The Regiochemistry of the Cycloaddition of 4-R-Phenacylpyridazinium Ylides to Nonsymmetrical Substituted Olefins

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The regiochemistry of the [3+2] cycloaddition reactions between 4-R-phenacylpyridazinium ylides and acrylonitrile has been studied. Theoretical and experimental studies have been performed, both of which show that the reaction is regiospecific. Four new tetrahydropyrrolopyridazine heterocycles have been obtained. The structures of the new compounds were established by elemental (C,H,N) and spectral analyses (IR, ^{1}H and ^{13}C NMR, MS).

Introduction

In a previous publication,[1] we described the cycloaddition of 4-R-phenacylpyridazinium ylides **1−4** to symmetrically substituted olefins (*E*/*Z*) and we demonstrated the stereospecificity of these reactions. The addition of pyridazinium ylides to nonsymmetrical substituted olefins is of theoretical and practical interest, both with regard to the reaction mechanism and owing to the possibility of synthesizing new heterocyclic structures that would otherwise be impossible or difficult to obtain. Therefore, we have conducted a theoretical and experimental study concerning the regiochemistry of addition of 4-R-phenacylpyridazinium ylides to acrylonitrile as a nonsymmetrical substituted olefin.

The problem of orientation in cycloaddition reactions of cycloimmonium ylides to nonsymmetrical olefins has interested many researchers.[2−6] This is because addition of the dipole to the dipolarophile in a double sense (Figure 3) has often been found, according to orbital, steric and electronic factors. Theoretical studies[4,6−9] of the orientation in cycloaddition reactions of ylides (as 1,3-dipoles) to nonsymmetrical substituted activated olefins (as dipolarophiles) have been carried out using the General Perturbation Theory Limited to the Frontier Molecular Orbitals.[9−13]

Results and Discussion

The first part of this paper concerns a theoretical study of the regiochemistry of cycloaddition reactions of 4-R-phenacylpyridazinium ylides to acrylonitrile. We used the General Perturbation Theory Limited to the Frontier Molecular Orbitals. The atomic charges, the coefficients of the atomic orbitals, and the energies of the frontier molecular orbitals were calculated using the AM1 method (Table 1).[14][15]

The geometries of pyridazinium ylides **1−4** and acrylonitrile were approximated using data taken from the literature.[4][5] Analysis of these data led to the conclusion that 4-R-phenacylpyridazinium ylides could have 1,3-dipolar structures of types **1b−4b**, thus making them suitable for use in cycloaddition reactions as 1,3-dipoles (Figure 4). In Table 1, we present the energies (in eV) of the frontier molecular orbitals (HOMO and LUMO), the coefficients of the atomic orbitals p_z, and the total atomic charges (in coulombs) of all the atoms involved in the cycloaddition reactions between ylides **1** and **2** and acrylonitrile. Making use of the data in Table 1, we have constructed correlation diagrams between the HOMO and LUMO orbitals of the ylides and dipolarophiles (Figure 1).

Analysis of the correlation diagrams shows that the HOMO(ylide)−LUMO(dipolarophile) interactions are characterized by the lowest interaction energies (ΔE_1 = 7.8321 eV for ylide **1** and ΔE_2 = 8.2440 eV for ylide **2**). This means that the most likely interaction will take place between C-3 of the ylide and C-2 of acrylonitrile (Figure 2).

As shown in Figure 3, in the case of reactions between cycloimmonium ylides and acrylonitrile, two reaction pathways (I and II) could theoretically be followed, leading to the formation of two pairs of regioisomers (A, A′ and B, B′). However, analyzing the data presented above, we find that in the case of 4-R-phenacylpyridazinium ylides, the bond is formed between the ylide carbon and the nonsubstituted carbon atom of the acrylonitrile. This is in accordance with the electronic effects exerted in the acrylonitrile (path I, stereoisomers A and A′, Figure 3).

In order to verify the theoretical data presented, we carried out [3+2] cycloaddition reactions between 4-R-phenacylpyridazinium ylides **1b−4b** (which were obtained in situ from the corresponding cycloimmonium salts[1]) and acrylonitrile (Figure 4).

As can be seen in Figure 1, a single stereoisomer **A** of a single regioisomer is obtained, according to pathway **I** in Figure 4.

The structures of **A**-type products **5−8** were proven by elemental and spectral analyses (IR, ^{1}H NMR, ^{13}C NMR, and MS). Obviously, the data generated by the elemental analysis are compatible with both possible regioisomers. However, the spectroscopic data confirm that **A**-type prod-

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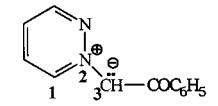
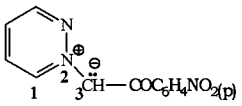
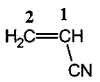
Table 1. The coefficients of atomic orbitals (p_z), the total atomic charge (in Q) and energies (in eV) of ylides **1**, **2** and acrylonitrile

Molecule	Orbital and atomic charge (Q)	E/eV	Coefficients of atomic orbitals (p_z)		
			C^1	N^2	$C^3_{(i)}$
	HOMO	–7.8549	0.459	–0.021	–0.636
	LUMO	–0.9570	–0.198	0.466	–0.385
	Q		–0.136	0.155	–0.195
	HOMO	–8.2228	0.451	–0. 008	–0.635
	LUMO	–1.6010	0.157	–0. 282	0.166
	Q		–0.125	0. 158	–0.216
	HOMO	–10.6123	–0.647	–0.648	–
	LUMO	0.0228	0.571	–0.674	–
	Q		–0.030	–0.011	

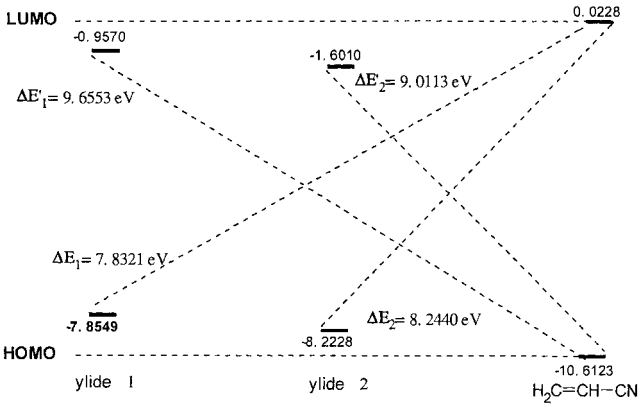


Figure 1. Correlation diagram between the HOMO and LUMO orbitals of the ylides and dipolarophiles

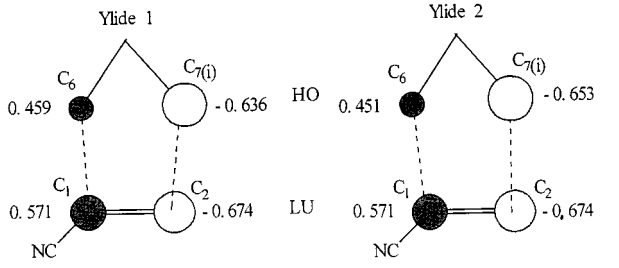


Figure 2. HOMO−LUMO interaction of ylides and acrylonitriles

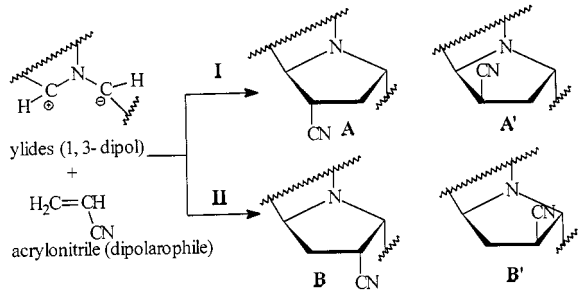


Figure 3. Reaction pathway between ylides and acrylonitrile

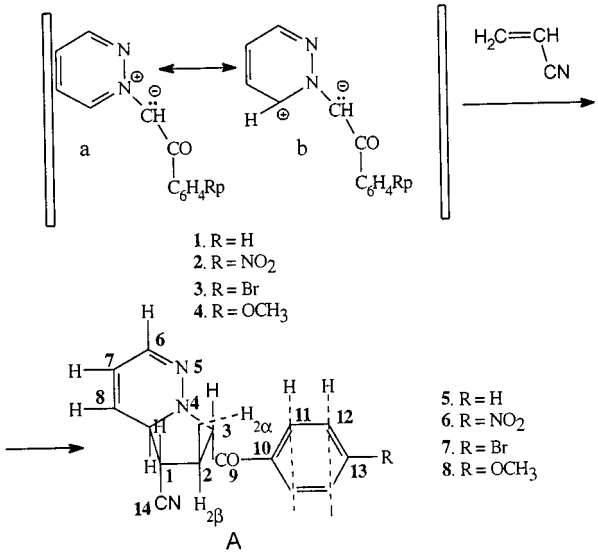


Figure 4. Reaction pathway between 4-R-phenacylpyridazinium ylides and acrylonitrile

ucts are obtained, according to route **I**, indicating that the reaction is charge-controlled. Thus, analysis of the spectra, such as that of product **5** as a representative of the series, reveals the following data:

In the IR spectra, the most notable signals are those of the cyano group at 2230 cm^{-1} (low intensity) and the oxo group at 1700 cm^{-1} (very intense).

The ^{1}H-NMR spectra provide essential data concerning the structures of the products. The most important protons in assigning the structure of product **5** are 1-H, 2-H$^{\alpha}$, 2-H$^{\beta}$, 3-H, 8a-H and 8-H. Thus, the 3-H proton gives rise to two doublets in the region δ = 5.61−5.55, which rules out the **B** and **B′** structures (where these protons should give rise simply to doublets). The 3-H proton exhibits two different coupling constants, $J_{3,2b}$ = 8.4 Hz and $J_{3,2a}$ = 3.0 Hz, which show that it is *trans* to 2-H$^{\beta}$ and on the same side of the pyrrolino ring as 2-H$^{\alpha}$. 2-H$^{\alpha}$ and 2-H$^{\beta}$ appear as nonequivalent protons: the signal due to 2-H$^{\alpha}$ is seen at

δ = 2.20−2.05 (seven lines ddd, $J_{2\alpha,3}$ = 3.0 Hz, $J_{2\alpha,1}$ = 3.5 Hz, $J_{2\alpha,2\beta}$ = 13.2 Hz), while that due to 2-H$^{\beta}$ is seen at δ = 2.78−2.65 (seven lines ddd, $J_{2\beta,3}$ = 8.4 Hz, $J_{2\beta,1}$ = 9.4 Hz, $J_{2\beta,2\alpha}$ = 13.2 Hz). The coupling constants confirm their orientation on the pyrrolino ring (2-H$^{\alpha}$ is up and 2-H$^{\beta}$ is down) and show that 1-H resides above the ring (this is also confirmed by the chemical shift, δ = 3.26−3.16, of this proton and its coupling constants, eight lines ddd, $J_{1,2\alpha}$ = 3.5 Hz, $J_{1,2\beta}$ = 9.4 Hz, $J_{1,8a}$ = 7.1 Hz). At δ = 4.05−4.00, a signal due to 8a-H is seen (sept, $J_{8a,1}$ = 7.1 Hz, $J_{8a,8}$ = 4.4 Hz, and a long-range coupling $J_{8a,7}$ = 2.6 Hz), which shows that 8a-H resides below the ring. On the basis of these data, we conclude that isomer **5** has a tetrahydropyrrolopyridazine structure, in which the cyano group is below the ring and the protons are above and below the ring as shown in Figure 5.

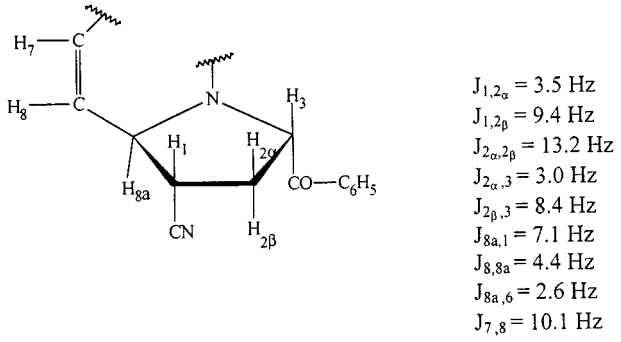


Figure 5. Structure and coupling constants of isomer 5

In the ^{13}C-NMR spectra, the most important signals are those of the ketone carbon atom (C-9, δ = 195.11), the cyano carbon atom (C-14, δ = 119.98), and the carbon atoms of the pyrrolino ring [C-1, δ = 35.69 (β-pyrrolino ring, α-cyano carbon atom); C-2, δ = 28.42 (β-pyrrolino ring, α-aliphatic carbon atom); C-3, δ = 70.62 (α-pyrrolino ring, α-oxo carbon atom); C-8a, δ = 56.03 (α-pyrrolino and α-pyridazine)].

MS data are also supportive of the proposed structures. Thus, the molecular ion, the [M + 1], [M + 2], [M − 1] and [M − 2] peaks, the main fragmentation reaction (α to the oxo group), and the remaining fragments confirm the structures as illustrated in Figure 6.

All other signals in the IR, ^{1}H- and ^{13}C-NMR and mass spectra are in accordance with the proposed structure.

Conclusions

1. Cycloaddition reactions between 4-R-phenacylpyridazinium ylides and acrylonitrile are highly regiospecific. The reaction is HOMO-controlled on the side of the ylides, and only one regioisomer is formed, namely that in which the ylide carbanion forms a new bond to the most electrophilic carbon atom of acrylonitrile. The theoretical and experimental data are in good agreement.

2. Four new tetrahydropyrrolopyridazine heterocycles have been obtained.

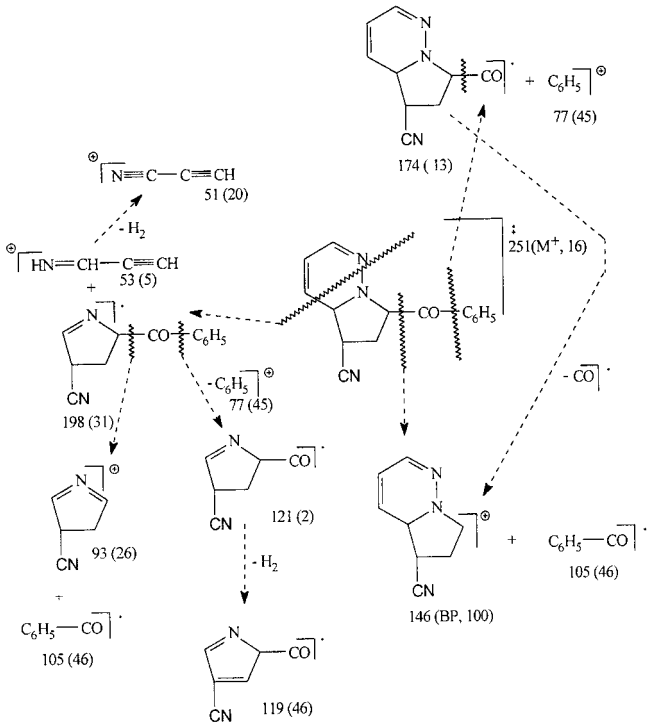


Figure 6. Fragmentation pattern of compound **5**

Experimental Section

General Remarks: ^{1}H- and ^{13}C-NMR spectra were recorded with a Gemini 200 MHz spectrometer in $CDCl_3$ solution; shifts are reported in ppm downfield from $SiMe_4$ as internal standard. Coupling constants are given in Hz. − Mass spectra were recorded at an ionizing voltage of 10 kV using field desorption (FD). − IR spectra were recorded with a Specord-71 spectrometer in KBr pellets. − Melting points are uncorrected.

General Procedure: The appropriate cycloimmonium salt (10 mmol) was suspended in 50 mL of anhydrous benzene. Acrylonitrile (10 mmol) and triethylamine (10 mmol), dissolved in 10 mL of benzene, were then added. The resulting mixture was heated to reflux for 2 h and then the solvent was evaporated using a steam bath. The crude product was recrystallized from an appropriate solvent.

3-Benzoyl-1-cyano-1,2,3,8a-tetrahydropyrrolo[2,1-*b*]pyridazine (5): Recrystallized from methanol. Cream-coloured crystals. Yield 2.06 g (82%); m.p. 121−122°C. − IR (KBr): ṽ = 2230 (w), 1700 (s), 1605, 1565, 1460, 1405 (s to m); 3050−3000 (m to w), 2950 cm^{-1} (w). − ^{1}H NMR ($CDCl_3$): δ = 8.13−8.09 (dd, 2 11-H, $J_{11,12}$ = 8.5, $J_{11,13}$ = 2.0), 7.63−7.55 (dd, 1 13-H, $J_{13,11}$ = 2.0, $J_{13,12}$ = 7.5), 7.54−7.43 (dd, 2 12-H, $J_{12,11}$ = 8.5, $J_{12,13}$ = 7.5), 6.87−6.85 (dd, 1 6-H, $J_{6,7}$ = 4.7, $J_{6,8}$ = 1.4), 6.14−6.08 (dd, 1 7-H, $J_{7,6}$ = 4.7, $J_{7,8}$ = 10.1, $J_{7,8a}$ = 2.6), 6.06−5.96 (8 signals ddd, 1 H-8, $J_{8,8a}$ = 4.4, $J_{8,7}$ = 10.1, $J_{8,6}$ = 1.4), 5.61−5.55 (dd, 1 H-3, $J_{3,2\alpha}$ = 3.0, $J_{3,2\alpha}$ = 8.4), 4.05−4.00 (sept, 1 8a-H, $J_{8a,1}$ = 7.1, $J_{8a,8}$ = 4.4, $J_{8a,7}$ = 2.6), 3.26−3.16 (8 signals ddd, 1 1-H, $J_{1,2\alpha}$ = 3.5, $J_{1,2\beta}$ = 9.4, $J_{1,8a}$ = 7.1), 2.78−2.65 (7 signals ddd, 1 2-H$^{\beta}$, $J_{2\beta,3}$ = 8.4, $J_{2\beta,1}$ = 9.4, $J_{2\beta,2\alpha}$ = 13.2), 2.20−2.05 (7 signals ddd, 1 2-H$^{\alpha}$, $J_{2\alpha,3}$ = 3.0, $J_{2\alpha,1}$ = 3.5, $J_{2\alpha,2\beta}$ = 13.2). − ^{13}C NMR ($CDCl_3$): δ = 195.11 (C-9), 135.39 (C-13), 134.42 (C-10), 133.25 (C-6), 128.77 (C-11), 128.17 (C-12), 123.51 (C-7), 119.98 (C-14), 119.47 (C-8), 70.62 (C-3), 56.03 (C-8a), 35.69 (C-1), 28.42 (C-2). − MS (EI); *m/z* (%): 251 [M$^+$] (16), 252 (3), 253 (1), 250 (1), 249 (1.5), 198 (31), 174 (13), 146 (base peak, 100), 121 (2), 119 (46), 105 (46),

93 (26), 77 (45), 53 (5), 51 (20). − $C_{15}H_{13}N_3O$ (251): calcd. C 71.71, H 5.17, N 16.73; found C 71.50, H 5.30, N 16.52.

1-Cyano-3-(4-nitrobenzoyl)-1,2,3,8a-tetrahydropyrrolo[2,1-*b*]-pyridazine (6): Recrystallized from methanol. Greenish crystals. Yield 2.31 g (78%); m.p. 152°C. − IR (KBr): $\tilde{\nu}$ = 2225 (w), 1695 (s), 1535, 1350 (s), 1605, 1450, 1420, 1400 (s to m); 3050−3000 (m to w), 2950 cm^{-1} (w). − ^1H NMR ($CDCl_3$): δ = 8.30−8.00 (m, 4 H, 2 11-H, 2 12-H), 6.90−6.87 (dd, 1 6-H, $J_{6,7}$ = 3.1, $J_{6,8}$ = 1.9), 6.17−6.10 (dd, 1 7-H, $J_{7,6}$ = 3.1, $J_{7,8}$ = 10.1, $J_{7,8a}$ = 2.1), 6.10−6.00 (8 signals ddd, 1 8-H, $J_{8,8a}$ = 4.5, $J_{8,7}$ = 10.1, $J_{8,6}$ = 1.9), 5.59−5.52 (dd, 1 3-H, $J_{3,2\alpha}$ = 3.0, $J_{3,2\alpha}$ = 8.4), 3.91−3.86 (sept, 1 8a-H, $J_{8a,1}$ = 6.8, $J_{8a,8}$ = 4.5, $J_{8a,7}$ = 2.1), 3.28−3.17 (8 signals ddd, 1 1-H, $J_{1,2\alpha}$ = 4.3, $J_{1,2\beta}$ = 9.4, $J_{1,8a}$ = 6.8), 2.88−2.75 (7 signals ddd, 1 2-H^{β}, $J_{2\beta,3}$ = 8.4, $J_{2\beta,1}$ = 9.4, $J_{2\beta,2\alpha}$ = 13.3), 2.12−2.07 (7 signals ddd, 1 2-H^{α}, $J_{2\alpha,3}$ = 3.0, $J_{2\alpha,1}$ = 4.3, $J_{2\alpha,2\beta}$ = 13.3). − ^{13}C NMR ($CDCl_3$): δ = 182.31 (C-9), 147.82 (C-13), 139.47 (C-10), 136.77 (C-6), 130.84 (C-11), 124.49 (C-7), 124.39 (C-12), 121.04 (C-14), 120.38 (C-8), 71.80 (C-3), 56.59 (C-8a), 36.34 (C-1), 27.72 (C-2). − MS EI; *m/z* (%): 296 [M^+] (12), 297 (2.5), 295 (1.5), 243 (40), 150 (22), 146 (base peak, 100), 119 (53), 93 (42), 76 (26). − $C_{15}H_{12}N_4O_3$ (296): calcd. C 60.81, H 4.05, N 18.91; found C 60.57, H 4.20, N 18.67.

3-(4-Bromobenzoyl)-1-cyano-1,2,3,8a-tetrahydropyrrolo[2,1-*b*]-pyridazine (7): Recrystallized from methanol. White crystals. Yield 2.74 g (83%); m.p. 139°C. − IR (KBr): $\tilde{\nu}$ = 2230 (w), 1705 (s), 1595, 1490, 1405 (s to m); 3050−3000 (m to w), 2950 cm^{-1} (w). − ^1H NMR ($CDCl_3$): δ = 8.00−7.96 (d, 2 11-H, $J_{11,12}$ = 8.9), 7.63−7.59 (d, 1 12-H, $J_{12,11}$ = 8.9), 6.87−6.84 (dd, 1 6-H, $J_{6,7}$ = 3.2, $J_{6,8}$ = 1.8), 6.16−6.09 (dd, 1 7-H, $J_{7,6}$ = 3.2, $J_{7,8}$ = 10.2, $J_{7,8a}$ = 2.2), 6.06−5.96 (8 signals ddd, 1 8-H, $J_{8,8a}$ = 4.6, $J_{8,7}$ = 10.2, $J_{8,6}$ = 1.8), 5.53−5.47 (dd, 1 3-H, $J_{3,2\alpha}$ = 3.2, $J_{3,2\beta}$ = 8.4), 3.96−3.91 (sept, 1 8a-H, $J_{8a,1}$ = 6.9, $J_{8a,8}$ = 4.6, $J_{8a,7}$ = 2.2), 3.25−3.15 (8 signals ddd, 1 1-H, $J_{1,2\alpha}$ = 4.0, $J_{1,2\beta}$ = 9.5, $J_{1,8a}$ = 6.9), 2.81−2.69 (7 signals ddd, 1 2-H^{β}, $J_{2\beta,3}$ = 8.4, $J_{2\beta,1}$ = 9.5, $J_{2\beta,2\alpha}$ = 13.1), 2.15−2.03 (7 signals ddd, 1 2-H^{α}, $J_{2\alpha,3}$ = 3.2, $J_{2\alpha,1}$ = 4.0, $J_{2\alpha,2\beta}$ = 13.1). − ^{13}C NMR ($CDCl_3$): δ = 194.32 (C-9), 135.82 (C-6), 132.47 (C-10), 131.47 (C-12), 130.55 (C-11), 128.97 (C-13), 123.79 (C-7), 119.94 (C-14), 119.65 (C-8), 70.72 (C-3), 55.90 (C-8a), 35.57 (C-1), 27.71 (C-2). − MS EI; *m/z* (%): 331 [M^+] (9), 332 (2), 330 (2), 329 (9), 278 (14), 276 (14), 185 (24), 183 (25), 157 (17), 155 (17), 146 (base peak, 100), 119 (67), 93 (26), 76 (16). − $C_{15}H_{12}BrN_3O$ (330): calcd. C 54.59, H 3.63, N 12.72; found C 54.72, H 3.72, N 12.57.

1-Cyano-3-(4-methoxybenzoyl)-1,2,3,8a-tetrahydropyrrolo[2,1-*b*]-pyridazine (8): Recrystallized from methanol. White crystals. Yield 2.25 g (80%); m.p. 143−145°C. − IR (KBr): $\tilde{\nu}$ = 2210 (w), 1680 (s), 1265, 1025 (s to m), 1610, 1575, 1500, 1430, 1395 (s to m); 3050−3000 (m to w), 2950 cm^{-1} (w). − ^1H NMR ($CDCl_3$): δ = 8.39−8.35 (d, 2 11-H, $J_{11,12}$ = 9.1), 7.24−7.19 (d, 1 12-H, $J_{12,11}$ = 9.1), 7.14−7.11 (dd, 1 6-H, $J_{6,7}$ = 4.3, $J_{6,8}$ = 1.8), 6.45−6.35 (dd, 1 7-H, $J_{7,6}$ = 4.3, $J_{7,8}$ = 10.2, $J_{7,8a}$ = 2.6), 6.36−6.25 (8 signals ddd, 1 8-H, $J_{8,8a}$ = 4.6, $J_{8,7}$ = 10.2, $J_{8,6}$ = 1.8), 5.84−5.78 (dd, 1 3-H, $J_{3,2\alpha}$ = 2.8, $J_{3,2\beta}$ = 8.4), 4.33−4.27 (sept, 1 8a-H, $J_{8a,1}$ = 6.8, $J_{8a,8}$ = 4.6, $J_{8a,7}$ = 2.6), 4.13 (s, OCH_3), 3.54−2.94 (8 signals ddd, 1 1-H, $J_{1,2\alpha}$ = 4.7, $J_{1,2\beta}$ = 9.5, $J_{1,8a}$ = 6.8), 3.07−2.94 (7 signals ddd, 1 2-H^{β}, $J_{2\beta,3}$ = 8.5, $J_{2\beta,1}$ = 9.5, $J_{2\beta,2\alpha}$ = 13.2), 2.42−2.29 (7 signals ddd, 1 2-H^{α}, $J_{2\alpha,3}$ = 2.8, $J_{2\alpha,1}$ = 4.7, $J_{2\alpha,2\beta}$ = 13.2). − ^{13}C NMR ($CDCl_3$): δ = 193.84 (C-9), 163.52 (C-13), 135.50 (C-6), 131.38 (C-11), 127.69 (C-10), 123.73 (C-7), 120.29 (C-14), 119.60 (C-8), 113.65 (C-12), 70.42 (C-3), 55.66 (C-8a), 35.50 (C-1), 28.30 (C-2, methoxy). − MS (EI): *m/z* (%) = 281 [M^+] (23), 282 (4), 280 (1), 228 (14), 146 (97), 135 (base peak, 100), 119 (36), 93 (18), 76 (19). − $C_{16}H_{15}N_3O_2$ (281): calcd. C 68.31, H 5.37, N 14.94; found C 68.00, H 5.30, N 14.68

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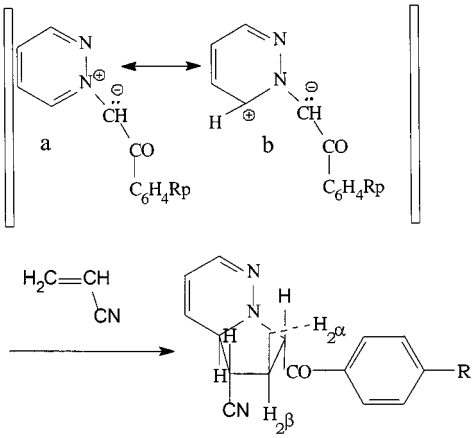
3501 **M. D. Caprosu, I. G. Olariu, I. I. Mangalagiu,* M. A. Constantinescu, M. G. Petrovanu**

The Regiochemistry of the Cycloaddition of 4-R-Phenacylpyridazinium Ylides to Nonsymmetrical Substituted Olefins

Keywords: Pyridazine / Ylides / Tetrahydropyrrolopyridazine / Regiospecificity / Structure / Semiempirical calculations



Regiochemistry of the reaction between 4-R-phenacylpyridazinium ylides and acrylonitrile