Nucleophilic Displacements of *N*-Aryl and Heteroaryl Groups. Part 1. Pyrylium-mediated Transformation of Anilines into Phenols

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Aromatic amines with 2,4-diphenyl-5,6,7,8-tetrahydrochromenylium trifluoromethanesulphonate (5) gave the corresponding pyridinium salts (6; R = aryl) which were converted by base into the anhydrobases (7). Benzoyl chloride converted (7) into the new pyridinium anhydrobases (9). These anhydrobases (9) rearranged at 150 °C into the isomeric phenol enol ethers (10) which were readily hydrolysed to yield the corresponding phenols. The mechanistic and synthetic significance of the results are assessed.

The classical activation of the amino group by diazotisation has been extensively applied to the transformations of arylamines and interest in this area remains widespread.[1] However the diazotisation process is unsuccessful for many phenylenediamines [2] and heteroarylamines (the latter leading to over activated diazoniums [3]).

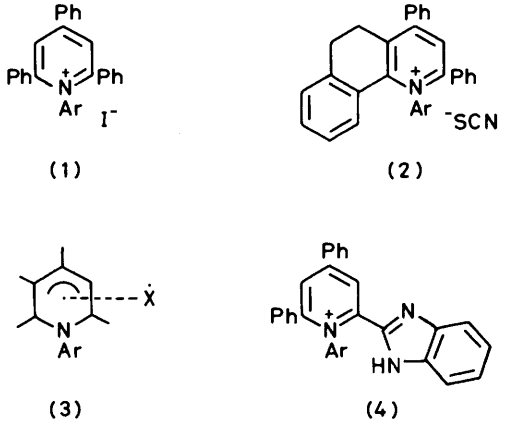
From our laboratories over the last few years [4] has emerged a new amine transformation scheme utilising the facile reaction of primary amines with pyrylium salts to give pyridinium salts which can then be treated with nucleophiles. This scheme is general for aliphatic amines (being complementary in scope to diazotisation). Our attempts to extend the method to arylamines are presented in the present set of papers.

Previously we have shown that 2,4,6-triphenylpyrylium iodide and 2,4-diphenyldihydrobenzochromenylium † thiocyanate react with arylamines and heteroarylamines. Pyrolysis of the neat 1-aryl(heteroaryl)pyridinium iodides (1) at *ca.* 250 °C [6] and of the dihydrobenzoquinolinium thiocyanates (2) in a melt of KSCN–NaSCN at 200 °C [7] gives moderate to good yields of the corresponding aryl iodides and aryl thiocyanates. Extension of the same procedure to transformations of arylamines into the other halogenaryls was unsuccessful, yielding hydrocarbons from fluorides [8a] and no useful products from chlorides and bromides.[8b] The iodide and thiocyanate pyrolyses probably involve charge-transfer complexes (3) and radical intermediates.[8b]

To facilitate *N*-aryl bond cleavage we have therefore designed systems in which the attacking ' nucleophile ' was held in close proximity to the aryl–nitrogen bond, to promote intramolecular rearrangement. We have reported a photorearrangement of an *N*-aryl group *via* a *N* to *N'*-1,4 shift in 1-aryl-2-benzimidazol-2-ylpyridinium salts (4).[9]

Anhydrobases of type (7; R = aryl) could form, it was rationalised, the basis for a more general method. It is known that the enamine (7c) reacts with carbon electrophiles (benzoyl chloride, carbon disulphide, phenyl isocyanate and isothiocyanate) and nitrogen electrophiles (phenyldiazonium tetrafluoroborate) to yield 8-substituted quinolinium salts (8).[10] [*N*-Alkyl groups have been rearranged onto the 8-position of the anhydrobase (7; R = alkyl) thermally, *via* a radical intermolecular pathway, but such rearrangements do not occur for *N*-aryl compounds.[11]]

Conversion of Anilines into Phenols.—2,4-Diphenyl-5,6,7,8-tetrahydrochromenylium trifluoromethanesulphonate (5) condensed readily with a series of aromatic amines to give the corresponding quinolinium salts (6) (Table 1). On treatment with sodium ethoxide the quinolinium salts (6) were readily converted into the corresponding anhydrobases. The anhydrobases (7) (Table 2) are light sensitive, decompose on attempted crystallisation, and gave unsatisfactory elemental analyses and were therefore characterised by their ^{1}H n.m.r. spectra (Table 3). The 8-CH is found as a triplet at δ 3.8—3.9 and the 3-CH as a singlet at δ 5.2—5.3. The three methylene groups were each distinct: 5-CH_2 as a triplet at δ 2.5 and the 6- and 7-CH_2 as multiplets centred near δ 1.6 and 2.1, respectively.



Treatment of the anhydrobases (7) with benzoyl chloride gave products (8; E = PhCO) which were converted without isolation by further base into the benzoyl enamines (9). Comparison of the spectra of these compounds (Table 5) with those of the parent anhydrobases (Table 3) is instructive. In particular, the peak for 8-CH has disappeared. The 5-CH_2 and 7-CH_2 now appear together as a complex multiplet. The 3-CH singlet is still easily distinguished, and the 2'-CH and 6'-CH are also separated from the other aromatic protons signals. The i.r. spectra show a combination of variable absorptions in the region 1 670—1 590 cm^{-1} due to the conjugated alkene C=C stretch and α,β unsaturated ketone C=O stretch.

Internal aryl migration to yield the enol ether (10) was effected initially by heating at 210 °C but is more conveniently carried out in refluxing dimethylformamide. The structure of these compounds (10) is supported by their ^{1}H n.m.r. spectra (Table 7). In contrast to the two series of anhydrobases (7) and (9), the 3-CH signal has become more deshielded, so that it appears in the aromatic region. The methylene protons have similar shifts to those in the precursors. The i.r. spectra show ν 1 640—1 630m (acyclic C=C str.), 1 605—1 585s (aromatic C=C str and C=N str), and 1 230—1 220s cm^{-1} (C–O str in

† This salt gives with amines quinolinium salts which are significantly more activated towards nucleophiles than 2,4,6-triphenylpyridinium salts.[5]

Table 1. Preparation of *N*-aryl-2,4-diphenyl-5,6,7,8-tetrahydroquinolinium trifluoromethanesulphonate (6)

No.	Substituent R	Yield (%)	M.p. (°C)	Recryst. solvent [d]	Found (%) C	H	N	Molecular formula	Required (%) C	H	N
(6a)	Ph	87	203—205	Et_2O	65.7	4.7	2.7	$C_{28}H_{24}F_3NO_3S$	65.8	4.7	2.7
(6b)	Ph	85	188—190	Et_2O	72.0	5.4	3.2	$C_{27}H_{24}BF_4N$	72.2	5.4	3.1
(6c)	4-C_6H_4Me	83	171—173 [b]	CH_2Cl_2–Et_2O	66.1	5.0	2.6	$C_{29}H_{26}F_3NO_3S$	66.3	5.0	2.7
(6d)	3-C_6H_4Me	83	143—145	CH_2Cl_2–Et_2O	66.4	4.9	2.7	$C_{29}H_{26}F_3NO_3S$	66.3	4.9	2.7
(6e)	4-C_6H_4Cl	84	146—148	*c*	61.5	4.3	2.6	$C_{28}H_{23}ClF_3NO_3S$	61.6	4.2	2.6
(6f)	4-C_6H_4Br	79	156—158	*c*	56.9	3.9	2.4	$C_{28}H_{23}BrF_3NO_3S$	56.9	3.9	2.4
(6g)	4-C_6H_4Ph	81	137—139	CH_2Cl_2–Et_2O	69.2	4.8	2.3	$C_{34}H_{28}F_3NO_3S$	69.5	4.8	2.4
(6h)	4-$C_6H_4CO_2H$	82	230—232	CH_2Cl_2–Et_2O	62.7	4.3	2.5	$C_{29}H_{24}F_3NO_5S$	62.7	4.3	2.5

[a] Physical data for the tetrafluoroborate salt. [b] Lit.,[10] m.p. 175 °C. [c] Triturated with ether. [d] All compounds crystallised as prisms.

Table 2. Preparation of *N*-aryl-2,4-diphenyl-1,5,6,7-tetrahydroquinolines (7)

No.	Substituent R	Yield (%)	M.p. (°C)	Crystal form	Found (%) C	H	N	Molecular formula	Required (%) C	H	N
(7a)	Ph	72	110—112	Prisms	88.0	6.5	— [a]	$C_{27}H_{23}N$	89.7	6.4	3.9
(7c)	4-C_6H_4Me	93	130—132	Plates	—	—	— [b]	$C_{28}H_{25}N$	—	—	—
(7d)	3-C_6H_4Me	99	98—103	Prisms	84.3	6.6	3.5 [a]	$C_{28}H_{25}N$	89.6	6.7	3.7
(7e)	4-C_6H_4Cl	88	146—148	Prisms	82.0	5.6	3.5 [c]	$C_{27}H_{22}ClN$	81.9	5.6	3.5
(7f)	4-C_6H_4Br	92	125—127	Prisms	72.2	5.2	— [a]	$C_{27}H_{22}BrN$	73.6	5.0	3.2
(7g)	4-C_6H_4Ph	90	134—136	Needles	89.1	6.4	— [a]	$C_{33}H_{27}N$	90.6	5.2	3.2

[a] Data for crude material from EtOH. Recrystallisation led to decomposition. [b] Lit.[10] m.p. 130—135 °C. [c] Recrystallised from ether.

Table 3. ^1H N.m.r.[a] of *N*-aryl-2,4-diphenyl-1,5,6,7-tetrahydroquinolines (7)

No.	Substituent R	5-CH_2 (2 H, t) δ	*J*	6-CH_2 (2 H, m) δ	7-CH_2 (2 H, m) δ	8-CH (1 H, t) δ	*J*	3-CH (1 H, s) δ	Aromatics (m) δ	H	Other
(7a)	Ph	2.5	6	1.7	2.2	3.9	4	5.3	7.1—7.5	15	—
(7c)	4-C_6H_4Me	2.4	6	1.6	2.1	3.8	4	5.2	7.0—7.6	14	2.2 (3 H, s)
(7d)	3-C_6H_4Me	2.5	6	1.6	2.1	3.8	4	5.2	6.8—7.6	14	2.2 (3 H, s)
(7e)	4-C_6H_4Cl	2.5	6	1.7	2.1	3.8	4	5.3	7.0—7.4	14	—
(7f)	4-C_6H_4Br	2.5	5	1.6	2.1	3.8	4	5.2	7.0—7.5	14	—
(7g)	4-C_6H_4Ph	2.5	5	1.6	2.1	3.9	4	5.2	6.9—7.6	19	—

[a] δ($CDCl_3$), *J* in Hz.

Table 4. Preparation of 8-benzoyl-*N*-aryl-2,4-diphenyl-1,5,6,7-tetrahydroquinolines (9)

No.	Substituent 4-R′	Yield (%)	M.p. (°C)	Recryst. solvent	Crystal form	Found (%) C	H	N	Molecular formula	Required (%) C	H	N
(9a)	H	93	173—175	Cyclohexane	Prisms	87.6	5.9	3.0	$C_{34}H_{27}NO$	87.7	5.9	3.0
(9c)	Me	73	163—165	EtOH	Plates	—	—	— [a]	$C_{35}H_{29}NO$	—	—	—
(9e)	Cl	71	172—174	*b*	Prisms	81.5	5.3	2.8	$C_{34}H_{26}ClNO$	81.7	5.2	2.8
(9f)	Br	70	197—199	Et_2O	Prisms	74.9	4.8	2.6	$C_{34}H_{26}BrNO$	75.0	4.8	2.6
(9g)	Ph	86	167—169	Cyclohexane	Prisms	88.6	5.8	2.5	$C_{40}H_{31}NO$	88.7	5.7	2.6

[a] Lit.[10] m.p. 159—161 °C. [b] Triturated with ether.

Table 5. ^1H N.m.r.[a] of 8-benzoyl-*N*-aryl-2,4-diphenyl-1,5,6,7-tetrahydroquinolines (9)

No.	Substituent 4-R′	5-CH_2, 7-CH_2 (4 H, m) δ	6-CH_2 (2 H, m) δ	3-CH (1 H, s) δ	2′,6′-CH (2 H) δ	m	*J*	Aromatics (m) δ	H
(9a)	H	2.6	1.7	6.1	6.5	m	—	6.8—7.5	18
(9c)	Me [b]	2.6	1.7	6.1	6.3	d	9	6.6—7.5	17
(9e)	Cl	2.5	1.7	6.1	6.4	d	9	6.7—7.5	17
(9f)	Br	2.5	1.7	6.0	6.3	d	9	6.7—7.4	17
(9g)	Ph	2.6	1.7	6.1	6.5	d	8	6.9—7.6	22

[a] δ($CDCl_3$), *J* in Hz. [b] Me peak at δ 2.1 (3 H).

Table 6. Preparation of 8-(α-aryloxybenzylidene)-2,4-diphenyl-5,6,7,8-tetrahydroquinolines (10)

No.	Substituent R	Procedure	Yield (%)	M.p. (°C)	Recryst. solvent	Crystal form	Found (%) (Required %) C	H	N	Molecular formula
(10a)	Ph	B	82	210—212	EtOAc	Needles	87.6 (87.7	5.9 5.8	3.0 3.0)	$C_{34}H_{27}NO$
(10e)	4-C_6H_4Cl	A	83	155—157	L.p. [b]	Prisms	81.5 (81.7	5.3 5.2	2.8 2.8)	$C_{34}H_{26}ClNO$
(10f)	4-C_6H_4Br	A, B	79 [a]	214—216	EtOAc	Prisms	74.7 (75.0	4.9 4.8	2.5 2.6)	$C_{34}H_{26}BrNO$
(10g)	4-C_6H_4Ph	B	80	248—250	CH_3CN	Prisms	88.5 (88.7	5.8 5.7	2.5 2.6)	$C_{40}H_{31}NO$

[a] Procedure A, yield 72%. [b] Light petroleum (b.p. 50—110 °C).

Table 7. ^{1}H N.m.r.[a] of 8-(α-aryloxybenzylidene)-2,4-diphenyl-5,6,7,8-tetrahydroquinolines (10)

No.	Substituent R	5-CH_2, 7-CH_2 (4 H, m) δ	6-CH_2 (2 H, m) δ	Aromatics, (m) δ	3-CH H
(10a)	Ph	2.7	1.8	6.9—7.7	21
(10e)	4-C_6H_4Cl	2.7	1.8	6.9—7.5	20
(10f)	4-C_6H_4Br	2.7	1.7	6.6—7.5	20
(10g)	4-C_6H_4Ph	2.8	1.8	7.2—7.8	25

[a] δ($CDCl_3$).

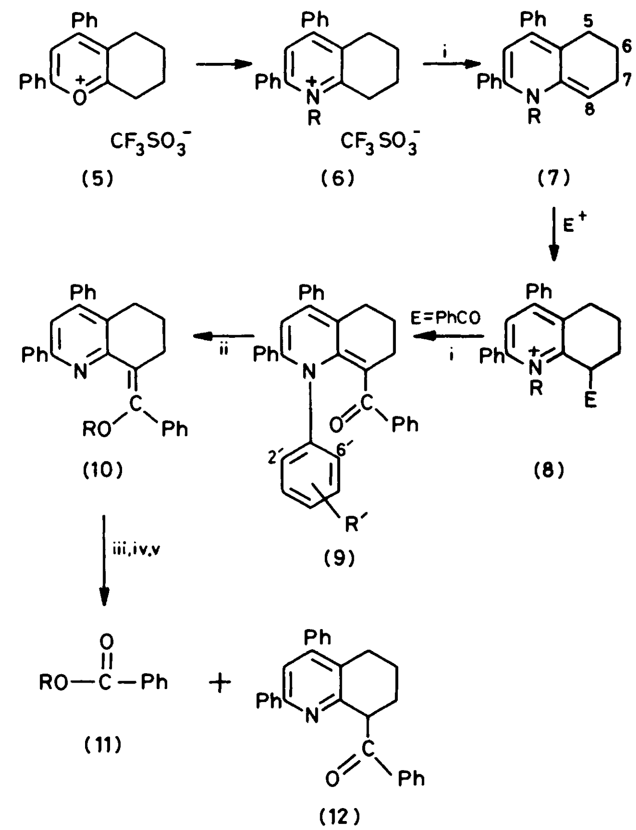
vinyl ethers). Particularly striking is the loss of the chromophore from $\lambda_{max.}$ 510 for (9) to *ca.* 375 for (10) (Table 8).

The conversion (9) into (10) takes place under surprisingly mild conditions considering that the *N*-aryl rings in (9) are unactivated towards nucleophilic substitution. Evidently, the system is so aligned that the transition state is relatively easily reached: recently an example of the shift of an unsubstituted phenyl group has been reported in a quite different system.[12]

Acid hydrolysis of the enol ethers (10) gave the phenols, isolated as their benzoyl esters (11, Table 9) after Schotten-Baumann acylation, and the β-benzoyltetrahydroquinoline (12). The phenols were identified spectrally and by their known melting points: this proves also the *para*-orientation of the groups in compounds (10).

Assessment of the Synthetic Results.—The work just described cannot be considered a practical synthetic method for the conversion of anilines into phenols since it suffers from a number of disadvantages. (i) It comprises a six-step sequence (although it is possible to do some of the stages without isolation). (ii) The conversion of anilines with electron-withdrawing groups (4-cyano and 4-nitro) into pyridinium salts (6) did not proceed smoothly and neither did that of aminopyridines nor aminopyrimidines. (iii) *p*-Aminobenzoic acid formed a pyridinium salt (6h) but it was difficult to convert this into the anhydrobase. (iv) Attempted rearrangement of the *N*-4-methylphenyl derivative (9c) gave a complex mixture of products.

This work is important, in our view, because it shows that, in principle, nucleophilic substitutions are possible on unactivated aromatic rings under rather mild conditions. Subsequent work disclosed systems where this potential may be harnessed in synthetically useful ways, by reducing the number of steps. This allowed us to realise our goal of making available an alternative to the diazonium reaction for the synthetic transformation of aromatic amines; this is described in the following papers.



(For designation of R in (6), (7), (10), and (11) and R′ in (9) see Tables 1, 2, 6, 9, and 4 respectively)

Scheme. *Reagents:* i, Base; ii, Heat; iii, H$^+$; iv, NaOH; v, BzCl

Experimental

^{1}H N.m.r. spectra were recorded with either a Varian EM 360L spectrometer or a Varian A-60A spectrometer using internal $SiMe_4$ as a standard. I.r. spectra were run using NaCl plates on a Perkin-Elmer 283 B spectrophotometer as solutions in $CHBr_3$. U.v. spectra were obtained on a Perkin-Elmer 330 spectrophotometer, as solutions in absolute ethanol. Mass spectral measurements were made on an AEI MS 30 spectrometer. M.p.s were recorded on a Kofler hot-stage apparatus and are uncorrected.

Benzylideneacetophenone (chalcone) (75%), m.p. 56—58 °C (lit.,[13] m.p. 56—57 °C) and 2,4-diphenyl-5,6,7,8-tetrahydrochromenylium trifluoromethanesulphonate (31%), m.p. 182—184 °C (lit.,[10] m.p. 187 °C) were prepared using the literature procedures quoted.

Table 8. U.v. data for 8-benzoyl-*N*-aryl- (9) and 8-(α-aryloxybenzylidene)-2,4-diphenyltetrahydroquinolines (10)

No.	Substituent R	(9)				(10)			
		$\lambda_{max.}$/nm	ε	$\lambda_{max.}$/nm	ε	$\lambda_{max.}$/nm	ε	$\lambda_{max.}$/nm	ε
a	Ph	390	3 840	515	10 750	290	34 900	375	22 400
e	4-C_6H_4Cl	380	2 620	510	6 900	285	22 500	370	7 950
f	4-C_6H_4Br	380	3 270	510	5 400	285	31 850	370	13 400
g	4-C_6H_4Ph	390	3 450	515	8 700	290	32 450	375	15 750

Table 9. Preparation of aryl benzoates (11)

No.	Substituent R	Yield (%)	M.p. (°C)	Recryst. solvent	Crystal form	Lit. m.p. (°C)
(11e)	4-C_6H_4Cl	75	88—90	L.p.[d]	Needles	86—87 [a]
(11f)	4-C_6H_4Br	48	102—104	L.p.[d]	Needles	102 [b]
(11g)	4-C_6H_4Ph	24	146—148	Hexane	Prisms	150 [c]

[a] J. R. Norell, *J. Org. Chem.*, 1973, **38**, 1924. [b] W. Utermark and W. Schicke, 'Melting Point Tables of Organic Compounds,' Wiley Interscience, New York, 1963, p. 185. [c] J. Kaiser, *Liebigs Ann. Chem.*, 1890, **257**, 95. [d] Light petroleum (b.p. 37—52 °C).

General Procedure for Preparation of N-*Aryl*-2,4-*diphenyl*-5,6,7,8-*tetrahydroquinolinium Trifluoromethanesulphonates* (6).—To the chromenylium salt (1.0 g, 2.3 mmol) in dichloromethane (50 ml) was added dropwise a mixture of the arylamine (2.3 mmol) and triethylamine (0.23 g, 2.3 mmol). The solution was refluxed 3 h, cooled, and treated dropwise with acetic acid (0.55 g, 9.2 mmol). After being stirred for 3 h at 25 °C, the solution was washed with water (2 × 25 ml) and dried (Na_2SO_4). Dilution with ether (200 ml) afforded the quinolinium salt as white prisms (Table 1).

General Procedure for Preparation of N-*Aryl*-2,4-*diphenyl*-1,5,6,7-*tetrahydroquinolines* (7).—To the quinolinium salt (2.3 mmol) in absolute ethanol (50 ml) was added portionwise 99% sodium hydride (0.11 g, 4.6 mmol). After the mixture had been stirred for 15 min at 25 °C the orange prisms were filtered off and washed with absolute ethanol (10 ml) (Table 2).

General Procedure for Preparation of 8-*Benzoyl*-N-*aryl*-2,4-*diphenyl*-1,5,6,7-*tetrahydroquinolines* (9).—To the enamine (5 mmol) in tetrahydrofuran (75 ml) was added benzoyl chloride (0.84 g, 6 mmol) dropwise. The red colour faded after the mixture had been stirred for 20 min at 25 °C. Sodium hydride (0.24 g, 10 mmol) in absolute ethanol (10 ml) was added dropwise and the solution stirred a further 20 min. The solvent was removed under reduced pressure (15 mmHg) and the residue washed with water (2 × 25 ml) and dried *in vacuo* (0.5 mmHg) over phosphorus pentoxide (Table 4).

General Procedure for Preparation of 8-(α-*Aryloxybenzylidene*)-2,4-*diphenyl*-5,6,7,8-*tetrahydroquinolines* (10).—*Procedure A.* The benzoyl enamine (2.4 mmol) in a pyrolysis apparatus under nitrogen was heated at 210 °C for 2 h. After cooling the residue was dissolved in dichloromethane (25 ml), filtered, and the solvent removed under reduced pressure (15 mmHg) to afford the enol ether (Table 6).

Procedure B. The benzoyl enamine (2.4 mmol) in dimethylformamide (15 ml) was refluxed 18 h. The solvent was removed under reduced pressure (5 mmHg) and the residue washed with water (2 × 10 ml) and dried *in vacuo* (0.5 mmHg) over phosphorus pentoxide (Table 6).

General Procedure for Preparation of Aryl Benzoates (11).—The enol ether (2 mmol) in acetic acid (10 ml) was treated dropwise with concentrated hydrochloric acid (5 ml) and refluxed for 10 min. The solution was cooled and basified at 5 °C with cold aqueous sodium hydroxide (8.0 g in 10 ml water). The 8-benzoyl-2,4-diphenyl-5,6,7,8-tetrahydroquinoline (12) precipitated and was filtered off and washed with water (5 ml). Recrystallisation from n-hexane gave prisms (0.5 g, 64%), m.p. 62—64 °C, *m/z* 389.1807 (M^+. Calc. for $C_{28}H_{33}NO$: *M*, 389.1779), δ($CDCl_3$) 8.2 (1 H, m), 7.8—7.0 (15 H, m), 2.8 (2 H, m), 2.3 (2 H, m), and 1.8 (2 H, m). The filtrate was treated dropwise with benzoyl chloride (0.42 g, 3 mmol) and stirred 30 min at 25 °C. Ether extraction (3 × 20 ml) afforded the aryl benzoates (Table 9).

Acknowledgements

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