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HETEROCYCLES FROM YLIDES. PART IX[1]. A CONVENIENT SYNTHESIS OF 1-SULFONYL-2,3-DISUBSTITUTED 2,3-DIHYDROINDOLES[‡]

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Abstract – The reaction of sulfur ylides (**1**) with *N*-(2-bromomethyl-phenyl)benzenesulfonamides (**4**) gives 2,3-dihydroindoles (**5**) whose structure and stereochemistry were assigned on the basis of analytical and spectroscopic data. Some chemical transformations of **5** are reported.

INTRODUCTION

As part of our interest concerning the synthesis of heterocyclic derivatives through addition-cyclocondensation reactions of ylides, we examined their reactivity towards different compounds. Some our previous results concerned the reaction of ylides (**1**) with 2-arylmethylenebenzofuran-3-ones, phenolic Mannich base methiodides and 3-arylmethyleneindolin-2-ones to give spiro [cyclopropane-1,2'-benzofuran-3'-ones],[1] 2-acyl-2,3-dihydrobenzofurans,[2] spiro [cyclopropane-1,3'-indolin-2'-ones][3] respectively. We now report a simple and new method for the preparation of 2,3-dihydroindole derivatives (**5**) based on the reaction of stabilized sulfur ylides (**1**) with benzyl bromides (**4**) prepared starting from *N*-sulfonylamidoketones (**2**), *via* reduction to alcohols (**3**), and their transformation into bromides (**4**).

RESULTS AND DISCUSSION

In a preliminary experiment to a solution of dimethylsulfonium 2-oxo-2-phenylethylide (**1a**) in acetonitrile was added *N*-(2-bromophenylmethylphenyl)benzenesulfonamide (**4a**) (molar ratio **1a**/**4a** = 2/1) and, after conventional work-up, 2-benzoyl-3-phenyl-1-phenylsulfonyl-2,3-dihydroindole (**5a**) was isolated directly by crystallisation of the crude reaction mixture in 85% yield. Further experiments to

‡ This paper is dedicated to the memory of the late Professor Kenji Koga.

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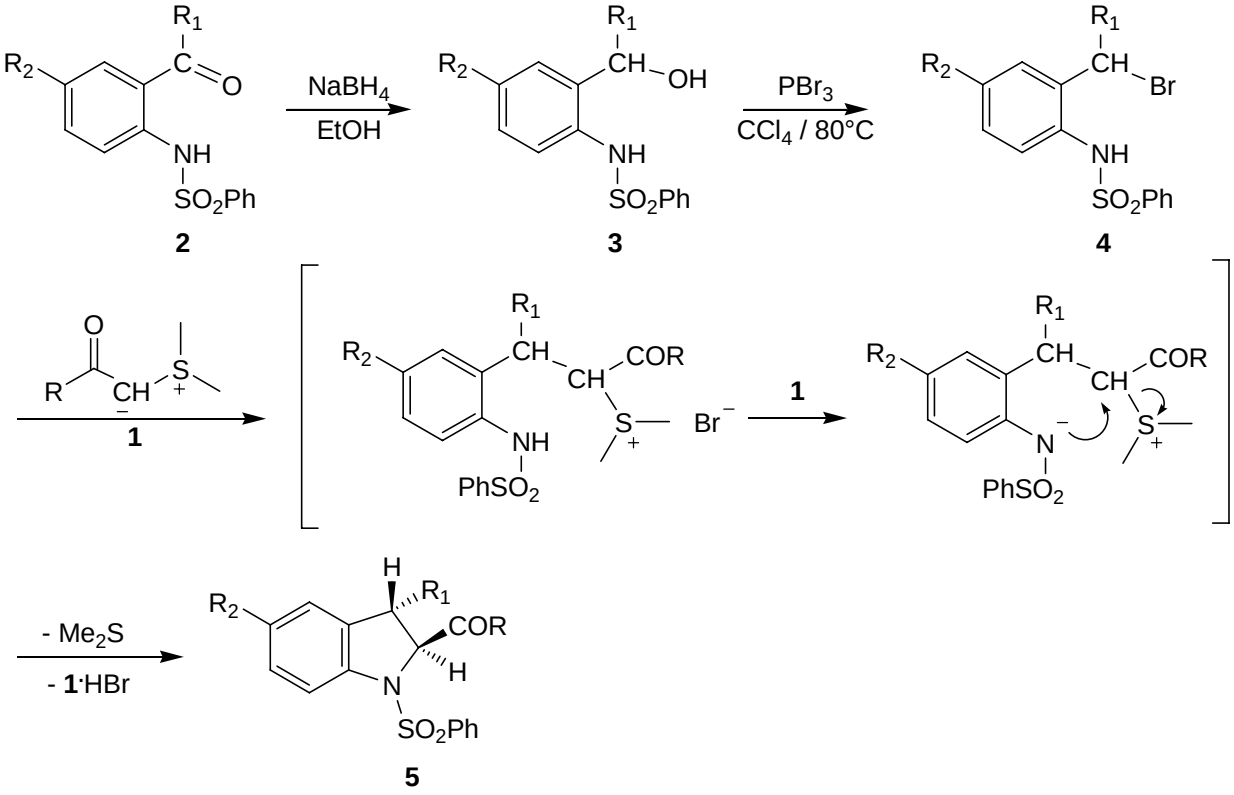
evaluate the scope of the reaction concerned both substituents on *N*-sulfonylamidoketones and ylides. In all the case investigated the sequence alkylation-cyclocondensation gave 2,3-dihydroindole derivatives (**5**) (**Scheme 1**) in fair to good yields. (**Table 1**)

Scheme 1



1a : R = C_6H_5
1b : R = OEt

4a : R_1 = C_6H_5; R_2 = H
4b : R_1 = C_6H_5; R_2 = Cl
4c : R_1 = Me; R_2 = H

5a : R = C_6H_5; R_1 = C_6H_5; R_2 = H
5b : R = C_6H_5; R_1 = C_6H_5; R_2 = Cl
5c : R = C_6H_5; R_1 = Me; R_2 = H
5d : R = OEt; R_1 = C_6H_5; R_2 = Cl

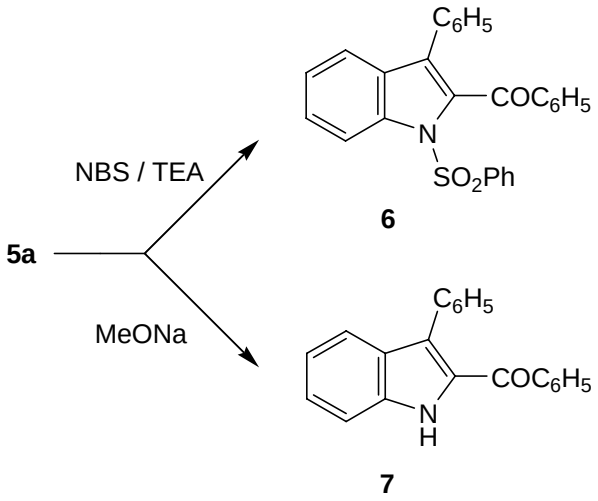
Table 1

Entry	**Reagents**	**Products**	**Yield** (%)	**Time** (hs)
1	**1a+4a**	**5a**	85	12
2	**1a+4b**	**5b**	82	16
3	**1a+4c**	**5c**	80	18
4	**1b+4b**	**5d**	65	12

The formation of the products can be rationalized by assuming the known behavior of sulfonium ylides towards systems bearing an electrophilic center and a nucleophilic heteroatom.[4] Analytical and

spectroscopic data of the compounds prepared are consistent with the assigned structures. In particular a *trans* relationship was assigned to H-2 and H-3 on the basis of the values of their coupling constants.[5] Compounds (**5**) may be useful intermediates for the preparation of other classes of indole derivatives. The dehydrogenation with NBS/TEA gives the corresponding indoles (**6**) whereas the elimination of sulfonyl group, under basic conditions, affords *N*-unsubstituted indoles (**7**) proving the role of sulfonyl residue, as leaving group, in the aromatization of heterocyclic compounds.[6] (**Scheme 2**)

Scheme 2



The reported reaction provides a ready, simple and mild access to 1-phenylsulfonyl-2,3-disubstituted 2,3-dihydroindoles.

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 and ^{13}C 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 spectrophotometer. The sulfonium bromide (**1a**[7], **1b**[8]) and the benzenesulfonamides (**2a**[9], **2b**[10], **2c**[11]) were prepared according to the reported procedures.

Preparation of benzyl alcohol (3a-c): general procedure.

To a suspension of sodium borohydride (4.62 g, 0.125 mol) in EtOH (50 mL), solid benzenesulfonamide (**2a-c**) (0.1 mol) was added portionwise and the mixture was stirred 12 h at rt. Ethanol was removed under reduced pressure and the residue was treated with a 10% hydrochloric acid solution (25 mL) and ethyl acetate (50 mL). The organic layer was separated, dried (Na_2SO_4), filtered and the solvent was evaporated:

***N*-[2-(Hydroxyphenylmethyl)phenyl]benzenesulfonamide (3a).**

Solid, mp 110-112°C (toluene). Yield 90%. ^{1}H NMR δ: 2.70 (s, 1H, OH); 5.65 (s, 1H, C*H*OH); 6.90-7.20 (m, 14H, Ph); 8.10 (s, 1H, NH). IR (*nujol*, *cm*$^{-1}$): 3255 (OH). *Anal.* Calcd for $C_{19}H_{17}NO_3S$: C, 67.25; H, 5.01; N, 4.12. Found: C, 67.32; H, 4.95; N, 4.23.

***N*-[2-(Hydroxyphenylmethyl)-4-chlorophenyl]benzenesulfonamide (3b).**

Solid, mp 121-123°C (toluene). Yield 95%. ^{1}H NMR δ: 2.90 (s, 1H, OH); 5.62 (s, 1H, C*H*OH); 6.80-7.30 (m, 13H, Ph); 8.20 (s, 1H, NH). IR (*nujol*, *cm*$^{-1}$): 3250 (OH). *Anal.* Calcd for $C_{19}H_{16}NO_3ClS$: C, 61.04; H, 4.28; N, 3.74. Found: C, 61.18; H, 4.22; N, 3.62.

***N*-[2-(α-Hydroxyethyl)phenyl]benzenesulfonamide (3c).**

Solid, mp 103-104°C (*i*-Pr_2O). Yield 90%. ^{1}H NMR δ: 1.38 (d, 3H, *J* = 6.6 Hz, CH_3); 2.20 (s, 1H, OH); 4.76 (s, 1H, *J* = 6.6 Hz, C*H*OH); 7.00-7.90 (m, 9H, Ph); 8.50 (s, 1H, NH). IR (*nujol*, *cm*$^{-1}$): 3260 (OH). *Anal.* Calcd for $C_{14}H_{15}NO_3S$: C, 60.64; H, 5.41; N, 5.05. Found: C, 60.41; H, 5.31; N, 5.01.

Preparation of benzyl bromides (4a-c): general procedure.

A mixture of **3a-c** (0.05 mol) in CCl_4 (20 mL) and phosphorus tribromide (6.76 g, 0.025 mol) was heated to 80°C for 16-18h. After cooling to 0°C the mixture was treated with water (20 mL). The organic phase was separated, dried (Na_2SO_4) and the solvent was evaporated off. The reaction progress was monitored by TLC. NMR spectra confirmed the structure of crude bromides which were used directly in the next step without purification.

***N*-[2-(Bromophenylmethyl)phenyl]benzenesulfonamide (4a).**

Oil. Yield 85%. ^{1}H NMR δ: 5.97 (s, 1H, CHBr); 7.00-8.00 (m, 14H, Ph); 8.10 (s, 1H, NH).

***N*-[2-(Bromophenylmethyl)-4-chlorophenyl]benzenesulfonamide (4b).**

Wax. Yield 80%. ^{1}H NMR δ: 6.05 (s, 1H, CHBr); 7.00-8.00 (m, 13H, Ph); 8.20 (s, 1H, NH).

***N*-[2-(α-Bromoethyl)phenyl]benzenesulfonamide (4c).**

Foam. Yield 85%. ^{1}H NMR δ: 1.15 (d, 3H, *J* = 5.9 Hz, CH_3); 5.17 (t, 1H, *J* = 6.0 Hz, $CHCH_3$); 7.00-8.00 (m, 9H, Ph); 8.40 (s, 1H, NH).

Synthesis of products (5a-d): general procedure.

To a solution of **1a-b** (10 mmol) in acetonitrile (25 mL), cooled to 0°C, **4a-c** (5 mmol) was added and the mixture stirred at rt for 12h. The solvent was evaporated and the residue was taken up with 5% hydrochloric acid solution (20 mL) and ethyl acetate (25 mL). The organic phase was separated and the solvent was evaporated off. The residue was purified by recrystallization. In this way were prepared:

2-Benzoyl-3-phenyl-1-phenylsulfonyl-2,3-dihydroindole (5a):

Solid, mp 121-123°C (EtOH). Yield 85%. ^{1}H NMR δ: 4.20 (d, 1H, *J* = 5.1 Hz, H-3 indole); 5.55 (d, 1H, *J* = 5.1 Hz, H-2 indole); 6.50-7.75 (m, 19H, Aromatics). *Anal.* Calcd for $C_{27}H_{21}NO_3S$: C, 73.80; H, 4.78; N, 3.18. Found: C, 73.60; H, 4.85; N, 3.15.

2-Benzoyl-5-chloro-3-phenyl-1-phenylsulfonyl-2,3-dihydroindole (5b):

Solid, mp 205-206°C (EtOH). Yield 82%. ^{1}H NMR δ: 4.18 (d, 1H, *J* = 4.9 Hz, H-3 indole); 5.44 (d, 1H, *J* = 4.9 Hz, H-2 indole); 6.50-7.90 (m, 18H, Ph). *Anal.* Calcd for $C_{27}H_{20}NO_3ClS$: C, 68.42; H, 4.22; N, 2.95. Found: C, 68.21; H, 4.18; N, 2.77.

2-Benzoyl-3-methyl-1-phenylsulfonyl-2,3-dihydroindole (5c):

Solid, mp 140-142°C (EtOH). Yield 80%. ^{1}H NMR δ: 1.10 (d, 3H, *J* = 6.9 Hz, C*H*$_3$CH); 3.35 (m, 1H, CH$_3$C*H*); 5.11 (d, 1H, *J* = 5.1 Hz, CHCO); 7.00-8.00 (m, 14H, Ph). *Anal.* Calcd for $C_{22}H_{19}NO_3S$: C, 70.02; H, 5.03; N, 3.71. Found: C, 70.10; H, 5.09; N, 3.79.

2-Ethoxycarbonyl-5-chloro-3-phenyl-1-phenylsulfonyl-2,3-dihydroindole (5d):

Solid, mp 82-83°C (*i*-Pr$_2$O). Yield 65%. ^{1}H NMR δ: 1.30 (t, 3H, *J* = 7.1 Hz, CH$_3$); 4.10 (q, 2H, *J* = 7.1 Hz, CH$_2$); 4.25 (d, 1H, *J* = 5.1 Hz, H-3 indole); 5.55 (d, 1H, *J* = 5.1 Hz, H-2 indole); 6.50-7.75 (m, 13H, Ph). *Anal.* Calcd for $C_{23}H_{20}NO_4ClS$: C, 62.51; H, 4.53; N, 3.17. Found: C, 62.43; H, 4.49; N, 3.12.

2-Benzoyl-3-phenyl-1-phenylsulfonylindole (6).

A solution of **5a** (0.439 g, 1 mmol) in CCl_4 (20 mL) was treated with *N*-bromosuccinimide (0.19 g, 1.1 mmol) and refluxed for 2 h. Triethylamine (0.11 g, 1.1 mmol) was added and the reaction mixture was heated for further 2 h. The mixture was cooled, succinimide and TEA·HBr were removed by filtration and the solvent was evaporated. The product was crystallized. Yield 90%. mp 166-168°C (EtOH). ^{1}H NMR δ: 7.25-8.24 (m, 19H, Ph). *Anal.* Calcd for $C_{27}H_{19}NO_3S$: C, 74.14; H, 4.34; N, 3.20. Found: C, 74.24; H, 4.41; N, 3.12.

2-Benzoyl-3-phenylindole (7).

A solution of **5a** (0.439 g, 1 mmol) in MeOH (20 mL) was treated with sodium methoxide (0.054 g, 1 mmol) and the mixture was stirred at rt overnight. The solvent was evaporated off and the residue was taken up with water. The product was filtered and crystallized. Yield 90%. mp 204-206°c (MeOH). lit.,[12] mp 203-204°C.

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