TRIAZOLOPYRIDINES. PART 12: A NEW SYNTHESIS OF INDOLIZINES FROM TRIAZOLOPYRIDINIUM YLIDES

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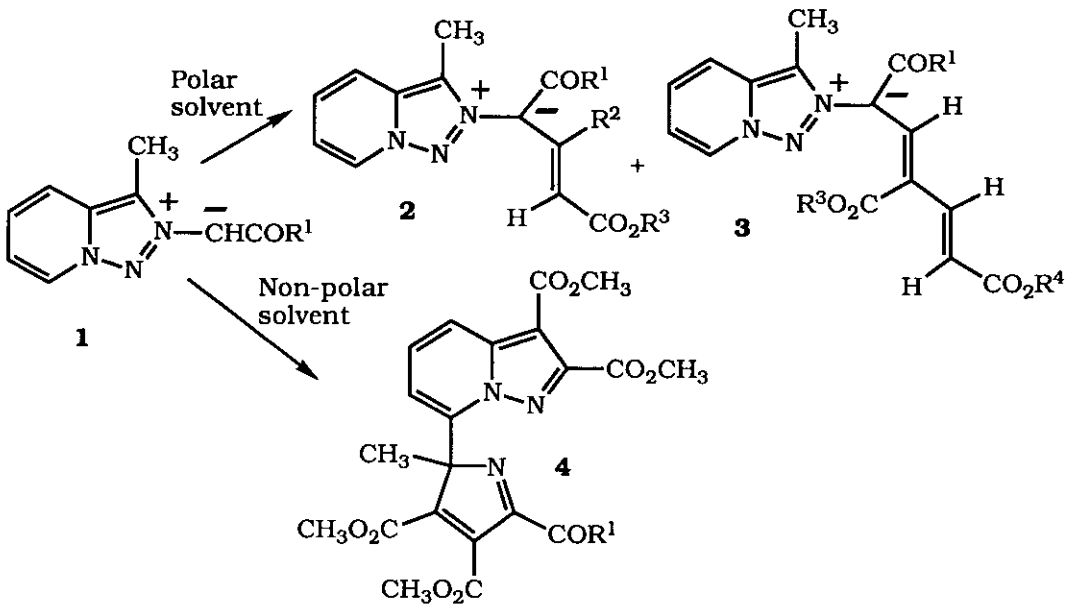
Abstract Treatment of 2-acylmethyl-1,2,3-triazolo[1,5-*a*]-pyridinium ylides (**1**) with methyl propiolate in non-polar solvent gives good yields of 1,2,3-trisubstituted indolizines (**5**). A mechanism for the transformation is suggested.

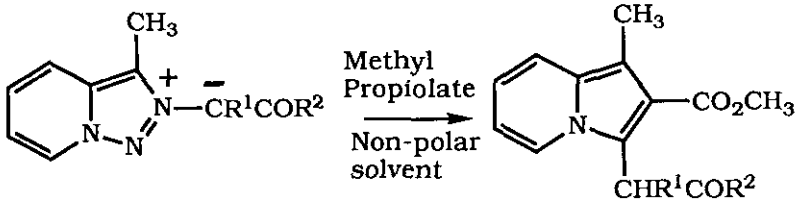
We have recently reported[1] that ylides of general type (**1**) derived from 2-acylmethyl-1,2,3-triazolo[1,5-*a*]pyridines react with acetylenic esters in acetonitrile to give new ylides of type (**2**) and (**3**). We have further reported [2] that a change in the reaction of the ylides with dimethyl acetylenedicarboxylate (DMAD) gives rise to pyrroleninylpyrazolo[5,1-*a*]pyridines of type (**4**) in excellent yields. We report here that a change in the acetylenic ester component again alters the course of the reaction producing indolizines in good to excellent yields.

We have previously noted[2] that the ylides (**1**) are not formed in toluene solution unless anhydrous potassium carbonate and triethylamine are present. This may be because the active base (the carbonate) is solubilized by the triethylamine, and we have confirmed the generation of ylides in toluene by the soluble strong base 4-dimethylaminopyridine (DMAP). With DMAP as base some indolizine was formed, but the yields are better and the reaction cleaner with the triethylamine/potassium carbonate mixture The products (**5**) obtained in yields of 82, 82, 65, and 90%, were colourless solids analysing for adducts containing one ylide (**1**) and one methyl Dedicated to Dr. Masatomo Hamana.



propiolate molecule, but with loss of two nitrogen atoms, thus immediately distinguishing them from the DMAD adducts. The ^{1}H nmr spectra of the new adducts (Table 1) showed four protons in the aromatic region (doublets at 7.68 and 7.37, double doublets at 6.55 and 6.66) in a pattern characteristic of a fused pyridine ring with a bridgehead nitrogen, but noticeably upfield of the equivalent signals in a triazolopyridine. The other signals in compound (**5a**), which we used as an example, were at 2.50, 3.68 and 3.89 (all 3H, s). The upfield signal was due to a methyl group attached to an aromatic system, the two near 3.70 to methyl ester groups. The only other signal (2H) was at 4.35; a DIFNOE experiment showed that irradiation at 2.50 (CH_3) produced enhancement only of the doublet at 7.37, while irradiation of the signal at 4.35 caused enhancement of the doublet at 7.68. The second observation immediately raises questions if we assume the methylene group to be that originally present in the triazolopyridinium salt, since the 'ylide' group must have migrated, being now attached in a peri position to the pyridine ring in the new heterocycles. The ^{13}C nmr spectrum of compound (**5a**) (Table 2) showed the expected 14 peaks, with methyl group signals at 10.43, 51.13 and 52.29 and a methylene signal at 30.85. Again the aromatic CH signals showed upfield shifts from those of triazolopyridine

indicating a π-excessive heterocycle, and the combined spectral evidence was best accommodated by the indolizine structures (**5a**)-(**5d**). In the case of the indolizine (**5d**) irradiation of the methyl doublet signal at 1.55 produced DIFNOE enhancement of the H5 doublet at 7.80, and for compound (**5c**) irradiation of the methylene signal at 5.03 produced enhancement of the doublet (H5) at 7.64 and of the 2H multiplet at 8.11 due to the *ortho* protons of the benzoyl group. The mass spectra show substantial peaks for the loss of the group COR^2 but few other significant peaks, reflecting the aromatic stability of the indolizines.

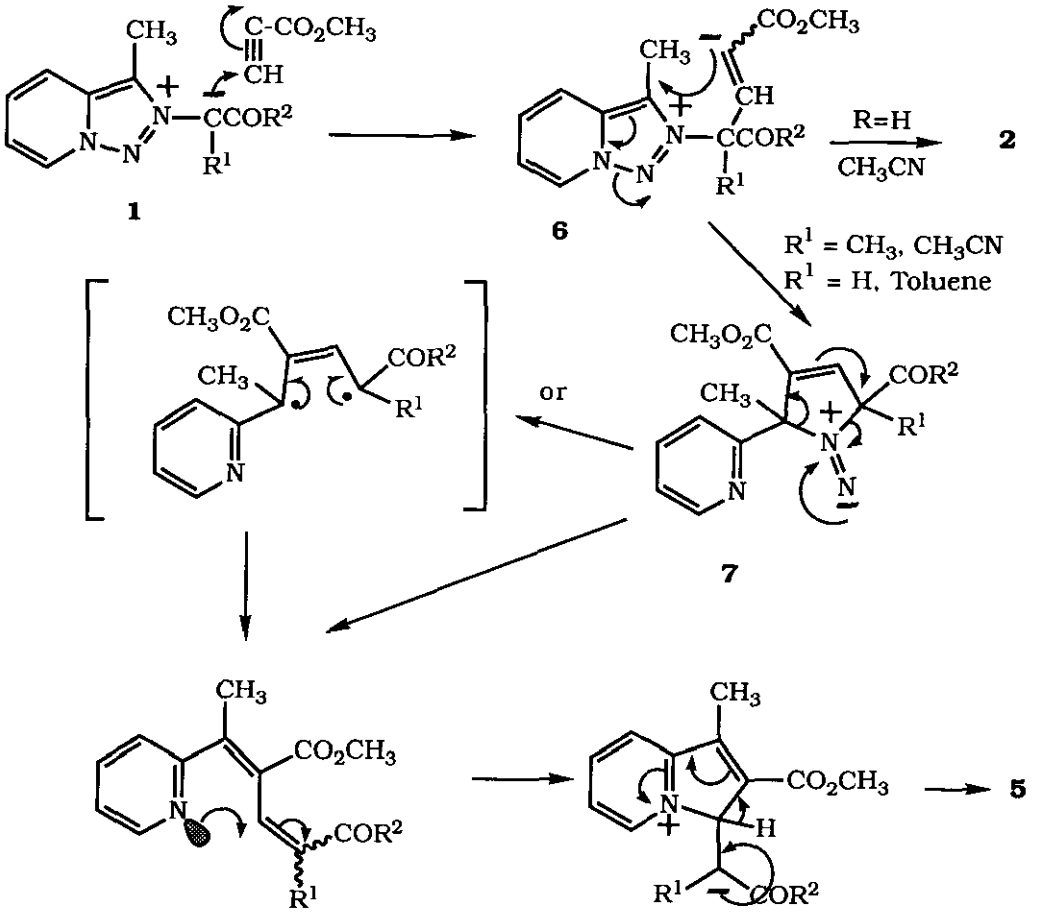


1a, R^1=H, R^2=OCH_3
1b, R^1=H, R^2=OC_2H_5
1c, R^1=H, R^2=C_6H_5
1d, R^1=CH_3, R^2=C_6H_5

5a, R^1=H, R^2=OCH_3
5b, R^1=H, R^2=OC_2H_5
5c, R^1=H, R^2=C_6H_5
5d, R^1=CH_3, R^2=C_6H_5

A mechanistic explanation is required to account for these three differing modes of reaction between ylides (**1**) and acetylenic esters to give compounds (**2**) and (**3**), compounds (**4**), and compounds (**5**). The only difference in the reactions which give compounds (**4**) from DMAD and compounds (**5**) from methyl propiolate appears to be in the relative reactivity of the two esters as dienophiles and we have suggested[2] that acetylenedicarboxylate causes (8 + 2) cycloaddition to initiate formation of compounds (**4**). It is probable that the first stage with methyl propiolate is the same whether the solvent is polar or non-polar, and results in formation of the ylide (**6**). In polar solvents a hydrogen transfer rapidly stabilizes the system to give the ylide (**2**), but in non-polar medium this process is slowed and attack on the C3 carbon allows cleavage of the N_1-N_8 bond giving the diazene (**7**). Support for this suggestion is provided by the observation that the ylide (**1d**) gives indolizine (**5d**) even in polar media, since a route to stabilized ylide via hydrogen shift is here not available. Fragmentation of acyclic 1,1-diazenes derived from pyrrolidine[3] has been shown to give a 1,4-diradical

and thence to alkenes and cyclobutanes. Our diazene (**7**) could fragment to a 1,4-diene directly or via a diradical, and recyclization of the resulting butadiene could produce the indolizine skeleton. This pathway is shown in the Scheme.



Scheme

ACKNOWLEDGEMENTS

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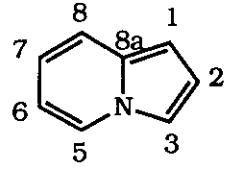
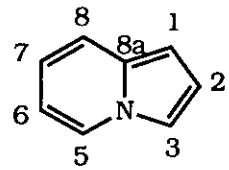
Table 1 ^{1}H Nmr shifts (δ) and J values (Hz) for Indolizines (**5**)



Compd	H5	H6	H7	H8	1-CH_3	Other	J values
5a	7.68d	6.55dd	6.66dd	7.37d	2.50s	3.68 (3H, s); 3.89 (3H, s); 4.35 (2H, s)	$J_{5,6}$=7.3; $J_{6,7}$=6.3; $J_{7,8}$=9.0
5b	7.68d	6.54dd	6.63dd	7.37d	2.50s	1.23 (3H, t); 3.89 (3H, s); 4.16 (2H, q); 4.33 (2H, s)	$J_{5,6}$=7.1; $J_{6,7}$=5.9; $J_{7,8}$=8.8; J_{CH_3,CH_2}=7.1
5c	7.64d	6.50dd	6.62dd	7.37d	2.50s	3.84 (3H, s); 5.03 (2H, s); 7.45-7.51 (2H, m); 7.55-7.61 (1H, m); 8.11 (2H, m)	$J_{5,6}$=7.1; $J_{6,7}$=7.1; $J_{7,8}$=9.0; J_{ortho}=6.8; J_{meta}=7.8
5d	7.80d	6.55dd	6.48dd	7.40d	2.45d	1.55 (3H, d); 4.00 (3H, s); 6.25 (1H, q); 7.20-7.31 (3H, m); 8.00 (2H, br d)	$J_{5,6}$=7.2

Table 2 ^{13}C Nmr shifts (δ) for Indolizines (**5**)



Compd	C1	C2	C3	C5	C6	C7	C8	C8a	Others
5a	110.70s	119.59s	116.15s	121.70d	112.57d	116.15d	118.85d	130.18s	10.43q; 30.85t; 51.13q; 52.29q;166.66s; 170.29s
5b	110.68s	119.76s	116.15s	121.73d	112.42d	116.07d	118.81d	130.13s	10.43q; 14.20q; 31.05t; 51.09q; 61.16t; 166.64s; 169.79s
5c	110.68s	120.78s	116.02s	122.06d	112.40d	116.15d	118.93d	130.37s	10.61q; 35.72t; 51.08q; 128.54d;128.70d; 133.42d; 136.48s; 166.97s; 195.67s
5d	111.01s	125.89s	114.59s	122.83d	116.13d	116.13d	118.83d	130.37s	10.50q; 12.82q; 39.79; 51.08q; 128.42d;128.48d; 133.01d; 136.62s; 167.39s; 200.44s

EXPERIMENTAL

Mps were recorded on a heated stage, and are uncorrected. Nmr spectra were determined on solutions in $CDCl_3$, and uv spectra in absolute ethanol.

General Procedure for Preparation of Indolizines (**5a**)-(**5d**)

A suspension of the appropriate salt (preparations previously described[4]) (0.003 mol) in anhydrous toluene (30 ml) with triethylamine (0.45 ml, 0.003 mol) and anhydrous potassium carbonate (0.5 g, 0.0036 mol) was stirred vigorously at room temperature for 4 h, during which time a yellow paste was formed. After addition of methyl propiolate (0.3 ml, 0.0035 mol) a red colour formed. The mixture was stirred overnight at room temperature, filtered, and the filtrate was evaporated. Purification was by chromatography on a column of alumina (activity IV) using hexane:ethyl acetate (9:1) as eluent, followed by recrystallization.

Methyl 3-Methoxycarbonylmethyl-1-methylindolizine-2-carboxylate (**5a**): Crystallized from hexane in 82% yield, mp 110-111°C. Found: C, 64.84; H, 5.74; N, 5.34. $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.74; N, 5.36. ν_{max} (KBr) 1726, 1699 cm^{-1}. λ_{max} 260.0, 308.0, 379.2 nm.

Methyl 3-Ethoxycarbonylmethyl-1-methylindolizine-2-carboxylate (**5b**): Crystallized from hexane in 82% yield, mp 121-122°C. Found: C, 65.68; H, 5.99; N, 5.23. $C_{15}H_{17}NO_4$ requires C, 65.45; H, 6.18; N, 5.09. ν_{max} (KBr) 1720, 1699 cm^{-1}. λ_{max} 265.6, 308.0, 379.2 nm.

Methyl 3-Benzoylmethyl-1-methylindolizine-2-carboxylate (**5c**): Recrystallized from ethanol in 65% yield, mp 190-191°C. Found: C, 74.44; H, 5.38; N, 4.62. $C_{19}H_{17}NO_3$ requires C, 74.26; H, 5.53; N, 4.56. ν_{max} (KBr) 1696, 1671 cm^{-1}. λ_{max} 245.6, 296.0, 381.6 nm.

Methyl 3-(1-Benzoylethyl)-1-methylindolizine-2-carboxylate (**5d**): Crystallized from petroleum (bp 40-60°C) in 90% yield, mp 103-105°C. Found: C, 74.65; H, 5.85; N, 4.33. $C_{20}H_{19}NO_3$ requires C, 74.74; H, 5.92; N, 4.35. ν_{max} (KBr) 1691, 1676 cm^{-1}. λ_{max} 255.2, 305.6.0, 366.4 nm.

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