Preparation and Reactions of Pyridinium Tetrazol-5-ylmethylides [1]

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Pyridinium 1- and 2-phenyltetrazol-5-ylmethylide have been prepared and successfully alkylated, acylated, carbamoylated, and thiocarbamoylated.

PYRIDINIUM ylides (1) are related to pyridine *N*-oxides [2] and pyridine *N*-imides,[3] but have on the whole attracted less attention, with the exception of the work of Kröhnke.[4] A recent review of pyridinium ylides (in Rumanian) [5] (see also ref. 6) demonstrates that most stable examples contain two electron-withdrawing substituents attached to the α-carbon atom [R and R′ in (1)]. Singly-substituted stable ylides (2) include the phenacyl (R = COPh) [7] and alkylthiothiocarbonyl compounds (R = CS_2Alk).[8] Heteroaromatic rings have rarely been used to stabilise ylides: in view of our investigations on the use of tetrazolylpyridinium salts (3a) [9] and (4a) [10,§] in the Kröhnke reaction [4d] we have now investigated the preparation and reactions of the corresponding ylides (5a) and (6a).

Application of the preparative methods of Kröhnke [7] and Henrick *et al.*[11] gave orange amorphous solids having analytical composition close to that expected for the free ylides (5a) and (6a). However, the n.m.r. spectra showed clearly that, at least in $CDCl_3$ as solvent, the ylides (5a) and (6a) are extensively dimerised or oligomerised: well resolved signals attributable to the five

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§ Recently other workers [E. Lippmann, A. Könnecke, and G. Beyer, *Monatsh.*, 1975, **106**, 443] have prepared (4a) and submitted it to the Kröhnke reaction but have reported a different m.p. During the present work we synthesised (4a) again and confirmed the m.p. previously reported in ref. 10.

[1] This is considered as Part LIV of the series ' *N*-Oxide and Related compounds.' For Part LIII see A. Maquestiau, Y. van Haverbeke, R. Flammang, S. O. Chua, M. J. Cook, and A. R. Katritzky, *Bull. Soc. chim. belges*, 1974, 105.

[2] A. R. Katritzky and J. M. Lagowski, ' Chemistry of the Heterocyclic *N*-Oxides,' vol. 19 of ' Organic Chemistry,' ed. A. T. Blomquist, Academic Press, New York and London, 1971.

[3] H.-J. Timpe, *Adv. Heterocyclic Chem.*, 1974, **17**, 213.

[4] (*a*) F. Kröhnke, *Angew. Chem.*, 1953, **65**, 605; (*b*) F. Kröhnke and W. Zecher, *Angew. Chem. Internat. Edn.*, 1962, **1**, 626; (*c*) F. Kröhnke, *ibid.*, 1963, **2**, 225; (*d*) F. Kröhnke, *ibid.*, p. 380.

[5] I. Zugrăvescu and M. Petrovanu, ' Chimia N-Ilidelor,' Editura Academiei Republicii Socialiste România, Bucharest, 1974, p. 147.

[6] A. W. Johnson, ' Ylid Chemistry,' vol. 7 in the series ' Organic Chemistry,' ed. A. T. Blomquist, Academic Press, New York and London, 1966, p. 260.

[7] F. Kröhnke, *Ber.*, 1935, **68**, 1177.

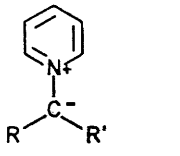
[8] F. Kröhnke and K. Gerlach, *Chem. Ber.*, 1962, **95**, 1108; F. Kröhnke, K. Gerlach, and K.-E. Schnalke, *ibid.*, p. 1118.

[9] D. Moderhack, *Annalen*, 1972, **758**, 29.

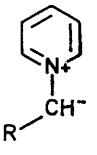
[10] D. Moderhack, *Chem. Ber.*, 1975, **108**, 887.

[11] C. A. Henrick, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1967, **20**, 2441.

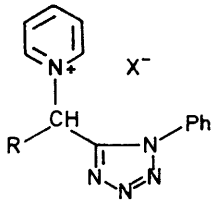
protons of the phenyl groups were found, but the other six protons showed broader absorption upfield of the region expected for a pyridinium ring (see Experimental section). Although observations of dimerisation of *N*-ylides are numerous [5] (for a recent example see ref. 12) they refer to heterocycles other than pyridine for which we are aware of no precedent. The ' free ylides ' (or dimers) were used for further reactions within a few hours; otherwise they gradually decomposed, changing colour and evolving pyridine.



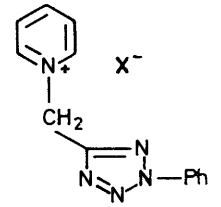
(1)



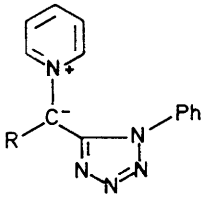
(2)



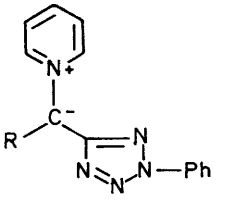
(3) a; R = H, X = Cl
b; R = Me, X = I
c; R = CH_2•CH:CH_2, X = Br
d; R = CH_2Ph, X = Br
e; R = H, X = Br



(4) a; X = Cl
b; X = I
c; X = Br



(5) a; R = H
b; R = COPh
c; R = CO•NHPh
d; R = CS•NHPh

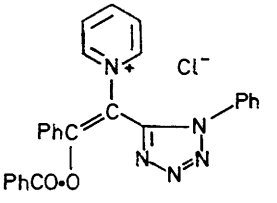


(6) a; R = H
b; R = COPh
c; R = CO•NHPh
d; R = CS•NHPh

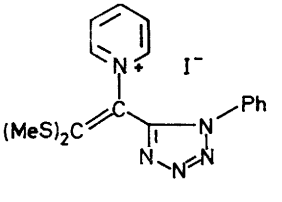
Alkylation at the ylide carbon atom is advantageously carried out in dimethylformamide: [11] we find that the ylide (5a) gives 65—70% yields of the *C*-alkylated pyridinium salts (3b, c, and d) with methyl iodide and allyl and benzyl bromides, respectively. However, with the isomeric ylide (6a) none of the expected products could be isolated, although n.m.r. gave indications that some were formed: the reactions with methyl iodide and allyl and benzyl bromides each caused anion exchange to give the pyridinium iodide (4b) and bromide (4c) [a small amount of the comparable by-product (3e) was also produced from (5a) with benzyl bromide].

Aroylation [13] of the pyridinium salts (3a) and (4a) under Schotten–Baumann conditions in the presence of 2 equiv. of base leads to the ylides (5b) and (6b) (50 and 26% yields, respectively). These compounds show a markedly different stability toward protic solvents, the benzoyl group of (6b) being split off in solution in neutral ethanol within a few hours at room temperature. This sensitivity to hydrolysis, which accounts for the low yield of (6b), is rationalised in terms of a weaker electron-withdrawing effect (inductively and by resonance) of the 2-substituted tetrazol-5-yl system [14] and is paralleled by a considerable shift of the visible charge-transfer absorption band [15] to longer wavelengths (*cf.* ref. 16).

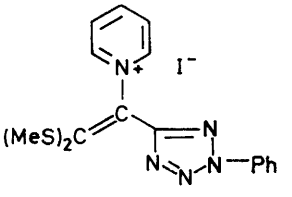
With benzoyl chloride alone the ylides (5a) and (6a) do not give salts of (5b) and (6b), instead—as is shown in detail for (5a)—a 1 : 1 mixture of (3a) and the enol ester (7) results by transylidation.[11,16,17] The salt (7) is converted into the ylide (5b) by treatment with aqueous base.



(7)



(8)



(9)

A mixture of carbon disulphide and methyl iodide (1 : 2) in the presence of 1 equiv. of base (*cf.* ref. 8) smoothly converts the ylides (5a) and (6a) into the orange-yellow keten thioacetals (8) and (9) (yield 40—60%), whose reactions are under investigation.

The ylides (5a) and (6a) were converted rapidly by reaction with phenyl isocyanate [18] in good yield to the deep red carbamoylated ylides (5c) and (6c). Similar reactions with phenyl isothiocyanate [19] give the analo-

[12] B. E. Landberg and J. W. Lown, *J.C.S. Perkin I*, 1975, 1326.
[13] F. Kröhnke, *Ber.*, 1937, **70**, 1114.
[14] M. A. Schroeder and R. A. Henry, Abstracts of the 156th National Meeting of the American Chemical Society, Atlantic City, New Jersey, Sept. 1968, ORGN 80.
[15] E. M. Kosower and B. G. Ramsey, *J. Amer. Chem. Soc.*, 1959, **81**, 856.
[16] C. A. Henrick, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1967, **20**, 2455.
[17] F. Weygand and H. Daniel, *Chem. Ber.*, 1961, **94**, 3147.
[18] F. Kröhnke and H. Kübler, *Ber.*, 1937, **70**, 538.
[19] F. Fröhlich, U. Habermalz, and F. Kröhnke, *Tetrahedron Letters*, 1970, 271; S. Sato and M. Ohta, *Bull. Chem. Soc. Japan*, 1969, **42**, 2054.

gous thiocarbamoyl derivatives (5d) and (6d). Our work shows that the starting pyridinium ylides (5a) and (6a) show the expected properties. The different electronic influence exerted by the 1- and 2-substituted tetrazol-5-yl systems is best demonstrated by comparison of the u.v. spectroscopic data (see Experimental section) and the behaviour of the benzoylated ylides (5b) and (6b) toward protic solvents such as ethanol [greater ease of hydrolysis with (6b)].

EXPERIMENTAL

I.r. spectra were measured with a Perkin-Elmer 237 instrument, n.m.r. spectra with a Perkin-Elmer R 12 instrument (Me_4Si as internal standard), and u.v. spectra on a Unicam SP 800 spectrophotometer (individual $\varepsilon_{max.}$ values were obtained with a manual SP 500 instrument).

Pyridinium 1-Phenyl- (5a) and 2-Phenyl-tetrazol-5-yl-methylide (6a).—K_2CO_3 (5 g) in water (7—8 ml) was added to the pyridinium salt (3a) [9] or (4a) [10] (2.74 g) in water (10 ml) at 0 °C with vigorous stirring. The mixtures were stirred at 0 °C for 20 min more, then extracted with CH_2Cl_2 (5 × 5 ml). The combined extracts were dried (K_2CO_3) and evaporated to give orange amorphous solids (2.0—2.1 g, 84—89%). The ylides were used for further reactions soon after their preparation. Attempted recrystallisation was unsatisfactory and analytical figures were only approximate: (5a) had m.p. 135—150 °C; $\nu_{max.}$ (Nujol) 1 675 cm^{-1}; τ ($CDCl_3$) 2.2—3.0 (*ca.* 5 H, m), 3.9—4.5 (2 H, m), and 5.2—6.4 (4 H, m); $\lambda_{max.}$(CH_2Cl_2) 431 nm; (6a) had m.p. 115—130 °C; $\nu_{max.}$ (Nujol) 1 680 cm^{-1}; τ ($CDCl_3$) 1.92 (2 H, m), 2.48 (3 H, m), 3.5—4.1 (2 H, m), and 5.0—6.3 (4 H, m); $\lambda_{max.}$(CH_2Cl_2) 447 nm.

1-Phenyl-5-(1-pyridinioethyl)tetrazole Iodide (3b).—The ylide (5a) (1.19 g) and MeI (*ca.* 0.8 g) in pure dimethylformamide (DMF) (7 ml) were kept at 20 °C under nitrogen for 36 h. On addition of ether and cooling to 0—5 °C, the *product* separated readily (1.20 g, 63%); it crystallised from EtOH as pale yellow plates, m.p. 197—200 °C (decomp.) (Found: C, 43.9; H, 3.7; N, 18.5. $C_{14}H_{14}IN_5$ requires C, 44.3; H, 3.7; N, 18.5%); τ ($CF_3{\cdot}CO_2H$) 0.91 (2 H, m), 1.30 (1 H, m), 1.78 (2 H, m), 2.30 (5 H, m), 3.14 (1 H, q, *J* 7 Hz, N^+ –CH), and 7.63 (3 H, d, *J* 7 Hz, CH_3).

A parallel run with (6a) afforded *2-phenyl-5-pyridiniomethyltetrazole iodide* (4b) (0.50 g), pale yellow needles, m.p. 221—222 °C (decomp.) (from EtOH) (Found: C, 43.0; H, 3.5; N, 19.0. $C_{13}H_{12}IN_5$ requires C, 42.8; H, 3.3; N, 19.2%); τ ($CF_3{\cdot}CO_2H$) 0.77 (2 H, m), 1.30 (1 H, m), 1.81 (4 H, m), 2.36 (3 H, m), and 3.49 (2 H, s).

5-(1-Pyridiniobut-3-enyl)-1-phenyltetrazole Bromide (3c).—The ylide (5a) (2.01 g) and allyl bromide (1.12 g) in DMF (12 ml) were kept at 20 °C as above. Evaporation under reduced pressure (bath at 80 °C) then gave a brown oil which was dissolved in CH_2Cl_2 (3 ml). After some days the *product* separated as coarse prisms (2.06 g, 68%) and was recrystallised from EtOH–Et_2O; m.p. 209—211 °C (Found: C, 53.4; H, 4.6; N, 19.6. $C_{16}H_{16}BrN_5$ requires C, 53.6; H, 4.5; N, 19.6%); τ ($CF_3{\cdot}CO_2H$) 0.94 (2 H, m), 1.30 (1 H, m), 1.80 (2 H, m), 2.35 (5 H, m), 3.42 (1 H, m), 4.20 (1 H, m), 4.86 (2 H, m), and 6.50 (2 H, m).

Treatment of the ylide (6a) under the same conditions gave *2-phenyl-5-pyridiniomethyltetrazole bromide* (4c) (0.56 g), needles, m.p. 229—230 °C (decomp.) (from EtOH) (Found: C, 48.6; H, 3.8; N, 21.6. $C_{13}H_{12}BrN_5$ requires C, 49.1; H, 3.8; N, 22.0%); n.m.r. spectrum as quoted before with (4b).

1-Phenyl-5-(2-phenyl-1-pyridinioethyl)tetrazole Bromide (3d).—The ylide (5a) (2.04 g) and benzyl bromide (1.65 g) under conditions analogous to the preparation of (3c) gave the *product* as flat prisms (2.5 g, 71%), m.p. 178—180 °C (from EtOH–tetrahydrofuran) (Found: C, 58.9; H, 4.5; N, 17.3. $C_{20}H_{18}BrN_5$ requires C, 58.8; H, 4.4; N, 17.2%); τ ($CF_3{\cdot}CO_2H$) 0.97 (2 H, m), 1.40 (1 H, m), 1.91 (2 H, m), 2.40 (3 H, m), 2.85 (7 H, m), 3.54 (1 H, t, *J* 7 Hz, N^+–CH), and 5.96 and 6.04 (2 H, dd, *J* 7 Hz, CH_2).

Pyridinium α-(1-Phenyltetrazol-5-yl)phenacylide (5b) *and its 2-Phenyl Isomer* (6b).—Benzoyl chloride (1.41 g) in CH_2Cl_2 (15 ml) and K_2CO_3 (2.8 g) in water (10 ml) were added to the pyridinium salt (3a) or (4a) (2.74 g) in water (20 ml). The mixture was shaken vigorously for 7 min and the organic layer was separated (part of the product crystallised out). Evaporation of solvent after drying (Na_2SO_4) gave a yellow solid which was recrystallised from EtOH to give (i) the *phenacylide* (5b) (1.70 g, 50%) as orange prisms, m.p. 227—229 °C (decomp. with evolution of phenyl isocyanide) [Found (after drying at 80 °C and 0.5 mmHg): C, 69.7; H, 4.5; N, 20.7. $C_{20}H_{15}N_5O$ requires C, 70.4; H, 4.4; N, 20.5%]; $\nu_{max.}$ (Nujol) 1 515 cm^{-1}; τ [$(CD_3)_2SO$] 0.94 (2 H, m), 1.73 (1 H, m), 2.12 (2 H, m), and 2.89 (10 H, m); $\lambda_{max.}$ (95% EtOH) 240 (log ε 4.13), 320 (3.80), and 419 nm (3.71); $\lambda_{max.}$ (dioxan) 333 (log ε 3.75) and 454 nm (3.97); and (ii) the *isomeric ylide* (6b) (0.9 g, 26%) as deep orange needles, m.p. 145—146 °C (decomp.) [Found (after drying at 80 °C and 0.5 mmHg): C, 70.2; H, 4.6; N, 20.0%]; $\nu_{max.}$ (Nujol) 1 525 cm^{-1}; τ ($CDCl_3$) 1.03 (2 H, m), 2.32 (5 H, m), and 2.61 (8 H, m); $\lambda_{max.}$ (95% EtOH) 243, 330, and 428 nm; $\lambda_{max.}$ (dioxan) 362 (log ε 3.89) and 478 nm (3.74).

Ethanolysis of the Phenacylide (6b).—The ylide (6b) (0.1 g) in EtOH (5 ml) after being kept at 20 °C for 40 h deposited the dimerised ylide (6a) (0.06 g), m.p. 130—132 °C, identical (i.r. spectrum) with authentic material (Found: C, 65.3; H, 4.8; N, 29.3. Calc. for $C_{13}H_{11}N_5$: C, 65.8; H, 4.7; N, 29.5%). The filtrate was evaporated to give ethyl benzoate, identified by comparison (i.r. spectrum) with an authentic sample.

N-[2-Benzoyloxy-2-phenyl-1-(1-phenyltetrazol-5-yl)vinyl]-pyridinium Chloride (7).—(*a*) K_2CO_3 (1 g) in water (2 ml) was added at 0 °C with shaking to the pyridinium salt (3a) (0.55 g) in water (2 ml). After 5—10 min the mixture was extracted with CH_2Cl_2 (5 × 5 ml). The extracts were dried (K_2CO_3) and then mixed with benzoyl chloride (0.3 g) in CH_2Cl_2 (5 ml). The solution rapidly deposited starting pyridinium salt (3a) (0.20 g, 36%). After 12 h ether (25 ml) was added to the filtrate, to give the *product* (0.30 g, 31%), which crystallised as needles, m.p. 147—149 °C (decomp.) (from EtOH–Et_2O) (Found: C, 64.8; H, 4.5; N, 14.3. $C_{27}H_{20}ClN_5O_2,H_2O$ requires C, 64.9; H, 4.4; N, 14.0%); $\nu_{max.}$ (Nujol) 1 745 cm^{-1} (C=O).

(*b*) Benzoyl chloride (0.35 g) was added to a suspension of (5b) (0.83 g) in CH_2Cl_2 (25 ml). The mixture was kept at 20 °C with shaking for 1 h and evaporated to 8 ml. Addition of ether (15 ml) precipitated the product (1.19 g, 98%).

Hydrolysis of the Benzoyloxy-compound (7).—K_2CO_3 (1.7 g) in water (5 ml) was added with stirring at 0 °C to (7) (0.5 g) in water (15 ml). A yellow solid immediately separated. After 20 min the mixture was extracted with CH_2Cl_2 (4 × 15 ml) to give 0.33 g (97%) of crude ylide (5b), identified by i.r. comparison with an authentic sample.

N-[2,2-*Bis*(*methylthio*)-1-(1-*phenyltetrazol*-5-*yl*)*vinyl*]*pyridinium Iodide* (8) *and the* 2-*Phenyl Isomer* (9).—Methyl iodide (0.75 ml), followed by carbon disulphide (0.5 ml) in CH_2Cl_2 (10 ml), and then K_2CO_3 (1.4 g) in water (5 ml) was added to the pyridinium salt (3a) (1.37 g) in water (5 ml) and the mixture was vigorously shaken for 20 min. The orange-red organic layer was dried (Na_2SO_4); the *iodide* (8) (1.29 g, 55%) slowly separated and crystallised as yellow-orange prisms, m.p. 185—190 °C (decomp.) (from EtOH) (Found: C, 41.2; H, 3.7; N, 15.3. $C_{16}H_{16}IN_5S_2$ requires C, 40.9; H, 3.4; N, 14.9%); τ ($CF_3{\cdot}CO_2H$) 0.93 (2 H, m), 1.21 (1 H, m), 1.64 (2 H, m), 2.21 (5 H, s), 7.40 (3 H, s), and 7.73 (3 H, s).

Similar treatment of pyridinium salt (4a) gave an organic layer which deposited the pyridinium salt (4b) (0.7 g, 38%). Addition of ether (30 ml) to the filtrate gave the *isomeric iodide* (9) (0.87 g, 37%) which crystallised as orange prisms, m.p. 172—181 °C (decomp.) (from EtOH) (Found: C, 40.7; H, 3.6; N, 15.1%); τ ($CDCl_3$) 0.60 (2 H, m), 1.05 (1 H, m), 1.43 (2 H, m), 1.96 (2 H, m), 2.45 (3 H, m), 7.30 (3 H, s), and 7.40 (3 H, s).

Pyridinium Phenylcarbamoyl-(1-*phenyltetrazol*-5-*yl*)*methylide* (5c) *and the* 2-*Phenyl Isomer* (6c).—Phenyl isocyanate (0.53 g) in CH_2Cl_2 (5 ml) was added with stirring and cooling to the ylide (5a) (1.19 g) in CH_2Cl_2 (5 ml). The solution turned red and soon deposited crystals; 1—2 h later light petroleum (*ca.* 5 ml) was added and the mixture kept for 12 h at 0—5 °C. The *product* (5c) (1.51 g, 85%) separated, and crystallised as deep red prisms, m.p. 193—198 °C (decomp.) (from EtOH) (Found: C, 67.0; H, 4.7; N, 23.4. $C_{20}H_{16}N_6O$ requires C, 67.4; H, 4.5; N, 23.6%); τ [$(CD_3)_2SO$] −0.66 (1 H, s), 1.45 (2 H, m), and 2.30—2.93 (13 H, m); $\lambda_{max.}$ (95% EtOH) 232 (log ε 4.21), 277 (4.13,) 314 (4.32), and 469 nm (3.55).

Similar treatment of the isomeric ylide (6a) gave the *isomeric carbamoylylide* (6c) (1.55 g, 87%) as violet-red needles, m.p. 172—174 °C (decomp.) (from EtOH) (Found: C, 67.3; H, 4.7; N, 22.9%); τ ($CDCl_3$) 0.15 (1 H, s), 1.02 (2 H, m), and 1.55—3.00 (13 H, m); $\lambda_{max.}$ (95% EtOH) 241 (log ε 4.39), 288 (4.36), 375 (3.72), and 486 nm (3.51).

Pyridinium 1-*Phenyltetrazol*-5-*yl*(*phenylthiocarbamoyl*)*methylide* (5d) *and the* 2-*Phenyl Isomer* (6d).—Use of phenyl isothiocyanate in place of phenyl isocyanate with (5a) and (6a) gave under the same conditions the *thiocarbamoylylide* (5d) (1.49 g, 80%) as scarlet prisms, m.p. 141—143 °C (decomp.) (from EtOH) (Found: C, 64.3; H, 4.5; N, 22.6. $C_{20}H_{16}N_6S$ requires C, 64.5; H, 4.3; N, 22.6%); τ[$(CD_3)_2SO$] −1.55 (1 H, s), 1.25 (2 H, m), 1.84 (1 H, m), and 2.16—3.00 (12 H, m); $\lambda_{max.}$ (95% EtOH) 280 (log ε 4.01), 338 (4.35), and 466 nm (3.02), and the *isomeric ylide* (6d) (1.40 g, 75%) as red needles, m.p. 128—129 °C (decomp.) (from EtOH) [Found (after drying at 80 °C at 0.5 mmHg): C, 65.2; H, 4.4; N, 22.6%]; τ [$(CD_3)_2SO$] −0.15 (1 H, s), 1.00 (2 H, m), 1.37 (1 H, m), and 1.75—3.02 (12 H, m); $\lambda_{max.}$ (95% EtOH) 255 (log ε 4.34), 316 (4.33), 375sh (4.01), and 480 nm (2.87).

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