The Regioselectivity in the Formation of Pyrazolines and Pyrazoles from Nitrile Imines

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The 1,3-cycloaddition of the nitrile imines **2a-e** to the carbon-carbon double bond in benzalacetophenone leads to the formation of 4-phenyl-5-benzoylpyrazolines **3a-e** which were converted into 4-phenyl-5-benzoylpyrazoles **5a-e** upon treatment with chloranil in xylene. However, the cycloaddition of **2a-e** to the carbon-carbon double bond in the enol tautomer of dibenzoylmethane gives the regioisomers 5-phenyl-5-hydroxy-4-benzoylpyrazolines which loose elements of water to yield 4-benzoyl-5-phenylpyrazoles **6a-e**. The orientations in these reactions are interpretted in terms of the Frontier Molecular Orbital theory. The structures of the products **3, 5** and **6** were substantiated by their chemical reactions and alternate synthesis wherever possible.

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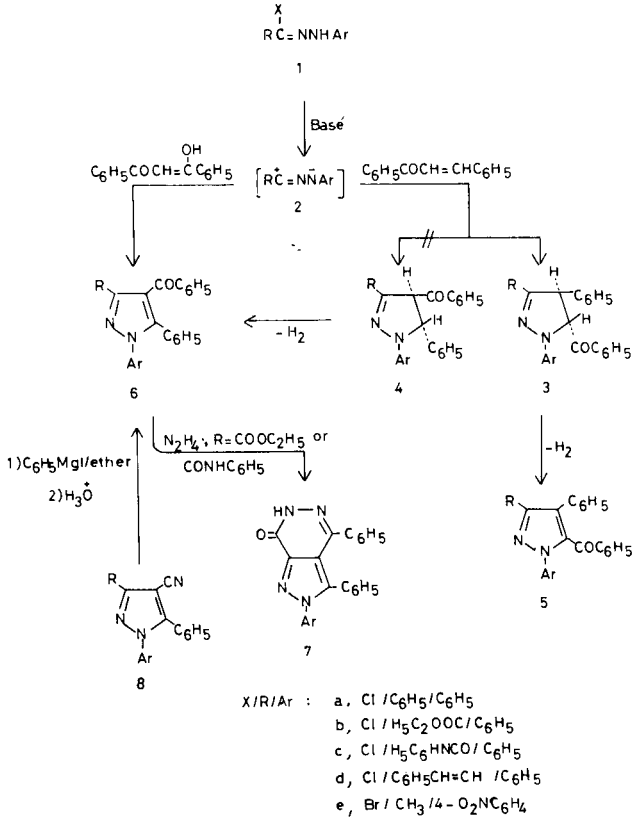
Introduction.

In this decade 1,3-dipolar cycloaddition reactions of 1,3-dipoles such as nitrile oxide and nitrile imines have proved to be very useful in synthesis of numerous heterocyclic systems [2-9]. One of the most interesting aspect of these reactions is their regioselectivity. The origin of the latter phenomenon has remained the greatest unsolved problem in this area of chemistry [7-16]. Our interest in the chemistry of hydrazidoyl halides **1** [6], which are versatile precursors for nitrile imines, prompted us to examine the cycloaddition reactions of five different nitrile imines **2a-e** to the carbon-carbon double bond in benzalacetophenone and the enol tautomer of dibenzoylmethane (Scheme 1). Our objective is to determine the effects of both the hydroxyl group in the enol tautomer of dibenzoylmethane and the C-substituent in the nitrile imine on the regioselectivity in the 1,3-dipolar cycloaddition to the carbon-carbon double bond.

Results and Discussion.

Treatment of **1a-e** with benzalacetophenone in toluene in the presence of triethylamine gave, in each case, one product as evidenced by tlc analysis. The structures of the products obtained were identified as 4-phenyl-5-benzoyl-1,3-disubstituted pyrazolines **3a-e** respectively (Scheme 1) (Table I). The structures of **3a-e** were assigned on the basis of their elemental analyses and spectral data (Table II). In the pmr spectra each compound in series **3** showed two characteristic doublets (J = 5-7 Hz) due to the protons at C4 and C5 of the pyrazoline ring (Table II). On the basis of the coupling constant values, these cycloadducts **3a-e** were assigned the trans configuration. The pmr spectroscopy has been shown to be a convenient method for establishing the stereochemistry of cycloadducts of type **3** since the values of the coupling constants between *trans*- and *cis*-protons at C4 and C5 are 6 and 12 Hz respectively [12,13].

2-Pyrazolines can be easily aromatized by autoxidation or thermal dehydrogenation, even in the absence of oxygen, or by some reagents such as choranil [17,18]. The pyrazoles **5a-e** were found to be the products from the treatment of the pyrazolines **3a-e** with chloranil in refluxing xylene. The structures of the pyrazole derivatives **5a-e**



Scheme 1

Table I

Synthesized Pyrazolines and Pyrazoles

Compound No.	Mp °C (Solvent) [a]	Molecular Formula	*Anal.* Calcd.(Found) % C	% H	% N
3a	175 (M)	$C_{28}H_{22}N_2O$ [b]			
3b	127 (M)	$C_{25}H_{22}N_2O_3$	75.35 (75.21)	5.56 (5.41)	7.03 (7.12)
3c	204 (A)	$C_{29}H_{23}N_3O_2$	78.18 (78.20)	5.20 (5.25)	9.43 (9.31)
3d	192 (A)	$C_{30}H_{24}N_2O$	84.08 (84.21)	5.64 (5.50)	6.54 (6.41)
3e	182 (A)	$C_{23}H_{19}N_3O_3$ [c]			
5a	161 (A)	$C_{28}H_{20}N_2O$	83.97 (83.81)	5.03 (5.00)	7.00 (6.92)
5b	142 (M)	$C_{25}H_{20}N_2O_3$	75.74 (75.61)	5.08 (4.98)	7.07 (7.10)
5c	167 (E)	$C_{29}H_{21}N_3O_2$	78.53 (78.44)	4.77 (4.65)	9.48 (9.41)
5d	146 (M)	$C_{30}H_{22}N_2O$	84.48 (84.42)	5.20 (5.18)	6.57 (6.49)
5e	191 (A)	$C_{23}H_{17}N_3O_3$	72.05 (72.21)	4.47 (4.50)	10.96 (10.90)
6a	168 (M)	$C_{28}H_{20}N_2O$ [d]			
6b	157 (M)	$C_{25}H_{20}N_2O_3$ [e]			
6c	128 (M)	$C_{29}H_{21}N_3O$	78.53 (78.46)	4.77 (4.80)	9.48 (9.38)
6d	177 (E)	$C_{30}H_{22}N_2O$	84.48 (84.37)	5.20 (5.29)	6.57 (6.49)
6e	148 (E)	$C_{23}H_{17}N_3O_3$ [f]			

[a] M, methanol; E, ethanol; A, acetic acid. [b] Lit mp 175° [17]. [c] Lit mp 182° [32]. [d] Lit mp 168° [33]. [e] Lit mp 157° [34]. [f] Lit mp 148° [32].

Table II

The Spectral Data of Compounds Under Study

Compound No.	λ_{max}(log e)[a] [a]	ν_{CO}(cm^{-1})[b] [b]	δ ppm
3a	282 (4.60), 230 (4.85)	1700	4.6 (d, 1H, CHAr), 5.6 (d, 1H, CHCOAr), 6.8-8.1 (m, 20H, ArH),
3b	278 (4.74), 228 (4.95)	1720, 1700	1.2 (t, 3H, CH_3CH_2), 4.1 (q, 2H, CH_3CH_2), 4.4 (d, 1H, CHAr), 5.8 (1H, d, CHCOAr), 7.0-8.0 (15H, ArH)
3c	284 (4.69), 228 (4.99)	1700, 1660	4.75 (d, 1H, CHAr), 5.9 (d, 1H, CHCOAr), 7.0-8.2 (m, 21H, ArH + CONH)
3d	372 (4.38), 254 (4.37)	1690	4.5 (d, 1H, CHAr), 5.6 (d, 1H, CHCOAr), 6.5 (d, 1H, CH=CHAr), 6.0-8.0 (m, 21H, ArH and CH-CHAr)
3e	334 (5.00), 228 (4.93)	1700	2.0 (s, 3H, CH_3), 4.2 (d, 1H, CHAr), 5.7 (d, 1H, CHCOAr), 6.9-8.0 (m, 14H, ArH + -CH=CHAr)
5a	260 (4.55)	1660	7.0-8.0 (m, ArH)
5b	344 (4.19), 249 (4.53)	1720, 1660	1.1 (t, 3H, CH_3CH_2), 4.2 (q, 2H, CH_3CH_2), 7.2-8.1 (15H, ArH)
5c	254 (4.51)	1660, 1650	6.9-8.1 (m, ArH)
5d	304 (4.20), 258 (4.25)	1660	6.6 (d, 1H, CH=CHAr), 7.1-7.9 (m, 21H, ArH + CH=CHAr)
5e	328 (4.20), 254 (4.25)	1660	2.0 (s, 3H, CH_3),7.0-8.0 (m, 14H, ArH)
6a	245 (4.85)	1650	7.1-8.1 (m, ArH)
6b	250 (4.36)	1710, 1670	1.05 (t, 3H, CH_3CH_2), 4.2 (q, 2H, CH_3CH_2), 6.7-8.0 (m, 15H, ArH)
6c	278 (4.65), 232 (4.93)	1680, 1640	7.3-8.4 (m, ArH)
6d	350 (4.47), 257 (4.49)	1645	6.55 (d, 1H, CH=CHAr), 7.1-7.8 (m, 21H, ArH + -CH=CHAr)
6e	298 (4.30), 253 (4.26)	1700	2.0 (s, 3H, CH_3), 7.2-8.3 (m, 14H, ArH)

[a] In Ethanol. [b] In Potassium Bromide. [c] In deuteriochloroform.

were established by elemental analyses, spectra (pmr, ir and uv), and comparison with the isomeric pyrazoles **6a-e** described below (Tables I and II).

Addition of hydrazidoyl halides **1a-e** to an equivalent amount of the sodium salt of dibenzoylmethane in ethanol at room temperature afforded 1,3-disubstituted 5-phenyl-4-benzoylpyrazoles **6a-e** respectively. The formation of the latter indicates the intermediacy of the corresponding 4-benzoyl-5-hydroxy-5-phenylpyrazoline derivatives which probably undergo spontaneous dehydration to give **6a-e**. The pmr data of **6a-e** (Table II) are compatible with the structures assigned. The structures of **6a-e** were further confirmed by their reaction with hydrazine hydrate. Thus hydrazinolysis of both **6b** and **6c** gave one product identified as 2*H*-pyrazolo[3,4-*d*]pyridazine derivative **7**. Also, the structure of **6a** was confirmed by its alternate synthesis from 1,3,5-triphenyl-4-cyanopyrazole **8** (R = Ar = C_6H_5) and phenylmagnesium iodide (Scheme 1).

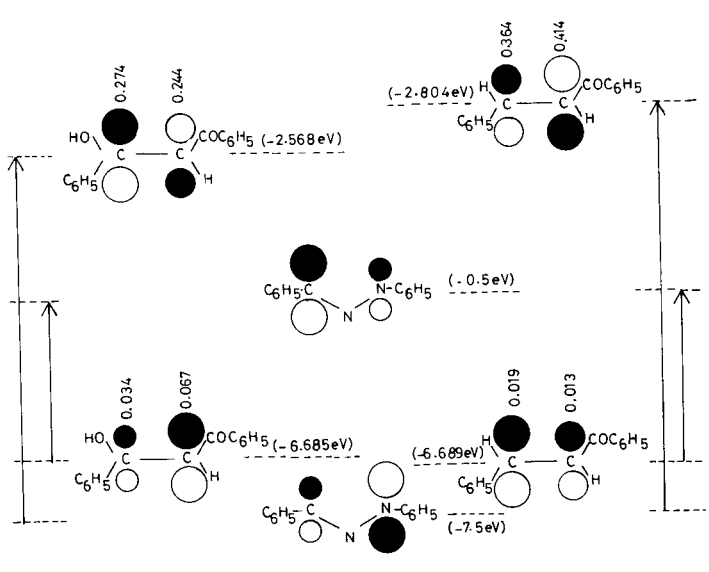
The difference in the regioselectivity of the cycloaddition of benzalacetophenone and the enol tautomer of dibenzoylmethane may be explained in terms of the frontier molecular orbital interactions (Scheme 2). In a recent report [19] it was indicated that in the cycloaddition of diphenylnitrile imine (DPNI) to the carbon-carbon double bond of α,β-unsaturated ketones, the interactions $LUMO_{[DPNI]}$-$HOMO_{[alkenone]}$ and $HOMO_{[DPNI]}$-$LUMO_{[alkenone]}$ favour the formation of the 5-acyl and 4-acyl regioisomers respectively. Furthermore, based on the assumption that in the LUMO of alkenone the orbital coefficient of C_B is larger than that of C_α, it was concluded that the coefficient c_C is bigger than the coefficient $c_{NC_6H_5}$ in the HOMO of diphenylnitrile imine contrary to the most widely accepted view that $c_{NC_6H_5} > c_C$ [14,15,19]. To shed more light on this problem, it was thought necessary to compute the energies and orbital coefficients of both benzalacetophenone and the enol tautomer of dibenzoylmethane. The results of such computations are summarized in Scheme 2.

According to the frontier orbital theory of 1,3-dipolar cycloadditions [14-16, 22,23], the regiochemistry will be determined by the relative magnitudes of the coefficients in the HOMO's and LUMO's of the 1,3-dipole and dipolarophile. The favoured cycloadduct will be that formed by union of the atoms with the largest coefficients. The data reproduced in Scheme 2 indicate that the reactions of **2a** are controlled by the interaction between its LUMO and the HOMO of the dipolarophile used. Since in the HOMO of benzalacetophenone, the coefficient of C_β is larger than that of C_α, the reaction between **2a** and benzalacetophenone should favour the 5-benzoyl regioisomer. On the other hand, since in the HOMO of the enol tautomer of dibenzoylmethane, the larger coefficient is on C_α, its interaction with the LUMO of nitrile imine **2a** should favour the 4-benzoyl regioisomer. These predictions are consistent with the experimental data outlined above. Also, the results obtained in this work indicate that the relative order of the orbital coefficients in the HOMO and LUMO of other nitrile imines **2b-e** is similar to that in **2a**.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra (potassium bromide disc) were recorded on Perkin Elmer 257 spectrophotometer and the electronic absorption spectra were obtained in ethanol using Pye Unicam SP8000 spectrophotometer. The pmr spectra in deuterated chloroform were recorded on a Varian T60-A spectrometer using tetramethylsilane as the internal reference. The spectral data are summarized in Table II. Elemental analyses were performed by the microanalytical Laboratory, University of Cairo, Giza, Egypt. The hydrazidoyl halides **1a-e** were prepared as previously described [13,24-28].

Scheme 2



Reaction of **1a-e** with Benzalacetophenone.

To a stirred solution of *trans*-benzalacetophenone (1.1 g, 0.005 mole) and triethylamine (1 ml) in toluene (50 ml) at 50° was added in small portions the appropriate hydrazidoyl halide (0.005 mole) over a period of 30 minutes. The mixture was refluxed for 5 hours. The precipitated triethylamine hydrohalide was filtered, and the filtrate was evaporated *in vacuo*. The residue which solidified on cooling was collected and crystallized from methanol or acetic acid to give the corresponding pyrazoline derivatives **3a-e** in 70-80% yields. Thin layer chromatographic analysis of each product obtained using silica gel as adsorbent and benzene as eluent indicates the presence of one component. The pyrazoline derivatives **3a-e** prepared are listed in Table I together with their physical constants and their spectra are summarized in Table II.

Dehydrogenation of Pyrazolines **3a-e**.

A stirred solution of the appropriate pyrazoline derivative **3** (0.005 mole) and chloranil (0.0052 mole) in xylene was refluxed until the complete disappearance of pyrazoline was shown by tlc (48 hours). The solution was extracted with aqueous sodium hydroxide solution (5%). The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo*. The solid left was collected and crystallization from ethanol or acetic acid gave the corresponding pyrazole derivatives **5**. The compounds prepared are listed in Table I and their spectral data are summarized in Table II.

Reaction of **1a-e** with Dibenzoylmethane.

To an ethanolic solution of sodium ethoxide (prepared from sodium (0.11 g, 0.005 g atom) and absolute ethanol (20 ml)) was added dibenzoylmethane (0.005 mole). After stirring the mixture for 30 minutes at room temperature, the hydrazidoyl halide **1** (0.005 mole) was added and stirring was continued for 3 hours during which the halide **1** dissolved and a solid product separated out. The latter was filtered and crystallized from ethanol. Analysis (tlc) of each product using silica gel as adsorbent and benzene-chloroform (1:1) as eluent showed a single isomer in each case. The compounds **6a-e** prepared by this reaction are listed in Table I and their spectra are in Table II.

Hydrazinolysis of **6b,c**.

A mixture of **6b** (0.005 mole) and hydrazine hydrate (10 ml) was refluxed for 30 minutes and then cooled. The solid which formed was collected, washed with water and crystallized from ethanol. The 2*H*-pyrazolo[3,4-*d*]pyridazine derivative **7** was obtained in 85% yield, mp 290°.

Anal. Calcd. for $C_{23}H_{16}N_4O$: C, 75.80; H, 4.42; N, 15.37. Found: C, 75.77; H, 4.57; N, 15.27.

Repitition of this experiment using compound **6c** in place of **6b** gave also the product **7** in 82% yield. Its melting point and mixed melting point with the sample above showed no depression.

Alternate Synthesis of **6a**.

To a cold solution of phenylmagnesium iodide (prepared from iodobenzene (0.005 mole) and magnesium (1 g) in dry ether (50 ml)) was added a solution of 1,3,5-triphenyl-4-cyanopyrazole (0.005 mole) in dry ether (50 ml). The mixture was refluxed for 2 hours, then left at room temperature overnight. The mixture was decomposed by aqueous ammonium chloride solution, and the ether layer was separated. The aqueous layer was extracted three times with 100 ml of ether. The ether extracts were combined and dried over anhydrous sodium sulfate and then filtered. The residue left after evaporating the solvent was suspended in hydrochloric acid (10 *M*, 20 ml) and refluxed for 30 minutes and cooled. The solid that precipitated was collected and washed with water. Crystallization from methanol gave **6a** in 70% yield. Its melting point and mixed melting point with the sample prepared from **1a** and dibenzoylmethane were 168°.

Method of Calculations.

All calculations have been carried out within the extended Hückel theory framework [29]. All s and p orbitals have been considered. Throughout the calculations standard exponents and parameters [30] have been employed. Overlap integrals were evaluated exactly using Orloff's formulas [31]. Computations have been carried out on the IBM machine at King Abdulaziz University, Jeddah, Saudi Arabia.

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