Synthetic Applications of *N–N* Linked Heterocycles. Part 11.[1] Regiospecific Synthesis of Dialkyl Pyridin-4-yl-, Quinolin-4-yl-, and Isoquinolin-1-yl-phosphonates

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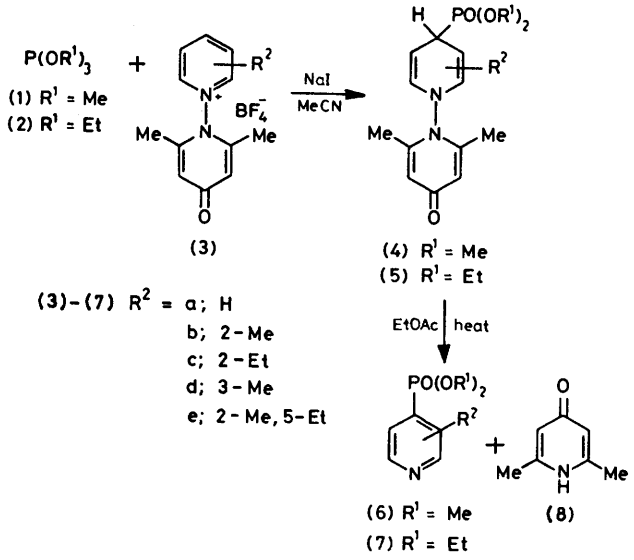
Treatment of *N*-(2,6-dimethyl-4-oxopyridin-1-yl)-pyridinium, -quinolinium, and -isoquinolinium salts with trialkyl phosphites in the presence of sodium iodide gives regiospecifically dihydro-intermediates, which may be decomposed in good yields to dialkyl pyridin-4-yl-, quinolin-4-yl-, and isoquinolin-1-yl-phosphonates respectively. The reaction may also be carried out in one step without isolating the dihydro-intermediate.

We have recently demonstrated the versatility of the *N*-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium salts (3) in the regiospecific synthesis of a variety of 4-substituted pyridines.[2] The pyridone methyl groups in the salts sterically shield the 2- and 6-positions of the pyridinium ring, thus directing an attacking nucleophile into the 4-position. The pyridone moiety then serves as a leaving group in rearomatising the pyridine ring. This synthetic strategy has now been developed further to include the preparation of pyridin-4-yl-, quinolin-4-yl-, and isoquinolin-1-yl-phosphonates.



Redmore [3] has shown that the reaction between diethyl sodio- or lithio-phosphonates and *N*-methoxypyridinium salts gives pyridin-2-ylphosphonates in moderate yields. When the 2- and 6-positions of the salt were blocked with methyl groups, a low yield of a pyridin-4-ylphosphonate (7; $R^2 = 2,6\text{-}Me_2$) was obtained. The method has also been used to prepare diethyl isoquinolin-1-ylphosphonate and a mixture of the diethyl esters of quinolin-2-yl- and quinolin-4-yl-phosphonic acids.[4] It was later reported [5] that dialkyl pyridin-4-ylphosphonates could be prepared from dialkyl sodiophosphonates and (triphenylmethyl)pyridinium salts, the bulky triphenylmethyl group sterically shielding the 2- and 6-positions from attack. Yields, however, were low to moderate. Pyridin-4-ylphosphonates, or the parent acids, have also been prepared by nucleophilic displacement of a suitable leaving group at the 4-position of the pyridine ring.[6,7]

Recently, Akiba and his co-workers [8] reported the preparation of 9,10-dihydro-10-dimethoxyphosphinyl derivatives of acridinium, xanthylium, and thioxanthylium salts in high yields by treatment of the salts with trimethyl phosphite (1) and sodium iodide under mild conditions. We have used this approach in the present work.

RESULTS AND DISCUSSION

Treatment of oxopyridinylpyridinium salts (3) in dry MeCN with one equivalent each of trialkyl phosphite (1) or (2) and of sodium iodide, gave, after stirring under nitrogen at 25 °C, the dihydro-intermediates (4) or (5). Generally, these were too unstable to be characterised by microanalysis, and after isolation were converted in high yield into the pyridin-4-ylphosphonates (6) or (7) and the pyridone (8) by heating under reflux in ethyl acetate. Likewise the corresponding *N*-(2,6-dimethyl-4-oxopyridin-1-yl)-quinolinium and -isoquinolinium salts gave the intermediates (9) and (10), though the latter, due to instability, was isolated in admixture with the final product (12). These intermediates also decomposed smoothly in ethyl acetate to give the phosphonates (11) and (12), the former being, to our knowledge, the first-recorded preparation of a quinolin-4-ylphosphonate free from other isomers. This isolation of the 4-isomer makes an interesting contrast with the reaction between the same quinolinium salt and cyanide ion, in which only 2-cyanoquinoline was formed.[1] A reaction using the pyridinium salt (3a) having iodide as counter ion in place of tetrafluoroborate also gave intermediate (4a) with trimethyl phosphite in essentially the same yield, in the absence of added NaI. Analogous reactions have been carried out by Sheinkman and co-workers [9] using the chloride counter ion in acridinium, quinolinium, and pyridinium salts.

In an experiment to evaluate the effectiveness of an alternative *N*-substituent to the pyridone moiety in the salts (3), *N*-(2,5-dimethylpyrrol-1-yl)pyridinium iodide [1] was converted into the intermediate (13) using trimethyl

TABLE 1

I.r. and ^{1}H n.m.r. spectroscopic data for dihydro-intermediates (4), (5), (9), (10), and (13)

Compound	R^1	R^2	I.r. ($\nu_{max.}$/cm^{-1}) [a] Pyridone	1,4-Dihydro	P=O	P–O–C	^{1}H N.m.r. (δ) [b] Pyridone ring 2′, 6′	3′, 5′	1-4,Dihydropyridine ring 2,6	3,5	4	O–R^1 [c]
(4a)	Me	H	1.635 1 520	1 675	1 245	1 045 1 025	*2.30* *2.37*	6.10	6.09	4.70 [d]	3.6 [e]	*3.83*
(4b)	Me	2-Me	1 640 1 525	1 684	1 245	1 050 1 028	*2.45* *2.51*	6.46	6.22 [f] *1.56* [g]	4.62	3.5 [e]	*3.78*
(4c)	Me	2-Et	1 632 1 562	1 687	1 250	1 040	*2.45* *2.52*	6.65	6.15 *2.55* *1.05*	4.81	3.6 [e]	*3.75*
(4d)	Me	3-Me	1 638 1 568	1 688	1 245	1 050 1 030	*2.28* *2.39*	6.14	5.9	4.69 *1.88*	3.46 [h]	*3.85*
(4e)	Me	2-Me,5-Et	1 636 1 568	1 693	1 250	1 046 1 030	*2.31* *2.42*	6.35	6.00 [f] *1.56* [g]	4.55 *2.38* *1.03*	3.5 [e]	*3.76*
(5a)	Et	H	1 645 1 575	1 680	1 250	1 050 1 020	*2.38* *2.42*	6.32	6.06 [f]	4.72 [d]	3.55 [h]	*4.17* *1.35*
(9)			1 644 1 570	1 668	1 248	1 055 1 030	*2.29* *2.54*	6.77	6.06	4.98	4.25 [j]	*3.75* [k]
(10)			1 639 1 565	1 666	1 252		*2.01* *2.25*	6.10	*l*	6.29	5.92	*3.78*
(13) [m]			1 614 [n] 1 524 [n]	1 679	1 249	1 055 1 030	*2.12* [n] *2.16* [n]	5.61 [n]	5.94	4.55 [d]	3.55 [h]	*3.78*

[a] $CHBr_3$ Mulls. [b] In $CDCl_3$ with internal $SiMe_4$. Values in italics refer to alkyl substituents. The pyridone Me groups give separate signals due to restricted rotation about the N–N bond. [c] J_{POCH} 10.5 Hz for all $POCH_3$ groups. [d] J_{PCCH} 4 Hz. [e] Approximate value; second half of signal masked by OMe. [f] J_{PCCCH} 5 Hz. [g] J_{PCCCCH} 4.5 Hz. [h] J_{PCH} 24 Hz. [i] J_{POCH} 7 Hz. [j] J_{PCH} 25 Hz. [k] Aryl H δ 7.1—7.5 (3 H, m), 6.5 (1 H, d). [l] Not applicable, 1-H occurs at δ 5.33. [m] 100 MHz ^{1}H N.m.r. spectrum. J_{PCCCXH} 4.5 Hz; $J_{2,3}$ 8 Hz; $J_{2,4}$ 1 Hz; $J_{3,4}$ 4 Hz. [n] Bands arising from pyrrole ring.

phosphite, again in the absence of added sodium iodide. The intermediate, though formed in 58% yield, was very much more stable than those formed from the salts (3), and gave only 47% of product (6a) even after refluxing for 72 h in chloroform, and in the presence of a radical initiator.

Although dihydro-intermediates were isolated above for the purposes of characterisation, this was found to be unnecessary for the successful preparation of the heteroarylphosphonates. Thus, the acetonitrile solution from reaction of the salt (3a) with trimethyl phosphite was heated under reflux for 4 h, and gave on evaporation and subsequent purification the pyridin-4-ylphosphonate (6a) directly in 59% overall yield from the pyridinium salt, as compared with 64% when the reaction was carried out in two steps. Also, a reaction scaled up five times gave the phosphonate (6d) in an overall yield of 65%.

Finally, an attempt was made to prepare pyridin-4-ylphosphonates by a method analogous to that described for 4-(α-acylalkyl)pyridines.[10] Diethyl phosphonate was added to a solution of lithium di-isopropylamide (LDA) in tetrahydrofuran (THF). However, diethyl lithiophosphonate precipitated from solution, and failed to react with the subsequently added pyridinium salt (3a).

I.r. and ^{1}H n.m.r. spectroscopic data, and physical and microanalytical data for the dihydro-intermediates are presented in Tables 1 and 2 respectively. Likewise, analogous data for the heteroarylphosphonates are given in Tables 3 and 4 respectively. Overall yields of products from pyridinium salts are thus found to be 38—72%, which are substantially higher than those reported by the alternative method.[5] In all cases the product consisted of only one isomer.

TABLE 2

Physical and analytical data for dihydro-intermediates (4), (5), (9), (10), and (13)

Compound	R^1	R^2	Yield (%)	M.p. (°C)	Crystal form
(4a) [a]	Me	H	68 [b]	113—114 [c]	needles
(4b)	Me	2-Me	71		oil
(4c)	Me	2-Et	47		oil
(4d)	Me	3-Me	68	121—123	prisms
(4e)	Me	2-Me, 5-Et	58		oil
(5a)	Et	H	88	125—127	needles
(9)			83	84—85	plates
(13)			58	57—60	plates

[a] Found: C, 54.1; H, 6.1; N, 8.5. $C_{14}H_{19}N_2O_4P$ requires C, 54.2; H, 6.2; N, 9.0%). [b] Yield from iodide salt without addition of NaI was 60%. [c] From EtOAc.

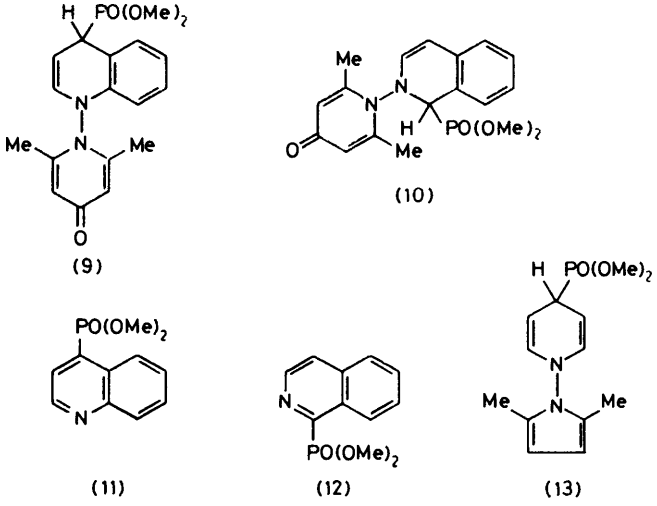


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TABLE 3

I.r. and ^{1}H n.m.r. spectroscopic data for heteroarylphosphonates (6), (7), (11), and (12)

			I.r. ($\nu_{max.}$/cm^{-1}) [a]		^{1}H N.m.r. (δ) [b] Ring substituents [c]				
Compound	R^1	R^2	P=O	P–O–C	2-	6-	3-	5-	OR^1 [d]
(6a)	Me	H	1 255	1 055 1 030		8.79		7.59	*3.74*
(6b)	Me	2-Me	1 260	1 060 1 035	*2.64*	8.67	7.57	7.48	*3.81*
(6c)	Me	2-Et	1 258	1 055 1 032	*2.93* *1.36*	8.70	7.60	7.46	*3.83*
(6d)	Me	3-Me	1 255	1 055 1 035		8.60 [e]	*2.55*	7.71	*3.80*
(6e)	Me	2-Me,5-Et	1 255	1 045 1 025	*2.59*	8.55	7.60	*2.86* *1.28*	*3.81*
(7a)	Et	H	1 260	1 050 1 022		8.81		7.71	*4.19* [f] *1.35*
(11)			1 255	1 050 1 025	9.05	*g*	7.8 [h]	g	*3.83*
(12)			1 245	1 050 1 030	*i*	*i*	8.97	*i*	*3.95*

[a] $CHBr_3$ Mulls. [b] In $CDCl_3$ with internal $SiMe_4$. Values in italics are for alkyl substituents. [c] J_{PCCH} 4.5—6.5 Hz for 2-H and 6-H; J_{PCH} 12—14.5 Hz for 3-H and 5-H. [d] J_{POCH} 11.3 Hz for all $POCH_3$ groups. [e] Multiplet comprising 2-H and 6-H. [f] J_{POCH} 7.2 Hz. [g] Aryl H δ 7.5—8.6. [h] Approximate value; masked by aryl H signals. [i] 8-H appears at δ 8.73 (d); 4-H, 7-H appear at δ 7.6—7.9 (4 H, m).

TABLE 4

Physical and analytical data for dialkyl heteroarylphosphonates (6), (7), (11), and (12)

						Picrate derivative						
						Found (%)				Required (%)		
Compound	R^1	R^2	Yield (%) [a]	M.p. (°C)	Crystal form [b]	C	H	N	Formula	C	H	N
(6a)	Me	H	96 [c,d]	139—140	plates	37.4	2.8	13.1	$C_{13}H_{13}N_4O_{10}P$	37.5	3.1	13.5
(6b)	Me	2-Me	60	112—114	plates	39.5	3.7	12.7	$C_{14}H_{15}N_4O_{10}P$	39.1	3.5	13.0
(6c)	Me	2-Et	81	123	plates	40.6	3.8	12.5	$C_{15}H_{17}N_4O_{10}P$	40.6	3.9	12.6
(6d)	Me	3-Me	73	93—94	plates	38.9	3.7	12.9	$C_{14}H_{15}N_4O_{10}P$	39.1	3.5	13.0
(6e)	Me	2-Me,5-Et	78 [e]	168	needles	41.9	4.2	12.1	$C_{16}H_{19}N_4O_{10}P$	41.9	4.2	12.2
(7a)	Et	H	82	152—153 [f]	needles	40.6	3.7	12.4	$C_{15}H_{17}N_4O_{10}P$	40.6	3.9	12.6
(11)			84	145—147	needles	43.8	3.1	11.9	$C_{17}H_{15}N_4O_{10}P$	43.8	3.2	12.0
(12)			53 [g]	112—112.5	plates	43.8	3.1	12.1	$C_{17}H_{15}N_4O_{10}P$	43.8	3.1	12.0

[a] Based on dihydro-intermediate. [b] From EtOH. [c] From intermediate (4a). Intermediate (13) gave only 47%. [d] Overall yield from salt (3a) without isolating intermediate was 59%. [e] Also analysed as the free base (Found: C, 49.9; H, 7.3; N, 5.5. $C_{10}H_{16}NO_3P\cdot\frac{2}{3}H_2O$ requires C, 49.8; H, 7.2; N, 5.8%). [f] Lit., [5] 152—153 °C. [g] Overall yield from isoquinolinium salt.

Spectroscopic Data.—The data presented in Tables 1 and 3 are fully consistent with proposed structures. However, some comments on the phosphorus couplings in the dihydro-intermediates are appropriate. Couplings between P and H are observable over two to five bonds, 3-, 4-, and 5-bond couplings being of similar magnitude (4—5 Hz), whereas 2-bond couplings (24—25 Hz) are much larger. These data compare well with those for analogous structures recorded by Akiba and his co-workers,[8] but differ significantly from the values reported recently for a 4-diethylphosphinyl-1,4-dihydropyridine.[11] The authors assign 3-H and 5-H to a signal at δ 3.49 (J_{PCCH} 15 Hz), and 4-H to a signal at δ 4.49. In view of our findings (Table 1) it is possible that these latter assignments should be reversed.

EXPERIMENTAL

I.r. spectra were recorded for $CHBr_3$ mulls on a Perkin-Elmer 257 instrument, and ^{1}H n.m.r. spectra on a Perkin-Elmer R-12 spectrometer for solutions in $CDCl_3$ with Me_4Si as internal reference.

Acetonitrile was redistilled from P_4O_{10} and stored over molecular sieves; sodium iodide was dried in a desiccator over $CaCl_2$ before use; and phosphite esters (1) and (2) were used as supplied. 4-Oxopyridinylpyridinium salts (3) were prepared as described previously,[12] salt (3c), reported here for the first time, being prepared analogously (42%) as *needles*, m.p. 172—173 °C (from 95% EtOH) (Found: C, 46.4; H, 4.9; N, 7.6. $C_{14}H_{17}BF_4N_2O\cdot\frac{1}{2}HBF_4$ requires C, 46.7; H, 4.9; N, 7.8%). Likewise, the *N*-(2,6-dimethyl-4-oxopyridin-1-yl)-quinolinium and -isoquinolinium salts, and the *N*-(2,5-dimethylpyrrol-1-yl)pyridinium iodide were prepared as reported.[1] Salts were all dried *in vacuo* before use.

General Procedure for the Preparation of Dihydro-intermediates (4), (5), (9), (10), *and* (13).—To a stirred suspension of the appropriate pyridinium or quinolinium salt (2 mmol) in dry MeCN (20 ml) under N_2 was added $P(OMe)_3$ (0.25 g, 2 mmol) followed by finely divided NaI (0.30 g, 2 mmol). After 1 h at 25 °C the solvent was removed *in vacuo*, water (20 ml) was added, the mixture was extracted with CH_2Cl_2 (3 × 15 ml), and the extracts were dried ($MgSO_4$), filtered, and evaporated to give the dihydro-intermediate as a hygroscopic oil or solid. Spectra of oils were recorded for crude products; solids were purified by dissolving in CH_2Cl_2 and reprecipitating by slow addition of dry Et_2O.

General Procedure for the Decomposition of Intermediates to Dialkyl Heteroarylphosphonates (6), (7), (11), *and* (12).—The crude dihydro-intermediate obtained by evaporation of the CH_2Cl_2 was dissolved in EtOAc (40 ml), heated under reflux (4 h), cooled, evaporated, and eluted on an alumina column (grade I; neutral) with $CHCl_3$. Products were obtained as colourless oils, some of which solidified on

standing. They were converted into picrate derivatives in the usual manner.

Large Scale Preparation of Phosphonate (6d).—This preparation was performed as above but scaled up five times. The intermediate (4d) (2.85 g, 66%), was decomposed to give the *phosphonate* (6d) (1.73 g, 98%), b.p. 109 °C at 0.7 mmHg, which solidified on standing, m.p. 36—38 °C (Found: C, 47.4; H, 6.4; N, 6.9. $C_8H_{12}NO_3P$ requires C, 47.8; H, 6.0; N, 7.0%).

Reactions with Pyridinium Iodides.—N-(2,6-*Dimethyl*-4-*oxopyridin*-1-*yl*)*pyridinium iodide*. The iodide salt (0.66 g, 2 mmol) in dry MeCN was treated with $P(OMe)_3$ as above, but no NaI was added. Work-up gave the intermediate (4a) (60%).

N-(2,5-*Dimethylpyrrol*-1-*yl*)*pyridinium iodide*. Treated likewise with $P(OMe)_3$ in the absence of NaI, the iodide salt required a longer reaction time (4 h). Work-up gave the intermediate (13) (58%) as buff plates, m.p. 57—60 °C (decomp.), which was dissolved in $CHCl_3$ (30 ml) and heated under reflux for 72 h in the presence of azobisisobutyronitrile. Isolation of the product as above yielded the phosphonate (6a) (47%).

One-pot Synthesis of Phosphonate (6a).—The reaction was performed as for the general preparation of the dihydro-intermediates, except that the reaction mixture from stirring together salt (3a), $P(OMe)_3$, and NaI in MeCN for 1 h was refluxed for 4 h, cooled, evaporated *in vacuo*, and the residue eluted through an alumina column with $CHCl_3$ to give the phosphonate (6a) (59%).

Attempted Reaction with Dimethyl Lithiophosphonate in THF.—To a stirred solution of $HPO(OMe)_2$ (0.22 g 2 mmol) in dry THF at −78 °C under N_2 was added BuLi (1.6M in hexane; 1.25 ml, 2 mmol). After 10 min, the white suspension was warmed to 25 °C, added to a suspension of the salt (3a) (0.58 g, 2 mmol) in dry THF (20 ml) and the mixture stirred for 2 h. The solvent was removed *in vacuo*, water (20 ml) was added, the mixture was extracted with CH_2Cl_2 (3 × 15 ml), and the extracts were dried and evaporated. Only $HPO(OMe)_2$ was isolated.

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