β-Acylation of Ethyl Pyrrole-2-carboxylate by Friedel–Crafts Acylation: Scope and Limitations (Synthetic Studies on Indoles and Related Compounds. XXXVIII[1])

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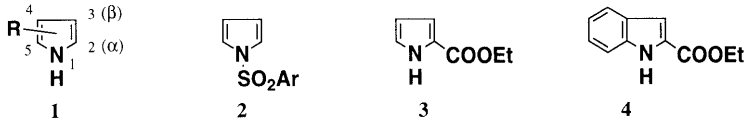
The Friedel–Crafts acylation of ethyl pyrrole-2-carboxylate (3) was studied under several conditions using various Lewis acids and acyl chlorides. The acylation with various acyl chlorides in the presence of aluminum chloride gave exclusively ethyl 4-acylpyrrole-2-carboxylate (5), whereas weaker Lewis acids such as zinc chloride and boron trifluoride etherate gave a mixture of ethyl 4- and 5-acylpyrrole-2-carboxylates.

Key words pyrrole; acylation; Friedel–Crafts reaction; regioselective; ethoxycarbonyl; trichloroacetyl

Electrophilic substitution in five-membered heteroaromatic compounds with one hetero atom, pyrrole (**1**) for example, occurs predominantly at the α- (C_2) position.[2] Thus, an efficient method for preparing β- (C_3) substituted pyrroles is an important goal in five-membered heteroaromatic chemistry. Two methods for acylation at the β- (C_3) position on the pyrrole ring (**1**) have been found: 1) Friedel–Crafts acylation[3] of pyrroles with an electron-withdrawing substituent at C_2 [for example, ethyl pyrrole-2-carboxylate (**3**)]; 2) Friedel–Crafts acylation of 1-(arylsulfonyl)pyrrole (**2**). The latter method has been studied extensively,[4] whereas the former is less well explored.[5] In connection with studies on the Friedel–Crafts acylation[6] of ethyl indole-2-carboxylate (**4**), we are interested in the regioselectivity in the Friedel–Crafts acylation of ethyl pyrrole-2-carboxylate (**3**). We report here a detailed study on the Friedel–Crafts acylation of **3** and related compounds.

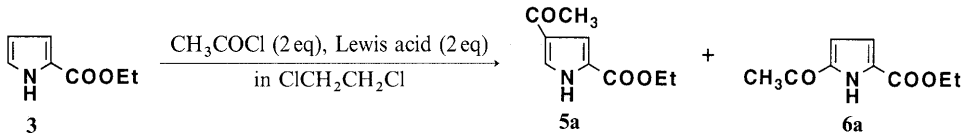
The Friedel–Crafts acylation of **3** was carried out with acetyl chloride as the reagent and Lewis acid as the catalyst in 1,2-dichloroethane under usual Friedel–Crafts conditions. First, the effect of Lewis acid was examined. The ethyl pyrrole-2-carboxylate (**3**, 1 eq) was treated with acetyl chloride (2 eq) in the presence of various Lewis acids (2 eq) until the reaction proceeded no longer. Generally, two products, ethyl 4- and 5-acetylpyrrole-2-carboxylates (**5a** and **6a**), were formed, but no 3-acetyl isomer was found. They could be separated easily by column chromatography over silica gel. The results are summarized in Table 1. Entry numbers are arranged in the order of higher ratio of the 4-acetylpyrrole (**5a**). In contrast to the Friedel–Crafts acylation of ethyl indole-2-carboxylate[6] (**4**), aluminum chloride showed complete regioselectivity for 4-acetylation, whereas boron trifluoride etherate and zinc chloride gave more of the 5-acetylpyrrole (**6a**) than the 4-acetyl one (**5a**). This tendency is similar to the Friedel–Crafts acylation of *N*-benzenesulfonylpyrrole[4] (**10**), where boron trifluoride etherate gave exclusively the



1 **2** **3** **4**

Fig. 1

Table 1. The Friedel–Crafts Acetylation of **3** Using Various Lewis Acids



3 **5a** **6a**

Entry	Lewis acid	Conditions		Products (**5a** and **6a**)	
		Temperature[a]	Time	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. r.t. = room temperature.

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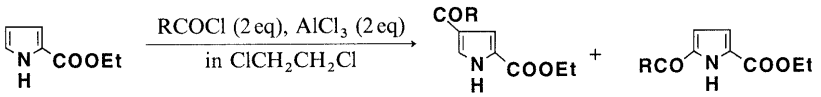
Table 2. The Friedel–Crafts Acylation of **4** with Various Acyl Chlorides in the Presence of $AlCl_3$



Entry	Acyl chloride R	Conditions		Product (**5** and **6**)	
		Temperature[a]	Time (h)	Total yield (%)	Ratio (**5**:**6**)
1[b]	CH_3 (a)	r.t.	1.0	99.9	**5a**:**6a** = 100:0
2	C_3H_7 (b)	75 °C	2.5	86.7	**5b**:**6b** = 93:7
3	$ClCH_2$ (c)	Reflux	1.0	47.2	**5c**:**6c** = 100:0
4	4-MeO–C_6H_4 (d)	80 °C	2.5	78.0	**5d**:**6d** = 91:9
5	C_6H_5 (e)	Reflux	2.5	71.7	**5e**:**6e** = 100:0
6	4-NO_2–C_6H_4 (f)	Reflux	2.0	78.3	**5f**:**6f** = 100:0

a) Bath temperature. *b*) Taken from Table 1. r.t. = room temperature.

Table 3. Comparison of Acetyl Chloride and Acetic Anhydride, and the Effect of Catalyst on the Acetylation of **3**

Entry	Reagent	Catalyst (mol eq to **3**)	Conditions		Products (**5a** and **6a**)	
			Temperature	Time	Total yield (%)	Ratio (**5a**:**6a**)
1[a]	CH_3COCl	$AlCl_3$ (2.0)	r.t.	1.0 h	88.9	100:0
2	$(CH_3CO)_2O$	$AlCl_3$ (2.0)	r.t.	6.0 h	80.6	88:12
3	$(CH_3CO)_2O$	$AlCl_3$ (6.0)	0 °C	15 min	92.9	100:0
4[a]	CH_3COCl	$BF_3 \cdot OEt_2$ (2.0)	80 °C	1.25 h	88.2	43:57
5	$(CH_3CO)_2O$	$BF_3 \cdot OEt_2$ (2.0)	r.t.	1.5 h	88.0	53:47
6	$(CH_3CO)_2O$	$BF_3 \cdot OEt_2$ (6.0)	0 °C	30 min	89.3	48:52
			r.t.	30 min		

a) Taken from Table 1. r.t. = room temperature.

α-acyl derivative [corresponding to the 5-acetylpyrrole (**6a**)]. These data indicate that regioselectivity toward the β-position of ethyl pyrrole-2-carboxylate (**3**) was superior to that of *N*-benzenesulfonylpyrrole[4] (**10**) with various Lewis acids.

Next, in order to examine the effect of acyl chloride, the ethyl pyrrole-2-carboxylate (**3**) was treated with various acyl chlorides (2 eq) in the presence of aluminum chloride, which was the catalyst giving the highest regioselectivity toward the C_4-position, as shown in Table 1. The results are summarized in Table 2. The reactions gave the corresponding 4-acylpyrroles (**5**) exclusively or with overwhelming regioselectivity. The reactions with acyl chlorides derived from weaker acids tended to yield a small amount of the 5-acyl isomer (**6**) (entries 2 and 4).

In Table 3, we show the results of comparative acetylation with acetic anhydride and acetyl chloride. The experiment in entry 2 should be compared with that in entry 1. The ratio of the desired 4-acetyl compound (**5a**) in the experiment with acetic anhydride was slightly lower than that in the experiment with acetyl chloride. The ratio of 4-acetylpyrrole (**5a**) increased with the use of increased amounts of aluminum chloride.

On the other hand, the use of boron trifluoride etherate as a catalyst increased the ratio of the undesired 5-acetylpyrrole (**6a**) to some extent, irrespective of the acylating reagent. The use of increased amounts of boron trifluoride etherate resulted in an increase of 5-acetylpyrrole (**6a**).

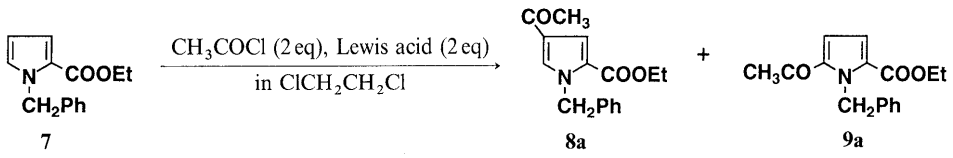
Next, the acetylation of *N*-benzylpyrrole (**7**) was examined. The *N*-benzyl group is known[6b] to increase the yield in C_3-acylation of ethyl indole-2-carboxylate (**4**). The reaction was carried out with four kinds of Lewis acids in the same way as in the case of the NH-pyrrole (**3**), and the results are summarized in Table 4.

The reaction conditions required for completion were similar to or somewhat milder than those in the NH-series (Table 1). The reactions with aluminum chloride and titanium tetrachloride gave exclusively the 4-acetylpyrrole (**8a**), and those with boron trifluoride etherate and zinc chloride also gave **8a** predominantly, whereas the same Lewis acids gave the 5-acetylpyrrole (**6a**) predominantly in the NH-series. These results show that the *N*-benzyl group accelerates C_4-acylation of the pyrrole.

In relation to the synthesis of pyrrolomycin C analogues, Ezaki and Sakai[7] reported that the Friedel–Crafts acylation of *N*-benzenesulfonylpyrrole (**10**) with 3,5-dichloro-2-methoxybenzoyl chloride (**11**) in the presence of aluminum chloride gave the desired 3-acylpyrrole (β-isomer) (**12**) in only 12% yield with the undesired 2-acyl isomer (α-isomer) (**13**) in 45% yield, whereas the present Friedel–Crafts acylation of ethyl pyrrole-2-carboxylate (**3**) gave the desired 4-acylpyrrole (**14**) exclusively in 63% yield (Chart 1).

The structures of the two β-acylpyrroles (**12** and **14**) were correlated by converting them into **15**. Thus, we can claim that ethyl pyrrole-2-carboxylate (**3**) is superior to *N*-benzenesulfonylpyrrole (**10**) as a substrate for β-acylation (Table 2). The regioselectivity for substitution

Table 4. The Friedel–Crafts Acetylation of **7** with Various Lewis Acids



Entry	Lewis acid	Conditions		Products (**8a** and **9a**)	
		Temperature	Time (min)	Total yield (%)	Ratio (**8a**:**9a**)
1	$AlCl_3$	Reflux	20	81.8	100:0
2	$TiCl_4$	0 °C	20	89.6	100:0
3	$BF_3 \cdot OEt_2$	85 °C	55	80.7	77:23
4	$ZnCl_2$	r.t.	80	95.8	65:35

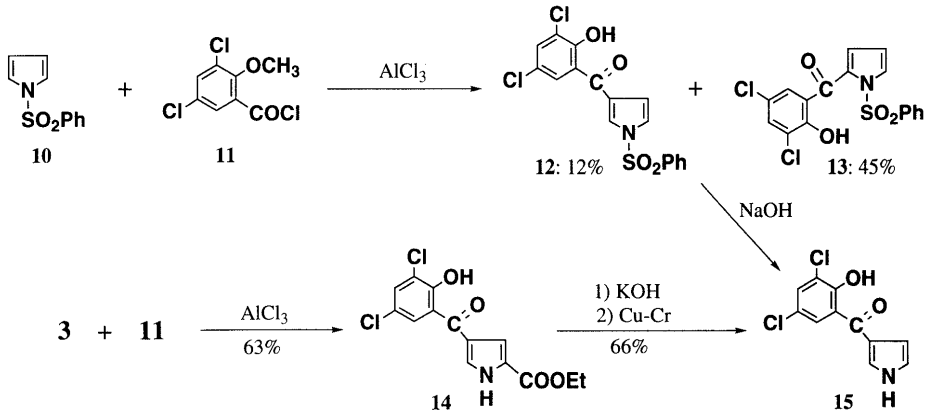


Chart 1

position in the Friedel–Crafts acylation of ethyl pyrrole-2-carboxylate (**3**) was little affected by the kind of acyl chloride, whereas the Friedel–Crafts acylation of ethyl indole-2-carboxylate[6] (**4**) was greatly affected.

Determination of the position of the acyl group in the acylpyrroles (**5** and **6**) was generally achieved by comparison of the chemical shifts of the 3-, 4-, and 5-protons in the ^{1}H-NMR spectra with those of ethyl 3- and 4-acetylpyrrole-2-carboxylates (**5a** and **6a**) as references. The structure of **5a** was established by converting it into 3-acetylpyrrole[8] (**16**). The structures of *N*-benzylpyrroles (**8a** and **9a**) were determined by comparison with the samples prepared from the 4- and 5-acetylpyrroles (**5a** and **6a**) by benzylation.

As shown in Table 5, the signals of the C_3- and C_5-protons of the 4-acylpyrroles (**5**) appeared separately in the δ 7.16—7.32 and 7.32—7.60 ppm area, whereas those of the C_3- and C_4-protons of the 5-acylpyrroles (**6**) appeared as equivalent in δ 6.80—6.94 ppm area. Thus, the two kinds of acylpyrroles were easily differentiated.

As shown in Tables 1 and 4, stronger Lewis acids tended to give more of the desired 4-acylpyrrole. This might be explained as follows. The Lewis acid would associate with the carbonyl of ethyl pyrrole-2-carboxylate (**3**) to give a complex similar to the complex[9] between an ethyl indole-2-carboxylate derivative and a shift reagent. The coordinated carbonyl acts as a stronger electron-attracting substituent. Thus, the 3- and 5-positions are deactivated and the 4-position is relatively activated for acylation. This

Table 5. ^{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		5-Acylpyrrole (**6**) Chemical shift
	C_3-H	C_5-H	C_3- and C_4-H
CH_3 (a)	7.24	7.52	6.84
C_3H_7 (b)	7.25	7.51	6.80
$ClCH_2$ (c)	7.25	7.60	—
4-MeO–C_6H_4 (d)	7.29	7.32	6.94
C_6H_5 (e)	7.32	7.52	—
4-NO_2–C_6H_4 (f)	7.16	7.58	—

supposition is supported by the fact that acetylation by the mixed anhydride method with a combination of acetic acid and trifluoroacetic anhydride[10] gave worse regioselectivity (36.2% of **5a** and 22.7% of **6a** from **3**, and 62.7% of **8a** and 27.3% of **9a** from **7**).

From this point of view the acylation of the pyrrole with a more electron-attracting C_2-substituent would lead to a greater amount of 4-acylated pyrrole. Thus, we finally examined the acylation of 2-trichloroacetylpyrrole[11] (**17**), since the trichloroacetyl group has been reported to be more electron-withdrawing than the 2-ethoxycarbonyl group.

The Friedel–Crafts acylation of 2-trichloroacetylpyrrole[11] (**17**) with three acyl chlorides was conducted under the same reaction conditions (in respect of molar ratios of the substrate and reagents) as those in Tables 1

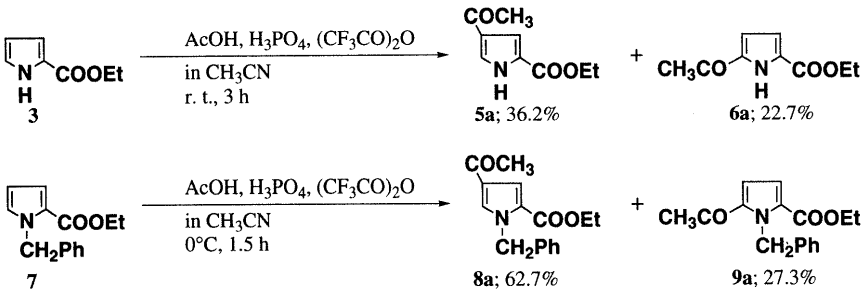
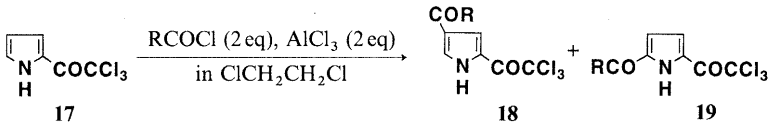


Chart 2

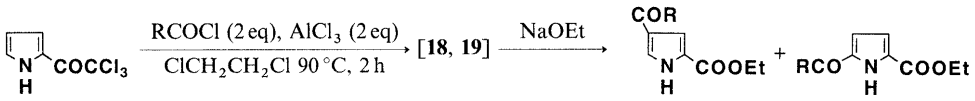
Table 6. The Friedel–Crafts Acetylation of **17** in the Presence of $AlCl_3$



Entry	Acyl chloride R	Conditions		Products (**18** and **19**)	
		Temperature	Time (h)	Total yield (%)	Ratio (**18**:**19**)
1[11]	CH_3 (a)	r.t.	1.25	96.7	100:0
2	$CH_3CH_2CH_2$ (b)	80 °C	1	86.2	98.5:1.5
3	4-MeO–C_6H_4 (d)	80 °C	1.5	96.0	98.0:2.0

r.t. = room temperature.

Table 7. Acylation and Conversion of Trichloroacetyl Group to Ethoxycarbonyl Group



Entry	Acyl chloride R	Reaction conditions from **18**, **19** to **5**, **6**		Products (**5** and **6**)	
		Temperature (°C)	Time (h)	Total yield (%)	Ratio (**5**:**6**)
1	$CH_3CH_2CH_2$ (b)	0	1.25	63.6	100:0
2	4-MeO–C_6H_4 (d)	100	1.1	92.7	96.5:3.5

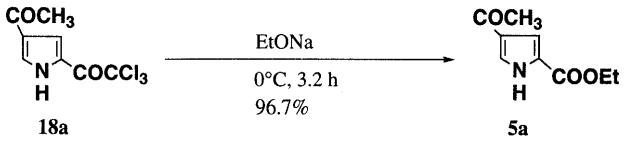


Chart 3

and 2. Butyryl and 4-methoxybenzoyl chloride were selected as reagents, because they showed poorer ratios of C_4-acylation than the others (Table 2), and acetyl chloride[11] was used as a reference. The reactions generally proceeded with high regioselectivity and in excellent yield, as described by Bélanger.[11] Next, ethyl 4-acetyl-2-trichloroacetylpyrrole (**18a**) was treated with sodium ethoxide to yield the corresponding 2-ethoxycarbonyl product (**5a**) in excellent yield. Thus, 2-trichloroacetylpyrrole (**17**) was treated with the two kinds of acyl chlorides to yield acylated pyrroles (**18** and **19**), which, without purification, were treated with sodium ethoxide to yield the corresponding ethyl acylpyrrole-2-carboxylates (**5** and **6**). Both the overall yields and the ratios of the 4-acylpyrrole were excellent. This experiment showed that the acylation of **17** is similar or superior to that of **3** in respect of C_4-acylation, although it requires more steps.

The present experiment revealed that ethyl pyrrole-2-carboxylate (**3**) is a good substrate for preparation of 3-(or β-)acylpyrroles. In the accompanying paper, we will describe a new synthetic methodology for indoles variously modified on the benzene ring by applying the present acylation.

Experimental

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-400 spectrometer (in Nujol, unless otherwise stated). ^{1}H-NMR spectra were measured on a Hitachi R-24B (60 MHz) spectrometer unless otherwise stated, or on a JEOL GX-400 (400 MHz). Deuteriochloroform was used as the solvent, with tetramethylsilane as an internal reference, unless otherwise stated. The assignments of NH signals were confirmed by disappearance of the signals after addition of deuterium oxide. Mass spectra (MS) were measured on JEOL JMS-01-SG-2, JEOL JMS-D300, and JEOL JMS-DX303 spectrometers with a direct inlet system. For column chromatography, Silica gel 60 (70—230 mesh ASTM, Merck, unless otherwise stated), and for thin

layer chromatography (TLC), Silica gel 60 F_{254} (Merck) were used. All identifications of products were done by examination of MS, IR spectra, and especially NMR spectra. When products were difficult to separate, their ratios were measured by comparison of the intensity of the signals of each compound in the 400 MHz ^{1}H-NMR spectrum. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad; dif., diffused; arom., aromatic; BP, base peak; dec., decomposition.

General Procedure for the Friedel–Crafts Acylation of Ethyl Pyrrole-2-carboxylate (3) A solution of ethyl pyrrole-2-carboxylate (**3**) (209 mg, 1.5 mmol) in 1,2-dichloroethane (4 ml) was added dropwise to the ice-cooled solution of an acylating agent (3 mmol) and a Lewis acid (3 mmol) in 1,2-dichloroethane (4 ml) under an argon atmosphere, or **3** (209 mg, 1.5 mmol) was added to a solution of an acylating agent (9 mmol) and a Lewis acid (9 mmol) in 1,2-dichloroethane (6 ml) in the same way, and the reaction mixture was stirred under the conditions given in the tables, until the formation of the products ceased as determined by TLC monitoring. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the residue. The residue was subjected to column chromatography on silica gel; gradient elution with hexane–ethyl acetate or benzene–ethyl acetate gave the products shown in the tables.

The Products Obtained from the Friedel–Crafts Acylation of Ethyl Pyrrole-2-carboxylate (3) Ethyl 4-Acetylpyrrole-2-carboxylate (**5a**): Colorless needles from benzene, mp 108—109 °C. *Anal.* Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.82; H, 6.18; N, 7.78. IR ν_{max} cm^{-1}: 3250 (NH), 1690, 1660 (CO). ^{1}H-NMR δ: 1.34 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.42 (3H, s, $COC\underline{H}_3$), 4.33 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.28 (1H, m, C_3-H), 7.53 (1H, dd, J=4, 1.5 Hz, C_5-H), 10.40 (1H, br s, NH). MS *m/z*: 181 (M^+, 35% of BP), 120 (BP).

Ethyl 5-Acetylpyrrole-2-carboxylate (**6a**): Pale yellow needles from hexane, mp 60—60.5 °C. *Anal.* Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.67; H, 6.13; N, 7.78. IR ν_{max} cm^{-1}: 3290 (NH), 1710, 1650 (CO). ^{1}H-NMR δ: 1.37 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.47 (3H, s, $COC\underline{H}_3$), 4.38 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.86 (2H, d, J=3 Hz, C_3- and C_4-H), 10.00 (1H, br s, NH). MS *m/z*: 181 (M^+, 35% of BP), 120 (BP).

Ethyl 4-Butyrylpyrrole-2-carboxylate (**5b**): Colorless needles from benzene–hexane, mp 71—72 °C. *Anal.* Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.05; H, 7.26; N, 6.65. IR ν_{max} cm^{-1}: 3210 (NH), 1710, 1645 (CO). ^{1}H-NMR δ: 0.99 (3H, t, J=7 Hz, $CH_2CH_2C\underline{H}_3$), 1.37 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.51—2.09 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.75 (2H, t, J=7 Hz, $COC\underline{H}_2CH_2$), 4.33 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.25 (1H, dd, J=3, 1 Hz, C_3-H), 7.51 (1H, dd, J=4, 1 Hz, C_5-H), 9.90 (1H, br s, NH). MS *m/z*: 209 (M^+, 27% of BP), 120 (BP).

Ethyl 5-Butyrylpyrrole-2-carboxylate (**6b**): Colorless needles from hexane, mp 54.5—55 °C. High-resolution MS: Calcd for $C_{11}H_{15}NO_3$: 209.1051. Found: 209.1032. IR ν_{max} cm^{-1}: 3250 (NH), 1710, 1665 (CO). ^{1}H-NMR δ: 1.00 (3H, t, J=7 Hz, $CH_2CH_2C\underline{H}_3$), 1.39 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.51—2.11 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.78 (2H, t, J=7 Hz, $COC\underline{H}_2CH_2$), 4.34 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.81 (2H, m, C_3- and C_4-H), 9.60 (1H, br s, NH). MS *m/z*: 209 (M^+, 18% of BP), 120 (BP).

Ethyl 4-Chloroacetylpyrrole-2-carboxylate (**5c**): Colorless prisms from benzene-hexane, mp 114.5—116.5 °C. *Anal.* Calcd for $C_9H_{10}ClNO_3$: C, 50.13; H, 4.67; N, 6.50. Found: C, 50.04; H, 4.63; N, 6.40. IR ν_{max} cm^{-1}: 3240 (NH), 1719, 1679 (CO). ^{1}H-NMR δ: 1.37 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.36 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.44 (2H, s, $COC\underline{H}_2Cl$), 7.27 (1H, dd, J=4, 1 Hz, C_3-H), 7.61 (1H, dd, J=3, 1 Hz, C_5-H), 9.90 (1H, br s, NH). MS *m/z*: 217 (M^++2, 5% of BP), 215 (M^+, 15% of BP), 120 (BP).

Ethyl 4-(4-Methoxybenzoyl)pyrrole-2-carboxylate (**5d**): Colorless prisms from benzene–hexane, mp 107—108 °C. *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.84; H, 5.53; N, 5.06. IR ν_{max} cm^{-1}: 3260 (NH), 1690 (CO). ^{1}H-NMR δ: 1.38 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.88 (3H, s, $OC\underline{H}_3$), 4.36 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.94 (2H, d, J=8 Hz, arom.-H), 7.29 (1H, dd, J=4, 1 Hz, C_3-H), 7.51 (1H, dd, J=3, 1 Hz, C_5-H), 9.82 (1H, br s, NH). MS *m/z*: 273 (M^+, 91% of BP), 120 (BP).

Ethyl 5-(4-Methoxybenzoyl)pyrrole-2-carboxylate (**6d**): Colorless needles from benzene–hexane, mp 65.5—67 °C. *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.84; H, 5.45; N, 5.09. IR ν_{max} cm^{-1}: 3245 (NH), 1700 (CO). ^{1}H-NMR δ: 1.38 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.87 (3H, s, $OC\underline{H}_3$), 4.37 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.71—7.15 (4H, m, arom.-H), 7.90 (2H, d, J=8.5 Hz, arom.-H), 10.02 (1H, br s, NH). MS *m/z*: 273 (M^+, BP).

Ethyl 4-Benzoylpyrrole-2-carboxylate (**5e**): Colorless prisms from benzene–hexane, mp 99.5—101 °C. *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.26; H, 5.43; N, 5.67. IR ν_{max} cm^{-1}: 3240 (NH), 1692 (CO). ^{1}H-NMR δ: 1.34 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.33 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.19—7.95 (7H, m, arom.-H), 9.97 (1H, br s, NH). MS *m/z*: 243 (M^+, 73% of BP), 120 (BP).

Ethyl 4-(4-Nitrobenzoyl)pyrrole-2-carboxylate (**5f**): Pale yellow prisms from ethyl acetate, mp 172.5—174 °C. *Anal.* Calcd for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.37; H, 4.21; N, 9.50. IR ν_{max} cm^{-1}: 3210 (NH), 1690 (CO). ^{1}H-NMR [$(CD_3)_2SO$] δ: 1.30 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.27 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.10 (1H, m, arom.-H), 7.57 (1H, m, arom.-H), 7.92 (2H, d, J=8 Hz, arom.-H), 8.31 (2H, d, J=8 Hz, arom.-H), 12.72 (1H, br s, NH). MS *m/z*: 288 (M^+, BP).

General Procedure for the Acetylation of Ethyl 1-Benzylpyrrole-2-carboxylate (7) A solution of ethyl 1-benzylpyrrole-2-carboxylate (**7**) (229 mg, 1 mmol) in 2 ml of 1,2-dichloroethane was added to a mixture of a Lewis acid (2 mmol) and acetyl chloride (2 mmol) in 1,2-dichloroethane (2 ml), and the whole was stirred under the conditions given in Table 4, until the formation of the products ceased as determined by TLC monitoring. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the residue. The residue was subjected to column chromatography on silica gel; gradient elution with hexane–ethyl acetate gave the products (**8a** and **9a**) listed in Table 4.

Ethyl 4-Acetyl-1-benzylpyrrole-2-carboxylate (**8a**): Pale yellow needles from hexane–ethyl acetate, mp 95.5—97.2 °C. *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.01; H, 6.35; N, 5.06. IR ν_{max} cm^{-1}: 1720, 1665 (CO). ^{1}H-NMR δ: 1.31 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.39 (3H, s, $COC\underline{H}_3$), 4.25 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.54 (2H, s, $NC\underline{H}_2Ph$), 6.95—7.50 (7H, m, arom.-H). MS *m/z*: 271 (M^+, 18% of BP), 243 (BP).

Ethyl 5-Acetyl-1-benzylpyrrole-2-carboxylate (**9a**): Colorless prisms from benzene-hexane, mp 78.0—79.5 °C. *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.94; H, 6.37; N, 5.17. IR ν_{max} cm^{-1}: 1710, 1670 (CO). ^{1}H-NMR δ: 1.29 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.44 (3H, s, $COC\underline{H}_3$), 4.24 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.16 (2H, s, $NC\underline{H}_2Ph$), 6.80—7.45 (7H, m, arom.-H). MS *m/z*: 271 (M^+, 52% of BP), 91 (BP).

Benzylation of Ethyl 4-Acetylpyrrole-2-carboxylate (5a) Benzyl chloride (138 μl, 1.2 mmol) was added to a mixture of NaH (60%, 48 mg, 1.2 mmol) and **5a** (177 mg, 1 mmol) in dimethyl sulfoxide (1.4 ml). The whole was stirred for 2.3 h at room temperature, poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the residue. The residue was subjected to column chromatography on silica gel with benzene to give ethyl 4-acetyl-1-benzylpyrrole-2-carboxylate (**8a**) (180 mg, 66%). Recrystallization from hexane–benzene gave a pure sample of **8a** (mp 95.0—97.3 °C). Compound **8a** was identical with **8a** obtained from the Friedel–Crafts acetylation of ethyl 1-benzylpyrrole-2-carboxylate (**7**) by comparison of TLC behavior and IR and ^{1}H-NMR spectra.

Benzylation of Ethyl 5-Acetylpyrrole-2-carboxylate (6a) Benzyl chloride (138 μl, 1.2 mmol) was added to a mixture of NaH (60%, 48 mg, 1.2 mmol) and **6a** (177 mg, 1 mmol) in dimethyl sulfoxide (1.4 ml). The whole was stirred for 4 h at 200 °C (oil-bath temperature), then worked up as described above to give the residue. The residue was subjected to column chromatography on silica gel; gradient elution with benzene–ethyl acetate gave ethyl 5-acetyl-1-benzylpyrrole-2-carboxylate (**9a**) (61 mg, 23%). Recrystallization from hexane-benzene gave a pure sample of **9a** (mp 78.3—79.5 °C). Compound **9a** was identical with **9a** obtained from the Friedel–Crafts acetylation of ethyl 1-benzylpyrrole-2-carboxylate (**7**) by comparison of TLC behavior and IR and ^{1}H-NMR spectra.

Ethyl 4-(3,5-Dichloro-2-hydroxybenzoyl)pyrrole-2-carboxylate (14) Oxalyl chloride (2.2 ml, 24 mmol) was added to a solution of 3,5-dichloro-2-methoxybenzoic acid[12] (1.768 g, 8 mmol) in chloroform (40 ml) under an argon atmosphere at 0 °C. The reaction mixture was refluxed for 1.5 h, and then evaporated to dryness *in vacuo* to give the residue. A solution of ethyl pyrrole-2-carboxylate (**3**) (557 mg, 4 mmol) in 1,2-dichloroethane (14 ml) was added dropwise to a mixture of the residue obtained above and aluminum chloride (1.616 g, 12 mmol) in 1,2-dichloroethane (20 ml) under an argon atmosphere at 0 °C. The whole was stirred for 3.2 h at room temperature, then poured into ice-water,

and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the residue. The residue (1.670 g) was subjected to silica gel column chromatography under gradient elution (methylene chloride-ethyl acetate) to give ethyl 4-(3,5-dichloro-2-hydroxybenzoyl)pyrrole-2-carboxylate (**14**) (821 mg, 63%) and **3** (24 mg, 4.3% recovery). The product (**14**) was recrystallized from ethyl acetate to give a pure sample of **14** as yellow needles, mp 221.5—223.5 °C. *Anal.* Calcd for $C_{14}H_{11}Cl_2NO_4$: C, 51.24; H, 3.38; N, 4.27. Found: C, 51.44; H, 3.34; N, 4.34. IR ν_{max} cm^{-1}: 3255 (NH), 1680 (CO). ^{1}H-NMR [$(CD_3)_2SO$] δ: 1.28 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.27 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.08 (1H, m, C_3-H), 7.43 (1H, d, J=2.5 Hz, arom.-H), 7.58 (1H, m, C_5-H), 7.68 (1H, d, J=2.5 Hz, arom.-H), 10.85 (1H, br s, OH or NH), 12.60 (1H, br s, NH or OH). MS *m/z*: 331 (M^++4, 6% of BP), 329 (M^++2, 30% of BP), 327 (M^+, 44% of BP), 139 (BP).

3-(3,5-Dichloro-2-hydroxybenzoyl)pyrrole (15)[7] Ethyl 4-(3,5-dichloro-2-hydroxybenzoyl)pyrrole-2-carboxylate (**14**) (394 mg, 1.20 mmol) was added to a solution of KOH (85%, 1.16 g, 17.6 mmol) in ethanol (34 ml), and the mixture was stirred for 7.5 h under reflux, then evaporated to remove ethanol. Water (250 ml) was added to the residue and the whole was extracted with ethyl acetate. The inorganic layer was separated, acidified with 10% HCl, and extracted with ethyl acetate. The latter organic layer was washed with saturated NaCl, dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give 4-(3,5-dichloro-2-hydroxybenzoyl)pyrrole-2-carboxylic acid (324 mg, 90%). A part of the 4-(3,5-dichloro-2-hydroxybenzoyl)pyrrole-2-carboxylic acid was recrystallized for characterization from 95% ethanol to give a pure sample as yellow needles, mp 288.5—290.5 °C. *Anal.* Calcd for $C_{12}H_7Cl_2NO_4$: C, 48.03; H, 2.35; N, 4.67. Found: C, 47.90; H, 2.35; N, 4.52. IR ν_{max} cm^{-1}: 3290 (NH), 3300—2050 (OH), 1685 (CO). ^{1}H-NMR [$(CD_3)_2SO$] δ: 7.09 (1H, m, arom.-H), 7.40—7.56 (2H, m, arom.-H), 7.69 (1H, d, J=2 Hz, arom.-H), 11.00 (1H, br s, OH, COOH or NH), 12.49 (1H, br s, NH, COOH or OH). MS *m/z*: 303 (M^++4, 6% of BP), 301 (M^++2, 38% of BP), 299 (M^+, 51% of BP), 94 (BP).

A mixture of 4-(3,5-dichloro-2-hydroxybenzoyl)pyrrole-2-carboxylic acid (184 mg, 0.61 mmol) and cupric chromite (26 mg, 0.08 mmol) in quinoline (1.9 ml) was stirred at 190—220 °C for 1 h under an argon atmosphere, then poured into 50 ml of water and extracted with ethyl acetate. The organic layer was washed with 10% HCl and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the residue. The residue was subjected to column chromatography on silica gel under gradient elution (benzene–ethyl acetate) to give 3-(3,5-dichloro-2-hydroxybenzoyl)pyrrole (**15**) (114 mg, 73%). The product was recrystallized from benzene-ethyl acetate to give a pure sample of **15** as yellow needles, mp 184.5—186.5 °C, (lit.,[7] mp 185—186 °C). *Anal.* Calcd for $C_{11}H_7Cl_2NO_2$: C, 51.59; H, 2.76; N, 5.47. Found: C, 51.75; H, 2.74; N, 5.52. IR ν_{max} cm^{-1}: 3375 (NH), 3400—2000 (OH), 1612 (CO). ^{1}H-NMR δ: 6.77 (1H, m, arom.-H), 6.91 (1H, m, arom.-H), 7.49 (1H, m, arom.-H), 7.56 (1H, d, J=2.5 Hz, arom.-H), 7.86 (1H, d, J=2.5 Hz, arom.-H), 8.80 (1H, br s, NH), 12.66 (1H, br s, OH). MS *m/z*: 259 (M^++4, 6% of BP), 257 (M^++2, 33% of BP), 255 (M^+, 50% of BP), 67 (BP).

3-Acetylpyrrole (16)[8] **from Ethyl 4-Acetylpyrrole-2-carboxylate (5a)** A mixture of ethyl 4-acetylpyrrole-2-carboxylate (**5a**) (219 mg, 1.21 mmol) and 23 ml of 15% aqueous KOH was stirred for 1 h at 55 °C. After cooling, the reaction mixture was extracted with ether. The inorganic layer was acidified with 10% HCl and extracted with ethyl acetate. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the crude 4-acetylpyrrole-2-carboxylic acid (145 mg, 78%) as a pale brown powder, mp 218—228 °C (dec.), [lit.,[8] mp 221.5—223 °C (dec.)].

A mixture of the crude 4-acetylpyrrole-2-carboxylic acid (61 mg, 0.4 mmol) and Dowtherm-A (a mixture of 669 mg of biphenyl and 1.847 g of diphenyl ether) was stirred for 6.3 h at 194—208 °C under an argon atmosphere. After cooling, the reaction mixture was subjected to silica gel column chromatography under gradient elution (hexane–benzene) to give 3-acetylpyrrole (**16**) (17 mg, 39%). The product was recrystallized from hexane–benzene to give a pure sample of **16** as colorless prisms, mp 113.5—115 °C, (lit.,[8] mp 114—115 °C). *Anal.* Calcd for C_6H_7NO: C, 66.04; H, 6.47; N, 12.83. Found: C, 65.79; H, 6.46; N, 12.70. IR ν_{max} cm^{-1}: 3200 (NH), 1640 (CO). ^{1}H-NMR δ: 2.40 (3H, s, $COC\underline{H}_3$), 6.60 (1H, m, C_4-H), 5.72 (1H, m, C_5-H), 7.38 (1H, m, C_2-H), 9.60 (1H, br s, NH). MS *m/z*: 109 (M^+, 58% of BP), 94 (BP).

Acetylation of Ethyl Pyrrole-2-carboxylate Derivatives (3 and 7) by the Mixed Anhydride Method A solution of ethyl pyrrole-2-carboxylate derivative (1 mmol) in CH_3CN (2 ml) was added to a solution of acetic acid (172 μl, 3 mmol), trifluoroacetic anhydride (424 μl, 3 mmol) and phosphoric acid (85 wt.%, 35 mg, 0.3 mmol) in CH_3CN (2 ml) at 0 °C under an argon atmosphere, and the mixture was stirred under the conditions given in Chart 2. Then the reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give a residue. The residue was subjected to column chromatography on silica gel with benzene–ethyl acetate to give the products shown in Chart 2. The products were identical with the compounds obtained from the Friedel–Crafts acetylation of **3** and **7** (Tables 1 and 7) by comparison of TLC behavior and IR and ^{1}H-NMR spectra.

General Procedure for the Friedel–Crafts Acylation of 2-Trichloroacetylpyrrole (17)[11] A solution of 2-trichloroacetylpyrrole (**17**) (212 mg, 1 mmol) in 1,2-dichloroethane (4 ml) was added dropwise to the ice-cooled mixture of an acyl chloride (2 mmol) and a Lewis acid (2 mmol) in 1,2-dichloroethane (4 ml) under an argon atmosphere. The mixture was stirred under the conditions given in Table 6, then poured into ice-water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the residue. The residue was subjected to column chromatography on silica gel; gradient elution with toluene–ethyl acetate or hexane–ethyl acetate gave the products shown in Table 6.

The Products Obtained from the Friedel–Crafts Acylation of 2-Trichloroacetylpyrrole (17)[11] 4-Acetyl-2-trichloroacetylpyrrole (**18a**)[11]: Colorless needles from ethyl acetate, mp 201—203 °C (lit.,[11] mp 193—194 °C). *Anal.* Calcd for $C_8H_6Cl_3NO_2$: C, 37.76; H, 2.38; N, 5.50. Found: C, 37.48; H, 2.43; N, 5.46. IR ν_{max} cm^{-1}: 3200 (NH), 1670, 1655 (CO). ^{1}H-NMR [400 MHz, $(CD_3)_2SO$] δ: 2.42 (3H, s, $COC\underline{H}_3$), 7.59 (1H, d, J=1.5 Hz, C_3-H), 8.06 (1H, d, J=1.5 Hz, C_5-H), 13.02 (1H, br s, NH). MS *m/z*: 257 (M^++4, 3% of BP), 255 (M^++2, 9% of BP), 253 (M^+, 9% of BP), 136 (BP).

4-Butyryl-2-trichloroacetylpyrrole (**18b**): Colorless needles from ethyl acetate–hexane, mp 125—128 °C. *Anal.* Calcd for $C_{10}H_{10}Cl_3NO_2$: C, 42.51; H, 3.57; N, 4.96. Found: C, 42.38; H, 3.44; N, 4.93. IR ν_{max} cm^{-1}: 3200 (NH), 1680, 1660 (CO). ^{1}H-NMR δ: 1.00 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.45—2.10 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.81 (2H, t, J=7.5 Hz, $COC\underline{H}_2CH_2$), 7.71 (2H, d, J=3.5 Hz, arom.-H), 10.10 (1H, br s, NH). MS *m/z*: 287 (M^++6, 4% of BP), 285 (M^++4, 37% of BP), 283 (M^++2, BP), 281 (M^+, 88% of BP).

5-Butyryl-2-trichloroacetylpyrrole (**19b**): Colorless plates from hexane–benzene, mp 92.5—94.5 °C. *Anal.* Calcd for $C_{10}H_{10}Cl_3NO_2$: C, 42.51; H, 3.57; N, 4.96. Found: C, 42.35; H, 3.54; N, 4.85. IR ν_{max} cm^{-1} ($CHCl_3$): 3390 (NH), 1685, 1665 (CO). ^{1}H-NMR (400 MHz) δ: 1.01 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.78 (2H, sextet, J=7.5 Hz, $CH_2C\underline{H}_2CH_3$), 2.83 (2H, t, J=7.5 Hz, $COC\underline{H}_2CH_2$), 6.89 (1H, dd, J=4.0, 2.5 Hz, arom.-H), 7.31 (1H, dd, J=4.0, 2.5 Hz, arom.-H), 10.03 (1H, br s, NH). MS *m/z*: 285 (M^++4, 1% of BP), 283 (M^++2, 3% of BP), 281 (M^+, 3% of BP), 164 (BP).

4-(4-Methoxybenzoyl)-2-trichloroacetylpyrrole (**18d**): Colorless needles from ethyl acetate–hexane, mp 150.5—153 °C. *Anal.* Calcd for $C_{14}H_{10}Cl_3NO_3$: C, 48.52; H, 2.91; N, 4.04. Found: C, 48.60; H, 2.90; N, 4.02. IR ν_{max} cm^{-1}: 3160 (NH), 1680 (CO). ^{1}H-NMR δ: 3.77 (3H, s, arom.-$OC\underline{H}_3$), 6.94 (2H, d, J=8.5 Hz, arom.-H), 7.60—7.77 (2H, m, C_3- and C_5-H), 7.85 (2H, d, J=8.5 Hz, arom.-H), 10.15 (1H, br s, NH). MS *m/z*: 349 (M^++4, 3% of BP), 347 (M^++2, 9% of BP), 345 (M^+, 9% of BP), 228 (BP).

5-(4-Methoxybenzoyl)-2-trichloroacetylpyrrole (**19d**): Colorless needles from benzene–hexane, mp 139—142 °C. High-resolution MS: Calcd for $C_{14}H_{10}Cl_3NO_3$: 344.9726. Found: 344.9751. IR ν_{max} cm^{-1} ($CHCl_3$): 3310 (NH), 1708 (CO). ^{1}H-NMR (400 MHz) δ: 3.91 (3H, s, arom.-OCH_3), 6.89 (1H, dd, J=4.0, 2.5 Hz, arom.-H), 7.02 (2H, d, J=9.0 Hz, arom.-H), 7.36 (1H, dd, J=4.0, 2.5 Hz, arom.-H), 7.97 (2H, d, J=9.0 Hz, arom.-H), 10.26 (1H, br s, NH). MS *m/z*: 349 (M^++4, 2% of BP), 347 (M^++2, 6% of BP), 345 (M^+, 6% of BP), 120 (BP).

Ethyl 4-Acetylpyrrole-2-carboxylate (5a) from 4-Acetyl-2-trichloroacetylpyrrole (18a)[11]: A solution of pure **18a** (100 mg, 0.39 mmol) in absolute EtOH (4.5 ml) was added dropwise to an ice-cooled solution of sodium ethoxide prepared from Na (1.2 mg, 0.05 mmol) in absolute EtOH (1.2 ml). The mixture was stirred for 3.2 h at 0 °C, poured into ice-water, acidified with 10% HCl, and extracted with ethyl acetate. The

organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the residue. The residue was subjected to column chromatography on silica gel (benzene : ethyl acetate = 4 : 1 as eluent) to give ethyl 4-acetylpyrrole-2-carboxylate (**5a**) (69 mg, 97%). The product was recrystallized from benzene–hexane to give a pure sample of **5a** as colorless needles, mp 107—109.5 °C. This **5a** was identical with the **5a** obtained from the Friedel–Crafts acetylation of ethyl pyrrole-2-carboxylate (**3**), by comparison of TLC behavior and IR and ^{1}H-NMR spectra.

Acylation, and Conversion of Trichloroacetyl Group to Ethoxycarbonyl Group without Isolation 2-Trichloroacetylpyrrole (**17**) (202 mg, 0.95 mmol) was allowed to react with acyl chloride (1.9 mmol) in 1,2-dichloroethane (8 ml) in the presence of aluminum chloride (253 mg, 1.9 mmol) for 2 h at 90 °C. Work-up as described in the general procedure gave the residue. A solution of the residue obtained after acylation in absolute EtOH (4 ml) was added dropwise to an ice-cooled solution of sodium ethoxide prepared from Na (3.0 mg, 0.13 mmol) in absolute EtOH (3 ml). The mixture was stirred under the conditions given in Table 7, then worked up as described in the case of the conversion of **18a** to **5a**, and subjected to column chromatography on silica gel to give the compounds shown in Table 7. The compounds were identical with those obtained from the Friedel–Crafts acylation of ethyl pyrrole-2-carboxylate (**3**), by comparison of TLC behavior and IR and ^{1}H-NMR spectra.

References and Notes

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