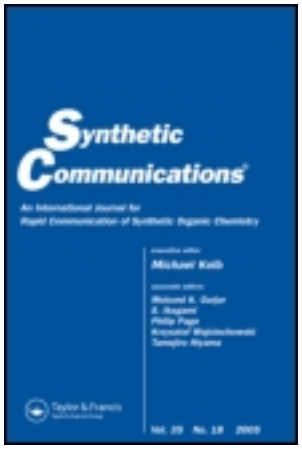

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GENERAL AND EFFICIENT SYNTHESIS OF O-SULFONYLHYDROXYLAMINE DERIVATIVES

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A general and efficient synthetic route to O-sulfonylhydroxylamine derivatives is described. The approach involves acylation of hydroxylamine with benzyl chloroformate to give N-carbobenzoxy hydroxylamine, followed by sulfonation and hydrogenolysis to give products.

Keywords: Benzyl chloroformate; hydrogenolysis; O-sulfonylhydroxylamine derivatives; sulfonation

INTRODUCTION

Recently, O-sulfonylhydroxylamine derivatives have attracted considerable attention in heterocyclic synthesis. O-Tosylhydroxylamine reacted with olefine to give azidines stereospecifically in moderate to high yield.[1] It can also react with 1,5-diaryl-1,5-diazapenta-1,3-diene in spontaneous cyclization to give pyrazole derivative.[2] As aminating regents, O-sulfonylhydroxylamine derivatives can react with pyridine, quinoline, and isoquinoline to give corresponding N-imines,[3,4] which are important intermediates in heterocyclic synthesis. Hajos et al. prepared a series of pyrido[1,2-*b*]-as-triazinium salts by condensation α-dioxo regents with diamino-pyridium salt, which resulted from aminating 2-aminopyridine with tosyl hydroxyl-amine.[5] With the same strategy, [1,2,4]-triazole-[1,5-*a*]-quinoline and [1,2,4]-triazole [5,1-*a*]-isoquinoline derivatives were also obtained.[6]

The traditional methods for synthesis of O-sulfonylhydroxylamine derivatives involve masking the amine function, sulfonation, and deprotection.[1,7,8] In the present communication, we describe a general and efficient synthesis of O-sulfonylhydroxylamine derivatives in which benzyl chloroformate is used to protect the amine group.

The O-sulfonylhydroxylamine derivatives were synthesized via the general route depicted in Scheme 1. Benzyl chloroformate reacted with hydroxylamine in CH_2Cl_2/H_2O at room temperature to give N-carbobenzoxy hydroxylamine,

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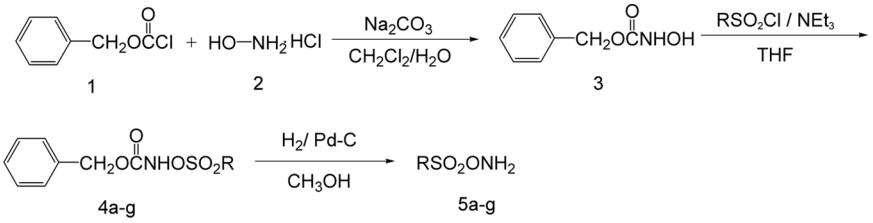

Scheme 1. Synthesis of O-sulfonylhydroxylamine derivatives.

which could be used for the next step without further purification. N-Carbobenzoxyhydroxylamine was converted into O-sulfonyl hydroxamic esters by treatment with various sulfonyl chlorides. The high reactivity of both enabled their complete conversion after the addition of sulfonyl chlorides. O-Sulfonyl hydroxamic esters were deprotected by hydrolysis with hydrogen and Pd-C to furnish almost quantitative products of O-sulfonylhydroxylamine derivatives. In comparison with other methods, O-sulfonylhydroxylamine derivatives prepared by this method are more stable and can be kept at low temperature for several days with no decomposition.

EXPERIMENTAL

Melting points were determined on an XT4A microscopic digital melting-point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Varian Inova 400 spectrometer in $CDCl_3$ or dimethylsulfoxide (DMSO-d_6) (with tetramathylsilane as internal standard). Infrared (IR) spectra were recorded on a Nicolet Fourier transform (FT)–IR 5700 spectrophotometer using KBr pellets. Mass spectra (MS) were recorded on a Thermo Scientific LTQ Orbitrap XLM mass spectronmeter.

N-Carbobenzoxyhydroxylamine (3)

Hydroxylamine hydrochloride (3.2 g, 0.046 mol) was added to a solution of 6.5 g (0.06 mol) Na_2CO_3 in 20 ml H_2O with continuous stirring. Subsequently, 6.82 g (0.04 mol) benzyl chloroformate in 15 ml CH_2Cl_2 were added slowly. The mixture was stirred at room temperature for 4 h, after which the reaction mixture was acidified with concentrated hydrochloric acid. The reaction mixture was then extracted with CH_2Cl_2, and CH_2Cl_2 solution was dried and concentrated under reduced pressure to give the crude product, which was recrystallized with ether and hexane to afford N-carbobenzoxyhydroxylamine. Mp 62–64°C (lit. 65–70), yield: 83.6%. IR (KBr) 3373, 3300, 1703, 1502, 1398, 1288, 1119 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.19 (s, 2H), 6.70 (s, 1H), 7.21 (s, 1H), 7.36 (s,5H). ESI-MS: 190 $(M + Na)^+$.

Sulfonation of N-Carbobenzoxyhydroxylamine (2)

A solution of 2.8 mmol substituted sulfonyl chloride in 4 ml THF was added dropwise to a solution of 3 mmol N-carbobenzoxyhydroxylamine and 3.2 mmol

triethylamine in 8 ml tetrahydrofuran (THF) at a temperature of −15°C. After addition, the reaction mixture was kept at this temperature for 0.5 h. After that, the precipitate triethylamine hydrochloride was filtered off, and the filtrate was concentrated under vacuum to give crude products. The crude material was purified by flash chromatography on silica gel.

Selected Data

O-p-Toluenesulfonyl benzyloxyhydroxamate (4a). Flash chromatography gave white solid, mp 120–123°C. Yield: 82.5%. IR (KBr) 3138, 2938, 1759, 1732, 1595, 1484, 1365, 1261, 1198, 1181, 1077 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.431 (s, 3H), 5.035 (s, 2H), 7.190–7.213 (m, 2H), 7.260 (d, 2H), 7.335–7.357 (m, 3H), 7.754 (s, 1H), 7.830 (d, 2H). ESI-MS: 344 $(M + Na)^+$.

O-Benzenesulfonyl benzyloxyhydroxamate (4b). Flash chromatography gave pale yellow solid, mp 65–68°C. Yield: 89.9%. IR (KBr) 3284, 1749, 1451, 1384, 1239, 1187, 1174, 1071 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 5.036 (s, 2H), 7.194–7.218 (m, 2H), 7.342–7.359 (m, 3H), 7.478–7.517 (m, 2H), 7.664–7.681 (m, 1H), 7.795 (s, 1H), 7.959–7.983 (m, 2H). ESI-MS: 330 $(M + Na)^+$.

O-Methanesulfonyl benzyloxyhydroxamate (4c). Flash chromatography gave white solid, mp 85–87°C. Yield: 73.2%. IR (KBr) 3237, 2941, 1740, 1490, 1455, 1361, 1247, 1150, 1100 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.171 (s, 3H), 5.270 (s, 2H), 7.380–7.396 (m, 5H), 8.024 (s, 1H). ESI-MS: 268 $(M + Na)^+$.

O-3,4-Difluorobenzenesulfonyl benzyloxyhydroxamate (4d). Flash chromatography gave pale yellow oil. Yield: 78.8%. IR (KBr) 3284, 1770, 1603, 1510, 1457, 1379, 1281, 1245, 1184, 1119, 1063 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 5.043 (s, 2H), 7.170–7.210 (m, 3H), 7.335–7.362 (m, 3H), 7.770–7.773 (m, 1H), 7.752–7.797 (m, 1H), 8.329 (s, 1H). ESI-MS: 366 $(M + Na)^+$.

O-p-Trifluoromethylbenzenesulfonyl benzyloxyhydroxamate (4e). Flash chromatography gave pale yellow solid, mp 57–59°C. Yield: 73.4%. IR (KBr) 3302, 1766, 1498, 1433, 1407, 1376, 1328, 1243, 1193, 1066, 1016 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 5.020 (s, 2H), 7.173–7.199 (m, 2H), 7.342–7.36 (m, 3H), 7.706 (d, 2H), 7.955 (s, 1H), 8.066 (d, 2H). ESI-MS: 398 $(M + Na)^+$.

O-m-Fluorobenzenesulfonyl benzyloxyhydroxamate (4f). Flash chromatography gave pale yellow solid, mp 76–77°C. Yield: 84.2%. IR (KBr) 3285, 1774, 1594, 1478, 1459, 1430, 1378, 1309, 1244, 1223, 1186, 1083, 1059 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 5.052 (s, 2H), 7.198–7.221 (m, 2H), 7.343–7.359 (m, 4H), 7.431–7.484 (m, 1H), 7.669 (d, 1H), 7.759 (d, 1H), 7.902 (s, 1H). ESI-MS: 348 $(M + Na)^+$.

O-2,5-Difluorobenzenesulfonyl benzyloxyhydroxamate (4g). Flash chromatography gave pale yellow oil. Yield: 66.8%. IR (KBr) 3307, 1775, 1494, 1458, 1423, 1382, 1241, 1256, 1201, 1185, 1059 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 5.073 (s, 2H), 7.018–7.072 (m, 1H). ESI-MS: 366 $(M + Na)^+$.

Hydrogenolysis of O-Sulfonyl Hydroxamic Esters

Substituted O-sulfonyl hydroxamic esters **5a–g** (1.5 mmol) and 0.5 g 10% Pd-C were dissolved in 8 ml absolute methanol at room temperature. A gentle stream of hydrogen was passed through the reaction mixture; the reaction proceeded for about 0.5 h. After the hydrolysis was completed (as monitored by thin-layer chromatography), the catalyst was removed by filtration through celite, and the filtrate was concentrated to give products with no workup.

Selected Data

O-p-Tolenesulfonylhydroxylamine (5a). White solid, mp 200°C (Dec). Yield: 98%. IR (KBr) 3426, 3179, 3070, 1599, 1457, 1163, 1127, 1036, 1010 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 2.287 (s, 3H), 7.115 (d, 2H), 7.472 (d, 2H). ESI-MS: 171 $(M\text{-}NH_2)^-$.

O-Benzenesulfonylhydroxylamine (5b). White solid, mp 195°C (Dec). Yield: 100%. IR (KBr) 3424, 3187, 3065, 1445, 1222, 1189, 1131, 1041, 1019 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.315 (m, 3H), 7.59 (m, 2H). ESI-MS: 157 $(M\text{-}NH_2)^-$.

O-Methanesulfonylhydroxylamine (5c). White solid, mp 177–179°C (Dec). Yield: 100%. IR (KBr) 3183, 3103, 1436, 1404, 1345, 1326, 1192, 1049 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 2.312 (s, 3H). ESI-MS: 95 $(M\text{-}NH_2)^-$.

O-3,4-Difluorobenzenesulfonylhydroxylamine (5d). White solid, mp 178°C (Dec). Yield: 98%. IR (KBr) 3408, 3243, 3089, 1644, 1611, 1516, 1417, 1282, 1259, 1231, 1106 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.374–7.489 (m, 3H). ESI-MS: 193 $(M\text{-}NH_2)^-$.

O-p-Trifluoromethylbenzenesulfonylamine (5e). White solid, mp > 300°C. Yield: 99%. IR (KBr) 3437, 1669, 1434, 1406, 1331, 1225, 1202, 1173, 1131, 1065, 1051 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.661 (d, 2H), 7.748 (d, 2H). ESI-MS: 225 $(M\text{-}NH_2)^-$.

O-m-Fluorobenzenesulfonylamine (5f). White solid, mp 230°C (Dec). Yield: 96%. IR (KBr) 3424, 3189, 3069, 1680, 1655, 1589, 1476, 1427, 1272, 1223, 1179, 1107, 1075, 1060, 1039 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.138–7.180 (m, 1H), 7.280–7.306 (m, 1H), 7.358–7.441 (m, 2H). ESI-MS: 175 $(M\text{-}NH_2)^-$.

O-2,5-Difluorobenzenesulfonylamine (5g). White solid, mp 238°C (Dec). Yield: 100%. IR (KBr) 3438, 3203, 3079, 1672, 1640, 1598, 1481, 1434, 1408, 1251, 1213, 1192, 1120, 1083, 1032 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.195–7.271 (m, 2H), 7.337–7.372 (m, 1H). ESI-MS: 193 $(M\text{-}NH_2)^-$.

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