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REGIOSELECTIVE NITRATION OF 3-ACETYLINDOLE AND ITS N-ACYL AND N-SULFONYL DERIVATIVES.

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3-Acetylindole reacts regioselectively with NO_2BF_4 in the presence of $SnCl_4$ to produce 3-acetyl-5-nitroindole or 3-acetyl-6-nitroindole, depending on the temperature, both in excellent yields.

The indolic ring system is quite activated towards electrophilic substitution but it also undergoes undesirable oxidations and oligomerizations readily. The nitration of indoles, even those substituted with withdrawing groups[1] such as -CN, COOR, NO_2, COH[2]or COR, leads to poor yields of the desired nitro products, probably due to the undesirable reactions mentioned above.

Noland[3] reported the nitration of indoles substituted by withdrawing groups at the 2 and at the 3-positions. He employed different nitration media such as HNO_3/H_2SO_4, HNO_3/CH_3COOH, $NaNO_3/ H_2SO_4$, the total yield varying from 18% to 52%. In a similar way, Nakatsuka,[4] by using HNO_3/CH_3COOH in the nitration of indole-3-ethylcarboxylate, obtained a mixture of 4 and 6 nitro derivatives in 60% total yield. These low yields, as well as the harshness of the conditions, preclude the use of these procedures synthetically. Therefore, we decided to search for new and more efficient nitration conditions for these systems. Thus, the study of the nitration of 3-acetylindole, 1,3-diacetylindole and 3-acetyl-1-benzosulfonylindole, which were prepared as described before,[5] was carried out by using $NO_2^+BF_4^-$ as a nitrating agent. The substrates were chosen in order to verify the effect of withdrawing groups on the efficiency and regioselectivity of the reactions. By varying the reaction conditions and the nature of the substrate it was possible to control the regioselectivity of the process, and the results are summarized in Table 1.

Under the conditions studied, three compounds (2,[6] 3[7] and 4[8]) can be formed (Scheme 1) and the predominance of one or another was dependent on the reaction condition and substrate nature.

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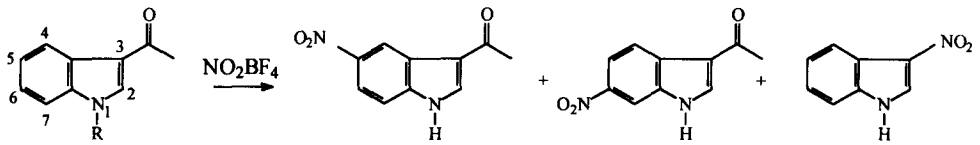
Scheme I.



1a R = H
1b R = $COCH_3$
1c R = SO_2Ph

2 3 4

Table 1. Nitration of 3-Acetylindole and Derivatives.

Substrate	medium	temperature ^0C	2	3	4	ratio 2/3
1a	CH_2Cl_2, CH_3NO_2	0	50%	40%	10%	1.25
1a	CH_2Cl_2, CH_3NO_2,	10	40%	35%	20%	1.14
1a	$SnCl_4$,$(CH_2Cl)_2$, CH_3NO_2,	-15 →-10	85%	-	-	-
1a	$SnCl_4$, CH_2Cl_2, CH_3NO_2,	rt	47%	45%	-	0.95
1a	$SnCl_4$, $CHCl_3$, CH_3NO_2	60	-	85%	-	-
1b*	CH_2Cl_2,	-5	60%	35%	-	0.58
1b*	CH_2Cl_2,	0 → rt	45%	42%	-	1.07
1c*	CH_2Cl_2,	0 → rt	80%	10%	-	1.12
1c*	CH_2Cl_2,	10 →15	45%	45%	-	1.0

**The yields were calculated after the hydrolysis of the protecting group.*

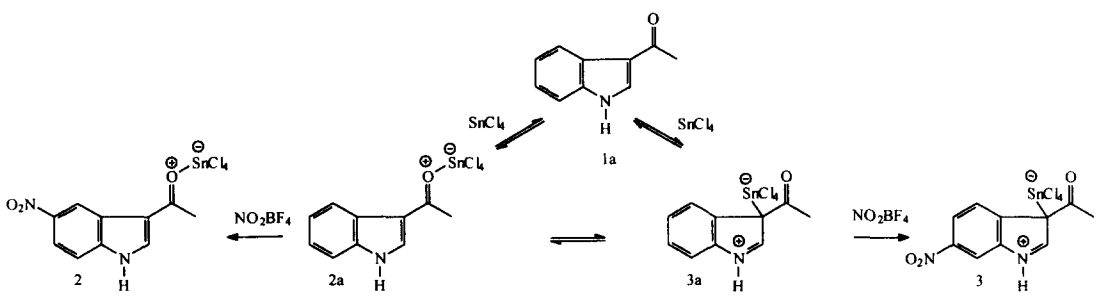
The total yields of the reactions were excellent, ranging from 90-100%, and the regioselectivity observed was quite different from that reported by Noland using HNO_3. While he obtained a mixture of 4 and 6 nitro derivatives for the nitration of 3-acetylindole, we isolated the 5 and 6 nitro substituted compounds as the main products. However, as Noland did, we obtained 3-nitroindole (4) as a by-product under some conditions. The 3-nitro compound 4 is formed through an ipso attack and, from examination of Table 1, it can be found that by increasing the temperature its formation increases. On the other hand, the presence of a withdrawing group such as acyl or benzosulfonyl on the indole nitrogen avoids ipso attack, even at rt. Another way to avoid the formation of 4, without carrying out a separate protection step, is by adding $SnCl_4$ to a suspension of 3-acetylindole before to the addition of $NO_2^+BF_4^-$.

It is worthy of mention that compounds 2 and 3 substituted at the nitrogen by the benzosulfonyl or acetyl groups have the same Rf's on SiO_2 or Al_2O_3 plates with all of the solvent systems examined. It was however possible to separate the regioisomers on alumina columns after hydrolysis of the protecting group.

The most important results were obtained from the reactions performed in the presence of $SnCl_4$. Under these conditions, it was not only possible to avoid the formation of by-product 4, but also to control the regioselectivity of the process by simply varying the temperature.

It seems the course of the reaction was changed considerably in the presence of $SnCl_4$ since the 3-acetylindole in its absence does not react below O ^{0}C, but, in its presence, forms 3-acetyl-5-nitroindole at -15^0 C. Moreover, in the presence of $SnCl_4$ it was possible to control the regioselectivity of the reaction, by varying the temperature. At low temperatures (-15 to -10^0 C), the only product obtained was 3-acetyl-5-nitroindole while, at 60 ^{0}C, only the 3-acetyl-6-nitroindole derivative was isolated. The introduction of nitro substituents on the carbocyclic ring of indoles in regiochemical fashion and in good yields has not been reported previously. The mechanistic basis of the regioselectivity is not clear yet since attempts to convert 3-acetyl-5-nitroindole to 3-acetyl-6-nitroindole by refluxing the first in $CHCl_3/CH_3NO_2$ in the presence of $SnCl_4$ failed, starting material being recovered. Even though, some points about the regioselectivity observed in the presence of $SnCl_4$ are obscure yet, some evidences leads us to think that the products 2 and 3 are formed from different intermediates, as shown in Scheme II.

Scheme II



The complex 2a might be favoured at lower temperatures, leading to product 2. At high temperatures, the Lewis acid could react at the 3 position of indole, thus deactivating the 5 position.

A typical experimental procedure for the nitration of 3-acetylindole and hydrolysis of the N-substituted 5 and 6 nitro-3-acetylindoles is described below.

Nitration of 3-acetylindole - To a stirred suspension of 3-acetylindole (800 mg, 5 mmol) in CH_2Cl_2 (30 mL), $SnCl_4$ (0,64 mL, 5,3 mmol) was added resulting in a pink suspension. After 30 minutes, at -15 ^{0}C, $NO_2^+BF_4^-$ (870 mg, 6,5 mmol) was added in small portions followed by 5 ml of CH_3NO_2. The reaction was stirred at -10^{0}C until no starting material could be detected by TLC (15 minutes). The mixture was poured into water (40 mL), the organic layer was separated and the aqueous solution extracted twice with 25 mL of ethyl acetate. The organic extracts were dried with Na_2SO_4 and the solvent removed in vacuum. The product was crystallized from CH_2Cl_2 to give 870 mg (85%) of 3-acetyl-5-nitroindole.

Hydrolysis of 3-acetyl-5-nitro-1-sulfonylindole - To a stirred solution of 3-acetyl-5-nitro-1-sulfonylindole (500 mg, 1,5 mmol) in MeOH (20 mL), NaOH 50% (5 mL) was added and, after 15 minutes, at

room temperature, no starting material could be detected by TLC. The MeOH was evaporated and the aqueous solution extracted twice with 25 mL of ethyl acetate. The organic extracts were dried with Na_2SO_4 and the solvent removed in vacuum, giving 301 mg (98%) of 3-acetyl-5-nitroindole as yellow powder.

In summary, we have described a regioselective procedure for obtaining 5 and 6 nitro-3-acetylindole in yields superior to all the currently reported procedures. This represents an advance in indole chemistry from the synthetic point of view, since the corresponding diazonium salts can be transformed into several different 5 and 6 substituted indoles. The reduction of the nitro derivatives to the corresponding amines has already been accomplished quite successfully in our laboratory. Detailed studies are underway in order to explain the regiochemistry of the nitration process.

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6. Compound **2**. mp 294-296 ^{0}C (lit.[3a] mp 295-297 ^{0}C). IR (KBr) 3080 (NH), 1633 (C=O), 1510, 1333 (NO_2) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 2.50 (s, 3 H), 7.65 (d, 1 H, J = 9.0 Hz), 8.07 (d, 1 H, J = 9.0 Hz), 8.54 (s, 1 H), 9.01 (s, 1 H). ^{13}C NMR (DMSO-d_6) δ 27.72, 113.57, 118.15, 118.40, 118.48, 125.31, 138.97, 141.02, 142.96, 193.31.
7. Compound **3**. mp 337-340 ^{0}C (lit.[3a] mp 340-342 ^{0}C). IR (KBr) 3150 (NH), 1632 (C=O), 1511, 1317 (NO_2) cm^{-1}. ^{1}H RMN (DMSO-d_6) δ 2.47 (s, 3 H), 8.00 (d, 1 H, J = 8.5 Hz), 8.26 (d, 1 H, J = 8.5 Hz), 8.32 (s, 1 H), 8.61 (s, 1 H). ^{13}C NMR (DMSO-d_6) δ 27.88, 109.11, 117.13, 117.48, 121.93, 130.51, 135.78, 139.76, 143.48, 193.26.
8. Compound **4**. mp 210-212 ^{0}C (lit.[3a] mp 213-214 ^{0}C). IR (KBr) 3215 (NH), 1506, 1370 (NO_2) cm^{-1}. ^{1}H RMN (DMSO-d_6) δ 7.30-7.35 (m, 2 H), 7.56 (d, 1 H, J = 10.00 Hz), 8.08 (d, 1 H, J = 7.50 Hz), 8.62 (s, 1 H). ^{13}C NMR (DMSO-d_6) δ 113.75, 119.80, 120.24, 124.08, 124.54, 128.87, 130.81, 135.44.