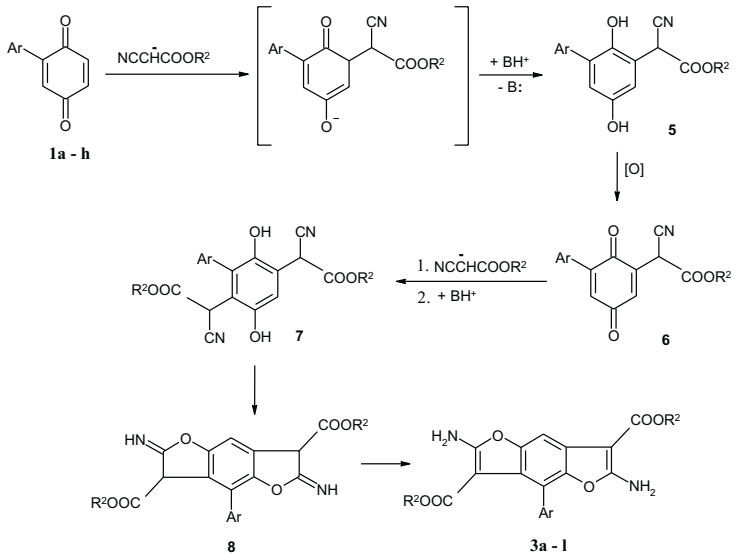
Probable mechanism of this reaction includes several steps (Scheme 3). Carbanion of cyanoacetic ester reacts with quinones **1a–h** by the type of Michael reaction with the formation of hydroquinone **5**. The latter is oxidized by starting quinone to substituted quinone **6**. In the next stage another molecule of cyanoacetic ester is added to quinone **6**. Finally, intramolecular cyclization takes place due to interaction of hydroxy and nitrile groups of hydroquinone **7**.

Scheme 2



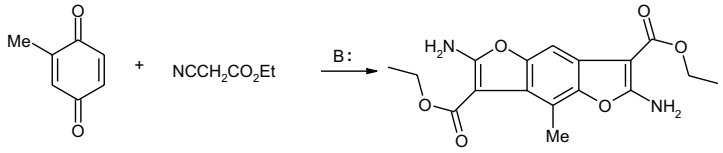
The principal stage of this process evidently is fast oxidation of adduct **5** to substituted quinone **6**. In that case when primary addition product **5** had not time to oxidize, its intramolecular cyclization takes place to form benzofuran derivative **4**. Electron-withdrawing substituents in aromatic ring of compounds **1a–h** (R^1=NO_2) naturally favour such reaction route.

Scheme 3



In ^{1}H NMR spectra of compounds **3a–l** two sets of signals of ester groups protons are observed. It is explained by shielding of one of ester groups by aryl substituent. Indeed in ^{1}H NMR spectrum of diethyl 2,6-diamino-4-methylfuro[2′,3′:4,5]benzo-[b]furan-3,7-dicarboxylate **9**, prepared from ethyl cyanoacetate and toluoquinone (Scheme 4), signals of CO_2Et-groups protons practically coincide.

Scheme 4



9

So, during the interaction of arylquinones with cyanoacetic esters the reaction is not stoped on the stage of the addition of one molecule of nucleophilic reagent. Adduct 1:2 is formed and its intramolecular cyclization leads to benzodifuran derivatives.

EXPERIMENTAL

All melting points are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker DRX500 or Bruker WP300 spectrometer in DMSO-d_6. Chemical shifts are reported in ppm relative to the residual signal of the solvent. Mass spectra were obtained using an Finnigan MAT INKOS-50 chromatomass spectrometer at 70 eV. The starting 2-aryl-1,4-benzoquinones **1a–h** were prepared as described earlier [15,16]. Melting points: **1c** – 60–61°C; **1g** – 155°C.

General procedures for the reaction of 2-aryl-1,4-benzoquinones with cyanoacetic esters: To a suspension of 0.01 mole 2-aryl-1,4-benzoquinone **1a-h** and 0.03 mole methyl or ethyl cyanoacetate **2a, b** in 30 ml of ethanol was added 5 ml of ammonium hydroxide at room temperature. After stirring for 30 minutes the mixture was diluted with water and acidified by diluted sulfuric acid. The residue was separated, washed with hot ethanol and recrystallized from appropriate solvent.

Dimethyl 2,6-diamino-4-phenylfuro[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylate (3a): Yield 50%; m.p. (dec.) 219–220°C (acetone); ^{1}H NMR δ: 3.02 (s, 3H, 3-CO_2CH_3), 3.83 (s, 3H, 7-CO_2CH_3), 7.22–7.31 (m, 7H, NH_2 and C_6H_5), 7.37 (s, 1H, 8-H), 7.39 (s, 2H, NH_2). Anal. Calcd. for $C_{20}H_{16}N_2O_6$: C, 63.16; H, 4.24; N, 7.37. Found: C, 62.94; H, 4.18; N, 7.23

Dimethyl 2,6-diamino-4-(4-methylphenyl)furo[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylate (3b): Yield 48%; m.p. (dec.) 220–221°C (acetone); ^{1}H NMR δ: 2.42 (s, 3H, $ArCH_3$), 3.02 (s, 3H, 3-CO_2CH_3), 3.84 (s, 3H, 7-CO_2CH_3), 7.17–7.24 (m, 4H, C_6H_4), 7.28 (s, 2H, NH_2), 7.36 (brs, 3H, 8-H and NH_2); MS, m/z (I, %): 394 (M^+, 53), 362 (13), 331 (19), 330 (100), 302 (25), 190 (13), 165 (23), 151 (14), 137 (10), 44 (13), 40 (16). Anal. Calcd. for $C_{21}H_{18}N_2O_6$: C, 63.96; H, 4.60; N, 7.10. Found: C, 63.81; H, 4.58; N, 6.97.

Dimethyl 2,6-diamino-4-(3-trifluoromethylphenyl)furo[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylate (3c): Yield 42%; m.p. (dec.) 244°C (acetone); ^{1}H NMR δ: 3.03 (s, 3H, 3-CO_2CH_3), 3.84 (s, 3H, 7-CO_2CH_3), 7.33 (s, 2H, NH_2), 7.42 (s, 1H, 8-H), 7.48 (s, 2H, NH_2), 7.59–7.70 (m, 4H, C_6H_4); MS, m/z (I, %): 449 (M^++1, 19), 448 (M^+, 100), 417 (12), 416 (51), 384 (23), 364 (45), 363 (10), 336 (38), 65 (10), 44 (24), 40 (31). Anal. Calcd. for $C_{21}H_{15}F_3N_2O_6$: C, 56.26; H, 3.37; N, 6.25. Found: C, 56.01; H, 3.39; N, 6.12.

Dimethyl 2,6-diamino-4-(4-chlorophenyl)furo[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylate (3d): Yield 48%; m.p. (dec.) 226–226.5°C (acetone); ^{1}H NMR δ: 3.10 (s, 3H, 3-CO_2CH_3), 3.84 (s, 3H, 7-CO_2CH_3), 7.31 (s, 2H, NH_2), 7.32–7.42 (m, 4H, C_6H_4), 7.39 (s, 1H, 8-H), 7.43 (s, 2H, NH_2); MS, m/z (I, %): 416 (M^++2, 12), 415 (M^++1, 10), 414 (M^+, 46), 382 (21), 352 (12), 351 (11), 350 (39), 349 (11), 322 (26), 315 (19), 321 (12), 203 (11), 177 (18), 176 (21), 175 (25), 162 (10), 161 (15), 92 (12), 77 (13), 75 (13), 65 (27), 64 (21), 59 (30), 44 (69), 43 (36), 40 (100). Anal. Calcd. for $C_{20}H_{15}ClN_2O_6$: C, 57.91; H, 3.64; N, 6.75. Found: C, 57.74; H, 3.47; N, 6.81.

Dimethyl 2,6-diamino-4-(4-fluorophenyl)furo[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylate (3e): Yield 54%; m.p. (dec.) 212–213°C (dioxane–DMF, 5:1); ^{1}H NMR δ: 3.10 (s, 3H, 3-CO_2CH_3), 3.82 (s, 3H, 7-CO_2CH_3), 7.12–7.22 and 7.31–7.36 (m, 4H, C_6H_4), 7.37 (s, 1H, 8-H), 7.41 (s, 2H, NH_2), 7.51 (s, 2H, NH_2). Anal. Calcd. for $C_{20}H_{15}FN_2O_6$: C, 60.30; H, 3.80; N, 7.03. Found: C, 60.43; H, 3.74; N, 6.89.

Diethyl 2,6-diamino-4-phenylfuro[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylate (3f): Yield 49%; m.p. (dec.) 200–201°C (acetone); ^{1}H NMR δ: 0.72 (t, 3H, 3-$CO_2CH_2\underline{CH_3}$), 1.38 (t, 3H, 7-$CO_2CH_2\underline{CH_3}$), 3.58 (q, 2H, 3-$CO_2\underline{CH_2}CH_3$), 4.28 (q, 2H, 7-$CO_2\underline{CH_2}CH_3$), 7.25 (s, 2H, NH_2), 7.26–7.36 (m, 7H, NH_2 and C_6H_5), 7.36 (s, 1H, 8-H). Anal. Calcd. for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86. Found: C, 64.54; H, 5.01; N, 6.69.

Diethyl 2,6-diamino-4-(4-methylphenyl)furo[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylate (3g): Yield 56%; m.p. (dec.) 211.5–212°C (EtOH–DMF, 5:1); ^{1}H NMR δ: 0.71 (t, 3H, 3-$CO_2CH_2\underline{CH_3}$), 1.39 (t, 3H, 7-$CO_2CH_2\underline{CH_3}$), 2.41 (s, 3H, $ArCH_3$), 3.58 (q, 2H, 3-$CO_2\underline{CH_2}CH_3$), 4.30 (q, 2H, 7-$CO_2\underline{CH_2}CH_3$), 7.17–7.26 (m, 4H, C_6H_4), 7.34 (s, 2H, NH_2), 7.35 (s, 1H, 8-H), 7.43 (s, 2H, NH_2). Anal. Calcd. for $C_{23}H_{22}N_2O_6$: C, 65.40; H, 5.25; N, 6.63. Found: C, 65.54; H, 5.19; N, 6.50.

Diethyl 2,6-diamino-4-(4-carboxyphenyl)furo[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylate (3h): Yield 46%; m.p. (dec.) 285–286°C (MeOH–DMF, 5:2); ^{1}H NMR δ: 0.72 (t, 3H, 3-$CO_2CH_2\underline{CH_3}$), 1.39 (t, 3H, 7-$CO_2CH_2\underline{CH_3}$), 3.59 (q, 2H, 3-$CO_2\underline{CH_2}CH_3$), 4.30 (q, 2H, 7-$CO_2\underline{CH_2}CH_3$), 7.32 (s, 2H, NH_2), 7.39 (s, 1H, 8-H), 7.45 (s, 2H, NH_2) 7.44–7.50 and 7.97–8.03 (m, 4H, C_6H_4). Anal. Calcd. for $C_{23}H_{20}N_2O_8$: C, 61.06; H, 4.46; N, 6.19. Found: C, 60.79; H, 4.38; N, 6.17.

Diethyl 2,6-diamino-4-(3-chlorophenyl)furo[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylate (3i): Yield 44%; m.p. (dec.) 180°C (MeOH); ^{1}H NMR δ: 0.77 (t, 3H, 3-$CO_2CH_2\underline{CH_3}$), 1.35 (t, 3H, 7-$CO_2CH_2\underline{CH_3}$), 3.65 (q, 2H, 3-$CO_2\underline{CH_2}CH_3$), 4.27 (q, 2H, 7-$CO_2\underline{CH_2}CH_3$), 7.30–7.38 (m, 2H, C_6H_4), 7.41 (s, 1H, 8-H), 7.42–7.50 (m, 2H, C_6H_4), 7.63 (s, 2H, NH_2), 7.73 (s, 2H, NH_2). Anal. Calcd. for $C_{22}H_{19}ClN_2O_6$: C, 59.67; H, 4.32; N, 6.33. Found: C, 59.83; H, 4.29; N, 6.18.

Diethyl 2,6-diamino-4-(4-chlorophenyl)furo[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylate (3j): Yield 60%; m.p. (dec.) 211–212°C (EtOH–acetone, 1:1); ^{1}H NMR δ: 0.78 (t, 3H, 3-$CO_2CH_2\underline{CH_3}$), 1.37 (t, 3H, 7-$CO_2CH_2\underline{CH_3}$), 3.66 (q, 2H, 3-$CO_2\underline{CH_2}CH_3$), 4.29 (q, 2H, 7-$CO_2\underline{CH_2}CH_3$), 7.34–7.39 (m, 3H, 8-H and C_6H_4), 7.41–7.47 (m, 4H, NH_2 and C_6H_4), 7.57 (s, 2H, NH_2). Anal. Calcd. for $C_{22}H_{19}ClN_2O_6$: C, 59.67; H, 4.32; N, 6.33. Found: C, 59.45; H, 4.34; N, 6.25.

Diethyl 2,6-diamino-4-(4-fluorophenyl)furo[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylate (3k): Yield 58%; m.p. (dec.) 213–213.5°C (acetone); ^{1}H NMR δ: 0.79 (t, 3H, 3-$CO_2CH_2\underline{CH_3}$), 1.38 (t, 3H, 7-$CO_2CH_2\underline{CH_3}$), 3.65 (q, 2H, 3-$CO_2\underline{CH_2}CH_3$), 4.29 (q, 2H, 7-$CO_2\underline{CH_2}CH_3$), 7.16–7.26 (m, 2H, C_6H_4), 7.34–7.40 (m, 3H, 8-H and C_6H_4), 7.42 (s, 2H, NH_2), 7.54 (s, 2H, NH_2). Anal. Calcd. for $C_{22}H_{19}FN_2O_6$: C, 61.97; H, 4.49; N, 6.57. Found: C, 62.05; H, 4.42; N, 6.39.

Diethyl 2,6-diamino-4-(4-nitrophenyl)furo[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylate (3l): Yield 31%; ^{1}H NMR δ: 0.75 (t, 3H, 3-$CO_2CH_2\underline{CH_3}$), 1.38 (t, 3H, 7-$CO_2CH_2\underline{CH_3}$), 3.65 (q, 2H, 3-$CO_2\underline{CH_2}CH_3$), 4.29 (q, 2H, 7-$CO_2\underline{CH_2}CH_3$), 7.43 (s, 1H, 8-H), 7.47 (s, 2H, NH_2), 7.62–7.67 (m, 4H, NH_2 and C_6H_4), 8.24–8.30 (m, 2H, C_6H_4).

Ethyl 2-amino-5-hydroxy-4-(4-nitrophenyl)benzo[b]furan-3-carboxylate (4): Yield 9%; ^{1}H NMR δ: 0.75 (t, 3H, $CO_2CH_2\underline{CH_3}$), 3.56 (q, 2H, 3-$CO_2\underline{CH_2}CH_3$), 6.62 (d, $J_{6,7}$ = 8.8 Hz, 1H, 6-H), 7.12 (d, 1H, 7-H), 7.61 (s, 2H, NH_2), 7.67–7.71 (m, 2H, C_6H_4), 8.16–8.20 (m, 2H, C_6H_4), 8.99 (s, 1H, OH). Anal. Calcd. for (**3l**:**4** = 77:23): C, 58,52; H, 4.20; N, 9,07. Found: C, 58.41; H, 4.15; N, 9.13.

Diethyl 2,6-diamino-4-methylfuro[2′,3′:4,5]benzo[b]furan-3,7-dicarboxylate (9). This compound was obtained using 2-methyl-1,4-benzoquinone and ethyl cyanoacetate like in the case of compounds **3a–l**. Yield: 42%; m.p. (dec.) 225.5–226.5°C (MeOH–acetone, 1:1); ^{1}H NMR δ: 1.37 (t, 3H, CH_3), 1.39 (t, 3H, CH_3), 2.69 (s, 3H, $ArCH_3$), 4.29 (q, 4H, $2CH_2$), 7.16 (s, 1H, 8-H), 7.31 (s, 2H, NH_2), 7.33 (s, 2H, NH_2). Anal. Calcd. for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.86; H, 5.13; N, 7.94.

REFERENCES

1. Synthesis of Heterocycles on the Basis of Arylation Products of Unsaturated Compounds. Part 8. Obushak M.D., Matiychuk V.S. and Martyak R.L., *ARKIVOC* (2002), in press.
2. Kutyrev A.A. and Moskva V.V., *Usp. Khim*., **60**, 134 (1991).
3. Grinev A.N. and Terent'ev A.P., *Zh. Obshch. Khim*., **28**, 78 (1958).
4. Grinev A.N., Pan Bon-Khvar, Frosin V.N. and Terent'ev A.P., *Zh. Obshch. Khim*., **26**, 561 (1956).
5. McPherson H.L. and Ponder B.W., *J. Heterocycl. Chem*., **15**, 43 (1978).
6. Grinev A.N., Venevtseva N.K. and Terent'ev A.P., *Zh. Obshch. Khim*., **28**, 1850 (1958).
7. Kornilov M.Yu., Makovetskii V.P., Turov A.V. and Dzvinchuk I.B., *Khim. Geterotsikl. Soedin*., 22 (1980).
8. Jeffreys J.A.D., *J. Chem. Soc*., 2153 (1959).
9. Fumagalli S.E. and Eugster C.H., *Helv. Chim. Acta*, **54**, 959 (1971).
10. Kuckländer U., Herweg-Wahl U., Massa W. and Baum G., *Chem. Ber.*, **120**, 1791 (1987).
11. Kuckländer U., Herweg-Wahl U., Poll W. and Rickerich L., *Chem. Ber.*, **121**, 1841 (1988).
12. Derkosch J. and Specht I., *Monatsh. Chem*., **92**, 542 (1961).
13. Napier R.J., Shand C.A., Thomson R.H., Cheng L., Griffiths J. and Greenhalgh C.W., *J. Chem. Res. Miniprint,* 480 (1983).
14. Obushak M.D., Matiychuk V.S. and Martyak R.L., *Khim. Geterotsikl. Soedin*., 986 (2001).
15. Brassard P. and L'Écuyer P., *Can. J. Chem*., **36**, 700 (1958).
16. Kvalnes D.E., *J. Am. Chem. Soc*., **56**, 2478 (1934).
17. Christoffers J., *Synlett*, **6**, 723 (2001).
18. King T.J. and Newall C.E., *J. Chem. Soc*., 974 (1965).
19. Makovetskii V.P., Dzvinchuk I.B., Yaremenko V.V. and Svishchuk A.A., *Ukrainian Khim. Zh*., **45**, 652 (1979).
20. Makovetskii V.P., Dzvinchuk I.B., Volovenko Yu.M. and Svishchuk A.A., *Khim. Geterotsikl. Soedin*., 129 (1979).