Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 6425–6427
Tetrahedron Letters

Deprotection of N-tosylated indoles and related structures using cesium carbonate

Joginder S. Bajwa,* Guang-Pei Chen, Kapa Prasad, Oljan Repič and Thomas J. Blacklock

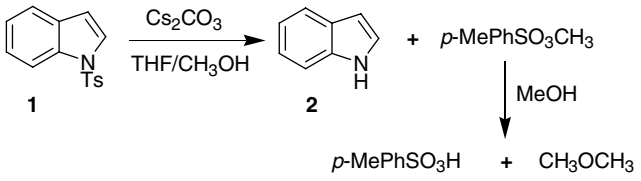
Process R&D, Chemical and Analytical Development, Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936, USA

Received 12 June 2006; revised 22 June 2006; accepted 23 June 2006

Abstract—A very mild, efficient, and convenient method for deprotection of N-tosylated indoles and related structures by cesium carbonate in THF–MeOH is described.

Many compounds in medicinal chemistry contain heteroaromatics as part of the structure and the NH-functionality, that is, present in some of these molecules needs to be protected during the synthesis by a suitable group, that is, easily removable. Tosyl group is one such blocking group, and its deprotection is usually accomplished by one of following methods: dissolving metal reductions (Li or Na) in ammonia, alcohol or HMPA; single electron transfer reagents such as sodium naphthalenide, Na–Hg, *n*-Bu_3SnH; reducing agents L-Selectride, Red-Al; photolysis.[1,2] Other reagents used for this deprotection are highly nucleophilic Gilman's reagent $PhMe_2SiLi$,[1] highly basic NaOH (or KOH) in alcohol solvents at high temperature,[3,4] KF[5] on alumina under microwaves, *n*-Bu_4NF in refluxing THF,[6] Mg–MeOH,[7] polymer-supported potassium thiophenolate,[8] and $HSCH_2COOH$/LiOH.[9]

Most of these methods, while effective in a number of cases, have serious incompatibilities with other functional groups. While making an indole derived drug substance, we needed to effect N-detosylation. Several literature methods were tried which invariably gave low yields due to the formation of many by-products. This led to the development of a new and a very mild method for N-detosylation of indoles and related structures using cesium carbonate (Scheme 1). To determine the optimum stoichiometry of cesium carbonate, a set of



Scheme 1.

experiments was performed with *N*-tosyl-5-bromoindole **9**, and the results are shown in Table 1. The reactions were carried out in a mixed solvent THF–MeOH (2:1). Ideally, the solvent of choice is methanol but simple *N*-tosyl indoles (such as **9**) are highly liphophilic and are not soluble in methanol. When the reactions were carried out in a single solvent methanol or ethanol, the reactions times were longer. The reaction did not work when carried out in *iso*-propanol.

It is apparent from the results in Table 1 that 3 equiv of cesium carbonate are required to achieve a reasonable reaction rate for N-detosylation of indole **9**. It is also

Table 1. Reaction[a] of *N*-tosyl-5-bromoindole **9** with varying amounts of cesium carbonate in THF–MeOH

Entry	Amount of Cs_2CO_3 (equiv)	Reaction time (h)	Conversion[b] **10/9**
1	1.0	15	69/31
2	2.0	15	95/5
3	3.0	15	99/1

[a] A mixture of **9** (0.25 mmol) and Cs_2CO_3 (1–3 equiv) in THF–MeOH (3 mL, 2:1) was stirred at 22 °C and followed by HPLC.
[b] Determined by HPLC.

Keywords: N-detosylation; Azaindoles; Indoles; Imidazoles; Cesium carbonate.
* Corresponding author. Tel.: +1 862 778 3474; fax: +1 973 781 4384; e-mail: joginder.bajwa@novartis.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.06.132

Table 2. Reaction[a] of *N*-tosyl-5-bromoindole **9** with various alkali metal carbonates in THF–MeOH in the presence/absence of water

Entry	Alkali metal carbonate (3.0 equiv)	Additive (equiv)	Conversion[b] **10/9**
1	Li_2CO_3	—	⟨0.1/⟩ 99.9
2	Na_2CO_3	—	⟨0.1/⟩ 99.9
3	K_2CO_3	—	24/76
4	Cs_2CO_3	—	99.8/0.2
5	Li_2CO_3	H_2O (1.0)	⟨0.1/⟩ 99.9
		H_2O (40.0)	⟨0.1/⟩ 99.9
6	Na_2CO_3	H_2O (1.0)	⟨0.1/⟩ 99.9
		H_2O (40.0)	⟨0.1/⟩ 99.9
7	K_2CO_3	H_2O (1.0)	23/77
		H_2O (40.0)	0.4/99.6
8	Cs_2CO_3	H_2O (1.0)	99.7/0.3
		H_2O (40.0)	7/93

[a] A mixture of **9** (0.25 mmol), alkali metal carbonate (3 equiv) and water (0, 1 or 40 equiv) in THF–MeOH (3 mL, 2:1) was stirred at 22 °C for 15 h.
[b] Determined by HPLC.

interesting to note that the initial by-product observed in this reaction is methyl *p*-toluenesulfonate (Scheme 1). If the reaction rate is slow enough as it is in the present case, the *p*-$MePhSO_3Me$ formed reacts further with methanol to give *p*-$MePhSO_3H$ and MeOMe. On the other hand, *p*-toluenesulfonic acid and dimethyl ether are the only by-products observed when the reaction was carried out at reflux temperature.[10]

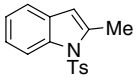
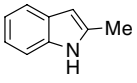
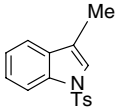
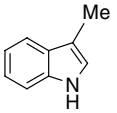
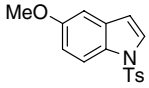
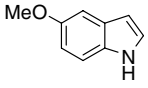
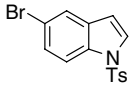
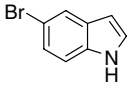
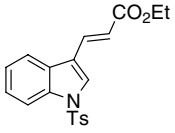
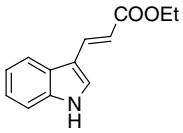
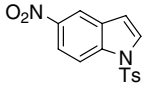
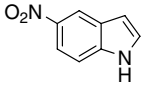
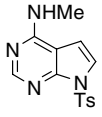
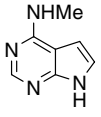
Next we examined N-detosylation of *N*-tosyl-5-bromoindole **9** with different alkali metal carbonates. The effect of water on this reaction was also studied. The results are shown in Table 2.

It is clear from the results in Table 2 (entries 1, 2, 5, and 6) that Li_2CO_3 and Na_2CO_3 with or without water are totally ineffective in deprotection of tosyl group in **9**. Potassium carbonate does effect detosylation of **9** (entry 3) but it is much less effective than Cs_2CO_3 (entry 4). While the use of one equivalent of water in the reaction mixture has practically no effect, excess of water (40 equiv) virtually shuts down the reaction (entry 3 vs 7 and entry 4 vs 8).

Based upon the optimized conditions with respect to the solvent, the stochiometry, and the alkali metal carbonate described above (Tables 1 and 2), a variety of substituted indoles and azaindoles were subjected to N-detosylation with Cs_2CO_3. The results are shown in Table 3.[11]

The reaction of unactivated *N*-tosyl indole **1** with cesium carbonate in THF–MeOH at room temperature was rather slow and gave 95% conversion after 90 h. However, when the reaction mixture was heated at reflux (64 °C), complete deprotection of the tosyl group was achieved in just 0.5 h. The reaction is slower in MeOH alone as compound **1** has limited solubility in MeOH. The reaction rate as expected is very sensitive to both electronic and steric effects of the substituents. For example, with indole **3** there is no reaction at ambient temperature for up to 70 h. Even at reflux, the reaction

Table 3. Deprotection of *N*-tosyl indoles and related heterocycles[a]

Substrate[12]	Temperature (°C)/ reaction time (h); conversion[b]	Product
 **1**	22/90; 95/5 (**2/1**) 64/0.5; >99/1 (**2/1**)	 **2**
 **3**	22/70; 2/98 (**4/3**) 64/48; 97/3 (**4/3**)	 **4**
 **5**	22/70; 12/88 (**6/5**) 64/8; 98/2 (**6/5**)	 **6**
 **7**	22/18; 7/93 (**8/7**) 64/2.5; >99/1 (**8/7**)	 **8**
 **9**	22/15; >99/1 (**10/9**)	 **10**
 **11**	22/1; >99/1 (**14/13**)	 **12**
 **13**	0–5/5; >99/1 (**12/11**)	 **14**[c]
 **15**	22/2; >99/1 (**16/15**)	 **16**
 **17**	22/0.5; >99/1 (**18/17**)	 **18**
 **19**	22/0.5; >99/1 (**20/19**)	 **20**

[a] A mixture of *N*-tosylindole (0.5 mmol) and Cs_2CO_3 (1.5 mmol) in THF–MeOH (3 mL, 2:1) was stirred at a specified temperature and progress of the reaction was followed by HPLC.
[b] Determined by HPLC.
[c] Unidentified by-product (9.6%) was also formed.

was slow, and it took 48 h to effect 97% conversion of **3** to **4**. In contrast, the deprotection of *N*-tosyl-3-methyl-

indole **5** was essentially complete in 8 h at reflux. Electron-donating substituents such as methoxy group in **7** also slow down the reaction. Nevertheless, complete deprotection of the tosyl group was achieved at reflux in 2.5 h. Electron withdrawing substituents such as bromo, vinyl ester, and nitro groups greatly facilitate the nucleophilic attack. For example, *N*-tosyl-5-bromoindole **9** and the unsaturated ester derivative **13** were converted into the corresponding free indoles **10** and **12** in quantitative yields in 15 h and 1 h, respectively. Deprotection of **11** was carried out in THF–EtOH rather than in THF–MeOH to avoid any trans-esterification by-products. Also, it is interesting to note that no Michael addition by-product(s) was observed.[5,9] The deprotection of *N*-tosyl-5-nitroindole **13** was complete in 0.5 h at 22 °C but it also gave an unidentified by-product. To minimize the formation of the by-product the reaction was carried out at 0–5 °C and the product **14** was formed in 90.4% yield.

We have successfully extended this methodology to N-detosylation of azaindoles. Azaindoles have lower pKa values compared to indoles[13] and thus are expected to be better leaving groups. Indeed, detosylation of azaindoles **15** and **17** were complete at ambient temperature in only 2 h and 0.5 h, respectively.

Imidazole also acts as a good leaving group and as a result, detosylation of 2-phenylimidazole derivative **19** proceeded very rapidly at room temperature to give product **20** in quantitative yield. It is interesting to note that the reaction time (0.5 h) is much shorter than 2.5 h as reported by the thioglycolate method.[9]

In summary, we have developed a very mild and efficient method for detosylation of a wide range of indoles, azaindoles, and imidazoles. Cesium carbonate is readily available, inexpensive, and easy to handle. This method should prove useful for deprotection of tosyl groups in indoles, azaindoles, and in situations where the other methods are not selective.

References and notes

1. Fleming, I.; Frackenpohl, J.; Ila, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1229–1235, and Ref. 8 cited there in.
2. (a) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*, 3rd ed.; Wiley Interscience: New York, 2005; (b) Kocieński, P. J. *Protective Groups*, 3rd ed.; Thieme: New York, 2003.
3. Gilbert, E. J.; Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem.* **1999**, *64*, 5670–5676.
4. Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179–13184.
5. Sabitha, G.; Abraham, S.; Subba Reddy, B. V.; Yadav, J. S. *Synlett* **1999**, *1*, 1745–1746.
6. Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281–3284.
7. (a) Nyasse, B.; Grehn, L.; Ragnarsson, U. *Chem. Commun.* **1997**, 1017–1018; (b) Muratake, H.; Natsume, M. *Hetrocycles* **1989**, *29*, 783–794.
8. MacCoss, R. N.; Henry, D. J.; Brain, C. T.; Ley, S. V. *Synlett* **2004**, 675–678.
9. Haskins, M. C.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 599–601.
10. The formation of *p*-$MePhSO_3Me$ and *p*-$MePhSO_3H$ in the reaction mixture was confirmed by comparison of HPLC analysis of the reaction mixture with authentic samples. The formation of dimethyl ether was assumed on the basis of the corresponding reaction carried out in *n*-butanol where the formation of the dibutyl ether by-product was confirmed by GC–MS.
11. A representative procedure is as follows: *N*-Tosyl 5-bromoindole **9** (2.1 g, 6.0 mmol) was dissolved in a mixture of THF (50 mL) and MeOH (25 mL) at ambient temperature. Cesium carbonate (5.85 g, 18.0 mmol) was added to the clear solution. The resulting mixture was stirred at ambient temperature and the progress of the reaction was monitored by HPLC. When the reaction was complete (18 h), the mixture was evaporated under vacuum. To the residue was added water (25 mL) and the mixture was stirred at ambient temperature for 10 min. The solids were filtered, washed with water (15 mL) and dried at 45 °C/1.5 mbar/18 h to give crude product **10** (1.156 g, 98.3%). An analytically pure sample was obtained in 88.2% yield and 100% purity (HPLC) by recrystallization of crude product (1.156 g) from *n*-heptane (15 mL).
12. All *N*-tosyl derivatives were prepared by following the procedure described in Poissonnet, G.; Théret-Bettiol, M.-H.; Dodd, R. H. *J. Org. Chem.* **1996**, *61*, 2273–2282.
13. The pKa of indole is reported to be 20.95 according to: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463; The pKa's of azaindoles are reported to be 4.50–8.26 according to: LeHyaric, M.; Vieira de Almeida, M.; Nora de Souza, M. V. *Quim. Nova* **2002**, *25*, 1165–1171.