Generation and 1,3-Dipolar Behavior of Pyridinium Arylsulfonylmethylides. A Simple Route to Indolizines

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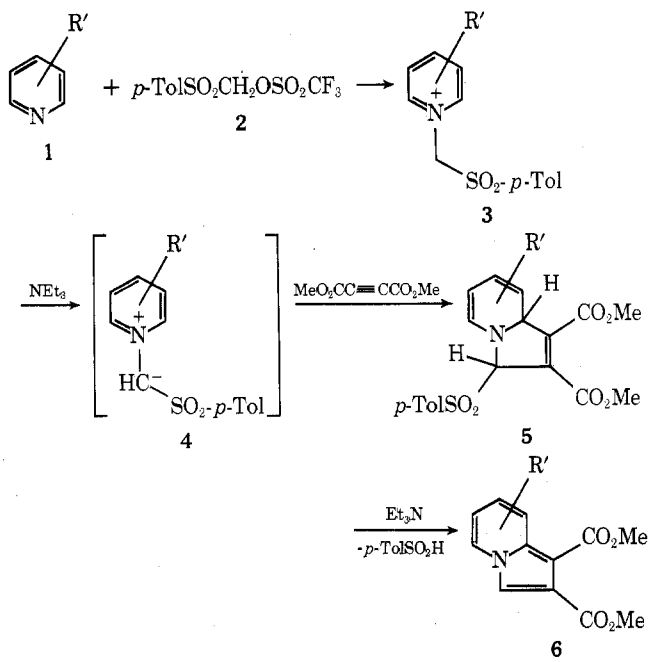
Received January 20, 1976

1-Pyridinium arylsulfonylmethylides (4) were generated by deprotonation of the corresponding pyridinium salts (3). 1,3-Dipolar cycloaddition of the ylides with acetylenes led to dihydroindolizines (5) which aromatized to indolizines by 1,4 elimination of *p*-toluenesulfinic acid. The *p*-toluenesulfonylmethylpyridinium trifluoromethanesulfonates (3) were prepared by the reaction of pyridines and *p*-toluenesulfonylmethyl trifluoromethanesulfonate (2). A new, simple synthesis of 2 was also developed.

There are a number of classical methods[1] and more recent syntheses of indolizines.[2-4] The ring system has recently been obtained from pyridinium ylides by their 1,3-dipolar cycloaddition to acetylenes followed by a 1,4 elimination of hydrogen cyanide from the initially formed dihydro adduct.[2] Intramolecular cyclization of pyridinium allylides[4,8] has also been reported to lead to indolizines in relatively low yield.[5] Several other, less general, methods which take advantage of a specific feature of the intermediates employed have also appeared in the literature,[9,10] some of which[1,9] require elaborate substituents on the pyridine ring. We report a simple, two-step synthesis that affords indolizines in good yield starting from pyridines and *p*-toluenesulfonylmethyl trifluoromethanesulfonate (2) via the intermediacy of pyridinium arylsulfonylmethylides (4), a novel class of unstable reactive intermediates.

The strategy followed involved cycloaddition of a pyridinium arylsulfonylmethylide to a 1,3-dipolarophile such as dimethyl acetylenedicarboxylate, followed by 1,4 elimination of a good leaving group. The sulfonyl group served the dual functions of activating the methylene protons toward deprotonation, and hence stabilizing the resulting ylide by delocalization of the negative charge at the α position, and as the leaving group in the elimination step leading to indolizines (6). It was hoped that the better leaving ability of the sulfinate group relative to cyanide[12] would facilitate the elimination step, thus reducing the competition from aromatization by oxidation.[2-4] The reaction sequence is depicted in Scheme I.

Scheme I



p-Toluenesulfonylmethyl trifluoromethanesulfonate (2) had been prepared in low yield (ca. 25%) from *p*-toluenesulfonyldiazomethane, a compound that is relatively tedious to prepare.[13] On the other hand, the reaction of *p*-toluenesulfinic acid with formaldehyde, followed by esterification with trifluoromethanesulfonic anhydride, gave 2 conveniently in 70% yield.

Scheme II

$$p\text{-TolSO}_2\text{H} \xrightarrow[\text{H}_2\text{O}]{\text{CH}_2\text{O}} p\text{-TolSO}_2\text{CH}_2\text{OH} \xrightarrow[\text{C}_5\text{H}_5\text{N, ether}]{(\text{CF}_3\text{SO}_2)_2\text{O}} p\text{-TolSO}_2\text{CH}_2\text{OSO}_2\text{CF}_3$$

2

Treatment of 2 with substituted pyridines afforded the corresponding pyridinium salts in excellent yields. Table I summarizes the yields and some infrared absorption bands of these compounds, and Table II summarizes the ^{1}H NMR chemical shifts and the coupling constants of the various protons. The pyridine protons in the pyridinium triflates were assigned by analogy with those of other pyridinium salts. The methylene protons absorbed in the region δ 6.20–6.50, consistent with the strong deshielding provided by both the SO_2 and pyridinium groups. The chemical shifts of the methylene protons do not correlate with the σ or σ^+ values of the substituents at the 4 position.

The mass spectrum of the pyridinium salts generally exhibited the M^+ ions arising from the cationic portion of the salts, except in the case of the unsubstituted salt 3 (R^1 = H) which exhibited a signal at *m/e* 278 instead of the expected M^+ at *m/e* 248. The signal at *m/e* 278 is compatible with the $(TolSO_2STol)\cdot^+$ ion, conceivably arising from thermal processes. The recurring features of the mass spectra of the pyridinium salts are summarized in Table III, and some of the plausible patterns are illustrated in Scheme III.

Scheme III

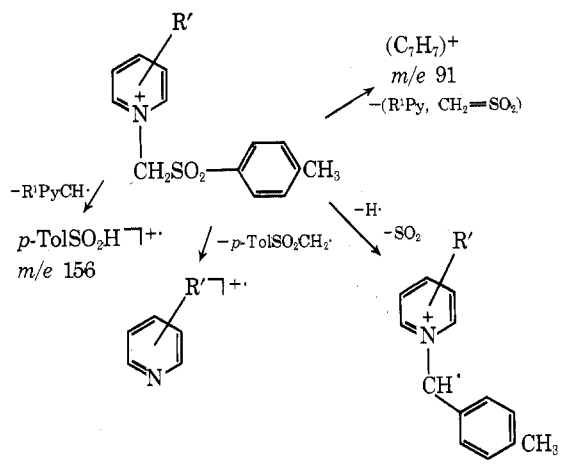
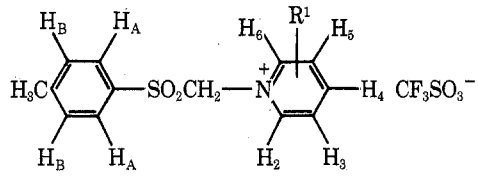


Table I. Synthesis and Infrared Absorption Frequencies (cm^{-1}) of 1-*p*-Toluenesulfonylmethylpyridinium Trifluoromethanesulfonates (3)

R^1	Temp, °C	Time, h	Yield of 3, %	Registry no.	$\nu_{as}SO_2$	ν_{CF_3}	$\nu_{sym}SO_2$	Other
H	140	2	95	58747-50-5	1338	1245	1165	
4-Me	120	2	90	58747-52-7	1335	1260	1150	
4-CN	145	4	97	58747-54-9	1332	1240	1170	ν_{CN} not observed[14]
4-PhCO	145	4	95	58747-56-1	1346	1235	1165	1687 (C=O)
4-*t*-Bu	120	2	85	58747-58-3	1345	1260	1162	
3,5-Cl_2	145	8	92	58747-60-7	1345	1260	1160	
3,5-Me_2	120	2	96	58747-62-9	1350	1270	1165	

Table II. Chemical Shifts (δ) and Coupling Constants (Hz) of 3 in Acetone-d_6



R^1	H_A (J_{AB})	H_B	H_2, H_6 ($J_{2,3} = J_{5,6}$)	H_3, H_5 ($J_{2,4} = J_{4,6}$)	H_4 ($J_{3,4} = J_{4,5}$)	CH_2	CH_3	R^1
H	7.72 (8)	7.43	8.94 (6)	8.25	8.80 (6)	6.38	2.40	
4-Me	7.74 (8)	7.47	8.78 (6)	8.10		6.30	2.44	2.77
4-CN	7.87 (8)	7.47	9.28 (6)	8.72		6.49	2.46	
4-PhCO	8–7.4[b]	8–7.4[b]	9.23 (6)	8.51		6.53	2.48	8–7.4
4-*t*-Bu[a]	7.72 (8)	7.32	8.81 (6)	7.94		6.20	2.41	1.36
3,5-Cl_2	7.82 (8)	7.51	9.21	(1.5)	9.11	6.36	2.47	
3,5-Me_2	7.74 (8)	7.52	8.64	(0.7)	8.57	6.24	2.49	2.54

[a] In $CDCl_3$. [b] Unresolved.

Table III. Values of *m/e* and Relative Abundances (%) of Some Fragments in the Mass Spectra of 3

R^1 in 3	M^+[a]	Base peak	$M^+ - H\cdot, -SO_2$	$M^+ - TosCH_2\cdot$	$M^+ - (PyCH)\cdot$	$M^+ - (Py, CH_2{=}SO_2)$
H		107		79 (52)	156 (10)	91 (85)
4-Me	262 (7)	$(4\text{-MePy})\cdot^+$		93 (100)	156 (20)	91 (80)
4-CN	273 (1)	$(C_7H_7)^+$			156 (10)	91 (100)
4-PhCO	352 (18)	105	287 (6)	183 (35)		91 (78)
4-*t*-Bu	304 (31)	$(C_7H_7)^+$	239 (5)	135 (24)		91 (100)
3,5-Cl_2[b]	316 (12)	$(C_7H_7)^+$	251 (8)	147 (78)	156 (14)	91 (100)

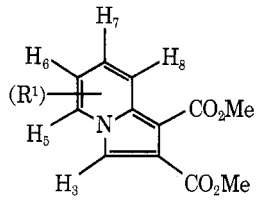
[a] $M^+ \equiv p\text{-TolSO}_2CH_2Py^+$. [b] For ^{35}Cl.

Deprotonation of the salts (3) with triethylamine in chloroform in the presence of dimethyl acetylenedicarboxylate gave the indolizines (6). The yields and some infrared absorptions of 6 and their proton chemical shifts and coupling constants are summarized in Tables IV and V, respectively. The indolizines exhibited two carbonyl absorptions for the carbomethoxy groups.[2,16] A good correspondance between the reported[16] and observed values of the chemical shifts and the coupling constants was obtained for 1,2-dicarbomethoxyindolizine (6, R^1 = H). The presence of a small ($J_{5,8}$ = 1 Hz) but distinct 1,4 coupling, previously unreported,[16] was also observed. 1,4 coupling was similarly observed for the H_5 and H_8 protons in 7-benzoyl- and 7-*tert*-butylindolizines ($J_{5,8}$ = 1 Hz), but not in 7-cyanoindolizine.

The H_3, H_5, H_6, and H_8 protons in the series of indolizines studied here were assigned on the basis of the comparison of their chemical shifts with those in 1,2-dicarbomethoxyindolizine (6, R^1 = H).[16–18] Assignment of H_6 was confirmed by the observation of a pronounced dependence of its chemical shift upon the nature of the substituent at the 7 position. H_5 protons, on the other hand, exhibited a less pronounced dependence. The observed dependence of the H_5, H_6, and H_8 chemical shifts in 7-*tert*-butylindolizine (6, R^1 = 7-Me) on the substituent was small in agreement with the downfield shifts in *tert*-butylbenzene relative to benzene.[19] The methyl protons in the carbomethoxy groups were usually resolved singlets. The lower field singlet is thought to arise from the 2-carbomethoxy protons, on the basis of the greater electron density of C_1 than at C_2 in indolizines.[20] Owing to the very small difference in their chemical shifts, an unequivocal assignment was not possible.

The mass spectrum of the indolizines (6) exhibited the

Table IV. Formation and Infrared Absorption Frequencies (cm^{-1}) of 1,2-Dicarbomethoxyindolizines



Registry no.	R^1	% yield	$\nu_{C=O}$ (CO_2Me)		Other
16959-60-7	H	72	1740 (1738)[a]	1695 (1689)[a]	
58747-63-0	7-CN	78	1720	1697	2217 ($\nu_{C\equiv N}$)
58747-64-1	7-PhCO	82	1730	1695	1650 ($\nu_{C=O}$, PhCO)
58747-65-2	7-*t*-Bu	64	1730	1697	
58747-66-3	6,8-Cl_2	85	1725	1700	
58747-67-4	6,8-Me_2	88	1730	1700	

[a] Reported values.[16]

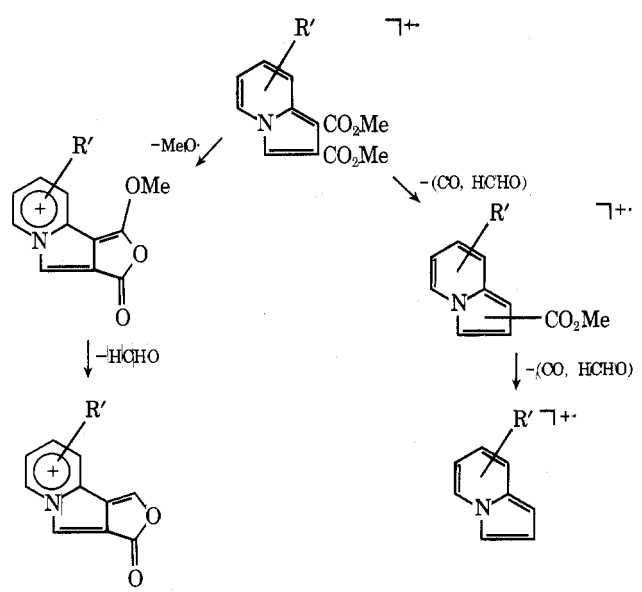
Table V. Chemical Shifts (δ) and Coupling Constants of the Protons in 6 in $CDCl_3$

R^1	H_3 ($J_{5,6}$)	H_5 ($J_{5,7}$)	H_6 ($J_{5,8}$)	H_7 ($J_{6,7}$)	H_8 ($J_{6,8}$; $J_{7,8}$)	1-CO_2CH_3	2-CO_2CH_3	Other
H	7.58 (7)	7.90 (1)	6.64 (1)	6.96 (7)	8.04 (1; 9)	3.86	3.86	
H[e]	(7.61) (7)	(7.93) (1)	(6.71)	(7.03) (7)	(8.10) (1; 9)	(3.90)	(3.90)	
7-CN	7.74 (7)	8.00	6.80		8.45 (2)	3.90	3.92	
7-PhCO	7.72 (8)	7.98	7.26 (1)		8.48 (2)	3.82	3.88	7.80—7.40[a]
7-*t*-Bu	7.50 (8)	7.84	6.75 (1)		8.03 (2)	3.87	3.86	1.30[b]
6,8-Cl_2	7.64	7.83 (2)		6.78		3.84	3.95	
6,8-Me_2[d]	7.78	7.85		6.56		3.81	3.85	3.37 and 3.19[c]

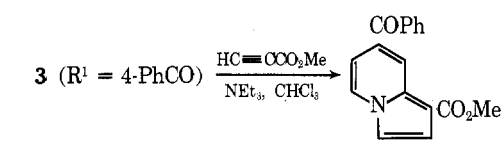
[a] PhCO. [b] *t*-Bu. [c] 6, 8-Me_2. [d] In acetone-d_6. [e] Literature values.[16]

molecular ion in all cases. The recurring features of the mass spectra of the indolizines are summarized in Table VI and possible fragmentation patterns are illustrated in Scheme IV.

Scheme IV



Treatment of **3** (R^1 = 4-PhCO) with triethylamine in the presence of methyl propiolate gave **7** in 65% yield. The infrared spectrum of **7** exhibited only two carbonyl absorptions at 1700 ($\nu_{C=O}$, ester) and 1650 cm^{-1} ($\nu_{C=O}$, benzoyl), respectively. The absorption present at ca. 1730 cm^{-1} in all 1,2-dicarbomethoxyindolizines studied here was absent. This, and the reported ester absorption for 3-benzoyl-1-carbomethoxyindolizine (1697 cm^{-1}),[21] for 1-benzenesulfonyl-2-carbomethoxyindolizine (1715 cm^{-1}),[22] and for 2-carbomethoxyindolizine (1714 cm^{-1}),[16] suggested that the indolizine in question was the 1-carbomethoxy isomer **7**. The NMR spectrum of **7** was similar to that of **6** (R^1 = 7-PhCO) except that the H_2 and H_3 protons appeared as a singlet at δ 7.33. The difference in chemical shifts between H_2 and H_3 protons in indolizine is only 0.50, and is expected to decrease in 1-carbomethoxyindolizine owing to the greater deshielding effect of a 1-carbomethoxy substituent on H_2 than on H_3, and hence the accidental degeneracy of H_2 and H_3 is not unreasonable. Furthermore, **7** is different from authentic 7-benzoyl-2-carbomethoxyindolizine.[23]



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The only failure to date occurred in the attempted synthesis of **6** (R^1 = 4-Me). Other failures have been reported[4] in the

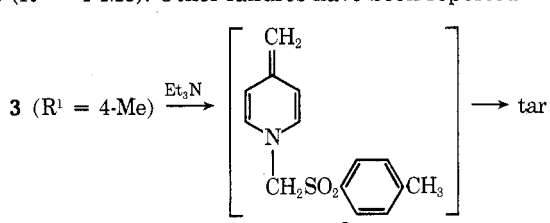

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Table VI. Values of *m/e* and Relative Abundances (%) of Some Fragments in the Mass Spectrum of 6

R^1	$M\cdot^+$	$M\cdot^+ - MeO\cdot$	$M\cdot^+ - MeO\cdot -$ HCHO	$M\cdot^+ -$(CO, HCHO)	$M\cdot^+ - 2$ (CO, HCHO)	Base Peak
H	233 (70)	202 (100)	172 (33)	175 (15)	117 (16)	202
7-CN	258 (46)	227 (100)	197 (32)	200 (8)	142 (18)	227
7-PhCO	337 (5)	306 (6)				163
7-*t*-Bu	289 (28)	258 (13)	228 (5)			91
6,8-Cl_2[a]	301 (45)	270 (100)	240 (17)	243 (15)	185 (13)	270
6, 8-Me_2	261 (45)	230 (7)	200 (15)	203 (6)	145 (11)	229

[a] For ^{35}Cl.

synthesis of 7-methylindolizines from 4-methylpyridinium ylides and were attributed to the instability of the ylide. It seems more likely that deprotonation of the 4-methyl rather than the methylene group is occurring to give 8 which goes on to tarry by-products in the presence of the acetylenedicarboxylate.

The 1-pyridinium *p*-toluenesulfonylmethylides (4) were investigated briefly as a possible source of sulfonylcarbenes. The ylide (4, R^1 = H) was generated from 3 (R^1 = H) and base in a two-phase system (water–cyclohexene or water–benzene) but none of the known[24] products of reaction of a sulfonylcarbene with these solvents were observed.

Experimental Section

Melting points are uncorrected. Infrared spectra were determined on a Perkin-Elmer 257 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates HA-100 spectrometer using tetramethylsilane as the internal standard. Mass spectra were recorded on a Perkin-Elmer RMU-6M spectrometer. Basic alumina for chromatography was Alcoa F-20.

***p*-Toluenesulfonylmethyl Trifluoromethanesulfonate (2).** A solution of *p*-toluenesulfonylmethanol[25] (1.00 g, 0.00537 mol) in dry ether (25 ml) was added to a suspension of trifluoromethanesulfonic anhydride[26,27] (1.51 g, 0.0058 mol) and pyridine (0.60 g, 0.0076 mol) in ether (25 ml) at −78 °C with vigorous stirring. After 1 h, the mixture was warmed to room temperature. After 24 h, water (50 ml) was added to the mixture and the organic material was extracted with methylene chloride (3 × 75 ml). The solvent was evaporated in vacuo and the crude product was recrystallized from a mixture of ether and light petroleum (1:2 v/v) to give *p*-toluenesulfonylmethyl trifluoromethanesulfonate (2, 1.37 g, 80%) as colorless needles: mp 88–89 °C (lit.[13] not reported); ir (KBr) 1338 (ν_{as} SO_2), 1208 (ν_{CF_3}), 1148 cm^{-1} (ν_{sym} SO_2); NMR (CCl_4–$CDCl_3$, 1:1 v/v) δ 7.82 (d, 2 H, J_{AB} = 8 Hz, H_A), 7.38 (d, 2 H, J_{AB} = 8 Hz, H_B), 5.10 (s, 2 H, CH_2), 2.46 (s, 3 H, CH_3); mass spectrum *m/e* 318 ($M\cdot^+$, 5), 155 (50), 139 (35), 99 (7), 92 (10), 91 (100), 90 (5), 89 (7.5), 69 (42), 65 (32), 63 (9).

Anal. Calcd for $C_9H_9F_3O_5S_2$: C, 33.96; H, 2.82. Found: C, 34.22; H, 2.89.

Reaction of 2 with Substituted Pyridines. General Procedure. *p*-Toluenesulfonylmethyl trifluoromethanesulfonate (2, 0.10 mol), the pyridine (0.012 mol), and absolute ethanol (ca. 20 ml) were heated in a Fischer-Porter tube under the conditions specified in Table I and the resulting mixture was poured into anhydrous ether (500 ml) in small portions with stirring to give colorless crystals of the pyridinium salts (3).

1-*p*-Toluenesulfonylmethylpyridinium trifluoromethanesulfonate (3, R^1 = H) (3.77 g, 95%), mp 135–136 °C.

Anal. Calcd for $C_{14}H_{14}F_3NO_5S_2$: C, 42.34; H, 3.55. Found: C, 42.46; H, 3.81.

1-*p*-Toluenesulfonylmethyl-4-methylpyridinium trifluoromethanesulfonate (3, R^1 = 4-Me) (3.70 g, 90%), mp 148–150 °C.

Anal. Calcd for $C_{15}H_{16}F_3NO_5S_2$: C, 43.79; H, 3.97. Found: C, 43.77; H, 4.18.

1-*p*-Toluenesulfonylmethyl-4-cyanopyridinium trifluoromethanesulfonate (3, R^1 = 4-CN) (4.09 g, 97%), mp 200–201 °C.

Anal. Calcd for $C_{15}H_{13}F_3N_2O_5S_2$: C, 42.66; H, 3.10. Found: C, 42.85; H, 3.09.

1-*p*-Toluenesulfonylmethyl-4-benzoylpyridinium trifluoromethanesulfonate (3, R^1 = 4-PhCO) (4.76 g, 95%), mp 188–189 °C.

Anal. Calcd for $C_{21}H_{18}F_3NO_6S_2$: C, 50.29; H, 3.62; N, 2.79. Found: C, 50.36; H, 3.73; N, 2.59.

1-*p*-Toluenesulfonylmethyl-4-*tert*-butylpyridinium trifluoromethanesulfonate (3, R^1 = 4-*t*-Bu) (3.85 g, 85%): mp 107–108 °C.

Anal. Calcd for $C_{18}H_{22}F_3NO_5S_2$: C, 47.67; H, 4.89; N, 3.09. Found: C, 47.67; H, 4.96; N, 3.21.

1-*p*-Toluenesulfonylmethyl-3,5-dichloropyridinium trifluoromethanesulfonate (3, R^1 = 3,5-Cl_2) (4.26 g, 92%), mp 196–198 °C.

Anal. Calcd for $C_{14}H_{12}Cl_2F_3NO_5S_2$: C, 36.06; H, 2.59; N, 3.00. Found: C, 36.32; H, 2.68; N, 2.80.

1-*p*-Toluenesulfonylmethyl-3,5-dimethylpyridinium trifluoromethanesulfonate (3, R^1 = 3,5-Me_2) (4.08 g, 96%), mp 202–204 °C.

Anal. Calcd for $C_{16}H_{18}F_3NO_5S_2$: C, 45.17; H, 4.26; N, 3.29. Found: C, 45.22; H, 4.25; N, 3.33.

1,2-Dicarbomethoxyindolizines (6). General Procedure. Triethylamine (3.03 g, 0.030 mol) in chloroform (20 ml) was added dropwise over a period of 10 min to a stirred suspension of the 1-arylsulfonylmethylpyridinium trifluoromethanesulfonates (0.0050 mol) and dimethyl acetylenedicarboxylate (5.0 g, 0.035 mol) in chloroform (100 ml) at room temperature. When the addition of the triethylamine was complete, the reaction mixture was boiled under reflux for 30 min, basic alumina (ca. 20 g) was added, and the solvent was evaporated to dryness. The residue was chromatographed over basic alumina. Elution with ether gave unreacted dimethyl acetylenedicarboxylate (ca. 4 g). Continued elution gave the 1,2-dicarbomethoxyindolizines (6).

1,2-Dicarbomethoxyindolizine (6, R^1 = H) was prepared from 3 (R^1 = H). Elution with ether gave a yellow solid which was recrystallized from a mixture of ether and light petroleum (1:4 v/v) to give 6 (R^1 = H) (0.84 g, 72%), mp 88–90 °C (lit.[16] mp 89–91 °C).

1,2-Dicarbomethoxy-7-*tert*-butylindolizine (6, R^1 = 7-*t*-Bu) was prepared from 3 (R^1 = 4-*t*-Bu). Elution with a mixture of ether and methylene chloride (9:1 v/v) gave yellow crystals which were recrystallized from a mixture of ether and light petroleum (2:98 v/v) to give 6 (R^1 = 7-*t*-Bu) (0.96 g, 64%), mp 84–86 °C.

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.53; H, 6.63; N, 4.95.

1,2-Dicarbomethoxy-7-benzoylindolizine (6, R^1 = 7-PhCO) was prepared from 3 (R^1 = 4-PhCO). Elution with methylene chloride gave pale yellow crystals which were recrystallized from ether to give 6 (R^1 = 7-PhCO) (1.38 g, 82%), mp 123–124 °C.

Anal. Calcd for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.58; H, 4.42; N, 4.23.

1,2-Dicarbomethoxy-6,8-dimethylindolizine (6, R^1 = 6,8-Me_2) was prepared from 3 (R^1 = 3,5-Me_2). Elution with a mixture of ether and methylene chloride (1:1 v/v) gave colorless crystals which were recrystallized from ether to give 6 (R^1 = 6,8-Me_2) (1.15 g, 88%), mp 135–136 °C.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.36; H, 5.80; N, 5.23.

1,2-Dicarbomethoxy-6,8-dichloroindolizine (6, R^1 = 6,8-Cl_2) was prepared from 3 (R^1 = 3,5-Cl_2). Elution with a mixture of ether and methylene chloride (1:1 v/v) gave colorless crystals which were recrystallized from ether to give 6 (R^1 = 6,8-Cl_2) (1.28 g, 85%), mp 127–128 °C.

Anal. Calcd for $C_{12}H_9Cl_2NO_4$: C, 47.70; H, 3.00; N, 4.64. Found: C, 48.01; H, 3.12; N, 4.57.

1,2-Dicarbomethoxy-7-cyanoindolizine (6, R^1 = 7-CN) was prepared from 3 (R^1 = 4-CN). The crude reaction mixture was triturated with methanol (20 ml) to give yellow crystals, which were recrystallized from methanol to give 6 (R^1 = 7-CN) (1.05 g, 78%), mp 169 °C.

Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.90. Found: C, 60.45; H, 3.94.

Attempted Synthesis of 1,2-Dicarbomethoxy-7-methylindolizine (10). Treatment of 3 (R^1 = 4-Me) with triethylamine in the presence of dimethyl acetylenedicarboxylate under the conditions described in the general procedure gave intractable materials.

1-Carbomethoxy-7-benzoylindolizine (7) was prepared from

3 (R^1 = 4-PhCO) (1.25 g, 0.0025 mol) and methyl propiolate (0.42 g, 0.0050 mol). Elution with a mixture of ether and methylene chloride (1:5 v/v) gave yellow crystals which were recrystallized from a mixture of ether and light petroleum (1:4 v/v) to give 7 (0.454 g, 65%): mp 174–175 °C; ir (KBr) 1700 ($\nu_{C=O}$, ester), 1650 cm^{-1} ($\nu_{C=O}$, benzoyl); NMR ($CDCl_3$) δ 8.60 (s, 1 H, H_9), 8.03 (d, 1 H, $J_{5,6}$ = 7 Hz, H_5), 7.82 (dd, 2 H, J_{AB} = 8, J_{AC} = 2 Hz, H_A, ortho H in benzoyl), 7.60–7.45 (m, 3 H, meta and para H in benzoyl), 7.33 (s, 2 H, H_2 and H_3), 7.27 (d, 1 H, $J_{5,6}$ = 7 Hz, H_6) 3.83 (s, 3 H, CH_3); mass spectrum *m/e* 279 ($M^{\cdot+}$, 100), 249 (15), 248 ($M^{\cdot+}$ – MeO·, 90), 221 ($M^{\cdot+}$ – CO – HCHO, 7), 202 (15), 165 (13).

Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.10; H, 4.69; N, 5.01. Found: C, 72.80; H, 4.78; N, 4.86.

Acknowledgments. This work was supported by grants from the National Science Foundation and from the National Institutes of Health (GM 16626) for which we are grateful, and during the tenure (by V.A.) of a University of Alabama Graduate School Fellowship (1973–1974).

Registry No.—1 (R′ = H), 110-86-1; 1 (R′ = 4-Me), 108-89-4; 1 (R′ = 4-CN), 100-48-1; 1 (R′ = 4-PhCO), 14548-46-0; 1 (R′ = 4-*t*-Bu), 3978-81-2; 1 (R′ = 3,5-Cl_2), 2457-47-8; 1 (R′ = 3,5-Me_2), 591-22-0; **2**, 37891-93-3; **7**, 58747-68-5; *p*-toluenesulfonylmethanol, 2182-69-6; trifluoromethanesulfonic anhydride, 358-23-6.

References and Notes

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Phosphorus Derivatives of Nitrogen Heterocycles. 4. Pyridyl-4-phosphonates

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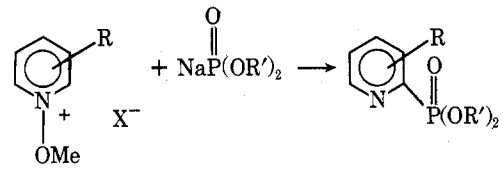
Received November 20, 1975

The reaction of 1-triphenylmethylpyridinium salts, e.g., **1**, with sodio diisopropylphosphonate yields diisopropyl pyridyl-4-phosphonates, e.g., **3**. The reaction is applicable to pyridinium salts having no α substituents. The esters are characterized by ^1H, ^{13}C, and ^{31}P NMR spectra. Hydrolysis of the esters yields the corresponding pyridyl-4-phosphonic acids whose dissociation constants are reported.

Previously we have described a general route for the synthesis of pyridyl-2-phosphonates (eq 1) and reported some of



(1)

the properties of these compounds.[1,2] Although numerous attempts were made to induce attack at the 4 position by changes in solvent, reaction temperature, etc., this was completely unsuccessful[3] and only where both positions α to nitrogen are substituted does attack by the phosphonate anion occur at the 4 position. The present paper describes a new approach which yields exclusively pyridyl-4-phosphonates and thus complements the earlier method.

The approach taken was to attach a bulky substituent to nitrogen, namely triphenylmethyl, to shield the 2 positions of the pyridine from nucleophilic attack, an approach which was partially successful for hydride attack.[4] Thus, triphenylmethylpyridinium tetrafluoroborate (1) upon treatment with the sodio derivative of diisopropyl phosphite yielded diisopropyl pyridyl-4-phosphonate (3). The 1,4-dihydropyridine 2 is presumably an intermediate but decomposes to 3 under the reaction conditions. The ^1H NMR spectrum of 3 fully supports the assigned structure showing a multiplet, δ 7.65, for the protons at C_3 and C_5 and a multiplet, δ 8.75, for the protons at C_2 and C_6, in addition to isopropoxy groups.[5] The ^{13}C NMR spectrum further supports the structural as-