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THE STRUCTURE OF THE CYCLOADDITION PRODUCTS OF α-KETONITRILIMINES TO α,β-UNSATURATED KETONES

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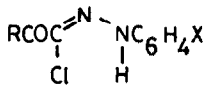
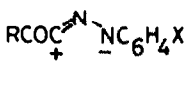
Abstract- The cycloaddition of C-ethoxycarbonyl-N-aryl-nitrilimines 3 and their C-acetyl analogs 4 to α,β-unsaturated ketones 5 give predominantly the 5-acyl-4-aryl-2-pyrazoline derivatives 8 and 9 respectively. The structures of the cycloadducts 8 and 9 were supported by spectral (^{13}C NMR, ^{1}H NMR and IR) and analytical data. Tewari and Parihar's conclusions about the regiochemistry of these reactions cannot be sustained.

A recent report[1] in this journal has claimed that the cycloaddition of benzalacetophenones 5a-c to the nitrilimines 3 and 4 afforded exclusively the corresponding 4-aroyl-5-aryl-2-pyrazoline derivatives 6a-c and 7a-c respectively. In addition, it was reported that the cycloaddition of ethyl cinnamate 5j to C-ethoxycarbonyl-N-(p-tolyl)nitrilimine 3B afforded 1-p-tolyl-3,4-bis(ethoxy-carbonyl)-5-phenyl-2-pyrazoline 6Bj as the only isolable product (Scheme 1).[1] These results are surprising since they are contrary to the earlier findings that cycloaddition of nitrilimines to α,β-unsaturated ketones are regioselective yielding 5-acyl-4-aryl-2-pyrazoline derivatives.[2] However, the enones 5a-c studied by Tewari and Parihar[1] are substituted with electron-donating groups which might possibly lead to abnormal products. Intrigued by these results, we were prompted to reinvestigate the regioselectivity in the cycloadditions of the nitrilimines 3 and 4 to α,β-unsaturated carbonyl compounds. We repeated the cycloadditions of 3 and 4 to the enones 5a-c and ethyl cinnamate 5j. In addition the reactions of 3 with six other enones namely 5d-i were investigated (Scheme 1).

RESULTS AND DISCUSSION

The reactions of C-ethoxycarbonyl-N-arylnitrilimines 3 and C-acetyl-N-arylnitri-limines 4, generated in situ by treatment of the corresponding hydrazidoyl chlorides 1 and 2 respectively with triethylamine, with the α,β-unsaturated carbonyl compounds 5a-i and ethyl cinnamate 5j were carried out in refluxing chloroform. The results are summarized in Table 1. The results show that the reactions studied are regioselective yielding only one of the two possible



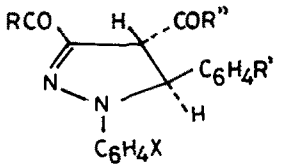


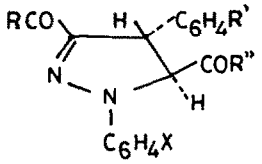
1, R = C_2H_5O 3, R = C_2H_5O

2, R = CH_3 4, R = CH_3

$R'C_6H_4CH = CHCOR''$

5





6, R = C_2H_5O 8, R = C_2H_5O

7, R = CH_3 9, R = CH_3

1-9	X
A	4-Br
B	4-CH_3
C	4-Cl

5-9	R' / R''
a	H / C_6H_5
b	3,4-$(CH_3O)_2$ /4-$CH_3OC_6H_4$
c	3,4-CH_2O_2 / 4-$CH_3OC_6H_4$
d	4-CH_3O / C_6H_5
e	4-Cl / C_6H_5
f	4-O_2N / C_6H_5
g	4-CH_3O / 4-$CH_3OC_6H_4$
h	H / CH_3
i	4-CH_3O / 4-BrC_6H_4
j	H / C_2H_5O

Scheme 1

regioisomers, namely 5-aroyl-4aryl-2-pyrazoline derivatives 8 and 9 regardless the nature of the C-substituent in the nitrilimine. Only in two cases, namely the reactions of 3A with benzalacetophenone 5a and ethyl cinnamate 5j (see entries nos.1 and 10 in Table 1), were mixtures of the two possible regioisomers produced. The two cycloadducts were separated, in each case, by preparative thin layer chromatography.

To explore the effect of solvent polarity on the regiochemistry of the reactions studied, the reaction of 3A and benzalacetophenone 5a was studied in benzene, 1,2-dichloroethane, and acetonitrile. In all solvents the reactions yielded mixtures of the cycloadducts 6Aa and 8Aa whose ratios were constantly around the ratio 25:75 obtained in chloroform. This finding suggests that the regiochemistry of the cycloaddition of 3 to 5 is independent on the solvent polarity.

Table 1. Cycloadducts from the reactions of nitrilimines 3 and 4 with the enones 5a-i and ethyl cinnamate 5j.

Entry No.	Reactions	Reaction time,h	Products (s) , (Yield %)[a]
1	3A + 5a	19	6Aa(25) + 8Aa(75)[b]
2	3A + 5b	10	8Ab(60)
3	3A + 5c	48	8Ac(44)
4	3A + 5d	30	8Ad(69)
5	3A + 5e	20	8Ae(71)
6	3A + 5f	16	8Af(59)
7	3A + 5g	96	8Ag(80)
8	3A + 5h	12	8Ah(48)
9	3A + 5i	30	8Ai(50)
10	3B + 5j	24	6Bj(54) + 8Bj(46)[b]
11	3B + 5b	24	8Bb(85)
12	4A + 5d	20	9Ad(70)
13	4B + 5a	16	9Ba(80)
14	4C + 5a	13	9Ca(70)

a, isolated yield
b, the ratio was determined by ^{1}H NMR analysis.

The assigned structures of the cycloadducts 8 and 9 isolated are consistent with the following data. In ^{13}C nmr spectra each of the cycloadducts 8Aa-i revealed three lines assignable to C-3 (s,δ 140.7 - 142.0), C-4 (d,δ 54.2 - 55.9) and C-5(d, δ 73.6 - 74.7) ppm (Table 2)[3]. The ^{1}H nmr spectra of 8 and 9 were characterized, in each case, by the presence of two doublets (J=6 Hz) near δ 4.40-4.55 and 5.60-5.78 ppm due to H-4 and H-5 respectively.[4] On the other hand, the cycloadduct 6Aa had its signals at δ 5.10(d,J=6 Hz, 1H)and 5.45(d,J Hz,1H)ppm. On the basis of coupling constant value ($J_{4,5}$= 6Hz) the cycloadducts 6, 8 and 9 were assigned the trans configuration indicated[6] (Scheme 1).

The structures of the two cycloadducts 6Bj and 8Bj were supported by analytical and spectral data. The cycloadduct 6Bj shows in its ^{1}H nmr spectrum two doublets with J=6 Hz at δ 4.00 and 5.50 ppm. On the other hand, the regioisomer 8Bj exhibits its two doublets at δ 4.90 and 4.82 ppm for H-4 and H-5 respectively. The values of the chemical shifts of H-4 and H-5 in 6Bj and 8Bj are similar to those reported for 1,3,5-triphenyl-4-ethoxycarbonyl-2-pyrazoline (δ 4.30 and 5.53 ppm) and its regiosomer 1,3,4-triphenyl-5-ethoxycarbonyl-2-pyrazolines (δ 4.65 and 4.82 ppm)[5] respectively. This similarity substantiates thus the assigned structures for 6Bj and 8Bj.

The structure of the cycloadducts 8 was substantiated further by the fact that treatment of 8Aa with phenylhydrazine in refluxing ethanol afforded the hydrazone derivative 10. However, similar treatment of 6Aa gave the pyrazolo[3,4-d] pyridazine derivative 11, probably via the oxidation of 6Aa to the corresponding pyrazole 12. An authentic sample of 12 was prepared by a known procedure[7] from the sodium salt of dibenzoylmethane and the hydrazidoyl chloride 1A. Treatment of 12 with phenylhydrazine in refluxing ethanol yielded 11 in almost quantitative yield (Scheme 2).

Table 2. Characteristic ^{13}C NMR Spectral Data of the Cycloadducts (8 and 9)[a,b]

Compound No.	δ, ppm C-3	C-4	C-5	COOR	COR	OCH_2R	CH_3R	Other Carbons
8Aa	141.4(s)	54.7(d)	73.5(d)	161.2(s)	191.1(s)	61.0(t)	14.0(q)	
8Ab	141.0(s)	55.7(d)	73.6(d)	161.3(s)	190.1(s)	61.1(t)	14.1(q)	55.5, 55.3(q, CH_3OAr)
8Ac	141.4(s)	55.5(d)	73.6(d)	163.2(s)	190.2(s)	61.0(t)	14.0(q)	55.3(q, CH_3OAr), 101.5(t,CH_2O_2)
8Ad	141.3(s)	54.8(d)	73.7(d)	161.2(s)	191.4(s)	61.0(t)	14.0(q)	55.2(q,CH_3OAr)
8Ae	141.1(s)	54.6(d)	73.4(d)	161.0(s)	191.1(s)	61.2(t)	14.0(q)	
8Af	141.7(s)	55.8(d)	73.9(d)	161.5(s)	191.1(s)	62.0(t)	14.6(q)	
8Ag	141.4(s)	55.6(d)	73.7(d)	161.3(s)	191.1(s)	61.0(t)	14.0(q)	55.2, 55.1(q, CH_3OAr)
8Ah	142.0(s)	55.8(d)	76.2(d)	161.8(s)	203.6(s)	61.9(t)	14.7(q)	26.3(q, CH_3CO)
9Ba	139.6(s)	53.7(d)	74.4(d)		191.6(s) 192.0(s)			25.7(q, CH_3CO), 20.6(q,CH_3Ar)
9Ca	140.6(s)	54.0(d)	74.2(d)		192.1(s) 191.1(s)			25.8(q,CH_3CO)

a, All resonances im ppm from internal $(CH_3)_4Si$ in $CDCl_3$.

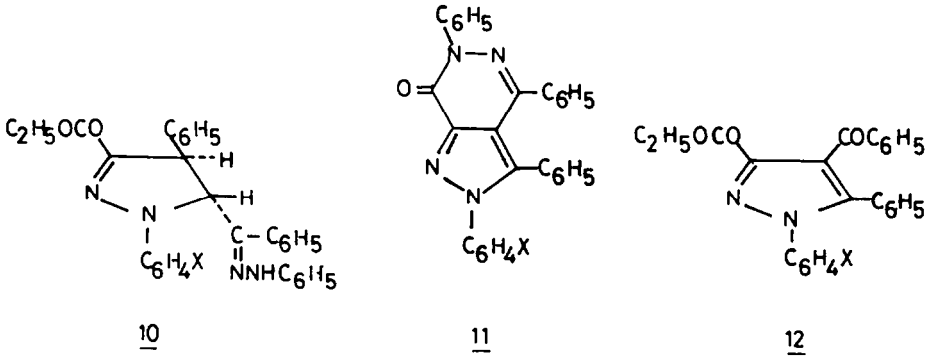
b, In addition to the indicated signals each compound exhibits also signals corresponding to the phenylcarbons in the region 113.0 - 160.0 ppm.

Table 3. Characteristic ^{1}H NMR and IR Spectral Data of the Cycloadducts (6,8,11)

Compound No.	^{1}H NMR ($CDCl_3$)[a,b] δ, ppm.	IR(KBr) ν_{CO}, cm^{-1}
6Aa	5.40 (d,1H), 5.10(d,1H), 4.20(q,2H), 1.20(t,3H)	1685, 1700
8Aa	5.72 (d,1H), 4.44(d,1H),4.20(q,2H), 1.27(t,3H)	1680, 1715
8Ab	5.70 (d,1H), 4.40(d,1H), 4.20(q,2H),3.90(s,6H),3.85(s,3H),1.20(t,3H)	1680, 1710
8Ac	6.00 (s,2H), 5.70(d,1H), 4.40(d,1H), 4.20(q,2H), 3.85(s,3H), 1.20(t,3H)	1675, 1700
8Ad	5.73 (d,1H), 4.45(d,1H), 4.20(q,2H), 3.83(s,3H),12.0(t,3H)	1690, 1700
8Ae	5.69 (d,1H), 4.40(d,1H), 4.19(q,2H), 1.20(t,3H)	1690, 1700
8Af	5.72 (d,1H), 4.53(d,1H), 4.20(q,2H), 1.22(t,3H)	1680, 1700
8Ag	5.70 (d,1H), 4.43(d,1H), 4.20(q,2H), 3.90(s,3H), 3.85(s,3H), 1.20(t,3H)	1680, 1700
8Ah	4.77 (d,1H), 4.45(d,1H), 4.20(q,2H), 2.15 (s,3H), 1.20(t,3H)	1700
8Ai	5.65 (d,1H), 4.42(d,1H), 4.20(q,2H), 3.85(s,3H), 1.25(t,3H)	1680, 1695
8Bb	5.70 (d,1H), 4.40(d,1H), 4.20(q,2H), 3.90(s,6H), 3.8(s,3H), 2.20(s,3H),1.15(t,3H)	1680, 1715
9Ad	5.70 (d,1H), 4.47(d,1H), 3.90(s,3H), 2.50(s,3H)	1653, 1685
9Ba	5.80 (d,1H), 4.50(d,1H), 2.45(s,3H), 2.30(s,3H)	1652, 1685
9Ca	5.73 (d,1H), 4.50(d,1H), 2.45(s,3H)	1655, 1690
6Bj	5.50 (d,1H), 4.00(d,1H), 4.23(two q,4H), 2.18(s,3H), 1.25(2t,6H)	1710, 1725
8Bj	4.82 (d,1H), 4.59(d,1H), 4.25(q,2H), 2.28(s,3H), 1.22(2t,6H)	1715

a, The value of J for the doublet (d), signal is 6Hz, whereas for the triplet (t) and the quartet (q) signals in 7 Hz,

b, All compounds exhibit proton multiplet in the region 6.8 - 7.9 ppm.



10 11 12

X = 4-Br

Scheme 2

The predominant formation of 5-aroyl-2-pyrazolines 8 and 9 in the reaction of the studied nitrilimines with α,β-unsaturated ketones is contrary to the results previously reported in the literature.[1] The erroneous assignment[1] of the regiochemistry of the cycloadducts probably resulted from the complete overlook by the authors[1] of the factors controlling the regioselectivity in 1,3-dipolar cycloadditions. The regioselective formation of 8 and 9 can be satisfactorily explained by taking into account the HOMO of nitrilimines where the coefficient of the carbon atom is larger than that of the nitrogen atom,[2,11] and the LUMO of enones where the coefficient of the α-carbon is smaller than that of β-carbon atom.[2] Thus, the overlap of orbitals with comparable coefficients, i.e. orbitals of nitrogen and carbon atoms in the nitrilimine HOMO with orbitals of the α-and β-carbon atoms of the enone LUMO, respectively will lead to 5-aroyl-4-aryl-2-pyrazoline derivatives 8 and 9.

EXPERIMENTAL

Melting points were determined on a Bockmonoscop appratus (hot stage type) and are uncorrected. Infrared spectra were recorded on Zeiss infrarot spectrophotometer model LMT16. ^{1}H NMR spectra were recorded on a Varian EM 390-90 MHz spectrometer, while ^{13}C nmr spectra were obtained from 1 M deuterated chloroform solution on Joel JUM FX100 spectrometer using tetramethylsilane as internal reference. All spectral chemical shifts are given in parts per million (δ) downfield from tetramethylsilane. Microanalyses were performed with Perkin-Elmer elemental analyzer, model 240-B at King Abdulaziz University. C-Ethoxycarbonyl-N-arylformohydrazidoyl chlorides 1A-B and their C-acetyl analogs 2A-C were prepared by a known proceudre.[8,9] Benzalacetophenone 5a,benzalacetone 5h and ethyl cinnamate 5j were obtained from Merck, and the remaining substituted benzalacetophenones 5b-g were prepared by condensation of the appropriate aromatic aldehyde with acetophenone following known procedure.[10] Reaction mixtures were analyzed on Fluka silica gel cards with fluorescent indicator 254 on aluminum cards and the spots were detected under UV light 254 nm. The preparative thin layer chromatographic separation was carried out on glass plates (20 x 20 cm) covered with Fluka silica gel G with 13% gypsum and using a mixture of carbon tetrachloride and chloroform in ratio of 5 : 1.5 (v/v)as eluent.

Reaction of Nitrilimines 3 and 4 with α,β-unsaturated ketones 5a-i and ethyl cinnamate 5-j. General method - Triethylamine (0.7 ml, 5 mmoles) was added to a chloroform solution (50 ml) of the appropriate hydrazidoyl chlroide 1 or 2 (5 mmoles) and the dipolarophile 5 (5 mmoles) at room temperature. The mixture was refluxed until the complete disappearance of 1 or 5 as indicated by thin layer chromatographic analysis. The mixture was cooled, washed with water three times, and the chloroform layer was collected, dried over anhydrous sodium sulfate, then filtered. The solvent in the filtrate was evaporated under reduced pressure and the residue left was triturated with little methanol where it solidified. The crude solid was collected and its ^1H nmr spectrum in deuterated chloroform was recorded. When the spectrum shows the presence of one regioisomer, the product was crystallized directly from ethanol. When the reaction yielded a mixture of two regioisomers as indicated by ^1H nmr analysis, they were separated by preparative thin layer chromatography in the usual way and were fully characterized by spectral and elemental analyses.

The ratios of 8Aa/6Aa were found to practically independent of solvent polarity: benzene (70/30), acetonitrile (75/25) and 1,2-dichloroethane (70/30). The physical constants are listed in Table 4.

Reaction of 8Aa with phenylhydrazine - A mixture of 8Aa (0.9 g, 2 mmole), phenylhydrazine (0.4 g, 3 mmole) and one drop of acetic acid in ethanol (30 ml) was refluxed for 3 h and cooled. The solid that precipitated was filtered,washed and crystallized from ethanol to give 1-(p-bromophenyl)-3-ethoxycarbonyl-4-phenyl-5-benzoyl-2-pyrazoline phenylhydrazone 10 in 50% yield.

Compound 10 had mp. 150-1°(ethanol), ^1H nmr ($CDCl_3$) δ1.21 (t, J=7Hz, 3H), 4.35 (q, J=7Hz, 2H), 4.70 (d, J=6Hz, 1H), 5.45 (d,J=6Hz,1H), 6.95-8.00(m,19H)ppm, IR (KBr) ν 1715 (CO cm^{-1}. Anal. Calcd. for $C_{31}H_{27}BrN_4O_2$: C, 65.61; H, 4.97; N,9.87, Found : C, 66.00 ; H, 4.85; N, 9.64.

1-(p-Bromophenyl)3-ethoxycarbonyl-4-benzoyl-5-phenylpyrazole 12-Dibenzoylmethane (1.1g, 5mmole) was added to sodium ethoxide solution, prepared from ethanol (50 ml) and sodium metal (0.11 g, 5 mmole) at room temperature, and the mixture was stirred for 10 min. To the resulting stirred solution was added the hydrazidoyl chloride 1A (1.5 g, 5 mmole) and stirring continued at room temperature for 24 h. The solid that precipitated was collected, washed and dried. Crystallization from ethanol-chlcroform mixture gave 12 in 75% yield.

Compound 12 had mp. 174-5° (ethanol-chloroform), IR(KBr) ν 1655(CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.2 (t, J=7Hz, 3H), 4.35 (q, J=7 Hz, 2H), 7.3-8.2(m,14H)ppm. Anal. Calcd. for $C_{25}H_{19}BrN_2O_2$: C, 63.17; H, 4.03; N, 5.89. Found: C, 63.31; H, 4.02; N, 5.93.

1,3,4-Triphenyl-5-(p-bromophenyl)-1H,5H-pyrazolo[3,4-d]pyridazin-7-one, 11- To a solution of 12 (2.4 g, 5 mmole) in ethanol (30 ml) was added phenylhydrazine (1.2 g, 10 mmole) and the mixture was refluxed for 10 h. The crude solid that precipitated was collected and crystallization from dimethylformamide (DMF) gave 11 in almost quantitative yield.

Compound 11 had mp. > 310°(DMF); IR(KBr) ν 1675(CO) cm^{-1}; Anal. Calcd. for $C_{23}H_{15}BrN_4O$: C, 62.31; H, 3.41; N, 12.64. Found: C, 61.99; H, 3.36; N, 12.73

Alternatively compound 11 was obtained in 45% yield when an equimolar mixture of 6Aa and phenylhydrazine (5 mmole each)in ethanol (40 ml) was refluxed for 48h. The product isolated was identical in all respects with 11 prepared above.

Table 4. Substituted 2-Pyrazolines 6-9 .

Compound No.	M.p. °C.	Molecular formula	Anal. Calcd. (Found) C,%	H,%	N,%
6Aa	137	$C_{25}H_{21}BrN_2O_3$	62.90(62.65)	4.43(4.42)	5.86(5.82)
8Aa	147[a]	$C_{25}H_{21}BrN_2O_3$	62.90(62.87)	4.43(4.38)	5.86(5.87)
8Ab	175[b]	$C_{28}H_{27}BrN_2O_6$	59.26(59.15)	4.80(4.91)	4.94(5.04)
8Ac	180[c]	$C_{27}H_{23}BrN_2O_6$	58.81(58.70)	4.20(4.11)	5.08(5.00)
8Ad	184	$C_{26}H_{23}BrN_2O_4$	61.55(61.60)	4.57(4.74)	5.52(5.77)
8Ae	151	$C_{25}H_{20}BrClN_2O_3$	58.67(58.32)	3.94(3.88)	5.47(5.49)
8Af	222	$C_{25}H_{20}BrN_3O_5$	57.48(57.86)	3.86(3.86)	8.04(8.02)
8Ag	197	$C_{27}H_{25}BrN_2O_5$	60.34(60.40)	4.69(4.73)	5.21(5.13)
8Ah	173	$C_{20}H_{19}BrN_2O_3$	57.84(57.87)	4.61(4.45)	6.74(6.82)
8Ai	183	$C_{26}H_{22}Br_2N_2O_4$	53.26(53.06)	3.78(3.81)	4.78(4.87)
8Bb	172	$C_{29}H_{30}N_2O_6$	69.31(69.20)	6.01(6.04)	5.57(5.53)
9Ad	200	$C_{25}H_{21}BrN_2O_3$	62.90(62.45)	4.43(4.38)	5.86(5.80)
9Ba	186	$C_{25}H_{22}N_2O_2$	78.51(77.88)	4.79(5.84)	7.32(7.12)
9Ca	203	$C_{24}H_{19}ClN_2O_2$	71.55(71.81)	4.75(4.77)	6.95(6.78)
6Bj	117	$C_{22}H_{24}N_2O_4$	69.45(69.55)	6.35(6.21)	7.36(7.40)
8Bj	113	$C_{22}H_{24}N_2O_4$	69.45(69.61)	6.35(6.16)	7.36(7.23)

a, Lit. mp. 136°; b, Lit. mp. 182°; c, Lit. mp. 119°(ref.1).

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