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THE FRIEDEL-CRAFTS ACYLATION OF ETHYL INDOLE-2-CARBOXYLATE. AN UNUSUAL SUBSTITUTION ON THE BENZENE MOIETY

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Abstract——Ethyl indole-2-carboxylate can be acylated with a variety of acyl chlorides under Friedel-Crafts conditions to give mono-acyl indole derivatives. However, the acyl chloride derived from a stronger acid tends to substitute at the C-5 position rather than at the C-3, a usual nucleophilic center of indoles.

There have been many methods[1] for the acylation of indoles at the C-3 position, as it is very important and fundamental reaction in indole chemistry. In a previous paper we ourselves reported[2] the acylation of ethyl indole-2-carboxylate (1) which is a stable equivalent of indole itself, and its derivatives with $RCO_2H/(CF_3CO)_2O/H_3PO_4$. In this paper we wish to report an unusual result regarding the Friedel-Crafts acylation[3] of 1.

As there is no example reported about the Friedel-Crafts acylation of 1, we aimed to examine it and compare with our previous method[2]. We undertook Friedel-Crafts acylation of the indole(1) with acyl chlorides(RCOCl), using $AlCl_3$ as a catalyst in ethylene chloride(molar ratio; 1:reagent:$AlCl_3$=1:2:2), and found that mono-acylation took place in fairly good yields, as shown in Table I. However, the position of the substitution is not limited to the most reactive C-3 position: the benzene moiety(C-5 as major and C-7 as minor) was also substituted, while the C-3 position was kept unsubstituted.

With simple alkyl(R=methyl or n-propyl) acyl chlorides the acylation occurred at the C-3 position and the benzene moiety in a ratio of nearly 1:1(Runs 1 and 4),

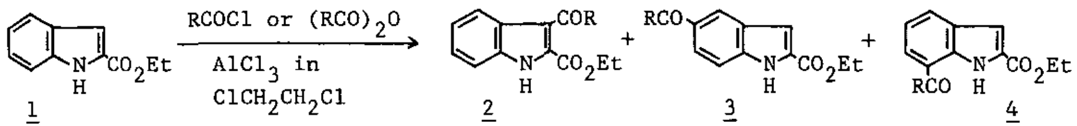

Table I The Results of the Friedel-Crafts Acylation of Ethyl Indole-2-carboxylate(1).

Run	Reagent[a] R=	A or B	Reaction conditions temp.	time(h)	Products[4,5] Total yield (%)	Product ratio 2 : 3 : 4	Recov. 1 (%)
1	CH_3-	A	r.t.[c]	1.0	73.2	55 : 31 : 14	0
2		A[b]	r.t.	1.0	77.6	81 : 15 : 4	0
3		B	reflux	1.0	72.7	98 : 2 : 0	trace
4	$CH_3(CH_2)_2$-	A	0°C	1.5	72.3	51 : 34 : 15	7.1
5		A[b]	r.t.	1.0	95.3	87 : 10 : 3	trace
6	$ClCH_2$-	A	r.t.	1.0	62.8	1 : 86 : 13	29.1
7		B	reflux	1.5	25.8	11 : 76 : 12	70.4
8		B[b]	110°C	2.0	41.5	23 : 68 : 9	trace
9	p-$NO_2C_6H_4$-	A	reflux	1.0	67.7	9 : 72 : 19	19.3
10	Ph-	A	reflux	1.0	78.5	51 : 31 : 18	trace
11		B	reflux	1.0	64.5	99 : 1 : 0	25.5
12	p-$CH_3C_6H_4$-	A	reflux	1.0	72.9	80 : 13 : 7	trace
13	p-$CH_3OC_6H_4$-	A	reflux	1.0	69.7	100 : 1 : 0	0

a) A: Acyl chloride(RCOCl), B: Acid anhydride[$(RCO)_2O$]

b) Nitrobenzene was used as the solvent for the reaction.

c) r.t.: room temperature

whereas with the acyl chloride(R=CH_2Cl) derived from a stronger acid the substitution occurred exclusively at the benzene moiety(mainly at the C-5 position) (run 6). This tendency[6] toward the acylation of 1 was clearly confirmed by experiments using p-substituted benzoyl chlorides(Runs 9, 10, 12, 13).
Indoles are usually attacked by an electrophile exclusively at the C-3 position, if it is vacant[7]. The Friedel-Crafts acylation of indoles is also known[1c] to take place at the C-3 position, except for only a few examples.[7b] Ethyl indole-

2-carboxylate(1) is also in the same situation for formylation[8a], halogenation[8b], Mannich reaction[8c], azo coupling reaction[8d], and so on, except for nitration[8e]. Noland[8e] described that the nitration of 1 gave a 4-nitro compound due to the steric hindrance of the 2-ethoxycarbonyl group. The present results show that the Friedel-Crafts acylation of 1 can take place at the benzene moiety while the C-3 position was kept unsubstituted, and that the regioselectivity for it markedly depends on the reactivity of reagents in contrast with the Noland's description. Although no theoretical explanation is available at the present time, this result suggests that the present procedure provides a promising method for preparing 5-acylindole derivatives, because the known method for it involves a roundabout route via acylation of N-acylindoline derivatives.[9]

Apart from the results described above, regioselective acylation toward the C-3 position of 1 is important from the viewpoint of synthetic chemistry. Thus, we changed the reagent from acyl chloride to acid anhydride, because the acylation with a mixed anhydride has been found[2] to give 3-acylindole derivatives exclusively. As expected, the Friedel-Crafts acylation with acid anhydride greatly increased the regioselectivity for acylation at the C-3 position(Runs 3 and 11). The use of nitrobenzene as a solvent also made the C-3 acylation more favorable (Runs 2 and 5). These devices should make the present method synthetically useful. However, there was evidently no effective improvement in the case of chloroacetylation(Runs 6,7, and 8).

We are now under investigation to accomplish the generality of regioselective preparation of 3- and 5-acylindoles.

Table II Melting Points of the Acyl Indoles Obtained in the Present Work.

Compound / Substituent	2[2]	3	4
R= CH_3	91.5-93°C	136.5-138°C[10]	49.5-51°C
$CH_3(CH_2)_2$	56-58°C	127-129.5°C	64-65°C
$ClCH_2$-	111-113.5°C	185-187°C	100-101°C
p-$NO_2C_6H_4$-	---	228-229.5°C	145-146.5°C
C_6H_5-	134-136°C	163.5-165.5°C	72-74°C
p-$CH_3C_6H_4$-	177-179°C	169-170.5°C	116-118.5°C
p-$CH_3OC_6H_4$-	131-133°C	---	---

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4) The isolation of acylated products(2, 3, and 4) could practically be achieved by usual column chromatography on silica gel, although the ratio of the products in the table was measured by HPLC.

5) All new compounds gave satisfactory elemental analyses and spectral data, and were identified with or correlated chemically to authentic compounds for 5-acetyl[10], 5-benzoyl-, and 5-chloroacetyl-1.

6) The isolated 3-benzoyl-(2) and 5-benzoyl-(3) indoles were submitted to the respective acylation conditions, but were recovered unchanged.

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