Synthetic Applications of *N-N* Linked Heterocycles. Part 15.[1] A Facile Synthesis of 4-Pyridyl(aryl)amines *via* the Reaction between 4-Chloro-1-pyridiniopyridinium Salts and Aryl Amines

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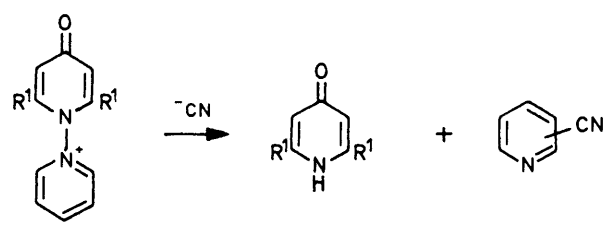
4-Chloro-1-pyridiniopyridinium salts (7) and (8) react with primary and secondary arylamines to give high yields of isolable 4-aryliminium salts (9) and (10). These are readily fragmented into 4-pyridyl(aryl)-amines (11) and (12) in excellent yields on treatment with sodium cyanide or sodium salts of sulphinic acids. The method fails with the more basic aliphatic amines, since these apparently attack the 2-position of the chloropyridinium ring giving products resulting from ring-opening. Mechanisms of the reactions are discussed.

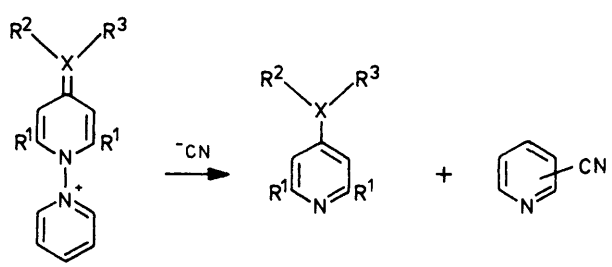
In Part 4 of this series [2] we described the reaction between cyanide ion and the *N*-(4-oxopyridin-1-yl)pyridinium salts (1) and (2). The salt (1) was shown to fragment into 4-pyridone (3) and a mixture of 2- and 4-cyanopyridines, while salt (2) gave 2,6-dimethyl-4-pyridone (4) and (regiospecifically) 4-cyanopyridine. It seemed likely that compounds (5), having X = N^+ or C, would give 4-substituted pyridines (6) (X = N, or CH) on reaction with cyanide ion, *via* an analogous fragmentation process. We have already shown [3] that the 4-chloro-1-pyridiniopyridinium salt (7) reacts with 4-nitroaniline to give the 4-nitrophenyliminium salt (9a) in high yield. We now report the analogous preparation of a wide range of aryliminium salts, and their fragmentation into 4-pyridyl(aryl)amines.

Some substituted 4-pyridyl(aryl)amines have been tested for antitubercular activity,[4] while certain *N*-(3-aminopropyl)-derivatives have shown useful central nervous system activity.[5] There exists the further possibility that reaction with sulphur might lead to potentially biologically active azaphenothiazines.[6] Previous syntheses of 4-pyridyl(aryl)amines have been by the reaction of substituted anilines with 4-chloropyridine [4,7] or its hydrochloride salt,[8] with 1-(4-pyridyl)pyridinium salts,[9] or with 4-phenoxypyridine hydrochloride; [10] and between 4-aminopyridine and an active aryl halide.[8a] These methods suffer from the disadvantages of low yields, vigorous conditions and/or long reaction times. Where yields are high, the key intermediate is available from pyridine only by a long sequence of synthetic steps. Thus, a simple high-yielding synthetic route to 4-pyridyl(aryl)amines is a desirable goal.



(1) R^1 = H
(2) R^1 = Me

(3) R^1 = H
(4) R^1 = Me



(5) (6)

Results

Crude pyridone salts (1) and (2) (as chloride hydrochlorides; prepared as described previously [3]) were carefully neutralised to pH 5 to 6 with aqueous $NaHCO_3$, and then recrystallised and dried before conversion into the 4-chloro-1-pyridiniopyridinium salts (7) and (8) with $POCl_3$. This modified procedure gave consistently higher yields of the salts (7) and (8) than that reported previously.[3]

Iminium Salts (9) *and* (10).—Generally, when equimolar amounts of a chloropyridinium salt [(7) or (8); Y = BF_4] and a substituted aniline were heated together under reflux in absolute ethanol for 5 min (Method A), the intermediate iminium salt (9) or (10) was precipitated in high yield on cooling.† In certain cases, however, especially with more basic anilines, better results were obtained by refluxing in dry acetonitrile for 1 h (Method B). In these cases the product was precipitated by the addition of dry benzene. Aliphatic primary amines, in contrast, gave highly coloured reaction mixtures, from which only tarry products could be isolated; though morpholine gave a hygroscopic product which may have been the iminium salt. The yields, and methods of preparation for 50 iminium salts are recorded in Table 1, the examples chosen being derived from a wide range of anilines bearing groups with electron attracting and releasing properties, and substituted at the *ortho*-, *meta*-, or *para*-positions, as well as on nitrogen. Yields were consistently greater than 80%, with the exception of the 2-nitro- and *N*-phenyl-derivatives. Physical and analytical data are displayed in Table 2.

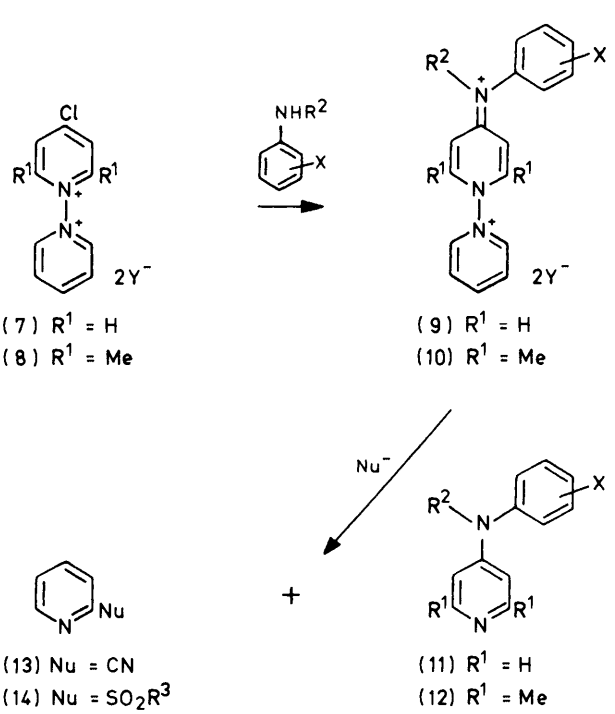
I.r. spectra of all iminium salts had intense bands in the ranges 1 650—1 640, 1 070—1 050, and 795—785 cm^{-1}, characteristic of the iminiopyridinyl ring C=C, the BF_4^- anion, and the pyridinium ring respectively. Absorption due to NH appeared in the range 3 320—3 290 cm^{-1}. In the ^1H n.m.r. spectra, in CF_3CO_2H, the pyridinium ring α-, γ-, and β-proton signals were observed respectively in the ranges δ 9.5—8.8, 9.2—8.2, and 8.7—8.1, and the NH signal

† The chlorides [(7) or (8) Y = Cl], in contrast, were very hygroscopic and gave unsatisfactory results.

Table 1. Yields of iminium salts (9) and (10), and of 4-pyridyl(aryl)amines (11) and (12), and methods of preparation

Substituents		$R^1 = H$						$R^1 = Me$					
X	R^2	Iminium salt	Method	Yield (%) [a]	Pyridyl-amine	Method	Yield (%) [b]	Iminium salt	Method	Yield (%) [a]	Pyridyl-amine	Method	Yield (%) [b]
4-NO_2	H	(9a)	A	90	(11a)	C	90	(10a)	A	89	(12a)	C	95
3-NO_2	H	(9b)	A	97	(11b)	C	87	(10b)	A	91	(12b)	C	92
2-NO_2	H	(9c)	A	26	(11c)	C	77	(10c)	A	45	(12c)	C	89
4-Ac	H	(9d)	A	94	(11d)	C	75	(10d)	A	95	(12d)	C	90
4-CO_2Me	H	(9e)	A	95	(11e)	C	79	(10e)	A	97	(12e)	C	98
4-CO_2H	H	(9f)	A	85	(11f)	C	89	(10f)	A	96	(12f)	C	95
4-Br	H	(9g)	A	90	(11g)	C	91	(10g)	A	96	(12g)	C	87
3-Br	H	(9h)	A	92	(11h)	C	78	(10h)	A	96	(12h)	C	85
2-Br	H	(9i)	A	89	(11i)	D	62	(10i)	A	89	(12i)	D	81
4-Cl	H	(9j)	A	90	(11j)	C	91	(10j)	A	95	(12j)	C	94
3-Cl	H	(9k)	A	94	(11k)	C	81	(10k)	A	94	(12k)	C	80
2-Cl	H	(9l)	A	91	(11l)	D	64	(10l)	A	90	(12l)	D	75
4-F	H	(9m)	A	93	(11m)	C	93	(10m)	A	87	(12m)	C	82
H	H	(9n)	B	89	(11n)	C	92	(10n)	A	96	(12n)	C	89
4-Me	H	(9o)	B	90	(11o)	C	90	(10o)	A	93	(12o)	C	91
3-Me	H	(9p)	A	85	(11p)	D	71	(10p)	A	94	(12p)	C	78
2-Me	H	(9q)	A	89	(11q)	D	62	(10q)	A	88	(12q)	D	72
4-OMe	H	(9r)	B	85	(11r)	D	69	(10r)	A	85	(12r)	E	70
3-OMe	H	(9s)	A	80	(11s)	D	81	(10s)	A	95	(12s)	D	84
2-OMe	H	(9t)	A	84	(11t)	E	65	(10t)	A	89	(12t)	D	81
4-OH	H	(9u)	A	90	(11u)	C	92	(10u)	A	87	(12u)	C	90
3-OH	H	(9v)	A	70	(11v)	D	87	(10v)	A	84	(12v)	D	79
H	Me	(9w)	B	90	(11w)	E	61	(10w)	A	91	(12w)	E	68
H	Et	(9x)	B	91	(11x)	E	*c*	(10x)	A	82	(12x)	E	*c*
H	Ph	(9y)	B	57	(11y)	E	*c*	(10y)	B	34	(12y)	E	*c*

[a] Based on chloropyridiniopyridinium salts (7) or (8). [b] Based on iminium salts (9) or (10). [c] Products were identified from spectroscopic data, but were not isolated pure.



(7) R^1 = H
(8) R^1 = Me
(9) R^1 = H
(10) R^1 = Me
(13) Nu = CN
(14) Nu = SO_2R^3
(11) R^1 = H
(12) R^1 = Me

in the range δ 8.9—7.0. For the iminiopyridinyl ring,* the α- and β-proton signals in salts (9) appeared in the ranges δ 8.4—8.1 and 8.7—8.3 respectively; and for salts (10) the α-methyl groups were observed in the range δ 2.4—2.0, and the β-protons in the range δ 7.5—6.2. Parent peaks $M^{+\cdot}$ were observed in the mass spectra of all salts.

4-Pyridyl(aryl)amines (11) *and* (12).—When the iminium salts were stirred with methanol containing an excess of sodium cyanide, cleavage to the pyridylamines (11) and (12) took place in high yield. Chromatography of the crude products by t.l.c. showed the other fragment to be 2-cyanopyridine (13), no trace of 4-cyanopyridine being detected. The same results were obtained using aqueous sodium cyanide, although in this case the product was more discoloured. Generally, the pyridylamine could be precipitated by addition of water (Method C), and was purified further by sublimation, followed by recrystallisation. Where Method C gave a gum, a crystalline product could usually be obtained by precipitation with water from acetonitrile (Method D). In cases where the product amine was low melting, it was purified by chromatography on alumina (Method E). Yields, and methods of isolation for 29 new and 17 known 4-pyridyl(aryl)amines are recorded in Table 1. Products were characterised by i.r. and ^1H n.m.r. spectroscopy, and further by comparison of melting points with published values (in the case of known compounds) or by microanalysis (in the case of new compounds). Satisfactory analyses were not obtained, however, for the new tertiary amines, these being characterised only by i.r. and ^1H n.m.r. spectroscopy. Physical and analytical data for new compounds are recorded in Table 3.

I.r. absorptions due to NH were observed in the range 3 340—3 180 cm^{-1}, the corresponding signal in the ^1H n.m.r. spectra [$(CD_3)_2SO$] being found between δ 8.0 and 9.5. For amines (11) the α- and β-proton signals appeared as an $(AB)_2$ system respectively near δ 8.3—8.1 and 7.1—6.8; and the methyl- and β-hydrogen signals for amines (12) were observed

* Signals arising from this ring were either broadened or split into two groups of lines, indicating restricted rotation about the iminium C=N$^+$ bond. Results from rotational energy barrier measurements will be reported later.

Table 2. Physical and analytical data for iminium salts (9) and (10)

Iminium salt	Substituent X	M.p. (°C)	Crystal form *	Found (%)			Formula	Requires (%)		
				C	H	N		C	H	N
(9a)	4-NO_2	251—254	Pr	41.4	3.3	12.0	$C_{16}H_{14}B_2F_8N_4O_2$	41.1	3.0	12.0
(9b)	3-NO_2	233—235	Pr	41.0	3.1	12.1	$C_{16}H_{14}B_2F_8N_4O_2$	41.1	3.0	12.0
(9c)	2-NO_2	211—213	Pr	40.9	2.9	11.7	$C_{16}H_{14}B_2F_8N_4O_2$	41.1	3.0	12.0
(9d)	4-Ac	189—190	Pl	46.4	3.7	9.1	$C_{18}H_{17}B_2F_8N_3O$	46.5	3.7	9.0
(9e)	4-CO_2Me	190—191	Pl	44.8	3.5	8.5	$C_{18}H_{17}B_2F_8N_3O_2$	45.0	3.6	8.7
(9f)	4-CO_2H	226—227	Pr	43.4	3.0	9.0	$C_{17}H_{15}B_2F_8N_3O_2$	43.7	3.2	9.0
(9g)	4-Br	254—260	Pl	38.5	3.3	8.1	$C_{16}H_{14}B_2BrF_8N_3$	38.3	2.8	8.4
(9h)	3-Br	221—222	Pr	38.6	3.0	8.5	$C_{16}H_{14}B_2BrF_8N_3$	38.3	2.8	8.4
(9i)	2-Br	235—236	Pr	38.1	3.4	8.0	$C_{16}H_{14}B_2BrF_8N_3$	38.3	2.8	8.4
(9j)	4-Cl	236—238	Pl	42.2	3.1	9.1	$C_{16}H_{14}B_2ClF_8N_3$	42.0	3.1	9.2
(9k)	3-Cl	230—231	Pl	41.7	3.3	9.2	$C_{16}H_{14}B_2ClF_8N_3$	42.0	3.1	9.2
(9l)	2-Cl	195—196	Pl	41.7	3.4	9.0	$C_{16}H_{14}B_2ClF_8N_3$	42.0	3.1	9.2
(9m)	4-F	236—237	Pl	43.4	3.2	9.4	$C_{16}H_{14}B_2F_9N_3$	43.6	3.2	9.5
(9n)	H	211—214	Pl	45.3	3.8	10.2	$C_{16}H_{15}B_2F_8N_3$	45.4	3.6	9.9
(9o)	4-Me	225—228	Pl	46.2	3.9	9.9	$C_{17}H_{17}B_2F_8N_3$	46.7	3.9	9.6
(9p)	3-Me	180—181	Pl	46.5	3.9	9.8	$C_{17}H_{17}B_2F_8N_3$	46.7	3.9	9.6
(9q)	2-Me	210—211	Pl	46.4	3.8	9.9	$C_{17}H_{17}B_2F_8N_3$	46.7	3.9	9.6
(9r)	4-OMe	200—205	Pr	45.1	3.9	9.3	$C_{17}H_{17}B_2F_8N_3O$	45.1	3.8	9.3
(9s)	3-OMe	205—206	Pr	45.0	3.9	9.3	$C_{17}H_{17}B_2F_8N_3O$	45.1	3.8	9.3
(9t)	2-OMe	185—186	Pr	44.8	3.8	9.3	$C_{17}H_{17}B_2F_8N_3O$	45.1	3.8	9.3
(9u)	4-OH	244—245	Pl	43.6	3.4	9.5	$C_{16}H_{15}B_2F_8N_3O$	43.8	3.4	9.6
(9v)	3-OH	235—236	Pl	43.9	3.5	9.6	$C_{16}H_{15}B_2F_8N_3O$	43.8	3.4	9.6
(9w)	H [a]	220—224	Pr	46.3	4.2	9.4	$C_{17}H_{17}B_2F_8N_3$	46.7	3.9	9.6
(9x)	H [b]	230—231	Pr	47.6	4.3	9.1	$C_{18}H_{19}B_2F_8N_3$	47.9	4.3	9.3
(9y)	H [c]	230—232	Pl	52.0	3.7	8.2	$C_{22}H_{19}B_2F_8N_3$	52.0	3.8	8.4
(10a)	4-NO_2	224—225	Pr	43.5	3.9	11.2	$C_{18}H_{18}B_2F_8N_4O_2$	43.6	3.7	11.3
(10b)	3-NO_2	222—223	Pl	43.4	3.8	11.2	$C_{18}H_{18}B_2F_8N_4O_2$	43.6	3.7	11.3
(10c)	2-NO_2	221—222	Pl	43.2	4.0	11.0	$C_{18}H_{18}B_2F_8N_4O_2$	43.6	3.7	11.3
(10d)	4-Ac	155—156	Pr	48.5	4.3	8.4	$C_{20}H_{21}B_2F_8N_3O$	48.7	4.3	8.5
(10e)	4-CO_2Me	230—231	Pl	46.9	4.0	8.3	$C_{20}H_{21}B_2F_8N_3O_2$	47.2	4.2	8.3
(10f)	4-CO_2H	183—184	Pl	45.7	4.2	8.2	$C_{19}H_{19}B_2F_8N_3O_2$	46.1	3.9	8.5
(10g)	4-Br	204—205	Pl	40.5	3.5	7.9	$C_{18}H_{18}B_2BrF_8N_3$	40.8	3.4	7.9
(10h)	3-Br	186—187	Pl	41.0	3.7	8.1	$C_{18}H_{18}B_2BrF_8N_3$	40.8	3.4	7.9
(10i)	2-Br	214—215	Pr	40.9	3.5	7.9	$C_{18}H_{18}B_2BrF_8N_3$	40.8	3.4	7.9
(10j)	4-Cl	201—202	Pl	44.2	3.8	8.6	$C_{18}H_{18}B_2ClF_8N_3$	44.5	3.7	8.7
(10k)	3-Cl	189—190	Pl	44.8	3.7	8.6	$C_{18}H_{18}B_2ClF_8N_3$	44.5	3.7	8.7
(10l)	2-Cl	217—218	Pl	44.5	3.7	8.4	$C_{18}H_{18}B_2ClF_8N_3$	44.5	3.7	8.7
(10m)	4-F	236—237	Pl	45.8	3.8	8.8	$C_{18}H_{18}B_2F_9N_3$	46.1	3.9	9.0
(10n)	H	226—227	N	47.9	4.4	9.3	$C_{18}H_{19}B_2F_8N_3$	47.9	4.3	9.3
(10o)	4-Me	181—182	Pr	49.3	4.5	9.3	$C_{19}H_{21}B_2F_8N_3$	49.1	4.6	9.0
(10p)	3-Me	168—169	Pl	49.0	4.8	9.3	$C_{19}H_{21}B_2F_8N_3$	49.1	4.6	9.0
(10q)	2-Me	225—226	Pl	49.1	4.9	8.6	$C_{19}H_{21}B_2F_8N_3$	49.1	4.6	9.0
(10r)	4-OMe	225—226	Pr	47.1	4.3	8.7	$C_{19}H_{21}B_2F_8N_3O$	47.4	4.4	8.7
(10s)	3-OMe	228—229	Pl	47.1	4.5	8.7	$C_{19}H_{21}B_2F_8N_3O$	47.4	4.4	8.7
(10t)	2-OMe	224—225	Pl	47.2	4.6	8.7	$C_{19}H_{21}B_2F_8N_3O$	47.4	4.4	8.7
(10u)	4-OH	230—231	Pl	46.4	4.2	8.7	$C_{18}H_{19}B_2F_8N_3O$	46.3	4.1	9.0
(10v)	3-OH	210—211	N	46.1	4.0	9.2	$C_{18}H_{19}B_2F_8N_3O$	46.3	4.1	9.0
(10w)	H [a]	234—235	Pr	48.8	4.5	9.1	$C_{19}H_{21}B_2F_8N_3$	49.1	4.6	9.0
(10x)	H [b]	232—233	Pl	49.9	4.9	8.5	$C_{20}H_{23}B_2F_8N_3$	50.1	4.8	8.8
(10y)	H [c]	200—201	Pr	54.4	4.3	8.1	$C_{24}H_{23}B_2F_8N_3$	54.7	4.4	8.0

[a] R^2 = Me. [b] R^2 = Et. [c] R^2 = Ph.

* Pl = plates, Pr = prisms, N = needles.

as broadened singlets respectively near δ 2.4—2.1 and 6.9—6.3. The parent ion was observed in the mass spectra of all amines.

Fragmentations of the iminium salts (9) and (10) were also attempted using methanolic solutions of the sodium salts of sulphinic acids in place of sodium cyanide. Sodium methane-, sodium benzene-, and sodium toluene-*p*-sulphinates each cleaved iminium salts successfully, giving high yields of pyridyl(aryl)amines, and the 2-pyridyl sulphones (14). Amines were purified by sublimation, and sulphones by recrystallisation, and the latter were identified by comparison of melting points and spectra with those of authentic samples. No 4-pyridyl sulphones were observed.

Discussion

Formation of Iminium Salts (9) *and* (10).—With few exceptions,† iminium salts were formed from arylamines rapidly, and in excellent yields. Consequently, the ethoxypyridinium salts (15a, b) [formed in high yield from the chloro-salts (7) and (8) by refluxing in ethanol [11]] were not observed as by-products. The amine when mixed with the chloro-salt (7) [though not with the 2,6-dimethyl analogue (8)], gave an

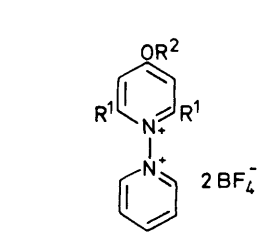
† The low yields of iminium salts (9c) and (10c) from 2-nitroaniline probably arose from the latter's low basicity, rather than from a steric effect. 2-Bromoaniline gave high yields of iminium salts (9i) and (10i).

Table 3. Physical and analytical data for novel 4-pyridyl(aryl)amines (11) and (12) [a]

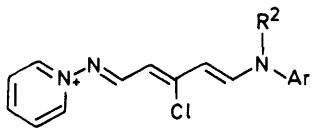
Pyridyl amine	Substituent X	M.p. (°C)	Crystal form [b]	Found (%) C	H	N	Formula	Requires (%) C	H	N
(11d)	4-Ac	258—259	Pr	73.5	5.7	13.2	$C_{13}H_{12}N_2O$	73.6	5.7	13.2
(11e)	4-CO_2Me	202—203	Pl	68.2	5.1	12.1	$C_{13}H_{12}N_2O_2$	68.4	5.3	12.3
(11g)	4-Br	264—265	Pr	52.5	4.0	11.4	$C_{11}H_9BrN_2$	53.0	3.6	11.3
(11h)	3-Br	175—176	N	53.1	3.9	11.3	$C_{11}H_9BrN_2$	53.0	3.6	11.3
(11i)	2-Br	101—102	Pr	53.0	3.5	11.4	$C_{11}H_9BrN_2$	53.0	3.6	11.3
(11k) [c]	3-Cl	181—182	Pr	64.3	4.4	13.6	$C_{11}H_9ClN_2$	64.6	4.4	13.7
(11l) [c]	2-Cl	134—135	Pl	64.5	4.6	13.7	$C_{11}H_9ClN_2$	64.6	4.4	13.7
(11m)	4-F	200—201	N	69.9	4.9	14.9	$C_{11}H_9FN_2$	70.2	4.8	14.9
(11t)	2-OMe	97—99	Pr	71.7	6.1	13.9	$C_{12}H_{12}N_2O$	72.0	6.0	14.0
(12a)	4-NO_2	250—252	N	64.0	5.5	17.1	$C_{13}H_{13}N_3O_2$	64.2	5.4	17.3
(12b)	3-NO_2	170—171	Pl	64.0	5.6	17.3	$C_{13}H_{13}N_3O_2$	64.2	5.4	17.3
(12c)	2-NO_2	160—161	N	64.0	5.3	17.3	$C_{13}H_{13}N_3O_2$	64.2	5.4	17.3
(12d)	4-Ac	155—156	N	74.8	6.7	11.8	$C_{15}H_{16}N_2O$	75.0	6.7	11.7
(12e)	4-CO_2Me	230—231	N	70.0	6.1	11.0	$C_{15}H_{16}N_2O_2$	70.3	6.3	10.9
(12f)	4-CO_2H	>300	Pr [d]	68.9	6.1	11.3	$C_{14}H_{14}N_2O_2$	69.4	5.8	11.6
(12g)	4-Br	200—201	N	56.0	4.7	10.1	$C_{13}H_{13}BrN_2$	56.3	4.7	10.1
(12h)	3-Br	164—165	Pr	56.6	4.7	10.1	$C_{13}H_{13}BrN_2$	56.3	4.7	10.1
(12i)	2-Br	163—164	N	56.4	4.7	9.9	$C_{13}H_{13}BrN_2$	56.3	4.7	10.1
(12k)	3-Cl	158—159	Pl	67.5	6.0	12.1	$C_{13}H_{13}ClN_2$	67.1	5.6	12.0
(12l)	2-Cl	154—155	N	67.2	5.7	12.1	$C_{13}H_{13}ClN_2$	67.1	5.6	12.0
(12m)	4-F	130—131	Pl	72.3	6.2	12.2	$C_{13}H_{13}FN_2$	72.2	6.1	12.0
(12p)	3-Me	135—136	Pl	79.4	7.8	13.5	$C_{14}H_{16}N_2$	79.2	7.6	13.2
(12q)	2-Me	175—176	N	79.1	7.9	13.1	$C_{14}H_{16}N_2$	79.2	7.6	13.2
(12r)	4-OMe	117—118	Pl	73.8	7.1	12.3	$C_{14}H_{16}N_2O$	73.7	7.1	12.3
(12s)	3-OMe	155—156	Pl	73.8	7.1	12.3	$C_{14}H_{16}N_2O$	73.7	7.1	12.3
(12t)	2-OMe	108—109	Pl	74.0	7.1	12.3	$C_{14}H_{16}N_2O$	73.7	7.1	12.3
(12u)	4-OH	265—266	Pl	72.8	6.9	13.0	$C_{13}H_{14}N_2O$	72.9	6.6	13.1
(12v)	3-OH	175—176	Pr	72.7	6.7	13.1	$C_{13}H_{14}N_2O$	72.9	6.6	13.1

* Pl = plates, Pr = prisms, N = needles.

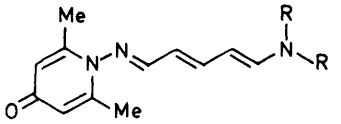
[a] For observed and literature m.p. of known compounds, see Experimental section. [b] Purified by sublimation, followed by recrystallisation (MeCN). [c] Compound mentioned by J. L. Delarue and A. Debarge, U.S. Patent 3 928 341/1975 (*Chem. Abstr.*, 1976, **84**, 180058r). [d] From Me_2SO.



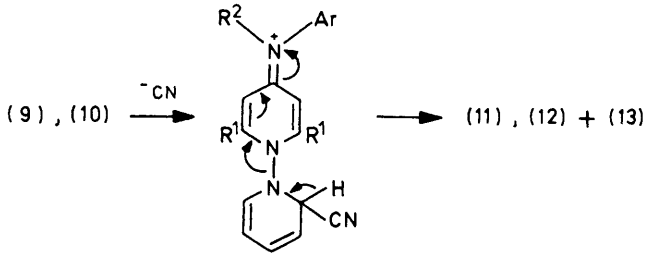
(15) a ; R^1 = H , R^2 = Et
b ; R^1 = Me, R^2 = Et
c ; R^1 = H , R^2 = Me
d ; R^1 = R^2 = Me



(16)



(17)



(18)

initial dark red colour, which faded when the solution was boiled. This is indicative of initial attack at the chloropyridinium ring α-position, followed by electrocyclic ring-opening to give a highly conjugated intermediate such as (16). However, it appears from the experimental results that the ring-opening reaction is reversible under the prevailing conditions, whereas that leading to iminium salts (9) is not, for only the latter are isolated.

With aliphatic primary and secondary amines, it seems that either the electrocyclic ring-opening step is irreversible, or that it is followed by a second irreversible reaction, since iminium salts were not isolated (except possibly with morpholine). We have found previously that the reaction between secondary aliphatic amines and the pyridone salt (2) gives high yields of isolable ring-opened products (17).[11]

Decomposition of Iminium Salts to 4-Pyridyl(aryl)amines.— The fragmentation of the iminium salts with cyanide ion also occurs rapidly and in high yield under very mild conditions. This makes the synthesis of 4-pyridyl(aryl)amines by this route [average over all yields of 74% from salts (7) and (8), or 44% from pyridine] an attractive procedure. Cyanide ion appears to add to the iminium salts (9) and (10) to give an intermediate adduct (18), which subsequently fragments to the pyridyl(aryl)amine and 2-cyanopyridine (13). The absence of 4-cyanopyridine shows that attack at the pyridinium α-positions of the iminium salts is strongly favoured kinetically over attack at the γ-position. In this respect the behaviour of the iminium salts (9) with cyanide ion is consistent with that of

the pyridone salt (1).[2] However, the methyl groups in the pyridone salt (2) sterically shield the pyridinium α-positions, directing cyanide ion [2] and other nucleophiles [12] regiospecifically to the γ-position. The failure to observe 4-cyanopyridine from the salts (10) is thus surprising. The extra positive charge on the salts (10), as compared with the pyridone (2), could result both in a lengthening of the N–N bond with concomitant reduction in steric shielding by the methyl groups, and in higher charge density at the pyridinium α-positions. Both effects would favour 2-cyanopyridine formation. This suggestion is consistent with our observation [11] that both of the methoxypyridinium salts (15c) and (15d) give 2-cyanopyridine on reaction with cyanide ion in methanol. The effect is apparently of sufficient magnitude to direct the large sulphinate anions also to the pyridinium α-positions, giving the sulphones (14).

Experimental

I.r. spectra were recorded as Nujol mulls on a Perkin-Elmer 577 spectrometer; and ^{1}H n.m.r. spectra on a JEOL FX90Q instrument as solutions in CF_3CO_2H for iminium salts (9) and (10), and in $CDCl_3$ for amines (11) and (12). Mass spectra were run on a Hitachi RMS-4 spectrometer. The pyridone salts (1) and (2) were prepared as chloride hydrochlorides as described previously.[3]

4-Chloro-1-pyridiniopyridinium Salts (7) *and* (8).—*Neutralisation of pyridone chlorides.* Crude pyridone chloride hydrochloride salts (1) or (2) (prepared from 0.1 mol 1-aminopyridinium chloride [3]) were dissolved in water (50 ml), and saturated $NaHCO_3$ solution was added dropwise until the pH had increased to 6. The solvent was removed under reduced pressure and the residue recrystallised (95% EtOH) to give the pure chlorides (1) or (2) (75% based on 1-aminopyridinium chloride). The salts were dried *in vacuo* at 100 °C before conversion into the chloro-salts (7) and (8).

Conversion into chloropyridiniopyridinium salts. Dry pyridone chloride (1) (5 g) was suspended in $POCl_3$ (100 ml) and stirred at 25 °C in a flask, protected by a drying tube, for 72 h. Anhydrous Et_2O (100 ml) was added, the mixture was filtered under suction, and the residue washed with dry Et_2O (2 × 30 ml). All operations were carried out under a rubber dam to minimise exposure to moist air. For the salt (2) it was necessary to use $POCl_3$ (120 ml) to prevent caking. The crude 4-chloro-1-pyridiniopyridinium dichlorides were converted into the bistetrafluoroborates (7) and (8) by trituration with ice-cold 50% HBF_4 (5 ml), followed by addition of absolute EtOH (50 ml) and further trituration in an ice–salt bath; the total time did not exceed 10 min. The suspension was filtered, and the residue was washed with ice-cold absolute EtOH (5 ml) followed by dry Et_2O (2 × 10 ml), and dried *in vacuo*. Yields varied between 72—85% based on the recrystallised pyridone chloride. The products were sufficiently pure for conversion into iminium salts (9) and (10).

Preparation of Iminium Salts (9) *and* (10).—*Method A.* The appropriate aniline (1 mmol) was dissolved in absolute EtOH (20 ml), the 4-chloro-1-pyridiniopyridinium salt (7) or (8) (1 mmol) was added, and the mixture was heated under reflux for 5 min. The solution was cooled, filtered, and the residue washed with ice-cold absolute EtOH (2 × 2 ml), and dried. Yields are recorded in Table 1. Products were sufficiently pure for conversion into 4-pyridyl(aryl)amines, but were recrystallised for microanalysis, first from a mixture of 95% EtOH and 50% HBF_4 (17 : 3 by volume), and then by dissolution in dry MeCN and reprecipitation by slow addition of dry benzene. Samples were dried *in vacuo* at 100 °C. Physical and analytical data are recorded in Table 2.

Method B. As for Method A, only dry MeCN (10 ml) was used as the solvent, and heating was continued for 1 h. After the solution had been cooled, the product was precipitated by slow addition of dry benzene (20 ml) with stirring. Samples for analysis were recrystallised from MeCN and benzene as above.

Preparation of 4-Pyridyl(aryl)amines (11) *and* (12).—*Method C.* The appropriate iminium salt (1 mmol) was added to a stirred solution of NaCN (0.1 g, 2 mmol) in absolute MeOH (10 ml) at 25 °C, and stirring was continued for 10 min. Water (20 ml) was added, and the deposited product was separated and purified by sublimation followed by recrystallisation. Details, together with analytical data, are given in Table 3.

Method D. As for Method C, except that when the reaction was complete, the MeOH was removed under reduced pressure, MeCN (10 ml) was added, and the product deposited by slow addition of ice-cold water (20 ml), with cooling and scratching. Products were purified as above.

Method E. As for Method C, only the reaction solvent was removed under reduced pressure; the residue was triturated with dry Et_2O, and the Et_2O extract concentrated, and eluted through an Al_2O_3 column (Grade V), first with light petroleum (b.p. 60—80 °C) to remove 2-cyanopyridine (13), and then with dry Et_2O. Products isolated as oils or low-melting solids were converted into picrates by standard procedures.

M.p.s of known compounds. Observed, and literature (in parentheses) m.p.s (°C) of known compounds were as follows (11a) 309—310 (298); [8a] (11b) 150—152 (150—151); [8a] (11c) 94—95 (95); [8b] (11f) >300 (>250); [4] (11j) 244—245 (245—247); [4] (11n) 175—176 (175—176); [13] (11o) 200—202 (201—202); [10] (11p) 165—166 (163—166); [10] (11q) 163—164 (163); [14a,*] (11r) 177—178 (178—179); [4] (11s) 154—155 (153—155); [14b] (11u) 236—237 (235); [14b] (11v) 210—211 (210—212); [4] (11w) 165—166 (164—166); [14a] (12c) 138—140 (138.5); [15] (12j) 186—187 (180—185); [7c] (12n) 148—149 (148—149); [16] (12o) 168—169 (168—169); [7c] (12w) picrate 154—155 (picrate 152—153).[17]

Identification of 2-Cyanopyridine.—The Et_2O extract of the crude reaction residue (Method C) was spotted onto a t.l.c. plate (Al_2O_3) side by side with authentic samples of 2- and 4-cyanopyridines. On elution with light petroleum (b.p. 60—80 °C), a spot corresponding to 2-cyanopyridine (R_F 0.72) was observed, but none for 4-cyanopyridine (R_F 0.84). 2-Cyanopyridine, isolated by column chromatography (Method C) was further characterised by comparison of i.r. and ^{1}H n.m.r. spectra with those for an authentic sample.

Reactions of Iminium Salts with Sodium Sulphinates.—To a solution of sodium benzenesulphinate (0.39 g, 2.4 mmol) in dry MeOH (10 cm^3) was added portionwise with stirring the iminium salt (10j) (0.4 g, 0.82 mmol). Saturated $NaHCO_3$ was added dropwise until the yellow solution just turned orange, the mixture was cooled in ice, and the pyridylamine (12j) filtered off, purified as above, and identified by m.p. and spectral comparison with an authentic sample. The filtrate was extracted with $CHCl_3$ and the extract was eluted through an Al_2O_3 column; the eluant was stripped to give 2-phenylsulphonylpyridine, m.p. 88—90 °C (benzene) (lit.,[18] 89—90 °C), i.r. and ^{1}H n.m.r. spectra identical with an authentic sample. Similarly, sodium methanesulphinate, and sodium toluene-*p*-sulphinate gave respectively 2-methylsulphonyl- and 2-(*p*-tolylsulphonyl)-pyridine.

* Vompe and co-workers [10] report 136—137 °C.

Acknowledgement

We thank the University of Hong Kong for a research grant (for M. L. T.).

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Received 27*th August* 1982; *Paper* 2/1489