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The Reaction of Nitrones with Indoles. Synthesis of asymmetrical diindolylalcanes

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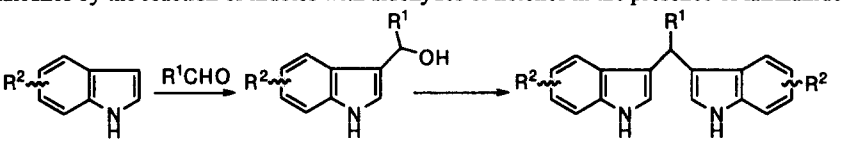
Abstract: The reaction of nitrones with indoles in the presence of HCl gives indolyl *N*-hydroxylamines. In the presence of Me_3SiCl symmetrical diindolylalcanes are obtained. A synthesis of asymmetrical diindolylalcanes and the syntheses of three natural symmetrical diindolylalcanes are reported.

The condensation of indole and of its substituted derivatives with electrophiles allows the preparation of important synthetic intermediates en route to naturaly occurring alkaloïds or to structuraly related compounds of pharmaceutical interest.[1] Condensations generally take place at position 3, when it is free. Among the various tested electrophiles, aldehydes are the most important (Scheme 1). A carbinol is thus formed which, generally, readily gives a symmetrical 'dimeric' diindolylalcane. The easy formation of the diindolylalcane is due to the propency of the first formed carbinol to form a stabilized carbocation which then reacts as the electrophile with another indole molecule. Recently, Wang *et al.* have reported a general synthesis of diindolylalcanes by the reaction of indoles with aldehydes or ketones in the presence of lanthanide triflates.[2]



Scheme 1

The condensation of indole derivatives with compounds containing a C=N double bond has been mainly limited to reactions with iminium derivatives of formaldehyde.[3] Recently, Grumbach *et al.* prepared indolylamines using iminium salts derived from various aldehydes.[4] The same reaction applied to nitrones should give indolyl *N*-hydroxylamines. However, this reaction has been poorly studied and Banerji and Mukhopadhyay have described the condensation of some activated aromatic nitrones with indoles to give 3,3'-diindolylalcanes.[5]

In this communication, we present our first results about the condensation of nitrones derived from various aliphatic aldehydes[6] with indoles. Depending on conditions, indolyl *N*-hydroxylamines or diindolylalcanes have been obtained. The syntheses of three natural products are presented and a two step strategy leading to asymmetrical 3,3'-diindolylalcanes is described.

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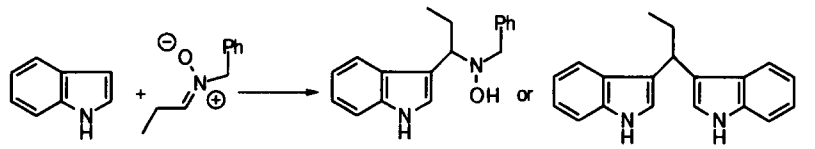


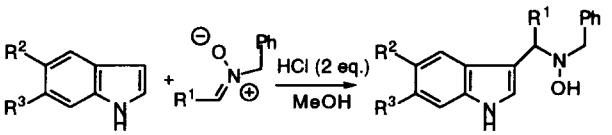
conditions		isolated yields
HCl (2 eq.), MeOH, 0°C, 2h	82%	
CF_3CO_2H (3 eq.), MeOH, O°C, 1h	70%	
pyridinium paratoluenesulfonate (1.5 eq.), r.t., 20h	41%	> 5%
Me_3SiCl (1 eq.), pyridine, toluene, r.t., 48h	55%	
Me_3SiCl (1 eq.), CH_2Cl_2, r.t., 2h, indole/nitrone = 2/1		85%

Scheme 2

Various activation reagents were tested. Representative results obtained with the *N*-benzyl nitrone derived from propanal and indole are presented in Scheme 2. As expected, condensation occurred on position 3. When a proton donor was used, the isolated product was the expected *N*-hydroxylamine. The best result was obtained with 2 eq. of HCl. These conditions were then applied to a series of nitrones and indoles.[7] Even the poorly reactive bromoindoles gave good yields. In the case of the very reactive 5-methoxyindole, the reactions were run at -10°C, in order to minimize the formation of by-products. The obtained *N*-hydroxylamines are stable and crystalline. They are easily isolated and purified by liquid chromatography or a simple washing with pentane.

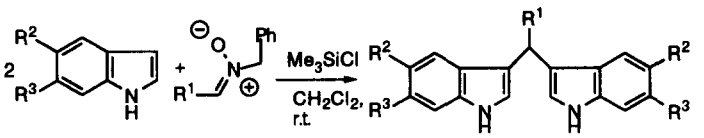
On the other hand, we noticed that, in the presence of 1 eq. of chlorotrimethylsilane in anhydrous dichloromethane, indole reacted with the nitrone of propanal to yield the corresponding diindolylpropane. The use of one equivalent of nitrone led to an equimolar mixture of diindolylpropane and the starting nitrone. When using two equivalents of indole, diindolylpropane was isolated in 85% yield. These conditions were applied to a variety of indoles and nitrones (Table 2). All the reactions were carried out at room temperature in anhydrous dichloromethane. The diindolylalcanes were isolated with medium to excellent yields.

Table 1



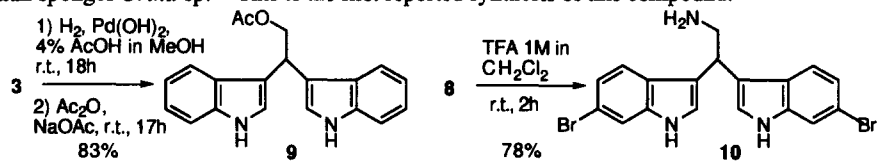
R^1	R^2	R^3	temperature	reaction time (h)	yield (%)
Me	H	H	0 °C	2	87
CH_2NHBoc	H	H	0 °C	1	92
CH_2OCH_2Ph	H	H	0 °C	1	88
Me	Br	H	r.t.	2	82
Et	Br	H	r.t.	3	70
CH_2NHBoc	H	Br	0 °C	4	81
Me	MeO	H	-10 °C	1	88

Table 2



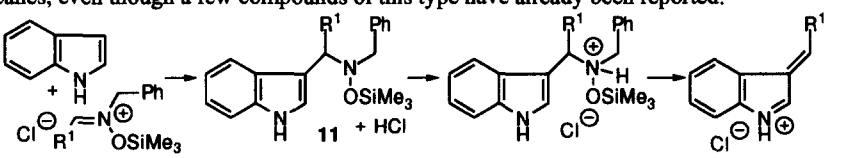
R^1	R^2	R^3	reaction time (h)	product number	yield (%)
Me	H	H	17	**1**	83
i-Pr	H	H	32	**2**	82
CH_2OCH_2Ph	H	H	24	**3**[9]	91
CH_2NHBoc	H	H	8.5	**4**	55
Et	MeO	H	8.5	**5**	86
Et	Br	H	72	**6**	87
CH_2NHBoc	Br	H	48	**7**	46
CH_2NHBoc	H	Br	54	**8**[9]	31

Compound **1** is a natural product named vibrindole A.[8] It has been isolated from the toxic mucus of the box fish *Ostracion cubicus*. Debenzylation of compound **3**[9], followed by acetylation of the resulting alcohol gave streptindole **9**[10] (Scheme 3), a genotoxic metabolite isolated from the intestinal bacteria *Streptococcus faecium* IB37 in 1983. The obtained overall yield from indole (3 steps, 75%) compares favorably with the best previously reported synthesis.[11] Deprotection of the amino group of compound **8**[9] gave the amine **10** which has been previously isolated from the californian tunicate *Didemnum candidum* and from the New Caledonian sponges *Orina* sp. [12]This is the first reported synthesis of this compound.



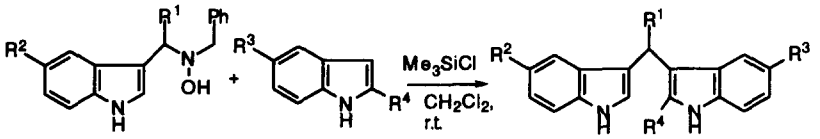
Scheme 3

From a mechanistic point of view, the striking difference between the HCl and Me_3SiCl promoted reactions is probably due to the basicity of the *O*-silyl-*N*-hydroxylamine intermediate **11** (Scheme 4) formed in the later case. The electron-donating trimethylsilyl group enhances the electronic density on the nitrogen atom, thus making it more basic than the corresponding nitrogen atom of the free *N*-hydroxylamine and rendering its protonation and subsequent elimination easier. We took advantage of this different behaviour by treating some of the previously isolated *N*-hydroxylamines with Me_3SiCl in the presence of various indole derivatives. Results are summarized in Table 3. This method is the first described general synthesis of asymmetrical 3,3'-diindolylalcanes, even though a few compounds of this type have already been reported.[13]



Scheme 4

Table 3



R^1	R^2	R^3	R^4	reaction time (h)	yield (%)
Et	H	Br	H	24	76
Et	H	MeO	H	24	83
Et	H	H	Me	18	74
Me	H	H	Me	24	75
Me	MeO	H	H	18	57
CH_2OCH_2Ph	H	Br	H	24	83
CH_2OCH_2Ph	H	MeO	H	24	77
CH_2OCH_2Ph	H	H	Me	22	55

We are currently working on other applications of these reactions to the synthesis of naturally occurring indoles, including annonidine B[14] and the antitumoral agents topsentins and nortopsentins.[15]

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7. Experimental procedure : To a methanolic solution of HCl (2 mmol, prepared *in situ* from AcCl + MeOH) stirred under N_2 at 0°C was added dropwise the nitrone and the indole (1mmol each). The resulting solution was stirred at 0°C for a period determined by TLC. After a conventionnal work up, the *N*-hydroxylamine was purified by chromatography on silica gel or by washing with pentane. The obtained products gave satisfactory ^1H and ^{13}C NMR and M.S. data.
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9. **3** : ^1H NMR (250 MHz, $CDCl_3$) : 4.04 (d, 2H, J = 7.1 Hz), 4.51 (s, 2H), 4.82 (t, 1H, J = 7.1 Hz), 6.63-7.49 (m, 15H), 7.59 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) : 34.41 ($\underline{C}HCH_2$), 72.84 ($CH\underline{C}H_2$), 73.34 ($O\underline{C}H_2C_6H_5$), 111.10 (2CH), 116.59 (2C), 118.92 (2CH), 119.31 (2CH), 121.58 (2CH), 122.47 (2CH), 126.85 (2C), 127.46 (CH), 127.74 (2CH), 128.24 (2CH), 136.22 (2C), 138.22 (C). **8** : ^1H NMR (200 MHz, $CDCl_3$) : 1.42 (s, 9H), 3.86 (t, 2H, J = 6.5 Hz), 4.55-4.71 (m, 2H), 7.00 (d, 2H, J = 2.0 Hz), 7.14 (dd, 2H, J = 1.7 et 8.6 Hz), 7.39 (d, 2H, J = 8.6 Hz), 7.51 (d, 2H, J = 1.7 Hz), 8.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) : 28.22 ($(CH_3)_3$), 33.55 (CH_2), 44.89 (CH), 77.51 (C), 113.58 (2C), 113.88 (2CH), 116.39 (2C), 120.50 (2CH), 120.95 (2CH), 123.47 (2CH), 125.86 (2C), 137.27 (2C), 155.67 (C=O).
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