Heterocycles in Organic Synthesis. Part 42.[1] Preparation of Azides, Phthalimides, and Sulphonamides from Primary Amines

By Alan R. Katritzky,* Gaietano Liso, Edward Lunt, Ranjan C. Patel, Sukhpal S. Thind, and Abid Zia, School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ

N-Alkyl and *N*-benzyl substituents are displaced from 2,4,6-triphenylpyridinium cations by nucleophilic azide, phthalimide, succinimide, and sulphonamide anions. This enables the conversion of primary alkyl- and benzylamines into azides, and primary (with potential for inversion or labelling) and secondary amines.

THE conversion of alkyl halides, sulphonates, *etc.* into primary amines *via* the Gabriel reaction [2] with potassium phthalimide or some modification thereof [2a-d] has been given renewed impetus lately by the discovery of easier methods of removal of the phthalimido residue using the sodium sulphide procedure,[2e] 40% methylamine,[2f] n-pentylamine,[2g] or *N*-methylhydrazine,[3] in place of the hydrazinolysis formerly used.[4] Their conversion into both primary and secondary amines *via* reactions with sulphonamides,[5] saccharin,[6] *N*-trifluoroacetyl derivatives,[7] triflamides,[8] and iminodicarboxylates [9] is also well known.

The replacement of an amino-group directly by another amino-group can invert an optically-active alkylamine or yield an ^{15}N-enriched amine,[10] introducing the label at a late stage in the synthesis. Replacement by a substituted amino-group (*cf.* ref. 11) enables the conversion of primary into secondary amines, useful where other precursors are unstable or inaccessible. Such synthetic transformations of primary amines have been foreshadowed: earlier papers [12] deal with their conversion into a variety of functionalised derivatives, by nucleophilic displacement of the *N*-substituent of 2,4,6-triarylpyridinium salts (3) obtained by reaction of the amines with the corresponding arylpyryliums (1).

The present paper describes the reaction of pyridinium salts (3) with phthalimide, succinimide, and primary and secondary sulphonamide anions. Primary amines are also converted into azides by reaction of pyridinium salts with sodium azide; azides can be reduced to primary amines,[13] or converted into secondary amines with organoboranes.[14] The 2,4,6-triarylpyridinium tetrafluoroborates [12,15] used were prepared from 2,4,6-triphenylpyrylium tetrafluoroborate [16] and the amine as previously described;[12a,c] novel derivatives are described in Table 1.

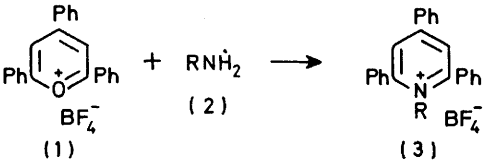
TABLE 1

Preparation of *N*-substituted succinimides and *N*-substituted phthalimides

	N-Substituted-2,4,6-triphenylpyridinium tetrafluoroborate M.p./°C				*N*-Substituted succinimide M.p./°C				*N*-Substituted phthalimide M.p./°C		
Compound	Found	Lit.	Ref.	Yield	Found	Lit.	Ref.	Yield	Found	Lit.	Ref.
(3a)	216	215—216	*a*	75	64	66	*f*	75	132	132	*i*
(3b)	164—165	164—165	*a*	66			*g*	75	78—80	78—79	*j*
(3c)	136		*b*	64			*g*	86			*g*
(3d)	171—173		*c*								
(3e)	200—201	201—202	*a*	90			*g*				
(3f)	236—238		*d*	65			*g*	60	38	38	*k*
(3g)	196	196	*a*	80	103	98	*h*	98	113	113	*l*
(3h)	206	200	*e*					65	122—123	124	*m*

[a] R. Lombard and A. Kress, *Bull. Soc. chim. France*, 1960, 1528; ref. 12*a*. [b] 63% Yield, needles (from absolute EtOH) (Found: C, 71.1; H, 5.3; N, 3.2. $C_{26}H_{24}BF_4N$ requires C, 71.4; H, 5.5; N, 3.2%). [c] 44% Yield, needles (from absolute EtOH) (Found: C, 71.1; H, 5.6; N, 2.9. $C_{26}H_{24}BF_4N$ requires C, 71.4; H, 5.5; N, 3.2%). [d] 60% Yield, needles (from absolute EtOH) (Found: C, 72.6; H, 6.4; N, 2.9. $C_{29}H_{30}BF_4N$ requires C, 72.6; H, 6.3; N, 29%). [e] Ref. 12*c*. [f] S. S. G. Sircar, *J. Chem. Soc.*, 1927, 1252. [g] Characterised by ^1H n.m.r. and i.r. spectra. [h] Mme. Ramart-Lucas and M. Z. Papadakis, *Ann. Chim.* (*France*), 1932, **18**, 32 (*Chem. Abs.*, 1932, **26**, 5609 [4]). [i] M. Freund and H. Beck, *Chem. Ber.*, 1904, **37**, 1942. [j] A. Michael, *Chem. Ber.*, 1877, **10**, 1644. [k] J. H. Billman and R. V. Cash, *Proc. Indiana Acad. Sci.*, 1952, **62**, 158 (*Chem. Abs.*, 1954, **48**, 12038*d*). [l] 'Beilsteins Handbuch der Organischen Chemie,' ed. F. Richter, Verlag von Julius Springer, Berlin, 1935, Vol. XXI, p. 467. [m] C. W. Shoppee, *J. Chem. Soc.*, 1931, 1225.

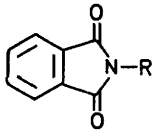
N-*Substituted Phthalimides*.—Melting *N*-alkyl- and *N*-benzyl-2,4,6-triphenylpyridinium salts (3) with potassium phthalimide, using 2,4,6-triphenylpyridine as a



R	R
a; Me	h; $ClC_6H_4CH_2$(*o*)
b; Et	i; $ClC_6H_4CH_2$(*p*)
c; Pr^n	j; $MeC_6H_4CH_2$(*p*)
d; Pr^i	k; $PhCH_2CH_2$
e; Bu^n	l; n-Pentyl
f; n-Hexyl	m; n-Octyl
g; $PhCH_2$	n; 2,4-$Cl_2C_6H_3CH_2$

flux (method A), gave the *N*-alkyl- and *N*-benzylphthalimides (4) in good yield (Table 1). The reaction also succeeds in dipolar aprotic solvents. Thus *N*-benzylpyridinium salt (3g) gave the corresponding

phthalimide (77%) by refluxing with potassium phthalimide in dimethylformamide for 2.5 h; *p*-chlorobenzylphthalimide (65%) was prepared similarly (method B).



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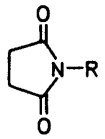

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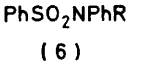
N-*Substituted Succinimides*.—When sodium succinimide was used in the above reactions the *N*-alkyl- and *N*-benzyl-succinimides (5) were isolated in good yields (Table 1) after vacuum distillation and/or crystallisation. Low-boiling alkyl succinimides are obtained directly as distillates during the pyrolysis reaction. The reaction with 1,2,4,6-tetraphenylpyridinium tetrafluoroborate resulted only in proton abstraction to give succinimide: no *N*-phenyl bond fission was observed.

N-*Substituted and* NN-*Disubstituted Sulphonamides*.—The use of sodium *N*-phenylbenzenesulphonamide or



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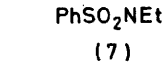

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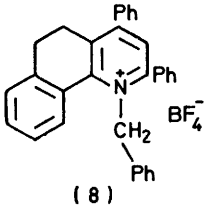
sodium *N*-ethylbenzenesulphonamide similarly (method A) gave the corresponding *N*-alkyl-, *N*-phenyl-, or *NN*-dialkyl-benzenesulphonamides (6) and (7) (Table 2) in fair to excellent yields. Pyrolysis of 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate with sodium benzenesulphonamide resulted only in the isolation of benzenesulphonamide.

Azides.—The reactions with sodium azide were performed in dry dimethylformamide: 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate gave benzyl azide (85%) after 4 h at 130 °C. Reactions giving alkyl azides were slower (*ca.* 6 h); high yields were usually obtained (Table 3). In difficult cases, the alternative tricyclic pyridinium salts [15], *e.g.* (8), which contain a better leaving group, may be advantageous: a single experiment gave benzyl azide (63%) at 100 °C. Most azides were identified by comparison (i.r. and ^{1}H n.m.r. spectra) with authentic samples prepared from alkyl halides and sodium azide in dimethylformamide or carbitol,[16] and



(8)

were >95% pure by ^{1}H n.m.r.; complete removal of dimethylformamide was hindered by co-distillation. An improved method to obtain these alkyl azides avoiding use of dimethylformamide is the reaction of alkyl-2,4,6-triphenylpyridinium tetrafluoroborate with sodium azide in dioxan at reflux using a phase transfer reagent (tetrabutylammonium tetrafluoroborate).

TABLE 2

Preparation of *N*-substituted-*N*-phenylbenzenesulphonamides and *N*-ethylbenzenesulphonamides

			N-Substituted-*N*-phenylbenzenesulphonamides M.p./°C or b.p./°C (mmHg)			*N*-Substituted-*N*-ethylbenzenesulphonamides M.p./°C or b.p./°C (mmHg)				
Compound	Method	Yield	Found	Lit.	Ref.	Method	Yield	Found	Lit.	Ref.
(3a)	A	69	75	79	*a*	A	38	116—120 (1.2)	120 (1.5)	*d*
	B	60								
(3b)	A	71	180—182 (1.5—2.0)	187—189 (3.0)	*a*	A	42	40	42	*e*
(3c)	A	75	52	54	*a*					
(3d)	A	33	70	71—72	*b*					
(3e)	A	65	186—189 (1.5—2.0)	182—184 (1.0)	*a*					
(3g)	A	65	116	118	*c*	A	48	226—228 (9—10)		*f*
	B	55								

[a] R. L. Shriner, J. D. Oppenlander, and R. S. Schreiber, *J. Org. Chem.*, 1939, **4**, 588. [b] R. J. Bates, J. Cymerman-Craig, M. Moyle, and R. J. Young, *J. Chem. Soc.*, 1956, 388. [c] G. W. Stacy, R. I. Day, and R. J. Morath, *J. Amer. Chem. Soc.*, 1955, **77**, 3869. [d] T. L. Cairns and J. C. Sauer, *J. Org. Chem.*, 1955, **20**, 627. [e] G. W. Watt and J. B. Otto, jun., *J. Amer. Chem. Soc.*, 1947, **69**, 836. [f] Found: C, 65.1; N, 4.9; H, 5.9. $C_{15}H_{17}NO_2S$ requires C, 65.5; N, 5.1; H, 6.2%.

TABLE 3

Preparation of azides from 1-substituted-2,4,6-triphenylpyridinium salts

	Pyridinium salt			Alkyl azide	
Compound	M.p./°C	Lit. m.p./°C	Reaction time (h)	Yield (%)	^{1}H N.m.r. chem. shifts (δ) [a]
(3g)			3	85 [b]	*c*
(3h)	200	200 [d]	3	77	4.35 (2 H, s), 7.0—7.5 (4 H, m)
(3j)	134	134 [e]	3	73	2.28 (3 H, s), 4.47 (2 H, s), 7.06 (4 H, s)
(3k)	273	274 [f]	6	73 [b]	2.8 (2 H, t), 3.45 (2 H, t), 7.25 (5 H, s)
(3l)	245—246	245—246 [e]	6	74	0.8—1.7 (9 H, m), 3.25 (2 H, t)
(3m)	155	155 [e]	8	65	0.5—1.5 (15 H, m), 3.2 (2 H, t)
(3n)	235—236	239 [g]	6	69	4.33 (2 H, s), 7.1—7.5 (3 H, m)

[a] In $CDCl_3$. [b] Identical with authentic sample prepared from chloride. [c] Characterised by i.r. spectrum. [d] Table 1, footnote *e*. [e] Ref. 15. [f] Ref. 12*a*. [g] Ref. 12*c*.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded with a Perkin-Elmer R-12 spectrometer using internal Me_4Si as a standard. I.r. spectra were obtained on a Perkin-Elmer 257 spectrophotometer.

Preparation of N-*Substituted*-2,4,6-*triphenylpyridinium Tetrafluoroborates*.—Following the general procedure reported in previous papers,[12] the 1-substituted-2,4,6-triphenylpyridinium tetrafluoroborates (3a, b, and d—g) reported in Table 1 were prepared.

2,4,6-*Triphenyl*-1-*propylpyridinium Tetrafluoroborate* (3c).—To a solution of 2,4,6-triphenylpyrylium tetrafluoroborate [17] (3.96 g, 0.01 mol) in absolute EtOH (50 ml) was added n-propylamine (0.8 g, 0.013 mol), dropwise with stirring. After standing at room temperature for 24 h the separated salt was filtered off, the filtrate evaporated to dryness, and the residue triturated with dry ether to give further product, total yield 2.98 g (68%). Recrystallisation from MeOH gave *prisms*, m.p. 136 °C (Found: C, 71.2; H, 5.3; N, 3.2. $C_{26}H_{24}BF_4N$ requires C, 71.4; H, 5.5; N, 3.2%); δ(CF_3CO_2H) 0.55 (t, Me), 1.55 (m, CH_2), 4.49 (t, CH_2), 7.7 (m, 15 H), and 8.12 (m, 2 H).

Preparation of N-*Substituted Phthalimides and Succinimides*.—*Method* A (*by pyrolysis*). The mixture of the 2,4,6-triphenylpyridinium tetrafluoroborate (1 mol), potassium phthalimide (2 mol), and 2,4,6-triphenylpyridine flux (1 mol) was heated under vacuum (15 mmHg) for 4 h at 80 °C and pyrolysed at 180—220 °C for 2 h. The cooled melt was triturated with $CHCl_3$, filtered to remove KBF_4, the solvent evaporated, and the residue dissolved in absolute EtOH (30 ml). Concentrated HCl (1.5 ml) was added, followed by an excess of ether to give a gummy precipitate of triphenylpyridine hydrochloride. The sulphonated liquid was decanted and the solvent removed to give substantially pure *N*-alkylphthalimide, having the expected i.r. and n.m.r. spectral characteristics.

Method B (*in solution*). The pyridinium salt was refluxed in dry $HCONMe_2$ under N_2 with an excess of potassium phthalimide for 2—4 h. The solution was poured into H_2O and extracted with Et_2O. The ethereal solution was dried over $MgSO_4$ and dry HCl gas was passed through to precipitate the substituted pyridine. The solution was filtered and evaporated to give the crude product which was purified by distillation at 0.5 mmHg. Other *N*-substituted phthalimides and succinimides prepared by these methods are shown in Table 1.

N-*Alkylation of Benzenesulphonamides*.—The sodium salts of *N*-ethyl- or *N*-phenyl-benzenesulphonamide were pyrolysed with an equivalent quantity of the appropriate *N*-alkylpyridinium tetrafluoroborate as described in Method A above. The *NN*-disubstituted sulphonamides prepared in this way are shown in Table 2.

Preparation of Azides.—The preparation of 2-phenylethyl azide is typical. 2,4,6-Triphenyl-1-(2-phenylethyl)-pyridinium tetrafluoroborate [12a] (4 g, 0.008 mol) and dried sodium azide (2 g, 0.025 mol) in dry $HCONMe_2$ (20 ml) were heated at 130 °C for 6 h. The mixture was cooled and water (100 ml) added. The product was extracted with hexane (2 × 50 ml), and the extract was washed with water (50 ml), dried ($MgSO_4$), and evaporated at 40 °C and 10 mmHg to give the azide (0.84 g, 73%).

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