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A new protecting-group strategy for indoles

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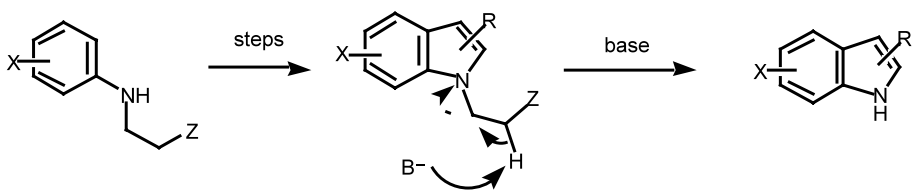
Abstract—The 2-phenylsulfonylethyl group is a useful alkyl protecting group for nitrogen during indole synthesis; it is readily removed from the indole nitrogen under basic conditions.

The wide-ranging biological activity associated with many indole derivatives, both naturally occurring and synthetic, ensures that the synthesis of this important ring system remains a topic of current interest.[1,2] Although many synthetic routes to indoles lead directly to *N*-unsubstituted derivatives, many also lead to *N*-substituted or -protected indoles, and whereas protecting group strategies for basic nitrogen atoms are well worked out,[3,4] the choice of suitable protecting groups for non-basic heterocyclic NH groups is more problematic. Electron-withdrawing carbonyl or sulfonyl based protecting groups, although easy to remove, often markedly affect the reactions leading to, and the reactivity of, the heterocyclic ring, and therefore one usually has to resort to alkyl-based groups, which are often less easy to remove.[5]

We recently encountered this exact problem in our modified version of the Bischler indole synthesis.[6] Whereas *N*-methylanilines were readily converted into *N*-methylindoles by dirhodium(II) acetate catalysed reaction with diazoketones to give α-(*N*-arylamino)ketones followed by cyclisation, the corresponding sequence with *N*-acetyl- or -tosyl anilines was unsatisfactory, and hence *N*-unsubstituted indoles could not be obtained. Therefore, in order to extend the methodology, we required an alkyl protecting group that functioned as a simple *N*-alkylaniline but was readily removable following the conversion of the aniline into the corresponding indole. Since indole is a much better leaving group than aniline in a 1,2-elimination reaction, as reflected in the difference of ca. 15 in their pK_a values, it seemed that a protecting group that could be removed in a base-mediated elimination reaction would be suitable. Therefore, a retro-Michael strategy involving a CH_2CH_2Z group ($Z = SO_2R$, CO_2R) was considered (Scheme 1). Although there are reports of the 2-arenesulfonylethyl group being used as a protecting group for the NH group of other heterocyclic rings,[7–9] and also for amides, carbamates and β-lactams,[10] it has apparently not been used for indoles. We now report the use of this alkyl protecting group for nitrogen during indole synthesis, its facile introduction into preformed indoles, and its base-mediated removal.

The starting *N*-alkylanilines **1** were readily prepared by reaction of the corresponding anilines with commercially available phenyl vinyl sulfone and treated with methyl 2-diazo-3-oxo-butanoate or -pentanoate in boiling chloroform in the presence of dirhodium(II) acetate. This resulted in N–H insertion reaction of the interme-



Scheme 1. $-CH_2CH_2Z$ group stable to base when attached to aniline (p$K_a \sim 31$) but labile to base when attached to indole (p$K_a \sim 16$).

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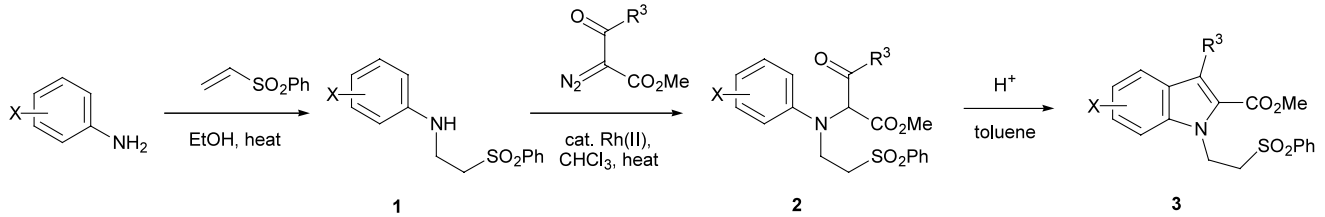


Scheme 2.

Table 1. Synthesis of *N*-(2-phenylsulfonylethyl)indoles

Entry	X	**1** Yield (%)	R^3	**2** Yield (%)[a]	**3**	X	**3** Yield (%)
1	4-Me	99	Me	62	**a**	5-Me	71
2	–	–	Et	63	**b**	5-Me	66
3	4-MeO	68	Me	78	**c**	5-MeO	49
4	2-Me	68	Me	73	**d**	7-Me	51
5	2-MeO	74	Me	90	**e**	7-MeO	48
6	4-Br	17	Me	36	**f**	5-Br	79
7	3-MeO	75	Me	63	**g**	4-MeO (6%)	30
					h	6-MeO (24%)	

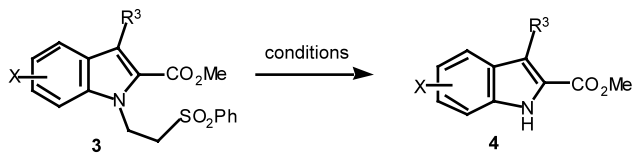
[a] Compounds not characterised; yields refer to partially purified material.

diate rhodium carbene, and gave the *N*-arylamino ketones **2** in reasonable yield. The intermediate *N*-arylamino ketones **2** were not completely purified, but were cyclised by treatment with acidic ion-exchange resin Amberlyst 15® in toluene to give the required indoles **3** (Scheme 2, Table 1).[11]

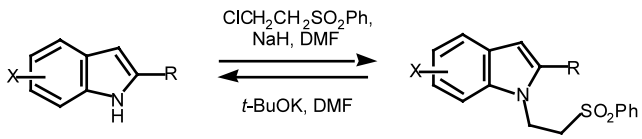
The base mediated deprotection of the 1-alkylindoles **3** was first investigated with the 1-(2-phenylsulfonylethyl) derivative **3a**, the most suitable conditions being potassium *tert*-butoxide in DMF (Table 2). These conditions were applied to a range of indoles **3**, and resulted in deprotection to give the *N*-unsubstituted compounds **4** in variable yield (Table 2).

Finally, the use of the 2-phenylsulfonylethyl protecting group on preformed indoles was briefly investigated. The group was readily introduced by reaction of the indole with 2-chloroethyl phenyl sulfone in DMF using sodium hydride as base, and removed using potassium *tert*-butoxide in DMF (Scheme 3).

Table 2. Deprotection of *N*-(2-phenylsulfonylethyl)indoles



3	X	R^3	Conditions	Yield (%)
a	5-Me	Me	*t*-BuOK, DMF/DBN	87
			Et_3N, DMF/DBU	59
			Et_3N, DMF	42
b	5-Me	Et	DBN, toluene	27
e	7-MeO	Me	*t*-BuOK, DMF	55
h	6-MeO	Me	*t*-BuOK, DMF	34



X= 5-MeO, R = H; protection 73%; deprotection 91%
X= H, R = CO_2Et; protection 67%; deprotection 100%

Scheme 3.

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11. *Typical experimental procedure:* A solution of **1** (1.25 mmol), diazo compound (2.50 mmol, 2 equiv.) and dirhodium(II) acetate (10 mg) in distilled chloroform (10 ml) was heated at reflux for 1.5 h. The reaction mixture was concentrated in vacuo and passed through a silica gel column eluting with ethyl acetate–light petroleum (1:9) to give the intermediate **2**, which was dissolved in toluene (3 ml) and heated under reflux overnight in the presence of Amberlyst 15® (110 mg). The reaction mixture was filtered, concentrated in vacuo and purified on silica gel eluting with ethyl acetate–light petroleum (1:9) to give the indole **3**.