THE FRIEDEL-CRAFTS ACYLATION OF ETHYL PYRROLE-2-CARBOXYLATE. SCOPE, LIMITATIONS, AND APPLICATION TO SYNTHESIS OF 7-SUBSTITUTED INDOLES[1]

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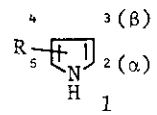
Abstract---The Friedel-Crafts acylation of ethyl pyrrole-2-carboxylate (3) was studied under a variety of conditions using various Lewis acids and acyl chlorides. The acylation with some Lewis acids such as BF_3 OEt_2 gave a mixture of 4- and 5-acyl derivatives (5 and 6), whereas the acylation with various acyl chlorides in the presence of $AlCl_3$ gave exclusively 4-acyl derivatives (5). Acylation in this experiment was applied to a new methodology for synthesis of 7-substituted indoles.

It is well known[2,3,4] that pyrroles (1) react with electrophiles exclusively at the 2- (or α) position. Thus, the method for preparing 3-substituted pyrroles has been one of the targets[3] of heterocyclic chemistry. The representative methods reported so far are electrophilic reaction (mostly Friedel-Crafts acylation) of N-phenyl (or aryl) sulfonylpyrroles (2) and ethyl pyrrole-2-carboxylate (3) (or pyrroles having an electron-withdrawing substituent at the 2-position). The Friedel-Crafts (FC) acylation of the former (2) has been studied in some detail,[3] whereas that of the latter (3) has not so much.[3,5] In connection with the FC acylation of ethyl indole-2-carboxylate[6] (4), we are interested in the regioselectivity in the FC acylation of ethyl pyrrole-2-carboxylate (3).



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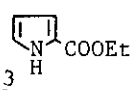

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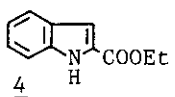

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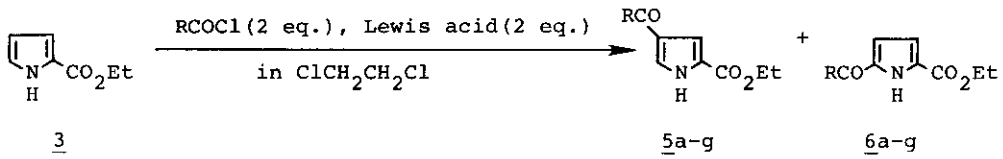
We wish to report the scope and limitations of the FC acylation of the pyrrole ester (3) and its application to a new methodology for synthesis of 7-substituted ethyl indole-2-carboxylates.

We first examined the effect of Lewis acids for the FC acylation. The pyrrole ester (3, 1 eq.) was treated with acetyl chloride (2 eq.) in the presence of various Lewis acids (2 eq.) until the reaction ceased. Two products, the 4- and 5-acetylpyrrole (5a and 6a), were formed and could be separated easily by column chromatography. The result is summarized in Table 1. Run number is arranged in the order of high ratio of the 4-acetylpyrrole (5). $AlCl_3$ showed complete regioselectivity for 4-acetylation, whereas $BF_3 \cdot OEt_2$ and $ZnCl_2$ gave the 5-acetylpyrrole (6) more than the 4-acetyl one (5). This tendency is similar to the FC acylation of N-phenylsulfonylpyrrole[7] (2), where $BF_3 \cdot OEt_2$ gave the α-acyl derivative (corresponding to 5-acetylpyrrole (6)) exclusively. However, it is worth noting that regioselectivity toward the β-position of the pyrrole ester (3) was superior to that of the sulfonyl compounds[7] (2) in the experiment using various Lewis acids.

Next, we examined the effect of acyl chlorides as reagent. $AlCl_3$ was used as a Lewis acid catalyst because it showed the highest regioselectivity toward 4-acylation. The pyrrole ester (3, 1 eq.) was treated with various acyl chlorides (2 eq.) in the presence of $AlCl_3$ (2 eq.) until the reaction ceased and the result is summarized in Table 2. The reactions gave corresponding 4-acylpyrroles (5) exclusively or overwhelmingly. The reactions with acyl chlorides derived from weaker acids tended to be accompanied by only a small amount of the 5-acyl derivative (6). In relation to the synthesis of a pyrrolomycin C analogue, Ezaki and Sakai[8] reported that the FC acylation of N-phenylsulfonylpyrrole (2) with 3,5-dichloro-2-methoxybenzoyl chloride in the presence of $AlCl_3$ gave the desired 3-acyl derivative (β-isomer) in 12% yield accompanied by an undesired 2-acyl derivative (α-isomer) in 45% yield, whereas the present FC acylation of the pyrrole ester (3) gave the desired 4-acylpyrrole (5g, β-isomer) exclusively in 61.9% yield. Thus, we can claim that ethyl pyrrole-2-carboxylate (3) is superior to N-phenylsulfonylpyrrole (2) for a substrate in β-acylation. The substitution position in the FC acylation of the pyrrole ester (3) was little affected by the kind of acyl chlorides, in contrast to the FC acylation of the indole (4).[6]

The structures of all new compounds in this paper were satisfactorily identified by elemental analyses and spectral means. Especially, as to the position of the substitution at 4- or 5-position in the acylpyrroles, the 4- or 5-acylpyrroles (5



3 5a-g 6a-g

Table 1. The Friedel-Crafts Acetylation of 3 Using Various Lewis Acids (R=CH_3)

Run	Lewis acid	Condition temp.[a], time	Products (5a and 6a) total yield (%)	ratio (5a : 6a)
1	$AlCl_3$	r.t., 1.0 h	88.9	100 : 0
2	$SbCl_5$	r.t., 30 min	85.5	98 : 2
3	$TiCl_4$	50°C, 1.0 h	88.2	94 : 6
4	$FeCl_3$	0°C, 3 min	98.6	88 : 12
5	$SnCl_4$	0°C, 20 min	99.1	83 : 17
6	$BF_3 \cdot OEt_2$	80°C, 1.25 h	88.2	43 : 57
7	$ZnCl_2$	50°C, 30 min	87.2	36 : 64

a) Bath temperature

Table 2. The Friedel-Crafts Acylation of 3 Using Various Acyl Chlorides in the Presence of $AlCl_3$

Run	Acyl chloride R=	Condition temp.[b], time	Products (5 and 6) total yield (%)	ratio (5 : 6)
1[a]	CH_3- (a)	r.t., 1.0 h	88.9	100 : 0
2	C_3H_7- (b)	75°C, 2.5 h	86.7	93 : 7
3	$ClCH_2$- (c)	reflux, 1.0 h	47.2	100 : 0
4	4-$MeOC_6H_4$- (d)	80°C, 2.5 h	78.0	91 : 9
5	C_6H_5- (e)	reflux, 2.5 h	71.7	100 : 0
6	4-$NO_2C_6H_4$- (f)	reflux, 2.0 h	78.3	100 : 0
7	3,5-diCl-2-$MeOC_6H_2$- (g)	50°C, 3.0 h	61.9[c]	100 : 0

a) Taken from Table 1

b) Bath temperature

c) The product was the demethylated 3,5-dichloro-2-hydroxy compound.

and 6) are identified by comparison of their chemical shifts of 3-, 4-, and 5-protons in the ^{1}H-nmr spectra with those of the 4- and 5-acetylpyrroles (5a and 6a) as references, whose structures were chemically identified by conversion of 5a to known 3-acetylpyrrole as reported.[5a] As shown in Table 3, the position of acyl group in each compound was firmly identified by ^{1}H-nmr spectra.

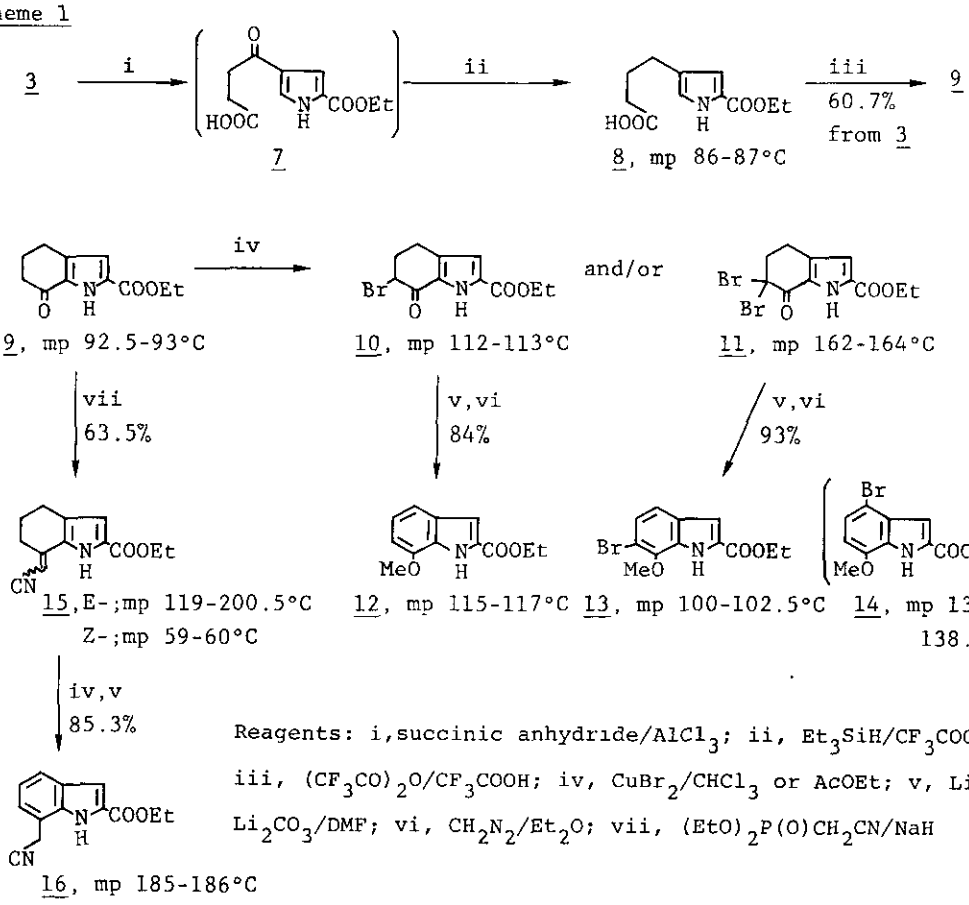
On the basis of thus established C-4 acylation of 3 we wanted to develop a new synthetic route for 7-substituted indoles. Although some 4-substituted indole syntheses[9] starting from pyrrole derivatives are reported, there is no report concerning the synthesis of 7-substituted indoles from them. The FC acylation of the pyrrole (3) with succinic anhydride gave the 4-succinoyl pyrrole (7) exclusively in a good yield. The reduction of 7 with Et_3SiH in CF_3CO_2H followed by cyclization with $(CF_3CO)_2O$ gave the ketone (9) as the key compound, which was treated with $CuBr_2$ (2 eq.) in AcOEt to give the monobromo ketone (10) exclusively in 89.3 % yield. The use of 4 eq. of $CuBr_2$ in $CHCl_3$ gave the dibromoketone (11) in 51% and the monobromoketone (10) in 15.1% yield, whereas the same reaction in AcOEt gave only dibromoketone (11) in 92.4% yield. Aromatization of the monobromoketone (10) by dehydrobromination with $LiBr/Li_2CO_3$ in DMF,[10] followed by methylation with CH_2N_2 gave the 7-methoxyindole (12) in 83% yield. The overall yield of 12 from 3 was 45.2%, which is comparable to that reported of 47.3%[11] by Reissert method starting from 3-methoxy-2-nitrotoluene. Aromatization of the dibromoketone (11) by the same reagent at 105°C for 22 min, followed by methylation with CH_2N_2 gave the 6-bromo-7-methoxyindole (13) in 93% yield. On the other hand, it is interesting to note that the aromatization by higher temperature and longer reaction time, 145°C for 5 h, gave the 6-bromo-7-methoxyindole (13) in only 11.1% and 4-bromo-7-methoxyindole (14) in 42.3% yield, probably via migration of the bromine atom. The mechanism of this migration is now under investigation. Finally, a synthesis of the 7-alkylindole (16) was conducted. The key intermediate ketone (9) was treated with a Wittig reagent to give a mixture of E- and Z-olefin (15) in 63.5% yield. The aromatization of 15 to the 7-functionalized alkylindole (16) was successful by bromination with $CuBr_2$ at the γ-position of the cyano group, followed by dehydrobromination in the same way as the preparation of 12 and 13, whereas the usual aromatization condition such as dehydrogenation by Pd-C or DDQ oxidation resulted in recovery of the starting material (15).

In summary we developed a new method for synthesis of some 7-substituted indoles. Skilled use of the present reaction sequence or the ketone (9) would afford more

Table 3. Physical and ^{1}H-Nmr Spectral Data (δ value in $CDCl_3$) of the 4- and 5-Acylpyrroles (5 and 6)

R	4-Acylpyrrole (5) Chemical shift, (mp, °C) C_3-H	C_5-H	5-Acylpyrrole (6) Chemical Shift, (mp, °C) C_3- and C_4-H
CH_3- (a)	7.24	7.52 (108-109)	6.84 (60-60.5)
C_3H_7- (b)	7.25	7.51 (71-72)	6.80 (54.5-55)
$ClCH_2$- (c)	7.25	7.60 (114.5-116.5)	---
4-$MeOC_6H_4$- (d)	7.29	7.32 (107-108)	6.94 (65.5-67)
C_6H_5- (e)	7.32	7.52 (99.5-101)	---
4-$NO_2C_6H_4$- (f)	7.16	7.58 (172.5-174.5)	---
3,5-diCl-2-OH-C_6H_2- (g)	7.08	7.59 (222-224)	---

Scheme 1



Reagents: i, succinic anhydride/$AlCl_3$; ii, Et_3SiH/CF_3COOH; iii, $(CF_3CO)_2O/CF_3COOH$; iv, $CuBr_2/CHCl_3$ or AcOEt; v, LiBr/Li_2CO_3/DMF; vi, CH_2N_2/Et_2O; vii, $(EtO)_2P(O)CH_2CN$/NaH

useful 7-substituted indoles.

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