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# NOVEL AZA AND OXA WITTIG-HORNER REACTIONS OF DIETHYL (1-BENZENESULFONYL)INDOL-2-YL METHYL PHOSPHONATE

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**Abstract**: Aza and oxa Wittig-Horner reactions of diethyl (1-benzenesulfonyl)indol-2-yl methyl phosphonate with arylnitroso compounds and oxygen have been reported.

In general vinylindoles [1,2] are excellent synthetic tools for the construction of indole alkaloids and have been well exploited for the synthesis of pharmacologically interesting lead structures. Despite the abundant reports on the synthesis on the 2-vinylindoles in literature, it still remains an attractive molecule for the researchers. Our earlier synthesis of quinolono carbazoles[3], *via* 2-vinylindoles involved diethyl (1-benzenesulfonyl)indol-2-yl methyl phosphonate **2**.

Diethyl phosphonate ester[4] **1** reported from our laboratory on treatment with Raney nickel in boiling ethanol followed by work-up and crystallization

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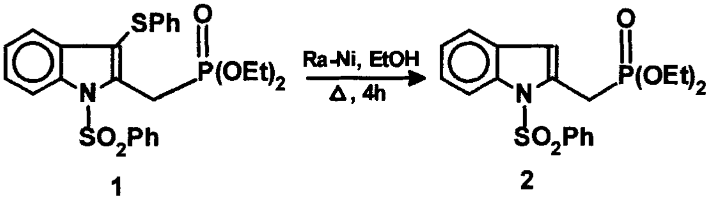
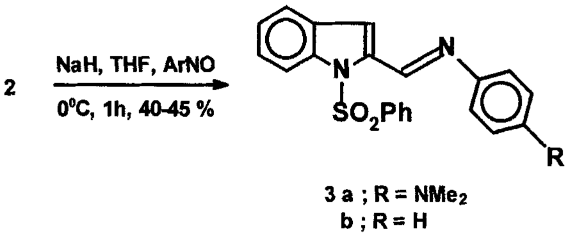
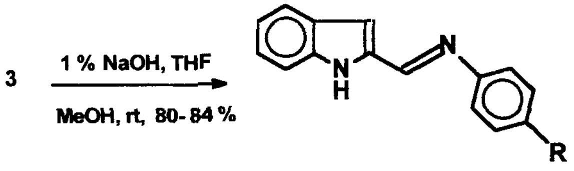
afforded 3-free indole phosphonate ester **2** as a crystalline solid in 85% yield. The advantage of this phosphonate ester is that it will not suffer N-deprotonation unlike the corresponding N-free indole during Wittig-Horner reaction. The N-free analog of **2** namely diethyl indol-2-yl methyl phosphonate has been reported [5] through different route.



Only a few reports on Wittig or Wittig-Horner reactions are available for the formation of carbon-nitrogen bond [6-8]. The objective of the present study was to use the phosphonate ester **2** for the preparation of an aza diene through Wittig-Horner reaction using arylnitroso compounds. Phosphonate ester **2** was reacted with arylnitroso compounds using NaH in THF to yield the imine **3** in 40-45% yield.

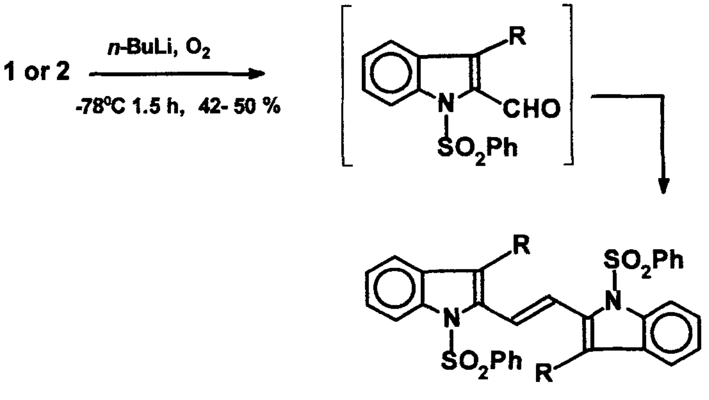


Selective cleavage of N-phenylsulfonyl group in **3a** was effected with 1 % NaOH in THF/MeOH mixture (ratio 2:1). NOE study of aza diene **4** revealed the anti configuration of the imine substituents. When the imine hydrogen at δ 8.6 was irradiated there was enhancement of peaks at δ 6.93 (11 %) and δ 7.29 (18 %) due to indole 3-H and the hydrogens meta to $NMe_2$ group in the aryl ring respectively.



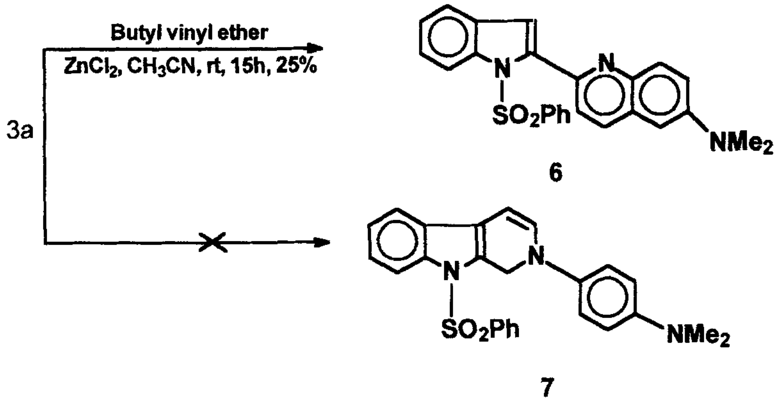
**4a** = $NMe_2$
**b** = H

The anion from the phophonate ester **1** or **2** (generated by *n*-BuLi in THF) was treated with dry oxygen. Work up of the reaction gave a compound in 40-45% yield which was identified to be biindolylethene **5**. It is possible that **5a,b** might form either via the intermediacy of the aldeyde or by the direct oxidative coupling of the carbanion from **1** or **2**.



**5a** ; R = H
**b** ; R = SPh

The imine **3a** underwent a facile regioselective cycloaddition with *n*-butyl vinyl ether to give a quinoline derivative **6** rather than a β-carboline derivative **7**. Imines from an aryl aldehyde and aniline are known [8] to behave as 2-aza-1,3-butadiene rather than a 1-aza-1,3-butadiene.



**Experimental :**

**Diethyl (1-benzenesulfonyl)indol-2-yl methyl phosphonate 2**

To a solution of diethyl (1-benzenesulfonyl-3-phenylthio)indol-2-yl methyl phosphonate **1** (5.16 g, 10 mmol) in ethanol (100 mL) was added the Raney nickel (~ 15 g) and the resulting mixture was refluxed for 4 h. Then it was cooled and nickel was filtered off and washed with hot ethanol ( 4 X 25 mL). The solvent was removed from the combined filtrate under reduced pressure. The yellow liquid obtained was crystallized from benzene-petrol to give phosphonate ester **2** as a white crystalline solid.

(3.47g, 85%); mp 84°C (benzene-petrol)

IR (KBr) cm$^{-1}$ : 1460, 1360, 1350, 1150; $^1$H NMR (CDCl$_3$/TMS) δ 1.3 (t, 6H); 3.4 (d, $J$ = 27 Hz, 2H); 4.2 (m, 4H); 6.95 (s, 1H); 7.3-8.3 (m, 9H);

HRMS: $C_{19}H_{22}NO_5PS$ Calcd. : 407.09567; Found : 407.10028

**General procedure for Aza Wittig-Horner reaction of 2**

To a well stirred suspension of sodium hydride (0.25 g, 5 mmol) in dry tetrahydrofuran (5 mL) under nitrogen at 0°C, a solution of **2** (2.04 g, 5 mmol) in the same solvent (15 mL) was added slowly. After the evolution of hydrogen ceased, the arylnitroso compound (5 mmol) in the same solvent (10 mL) was added and stirred further for 1h. The mixture was poured over crushed ice. The sticky material was extracted with methylene chloride (2 X 25 mL) and the extract was wahsed with water (2 X 20 mL) and dried ($MgSO_4$). The residue obtained after removal of the solvent was column chromatographed (benzene-petrol = 1:4) to give the imine **3** as a crystalline solid.

**N-(1-Benzenesulfonylindol-2-ylmethylene)-4-(N',N'-dimethylamino)aniline 3a**

(0.9g, 45%); mp 112 °C (ethanol)

IR (KBr) cm$^{-1}$ : 1610, 1360, 1180; $^1$H NMR (400MHz) (CDCl$_3$/TMS) δ 3.03 (s, 6H); 6.80 (d, $J$ = 8.6 Hz); 7.28-7.56 (m, 9H); 7.75 (d, $J$ = 8.6 Hz, 2H); 8.25 (d, 1H); 9.27 (s, 1H); HRMS: $C_{23}H_{21}N_3SO_2$ Calcd. : 403.13545; Found : 403.13217

**N-(1-Benzenesulfonylindol-2-ylmethylene)aniline 3b**

(0.72g, 40%); mp 140 °C (benzene-petrol)

IR (KBr) cm$^{-1}$ : 1610, 1355, 1170; $^1$H NMR (CDCl$_3$/TMS) δ 7.2-7.9 (m, 14H) ; 8.3 (d, 1H); 9.3 (s, 1H); HRMS $C_{21}H_{16}N_2SO_2$ Calcd. : 306.09325; Found : 360.08645

## Diels -Alder reaction of 3a

To a solution of imine **3a** (0.8g, 2mmol) in dry acetonitrile was added n-butyl vinyl ether (0.26mL, 2mmol) followed by finely powdered anhydrous zinc chloride (0.5g). This was stirred at room temperature for 15 h. Most of the solvent was removed by distillation and the residue was treated with ice. The sticky product was extracted with methylene chloride (3 X 25 mL) and the extract was washed with water (2 X 20mL) and dried ($MgSO_4$). The residue obtained after removal of solvent was chromotographed (benzene – petrol = 3:2) to give 1-benzenesulfonyl-2-(6–dimethylaminoquinolin-2-yl)indole **6** as a crystalline solid (0.21g, 25%).mp.172°C (ethyl acetate – petrol)

IR (KBr) $cm^{-1}$ : 1615, 1360 and 1170; $^1H$ NMR (300MHz) ($CDCl_3$/TMS) $\delta$ 3.1 (s, 6H,$NMe_2$); 6.87 (d, J = 3Hz, 1H); 6.92 (s, 1H); 7.26-7.41 (m, 7H); 7.64-7.72 (m, 3H); 7,99- 8.02 (m, 2H); 8.23-8.26 (d, J = 9Hz, 1H); MS m/e 437 (83, m+), 426 (75), 287 (60), 288 (91), 285 (100); HRMS $C_{25}H_{21}N_3SO_2$ calcd 427.13544; Found: 427.13524

## Hydrolysis of benezenesulfonyl group in 3

A solution of imine **3** (2 mmol) in a mixture of tetrahydrofuran and methanol (2:1, 30 mL) and 50 % sodium hydroxide solution (1 mL) was stirred at room temperature for 1h. The solution was poured over ice and the precipitated solid was filtered, washed with water (2 X 10 mL) and dried over calcium chloride. It was recrystallized from benzene-petrol to give **4** as a crystalline solid.

## N-(Indol-2-ylmethylene)-(4-dimethylaminoaniline) 4a

(0.44 g, 84%); mp 208 °C (benzene-petrol)

IR (KBr) cm$^{-1}$ : 3200, 1600; $^1$H NMR (400MHz)(DMSO-$d_6$/TMS) δ: 2.91 (s, 6H); 6.75 (d, *J* = 9 Hz, 2H); 6.93 (s, 1H); 7.02-7.59 (m, 4H); 7.29 (d, *J* = 9 Hz, 2H); 8.6 (s, 1H); 1.55 (s, 1H); NOE: δ 8.6 (6.75, 11%; 7.29, 18%); HRMS: $C_{17}H_{17}N_5$ Calcd. : 263.14225; Found : 263.14023

**N-(Indol-2-ylmethylene)aniline 4b**

(0.35 g, 80%); mp 104 °C (benzene-petrol)

IR (KBr) cm$^{-1}$ : 3350, 1615; $^1$H NMR (CDCl$_3$/TMS) δ : 6.95 (s, 1H); 7.10-7.45) (m, 8H); 7.65 (d, 1H); 8.47 (s, 1H); 9.5 (s, 1H); HRMS $C_{15}H_{12}N_2$ Calcd. : 220.10005; Found : 219.99152

**General procedure for oxa Wittig-Horner reaction of 1 & 2**

To a solution of *n*-butyllithium (15% solution in *n*-hexane, 0.9 mL, 2 mmol) tetrahydrofuran (5 mL) at 0°C under nitrogen, was added 2 (0.82 g, 2 mmol)or 1 (1 g, 2 mmol) in the same solvent (40 mL) stirred for 0.5h. Dry oxygen was bubbled into the solution at -78°C for 0.5h and then at room temperature for 1h with continued stirring. The reaction mixture was poured over ice water (40 mL). The sticky matter was extracted with methylene chloride (2 X 20 mL) extract washed with water (2 X 10 mL) and dried (MgSO$_4$). The thick liquid obtained after removal of the solvent was crystallized from methanol to afford **5** as a crystalline solid.

**1,2 Bis (1-benzenesulfonyl-3-phenylthioindol-2-yl)ethene 5b**

(0.38g, 59%); mp 194°C (methanol)

IR (KBr) cm$^{-1}$ : 1580, 1380, 1170; $^1$H NMR (DMSO-$d_6$/TMS) δ 6.35-8.2 (m)

MS : 754 (9), 615 (31), 364 (73), 363 (47), 332 (25), 287 (44), 256 (35), 218

(100), 109 (63), 77 (48); HRMS $C_{42}H_{30}N_2S_4O_4$ Calcd. : 754.10885; Found : 754.10982

**1,2 Bis (1-benzenesulfonylindol-2-yl)ethene 5a**

(0.22g, 40%); mp 244°C (methanol)

IR (KBr) cm$^{-1}$ : 1575, 1355, 1170; $^1$H NMR (DMSO-$d_6$/TMS) δ 7.29 (s, 2H); 7.27-7.81 (m, 16H); 7.70 (s, 2H); 8.09 (d, 2H); CMR: (DMSO-$d_6$/TMS) δ : 110.538, 114.624, 121.454, 121.516, 124.527, 125.499, 126.190, 126.364, 128.792, 134.728, 136.775, 136.965, 138.376; MS : 538 (30), 537 (70), 396 (92), 256 (100), 77 (48); HRMS: $C_{30}H_{22}N_2S_2O_4$ Calcd. : 538.10211 ; Found : 538.11143

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