A Two-stage Conversion of Primary-alkyl Primary-amines into Alcohols and Further Examples of Transfunctionalisation of Amines under Mild Conditions

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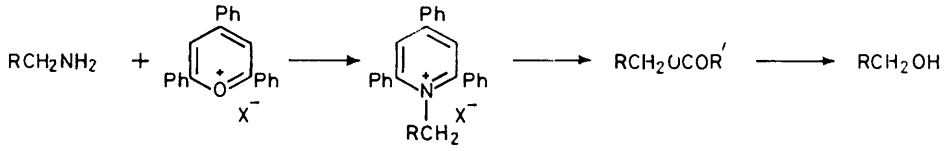
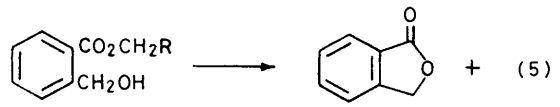
Phase-transfer catalysts allow the conversion of primary-alkyl primary-amines into primary alcohols, sulphones, sulphides, and ethers at ⩽100 °C *via* the pentacyclic pyridiniums (9).

THE conversion of primary-alkyl primary-amines into primary alcohols has been difficult: reaction of primary-alkyl primary-amines with nitrous acid has led usually to a complex mixture of products.[1] Primary amine ditoluenesulphonate derivatives have been converted into acetates by potassium acetate in HMPA.[2]



(1) (2) (3) (4) (5)



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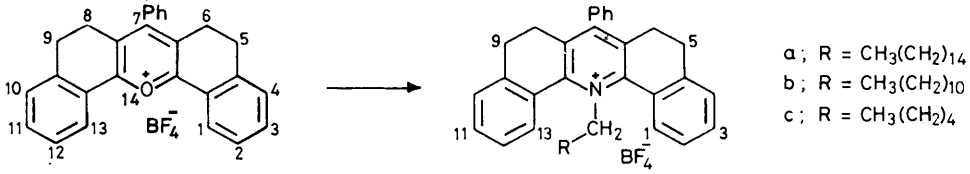

(8) (9)

Pyrylium-mediated transfunctionalisation of amines [3] was used to effect a three-stage conversion (1) + (2) ⟶ (3) ⟶ (4) ⟶ (5) *via* acetates [4] or trifluoroacetates.[5] We reasoned that if the carboxylate nucleophile used for (3) ⟶ (4) was *o*-hydroxymethylbenzoate, the resulting esters (6) should spontaneously [6] yield phthalide (7) and the desired alcohol (5), thus saving a step. However, attempts to effect this transformation using 2,4,6-triphenylpyryliums and sodium *o*-hydroxymethylbenzoate failed: it was shown that sodium *o*-hydroxymethylbenzoate when heated at 190 °C alone yielded considerable quantities of water and phthalide.[7]

The advent of the tetrahydrodibenzoacridiniums, *e.g.* (9), shown kinetically to be 900 times more reactive than (8),[8] has led to significantly milder conditions for amine transformations,[9] and we now show that it enables a convenient two-stage method for RCH_2NH_2 ⟶ RCH_2OH, as well as other transformations.

Preparation of Pyridiniums.—Pyrylium (8) reacted with amines under the standard conditions [10] to give the pentacyclic pyridiniums (9) in the following yields: n-hexadecyl 72%, n-dodecyl 70%, and n-hexyl 71%.

Preparation of Primary Alcohols.—Sodium *o*-hydroxymethylbenzoate (10b) (prepared from phthalide and NaOH [7]) was refluxed in dioxan with the *N*-n-hexadecylpyridinium (9a) and commercial tetra-n-butyl-

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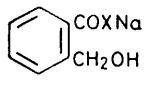
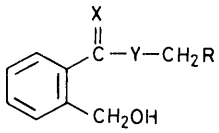
ammonium tetrafluoroborate as a phase-transfer catalyst to give cetyl alcohol (74%). In an attempt to extend this method to the preparation of the corresponding thiol, sodium *o*-hydroxymethylthiobenzoate (10a) (prepared from phthalide and sodium hydrosulphide) was





(10)

a; X = S
b; X = O

(11) X = S, Y = O
(12) X = O, Y = S

allowed to react with (9a) under the same conditions; but, unexpectedly, the product was again cetyl alcohol (72%). This suggests that (11) rather than (12) may have been formed as the intermediate: by contrast *N*-alkyl-2,4,6-triphenylpyridiniums reacted with potassium thiobenzoate to give *S*-alkyl products.[11]

Preparation of Sulphones, Sulphides, and Ethers.—Compounds of these types have been prepared from amines *via* the 2,4,6-triphenylpyridiniums (3), but the conditions were rather severe. Thus, transfer of *N*-alkyl and *N*-benzyl groups to phthalimide required heating at 180—220 °C with potassium phthalimide:[12] sodium arylsulphinites[13,14] and sodium β-naphthoxide[14] reacted at 80 °C but the reaction reported only the transfer of *N*-benzyl groups.[13]

We now find that the *N*-n-dodecyl- (9b) and *N*-n-hexyl-pyridiniums (9c) can be converted into compounds of each of these classes under conditions far milder than used previously (see Table 1). In each reaction, tetra-n-butylammonium tetrafluoroborate was used as a phase-transfer catalyst. Table 2 reports ^{1}H n.m.r. data for the products obtained.

Phenyl sulphones RSO_2Ph were prepared using sodium sulphinite in refluxing dioxan for 12 h in yields of 58—65%: alcohols (presumably formed from hydrolysis of sulphite esters) were side products as evidence by the i.r. and n.m.r. spectroscopy. The superior nucleophile NaSPh reacted at 20 °C in dioxan to form the alkyl phenyl sulphides RSPh in 80—82% yield. Sodium β-naphthoxide reacted readily with acridiniums (9) to the ethers (69—70%).

Potassium phthalimide gave with (9b, c), instead of *N*-alkylphthalimides, 2-(*N*-alkylcarbamoyl)benzoic acids as

TABLE 1

Reactions of phenylsulphinite, thiophenate, phthalimide, β-naphtholate, and *o*-hydroxymethylbenzoate with acridiniums

Nucleophilic anion	Cation	Substrate	Product	Method	Reaction Time (h)	Reaction Temp. (°C)	Yield (%)	M.p./b.p. (°C/mmHg)
Phenylsulphinite	Na	(9b)	$PhSO_2(CH_2)_{11}CH_3$	A	10	101	58	180—181/0.5 [a]
		(9c)	$PhSO_2(CH_2)_5CH_5$	A	12	101	65	160—161/2 [b]
Thiophenate	Na	(9b)	$PhS(CH_2)_{11}CH_3$	A	0.5	20	80.5	135—140/0.5 [c]
		(9c)	$PhS(CH_2)_5CH_3$	A	0.13	20	82	90—100/2 [d]
Phthalimide	K	(9b)	$CH_3(CH_2)_{11}NHC(O)Ph\text{-}2\text{-}CO_2H$ [e]	A	4	101	59	74—75 [f]
		(9c)	$CH_3(CH_2)_5NHC(O)Ph\text{-}2\text{-}CO_2H$ [e]	A	2.5	101	62	84—85 [g]
β-Naphtholate	Na	(9b)	2-Naphth-O-$(CH_2)_{11}CH_3$	A	12	101	68.7	110—115/0.5 [h]
		(9c)	2-Naphth-O-$(CH_2)_5CH_3$	A	4	101	70	185—186/10 [i]
o-Hydroxymethylbenzoate	Na	(9a)	$CH_3(CH_2)_{15}OH$	B	12	101	74	49 [j]
		(9b)	$CH_3(CH_2)_{11}OH$	B	12	101	77	140/10 [k]

[a] Found: C, 69.7, H, 10.2. $C_{18}H_{30}O_2S$ requires C, 69.7, H, 9.7%. [b] Lit. b.p. 195 °C at 9 mmHg (O. Eisleb, Ger. P. 735,866, 1943 [*Chem. Abstr.*, 1944, **38**, 4101 [8]]). [c] Lit. m.p. 33—34 °C (R. Adams and A. Ferretti, *J. Am. Chem. Soc.*, 1959, **81**, 4927). [d] Lit., b.p. 133 °C (J. M. Hoeffelman and R. Berkenbosch, U.S.P. 2,352,435, 1944 [*Chem. Abstr.*, 1944, **38**, 5506 [9]]). [e] The products were purified by column chromatography (silica gel, eluant: CH_2Cl_2-EtOAc 1 : 3) and recrystallised from n-hexane, EtOAc 1 : 1, plates. [f] Found: C, 71.8; H, 9.5; N, 4.1. $C_{20}H_{31}NO_3$ requires C, 72.0; H, 9.4; N, 4.2%. [g] Found: C 68.1; H, 7.4; N, 5.3. $C_{14}H_{19}NO_3$ requires C, 67.5; H, 7.7; N, 5.6%. [h] Found: C. 84.7; H, 10.8. $C_{22}H_{32}O$ requires C, 84.6; H, 10.3%. [i] Lit. b.p. 185—186 °C at 10 mmHg (R. Royer, J.-P. Buisson, P. Demerseman, and A. Cheutin, *Bull. Soc. Chim. Fr.* 1970, 3647). [j] Found: C, 79.0; H. 14.1. $C_{16}H_{34}O$ requires C, 79.3; H, 14.1%. Lit. m.p. 45—46 °C (M. A. Youtz, *J. Am. Chem. Soc.*, 1925, **47**, 2253.) [k] Lit. b.p. 151—152 °C at 21 mmHg (' Beilsteins Handbuch der Organischen Chemie ', Suppl. 2, ed. F. Richter, Springer-Verlag, Berlin, 1941, vol. I, p. 463).

TABLE 2

^{1}H N.m.r. [a] of products (RNu)

Product	R: CH_2Nu	R: Other	Nu
n-Dodecyl phenyl sulphone	3.02 (2 H, t) [b]	0.85—1.5 (23 H, m)	7.4—7.9 (5 H, m)
n-Hexyl phenyl sulphone [c]	2.97 (2 H, t) [b]	0.85—1.5 (11 H, m)	7.3—7.9 (5 H, m)
n-Dodecyl phenyl sulphide [c]	2.81 (2 H, t, *J* 6 Hz)	0.86—1.7 (23 H, m)	7.0—7.28 (5 H, m)
n-Hexyl phenyl sulphide [c]	2.81 (2 H, t, *J* 6 Hz)	0.83—1.7 (11 H, m)	6.95—7.25 (5 H, m)
2-(n-Dodecylcarbamoyl)benzoic acid	4.25 (2 H, t, *J* 6 Hz)	0.86—1.8 (23 H, m)	7.33—7.85 (4 H, m)
2-(n-Hexylcarbamoyl)benzoic acid	4.25 (2 H, t, *J* 6 Hz)	0.76—1.8 (11 H, m)	7.33—7.85 (4 H, m)
n-Dodecyloxy-2-naphthalene	4.0 (2 H, t, *J* 6 Hz)	0.8—1.8 (23 H, m)	7.0—7.8 (7 H, m)
n-Hexyloxy-2-naphthalene	4.05 (2 H, t, *J* 6 Hz)	0.8—1.5 (11 H, m)	7.0—7.8 (7 H, m)
Cetyl alcohol [c]	3.53 (2 H, t, *J* 5 Hz)	0.9—1.27 (31 H, m)	
Lauryl alcohol [c]	3.49 (2 H, t, *J* 5 Hz)	0.9—1.25 (23 H, m)	

[a] In $CDCl_3$, unless otherwise stated. [b] Virtual coupling. [c] In CCl_4.

deduced from analysis and i.r. (OH/NH 3 300—3 100 cm^{-1}). The alternative isomer [2-(*O*-alkylcarbonyl)-benzamide] is thought not likely because of its rapid decomposition to alcohol and phthalimide.[15]

EXPERIMENTAL

I.r. and n.m.r. spectra were measured with Perkin-Elmer 157, 257, R12 and Varian T60 respectively ($SiMe_4$ as internal n.m.r. standard). Melting points (uncorrected) were determined on a Kofler hot-stage apparatus.

The following compounds were prepared using standard literature methods: 5,6,8,9-tetrahydro-7-phenyldibenzo-[*c,h*]xanthylium tetrafluoroborate, m.p. 259—260 °C (lit.,[9] m.p. 265 °C); *N*-n-hexadecyl-5,6,8,9-tetrahydro-7-phenyldibenzo[*c,h*]acridinium tetrafluoroborate, m.p. 175 °C (lit.,[16] m.p. 175 °C); sodium 2-hydroxymethylbenzoate.[7]

N-n-Dodecyl-5,6,8,9-tetrahydro-7-phenyldibenzo[c,h]-*acridinium Tetrafluoroborate.*—To 5,6,8,9-tetrahydro-7-phenyldibenzo[*c,h*]xanthylium tetrafluoroborate (10 g) in CH_2Cl_2 (100 ml), dodecylamine (6 g), and Et_3N (3 ml) were added with stirring. After 12 h stirring at 20 °C the solvent was removed and the residue extracted with Et_2O (50 ml), the solid *product* obtained was filtered (10 g, 70%) and recrystallised as prisms from Me_2CO–Et_2O (1 : 5, 300 ml), m.p. 159—160 °C (Found: C, 76.1; H, 7.6; N, 2.2. $C_{39}H_{46}BF_4N$ requires C, 76.1; H, 7.5; N, 2.3%).

N-n-Hexyl-5,6,8,9-tetrahydro-7-phenyldibenzo[c,h]*acridinium tetrafluoroborate* was prepared as above (70%), and recrystallised from Me_2CO–Et_2O as yellow prisms, m.p. 174—175 °C (Found: N, 2.5. $C_{33}H_{34}BF_4N$ requires N, 2.6%).

General Procedure for Reaction of Acridiniums with Anions.—Method A. The acridinium tetrafluoroborate (*ca.* 5×10^{-2}M), $Bu^n_4N^+BF_4^-$ (3 equiv.), and sodium or potassium salt of nucleophile (3 equiv.) were allowed to react in dioxan (*ca.* 50 ml). When t.l.c. [silica gel, light petroleum (b.p. 40—60 °C)–Et_2OAc 3 : 1] showed absence of acridinium, dioxan was removed *in vacuo* (25 °C at 25 mmHg). The residue was extracted with Et_2O (sodium dried) (3 × 25 ml). Anhydrous HCl gas was passed through and the by-product hydrochloride filtered off. Distillation gave pure products (Tables).

Method B. As above. Instead of distillation the crude product was refluxed for 10 min in EtOH (5 ml) containing NaOH (0.15 g). EtOH was removed, water (20 ml) was added, and the whole extracted with Et_2O (3 × 10 ml). Removal of solvent from the dried ($MgSO_4$) extracts gave the pure alcohols.

We thank the Italian Research Council (CNR), Rome, for a grant (to A. S.).

[0/1653 *Received*, 30*th October*, 1980]

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