mixture was stirred for 16 h at room temperature. Evaporation of the unreacted acetic anhydride–pyridine mixture under reduced pressure afforded the phthalimido product. Crystallization from the appropriate solvent (Table I) gave pure phthalimido compounds.

The IR spectra of compounds **7–10** showed NH stretching at 3350–3365 cm^{-1} and the amide carbonyl at 1680 cm^{-1}. The carbonyl groups of the carboxylic acids of compounds **7–11** disappeared, and a new band appeared at ~1700 cm^{-1} corresponding to the imido group (–CONH–CO–).

^1H NMR spectra of compounds **7–11** were in full agreement with these for compounds **1–6** except for the disappearance of the carboxylic and amide protons.

Registry No. **1**, 16067-61-1; **2**, 118071-17-3; **3**, 118071-18-4; **4**, 118071-19-5; **5**, 70988-26-0; **6**, 19357-13-2; **7**, 16067-65-5; **6**, 118071-20-8; **9**, 118071-21-9; **10**, 100873-73-2; **11**, 60945-03-1; phthalic anhydride, 85-44-9; benzoylhydrazine, 613-94-5; *p*-methylbenzoylhydrazine, 3619-22-5; *p*-methoxybenzoylhydrazine, 3290-99-1; *p*-bromobenzoylhydrazine, 5933-32-4; 4-pyridinecarboxylic acid hydrazide, 54-85-3; 2-aminobenzothiazole, 136-95-8.

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Regioselectivity of 1,3-Dipolar Cycloaddition Reactions of *C*-Acetyl-*N*-arylnitrilimines with Acrylic Acid Derivatives and α,β-Unsaturated Ketones

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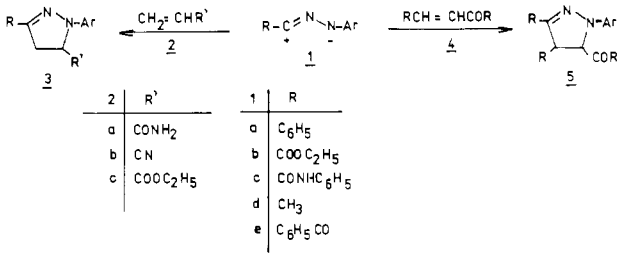
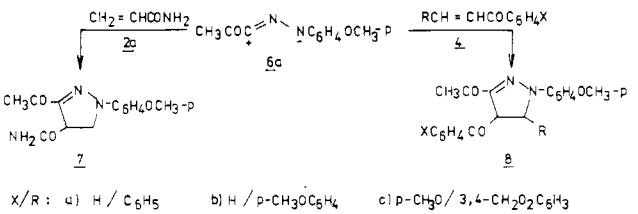
The cycloaddition of a series of *C*-acetyl-*N*-arylnitrilimines 6a–e to acrylamide (2a), acrylonitrile (2b), and substituted benzylideneacetophenones 4a–d has been studied. Under thermal conditions, these 1,3-dipolar cycloadditions proceed with absolute regioselectivity to yield 5-$CONH_2$-, 5-CN-, and 5-COAr-substituted 2-pyrazolines 3A, 3B, and 5, respectively. The structures of the cycloadducts 3A, 3B, and 5 were assigned on the basis of their ^1H NMR and IR spectra.

Nitrilimines **1a–e** have been known to react with acrylic acid derivatives **2a–c** to give predominantly 5-substituted 2-pyrazolines **3** (Scheme I) (*1*). Also, the reactions of **1a–c** with benzylideneacetophenone (**4**; R = C_6H_5) have been reported to give predominantly 5-benzoyl-4-phenyl-2-pyrazolines **5** (Scheme I) (*2*, *3*, *7*). The regioselectivity of these reactions was satisfactorily rationalized in terms of the nitrilimine HOMO–dipolarophile LUMO interaction (*2*, *3*). A recent report (*4*) indicated, however, that the reaction of *C*-acetyl-*N*-(*p*-methoxyphenyl)-nitrilimine (**6a**) with acrylamide (**2a**) and the substituted benzylideneacetophenones **4a–c** gave exclusively 1-aryl-3-acetyl-5-aminocarbonyl-2-pyrazoline **7** and 1,5-diaryl-3-acetyl-4-aroyl-2-pyrazolines **8a–c**, respectively (Scheme II). The regiochemistry of such products is contrary to our expectation; therefore, we reexamined the regiochemistry of the cycloadditions of *C*-acetyl-*N*-arylnitrilimines **6a–e** to acrylic acid derivatives and α,β-unsaturated ketones. In this article we report on the results of the study of the reactions of **6a–e** with acrylamide (**2a**), acrylonitrile (**2b**), and a series of four substituted benzylideneacetophenones **4a–d** (Scheme III).

Scheme I



Scheme II



Results and Discussion

The reactions of *C*-acetyl-*N*-arylnitrilimines **6a–e**, generated in situ by treatment of *C*-acetyl-*N*-arylformohydrazidoyl chlorides **9a–e** with triethylamine, with the dipolarophiles **2a**, **2b**, and **4a–d** were carried out in refluxing chloroform. The results are summarized in Table I. These results indicate that the cycloadditions of **6** with acrylamide (**2a**), acrylonitrile (**2b**), and α,β-unsaturated ketones **4a–d** are regioselective, yielding exclusively the corresponding 5-$CONH_2$, 5-CN, and 5-COC_6H_4R

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Table I. Cycloadducts from the Reactions of 9a–e with Acrylic Acid Derivatives 2a,b and α,β-Unsaturated Ketones 4a–d

entry	reactants	reaction time, h	cycloadduct	mp, °C	yield,[a] %
1	**9a + 2a**	5	**3Aa**	223[b]	70
2	**9b + 2a**	5	**3Ab**	255	65
3	**9c + 2a**	5	**3Ac**	269[c]	70
4	**9d + 2a**	8	**3Ad**	255	55
5	**9a + 2b**	9	**3Ba**	96	80
6	**9b + 2b**	4	**3Bb**	111	75
7	**9c + 2b**	5	**3Bc**	123	73
8	**9d + 2b**	8	**3Bd**	110	70
9	**9e + 2b**	4	**3Be**	122	70
10	**9a + 4a**	19	**5a**	178	45
11	**9b + 4a**	18	**5b**	159	50
12	**9a + 4b**	20	**5c**	153	43
13	**9a + 4c**	18	**5d**	134	48
14	**9a + 4d**	29	**5e**	164	40

[a] Isolated yield. [b] Lit. mp 240 °C (*4*). [c] Lit. mp 200 °C (*4*).

substituted 2-pyrazolines **3A**, **3B**, and **5**, respectively (Scheme III). When these reactions were carried out in benzene, similar regiochemical results were obtained, indicating that the regiochemistry of the cycloaddition reactions of **6** is independent of the solvent polarity.

The regiochemistry of the cycloadducts **3Aa–e** was assigned on the basis of the chemical shifts of the methylene (4-CH_2) and methine (5-CH) protons (Table II). Literature ^{1}H NMR data of

Scheme III

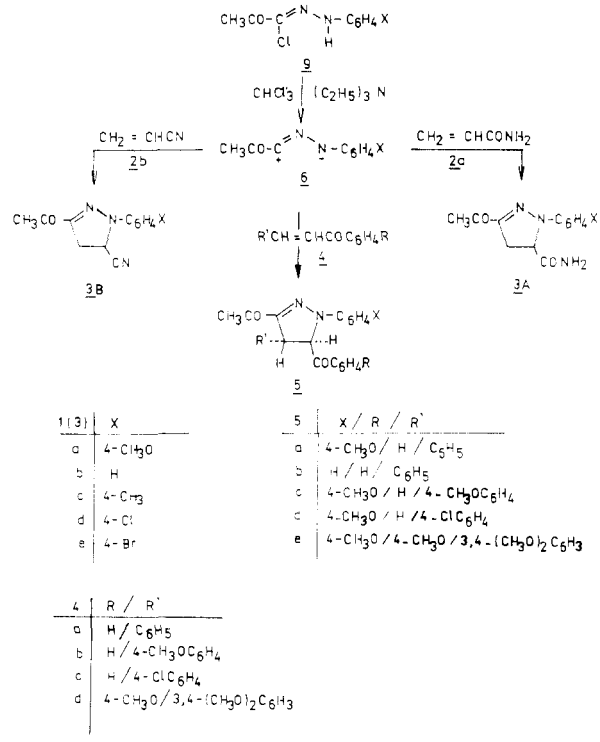
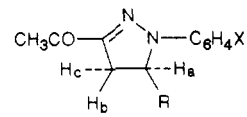


Table II. ^{1}H NMR and IR Spectral Data of the Cycloadducts 3Aa–d and 3Ba–e

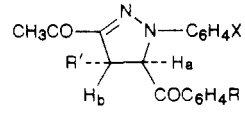


3A, R = $CONH_2$
3B, R = CN

compd no.	δ,[a–c] ppm (multiplicity) H_a	H_b	H_c	CH_3CO	ν̄,[d] cm^{-1}
3Aa	4.87 (dd)	3.68 (dd)	2.89 (dd)	2.40 (s)	1670, 1630, 3190, 3260, 3360
3Ab	4.90 (dd)	3.54 (dd)	2.67 (dd)	2.47 (s)	1675, 1640, 3200, 3320, 3400
3Ac	4.90 (dd)	3.68 (dd)	2.88 (dd)	2.43 (s)	1670, 1640, 3180, 3240, 3360
3Ad	4.95 (dd)	3.55 (dd)	2.80 (dd)	2.45 (s)	1665, 1630, 3200, 3300, 3380
3Ba	5.02 (dd)	3.51 (d)	3.50 (d)	2.52 (s)	1650
3Bb	5.07 (dd)	3.57 (d)	3.55 (d)	2.55 (s)	1660
3Bc	5.05 (dd)	3.57 (d)	3.56 (d)	2.50 (s)	1660
3Bd	5.07 (dd)	3.55 (d)	3.50 (d)	2.50 (s)	1660
3Be	5.08 (dd)	3.72 (d)	3.60 (d)	2.55 (s)	1665

[a] All compounds exhibit aromatic proton multiplet in the region 7.0–8.0 ppm. [b] For compounds **3Aa–d**: $J_{a,b}$ = 12 Hz; $J_{a,c}$ = 7 Hz; $J_{b,c}$ = 18 Hz. For compounds **3Ba–e**: $J_{a,b}$ = 10.8 Hz; $J_{a,c}$ = 9 Hz; $J_{b,c}$ = 0.0 Hz. [c] Compounds **3Aa** and **3Ba** exhibit a singlet near 3.75–3.84 ppm for CH_3OAr protons, whereas compounds **3Ac** and **3Bc** show a singlet near 2.27–2.35 ppm for CH_3Ar protons. [d] For compounds **3Ba–e** the nitrile absorption is either absent or very weak near 2220 cm^{-1}.

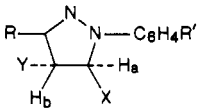
Table III. ^{1}H NMR and IR Spectral Data of the Cycloadducts 5a–e



compd no.	δ,[a,b] ppm (multiplicity) H_a	H_b	CH_3CO	CH_3OAr	ν̄, cm^{-1}
5a	5.77 (d)	4.50 (d)	2.48 (s)	3.80 (s)	1680, 1650
5b	5.75 (d)	4.50 (d)	2.47 (s)		1680, 1650
5c	5.68 (d)	4.40 (d)	2.40 (s)	3.73 (s) 3.75 (s)	1685, 1640
5d	5.68 (d)	4.45 (d)	2.45 (s)	3.75 (s)	1680, 1640
5e	5.67 (d)	4.40 (d)	2.44 (s)	3.74 (s) 3.80 (s) 3.88 (s)	1670, 1645

[a] $J_{a,b}$ = 6 Hz. [b] All compounds exhibit aromatic proton multiplet in the region 6.9–8.2 ppm.

Table IV. Characteristic ^{1}H NMR Data of Some 2-Pyrazoline Derivatives



entry	R/R'/X/Y	δ, ppm H_a	H_b	H_c	ref
		Y = H_c			
1	C_2H_5OOC/H/$CONH_2$	4.90	3.54	2.97	*3, 15*
2	2-thienyl/H/$CONH_2$	4.66	3.74	3.26	*8*
3	2-thienyl/4-NO_2/$CONH_2$	4.90	3.60	3.00	*8*
4	CH_3CO/H/$CONH_2$	4.90	3.54	2.67	*a*
5	C_6H_5/H/CN	4.88	3.55	3.55	*5*
6	$COOC_2H_5$/H/CN	5.04	3.50	3.50	*3, 15*
7	COC_6H_5/H/CN	5.12	3.77	3.77	*9*
8	CH_3/4-NO_2/CN	5.03	3.45	3.45	*10*
9	2-thienyl/H/CN	4.91	3.61	3.61	*8*
10	2-thienyl/4-NO_2/CN	5.10	3.60	3.60	*8*
11	CH_3CO/H/CN	5.07	3.57	3.55	*a*
		Y ≠ H			
12	C_6H_5/H/$COOCH_3$/$COOCH_3$	5.17	4.57		*5*
13	C_6H_5/H/C_6H_5CO/C_6H_5CO	5.75	5.26		*6*
14	C_6H_5/H/C_6H_5/C_6H_5	5.09	4.48		*5*
15	C_6H_5/H/$COOCH_3$/C_6H_5	5.57	4.24		*5, 11*
16	C_6H_5/H/C_6H_5/$COOCH_3$	4.79	4.67		*5, 11*
17	$COOC_2H_5$/H/COC_6H_5/C_6H_5	5.77	4.43		*3, 7*
18	$COOC_2H_5$/H/C_6H_5/COC_6H_5	5.47	5.07		*3, 7*
19	CH_3CO/H/COC_6H_5/C_6H_5	5.75	4.50		*a*

[a] This work.

5-substituted and 4,5-disubstituted 2-pyrazoline derivatives indicate that the chemical shift of 5-H appears in general at lower field than that of 4-H (*3*, *5–11*) (Table III). Comparison of the spectral data of **3Aa–e** with those reported for 2-pyrazoline-5-carboxamides (see entries 1–3 in Table III) shows that each of the methine and methylene protons shows comparable chemical shifts. Such similarity between the chemical shifts of the 2-pyrazoline ring protons in 2-pyrazoline-5-carboxamides and those of the cycloadducts **3Aa–e** substantiates the assigned regiochemistry of the latter.

The geminal protons 4-H_b and 4-H_c in **3Aa–e** constitute the AB part of an ABX pattern, and their signals appear as two double doublets (dd). The proton 4-H_c was assigned the high field signal due to shielding by the proton 5-H_a with which it has a smaller coupling constant $J_{a,c}$ = 7 Hz, by comparison to 4-H_b, which by virtue of its transdiaxial disposition to 5-H_a had a $J_{a,b}$ of 12 Hz (*3*, *5–12*).

The structure of the adducts **3Ba–e** was established on the basis of the absence of the nitrile absorption in their infrared spectra. Aliphatic nitriles activated by a nitrogen or an oxygen atom in the α-position (*13*, *14*) such as the 5-cyano-2-pyrazoline derivatives exhibit no nitrile absorption in their IR spectra (*9*, *15*). On the other hand, the nitrile group in the 4-cyano-substituted 2-pyrazoline and pyrazole derivatives is IR active, showing a strong band in the 2400–2000-cm^{-1} region (*16*). In the infrared spectra of the cycloadducts isolated from the reaction of **6** with acrylonitrile, the nitrile absorption was absent or very weak if present. Therefore, they were assigned the 5-cyano-3-acetyl-1-aryl-2-pyrazoline structure **3B**.

The assigned structure **3B** is further supported by a comparison of the chemical shifts of the 2-pyrazoline ring protons with those in the literature (*5*, *7–10*). The chemical shifts observed at δ 5.02–5.08, 3.51–3.72, and 3.5–3.60 ppm in ^{1}H NMR spectra of **3Ba–e** (Table II) correspond well with the reported values of the 2-pyrazoline ring protons of other 3-R-substituted 1-aryl-5-cyano-2-pyrazolines (see enteries 5–10 in Table III). It is noteworthy to mention that the diastereotopic protons 4-H_b and 4-H_c in **3Ba–e** give different signals but with little chemical shift difference (Δδ 0.01–0.08 ppm); each splits into a doublet by the methine proton 5-H_a, and the downfield lines of the two doublets happen to coincide. Under the conditions of measurement, the spectra showed no splitting due to coupling between 4-H_b and 4-H_c, which is expected to appear at higher gain. That the geminal protons 4-H_b and 4-H_c of **3Ba–e** are the AB part of the ABX system is substantiated by the appearance of a four-line pattern for the 5-H_a due to successive splitting by 4-H_b and 4-H_c protons (Table II). The latter was identified by their chemical shifts and vicinal coupling constants with 5-H_a (*12*).

Direct evidence in support of the structure **5** for the cycloadducts obtained from the reaction of **6** with **4** was obtained from the spacing between the chemical shifts of the pyrazoline protons 4-H and 5-H and the stereochemistry from the comparison of the coupling constants. In their ^{1}H NMR spectra the signals for 4-H and 5-H protons of **5a–e** appeared as a pair of doublets with a chemical shift difference of about 1.3 ppm (Table III). The latter value corresponds well with the reported value (Δδ > 1.0 ppm) of other related 3-R-substituted 4-aryl-5-aroyl-2-pyrazolines and not with the value of Δδ < 0.1 reported for 4-aroyl regioisomers (Table IV) (*3*, *5*, *7*, *11*).

The stereochemistry of the cycloadducts **5a–e** has been unequivocally made by means of the vicinal coupling constants between 4-H and 5-H protons. The vicinal couplings have been shown to be stereospecific J_{trans} (6 Hz) < J_{cis} (12 Hz) (*5*, *6*). Thus, on the basis of the coupling constant value $J_{4,5}$ = 6 Hz, the cycloadducts **5a–e** were assigned the *E*-configuration indicated.

Experimental Section

Melting points were determined on a Bockmonoscop apparatus (hot stage type) and are uncorrected. Infrared spectra were recorded on Zeiss infrared spectrophotometer Model IMT6. ^{1}H NMR spectra were recorded on a Varian EM 390–90-MHz spectrometer. All special chemical shifts are given in parts per million downfield from TMS. Microanalytical analyses were performed with the Perkin-Elmer elemental analyzer Model 240-B at King Abdulaziz University. The elemental analysis data

were submitted for review. *C*-Acetyl-*N*-arylformohydrazidoyl chlorides **9a–e** were prepared according to known procedure (*17*). Acrylamide and acrylonitrile were Aldrich laboratory reagents. Benzylideneacetophenone (**4a**) was obtained from Merck. The other substituted benzylideneacetophenones **4b–d** were prepared according to literature procedures (*18*). 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 × 20 cm) covered with Fluka silica gel G with 13% gypsum and with a mixture of carbon tetrachloride and chloroform in ratio of 5:1.5 (v/v) as eluent.

Reaction of 9 with 2 or 4. General Method. Triethylamine (0.7 mL, 5 mmol) was added to a chloroform solution (50 mL) of **9** (5 mmol) and **2** (or **4**) (5 mmol) at room temperature. The mixture was refluxed until the complete disappearance of **9** or the dipolarophile **2** (or **4**) as indicated by thin-layer-chromatographic analysis. The mixture was cooled and then washed with water three times, and the chloroform layer was collected, dried over anhydrous sodium sulfate, and then filtered. The solvent in the filtrate was evaporated under reduced pressure, and the residue left was triturated with methanol, where it solidified. The crude solid was collected, and its ^{1}H NMR spectrum in deuterated chloroform was recorded. The spectra showed the presence of only one regioisomer in each case. The product was crystallized from ethanol or a mixture of ethanol and chloroform. Only the products **5c** and **5e** were separated by preparative thin-layer chromatography. The physical constants of the products are given in Table I, and their spectral data are gathered in Tables II and III.

Registry No. **2a**, 79-06-1; **2b**, 107-13-1; **3Aa**, 118317-92-3; **3Ab**, 118317-93-4; **3Ac**, 118317-94-5; **3Ad**, 118317-95-6; **3Ba**, 118317-96-7; **3Bb**, 118317-97-8; **3Bc**, 118317-98-9; **3Bd**, 118317-99-0; **3Be**, 118318-00-6; **4a**, 94-41-7; **4b**, 959-33-1; **4c**, 956-04-7; **4d**, 36685-66-2; **5a**, 118318-01-7; **5b**, 118318-02-8; **5c**, 118318-03-9; **5d**, 118318-04-0; **5e**, 118318-05-1; **9a**, 56886-07-8; **9b**, 18440-58-9; **9c**, 18440-55-6; **9d**, 18247-78-4; **9e**, 18247-79-5.

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