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Communications to the Editor

A Green *N*-Detosylation of Indoles and Related Heterocycles Using Phase Transfer Catalysis

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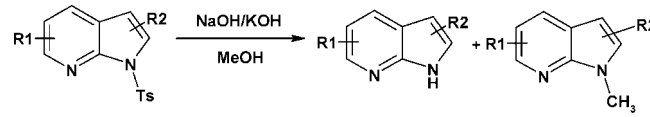
Abstract:

A practical method for the *N*-detosylation of indoles and related heterocycles with KOH in THF and water in the presence of a phase transfer catalyst is described. Using a nonalcoholic solvent, this method prevents the formation of toxic alkyl *p*-toluenesulfonate and consequently eliminates the formation of even traces of *N*-alkyl byproduct. This green method is particularly useful for indoles bearing electron-withdrawing groups and for azaindoles.

Introduction

Indoles and related structures are widely found in many active pharmaceutical ingredients. The NH groups are often protected as *p*-toluenesulfonamides along the synthetic pathways when incompatibilities with other functionalities or reagents arise. One has to deal with the eventual removal of the tosyl group, usually at a later stage of the synthesis. Not surprisingly, many protocols for the *N*-detosylation of indoles have been reported, such as reductive cleavage by dissolving metals in ammonia, HMPA, or alcohol,[1] single-electron transfer reagents including sodium naphthalenide, sodium amalgam, and Bu_3SnH,[2] and those involving the use of special devices, for example, electrolysis, microwave activation (KF/Al_2O_3), and sonication (Mg/MeOH).[3] Deprotections under nucleophilic conditions, such as $PhMe_2SiLi$, $HSCH_2CO_2H/LiOH$, tetra-*n*-butlyammonium fluoride,[6] sodium or potassium hydroxide/alcohol, and Cs_2CO_3/THF/MeOH[4] have also been reported.

Scheme 1



Despite the many *N*-detosylation methods, very few are really useful in industries where safety, simplicity and reliability are desired. While making an azaindole-containing active pharmaceutical ingredient, we needed to cleave the *N*-tosyl group without producing impurities that were difficult to remove. We tried several methods reported in the literature, and none of them gave satisfactory results. The best results were obtained using KOH/MeOH or Cs_2CO_3/THF/MeOH, but they generated an *N*-methylated impurity, which was very difficult to remove by crystallization or by chromatography. Methanol as solvent led to the formation of toxic methyl *p*-toluenesulfonate as the byproduct in this detosylation reaction, as a consequence of esterification of liberated *p*-toluenesulfonic acid, which acted as the *N*-alkylating agent on the deprotected indole[5] (Scheme 1). When difficult to remove, even 1−2% of such an *N*-alkylated byproduct could be a serious problem in achieving the desired purity specifications of drug substances. Additionally, special measures are required on large scale due to the carcinogenic nature of these alkyl *p*-toluenesulfonates.

Therefore, we needed to develop a convenient and practical method for the *N*-detosylation that avoided the formation of toxic alkyl *p*-toluenesulfonate, and subsequently formation of even traces of *N*-alkylated byproduct. Herein, we describe our results on the development of a green method for this

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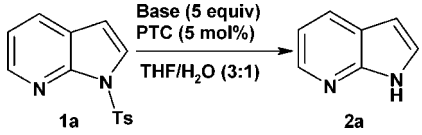
Table 1. ***N*-Detosylation[a] of *N*-tosyl-7-azaindole (1a)**



entry	base	catalyst	rxn temp (°C)	rxn time (h)/ conversion (%)
1	KOH	none	20	20/0.3
2	KOH	none	65	48/95.0
3	KOH	CTAB	20	20/2.0
4	**KOH**	**CTAB**	**65**	**10/100**
5	KOH	Me_4NCl	65	20/100
6	KOH	Bu_4NBr	20	20/2.2
7	KOH	Bu_4NBr	65	15/100
8	KOH	TDA-1	20	20/0.3
9	KOH	TDA-1	65	20/78.0
10	NaOH	CTAB	20	20/2.0
11	NaOH	CTAB	65	20/100
12	Na_2CO_3	CTAB	20	20/0.1
13	Na_2CO_3	CTAB	65	20/0.1
14	K_2CO_3	CTAB	20	20/0.1
15	K_2CO_3	CTAB	65	20/5.0
16	Cs_2CO_3	CTAB	20	20/0.1
17	Cs_2CO_3	CTAB	65	20/6.0

[a] Conditions: 1 mmol of *N*-tosyl-7-azaindole, 5 mmol of base, 1.5 mL of THF and 0.5 mL of water were mixed and treated with or without phase transfer catalyst at 20 °C or at reflux. The conversion was determined by HPLC @ 280 nm.

transformation using KOH in THF and H_2O under phase transfer catalysis (PTC) conditions.

Results and Discussion

We first investigated the *N*-detosylation of *N*-tosyl-7-azaindole in THF and water using KOH (Table 1). The reaction mixture showed two clear layers when settled, and almost no detosylation was observed (entry 1) under vigorous stirring at room temperature. The reaction did occur at 65 °C, but took 48 h to achieve 95% conversion (entry 2). However, the use of a phase transfer catalyst cetyltrimethylammonium bromide (CTAB) was found to significantly accelerate the reaction, leading the completion of reaction in only 10 h (entry 4). Other phase transfer catalysts, e.g., tetramethylammonium chloride, tetramethylammonium bromide and tris(dioxa-3,6-heptyl)amine (TDA-1) were not as effective as CTAB (entries 5−9). The reason for the rate differences was probably due to the fact that CTAB has a more lipophilic cetyl group, as suggested by the trend going from tetramethylammonium chloride to CTAB. No emulsion was observed with either of the catalysts. Interestingly, the *N*-detosylation took much longer if the base was changed to NaOH (entries 10−11). As expected, weaker bases such as Na_2CO_3, K_2CO_3 and Cs_2CO_3 led to negligible *N*-detosylation (entries 12−17).

To test the scope and limitations of this *N*-detosylation method, a variety of indole derivatives were subjected to the above reaction conditions. The results are summarized in Table 2. A complete *N*-detosylation of *N*-tosyl indole (**1b**) was achieved in 72 h in the presence of CTAB, whereas only 15% conversion was observed without CTAB under identical conditions (entry 2). Again CTAB accelerated the *N*-detosylation reaction. The *N*-detosylation of *N*-tosyl indoles bearing an electron-withdrawing group, e.g., aza (**1a**), 5-nitro (**1c**), and

Table 2. ***N*-Detosylation[a] of indoles and related heterocycles**

Entry	Substrate	Product	% Conversion with CTAB (reaction time)	% Conversion without CTAB (reaction time)
1	**1a**	**2a**	100 (10 h)	53 (10 h)
2	**1b**	**2b**	100 (72 h)	15 (72 h)
3	**1c**	**2c**	100 (1.5 h)	90 (1.5 h)
4	**1d**	**2d**	100 (26 h)	39 (26 h)
5	**1e**	**2e**	35 (120 h)	1.5 (120 h)
6	**1f**	**2f**	73 (120 h)	8 (120 h)
7	**1g**	**2g**	100 (7 h)	61 (7 h)
8	**1h**	**2h**	100 (3.5 h)	90 (3.5 h)
9	**1i**	**2i**	100 (4 h, rt)	15 (4 h, rt)
10	**1j**	**2j**	100 (40 min, rt)	100 (60 min, rt)

[a] Conditions: 1 mmol of substrate, 5 mmol of KOH, 1.5 mL of THF and 0.5 mL of water were mixed and treated with or without 0.05 mmol of CTAB at reflux.[7] The conversion was determined by HPLC @ 280 nm. rt = room temperature.

5-bromo (**1d**), were relatively faster compared to *N*-tosyl indole (**1b**) itself, and went to completion in 10, 1.5, and 26 h, respectively (entries 1, 3−4). Without CTAB, the conversions were 53, 90, and 39%, respectively. However, the reactions of *N*-tosyl indoles bearing an electron-donating group, such as 3-methyl (**1e**) and 5-methoxy indoles (**1f**) (entries 5−6), were quite slow, giving only 35% and 73% conversion, respectively, after 120 h in the presence of CTAB, and 1.5% and 8% without CTAB. Deprotection of *N*-tosyl imidazoles, indazoles, and triazoles was significantly faster compared to *N*-tosyl indole (**1b**). However, the reactions without CTAB were also quite fast. Detosylation of 2-phenylimidazole (**1g**) proceeded to completion in 7 h with the catalyst, while only 61% conversion was observed without CTAB (entry 7). For *N*-tosyl indazole (**1 h**), the deprotection was complete in 3.5 h with CTAB and

90% conversion without catalyst (entry 8). In case of *N*-tosyl benzimidazole (**1i**) (entry 9), the deprotection was carried out at room temperature and was complete in 4 h, while 15% conversion occurred without CTAB. Deprotection of *N*-tosyl-1*H*-benzotriazole (**1j**) (entry 10) was complete in 40 min at room temperature with CTAB and in 1 h without CTAB. Thus, CTAB consistently accelerated the *N*-detosylation reaction in all cases.

In summary, we demonstrated that the *N*-detosylation of a wide range of indole derivatives was accomplished with KOH in THF and water in the presence of a phase transfer catalyst. This method eliminates the formation of toxic alkyl *p*-toluenesulfonates and, consequently, even traces of *N*-alkyl byproduct formed in alcoholic solvents. This green method is particularly useful for indoles bearing electron-withdrawing groups and for azaindoles.

Experimental Section

All products are catalogued compounds and have been verified to be identical with the commercial materials.

A Typical Procedure of *N*-Detosylation. To a solution of *N*-tosyl-7-azaindole (100 g, 367 mmol) in THF (540 mL) and water (180 mL) was added CTAB (6.7 g, 0.05 equiv) and KOH (103.0 g, 5 equiv). The mixture was heated at refluxing until HPLC indicated the completion of the reaction. Water (300 mL) and *i*-PrOAc (500 mL) were added to the reaction mixture upon cooling to room temperature. The organic layer was separated and washed with water (2 × 300 mL). It was then concentrated under reduced pressure to a batch volume of ~100 mL. Heptanes (400 mL) was added to the residue. The resulting suspension was distilled under reduced pressure to a batch volume of ~300 mL. The suspension was cooled to room temperature and filtered. The filtered cake was washed with heptanes (50 mL) and dried under reduced pressure at 55 °C for 2 h to afford 7-azaindole (39.0 g, 90% yield).

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