Reactions of *N*-Substituted Pyridinium Cations with Carbanions: 5,6,8,9-Tetrahydro-7-phenylbisbenzo[*ah*]acridine, a Superior Leaving Group[1]

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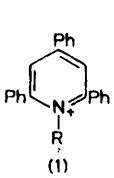
N-Substituents are transferred from pyridinium cations to malonate, cyanoacetate, and acetoacetate carbanions: for alkyl substituents the pentacyclic derivatives (4) attain the required activity.

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) rates[3] 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.



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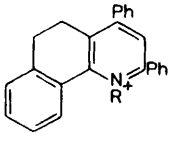

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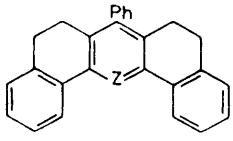
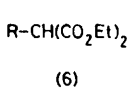


(3) Z = $O^+CF_3SO_3^-$
(4) Z = N^+R
(5) Z = N



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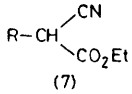

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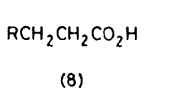

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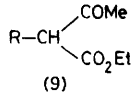

(9)

a, R = CH_2Ph; b, R = $ClC_6H_4CH_2$ (*o*); c, R = $MeC_6H_4CH_2$ (*p*); d, R = $Cl_2C_6H_3CH_2$ (*o*,*p*); e, R = benzothiazol-2-yl; f, R = 4-pyridyl; g, R = MeC_6H_4 (*p*); h, R = n-C_6H_{13}; i, R = n-C_8H_{17}; j, R = 2-pyridyl.

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 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 ($Bu^n_4N^+BF_4^-$). 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

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TABLE 1

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_3SO_3	C	78	252		*d*
(2f)	CF_3SO_3	C	72	134—135		*e*
(2j)	BF_4	B	95	258	258	*f*
(4g)	CF_3SO_3	C [g]	84	321—322		*h*
(4h)	CF_3SO_3	A	88	101—102		*i*
(4i)	CF_3SO_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. $C_{31}H_{26}ClNO_4,0.5C_2H_5OH$ requires C, 71.8; H, 5.5; N, 2.6%. EtOH νOH found in i.r. spectrum at 3 450br 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. $C_{33}H_{23}F_3N_2O_3S_2$ requires C, 64.2; N, 4.6; H, 3.8; S, 10.5%). [e] From EtOH (prisms) (Found: N, 4.6; S, 5.5. $C_{31}H_{23}F_3N_2SO_3$ requires N, 4.5; S, 5.7%). [f] Ref. 4. [g] Prepared in $HCONMe_2$ at reflux temp. for 2.5 h. [h] From EtOH (needles) (Found: C, 69.9; N, 2.4; H, 4.7. $C_{35}H_{28}F_3NO_3S$ requires C, 70.1; N, 2.3; H, 4.7). [i] From EtOH (prisms) (Found: C, 68.5; H, 5.8; N, 2.1. $C_{34}H_{34}F_3NSO_3$ requires C, 68.8; H, 5.8; N, 2.4%). [j] From EtOH (prisms) (Found: C, 69.6; H, 6.2; N, 2.1. $C_{36}H_{38}F_3NSO_3$ requires C, 69.5; H, 6.2; N, 2.3%).

TABLE 2

Preparation of diesters, cyanoesters, and acids

Compound prepared	Subst. transferred	Starting materials: Pyridinium	Starting materials: Sodio-deriv. of	Solvent [a]	Yield	M.p. or b.p. °C (mmHg)	Lit. m.p. or b.p. °C (mmHg)	Ref.
(6a)	$PhCH_2$	(1a)	$CH_2(CO_2Et)_2$	W	73	134—140 (3)	300	*b, c*
(6b)	*o*-$ClC_6H_4CH_2$	(1b)	$CH_2(CO_2Et)_2$	X	55	125 (5—8)	140—148 (12)	*d*
(6c)	*p*-$MeC_6H_4CH_2$	(1c)	$CH_2(CO_2Et)_2$	W	70	185—190 (15)	208 (20)	*d*
(6d)	2,4-di-$ClC_6H_4CH_2$	(1d)	$CH_2(CO_2Et)_2$	X	65	170—185 (8—12)		*e*
(6h)	n-C_6H_{13}	(4h)	$CH_2(CO_2Et)_2$	Y	80	125 (10—12)	143 (15)	*f, g*
(6j)	2-Pyridyl	(2j)	$CH_2(CO_2Et)_2$	W	40	140 (2)	130—132 (1)	*h*
(7a)	$PhCH_2$	(1a)	$CH_2(CN)CO_2Et$	X	68	160 (2—3)	242	*i*
(7d)	2,4-di-$ClC_6H_4CH_2$	(1d)	$CH_2(CN)CO_2Et$	X	84	194—206 (5—7)		*c, e*
(8h)	n-C_6H_{13}	(4h)	$CH_2(CO_2Et)_2$	Z/Y	85	150—160 (5)	223	*j*
(8i)	n-C_8H_{17}	(4i)	$CH_2(CO_2Et)_2$	Y	70	148—150 (13) [k]	167 (16)	*l*
(8k)	2,4-di-$ClC_6H_4CH_2$	(1d)	$CH_2(CO_2Et)_2$	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.

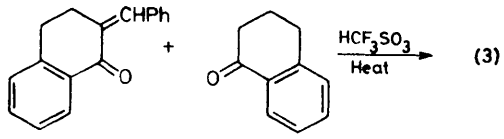
TABLE 3

^1H Chemical shifts (δ on Me_4Si scale) and coupling constants (Hz) for esters and acids prepared [a]

Compound no.	Aromatics (m)/*OH* * (s): H	Aromatics (m)/*OH* * (s): δ	OCH_2CH_3 (q): H	OCH_2CH_3 (q): δ	OCH_2CH_3 (q): *J*	OCH_2CH_3 (t): H	OCH_2CH_3 (t): δ	OCH_2CH_3 (t): *J*	CH_2CO_2H / CH_2CHXY (m): H	CH_2CO_2H / CH_2CHXY (m): δ	Alkyl (m): H	Alkyl (m): 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		*c*		3	2.43	17	1.45

[a] Solvent $CDCl_3$. [b] Solvent CCl_4. [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]



(3)

(10)

EXPERIMENTAL

I.r. and n.m.r. spectra were measured with Perkin-Elmer 237 and R12 instruments respectively (Me_4Si 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 perchlorate [9] (71%), m.p. 290 °C (lit.,[9] m.p. 290 °C); 2,4,6-triphenylpyrylium tetrafluoroborate [10] (65%), m.p. 257 °C (lit.,[10] m.p. 251—257 °C); 5,6-dihydro-2,4-diphenylnaphtho[1,2-*b*]pyrylium tetrafluoroborate [4] (68%), m.p. 270 °C (lit.,[4] m.p. 270 °C).

Preparation of 5,6,8,9-Tetrahydro-7-phenyldibenzo[ah]-*xanthylium Trifluoromethanesulphonate* (3).—2-Benzylidene-1-tetralone [11] (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 Et_2O (200 ml). The product was filtered and washed with Et_2O giving bright yellow prisms (18.5 g, 51%), m.p. 304 °C (Found: C, 65.8; H, 4.0. $C_{28}H_{21}F_3O_4S$ requires C, 65.9; H, 4.2%); $\nu_{max.}$ ($CHBr_3$) 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 (CF_3CO_2H) 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 Et_2O (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 Et_3N (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 Et_2O (60 ml), filtered, and recrystallised from absolute EtOH (Table 1).

Method C. The procedure was the same as B without Et_3N. The solution was refluxed in EtOH for 3—6 h, cooled, and the product precipitated by addition of Et_2O.

Reactions of Diethyl Sodiomalonate and Ethyl Sodiocyanoacetate: General Procedure for (6a—d, 7a, 7d).—NaH (0.03 mol) was added to diethyl malonate or ethyl cyanoacetate (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 Et_2O (2 × 40 ml). The ether extracts were washed with water (2 × 20 ml), and dried ($MgSO_4$). 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 BF_4^- (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 CH_2Cl_2 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 Et_2O 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 Et_2O (2 × 30 ml) followed. The Et_2O 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*, 4*th March*, 1980]

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