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Synthesis of 7,7'-Bisindolizines by the Reaction of 4,4'-Bipyridinium-Ylides with Activated Alkynes

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Abstract: Eight new bis-indolizine heterocycles were prepared. We have accomplished a theoretical and experimental study looking at the regiochemistry of 3+2 dipolar cycloadditions of 4,4'-bipyridinium ylides (6-10)[1,2] to ethyl propiolate and dimethyl acetylenedicarboxylate.

Introduction

In view of the biological[3,4] and chemical[5-7] widespread importance of compounds having the bipyridyl framework, we deemed it of interest to make an addition to the synthetic methods of preparation of bis-indolizine, which is the subject of the present report.

In previous publications we have already presented the synthesis of diquaternary salts of 4,4'-bipyridine.[1,2]

By studying the reactivity of diquaternary salts of 4,4'-bipyridine, it can be observed, by their treatment with alkali, a succession of zwitterionic structure compounds formed of ylidic type.

The addition of 4,4'-bipyridinium ylides to substituted olefins and alkynes presents interest because of the reaction pathway and because of possibility of preparing new bisindolizine heterocycles which are difficult to obtain otherwise.

We therefore decided to conduct in a series of 4,4'-bipyridinium ylides, a theoretical and experimental study regarding the regiochemistry of the reactions of 4,4'-bipyridinium ylides with ethyl propiolate and dimethyl acetylenedicarboxylate.

The problem of orientation in cycloaddition reactions of cycloimmonium ylides to activated non-symmetrical alkynes has interested many researchers[8-12] because addition of the dipole is affected by orbital, steric and electron factors.

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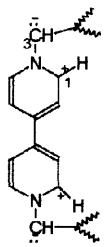
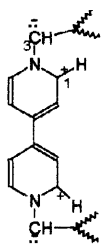
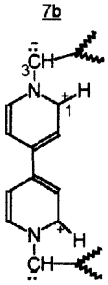
The theoretical studies which have been realised over a period time, regarding the regiochemistry of cycloaddition reactions of ylides (as 1,3-dipoles) to non-symmetrical activated alkynes (as dipolarophiles), have made use of the General Theory of Perturbation of the Molecular Frontier Orbitals.

Results and discussion

The first part of the paper contains a theoretical study concerning the regiochemistry of cycloaddition reactions of 4,4'-bipyridinium ylides to ethyl propiolate. We have used the General Theory of Perturbation of the Molecular Frontier Orbitals.

The atomic charges, the coefficient of atomic orbitals and the values of the energy from the frontier molecular orbitals, have been calculated using the MNDO method. [11,12] (Table 1).

Table 1

Molecule	Orbital	Energy,eV	C_1	C_2	C_3
 6b	HOMO	-7,2859	0,225	-	-0,458
	LUMO	-1,5401	-0,131	-	-0,276
	Q		-0,179	-	-0,387
 7b	HOMO	-7,595	0,203	-	-0,412
	LUMO	-1,507	-0,117	-	-0,249
	Q		-0,180	-	-0,387
 8b	HOMO	-7,809	0,206	-	-0,449
	LUMO	-1,463	-0,137	-	-0,259
	Q		-0,175	-	-0,396
$CH^{2}{\equiv}C^{1}O_2C_2H_5$	HOMO	-11,3143	-0,1791	-0,1794	
	LUMO	+0,4186	+0,5655	-0,5621	
	Q		-0,1856	-0,0311	

The geometry of 4,4'-bipyridinium ylides **6-8b** and ethyl propiolate has been approximated using the data from chemistry literature. [9-13]

Analysis of these data leads to the conclusion that 4,4'-bipyridinium ylides could have 1,3-dipolar structure of type **6-10b**, and, therefore, they can be used in cycloaddition reactions as 1,3-dipoles. In Table 1, we present the energies (in eV) of frontier molecular orbitals (HOMO and LUMO), the coefficients of atomic orbitals p_z, and the total atomic charges (in coulombs) of all the atoms involved in the cycloaddition reactions between ylides **6-8b** and ethyl propiolate.

Making use of the data in Table1, we have elaborated the correlation diagram between HOMO and LUMO orbitals from ylides and dipolarophiles (figure 1).

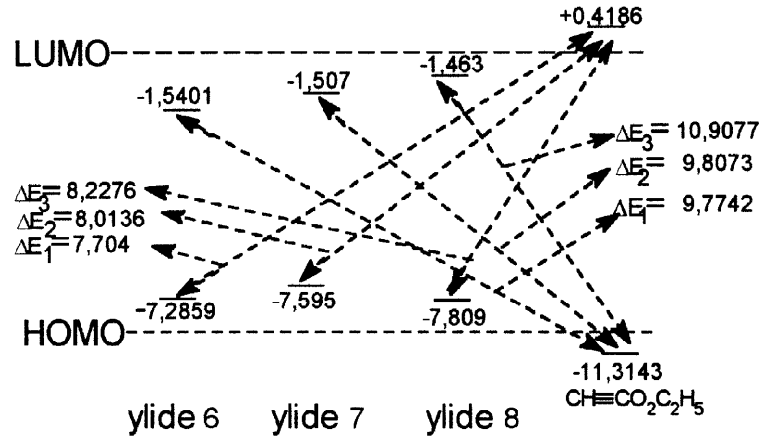


Figure 1

Correlation diagram between ylides **6-8b** and ethyl propiolate

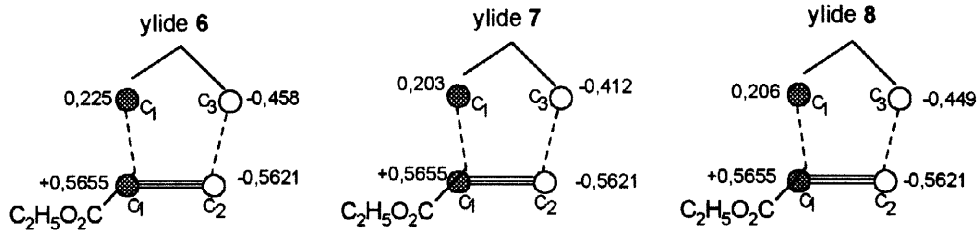


Figure 2

Graphical representation of the interaction between the frontier molecular orbitals

The analysis of the correlation diagrams shows that the interactions HOMO ylide-LUMO dipolarophile are characterised by the lowest interaction energies (ΔE_1=7,704 for ylide **6b**, ΔE_2=8, 0136 for ylide **7b** and ΔE_3=8, 2276 for ylide **8b**). This means that , in a reaction ylide (donor)-dipolarophile (acceptor), under orbital or charge control, the most likely interaction will take place between the C_3 atom from ylide and C_2 from ethyl propiolate (figure 2)

As figure 2 shows, in the case of reactions between cycloimmoniumylides and ethyl propiolate, theoretically, there could be two reaction pathways (I and II) with the formation of two regioisomers (**A** and **B**).

The second part of the paper describes the course of the reaction between 4,4'-bipyridinium ylides **6-10b** with ethyl propiolate and dimethyl acetylenedicarboxylate. 4,4'-Bipyridinium salts **1-5**, were synthesized by reaction of 4,4'-bipyridine with reactive halide derivatives. [1,2] Ylides **6-10** were obtained *in situ* by the reaction between salts **1-5** and triethylamine , in anhydrous benzene or N-methyl pyrrolidone (figure 4).

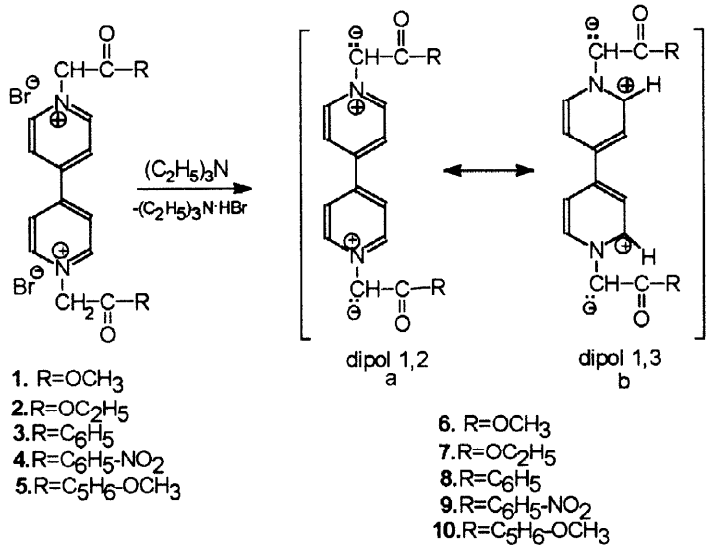


Figure 4. Zwitterionic structure of 4,4'-bipyridinium ylides

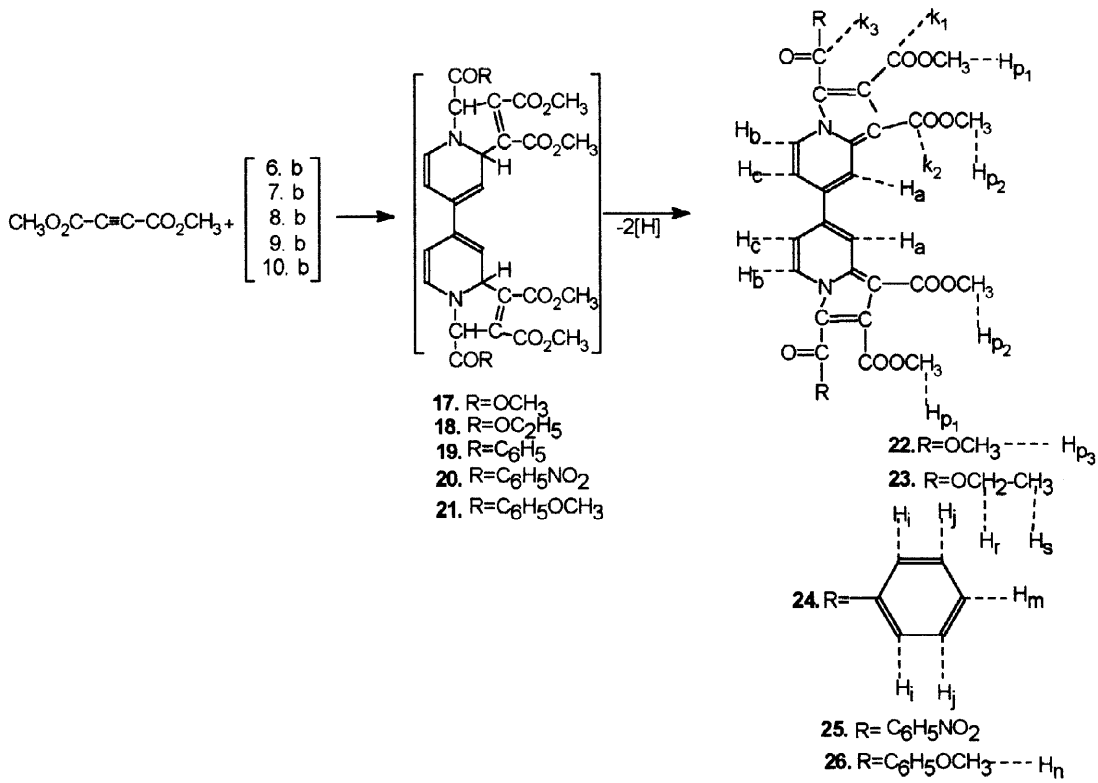


Figure 5. Reaction between 4,4'-bipyridinium ylides and dimethyl acetylendicarboxylate

4,4'-Bypiridinium ylides **6-10b** react with dimethyl acetylenedicarboxylate to give cycloadducts. As figure 5 shows, ylides obtained *in situ* were likely to form unisolable intermediate cycloadducts of type **17-21**, which due to the stabilisation by aromatisation, suffer a dehydrogenation process. As we worked in ambient conditions, it is possible an oxidative dehydrogenation occurred, too. Finally, isolable cycloadducts **22-26** were obtained. These products contain a system of conjugated double bonds.

The structure of **14-16** and **22-26** compounds were proved by elemental and spectral methods. The IR spectra of the compounds **14-16** sustain the structure of type **A** of these products. The esteric carbonyl group absorbs at 1697-1700cm^{-1}. If the compound structures had been of type **B**, the esteric carbonyl group should have absorbed at higher wave numbers. The ketone band is present at wave number 1656 cm^{-1}. IR spectra for compounds **22-26** show absorption bands between 1658cm-1 and 1680cm-1 which are characteristic for the ketonic carbonylic groups. The esteric carbonyl groups absorb at different frequencies. The appearance of two absorption bands shows that the two esteric groups are not in the same plane.

The structure of the compounds **14-16** and **22-26** were also investigated by ^{1}HNMR spectroscopy. For the compounds **14-16**, in the multiplet at δ=7,78-7,82 ppm, there is a clear singlet of the H_d proton. In the multiplet at δ=7,42-7,73 ppm, we have established that the doublet of doublets which appears at δ=7,52, with J=7,5 and J=1,2, is assigned to H_c proton. The Hr and Hs protons gave a quartet at δ=4,38-4,4 ppm and a triplet at δ=1,40-1,43 ppm.

For the compounds **22-26** two singlets corresponding to methylic protons appear: δ=3,65-4,13 ppm for the H_{p1} protons and δ=4,05-4,13 ppm for the H_{p2} protons. We have established that the doublet of doublets which appears at δ=8,58-8,78 ppm is assigned to H_a proton. Each signal for pyridinic protons was attributed taking into account the literature data available. [5-8]

Experimental

Materials. Diquaternary salts of 4,4'-bipyridine 1-5[1] were prepared according to described procedures. Other common reagents and solvents were purchased from commercial sources as received.

Equipment IR spectra were obtained with a SPECORD 71 spectrometer using KBr for solids.

^{1}H NMR spectra were recorded in $CDCl_3$, DMSO-d_6 or DMF-d_7-D_2O depending on solubility, at room temperature on a VARIAN-GEMINI-200 spectrometer. NMR peak locations are reported as δ values from TMS. The coupling constants are given in Hertz.

General procedure for the preparation of 14-16 and 24-26. 1Mmol 4,4'-bipyridinium diquaternary salts and 2 mmoles ethyl propiolate or dimethyl acetylenedicarboxylate was suspended in 10 ml N-methyl pyrrolidone. Then,2 mmoles triethylamine (dissolved in 3 ml benzene) was added, under vigorous stirring. The solution was slowly heated. The reaction product was separated by filtration and washed with methanol.

General procedure for the preparation of 22-23. 1Mmol 4,4'-bipyridilium diquaternary salts and 2 mmoles dimethyl acetylenedicarboxylate was suspended in 10 ml anhydrous benzene. Then,2 mmoles triethylamine (dissolved in 3 ml benzene) was added, under vigorous stirring. The solution was slowly heated.

Then the solvent was evaporated on a steam bath. After solvent removal, the reaction product was obtained by crystallisation from methanol.

1,1'-Di(ethoxycarbonyl)-3,3'-di(methoxycarbonyl)- 7,7'-bisindolizine (14). The product was recrystallized from methanol and yellow crystals were obtained.Yield 52%,mp 235-236^{0}C. Anal. $C_{26}H_{24}N_2O_8$.Calcd. C 67,24; H 5,17; N 6,03. Found C 67,17; H 5,10; N 5,58. IR(KBr,cm^{-1}): 1697-1700(C=O ester k_1,k_2) .^{1}HNMR ($CDCl_3$):δ:9,54 (d,2H_b, J_{bc}=7,6); 8,7(d,2Ha, J_{ac}=1,2); 7,97 (s,2H_d); 7,37 (q,2H_c, J_{cb}=7,6, Jca=1,2); 4,4 (q,4H_r, J_{rs}=7,2); 4,06 (s,6H_p); 1,40 (t,6H_s, J_{sr}=7,2).

7,7'-bisindolizine-1,3,1',3'-tetraethyltetracarboxylate (15). The product was recrystallized from methanol and yellow crystals were obtained.Yield 58%,mp 274-275^{0}C. Anal. $C_{28}H_{28}N_2O_8$Calcd. C 64,46; H 5,38; N 5,38. Found C 64,41; H 5,21; N 5,27. IR(KBr,cm^{-1}): 1696-1700(C=O ester k_1,k_2). .$_1$HNMR ($CDCl_3$):δ:9,54 (d,2H_b, J_{bc}=7,6); 8,69(d,2H_a, J_{ac}=1,2); 7,97 (s,2H_d); 7,37 (q,2H_c, J_{cb}=7,6, J_{ca}=1,2); 4,38 (q,8H_r, $J_{rs(s')}$=7,2); 1,43 (t,6$H_{s'}$, $J_{s'r'}$=7,2); 1,40 (t,6H_s, J_{sr}=7,2).

1,1'-Di(ethoxycarbonyl)-3,3'-benzoyl- 7,7'-bisindolizine (16). The product was recrystallized from methanol and yellow crystals were obtained.Yield 55%,mp 273-274°C. Anal $C_{36}H_{28}N_2O_6$.Calcd. C 73,97; H 4,79; N 4,79. Found C 73,85; H 4,69; N 4,68. IR(KBr,cm-1):1700(C=O ester), 1656 (C=O ketone). .^{1}HNMR ($CDCl_3$):δ:9,98 (d,2H_b, J_{bc}=7,5); 8,77(d,2H_a, J_{ac}=1,2); 7,78-7,88 (m, 6H: 4H_i,2H_d (7,82)); 7,42-7,73 [m,8H:4H_j,2H_m,2H_c (7,52, J_{cb}=7,5, J_{ca}=1,2)]; 4,4 (q,4H_r, J=7,2); 1,43 (t,6H_s, J=7,2).

1,2,3,1',2',3'-Hexa(methoxycarbonyl)-7,7'-bisindolizine (22). The product was recrystallized from methanol and yellow crystals were obtained.Yield 50%,mp 210-211^{0}C. Anal$C_{28}H_{24}N_2O_{12}$.Calcd. C 57,93; H 4,13; N 4,82 Found C 57,97; H 4,10; N 4,78. IR(KBr,cm^{-1}): 1738(C=O ester k_1), 1697-1701(C=O ester k_2, k_3).^{1}HNMR ($CDCl_3$):δ:9,7 (d,2H_b, J_{bc}=7,5); 8,78(d,2Ha, J_{ac}=1,2); 7,5 (q,2H_c, J_{cb}=7,5, Jca=1,2); 4,13 (s,6H_{p1}); 4,05(s,12$H_{p2,p3}$).

1,2,1',2'-Tetra(methxoycarbonyl)-3,3'-di(ethoxycarbonyl)-7,7'-bisindolizine (23). The product was recrystallized from methanol and yellow crystals were obtained.Yield 55%,mp 230-231^{0}C. Anal$C_{30}H_{28}N_2O_{12}$.Calcd. C 59,21; H 4,60; N 4,60 Found C 59,11; H 4,50; N 4,51. IR(KBr,cm^{-1}): 1742(C=O ester k_1), 1696-1700 (C=O ester k_2, k_3). ^{1}HNMR ($CDCl_3$): δ: 9,7 (d, 2H_b, J_{bc}=7,5); 8,78 (d, 2Ha, J_{ac}=1,1); 7,5 (q, 2H_c, J_{cb}=7,5, Jca=1,1); 4,5 (q, 4H_r) ; 4,13 (s, 6H_{p1}); 4,05(s, 6H_{p2}); 1,5 (t, 6H_s, J_{rs}=7,1).

1,2,1', 2'-Tetra(methoxycarbonyl)-3,3'-bis(benzoyl)-7,7'-bisindolizine (24). The product was recrystallized from methanol and yellow crystals were obtained.Yield 60%,mp 280-281^{0}C. Anal$C_{38}H_{28}N_2O_{10}$.Calcd. C 67,85; H 4,16; N 4,16 Found C 67,77; H 4,01; N 4,08. IR(KBr,cm^{-1}): 1741(C=O ester k_1), 1702 (C=O ester k_2), 1658 (C=O ketone). ^{1}HNMR (DMF-d_7): δ: 9,12 (d, 2H_b, J_{bc}=7,4); 8,4 (d, 2Ha, J_{ac}=1,2); 7,7 (q, 2H_c, J_{cb}=7,4, Jca=1,2); 7,3-7,61 (m, 5$H_{i,j,m}$); 4,14 (s, 6H_{p2}); 3,65(s, 6H_{p1}) .

1,2,1', 2'-Tetra(methoxylcarbonyl-3,3'-bis(p-nitrobenzoyl) -7,7'-bisindolizine (25). The product was recrystallized from methanol and yellow crystals were obtained.Yield 68%,mp 290-291^{0}C. Anal$C_{38}H_{26}N_2O_{14}$.Calcd. C 62,12; H 3,54; N 7,62. Found C 62,07; H 3,48; N 7,58. IR(KBr,cm^{-1}): 1743(C=O ester k_1), 1706 (C=O ester k_2), 1680 (C=O ketone). ^{1}HNMR (DMF-d_7+D_2O): δ: 9,31 (d, 2H_b, J_{bc}=7,3); 8,50 (d,

2Ha, J_{ac}=1,1); 8,21 (d, 4H_j, J_{ji}=7,0); 7,82 (d, 4H_i, J_{ij}=7,0); 7,73 (q, 2H_c, J_{cb}=7,3, Jca=1,1) ; 4,15 (s, 6H_{p2}); 3,68(s, 6H_{p1}) .

1,2,1', 2'-Tetra(methoxycarbonyl)-3,3'-bis(p-methoxybenzoyl) -7,7'-bisindolizine (26). The product was recrystallized from methanol and yellow crystals were obtained.Yield 50%, mp 270-271^{0}C. Anal$C_{38}H_{32}N_2O_{12}$.Calcd. C 64,40; H 4,51; N 3,95 Found C 64,31; H 4,41; N 3,88. IR(KBr,cm^{-1}): 1739(C=O ester k_1), 1697 (C=O ester k_2),1651(C=O ketone). ^{1}HNMR (DMF-d_7+D_2O): δ: 9,o7 (d, 2H_b, J_{bc}=7,5); 8,38 (d, 2Ha, J_{ac}=1,3); 7,8 (q, 2H_c, J_{cb}=7,5, Jca=1,3) ; 7,32 (d, 4H_i, J_{ij}=7,3); 6,93 (d, 4H_j, J_{ji}=7,3); 4,14 (s, 6H_{p2}); 3,8 (s,3H_n); 3,65(s, 6H_{p1}) .

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