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N-(*tert*-Butoxycarbonyl)-*N*-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-ylsulfonyl]azanide: A New Sulfamoylating Agent. Structure and Reactivity toward Amines

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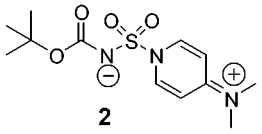
ABSTRACT



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Synthesis, structure, and reactivity toward amines of the new sulfamoylating reagent 2 are described. Compound 2 allowed sulfamoylation of amines under very mild conditions to give sulfamide derivatives in good yields.

The sulfamoyl moiety is an important structural element in numerous compounds of biological interest.[1] During our efforts toward efficient synthesis of sulfamide or sulfamate derivatives, we demonstrated that chlorosulfonyl isocyanate (CSI), the strongest bielectrophile, is the reagent of choice for the preparation of such compounds.[2] Previously, we demonstrated that according to the difference of reactivity between both the isocyanate and the chlorosulfonic acid group, it was possible to synthesize ab initio the unstable *N*-(*tert*-butoxycarbonyl)sulfamoyl chloride **1** (Scheme 1). This compound was allowed to react in a one-pot reaction with an amine or an alcohol to lead to a sulfamide or sulfamate derivatives.[1,2] This strategy has already been successfully applied in the synthesis of new anticancerous agents such as chloroethylnitrososulfamide[2] analogues of the chloroethylnitrosoureas.

The instability of compound **1** and the too strong reactivity of CSI limited the application of this methodology for introduction of a sulfamoyl moiety on polyfonctionnal compounds and its use in solid-phase synthesis of sulfamide (degradation of the resin by CSI).

These problems led us to develop a convenient means to access a sulfamide and to avoid the use of the sensitive intermediate **1**. Our approach was to try to stabilize compound **1** by treatment with (dimethylamino)pyridine (DMAP)

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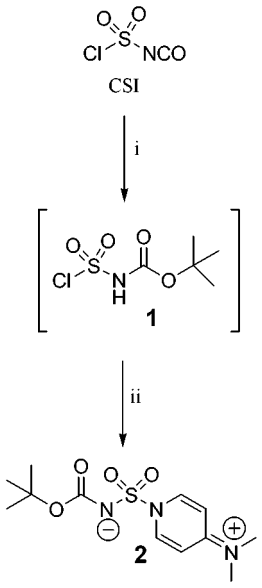
Scheme 1[a]



[a] Reagents and conditions: (i) *t*BuOH, CH_2Cl_2; (ii) DMAP, 2 equiv.

(Scheme 1). Indeed, DMAP is well-known for its remarkable properties in acyl[3] or sulfonyl transfer.[4] Moreover, some arylsulfonyl(dimethylamino)pyridinium salts are isolable and stable.[4] Thus, product **2**, *N*-(*tert*-butoxycarbonyl)-*N*-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-ylsulfonyl]-azanide, was obtained in good yield as colorless crystals, non-moisture sensitive, stable at ambient temperature.

The structure of the product **2** was elucidated using ^{1}H NMR spectroscopy, mass spectrometry,[5] and X-ray crystal crystallography.[6]

^{1}H NMR of compound **2** showed proton chemical shifts of the aromatic ring and dimethylamino groups which were more deshielded than those of DMAP. This result was in accordance with a structure in which the positive charge is on the nitrogen N_1. The X-ray analysis confirmed the zwitterionic structure of **2** (Figure 1). The structure found

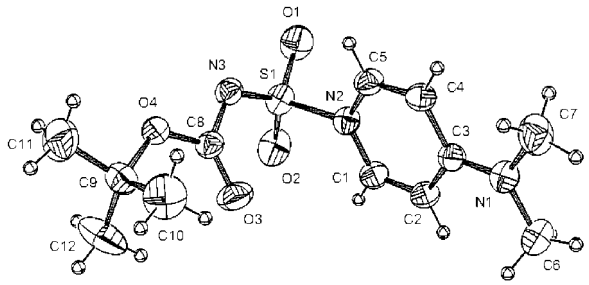


Figure 1. X-ray crystal structure of compound **2**.

gives a maximum distance between the two charges, which is favorable for the electronic stabilization of the molecule. All results were correlated by mass spectrometry, which showed a molecular ion at 301 Da.

It is worth pointing out the structural analogy between **2** and the Burgess reagent[12] (methyl *N*-(triethylammonium sulfonyl)carbamate), which also presents a zwitterionic form.

As delineated in Table 1, the newly developed reagent **2**

Table 1. Reactivity of **2** toward Diverse Amines

products[a]	amines	time, h	yield,[b] %
3a	butylamine	2	100
3b	4-methlcyclohexylamine	2	80
3c	benzylamine	4	90
3d	2-adamantanamine	4	88
3e	diisobutylamine	4	94
3f	diisopropylamine	4	78
3g	dibenzylamine	4	91
3h	aniline	12	50
3i	4-bromoaniline	12	35
3j	4-methoxyaniline	12	40

[a] The reactions were generally performed on a 0.3−0.5 mmol scale in 1.5 mL of CH_2Cl_2 using 1 equiv of compound **2** and 1 equiv of amine at room temperature. [b] Yield of isolated product.

was allowed to react with various amines and anilines in methylene chloride (Scheme 2). The reaction proceeds under

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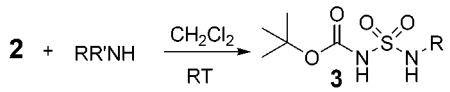
(5) **Typical procedure for synthesis of compound 2**: 1.2 mL (1 equiv) of CSI was added dropwise to a cold solution of *tert*-butyl alcohol (1.3 mL, 1 equiv) in anhydrous methylene chloride (10 mL). Then DMAP (3.45 g, 2 equiv) was added. The mixture was stirred for 1 h at room temperature and washed several times with water. The organic layer was dried on anhydrous sodium sulfate and concentrated in vacuo. The colorless powder was then crystallized from acetonitrile to afford compound **2** in 80% yield. Mp = 178−180 °C (acetonitrile); ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.5 (d, J = 7 Hz, 2H), 7.0 (d, J = 7 Hz, 2H), 3.2 (s, 6H), 1.2 (s, 9H); MS (FAB positive mode, NOBA), m/z 301 M^+, 302 $(M + H)^+$, 324 $(M + Na)^+$.

(6) Detailed X-ray crystallographic data are available free of charge on application to the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK. E-mail: deposit@ccdc.cam.ac.uk (for compound **2** CCDC # 162525). Compound **2**: $C_{12}H_{19}N_3O_4S$, M_r = 301.36, orthorhombic, $P2_12_12_1$, a = 10.4262(2), b = 10.4455(2), and c = 13.7652(3) Å, V = 1498.70(5) Å^3, Z = 4, D_x = 1.336 Mg·m^{-3}, λ(Mo Kα) = 0.71073 Å, μ = 2.32 cm^{-1}, F(000) = 640, T = 293 K. The sample (0.35 × 0.35 × 0.15 mm) was studied on a NONIUS Kappa CCD with graphite-monochromatized Mo Kα radiation. The cell parameters were obtained by following methods of Denzo and Scalepack[7] with 10 frames (psi rotation: 1° per frame). The data collection[8] ($2\theta_{max}$ = 60°, 143 frames via 2° ω rotation and 80 s per frame, range hkl h = 0.13, k = 0.13, l =0.17) gives 10682 reflections. The data reduction by the Denzo and Scalepack[7] methods leads to 1971 independent reflections from which 1860 have $I > 2.0\sigma(I)$. The structure was solved with SIR-97[9], which reveals the non-hydrogen atoms of structure. After anisotropic refinement, many hydrogen atoms can be determined using Fourier difference. The whole structure was refined using SHELXL97[10] by the full-matrix least-squares techniques (use of F square magnitude; x, y, z, β_{ij} for S, O, C, and N atoms, x, y, z in riding mode for H atoms; 182 variables and 1860 observations with $I > 2.0\sigma(I)$; calc $w = 1/[\sigma^2(F_o^2) + (0.085P)^2 + 0.10P]$ where $P = (F_o^2 + 2F_c^2)/3$ with the resulting R =0.036, R_w = 0.107, and S_w = 1.009 (residual around solvent molecules) $\Delta\rho$ < 0.18 e Å^{-3}). Atomic scattering factors are from *International Tables for X-ray Crystallography*, 1992. Ortep views were realized with PLATON98.[11] All the calculations were performed on a Pentium NT Server computer.

Scheme 2



very mild conditions at room temperature. The resulting products are easily isolable by flash chromatography on silica gel. The different sulfamides have been obtained in good yields after 2 or 4 h of reaction at room temperature, independent of the primary or secondary aliphatic amines used (**3a**−**3g**). When the reaction was performed with anilines (**3h**−**3j**), sulfamides were obtained in moderate yields after 12 h. No yield improvement was noted after thermal activation. The poor nucleophilic nature of the -NH_2 function in aniline derivatives can easily explain these results. Attempted reactions with a series of nitroanilines did not result in the isolation of the expected sulfamide.

In summary, we describe here the preparation and the structure of a new sulfamoylating reagent, **2**. Its reactivity toward amines demonstrates the great potential of this compound in the synthesis of sulfamides.

Thus, the scope of the reaction (Scheme 2) is broad because any primary or secondary aliphatic amine can be converted into a sulfamide by performing a simple and straightforward synthesis in very mild conditions. Moreover, the reactivity of compound **2** toward different nucleophiles is currently in progress and will be reported in due course.

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Supporting Information Available: Analytical data of sulfamides **3a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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