Homolytic Acylation of Protonated Pyridine and Pyrazine Derivatives

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The results of the homolytic acylation of compounds containing pyridine and pyrazine rings are reported, aldehydes being used as source of acyl radicals. The reactions proceed in high yields and with complete selectivity at positions α and γ to a heterocyclic nitrogen atom. The factors affecting mono- and poly-substitution and the formation of 9-acyl-9,10-dihydro-derivatives with acridine are discussed. A new process of homolytic acylation, based on decarboxylation of α-keto-acids, is also reported.

THE homolytic acylation of protonated heteroaromatic bases is potentially of synthetic value.[1] We have previously reported the results obtained with an aldehyde radical source and quinoxaline [2] and benzothiazole [3] as substrates, which were of interest in that only one reactive position is present in each substrate. We now report results obtained with pyridine and pyrazine derivatives containing one or more free reactive positions (α or γ to a heterocyclic nitrogen atom). We also report a new process of homolytic acylation of heteroaromatic bases, based on the silver-catalysed decarboxylation of α-keto-acids.

The results obtained from a number of aldehydes and heteroaromatic substrates are reported in Table 1. Yields are based on crystallized product; monoacyl derivatives are neglected in the cases of quinoline and pyrazine. Standard conditions were used with a 2 : 1 ratio of t-butoxyl radical to heteroaromatic base. The yields increase with increase of this ratio; for example with quinoline a 70% yield of 2,4-diacetylquinoline is obtained with a 4 : 1 ratio of t-butoxyl radical to quinoline. As regards the yields based on amount of base converted, g.l.c. shows that the reaction is very clean and selective; only products acylated α and γ to a heterocyclic nitrogen atom and the substrate are present.

Two synthetic aspects emphasize the importance of the polar factor(s) in homolytic acylation. High yields are obtained with substrates containing electron-withdrawing ring substituents (CN, CO_2R). A quantitative study of substituent effects has confirmed the strong influence of substituent polarity on acylation rates.[4] This is supported by the behaviour of heteroaromatic compounds such as quinoline or pyrazine with more free reactive positions. In these cases the introduction of an acyl group activates the heteroaromatic ring towards further acylation, so that polyacylation occurs even in cases with low overall conversions. The behaviour in homolytic alkylation and acylation of protonated heteroaromatic bases is therefore opposite to that in the electrophilic alkylation and acylation of homocyclic aromatic compounds. The alkyl groups deactivate the heteroaromatic ring towards further alkylation [4-6] so that it is relatively easy to obtain monosubstitution with partial conversion. This behaviour must be ascribed to the nucleophilic character of the alkyl and acyl radicals and to the sensitivity of these reactions to polar effects.[4-6] From a synthetic point of view this means that it is easy, for example with quinoline and pyrazine, to obtain diacyl derivatives by using an excess of acylating agent, whereas the monoacyl derivatives prevail

[1] T. Caronna, G. P. Gardini, and F. Minisci, *Chem. Comm.*, 1969, 201.
[2] G. P. Gardini and F. Minisci, *J. Chem. Soc.* (*C*), 1970, 229.
[3] T. Caronna, R. Galli, V. Malatesta, and F. Minisci, *J. Chem. Soc.* (*C*), 1971, 1747.
[4] T. Caronna, G. Fronza, F. Minisci, O. Porta, and G. P. Gardini, *J.C.S. Perkin I*, in the press.
[5] G. P. Gardini, F. Minisci, and G. Palla, *Chimica e Industria*, 1971, **53**, 263.
[6] F. Minisci, R. Mondelli, G. P. Gardini, and O. Porta, *Tetrahedron*, 1972, **28**, 2403.

only at very low conversions. Thus with 6% conversion of quinoline in the acetylation, 0·7% of 2,4-diacetylquinoline is formed. The ratio of 4-acyl- to 2-acyl-quinoline is 1·3 : 1 with the acetyl radical and 2·8 : 1 with the benzoyl radical. No other isomer is formed.

The activating influence of the acetyl group was directly confirmed in a competitive experiment with 4-acetyl- and 4-methyl-pyridine. Under conditions of very low conversion (used in order to minimize the formation of 2,6-diacetylpyridines), 4-acetylpyridine was 20 times more reactive than 4-methylpyridine; only position 2 is attacked in both substrates.

It is possible to obtain selective monoacylation even if the heteroaromatic base has more free reactive positions, by taking advantage of hydrolytic equilibria of the starting base and of the products. Thus with 4-cyanopyridine, which has two free reactive positions, the introduction of an acyl group in position 2 decreases the basic character and causes precipitation by hydrolysis of the unprotonated reaction product; thus selective monoacylation is achieved.

The acylation of acridine gave results which allowed us to obtain significant indications concerning the final step of the homolytic acylation. The first two steps of the general process can be interpreted in terms of formation of the acyl radical by hydrogen abstraction from the aldehyde [equation (1)] and addition of the acyl radical to the heteroaromatic ring [equation (2)]. The final step, rearomatization of the radical (I), can occur through several paths: (*a*) hydrogen abstraction from the radical (I) by an intermediate radical X·; (*b*) disproportionation of the radical (I); (*c*) oxidation of the radical (I) by iron(III); or (*d*) reduction of the radical (I) by iron(II) or by hydrogen abstraction from the aldehyde, followed by oxidation of the dihydro-

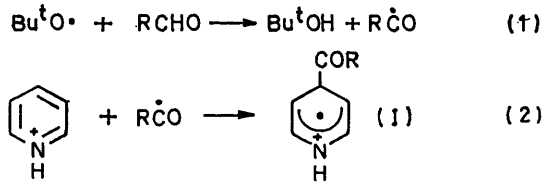


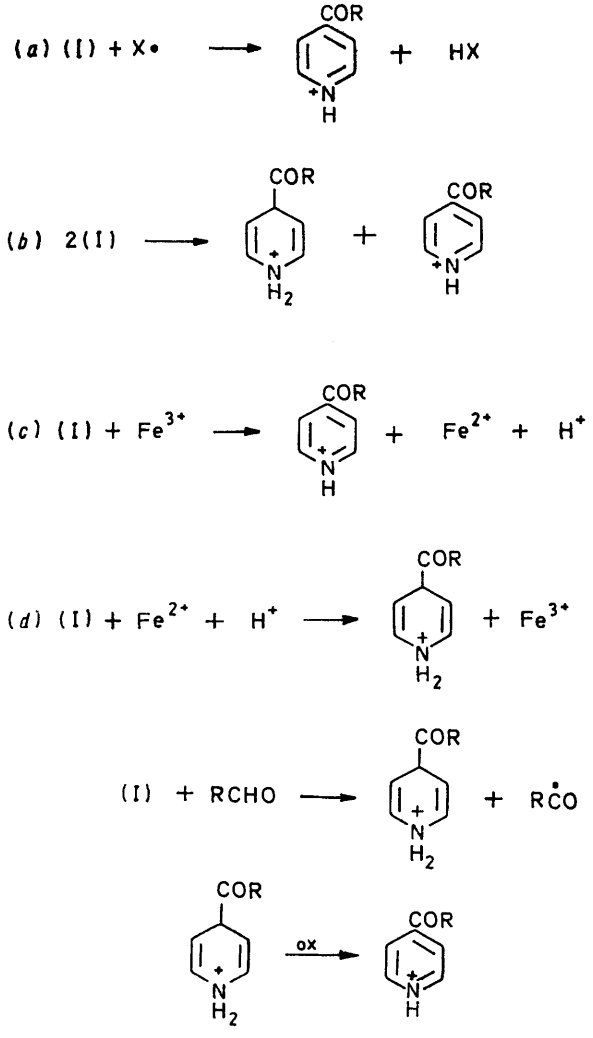
TABLE 1

Acetylation by aldehydes

Substrate	Acyl radical	Products	M.p. (°C)	Yield (%)
Quinoline	Acetyl	2,4-Diacetyl (1)	69	41
	Propionyl	2,4-Dipropionyl (2)	64	40
	Benzoyl	2,4-Dibenzoyl (3)	128	50
	p-Chlorobenzoyl	2,4-Bis-(*p*-chlorobenzoyl) (4)	160	69
	p-Methoxybenzoyl	2,4-Bis-(*p*-methoxybenzoyl) (5)	147	25
	p-Methylbenzoyl	2,4-Bis-(*p*-methylbenzoyl) (6)	134	25
	o-Hydroxybenzoyl	2,4-Bis-(*o*-hydroxybenzoyl) (7)	107	24
4-Cyanoquinoline	Acetyl	2-Acetyl (8)	168	93
	Benzoyl	2-Benzoyl (9)	142	86
	m-Chlorobenzoyl	2-*m*-Chlorobenzoyl (10)	187	69
	p-Chlorobenzoyl	2-*p*-Chlorobenzoyl (11)	193	81
	m-Methoxybenzoyl	2-*m*-Methoxybenzoyl (12)	188	88
	p-Methoxybenzoyl	2-*p*-Methoxybenzoyl (13)	138	73
	m-Methylbenzoyl	2-*m*-Methylbenzoyl (14)	156	87
	p-Methylbenzoyl	2-*p*-Methylbenzoyl (15)	149	83
4-Chloroquinoline	Acetyl	2-Acetyl (16)	99	71
	m-Methylbenzoyl	2-*m*-Methylbenzoyl (17)	107	64
	p-Methylbenzoyl	2-*p*-Methylbenzoyl (18)	104	67
2-Cyanoquinoline	Acetyl	4-Acetyl (19)	160	90
	Benzoyl	4-Benzoyl (20)	123	70
2-Carboxyethylquinoline	Acetyl	4-Acetyl (21)	79	79
	Benzoyl	4-Benzoyl (22)	60	70
2-Methoxyquinoline	Acetyl	4-Acetyl (23)	75	75
	Benzoyl	4-Benzoyl (24)	140	35
2-Chloroquinoline	Acetyl	4-Acetyl (25)	100	47
	Propionyl	4-Propionyl (26)		52
	Benzoyl	4-Benzoyl (27) *	115	80
4-Cyanopyridine	Propionyl	2-Propionyl (28)	105	57
Pyrazine	Acetyl	2,5-Diacetyl (29)	158	30
	Propionyl	2,5-Dipropionyl (30)	115	47
	Benzoyl	2,5-Dibenzoyl (31)	176	30
	p-Chlorobenzoyl	2,5-Bis-(*p*-chlorobenzoyl) (32)	229	40
	p-Methoxybenzoyl	2,5-Bis-(*p*-methoxybenzoyl) (33)	>270	30
Phenanthridine	Acetyl	9-Acetyl (34)	99	62
	Benzoyl	9-Benzoyl (35)	135	50
Acridine	Acetyl	9-Acetyl (36) †	111	15
	Acetyl	9-Acetyl-9,10-dihydro (37)	85	15
	Benzoyl	9-Benzoyl (38) ‡	225	54
	Propionyl	9-Propionyl (39)	109	38
	Propionyl	9,10-Dihydro-9-propionyl (40)	115	38
	Propionyl §	9,10-Dihydro-9-propionyl (40)	115	51

* Lit., m.p. 105—107° (A. Borsche and W. Noll, *Annalen*, 1937, **532**, 127). † Lit., m.p. 109° (O. Eisleb, (*Chem. Abs.*, 1937, **31**, 5803 [9])]. ‡ Lit., m.p. 217° (K. Lehinstedt and F. Dostal, *Ber.*, 1939, **72***B*, 804). § $Ti_2(SO_4)_3$ was used instead of $FeSO_4$ in the redox system.

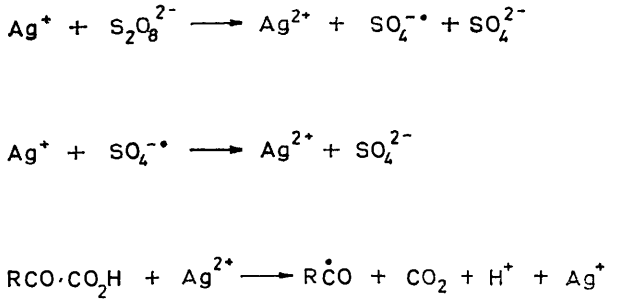
derivative. In the reactions of acridine with acetaldehyde and propionaldehyde the 9-acyl-9,10-dihydroacridines were also isolated. These compounds undergo spontaneous oxidation to 9-acylacridines by oxygen, indicating that a mechanism of type (*b*) or (*d*) may be



operating. By using the redox system $Bu^tO{\cdot}OH$–Fe^{2+} a 1 : 1 ratio of dihydro- and oxidized product was obtained. This ratio could support a mechanism of type (*b*); it could however be accidental, owing to the easy oxidisability of the dihydro-derivatives. We have therefore used a different redox system for generating the t-butoxyl radical, with a metal salt more reducing than iron(II), *viz.* $Bu^tO{\cdot}OH$–Ti^{3+}. In this case the dihydro-derivative was the only product; this result excludes, at least in this case, a type (*b*) mechanism and strongly supports the reduction of the radical (I) by the metal salt according to mechanism (*d*). A high ionization potential of the protonated radical (I) would result in such behaviour.

With pyrazine only one diacyl derivative was formed. It was difficult to predict its structure, because four positions of the pyrazine ring are apparently activated towards homolytic acylation. Owing to the symmetrical structure of the three possible isomers (2,3-, 2,5-, and 2,6-diacylpyrazines), the n.m.r. spectrum of the aromatic protons (A_2 type) shows only a singlet; it is not possible therefore to determine $J_{AA'}$ and the relative position of the acyl groups. However, the presence of a ^{13}C atom in natural abundance destroys the symmetry of the molecule and the corresponding n.m.r. spectrum becomes of the AA'X type (X being the ^{13}C nucleus). In the ^1H spectrum of the external satellites of ^{13}C it is possible to determine $J_{AA'}$, because the value of J_{AX} ($J_{^{13}C-H}$ 189 Hz) is very high in comparison with those of $J_{AA'}$ and $J_{A'X}$. A value of 1·25 Hz for $J_{AA'}$ was found for the dipropionylpyrazine; it is in agreement with the structure of 2,5-diacylpyrazine (the coupling constants of a series of monosubstituted pyrazines are known:[7] J_{ortho} 2·4—2·8, J_{meta} (0·01—0·5, and J_{para} 1·3—1·5 Hz). Steric and polar factors probably contribute to the introduction of the second acyl group at position 5.

We have also carried out homolytic acylation by the silver-catalysed decarboxylation of α-keto-acids. The reaction takes place at 40° in aqueous solution and the formation of the acyl radical can be interpreted on the



grounds of the mechanism shown. Results with protonated heteroaromatic bases are shown in Table 2.

TABLE 2

Acylation by α-keto-acids

Substrate	Acyl radical	Products	Yields based on initial base
Quinoline	Acetyl	2-Acetyl- (21·9%) 4-Acetyl- (25·6%) 2,4-Diacetyl- (52·5%)	53
2-Methylquinoline	Acetyl	4-Acetyl	43
Quinoxaline	Acetyl	2-Acetyl	42
Benzothiazole	Acetyl	2-Acetyl	40
Quinoline	Benozyl	2,4-Dibenzoyl	41

EXPERIMENTAL

N.m.r. spectra were recorded on a Varian A-60 spectrometer with tetramethylsilane as internal standard. The spectrum of 2,5-dipropionylpyrazine (2·6M in [^2H]chloroform) was recorded on a Varian XL-100-15 spectrometer at 30°. Mass spectra were obtained on a Hitachi–Perkin-Elmer RMU-6D spectrometer operating with an ionization energy of 70 eV. G.l.c. analyses were performed on a Varian Aerograph, series 1200, equipped with a flame

[7] R. H. Cox and A. A. Bothner-By, *J. Phys. Chem.*, 1968, **72**, 1646.

ionization detector, using a column packed with 2% Silicone XE-60 on silanized GasChrom P (60—80 mesh).

General Procedure for Acylation with Aldehydes.—To an ice-cooled solution heteroaromatic base (0·01 mol) and aldehyde (0·05 mol) in water (15 ml), acetic acid (15 ml), and conc. sulphuric acid (3 ml) was added a solution of t-butyl hydroperoxide (0·02 mol) and iron(II) sulphate (0·02 mol) in water (10 ml) with stirring. The reaction product was either directly precipitated or separated after dilution with water. Yields and analytical characteristics are shown in Tables 1 and 3.

General Procedure for Acylation with α-Keto-acids.—To a solution of the heteroaromatic base (0·01 mol), silver nitrate (0·001 mol) and the α-keto-acid (0·02 mol) in water (30 ml) and conc. sulphuric acid (3 ml) was added a solution of ammonium peroxydisulphate (0·01 mol) in water (20 ml) at 40°. The cooled mixture was basified and extracted with ether, and the product was analysed by g.l.c. The results are shown in Table 2.

Competitive Acetylation of 4-Methyl- and 4-Acetyl-pyridine with Acetaldehyde.—4-Methylpyridine (0·01 mol), 4-acetylpyridine (0·01 mol) and of acetaldehyde (0·05 mol) were dissolved in water (30 ml) and conc. sulphuric acid (6 ml). Iron(II) sulphate (0·002 mol) in water (8 ml) and t-butyl hydroperoxide (0·002 mol) were added with stirring. The mixture was basified and exhaustively extracted with ether, and the products were analysed by g.l.c.

TABLE 3

Spectral and analytical data for products in Table 1

Products	δ (p.p.m.)	*m/e*	Found (%) C	H	N	Calc. (%) C	H	N
(1)	2·8 (s), 2·9 (s), 7·5—8·6 (m)	213, 185, 171, 143, 128	73·4	5·2	6·5	73·2	5·2	6·6
(2)	1·28 (t), 2·9—3·6 (2q), 7·6—8·4 (m)	241, 226, 213, 185, 156, 128	75·0	6·5	5·6	74·7	6·3	5·8
(3)	7·4—8·4 (m)	337, 308, 280, 232, 204	81·7	4·4	4·2	81·9	4·5	4·1
(4)	7·3—8·6 (m)	405, 377, 263, 249, 221, 139	67·7	3·6	3·7	68·0	3·2	3·4
(5)	3·85 (s), 3·88 (s), 6·8—8·4 (m)	397, 369, 340, 242, 135	75·9	5·0	3·5	75·6	4·8	3·5
(6)	2·4 (s), 7·2—8·4 (m)	365, 337, 322, 294, 246, 217, 203, 189	82·0	5·5	3·5	82·2	5·3	3·8
(7)	11·9 (s), 12·3 (s), 6·7—8·6 (m)	369, 340, 312, 248, 193	74·5	4·3	3·9	74·8	4·1	3·8
(8)	2·8 (s), 7·7—8·7 (m)	196, 181, 154	73·7	4·0	14·5	73·5	4·1	14·3
(9)		258, 230, 105	79·1	3·7	11·2	79·1	3·9	11·2
(10)		292, 264, 139	69·7	3·1	9·5	69·8	3·1	9·6
(11)		292, 264, 139	70·0	3·2	9·4	69·8	3·1	9·6
(12)	4·0 (s), 7·5—8·5 (m)	288, 260, 77	74·8	4·1	9·8	75·0	4·2	9·7
(13)	4·0 (s), 7·5—8·5 (m)	288, 260, 77	74·9	4·3	9·6	75·0	4·2	9·7
(14)	2·5 (s), 7·5—8·5 (m)	272, 244, 91	79·7	4·5	10·1	79·4	4·4	10·3
(15)	2·5 (s), 7·5—8·5 (m)	272, 244, 91	79·2	4·5	10·0	79·4	4·4	10·3
(16)	2·8 (s), 7·7—8·7 (m)	205, 163, 101	63·9	4·1	6·8	64·2	3·9	6·8
(17)	2·5 (s), 7·5—8·5 (m)	281, 253, 91	72·5	4·2	4·9	72·5	4·3	5·0
(18)	2·5 (s), 7·5—8·5 (m)	281, 253, 91	72·3	4·4	5·0	72·5	4·3	5·0
(19)	2·8 (s), 7·5—8·5 (m)	196, 181, 168, 154, 140, 127	73·7	4·3	14·3	73·5	4·1	14·3
(20)		258, 241, 229, 168, 153	78·9	4·1	11·2	79·1	3·9	11·2
(21)	1·5 (t), 4·6 (q), 2·8 (s), 7·5—8·5 (m)	243, 199, 171, 156, 143, 128	69·4	5·4	5·6	69·1	5·4	5·8
(22)	1·5 (t), 4·6 (q), 7·3—8·5 (m)	305, 261, 233, 204, 128	74·6	5·1	4·4	74·7	5·0	4·6
(23)	2·6 (s), 4·1 (s), 7·1—8·4 (m)	201, 186, 171, 158, 143, 128	71·5	5·4	7·1	71·6	5·5	7·0
(24)	4·1 (s), 6·9—8·1 (m)	263, 234, 204, 143	77·5	5·1	5·5	77·6	5·0	5·3
(25)	2·9 (s), 7·2—8·4 (m)	205, 190, 162, 140, 127	64·1	4·1	6·9	64·2	3·9	6·8
(26)		219, 190, 177, 163, 128	65·6	4·6	6·4	65·6	4·6	6·4
(28)	1·3 (t), 3·3 (q), 7·7—8·9 (m)	160, 146, 131, 118	67·5	4·9	17·7	67·5	5·0	17·5
(29)	2·8 (s), 9·3 (s)	164, 149, 136, 122	58·3	4·9	17·0	58·9	4·9	17·1
(30)	1·2 (t), 3·5 (q), 9·3 (s)	192, 164, 136, 108	62·4	6·2	14·6	62·5	6·3	14·6
(31)		288, 240, 232, 105	75·1	4·1	9·6	75·0	4·2	9·7
(32)		356, 328, 218, 156, 139, 111	60·3	2·9	8·0	60·5	2·8	7·8
(33)	4·1 (s), 7·0—8·4 (m), 9·7 (s)	348, 320, 135, 107	69·1	4·5	8·2	69·0	4·6	8·0
(34)	2·9 (s), 7·5—9·0 (m)	221, 193, 178, 151	81·6	4·9	6·2	81·5	5·0	6·3
(35)		283, 254, 177, 151	84·9	4·6	4·8	84·8	4·6	4·9
(37)	2·0 (s), 4·9 (s), 6·3 (s), 6·6—7·3 (m)	223, 208, 194, 179, 152	80·6	5·8	6·3	80·7	5·9	6·3
(39)	1·3 (t), 3·0 (q), 7·4—8·3 (m)	235, 220, 206, 178, 151	81·8	5·6	5·9	81·7	5·6	5·9
(40)	0·8 (t), 2·4 (q), 5·0 (s), 6·5—7·3 (m)	237, 207, 181, 152	80·9	6·4	5·7	81·0	6·4	5·9

Acylation of Acridine.—(a) *With acetaldehyde or propionaldehyde and iron(II) salt.* The reaction was carried out according to the general procedure. The product was chromatographed on silica gel. With hexane as eluant the 9-acyl-9,10-dihydroacridine was separated. Elution with 8 : 2 hexane–ethyl acetate gave the 9-acylacridine.

(b) *With propionaldehyde and titanium(III) salt.* The reaction was carried out as in (a) with titanium(III) sulphate instead of iron(II) sulphate. Only 9,10-dihydro-9-propionylacridine was formed.

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