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Deprotection of 2-nitrobenzenesulfonamides using fluorous and solid phase reagents

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Abstract—The 2-nitrobenzenesulfonyl group was efficiently removed from primary and secondary amines as well as amides with a perfluorinated thiol under mild conditions. The resulting perfluorinated byproduct was removed via a solid phase extraction through perfluorinated silica gel making this a fast and simple procedure for parallel deprotection.
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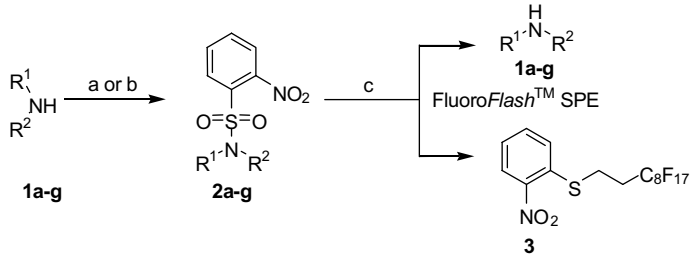
The monoalkylation of primary amines is a simple, yet challenging transformation, and many solutions to this problem have been reported. Very often this has involved protection of the primary amine followed by alkylation and subsequent deprotection. Various protecting groups have been used in this sequence, but especially the 2-nitrobenzenesulfonamides introduced by Fukuyama and co-workers have become very popular, due to ease of synthesis, enhanced nucleophilicity and mild deprotection.[1,2]

Recently, perfluorinated reagents and scavengers have emerged as an attractive alternative to solid phase synthesis, combining solution-phase and solid-phase advantages.[3] Highly fluorinated compounds are readily separated from nonfluorinated products using an orthogonal fluorous phase or through fluorous solid phase extraction (F-SPE).[4]

We became interested in perfluorinated thiols for the deprotection of 2-nitrobenzenesulfonamides as the formed perfluorinated 2-nitrobenzenethioether **3** (Scheme 1) could in principle be removed via a simple F-SPE.

A series of 2-nitrobenzenesulfonamides **2a**–**g** was therefore prepared (Scheme 1). The 2-nitrobenzenesulfonamides **2a**–**g** were treated with the commercially available perfluorinated thiol, $C_8F_{17}CH_2CH_2SH$ (2.5 equiv) and K_2CO_3 (5 equiv) in MeCN at 50 °C overnight.



Scheme 1. Reagents and conditions: (a) 2-nitrobenzenesulfonyl chloride 1.2 equiv, K_2CO_3 (aq) or Et_3N (**a**–**f**); (b) AcCl, DMAP (cat.), Et_3N, CH_2Cl_2 (**g**); (c) $C_8F_{17}C_2H_4SH$ (2.5 equiv)/K_2CO_3 (5 equiv) in MeCN, followed by F-SPE.

Keywords: Fluorous reagents; 2-Nitrobenzenesulfonamides; Deprotection.
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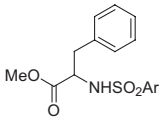
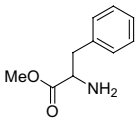
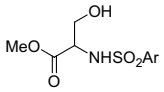
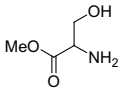
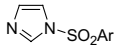
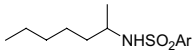
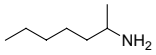
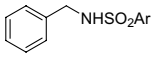
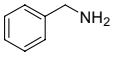
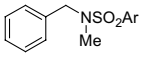
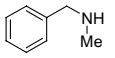
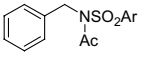
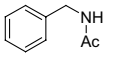
Table 1. Deprotection of 2-nitrobenzenesulfonamides **2a**–**g**[5]

Entry	Sulfonamide **2**	Product **1**	Yield[a] (%)
2a			91 (>95)
2b			96 (>95)
2c			76 (86)
2d			43[b] (>95)
2e			72 (>95)
2f			77 (>95)
2g			81 (>95)

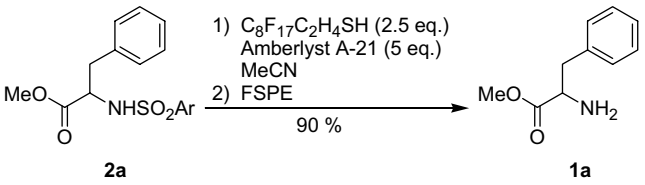
[a] Yields in brackets refer to isolated yields of the fluorinated byproduct **3**. Ar = 2-NO_2–C_6H_4.

[b] The modest yield is due to the volatility of the product.

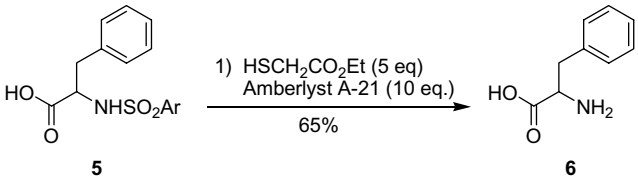
TLC showed full conversion of **2a**–**g** to **1a**–**g** and **3**. The fluorinated byproduct **3** was readily removed by Fluoro*Flash*™ SPE to afford the desired compounds in high yield and purity (Table 1).

This procedure is well suited for parallel synthesis, as the products are obtained in sufficient purity for subsequent manipulation or biological screening. However, it cannot be excluded that the products may contain traces of K_2CO_3. Although this is usually not a problem, we probed the possibility of employing a solid-supported base instead of K_2CO_3, thus immobilizing everything but the product. Indeed, deprotection of **2a** using Amberlyst A-21 as base gave **1a** in identical yield, free of organic or inorganic impurities (Scheme 2).

The use of a solid-supported base enables immobilization of the product when an acidic group is present in the molecule. In the deprotection of the amino acid derivative **5** (Scheme 3) ethyl thioglycolate was used in excess, in the presence of Amberlyst A-21. The formed thioether and excess ethyl thioglycolate were washed



Scheme 2. Deprotection with solid-supported base and fluorinated thiol.



Scheme 3. Purification via product immobilization.

from the solid support, while the free amino acid **6** was retained.

Subsequently, **6** was isolated simply by washing the solid support with excess of AcOH/MeCN (1:1) followed by evaporation of the solvent.[6]

In conclusion, we have demonstrated that 2-nitrobenzenesulfonamides are readily cleaved by the commercially available perfluorinated thiol, $C_8F_{17}(CH_2)_2SH$, in the presence of K_2CO_3 or a solid-supported base. The fluorinated byproduct can be easily separated via a Fluoro*Flash*™ SPE to afford the free amine or amide in high purity and yield. In addition, the use of a solid-supported base and ethyl thioglycolate allows for the direct isolation of free amino acids.

Acknowledgements

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References and notes

1. Fukuyama, T.; Cheung, M.; Jow, C. K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831–5834.
2. Review: Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353–359.
3. Perfluorinated compounds and cartridges can be obtained from Fluorous Technologies Inc.
4. Review: Zhang, W. *Tetrahedron* **2003**, *59*, 4475–4489.
5. *Representative experimental procedure*: To a solution of *N*-(2-nitrobenzenesulfonyl)-serine methyl ester (100 mg, 0.33 mmol) and K_2CO_3 (227 mg, 5 equiv) in MeCN (3 mL), 1*H*,1*H*,2*H*,2*H*-perfluorodecane-1-thiol (289 μL, 2.5 equiv) was added, and the mixture was stirred at 50 °C for 16 h. The resulting yellow solution was filtered, evaporated in vacuo, redissolved in MeOH/H_2O (4/1), loaded onto a 5 g Fluoro*Flash*™ SPE cartridge pre-conditioned with MeOH/H_2O (4/1). The cartridge was eluted with 15 mL MeOH/H_2O (4/1). Evaporation of the solvent afforded serine methyl ester in 96% yield with spectral data identical to those of an authentic sample. The yellowish cartridge was then washed with MeOH (10 mL) and acetone until it was colourless. Evaporation of the solvent afforded the perfluorinated thioether adduct **3** in quantitative yield as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.25 (1H, dd, J = 8.2, 1.5 Hz), 7.63 (1H, m), 7.41–7.31 (m, 2H), 3.26–3.20 (m, 2H), 2.59–2.42 (m, 2H).
6. *Representative experimental procedure*: To a solution of *N*-(2-nitrobenzenesulfonyl)-phenylalanine (100 mg, 0.29 mmol)

and Amberlyst A-21 ($L = 1$ mmol/g, 10 equiv) in MeCN (3 mL) ethyl thioglycolate (170 mg, 5 equiv) was added and the mixture was stirred at rt for 48 h. The resulting yellow solution was filtered and the resin eluted with MeCN. Then, the resin was eluted with AcOH/MeCN (1/1) and the resulting filtrate was evaporated in vacuo to afford pure phenylalanine in 65% yield with spectral data identical to those of an authentic sample.