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# HETEROCYCLES FROM YLIDES. PART X.[1] SYNTHESIS OF 3-HYDROXY-2,3-DIHYDROINDOLES BY A DOMINO REACTION [§]

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**Abstract** – A domino reaction between 2-*N*-phenylsulfonylaminobenzaldehyde **(1)** and sulfonium ylides **(2)** leads to 3-hydroxy-2,3-dihydroindoles **(3)** whose structure was confirmed on the basis of analytical and spectroscopic data.

## INTRODUCTION

Among the general methods for the synthesis of indole derivatives, one tactic is to effect the direct functionalization of the ring system during its construction. In this regard and as a part of our studies concerning the synthesis of heterocyclic compounds from ylides, we report the reaction of 2-*N*-phenylsulfonylaminobenzaldehyde (**1**) with sulfonium ylides (**2**). Taking into account the predictable reactivity of sulfonium ylides towards carbonyl group and the behaviour of oxirane system we planned to use the emerging strategy of domino reactions.[2]

## RESULTS AND DISCUSSION

The treatment of **1** with preformed ylides (**2**) (molar ratio **1**/**2** = 1/2), in acetonitrile solution leads to the formation of 3-hydroxy-1-phenylsulfonyl-2,3-dihydroindoles (**3**). In all cases the reaction proceeds between 0°C and rt and gives compounds **3** in fair to good yields (**Scheme 1**).

The formation of the products can be rationalized by assuming the known behaviour of sulfonium ylides towards carbonyl group to give an oxirane [$\alpha$] (*Step A*) from which the final compounds **3** are obtained by a nucleophilic ring opening mediated by nitrogen anion (*Step B*). The structure of products **3** was assigned on the basis of the analytical and spectroscopic data IR, MS and $^1$H NMR.

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[§] This paper is dedicated to the memory of the late Dr. Ivar Ugi.

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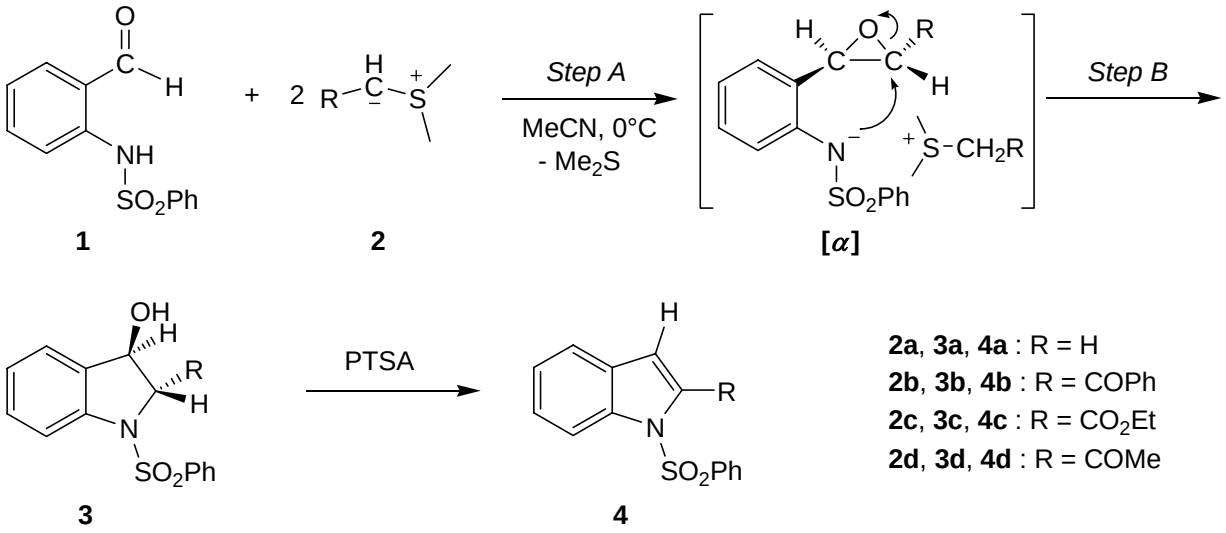
**Scheme 1**




Also the relative *trans* configuration of the H-2 and H-3 was attributed by their coupling constant values, according to the *Karplus* rule (see experimental).

The 3-hydroxy-2,3-dihydroindoles **(3)** can be considered useful intermediates for the preparation of the corresponding indoles **4** by a dehydration reaction according to E1 process. To this purpose the treatment of **3** in toluene or acetonitrile solution, at 60°C, in presence of catalytic amount of PTSA leads to indoles in almost quantitative yields. It is possible to gain aromaticity directly, running our protocol in one pot.

After completion of the Step B the reaction mixture was treated with HCl 10% solution and heated to 60°C for 1h. Conventional work-up gives **4** and this method represent an application of domino reaction to the synthesis of functionalized indoles.

## EXPERIMENTAL

Melting points were determined on a *Büchi* B-540 apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the Department. $^1$H NMR spectra were recorded in $CDCl_3$ solution using a *Bruker AC 300 MHz* spectrometer, and chemical shifts are given in ppm relative to TMS. IR spectroscopy was performed using a *Perkin-Elmer 1725X FT-IR* spectrometer.

**2-*N*-Phenylsulfonylaminobenzaldehyde (1)** was prepared according to the reported procedure.[3]

**Ylides 2a**[4], **2b**[5], **2c**[6], **2d**[7] were prepared from the corresponding salts (halides) in $CHCl_3$ by treatment with $K_2CO_3$ 50% solution. The solvent was evaporated off and the residue used directly.

**Synthesis of products (3a-d): general procedure.**

To a solution of ylide **2a-d** (6.0 mmol) in MeCN (20 mL) cooled to 0-5°C, a solution of **(1)** (3.0 mmol) in the same solvent was added dropwise. The mixture was stirred 48h at rt. The solvent was evaporated off and the residue taken up with AcOEt (20 mL) and AcOH (5% aqueous solution) to pH 6. The organic layer was separated, dried ($Na_2SO_4$), filtered and the solvent was evaporated off. The residue was purified by recrystallization. In this way were prepared:

**3-Hydroxy-1-phenylsulfonyl-2,3-dihydroindole (3a):** Solid, mp 63-65°C (*i*-$Pr_2O$). Yield 55%. $^1$H NMR $\delta$: 4.25 (m, 2H, H-2); 5.03 (m, 1H, H-3); 7.00-8.00 (m, 10H, Ar, OH). IR (*nujol*, $cm^{-1}$): 3495 (OH). *Anal.* Calcd for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.09. Found: C, 61.12; H, 4.68; N, 4.98.

**2-Benzoyl-3-hydroxy-1-phenylsulfonyl-2,3-dihydroindole (3b):** Solid, mp 162-164°C (toluene). Yield 88%. $^1$H NMR $\delta$: 5.05 (d, 2H, $J$ = 2.1 Hz, H-3); 5.70 (d, 1H, $J$ = 2.1 Hz, H-2); 7.00-8.20 (m, 15H, Ar, OH). IR (*nujol*, $cm^{-1}$): 3481 (OH), 1698 (CO). *Anal.* Calcd for $C_{21}H_{17}NO_4S$: C, 66.47; H, 4.52; N, 3.69. Found: C, 66.50; H, 4.52; N, 3.65.

**2-Ethoxycarbonyl-3-hydroxy-1-phenylsulfonyl-2,3-dihydroindole (3c):** Solid, mp 116-118°C (toluene). Yield 83%. $^1$H NMR $\delta$: 1.30 (t, 3H, $J$ = 7.2 Hz, $CH_3$); 4.25 (q, 2H, $J$ = 7.2 Hz, $CH_2$); 4.65 (d, 1H, $J$ = 2.0 Hz, H-2); 5.15 (d, 1H, $J$ = 2.0 Hz, H-3); 7.00-8.20 (m, 10H, Ar, OH). IR (*nujol*, $cm^{-1}$): 3390 (OH), 1710 (CO). *Anal.* Calcd for $C_{17}H_{17}NO_5S$: C, 58.78; H, 4.93; N, 4.03. Found: C, 58.84; H, 4.98; N, 4.03.

**2-Acetyl-3-hydroxy-1-phenylsulfonyl-2,3-dihydroindole (3d):** Solid, mp 96-98°C (*i*-$Pr_2O$). Yield 65%. $^1$H NMR $\delta$: 2.30 (s, 3H, $CH_3$); 4.25 (d, 1H, $J$ = 1.95 Hz, H-2); 5.09 (d, 1H, $J$ = 1.95 Hz, H-3); 7.00-8.00 (m, 10H, Ar, OH). IR (*nujol*, $cm^{-1}$): 3485 (OH), 1700 (CO). *Anal.* Calcd for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41. Found: C, 60.48; H, 4.91; N, 4.35.

**Preparation of indoles (4a-d): general procedure.**

A mixture of **3** (1.5 mmol) and catalytic amount of PTSA in toluene (15 mL) was heated to 80°C for 2h. The reaction mixture was cooled to rt and washed with $NaHCO_3$ (5% aqueous solution). The organic phase was dried ($Na_2SO_4$), filtered and the solvent evaporated off. The residue was purified by crystallization. In this case the products are known compounds and the physical constants are in satisfactory agreement with literature data.

**1-Phenylsulfonylindole (4a):** Solid, mp 75-77°C (*i*-$Pr_2O$). Yield 86%. Lit.,[8] 76-78°C.

**2-Benzoyl-1-phenylsulfonylindole (4b):** Solid, mp 140-142°C (toluene). Yield 90%. Lit.,[9] 142-144°C.

**2-Etoxycarbonyl-1-phenylsulfonylindole (4c):** Solid, mp 89-91°C (MeOH). Yield 95%. Lit.,[9] 89-91°C.

**2-Acetyl-1-phenylsulfonylindole (4d):** Solid, mp 86-88°C (EtOH). Yield 92%. Lit.,[10] 89-90°C.

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