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CONVERSIONS OF PRIMARY AMINO GROUPS INTO OTHER FUNCTIONALITY MEDIATED BY PYRYLIUM CATIONS

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Abstract—Primary amines react with pyrylium cations to give pyridiniums which transfer the N-substituent to a wide range of halide, O-, S-, N-, C- and H-nucleophiles and undergo elimination and rearrangement reactions.

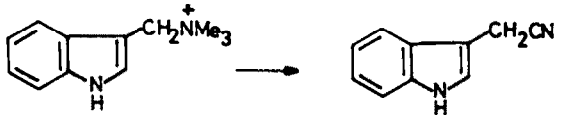
Kinetic study of the formation and displacement steps has enabled the selection of substituents on the original pyrylium to optimise conditions for both steps. The procedure represents a widely applicable two-step sequence for the selective conversion of primary amino groups into many other functionalities under mild conditions in high yields.

I. INTRODUCTION

1. *Leaving groups in synthetic chemistry*

Organic synthetic operations can conveniently be divided into the construction of carbon skeletons and the introduction of functionality. Of the methods for the introduction of functionality perhaps the most important is by nucleophilic displacement. In aliphatic compounds or generally when dealing with hybridised C atoms, the general methods of the introduction of functionality by nucleophilic displacement have been the displacement of a halogen atom or an activated derivative of an OH group, for example a tosylate. For aromatic compounds, by contrast it has been the displacement of an amino group via the diazonium function that has been the most useful.

The conversion of aliphatic amino groups into other functionality by means of a nucleophilic displacement on an activated derivative has been rare: displacements on trimethylammonio-derivatives, nitrosoamide decomposition and the triazene method all suffer from poor yields, lack of generality or other disadvantages.[1] Isolated useful examples, however, have been known for a long time: examples are (i) the conversion of amino groups into unsaturation by Hoffmann elimination reactions,[2] and (ii) the nucleophilic displacements on gramine quaternary salts (e.g. 1→2).[3]



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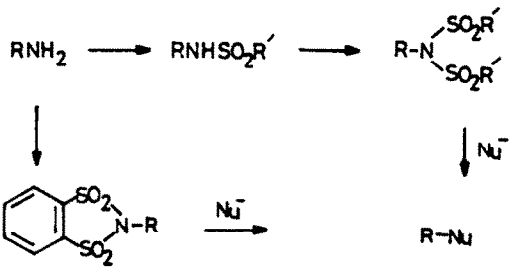
2. *The conversion of a primary amino into a leaving group*

Previous work. Over the last ten years several groups have looked at the possibility of the conversion of primary aliphatic amino into leaving groups (see Scheme 1). Good yields of n-hexyl acetate were



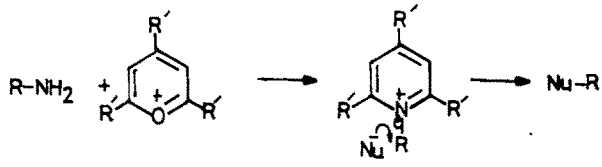
(R' = CF_3, Ph, C_6H_4Me)

Scheme 1. Literature conversions of amino into leaving groups.

obtained with $N(SO_2C_6H_4Me)_2$ or $N(SO_2C_6H_4NO_2)_2$ as leaving group, provided hexamethylphosphoric triamide was used as solvent[4] and also fair yields of n-hexyl iodide and bromide with $N(SO_2C_6H_4Me_2)_2$ whereas saccharine was poor as leaving group.[5] Similar replacements of NTs_2 by H have been reported,[6] and also limited success for displacement reactions of $N(SO_2CF_3)_2$.[7] However, in general cyclic groups such as benzene-1,2-disulphonimide do not appear to be promising for nucleophilic displacement.[8]

3. *Conversion of primary amino into a leaving group by pyrylium*

The concept. Over the last five years at the University of East Anglia we have developed a general method for the conversion of primary aliphatic amino groups into other functionality via a 2-stage sequence: (i) the reaction of the amine with a pyrylium cation to give a pyridinium cation (see 3+4→5) followed by (ii) nucleophilic displacement of the N-substituent on the pyridinium cation (see 5→6).



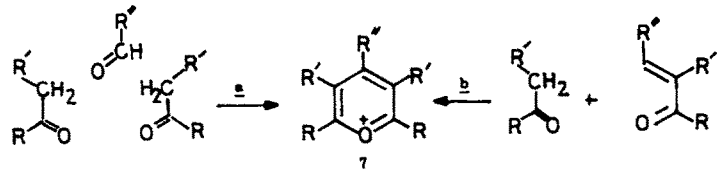
Prior to our work there were only two reports of reaction sequences of this type. In 1926, Ziegler and Fries[9] showed that 1-methyl-2,4,6-triphenylpyridinium chloride thermolysed to 2,4,6-triphenylpyridine and (presumably) methyl chloride. More recently Susan and Balaban[10] recognised the synthetic possibilities of this type of transformation for converting alkyl- or benzyl-amines into their halides and demonstrated the expected thermal weight loss for 1-methyl-2,4,6-triphenylpyridinium chloride and iodide, but this procedure has not received detailed examination.

For the development of this reaction into a general synthetic method three separate investigation directions were needed: (i) the preparation of the reagent pyrylium salts, (ii) a study of the reaction of amines with pyrylium salts to determine optimum conditions for the preparation of pyridinium intermediates and (iii) a study of the nucleophilic displacements. Sections on each of these topics follow, and are then succeeded by a general survey of the functionality which has been introduced by this method.

4. *Preparation of pyrylium salts*

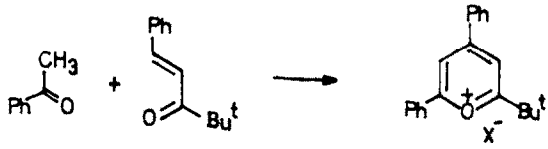
(i) *The formation of the carbon skeleton.* Numerous methods are available for the preparation of pyrylium salts, and the subject has been reviewed.[11] In our laboratory we have found three reaction sequences of particular value for the preparation of a wide range of pyrylium salts in large quantities:

(a) For symmetrical systems, in a classical reaction,[12] two moles of a methyl or methylene ketone are condensed with one mole of aldehyde, often in the presence of perchloric acid or boron trifluoride etherate (Scheme 2). The yield is often improved by using a modification of the above sequence (see Ref. 13), in which 1.5–2 moles of the intermediate chalcone is reacted with one further mole of ketone. In both versions, the chalcone also acts as a hydride abstracting agent.



Scheme 2. Preparation of *a* symmetrical and *b* symmetrical *or* unsymmetrical pyrylium cations.

(b) For the preparation of unsymmetrical systems, the chalcone of Scheme 2 must be derived from the *less reactive* ketone. For example, in the preparation of 2-t-butyl-4,6-diphenylpyrylium (**10**) only the sequence shown (**8**+**9**→**10**) gives the right product. The reverse sequence (Bu^{t}COPh and PhCH:CHCOPh) gives a mixture of **10** with much 2,4,6-triphenylpyrylium resulting from the retro-aldol reaction of the chalcone into acetophenone and benzaldehyde (relevant references are given later in Table 7).



8 9 10

(c) When neither of the above sequences is satisfactory, it is often possible to isolate the symmetrical 1,5-diketone formed from the base-catalysed reaction of the aldehyde with two molecules of ketone (see Ref. 14), or the unsymmetrical 1,5-diketone from one mole of an α,β-unsaturated ketone with one mole of ketone, and to dehydrogenate and ring-close these diketones in a separate step. Triphenylmethyl perchlorate has been used previously as hydride-ion acceptor,[15] and we have also found triphenylmethyl borofluoride and bromine to be useful hydride acceptors giving yields of ~80% of pyrylium salt from the diketone.[16] Recently we have found that chalcone (PhCH:CHCOPh) can be used as a hydride acceptor in pyrylium syntheses for symmetrical and unsymmetrical 1,5-diketones.[17]

References to preferred methods for the preparation of some of the most useful pyrylium salts are collected in Table 1.

Table 1. Preparation of pyrylium salts

Cation	Ref. for preparation of	
	ClO_4^-	BF_4^-
2,4,6-Trimethylpyrylium	a	b
2,4,6-Triphenylpyrylium	c	d
2,3,5,6-Tetraphenylpyrylium	-	54
5,6-Dihydro-2,4-diphenylnaphtho[1,2-b]pyrylium	48	48
5,6,8,9-Tetrahydro-7-phenyldibenzo[c,h]xanthylium	48	48

a A. T. Balaban and C. D. Nenitzescu, Org. Synth. Coll. Vol. V, 1106 (1973).
b A. T. Balaban and A. J. Boulton, Org. Synth. Coll. Vol. V, 1112 (1973).
c J. A. Van Allan and G. A. Reynolds, J. Org. Chem. 33, 1102 (1968).
d K. Dimroth, C. Reichardt and K. Vogel, Org. Synth. Coll. Vol. V 1135 (1973).

(ii) *Anion exchange.* The readily available pyrylium tetrafluoroborates and perchlorates are converted by weak bases into alk-2-en-1,5-diones (pseudo bases). These unsaturated 1,5-diketones react readily with a wide variety of acids to regenerate the pyrylium cation now associated with any required anion. Such reactions generally take place in high yield. Salts of unstable acids (e.g. thiocyanic) can be made using an appropriate ammonium salt and sulphuric acid. Relevant work from our laboratory and from published literature is gathered in Table 2.

II. REACTION OF PRIMARY AMINES WITH PYRYLIUM SALTS TO GIVE PYRIDINIUM COMPOUNDS

1. *Mechanistic pathways*

(i) *Previous work in the literature.* Balaban and Susan[10] studied the reaction of 2,4,6-triphenylpyrylium perchlorate with methylamine, isolated the vinylogous amide intermediate and outlined a probable reaction mechanism. Williams[18] studied the kinetics of the hydrolysis of pyrylium salts to 2-ene-1,5-diones and the reverse reaction has also been examined, [19] but there were no kinetic reports of reactions with amines.

(ii) *Preliminary investigations.* We initially investigated[20] the reaction of 2,4,6-triphenylpyrylium cation with methoxide ion and found that the product was the 2-adduct (11), as shown clearly by ^{13}C NMR. Comparisons with the tris-parafluorophenyl and tris-paramethylphenyl analogues were parti-

Table 2. Pyrylium salts of various anions prepared from 2-ene-1,5-diones

Anion	Method[a]	Yield	Ref.
2,4,6-Triphenylpyrylium			
F_3CSO_3	A	96	b
FSO_3	A	89	b
β-naphthyl-SO_3	A	99	b
$EtOSO_3$	A	85	b
F_3CCO_2	A	72	c
Cl_3CCO_2	A	75	c
NO_3	A	70	c, d
Cl	A	97	e
Br	A	70	f
I	A	99	g
SCN	B	93	h
F	A	88	i
$SnCl_3$	B	80	c
2,4-Diphenyl-5,6-dihydronaphtho-[1,2-b]pyrylium			
F_3CSO_3	A	95	j
Br	A	98	j
SCN	B	85	j
F	A	88	k
5,6,8,9-Tetrahydro-7-phenyldibenzo[c,h]xanthylium			
Br	A	85	j
F	A	80	k

[a] A = pseudo-base, acid; B = pseudo-base, acidic-aqueous solution of the appropriate inorganic salt.

[b] A.M. El-Mowafy, M.Sc. Thesis, University of East Anglia, 1978.

[c] Ref. 39.

[d] Cf. C. Gastaldi, Gazz. chim. Ital. 51 (II), 289 (1921).

[e] Ref. 33, cf. T.C. Chadwick, Anal. Chem. 45, 985 (1973) quotes 96% yield.

[f] Ref. 31, cf. Ref. 15b quotes 27% yield.

[g] Ref. 27b.

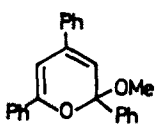
[h] Ref. 49b, cf. A.T. Balaban and M. Paraschiv, Rev. Roumaine Chim. 19 (11), 1731 (1974).

[i] A. Chermprapai, M.Sc. Thesis, University of East Anglia, 1978.

[j] Ref. 48.

[k] Ref. 58.

cularly helpful, and demonstrated that none of the 4-adduct (12) or the open chain compound (13) was formed.



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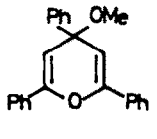

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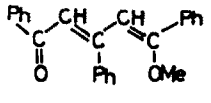

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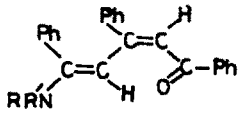
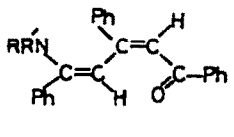


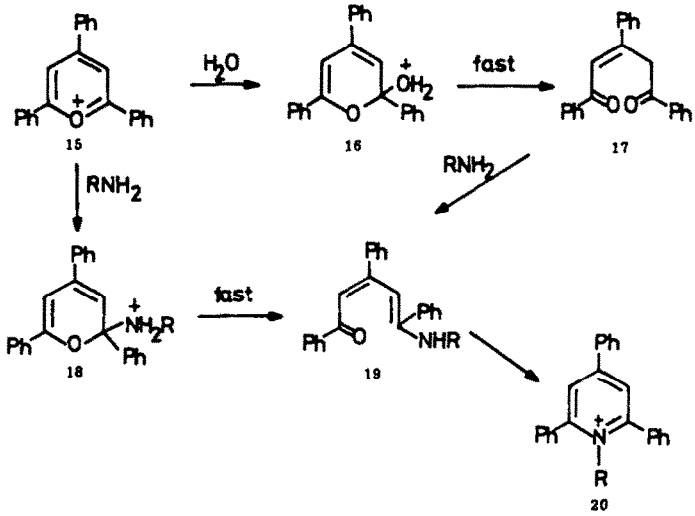
14a



14b

By contrast the reaction of secondary amines with 2,4,6-triphenyl pyrylium cation gave the open-chain vinylogous amide. Significant ^{13}C chemical shift differences suggest that the piperidine compound adopts predominantly structure **14a**, with the pyrrolidine analogue existing mainly as **14b**.[21]

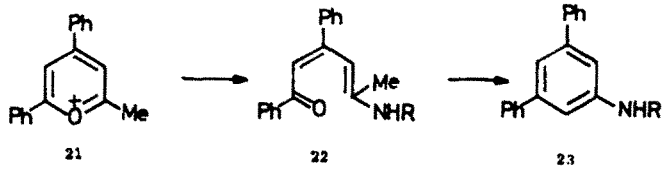
(iii) *^{13}C NMR investigation of reaction of n-butylamine with 2,4,6-triphenyl pyrylium cation.* This reaction is more complex, and the pattern that has now been established by ^{13}C NMR is shown in Scheme 3.[21] Initial reaction of n-butylamine with the pyrylium cation is rapid as is deprotonation and ring-opening: the first product that can be detected after mixing is the vinylogous amide **19**. If the amine:pyrylium ratio is at least 2:1 (one mole of primary amine can be replaced by e.g. NEt_3), then all the pyrylium salt is converted into **19**. However, for lower amine:pyrylium ratios, the diketone **17** (pseudo-base) is also formed, presumably from traces of water present. The vinylogous amide **19** is converted at a measurable rate into the pyridinium salt **20**. The diketone **17**, also reacts with amine to give **20** (probably via **19**), but at a slow rate.



Scheme 3. Reaction of pyrylium salts with amines.

We believe that in this sequence the function of the second molecule of amine is to deprotonate the intermediate **18**: indeed NEt_3 can be substituted for the 2nd mole of amine with identical results.

(iv) *Conversion of 2-alkylpyrylium cations into anilines by primary amines.* 2-Methyl-4,6-diphenyl-pyrylium cation (**21**) reacts with cyclohexylamine to give exclusively the aniline **23** by alternative ring closure of intermediate **22**.[22] Balaban[23] had earlier reported mixtures of the aniline and pyridinium salt in ratios which depended on the bulk of the amine R group, in reactions with 2,4,6-trimethylpyridinium



2. *Ultraviolet investigation of the kinetic dependence of the reaction of pyrylium compounds with primary amines*

(i) *Mechanism of reaction.* UV investigation[24] of the mechanism of reaction confirms and extends the conclusions from the ^{13}C work (Scheme 1). In dichloromethane as a solvent, provided that at least 2 moles of amine are used per mole of pyrylium salt and up to an excess of 10 moles of amine, the rate is independent of the concentration of amine and is first order in pyrylium salt, indicating that the rate determining stage is the ring-closure step **19**→**20**. The reaction **19**→**20** is subject to acid catalysis, the rate being increased by $\sim 10^3$ by the addition of acetic acid to the intermediates.

(ii) *Dependence on solvent.* Relative rates for the reaction of 2,4,6-triphenylpyrylium perchlorate with n-butylamine in various solvents are given in Table 3. Clearly the reaction rate is considerably enhanced in non polar solvents; however, no obvious qualitative correlation was found with solvent characteristics.

Table 3. Relative rates for the reaction of 2,4,6-triphenylpyrylium perchlorate with excess n-butylamine (at 25°) in various solvents[24]

Solvent	PhCl	$(CH_2Cl)_2$	$CHCl_3$	CH_2Cl_2	DMSO	CH_3CN	DMF
Relative rate	22.8	15.6	14.7	13.5	1.6	1.0	0.05

(iii) *Dependence on nature of the anion.* Small but significant variations in rate were found with the anion of the pyrylium salt utilised. Thus for the reaction of 2,4,6-triphenylpyrylium salts with *n*-butylamine (2 moles) in dichloromethane, variations over a factor of ~2 were found (Table 4). This probably reflects ion pair association in the reaction. The absence of large rate effects of the anion is preparatively important.

Table 4. Reaction of 2,4,6-triphenylpyrylium salts with n-$BuNH_2$ (2 moles) at 25° in CH_2Cl_2: dependence on anion[24]

Salt	F^-	BF_4^-	SCN^-	ClO_4^-
k. 10^4 sec^{-1}	4.99	4.57	3.00	2.77

(iv) *Structure of pyrylium salt.* Some rate dependence is found with pyrylium cation structure (Table 5): preparative aspects are presently being studied.[24]

Table 5. Relative rates for the reaction of benzylamine with pyrylium tetrafluoroborates catalysed by acetic acid (0.065 mole) in dichloromethane at 25°[24]

Pyrylium cation substitution	Relative rate	Structure of product
2,4,6-triphenyl	1	24a
2,3,5,6-tetraphenyl	1.4	26
2-methyl-4,6-diphenyl	0.2	24b
6-t-butyl-4-phenyl-[2,3-b]-tetrahydronaphtho	0.3	33
2-(2,3-cyclohexeno)-4,6-diphenyl	1.8	28

(v) *Structure of amine.* Relevant rate data (Table 6) indicate that primary carbylamines react *ca.* 10^2 times faster than secondary carbylamines and that within each of these series steric hindrance has significant influence on the rates. Electronic effects are also significant, as shown by a comparison of the rates for aniline and its *p*- and *m*-nitro derivatives.

Table 6. Relative rates for the reaction of 2,4,6-triphenylpyrylium perchlorate (1 mole) with primary amines (2 moles) at 25° in dichloromethane[24]

R of RNH_2	Mol acetic acid	Rate (k.10^3 sec^{-1})	Relative rate
Et	0.0	2.35	102
n-Bu	0.0	1.73	83
	0.065	7.84	
$PhCH_2$	0.065	6.04	64
i-Pr	0.065	0.0949	1.00
	4.03	5.39	
Cyclo-C_6H_{11}	4.03	3.75	0.70
Cyclo-C_5H_{11}	4.03	3.02	0.56
PhCH(Me)	4.03	1.13	0.21
Ph	4.03	8.86	1.64

3. *Preparative aspects of conversion of amines into pyridinium salts*

(i) *Previous work.* Numerous examples of reactions of pyrylium salts with primary amines are found in the literature; generally the conditions reported are more severe than needed. Guided by the kinetic measurements above, and by experience we recommend the following sets of conditions.

(iii) 2,4,6-*Triphenylpyridiniums.* A slight excess of the amine (say 10%—this can be replaced by 10% of NEt_3) is stirred at 20° with the pyrylium salt in ether or dichloromethane. Other solvents can also be used, e.g. ethanol, but do not give as good results in some cases. For slow reactions, i.e. those involving secondary carbylamines and arylamines, the addition of acetic (or other) acid after the initial mixing helps speed up the reaction to a convenient rate. Typically such reactions are left for 3–12 hours: if ether is used as a solvent the product separates as formed. For other solvents, ether is normally added to give the product.

(iii) *Other pyridiniums.* The conditions described above can be used widely for primary carbylamines and for benzylamines. However, for arylamines increasing steric hindrance necessitates increasingly vigorous conditions.

(iv) *Influence of anions.* The conditions described do not depend in general on the anion: however, this does not apply to chlorides, fluorides, and tosylates. Many of the pyridinium salts of these anions are hygroscopic, and this quality makes them difficult to crystallise. In such cases, use of superdry ethanol or azeotropic removal of water may be needed.

(v) *Survey of pyridinium salts prepared.* Table 7 surveys the salts which have been prepared, classified according to pyridinium cation and anion.

III. MECHANISTIC ASPECTS OF NUCLEOPHILIC DISPLACEMENT OF N-SUBSTITUENTS IN PYRIDINIUM CATIONS

1. *Standard reaction investigated and ultraviolet technique*

Our initial kinetic experiments were carried out with 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate and piperidine, and utilised the ultraviolet technique to follow the disappearance of the pyridinium cation and the appearance of the pyridine. Reactions are 1st order in pyridinium compound, and 1st order in piperidine.[25] For reactions with anionic nucleophiles large salt effects occur, as expected for reactions between charged species,[26] which decrease the apparent second order rate constants markedly at higher concentrations.

2. *Dependence on the solvent*

The reaction of 1-benzyl-2,4,6-triphenylpyridinium perchlorate and tetra-n-butylammonium iodide was studied. For each of the two classes of (a) hydroxylic and (b) non-hydroxylic solvents, log k_2 decreases linearly with solvent dielectric constant. The rate is greater in a non-hydroxylic solvent for equal dielectric constant.[25]

3. *Dependence on the carbon substituents on the pyridinium ring*

The importance of the 2- and 6-phenyl groups in sterically accelerating the N–C bond heterolysis is clear from the relative rate data in Scheme 4. The rate for the 1-benzyl-2,4,6-triphenyl derivative **24a** at 100° with piperidine in chlorobenzene solvent is taken as standard. Replacement of the 2-phenyl group by a 2-methyl in **24b** reduces the rate considerably; when a cyclohexeno substituent occurs in the 2,3-positions (as in **28**) instead of the 2-phenyl then the rate reduction is considerably less ; for the 2,3-cyclopenteno substituent (in **29**) the rate drops again to near that for the 2-methyl analogue **24b**. In addition to the S_N2 mechanism shown by the 1-benzyl-2,4,6-triphenylpyridinium **24a**, some of the other compounds show S_N1 components which complicate precise rate comparisons.

However, an increasing number of substituents in the pyridinium ring does not of itself increase the rate. Thus the 2,3,5,6-tetraphenyl (**26**) and 2,3,4,5,6-pentaphenyl derivative (**27**) both react significantly more slowly than the triphenyl analogue. Introduction of alkyl groups into the 3-position of 2,4,6-triphenylpyridinium also causes rate slowing down as seen in the effect of 3-methyl (**25b**) and 3,5-dimethyl (**25c**) substitution.

The replacement of the 2-phenyl group by a tertiary butyl group in **24c** also slows the rate down, although by a much smaller factor than the corresponding methyl substitution. Replacement of the 2-phenyl group by thienyl (**24e**) or *o*-nitrophenyl (**24d**) has little effect on the rate.

A very significant rate enhancement by a factor of about 60 occurs when one of the phenyl groups in the 2-position is constrained into a more nearly planar situation by a CH_2CH_2 side chain in the tricyclic

Table 7. Preparation of pyridinium from pyrylium salts and amines

Pyridinium cation	Anion	Refs.
2, 4, 6-Trimethyl	ClO_4	a, b, 45, 59
2-Methyl-4, 6-diphenyl	ClO_4	c, 59
2-t-Butyl-4, 6-diphenyl	ClO_4	d, 54
	BF_4	d
2, 6-Di-t-butyl-4-phenyl	ClO_4	d
2, 4, 6-Triphenyl	ClO_4	a, b, c, d, 45, 49, 53, 54, 59, 61
	BF_4	d, 21, 30, 35, 36, 47, 49, 51, 52, 54, 59
	I	a, 27
	Br, Cl	30, 31, 33
	F	35
	SCN	49
	CF_3SO_3	61
2, 4, 6-Tri-(p-fluorophenyl)	BF_4	21
2, 4, 6-Tri-p-tolyl	ClO_4	b, c
2, 3, 5, 6-Tetraphenyl	ClO_4	54
	BF_4	54
2, 3, 4, 5, 6-Pentaphenyl	Br	30, 31
4-(2-Chlorophenyl)-2, 3, 5, 6-tetraphenyl	Br	31
4-(4-Chlorophenyl)-2, 3, 5, 6-tetraphenyl	BF_4	35
	Br	31
4-(4-Methoxyphenyl)-2, 3, 5, 6-tetraphenyl	Br	31
2, 3, 5, 6-Tetraphenyl-4-p-tolyl	Br	31
2, 4-Diphenyl-6-p-tolyl	ClO_4	c
2, 6-Diphenyl-4-p-tolyl	ClO_4	c
7, 8-Benzo-5, 6-dihydro-2, 4-diphenylquinolinium	ClO_4	d
	BF_4	c, d, 35
	SCN	50
	Br	31
5, 6, 8, 9-Tetrahydro-7-phenyldibenzo[c, h] acridinium	ClO_4	d
	Br	31

a A. R. Katritzky, A. Krutošíková, C. A. Ramsden, and J. Lewis. Coll. Czech. Chem. Comm., 43, 2046 (1978).

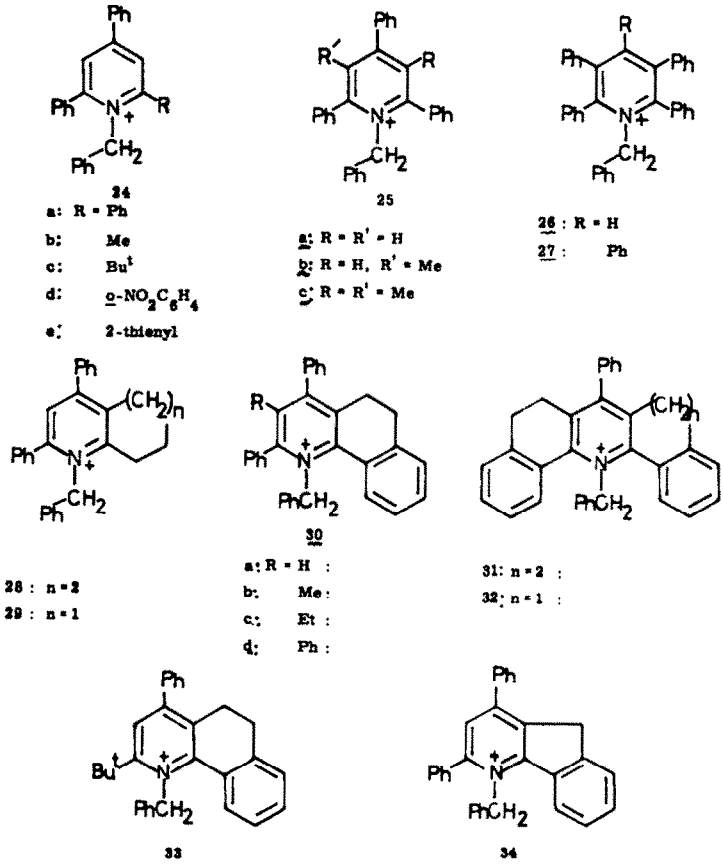
b A. R. Katritzky, C. A. Ramsden, Z. Zakaria, R. L. Harlow and S. H. Simonsen. J. Chem. Soc. Chem. Comm. 383 (1979); Ibid, in preparation for J. Chem. Soc. Perkin I.

c A. R. Katritzky, Z. Zakaria, E. Lunt, P. G. Jones, and O. Kennard J. Chem. Soc. Chem. Comm. 288 (1979); Ibid., in preparation for J. Chem. Soc. Perkin I.

d A. R. Katritzky and S. S. Thind, in preparation for J. Chem. Soc. Perkin I.

derivative **30a**. When this constraint is done for both the 2- and the 6-phenyl groups in **31**, the rate enhancement is about 1000 (see Scheme 4). Again in the tricyclic system **30** the presence of an additional substituent in the vacant position has a deleterious effect and the rates for the 3-methyl, 3-ethyl, and 3-phenyl compounds (**30b, c, d**) are each much less than that for the unsubstituted analogue (**30a**).

If instead of the ethano group we use a single CH_2 as a linking unit, then the rate enhancement is much less, as is shown in compounds **32** and **34**.



Scheme 4. Compounds used for kinetic studies (at 100°, piperidine, chlorobenzene solvent).

We have also investigated inductive effects on kinetic rates. One series is shown in Table 8: various substituents are placed in the 4-phenyl ring. The relative rates show clearly that electronic effects are relatively modest.

Table 8. Reaction of 1-benzyl-4-aryl-2,6-diphenylpyridinium tetrafluoroborates with piperidine: rate dependence on aryl group

4-(Substituted phenyl)	H	p-Me	p-F	p-Cl	p-Br	m-Cl	p-OMe	m-NO_2
Relative rate	1.00	0.9	1.2	1.5	1.5	1.4	0.7	1.6

4. *Dependence on the N-substituent*

As seen in Table 9, aliphatic N-substituents are transferred more slowly than benzyl to piperidine. The rate depression is least for methyl and greater for other n-alkyl groups.

Table 9. Relative rates for reaction of N-substituted-2,4,6-triphenylpyridinium tetrafluoroborates with piperidine in chlorobenzene[25]

N-Substituent	Me	Et and n-C_6H_{11}	$PhCH_2$
Relative rate	0.13	<0.01	1

5. *Dependence on displacing nucleophile*

The influence of steric hindrance is shown in Table 10.

Table 10. Relative rates for the reaction of 1-benzyl-2,4,6-triphenylpyridinium perchlorate with amine nucleophiles at 100° in chlorobenzene[25]

Nucleophile	Piperidine	Substituted pyridines		
		H	2-Me	2,6-diMe
Relative rate	10^4	65	16	5

IV. PREPARATIVE ASPECTS OF NUCLEOPHILIC DISPLACEMENTS OF N-SUBSTITUENTS IN PYRIDINIUM RINGS

1. *Replacement by halogen*

(i) *The conversion of aliphatic, aromatic and heteroaromatic primary amines into iodides.* 2,4,6-Triphenylpyrylium iodide reacts with aliphatic, aromatic and heterocyclic amines to give pyridinium salts in high yields.[27] For the aliphatic amines, ether was found to be a useful solvent; for the less nucleophilic amines reaction was attained in refluxing ethanol. On heating at temperatures between 135 and 180°, for aliphatic and benzyl derivatives, and at 200–300° for aromatic and heteroaromatic derivatives, the pyridinium iodides decomposed smoothly into 2,4,6-triphenylpyridine and the iodides corresponding to the original amines. Table 11 shows the wide range of compounds to which this method is applicable together with the yields over the two stages.

Table 11. Preparation of iodides (RI) by thermolysis of N-substituted-2,4,6-triphenylpyridinium iodides[27b]

R	n-Alkyl		2-Alkyl		Allyl	$(CH_2)_3OH$	α,ω-Di		Subst. benzyl		
	C2	C4	C3	C4			C4	C5	H	p-Me	p-Cl
Yield (%)	83	78	79	83	85	78	85	81	58	65	52

Subst. phenyl			m-Phenylene di	Subst. 2-pyridyl			Subst. 2-thiazolyl	
H	p-Me	p-Cl		H	3-Me	4-Me	H	4,5-Benzo
75	78	77	70	75	71	62	72	85

Useful preparative techniques for the conversion of non-diazotizable primary amines into iodides have previously been rare. N-Hexylamine was converted into the N,N-di-*p*-nitrobenzenesulphonyl derivative which gave N-hexyl iodide on nucleophilic displacement with KI, but this reaction was not generalised.[5] A recent method for the conversion of pyridylamines to the corresponding pyridyl iodides has involved heating the intermediate nitramines with phosphorus iodides.[28] Of course the conversion of anilines via benzenediazonium salts into iodobenzenes is generally applicable to diazotizable aromatic amines, but fails for example for metaphenylenediamines.[29] As discussed above, 1-methyl-2,4,6-triphenylpyrylium iodide had previously been pyrolysed by Balaban and Susan.[10]

(ii) *Conversion of primary alkyl and benzylamines into bromides.* Our initial work[30] showed that primary alkyl- and benzyl-amines reacted readily with 2,4,6-tri- and 2,3,4,5,6-pentaphenylpyrylium bromide to give the corresponding pyridinium bromides. The latter were pyrolysed at their melting point which gave bromides in an average yield of 60% in the triphenyl series; in the pentaphenyl series the higher melting points made the reaction less successful.

Later,[31] we showed that use of triphenylpyridine as a flux decreased the fusion and decomposition temperatures considerably: for the 2,4,6-triphenyl series and for the 2,3,5,6-tetraphenyl-4-*p*-chlorophenyl series the pyrolysis yields now averaged 80% (Table 12). However, attempts to prepare aryl and heteroaryl bromides in this way failed.

Table 12. Preparation of 1-substituted-4-(*p*-chlorophenyl)-2,3,5,6-tetraphenylpyridinium and 1-substituted-2,4,6-triphenylpyridinium bromides and pyrolysis to alkyl bromides[31]

Series	Yield (%)	Et	n-Bu	$PhCH_2CH_2$	$PhCH_2$	p-$MeC_6H_4CH_2$	p-$ClC_6H_4CH_2$
p-Chlorophenyl	pyridinium	86	75	-	88	73	86
	RBr	97	75	-	75	72	79
Triphenyl	pyridinium	-	-	83	-	74	83
	RBr	-	-	78	-	80	79

Few other methods are available for the conversion of primary aliphatic amines into bromides, but recently conversion via a triazene has been used to give yields of around 60% although olefins and secondary amines are formed as side products.[32]

(iii) *Conversion of primary alkyl and benzylamines into chlorides.* Our first procedure for this conversion[30] involved initial preparation of pyridinium tetrafluoroborates formed by reaction of the primary amines with 2,4,6-triphenylpyrylium tetrafluoroborate and pyrolysis of these salts with the KCl–NaCl–$ZnCl_2$ eutectic (m.p. 203°) at 200–240° when the corresponding alkyl or benzyl chloride distills out in yields of around 50%.

We had used this method of an external chloride nucleophile because initially we found it difficult to prepare the 2,4,6-triphenylpyridinium chlorides from the primary amine and 2,4,6-triphenylpyrylium chloride. However, it transpires that this reaction in fact goes readily[24] but that in order to get the pyridinium chloride to crystallise it is necessary to remove the water by azeotropic distillation.[33] When this was done it was found that thermolysis of the N-benzylpyridinium chlorides occured even below 100°, and for the N-alkyl compounds was complete in 20 minutes at 120–130° to produce the corresponding benzyl and alkyl halides in excellent yields. Details are given in Table 13.

Table 13. Thermolysis of N-substituted-2,4,6-triphenylpyridinium chlorides to alkyl and benzyl chlorides[33]

R	n-Alkyl			Subst. benzyl			
	C4	C7	C8	H	p-Me	o-Cl	p-Cl
Yield %	98	98	99	97	98	54[a]	86

[a] Reaction occurs in solution.

The most general previously available method for the conversion of primary and secondary alkyl amines into chlorides has been the von Braun acylation, and subsequent treatment with phosphorus pentachloride which has certain disadvantages.[34]

(iv) *The preparation of alkyl and benzyl fluorides from the corresponding primary amines.* Stable 2,4,6-triphenylpyrylium fluoride reacts under carefully defined conditions (continuous removal of water by azeotroping out with benzene and ethanol) with a variety of alkyl and benzyl primary amines to give the corresponding pyridinium fluorides as stable crystalline solids.[35] The melting points of these pyridinium fluorides lie in the range 80–120° and on heating to just above melting, the N-alkyl and N-benzyl derivatives decompose smoothly to give the corresponding fluorides. It is essential that fluorides are quite dry before pyrolysis (one week drying in vacuum was needed). Yields over the two stages are given in Table 14. Heating the tetrafluoroborate salts with KF and triphenylpyridine as flux gives some fluoride, but the yields are poor and the product is contaminated with hydrocarbon.

Table 14. Conversion of amines RCH_2NH_2 and bis-amines $[NH_2(CH_2)_nNH_2]$ into fluorides and α,ω-difluorides via the 2,4,6-triphenylpyridinium fluorides[35]

R	n-Alkyl			Bis-			Benzyl			
	C7	C8	C11	$(CH_2)_4$	$(CH_2)_5$	$(CH_2)_6$	H	p-Cl	o-Cl	2,4-DiCl
Yield of intermediate (%)	82	78	85	83	85	86	78	82	72	86
Yield of RF (%)	65	42	55	48	49	52	82	85	67	61

Previously no convenient method for the conversion of non-diazotisable primary amines into fluorides has been available, in contrast to the widely used Schiemann conversion of primary aromatic amines into aryl fluorides.

2. *Nucleophilic displacements by oxygen and sulphur nucleophiles*

(i) *Conversion of amines into esters and alcohols.* N-Alkyl and N-benzyl-2,4,6-triphenylpyridinium tetrafluoroborates when heated with an intimate mixture of sodium acetate, sodium benzoate, or sodium butyrate, to 180–220° together with a quantity of 2,4,6-triphenylpyridine which acts as a flux, yield the corresponding esters (Table 15).[36] Such reactions proceed in acetic acid at 100° if the more reactive pentacyclic system (see 31) is used. The hydrolysis of esters to alcohols proceeds in high yield.[37]

Table 15. Conversions of N-substituted 2,4,6-triphenylpyridinium tetrafluoroborates into acetate (CH_3CO_2R) and benzoate esters ($PhCO_2R$)[36b]

R	n-Alkyl			Subst. benzyl		$PhCH_2CH_2$	Picolyl	
	C1	C2	C4	H	o-Me		2	3
Yield of acetate (%)	65	79	75	70	70	70	60	78
Yield of benzoate (%)	70	60	85	85	-	-	68	75

Although elementary texts frequently show the conversion of primary amino compounds into their hydroxy analogues as being achieved by nitrous acid, in reality the products from such reactions of aliphatic amines are usually complex.[38] Previously, primary amine ditosyl derivatives have been converted into corresponding acetates by potassium acetate in hexamethylphosphoramide as solvent.[4]

More recently we have shown that 2,4,6-triphenylpyrylium trifluoroacetate reacts readily with primary amines to give the corresponding pyridinium trifluoroacetates as stable crystalline salts, which decompose on gentle thermolysis (~160°) to give the easily hydrolysable trifluoroacetate esters in high yield.[39]

(ii) *Conversion of primary amines into nitrate esters.* Nitrate esters can be prepared from alcohols by O-nitration with mixed nitric–sulphuric acid[40] (which requires elaborate safety precautions) or transfer nitration with N-nitrocollidinium tetrafluoroborates,[41] or by metathesis of the corresponding alkyl halides.[42] No general method for the conversion of primary carbylamines into nitrate esters has been previously reported: deamination with dinitrogen tetroxide[43] was limited to three examples.

N-Alkyl-2,4,6-triphenylpyridinium nitrates are easily prepared by the reaction of 2,4,6-triphenylpyrylium nitrate with primary amines, and their pyrolysis, under vacuum, leads to pure alkyl nitrate esters, in good yields (Table 16).[39]

Table 16. Conversion of primary alkyl amines RNH_2 to alkyl nitrates $RONO_2$ via 1-alkyl-2,4,6-triphenylpyridinium nitrates[39]

R		$PhCH_2$	p-$ClC_6H_4CH_2$	p-$MeC_6H_4CH_2$	n-C_6H_{13}
Yield (%)	Pyridinium salt	70	86	90	85
	$RONO_2$	85	60	73	68

(iii) *Conversion of primary amines into ethers.* 1-Benzyl - 2,4,6 - triphenylpyridinium tetrafluoroborate reacts with sodium-β-naphthoxide in refluxing dioxane with tetra-*n*-butylammonium bromide as a phase transfer agent to yield benzyl-β-naphthyl ether (71%).[44] 3- and 4-Picolylamine have also been converted via reaction of the corresponding 2,4,6-triphenylpyridinium cations with sodium phenoxide into the corresponding picolyl phenyl ethers.[45]

(iv) *Conversion of primary amines into aldehydes.* The pyrolysis of N-substituted 2,4,6-triphenylpyridinium tetrafluoroborates with sodium 1 - oxido - 4,6 - diphenyl - 2 - pyridone[46] affords a conversion of amines into aldehydes (Table 17) under neutral and non-oxidative conditions.[47]

Table 17. Conversion of amines RCH_2NH_2 into aldehydes RCHO[47]

R	n-Alkyl		Vinyl	Substituted phenyl				Pyridyl		
	C3	C7		H	4-Me	2-Cl	2,4-Cl_2	2	3	4
Yield %	20	3	9	47	59	42	36	27	42	32

1 - Benzyl - 2,4,6 - triphenylpyridiniums are oxidized to substituted benzaldehydes by $K_2Cr_2O_7$ in the presence of n-$Bu_4N^+BF_4^-$ in refluxing 1,2-dichloroethane. The yields are substantially increased by the use of 1 - benzyl - 2,4 - diphenyl - 5,6 - dihydrobenzo[h]quinoliniums.[48]

(v) *Conversion of primary alkyl, benzyl and aryl amines into thiocyanates.* Primary amines react readily with 2,4,6-triphenylpyrylium thiocyanate to form the corresponding 1 - substituted - 2,4,6-triphenylpyridinium thiocyanates.[49] In the case of the 1-alkyl and 1-benzyl derivates these, on heating with triphenylpyridine as a flux, smoothly decompose to give the corresponding alkyl and benzyl-

thiocyanates in high yields (Table 18). These thiocyanates contain only very small quantities of the corresponding isothiocyanates.

Table 18. Preparation of alkyl thiocyanates (RSCN) by thermolysis of 1-substituted 2,4,6-triphenylpyridinium thiocyanates[49b]

R	n-Alkyl					i-Butyl	$(CH_2)_3OH$	Subst. benzyl		$PhCH_2CH_2$
	C1	C2	C3	C4	C5			H	p-Me	
Yield %	95	90	81	87	82	87	67	83	84	65

The 1-aryl-2,4,6-triphenylpyridinium thiocyanates on thermolysis give only low yields of the corresponding aryl thiocyanates. However good yields of aryl thiocyanates were obtained by the thermolysis (using the KSCN–NaSCN eutectic as flux) of N-aryl-dihydrobenzoquinolinium thiocyanates at 220° (Table 19).[50]

Table 19. Preparation of substituted phenyl thiocyanates (XC_6H_4SCN) by thermolysis of 1 - aryl - 2,4 - diphenyl - 5,6 - dihydrobenzo[h]quinolinium thiocyanates[50b]

X	H	m-Cl	p-Cl	m-Me	p-Me	p-OMe	$m-NO_2$	3-Cl-4-Me
Yield (%)	98	94	88	72	84	96	60	80

(vi) *Reaction of ethyl xanthate anion with pyridinium salts.* N-Alkyl-2,4,6-triphenylpyridinium perchlorates or tetrafluoroborates undergo nucleophilic substitution to yield the corresponding O - ethyl - S - alkyl dithiocarbonates on refluxing with potassium ethyl xanthate in benzene. No reactions occur with these N-alkyl salts in ethanol, but the more reactive 1-benzyl analogues on refluxing in ethanol readily give the dithiocarbonates in good yield (Table 20).

Table 20. Preparation of alkyl and benzyl ethyl xanthates (RSCSOEt) from 1-substituted 2,4,6-triphenylpyridinium perchlorates[49b]

R	n-Alkyl			Substituted benzyl			
	C1	C2	C4	H	p-Me	p-Cl	p-OMe
Yield (%)	40	64	80	73	84	81	88

(vii) *Reaction with thiourea.* Thiourea and NN'-dimethylthiourea react with 1-substituted 2,4,6-triphenylpyridiniums and 2,4 - diphenyl - 5,6 - dihydrobenzo[h]quinoliniums in refluxing chlorobenzene to give the corresponding S-alkyl and S-benzyl thiouronium salts (>85%), which are readily hydrolysed to the thiols.[48]

(viii) *Reaction with sulphinite anion.* 1 - (4 - Pyridylmethyl) - 2,4,6 - triphenylpyridinium perchlorate reacts in refluxing ethanol with sodium toluene-*p*-sulphinate to give (4-pyridylmethyl)*p*-tolyl sulphone in high yield.[45]

3. *Reactions with nitrogen and phosphorus nucleophiles*

(i) *Reaction of 1-substituted pyridinium salts with sodium succinimide and potassium phthalimide.* These reactions take place readily on heating the pyridinium salt with triphenylpyridine as flux to give the corresponding N-substituted succinimides and phthalimides in yields around 75% (Table 21).[51]

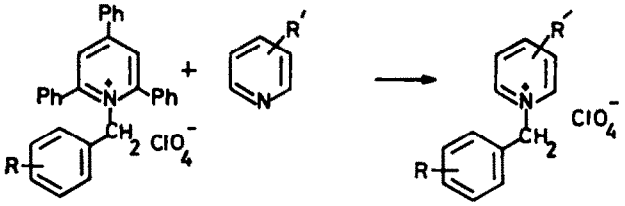
Table 21. Preparation of N-substituted succinimides, phthalimides, and benzenesulphonamides from N-substituted 2,4,6-triphenylpyridinium tetrafluoroborates[51]

N-Substituent	n-Alkyl					Pr^i	$PhCH_2$	$o-ClC_6H_4CH_2$
	C1	C2	C3	C4	C6			
Yield of succinimide (%)	75	66	64	90	65	-	80	-
Yield of phthalimide (%)	75	75	86	-	60	-	98	65
Yield of N-phenylbenzene-sulphonamide (%)	69	71	75	65	-	33	65	-
Yield of N-ethylbenzene-sulphonamide (%)	38	42	-	-	-	-	48	-

(ii) *Reaction with sodium salts of N-substituted sulphonamides.* These also occur in triphenylpyridine as flux: series of N - substituted - N - phenyl- and N - substituted - N - ethyl - benzenesulphonamides were prepared in this way (Table 21).[51] This reaction provides a method of conversion of primary into secondary amines by hydrolysis of the sulphonamide derivatives formed.

(iii) *Conversion of primary into tertiary amines.* 1 - Benzyl - 2,4,6 - triphenylpyridinium perchlorate reacts with secondary amines such as piperidine or morpholine, to give the corresponding tertiary amines in high yield without complications arising from the formation of quaternary salts. This is attributable to unfavourable steric interactions in the transition state. The 2- and 6-phenyl groups not only sterically accelerate the loss of the 1-benzyl group, but also shield it at the same time from the approach by bulky nucleophiles, thus the selectivity of the reaction is high. Similar reactions have been achieved with 2-, 3-, and 4-pyridyl methyl groups as 1-substituents in 2,4,6-triphenylpyridinium cations in reactions with secondary amines.

(iv) *Conversion of primary amines into quaternary salts.* 1-Substituents in 2,4,6-triphenylpyridinium salts are readily transferred to tertiary amines by heating with pyridine or its 2- or 4-Me derivatives.[45] Such reactions are illustrated in Scheme 5.



R	H	p-Me	p-Cl
Yield with pyridine as nucleophile	88	94	92

R'	2-Me	3-Me	4-Me
Yield with N-benzyl-pyridinium as substrate	90	72	81

Scheme 5. Conversion of primary amines to quaternary salts.

(v) *Conversion of primary amines into azides.* 1-Substituted 2,4,6-triphenylpyridinium salts react with sodium azide in dimethylformamide at 130° to yield alkyl and benzyl azides in high yields (see Table 22).[51]

Table 22. Preparation of azides from 1-substituted 2,4,6-triphenylpyridinium tetrafluoroborates[51]

R	n-Alkyl C5	n-Alkyl C8	$PhCH_2$	$Ph(CH_2)_2$	p-$MeC_6H_4CH_2$	o-$ClC_6H_4CH_2$	2,4-$Cl_2C_6H_3CH_2$
Yield azide (%)	74	65	85	73	73	77	69

(vi) *Reaction with triphenylphosphine.* 1 - Benzyl - 2,4,6 - triphenylpyridinium perchlorate reacts with triphenylphosphine to form the phosphonium perchlorate in quantitative yield, and similar reactions were discovered for the 2- and 4-picolyl analogues.[45] This reaction offers in principle a route to Wittig reagents.

4. *Reactions with carbon nucleophiles*

(i) *Nucleophilic displacements with malonate and analogous anions.* 1 - Benzyl - 2,4,6 - triphenylpyridiniums and 1 - benzyl - 2,4 - diphenyl - 5,6 - dihydrobenzo[h]quinoliniums react with sodio derivatives of diethyl malonate, ethyl cyanoacetate and ethyl phenylacetate in refluxing dioxane or 1,2-dimethoxyethane to give the corresponding monobenzylated esters ($\geq 70\%$). These reactions fail as

preparative methods for C-alkylation but N - alkyl - 7 - phenyl - 5,6,8,9 - tetrahydrodibenzo[c, h]acridiniums are sufficiently reactive and give high yields of diethyl alkylmalonates and ethyl alkylcyanoacetate in refluxing xylene.[48]

(ii) C-*Alkylation of nitronate anions.* Although nitronate anions are normally O-alkylated, we find that 1 - substituted - 2,4,6 - triphenylpyridinium cations react regiospecifically with simple nitronate anions to give the corresponding C-alkylated nitro compounds in yields which average 60% (see Table 23): benzylations proceeded in ethanol, for the alkylations dimethyl sulphoxide was preferable. At least some of these reactions probably involve a radical mechanism.[52]

Table 23. Yields (%) of C-alkylation products (RCH_2NO_2, $RCHMeNO_2$ and $RCMe_2NO_2$) of nitronate anions with N-substituted-2,4,6-triphenylpyridinium tetrafluoroborates[52b]

Anion of	N-Substituent of pyridinium cation					
	n-Butyl	n-Hexyl	Benzyl	p-Methylbenzyl	p-Chlorobenzyl	2,4-Dichlorobenzyl
Nitromethane	-	-	76	68	62	52
Nitroethane	46	38	53	54	57	35
2-Nitropropane	73	62	41	-	-	-

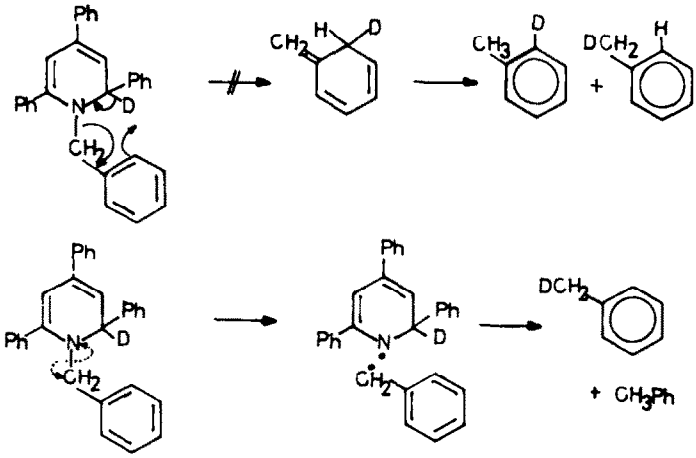
5. *Replacement of amino group by hydrogen*

(i) *Conversion of* N-*allyl,* N-*benzyl and* N-*heteroarylmethyl amines to the corresponding hydrogen compounds.* N-Substituted 2,4,6 - triphenylpyridinium salts are reduced by borohydride in good yield to the 1,2-dihydro derivatives. The behaviour of these compounds on heating depends on the nature of the N-substituent. If this is allyl, benzyl or heteroarylmethyl then the dihydropyridines decompose smoothly at around 200° to give 2,4,6-triphenylpyridine and the compound in which the original amino group has been replaced by an H atom (Table 24).[53]

Table 24. Yields of deaminated products (RCH_3) from the thermolysis of 1-(substituted methyl)-2,4,6-triphenyl-1,2-dihydropyridines[53a]

R	CH_2:CH	Ph	2-Furyl	2-Pyridyl	4-Pyridyl
Yield (%)	81	75	82	75	77

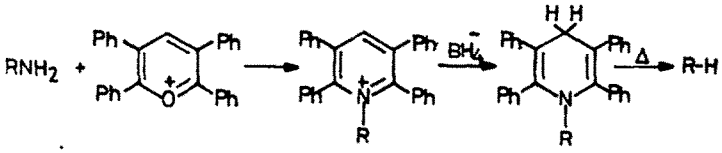
The mechanism of this reduction has been investigated by deuterium labelling for the case of the N-benzyl substituent. Heating the 2 - deuterio - 1,2 - dihydropyridine gives only ω-and no 2-monodeuteriotoluene as shown most convincingly by deuterium NMR. This strongly points to a radical mechanism for the reaction as the electrocyclic mechanism should give a mixture of *ortho*- and ω-deuterio derivatives (Scheme 6).[54] On the other hand, for an N-allyl type substituent the reaction may take an electrocyclic course.[55]



Scheme 6. Mechanism of deamination reaction.

By contrast 1 - aryl - 2,4,6 - triphenyl - 1,2 - dihydropyridines are thermally very stable compounds. 1 - Alkyl - 2,4,6 - triphenyl - 1,2 - dihydropyridines, although they decompose fairly readily on thermolysis, give a complex mixture of products.[53c]

(ii) *Conversion of primary alkylamines into the corresponding hydrocarbons.* Alkylamines react readily with 2,3,5,6-tetraphenylpyrylium cations to yield the corresponding pyridinium salts. These compounds are reduced regiospecifically by sodium borohydride to the 1,4-dihydropyridines; steric hindrance directs the attack by the borohydride nucleophile into the 4-position. In contrast to the 1,2-dihydro analogues mentioned above, these N-alkyl-1,4-dihydropyridines thermolyse smoothly at 180–200° to give the corresponding alkanes in synthetically useful overall yields (Scheme 7 and Table 25.[54]



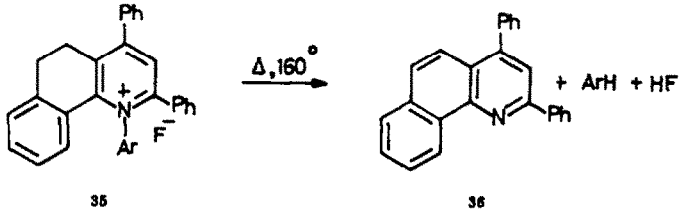
Scheme 7. Conversion of primary alkylamines into hydrocarbons.

Table 25. Yields of deaminated products (RH) from the thermolysis of 1-substituted-2,3,5,6-tetraphenyl-1,4-dihydropyridines[54]

R	n-C_6H_{13}	n-C_8H_{17}	Ph	$PhCH_2$	$Ph(CH_2)_2$	p-$ClC_6H_4CH_2$
Yield (%)	58	88	54	44	64	62

Few general methods are available for the transformation of saturated primary amines into corresponding hydrocarbons. One sequence used by Nickon *et al.*[56] has involved the reaction of sodium derivatives of sulphonamides with hydroxylamine-O-sulphonic acid salts, and another general method[57] enables the conversion in one step but utilises the difficulty available reagent difluoroamine (HNF_2). A third more recent method[6] is the reduction of N,N-disulphonimides with sodium borohydride.

(iii) *The conversion of primary arylamines into the corresponding hydrocarbons.* The method described above for saturated alkylamines can be applied to arylamines but very high temperatures of around 300° are required and the yields are variable. However, we have recently discovered that N - aryl - 2,4 - diphenyl - 5,6 - dihydrobenzo[h]quinolinium fluorides when heated at 160° give the corresponding arenes (**35** → **36**) in yields around 60% (Table 26). The mechanism of this reaction is not yet settled but is probably of radical type.[58]



35 36

Table 26. Reductive deamination of primary arylamines via N - substituted - 2,4 - diphenyl - 5,6 - dihydrobenzo[h]quinolinium fluroides[58]

N-Substituent (R)	C_6H_5	p-Cl-C_6H_4	p-Br-C_6H_4
Yield (%) RH	60	57	62

6. *Ring formation reactions using pyridinium salts*

Very little work has yet been carried out in this area: although initial attempts to prepare three-membered rings were only partially successful,[59] later work indicates that the intramolecular ring-closure of amines containing a nucleophilic group elsewhere in the molecule via pyridinium cations can give high yields.[60] Further work is planned.

7. Preparative advantages of transformations of amines mediated by pyrylium salts

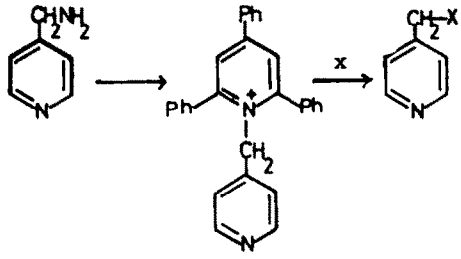
(i) *General advantages.* Obviously where an amino derivative is more readily available then a hydroxy compound or the halogen analogue, reactions of the types mentioned will be of considerable value. This applies, for example, to some amino acids and to certain natural products containing amino groups.

A second advantage lies in the greater selectivity of the reaction. The special steric factors not only accelerate the cleavage of the CN bond, but also hinder the approach of the nucleophile to the electrophilic centre and thus increases selectivity. An example was given in the discussion of the reactions of N-substituted pyridinium cations with secondary amines to give tertiary amines uncontaminated with quaternary salts (Section IV. 3. iii).

A third advantage of the reaction is that certain transformations are enabled with it which are otherwise not possible, for example, the C-alkylation of nitronate anions (Section IV. 4. ii).

In addition to these general advantages, certain specific advantages apply if the corresponding halogeno compounds are unstable or unpleasant to work with. Sections dealing with three examples of this now follow.

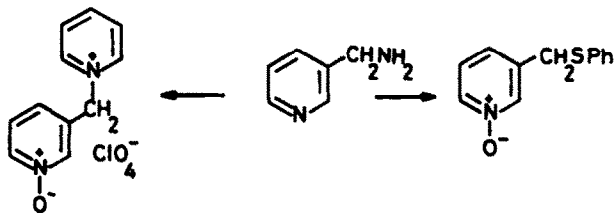
(ii) *The preparation of pyridylmethyl derivatives.* The pyridylmethyl halides are very unstable compounds which readily polymerise and also possess unpleasant physiological properties. Their use in the preparation of ω-substituted picolines can be avoided for each of 2-, 3- and 4-picolylamine is readily converted into the corresponding 2,4,6-triphenylpyridinium cation and these react with a wide variety of anionic and neutral nucleophiles to afford the desired ω-substituted 2-, 3- and 4-picolines in good yields (Scheme 8).[45]



X	pyridine,	morpholine,	4-picoline	$(Ph)_3P$	piperidine
Yield (%)	75	70	70	71	82
X	PhO^-,	PhS^-,	p-Me $C_6H_4SO_2$		isoquinoline
Yield (%)	75	76	82		83

Scheme 8. Preparation of 4-picolyl derivatives.

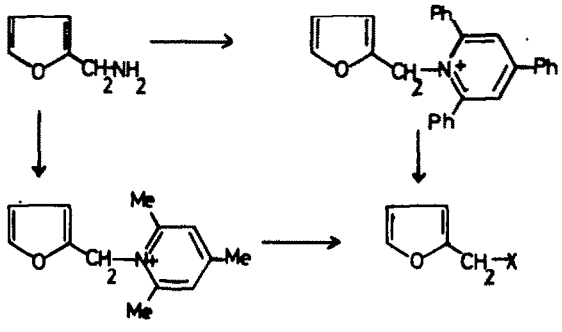
(iii) *Preparation of ω-substituted picoline* N-*oxides.* The 1 - (3 - picolyl-) and 1 - (4 - picolyl) - pyridinium cations mentioned in the preceding paragraph are oxidised by *m*-chloroperbenzoic acid into the corresponding N-oxides in high yield. These N-oxides now undergo the familiar nucleophilic displacement reactions to yield ω-substituted picoline N-oxides (see Scheme 9).[61] 3- and 4-Phenylthiomethylpyridine 1-oxides prepared in this way would be difficult to make by other methods.



Scheme 9. Preparation of 3-picolyl 1-oxides.

(iv) *Preparation of furfuryl derivatives.* Although the chloride is more stable than other furfuryl halides,[62] it polymerises on heating and cannot be stored for long periods, further it has a tendency to give 5-substituted products[63] by what are effectively S_N2' reactions.

In contrast furfurylamine is stable and readily available and is converted into the 2,4,6-triphenyl- and 2,4,6 - trimethyl - pyridinium salts by the appropriate pyrylium.[64] Both pyridiniums react readily with a range of nucleophiles to yield a wide variety of 2-furfuryl derivatives (see Scheme 10).



Nucleophile	Yield (triMe)	Yield (triPh)	Nucleophile	Yield (triPh)
Pyridine	94	90	Triphenylphosphine	98
α-Picoline	76	70	Quinoline	80
γ-Picoline	97	95	Diethylamine	63
Piperidine	55	75	Na thiophenate	55
Morpholine	67	78	Na phenate	53

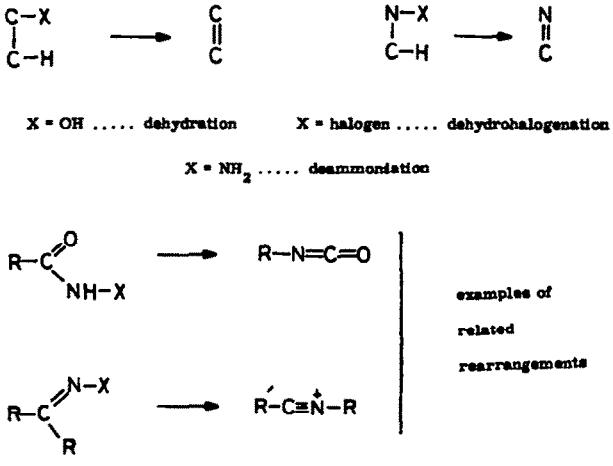
Scheme 10. Preparation of 2-furylmethyl derivatives.

In addition, the 2,4,6-triphenylpyridiniomethyl group also protects the furan ring in electrophilic substitution: 1 - furfuryl - 2,4,6 - triphenylpyridinium undergoes bromination smoothly to yield the 5'-bromo derivative (85%), which now reacts with nucleophiles to form the corresponding 5-bromofurfuryl derivatives.[64]

V. ELIMINATION AND FRAGMENTATION REACTIONS OF N-SUBSTITUTED PYRIDINIUM COMPOUNDS

1. *The concept of deammoniation*

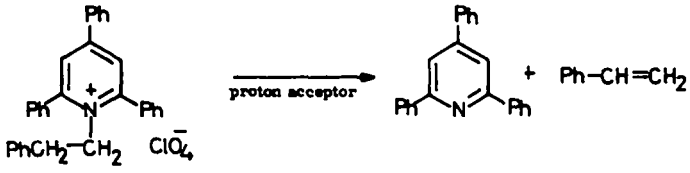
Whereas the concepts of "dehydration" and "dehydrohalogenation" are very familiar, that of "deammoniation", i.e. the loss of a molecule of NH_3, is not at all. In Scheme 11, these concepts are compared. Most dehydrations require a "dehydrating agent": it is the same for deamination: we can consider pyrylium salts to be "deammoniating agents" in this context.



Scheme 11. Deammoniation.

2. *Deammoniation without rearrangement*

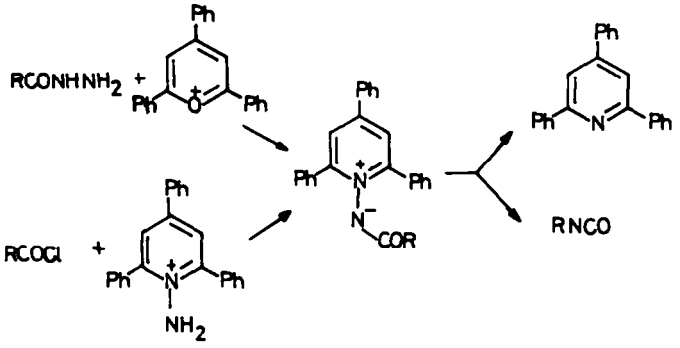
(i) *The preparation of olefines.* Reactions of type **37** → **38** + **39** offer considerable promise; our investigations in this area are proceeding.



37 38 39

3. *Deammoniation with rearrangement*

(i) *The preparation of isocyanates.* The reactions of Scheme 12 offer an alternative to the Curtius preparation of isocyanates from acid hydrazides or acid chlorides, avoiding the use of nitrous acid and azides. The yields are high (Table 27).[65]



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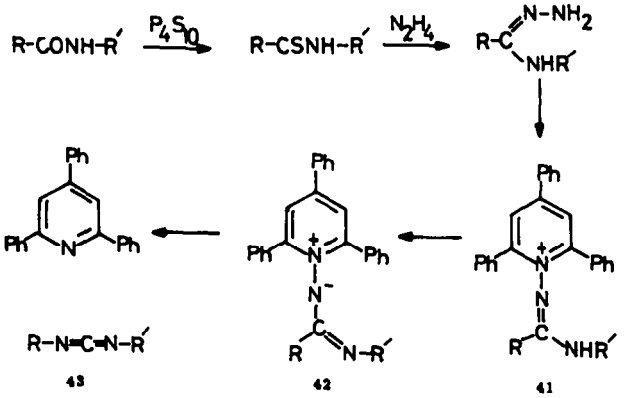
Scheme 12. Alternative to Curtius reaction.

Table 27. Preparation of isocyanates (RNCO) by thermolysis of acylimides (**40**)[65b]

R	Ph	p-MeC_6H_4	p-$MeOC_6H_4$	PhCH:CH	$PhCH_2$	n-Pr	p-ClC_6H_4
Yield (%)	86	95	93	90	76	94	89

(ii) *The preparation of carbodiimides.* Most methods for the preparation of carbodiimides start from *amines*: most reactions which start from carboxylic acid derivatives are of minor synthetic utility (exception: the thermolysis of 1,2,3,5-oxathiadiazole 2-oxides):[66] e.g. the pyrolysis of 1,5-diaryltetrazoles[67] is preparatively limited to *symmetrical* carbodiimides as disproportionation occurs. The sequence of Scheme 13 is a useful addition to methods for the preparation of unsymmetrical diarylcarbodiimides in good yield (Table 28).[68]



43 42 41

Scheme 13. Preparation of carbodiimides.

Table 28. Preparation of carbodiimides PhN=C=NC$_6$H$_4$X (see Scheme 13)[66b]

X	H	p-Me	p-Cl	p-MeO	o-Me	o-Cl
Yield of 41 (%)	92	89	90	90	93	90
42	87	92	85	87	90	92
43	86	96	95	95	92	95

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