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THE $AlCl_3$ CATALYZED BENZOYLATION OF ETHYL PYRROLE-2-ACETATE: AN UNUSUAL β-SUBSTITUTION

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ABSTRACT: In this study, synthetic methodologies have been developed which are potentially useful in preparing 4- and 5-aroylpyrrole-2-acetic acids bearing no alkyl substituents on the heterocyclic nitrogen. These compounds are structurally related to a class of NSAIDs.

A number of N-alkyl-4(or 5)-aroylpyrrole-2-acetic acids have been shown to possess prominent antiinflammatory and analgesic activities[1,2,3]. However, the synthesis and the biological properties of analogous N-unsubstituted derivatives have been little studied[4].

The scope of the present work was to develop methodologies that will give access to the isomeric 4- and 5-aroylpyrrole-2-acetic acids bearing no alkyl substituents on the heterocyclic nitrogen. For this purpose, the electrophilic benzoylation of ethyl pyrrole-2-acetate[5] was studied as a model synthetic route. Results are shown in Table I.

It was found that these reactions give mixtures mainly of the C-5 (1) and C-4 (2) isomers, while under Friedel-Crafts conditions and in the presence of a certain excess of $AlCl_3$ (runs 3 and 4) 2 was formed in synthetically useful yields.

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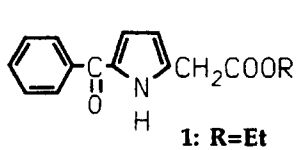
Table I. Electrophilic benzoylation reactions of ethyl pyrrole-2-acetate

	Procedure[a]	mol ratio of ethyl pyrrole-2-acetate / benzoyl chloride/ $AlCl_3$/nitromethane	Yield [%][b] 1	2	3	4
	Friedel-Crafts					
1	A	1/2/1.2/0	38	2	3	T
2	A	1/2/1.2/1.2	29	6	2	T
3	A	1/1.2/2/0	39	30	3	4
4	B	1/1.2/2/0	33	33	2	3
5	B	1/1.2/2.5/0	19	17	T	T
6	B	1/1/1.2/0	3	9	ND	ND
	Vilsmeier-Haack					
7	C		12	ND	ND	ND
8	D		74	ND	ND	ND
	Without catalysis					
9	E		19	ND	ND	ND

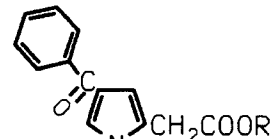
[a]A, B, C, D, E: see Experimental. [b]Yields refer to isolated products and are means of at least two experiments; T=traces; ND=not detected.

The reasons for the unusual, for pyrrole[6], β-substitution that leads to the formation of 2 in relatively large amounts is not yet clear. There is a possibility that this is formed by an intramolecular acyl migration catalyzed by the $AlCl_3$ and/or the HCl formed during the course of the benzoylation reaction[7]. However, evidence does not support this explanation, because 1 was not converted to 2 by the action of an excess $AlCl_3$, either in 1,2-dichloroethane or in 1,2-dichloroethane saturated with HCl. Furthermore, attempts to isomerize 1 with trifluoromethanesulfonic acid[8] or borontrifluride etherate[2] resulted in the formation of only trace amounts of 2.

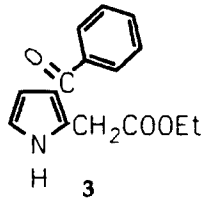
It has been reported[9] that a number of pyrrole derivatives substituted at the C-2 position with strong electron withdrawing groups react with electrophiles preferentially at C-4 position. It is proposed that a similar



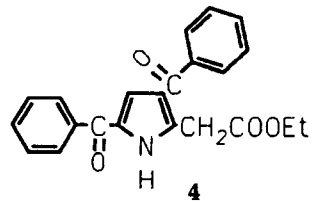
1: R=Et
1a: R=H



2: R=Et
2a: R=H



3



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phenomenon could operate for the formation of 2. Specifically, the excess of $AlCl_3$ employed in these reactions complexes with the acetate side chain of ethyl pyrrole-2-acetate, thus directing the incoming electrophile to C-4 position. 2-Ethylpyrrole was also used as a reactant, according to the procedure of run 3, in an attempt to assess the importance of the acetate ester side chain as a directing group. From this reaction the only product which could be isolated, in 17% yield, was the 2,4-dibenzoyl-5-ethylpyrrole [^{1}H-NMR ($CDCl_3$): δ 10.44(br s, 1H, NH), 7.94-7.16(m, 10H, C_6H_5), 7.02(s, 1H, H-3), 3.03(q, 2H, CH_2), 1.20(t, 3H, CH_3)]. This result gives further support to the above proposed mechanism for the formation of 2.

Finally, basic hydrolysis of the ester groups in 1 and 2 gave the target acids 1a and 2a.

In conclusion, synthetic methodologies have been developed which are potentially useful in preparing N-unsubstituted 4- and 5-aroylpyrrole-2-acetic acids structurally related to a class of nonsteroidal antiinflammatory and analgesic agents.

EXPERIMENTAL

Melting points are uncorrected and were determined in open glass capillaries using a Mel-Temp II apparatus. Infrared spectra were recorded with a Prerkin-Elmer 597 spectrophotometer, and nuclear magnetic resonance spectra were recorded with a Bruker AW-80 spectrometer with internal tetramethylsilane reference. Elemental analyses were performed on a Perkin-Elmer 2400 automated analyzer. Flash chromatography[10]

was carried out using Merck 9385 silica gel. Petroleum ether refers to the fraction of bp 40-60° C. Characteristic spectral and physical data of the intermediate and final compounds are compiled in Tables II and III.

Friedel-Crafts (procedure A)

A mixture of $AlCl_3$, benzoyl chloride and nitromethane (Table I) in 1,2-dichloroethane (16 ml) was stirred at room temperature for 10 min under a N_2 atmosphere. It was cooled (ice bath), a solution of ethyl pyrrole-2-acetate (0.31 g, 2 mmol) in 1,2-dichloroethane (4 ml) was added and the reaction was allowed to proceed for 12 h at room temperature. It was poured into a mixture of ice, CH_2Cl_2 (20 ml), triethylamine (4 ml), and EtOH (10 ml), stirred for 1 h and extracted with CH_2Cl_2 (3x40 ml). The combined organic extracts were washed with a saturated NaCl solution, dried (anhydrous Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was flash chromatographed on silica gel with petroleum ether/ethyl acetate (11:1->6:1) as the eluent to afford in this order: a) 1, b) a mixture of 3 and 4, c) 2. The mixture of 3 and 4 was rechromatographed with CH_2Cl_2/ethyl acetate (1:0->1:0.1) to afford first 3 and then 4.

Friedel-Crafts (procedure B)

To a stirred and cold (ice bath) solution of ethyl pyrrole-2-acetate (0.31 g, 2 mmol) in 1,2-dichloroethane (16 ml), under a nitrogen atmosphere, $AlCl_3$ and, after 10 min, a solution of benzoyl chloride in 1,2-dichloroethane (4 ml) were added (Table I). The reaction was allowed to proceed for 12 h at room temperature and the work up and isolation process were analogous to procedure A.

Vilsmeier-Haack (procedure C)

The method previously described[11] for pyrrole was employed using instead ethyl pyrrole-2-acetate (0.31 g, 2 mmol). The crude product was chromatographed as in procedure A.

Vilsmeier-Haack (procedure D)

A solution of N,N-dimethyl benzamide (0.6 g, 4 mmol) and $POCl_3$ (0.61 g, 4 mmol) in 1,2-dichloroethane (20 ml) was refluxed under a N_2 atmosphere for 1 h. A solution of ethyl pyrrole-2-acetate (0.31 g, 2 mmol) in 1,2-dichloroethane (10 ml) was added and heating at reflux was maintained for 4 h. It was cooled to room temperature, diluted with 1,2-dichloroethane (40 ml), treated with a solution of sodium acetate (5 g) in H_2O

Table II. Characteristic spectral data of the synthesized compounds

Compound	Solvent[a]	1H-NMR chemical shifts (δ)				IR (cm^{-1})
		H-3	H-4	H-5	$-CH_2COO-$	
1	A	6.16	6.77		3.76	(nujol): 1610, 1730
2	A	6.55		7.23	3.65	(nujol): 1630, 1705
3	A		6.40	6.87	4.43	(film): 1620, 1720
4	A		7.05		4.23	(nujol): 1610, 1640, 1745
1a	B	6.11	6.67		3.63	(nujol): 1610, 1710
2a	B	6.39		7.22	3.57	(nujol): 1605, 1720

[a]A=$CDCl_3$, B=DMSO-d_6.

Table III. Physical data of the synthesized compounds

Compound	mp (°C)[a]	R_f[b]	Formula	Calcd.			Found		
				C	H	N	C	H	N
1	123-124[A]	0.76	$C_{15}H_{15}NO_3$	70.02	5.88	5.44	70.43	5.87	5.37
2	92-93[A]	0.53	$C_{15}H_{15}NO_3$	70.02	5.88	5.44	69.66	5.86	5.56
3	oil	0.65	$C_{15}H_{15}NO_3$						
4	164-165[B]	0.72	$C_{22}H_{19}NO_4$	73.12	5.30	3.88	73.47	5.27	3.87
1a	168-170[B]		$C_{13}H_{11}NO_3$	68.11	4.84	6.11	68.21	4.78	6.00
2a	189-190[C]		$C_{13}H_{11}NO_3$	68.11	4.84	6.11	68.49	4.86	6.19

[a]Recrystallization solvent: A=ether/petroleum ether, B=$CHCl_3$/petroleum ether, C=2-propanol/petroleum ether. [b]Silica gel, ethylacetate/petroleum ether (1:1).

(20 ml) and the resulted mixture was refluxed for 2 h. The organic phase was separated, washed with a saturated NaCl solution, dried (anhydrous K_2CO_3) and treated with activated charcoal. The solvent was evaporated under reduced pressure and the residue was chromatographed as in procedure A.

Without catalysis (procedure E)

A solution of ethyl pyrrole-2-acetate (0.31 g, 2 mmol) and benzoyl chloride (0.82 g, 6 mmol) in xylene (20 ml) was refluxed for 24 h under a N_2 atmosphere. The solvent was removed under reduced pressure, the residue was mixed with EtOH (50 ml) $NaHCO_3$

(0.5 g) and stirred at room temperature for 12 h. It was taken up in ether, washed with a saturated NaCl solution, dried (anhydrous K_2CO_3) and treated with activated charcoal. The solvent was removed under reduced pressure and the residue was chromatographed as in procedure A.

Hydrolysis of 1 and 2

A mixture of 1 and 2 (0.2 g, 0.77 mmol), MeOH (5 ml) and a 5% aqueous NaOH solution (10 ml) was stirred at room temperature for 12 h. It was concentrated to approximately half of its volume under reduced pressure (bath temperature<30° C), cooled (ice bath) and acidified by the addition of concentrated aqueous HCl solution. The precipitate was collected by filtration, the filtrate was saturated with NaCl and extracted with ethyl acetate. The organic solvent was removed under reduced pressure and the residue was combined with the precipitate and recrystallized (Table III). Yields: 1a (79%), 2a (77%).

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