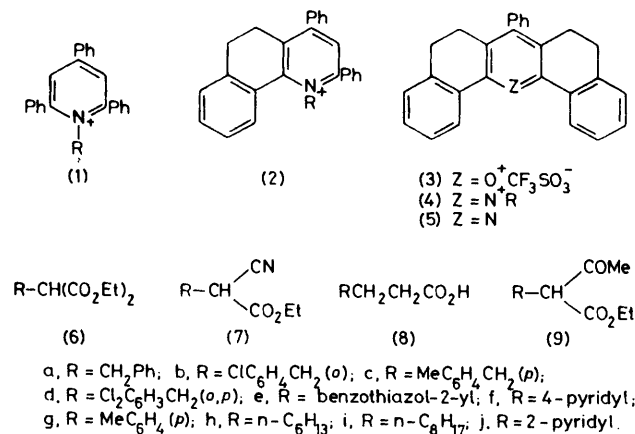


Reactions of *N*-Substituted Pyridinium Cations with Carbanions: 5,6,8,9-Tetrahydro-7-phenylbisbenzo[*ah*]acridine, a Superior Leaving Group¹

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N-Substituents are transferred from pyridinium cations to malonate, cyanoacetate, and acetoacetate carbanions: for alkyl substituents the pentacyclic derivatives (4) attain the required activity.

HALOGEN, oxygen, and nitrogen nucleophiles displace the *N*-substituent from suitable pyridinium cations allowing a two-step conversion of primary amines into other compound classes.² Much of our earlier work was carried out under pyrolysis conditions (*cf.* ref. 2) which are unsuitable for carbon nucleophiles. However, extensive kinetic and exploratory experiments have now disclosed more suitable conditions for reactions in solution including the discovery of superior leaving groups. Reactions in chlorobenzene solvent with piperidine as nucleophile displayed clean second-order kinetics for the reactions of the *N*-benzyl compounds (1a), (2a), and (4a) and (extrapolated) rates³ were in the approximate ratios 1 : 60 : 100 0. Rates for other 1-benzylpyridinium salts were considerably less; *e.g.*, the 1-benzyl-2-methyl-4,6-diphenyl derivative on this scale was 0.03.



Preliminary preparative experiments with tri- (2) and penta-cyclic pyridiniums (4) have also been reported.⁴ We now give further examples of their value in reactions involving carbon nucleophiles (*cf.* also ref. 5): whereas *N*-benzyl groups are transferred to diethyl sodiomalonate and similar anions from 2,4,6-triphenylpyridiniums (1), preparatively useful transfers of heteroaryl and alkyl groups require the use of systems (2) and (4) respectively. These reactions have considerable preparative significance: the preparation of carboxylic acids from primary amines is in this way easily accomplished in a two-step but one-pot reaction starting

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from the pyridinium salts. The method gives high yields of the acids without any dialkylation or *O*-alkylation.

The general procedure involves generation of diethyl sodiomalonate or ethyl sodiocyanoacetate with sodium hydride in an aprotic solvent and adding the *N*-substituted pyridinium salt in batches. Gentle refluxing for 2–6 h, depending on the pyridinium salt and the solvent, leads to *C*-alkylation. Completion of the reaction can be judged by one or more of the following methods: (i) t.l.c.; (ii) the initial brown colour becomes light yellow; (iii) precipitation of substituted pyridine is complete; (iv) addition of ether to a sample of the reaction mixture no longer precipitates starting material.

The solvent choice depends primarily on the solubility of the sodium enolate and pyridinium salt: preferably both, and at least one, must be partly soluble in the reaction medium. Protic solvents are unsuitable: they promote pseudobase formation, and themselves act as nucleophiles, *e.g.* alcohols as solvents form ethers. Although both enolate and pyridinium salts are highly soluble in dipolar aprotic solvents such as hexamethylphosphoramide, dimethylformamide, and dimethyl sulphoxide, these give poor yields of contaminated products, probably because both *C*- and *O*-alkylation occur.

For *C*-benzylation, use of *N*-benzyl-2,4,6-triphenylpyridiniums (1) (*cf.* Table 1) at relatively low reaction temperatures was satisfactory (Table 2). The preferred solvents are refluxing dioxan or 1,2-dimethoxyethane: compounds were characterised spectroscopically (*cf.* Table 3).

Under these conditions the *N*-alkyl- and *N*-(2-pyridyl)pyridiniums do not react well.⁶ The more reactive 5,6-dihydro-2,4-diphenyl-1-(2-pyridyl)benzo[*h*]quinolinium [*cf.* (2)] in refluxing dioxan gave diethyl 2-pyridylmalonate (40%): for this reaction, the solubility of the diethyl sodiomalonate was increased by tetra-*n*-butylammonium tetrafluoroborate (Bu₄N⁺BF₄⁻). However, such reactions to yield heteroarylmalonates were not general: the 4-pyridyl (2f) and benzothiazol-2-yl (2e) analogues on attempted reaction with malonate anion gave complex mixtures only.

For the synthesis of diethyl alkylmalonates, the still more reactive *N*-alkyl-5,6,8,9-tetrahydro-7-phenylbisbenzo[*ah*]acridiniums (4) give the best results. The pentacyclic pyrylium (3) trifluoromethanesulphonate was prepared from 2-benzylidene-1-tetralone (10) and

TABLE I
 Preparation of pyridinium salts

Compound no.	X-	Method of preparation	Yield (%)	M.p. (°C)	Lit. m.p. (°C)	Ref.
(1a)	ClO ₄	A	95	197	196—198	a
(1b)	BF ₄	A	75	200	200	b
(1c)	ClO ₄	A	95	134 ^c	174—176	a
(1d)	BF ₄	A	78	239	239	b
(2e)	CF ₃ SO ₃	C	78	252		d
(2f)	CF ₃ SO ₃	C	72	134—135		e
(2j)	BF ₄	B	95	258	258	f
(4g)	CF ₃ SO ₃	C ^g	84	321—322		h
(4h)	CF ₃ SO ₃	A	88	101—102		i
(4i)	CF ₃ SO ₃	A	93	147—148		j

^a A. R. Katritzky, J. B. Bapat, R. J. Blade, B. P. Leddy, P. L. Nie, C. A. Ramsden, and S. S. Thind, *J.C.S. Perkin I*, 1979, 418.
^b A. R. Katritzky, U. Gruntz, A. A. Ikizler, D. H. Kenny, and B. P. Leddy, *J.C.S. Perkin I*, 1979, 436. ^c Found: C, 71.7; H, 5.2; N, 2.7. C₃₁H₂₈ClNO₄·0.5C₂H₅OH requires C, 71.8; H, 5.5; N, 2.6%. EtOH·OH found in i.r. spectrum at 3450 cm⁻¹. The present is a different polymorphic form to that previously reported. ^d From EtOH (prisms) (Found: C, 63.8; N, 4.6; H, 3.7; S, 10.5. C₃₃H₂₃F₃N₂O₃S₂ requires C, 64.2; N, 4.6; H, 3.8; S, 10.5%). ^e From EtOH (prisms) (Found: N, 4.6; S, 5.5. C₃₁H₂₃F₃N₂SO₃ requires N, 4.5; S, 5.7%). ^f Ref. 4. ^g Prepared in HCONMe₂ at reflux temp. for 2.5 h. ^h From EtOH (needles) (Found: C, 69.9; N, 2.4; H, 4.7. C₃₅H₂₈F₃N₂O₃S requires C, 70.1; N, 2.3; H, 4.7). ⁱ From EtOH (prisms) (Found: C, 68.5; H, 5.8; N, 2.1. C₃₄H₃₄F₃NSO₃ requires C, 68.8; H, 5.8; N, 2.4%). ^j From EtOH (prisms) (Found: C, 69.6; H, 6.2; N, 2.1. C₃₆H₃₈F₃NSO₃ requires C, 69.5; H, 6.2; N, 2.3%).

 TABLE 2
 Preparation of diesters, cyanoesters, and acids

Compound prepared	Subst. transferred	Starting materials		Solvent ^a	Yield	M.p. or b.p. °C (mmHg)	Lit. m.p. or b.p. °C (mmHg)	Ref.
		Pyridinium	Sodio-deriv. of					
(6a)	PhCH ₂	(1a)	CH ₂ (CO ₂ Et) ₂	W	73	134—140 (3)	300	b, c
(6b)	<i>o</i> -ClC ₆ H ₄ CH ₂	(1b)	CH ₂ (CO ₂ Et) ₂	X	55	125 (5—8)	140—148 (12)	d
(6c)	<i>p</i> -MeC ₆ H ₄ CH ₂	(1c)	CH ₂ (CO ₂ Et) ₂	W	70	185—190 (15)	208 (20)	d
(6d)	2,4-di-ClC ₆ H ₄ CH ₂	(1d)	CH ₂ (CO ₂ Et) ₂	X	65	170—185 (8—12)		e
(6h)	<i>n</i> -C ₆ H ₁₃	(4h)	CH ₂ (CO ₂ Et) ₂	Y	80	125 (10—12)	143 (15)	f, g
(6j)	2-Pyridyl	(2j)	CH ₂ (CO ₂ Et) ₂	W	40	140 (2)	130—132 (1)	h
(7a)	PhCH ₂	(1a)	CH ₂ (CN)CO ₂ Et	X	68	160 (2—3)	242	i
(7d)	2,4-di-ClC ₆ H ₄ CH ₂	(1d)	CH ₂ (CN)CO ₂ Et	X	84	194—206 (5—7)		c, e
(8h)	<i>n</i> -C ₆ H ₁₃	(4h)	CH ₂ (CO ₂ Et) ₂	Z/Y	85	150—160 (5)	223	j
(8i)	<i>n</i> -C ₆ H ₁₇	(4i)	CH ₂ (CO ₂ Et) ₂	Y	70	148—150 (13) ^k	167 (16)	l
(8k)	2,4-di-ClC ₆ H ₄ CH ₂	(1d)	CH ₂ (CO ₂ Et) ₂	X	62	85—87	86—90	m

^a W = Dioxan; X = 1,2-dimethoxyethane; Y = xylene; Z = chlorobenzene. ^b I. Vogel, *J. Chem. Soc.*, 1928, 1019; 'Beilsteins Handbuch der Organischen Chemie,' eds. B. Prager, P. Jacobson, P. Schmidt, and D. Stern, Julius Springer, Berlin, 1926, vol. 9, p. 869. ^c R. O. Hutchins, D. Rotstein, N. Natale, J. Fanelli, and D. Dimmel, *J. Org. Chem.*, 1976, 41, 3328. ^d J. P. Trivedi and J. J. Trivedi, *J. Indian Chem. Soc.*, 1959, 35, 687. ^e Characterised by ¹H n.m.r., i.r., and hydrolysis to acid (8k). ^f G. I. Nikishin, Yu. N. Ogibin, and I. A. Palanuer, *Izvest. Akad. Nauk, S.S.S.R.*, 1967, 2478 [*Bull. Acad. Sci. U.S.S.R.*, 1967, 2360]; H.-H. Vogel, *Synthesis*, 1970, 120. ^g A. W. Dox, *J. Amer. Chem. Soc.*, 1924, 46, 1707, b.p. 268—270 (749 mmHg). ^h G. R. Newkome, J. M. Robinson, and N. S. Bhacca, *J. Org. Chem.*, 1973, 38, 2234. ⁱ H. Cassirer, *Chem. Ber.*, 1892, 25, 3018. ^j Z. Rappoport, 'CRC Handbook of Tables for Organic Compound Identification,' 3rd edn., CRC Press, Cleveland, Ohio, 1976, p. 191. ^k M.p. 31 °C. ^l K. Sisido, Y. Kazama, H. Kodama, and H. Nozaki, *J. Amer. Chem. Soc.*, 1959, 81, 5817. ^m P. Strehlke, G.-A. Hoyer, and E. Schröder, *Arch. Pharm.*, 1975, 308(2), 94.

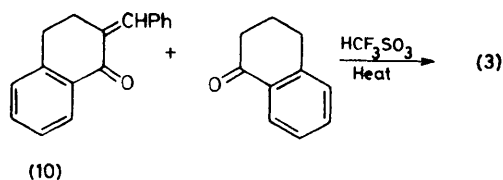
 TABLE 3
¹H Chemical shifts (δ on Me₄Si scale) and coupling constants (Hz) for esters and acids prepared^a

Compound no.	Aromatics (m)/OH [*] (s)		OCH ₂ CH ₃ (q)			OCH ₂ CH ₃ (t)			CH ₂ CO ₂ H } (m) CH ₂ CHXY		Alkyl (m)	
	H	δ	H	δ	J	H	δ	J	H	δ	H	δ
(6a)	5	7.23	4	4.1	7.7	6	1.2	7.7	3	3.5		
(6b)	4	7.22	4	4.05	7.7	6	1.15	7.7	3	3.45		
(6c)	4	6.94	4	3.85	7.3	6	0.82	7.3	3	3.05	3	1.83
(6d)	3	7.05	4	3.82	8.0	6	0.91	8.0	3	3.10		
(6j)	3	7.62	2	3.45	7.9	3	1.00	7.9	1	3.32		
(7a)	5	7.30	4	4.15	7.9	3	1.2	7.9	3	3.44		
(7d)	3	7.01	2	3.95	7.9	3	1.01	7.9	3	3.20		
(8h) ^b	1 [*]	11.52							2	2.31	13	1.22
(8i)	1 [*]	9.31							2	2.30	19	1.25
(9h)			4	4.05	8.0		<i>c</i>		3	2.43	17	1.45

^a Solvent CDCl₃. ^b Solvent CCl₄. ^c Appears with alkyl group.

1-tetralone by a method similar to that used for the corresponding tetrafluoroborate.⁴ It reacted readily with amines to form the corresponding pentacyclic pyridiniums (4). These trifluoromethanesulphonates are fairly soluble in xylene, the preferred solvent. As the

reaction proceeds the acridine (5) precipitates. No side reactions were detected: predominant carbon alkylation is ensured by the use of a non-polar solvent in which the metal enolate is undissociated and the sodium cation shields the enolate oxygen.⁷



EXPERIMENTAL

I.r. and n.m.r. spectra were measured with Perkin-Elmer 237 and R12 instruments respectively (Me₄Si as internal standard). Melting points are uncorrected and were determined on a Reichert hot-stage microscope.

The following compounds were prepared by reported methods: 2,4,6-triphenylpyrylium perchlorate⁹ (71%), m.p. 290 °C (lit.,⁹ m.p. 290 °C); 2,4,6-triphenylpyrylium tetrafluoroborate¹⁰ (65%), m.p. 257 °C (lit.,¹⁰ m.p. 251–257 °C); 5,6-dihydro-2,4-diphenylnaphtho[1,2-*b*]pyrylium tetrafluoroborate⁴ (68%), m.p. 270 °C (lit.,⁴ m.p. 270 °C).

Preparation of 5,6,8,9-Tetrahydro-7-phenyldibenzo[ah]xanthylum Trifluoromethanesulphonate (3).—2-Benzylidene-1-tetralone¹¹ (10) (15.5 g, 0.065 mol) and α -tetralone (8.8 g, 0.06 mol) were condensed in the presence of trifluoromethanesulphonic acid (9.0 g, 0.06 mol) on a steam-bath with mechanical stirring. After 4 h the reaction mixture was cooled to 20 °C and stirred with Et₂O (200 ml). The product was filtered and washed with Et₂O giving bright yellow prisms (18.5 g, 51%), m.p. 304 °C (Found: C, 65.8; H, 4.0. C₂₈H₂₁F₃O₄S requires C, 65.9; H, 4.2%); ν_{\max} . (CHBr₃) 1 618s, 1 605ms, 1 570ms, 1 510m, 1 478s, 1 440m, 1 420s, 1 320m, 1 270s, 1 210ms, 1 038s, 896m, 798m, 775m, and 758m cm⁻¹; δ (CF₃CO₂H) 8.39 (2 H, m), 7.55 (11 H, m), and 3.03 (8 H, s).

Preparation of Pyridinium Salts.—Method A. The appropriate pyrylium salt (0.005 mol) was stirred with amine (0.005 mol) in Et₂O (30 ml) at 20 °C for 8–12 h. The crystalline solid obtained was filtered and recrystallised from absolute EtOH (Table 1).

Method B. The pyrylium salt (0.005 mol) in absolute EtOH (20 ml) was treated with Et₃N (0.005 mol) followed by amine (0.005 mol). When all the suspension had turned into a red solution two drops of glacial HOAc were added. The solution was stirred until pale yellow in colour (0.5–1 h). The product was precipitated by addition of Et₂O (60 ml), filtered, and recrystallised from absolute EtOH (Table 1).

Method C. The procedure was the same as B without Et₃N. The solution was refluxed in EtOH for 3–6 h, cooled, and the product precipitated by addition of Et₂O.

Reactions of Diethyl Sodiomaltonate and Ethyl Sodiocyanacetate: General Procedure for (6a–d, 7a, 7d).—NaH (0.03 mol) was added to diethyl malonate or ethyl cyanacetate (0.03 mol), and stirred in dry dioxan or 1,2-dimethoxyethane (30 ml) at 40–50 °C. Hydrogen was evolved and a white precipitate formed. The pyridinium salt (0.01 mol) was added in portions during 20 min. The whole was refluxed for 6 h, poured into water at 0 °C, and extracted with Et₂O

(2 × 40 ml). The ether extracts were washed with water (2 × 20 ml), and dried (MgSO₄). Dry HCl was bubbled through the ether solution to precipitate the substituted pyridine hydrochloride. This was filtered off and the product was obtained by distillation, and characterised by i.r. and n.m.r. spectroscopy.

For compound (6j), the above procedure was modified by the use of tetra-*n*-butylammonium BF₄⁻ (1 mol equiv.) as phase-transfer catalyst. Additionally, instead of separating the pyridine hydrochloride by HCl, the reaction mixture after treatment with water was extracted with CH₂Cl₂ and the product distilled at reduced pressure.

For compound (9h) the general procedure was used except that after being poured into water the reaction mixture was brought to pH 7 with dilute HCl. Extraction with Et₂O and fractional distillation at 4–5 mmHg gave the diester.

Procedure for Compounds (8h) and (8i).—NaH (0.24 g, 0.01 mol) was added to a stirred solution of diethyl malonate (2.0 g, 0.01 mol) in the solvent indicated (30 ml). The temperature was raised to 60 °C and hydrogen was evolved. Compound (9a) was added (4.0 g, 0.008 mol) in portions during 15 min. The solution was refluxed for 3 h. Aqueous NaOH (10%, 40 ml) was added and the chlorobenzene or xylene azeotroped off (b.p. 90.2 °C, 94.5 °C). The complete removal of solvent was indicated by a rise in temperature of the distillate to 100 °C (remaining volume ca. 30 ml). The solution was again refluxed for 2 h, reduced to ca. 15 ml by distillation, cooled, filtered, and then the solid washed with water. To the filtrate conc. HCl was added carefully until pH 6.5. Extraction with Et₂O (2 × 30 ml) followed. The Et₂O was removed at 30 cmHg and the residue heated with a drop of conc. HCl to 140 °C. Carbon dioxide was evolved and some HOAc distilled followed by heptanoic acid, b.p. 238–248 °C (1.0 g, 85%).

For compound (8k) the same procedure as above was used except that the reaction was conducted in 1,2-dimethoxyethane and on completion 1,2-dimethoxyethane was removed at reduced pressure. The hydrolysis was done in EtOH (60%). Compound (8k) was obtained in 62% yield.

[0/353 Received, 4th March, 1980]

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