# 2,5-Disubstituted *s*-Triazolo[3,4-*b*][1,3,4]thiadiazoles

M. UHER and D. BERKEŠ

*Department of Organic Chemistry, Faculty of Chemical Technology, Slovak University of Technology, SK-812 37 Bratislava*

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A new simple "one-pot" method leading to *s*-triazolo[3,4-*b*][1,3,4]thiadiazoles by the reaction of 5-aryl- and heteroaryl-substituted tetrazoles resp. their sodium salts with thiophosgene in dioxane is described.

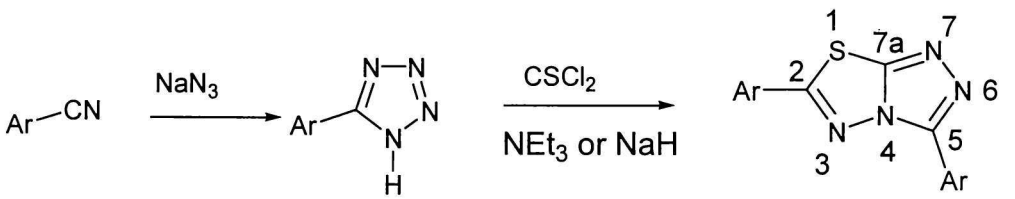
Heterocyclic compounds possessing thiazole, thiadiazole or oxadiazole ring system show antifungal, bacteriostatic as well as anthelmintic effects [1, 2]. Compounds containing the above rings also exhibit anti-inflammatory and antimicrobial [3] properties and the depression effect on the central nervous system [4].

The *s*-triazolo[3,4-*b*][1,3,4]thiadiazole ring system was successfully synthesized by the following three routes. The first one is the cyclocondensation of 4-amino-5-aryl-1,2,4-triazole-3-thiones with benzoic acid in the presence of phosphorus oxychloride at 120—130 °C [4—8, 10]. The second route involves a ring formation by the 5-substituted 2-hydrazino-1,3,4-thiadiazole reaction with phosphorus oxychloride in xylene [9]. The preparation of *s*-triazolo[3,4-*b*][1,3,4]thiadiazole ring system with two identical substituents is described by a "one-step" reaction from the corresponding carboxylic acids and hydrazide of appropriate thiocarboxylic acids in the presence of phosphorus oxychloride [6]. The recently published method is based on the oxidative cyclization of 3-substituted 5-mercapto-4-amino[1,2,4]triazole hydrazones [10] but the yields were low and the work-up was tedious.

This paper describes a new synthesis of such a potential antibacterial heterocyclic system with two identical halogenaryl resp. heteroaryl substituents in positions 2 and 5 by the reaction of 5-substituted tetrazoles or their sodium salts with thiophosgene (Scheme 1).

The reaction itself involves an action of thiophosgene on the corresponding tetrazoles in the presence of triethylamine resp. the heating of the appropriate tetrazole sodium salts with thiophosgene in anhydrous dioxane solution. Both the procedures give comparable yields of desired product, the first one has some advantages in work-up. The release of first nitrogen equivalent starts on addition of triethylamine to the cold mixture of tetrazole and thiophosgene in anhydrous dioxane. To finish the transformation the mixture must be heated up to reflux temperature for 3—5 h. This "one-pot" cyclization is compatible with aryl and heteroaryl substituents on tetrazole ring. Reaction of 5-benzyltetrazole leads to the complex mixture of unidentified products. The yields of 2,5-diaryl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazoles *IIa—IIg* rise up to 80 % of pure crystallized products.

The structure of prepared heterocycles has been fully certified by elemental analysis, IR and NMR spectra. The $^1$H NMR spectra reveal the presence




*Ia—Ig* *IIa—IIg*

Ar = *a*) $C_6H_5$ *e*) 4-$MeOC_6H_4$
*b*) 3-$FC_6H_4$ *f*) 3,4-$OCH_2OC_6H_3$
*c*) 3-$ClC_6H_4$ *g*) 5-Me-2-furyl
*d*) 4-$ClC_6H_4$

*Scheme 1*

of the twin set of aromatic substituent protons. For the first time the $^{13}C$ NMR spectra of *s*-triazolo[3,4-*b*][1,3,4]thiadiazole ring system have been measured. The three sets of carbon atom signals in relatively narrow region have been observed ($\delta$ = 144.4—145.6; 153.2—154.6; 165.8—166.9).

The signal assignment of *s*-triazolo[3,4-*b*][1,3,4]thiadiazole carbon atoms in $^{13}C$ NMR spectra was done on the basis of the long-range coupling constants $^4J$(C—F) in the fluorinated derivative *IIb*. The signals of C-2 (165.9) and C-5 (144.6) carbons were splitted by the interaction of 2.9 resp. 2.8 Hz and the only singlet at $\delta$ = 154.6 was assigned unambiguously to the carbon C-7a. The mass spectrum was measured for *IIa* ($I(M^{+\cdot})$/%: 278, 100). Ions in the range of lower masses were characteristic of the presence of benzene ring.

## EXPERIMENTAL

Melting points were measured on the Kofler hot stage apparatus. Elemental analyses were performed by the microanalysis service of the Department of Analytical Chemistry, Slovak University of Technology. IR spectra (0.5 mg in 300 mg KBr) were taken on a Philips PU 9800 FTIR spectrometer. $^1H$ NMR (300 MHz) and $^{13}C$ NMR (75 MHz) spectra were measured in DMSO-$d_6$ solution on a Varian VXR-300 spectrometer. Chemical shifts are given relative to TMS. Mass spectrum of *IIa* was recorded on MS 902S mass spectrometer (AS Kratos) using all glass heated system with the temperature of ion source 100—125 °C, electron energy 90 eV, and trap current 100 mA.

Starting 5-substituted tetrazoles *Ia—Ie* were prepared from the corresponding nitriles [11].

### 2,5-Disubstituted *s*-Triazolo[3,4-*b*][1,3,4]-thiadiazoles (*IIa—IIg*)

*A*. To the solution of tetrazole (0.01 mol) and thiophosgene (0.38 cm$^3$, 0.005 mol) in 50 cm$^3$ of anhydrous dioxane was dropwise added triethylamine (1.5 cm$^3$, 0.02 mol) in anhydrous dioxane (10 cm$^3$). The mixture was kept under reflux till the development of the gases ceased (3—5 h). The solvent was evaporated and the solid residue was triturated with 50 cm$^3$ of water. The resulted suspension was heated for additional 5 min, cooled and filtered off to give crude product. Purification was made by crystallization from corresponding solvents.

*B*. To the boiling solution of tetrazole sodium salt (prepared from corresponding tetrazole (0.01 mol) and sodium hydride (0.24 g; 0.01 mol) in anhydrous dioxane (30 cm$^3$)) was added thiophosgene (0.38 cm$^3$, 0.005 mol) in dioxane (10 cm$^3$). The reaction mixture was heated under reflux for 2 h. Benzene (10 cm$^3$) was added at 70 °C and the precipitated salts were removed by filtration.The filtrate was evaporated *in vacuo* to give crude product. The pure triazolothiadiazoles *IIa*, *IIc*, *IIe* were obtained by crystallization from appropriate solvents.

*IIa*: Yield = 2.23 g (80 %, method *A*), 1.78 g (64 %, method *B*), m.p. = 206—208 °C (dioxane), Ref. [3] gives m.p. = 201—202 °C. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 1603, 1470, 1437, 1177, 1075. $^1H$ NMR spectrum, $\delta$: 8.30—8.35 (m, 2H), 8.02—8.10 (m, 2H), 7.50—7.80 (m, 6H). $^{13}C$ NMR spectrum, $\delta$: 166.9 (C-2), 154.0 (C-7a), 145.6 (C-5), 133.0, 130.4, 129.7, 129.2, 127.3, 126.0, 129.0, 125.5 ($C_{arom}$). Mass spectrum, $m/z$ ($I_r$/%): 278 (100).

*IIb*: Yield = 1.79 g (57 %, method *A*), m.p. = 192—194 °C (dioxane). For $C_{15}H_8F_2N_4S$ ($M_r$ = 314.32) $w_i$(calc.): 57.32 % C, 2.57 % H, 17.83 % N, 10.20 % S; $w_i$(found): 57.65 % C, 2.65 % H, 17.92 % N, 10.41 % S. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 1591, 1480, 1460, 1453, 1291, 1198. $^1H$ NMR spectrum, $\delta$: 8.20 (bd, 1H, $J$ = 8.1 Hz), 7.90—8.10 (m, 3H), 7.65—7.77 (m, 2H), 7.53—7.62 (m, 1H), 7.40—7.49 (m, 1H). $^{13}C$ NMR spectrum, $\delta$: 165.9 (C-2, $^4J_{C\text{-}F}$ = 2.9 Hz), 154.6 (C-7a), 144.6 (C-5, $^4J_{C\text{-}F}$ = 2.8 Hz), 162.4 (C-3$_{arom}$, $J_{C\text{-}F}$ = 245 Hz), 162.3 (C-3$_{arom}$, $J_{C\text{-}F}$ = 244 Hz), 131.6 (C-5$_{arom}$, $J_{C\text{-}F}$ = 8.3 Hz), 132.0 (C-5$_{arom}$, $J_{C\text{-}F}$ = 8.3 Hz), 131.0 (C-1$_{arom}$, $J_{C\text{-}F}$ = 8.6 Hz), 127.4 (C-1$_{arom}$, $J_{C\text{-}F}$ = 8.9 Hz), 122.1 (C-6$_{arom}$, $J_{C\text{-}F}$ = 2.9 Hz), 123.8 (C-6$_{arom}$, $J_{C\text{-}F}$ = 2.8 Hz), 117.4 (C-4$_{arom}$, $J_{C\text{-}F}$ = 21 Hz), 120.0 (C-4$_{arom}$, $J_{C\text{-}F}$ = 21 Hz), 112.5 (C-2$_{arom}$, $J_{C\text{-}F}$ = 24 Hz), 114.2 (C-2$_{arom}$, $J_{C\text{-}F}$ = 24 Hz).

*IIc*: Yield = 2.25 g (65 %, method *A*) resp. 2.08 g (60 %, method *B*), m.p. = 202—204 °C (isopropanol—toluene, volume ratio = 1 2). For $C_{15}H_8Cl_2N_4S$ ($M_r$ = 347.23) $w_i$(calc.): 51.89 % C, 2.32 % H, 16.14 % N, 9.24 % S; w$_i$(found): 52.01 % C, 2.40 % H, 16.32 % N, 9.38 % S. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 1601, 1496, 1472, 1460, 1439, 1427, 1263, 1238, 1084. $^1H$ NMR spectrum, $\delta$: 8.25—8.40 (m, 2H), 8.00—8.20 (m, 2H), 7.60—7.85 (m, 4H). $^{13}C$ NMR spectrum, $\delta$: 165.8 (C-2), 154.5 (C-7a), 144.4 (C-5), 132.8, 131.7, 131.4, 130.3, 126.7, 126.3, 125.3, 124.6, 134.4, 130.8, 133.9, 127.3 ($C_{arom}$).

*IId*: Yield = 2.19 g (63 %, method *A*), m.p. = 239—239.5 °C (isopropanol—toluene, volume ratio = 1 2), Ref. [3] gives m.p. = 235—236 °C. IR spectrum (KBr disc), $\tilde{\nu}$/cm$^{-1}$: 1595, 1472, 1468, 1092. $^1H$ NMR spectrum, $\delta$: 8.33 (d, 2H, $J$ = 8.7 Hz), 8.10 (d, 2H, $J$ = 8.7 Hz), 7.73 (d, 2H, $J$ = 8.7 Hz), 7.71 (d, 2H, $J$ = 8.7 Hz). $^{13}C$ NMR spectrum, $\delta$: 166.0 (C-2), 154.5 (C-7a), 144.8 (C-5), 129.8, 129.3, 129.1, 127.8, 137.7, 135.0, 127.8, 124.3 ($C_{arom}$).

*IIe*: Yield = 2.40 g (71 %, method *A*) resp. 2.10 g (62 %, method *B*), m.p. = 234—237 °C (heptane—toluene, volume ratio = 1 1). For $C_{17}H_{14}N_4O_2S$ ($M_r$ = 338.39) $w_i$(calc.): 60.34 % C, 2.32 % H, 16.56 % N, 9.48 % S; $w_i$(found): 62.05 % C, 2.41 % H, 16.71 % N, 9.56 % S. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 1609, 1476, 1258, 1173. $^1H$ NMR spectrum, $\delta$: 8.22 (d, 2H, $J$ = 8.5 Hz), 7.95 (d, 2H, $J$ = 8.7 Hz), 7.17 (d, 2H, $J$ = 8.5 Hz),

7.15 (d, 2H, $J = 8.7$ Hz), 2.86 (s, 3H), 2.84 (s, 3H). $^{13}$C NMR spectrum, $\delta$: 166.2 (C-2), 153.4 (C-7a), 145.4 (C-5), 55.7 ($CH_3$), 55.4 ($CH_3$), 129.1, 127.6, 115.1, 114.6, 162.8, 160.8, 121.3, 118.0 ($C_{arom}$).

*IIf*: Yield = 2.56 g (70 %, method *A*), m.p. = 255—256 °C (heptane—toluene, volume ratio = 1 1). For $C_{17}H_{10}N_4O_4S$ ($M_r = 366.36$) $w_i$(calc.): 55.73 % C, 2.75 % H, 15.29 % N, 8.75 % S; $w_i$(found): 56.22 % C, 2.90 % H, 15.61 % N, 8.92 % S. IR spectrum, $\tilde{\nu}/cm^{-1}$: 1611, 1496, 1466, 1256, 1038. $^1$H NMR spectrum, $\delta$: 7.90 (dd, 1H, $J = 1.5$ Hz, $J = 8.1$ Hz), 7.74 (d, 1H, $J = 1.5$ Hz), 7.61 (d, 1H, $J = 1.5$ Hz), 7.57 (dd, 1H, $J = 1.5$ Hz, $J = 8.1$ Hz), 7.15 (d, 2H, $J = 8.4$ Hz), 6.20 (s, 2H), 6.15 (s, 2H). $^{13}$C NMR spectrum, $\delta$: 165.9 (C-2), 153.2 (C-7a), 145.1 (C-5), 102.2 ($CH_2$), 101.5 ($CH_2$), 122.8, 120.5, 108.9, 108.7, 106.4, 105.7, 151.1, 148.8, 148.3, 147.7, 122.7, 119.2 ($C_{arom}$).

*IIg*: Yield = 1.58 g (55 %, method *A*), m.p. = 206—208 °C (isopropanol—heptane, volume ratio = 1 1). For $C_{13}H_{12}N_4O_2S$ ($M_r = 288.33$) $w_i$(calc.): 54.53 % C, 3.52 % H, 19.57 % N, 11.20 % S; $w_i$(found): 55.41 % C, 3.61 % H, 19.90 % N, 10.98 % S. IR spectrum, $\tilde{\nu}/cm^{-1}$: 1603, 1578, 1545, 1437, 1206, 1022. $^1$H NMR spectrum, $\delta$: 7.44 (d, 1H, $J = 3.0$ Hz), 7.17 (d, 1H, $J = 3.0$ Hz), 6.50 (m, 1H), 6.41 (m, 1H), 2.44 (s, 3H), 2.43 (s, 3H). $^{13}$C NMR spectrum, $\delta$: 156.3 (C-2), 152.2 (C-7a), 141.2 (C-5), 13.2 ($CH_3$), 13.1 ($CH_3$), 116.4, 112.6, 109.7, 108.1, 157.4, 154.3, 139.2, 138.2 ($C_{arom}$).

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