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Reagent for Synthesis of Secondary Amines by Two Consecutive N-Alkylations and Its Application to Orthogonally Protected Spermidine†

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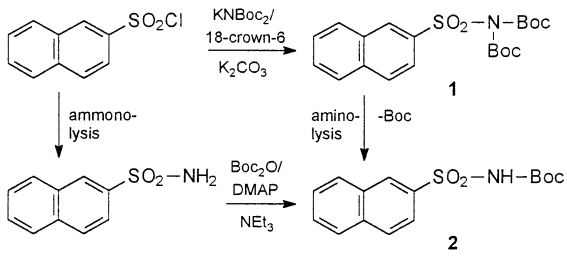
Abstract: A novel reagent, *tert*-butyl 2-naphthalenesulfonylcarbamate, has been designed to allow the stepwise synthesis of secondary aliphatic amines by two consecutive N-alkylations with intermediate Boc-cleavage and final desulfonylation under mild and experimentally convenient conditions. Its application was demonstrated to make an orthogonally protected spermidine derivative, suitable for further selective modification. Each individual step, including the final cleavage of 2-naphthalenesulfonyl to provide the secondary amine nitrogen, took place in high yield.

A very large number of procedures are now available for the synthesis of secondary aliphatic amines. Whereas in the majority of these cases free primary amines have been used as starting materials, protected derivatives of carbox- and sulfonamides, dialkylphosphoramidates, and carbamates, as well as others obtained by benzyl-, trityl- and silylation, have also been applied in this context.[1,2] Contrary to phthalimide,[3] the classical precursor for the synthesis of *primary* amines with a *divalent* protecting group on nitrogen, many other more recently developed reagents for this purpose with two *monovalent* orthogonal such groups[4] should in principle allow two subsequent alkylation steps to be performed, i.e., also synthesis of secondary amines. Among these reagents are imidodicarbonates and various acylcarbamates including phosphoramidates and sulfonylcarbamates,[5] many of which undergo facile alkylation and selective monodeprotection to give carbamates or the corresponding amides. Nevertheless, they have found limited application for direct double alkylation due to restrictions imposed in the second alkylation step or, alternatively, the need for harsh conditions for the final deprotection. This paper therefore addresses these issues.

SCHEME 1. Synthesis of 2-Ns-NH-Boc (2)



A major procedure to accomplish nitrogen alkylation by a primary or, especially, secondary alcohol is based on the Mitsunobu reaction,[6] which requires a relatively acidic nitrogen donor. Reagents of the imidodicarbonate type have been shown to be too weakly acidic, whereas sulfonylcarbamates proved to be more satisfactory in this context.[7,8] Ideally, sulfonamides may allow a second Mitsunobu reaction,[8−10] but as mentioned above, to be really useful they should allow deprotection under reasonably mild conditions afterward, which so far seems to be best fulfilled by the nitrobenzenesulfonyl group.[10] Recently, after systematic studies which included measuring the reduction potential of a large number of compounds by cyclic voltammetry, we came up with the 2-naphthalenesulfonyl group as a candidate for examination in this context.[11] 2-Naphthalenesulfonamides do not require sodium in liquid ammonia for reductive cleavage, which can be more conveniently accomplished by magnesium powder in methanol.[12] As a first step toward the exploration of this sulfonyl group for the synthesis of secondary amines by a double-alkylation approach, we have now prepared the reagent *tert*-butyl 2-naphthalenesulfonylcarbamate, 2-Ns-NH-Boc (**2**), the synthesis of which is outlined in Scheme 1.

The synthesis of **2** was performed in two steps. Initially, 2-Ns-Cl was reacted with the potassium salt of easily available di-*tert*-butyl imidodicarbonate.[13] Compounds such as **1**, a sulfonylimidodicarbonate, have to the best of our knowledge previously only been described in two patents.[14] By analogy with $NBoc_3$, **1** underwent facile *aminolysis* with cleavage of one Boc-group to give

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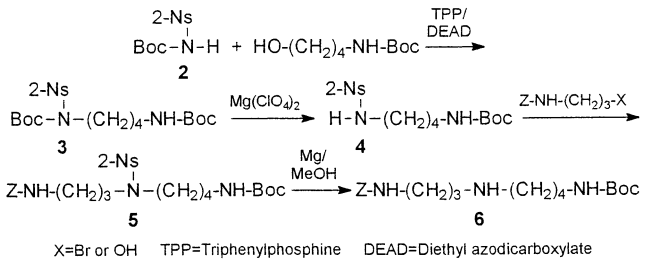
SCHEME 2. Synthesis of Protected Spermidines 5 and 6



2.[13d] This could also be prepared conveniently via the sulfonamide,[15] but in this experiment a small amount of N-*tert*-butylation was detected. Experimentally, both procedures are simple and go to completion. From compound **2** a stable, nonhygroscopic potassium salt can readily be prepared.

After several successful experiments starting from **2** had been performed, we decided to concentrate our efforts next on the polyamine spermidine, $H_2N-(CH_2)_3-NH-(CH_2)_4-NH_2$, which is known to be both involved in a variety of important biological functions and a component of alkaloids and toxins.[16] For the synthesis of substances of these types, selectively protected derivatives of spermidine are required and used.[16a,b] Several years ago, we converted spermidine to the N^1-Z,N^3-Boc-protected derivative by a multistep approach.[17] In Scheme 2, the synthesis of this substance (**6**) from the novel reagent **2** is outlined.

In the first step, the reagent **2** was condensed with 4-Boc-aminobutanol under Mitsunobu conditions to give the intermediate **3** in 97% yield. In the next step, by analogy with *tert*-butyl imidodicarbonates,[18] regiospecific sulfonylcarbamate cleavage could be effected by catalytic amounts of $Mg(ClO_4)_2$ without affecting the ordinary Boc-group on the other nitrogen. The resulting product **4** was obtained in 94% yield. This compound underwent alkylation under Mitsunobu conditions with 3-Z-aminopropanol in THF to give **5** in 60% yield. This figure is similar to those obtained by Weinreb et al. in Mitsunobu reactions with *N*-methyl-4-toluenesulfonamide,[8] but it could be raised to 94% or greater by alkylation with 3-Z-aminopropyl bromide instead, either with NaH as a base or under liquid−liquid phase-transfer catalysis conditions. The latter procedure turned out to be particularly attractive in this case. Finally, the 2-Ns-group of **5** was cleaved by magnesium in methanol to furnish **6** in 95% yield,[12] demonstrating practical reductive cleavage of 2-naphthalenesulfonyl for protection of amino functions.[11]

The physical and spectral data of **6** were in complete agreement with those of an authentic sample,[17] previously prepared by derivatization of commercial spermidine. The novel compound **5**, with its two additional classical protecting groups that can be manipulated at will and independently of the aromatic sulfonyl residue, should be useful for conjugation at N-1 and N-3 and, thus, useful together with **6** in future synthetic work.

From a synthetic and principle point of view, sulfonylcarbamates[8,19] and sulfonylimidodicarbonates are both interesting and useful. Therefore, when other sulfonyl protecting groups are required and suitable precursors become available, as long as bases and nucleophiles do not interfere with them, the sequence used to make **2** should be applicable. Also, as the corresponding N-15-labeled imidodicarbonate is readily available,[13d] a facile procedure for N-15 labeling is now also available.

Experimental Section

General Methods. Melting points are uncorrected. All solvents used as reaction media were of analytical quality and dried over molecular sieves (4 Å, activated at 320 °C overnight). Light petroleum refers to a fraction with a bp of 40−65 °C. All chemicals were of commercial grade and used as such, if not otherwise stated. Dry THF for the Mitsunobu syntheses was kept under argon. All glassware used were dried in a flame immediately before use, and all reactions were executed under dry argon. TLC analyses were performed on 0.25 mm thick precoated silica plates eluting with (A) 2:1 toluene/MeCN, (B) 19:1 CH_2Cl_2/Et_2O, (C) 19:1 CH_2Cl_2/MeOH, (D) 5:3:1:1 EtOAc/acetone/HOAc/water, or (E) 40:10:1 CH_2Cl_2/acetone/HOAc; spots were visualized by inspection under UV light and/or by Cl_2/dicarboxidine spray[20] and, for free amino compounds, also by ninhydrin spray. Preparative column chromatography was carried out on silica (70−230 mesh). IR spectra were recorded in KBr pellets. ^{1}H and ^{13}C specta were recorded at 400 and 100.4 MHz, respectively, in ~5% solution in $CDCl_3$ at 25 °C, when not otherwise stated. All shifts are given in parts per million using δ_H(TMS) = 0 and δ_C($CDCl_3$) = 77.02 as references.

Di-*tert*-butyl 2-naphthalenesulfonylimidodicarbonate (1). 2-Ns-Cl (2.82 g, 12.0 mmol) in CH_2Cl_2 (30 mL) was cooled in ice, and dry $KNBoc_2$[13e] (2.55 g, 10.0 mmol) was added in small portions with rapid stirring. The resulting slurry was treated with 18-crown-6 (264 mg, 1.00 mmol) in CH_2Cl_2 (3 mL). Finally, ground K_2CO_3 (276 mg, 2.00 mmol) was added in small portions, whereupon the mixture was stirred overnight. The turbid mixture was partitioned between Et_2O (150 mL) and 0.2 M citric acid (50 mL); ether was washed with 0.2 M citric acid, 1 M $NaHCO_3$, and brine (3 × each) and dried ($MgSO_4$). Evaporation furnished white solid **1** (2-$NsNBoc_2$, 3.87 g, 95%); essentially pure (TLC (A)), mp 119.5−120.5 °C (white needles from Et_2O/hexane). ^{1}H NMR: δ 1.48 (s, 18H), 7.63 and 7.68 (2 × dt, $J_1 \approx$ 7.5 Hz, $J_2 \approx$ 1 Hz, 1H + 1H), 7.93 and 8.00 (2 × perturbed d, $J \approx$ 8 Hz, 1H + 1H), 7.98 (d, J = 8.7 Hz, 1H), 8.07 (dd, J_1 = 8.7 Hz, J_2 = 1.9 Hz, 1H), 8.65 (pert d, J = 1.8 Hz, 1H). ^{13}C NMR (100.4 MHz): δ 27.55, 85.94, 123.07, 127.61, 127.96, 129.05, 129.41, 129.57, 130.80, 131.78, 135.41, 135.68, 147.66. FT IR ν (cm^{-1}): 1135, 1305, 1360, 1740, 1774, 2983. Anal. Calcd for $C_{20}H_{25}NO_6S$: C, 58.95; H, 6.18; N, 3.44. Found: C, 59.2; H, 6.2; N, 3.4.

***tert*-Butyl 2-naphthalenesulfonylcarbamate (2). (a) From 1.** Compound **1** (845 mg, 2.05 mmol) in MeCN (10 mL) was treated with 2-diethylaminoethylamine (302 mg, 2.60 mmol) and left overnight. Most of the solvent was evaporated and the oily residue redissolved in CH_2Cl_2 (50 mL) and then partitioned between EtOAc (200 mL) and 0.2 M citric acid (60 mL); EtOAc

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was washed with citric acid and brine as above and dried (Na_2SO_4). Evaporation furnished white solid **2**, which after careful trituration with light petroleum, was collected, rinsed, and dried; yield 612 mg (97%), pure by TLC (C,E), mp 170−173 °C dec (microcrystalline solid; from CH_2Cl_2/Et_2O). ^{1}H NMR: δ 1.36 (s, 9H), 7.34 (br s, 1H), 7.63 and 7.68 (2 × pert t, $J_1 \approx 7.5$ Hz, $J_2 \approx 1.5$ Hz, 1H + 1H), 7.94 (pert dd, $J_1 = 8.0$ Hz, $J_2 \approx 0.7$ Hz, 1H), 7.95−8.01 (sign overlap, ∼2H), 8.00 (pert dd, $J_1 = 8.9$ Hz, $J_2 \approx 0.6$ Hz, 1H), 8.61 (pert d, $J \approx 1$ Hz, 1H). ^{13}C NMR: δ 27.84, 84.23, 122.72, 127.65, 127.94, 129.21, 129.30, 129.48, 130.26, 131.86, 135.28, 135.67, 149.10. FT IR ν (cm^{-1}): 1128, 1142, 1343, 1745, 3234. Anal. Calcd for $C_{15}H_{17}NO_4S$: C, 58.62; H, 5.57; N, 4.56. Found: C, 58.8; H, 5.7; N, 4.6. **(b) From 2-Naphthalenesulfonamide.** Crude 2-Ns-NH_2 (12.85 g, 62.0 mmol) was suspended in CH_2Cl_2 (90 mL), and DMAP (756 mg, 6.2 mmol) and NEt_3 (6.89 g, 68.2 mmol) were added. The resulting mixture was treated dropwise with Boc_2O (14.89 g, 68.2 mmol) in CH_2Cl_2 (125 mL) with vigorous agitation (30 min). Evolution of CO_2 became brisk within a few min and gave a clear tan solution after 1 h. The next day, all starting material had been consumed (TLC (C,E)). Partitioning was performed with EtOAc and 0.2 M citric acid. The organic phase was washed with 0.2 M citric acid and brine (three times each) and dried (Na_2SO_4); the solid residue was carefully triturated with light petroleum, rinsed (five times), and dried under high vacuum; yield 18.31 g (96%), pure by TLC and suitable for further work. A recrystallized sample was identical in all respects to the product above. From the light petroleum used for trituration and rinsing of the crude product, a side product was isolated (See Supporting Information).

***N*^{1},*N*^{2}-Bis-*tert*-butyloxycarbonyl-*N*^{1}-2-naphthalenesulfonyl-1,4-diaminobutane (3).** A solution of **2** (738 mg, 2.40 mmol) and Boc-NH-$(CH_2)_4$-OH[21] (526 mg, ∼95%, 2.64 mmol) in THF (7 mL) was cooled in ice. Solid TPP (756 mg, 2.88 mmol) was added with thorough mixing followed by DEAD (0.511 mL, ∼3.12 mmol) at 0 °C over 20 min. After 1 h at 0 °C and 6 h at rt, reaction was complete (TLC (A,B)) and the solvent was stripped off. The oily residue was dissolved in CH_2Cl_2 (10 mL) and chromatographed on silica with 40:1 CH_2Cl_2/Et_2O as an eluent; yield of crude and chromatographically pure product 1.12 g (97%), mp 130.5−131.5 °C (white microcrystalline solid from Et_2O at −20 °C). ^{1}H NMR: δ 1.28 (s, 9H), 1.46 (s, 9H), 1.59 (pert m, $J \approx 7.3$ Hz, 2H), 1.85 (pert m, $J \approx 7.5$ Hz, 2H), 3.21 (br q, $J \approx 6$ Hz, 2H), 3.91 (t, $J = 7.5$ Hz, 2H), 4.65 (br sign, 1H), 7.62 and 7.67 (2 pert dt, $J_1 \approx 7$ Hz, $J_2 \approx 1.4$ Hz, 1H + 1H), 7.80 (dd, $J_1 = 8.7$ Hz, $J_2 = 1.9$ Hz, 1H), 7.92 (pert d, $J \approx 8$ Hz, 1H), 7.95 (d, $J = 8.5$ Hz, 1H), 7.97 (pert d, partly obscured, 1H), 8.50 (d, $J = 1.8$ Hz, 1H). ^{13}C NMR: δ 27.19, 27.50, 27.81, 28.41, 40.05, 46.83, 79.09, 84.31, 122.31, 127.65, 127.93, 128.99, 129.08, 129.24, 129.71, 131.74, 134.95, 137.08, 150.88, 155.95. FT IR ν (cm^{-1}): 1130, 1143, 1157, 1170, 1348, 1682, 1729, 3355. Anal. Calcd for $C_{24}H_{34}N_2O_6S$: C, 60.23; H, 7.16; N, 5.85**.** Found: C, 60.4; H, 7.2; N, 5.9.

***N*^{2}-*tert*-Butyloxycarbonyl-*N*^{1}-2-naphthalenesulfonyl-1,4-diaminobutane (4).** Recrystallized **3** (478 mg, 1.00 mmol) in MeCN (4 mL) was heated to 60 °C under N_2 and the solution treated with $Mg(ClO_4)_2$ (90 mg, 0.40 mmol) in portions and left under stirring. After 3 h, TLC (A,B) indicated that the reaction was about halfway complete and, after 15 h, virtually complete. The solvent was stripped off at reduced pressure, and the semisolid residue was dissolved in CH_2Cl_2 and partitioned between Et_2O and 1 M $KHSO_4$. The extract was washed in turn with 1 M $KHSO_4$, 1 M $NaHCO_3$, and brine (three times each), dried ($MgSO_4$) and evaporated; the solid residue was triturated with light petroleum, filtered, rinsed, and dried in vacuo; yield 356 mg (94%), pure by TLC (A), mp 85.5−86.5 °C (white fluffy needles from Et_2O at −20 °C). ^{1}H NMR: δ 1.41 (s, 9H), 1.43−1.55 (2 overlap m, 4H), 2.99 and 3.05 (2 pert t, 2H + 2H), 4.53 and 5.01 (2 br sign, 1H + 1H), 7.61 and 7.65 (2 pert dt, $J_1 \approx 7$ Hz, $J_2 \approx 1.5$ Hz, 1H + 1H), 7.84 (dd, $J_1 = 8.8$ Hz, $J_2 = 1.8$ Hz, 1H), 7.91 (pert dd, $J_1 \approx 8$ Hz, $J_2 \approx 1$ Hz, 1H), ∼7.96 (2 overlap d, $J \approx 8$ Hz, 1H + 1H), 8.44 (pert d, $J = 1.8$ Hz, 1H). ^{13}C NMR: δ 26.73, 27.25, 28.38, 39.84, 42.91, 79.29, 122.31, 127.54, 127.90, 128.39, 128.75, 129.22, 129.50, 132.16, 134.79, 136.73, 156.08. FT IR ν (cm^{-1}): 1162, 1331, 1527, 1686, 3227, 3370. Anal. Calcd for $C_{19}H_{26}N_2O_4S$: C, 60.29; H, 6.92; N, 7.40. Found: C, 60.4; H, 6.9; N, 7.4.

***N*^{1}-Benzyloxycarbonyl-*N*^{3}-*tert*-butyloxycarbonyl-*N*^{2}-2-naphthalenesulfonyl-spermidine (5). Phase Transfer-Induced Alkylation of Sulfonamide Function.** A mixture of compound **4** (757 mg, 2.00 mmol), chromatographed Z-NH-$(CH_2)_3$-Br[22] (653 mg, 2.40 mmol), and TBAHS (136 mg, 0.40 mmol) in benzene (10 mL) was treated with 50% NaOH (4 mL) with rapid stirring.[23] Traces of starting material remained after 4 h, but after 6 h, the reaction was completed (TLC (C)). After the mixture was diluted with CH_2Cl_2, the solution was partitioned between Et_2O and 1 M $KHSO_4$. The Et_2O extract was washed with 1 M $KHSO_4$, 1 M $NaHCO_3$, and brine (three times each), dried ($MgSO_4$), and evaporated; the sticky residue was triturated with light petroleum, filtered, repeatedly rinsed, and dried in vacuo; yield 1.13 g (98%), pure by TLC (C). A recrystallized specimen, mp 104−105 °C, was identical to an authentic sample (Supporting Information).

***N*^{1}-Benzyloxycarbonyl-*N*^{3}-*tert*-butyloxycarbonyl-spermidine (6).** To a suspension of **5** (1.14 g, 2.00 mmol) in dry MeOH (30 mL) was added Mg powder (0.15 g, 6.0 mmol) and the resulting slurry sonicated for 30 min,[11] when TLC (C,D) confirmed that most of the starting material had been consumed. The solvent was stripped off at reduced pressure; the residual sludge was partitioned between CH_2Cl_2 (150 mL) and 1:1 2 M NaOH/brine (300 mL) containing Na_2-EDTA (∼3.0 g, ∼8 mmol) and the aqueous layer further extracted with CH_2Cl_2 (2 × 75 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residual colorless viscous oil soon solidified upon trituration with light petroleum; the powder was collected by filtration, rinsed, and dried in vacuo, yield 723 mg (95%), essentially pure by TLC (D). ^{1}H NMR indicated that the product consisted of very pure title compound. The recrystallized product was identical to an authentic sample.[17]

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Supporting Information Available: Isolation of a side product and synthetic procedures for reference substances **4** and **5** and the potassium salt of **2**, as well as alternative procedures for synthesis of **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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