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METHOD FOR PREPARATION OF 4-METHYL-1,2-BENZOXATHIINE 2,2-DIOXIDE DERIVATIVES

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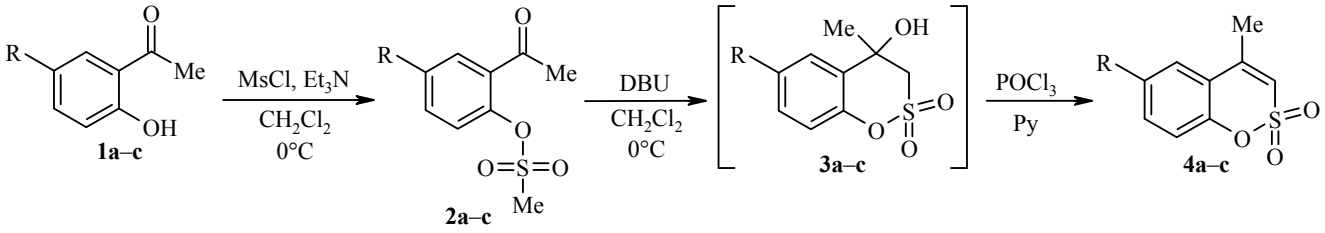
We propose an efficient method for the synthesis of 4-methyl-1,2-benzoxathiine 2,2-dioxides **4a-c** from the available 2-hydroxyacetophenones **1a-c**, which undergo mesylation to give compounds **2a-c**. Contrary to literature data [1], we have found that intramolecular condensation of compound **2a** [2] with formation of compound **4a** does not occur in pyridine in the presence of KOH. We have shown that this intramolecular cyclization of compounds **2a-c** occurs readily in the presence of the strong organic base 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) to give presumably the intermediate hydroxy derivatives **3a-c**. Subsequent dehydration of compounds **3a-c** using $POCl_3$ gives the compounds **4a-c**.



a R = H, **b** R = OMe, **c** R = NO_2

The structure of compounds **4a-c** obtained was confirmed from ^{1}H NMR and ^{13}C NMR spectroscopic data, elemental analysis, and also from an X-ray structural analysis of compound **4a** (Figure 1).

^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 spectrometer (400 MHz and 100 MHz, respectively) using DMSO-d_6 with the residual solvent signals for reference (2.50 ppm for the ^{1}H nuclei and 39.5 ppm for the ^{13}C nuclei). Elemental analysis was carried out on an Elemental Analyzer EA 1108 apparatus. Melting points of crystalline substances were determined using an SRS OptiMelt apparatus.

2-Acetylphenyl Methanesulfonate (2a). 2-Hydroxyacetophenone (**1a**) (1.77 ml, 14.70 mmol) was dissolved in absolute CH_2Cl_2 (25 ml), and Et_3N (2.45 ml, 17.64 mmol) was added. $MeSO_2Cl$ (1.83 ml, 23.67 mmol) was added dropwise to the obtained mixture at 0ºC. The reaction mixture was stirred at room temperature for 4 h, then water (50 ml) was added, and the product was extracted with ethyl acetate (100 ml).

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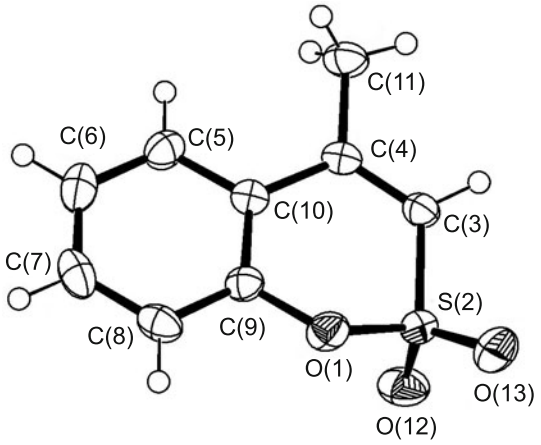

Fig. 1. Structure of the compound **4a** molecule with atoms represented by thermal vibrational atomic ellipsoids of 50% probability.

The organic layer was separated, washed with NaCl solution, and dried over Na_2SO_4. The solvent was evaporated *in vacuo*. Yield 2.88 g (>99%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.57 (3H, s, $COCH_3$); 3.45 (3H, s, SO_2CH_3); 7.47-7.52 (2H, m, H Ar); 7.65-7.70 (1H, m, H Ar); 7.78-7.82 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.2 ($COCH_3$); 38.0 (SO_2CH_3); 123.4; 127.5; 130.2; 133.3; 133.5; 145.9 (C Ar); 197.9 (CO).

2-Acetyl-4-methoxyphenyl Methanesulfonate (2b). Obtained similarly to compound **2a** from the 2-hydroxy-5-methoxyacetophenone (**1b**) (0.60 g, 3.61 mmol), Et_3N (0.75 ml, 5.42 mmol), and $MeSO_2Cl$ (0.45 ml, 5.81 mmol) in absolute CH_2Cl_2 (10 ml). Yield 0.84 g (96%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.56 (3H, s, $COCH_3$); 3.40 (3H, s, SO_2CH_3); 3.82 (3H, s, OCH_3); 7.20 (1H, dd, *J* = 3.2, *J* = 9.0, H-5); 7.26 (1H, d, *J* = 3.2, H-3); 7.41 (1H, d, *J* = 9.0, H-6). ^{13}C NMR spectrum, δ, ppm: 30.1 ($CO\underline{C}H_3$); 37.6 (SO_2CH_3); 55.8 (OCH_3); 114.5; 118.3; 124.7; 134.4; 139.1; 157.7 (C Ar); 197.8 (CO). Found, %: C 48.91; H 4.98. $C_{10}H_{12}O_5S$. Calculated, %: C 49.17; H 4.95.

2-Acetyl-4-nitrophenyl Methanesulfonate (2c). Obtained similarly to compound **2a** from the 2-hydroxy-5-nitroacetophenone (**1c**) (0.60 g, 3.31 mmol), Et_3N (0.69 ml, 4.97 mmol), and $MeSO_2Cl$ (0.41 ml, 5.33 mmol) in absolute CH_2Cl_2 (20 ml). Yield 0.87 g (> 99%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.65 (3H, s, $COCH_3$); 3.59 (3H, s, SO_2CH_3); 7.79 (1H, d, *J* = 9.0, H-6); 8.50 (1H, dd, *J* = 2.9, *J* = 9.0, H-5); 8.55 (1H, d, *J* = 2.9, H-3). ^{13}C NMR spectrum, δ, ppm: 30.3 ($CO\underline{C}H_3$); 38.4 (SO_2CH_3); 124.8; 125.3; 128.2; 133.9; 145.7; 150.0 (C Ar); 196.3 (CO). Found, % C 41.47; H 3.54; N 5.37. $C_9H_9NO_6S$. Calculated, %: C 41.70; H 3.50; N 5.40.

4-Methyl-1,2-benzoxathiine 2,2-Dioxide (4a). Compound **2a** (3.37 g, 15.72 mmol) was dissolved in absolute CH_2Cl_2 (11 ml), cooled to 0ºC, DBU (2.35 ml, 15.72 mmol) was added, and the reaction mixture was stirred at 0ºC for 3.5 h. Solvent was evaporated, pyridine (8 ml) and $POCl_3$ (1.85 ml, 19.85 mmol) were added. The reaction product was stirred at room temperature for 3 h and then poured into water. The precipitate formed was filtered off and recrystallized from EtOH. Yield 1.74 g (56%). Light-brown crystals, mp 87-88ºC (EtOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, d, *J* = 1.4, CH_3); 7.39 (1H, q, *J* = 1.4, H-3); 7.42-7.48 (2H, m, H Ar); 7.61 (1H, dt, *J* = 1.5, *J* = 7.8, H Ar); 7.78 (1H, dd, *J* = 1.5, *J* = 7.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 18.9 (CH_3); 118.7; 119.3; 120.5; 126.2; 127.2; 132.6; 145.5; 149.9. Found, %: C 55.12; H 4.23. $C_9H_8O_3S$. Calculated, %: C 55.09; H 4.11.

6-Methoxy-4-methyl-1,2-benzoxathiine 2,2-Dioxide (4b). Prepared similarly to compound **4a** from compound **2b** (0.83 g, 3.39 mmol) and DBU (0.51 ml, 3.39 mmol) in absolute CH_2Cl_2 (10 ml) and $POCl_3$ (0.95 ml, 10.17 mmol) in pyridine (8 ml). Yield 0.63 g (83%). Colorless crystals, mp 161-162ºC (EtOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.37 (3H, d, *J* = 1.4, CH_3); 3.84 (3H, s, OCH_3); 7.16 (1H, dd, *J* = 3.0, *J* = 9.0, H-7); 7.23 (1H, d, *J* = 3.0, H-5); 7.35-7.40 (2H, m, H-3,8). ^{13}C NMR spectrum, δ, ppm: 18.9 (CH_3); 55.9 (OCH_3);

111.5; 117.9; 119.7 (2C); 121.4; 143.6; 145.4; 156.8. Found, %: C 53.16; H 4.51. $C_{10}H_{10}O_4S$. Calculated, %: C 53.09; H 4.46.

4-Methyl-6-nitro-1,2-benzoxathiine 2,2-Dioxide (4c). Compound **2c** (0.86 g, 3.31 mmol) was dissolved in absolute CH_2Cl_2 (10 ml) and DBU (0.49 ml, 3.31 mmol) was added at 0ºC. The reaction mixture was stirred at 0ºC for 3.5 h, poured into a mixture of ice and 10% HCl, extracted with ethyl acetate (3×30 ml), washed with saturated aqueous ammonium chloride solution (4×40 ml), and dried over Na_2SO_4. Solvent was evaporated, and pyridine (5 ml) and $POCl_3$ (0.92 ml, 9.94 mmol) were added. The reaction mixture was stirred at room temperature for 4.5 h, poured into water, and the precipitate formed was filtered off and recrystallized from EtOH. Yield 0.27 g (34%). Light-brown crystals, mp 148-149ºC (EtOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.48 (3H, d, *J* = 1.4, CH_3); 7.66 (1H, q, *J* = 1.4, H-3); 7.74 (1H, d, *J* = 9.0, H-8); 8.44 (1H, dd, *J* = 2.8, *J* = 9.0, H-7); 8.54 (1H, d, *J* = 2.8, H-5). ^{13}C NMR spectrum, δ, ppm: 19.0 (CH_3); 120.3; 120.6; 121.1; 122.8; 127.5; 144.7; 144.9; 153.7. Found, %: C 44.96; H 2.86; N 5.72. $C_9H_7NO_5S$. Calculated, %: C 44.81; H 2.92; N 5.81.

X-ray Structural Analysis of Compound 4a. Single crystals of compound **4a** ($C_9H_8O_3S$) were grown from ethanol solution. The unit cell parameters and intensities of 1465 independent reflections with $I > 2\sigma(I)$ were measured at 190 K on a Bruker-Nonius KappaCCD automatic X-ray diffractometer (MoKα radiation, λ 0.71073 Å). Crystals of compound **4a** are monoclinic with: *a* 6.979(2), *b* 9.182(4), *c* 14.959(6) Å; β 114.420(17)º; *V* 872.8 (6) Å^3; M 196.21; *Z* 4; d_{calc} 1.493 g/cm^3; space group $P2_1/c$. The structure was solved by the direct method using the SIR2008 software [3] and refined by full-matrix least-squares analysis using the SHELXL97 software [4]. The final probability factors were *R* 0.0435 and R_w 0.1059. The crystallographic parameters, atomic coordinates and their thermal parameters, bond lengths, and valence angle values for the molecule of compound **4a** have been placed in the Cambridge Crystallographic Data Center (deposit CCDC 865817).

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