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Novel Synthesis of 2-Aryl and 2,3-Disubstituted Indoles by Modified Double Elimination Protocol

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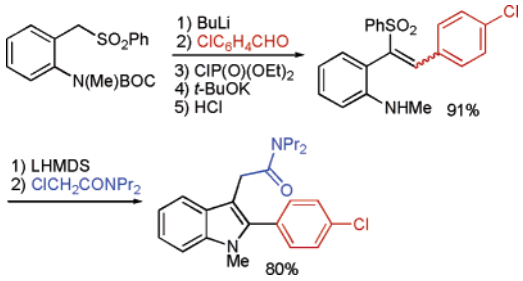
ABSTRACT



Syntheses of 2-aryl and 2,3-substituted indoles were realized by modified double elimination protocol. Under basic conditions, vinyl sulfones derived from the reaction of 2-aminobenzyl sulfone with benzaldehydes underwent cyclization and alkylation followed by elimination of sulfinic acid to afford 2,3-substituted indoles.

The indole nucleus is widely prevalent in many biologically active natural and unnatural products.[1] Numerous methods have been reported in the literature for the construction of the indole skeleton.[2] Apart from classical methods such as Fischer, Reissert, and Madelung protocols,[2a,3−5] many transition metal-assisted intermolecular annulation[6] and intramolecular cyclization[7] methods have been developed in the last two decades which provide indole derivatives efficiently and with different functional group compatibility. We have long been involved in the project on synthesis of polyenes and acetylenes by taking advantage of the double elimination reactions of β-substituted sulfones in which vinyl sulfones are readily generated as intermediates (Scheme 1).[8] In this context, we postulated that incorporation of an amino group to the ortho position of arylvinyl sulfones would lead to a

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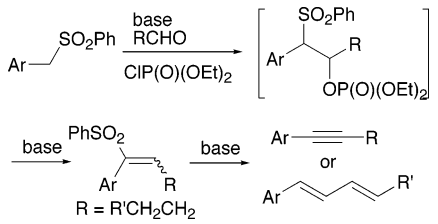
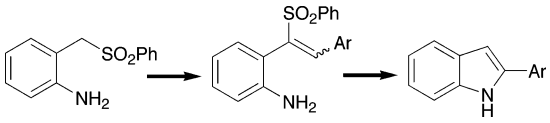
Scheme 1



new protocol for arylindole synthesis (Scheme 2). To our knowledge, no such cyclization mode has been exploited although the endo-mode cyclization of sulfonylallenes to

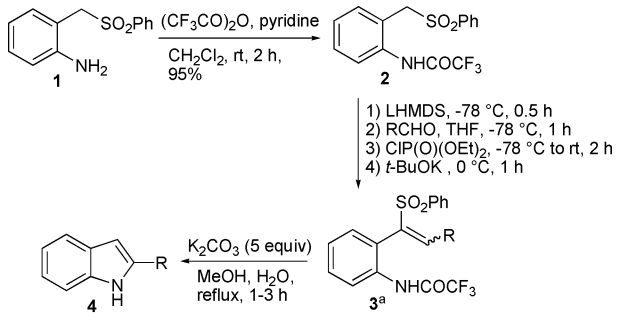
Scheme 2



construct nitrogen heterocycles[9] and intramolecular addition of amines to vinylsulfoxides leading to isoquinoline derivatives[10] are known. Furthermore, it is of practical use that the double elimination reaction is conducted by an organoalkali metal promoter while many intramolecular cyclizations so far known have recourse to transition metal catalysts, which are occasionally toxic.[11] In this letter, we wish to report a new strategy for synthesis of indoles consisting of two one-pot procedures for preparing *o*-amino vinyl sulfone and subsequent Michael addition of in situ-generated amino anion.[12]

First, we examined the synthesis of 2-phenylindole starting from sulfone **2** (Scheme 3). The anion of benzyl sulfone **2**

Scheme 3

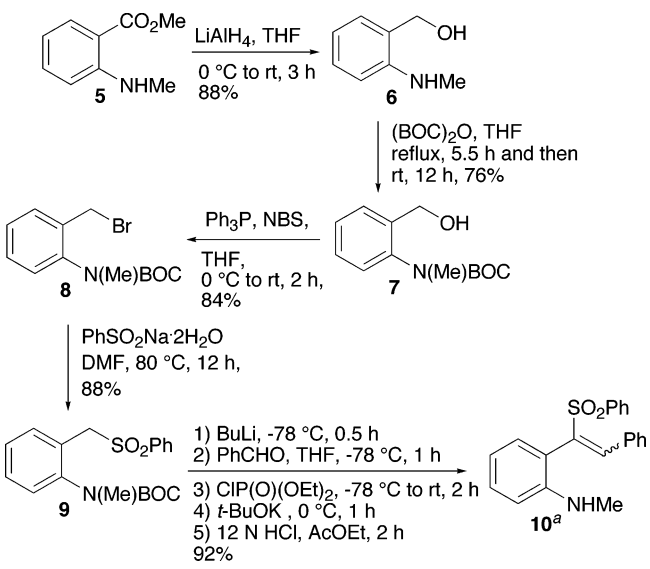


[a] One isomer (geometry not determined).

reacted with benzaldehyde at −78 °C, and the trapping of the resulting aldolate with diethyl chlorophosphate followed by the elimination of the phosphate with *t*-BuOK provided vinyl sulfone **3a**. The cleavage of the amino protecting group with potassium carbonate was accompanied by spontaneous cyclization to afford 2-phenyl indole **4a** in excellent yield. The reaction proceeded well with other aromatic aldehydes in good to moderate yields, thus providing a general method to synthesize 2-aryl indoles.

Next, we turned our attention to 2,3-disubstituted indoles through one-pot incorporation of a substituent at the 3-position. The synthetic route for requisite *o*-amino vinyl sulfone **10** is depicted in Scheme 4. The *N*-methyl group is the

Scheme 4



[a] One isomer (geometry not determined).

protection of choice because this group can survive under the double elimination conditions and, more preferably, there are many biologically important 1-methylindoles. The key sulfone **9** was prepared straightforwardly from commercially available *N*-methyl anthranillic acid methyl ester **5**. Then, **9** was converted to vinyl sulfone **10** by a one-pot sequence of reactions with benzaldehyde, diethyl chlorophosphate, and *t*-BuOK followed by cleavage of the BOC group by 12 N HCl/EtOAc. Remarkably, these four sequential reactions gave rise to a 92% overall yield. Treatment of vinyl sulfone **10** with lithium hexamethyldisilazide (LHMDS) and subsequent trapping of the carbanion generated after the Michael-type cyclization with methyl iodide afforded 1,3-dimethyl-2-phenyl indole **11a** in good yield (Table 1). The reaction went smoothly with many electrophiles as summarized in the table. In addition to simple alkyl and allyl iodides,

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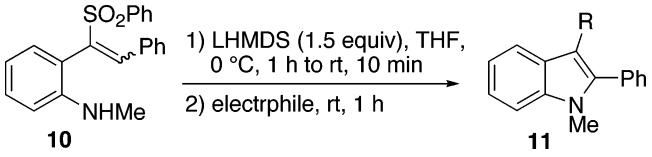
(11) Indole synthesis with the aid of lithium reagents: (a) Miyagi, T.; Hari, Y.; Aoyama, T. *Tetrahedron Lett.* **2004**, *45*, 6303. (b) Coleman, M. C.; O'Shea, D. F. *J. Am. Chem. Soc.* **2003**, *125*, 4054.

(12) α-Amino benzyl sulfones were converted to the corresponding Schiff bases, whose benzylic anions underwent intramolcular addition to the C=N bond at the ortho position to afford 2-arylindoles: Wojciechowski, K.; Makosza, M. *Bull. Soc. Chim. Belg.* **1986**, *95*, 671.

Table 1. Synthesis of 2,3-Disubstituted Indoles



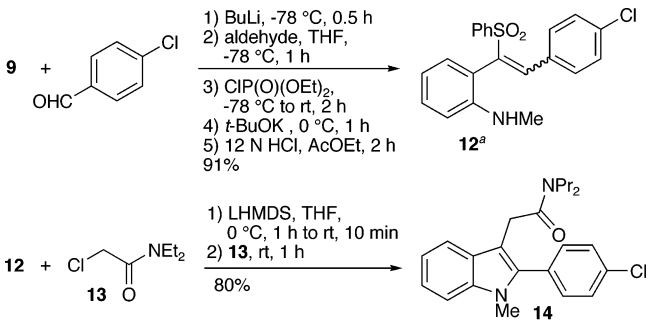
electrophile	R	product	yield (%)[a]
MeI (3 equiv)	CH_3	**11a**	82
C_2H_5I (4 equiv)	C_2H_5	**11b**	86
C_3H_7I (4 equiv)	C_3H_7	**11c**	84
allyl iodide (4 equiv)	$CH_2CH{=}CH_2$	**11d**	84
$BrCH_2CO_2C_2H_5$ (4 equiv)	$CH_2CO_2C_2H_5$	**11e**	81
$ClCH_2CON(C_2H_5)_2$ (4 equiv)	$CH_2CON(C_2H_5)_2$	**11f**	86
benzoyl chloride[b] (5 equiv)	COPh	**11g**	85

[a] Isolated yield. [b] Reagents and conditions: (i) LHMDS (1.5 equiv), 0 °C, 1 h to room temperature, 10 min, (ii) PhCOCl (5 equiv), rt, 1 h, (iii) LHMDS (5 equiv), rt, 1 h.

alkylation reagents with an ester or amide function were employable as well. It is to be noted that acylation also works smoothly because 3-acyl derivatives constitute an important class of the indole derivatives.

To exemplify the usefulness of the present protocol, we have chosen compound **14**, which is one of the better ligands for the antineophonic mitochondrial DBI receptor complex[13] (Scheme 5). Thus, the vinyl sulfone **12** was synthesized starting from **9** and 4-chlorobenzaldehyde according to our modified double elimination protocol. Upon treatment of the amino anion generated from **12** with LHMDS in the presence of chloroacetamide **13**,[14] the intramolecular Michael-type addition and in situ alkylation of the resulting carbanion occurred smoothly to provide compound **14** in good yield.[15]

Scheme 5



[a] One isomer (geometry not determined).

In conclusion we have shown a novel route to synthesize indole derivatives from easily accessible sulfones by a sequence of two one-pot procedures. The overall yields are high, in general, and the products are free from the residues of transition metal catalysts, offering a practical means for the indole synthesis. Efforts to synthesize other heterocycles are currently in progress.

Supporting Information Available: Experimental details and characterizaton data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) **Synthesis of 12:** BuLi (1.33 M in hexane, 1.45 mL, 1.93 mmol) was added to a THF solution (20 mL) of sulfone **9** (0.636 g, 1.76 mmol) at −78 °C, and the mixture was stirred for 30 min. 4-Chlorobenzaldehyde (0.296 g, 2.11 mmol) in THF (8 mL) was added dropwise at this temperature. After an additional 1 h, $ClP(O)(OEt)_2$ (0.305 mL, 2.11 mmol) was added at −78 °C and the mixture was stirred at room temperature for 2 h. Potassium *tert*-butoxide (0.645 g, 5.28 mmol) was added at 0 °C. After the mixture had been stirred at the same temperature for 1 h, the solvent was evaporated and the residue was dissolved in a premixed solution of ethyl acetate (29.4 mL)/12 M HCl (12.6 mL) and stirred at room temperature for 2 h. The reaction mixture was neutralized with solid $NaHCO_3$, extracted with ethyl acetate, dried over $MgSO_4$, and filtered. The solvent was evaporated and the residue was chromatographed (2.5:7.5 ethyl acetate/hexane) to give 0.614 g of **12** (91%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.65 (dd, 2H, J = 8.5, 1.5 Hz), 7.57 (m, 1H), 7.42 (t, 2H, J = 8.5 Hz), 7.28 (m, 1H), 7.18 (d, 2H, J = 8.5 Hz), 7.10 (d, 2H, J = 8.5 Hz), 6.58 (d, 1H, J = 8.0 Hz), 6.55 (dt, 1H, J = 7.0, 1.0 Hz), 6.47 (dd, 1H, J = 7.0, 1.0 Hz), 3.97 (br, 1H), 2.57 (d, 3H, J = 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 139.0, 138.2, 138.0, 136.5, 133.3, 131.4, 131.2, 131.1, 131.0, 128.9, 128.8, 128.6, 116.8, 115.0, 110.4, 30.4. **Synthesis of 14:**[13] A 50 mL flask was charged with **12** (0.306 g, 0.79 mmol) in THF (15 mL) and cooled to 0 °C. LHMDS (1 M in THF, 1.20 mL, 1.19 mmol) was added slowly. After the mixture had been stirred at 0 °C for 1 h, and then at room temperature for 10 min, **13** (0.566 g, 3.18 mmol) was added. After the mixture had been stirred at room temperature for 1 h, the reaction was quenched by the addition of aqueous NH_4Cl and extracted with ethyl acetate. The extract was dried over $MgSO_4$ and filtered. The solvent was evaporated and chromatographed (3:7 ethyl acetate/hexane) to give 0.244 g of **14** (80%) as a colorless solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, 1H, J = 7.5 Hz), 7.47 (d, 2H, J = 8.5 Hz), 7.40 (d, 2H, J = 8.5 Hz), 7.33 (d, 1H, J = 8.5 Hz), 7.25 (m, 1H), 7.14 (t, 1H, J = 8.0 Hz), 3.68 (s, 2H), 3.60 (s, 3H), 3.26 (t, 2H, J = 7.5 Hz), 3.10 (t, 2H, J = 7.5 Hz), 1.53 (m, 4H), 0.83 (t, 3H, J = 7.5 Hz), 0.74 (t, 3H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 137.3, 137.1, 134.3, 131.8, 129.9, 128.6, 127.6, 122.0, 119.6, 119.4, 109.3, 107.6, 49.6, 47.8, 30.9, 30.5, 22.1, 20.8, 11.3, 11.0.