Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 599–601
Tetrahedron Letters

Efficient indole *N*-detosylation using thioglycolate

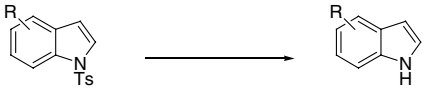
Charlotte M. Haskins and David W. Knight*

Cardiff School of Chemistry, Cardiff University, PO Box 912, Cardiff CF10 3TB, UK

Received 10 October 2003; revised 17 October 2003; accepted 24 October 2003

Abstract—The dilithium salt of thioglycolic acid in DMF can be used for the very efficient and convenient removal of *N*-*p*-toluenesulfonyl (tosyl) groups from a range of indoles at ambient temperature.

The very stability of sulfonamides, while rendering them attractive candidates for general amine protection, clearly poses the conundrum of their eventual removal, usually at a late stage in a synthetic scheme. A range of dissolving metal reductions of a more or less appealing nature can be effective such as sodium or lithium in ammonia, an alcohol or HMPA and potassium and 18-crown-6. Other single electron transfer reagents include sodium naphthalenide, sodium amalgam and tributyltin hydride, while photolysis and exposure to Red-Al provide contrasting alternatives.[1]



1 2

In the specific case of the *N*-detosylation of indoles **1**, other methods featuring nucleophilic attack at the sulfonyl group have proven viable, by reason of the lower pK_a value associated with the nitrogen function in this heterocycle **2** and hence its enhanced ability to act as a leaving group. These include L-selectride, amongst a number of hydride sources in some specific examples,[2] various concentrations of ethanolic hydroxide, which can require prolonged reflux,[3,4] and the highly nucleophilic Gilman reagent, $PhMe_2$ SiLi.[1] A recently reported protocol features an alternative dissolving metal method, that of magnesium in methanol,[5] while another nucleophile-based method uses fluoride, provided in the form of either potassium fluoride on alumina and requiring microwave activation[6] or tetrabutylammonium fluoride (TBAF) in refluxing THF.[7] Clearly, while effective in a number of cases, applications of such reagent combinations can be precluded because of the strongly basic conditions, which are incompatible with some functionality or which may epimerise stereogenic centres.

These constraints led Fukuyama[8] to develop a range of nitrophenylsulfonyl groups as alternatives for general amine protection. While clearly more vulnerable than tosyl groups to various conditions and reagents such as catalytic hydrogenation or nucleophiles, this latter reactivity was exploited in a very selective and mild method for their removal by *ipso* attack of thiophenolate followed by disintegration of the resulting nitronate to give a phenyl(nitrophenyl)sulfide, sulfur dioxide and the free amine. An even neater method employs thioglycolate as the sulfur nucleophile; clearly, the presence of the carboxylate group allows simple by-product removal during an aqueous work-up.

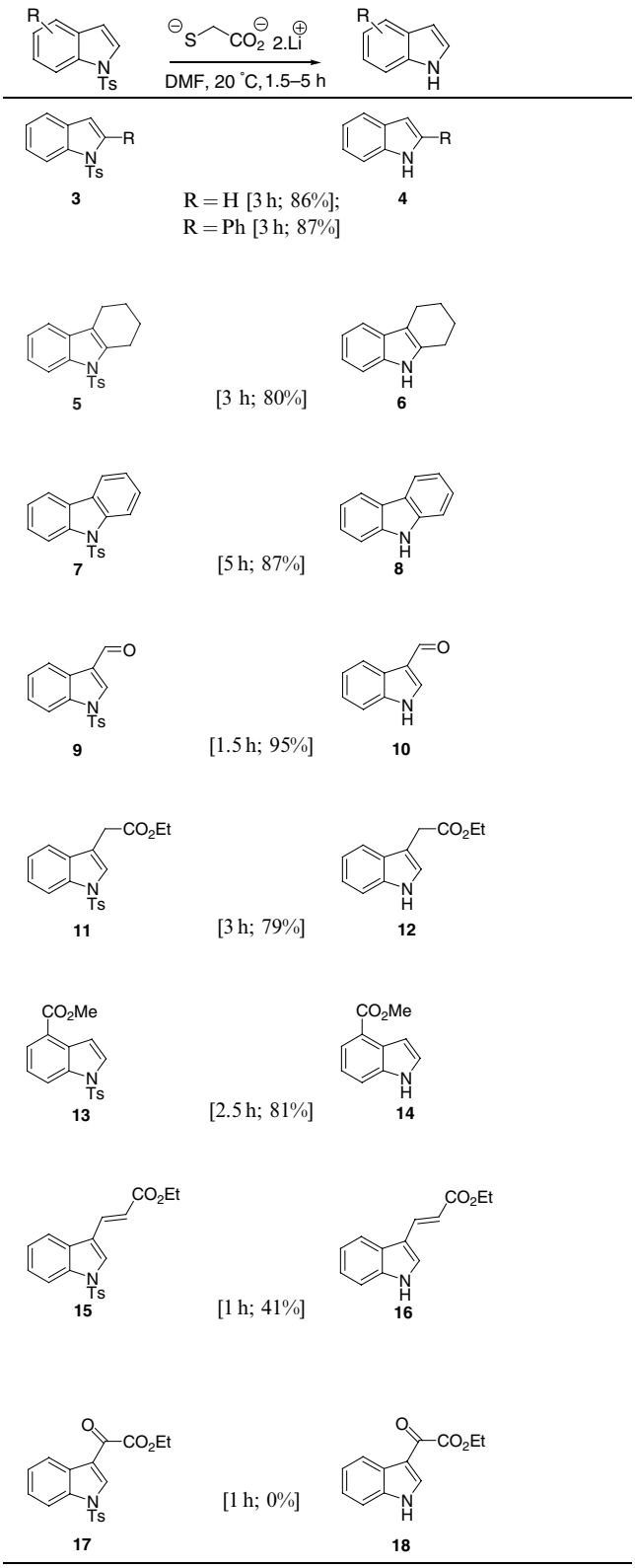
Herein, we report that thioglycolate can also be used for the *N*-detosylation of indoles, thereby adding a particularly mild and relatively selective reagent to the foregoing methods. The results of experiments with a variety of substituted indoles are presented in Table 1.[9]

Both *N*-tosylindole itself **3** and the 2-phenyl derivative [**3**; R = Ph] were deprotected to give purified yields of the corresponding free indoles **4** of just under 90% in 3 h at ambient temperature. Similarly, the tetrahydrocarbazole derivative **5** gave the NH derivative **6** in 80% yield in a similar time, while *N*-tosylcarbazole **7** itself took a little longer to react fully (5 h), but still the method delivered

* Corresponding author. Fax: +44-2920-874210; e-mail: knightdw@cf.ac.uk

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.10.154

Table 1. Detosylation of representative *N*-tosylindoles using thioglycolate

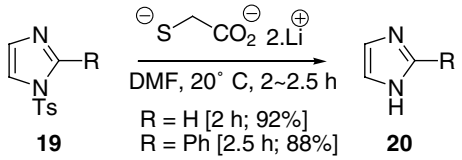


an excellent 87% return of the unprotected heterocycle **8**. Understandably, *N*-tosyl indoles having electron withdrawing substituents are more prone to this type of nucleophilic attack. For example, *N*-tosyl indole-3-carboxaldehyde **9** is converted into the free indole **10** in essentially quantitative yield in only 1.5 h. No products arising from other processes such as Cannizzaro reactions were detected. Ester groups remain very largely unattacked by thiogylcolate; thus, the 3-acetate derivative **11** is converted into the free indole ester **12** in 79% isolated yield. In this case, activation to nucleophilic attack was obviously much lower than that in the foregoing example and complete reaction took 3 h. Despite the basic conditions, there was no evidence for the formation of Claisen condensation products. In contrast, the indole-4-carboxylate **13** reacted a little faster to give the free indole **14** in 2.5 h and in an isolated yield of 80%.[10]

That the thiolate does indeed play a vital role in the detosylations was established by exposing the indole-3-carboxaldehyde derivative **9** to lithium hydroxide in DMF but in the absence of thioglycolic acid. After 24 h at ambient temperature, the usual work-up[9] delivered the free indole-3-aldehyde **10** in 82% yield. Hence, hydroxide alone in DMF is capable of removing *N*-tosyl groups from indoles at ambient temperature, but at a much slower rate (24 h compared with 1.5 h) in this case of a relatively activated example. Less activated substrates would clearly require even more prolonged reaction times. This observation seems consistent with the requirement for heating for extended periods when ethanolic hydroxide is employed.[3,4]

Inevitably, almost any synthetic method has its limitations, especially ones using nucleophiles. Thiolates in general are well known to be good Michael nucleophiles, so it did not come as much of a surprise to find that detosylation of the unsaturated ester derivative **15** gave a poor 41% purified yield of the free indole **16**. The material balance appeared to consist of Michael addition product(s) which, if derived from attack by thiolate, could perhaps be converted back into the unsaturated ester function by sequential oxidation and base treatment. Finally, a probably unrecoverable example was the attempted deprotection of the indole derivative **17** containing an α-keto-ester function. This resulted in no identifiable products and little evidence for the formation of any free indole **18**, presumably because of the electrophilicity of the central carbonyl group.

We have also examined similar detosylations of two imidazole derivatives **19**. In view of the relatively good leaving ability of the imidazole nucleus, it came as little surprise that the corresponding free heteroaromatics **20** were formed rapidly in around 90% purified yields.[10]



In conclusion, we suggest that this relatively very mild method will be useful for the *N*-detosylation of a very wide range of indole derivatives, within some fairly obvious constraints. Imidazoles can also be similarly deprotected and possibly some other nitrogen-based heteroaromatics. A particular advantage, certainly on a small scale, is that the other products are so easy removed from the free indoles using a simple wash with mild aqueous base.

Acknowledgements

We thank the EPSRC Mass Spectrometry Service, University College Swansea for the provision of high resolution Mass Spectrometric data and the EPSRC for generous financial support.

References and Notes

1. For a succinct summary, see Fleming, I.; Frackenpohl, J.; Ila, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1229.
2. Yang, C.-G.; Wang, J.; Tang, X.-X.; Jiang, B. *Tetrahedron: Asymmetry* **2002**, *13*, 383.
3. Gilbert, E. J.; Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem.* **1999**, *64*, 5670.
4. Gard, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179.
5. Muratake, H.; Natsume, M. *Heterocycles* **1989**, *29*, 783; Nyasse, B.; Grehn, L.; Ragnarsson, U. *Chem. Commun.* **1997**, 1017.
6. Sabitha, G.; Abraham, S.; Subba Reddy, B. V.; Yadav, J. S. *Synlett.* **1999**, *1*, 1745.
7. Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281.
8. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373; Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y. *Tetrahedron Lett.* **1997**, *38*, 5831; Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 1519; Kan, T.; Fujiwara, A.; Kobayashi, H.; Fukuyama, T. *Tetrahedron* **2002**, *58*, 6267; Kunosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112, and references cited therein.
9. A representative procedure is as follows: The *N*-tosyl indole or imidazole (0.5 mmol) was dissolved in DMF (2 mL). Lithium hydroxide (48 mg, 2.0 mmol) was added followed by thioglycolic acid (30 μl, 0.6 mmol). The resulting solution was stirred at ambient temperature and monitored by TLC (1.5–5 h). When the reaction was complete, the solution was diluted with ethyl acetate (4 mL) and water (2 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (4 mL) and the combined organic solutions washed with saturated aqueous sodium carbonate (3×5 mL) then dried ($MgSO_4$), filtered and evaporated. The residue was usually essentially pure indole or imidazole. Additional purification, if necessary, was then carried out by standard means (crystallisation, chromatography etc.).
10. All *N*-tosyl derivatives and the corresponding free indoles or imidazoles were identified by comparisons with authentic materials.