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Reactions of 5-mesyl-2-phenyl-4-tosyloxazole with N-, C-, and S-nucleophiles

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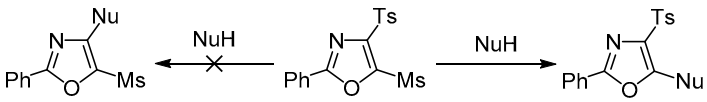


The reaction of 5-mesyl-2-phenyl-4-tosyloxazole with N-, C-, and S-nucleophiles led to products arising from substitution of the mesyl group at the C-5 position, while the tosyl group at the C-4 position was not affected.

Keywords: amines, Fischer's base, oxazoles, thiols, nucleophilic substitution.

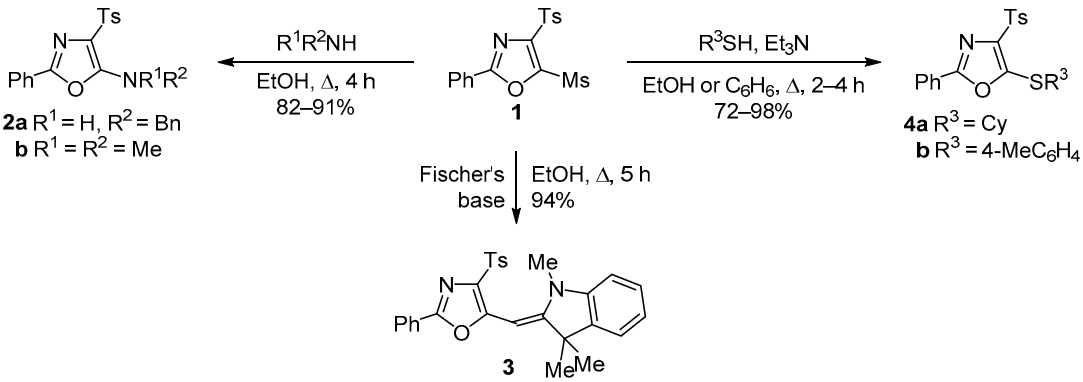
The sulfinate anion RSO_2^- is known as a good leaving group, which has been used for nucleophilic substitution reactions in oxazoles in the synthesis of promising pharmaceutical agents,[1,2] plant growth regulators,[3,4] and natural compounds.[5] Despite the fact that such applications of a sulfonyl group do not follow the atom economy principles, they are justified in the cases when the respective halogenated oxazoles are difficult to obtain.[6]

The earlier examples of such nucleophilic substitution reactions used oxazoles with one sulfonyl group, which was bonded either to the C-2 atom[1–5,7,8] or to the C-5 atom.[6,9,10] Later, in 2001 we reported the preparation of oxazoles containing two sulfonyl groups: one at the C-4 atom and the other at C-5 atom.[11] Each of these groups, on one hand, activates the respective β-carbon atom in the oxazole ring, making this ring highly electron-deficient, and on the other hand may act as a leaving group.

In the current work, we studied the reactions of 5-mesyl-2-phenyl-4-tosyloxazole (**1**) with amines, thiols, and the Fischer's base. All of these reactions proceeded under relatively mild conditions with cleavage of the mesyl group and gave high yields of substitution products **2**–**4** (Scheme 1).

It should be noted that transformation **1**→**2** is more of theoretical interest than preparative value: compounds **2** can be obtained more conveniently by cyclocondensation of *N*-(2,2-dichloro-1-tosylethenyl)benzamide with amines.[12] The reaction of oxazole **1** with the Fischer's base provided product **3**, which exists in the form of only one of the two possible geometric isomers according to NMR analysis. The reactions with thiols were more important and led to oxazoles **4a**,**b** containing a tosyl group at position 4 and a cyclohexyl or *p*-tolylsulfanyl group at position 5. Such compounds are difficult to obtain by using the known

Scheme 1



methods for the synthesis of 4,5-dimercaptooxazole derivatives.[11]

The direction of our discovered transformations was in agreement with previously reported experimental data. Thus, a research group from Japan studied the reactivity of isomeric halodiphenyloxazoles toward a carbanion generated from phenylacetonitrile[7] and demonstrated, in particular, that 5-bromo- and 5-chloro-2,4-diphenyloxazoles gave substitution products in significantly higher yields compared to the respective 4-halooxazoles. On the basis of these considerations, the authors concluded that the C-5 atom of the oxazole ring is more preferrable for nucleophilic attack compared to the C-4 atom.

Thus, the reactions of the 5-mesyl-2-phenyl-4-tosyloxazole with N-, C-, and S-nucleophiles do not involve the tosyl group and may provide a new regioselective method for the functionalization of a 4-arylsulfonyl-substituted oxazole ring.

Experimental

^{1}H and ^{13}C NMR spectra were acquired on Bruker Avance DRX 500 (500 and 126 MHz, respectively) and Varian Unity Plus 400 (400 and 101 MHz, respectively) spectrometers in DMSO-d_6 using the residual solvent signals as standards. LC-MS analysis was performed on an Agilent 1200 chromatograph with a G6130A mass spectrometer using electrospray ionization at atmospheric pressure, capillary voltage 4000 V. The carbon and hydrogen content was determined by the Pregl gravimetric method, nitrogen – by the Dumas gasometric method, and sulfur – by the Schöniger titration method. Melting points were determined on a Fisher-Johns apparatus.

5-Mesyl-2-phenyl-4-tosyloxazole (**1**) was obtained according to a previously described procedure.[11]

***N*-Benzyl-4-[(4-methylphenyl)sulfonyl]-2-phenyl-1,3-oxazol-5-amine (2a)**. Benzylamine (0.40 ml, 3.66 mmol) was added to a suspension of oxazole **1** (0.33 g, 0.87 mmol) in EtOH (5 ml), and the reaction mixture was refluxed with stirring for 4 h. The resulting solution was cooled to room temperature, the precipitated compound **2a** was filtered off. Yield 0.32 g (91%), colorless crystals, mp 185–186°C (mp 186–188°C[12]). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.35 (3H, s, CH_3); 4.58 (2H, d, *J* = 6.2, CH_2); 7.25 (1H, t, *J* = 7.3, H Ph); 7.30–7.52 (9H, m, H Ar and H Ph); 7.66–7.75 (2H, m, H Ph); 7.79 (2H, d, *J* = 8.1, H Ar); 8.19 (1H, t, *J* = 6.2, NH). ^{13}C NMR spectrum (126 MHz), δ, ppm: 21.0; 46.3; 108.8; 124.9; 125.7; 126.2; 127.2; 127.4; 128.4; 129.0; 129.8; 130.1; 139.0; 139.5; 143.5; 149.4; 156.6. Mass spectrum, *m*/*z* (I_{rel}, %): 405 $[M+H]^+$ (50), 403 $[M–H]^–$ (100). Found, %: C 68.07; H 5.36; N 6.82. $C_{23}H_{20}N_2O_3S$. Calculated, %: C 68.30; H 4.98; N 6.93.

***N,N*-Dimethyl-[(4-methylphenyl)sulfonyl]-2-phenyl-1,3-oxazol-5-amine (2b)** was obtained analogously to compound **2a** from compound **1** (0.38 g, 1.0 mmol) and aqueous 7.8 M dimethylamine solution (1.0 ml). Yield 0.28 g (82%), colorless crystals, mp 160–161°C (EtOH) (mp 174–176°C (EtOH)[12]). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.37 (3H, s, CH_3); 3.18 (6H, s, $N(CH_3)_2$); 7.36–7.55 (5H, m, H Ph); 7.80 (4H, d, *J* = 6.9, H Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 343 $[M+H]^+$ (100). Found, %: C 63.00; H 5.44; N 8.26. $C_{18}H_{18}N_2O_3S$. Calculated, %: C 63.14; H 5.30; N 8.18.

4-[(4-Methylphenyl)sulfonyl]-5-[(1,3,3-trimethylindolin-2-ylidene)methyl]-2-phenyl-1,3-oxazole (3). 1,3,3-Trimethyl-2-methyleneindoline (Fischer's base) (0.39 ml, 2.0 mmol) was added to a suspension of compound **1** (0.38 g, 1.0 mmol) in EtOH (5 ml), and the reaction mixture was refluxed for 5 h. The resulting solution was cooled to room temperature, the precipitated compound **3** was filtered off. Yield 0.44 g (94%), yellow crystals, mp 188–191°C. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.69 (6H, s, CH_3); 2.37 (3H, s, CH_3); 3.31 (3H, s, CH_3); 6.14 (1H, s, CH); 6.90–7.04 (2H, m, H Ar); 7.22 (1H, t, *J* = 7.6, H Ar); 7.33 (1H, d, *J* = 7.2, H Ar); 7.44 (2H, d, *J* = 7.9, H Ar); 7.49–7.62 (3H, m, H Ar); 7.84–7.97 (4H, m, H Ar). ^{13}C NMR spectrum (101 MHz), δ, ppm: 21.3; 24.7; 29.7; 46.4; 78.4; 107.9; 121.4; 122.0; 125.8; 125.9; 127.1; 128.1; 129.0; 129.6; 130.3; 131.2; 138.6; 139.1; 143.7; 144.4; 152.8; 156.6; 162.9. Mass spectrum, *m*/*z* (I_{rel}, %): 471 $[M+H]^+$ (100). Found, %: C 71.14; H 5.85; N 5.87. $C_{28}H_{26}N_2O_3S$. Calculated, %: C 71.47; H 5.57; N 5.95.

5-Cyclohexylsulfanyl-4-[(4-methylphenyl)sulfonyl]-2-phenyl-1,3-oxazole (4a). Triethylamine (0.13 ml, 1.0 mmol) was added to a mixture of compound **1** (0.30 g, 0.8 mmol) and cyclohexanethiol (0.12 ml, 1.0 mmol) in EtOH (4 ml), and the reaction mixture was refluxed for 4 h. The volatile compounds were removed by evaporation at reduced pressure, the oily residue was diluted with EtOH and, after the crystallization was complete, compound **4a** was filtered off. Yield 0.24 g (72%), colorless crystals, mp 94–95°C (EtOH). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.16–1.61 (6H, m, C_6H_{11}); 1.70 (2H, d, *J* = 9.1, C_6H_{11}); 1.94 (2H, d, *J* = 9.6, C_6H_{11}); 2.39 (3H, s, CH_3); 3.59 (1H, t, *J* = 9.9, C_6H_{11}); 7.41–7.64 (5H, m, H Ph); 7.81–7.99 (4H, m, H Ar). ^{13}C NMR spectrum (101 MHz), δ, ppm: 21.1; 24.8; 25.2; 33.0; 47.2; 125.2; 126.3; 127.4; 129.3; 130.1; 131.8; 137.1; 140.0; 145.1; 149.4; 161.5. Mass spectrum, *m*/*z* (I_{rel}, %): 414 $[M+H]^+$ (100). Found, %: C 63.92; H 5.22; N 3.16. $C_{22}H_{23}NO_3S_2$. Calculated, %: C 63.90; H 5.61; N 3.39.

5-[(4-Methylphenyl)sulfanyl]-4-[(4-methylphenyl)sulfonyl]-2-phenyl-1,3-oxazole (4b). Triethylamine (0.17 ml, 1.2 mmol) was added to a mixture of compound **1** (0.46 g, 1.2 mmol) and *p*-thiocresol (0.15 g, 1.2 mmol) in EtOH (4 ml), and the reaction mixture was refluxed for 2 h. The resulting solution was cooled to room temperature, the precipitated compound **4b** was filtered off. Yield 0.50 g (98%), colorless crystals, mp 116–117°C (EtOH). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.32 (3H, s, CH_3); 2.39 (3H, s, CH_3); 7.25 (2H, d, *J* = 7.8, H Ar); 7.34–7.61 (7H, m, H Ar and H Ph); 7.77 (2H, d, *J* = 7.1, H Ar); 7.86 (2H, d, *J* = 8.1, H Ar). ^{13}C NMR spectrum (126 MHz), δ, ppm: 20.7; 21.1; 124.9; 125.5; 126.3; 127.6; 129.3; 130.2; 130.4; 132.0; 136.6; 139.2; 140.3; 145.3; 147.8; 161.9. Mass spectrum, *m*/*z* (I_{rel}, %): 422 $[M+H]^+$ (100). Found, %: C 65.68; H 4.78; S 15.31. $C_{23}H_{19}NO_3S_2$. Calculated, %: C 65.54; H 4.54; S 15.21.

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