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Primary cycloadducts of 1,10-phenanthrolinium and phthalazinium phenacylides with DMAD

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Abstract—Primary cycloadducts *cis*-**2** and *trans*-**6** of monosubstituted cycloimmonium phenacylides **1** and **5** with DMAD have been obtained for the first time. They isomerise stereospecifically and regiospecifically by prototropic rearrangement to dihydro derivatives *cis*-**3** and *trans*-**7**, respectively. The new heterocyclic system of pyrrolo[1,2-*a*][1,10]phenanthroline was illustrated by a series of derivatives (**8a**–**f**). The ethyl (**8b**) and isopropyl (**8c**) esters exhibit helical chirality by ^{1}H NMR.

The unstable monosubstituted heteroaromatic *N*-ylides obtained in situ by deprotonation of the corresponding cycloimmonium salts in the presence of base (mostly triethylamine) are 1,3-dipoles which undergo cycloaddition with acetylenic dipolarophiles resulting in the formation of a fused five-membered nitrogen heterocycle. Aromatisation by loss of two hydrogen atoms occurs spontaneously during the reaction in the presence of oxygen. As a matter of fact, the primary cycloaddition product, a 2,5-dihydropyrrolo derivative has never been isolated or detected in the reaction mixture.[1–3] A claim[4] to have obtained such a product from an unsubtituted phthalazinium methylide lacks sufficient information (NMR spectral characterisation by only one chemical shift).

We have succeeded in obtaining the primary cycloadducts *cis*-**2** and *trans*-**6** from the title ylides **1** and **5** with dimethyl acetylenedicarboxylate (DMAD) by replacing the usual aprotic solvents used in the cycloaddition with methanol. The nucleophilicity of triethylamine is reduced by solvation so that further isomerisation by a contact ion-pair mechanism is obstructed. The reactions were performed with ice cooling and yields over 90% were registered. Under the same conditions, the quinolinium and isoquinolinium phenacylides led directly to the corresponding dehydrogenated pyrroloazines.

The cycloadditions are stereospecific with the cycloadducts *cis*-**2** and *trans*-**6** corresponding to the ylide geometries *syn*-**1** (**W**-dipole) and *anti*-**5** (**S**-dipole), respectively. NMR spectra of the free ylides could not be registered because of their instability.

Protrotropic rearrangements of *cis*-**2** and *trans*-**6** take place quantitatively to give the dihydro derivatives *cis*-**3** and *trans*-**7**, respectively, at room temperature in the presence of triethylamine in deuterochloroform. Considering the reacting dihydropyrrolo moieties of *cis*-**2** and *trans*-**6** as *cis*-*trans* isomers, their allylic rearrangements to *cis*-**3** and *trans*-**7** are stereospecific and regiospecific at the same time. In the former case the 3-H atom, geminal to the benzoyl group, migrates while in the latter the angular hydrogen atom (3a-H) is shifting. No traces of equilibrium products could be detected by ^{1}H NMR. Each one of the isomers *cis*-**2** and *trans*-**6**, under thermodynamic control, could afford two pairs of *cis*-*trans* regioisomers. In fact one single compound results from each primary cycloadduct. The pyrroline moieties of *cis*-**3** and *trans*-**7** are regioisomers to each other with opposite configurations. This possibility was anticipated by Epiotis[5] in 1978 who introduced a new term 'chorochemistry' which collectively describes stereochemistry and regiochemistry. We might say the reactions occur 'chorospecifically'. In the strict sense, *trans*-**7** is 'choroisomeric'

Keywords: heteroaromatic *N*-ylides; 1,3-dipolar primary cycloadducts; stereospecificity; regiospecificity; pyrrolo[1,2-*a*][1,10]phenanthrolines; helical chirality.

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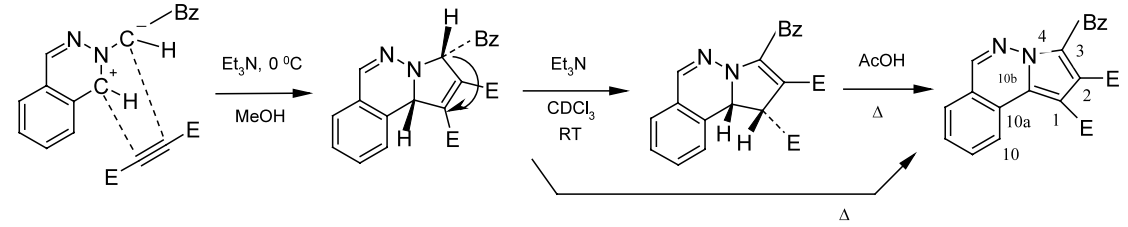
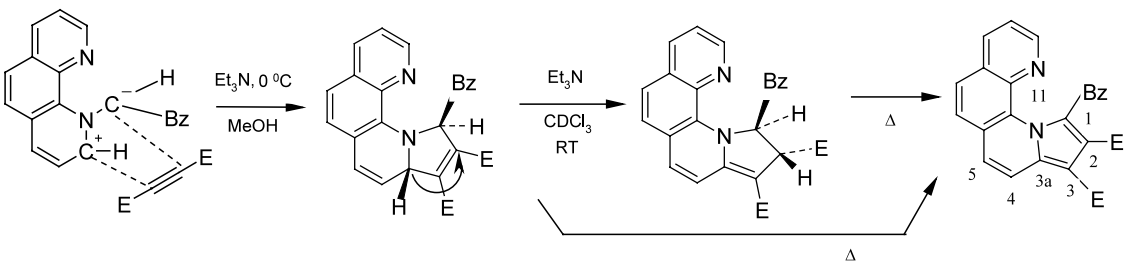
with *cis*-**9a** which has also been identified (see below). The exclusive formation of one isomer is also a good diagnosis for the *anti* or *syn* conformation of the initial reacting ylide.

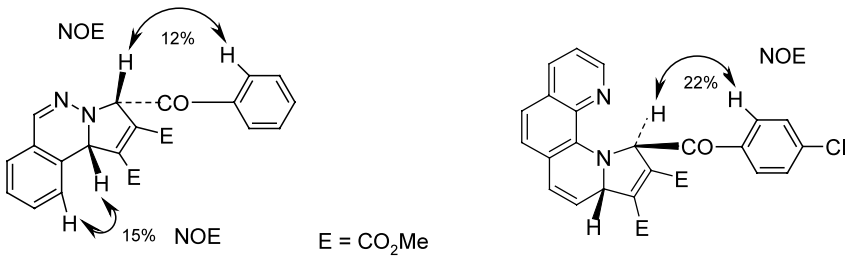
The primary cycloadduct *trans*-**6** melted at 157–160°C in a sealed tube and after resolidification the melting point rose to 257–259°C on the microplate, which corresponded to the dehydrogenated product **8a**. Compound *trans*-**7** (mp 222–225°C) displayed the same behaviour. The *cis*-cycloadduct **2** (mp 163–164°C) on melting rearranged to *cis*-**3** (mp 129–131°C) which dehydrogenated to **4**[6] by refluxing in acetic acid.



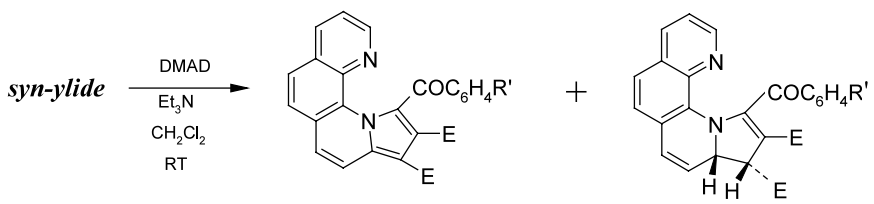
syn-**1** *cis*-**2** *cis*-**3** **4**



anti-**5** *trans*-**6** *trans*-**7** **8a**

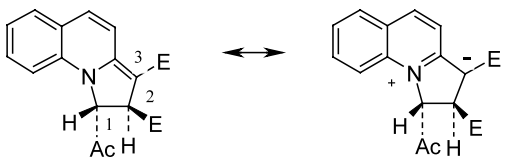


cis-**2** *trans*-**6e**



8 *cis*-**9**

a: E = CO_2Me; R' = H; **b:** E = CO_2Et; R' = H; **c:** E = CO_2iPr; R' = H
d: E = CO_2Me; R' = 4-F **e:** E = CO_2Me; R' =4-Cl; **f:** E = CO_2Me; R' = 4-Br



trans-**10** **11**

E = CO_2Me

Figure 1.

The relative stability of the dihydro derivatives *cis*-**3** and *trans*-**7** allowed us to draw the conclusion that they were the only by-products of the spontaneous dehydrogenation of *cis*-**2** and *trans*-**6**.

The reaction with phenanthroline was initially planned with the purpose of synthesising derivatives of a new heterocyclic system, pyrrolo[1,2-*a*][1,10]phenanthroline. The second nitrogen of the phenanthroline could not be made to react. Yields of over 80% were obtained for **8a**–**f**[7] by carrying out the reaction in methylene chloride at room temperature. ^{1}H NMR measurement on the crude products indicated the presence of the dihydro derivative *cis*-**9** in appreciable quantities (up to 80%). Its source is *syn*-**5** due to the protic polar solvent methanol. Refluxing the mixture in ethanol for a short time led to the dehydrogenation product **8**. However, in the case of quinolinium acetylmethylide an appreciable percentage (60%) of *trans*-**10** was obtained which could be separated by chromatography unlike the other dihydro derivatives which aromatised on the column. Therefore, the reacting species of the initial ylide is *anti*. The formation of isomers of the type *trans*-**7** and *trans*-**10** by ylide cycloaddition has not been observed until now.

Structures were assigned on the basis of the following criteria: the coupling constants of the two protons of the pyrroline nucleus, ^{1}H and ^{13}C NMR chemical shifts of the corresponding CH and N-CH groups, of the carbonyl groups and also of the enaminic quaternary carbons.

The most characteristic feature of **6** is the unusually large *trans*-homoallylic coupling, $J_{1,3a}=7.3$ Hz. This has been already encountered in *trans*-2,5-dihydropyrrolines in the range 7.0–7.6 Hz.[8–11] Its magnitude was explained by a dual path, the heteroatom being implicated in the mechanism of interaction by a synergistic four-bond coupling.[8] The *cis*-homoallylic coupling in **2** has a value of 1.5 Hz. The structures are confirmed by the presence of two N-CH groups, a benzoyl group bound to a saturated carbon, two esters groups grafted on a double bond and by the lack of a quaternary enaminic carbon. Supplementary evidence was given by COSY, HETCOR and NOE experiments (Fig. 1).[12] For isomers *cis*-**3** and *cis*-**9e** the following coupling constants were measured $J_{1,10b}=13.2$ and $J_{3,3a}=13.8$ Hz. The vicinal and allylic coupling constants of protons in positions 3a, 4 and 5 of *cis*-**9e** are quite similar to those of the dihydro derivative *trans*-**6**. They are not observed in *trans*-**7** whose chemical shifts and vicinal coupling constant, $J_{1,2}=4.5$ Hz, have values close to those of the analogous *trans*-**10** ($J_{1,2}=4.2$ Hz). All these coupling constants have close values to those of the corresponding dihydroindolizines derivatives (4.0–7.0 and 13–14 Hz)[13,14] and also to those of the analogous 2-pyrrolines (5.0–7.0 and 13.0–13.4 Hz)[9] to which the configurations *trans* and *cis* have been assigned, respectively. Compounds **3**, **7**, **9** and **10** possess one single N-CH group and also an enaminic quaternary carbon, the high field values observed for the 3-C_q in **7** and **10** being explained by the major contribution of the pyridinium canonical form **11**. This also explains the higher δ values for the protons of the N-CH groups. The 1-H protons of the pyrrolophenanthrolines **6** and **7** are strongly deshielded being in close vicinity to the nitrogen atom in position 11.[12]

Several dihydro derivatives of pyrrolo[2,1-*a*]isoquinoline[13,15] and pyrrolo[1,2-*b*]pyridazine[16,17] are described in literature and were obtained as mixtures with the dehydrogenated products, all corresponding to the same type of structure *cis*-**3** ($J_{vic}=13$–14 Hz). Also erroneous structures were proposed.[18,19] They can be diagnosed now as originating from a *syn*-ylide.

The ^{1}H NMR spectra at room temperature of the diethyl (**8b**) and diisopropyl (**8c**) esters of the new heterocyclic system exhibited helical chirality. The energy barrier of **8b** was calculated from the coalescence temperature and was found to be $\Delta G^{\ddagger}_{60°C}=16.5$ kcal/mol.

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12. NMR (δ, Hz, $CDCl_3$, 300 and 75 MHz). *cis*-**2**: 5.53 (3-H); 6.21 (10b-H); $J_{3,10b}=1.5$ (COSY); 64.8 (10b-C), 79.1 (3-C); HETCOR; 162.3 and 164.3 (1- and 2-E); 193.7 (Bz); *cis*-**3**: 4.52 (1-H); 5.32 (10b-H); $J_{1,10b}=13.2$; 51.3 (1-C); 61.8 (10b-C); 101.8 (2-C_q); 164.3 (2-E); 172.1 (1-E); 188.3 (Bz); **4**: 107.6 (1-C_q); 163.8 and 165.8 (1- and 2-E); 187.0 (Bz); *trans*-**6**: 5.92 (4-H); 6.38 (3a-H); 6.52 (5-H); 6.82 (1-H); $J_{1,3a}=7.3$; $J_{3a,4}=2.3$; $J_{3a,5}=2.7$; $J_{4,5}=9.7$ (COSY); 67.9 (3a-C); 75.6 (1-C); HETCOR; 162.6 and 163.9 (2- and 3-E); 194.5 (Bz); *trans*-**7**: 3.99 (2-H); 7.52 (1-H); $J_{1,2}=4.5$; 49.9 (2-C); 71.5 (1-C); HETCOR; 88.6 (3-C_q); 166.1 (3-E); 174.1 (2-E); 190.0 (Bz); **8a**: 104.0 (3-C_q); 164.8 and 167.3 (2- and 3-E); 187.3 (Bz); *cis*-**9e**: 4.55 (3-H); 5.40 (3a-H); 6.01 (4-H); 6.69 (5-H); $J_{3,3a}=13.8$; $J_{3a,4}=2.0$; $J_{3a,5}=2.6$; $J_{4,5}=9.8$; 51.1 (3-C); 61.5 (3a-C); *trans*-**10**: 3.96 (2-H); 5.06 (1-H); $J_{1,2}=4.2$; 48.9 (2-C);

70.1 (1-C); 89.9 (3-C_q); 165.6 (3-E); 172.6 (2-E); 201.8 (Ac).

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