# Synthetic Applications of *N*–*N* Linked Heterocycles. Part 14.[1] The Preparation of α-(4-Pyridyl)esters and α-(4-Pyridyl)nitriles by Regiospecific Attack of Ester and Nitrile Anions on Pyridinium Salts

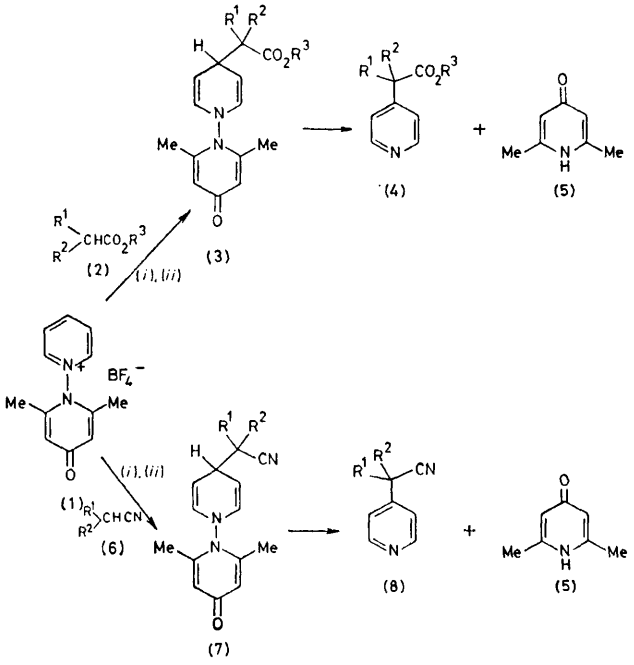
By **Michael P. Sammes** * and **Cheuk Man Lee**, Department of Chemistry, University of Hong Kong, Pokfulam Road, Hong Kong
**Alan R. Katritzky**,* Department of Chemistry, University of Florida, Gainesville, Florida 32611, U.S.A.

Reactions between *N*-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium tetrafluoroborate (1) and lithio-derivatives of esters and nitriles give only low yields of 1,4-dihydro-adducts (3) and (7) due apparently to competing proton abstraction from the pyridone methyl groups. This limitation with salt (1) appears only with C–H acids of $pK_a > 20$. Decomposition of the adducts under free-radical conditions yields α-(4-pyridyl)-esters (4) and -nitriles (8) essentially quantitatively. The same pyridyl-esters and -nitriles may be prepared conveniently in good overall yields by the reaction between the appropriate lithium salts and *N*-triphenylmethylpyridinium salts. The scope and limitations of the method are discussed. 2-Methyl-*N*-triphenylmethylpyridinium tetrafluoroborate is reported for the first time.



We described, in an earlier part of this series, a method for preparing regiospecifically 4-(α-acylalkyl)pyridines in high yields [2] by attack of lithium enolates of ketones on *N*-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium salts, *e.g.* (1). The pyridone methyl groups, by sterically shielding the α-positions of the pyridinium ring, directed the enolate anion to the γ-position, giving a 1,4-dihydro-intermediate, which was subsequently fragmented by a free-radical process to give the desired 4-(α-acylalkyl)-pyridine, and 2,6-dimethyl-4-pyridone (5). It seemed likely that the method could be extended, *via* the use of lithio-derivatives of esters and nitriles, to the synthesis of α-(4-pyridyl)esters and α-(4-pyridyl)nitriles [respectively (4) and (8), Scheme 1]. Surprisingly few examples of pyridyl esters and nitriles of these types have been reported, the few known synthetic routes being *via* (*a*) carboxylation of 4-methylpyridine in the presence of strong base with carbon dioxide or ethyl chloroformate; [3,4] (*b*) displacement of a 4-halogeno- [5] or 4-methoxy-group [6] with an ester or nitrile anion; or (*c*) elaboration of a different 4-substituent.[7] In all cases, however, a substituent must already be present at the pyridine 4-position, thus restricting the utility of the methods.

We report here the synthesis of α-(4-pyridyl)-esters and -nitriles as in Scheme 1, a limitation to the method, and the development of a more successful alternative route *via* *N*-triphenylmethylpyridinium salts (Scheme 2).




SCHEME 1 (*i*) Lithium di-isopropylamide (LDA) or lithium isopropylcyclohexylamide (LICA); (*ii*) THF

## RESULTS AND DISCUSSION

*Syntheses* via N-(2,6-*Dimethyl*-4-*oxopyridin*-1-*yl*)*pyridinium Tetrafluoroborate* (1).—*Preparation of dihydro-intermediates* (3) *and* (7). The pyridinium salt (1) was added to solutions containing an equimolar amount of the appropriate ester lithium salts, prepared [8] from the ester (2) and lithium *N*-isopropylcyclohexylamide (LICA), in tetrahydrofuran (THF) at −78 °C. Analysis of the product after 30 min showed it to contain unchanged (1) (60—70%), dihydro-intermediate (3) (30%), and products resulting from self-condensation of the ester. The use of an alternative method for generating the ester lithium salt,[9] or using t-butyl acetate as the ester,[9,10] both of which approaches, like that of ref. 8, were reported to eliminate ester self-condensation, also gave the same pattern of products. Ethyl phenylacetate, however, gave a high yield of the intermediate (3j) with no evidence of ester self-condensation. The results are given in Table 1. Likewise, the lithium salt af propanonitrile,

TABLE 1

Yields (%) of 1,4-dihydro-intermediates (3) and (7)

| Compound | $R^1$ | $R^2$ | $R^3$ | Yield (%) |
|---|---|---|---|---|
| (3a) | H | H | Et | 30 |
| (3b) | H | H | Bu$^t$ | 28 |
| (3e) | H | Pr$^n$ | Et | 30 |
| (3j) | H | Ph | Et | 72 |
| (3k) | Me | Me | Me | 27 |
| (7b) | H | Et | | 10 |
| (7d) | H | Ph | | 21 [a] |

[a] Product contaminated with *ca.* 75% benzyl cyanide.

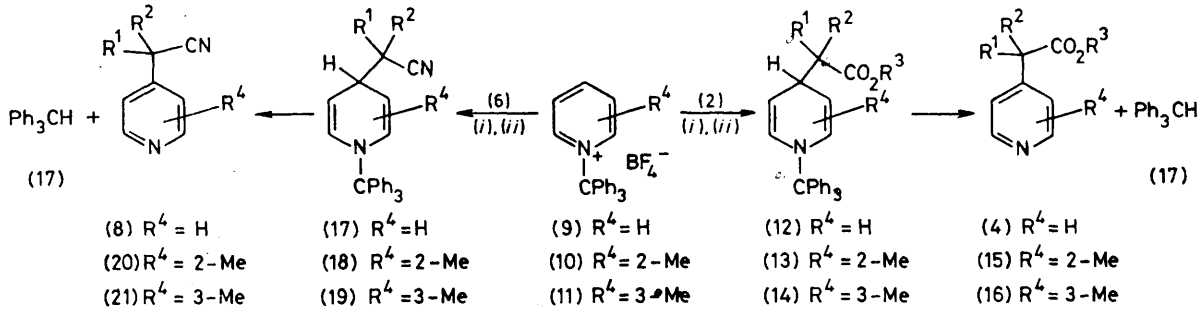
prepared analogously [11] from LICA in THF, gave a low yield of the dihydro-intermediate (7b) together with a large amount of product from self-condensation of the nitrile.

Dihydro-intermediates were isolated by column chromatography ($Al_2O_3$), and though too unstable to characterise by microanalysis, were shown to be essentially pure from their i.r. and $^1H$ n.m.r. spectra, which were entirely consistent with those for the analogous ketone intermediates.[2] Thus, characteristic i.r. absorptions for the pyridone and the dihydropyridine rings were found respectively near 1 630 and 1 560, and near 1 670 $cm^{-1}$, together with bands for the ester or nitrile groups; and in the $^1H$ n.m.r. spectra signals were found for the pyridone ring at δ 6.1 (3- and 5-H) and 2.2 (2- and 6-Me; sometimes as separate signals due to restricted rotation about the N–N bond); and for the dihydropyridine ring near δ 5.9 (2 H, d, 2- and 6-H), 4.6 (2 H, dd, 3- and 5-H), and 3.5 (1 H, m, 4-H).

*Decomposition of intermediates* (3) *and* (7). Although the intermediates (3) and (7) were prepared only in relatively low yield, they could nevertheless be fragmented into the product pyridines (4) and (8) essentially quantitatively under free-radical conditions, by boiling in $CCl_4$ in the presence of azoisobutyronitrile. If *N*-isopropylcyclohexylamine was not first removed by chromatography, however, the yields were reduced substantially. The products (4) and (8) were isolated by column chromatography ($Al_2O_3$) and characterised by their i.r. and n.m.r. spectra, which were identical with those for the same compounds prepared in the second part of this paper.

Thus, although the desired pyridines may readily be prepared from the intermediates (3) and (7), the synthesis of the intermediates presents a major problem. It seems that self-condensations of the esters and nitriles are competing seriously with addition of the lithium salts to the pyridinium salt (1) under conditions in which no free ester or nitrile should be present.[8–11] Esters and nitriles have p$K_a$ values for their α-hydrogen atoms near 25, and it is possible that proton exchange between the lithio-derivatives and the pyridone methyl groups in the salt (1) generates the free ester or nitrile essential for condensation. The observation that ethyl phenylacetate (p$K_a$ *ca.* 16) does not give products from self-condensation supports this suggestion, and the fact that ketones (p$K_a$ *ca.* 20) react cleanly without side-reactions [2] indicates that the upper p$K_a$ limit for reactions of this type using salt (1) lies between 20 and 25. Though benzyl cyanide (p$K_a$ *ca.* 16) gives only a low yield of intermediate (7d), this was not due to competing self-condensation of the nitrile, as evidenced by its recovery on a substantial scale unchanged. Instead, the isolation of highly coloured products from nucleophilic ring-opening of the salt (1) (not observed with the other esters and nitriles studied) indicates that the initially formed adduct (7b) reacted with traces of moisture during isolation, reverting to benzyl cyanide and products from attack of $OH^-$ on the salt (1). Such reversals have been reported in other papers in this series.[2,12]

The *N*-triphenylmethylpyridinium salts (9)—(11) were therefore selected as potential substrates in place of the salt (1) since the *N*-substituent, which may easily be attached, and might leave *via* free-radical cleavage, not only bears no hydrogen atoms with p$K_a$ in the range




(8) $R^4$ = H; (20) $R^4$ = 2-Me; (21) $R^4$ = 3-Me
(17) $R^4$ = H; (18) $R^4$ = 2-Me; (19) $R^4$ = 3-Me
(9) $R^4$ = H; (10) $R^4$ = 2-Me; (11) $R^4$ = 3-Me
(12) $R^4$ = H; (13) $R^4$ = 2-Me; (14) $R^4$ = 3-Me
(4) $R^4$ = H; (15) $R^4$ = 2-Me; (16) $R^4$ = 3-Me

SCHEME 2 (*i*) LDA or LICA; (*ii*) THF

under study, but also has been shown to sterically shield the pyridinium α-positions from nucleophilic attack. Thus, Lyle and Boyce [13] isolated a mixture of 77% of the 1,2- and 23% of the 1,4-dihydro-adducts from treatment of the salt (9) with sodium borohydride, rather than the 1,2-adduct alone; and Redmore [14] obtained 4-pyridylphosphonates in low to moderate yields regiospecifically by the reaction between the salt (9) and sodium dialkylphosphonates. Attempts were therefore made to prepare α-(4-pyridyl)-esters and -nitriles by the route shown in Scheme 2.

*Syntheses via N-Triphenylmethylpyridinium Tetrafluoroborates* (9)—(11).—*Preparation of the pyridinium salts.* The salts (9) [13–15] and (11) [14] were prepared from triphenylmethyl fluoroborate,[16,17] using a modification of the published procedures. Care was essential to exclude traces of moisture, which would cause slight hydrolysis to triphenylmethanol and pyridinium fluoroborate,* to the detriment of the subsequent nucleophilic addition step. The 3-methyl-derivative was isolated in a purer form than previously,[14] and the 2-methyl-analogue (10) was prepared successfully for the first time by using 10

* Detectable in the i.r. by absorptions at 3 460 and 3 240 $cm^{-1}$, respectively. Samples of triphenylmethylpyridinium salts used in this work were free from hydrolysis products.

mol-equiv. of 2-methylpyridine, and a longer reaction time. Attempts to extend the synthesis to the 3-chloro-, 3-cyano-, and 3-methoxycarbonyl-analogues, however, gave products contaminated with triphenylmethanol and the pyridinium fluoroborate under all conditions tried.* The successful preparation of these extremely moisture-sensitive salts will probably require the use of super-dry materials and apparatus in a dry box.

*Reactions of pyridinium salts* (9)—(11) *with lithium salts of esters and nitriles.* In most cases, addition of the appropriate triphenylmethylpyridinium salt to a solution containing an equimolar amount of the ester or nitrile lithium salt in THF at 0 °C under $N_2$ gave, after stirring for 4—6 h at 25 °C, a mixture from which the desired 4-substituted pyridine could be isolated in good yield by a stopped 20—40 min after addition of the pyridinium salt. In certain cases, especially when the ester or nitrile contained a branched chain, the dihydro-intermediate was significantly more stable, and it was necessary to isolate it prior to decomposition. The latter could be carried out *either* by stirring in $CCl_4$ at 25 °C in the presence of air † (Method B) *or* by refluxing in toluene with dibenzoyl peroxide (Method C).‡ For the intermediate (17d) scrupulous exclusion of moisture was essential, to prevent attack by water giving triphenylmethanol, pyridine, and benzyl cyanide. This is consistent with the observed result above for the preparation of intermediate (7d).

Methods for the decomposition of intermediates, and yields of product pyridines are given in Tables 3 and 4.

TABLE 2

$^1$H N.m.r. data (δ) [a] for some dihydro-intermediates derived from the pyridinium salt (9)

| Compound | Trityl group | Dihydropyridine ring 2,6 | 3,5 | 4 | R$^1$ | R$^2$ | R$^3$ |
|---|---|---|---|---|---|---|---|
| (12b) | 7.3 (m) | 6.05 (d) | 4.45 (dd) | 3.35 (m) | 2.20 (d) | | 1.08 (s) |
| (17c) | 7.3 (m) | 6.28 (d) | 4.40 (m) | 3.15 (m) | 2.10 (m) | 0.98 (dd), 1.30 (m) | |
| (17d) | 7.2 (m) | 6.20 (d) | 4.40 (m) | 3.45 (d) | 3.55 (d) | 7.30 (s) | |
| (17e) | 7.3 (m) | 6.30 (d) | 4.45 (dd) | 2.92 (t) | 1.15 (s) | | |
| (17g) | 7.2 (m) | 6.25 (d) | 4.40 (m) | 3.20 (m) | 3.55 (m) | 1.55 (m), 1.90 (m), 5.70 (m) | |

[a] In $CDCl_3$ on a Perkin-Elmer R-20 spectrometer.

TABLE 3

Yields [a] of α-(4-pyridyl)esters (4), (15), and (16), and products (22) and (24) from pyridinium salts (9)—(11)

| Pyridinium salt | Ester | Substituents R$^1$ | R$^2$ | R$^3$ | Method | Product | Yield (%) |
|---|---|---|---|---|---|---|---|
| (9) | (2b) | H | H | Bu$^t$ | B or C | (4b) | 60 |
| (9) | (2c) | H | Et | Et | A | (4c) | 62 |
| (9) | (2d) | H | Pr$^n$ | Me | A | (4d) | 70 |
| (9) | (2f) | H | Pr$^i$ | Me | C | (4f) | 58 |
| (9) | (2g) | H | $[CH_2]_2$ | | A | (4g) | 58 [b] |
| (9) | (2h) | H | $[CH_2]_3$ | | A | (4h) | 29 [b] |
| (9) | (2i) | H | $[CH_2]_4$ | | A | (4i) | 34 [b] |
| (9) | (2j) | H | Ph | Et | A | (4j) | 65 [c] |
| (9) | (2k) | Me | Me | Me | B or C | (4k) | 56 |
| (9) | (2l) | $[CH_2]_2CH=CHCH_2$ | | Me | C | (4l) | 72 |
| (9) | (2m) | H | $CO_2Et$ | | *d* | (22) | 82 |
| (9) | (2n) | MeCH= | | Me | C | (24) | 62 [e] |
| (10) | (2c) | H | Et | Et | A | (15c) | 21 [f] |
| (10) | (2j) | H | Ph | Et | A | (15j) | 19 [f] |
| (11) | (2c) | H | Et | Et | A | (16c) | 56 |
| (11) | (2j) | H | Ph | Et | A | (16j) | 60 |

[a] Based on pyridinium salts (9)—(11). [b] Significant amount of pyridine also present; see text. [c] Yield 60% on ×5 scale. [d] Ester anion attacked triphenylmethyl group; compound (22), m.p. 130 °C (Y. Ittah and I. Shahak, *Synthesis*, 1976, 320, report m.p. 133 °C); *m/e* 402 ($M^+$); $\nu_{max.}$ 1 756, 1 720, 1 594, 1 495, 1 445, and 1 230 cm$^{-1}$; δ ($CDCl_3$) 7.24 (15 H, m), 5.32 (1 H, s), 3.37 (4 H, q), and 0.97 (6 H, t). [e] Yield of intermediate (24). [f] 2-Methylpyridine [37—45% based on salt (10)] in admixture with product.

series of extraction steps (see Experimental section), followed by chromatographic purification (Method A). The 1,4-dihydro-intermediates (12)—(14) and (17)—(19) were thus not normally isolated, those from 2- and 3-methylpyridinium salts being particularly unstable. However, isolation and characterisation by $^1$H n.m.r. spectroscopy (Table 2) was possible if the reaction was

Most of the products, being oils, were characterised as crystalline derivatives. Generally, however, neither picrates nor methiodides would form satisfactorily, so methotetraphenylborates were prepared. Since analytical data for salts of such high molecular mass are not good criteria for establishing the identity of the new product

* Detectable in the i.r. by absorptions at 3 460 and 3 240 cm$^{-1}$, respectively. Samples of triphenylmethylpyridinium salts used in this work were free from hydrolysis products.

† Decomposition was much slower in the absence of air.

‡ Separation of the pyridine from oxidation products of $Ph_3CH$ was not possible by column chromatography, but was achieved by a series of extraction steps.

TABLE 4

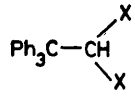
Yields [a] of α-(4-pyridyl)nitriles (8), (20), and (21), and products (23) and (26) from pyridinium salts (9)—(11)

| Pyridinium salt | Nitrile | Substituents R¹ | Substituents R² | Method | Product | Yield (%) |
|---|---|---|---|---|---|---|
| (9) | (6a) | H | Me | C | (8a) | 63 |
| (9) | (6b) | H | Et | B or C | (8b) | 60 |
| (9) | (6c) | H | Pr$^i$ | C | (8c) | 62 |
| (9) | (6d) | H | Ph | A [b] | (8d) | 63 [c] |
| (9) | (6e) | Me | Me | C | (8e) | 57 |
| (9) | (6f) | H | CN | *d* | (23) | 74 |
| (9) | (6g) | H | Cyclohexen-1-yl | C | (25) | 64 |
| (10) | (6b) | H | Et | A | (20b) | 19 [e] |
| (10) | (6d) | H | Ph | A | (20d) | 16 [e] |
| (11) | (6b) | H | Et | A | (21b) | 57 |
| (11) | (6d) | H | Ph | A | (21d) | 60 |

[a] Based on pyridinium salts (9)—(11). [b] Scrupulous exclusion of moisture essential; see text. [c] Yield 59% on ×5 scale. [d] Nitrile anion attacked triphenylmethyl group; compound (23) m.p. 160 °C (S. Patai and S. Dayagi, *J. Chem. Soc.*, 1962, 716; report m.p. 162 °C); $\nu_{max.}$ 2 260, 1 595, 1 495, and 1 445 cm$^{-1}$; δ ($CDCl_3$) 7.31 (15 H, m) and 5.15 (1 H, s). [e] 2-Methylpyridine [40—45% based on salt (10)] in admixture with product.

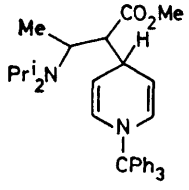
pyridines, i.r. and $^1$H n.m.r. data are recorded (Tables 5 and 6) in addition to physical and analytical data (Table 7) (see Experimental section). In no case were products observed from attack of the carbanion at the pyridinium α-positions.

In some reactions attack by the carbanion at the triphenylmethyl group competed with addition at the pyridinium γ-position, resulting in the formation of free pyridine by nucleophilic displacement. For example, all reactions with the salt (10) gave 35—45% of free 2-methylpyridine, possibly as a result of weakening of the N–triphenylmethyl bond by steric interaction involving the 2-methyl group. Since yields of products (15) and (20) were low (Tables 3 and 4), the by-product was not separated, and the compounds were identified only by i.r. and $^1$H n.m.r. spectra. Lactone anions also gave various amounts of by-product pyridine depending on the ring size, lactones (2g), (2h), and (2i) yielding 15, 50, and 40% of pyridine, respectively in addition to the desired products (4g—i). With anions derived from diethyl malonate (2m) and malononitrile (6f) reactions were very slow, and compounds (22) and (23), resulting from nucleophilic attack at the triphenylmethyl group, were the only isolable products. Their structures were confirmed by



(22) X = $CO_2Et$

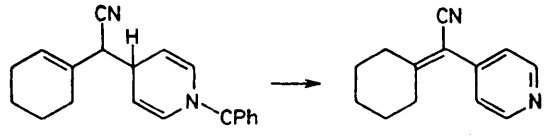
(23) X = CN



(24)

comparison of m.p. and spectroscopic data with literature values (Tables 3 and 4). In these two cases the outcome seems to be the result of thermodynamic rather than kinetic factors, since we have observed [18] that anions derived from C–H acids of $pK_a < 12$ can add reversibly to the salt (1).

Two research groups have reported [19,20] the successful alkylation of lithium enolates of αβ-unsaturated esters at the α-position. However, addition of the salt (9) to the lithio-derivative of methyl crotonate, prepared using LICA,[19] or LDA with or without added hexamethylphosphoramide,[20] gave only complex mixtures. The use of 2 mol equiv. of LDA, on the other hand, led to the intermediate (24),* formed by conjugate addition of the base to the ester, followed by attack of the resulting anion on the pyridinium salt. Conjugate addition of LDA to methyl crotonate has been reported before,[20] and examples in which the intermediate anion was trapped by alkylation have been published recently.[21] Attempts to extend this type of addition to methyl cinnamate were unsuccessful, probably due to steric interaction, and



(17g) (25)

(26) (27)

decomposition of the adduct (24) under a variety of conditions gave a mixture of products.

Borch and co-workers [22] have shown that for βγ-unsaturated nitriles, α-protons are abstracted faster than ε-protons, and that alkylation of lithium salts prepared under kinetic conditions occurs predominantly at the α-position. This is consistent with our observation that cyclohexen-1-ylacetonitrile (6g) adds to the salt (9) in the presence of LDA to give the intermediate (17g), which, however, fragmented to the exocyclic conjugated nitrile (25), rather than the isomer with an endocyclic double bond.

* δ ($CDCl_3$) 7.3 (15 H, m), 6.10 (2 H, d), 4.45 (2 H, m), 3.60 (3 H, s), 3.30 (1 H, m), 3.10 (3 H, m), 2.35 (1 H, dd), 1.0 (15 H, m).

*Reaction of the salt* (9) *with the lithium enolate of* 3,3-*dimethylbutan-2-one.* This was to compare the suitability of the salt (9) with that of salt (1) [2] as a substrate for preparing 4-(α-acylalkyl)pyridines. The lithium enolate of 3,3-dimethylbutan-2-one added to the salt (9) readily to give the intermediate (26), which, however, decomposed only after prolonged reflux in toluene (Method C) to give the ketone (27) in 68% yield.† From this experiment the salt (1) is the better substrate, both from the point of view of yield, and of ease of decomposition of the dihydro-intermediate.

*Conclusion.*—Subject to the limitations discussed above, simple triphenylmethylpyridinium salts are thus convenient substrates for the regiospecific synthesis of α-(4-pyridyl)-esters and -nitriles in average overall yields from the parent pyridine of *ca.* 50%.

## EXPERIMENTAL

Tetrahydrofuran (THF) was re-distilled from $LiAlH_4$ before use; n-butyl-lithium, di-isopropylamine, and *N*-isopropylcyclohexylamine were used as supplied by E. Merck Company. Esters and nitriles were dried and re-distilled before use. The pyridinium salt (1) was prepared as reported previously.[2] Triphenylmethyl tetrafluoroborate was best made (90—95%) by Dauber's method.[16] It was found that contamination of the product with $Ph_3COH$ could be avoided as long as $HBF_4$ of at least 48% concentration was used, and exposure to moisture was minimised. $(Pr^nCO)_2O$ could be used in place of $(EtCO)_2O$.

*Preparation of* N-*Triphenylmethylpyridinium Salts.*—*Parent salt* (9). Prepared by the method of Lyle and Boyce [13] (85%) as white prisms, m.p. 174—177 °C (decomp.) [lit.,[13] 177—186 °C (decomp.)]; $\nu_{max.}$ 1 630, 1 490, 1 470, and 1 050 $cm^{-1}$; δ ($CD_2Cl_2$) 8.7 (2 H, m), 8.4 (1 H, m), 8.0 (2 H, m), and 7.3 (15 H, m).

3-*Methyl-derivative* (11). As for salt (9), only addition of dry $Et_2O$ to the $CH_2Cl_2$ solution was necessary to precipitate the product (82%) as white prisms, m.p. 141—143 °C (decomp.); $\nu_{max.}$ 1 625, 1 600, 1 490, 1 450, and 1 050 $cm^{-1}$; δ ($CD_2Cl_2$) 8.5 (3 H, m), 8.0 (1 H, m), 7.3 (15 H, m), and 2.5 (3 H, s).

2-*Methyl-derivative* (10). To a solution of dry (KOH) 2-methylpyridine (20 ml, 0.2 mol) in dry $CH_2Cl_2$ (50 ml) was added [$Ph_3C$][$BF_4$] (7 g, 0.021 mol). The solution was stirred vigorously under dry $N_2$ until the colour was discharged (30 min), dry ether (150 ml) was added, and the deposited product filtered and washed (dry $Et_2O$) under a rubber dam. The *salt* (10) was obtained (75%) as pale yellow prisms, m.p. 146—148 °C (decomp.); $\nu_{max.}$ 1 625, 1 600, 1 490, 1 470, and 1 050 $cm^{-1}$; δ ($CD_2Cl_2$) 8.6 (2 H, m), 8.15 (2 H, m), 7.3 (15 H, m), and 2.8 (3 H, s).

*Reactions of Ester and Nitrile Anions with the Salt* (1).—*Dihydro-intermediates* (3) *and* (7). *N*-Isopropylcyclohexylamine (0.329 ml, 2.0 mmol) was added at −78 °C under dry $N_2$ to a solution of $Bu^nLi$ (15% in hexane; 1.20 ml, 2.0 mmol) in dry THF (10 ml), followed by the appropriate ester (2) or nitrile (6) during 2 min. The mixture was stirred for 20—40 min to ensure complete formation of the lithio-derivative, the pyridinium salt (1) (576 mg, 2.0 mmol)

† The same ketone was formed in 78% yield *via* the salt (1).[2]

TABLE 5

$^1H$ N.m.r. and i.r. spectroscopic data for α-(4-pyridyl)esters (4), (15), and (16)

| | $^1H$ N.m.r. (δ) [a] | | | | | $\nu_{max.}$ [b]/$cm^{-1}$ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Pyridine ring [c] | | | | | Ester group | | Pyridine ring | | |
| Compound | 2,6 | 3,5 | $R^1$ | $R^2$ | $R^3$ | | | | | |
| (4a) [d] | 8.45 (m) | 7.15 (m) | 3.50 (s) | | 1.20 (t), 4.10 (q) | 1.725 | 1 170 | 1 600 | 1 550 | 820 |
| (4b) | 8.55 (m) | 7.20 (m) | 3.50 (s) | | 1.40 (s), | 1 735 | 1 140 | 1 595 | 1 550 | 825 |
| (4c) | 8.55 (m) | 7.25 (m) | 3.42 (t) | 0.88 (t), 1.85 (m) | 1.10 (t), 4.15 (q) | 1 725 | 1 170 | 1 595 | 1 550 | 820 |
| (4d) | 8.45 (m) | 7.25 (m) | 3.62 (t) | 0.90 (t), 1.20 (m), 1.90 (m) | 3.65 (s) | 1 725 | 1 165 | 1 600 | 1 560 | 815 |
| (4e) [d] | 8.55 (m) | 7.25 (m) | 3.52 (t) | 0.90 (t), 1.20 (m), 1.90 (m) | 1.20 (t), 4.15 (q) | 1 725 | 1 165 | 1 595 | 1 555 | 820 |
| (4f) | 8.55 (m) | 7.25 (m) | 3.15 (d) | 0.82 (dd), 2.30 (m) | 3.65 (s) | 1 730 | 1 155 | 1 600 | 1 555 | 815 |
| (4g) | 8.60 (m) | 7.30 (m) | 4.10 (dd) [e] | 2.50 (m) | 4.10 (m) [e] | 1 765 | 1 170 | 1 590 | 1 550 | 815 |
| (4h) | 8.68 (m) | 7.20 (m) | 4.10 (m) [e] | 1.8 (m) | 4.10 (m) [e] | 1 725 | 1 160 | 1 600 | 1 560 | 815 |
| (4i) | 8.55 (m) | 7.20 (m) | 4.10 (m) [e] | 1.4 (m) | 4.10 (m) [e] | 1 720 | 1 160 | 1 595 | 1 550 | 825 |
| (4j) | 8.60 (m) | 7.25 (m) | 4.95 (s) | 7.30 (m) | 1.22 (t), 4.22 (q) | 1 725 | 1 150 | 1 600 | 1 550 | 830 |
| (4k) | 8.55 (m) | 7.25 (m) | 1.55 (s) | | 3.65 (s) | 1 725 | 1 150 | 1 595 | 1 550 | 820 |
| (4l) | 8.55 (m) | 7.30 (m) | | 2.15 (m), 2.60 (m), 5.70 (m) | 3.62 (s) | 1 725 | 1 170 | 1 600 | 1 550 | 825 |
| (15c) | 8.55 (d), *2.50* (s) | 7.25 (m) | 3.42 (t) | 0.85 (t), 1.80 (m) | 1.17 (t), 4.12 (q) | 1 730 | 1 165 | 1 590 | 1 555 | 820 |
| (15j) | 8.50 (d), *2.50* (s) | 7.25 (m) | 5.00 (s) | 7.30 (m) | 1.20 (t), 4.20 (q) | 1 725 | 1 170 | 1 600 | 1 560 | 805 |
| (16c) | 8.35 (m) | 7.25 (d), *2.30* (s) | 3.70 (t) | 0.89 (t), 1.80 (m) | 1.14 (t), 4.10 (q) | 1 725 | 1 180 | 1 590 | 1 560 | 835 |
| (16j) | 8.35 (m) | 7.20 (d), *2.15* (s) | 5.17 (s) | 7.22 (m) | 1.11 (t), 4.15 (q) | 1 730 | 1 150 | 1 595 | 1 550 | 840 |

[a] In $CDCl_3$ on a Perkin-Elmer R-20 spectrometer. [b] As neat liquids on a Perkin-Elmer 577 spectrometer. [c] Values in italics are for ring methyl groups. [d] Prepared from salt (1), characterised only by i.r. and $^1H$ n.m.r. spectroscopy. [e] Signals superimposed.

was added portionwise over 5 min, and stirring was continued for 30 min at −78 °C. The solvent was removed under reduced pressure at 25 °C, the residue extracted with $CHCl_3$ (2 × 30 ml), the solution evaporated, and the product was triturated with light petroleum to remove $Pr^iNHC_6H_{11}$. It was further purified by eluting through a short (10 cm) $Al_2O_3$ column (grade V; neutral) with $CHCl_3$. Yields are given in Table 1.

*Decomposition to products* (4) *and* (8). The intermediate (3) or (7) was refluxed in $CCl_4$ (25 ml) for 16 h in the presence of azoisobutyronitrile. Evaporation of the solvent and elution of the residue through an $Al_2O_3$ column with $CHCl_3$ gave the desired product (first to emerge) in essentially quantitative yield.

*Reactions of Ester and Nitrile Anions with Salts* (9)—(11). —*Method A*. The ester or nitrile lithio-derivative was prepared as above only using LDA [from $Pr^i_2NH$ (0.283 ml, 2.0 mmol)] in place of LICA. The appropriate pyridinium salt (9)—(11) (2.0 mmol) was added to the stirred solution over 2 min at 0 °C, the mixture was stirred at 25 °C for 4—6 h, $CHCl_3$ (30 ml) was added, and the product washed first with saturated $NH_4Cl$ solution (2 × 30 ml), and then with 2M HCl (2 × 30 ml). The HCl solution was washed with $Et_2O$ (30 ml), basified with $K_2CO_3$, and extracted with $CHCl_3$ (3 × 20 ml). The $CHCl_3$ solution was dried ($Na_2SO_4$), and evaporated to give the desired pyridyl ester or nitrile as an oil, which could be further purified by preparative t.l.c. on $SiO_2$ using $Et_2O$–$CHCl_3$ (3 : 7), or by column chromatography on $SiO_2$ [$Et_2O$–$CHCl_3$ (5 : 95)] or on $Al_2O_3$ (grade I; neutral) [$Et_2O$–$CHCl_3$ (1 : 9)].

TABLE 6

$^1H$ N.m.r. and i.r. spectroscopic data for α-(4-pyridyl)nitriles (8), (20), (21), and (25)

| | $^1H$ N.m.r. (δ) [a] | | | | $\nu_{max.}$ [b]/cm$^{-1}$ | | | |
|---|---|---|---|---|---|---|---|---|
| | Pyridine ring [c] | | | | Nitrile group | Pyridine ring | | |
| Compound | 2,6 | 3,5 | $R^1$ | $R^2$ | | | | |
| (8a) | 8.60 (m) | 7.30 (m) | 3.95 (q) | 1.60 (d) | 2 240 | 1 600 | 1 550 | 820 |
| (8b) | 8.65 (m) | 7.30 (m) | 3.80 (t) | 1.10 (t), 1.95 (m) | 2 240 | 1 600 | 1 550 | 815 |
| (8c) | 8.63 (m) | 7.30 (m) | 3.78 (d) | 1.00 (dd), 2.10 (m) | 2 240 | 1 600 | 1 560 | 820 |
| (8d) | 8.60 (m) | 7.28 (m) | 5.13 (s) | 7.35 (m) | 2 240 | 1 600 | 1 550 | 830 |
| (8e) | 8.65 (m) | 7.40 (m) | 1.70 (s) | | 2 240 | 1 600 | 1 550 | 820 |
| (20b) | 8.48 (d), *2.50* (s) | 7.10 (d), 7.18 (s) | 3.80 (t) | 1.12 (t), 1.90 (m) | 2 240 | 1 600 | 1 560 | 830 |
| (20d) | 8.32 (d), *2.50* (s) | *d* | 5.18 (s) | 7.20 (m) | 2 240 | 1 600 | 1 560 | 815 |
| (21b) | 8.35 (d), 8.40 (s) | 7.25 (d) *2.30* (s) | 3.90 (t) | 1.10 (t), 1.85 (m) | 2 240 | 1 595 | 1 550 | 820 |
| (21d) | 8.20 (d), 8.25 (s) | *d*, *2.20* (s) | 5.35 (s) | 7.30 (m) | 2 240 | 1 590 | 1 550 | 830 |
| (25) | 8.60 (m) | 7.25 (m) | | 2.2 (m) 2.7 (m) | 2 210 | 1 600 | 1 550 | 830 |

[a] In $CDCl_3$. [b] As neat liquids. [c] Values in italics are for ring methyl groups. [d] Hidden by phenyl signal.

TABLE 7

Physical and analytical data for derivatives of pyridine esters and nitriles

| | | | Found (%) | | | | Requires (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| Compound | Derivative [a] | M.p. (°C) [b] | C | H | N | Formula | C | H | N |
| (a) Esters | | | | | | | | | |
| (4b) | MB | 69—70 | 79.4 | 7.5 | 2.8 | $C_{36}H_{38}BNO_2$ [c] | 79.3 | 7.3 | 2.6 |
| (4c) | MB | 145—146 | 80.7 | 7.0 | 2.5 | $C_{36}H_{38}BNO_2$ [d] | 80.5 | 7.3 | 2.6 |
| (4d) | P | 137—137.5 | 48.4 | 4.3 | 13.3 | $C_{17}H_{18}N_4O_9$ | 48.3 | 4.3 | 13.3 |
| (4f) | P | 124—124.5 | 48.6 | 4.4 | 13.3 | $C_{17}H_{18}N_4O_9$ | 48.3 | 4.3 | 13.3 |
| (4g) | MB | 134—135 | 82.3 | 6.4 | 2.8 | $C_{34}H_{32}BNO_2$ | 82.1 | 6.5 | 2.8 |
| (4h) | MB | 219—220 | 82.4 | 6.5 | 2.8 | $C_{35}H_{34}BNO_2$ | 82.2 | 6.7 | 2.7 |
| (4i) | P | 182—183 | 49.0 | 4.2 | 13.4 | $C_{17}H_{16}N_4O_9$ | 48.6 | 3.8 | 13.3 |
| (4j) | MB [e] | 157—158 | 81.2 | 6.5 | 2.3 | $C_{40}H_{38}BNO_2$ | 80.9 | 6.7 | 2.4 |
| (4k) | MB | 192—193 | 81.7 | 7.3 | 2.9 | $C_{35}H_{36}BNO_2$ | 81.8 | 7.0 | 2.7 |
| (4l) | MI | 168—169 | 46.9 | 5.3 | 4.1 | $C_{14}H_{18}INO_2$ | 46.8 | 5.1 | 3.9 |
| (16c) | MB | 205—206 | 79.7 | 7.5 | 2.7 | $C_{37}H_{40}BNO_2$ [c] | 79.4 | 7.5 | 2.5 |
| (16j) | MB | 100—101 | 80.8 | 6.8 | 2.6 | $C_{41}H_{40}BNO_2$ [c] | 81.1 | 7.0 | 2.3 |
| (b) Nitriles | | | | | | | | | |
| (8a) | MB | 173—174 | 82.7 | 6.9 | 3.4 | $C_{33}H_{31}BN_2$ [f] | 82.8 | 6.5 | 3.4 |
| (8b) | MB | 189—190 | 84.8 | 7.0 | 5.6 | $C_{34}H_{33}BN_2$ | 85.0 | 6.9 | 5.8 |
| (8c) | P | 123—123.5 | 49.4 | 4.0 | 17.7 | $C_{16}H_{15}N_5O_7$ | 49.4 | 3.9 | 17.9 |
| (8d) | P [g] | 134—135 | 53.8 | 3.3 | 16.5 | $C_{19}H_{13}N_5O_7$ | 53.8 | 3.1 | 16.5 |
| (8e) | P | 124—125 | 48.2 | 3.9 | 18.5 | $C_{15}H_{13}N_5O_7$ | 48.0 | 4.2 | 18.7 |
| (21b) | P | 130—130.5 | 49.5 | 4.1 | 17.7 | $C_{16}H_{15}N_5O_7$ | 49.4 | 3.9 | 17.9 |
| (21d) | MB | 129—130 | 71.1 | 7.3 | 4.3 | $C_{39}H_{35}BN_2$ [h] | 71.0 | 7.3 | 4.2 |
| (25) | MB | 180—181 | 83.0 | 7.2 | 4.9 | $C_{38}H_{37}BN_2$ [c] | 82.9 | 7.1 | 5.1 |

[a] MB = Methotetraphenylborate; MI = methiodide; P = picrate. [b] Crystalline form, all prisms. [c] Analyses as monohydrate. [d] Analyses as hemihydrate. [e] Parent pyridine, m.p. 135—136 °C, see Experimental section. [f] Analyses as monohydrate + $NaBPh_4$. [g] Parent pyridine, m.p. 76—76.5 °C (lit.,[5c] 76—76.5 °C). [h] Analyses as hexahydrate.

*Method B*. The dihydro-intermediate was prepared as for method A. The THF was removed under reduced pressure at 25 °C as soon as all the pyridinium salt had dissolved. The residue was extracted with $CHCl_3$ (40 ml), the extract filtered, the filtrate mixed with $CCl_4$ (30 ml; AR grade), and stirred at 25 °C in the presence of air for 16 h. After evaporation of the solvent the residue was eluted through an $Al_2O_3$ column (grade I, neutral) first with $CCl_4$–$CHCl_3$ (2 : 8) to remove $Ph_3CH$, and then with $Et_2O$–$CHCl_3$ (1 : 9) to give the desired product.

*Method C*. As for method B, except that the $CHCl_3$ extract, instead of being mixed with $CCl_4$, was evaporated to dryness. The residue was eluted through an $Al_2O_3$ column (Grade IV: neutral) with $CHCl_3$, the eluant evaporated, and the residue refluxed in toluene (30 ml; AR grade) for 16 h together with a little dibenzoyl peroxide. The product was isolated by acid and base treatment as for method A.

Yields and methods of decomposition are given in Tables 3 and 4, and i.r. and $^1H$ n.m.r. spectra are recorded in Tables 5 and 6, respectively.

*Preparation of Derivatives*.—Picrates were prepared by mixing $Et_2O$ solutions of the pyridine and of picric acid, and were recrystallised from 95% EtOH. Methiodides were prepared with MeI in dry EtOAc. If the precipitated gum did not crystallise on trituration with dry $Et_2O$, a saturated aqueous solution of $NaBPh_4$ was added, and the precipitated tetraphenylborate salt was recrystallised from 95% EtOH, or acetone–ether. Analytical data and m.p. for derivatives are given in Table 7.

*Large-scale Preparations of Ester* (4j) *and Nitrile* (8d).—Prepared as above from ethyl phenylacetate (2j) and benzyl cyanide (6d), respectively, only on 0.01 mol (×5) scale. The *ester* (4j) (1.56 g; 65%) was isolated as pale yellow prisms, m.p. 97—98 °C (benzene–light petroleum) (Found: C, 71.0; H, 6.2; N, 5.3. $C_{15}H_{15}NO_2 \cdot 0.75H_2O$ requires C, 70.7; H, 6.2; N, 5.1%); *m/e* 241 ($M^+$); and the nitrile (8d) (1.04 g, 58%) as pale yellow prisms, m.p. 76—76.5 °C (benzene–hexane) (lit.,[5c] 76—76.5 °C); *m/e* 194 ($M^+$).

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