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PYRIDINES AS LEAVING GROUPS IN SYNTHETIC TRANSFORMATIONS: NUCLEOPHILIC DISPLACEMENTS OF AMINO GROUPS, AND NOVEL PREPARATIONS OF NITRILES AND ISOCYANATES[1]

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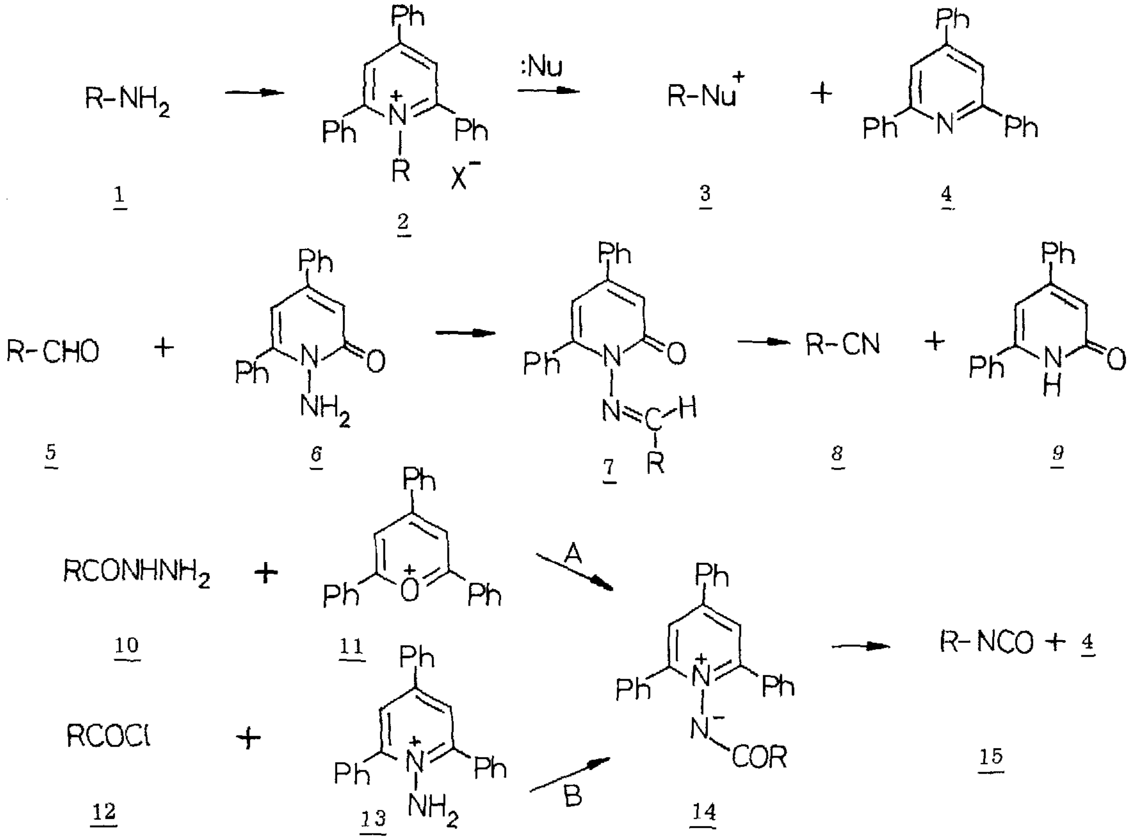
We have been investigating reactions of N-substituted pyridinium salts,[1] and find that the pyridine ring can act as leaving group in a variety of synthetically useful transformations. We here report three examples: (i) nucleophilic displacement of amino groups (1 → 3) via conversion to the triphenylpyridinium salts 2; (ii) the conversion of aldehydes into nitriles (5 → 8) by reaction with the 1-aminopyridone 6 and pyrolysis of the intermediates 7; (iii) the preparation of isocyanates (15) from the N-imines 14, themselves prepared either from acid hydrazides (10) or from acid chlorides (12).



Nucleophilic displacements. Primary amines (1) with triphenylpyrylium salts give the triphenylpyridinium salts in good yield.[3] We now show that triphenylpyridine (4) is displaced by nucleophiles from several of these cations (2 → 3 + 4). Typically, 1-benzyl-2,4,6-triphenylpyridinium perchlorate (2; R = CH_2Ph, X = ClO_4) with pyridine at 115°C forms N-benzylpyridinium perchlorate (3; R = CH_2Ph, Nu = C_5H_5N) and α- and γ-picoline react similarly (Table 1). Pyrolysis of the pyridinium iodide (2; R = CH_2Ph, X = I) gives benzyl iodide, exemplifying the conversion of primary amines into iodides.

Triphenylpyridine as a leaving group in S_N2 displacements is particularly attractive in two situations. The first covers derivatives such as those in which R is 2- and 4-picolyl and 2-furfuryl, where the corresponding halides are unstable, difficult of access, or undergo easy polymerisation or other side reactions. In these cases the primary amines 1 are often readily available, and by conversion into the pyridinium salts 2 can be transformed into other derivatives. The second area of applicability is in the ready formation of tertiary from secondary amines without the formation of quantities of quaternary salt by-products, as with the N-benzylation of piperidine and morpholine. Both areas are illustrated by the examples in Table 1.

TABLE 1. NUCLEOPHILIC DISPLACEMENTS OF TRIPHENYLPYRIDINE FROM SALTS 2

Amine 1	Salt 2	Nucleophile	Reaction	Product 3[a]	
R	X	Nu	temp. (°C)	Yield (%)	M.p./b.p. (°C)
$PhCH_2$	ClO_4	pyridine	115	88	82-84
$PhCH_2$	ClO_4	α-picoline	128	91	96
$PhCH_2$	ClO_4	γ-picoline	145	81	128
$PhCH_2$	ClO_4	piperidine	106	85	245/760 Torr
$PhCH_2$	ClO_4	morpholine	129	92	260/760 Torr
$PhCH_2$	I	I^-	250	32	25
Furfuryl	ClO_4	pyridine	115	61	137-138
γ-Picolyl	ClO_4	pyridine	115	75	104-105
γ-Picolyl	ClO_4	morpholine	129	70	65-70/5 Torr

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[a] New products had analytical and spectral data in accordance with their assigned structures, known ones had m.p.s in agreement with lit. values.

Preparation of nitriles. The aminopyridone 6[4] condenses with aldehydes (5) to give aldimine derivatives 7, which on thermolysis form the nitriles 8 and the pyridone 9.[5] Details are listed in Table 2. Although many reagents are available to effect the conversion of aldehydes to nitriles,[6] the majority are electrophilic in character, or require acidic conditions. Reagent 6 offers a useful alternative in cases where thermal lability or involatility does not offer an additional obstacle.

TABLE 2. CONVERSION OF ALDEHYDES INTO NITRILES

R	Aldimine 7[a]		Pyrolysis	Nitrile 8[b]
	M.p. (°C)	Yield (%)	temp. (°C)	Yield (%)
Ph	179-180	99	220	94
p-$\mathrm{MeC_6H_4}$	183	95	220	90
p-$\mathrm{MeOC_6H_4}$	181	97	220	72
p-$\mathrm{O_2NC_6H_4}$	257-258 (dec)	95	260	85
2-Furyl	187	93	220	73
3-Pyridyl	220 (dec)	81	230	97
n-$\mathrm{C_3H_7}$	[c]	-	200	71

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[a] Satisfactory analytical data were obtained, for all except the last entry. [b] Solid nitriles had m.p.s in agreement with lit values; liquids were identified by IR spectral comparison with authentic material. [c] Gummy product, not isolated pure.

TABLE 3. ISOCYANATES FROM ACID CHLORIDES AND HYDRAZIDES

R	N-Acylimide 14			Isocyanate 15
	M.p. (°C)	Yield (%)	Method[a]	Yield %
Ph	204	82	A	86[b]
p-$\mathrm{MeC_6H_4}$	201	79	A	95[b]
p-$\mathrm{MeOC_6H_4}$	201	78	A	93[b]
p-$\mathrm{ClC_6H_4}$	186	73	B	89[b]
PhCH:CH.	197	66	B	90
$\mathrm{PhCH_2}$	167	85	B	76[b]
Me	209	76	A	95
n-$\mathrm{C_3H_7}$	174	64	B	94

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[a] See footnote 7. [b] Characterised as ureas with aniline or *p*-toluidine.

Preparation of isocyanates. Pyrolysis (220°C)[7] of the N-acylimines 14 gives good yields of isocyanates 15, which were in some cases characterised as urea derivatives by reaction with amines. Details are given in Table 3. The preparation of the pyridine-N-acylimines 14 was achieved either by condensation of the acid hydrazide 10 with the pyrylium salt 11 (Method A), or by acylation of the N-aminopyridinium salt 13 (Method B).[7] The pyrolysis of pyridine N-benzoylimine has been studied previously,[8] but only pyridine (27%) and diphenylurea (30%) were isolated. The present route complements the Curtius reaction for forming isocyanates[9], and, for cases in which the use of azide ion or nitrous acid in the preparation of the acid azide is a source of difficulty, it may be the method of choice.

REFERENCES AND FOOTNOTES

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(5) In a typical experiment the aminopyridone 6 (3 g) condensed with benzaldehyde (2.3 g) on reflux 4 hr in ethanol. The resulting benzylideneamine 7 was heated to 220°C in vacuo (12 Torr) for 1 hr, collecting the benzonitrile as distillate in a trap cooled in liquid nitrogen. The 4,6-diphenyl-2-pyridone remained in the pyrolysis flask.

(6) See, e.g., I.T. Harrison and S. Harrison, Compendium of Organic Synthetic Methods, Vol. 1, p. 461. Wiley-Interscience, New York (1971).

(7) (Method A) The hydrazides 10 were refluxed 15 hr in ethanol with 2,4,6-triphenylpyrylium perchlorate[10] (1 mole). The N-acylamino-2,4,6-triphenylpyridinium perchlorates were separated by filtration, after cooling. The salts were dissolved in methanol and treated with an equimolar portion of KOH in methanol. $KClO_4$ was removed by filtration, the methanol was removed and the residue (14) was recrystallised from benzene. (Method B) N-amino-2,4,6-triphenylpyridinium perchlorate[11] (0.4 g) in acetone (5 ml) and water (1 ml) was stirred with K_2CO_3 (0.28 g) for 10 min. An acetone solution of the acid chloride (1 m mole) was added, and the mixture was stirred 1 hr. After solvent removal, the residue was extracted with chloroform, and the chloroform dried and removed.

The betaine 14, from method A or B, was dried in vacuo at 80-90°C for 24 hr. It was transferred to distillation apparatus and heated under 12-14 Torr pressure. Between 170°C and 250°C the isocyanate was evolved and collected in a trap cooled in liquid nitrogen. The ureas were prepared by condensing the trap contents with the appropriate amine in dry benzene.

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(11) t-Butyl carbazate (1.6 g) and 2,4,6-triphenylpyrylium perchlorate[10] (4.1 g) were refluxed 4 hr in isopentyl alcohol (25 ml). An oil which separated on cooling was crystallised from ethanol, to give the amino-pyridinium perchlorate 13 (2 g, 45%), m.p. 160-162°C.