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REGIOSELECTIVE SYNTHESIS OF 2,3,5-TRISUBSTITUTED INDOLES FROM *p*-SULFINYLANILINE BY DUAL USE OF THE SULFINYL GROUP†

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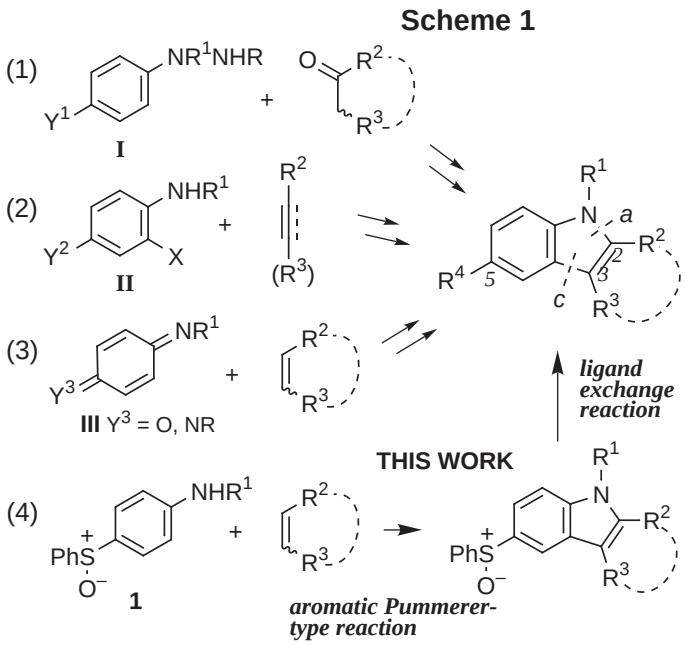
Abstract — A novel and convergent synthesis of 2,3,5-trisubstituted indoles (**6**) from *p*-sulfinylaniline (**1**) is described. The single *p*-sulfinyl group was repeatedly employed in two ways; viz., the construction of the 2,3-disubstituted indole/indoline skeleton and the introduction of a carbon substituent at the C-5 position.

Substituted indole and indoline moieties are the core structures of a broad range of biologically active compounds of both natural and synthetic origin, and the development of an effective synthetic method for these structures bearing diverse substituents is an important and interesting subject.[1] Among a large number of reported methods, the procedures that form both *a* and *c* bonds by the coupling of two components in one step feature the direct and convergent preparation of diverse 2- and/or 3-substituted indoles (Scheme 1). The Fischer indole synthesis (eq. 1) and the palladium-catalyzed cyclization of 2-haloanilines (**II**) (eq. 2) are typical examples with wide applicability. The cycloaddition of olefins to iminoquinone derivatives (**III**) were also disclosed (eq. 3).[2] On the other hand, the regioselective introduction of versatile carbon substituents at the C-5 position of the indoles sometimes becomes a significant issue for research towards the development of new drugs.[3] The direct introduction protocols such as the Friedel–Crafts reaction often suffer from unsatisfactory regioselectivity,[4] and the transformation of the functional group Y^3 in eq. 3 to a carbon substituent is not always easy.[2] Alternative approaches were reported using the indole synthesis having a precursor (**I** or **II**) with a functional group such as bromo or alkoxycarbonyl group as Y^1 or Y^2 followed by their transformation.[3a,5]

Scheme 1



As a part of our ongoing project on the functionalization of aromatic compounds by the aromatic Pummerer-type reaction,[6,7] we present here a new convenient methodology (eq. 4) for the regioselective synthesis of the diverse 2,3,5-

substituted indoles. Our method is unique among the existing methods in the sense that a single *p*-sulfinyl group of the aniline (**1**) effectively manages either the construction of the indole/indoline skeleton by the aromatic Pummerer-type reaction and the easy introduction of a carbon substituent at the C-5 position *via* the ligand exchange reaction.

First, a preliminary investigation on the feasibility of the Pummerer-type reaction of some *N*-protected anilines (**1**) (1 equiv.) with anethole (**2a**) (2 equiv.) was carried out in the presence of $(CF_3CO)_2O$ (2 equiv.),[7] and it was revealed that the reaction of the *N*-toluenesulfonyl- (Ts) (**1a**) or the *N*-(2,4-dinitrobenzenesulfonyl)- (DNs) aniline (**1b**) gave the corresponding *trans*-indolines (**3a** and **3b**) in 80% and 75% yields, respectively (Table 1, entries 1 and 2).[8–10] These reactions are plausibly accounted for by a stepwise mechanism through the intermediates (**A**–**C**). The use of other reagents, Tf_2O and $SOCl_2$, and solvents, CH_2Cl_2 and $CHCl_3$, was ineffective. The similar reactions of **1a** with the electron-rich olefin (**2b**) gave the product (**3c**) in high yield (entry 3), and the cinnamate (**2c**) could also be applied to this reaction (entry 4). The cycloadducts (**3**) were readily oxidized by DDQ in refluxing benzene to give the 2-arylindoles (**4**) (Scheme 2 and Table 1).[11]

Scheme 2

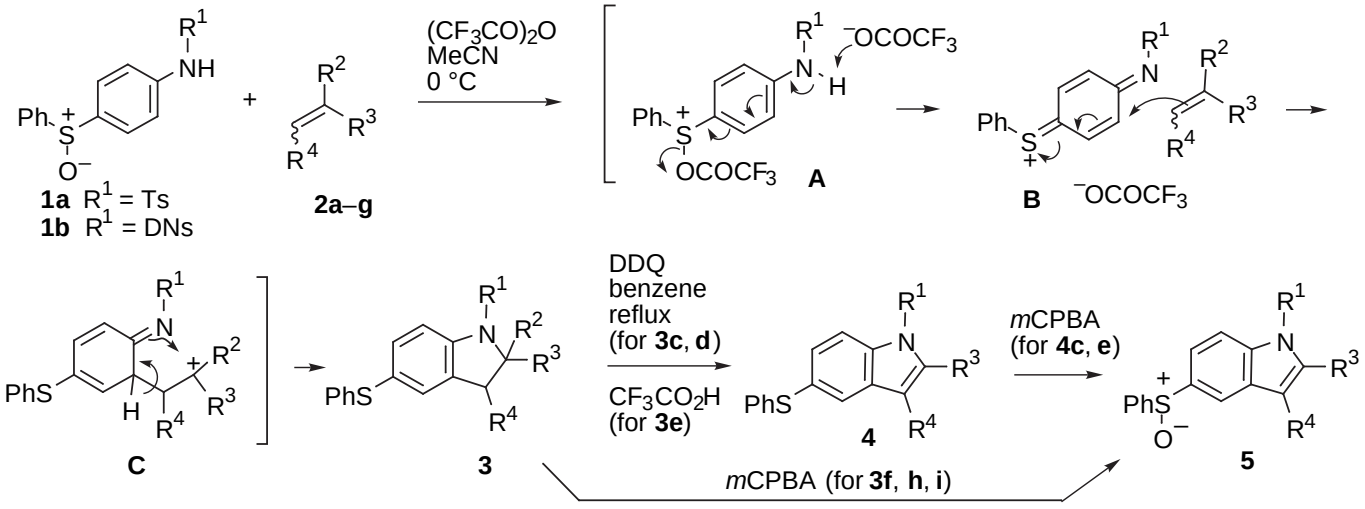


Table 1. Preparation of the indolines (**3**) and indoles (**4** and **5**).

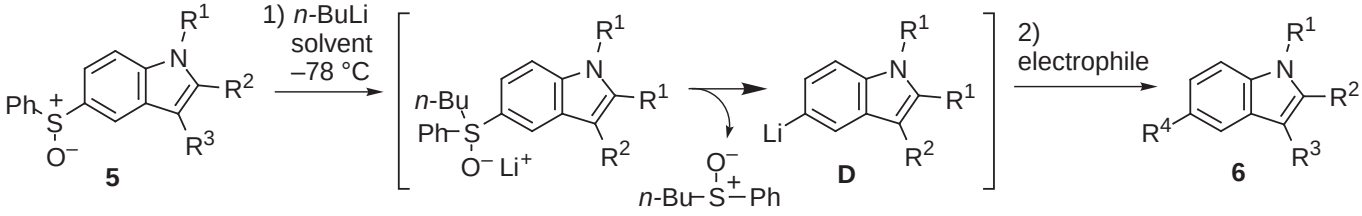
		2[a]				yield (%)		
entry	**1**, R^1	R^2	R^3	R^4		**3**[b]	**4**	**5**
1	Ts **1a**	H	C_6H_4-4-OMe	Me	**2a** (97:3)	**3a** 80 (>95:5)		
2	DNs **1b**	H	C_6H_4-4-OMe	Me	**2a** (97:3)	**3b** 75 (>95:5)		
3	Ts **1a**	H	C_6H_3-3,4-diOMe	Me	**2b** (95:5)	**3c** 75 (>95:5)	**4c** 50	**5c** 86
4	DNs **1b**	H	C_6H_4-4-OMe	CO_2Et	**2c** (>99:1)	**3d** 55 (>95:5)	**4d** 31	
5	Ts **1a**	SPh	H	H	**2d**	**3e** —	**4e** 65[c]	**5e** 90
6	DNs **1b**	SPh	H	H	**2d**	**3f** 85	**4f** —	**5f** 90
7	DNs **1b**	SPh	H	$C_3H_6CO_2Et$	**2e** (50:50)	**3g** 83 (41:59)	**4g** —	
8	Ts **1a**	SPh	H	*n*-C_6H_{13}	**2f** (67:33)	**3h** —[d]	**4h** —[d]	**5h** 41[e]
9	Ts **1a**	SPh	–$(CH_2)_4$–		**2g**	**3i** —[d]	**4i** —[d]	**5i** 57[e]

[a] Ratio of the *E*- and *Z*-**2** is shown in parenthesis. [b] Ratio of *trans*- and *cis*-**3** is shown in parenthesis. [c] Ten equiv. of CF_3CO_2H was added to the reaction mixture after consuming **1a**. [d] A mixture of **3** and **4** was obtained, which was treated with *m*CPBA to give **5**. [e] Yield based on **1a**.

For the preparation of **3** and **4** having the alkyl substituents at the C-2 and/or the C-3 positions, the (phenylthio)alkenes (**2d**–**g**) were effectively employed. Thus, the reaction of **1a** with **2d** afforded a mixture of **3e** and **4e**. The addition of trifluoroacetic acid (10 equiv.) to the crude reaction mixture accelerated the elimination of thiophenol to provide **4e** in 65% yield (entry 5). On the other hand, the use of the *N*-DNs aniline (**1b**) selectively gave **3f** in 85% yield (entry 6). The treatment of either **4e** or **3f** with *m*CPBA gave the 5-sulfinylindoles (**5e** and **5f**), the substrate for the subsequent ligand exchange reaction, in high yields. A similar reaction of **2e** with **1b** gave **3g** (entry 7), whereas those of **2f** or **2g** with **1a** gave a mixture of **3** or **4**, which was treated with *m*CPBA to give **5h** and **5i** in 41% and 57% yields, respectively (entries 8 and 9).

Next, the introduction of a carbon substituent at the C-5 position of **5** was examined (Table 2). When **5e** was treated with *n*-BuLi in THF at –78 °C,[7] the ligand exchange reaction quickly took place to give the lithio intermediate (**D**). Its generation was confirmed by the formation of the C-5 protonated product (**6a**) (67%) by quenching the reaction mixture with MeOH (entry 1). Changing the solvent to anhydrous toluene was found to give a better yield of **6a** (75%) (entry 2). On the other hand, a similar reaction of the *N*-DNs derivative (**5f**) in either THF or toluene caused cleavage of the DNs group rather than the ligand exchange reaction giving the *N*-H sulfoxide (**5j**) (R^1 = H) in 90% yield (entry 3). Therefore, the *N*-Ts indoles (**5c**, **5e**, and **5i**) were treated with *n*-BuLi in toluene followed by the addition of a carbon electrophile to give products (**6c**–**f**) in moderate to good yields (entries 4–7).[12]

Table 2. Introduction of a carbon substituent at the C-5 position.



							6		
entry	R^1	R^2	R^3		solvent	electrophile	R^4		yield (%)
1	Ts	H	H	**5e**	THF	MeOH	H	**6a**	67
2	Ts	H	H	**5e**	toluene	MeOH	H	**6a**	75
3	DNs	H	H	**5f**	toluene	MeOH	H	**6b**	—[a]
4	Ts	H	H	**5e**	toluene	DMF	CHO	**6c**	72
5	Ts	H	H	**5e**	toluene	$ClCO_2Me$	CO_2Me	**6d**	51
6	Ts	C_6H_3-3,4-diOMe	Me	**5c**	toluene	DMF	CH(OH)Et	**6e**	45
7	Ts	–$(CH_2)_4$–		**5i**	toluene	EtCHO	CHO	**6f**	48

[a] The deprotected sulfoxide (**5j**) (R^1 = R^2 = R^3 = H) was obtained as the only identified product in 90% yield.

The presented methodology will be effectively used for the preparation of the biologically significant indole derivatives such as 2-arylindoles,[3c,11] cycloalkane-ring-fused indoles,[3d,e,13] and their congeners. The optimization of each reaction and the total synthesis of the indole derivatives are now in progress.

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† Dedicated to Professor A. I. Meyers in celebration of his 70th birthday.

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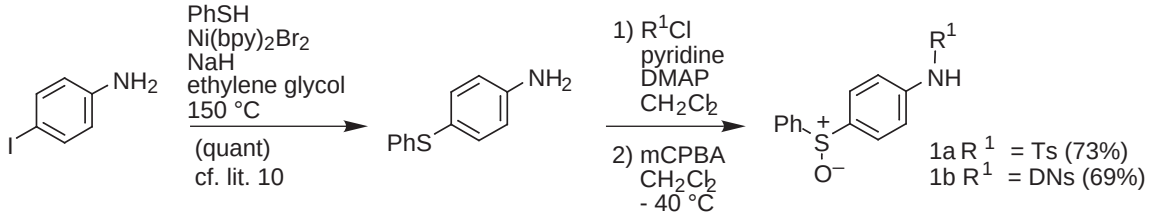
8. A similar reaction with other *N*-protected anilines (**1**) (R^1 = Ac, $COCF_3$, $CO_2{}^tBu$, CO_2CH_2Ph) did not give the expected products (**3**).
9. The *N*-protected *p*-sulfinylanilines (**1a** and **1b**) were prepared from commercial *p*-iodoaniline in three steps.



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12. The replacement of the *N*-DNs group of **3** or **4** to the Ts group was available in two steps (1. *n*-$PrNH_2$, CH_2Cl_2, rt; 2. TsCl, Bu_4NHSO_4, NaOH, toluene–H_2O, rt) in high yields.
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