

With compliments of the Author

Nucleophilic Aromatic Substitution on 4-Fluorophenylsulfonamides: Nitrogen, Oxygen, and Sulfur Nucleophiles

Elena Badetti, Marcial Moreno-Mañas,* Roser Pleixats, Rosa M. Sebastián, Anna Serra, Roger Soler, Adelina Vallribera

Department of Chemistry, Universitat Autònoma de Barcelona, Cerdanyola, 08193 Barcelona, Spain
Fax +34(9)35811254; E-mail: marcial.moreno@uab.es

Received 10 November 2004

Abstract: Improved conditions are reported for the stoichiometric reaction of nitrogen, oxygen, and sulfur nucleophiles with weakly activated 4-fluorophenylsulfonamides.

Key words: nucleophilic aromatic substitution, phase transfer catalysis, cesium, macrocycles, diaryl oxides, diarylamines

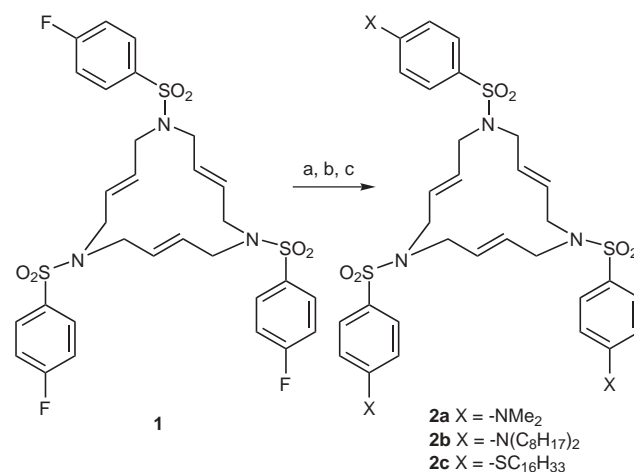
In the course of a project we sought substitution of fluorine with nucleophiles in triolefinic macrocycle **1** (Scheme 1).^{1,2} Large excesses of nucleophiles and harsh experimental conditions were required. This solution is not applicable to reactions of more valuable nucleophiles when only one mol of nucleophile per fluorine atom is preferred. Milder experimental conditions are also desirable.

Whereas nucleophilic aromatic substitution (S_NAr) on 4-nitrofluoroaromatics is a reaction of broad applicability,⁴ activation by electron-acceptor functional groups other than nitro has met with less success. This is a consequence of the decreased ability to stabilize the negative charge in the intermediate anion formed along S_NAr processes. The stabilizing power can be estimated from the σ_p^- values of the different groups: $-NO_2$ (1.27), $-SO_2-CH_3$ (1.13), and $-SO_2-NMe_2$ (0.99).⁵ Therefore it is not surprising that reports on replacement of fluorine on aromatic sulfones with nitrogen,⁶ oxygen,⁷ or sulfur⁸ nucleophiles are scarce. In these cases either large excess of nucleophiles, or severe experimental conditions, or both had to be introduced. Examples of such a reaction on 4-fluorophenylsulfonamides are even more rare.^{1,9}

We endeavored to find improved methods to perform S_NAr reactions on aromatic fluorosulfonamides choosing sulfonamide **3** as a model.¹⁰

We report here that fluorine can be exchanged in compound **3** with a variety of primary and secondary aliphatic and aromatic amines (Table 1) through their lithium amides formed with butyllithium in THF (method A).^{11,12} Thus, hexylamine, di-*n*-octylamine, and diethylamine react to afford **4a,b,d** in good yields (entries 1, 2, and 5). However, laurylamine did not react under conditions of method A. Nevertheless, reaction did occur in hot

DMF in the presence of potassium carbonate (method B) to afford **4c** (entries 3 and 4). Aniline and a *N*-substituted aniline, 4-chloro-*N*-methylaniline, were also active under method A (entries 6 and 7), diarylamines **4e,f** being isolated in reasonable yields. Finally, 1-aza-18-crown-6 gave **4g** (entry 8). Stoichiometric amounts or only slight excesses (1.2 molar) of amine were used in all cases. Cyclohexylamine and diphenylamine were inert under all tested conditions. Addition of tetramethylethylenediamine (TMEDA) did not improve the results. Even in one case, when working with di-*n*-octylamine, a small amount of **4** ($R^1 = R^2 = CH_3$) was isolated. Dimethylamine required for the formation of this by-product must come from TMEDA under BuLi initiation as suggested by one referee. Therefore this additive was not considered further.



Scheme 1 a) Excess 2 M HNMe₂ in THF, 100 °C, 6 d in closed reactor; b) excess HN(C₈H₁₇)₂, THF, 170 °C, 2 months in closed reactor; c) HSC₁₆H₃₃ (3-fold molar excess), K₂CO₃, DMSO, 100 °C, 2 d.³

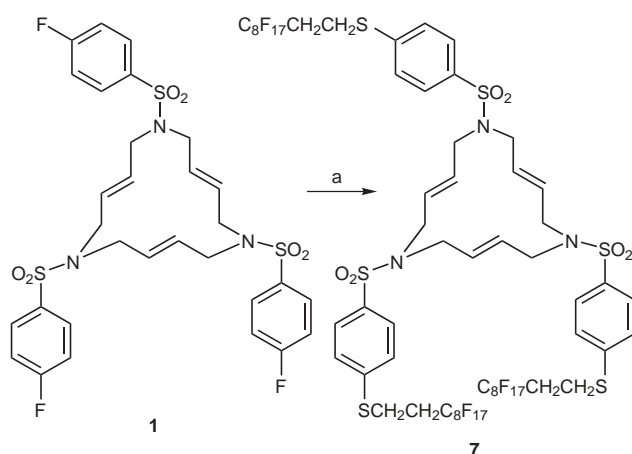
Oxygen nucleophiles react with **3** (Scheme 2 and Table 2) to afford the corresponding ethers. Thus, three aliphatic alcohols as well as phenol gave ethers **5a–d** in good yields when their sodium salts (HNa in THF) were treated with **3** (entries 1, 3–5, Table 2). We noticed that addition of tetrabutylammonium chloride (method C) improved the result. In theory the ammonium salt could be used in substoichiometric amounts since it is a catalyst. Indeed, formation of sodium chloride generates the quaternary salts Bu₄N(RX) which, upon reaction, regenerate the quaternary salt in the form of fluoride. We never made attempts to

Table 2 Replacement of Fluorine in Sulfonamides **1** and **3** with Oxygen and Sulfur Nucleophiles^a

Entry	Yield of 5–7 (%)	X-R	Bu ₄ NCl (mol)	Mp (°C)	Method
1	5a (61)	O-C ₄ H ₉	1	60–62	C
2	5b (83)	O-C ₁₂ H ₂₅	1	33–35	D
3	5b (80) ^b	O-C ₁₂ H ₂₅	1	– ^b	C
4	5c (76)	O-CH ₂ CH(Et)-C ₄ H ₉	1	Oil	C
5	5d (83)	O-Ph	1	80–82	C
6	6a (87)	S-C ₃ H ₇	0.01	59–61	C
7	6b (81)	S-C ₁₆ H ₃₃	0.06	41–43	C
8	6c (73)	S-Ph	1	63–66	C
9	6c (61)	S-Ph	1	63–66	D
10	6d (80) ^b	S-CH ₂ CH ₂ -C ₈ F ₁₇	1	56–58	C
11	6d (84)	S-CH ₂ CH ₂ -C ₈ F ₁₇	0.01	56–58	D
12	7 (95)	S-CH ₂ CH ₂ -C ₈ F ₁₇	0.1	187–192	D

^a Method C: NaH. Method D: Cs₂CO₃. In both methods: Bu₄NCl, THF.

^b Conversion. Product not isolated.



Scheme 3 Triple substitution. a) HSCH₂CH₂C₈F₁₇ (4.2 mol); conditions D.

References

- Moreno-Mañas, M.; Spengler, J. *Tetrahedron* **2002**, *58*, 7769.
- For reviews on 15-membered triolefinic macrocycles of type **1** see: (a) Moreno-Mañas, M.; Pleixats, R.; Sebastián, R. M.; Vallribera, A.; Roglans, A. *ARKIVOC* **2004**, *iv*, 109; available from <http://www.arkat-usa.org>. (b) Moreno-Mañas, M.; Pleixats, R.; Sebastián, R. M.; Vallribera, A.; Roglans, A. *J. Organomet. Chem.* **2004**, *689*, 3669.
- Compound **2a** (72%): mp 230 °C. Compound **2b** (40%): oil. Compound **2c** (65%): mp 84–85 °C.
- March, J. *Advanced Organic Chemistry. Reactions, Mechanism, and Structure*, 4th ed.; Wiley-Interscience: New York, **1992**, Chap. 13, 641–676.
- Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
- (a) Navidpour, L.; Karimi, L.; Amini, M.; Vosooghi, M.; Shafiee, A. *J. Heterocycl. Chem.* **2004**, *41*, 201. (b) Wang, C.-C.; Li, J. J.; Huang, H.-C.; Lee, L. F.; Reitz, D. B. *J. Org. Chem.* **2000**, *65*, 2711. (c) You, F.; Twieg, R. J. *Tetrahedron Lett.* **1999**, *40*, 8759. (d) Smith, W. J.; Scott Sawyer, J. *Tetrahedron Lett.* **1996**, *37*, 299. (e) Miller, A. O.; Furin, G. G. *J. Fluorine Chem.* **1995**, *75*, 169.
- (a) Koyama, H.; Boueres, J. K.; Han, W.; Metzger, E. J.; Bergman, J. P.; Gratale, D. F.; Miller, D. J.; Tolman, R. L.; MacNaul, K. L.; Berger, J. P.; Doebber, T. W.; Leung, K.; Moller, D. E.; Heck, J. V.; Sahoo, S. P. *Biorg. Med. Chem. Lett.* **2003**, *13*, 1801. (b) Zask, A.; Jirkovsky, I.; Nowicki, J. W.; McCaleb, M. L. *J. Med. Chem.* **1990**, *33*, 1418. (c) Markley, L. D.; Tong, Y. C.; Dulworth, J. K.; Steward, D. L.; Goralski, C. T.; Johnston, H.; Wood, S. G.; Vinogradoff, A. P.; Bargar, T. M. *J. Med. Chem.* **1986**, *29*, 427. (d) Idoux, J. P.; Madenwald, M. L.; Garcia, B. S.; Chu, D.-L.; Gupton, J. T. *J. Org. Chem.* **1985**, *50*, 1876.
- Baxter, I.; Ben-Haida, A.; Colquhoun, H. M.; Hodge, P.; Kohnke, F. H.; Williams, D. J. *Chem.-Eur. J.* **2000**, *6*, 4285.
- For examples with nitrogen nucleophiles see: (a) Pal, M.; Madan, M.; Padakanti, S.; Pattabiraman, V. R.; Kalleda, S.; Vanguri, A.; Mullangi, R.; Rao Mamidi, N. V. S.; Casturi, S. R.; Malde, A.; Gopalakrishnan, B.; Yeleswarapu, K. R. *J. Med. Chem.* **2003**, *46*, 3975. (b) Tollefson, M. B.; Kolodziej, S. A.; Fletcher, T. R.; Vernier, W. F.; Beaudry, J. A.; Keller, B. T.; Reitz, D. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3727. (c) Levin, J. I.; Chen, J. M.; Cheung, K.; Cole, D.; Crago, C.; Delos Santos, E.; Du, X.; Khafizova, G.; MacEwan, G.; Niu, C.; Salaski, E. J.; Zask, A.; Cummons, T.; Sung, A.; Xu, J.; Zhang, Y.; Xu, W.; Ayral-Kaloustian, S.; Jin, G.; Cowling, R.; Barone, D.; Mohler, K. M.; Black, R. A.; Skotnicki, J. S. *Biorg. Med. Chem. Lett.* **2003**, *13*, 2799. (d) Steffan, R. J.; Ashwell, M. A.; Solvibile, W. R.; Matelan, E.; Largis, E.; Han, S.; Tillet, J.; Mulvey, R. *Biorg. Med. Chem. Lett.* **2002**, *12*, 2963. (e) Morgan, T. K. Jr.; Lis, R.; Lumma, W. C. Jr.; Nickisch, K.; Wohl, R. A.;

Phillips, G. B.; Gomez, R. P.; Lampe, J. W.; Di Meo, S. V.; Marisca, A. J.; Forst, J. *J. Med. Chem.* **1990**, *33*, 1091.

(f) For example with oxygen nucleophile see: Levin, J. I.; Du, M. T. *Synth. Commun.* **2002**, *32*, 1401. (g) For example with sulfur nucleophile see ref. 9c.

(10) Compound **3**, mp 39–40 °C, was prepared by reaction of 4-fluorobenzenesulfonyl chloride with diethylamine in CH₂Cl₂.

(11) **Method A of Table 1. Typical Experiment:**

A 1.6 M solution of *n*-BuLi in hexane (3.4 mL, 5.34 mmol) was added dropwise into a solution of di-*n*-octyl amine (1.1 mL, 3.56 mmol) in anhyd THF (3 mL) cooled at –40 °C (MeCN–liquid nitrogen bath). The mixture was stirred at –40 °C for 15 min. Then, a solution of sulphonamide **3** (0.82 g, 3.56 mmol) in anhyd THF (5 mL) was added. The mixture was stirred at r.t. for one day and evaporated. The residue was partitioned between CHCl₃ and diluted HCl, the organic layer was dried (Na₂SO₄) and evaporated to afford 1.6 g (ca. 100%) of **4b** as an ochre oil. IR (Attenuated Total Reflectance, ATR): 2924, 2853, 1594, 1333, 1147 cm⁻¹. ¹H NMR (250 MHz, CDCl₃): δ = 0.88 (t, *J* = 6.6 Hz, 6 H), 1.12 (t, *J* = 7.2 Hz, 6 H), 1.29 (m, 20 H), 1.57 (m, 4 H), 3.18 (q, *J* = 7.2 Hz, 4 H), 3.26 (t, *J* = 7.1, 4 H), 6.56 (d, *J* = 9.1 Hz, 2 H), 7.57 (d, *J* = 9.1 Hz, 2 H). ¹³C NMR (62.5 MHz, CDCl₃): δ = 14.2, 14.4, 22.7, 27.2, 29.4, 29.5, 31.9, 42.1, 51.1, 110.5, 124.7, 129.1, 150.8. Anal. Calcd for C₂₆H₄₈N₂O₂S: C, 68.98; H, 10.69; N, 6.19; S, 7.08. Found: C, 68.79; H, 10.69; N, 6.05; S, 6.74.

Good elemental analyses (at least three elements) were secured for **4b, c, e–g** (with 0.5 mol of H₂O), and **4d** (as picrate, mp 109–110 °C). Product **4a**: HRMS: *m/z* calcd for C₁₆H₂₈N₂O₂S: 312.1871; found: 312.1867.

(12) When our work was finished a paper was published on similar results obtained with 2-fluoropyridine: Pasumansky, L.; Hernández, A. R.; Gamsey, S.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **2004**, *45*, 6417.

(13) **Method C of Table 2; Typical Experiment**

A solution of **3** (1.05 g, 4.55 mmol) and tetrabutylammonium chloride (1.52 g, 5.2 mmol) in anhyd THF (5.5 mL) was added under argon via cannula to a stirred suspension of sodium phenolate in anhyd THF (4 mL), made from NaH (60% suspension in mineral oil, 0.30 g, 7.55 mmol) and phenol (0.52 g, 5.52 mmol). The mixture was stirred overnight and MeOH (2 mL) was added. The solvents were evaporated and the residue was taken in EtOAc. The organic solution was washed with 5% aq NaOH, dried (Na₂SO₄), and evaporated to afford a dark yellow oil that crystallized upon standing (83%). It was recrystallized from *t*-butyl methyl ether to afford pure **5d** (52%); mp 80–82 °C. IR (ATR): 3090, 2972, 2932, 2879, 1579, 1491, 1332, 1238, 1200, 1169, 1089, 1014, 934 cm⁻¹. ¹H NMR (250 MHz, CDCl₃): δ = 1.14 (t, *J* = 7.0 Hz, 3 H), 3.23 (q, *J* = 7.0 Hz, 4 H), 7.02 (d, *J* = 9.0 Hz, 2 H), 6.94–7.08 (m, 2 H), 7.21 (tt, *J* = 6.9 and 1.2 Hz, 1 H), 7.40 (m, 2 H), 7.75 (d, *J* = 9.0 Hz, 2 H). ¹³C NMR (62.5 MHz, CDCl₃): δ = 14.2, 42.0, 117.6, 120.2, 124.8, 129.1, 130.1, 134.2, 155.3, 161.1. HRMS calcd for C₁₆H₁₉NO₃S: 305.1086; found: 305.1100.

Good elemental analyses (at least three elements) were secured for **5a–c, 6a–d**, and **7**.

(14) For recent examples on the use of cesium compounds in related substitutions see the following references.

(a) CsOH: Varala, R.; Ramu, E.; Alam, M. M.; Adapa, S. R. *Synlett* **2004**, 1747. (b) Cs₂CO₃: Cui, S.-L.; Jiang, Z.-Y.; Wang, Y.-G. *Synlett* **2004**, 1829.