

TRIAZOLOPYRIDINES. 13¹. REACTION BETWEEN TRIAZOLOPYRIDINIUM
YLIDES AND ELECTROPHILES

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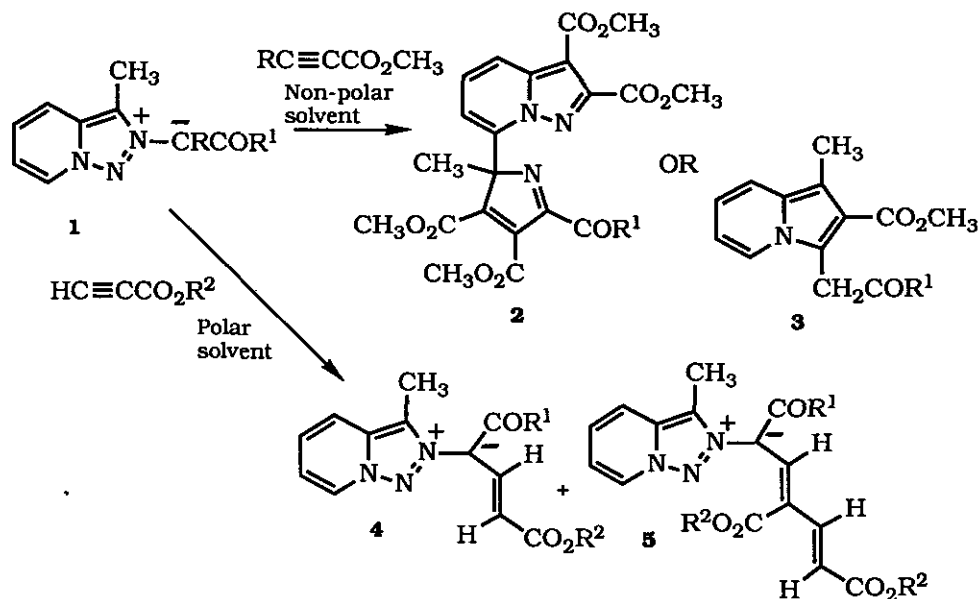
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Abstract – The triazolopyridinium ylides (**4**) are protonated and react with acylium and nitronium ions at the end of the side chain, giving acyl derivatives (**8a**, **8b**) and dinitro derivatives (**10a-10c**). The structure of the dinitro compound (**10b**) is confirmed by X-ray diffraction.

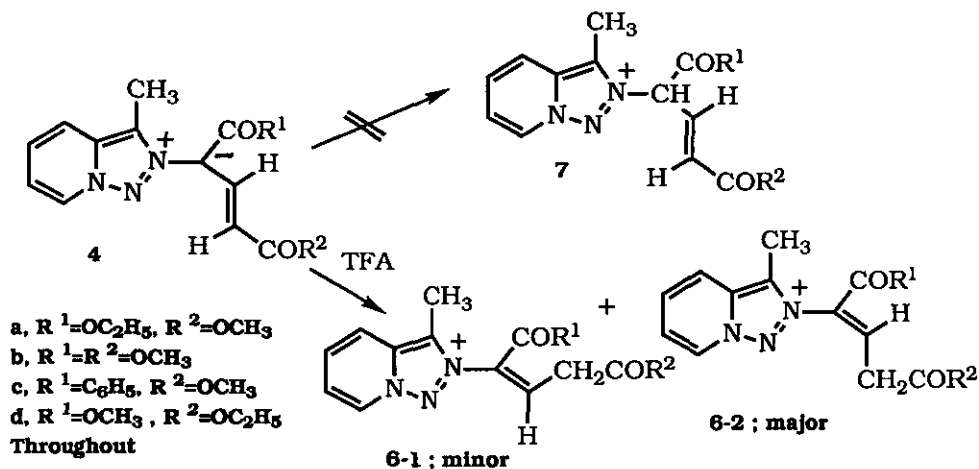
We have reported^{1,2} that triazolopyridinium ylides (**1**) are versatile synthons for the production of pyrazolopyridines (**2**)² and for indolizines (**3**); we also reported³ that ylides (**1**) where R¹ = H react with acetylenic esters in a polar solvent to give new ylides of type (**4**) and (**5**) with the addition of one or two acetylene units to the side chain. Ylides of type (**4**) were previously known, with pyridinium^{4a} or pyrazolium^{4b} ions, but their properties have not been extensively studied. We report here on the reaction between ylides of type (**4**) and electrophiles. A point of interest lies in the position of substitution, which gives an indication, in irreversible reactions, of the

distribution of electrical charge along the chain. Protonation has been examined first.



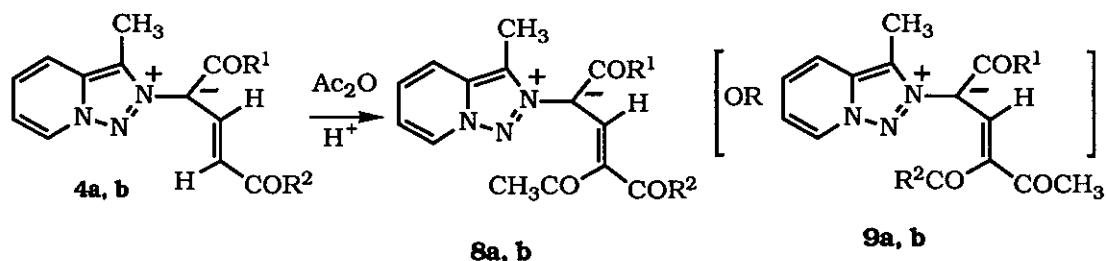
An immediate discharge of colour, with the loss of the longest wavelength band ($>350\text{nm}$) in the electronic absorption spectrum was observed when trifluoroacetic acid (TFA) was added to a solution of **4** in CDCl_3 and a change was observed in the ^1H and the ^{13}C nmr spectra, indicating that the ylides (**4**) were protonated to form the triazolopyridinium cations (**6**). The nmr data for **6** are shown in Table 2 (^1H) and in Table 3 (^{13}C). The spectra of **4a** and **4b** in the protonating medium showed the presence of two species, that of compound (**4c**) only one. There was no trace of the unprotonated form, easily distinguished by the AB pair of doublets at 4.10 and 7.85, due to the alkene protons on the side chain. Discussion will be concentrated on the spectra of compound (**4b**), with some notes about the single protonated form of compound (**4c**). In all cases the ylide could be recovered from the protonating solution unchanged. The two protonated species of compound (**4b**) were present in the proportion of 1:4. The major product had in its ^1H spectrum a doublet (2H) at 3.25 ($J=7$ Hz) and was coupled to a signal at 7.90 (1H, t). The only possible formulae

are **6-1** and **6-2**, the alternative **7** being incompatible with the spectrum. In the minor isomer the two equivalent signals are at 4.10 (2H, $J=7$ Hz) and 7.35 (1H, t , $J=7$ Hz). A decision on the stereochemistry can be reached by consideration of the chemical shifts. The deshielding effect of the ester carbonyl group sited at C1' causes the methylene group signal to shift downfield in the *E* form, and the alkene signal to shift downfield in the *Z* form; hence the major isomer is **6-2** (*Z*) and the minor form is **6-1** (*E*). The ^1H spectrum of compound (**4a**) in CDCl_3/TFA showed a similar pair of protonated forms, in the proportion 1:5. Protonation of the ylide (**4c**) gave a single isomer, with a methylene signal at 3.40 and an alkene signal at 7.70, sufficiently close to the signals of the other two major isomers for a confident assignment as the *Z* isomer. Since steric interference between the acyl group at C1' and the substituted methylene group appears to determine the configuration about the double bond, it is not surprising that the bulky benzoyl group produces only one of the possible isomers. The ^{13}C spectra require little comment, showing the expected double set of signals for **6a** and **6b**, with significant shift differences on the methylene and the C2' carbon signals between the isomers.



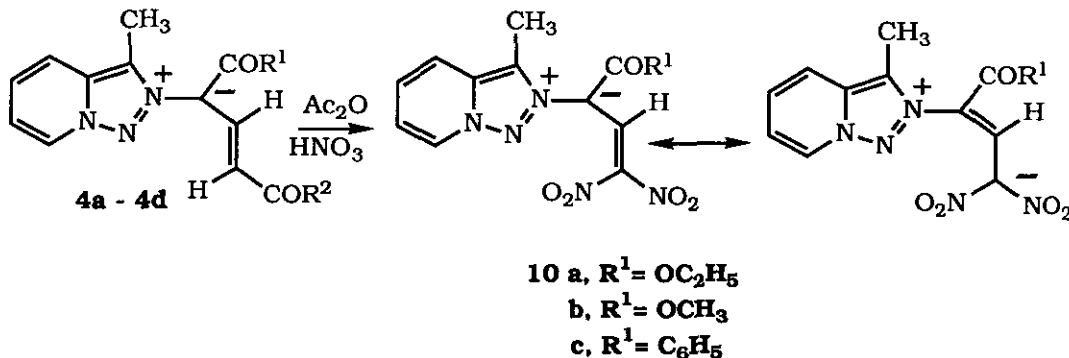
In the second series of experiments the ylides were subjected to potentially irreversible reactions. Alkylation was not achieved with a variety of alkylating agents under a range of conditions. The ylides (**4a**) and (**4b**) were treated with acetic

anhydride and a trace of concentrated sulphuric acid. Initial decolourisation was followed by the development of an orange colour; work-up gave yellow/orange products (**8a**) and (**8b**), with analysis figures which indicated that an acetyl group had, in each case, replaced a hydrogen atom. The ^1H nmr spectrum of compound (**8a**) showed four methyl signals, at 1.22 (t), 2.09 (s), 2.59 (s), and 3.70 (s), the latter two being due to the methyl group at position 3 of the triazolopyridinium ring and to the methyl ester respectively. The position of the second singlet is that expected for an acetyl substituent. The normal four proton pattern is interrupted by a singlet (1H) at 8.50 which must be due to the alkene proton on the side chain, and is similar to that found for H2' in ylides of type (**4**). The ^{13}C spectrum shows the signal for C2' at 142.04, again similar to those of ylides (**4**) but the two quaternary carbon signals for C1' and C3' are very similar in chemical shift, indicating a more even distribution of the negative charge. We prefer structures (**8a**) and (**8b**) to the alternative (**9a**) and (**9b**), because a DIFNOE spectrum irradiating at 3.65 (ester methyl) on the compound (**8d**) (characterised only by spectra) showed enhancement of signals at 2.10 (acetyl methyl), 2.60 (C3 methyl), and 8.50 (H2'), impossible with structure (**9**).



The most interesting reaction of the ylides (**4**) was that with acetic anhydride and nitric acid. The four ylides (**4a-4d**) reacted to give yellow crystalline products (**10**) in yields of 55, 60, 30, and 60%; the ylides (**4b**) and (**4d**) gave the same product. Microanalysis showed the formulae of the three products to be $\text{C}_{13}\text{H}_{13}\text{N}_5\text{O}_6$, $\text{C}_{12}\text{H}_{11}\text{N}_5\text{O}_6$, and $\text{C}_{17}\text{H}_{13}\text{N}_5\text{O}_5$, so that in all cases an ester group and a hydrogen atom had been replaced by nitro groups. The ^1H nmr spectrum of compound (**10a**) showed signals for the ethyl ester group at 1.25 and 4.28, for the methyl group at position 3 at

2.71, and aromatic proton signals at 7.80-8.00 (overlapping triplets, H5 and H6), 8.53 (H4, d), and 9.32 (H7, d). The only other signal was a singlet (1H) at 8.66, similar to that described for ylides (**8a**) and (**8b**). The aromatic proton shifts and the yellow colour indicated the presence of an ylide, but the spectroscopic evidence was insufficient for certainty in structure elucidation and the ylide (**10b**) was subjected to X-ray diffraction. The X-ray structure is shown in Figure 1 and the X-ray data are given at the end of the discussion and in Table 1.



The mechanism of reaction of the ylides with electrophiles is straightforward for the acetylation, as shown in the first steps of the Scheme. The mechanism of nitration is more interesting since it requires decarboalkoxylation. We suggest that the conjugate base causes dealkylation, and the resulting 3,3'-dinitro intermediate would decarboxylate readily to give product. The other point of interest concerns the degree of delocalisation of the negative charge in the ylide (**10b**). Examination of the angles between the dihedral planes N4-C10-C9 (numbers as in the X-ray diagram) and N5-C10-C9 shows only a slight departure from planarity, with a slightly larger difference between planes N3-C8-C9 and N3-C8-C11, but neither is sufficient to indicate a high degree of charge localisation.

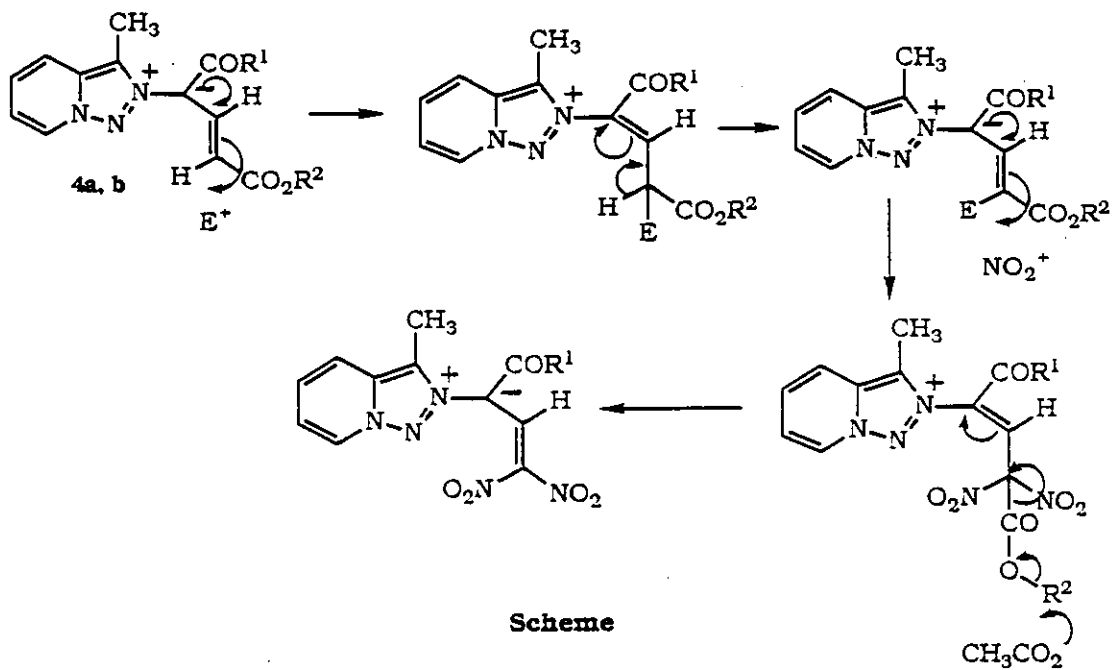


Figure 1: X-ray diffraction structure of ylide 10b

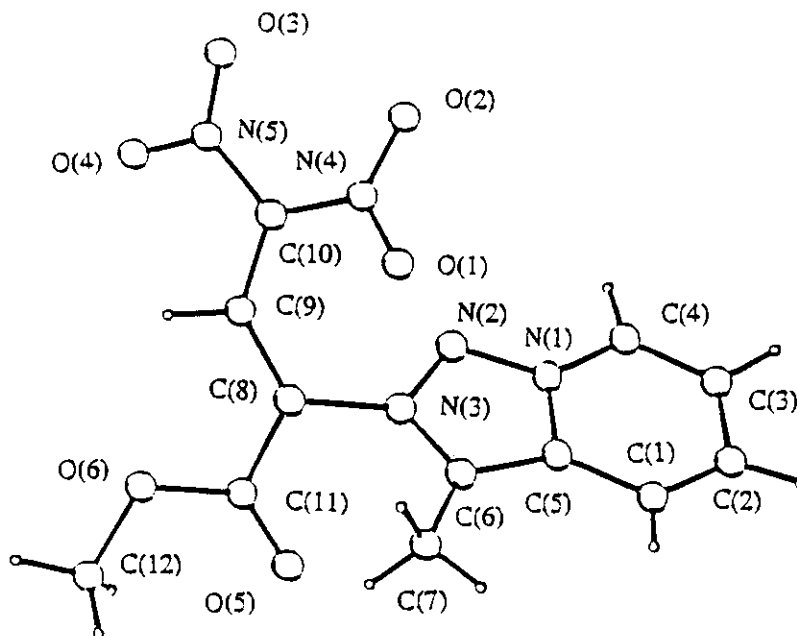


TABLE 1 Bond Lengths and Angles for Compound 10b

Bond lengths (Å)

C(2)-C(1)	1.325(10)	C(5)-C(1)	1.410(8)
C(3)-C(2)	1.403(10)	C(4)-C(3)	1.355(9)
N(1)-C(4)	1.368(8)	C(5)-N(1)	1.368(8)
N(2)-N(1)	1.333(7)	C(6)-C(5)	1.377(8)
N(3)-N(2)	1.339(6)	C(6)-N(3)	1.343(7)
C(8)-N(3)	1.438(7)	C(7)-C(6)	1.475(8)
C(9)-C(8)	1.349(7)	C(11)-C(8)	1.455(8)
C(10)-C(9)	1.400(8)	N(4)-C(10)	1.403(8)
N(5)-C(10)	1.399(7)	O(1)-N(4)	1.242(7)
O(2)-N(4)	1.229(7)	O(3)-N(5)	1.228(6)
O(4)-N(5)	1.245(7)	O(5)-C(11)	1.199(7)
O(6)-C(11)	1.341(7)	C(12)-O(6)	1.443(7)

Bond angles (deg.)

C(5)-C(1)-C(2)	119.6(7)	C(3)-C(2)-C(1)	120.1(7)
C(4)-C(3)-C(2)	122.4(7)	N(1)-C(4)-C(3)	116.3(7)
C(5)-N(1)-C(4)	123.5(6)	N(2)-N(1)-C(4)	123.6(6)
N(2)-N(1)-C(5)	112.8(5)	N(1)-C(5)-C(1)	118.2(6)
C(6)-C(5)-C(1)	136.4(5)	C(6)-C(5)-N(1)	105.3(5)
N(3)-N(2)-N(1)	102.8(5)	C(6)-N(3)-N(2)	114.0(5)
C(8)-N(3)-N(2)	117.5(5)	C(8)-N(3)-C(6)	128.4(5)
N(3)-C(6)-C(5)	105.1(5)	C(7)-C(6)-C(5)	129.6(6)
C(7)-C(6)-N(3)	125.1(6)	C(9)-C(8)-N(3)	121.8(5)
C(11)-C(8)-N(3)	112.6(5)	C(11)-C(8)-C(9)	124.3(6)
C(10)-C(9)-C(8)	133.8(5)	N(4)-C(10)-C(9)	122.6(5)
N(5)-C(10)-C(9)	118.5(6)	N(5)-C(10)-N(4)	118.7(5)
O(1)-N(4)-C(10)	117.4(5)	O(2)-N(4)-C(10)	121.2(6)
O(2)-N(4)-O(1)	121.3(6)	O(3)-N(5)-C(10)	122.8(6)
O(4)-N(5)-C(10)	116.7(5)	O(4)-N(5)-O(3)	120.5(5)
O(5)-C(11)-C(8)	124.4(6)	O(6)-C(11)-C(8)	112.1(5)
O(6)-C(11)-O(5)	123.6(6)	C(12)-O(6)-C(11)	115.3(5)

X-ray Crystal Structure Determination

The structure of the ylide (**10b**) has been determined by X-ray crystallography. Crystal Data: $C_{12}H_{11}N_5O_6$, $M_r = 321.25$, triclinic, space group P1, $a = 7.456(1)$, $b = 10.235(3)$, $c = 10.371(2)$ Å, $\alpha = 116.11(2)$, $\beta = 92.44(1)$, $\gamma = 92.29(1)^\circ$, $V = 1379.9(2)$ Å³, $Z = 2$, $D_x = 1.51$ g cm⁻³, $\mu(\text{Mo-K}\alpha) = 1.16$ cm⁻¹.

Intensity data were collected at 291 K on a crystal of dimensions 0.2 x 0.05 x 0.05 mm³ using a FAST TV area detector diffractometer and graphite monochromated Mo-K α radiation from a rotating anode generator operating at 50 KV, 55 mA with a 300 μ focus, following previously described procedures.⁵ A total of 3311 reflections which satisfied the conditions for acceptable measurement were merged ($R_{\text{int}} = 0.032$) to give only 1376 observed [$F_o > 3\sigma(F_o)$] data. The structure was solved by direct methods⁶ and refined by full matrix least squares.⁷ Non hydrogen atoms were refined anisotropically, aromatic hydrogens were freely refined isotropically and methyl hydrogens were included in idealised positions with group Uiso values. The final R value was 0.06 for 236 parameters and with unit weights. Final bond lengths and angles are given in Table 1; atomic coordinates and other crystallographic data are available on request from the Cambridge Crystallographic Data Centre.⁸

EXPERIMENTAL

Mps were determined on a heated stage, and are uncorrected. Nmr spectra were determined on a Jeol X270, Bruker WP-80-SY, or Bruker AM200 spectrometer, normally for solutions in CDCl₃, and electronic spectra for solutions in absolute ethanol.

Protonation Experiments.

A solution of the appropriate ylide in CDCl₃ was treated dropwise with trifluoroacetic acid until the solution was decolourised. Spectra are reported in Tables 2 and 3.

TABLE 2 ¹H Nmr Shifts for Compounds 6, 8 and 10

<u>Compd</u>	<u>Solvent</u>	<u>H4</u>	<u>H5 and H6</u>	<u>H7</u>	<u>CH₃(C3)</u>	<u>H2'</u>	<u>H3'</u>	<u>Other</u>
6a(Z)	C/TFA	8.00(d)	←7.55-7.70(m)→	8.70(d)	2.72	7.91(t)	3.25(2H,d)	1.21(3h,t);3.91(3H,s); 4.15(2H,q).
6a(E)^a	C/TFA	-	-	-	2.75	7.35(t)	-	3.86(s).
6b(Z)	C/TFA	8.15(d)	←7.70-7.90(m)→	8.85(d)	2.70	7.90(t)	3.25(2H,d)	3.71(3H,s);3.92(3H,s).
6b(E)	C/TFA	-	-	-	2.73	7.35(t)	4.10(2H,d)	3.80(3H,s);3.87(3H,s)
6c	C/TFA	8.15(d)	←7.60-8.00(m)→	8.90(d)	2.75	7.70(t)	3.40(2H,d)	3.75(3H,s);7.6- 8.0(5H,m)
8a	C	7.85(d)	←7.35-7.56(m)→	8.55(d)	2.59	8.50(s)	-	1.22(3H,q);2.09(3H,s); 3.7(3H,s);3.95(3H,q).
8b	C	7.85(d)	←7.32-7.52(m)→	8.55(d)	2.55	8.50(s)	-	2.07(3H,s);3.42(3H,s); 3.66(3H,s).
10a	D	8.53(d)	←7.83-8.05(m)→	9.32(d)	2.71	8.66(s)	-	1.25(3H,t);4.28(2H,q).
10b	D	8.55(d)	←7.75-8.00(m)→	9.33(d)	2.73	8.6f (s)	-	3.80(3H,s).
10c	D	8.56(d)	←7.80-7.96(m)→	9.30(d)	2.75	8.41(s)	-	7.35-7.70(3H,m);7.80- 7.96(2H,m).

^a Some peaks of the minor component were obscured

C=CDCl₃; TFA=CF₃CO₂H; D=d₆DMSO

TABLE 3 ^{13}C Nmr shifts for Compounds 6, 8, and 10

Compd	Solvent	C3	C3a	C4	C5	C6	C7	C1'	C2'	C3'	Other
6a(Z)	C/TFA	135.80(s)	133.95(s)	124.11(d)	125.58(d)	119.93(d)	129.98(d)	126.81(s)	144.00(d)	33.06(t)	8.81(q); 13.55(q); 53.88(q); 61.96(t); 160.11(s); 167.49(s).
6a(E)	C/TFA	-	-	123.901	125.33	119.702	129.809	126.044	149.357	33.966	
6b(Z)	C/TFA	135.80(s)	133.94(s)	124.12(d)	125.57(d)	119.81(d)	130.06(d)	126.95(s)	143.70(d)	32.79(t)	8.77(q); 53.93(q); 159.75(s); 167.97(s).
6b(E)	C/TFA	-	-	123.901	125.330	119.702	129.809	126.044	147.357	33.966	8.608; 53.759; 61.836; 160.117; 168.423.
6c(Z)	C/TFA	135.92(s)	134.04(s)	124.30(d)	125.79(d)	119.82(d)	130.33(d)	134.19(s)	144.97(d)	33.31(t)	8.85(q); 53.22(q); 129.53(d); 129.88(d); 130.03(d); 134.27(s); 169.14(s); 187.97(s).
8a	C	135.54(s)	132.81(s)	121.29(d)	124.90(d)	119.23(d)	126.87(d)	101.45(s)	142.04(d)	99.98(s)	9.70(q); 14.56(q); 29.76(q); 51.76(q); 59.23(t); 164.93(s); 169.32(s); 195.40(s).
8b	C	135.68(s)	133.02(s)	121.64(d)	125.14(d)	119.38(d)	127.27(d)	101.36(s)	142.07(d)	99.54(s)	9.86(q); 50.78(q); 51.93(q); 165.16(s); 169.98(s); 196.00(s).
10a	D	135.71(s)	133.35(s)	123.95(d)	126.18(d)	120.26(d)	128.31(d)	103.33(d)	125.92(d)	135.78(s)	8.99(q); 14.05(q); 61.82(t); 162.75(s).
10b	D	135.35(s)	132.97(s)	123.63(d)	125.83(d)	119.95(d)	127.99(d)	102.69(s)	129.19(d)	135.47(s)	8.97(q); 52.79(q); 162.21(s).
10c	D	135.68(s)	133.38(s)	123.88(s)	126.18(d)	120.25(d)	129.00(d)	112.42(s)	129.51(d)	137.39(s)	9.16(q); 129.09(d); 131.75(s); 132.31(d); 135.37(s); 187.44(s).

C = CDCl_3 TFA = $\text{CF}_3\text{CO}_2\text{H}$ D = d_6 -DMSO

Acetylation Procedure.

To a solution of the ylide (0.001 mol) in acetic anhydride (6 ml, 64 mmol) were added two drops of sulphuric acid (98%). The decolourised solution was stirred (2 h) and then poured into ice/water (40 ml), neutralized with a solution of potassium bicarbonate (10%) and extracted with chloroform. The dried (Na_2SO_4) chloroform solution was concentrated and purified on alumina (activity IV) using hexane/ethyl acetate (2:1) as eluent.

Ylide (8a) mp 178-179°C (ethanol), 82% yield. Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_5$: C, 59.13; H, 5.50; N, 12.17. Found: C, 58.83; H, 5.61; N, 11.84. ν_{max} (KBr) 1730, 1725, 1680 cm^{-1} . λ_{max} 213.6, 268.8, 343.2 nm.

Ylide (8b) mp 152-154°C (ethanol/hexane), 55% yield. Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_5 \cdot 0.5\text{H}_2\text{O}$: C, 56.40; H, 5.30; N, 12.30. Found: C, 56.41; H, 5.41; N, 11.37. ν_{max} (CHCl_3) 1790, 1770, 1670, 1634 cm^{-1} . λ_{max} 228, 256.8, 264.8 sh, 320.0, 350.4, 368.8 sh nm.

Nitration Procedure.

The ylide (0.001 mol) was added to a stirred mixture of acetic anhydride (6 ml) and nitric acid (2 ml, 31 mmol) at 0°C, and the mixture was then stirred at room temperature (4 h). The mixture was poured into ice/water (40 ml) neutralized with 10% potassium bicarbonate, and extracted with chloroform. The dried (Na_2SO_4) extracts were evaporated and the yellow residue was crystallized.

Ylide (10a): 55% yield, mp 214-215 °C (ethanol). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_5\text{O}_6$: C, 46.56; H, 3.88; N, 20.89. Found: C, 46.50; H, 3.65; N, 20.28. ν_{max} (CHCl_3) 1690, 1590, 1490 cm^{-1} . λ_{max} 216.8, 274.4, and 378.4 nm.

Ylide (10b): 60% yield, mp 215-216 °C (ethanol). Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{N}_5\text{O}_6 \cdot \text{H}_2\text{O}$: C, 42.47; H, 3.83; N, 20.64. Found: C, 42.80; H, 3.26; N, 20.47. ν_{max} 1690, (CHCl_3) 1590, 1490 cm^{-1} . λ_{max} 226.4, 268.8, 302.4, 400.8 nm. m/z 321 (M^+ , 14%), 275 ($\text{M}-\text{NO}_2$, 18%), 170 (14%), 105 (52%), 104 (100%), 79 (65%), 78 (52%).

Ylide (10c): 30% yield, mp 270-273°C (ethanol). Anal. Calcd for $C_{17}H_{13}N_5O_5 \cdot 0.5C_2H_6O$; C, 54.38; H, 4.10; N, 17.94; Found: C, 54.45; H, 3.74; N, 17.59. ν_{max} (KBr) 1580, 1570, 1500 cm^{-1} . λ_{max} 206.4, 269.6, 398.4 nm.

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REFERENCES

1. Part 12. B. Abarca, R. Ballesteros, M.R. Metni, and G. Jones, Heterocycles, 1992, **33**, 203.
2. B. Abarca, R. Ballesteros, M.R. Metni, D.J. Ando, M.B. Hursthouse, and G. Jones, Tetrahedron Lett., 1991, **32**, 4977.
3. B. Abarca, R. Ballesteros, F. Mojarrad, M.R. Metni, S. Garcia-Granda, E. Perez-Carreño, and G. Jones, Tetrahedron, 1991, **47**, 5277.
4. a) J.E. Douglass and J.M. Wesolosky, J. Org. Chem., 1971, **36**, 1165; b) V. Boekelheide and J.E. Nottke, J. Org. Chem., 1969, **34**, 4134.
5. A.A. Danopoulos, G. Wilkinson, B. Hussain-Bates and M.B. Hursthouse, J. Chem. Soc., Dalton Trans., 1991, 1855.
6. SHELX86S. G.M. Sheldrick. Program for Crystal Structure Solution. Univ. Gottingen, 1986.
7. SHELX76. G.M. Sheldrick. Program for Crystal Structure Determination. Univ. Cambridge, 1976.
8. List of structure amplitudes, anisotropic thermal parameters, H-atom parameters, distances and angles involving H atoms and least-squares-planes data and principal torsion angles, have been deposited in the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

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