THE REACTION OF INDOLYL GRIGNARD AND RELATED ORGANOMETALLIC REAGENTS WITH 2-PHENYLSULPHONYL-BUTA-1,3-DIENE AND 2,3-DIPHENYLSULPHONYLBUTA-1,3-DIENE

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Abstract - Indolyl Grignard reagents, and some related organometallic species, react with 2,3-diphenylsulfonylbuta-1,3-diene producing $RCH_2C(SO_2Ph)=C=CH_2$, where R is derived from the organometallic reagent.

This communication is dedicated to Professor Alan R. Katritzky, on the occasion of his 65th birthday, in acknowledgement of his major contributions to the development of new methods in, and the systematisation of, aromatic heterocyclic chemistry.

The structure of the unique marine alkaloid, hinckdentine A[1] (1) can be viewed as a fused 2,3-dihydroindole (indoline) carrying a 2-aryl substituent. Other significant structural aspects, which will need to be addressed for a synthesis of the system, are the dihydropyrimidine ring and the quaternary carbon at the indoline C-2 position. We envisage that hinckdentine could be approached synthetically from an intermediate of the form 2 (halogens omitted), in which substituent Y would be utilised for a ring expansion and the production of the seven-membered cyclic amide, and substituent X would be a nitrogen-containing group to allow late formation of the dihydropyrimidine ring.
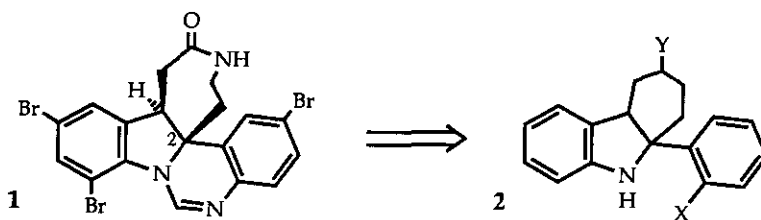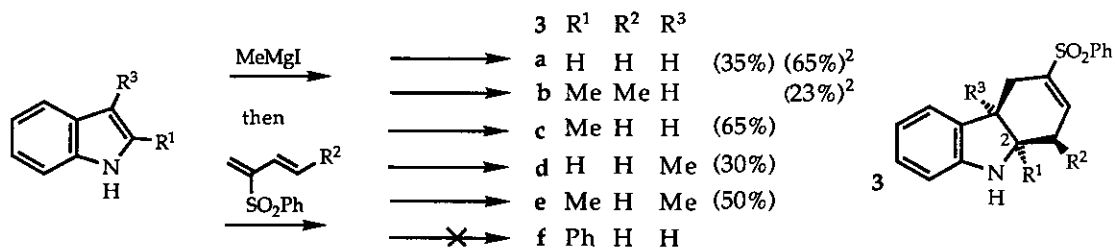

Accordingly, our attention was drawn to Bäckvall's reports[2] of the reactions of indolyl-magnesium iodide and in particular of 2-methylindolylmagnesium iodide, with 2-

phenylsulfonyl-buta-1,3-diene and with 2-phenylsulfonyl-penta-1,3-diene respectively, the former giving the tricyclic indoline (**3a**) and the latter the indoline (**3b**) *with a quaternary carbon at the indoline C-2.* We have repeated the former reaction and confirmed the structure and relative stereochemistry (**3a**) with a single crystal X-ray crystallographic determination.[3] The Figures, below, show PLUTO representations of the crystal structure which illustrate the relative stereochemistry of the molecule.
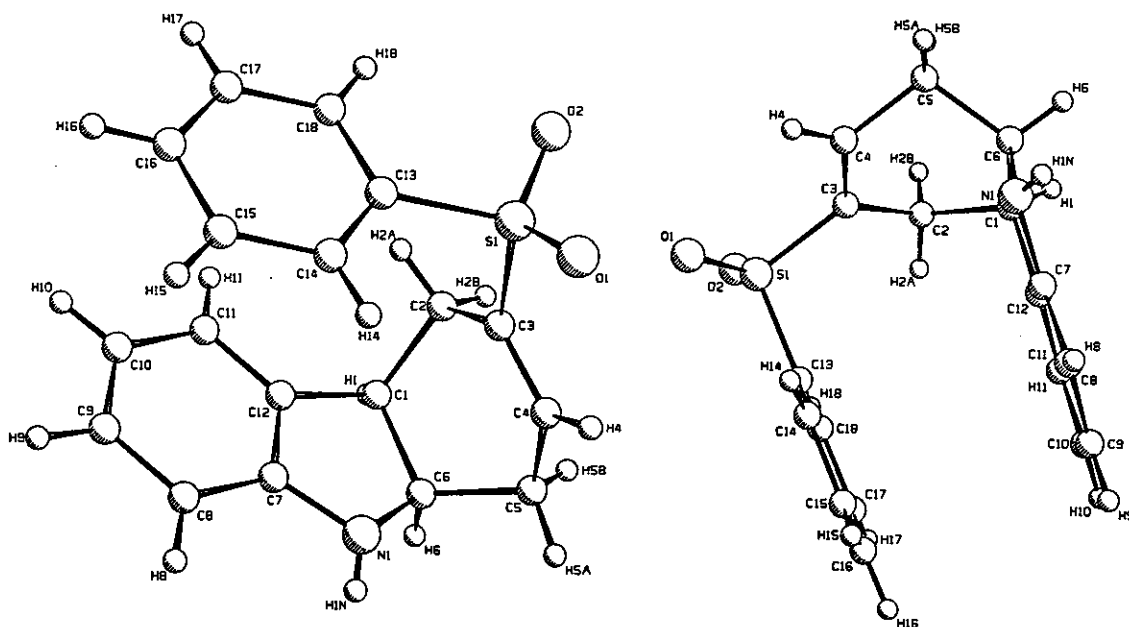

Figures: PLUTO drawings of **3a**.

We have now shown that the 'cycloaddition' also proceeds, using 2-phenylsulfonyl-1,3-butadiene, with the Grignard derivatives of 2-methylindole, 3-methylindole, and 2,3-dimethylindole, affording **3c**,[4] **3d**,[4] and **3e**[4] respectively.

| 3	R^1	R^2	R^3	
a	H	H	H	(35%) (65%)[2]
b	Me	Me	H	(23%)[2]
c	Me	H	H	(65%)
d	H	H	Me	(30%)
e	Me	H	Me	(50%)
f	Ph	H	H	

It seemed possible that application of this methodology to a suitable 2-*aryl*indole would allow the rapid generation of structures of the type (2). Unfortunately, we found that neither the Grignard derivative of 2-phenylindole, nor its lithio or potassio derivatives would react with 2-phenylsulfonyl-1,3-butadiene – 3f was *not* obtained. Similarly, the more ambitious use of the Grignard derivative of 2-(2-nitrophenyl)indole or the Grignard or lithio derivatives of 3-methyl-2-phenylindole were unsuccessful, the latter being recovered unchanged and the former giving rise to a very complex mixture, which may have resulted from interaction of the methyl magnesium iodide with the nitro group[5] of this substrate indole.

On the basis that increasing the reactivity of the diene might encourage the desired 'cycloaddition' we turned to the use of 2,3-diphenylsulfonylbuta-1,3-diene.[6] Reaction with the Grignard derivative of 2-phenylindole afforded a product which, from spectroscopic examination clearly did not contain an indoline nucleus; the structure was determined by X-ray crystallography,[7] and the product shown to be the indole-allene (4c).[4] Subsequently we showed that the Grignard derivative of 2-methylindole behaves in an exactly analogous fashion, giving 4b,[4] and, after our investigations were complete, Padwa reported the reaction of indole itself, with the same diene, giving 4a.[8]

$$4 \quad R$$
$$a \quad H \quad (45\%) \ (80\%)^8$$
$$b \quad Me \ (35\%)$$
$$c \quad Ph \ (70\%)$$
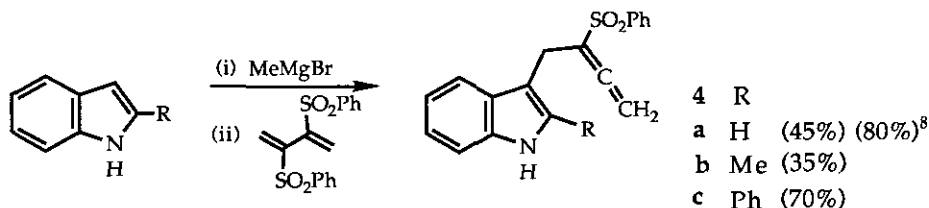
One may speculate about the sequence which leads to allenic products (4) in particular, the elimination of phenylsulfinate which is required may not necessarily be synchronous with the C-C bonding step, as implied by the curly arrows in the scheme below. An alternative is that an intramolecular proton transfer is required: the arrows on 5 illustrate this in the indole situation.

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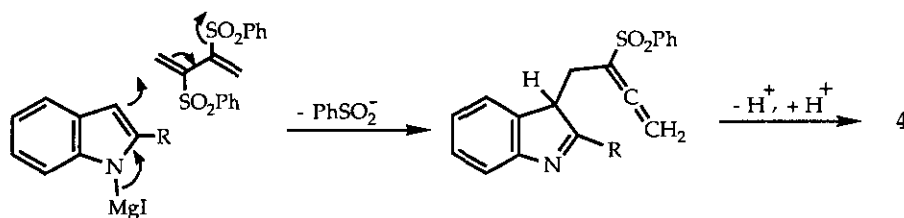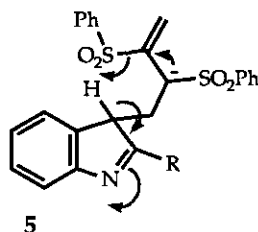
The intriguing process exemplified by these indole transformations demanded a broader assessment aimed at defining the generality of the transformation, and we have carried out a limited survey, though the results do not seem to fit a simple pattern. Both pyrrolyl and phenyl Grignard reagents *did* react comparably, producing phenylsulfonyl allenes (6a)[4] and (6b).[4]
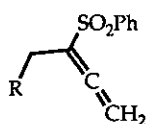
6 R
a pyrrol-2-yl (90%)
b Ph   (25%)
c n-Bu   (10%)

The reaction of n-butyllithium with 2-phenylsulfonyl-1,3-butadiene also afforded an allene (6c)[4] though in poor yield. Attempts to improve this yield by using n-butylzinc chloride or n-butyl-magnesium bromide failed – no allene at all was obtained. We also failed to obtain allenic products from attempts to utilise imidazole or benzimidazole, though it should be noted that in the latter case reaction would have had to take place at nitrogen. More surprising were the failures of attempts to utilise 2-lithio-1-methylpyrrole or 2-lithio-1-methylindole in a comparable manner. The enolate of indan-1-one also failed to produce an allenic product.

TYPICAL PROCEDURES

Synthesis of indoline, 3a.- (a slight modification of Bäckvall's procedure[2]) 2-Phenylsulfonylbuta-1,3-diene (*ca.* 1 g, *ca.* 5 mmol) in CH$_2$Cl$_2$ (100 ml) was canulated into preformed indolyl-magnesium iodide (from indole (1.41 g, 12 mmol) and methylmagnesium bromide (8.6 ml, 1.4M solution in THF)) in Et$_2$O (20 ml) at 0°C. After 45 min the resulting brown solution was washed with saturated aq. NH$_4$Cl, dried (MgSO$_4$), evaporated under reduced pressure and the crude product purified by chromatography over silica gel, elution with EtOAc/hexane (2:3), giving indoline (3a) (544 mg, 35%) as crystals, mp 132-134°C.

Synthesis of allene, 6a.- 2,3-Diphenylsulfonylbuta-1,3-diene (250 mg, 0.75 mmol) in CH$_2$Cl$_2$ (20 ml) was added to preformed pyrrolylmagnesium iodide (from pyrrole (54 μl, 0.75 mmol) and methyl magnesium bromide (0.6 ml, 1.4M solution in THF)) in Et$_2$O (5 ml) at -78°C. After 30 min the mixture was allowed to warm to room temperature, washed with saturated aq. NH$_4$Cl, dried (MgSO$_4$) and evaporated under reduced pressure. The resulting brown oil (almost pure

allene **6a**) was purified using chromatography over silica, eluting with EtOAc/40-60 petroleum ether (2:3), giving **6a** (168 mg, 90%) as a gum.

ACKNOWLEDGEMENT

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3. *Crystal data*: for **3a**: $C_{18}H_{17}NO_2S$, colourless prismatic, mp 132-134°C (from MeOH), crystal dimensions 0.30 x 0.30 x 0.60 mm, orthorhombic, $a = 12.650(1)$, $b = 19.663(1)$, $c = 6.078(1)$ Å, $U = 1512(3)$ Å^3, space group $P2_12_12_1$ (#19), $Z = 4$, $F(000) = 656$, $\omega/2\theta$ scans of $(1.21 + 0.30\tan\theta)$ were made at a speed of 4.0°min^{-1} at 296K; 1595 reflections were collected with 5° < 2θ < 100°; of these, 1017 which were unique, and had $F>6\sigma(F)$, were used in the analysis. The data were collected on a Rigaku AFC6S diffractometer using graphite-monochromated MoK$_\alpha$ radiation. Lorentz, polarisation and linear intensity drift (maximum -1.4%) corrections were applied. The structure was solved by direct methods. The refinement converged with $R = 0.061$, $R_w = 0.073$. All calculations were performed using the TEXSAN crystallographic software package of Molecular Structure Corporation (1985). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

4. All new compounds gave combustion analytical (or HRms) data consistent with the assigned structures. Compound (**3c**) was amorphous; compound (**3d**) had mp 129-131°C; compound (**3e**) had mp 140-142°C; **3c-e** had ^{1}H nmr data entirely comparable with those for **3a**; compound (**4b**) had mp 161-165°C, δ_H 3.76 and 5.25 (2x2H, 2xt, J = 3.2 Hz); **4c** had mp 178-180°C, δ_H 3.86 and 5.10 (2x2H, 2xt, J = 4.0 Hz); **6a** was a gum, δ_H 3.64 and 5.31 (2x2H, 2xt, J = 2.6 Hz); **6b** was a gum, δ_H 3.60 and 5.27 (2x2H, 2xt, J = 3.0 Hz); **6c** was a gum, δ_H 3.76 (2H, t, J = 2.0 Hz), 2.20 (2H, m).

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