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SHORT COMMUNICATIONS

Thietanyl Protection in the Synthesis of 5-Aryloxy(sulfonyl)-3-bromo-1,2,4-triazoles

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Abstract—Previously unknown 5-aryloxy- and 5-benzenesulfonyl-3-bromo-1*H*-1,2,4-triazoles have been synthesized starting from 3,5-dibromo-1,2,4-triazole by successive alkylation with 2-chloromethylthiirane, nucleophilic substitution of the 5-bromine atom by phenoxy or phenylsulfanyl group, oxidation of the thietane sulfur atom with hydrogen peroxide, and removal of the thietanyl protecting group by treatment with sodium ethoxide.

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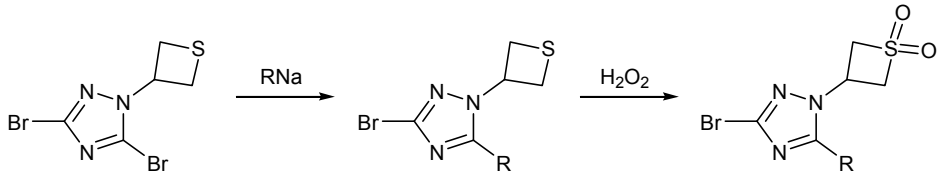
1,2,4-Triazole derivatives attract interest from both theoretical and practical viewpoints. In particular, these compounds are promising as pharmacologically active substances since they inhibit cytochrom P450-mediated processes [1] and synthesis of viral RNA and virus-specific proteins [2], selectively inhibit aromatase [3] and reuptake of serotonin at brain synapses, and act as 5-$HT_{2A/2C}$ serotonin receptor antagonists [4]. 1,2,4-Triazole ring is a structural unit of many medicines used for the treatment of fungal and viral infections, malignant tumors, and psychic disorders [5]. Furthermore, 1,2,4-triazole derivatives are extensively studied as potential antidepressants, analgesics, and anti-inflammatory agents [6].

3,5-Disubstituted 1*H*-1,2,4-triazoles are convenient building blocks for the creation of combinatorial libraries of potential biologically active compounds; these syntheses utilize various protecting groups such as 3-oxobutyl [7], benzyl [8], diphenylmethyl [9], 2-methoxypropan-2-yl [10], tetrahydrofuran-2-yl [11], and cyanoethyl [12].

Herein, we propose to use a thietanyl protecting group [13] for the synthesis of previously unknown 5-aryloxy(sulfonyl)-3-bromo-1*H*-1,2,4-triazoles. This protecting group can be easily introduced by alkylation of 3,5-dibromo-1*H*-1,2,4-triazole with 2-chloromethylthiirane, it ensures subsequent reactions with nucleophiles, and is readily removed by treatment with sodium alkoxide after oxidation of the sulfur atom.

5-Substituted 3-bromo-1*H*-1,2,4-triazoles were synthesized in several steps. Initially, the reaction of 3,5-dibromo-1*H*-1,2,4-triazole with 2-chloromethylthiirane gave 3,5-dibromo-1-(thietan-3-yl)-1*H*-1,2,4-triazole (**1**) [14] which was treated with sodium phenoxides and sodium benzenethiolate to obtain 5-aryloxy(sulfanyl)-3-bromo-1-(thietan-3-yl)-1*H*-1,2,4-triazoles (Scheme 1) [15]. Compounds **2a**–**2g** were oxidized with hydrogen peroxides to the corre-

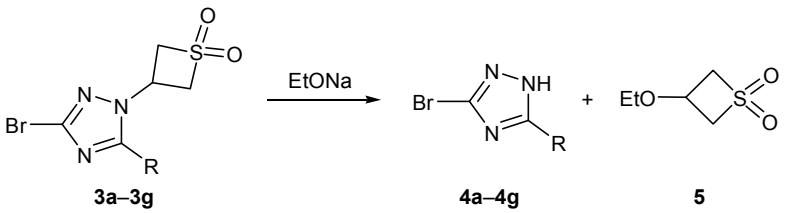
Scheme 1.



1 **2a–2g** **3a–3g**

2, **3**, R = PhO (**a**), 4-MeC_6H_4O (**b**), 3,4-$Me_2C_6H_3O$ (**c**), 2-*i*-Pr-5-MeC_6H_3O (**d**), 2,4-$Cl_2C_6H_3O$ (**e**), naphthalen-1-yloxy (**f**); **2g**, R = PhS; **3g**, R = $PhSO_2$.

Scheme 2.



R = PhO (**a**), 4-MeC_6H_4O (**b**), 3,4-$Me_2C_6H_3O$ (**c**), 2-*i*-Pr-5-MeC_6H_3O (**d**), 2,4-$Cl_2C_6H_3O$ (**e**), naphthalen-1-yloxy (**f**), R = $PhSO_2$ (**g**).

sponding thietane *S*,*S*-dioxides **3a**–**3g** [16]. The oxidation of the thietane sulfur atom in **2g** was accompanied by the transformation of the phenylsulfanyl group to benzenesulfonyl.

The thietanyl protection was readily removed by treatment of 5-substituted 3-bromo-1-(1,1-dioxo-λ^6-thietan-3-yl)-1*H*-1,2,4-triazoles **3a**–**3g** with sodium ethoxide. We thus isolated 20–80% of 3-bromo-5-aryloxy(benzenesulfonyl)-1*H*-1,2,4-triazoles **4a**–**4g** and 3-ethoxythietane 1,1-dioxide (**5**) (Scheme 2).

The structure of the synthesized compounds was confirmed by elemental analyses and NMR and IR spectra, and their purity was checked by TLC. Unlike compounds **3a**–**3g**, the IR spectra of triazoles **4a**–**4g** contained an absorption band at 2642–3093 cm^{-1} due to stretching vibrations of associated N–H group, whereas no bands assignable to vibrations of sulfonyl group were present; these data confirmed elimination of the thietane dioxide ring with formation of 5-substituted 3-bromo-1*H*-1,2,4-triazoles. The ^1H NMR spectra of **4a**–**4g** lacked proton signals typical of thietane 1,1-dioxide fragment, while signals from protons of the substituent on C^5 were present. For example, in the ^1H NMR spectrum of **4g** we observed three aromatic proton signals, a multiplet at δ 7.62–7.68 ppm, a triplet at δ 7.74 ppm, and a doublet at δ 7.95 ppm, which indicated conservation of the benzenesulfonyl group.

In keeping with the data of [17, 18], the ^{13}C NMR spectra of **4a**–**4f** in $CDCl_3$ displayed only signals of the aromatic substituent, whereas signals of C^3 and C^5 of the triazole ring were not observed. Presumably, this is due to fast tautomeric transformations of compounds **4a**–**4f** in solution, which leads to considerable broadening of the ring carbon signals. The two-dimensional ^1H–^{15}N HSQC and ^1H–^{15}N HMBC spectra of **4b** showed no cross peaks between the NH proton (it resonated as a broadened singlet at δ 10.39 ppm in the ^1H NMR spectrum) and nitrogen atoms, which can also be explained by exchange processes. The ^1H–^{13}C HMBC and ^1H–^{13}C HSQC spectra of **4b** displayed correlations of aromatic protons only with carbon atoms of the benzene ring and methyl group (Fig. 1).

Likewise, neither C^3 nor C^5 signal was detected in the ^{13}C NMR spectra of **4c** in CD_3COOD and DMSO-d_6. Only the ^{13}C NMR spectrum of **4g** in DMSO-d_6 showed signals at δ_C 134.08 and 161.67 ppm, which were assigned, respectively, to C^3 and C^5 of the triazole ring.

Thus, we have demonstrated the possibility of using thietanyl protection for the synthesis of difficultly accessible 5-aryloxy- and 5-benzenesulfonyl-3-bromo-1*H*-1,2,4-triazoles.

Compounds 4a–4g (*general procedure***).** Metallic sodium, 0.27 g (11.6 mmol), was added to 25 mL of anhydrous ethanol, and the mixture was heated until hydrogen no longer evolved. 5-Substituted 3-bromo-1-(1,1-dioxo-λ^6-thietan-3-yl)-1*H*-1,2,4-triazole **3a**–**3g**, 9.7 mmol, was then added, and the mixture was refluxed for 0.5 h. The solvent was distilled off under reduced pressure, the residue was treated with 5 mL of benzene and dissolved in 25 mL of water, and the mixture was acidified to pH 3 with dilute sulfuric acid. The precipitate was filtered off, washed with water, dried, and purified by reprecipitation with sulfuric acid from a solution in aqueous potassium hydroxide.

3-Bromo-5-phenoxy-1*H*-1,2,4-triazole (4a). Yield 0.84 g (36%), mp 95–97°C. IR spectrum, ν, cm^{-1}: 3065, 3036, 2945, 2842 (N–H), 1600, 1571, 1541, 1487 (C=N, C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.20–7.27 m (3H, H_{arom}), 7.36–7.41 m (2H,

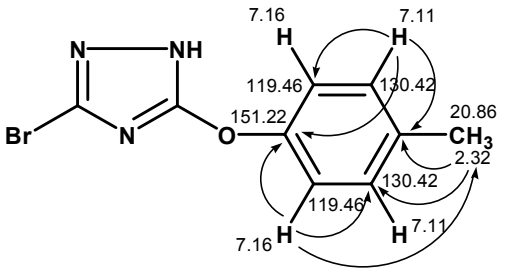


Fig. 1. Correlations in the ^1H–^{13}C HMBC spectrum of 3-bromo-5-(4-methylphenoxy)-1*H*-1,2,4-triazole (**4b**).

H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 119.53 ($C^{2'}$, $C^{6'}$), 125.91 ($C^{4'}$), 129.94 ($C^{3'}$, $C^{5'}$), 153.44 ($C^{1'}$). Found, %: C 39.62; H 2.50; N 18.02. $C_8H_6BrN_3O$. Calculated, %: C 40.03; H 2.52; N 17.50.

3-Bromo-5-(4-methylphenoxy)-1*H*-1,2,4-triazole (4b). Yield 1.16 g (47%), mp 120–122°C. IR spectrum, ν, cm^{-1}: 3030, 2926, 2853, 2820, 2743, 2653 (N–H), 1561, 1501, 1489 (C=N, C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.32 s (3H, CH_3), 7.11 d (2H, 3′-H, 5′-H, ^3J = 8.5 Hz), 7.16 d (2H, 2′-H, 6′-H, ^3J = 8.5 Hz), 10.39 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.86 (4′-CH_3), 119.46 ($C^{2'}$, $C^{6'}$), 130.42 ($C^{3'}$, $C^{5'}$), 135.80 ($C^{4'}$), 151.22 ($C^{1'}$). Found, %: C 42.87; H 3.10; N 16.83. $C_9H_8BrN_3O$. Calculated, %: C 42.54; H 3.17; N 16.54.

3-Bromo-5-(3,4-dimethylphenoxy)-1*H*-1,2,4-triazole (4c). Yield 1.85 g (71%), mp 133–134°C. IR spectrum, ν, cm^{-1}: 3023, 2939, 2918, 2848, 2734, 2642 (N–H), 1569, 1551, 1498, 1488 (C=N, C=C). ^1H NMR spectrum, δ, ppm: in $CDCl_3$: 2.22 s (3H, 4′-CH_3), 2.24 s (3H, 3′-CH_3), 6.95 d.d (1H, 6′-H, ^3J = 8.2, ^4J = 2.4 Hz), 6.99 d (1H, 2′-H, ^4J = 2.2 Hz), 7.11 d (1H, 5′-H, ^3J = 8.2 Hz); in CD_3COOD: 2.24 s (3H, 4′-CH_3), 2.25 s (3H, 3′-CH_3), 6.98 d.d (1H, 6′-H, ^3J = 8.2, ^4J = 2.4 Hz), 7.05 d (1H, 2′-H, ^4J = 2.1 Hz), 7.15 d (1H, 5′-H, ^3J = 8.3 Hz); in DMSO-d_6: 2.17 s (3H, 4′-CH_3), 2.19 s (3H, 3′-CH_3), 6.94 d.d (1H, 6′-H, ^3J = 8.2, ^4J = 2.1 Hz), 7.02 d (1H, 2′-H, ^4J = 2.7 Hz), 7.14 d (1H, 5′-H, ^3J = 8.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: in $CDCl_3$: 19.18 (4′-CH_3), 19.98 (3′-CH_3), 116.81 ($C^{2'}$), 120.68 ($C^{6'}$), 130.73 ($C^{5'}$), 134.52 ($C^{4'}$), 138.50 ($C^{3'}$), 151.30 ($C^{1'}$); in CD_3COOD (125 MHz): 18.07 (4′-CH_3), 18.77 (3′-CH_3), 116.87 ($C^{2'}$), 120.66 ($C^{6'}$), 130.49 ($C^{5'}$), 134.26 ($C^{4'}$), 138.40 ($C^{3'}$), 151.63 ($C^{1'}$); in DMSO-d_6: 19.13 (4′-CH_3), 19.87 (3′-CH_3), 116.92 ($C^{2'}$), 120.66 ($C^{6'}$), 130.88 ($C^{5'}$), 133.79 ($C^{4'}$), 138.50 ($C^{3'}$), 152.25 ($C^{1'}$). Found, %: C 44.98; H 3.71; N 15.80. $C_{10}H_{10}BrN_3O$. Calculated, %: C 44.80; H 3.76; N 15.67.

3-Bromo-5-[5-methyl-2-(propan-2-yl)phenoxy)-1*H*-1,2,4-triazole (4d). Yield 0.57 g (20%), mp 139–140°C. IR spectrum, ν, cm^{-1}: 2961, 2926, 2866, 2736, 2651 (N–H), 1567, 1491 (C=N, C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.20 d [6H, $CH(C\mathbf{H}_3)_2$, ^3J = 6.8 Hz], 2.32 s (3H, 5′-CH_3), 3.10 d.d [1H, $C\mathbf{H}(CH_3)_2$, ^3J = 6.8 Hz], 6.99 d (1H, 6′-H, ^4J = 2.4 Hz), 7.04 m (1H, 4′-H, ^3J = 8.4, ^4J = 2.6 Hz), 7.23 d (1H, 3′-H, ^3J = 8.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.43 (5′-CH_3), 23.22 [$CH(\mathbf{C}H_3)_2$], 28.91 [$\mathbf{C}H(CH_3)_2$], 117.14 ($C^{6'}$), 121.02 ($C^{4'}$), 126.21 ($C^{3'}$), 137.21 ($C^{2'}$), 144.78 ($C^{5'}$), 150.80 ($C^{1'}$). Found, %: C 49.01; H 4.57; N 14.21. $C_{12}H_{14}BrN_3O$. Calculated, %: C 48.67; H 4.76; N 14.19.

3-Bromo-5-(2,4-dichlorophenoxy)-1*H*-1,2,4-triazole (4e). Yield 1.17 g (39%), mp 126–128°C. IR spectrum, ν, cm^{-1}: 3093, 3068, 3021, 2962, 2853, 2737 (N–H), 1591, 1568, 1475 (C=N, C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.29 d (1H, 5′-H, J = 2.3 Hz), 7.31 s (1H, 3′-H), 7.45 d (1H, 6′-H, J = 2.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 123.00 ($C^{6'}$), 126.96 ($C^{4'}$), 128.34 ($C^{5'}$), 130.65 ($C^{3'}$), 132.12 ($C^{2'}$), 147.88 ($C^{1'}$). Found, %: C 30.94; H 1.30; N 13.48. $C_8H_4BrCl_2N_3O$. Calculated, %: C 31.10; H 1.31; N 13.60.

3-Bromo-5-(naphthalen-1-yloxy)-1*H*-1,2,4-triazole (4f). Yield 2.25 g (80%), mp 112–113°C. IR spectrum, ν, cm^{-1}: 3024, 2949, 2845, 2740, 2650 (N–H), 1582, 1557, 1489 (C=N, C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.32–7.52 m (4H, 2′-H, 3′-H, 6′-H, 7′-H), 7.70 d (1H, 4′-H, ^3J = 8.1 Hz), 7.83 d (1H, 8′-H, ^3J = 8.0 Hz), 8.00 d (1H, 5′-H, ^3J = 8.1 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 115.41 ($C^{8'}$), 120.99 ($C^{4'}$), 125.42 ($C^{7'}$), 125.89 ($C^{9'}$), 126.05 ($C^{3'}$), 126.73 ($C^{5'}$), 126.85 ($C^{2'}$), 127.95 ($C^{6'}$), 134.82 ($C^{10'}$), 149.23 ($C^{1'}$). Found, %: C 49.79; H 2.86; N 14.40. $C_{12}H_8BrN_3O$. Calculated, %: C 49.68; H 2.78; N 14.48.

3-Bromo-5-benzenesulfonyl-1*H*-1,2,4-triazole (4g). Yield 0.83 g (30%), mp 203–205°C. IR spectrum, ν, cm^{-1}: 3064, 2951, 2873, 2735, 2667 (N–H), 1421, 1373 (C=N, C=C), 1340, 1161 (SO_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.62–7.68 m (2H, 3′-H, 5′-H), 7.74 t (1H, 4′-H, ^3J = 7.4 Hz), 7.95 d (2H, 2′-H, 6′-H, ^3J = 7.2 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 127.80 ($C^{2'}$, $C^{6'}$), 129.62 ($C^{3'}$, $C^{5'}$), 134.08 (C^3), 134.20 ($C^{4'}$), 139.61 ($C^{1'}$), 161.67 (C^5). Found, %: C 33.31; H 2.43; N 14.77. $C_8H_6BrN_3O_2S$. Calculated, %: C 33.35; H 2.10; N 14.58.

The IR spectra were recorded in KBr on an Infralyum FT-02 spectrometer. The ^1H and ^{13}C NMR spectra were measured on a Bruker AV-500 instrument at 500 and 125 MHz, respectively, relative to the residual proton and carbon signals of the deuterated solvent. The elemental analyses were obtained on a Hekatech Euro 3000 CHNS analyzer. The melting points were determined with a Stuart SMP30 melting point apparatus.

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