ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 6, pp. 918–921. © Pleiades Publishing, Inc., 2006.
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Synthesis of Sulfonyl and Sulfenyl Derivatives of Pyridine and 1,2,4-Triazole

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Received July 18, 2005

Abstract—The corresponding sulfonamides and sulfenamides were synthesized from 5-methyl-4-phenyl-4*H*-1,2,4-triazole-3-thiol and 6-*tert*-butyl-3-cyano-4-phenylpyridine-2-thiol.

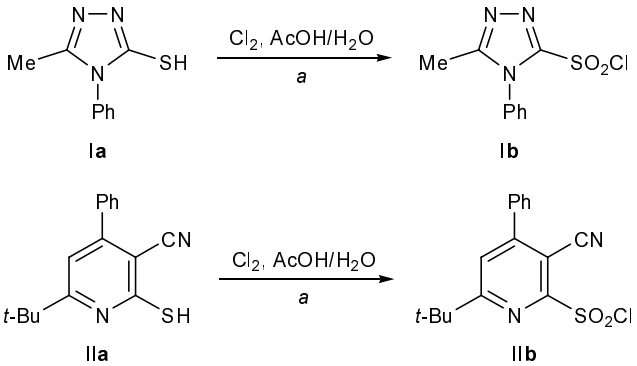
DOI: 10.1134/S1070428006060182

Many 1,2,4-triazole and pyridine derivatives exhibit a broad spectrum of biological activity, in particular antibacterial, neuroleptic, and spasmodic; some of these also stimulate cardiac function [1, 2]. In the present communication we report on the synthesis of new sulfonyl and sulfenyl derivatives possessing pyridine and 1,2,4-triazole fragments, which attract interest as potential biologically active substances. The syntheses were performed in two ways: (*a*) by reaction of the corresponding sulfonyl chlorides with amines and (*b*) by oxidation of sulfides obtained from 5-methyl-4-phenyl-4*H*-1,2,4-triazole-3-thiol and 6-*tert*-butyl-3-cyano-4-phenylpyridine-2-thiol and chloroacetic acid derivatives.

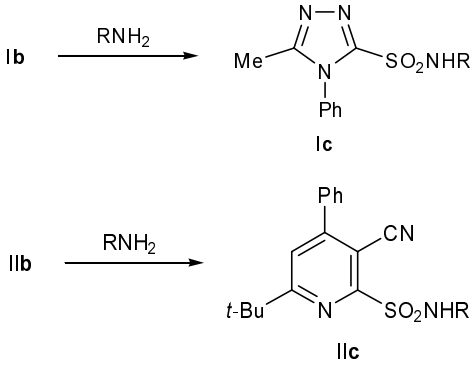
According to method *a*, 5-methyl-4-phenyl-4*H*-1,2,4-triazole-3-thiol (**Ia**) and 6-*tert*-butyl-3-cyano-4-phenylpyridine-2-thiol (**IIa**) were converted into the corresponding sulfonyl chlorides **Ib** and **IIb** (Scheme 1), and the latter were treated ethyl 4-aminobenzoate in dimethylformamide to obtain sulfonamides **Ic** and **IIc** having 1,2,4-triazole and pyridine fragments (Scheme 2).

According to method *b*, thiols **Ia** and **IIa** were alkylated with *N*-(4-bromophenyl)-2-chloroacetamide (Scheme 3). Sulfides **Id** and **IId** thus obtained were

Scheme 1.

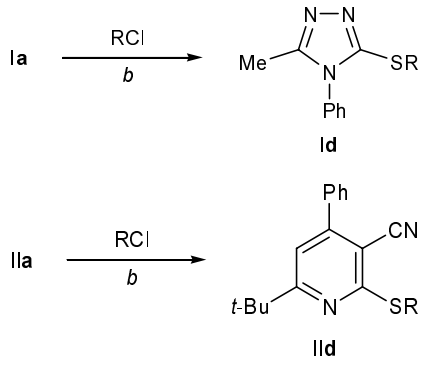


Scheme 2.



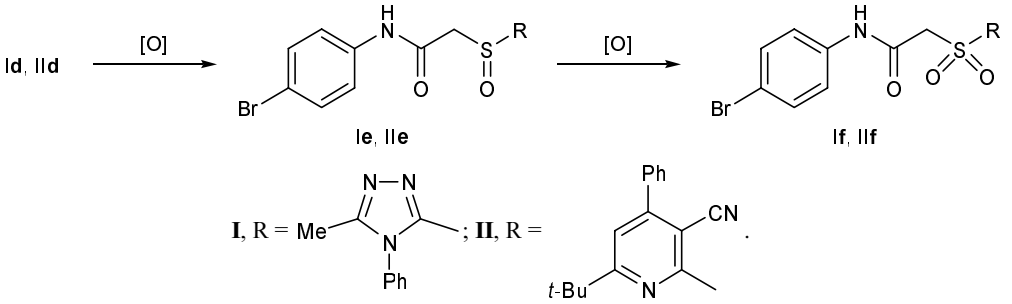
R = 4-EtOCOC$_6$H$_4$.

Scheme 3.



R = 4-BrC$_6$H$_4$NHC(O)CH$_2$.

Scheme 4.



subjected to oxidation using various oxidants and catalysts (Scheme 4, see table).

If the lone electron pair on the sulfur atom in a sulfide is involved in conjugation with an aromatic ring, the oxidation of both the sulfide to sulfoxide and the sulfoxide to sulfone is hindered. It is also known that the synthesis of sulfoxides by oxidation of sulfides with 1 equiv of an oxidant is accompanied by formation of some amount of the corresponding sulfone which is difficult to separate from the target sulfoxide [3]. Therefore, apart from common oxidants (such as hydrogen peroxide in acetic acid and *m*-chloroperoxybenzoic acid), we used hydrogen peroxide in the presence of anionic peroxo complexes of vanadium as catalysts; these complexes are known as highly selective oxidants toward organosulfur compounds in two-phase systems [4, 5]. An advantage of the procedure involving vanadium complexes is that it utilizes technical-grade 10–30% solutions of hydrogen peroxide without additional purification and concentration and relatively low-expensive weakly polar aprotic solvents.

As follows from the data in table, system nos. 3, 5, and 6 turned out to be the most effective and selective in the oxidation of sulfides **Id** and **IId**. The oxidation of these compounds with hydrogen peroxide in a two-phase system using pyridine vanadium peroxo complex (run no. 3) gave the corresponding sulfoxides **Ie** and **IIe** in almost quantitative yield. *m*-Chloroperoxybenzoic acid induced more profound oxidation: sulfones **If** and **IIf** were quantitatively obtained in a shorter time using 5 equiv of the oxidant. When the amount of the oxidant was reduced, the oxidation of the sulfides to sulfones was incomplete. In the presence of a catalytic amount of anionic vanadium peroxo complex with pyridine, the reaction time was considerably longer, but the corresponding sulfone was formed in almost quantitative yield using an equimolar amount of *m*-chloroperoxybenzoic acid (run no. 6).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian XR-400 spectrometer (400 MHz) using DMSO-d_6 as solvent and HMDS as internal reference. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates (ethyl acetate–benzene, 1:1. Initial compounds **Ia** and **IIa** were synthesized as described in [6] and [7], respectively.

5-Methyl-4-phenyl-4*H*-1,2,4-triazole-3-thiol (Ia). Yield 76%, mp 95–97°C. ^{1}H NMR spectrum, δ, ppm: 12.58 br.s (1H, NH), 7.2 m (5H, H_{arom}), 2.32 s (3H, Me). Found, %: C 56.44; H 4.72; N 21.93. $C_9H_9N_3S$. Calculated, %: C 56.52; H 4.74; N 21.99.

Oxidation of sulfides **Id** and **IId** (30°C, 8 h)

Run no.	Oxidant	Catalyst	Substrate–oxidant–catalyst molar ratio	Solvent	Product composition, %	
					sulfoxide	sulfone
1	$AcOH/H_2O_2$	–	1:1	AcOH	83 (**IIe**)	17 (**IIf**)
2	CF_3COOH/H_2O_2	$VO(O_2)_2Py_2$		CH_2Cl_2/H_2O	80 (**IIe**)	20 (**IIf**)
3	H_2O_2	$VO(O_2)_2Py_2$	1:1:0.03	CH_2Cl_2/H_2O	100 (**Ie**, **IIe**)	0
4	H_2O_2	$VO(acac)_2$	1:1:0.03	CH_2Cl_2	9 (**IIe**)	91 (**IIf**)
5[a]	$3\text{-}ClC_6H_4CO_3H$	–	1:5	CH_2Cl_2	0	100 (**If**, **IIf**)
6	$3\text{-}ClC_6H_4CO_3H$	$VO(O_2)_2Py_2$	1:1:0.03	CH_2Cl_2/H_2O	0	100 (**If**, **IIf**)

[a] Oxidation time 2 h.

6-*tert*-Butyl-3-cyano-4-phenylpyridine-2-thiol (IIa). Yield 98%, mp 235–237°C. ^{1}H NMR spectrum, δ, ppm: 13.70 br.s (1H, NH), 7.5 m (5H, H_{arom}), 6.47 s (1H, 5-H); 1.14 s (9H, *t*-Bu). Found, %: C 71.17; H 5.98; N 10.41. $C_{16}H_{16}N_2S$. Calculated, %: C 71.60; H 6.01; N 10.45.

Sulfonyl chlorides Ib and IIb (*general procedure*). Thiol **Ia** or **IIa**, 5 mmol, was dissolved in 80% acetic acid, and gaseous chlorine was passed through the solution over a period of 8–10 h at room temperature (until the initial thiol disappeared according to the TLC data). The precipitate was filtered off and recrystallized from benzene–hexane.

5-Methyl-4-phenyl-4*H*-1,2,4-triazole-3-sulfonyl chloride (Ib). Yield 37%, mp 125–127°C. ^{1}H NMR spectrum, δ, ppm: 7.3 m (5H, H_{arom}), 2.41 s (3H, Me). Found, %: C 41.92; H 3.20; N 16.28. $C_9H_8ClN_3O_2S$. Calculated, %: C 41.95; H 3.13; N 16.31.

6-*tert*-Butyl-3-cyano-4-phenylpyridine-2-sulfonyl chloride (IIb). Yield 45%, mp 246–248°C. ^{1}H NMR spectrum, δ, ppm: 7.98 s (1H, 5-H), 7.5 m (5H, H_{arom}), 1.32 s (9H, *t*-Bu). Found, %: C 57.50; H 4.48; N 8.32. Calculated, %: C 57.40; H 4.52; N 8.37.

Sulfonamides Ic and IIc (*general procedure*). Sulfonyl chloride **Ib** or **IIb** was dissolved in DMF, an equimolar amount of ethyl 4-aminobenzoate was added, and the mixture was heated for 35 min under reflux (TLC). After cooling, the precipitate was filtered off and recrystallized from isopropyl alcohol.

Ethyl 4-(5-methyl-4-phenyl-4*H*-1,2,4-triazol-3-ylsulfonylamino)benzoate (Ic). Yield 60%, mp 134–136°C. ^{1}H NMR spectrum, δ, ppm: 7.7 m (4H, H_{arom}), 7.3 m (5H, H_{arom}), 6.20 s (1H, NH), 4.30 d (2H, CH_2), 2.33 s (3H, Me), 1.35 t (3H, Me). Found, %: C 55.87; H 4.70; N 14.48. $C_{18}H_{18}N_4O_4S$. Calculated, %: C 55.95; H 4.70; N 14.51.

Ethyl 4-(6-*tert*-butyl-3-cyano-4-phenylpyridin-2-ylsulfonylamino)benzoate (IIc). Yield 35%, mp 225–227°C. ^{1}H NMR spectrum, δ, ppm: 8.0 s (1H, 5-H, Py), 7.95 m (4H, H_{arom}), 7.50 m (5H, H_{arom}), 4.32 d (2H, CH_2), 1.35 t (3H, Me), 1.32 s (9H, *t*-Bu). Found, %: C 64.76; H 5.48; N 9.04. $C_{25}H_{25}N_3O_4S$. Calculated, %: C 64.78; H 5.44; N 9.07.

Sulfides Id and IId (*general procedure*). Compound **Ia** or **IIa**, 1 equiv, was dissolved in a 1 N solution of potassium hydroxide (2 equiv), and 1 equiv of *N*-(4-bromophenyl)-2-chloroacetamide was added under stirring at room temperature. The precipitate was filtered off and dried under reduced pressure.

***N*-(4-Bromophenyl)-2-(5-methyl-4-phenyl-4*H*-1,2,4-triazol-3-ylsulfanyl)acetamide (Id).** Yield 98%, mp 187–189°C. ^{1}H NMR spectrum, δ, ppm: 9.50 br.s (1H, NH), 7.20 m (4H, H_{arom}), 7.00 m (5H, H_{arom}), 3.95 s (2H, CH_2), 2.34 s (3H, Me). Found, %: C 51.01; H 3.67; N 13.90. $C_{17}H_{15}BrN_4OS$. Calculated, %: C 50.63; H 3.75; N 13.89.

***N*-(4-Bromophenyl)-2-(6-*tert*-butyl-3-cyano-4-phenylpyridin-2-ylsulfanyl)acetamide (IId).** Yield 96%, mp 257–258°C. ^{1}H NMR spectrum, δ, ppm: 10.30 br.s (1H, NH), 7.50 m (5H, H_{arom}), 7.35 m (4H, H_{arom}), 7.27 s (1H, 5-H, Py), 4.33 s (2H, CH_2), 1.32 s (9H, *t*-Bu). Found, %: C 60.36; H 5.02; N 8.73. $C_{24}H_{22}BrN_3OS$. Calculated, %: C 60.00; H 4.62; N 8.75.

Oxidation of sulfides Id and IId with hydrogen peroxide in acetic acid (see table**).** *Run no. 1*. The procedure was the same as in [8]. Sulfide **Id** or **IId**, 10 mmol, was dissolved in 10 ml of acetic acid, 11 mmol of a 30% solution of hydrogen peroxide was added dropwise under stirring, and the mixture was stirred for 8 h. The organic phase was separated and evaporated, and the residue was analyzed by TLC using acetone–hexane (4:1) as eluent. The products were separated by column chromatography on silica gel (100–160 μm) using acetone–hexane (4:1) as eluent.

***N*-(4-Bromophenyl)-2-(5-methyl-4-phenyl-4*H*-1,2,4-triazol-3-ylsulfinyl)acetamide (Ie).** Yield 96%, mp 183–185°C. ^{1}H NMR spectrum, δ, ppm: 9.50 br.s (1H, NH), 7.20 m (4H, H_{arom}), 7.00 m (5H, H_{arom}), 3.95 s (2H, CH_2), 2.34 s (3H, Me). Found, %: C 48.70; H 3.58; N 13.34. $C_{17}H_{15}BrN_4O_2S$. Calculated, %: C 48.70; H 3.61; N 13.36.

***N*-(4-Bromophenyl)-2-(6-*tert*-butyl-3-cyano-4-phenylpyridin-2-ylsulfinyl)acetamide (IIe).** Yield 9–100%, mp 233–235°C. ^{1}H NMR spectrum, δ, ppm: 10.48 br.s (1H, NH), 7.70 m (5H, H_{arom}), 7.65 m (4H, H_{arom}), 7.50 s (1H, 5-H, Py), 4.60 d (2H, CH_2), 1.32 s (9H, *t*-Bu). Found, %: C 58.10; H 4.47; N 8.41. $C_{24}H_{22}BrN_3O_2S$. Calculated, %: C 58.07; H 4.47; N 8.46.

***N*-(4-Bromophenyl)-2-(5-methyl-4-phenyl-4*H*-1,2,4-triazol-3-ylsulfonyl)acetamide (If).** Yield 98%, mp 190–192°C. ^{1}H NMR spectrum, δ, ppm: 8.65 br.s (1H, NH), 7.91 m (5H, H_{arom}), 7.48 m (4H, H_{arom}), 5.04 s (2H, CH_2), 2.35 s (3H, Me). Found, %: C 47.20; H 3.56; N 12.89. $C_{17}H_{15}BrN_4O_3S$. Calculated, %: C 46.91; H 3.47; N 12.87.

***N*-(4-Bromophenyl)-2-(6-*tert*-butyl-3-cyano-4-phenylpyridin-2-ylsulfonyl)acetamide (IIf).** Yield

17–100%, mp 240–242°C. ^{1}H NMR spectrum, δ, ppm: 10.50 br.s (1H, NH), 7.90 s (1H, 5-H, Py), 7.70 m (5H, H_{arom}), 4.90 s (2H, CH_2), 1.34 s (9H, *t*-Bu). Found, %: C 56.09; H 4.25; N 8.22. $C_{24}H_{22}BrN_3O_3S$. Calculated, %: C 56.25; H 4.33; N 8.20.

Run no. 2. The oxidation was carried out according to a modified procedure [9]. To a mixture of 10 mmol of sulfide **IId**, 10 ml of trifluoroacetic acid, and 10 ml of methylene chloride we added 0.03 mmol of $NaVO_3 \cdot 2H_2O$ and 0.06 mmol of pyridine, and 11 mmol of 30% hydrogen peroxide was then added dropwise under stirring. The mixture was stirred for 8 h, and the products were isolated as in run no. 1.

Run no. 3. The oxidation was carried out according to the procedure described in [9]. To a mixture of 10 mmol of sulfide **Id** or **IId** and 10 ml of methylene chloride we added 0.03 mmol of $NaVO_3 \cdot 2H_2O$, 0.06 mmol of pyridine, and 11 mmol of 30% hydrogen peroxide. The mixture was stirred for 2 h, and the organic phase was separated, washed with water (2 × 10 ml), passed through a short column charged with 1 g of silica gel to remove excess water, and evaporated. The residue was analyzed by TLC (acetone–hexane, 4 : 1). The products were separated by column chromatography on silica gel (100–160 μm) using acetone–hexane (4 : 1) as eluent.

Run no. 4. The oxidation was carried out following a modified procedure [10]. Vanadium oxo complex $[VO(acac)_2]$ [11], 0.03 mmol, and 50% hydrogen peroxide, 11 mmol, were added to a mixture of 10 mmol of sulfide **IId** and 10 ml of methylene chloride. The mixture was stirred for 2 h, and the products were isolated as in run no. 3.

Run no. 5. The procedure was the same as in [12]. A solution of 50 mmol of *m*-chloroperoxybenzoic acid in 10 mmol of methylene chloride was added to a mixture of 10 mmol of sulfide **Id** or **IId** and 10 ml of methylene chloride. The mixture was stirred for 2 h, and the products were isolated as in run no. 1.

Run no. 6. The oxidation was carried out according to a modified procedure [9]. To a mixture of 10 mmol of sulfide **Id** or **IId** and 10 ml of methylene chloride we added 0.03 mmol of $NaVO_3 \cdot 2H_2O$, 0.06 mmol of pyridine, and 11 mmol of 50% hydrogen peroxide, and a solution of 10 mmol of *m*-chloroperoxybenzoic acid in 10 ml of methylene chloride was then added dropwise. The mixture was stirred for 8 h, and the products were isolated as in run no. 3.

This study was performed under financial support by the Ministry of Education of the Russian Federation in the framework of the program "Universities of Russia" (project no. UR.05.02.540).

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