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REDUCTIVE DEAMINATION OF ARYL- AND HETEROARYL-AMINES VIA PYRIDINIUM FLUORIDES

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Abstract - The corresponding "pseudobase" Δ^2-1,5-diketones (8) and (14) afford dihydrochromenylium (9b) and tetrahydroxanthylium monofluorides (15). These convert aryl- and heteroarylamines into dihydroquinolinium (10) and tetrahydroacridinium (16) monofluorides which at 130-250° give the deaminated arenes and heteroarenes (average overall yield 60%).

In the course of our work on the transformations of amines (2) into other functionality (5) mediated by pyrylium salts (cf. 1),[1] we have shown that allyl- and benzyl-amines can be reductively deaminated via 1,2-dihydropyridines (cf. 6)[2] and aliphatic amines via 1,4-dihydropyridines.[3] Although the latter method also succeeds for arylamines, high temperatures are required. We now report a milder reductive deamination procedure for aryl- and heteroaryl-amines.

The present work arose from our cognate investigations on the transformation of primary amines into halides. 2,4,6-Triphenylpyrylium fluoride converts aliphatic primary amines via pyridinium fluorides into alkyl fluorides.[4] Similar work with other halides, and particularly the discovery that 2,4,6-triphenylpyrylium iodide can be used not only for the preparation of alkyl iodides but also of aryl and heteroaryl iodides[5] led to attempts to prepare aryl and heteroaryl fluorides via the superior 5,6-tetrahydro-7,9-diphenylquinoliniums: while these attempts still continue, they have led

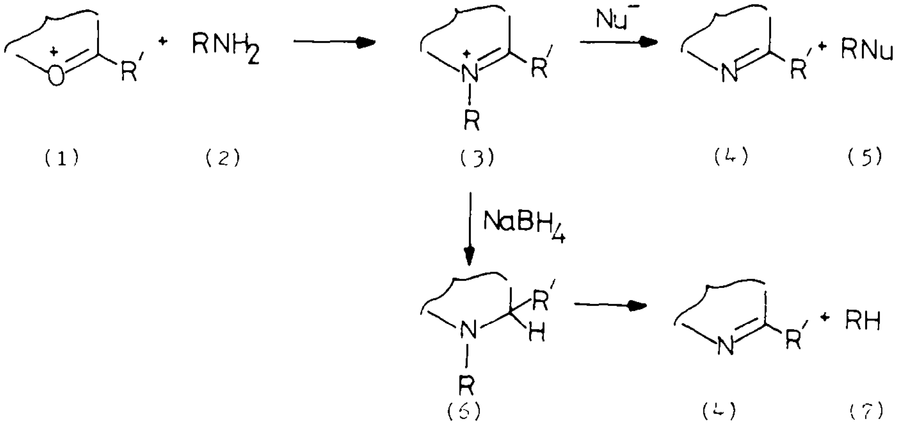


TABLE 1

Preparation of pyridinium fluorides[a]

N-Substituent	Yield (%)	M.p. (°C)	Found %				Formula	Required %			
			C	H	N	F		C	H	N	F
Compound (10a), Anion H_2F_3 by Procedure B.											
Ph	89	182-184[b]	-	-	2.9	12.4	$C_{31}H_{26}F_3N$	-	-	3.0	12.1
pyrid-2-yl	25	159-164[b]	-	-	5.9	12.5	$C_{30}H_{25}F_3N_2$	-	-	6.0	12.3
pyrid-4-yl	35	159-163[b]	-	-	6.4	12.6	$C_{30}H_{25}F_3N_2$	-	-	6.0	12.3
Compound (10b), Anion F by Procedure A.											
Ph	85	108-110	86.5	5.6	3.1	4.7	$C_{31}H_{24}FN$	86.7	5.6	3.3	4.4
4-ClC_6H_4	80	189-191	80.1	4.9	3.1	4.4	$C_{31}H_{23}ClFN$	80.3	5.0	3.0	4.1
4-BrC_6H_4	82	149-151	73.2	4.4	2.6	3.9	$C_{31}H_{23}BrFN$	73.4	4.5	2.8	3.8
pyrid-2-yl	40	159-161	83.2	5.1	6.2	4.8	$C_{30}H_{23}FN_2$	83.7	5.4	6.5	4.4
pyrid-4-yl	55	163-165	83.3	5.1	6.1	4.8	$C_{30}H_{23}FN_2$	83.7	5.4	6.5	4.4
pyrimid-2-yl	60	192-194	80.3	4.8	9.3	4.7	$C_{29}H_{22}FN_3$	80.7	5.1	9.7	4.4
benzothiazol-2-yl	65	152-154	78.7	4.3	5.5	4.3	$C_{32}H_{23}FN_2S$	79.0	4.7	5.8	3.9
Compound (16), Anion F by Procedure A.											
Ph	89	160-162	86.8	6.0	3.1	4.4	$C_{33}H_{26}FN$	87.0	5.7	3.1	4.2
4-ClC_6H_4	85	173-175	80.7	5.2	2.7	4.0	$C_{33}H_{25}ClFN$	80.9	5.1	2.9	3.9
4-BrC_6H_4	83	125-126	74.0	4.8	2.5	3.8	$C_{33}H_{25}BrFN$	74.3	4.7	2.6	3.6

Footnotes

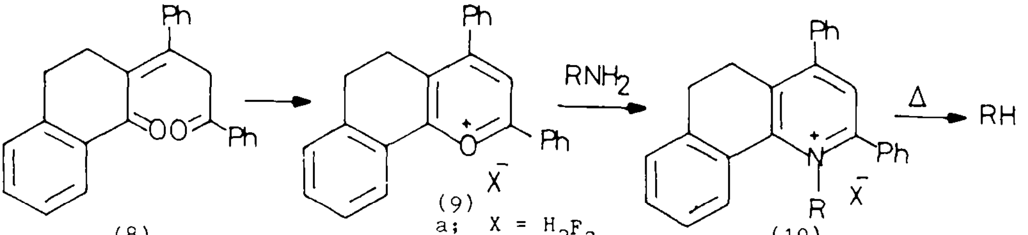
[a] Recrystallised from abs. EtOH as prisms unless otherwise indicated.

[b] Recrystallised from CH_2Cl_2 - Et_2O, prisms.

serendipitiously to a useful reductive deamination method for arylamines which we now report.

The Preparation of Chromenylium Fluorides and Hydrofluorides.- "Pseudobase" (8), obtained[6] from 5,6-dihydro-7,9-diphenylchromenylium tetrafluoroborate and NaOH, cyclises in aqueous HF (40%) yielding the chromenylium (9) as the trifluoride ($H_2F_3^-$) salt (9a), the i.r. of which shows the characteristic $FH...F^-$ H-bond[7] at ca. 1700 cm^{-1}: chemical analysis discloses the three atoms of fluorine. Under these conditions 1,3,5-triphenyl-2-pentene-1,5-dione previously[4] cyclised to give 2,4,6-triphenylpyrylium as the monofluoride F^-, as evidenced by absence of the $FH...F^-$ band in the i.r. and by the fluorine analysis. Apparently, chromenylium (9) requires the anion $H_2F_3^-$ to crystallise easily; however the chromenylium trifluoride $H_2F_3^-$ (9a) decomposes cleanly in refluxing magnesium dried ethanol to the monofluoride salt 9b (after ca. 12 h) and more slowly also in refluxing dichloromethane (ca. 24 h). Salt 9b has a lower m.p. than 9a and is hygroscopic.

The Preparation of Quinolinium Mono and Trifluorides.- Chromenylium $H_2F_3^-$ (9a) reacts readily with aniline and with 2- and 4-amino pyridine in refluxing dichloromethane to give 10-phenyl-, or 10-pyridyl-5,6-dihydro-



(8)

(9)
a; X = H_2F_3
b; X = F

(10)

7,9-diphenylbenzo[h]quinolinium trifluoride $H_2F_3^-$ (10 a) in moderate yields (50% average for 3 examples). The i.r. of these quinoliniums shows the retention of the $FH...F^-$ band. However, when chromenylium trifluoride 9a was reacted with aniline in refluxing magnesium dried ethanol and sodium dried benzene (1:1), with the object of removing the water of reaction by azeotropic distillation and thus improve yields,[4] the 10-phenylquinolinium monofluoride (10b) was obtained in 85% yield.

Chromenylium monofluoride (9b) reacts in the azeotroping medium of ethanol-benzene at 78 °C with aniline, 4-bromo- and 4-chloro-anilines, 2-pyridyl-, 2-pyrimidyl-, 2-benzothiazolyl-, and 4-pyridyl-amines to give the corresponding quinolinium monofluorides (10b) in good to excellent yields (average 70%).

Pyrolysis of Quinolinium Monofluorides and Trifluorides. Heating to just above their melting points the quinolinium fluorides (dried over P_2O_5 prior to pyrolysis) convert smoothly at 130-180 °C to arenes (Table 2). Good yields of pure products are obtained; g.l.c. shows them as single components. The benzothiazolyl derivative decomposes to a black tar from which benzothiazole was not isolated. The 2-pyrimidyl and 4-pyridylquinolinium fluorides were pyrolysed with 2,4,6-triphenylpyridine to lower the melt temperature: good yields of pyrimidine and pyridine were obtained.

The mechanism in Scheme 2 is postulated: fluoride anion removes the acidic proton at position 5 to give a dihydroquinoline (11) which aromatises with loss of the N-substituent as an arene. An alternative breakdown via a radical pathway is also possible. ^1H N.m.r. of the pyrolysis residue shows absence of the CH_2CH_2 protons (cf. 12) expected at ca. δ 3[8] for quinoline (13).

Quinolinium dihydrotrifluorides (10a) also decompose at their melting points [170-220 °C; i.e., higher than for (10b)] and arenes result in good to moderate yields (Table 2). However, since HF (3 equivalents) is evolved, this conversion of aryl-NH_2 to aryl-H via quinolinium trifluorides is not recommended.

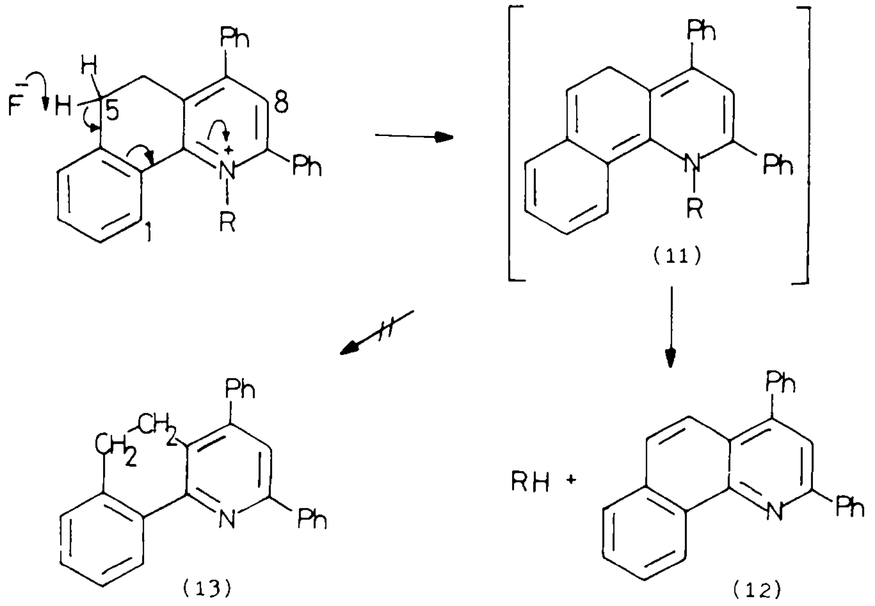


TABLE 2

Pyrolysis of pyridinium fluorides

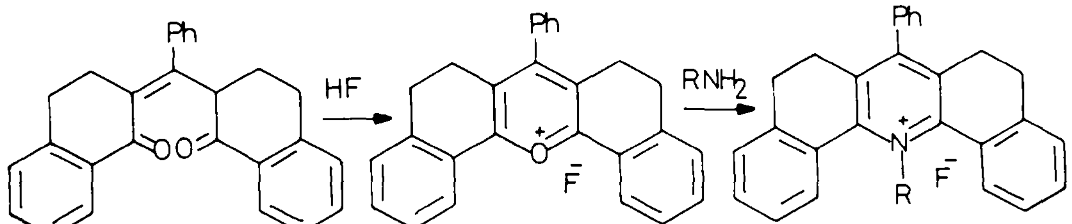
N-Substituent	Pyrolysis Temp(°C)	Time(h)	Product	Yield (%)	Characterisation[a]
Compounds (10a), Anion H_2F_3					
Ph	200-220	5	benzene	65	Ir, ^{1}H nmr
pyrid-2-yl	165	5	pyridine	60	Ir, ^{1}H nmr
pyrid-4-yl	165	5	pyridine	70	Ir, ^{1}H nmr
Compounds (10b), Anion F.					
Ph	130	6	benzene	60	Ir, ^{1}H nmr
4-ClC_6H_4	200	6	chlorobenzene	68	Ir, ^{1}H nmr
4-BrC_6H_4	170	6	bromobenzene	67	Ir, ^{1}H nmr
pyrid-2-yl	180	6	pyridine	62	Ir, ^{1}H nmr, glc[b](r_t=2.2min)
pyrid-4-yl	220[c]	6	pyridine	58	Ir, ^{1}H nmr, glc[b](r_t=2.2min)
pyrimid-2-yl	250[c]	6	pyrimidine	51	Ir, ^{1}H nmr, glc[b](r_t=4.5min)
benzothiazol-2-yl	180[d]	-	-	-	-
Compounds (16), Anion F.					
Ph	170-180	6	benzene	55	Ir, ^{1}H nmr
4-ClC_6H_4	180-200	6	chlorobenzene	53	Ir, ^{1}H nmr
4-BrC_6H_4	140	6	bromobenzene	50	Ir, ^{1}H nmr

[a] Compared with authentic samples. [b] CARBOWAX 20M, temp. 170 °C. [c] Due to high m.p., 1 equivalent of 2,4,6-triphenylpyridine added as flux.

[d] Benzothiazole not isolated: compound decomposed to black tar on heating.

Studies with 7-Phenyltetrahydrodibenzo[c,h] xanthylium fluoride.- This pyrylium is readily prepared from "pseudobase" (14)[8] and 40% aqueous HF as mainly the monofluoride salt (15). Recrystallisation from hot ethanol gives pure xanthylium monofluoride (15), which reacts readily with aniline and 4-chloro- and 4-bromo- anilines to give the corresponding 5,6,8,9-tetrahydro-7-phenyldibenzo[c,h]acridinium monofluorides (16) (average yield 86%). These acridinium monofluorides decompose to arenes (average 53%) and presumably the dehydrogenated acridine. A mechanism similar to that proposed for the decomposition of the quinolinium fluorides is likely: a recent basic decomposition of N-alkyl-5,6,8,9-tetrahydro-7-phenyldibenzo[c,h] acridiniums resulted in isolation of a mixture of alkanes,[9] formed via a similar breakdown.

Synthetic Applicability of Quinolinium Fluorides as Reductive Deaminating Agents.- Because of the mild conditions offered for aryl/heteroaryl $NH_2 \rightarrow H$ by use of chromenylium fluoride, the method has considerable potential for non-diazotisable amines: reductive deamination of aryl/heteroaryl amines via diazonium intermediates fails for heteroaryl amines which decompose in the diazotising medium into substituted heteroarenes.[10] The method described in this paper leads to clean separation of products.



(14) (15) (16)

EXPERIMENTAL

I.r. and n.m.r. spectra were measured with Perkin Elmer 237 and R12 instruments respectively ($SiMe_4$ as internal standard). Melting points (uncorrected) were determined on a Reichert hot-stage microscope.

5,6-*Dihydro*-7,9-*diphenylbenzo*[h]-*chromenylium Trifluoride* (9a).- A solution of pseudobase (8)[6] (14 g, 40 mmole) in toluene (50 ml) in a polyethylene beaker was treated with aqueous HF (40%, 2.5 ml, 50 mmol). After stirring for 12 h at 25 °C, to the resulting yellow crystalline mass was added Et_2O (50 ml). The crystals were filtered off and washed with Et_2O. Recrystallisation from CH_2Cl_2 gave the chromenylium $H_2F_3^-$ (11 g, 70%), yellow prisms, m.p. 210-212 °C (Found: C, 75.5; H, 5.6; F, 14.2. $C_{25}H_{21}F_3O$ requires C, 76.2; H, 6.3; F, 14.2%); ν_{max} ($CHBr_3$) 1700b, 1620s.

5,6-*Dihydro*-7,9-*diphenylbenzo*[h]-*chromenylium Monofluoride* (9b).- The chromenylium hydrofluoride (9a) was refluxed in magnesium dried EtOH for 12 h to give after addition of Et_2O the *chromenylium fluoride* (9b) (9 g, 92%), m.p. 141-143 °C from absolute ethanol (Found: C, 84.4; H, 5.0; F, 5.7. $C_{25}H_{19}FO$ requires C, 84.8; H, 5.4; F, 5.4%).

5,6,8,9-*Tetrahydro*-7-*phenyldibenzo* [c,h]*xanthylium Monofluoride* (15).- As for preparation of chromenylium fluoride (9*a*) but from corresponding "pseudobase" (14)[8], (15 g, 40 mmol) recrystallised from hot abs. EtOH as yellow prisms (12.2 g, 80%), m.p. 153-155 °C (Found: C, 85.1; H, 5.8; F, 5.9. $C_{27}H_{21}FO$ requires C, 85.3; H, 5.5; F, 5.0%). (The high F-analysis probably indicates the presence of some poly fluoride salt).

Procedures for Preparation of Quinoliniums and Acridiniums.- *Method A*. The amine (10 mmol) was added to a suspension of the chromenylium/xanthylium fluoride (10 mmol) in Mg dried EtOH and Na dried benzene (1:1, 40 ml). The reaction mixture was heated for 12-16 h in a Dean Stark apparatus. The solvents were removed *in vacuo* (20 mmHg) at 30 °C. The oily residue was triturated with Et_2O, and the resulting solid recrystallised from abs. EtOH (Table 1).

Method B. To the chromenylium hydrofluoride (2 mmol) in CH_2Cl_2 (10 ml) was added the amine (2 mmol) and Et_3N (2 mmol). The mixture was refluxed for 6 h. Acetic acid was added (4 mmol) and the solution was refluxed until t.l.c. (silica - EtOAc) showed the absence of starting pyrylium. After cooling, the quinolinium hydrofluoride was precipitated with Et_2O (50 ml) and recrystallised from CH_2Cl_2 - Et_2O (Table 1).

Pyrolysis of Quinoliniums and Acridiniums. The pyridinium salt was dried over P_2O_5 at 25 °C *in vacuo* (10 mmHg) for 3 days. It was melted in a flask attached to a trap (a micro Hickman can also be used). The heating at m.p. of the salts was maintained for 6 h. The distillate was collected, weighed, and analysed in the following order: (i) i.r. as liquid film, (ii) ^1H n.m.r. as solution in $CDCl_3$, and (iii) g.l.c. as solution in ether.

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