ORGANIC LETTERS

2001
Vol. 3, No. 26
4247−4249

# Highly Selective Synthesis of Heterosubstituted Aromatic Sulfamides

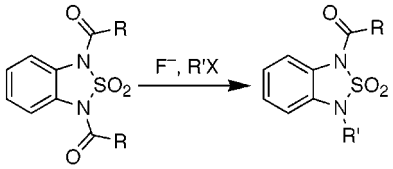
**Fraser Hof, Peter M. Iovine, Darren W. Johnson, and Julius Rebek, Jr.***

*The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, MB-26, La Jolla, California 92037*

*jrebek@scripps.edu*

**Received October 29, 2001**

## ABSTRACT




**The sulfamide functional group is increasingly relevant in both medicinal and supramolecular chemistry, yet few selective synthetic steps are available for its elaboration. We report here a mild, general, and efficient method for the selective differentiation of *N*-atom substituents of aromatic sulfamides.**

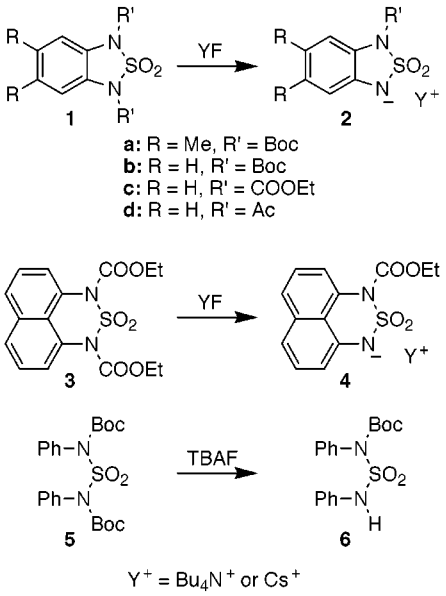
Sulfamides have enjoyed growing popularity in the field of medicinal chemistry as nonhydrolyzable components in peptidomimetics,[1] as well as active components in epinephrine analogues,[2] agonists of the 5-$HT_{1D}$ receptor (regulating serotonin levels),[3] and HIV protease inhibitors.[4,5] They have also recently enjoyed increasing representation in the field of supramolecular chemistry.[6−12] Reasonable synthetic routes exist for symmetric *N*,*N*′-substituted sulfamides;[13,14] however, syntheses of nonsymmetric *N*,*N*′-substituted sulfamides rely on low-yielding synthetic steps that are neither general nor selective.[15,16] We report herein a synthetically simple, mild, and efficient procedure for the generation of nonsymmetric aromatic sulfamides.

*N*,*N*′-Diacyl-protected sulfamides are easily prepared synthetic intermediates en route to elaborated sulfamides.[7,9,12,15] In the course of our investigations on the molecular recognition of sulfamides, we were surprised to discover that treatment of *N*,*N*′-di-(*tert*-butoxycarbonyl)-protected sulfamide **1a** with tetrabutylammonium fluoride (TBAF) led to the rapid (<10 min) and highly selective (>95%) production of the monoacyl protected anion **2a** as the tetrabutylammonium salt (Scheme 1). Since no selective and general transformation for the *N*-atom differentiation of sulfamides could be found in the literature, we set out to explore the scope of the reaction.[17] The results are summarized in Table 1.

(1) Dougherty, J. M.; Probst, D. A.; Robinson, R. E.; Moore, J. D.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron* **2000**, *56*, 9781−9790.
(2) Acheson, R. M.; Bite, M. G.; Kemp, J. E. G. *J. Med. Chem.* **1981**, *24*, 1300−1304.
(3) Castro, J. L.; Baker, R.; Guiblin, A. R.; Hobbs, S. C.; Jenkins, M. R.; Russell, M. G. N.; Beer, M. S.; Stanton, J. A.; Scholey, K.; Hargreaves, R. J.; et al. *J. Med. Chem.* **1994**, *37*, 3023−3032.
(4) Bäckbro, K.; Löwgren, S.; Österlund, K.; Atepo, J.; Unge, T.; Hultén, J.; Bonham, N. M.; Schaal, W.; Karlén, A.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 898−902.
(5) Hultén, J.; Bonham, N. M.; Nillroth, U.; Hansson, T.; Zuccarello, G.; Bouzide, A.; Åqvist, J.; Classon, B.; Danielson, U. H.; Karlén, A.; et al. *J. Med. Chem.* **1997**, *40*, 885−897.
(6) Gong, B.; Zheng, C.; Skrzypczak-Jankun, E.; Yan, Y.; Zhang, J. *J. Am. Chem. Soc.* **1998**, *120*, 11194−11195.
(7) Martín, T.; Obst, U.; Rebek, J., Jr. *Science* **1998**, *281*, 1842−1845.
(8) Gong, B.; Zheng, C.; Zeng, H.; Zhu, J. *J. Am. Chem. Soc.* **1999**, *121*, 9766−9767.
(9) Nuckolls, C.; Hof, F.; Martín, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 10281−10285.
(10) Gong, B.; Zheng, C.; Skrzypczak-Jankun, E.; Zhu, J. *Org. Lett.* **2000**, *2*, 3273−3275.
(11) Hof, F.; Nuckolls, C.; Craig, S. L.; Martín, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 10991−10996.
(12) Hof, F.; Nuckolls, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 4251−4252.
(13) Ohme, R.; Preuschhof, H. *Justus Liebigs Ann. Chem.* **1968**, *713*, 74−86.
(14) McDermott, S. D.; Spillane, W. J. *Org. Prep. Proced. Int.* **1984**, *16*, 49−77.
(15) Nodelman, N.; Martin, J. C. *J. Am. Chem. Soc.* **1976**, *98*, 6597−6608.
(16) Burke, P. O.; McDermott, S. D.; Hannigan, T. J.; Spillane, W. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1851−1854.

10.1021/ol0169731 CCC: $20.00 
**Published on Web 12/04/2001**

**Scheme 1**[a]




[a] Products isolated after workup with aqueous $NH_4Cl$.

We have developed two simple, mild, and efficient synthetic procedures to generate *N*-centered monoanionic species from diacylated sulfamides. Method A involves treatment of a 0.05 M solution of the *N*,*N*′-diacylated sulfamide with TBAF in THF whereas method B employs CsF as the fluoride source and DMF as the reaction solvent. The low solubility of CsF in DMF (method B) results in a slower reaction with slightly decreased yields relative to those of method A. In both cases, partitioning the crude reaction mixture between aqueous ammonium chloride and ethyl acetate is sufficient to give pure monodeprotected products with isolated yields in excess of 80%.

**Table 1.** Selective Monodeprotection of *N*,*N*′-Diacylsulfamides Mediated by Fluoride

| starting material | method[a] | product | time (min) | yield[b] (%) |
|---|---|---|---|---|
| **1a** | A | **2a** $Bu_4N^+$ | 10 | 96 |
| | B | **2a** $Cs^+$ | 90 | 81 |
| **1b** | A | **2b** $Bu_4N^+$ | 10 | 100 |
| | B | **2b** $Cs^+$ | 90 | 81 |
| **1c** | A | **2c** $Bu_4N^+$ | 10 | 99 |
| | B | **2c** $Cs^+$ | 20 | 80 |
| **1d** | A | **2d** $Bu_4N^+$ | 10 | 100 |
| | B | **2d** $Cs^+$ | 10 | 81 |
| **3** | A | **4** $Bu_4N^+$ | 10 | 86 |
| | B | **4** $Cs^+$ | 20 | 79 |
| **5** | A[c] | **6** | 1400 | 98 |
| | B | | 1400 | NR |

[a] All reactions were carried out with 0.25 mmol of starting material in 5 mL of solvent. Method A: 3 equiv of TBAF in THF, room temperature. Method B: 5 equiv of CsF in DMF, room temperature. [b] Isolated yields after aqueous workup without further purification (see text). [c] 5 equiv of TBAF were required for complete conversion.

The scope of the reaction was probed by examining the reactivity of a variety of aromatic sulfamide carbamates upon treatment with fluoride (Scheme 1). In all cases, treatment of the substrates with fluoride gave exclusively the monoanionic species in high yield. Surprisingly, even the relatively inert acetamide protecting group (compound **1d**) was selectively deprotected in the presence of fluoride. All acyl groups tested resulted in equally high yields and high selectivity (Table 1).

The X-ray structures of ethyl carbamate protected starting material **1c** and product **2c** are shown in Figure 1 and unambiguously verify the elemental composition and structure of the compounds.[18] The presence of a tetrabutylammonium cation (not shown) cocrystallized with **2c** confirms that the product is isolated as an anionic species.

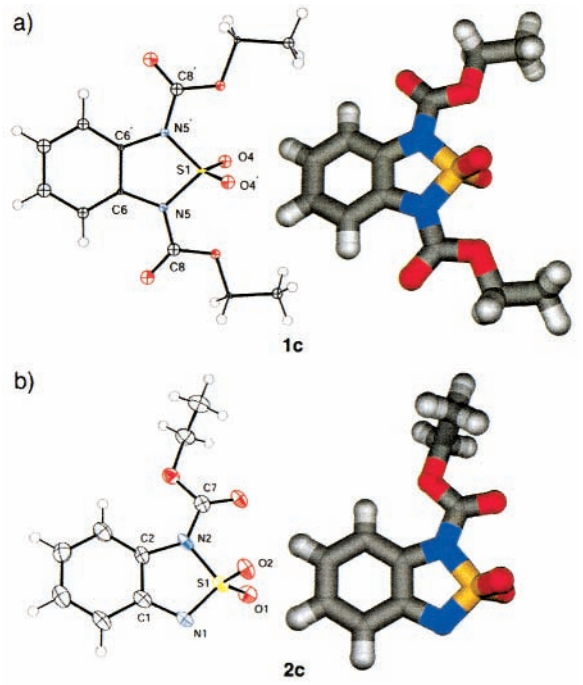


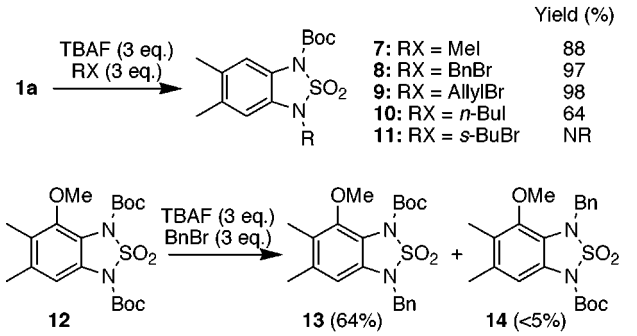

**Figure 1.** (a) Crystal structure of **1c** (ORTEP view with 50% thermal ellipsoids). Primes signify symmetry-equivalent atoms. Selected bond distances and angles (Å, deg): S1−O4 1.417(5), S1−N5 1.685(5), N5−C8 1.417(8), N5−C6 1.414(9), N5−S1−N5′ 90.6(4). (b) Crystal structure of **2c** anion (ORTEP view with 50% thermal ellipsoids, the tetrabutylammonium countercation is omitted for clarity). Selected bond distances and angles (Å, deg): S1−N1 1.555(4), S1−N2 1.737(4), N1−C1 1.389(6), N2−C2 1.428(6), N2−C7 1.389(6), N1−S1−N2 96.6(2).

(17) For a selective, yet specific example of this type of reaction see: Dewynter, G.; Abdaoui, M.; Toupet, L.; Montero, J.-L. *Tetrahedron Lett.* **1997**, *38*, 8691−8694.

(18) (a) $C_{12}H_{14}N_2O_6S$, **1c**: thin colorless plate, crystal size 0.10 × 0.10 × 0.02 mm, FW = 314.31, $T$ = −153 °C, monoclinic space group *C*2/*c*, $a$ = 14.877(1) Å, $b$ = 8.8583(5) Å, $c$ = 11.1192(7) Å, $\beta$ = 111.004(3)°, $V$ = 1368.0(2) Å$^3$, $Z$ = 4, $R1$ = 0.115, w$R2$ = 0.290, GOF = 1.447. (b) $C_{25}H_{45}N_3O_4S$, **2c**: thin colorless plate, crystal size 0.39 × 0.13 × 0.01 mm, FW = 483.70, $T$ = −155 °C, monoclinic space group $P2_1$, $a$ = 8.3003(5) Å, $b$ = 13.8825(8) Å, $c$ = 11.6167(7) Å, $\beta$ = 97.160(3)°, $V$ = 1328.1(1) Å$^3$, $Z$ = 2, $R1$ = 0.052, w$R2$ = 0.130, GOF = 1.022. Data were also collected for **1b**. See Supporting Information for full experimental details on all structures.

The highly stable anionic products proved to be excellent substrates for a variety of alkylating reactions. It therefore seemed advantageous to leverage this stability into a one-pot monodeprotection and alkylation reaction sequence. Treatment of compound **1a** with TBAF in the presence of a variety of alkylating agents selectively yields the mono-alkylated products in good yield with little or no purification (Scheme 2). Unactivated primary alkyl bromides give modest

**Scheme 2**




yields of 30−40%, while only trace product formation is observed when using secondary alkyl bromides. Activated alkylating reagents such as benzyl bromide, allyl bromide, and iodomethane give the desired product in high yield (>88%), while unactivated primary alkyl iodides result in moderate yields (60−70%). The one-pot reaction is not limited to *N*,*N*′-di-(*tert*-butoxycarbonyl)-protected sulfamides. Rather, high-yielding deprotection-alkylation is also observed for *N*,*N*′-diethylcarbamates as well as *N*,*N*′-diacetamides (results not shown). The electronic influence of substituents upon the reaction is demonstrated by treatment of compound **12** with TBAF and benzyl bromide (Scheme 2). Compound **13** is produced in >12:1 excess over product **14**, showing a bias against formation and subsequent alkylation of the resonance-destabilized isomeric anion.

The role of base and/or adventitious water in the deprotection reaction was examined by subjecting compound **1a** to a variety of other basic reaction conditions. A 24-h exposure of **1a** to NaH/DMF, LiOH/$H_2O$/THF, diisopropylethylamine/DMAP/THF, or tetrabutylammonium chloride/DMF resulted in little or no reaction. Even in cases where low reactivity was observed, these conditions did not yield selectivity comparable to that of the fluoride-mediated reaction. This lack of selectivity and/or reactivity in the above experiments, combined with the exclusive monoanionic product formation obtained under anhydrous conditions (method B), suggests, albeit tentatively, that the reaction is *not* simply a hydrolysis mediated by the basic fluoride reagents and adventitious water. Since fluoride is the only active nucleophilic species under rigorously anhydrous conditions, the most likely mechanism for the deacylation reaction is nucleophilic attack of fluoride anion at the extremely electron deficient acyl group.

The fluoride-induced cleavage of one acyl group of the sulfamide results in a highly stabilized α-monoanion, reminiscent of the α-anion stabilization observed in carbon sulfone analogues.[19] Negative charge on the sulfamide nitrogen is also stabilized by the neighboring aromatic groups and *N*-acyl sulfamide. The cyclic anions are especially well stabilized—the p$K_a$ of the conjugate acid of cyclic product **1d** is 3.40,[16] while the p$K_a$ of acyclic product **6** can be estimated at 7−9. The stability of the monoanionic products relative to the electron deficient diacyl sulfamide starting materials likely provides the thermodynamic driving force for the reaction, whereas the high stability of the monoanion relative to the dianion provides the selectivity for a single deprotection. The stabilized sulfamide anion inhibits further nucleophilic attack even in the presence of excess fluoride. That treatment of alkylated products such as **7** with fluoride results in no significant reaction after 24 h suggests that the presence of a charged center is not necessary to discourage further nucleophilic attack. The mere absence of the electron withdrawing effects of *two* acyl groups is sufficient to stop the reaction at the stage of monodeprotection.

The selective transformation of symmetric *N*,*N*′-substituted sulfamides into *N*-differentiated sulfamides described in this work utilizes mild reagents that are prized for their functional group compatibility.[20] The reaction proceeds in a highly selective manner, generating exclusively monodeprotected sulfamides while remaining general for a wide variety of aromatic sulfamide and protecting group combinations. As such, this reaction is uniquely positioned to advance the synthesis of complex aromatic sulfamides. Since the reaction proceeds rapidly and the products require little or no purification, this reaction should also prove useful in the generation of libraries of molecular diversity based on the pharmacologically important sulfamide scaffold.

**Acknowledgment.** This research was supported by the NIH and the Skaggs Institute for Chemical Biology. F.H. thanks NSERC for fellowship support, and P.M.I. thanks the Skaggs Institute for fellowship support. The authors thank Prof. Ian Wilson for use of the X-ray diffractometer and Dr. Xiaoping Dai for expert assistance with X-ray diffractometer configuration and data collection.

**Supporting Information Available:** Complete experimental procedures and characterization ($^1$H NMR, $^{13}$C NMR, and HRMS) for all new compounds, as well as experimental procedures for X-ray structure determination of compounds **1b**, **1c**, and **2c** $Bu_4N^+$. This material is available free of charge via the Internet at http://pubs.acs.org. All crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 173849 (**1b**), 173847 (**1c**), and 173848 (**2c** $Bu_4N^+$). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax int. code + (1223)336-033; email deposit@chemcrys.cam.ac.uk).

OL0169731

(19) In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: New York, 1979; Vol. 3, pp 171−197.

(20) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549−2550.