Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 4523–4525

TETRAHEDRON LETTERS

# Boron trichloride as an efficient and selective agent for deprotection of *tert*-butyl aryl sulfonamides

Yiqian Wan, Xiongyu Wu, Mahalingam A. Kannan and Mathias Alterman*

*Department of Organic Pharmaceutical Chemistry, BMC, Uppsala University, PO Box 574, SE-751 23 Uppsala, Sweden*

Received 12 March 2003; revised 7 April 2003; accepted 17 April 2003

**Abstract**—A fast, mild and selective method for deprotection of *tert*-butyl aryl sulfonamides utilizing $BCl_3$ as deprotection reagent has been developed. A variety of *tert*-butyl aryl sulfonamides used under these conditions gave the corresponding primary sulfonamides in high yields. The method does not cleave methoxy groups and prevents incorporation of *tert*-butyl groups onto electron-rich aromatic rings. © 2003 Elsevier Science Ltd. All rights reserved.

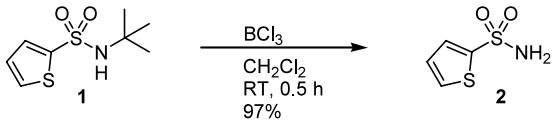
The sulfonamide and acylated sulfonamide groups are both common carboxylic acid bioisosteres,[1,2] and are widely used in many bioactive compounds, e.g. $AT_1$ antagonists,[3] endothelin antagonists,[4] and factor Xa antagonists.[5] In the synthetic routes to these drugs the sulfonamide groups often need to be protected. The most widely used sulfonamide protecting group is the *tert*-butyl group[3,5–10] and deprotection is generally executed with a strong acid, e.g. HCl[10,11] or more commonly TFA.[3,5–9] Unfortunately, long reaction times are often required for full conversion, i.e. from 6 to 18 h, and occasionally reflux is necessary.[12] When applying these conditions in a medicinal chemistry context we found that the deprotection had been achieved but that this reaction was also associated with concomitant formation of unacceptably high amounts of a *tert*-butylated side product, even in the presence of anisole as an electrophile scavenger.

We therefore felt prompted to search for more selective conditions. Recently, Chen et al. reported one example of deprotection of a *tert*-butyl arylsulfonamide with $BBr_3$ (excess) and that this reagent also promoted demethylation of a methoxy group.[13] These findings encouraged us to examine the less reactive $BCl_3$ as a potential reagent for selective and mild deprotection of *tert*-butyl sulfonamides.

*N*-*tert*-Butylthiophene-2-sulfonamide **1**, encompassing a nucleophilic aromatic ring system, was used as a model substrate. Compound **1** was dissolved in dichloromethane and a large excess of $BCl_3$ (5.5 equiv.) was added to the stirred solution at ambient temperature. The starting material was consumed after only 0.5 h. In following experiments the amount of $BCl_3$ was systematically reduced and it was found that only 0.5 equiv. of $BCl_3$ was required to obtain full conversion after 0.5 h.[14] After quenching the reaction with water the remaining boron residue was removed by extraction and the thiophene-2-sulfonamide **2** was isolated in 97% yield (Scheme 1).

To examine the scope and limitation of the deprotection procedure a series of electron-rich and electron-deficient *tert*-butyl aryl sulfonamides were selected for evaluation. The preparative results are shown in Table 1. In most cases, the reaction delivered good yields ranging from 74 to 97%. Notably, no demethylation of the methoxy group was observed in the deprotection of *tert*-butyl-4-methoxybenzenesulfonamide (Table 1, entry 5), not even when 5.5 equiv. of $BCl_3$ was employed.

When *tert*-butyl aryl sulfonamides containing electron-rich aromatic systems are subjected to TFA, undesired *tert*-butylation is prone to occur.[3,6,7] As a model of an electron-rich aromatic compound 1.0 equiv. of thiophene was added in the deprotection reaction of *N*-*tert*-butylthiophene-2-sulfonamide with TFA and 1.0 equiv.



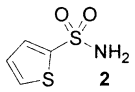
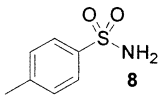
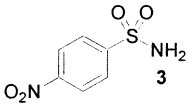
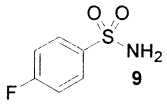
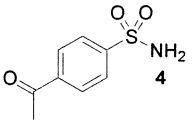
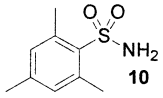
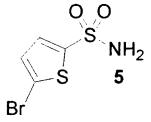
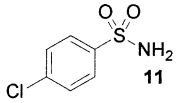
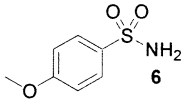
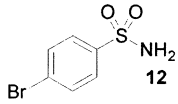
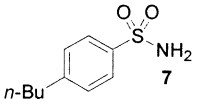
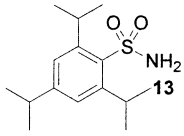

**Scheme 1.**

*Keywords*: boron trichloride; sulfonamides; *tert*-butyl deprotection.

* Corresponding author. Tel.: +46-18-471-4905; fax: +46-18-471-4474; e-mail: mathias@orgfarm.uu.se

0040-4039/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01020-7

**Table 1.** Selective deprotection of *tert*-butyl sulfonamides with $BCl_3$

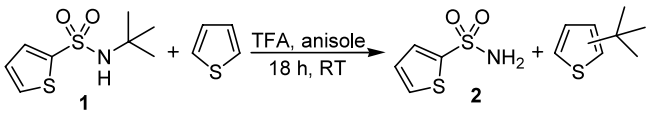
| Entry | Product | Isolated yield (%) | Entry | Product | Isolated yield (%) |
|---|---|---|---|---|---|
| 1 |  **2** | 97 | 7 |  **8** | 88 |
| 2 |  **3** | 78 | 8 |  **9** | 93 |
| 3 |  **4** | 74[a] | 9 |  **10** | 89 |
| 4 |  **5** | 96 | 10 |  **11** | 86 |
| 5 |  **6** | 95 | 11 |  **12** | 91 |
| 6 |  **7** | 94 | 12 |  **13** | 93 |

[a]1.2 equiv. of $BCl_3$ was required to obtain full conversion.

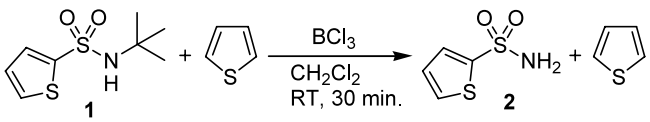
anisole (Scheme 2). Thus, while a substantial amount of *tert*-butylthiophene could be found (GC/MS) in the reaction mixture when TFA/anisole was employed, the same reaction with $BCl_3$ delivered no *tert*-butylated products. The favorable outcome with $BCl_3$ was demonstrated by conducting the deprotection in the presence of 1.0 equiv. of thiophene (Scheme 3).

The synthetic protocol with $BCl_3$ was applied in the synthesis of a key intermediate of the ANG II agonist L-162,313[15] (Scheme 4). The primary sulfonamide **15** was isolated in 90% yield.

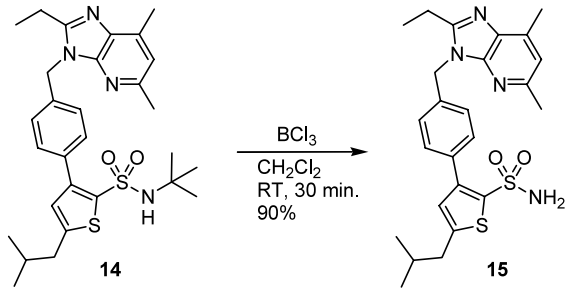
In summary, a fast, high-yield method for removal of the *tert*-butyl protecting group from sulfonamides has




**Scheme 2.**




**Scheme 3.**




**Scheme 4.**

been developed. This method additionally prevents incorporation of *tert*-butyl groups into electron rich aromatic moieties and dose not cleave methoxy groups.

**General procedure**: $BCl_3$ (1 M in $CH_2Cl_2$, 500 μL, 0.5 mmol) was added to a stirred solution of the *N*-*tert*-butylsulfonamide (1.0 mmol) in $CH_2Cl_2$ (2 mL) at room temperature under $N_2$(g). The reaction mixture was stirred for 30 min and then quenched with water (50 mL). The reaction mixture was extracted with ethyl acetate and washed with water, brine, dried and evaporated. The crude product was purified by column chromatography (hexane/acetone) to afford the desired products.[15–27]

## Acknowledgements

We gratefully acknowledge support from the Swedish Foundation for Strategic Research (SSF) and Professor Anders Hallberg for creative discussions.

## References

1. Patani, G. A.; LaVoie, E. J. *Chem. Rev*. **1996**, *96*, 3147–3176.
2. Thornber, C. W. *Chem. Soc. Rev*. **1979**, *8*, 563–580.
3. Le Bourdonnec, B.; Meulon, E.; Yous, S.; Goossens, J.; Houssin, R.; Henichart, J. *J. Med. Chem*. **2000**, *43*, 2685–2697.
4. Murugesan, N.; Gu, Z.; Spergel, S.; Young, M.; Chen, P.; Mathur, A.; Leith, L.; Hermsmeier, M.; Liu, E. C. K.; Zhang, R.; Bird, E.; Waldron, T.; Marino, A.; Koplowitz, B.; Humphreys, W. G.; Chong, S.; Morrison, R. A.; Webb, M. L.; Moreland, S.; Trippodo, N.; Barrish, J. C. *J. Med. Chem*. **2003**, *46*, 125–137.
5. Quan, M. L.; Ellis, C. D.; He, M. Y.; Liauw, A. Y.; Woerner, F. J.; Alexander, R. S.; Knabb, R. M.; Lam, P. Y. S.; Luettgen, J. M.; Wong, P. C.; Wright, M. R.; Wexler, R. R. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 369–373.
6. Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Naylor, E. M.; Chakravarty, P. K.; Patchett, A. A.; Greenlee, W. J.; Bendesky, R. J.; Chen, T. B.; Faust, K. A.; Kling, P. J.; Schaffer, L. W.; Schorn, T. W.; Zingar, G. J.; Chang, R. S. L.; Lotti, V. J.; Kivlighn, S. D.; Siegel, P. K. S. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 115–120.
7. Ashton, W. T.; Chang, L. L.; Flanagan, K. L.; Hutchins, S. M.; Naylor, E. M.; Chakravarty, P. K.; Patchett, A. A.; Greenlee, W. J.; Chen, T. B.; Faust, K. A. *J. Med. Chem*. **1994**, *37*, 2808–2824.
8. Naylor, E. M.; Chakravarty, P. K.; Costello, C. A.; Chang, R. S.; Chen, T.; Faust, K. A.; Lotti, V. J.; Kivlighn, S. D.; Zingaro, G. J.; Siegel, P. K. S.; Wong, P. C.; Carini, D. J.; Wexler, R. R.; Patchett, A. A.; Greenlee, W. J. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 69–74.
9. Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Rivero, R. A.; Chen, T. B.; O'Malley, S. S.; Zingaro, G. J.; Kivlighn, S. D.; Siegl, P. K. S.; Lotti, V. J.; Chang, R. S. L.; Greenlee, W. J. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 2787–2792.
10. Graham, S. L.; Scholz, T. H. *J. Org. Chem*. **1991**, *56*, 4260–4263.
11. Han, Q.; Dominguez, C.; Stouten, P. F. W.; Park, J. M.; Duffy, D. E.; Galemmo, R. A., Jr.; Rossi, K. A.; Alexander, R. S.; Smallwood, A. M.; Wong, P. C.; Wright, M. M.; Leuttgen, J. M.; Knabb, R. M.; Wexler, R. R. *J. Med. Chem*. **2000**, *43*, 4398–4415.
12. Fevig, J. M.; Pinto, D. J.; Han, Q.; Quan, M. L.; Pruitt, J. R.; Jacobson, I. C.; Galemmo, R. A., Jr.; Wang, S.; Orwat, M. J.; Bostrom, L. L.; Knabb, R. M.; Wong, P. C.; Lam, P. Y. S.; Wexler, R. R. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 641–645.
13. Chen, H. H.; Gross, S.; Liao, J.; McLaughlin, M.; Dean, T.; Sly, W. S.; May, J. A. *Bioorg. Med. Chem*. **2000**, *8*, 957–975.
14. In the case where the substrate was not adequately dried, 1–2 equiv. of $BCl_3$was required for full conversion.
15. Kivlighn, S. D.; Lotti, V. J.; Rivero, R. A.; Siegl, P. K. S.; Zingaro, G. J. In *Brit. UK Pat. Appl*.; (Merck and Co., Inc., USA). Gb, 1995, p 21 pp.
16. All the products are known and gave consistent analytical data. **2**: Meyer, V.; Kreis, H. *Ber*. **1883**, *16*, 2172–2176.
17. **3**: Ekbom, A. *Ber*. **1902**, *35*, 651–653.
18. **4**: Burton, H.; Hu, P. F. *J. Chem. Soc*. **1949**, 178–181.
19. **5**: Steinkopf, W.; Jacob, H.; Penz, H. *Ann*. **1934**, *512*, 136–164.
20. **6**: Gattermann, L. *Ber*. **1899**, *32*, 1136–1161.
21. **7**: Huntress, E. H.; Autenrieth, J. S. *J. Am. Chem. Soc*. **1941**, *63*, 3446–3448.
22. **8**: Chern, J. W.; Leu, Y. L.; Wang, S. S.; Jou, R.; Lee, C. F.; Tsou, P. C.; Hsu, S. C.; Liaw, Y. C.; Lin, H. M. *J. Med. Chem*. **1997**, *40*, 2276–2286.
23. **9**: Lenz, W. *Ber*. **1879**, *12*, 580–583.
24. **10**: Schreinemakers, F. A. H. *Recl. Trav. Chim. Pays-Bas*. **1897**, *16*, 411–424.
25. **11**: Paal, C. *Ber*. **1901**, *34*, 2748–2757.
26. **12**: Evans, T. W.; Dehn, W. M. *J. Am. Chem. Soc*. **1930**, *52*, 2531–2533.
27. **13**: Newton, A. *J. Am. Chem. Soc*. **1943**, *65*, 2439–2441.