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Efficient electrochemical cleavage of *N*,*N*-dimethylaminosulfonyl-protected indoles†

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Abstract

Indoles protected at the N-1 position with the *N*,*N*-dimethylaminosulfonyl group were efficiently deprotected by electrolysis. Yields were in the 80–90% range and the method was compatible with a number of functional groups (nitrile, ester, chloride, carboxamide).

The *N*,*N*-dimethylaminosulfonyl ($Me_2NSO_2^-$) group has been found to be an effective complement to the arsenal of protecting groups for the NH function of various heterocycles, being easy to incorporate and particularly stable to a variety of reaction conditions. Thus, it has been shown to be the optimal protecting group for the lithiation of imidazole, its powerful electron-withdrawing and *ortho*-directing properties allowing selective metallation at C-2 without having to use a large excess of metallating agent.[1] Its usefulness in the synthesis of di- and trisubstituted pyrrole derivatives has also recently been demonstrated.[2,3] We have shown that, in the case of 3-carboxy-β-carbolines, the *N*,*N*-dimethylaminosulfonyl group permits efficient *o*-metallation reactions in this family of compounds.[4]

A corollary of the stability of the *N*-sulfonyl bond is, of course, the difficulty encountered in the removal of this type of protecting group. In the case of *N*,*N*-dimethylaminosulfonyl imidazole derivatives, this was achieved by refluxing in 2 M aqueous hydrochloric acid.[1] For similarly protected pyrrole derivatives, tetrabutylammonium fluoride (TBAF) in THF at reflux was generally successful.[2,3] When this method failed, magnesium in methanol proved to be a good alternative.[3] In the case of β-carbolines, both a mixture (1:10) of triflic acid–trifluoroacetic

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acid or samarium diiodide in THF were shown to be particularly efficient in removing this protecting group.[4]

By analogy with our work with β-carbolines,[4,5] we have recently introduced the use of the *N*,*N*-dimethylaminosulfonyl group for the protection of the N-1 position of indole-5-carboxamides prior to effecting *o*-metallation reactions.[6] However, contrary to our experience with the β-carbolines, attempted removal of the sulfamoyl protecting group with triflic acid/TFA (or other acids) led mainly to decomposition of the substrate. Use of SmI_2, on the other hand, resulted unexpectedly in reduction of the *N*-protected indole to the corresponding indoline. The other reported methods for removal of the *N*,*N*-dimethylaminosulfonyl group (TBAF or Mg/MeOH) led to inconsistent results, the success of the procedures depending to a large degree on the pattern of substitution on the indole nucleus. Clearly, a cleaner and more generally applicable method of deprotection was required.

Electrochemical removal of protecting groups has been shown to display significant advantages over conventional methods.[7–9] The mild conditions of this kind of cleavage, and the possibility of smooth variation in the strength of the deprotecting reagent (electrode) by a simple variation of its potential, makes electrolysis an appealing approach for the selective removal of protecting groups.[10] Moreover, electrochemical reduction of arylsulfonamides, through direct or indirect electrolysis, is a well established reaction that leads to the corresponding amines and arylsulfinic acids in good yields.[11–15]

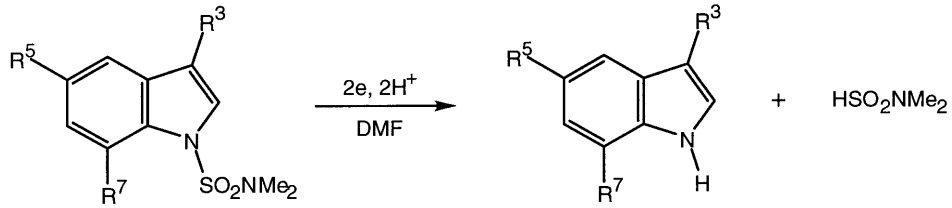
In this paper, we wish to report that use of controlled potential electrolysis has proven to be an efficient solution to the problems encountered in removing the *N*,*N*-dimethylaminosulfonyl protecting group by chemical methods in indole derivatives.

The *N*,*N*-dimethylaminosulfonyl protected indoles **1**–**12** (Table 1) were prepared by treating the indole derivative with sodium hydride (2 equiv.) and *N*,*N*-dimethylsulfamoyl chloride (2 equiv.) in THF for 4 h at room temperature. In some cases, concomitant chlorination of the initially unsubstituted C-3 position was observed to occur to a minor degree (**3**–**6**, **8**). Such a reaction has previously been reported during the course of the *N*-arylsulfonylation of indoles.[16,17]

In order to examine the ease of reduction of *N*,*N*-dimethylaminosulfonamides **1**–**12**, a preliminary voltammetric study was performed in DMF at a mercury cathode. Peak reduction potentials were found to be between −1.95 and −2.35 V, in the same range as that for arylsulfonamides.[14,15] The experiments were then run on a preparative scale (100–150 mg) allowing isolation of the expected *N*-deprotected indole in yields ranging from 76 to 91% (Table 1). By comparison, deprotection of compound **4** with TBAF gave only 30% of the desired product while with indole (compound **1**), only traces of the deprotected product were formed using this reagent. The *N*,*N*-dimethylaminosulfonyl group could, moreover, be cleaved selectively in the presence of other reducible functional groups such as nitrile (compounds **9** and **10**) or benzamide (compound **11**). In contrast, the presence of a bromo substituent (compounds **6** and **7**) was found to be incompatible with removal of the *N*,*N*-dimethylaminosulfonyl group owing to competitive cleavage of the C–Br bond. However, in no case was cleavage of C–Cl bonds observed (compounds **3**–**6**, **8**, **12**).

The electrochemical removal of the *N*,*N*-dimethylaminosulfonyl protecting group in indoles thus appears to be a preparatively useful, generally applicable and high-yielding procedure. The extension of this methodology to the deprotection of other so-protected heterocycles is currently under study.

Table 1
Electrochemical cleavage of *N*,*N*-dimethylaminosulfonamide derivatives **1**–**12** to the corresponding indoles



1-12

Compound	R^3	R^5	R^7	E^a (V)	Isolated yield (%) of indole
1	H	H	H	−2.50	76[b]
2	CO_2Me	H	H	−2.10	83
3	Cl	H	H	−2.50	83
4	Cl	OMe	H	−2.30	90
5	Cl	Cl	H	−2.20	91
6	Cl	Br	H	−2.15	[c]
7	H	Br	H	−2.15	[c]
8	Cl	H	Me	−2.40	90
9	CN	H	H	−2.10	87
10	H	CN	H	−2.30	90
11	H	CONHPh	H	−2.35	88
12	H	Cl	H	−2.40	81

[a] Electrolysis potential applied to the mercury working electrode.
[b] Significant amounts of indole were lost upon isolation due to its volatility.
[c] No trace of the expected product was obtained owing to competitive cleavage of the C–Br bonds.

General procedure for the electrochemical cleavage of the N,N-*dimethylaminosulfonyl group*

Using a cylindrical vessel fitted with two side arms separated from the main compartment with glass frits, a mercury pool electrode in the main compartment served as the cathode (working electrode) while a saturated calomel reference electrode was placed in one side arm, and a platinum sheet in the other side arm (anode, counter electrode). The electrolyte solution (0.2 mol L^{-1} tetraethylammonium perchlorate in DMF) was poured into the cell and the side arms. The *N*,*N*-dimethylaminosulfonyl derivative (0.35 mmol) was added to the solution in the main compartment (35 mL) and the resulting solution was then reduced (Table 1) under nitrogen at room temperature. After exhaustive electrolysis (2 Faraday mol^{-1}) and once a minimum value of the current was recorded, the solution was poured into water (350 mL) and extracted with diethyl ether (200 mL). The organic phase was washed vigorously with water and dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure at 30°C. The residue was chromatographed on silica gel to give the expected indole. Its structure was confirmed by comparison with an authentic sample.

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