Yields were between 60% and 75%. HPLC, TLC, and NMR characteristics are summarized in Tables I and II.

Ethyl 1-Thiotriphosphate (9). P^1-Ethyl P^2,P^3-Dioxocyclotriphophite (7). Dry ethyl alcohol (100 μmol) was reacted with 100 μmol of salicyl phosphorochloridite and pyrophosphate as described for the reaction with nucleosides. After reaction for 10 min with pyrophosphate, 200 μL of DMF-d_7 was added to the reaction solution, the solution transferred to a NMR tube that previously had been flushed with argon, and the ^{31}P NMR spectrum recorded (see Figure 1B).

Ethyl 1-Thiocyclotriphosphate (8). Addition of sulfur (6.4 mg, 200 μmol) to the above reaction solution resulted in the appearance of new peaks in the ^{31}P NMR spectrum as follows: δ(A) = 44.21 ppm, t (1 P); δ(B) = −23.01 ppm, d (2 P); J_{AB} = 34.44 Hz.

Ethyl 1-Thiotriphosphate (9). Water was added to the above reaction solution, which was evaporated to dryness after 1 h. The residue was dissolved in D_2O and the ^{31}P NMR spectrum recorded (see Table II).

Thymidine 5′-Triphosphate (6c). 3′-Acetylthymidine (1c) (100 μmol) was phosphitylated as described above. Pyrophosphate and tri-*n*-butylamine were added and the reaction mixture was stirred for 10 min. A solution of 1% iodine in pyridine/water (98/2, v/v) (2 mL, 157 μmol) was then added. After 15 min excess iodine was destroyed by adding a few drops of a 5% aqueous solution of $NaHSO_3$ and the reaction solution evaporated to dryness. The residue was dissolved in water (10 mL). After standing at room temperature for 30 min, concentrated ammonia (20 mL) was added. After 1 h the solution was evaporated to dryness, the residue dissolved in water, and the solution applied to a DEAE Sephadex column, which was eluted with a linear gradient of 800 mL each of 0.05 M and 1 M TEAB. The product was eluted between 0.50 and 0.55 M buffer, yield 72%. The product was compared by HPLC and ^{31}P NMR with a commercial sample.

Thymidine 5′-*O*-(1-Thiodiphosphate) (TDPαS). 3′-Acetylthymidine (1c) (100 μmol) was phosphitylated as described above for the synthesis of TTPαS. Instead of pyrophosphate a mixture of 0.5 M tri-*n*-butylammonium orthophosphate in anhydrous DMF (500 μL) and tri-*n*-butylamine (100 μL) was added. After addition of sulfur and removal of the protecting group, the reaction mixture was chromatographed on a DEAE-Sephadex column using a linear gradient of 800 mL each of 0.05 M and 0.8 M TEAB. TDPαS (yield 23%) was eluted between 0.52 and 0.55 M buffer and TTPαS (yield 22%) between 0.56 and 0.62 M buffer. HPLC, TLC, and NMR data are summarized in Tables I and II.

Adenosine and Cytidine 2′,3′-Cyclophosphorothioates. 5′-Acetyladenosine or 5′-*O*-,N^4-diacetylcytidine (100 μmol) was reacted with salicyl phosphorochloridite as described for the synthesis of the nucleoside thiotriphosphates. After being stirred for 5 min, a mixture of 0.3 mL of DMF and 0.1 mL of tri-*n*-butylamine was injected. After a further 10 min, a suspension of 10 mg of sulfur in 0.2 mL of DMF was added. After stirring for 30 min, 2 mL of a mixture of H_2O/dioxane (1:3, v/v) was added and the solution evaporated. The residue was dissolved in 10 mL of 25% aqueous ammonia. After reaction for 1 h at room tempeature for the reaction with 5′-acetyladenosine and reaction for 1.5 h for that with 5′-*O*,N^4-diacetylcytidine, the solution was evaporated to dryness, the residue dissolved in 5 mL of H_2O, any sulfur removed by filtration and the solution chromatographed on a DEAE-Sephadex column (2 × 30 cm) with a linear gradient of 1 L each of 0.05 and 0.4 M TEAB. The diastereomers of adenosine 2′,3′-cyclophosphorothioate eluted between 0.23 and 0.26 M buffer and those of cytidine 2′,3′-cyclophosphorothioate between 0.16 and 0.20 M buffer. Yield of 2′,3′ cAMPS 32%, of 2′,3′ cCMPS 45%. ^{31}P NMR (H_2O): δ 77.26 (exo isomer, S_p configuration) and 75.69 ppm (endo isomer, R_p configuration) for 2′,3′-cAMPS and 77.03 (exo isomer, S_p configuration) and 75.72 ppm (endo isomer, R_p configuration) for 2′,3′-cCMPS. HPLC data are in Table I.

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Registry No. **1a**, 25152-96-9; **1b**, 118275-88-0; **1c**, 21090-30-2; **1d**, 96666-99-8; **1e**, 29886-19-9; **1f**, 42167-65-7; **1g**, 16628-81-2; **1h**, 16628-82-3; **4a**, 118275-89-1; **4b**, 118275-90-4; **4c**, 118275-91-5; **4d**, 118275-92-6; **4e**, 118275-93-7; **4f**, 118275-94-8; **4g**, 118275-95-9; **4h**, 118275-96-0; (R_p)-**5a**, 87358-15-4; (S_p)-**5a**, 80875-87-2; (R_p)-**5b**, 80902-29-0; (S_p)-**5b**, 80902-28-9; (R_p)-**5c**, 83199-35-3; (S_p)-**5c**, 83199-32-0; (R_p)-**5d**, 80951-76-4; (S_p)-5d, 80951-75-3; (R_p)-**5e**, 58976-49-1; (S_p)-**5e**, 58976-48-0; (R_p)-**5f**, 81570-50-5; (S_p)-**5f**, 81570-51-6; (R_p)-**5g**, 71214-30-7; (S_p)-**5g**, 71214-29-4; (R_p)-**5r**, 118374-59-7; (S_p)-**5h**, 118353-34-7; **6c**, 365-08-2; **7**, 118297-34-0; **8**, 118275-97-1; **9**, 118275-98-2; (R_p)-2′,3′-cAMPS, 118275-99-3; (S_p)-2′,3′-cAMPS, 118276-00-9; (R_p)-2′,3′-cCMPS, 118276-01-0; (S_p)-2′,3′-cCMPS, 118276-02-1; TDPαs, 81811-21-4; 2-chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one, 5381-99-7; bis(tri-*n*-butylammonium)pyrophosphate, 5975-18-8; 5′-acetyladenosine, 2140-25-2; 5′-*O*,N^+-diacetylcytidine, 6554-13-8.

Products from Reactions of Methyl (*E*)-2-Cyano-3-(*p*-substituted-phenyl)acrylates with 1-Phenyldiazoethane and Cycloreversion of Secondary Pyrazolines

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In dichloromethane, the reaction of methyl (*E*)-2-cyano-3-(*p*-substituted-phenyl)acrylates (**2**) with 1-phenyldiazoethane (**1**), prepared from 2 molar equiv of acetophenone hydrazone, produced methyl 2-cyano-4-phenyl-4-(*p*-substituted-phenyl)-2-pentenoates (**3**), 1-cyano-1-(methoxycarbonyl)-2-methyl-2-phenyl-3-(*p*-substituted-phenyl)cyclopropanes (**4**), and 4-cyano-4-(methoxycarbonyl)-3-methyl-3-phenyl-5-(1-phenyl-1-(*p*-substituted-phenyl)ethyl)-1-pyrazolines (**5**). Compounds **5** were found to be derived from compounds **3** and **1**. Compounds **5** were different from the primary pyrazolines derived from compounds **1** and **2**, both in mode of formation and properties. Compounds **5**, when decomposed thermally or photochemically, produced the initial olefins **3**. This decomposition is an example of "true" cycloreversion.

The 1,3-dipolar cycloadditions of diazomethane derivatives to olefins activated by electron-attracting groups have been extensively studied, especially in connection with the preparation of cyclopropane derivatives.[1] In a previous paper,[2] we reported that the reaction of 1,1-disubstituted olefins containing electron-attracting substituents with 1-phenyldiazoethane produced both cyclopropane and olefin derivatives. In the reactions with 2-

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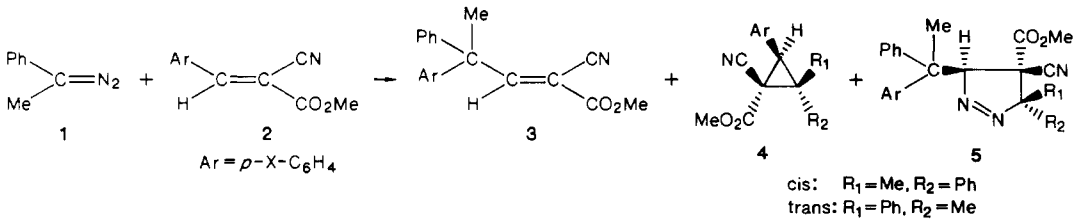
0022-3263/89/1954-0635$01.50/0

Table I. Reaction of Methyl 2-Cyano-3-(substituted-phenyl)acrylates with 1-Phenyldiazoethane



entry	X	yield, % 3	cis-4	*trans*-4	5	total	[3 + 5]:4
a	NO_2	45	29	9		83	54:46
b	Cl	36		20	17	73	73:27
c	H	5		7	54	66	89:11
d	CH_3	58		14	14	86	84:16
e	OCH_3	64		9	17	90	90:10

cyanoacrylate, the resulting olefin reacted with another mole of diazo compound to give a secondary cyclopropane derivative. In this paper, we describe the reaction of 2-cyano-3-(*p*-substituted-phenyl)acrylates with excess of 1-phenyldiazoethane.

Results

To a dichloromethane solution of 1-phenyldiazoethane (**1**),[3] prepared by treating 2 molar equiv of acetophenone hydrazone with manganese dioxide,[4] was added methyl (*E*)-2-cyano-3-(*p*-substituted-phenyl)acrylates (**2**) at −5 to 0 °C. The reaction mixture was left to stand overnight and then chromatographed on silica gel to give methyl 2-cyano-4-phenyl-4-(*p*-substituted-phenyl)-2-pentenoates (**3**), methyl 1-cyano-2-methyl-2-phenyl-3-(*p*-substituted-phenyl)cyclopropanecarboxylates (**4**), and 4-cyano-4-(methoxycarbonyl)-3-methyl-3-phenyl-5-(1-phenyl-1-(*p*-substituted-phenyl)ethyl)-1-pyrazolines (**5**). The results are summarized in Table I.

Structure of Olefinic Products 3. Although compounds **3** are oils, they are composed of a single isomer on the basis of their NMR spectra. Compound **3a** showed a singlet signal at 108.6 ppm and a doublet at 166.3 ppm in the ^{13}C NMR spectrum. These chemical shifts correspond to the α- and β-carbon atoms of 2-cyanoacrylates.[5] On the other hand, the ^1H NMR spectrum for **3a** showed a singlet signal for an olefinic proton at 8.23 ppm. Selective irradiation of the olefinic proton revealed that the proton is attached to β-carbon atom having a doublet at 166.3 ppm. The remaining groups, two phenyls and one methyl, must be located on the quaternary carbon atom. The extraordinarily low-field chemical shift of the β-proton seems to be due to deshielding by one or both of the two phenyls of the quaternary carbon atom. The structures of compounds **3** were further confirmed by an independent synthesis of **3c** by the Cope–Knoevenagel reaction of 2,2-diphenylpropionaldehyde and methyl cyanoacrylate in 93% yield. Regarding the stereochemistry of alkyl 2-cyano-3-phenylacrylates, Cope–Knoevenagel reaction was reported to give products of *E* configuration.[6] On this basis, compounds **3** produced by the diazo compound reaction are assigned the *E* configuration.

Structure of Cyclopropane Derivatives 4. In the case of nitro compound **2a**, **4a** was obtained in two forms (A and B). While the ester methyl signal of isomer A appeared at 3.94 ppm in the ^1H NMR spectrum, that of isomer B was at 3.61 ppm. According to the literature,[7] the ester methyl on a cyclopropane ring is shielded (ca. 0.26–0.55 ppm) by the cis phenyl group. Therefore, the isomer A has no aromatic ring on the cis position of the ester function. On the other hand, the ester group of isomer B should be shielded by at least one aromatic nucleus on the cis position. The phenyl ring cis to a methyl group gave less shielding effect (0.11 ppm) to cis ester methyl group than that cis to hydrogen.[7b] Thus, isomers A and B were assigned structure *trans*-**4** and *cis*-**4**, respectively.[8] The structure of the isomer A was further supported by X-ray crystallography (Figure 1).[9]

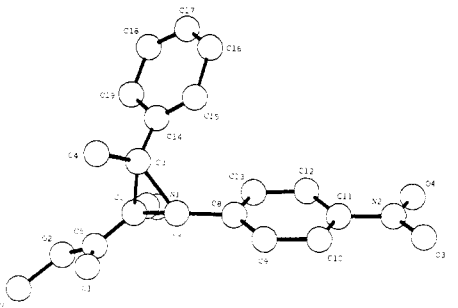


Figure 1. The X-ray crystal structure of *trans*-**4a**.

In other cases, only trans isomer A was obtained; however, we could not exclude the possibility of formation of the cis isomer in other cases.

Structure of Secondary Pyrazolines 5. The composition of compounds **5** corresponded to the adduct of another mole of **1** to the olefinic compounds **3**. In separate experiments, the pyrazolines **5** were also obtained from alkenes **3** prepared by Cope–Knoevenagel condensation. Compounds **5** showed an N=N absorption near 1580 cm^{-1} but no NH absorption, indicating Δ^1-pyrazoline structures. The ^{13}C NMR spectrum for compound **5b** showed tertiary and quaternary carbon signals at 99.6 and 100.9 ppm, respectively, characteristic for carbon atoms attached to the diazo group in a pyrazoline ring.[10] A selective de-

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(8) Cis and trans configurations refer to the relationship between the phenyl group derived from the diazoalkane and methoxycarbonyl group through the paper.
(9) This X-ray structural analysis was kindly provided by Professor Taiichi Higuchi (Osaks City University); the details will be published independently elsewhere.
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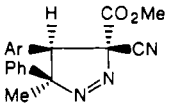
coupling experiment indicated that a proton showing a singlet at 6.25 ppm was attached to the tertiary carbon atom described above.[11] This information established unequivocally that the adducts **5** are formed in the abnormal regiochemistry of 1,3-addition. Apparently, the anomaly is due to the bulky substituent on the β-carbon atom of the olefinic linkage of compounds **3** as well as to the bulky diazo compound. The reverse addition caused by the steric crowding has a precedent.[12]

In the reaction of 2-cyano-3-phenylacrylates **2** with **1**, compounds **5** were isolated as a sole isomer; however, in the reaction of **3c** with **1**, two isomers of **5c** were obtained. The major product was identical with that obtained from **2c**. The major product showed the ester methyl signal at 2.66 ppm (in benzene) different from that (2.92 ppm in benzene) of the minor product. The ester methyl group on the pyrazoline ring also was known to be shielded by a cis phenyl group.[7a,13] Since the addition of diazo compounds to olefins has been established to be stereoselective,[14] the major and minor products isolated here should have structures *cis*-**5c** and *trans*-**5c**, respectively. Other compounds **5** also showed the ester methyl signal at a similar position as the major product here; therefore, these compounds have the cis configuration.

Cycloreversion of Compounds 5. Compound **5c**, under either photolysis or thermolysis, produced olefin **3c** and acetophenonazine,[15] which was formed from the released diazo compound. The ^{1}H NMR spectrum and MS of benzene-d_6 solutions of compound **5c** were measured after the solution had been either irradiated with a high-pressure mercury lamp or heated in an oil bath. In addition to the signals of compound **5c**, new signals were recognized in the ^{1}H NMR spectrum of this solution. These signals corresponded to those of **3c** and acetophenonazine. As the period of irradiation or heating was prolonged, the methine signal at 6.60 ppm of **5c** became weak and the olefinic signal at 8.27 ppm stronger. In the MS, the M^+ of **5c** was not observed, but the parent peak (*m/e* 291) of **3c** was found. Furthermore, in the MS of the thermolysis product of **5f**, prepared from **3c** and 1-(*p*-chlorophenyl)diazoethane, the peaks at *m/e* 291 (M^+ of **3c**) and 259 ([M^+ of **3c**] minus MeOH, base peak) showed the absence of chlorine atom, while a pair of peaks at *m/e* 140 and 138, corresponding to CH_3–C–C_6H_4Cl due to from *p,p'*-dichloroacetophenonazine was observed. Consequently, the photolysis or thermolysis of compounds **5** resulted in "true" cycloreversion to form olefins **3** and acetophenonazines derived from the 1-phenyldiazoethane derivatives.

Discussion

According to McGreer et al.,[16] the rates of decomposition of 3-acetyl- and 3-(methoxycarbonyl)-Δ^1-pyrazolines are enhanced by the alkyl substitution at C-5. This effect is apparently attributable to the stabilization of positive charge at C-5, assisting the cleavage of diazo group polarized at the N to C-3 bond by the electron-attracting group.[17] Substitution with aryl group at C-5 in this system will cause rate enhancement. For instance, 3-acetoxy-3-cyano-5-phenyl-Δ^1-pyrazoline decomposes at −20 °C.[18] In the reaction of 2-cyano-3-phenylacrylates (**2**) with 1-phenyldiazoethane (**1**), no pyrazoline derivatives were isolated because of the instability of these adducts. Equimolar amount of **2a** was added to a dichloromethane solution of **1** and kept at −70 °C for 3 days, during which the violet color of **1** disappeared completely. After removal of the solvent at −50 °C, the ^{13}C NMR spectrum ($CDCl_3$) of the reaction mixture was measured at −40 °C. The spectrum showed different peaks from **3a** and *cis*- and *trans*-**4a**. No products were definitely identified, but evolution of nitrogen during the measurement and the spectrum after complete decomposition indicated clearly the formation of the pyrazoline **6**.



6

Formation of the compounds **3** deserve some commment. The pyrolysis of the pyrazolines formed by the reaction of 2-cyano-[19] or 2-(acetylamido)cinnamates[20] with diazomethane provide a good preparative method for the corresponding 3-methylcinnamates. Crystal structure data of pyrazoline derivatives indicated preferential location of the 4-phenyl group in pseudoaxial position of the envelope form even in the presence of another axial phenyl in the 3-position, provided that the latter phenyl group has no syn substituent on the 5-position.[21] For this reason, the hydrogen, assuming the pseudoequatorial position, migrates easily to form 3-methylcinnamate. However, if the 5-position of a *trans*-3,4-diphenylpyrazoline has a substituent syn to the 3-phenyl group, both of the phenyl groups assume equatorial positions.[22] Therefore, in our case, the aryl group on the 4-carbon migrated stereoselectively to give compounds **3**.

A survey of Table I indicates a trend in product distribution with changing para substituent. Since compounds **5** were certainly derived from compounds **3**, the sum of the yields of **3** and **5** was compared with the yield of **4**. Because of the low yield in entry c, irregularity was observed there; however, the yield of compounds **3** increased as the electron-donating ability of the 3-aryl group of the pyrazoline **6** increased, since the liberation of the nitrogen will be assisted by the neighboring participation of the aromatic group at C-4.[23]

Parham et al.[24] reported the formation of abnormal adduct from 1-nitroalkenes and diphenyldiazomethane and

(11) On the irradiation of this proton, one of the methyl signals (24.45 ppm) and a quaternary carbon (49.37 ppm) as well as the signal for a cyano group (115.07 ppm) also decoupled in accord with the structure. Because of the proximity of the proton signals of two *C*-methyl groups, the irradiation on these protons gave definite conclusion on the structure; however, in both cases, some decoupling was observed on the quaternary carbons at 55.98, 100.15, and 115.07 ppm.

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their thermolysis of cyclopropanes. In this reaction, nitroethylene did not yield stable pyrazoline, but cyclopropane was obtained immediately. In this case also, an unstable adduct of normal mode might be produced for steric reason.

Wilt et al.[25] reported the reaction of a norbornenecarboxylate with diaryldiazomethane to form both normal and abnormal adducts, and they claimed the latter to undergo "true" cycloreversion.[26] In their case, the cycloreversion was accompanied by reversion to the normal adduct. In our case, no normal addition occurred, and the thermal and photochemical decomposition of compounds **5** have added a clear-cut example of "true" cycloreversion.

Experimental Section

Proton NMR spectra were obtained with a Hitachi R-20B (60 MHz) or a Hitachi R-22 (90 MHz) instrument. Carbon-13 NMR spectra were obtained with a JEOL PFT-100. IR spectra were determined with a JASCo A-100 instrument, and a Perkin-Elmer 202 recording spectrophotometer was used for UV absorption spectra. Mass spectra were recorded on a Hitachi RMU-6 spectrometer.

General Procedure. Reactions of Methyl (*E*)-3-Aryl-2-cyanoacrylates with 1-Phenyldiazoethane. To the deep red-violet color solution of 1-phenyldiazoethane (1),[2] which was prepared from the reaction in which 25.7 g of activated MnO_2 was added to a mixture of 0.06 mol (8 g) of acetophenone hydrazone and 6.2 g of anhydrous $MgSO_4$ in 60 mL of dichloromethane at −5 to 0 °C, was added the solution 0.03 mol of methyl (*E*)-2-cyano-3-(*p*-substituted-phenyl)acrylates (**2**) in 25 mL of dichloromethane at −5 to 0 °C. (This 1-phenyldiazoethane solution contained about 0.042 mol of 1-phenyldiazoethane.[27]) The deep color of the diazo compound disappeared gradually and became light yellow. In the case of 2-cyano-3-(*p*-nitrophenyl)acrylate (**2a**) with 1-phenyldiazoethane (1), compared to the reaction of *p*-methoxy compound **2e** with compound 1, the decoloration was very rapid. After the reaction mixture stood overnight at room temperature, the solvent was evaporated under reduced pressure (20–25 mmHg) at 40–50 °C, and 12–15 g of crude products was obtained. The crude products were separated by chromatography on silica gel with the mixture of $CHCl_3$ and CCl_4 as eluant. The isolated compounds in solid states were recrystallized from 95% ethanol or from benzene. The isolated products **3**, **4**, and **5** are described below.

Reaction of Methyl (*E*)-2-Cyano-3-(*p*-nitrophenyl)acrylate (2a) with 1. (*E*)-3a (4.6 g; 45%): ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3 H), 3.87 (s, 3 H, OMe), 7.30 (s, 5 H, Ph), 7.35 and 8.18 (A_2B_2, 4 H, Ph), 8.23 (s, 1 H); ^{13}C NMR δ 27.2, 51.1, 53.5, 108.6, 112.5, 143.3, 146.8, 152.2, 161.9, 166.3; MS, *m/e* (relative intensity) 336 (95, M^+), 319 (75), 304 (50), 276 (60), 259 (45), 231 (50), 200 (45), 77 (100); IR (neat) 2248 (C≡N), 1730 cm^{-1} (C=O); UV (EtOH) λ_{max} (log ε) 209 (4.38), 270 nm (4.09). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.76; N, 8.33. Found: C, 67.55; H, 5.10; N, 8.08.

***trans*-4a** (0.9 g; 9%): mp 210–212 °C; ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 3 H), 3.52 (s, 1 H), 3.94 (s, 3 H, OMe), 7.12 and 8.03 (A_2B_2, 4 H, Ph), 7.30 (s, 5 H, Ph); MS, *m/e* (relative intensity) 336 (3, M^+), 231 (99), 230 (100), 200 (39); IR (Nujol) 2250 (C≡N), 1742 cm^{-1} (C=O); UV (EtOH) λ_{max} (log ε) 207 (4.20), 278 nm (3.93). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.76; N, 8.33. Found: C, 67.75; H, 4.66; N, 8.40.

***cis*-4a** (3.0 g; 29%): mp 204–205 °C; ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 3 H), 3.61 (s, 3 H, OMe), 3.95 (s, 1 H), 7.34 (s, 5 H, Ph), 7.62 and 8.31 (A_2B_2, 4 H, Ph); MS, *m/e* (relative intensity) 336 (18, M^+), 231 (47), 230 (53), 200 (100); IR (Nujol) 2245 (C≡N), 1735 cm^{-1} (C=O); UV (EtOH) λ_{max} (log ε) 207 (4.02), 267 nm (3.86). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.76; N, 8.33. Found: C, 67.56; H, 4.74; N, 8.40.

Reaction of Methyl (*E*)-2-Cyano-3-(*p*-chlorophenyl)acrylate (2b) with 1. (*E*)-3b (3.6 g; 36%): ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3 H), 3.84 (s, 3 H, OMe), 7.1–7.4 (5 H, Ph), 8.20 (s, 1 H).

***trans*-4b** (2.0 g; 20%): mp 189–190 °C; ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 3 H), 3.44 (s, 1 H), 3.98 (s, 3 H, OMe), 6.97 and 7.22 (A_2B_2, 4 H), 7.32 (s, 5 H); MS, *m/e* (relative intensity) 327 (24, M^+), 325 (71, M^+), 200 (100); IR (Nujol) 2250 (C≡N), 1735 cm^{-1} (C=O); UV (EtOH) λ_{max} (log ε) 210 (4.21), 231 (4.15), 270 nm (sh) (2.63). Anal. Calcd for $C_{19}H_{16}NO_2Cl$: C, 70.15; H, 4.92; N, 4.30; Cl, 10.77. Found: C, 69.75; H, 4.91; N, 4.48; Cl, 11.04.

***cis*-5b** (2.3 g; 17%): mp 148–150 °C; ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3 H), 2.01 (s, 3 H), 3.16 (s, 3 H, OMe), 6.25 (s, 1 H), 7.0–7.5 (14 H, Ph); ^{13}C NMR ($CDCl_3$) δ 24.83, 49.02, 53.78, 55.88, 99.57, 100.86, 114.96, 132.86, 135.74, 142.84, 146.36, 166.27; MS, *m/e* (relative intensity) 457 (1, M^+), 429 (0.1), 228 (100), 208 (4); IR (Nujol) 2250 (C≡N), 1738 (C=O), 1580 cm^{-1} (N=N); UV (EtOH) λ_{max} (log ε) 210 (4.45), 235 (sh) (4.14), 260 nm (sh) (3.29). Anal. Calcd for $C_{27}H_{24}N_3O_2Cl$: C, 70.90; H, 5.25; N, 9.19; Cl, 7.66. Found: C, 70.50; H, 5.11; N, 9.61; Cl, 7.82.

Reaction of Methyl (*E*)-2-Cyano-3-phenylacrylate (2c) with 1. (*E*)-3c (0.4 g; 5%): mp 74–75 °C; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3 H), 3.84 (s, 3 H, OMe), 7.18–7.40 (10 H, Ph), 8.26 (s, 1 H); MS, *m/e* (relative intensity) 291 (49, M^+), 259 (100), 232 (51), 205 (23), 200 (75), 187 (27); IR (Nujol) 2240 (C≡N), 1735 cm^{-1} (C=O); UV (EtOH) λ_{max} (log ε) 213 (4.36), 245 (sh) (3.92), 275 nm (sh) (3.62). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.35; H, 5.84; N, 4.81. Found: C, 78.18; H, 5.87; N, 4.78.

***trans*-4c** (0.6 g; 7%): mp 106–108 °C; ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 3 H), 3.47 (s, 1 H), 3.96 (s, 3 H, OMe), 7.0–7.4 (10 H, Ph); MS, *m/e* (relative intensity) 291 (67, M^+), 259 (100), 200 (85), 154 (81); IR (Nujol) 2250 (C≡N), 1730 cm^{-1} (C=O); UV (EtOH) λ_{max} (log ε) 212 (4.19), 260 nm (sh) (2.70). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.35; H, 5.84; N, 4.81. Found: C, 77.88; H, 5.86; N, 4.74.

***cis*-5c** (6.9 g; 54%) mp 131–132 °C; ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3 H), 2.02 (s, 3 H), 3.13 (s, 3 H, OMe), 6.33 (s, 1 H), 7.0–7.6 (15 H, Ph); ^{13}C NMR ($CDCl_3$) δ 24.45 (qm, J = 129.4, $MeCPh_2$), 24.97 (q, J = 131, MeCPh), 49.37 (m, J = 4, CMePh), 53.64 (q, J = 149, MeOOC), 55.98 (m, J = 3, C(CN)COOMe), 100.15 (dq, J = 144.4, CHN=N), 100.79 (q, J = 4, CN=N), 115.07 (d, J = 7, CN), 166.43 (sm, J = 4, COOMe); aromatic carbons 126.13, 126.77, 127.00, 128.00, 128.23, 128.41, 128.59, 128.82, 128.99, 136.13, 144.14, 146.89; MS, *m/e* (relative intensity) 423 (1, M^+), 395 (2), 208 (6), 194 (95), 104 (100); IR (Nujol) 2250 (C≡N), 1750 (C=O), 1580 cm^{-1} (N=N); UV (EtOH) λ_{max} (log ε) 216 (4.29), 235 nm (sh) (3.61). Anal. Calcd for $C_{27}H_{25}N_3O_2$: C, 76.60; H, 5.91; N, 9.93. Found: C, 76.29; H, 6.02; N, 9.80.

Reaction of Methyl (*E*)-2-Cyano-3-(*p*-methylphenyl)acrylate (2d) with 1. (*E*)-3d (5.3 g; 58%): ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3 H), 2.31 (s, 3 H, *p*-CH_3), 3.85 (s, 3 H, OMe), 7.1–7.38 (9 H, Ph), 8.24 (s, 1 H); MS, *m/e* (relative intensity) 305 (44, M^+), 274 (75), 246 (65), 215 (100), 201 (44); IR (Nujol) 2220 (C≡N), 1723 cm^{-1} (C=O).

***trans*-4d** (1.3 g; 14%): mp 161–163 °C; ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 3 H), 2.28 (s, 3 H, *p*-CH_3), 3.42 (s, 1 H), 3.93 (s, 3 H, OMe), 6.89 and 7.03 (A_2B_2, 4 H), 7.1–7.45 (5 H, Ph); MS, *m/e* (relative intensity) 305 (33, M^+), 200 (35), 154 (100); IR (Nujol) 2255 (C≡N), 1740 cm^{-1} (C=O); UV (EtOH) λ_{max} (log ε) 208 (4.37), 230 nm (sh) (4.07). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.69; H, 6.23; N, 4.59. Found: C, 78.39; H, 6.31; N, 4.57.

***cis*-5d** (1.8 g; 14%): mp 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3 H), 2.00 (s, 3 H), 2.29 (s, 3 H, *p*-CH_3), 3.12 (s, 3 H, OMe), 6.34 (s, 1 H), 7.0–7.55 (Ph); ^{13}C NMR ($CDCl_3$) δ 24.57, 25.10, 53.70, 100.54, 100.86, 115.16, 128.11, 136.27, 136.62, 141.30, 147.19, 166.65; MS, *m/e* (relative intensity) 208 (100); IR (Nujol) 2250 (C≡N), 1730 (C=O), 1578 cm^{-1} (N=N); UV (EtOH) λ_{max} (log ε) 213 (4.38), 270 nm (sh) (3.10). Anal. Calcd for $C_{28}H_{27}N_3O_2$: C, 76.89; H, 6.18; N, 9.61. Found: C, 76.96; H, 6.16; N, 9.57.

Reaction of Methyl (*E*)-2-Cyano-3-(*p*-methoxyphenyl)acrylate (2e) with 1. (*E*)-3e (6.1 g; 64%): ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3 H), 3.79 (s, 3 H, *p*-OMe), 3.84 (s, 3 H, OMe), 6.38 and 7.13 (10 H, Ph), 8.22 (s, 1 H).

***trans*-4e** (0.9 g; 9%): mp 152–153 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 3 H), 3.41 (s, 1 H), 3.72 (s, 3 H, *p*-OMe), 3.90 (s, 3 H, OMe), 6.95 and 6.98 (A_2B_2, 4 H, Ph), 7.2–7.3 (5 H, Ph); MS, *m/e* (relative intensity) 321 (66, M^+), 260 (69), 235 (100); IR (Nujol) 2250 (C≡N), 1738 cm^{-1} (C=O); UV (EtOH) λ_{max} (log ε) 210 (4.3), 230

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nm (4.0). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.74; H, 5.96; N, 4.36. Found: C, 74.20; H, 5.87; N, 4.49.

***cis*-5e** (2.1 g; 16%): mp 145–147 °C; ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3 H), 3.12 (s, 3 H, OMe), 3.78 (s, 3 H, *p*-OMe), 6.29 (s, 1 H), 6.8 and 7.2 (A_2B_2, 4 H, Ph), 7.3–7.6 (10 H, Ph); MS, *m/e* (relative intensity) 453 (2, M^+), 425 (2), 321 (45), 224 (100); IR (Nujol) 2250 (C≡N), 1730 (C=O), 1580 cm^{-1} (N=N); UV (EtOH) λ_{max} (log ε) 213 (4.4), 265 nm (3.1). Anal. Calcd for $C_{28}H_{27}N_3O_3$: C, 74.15; H, 6.00; N, 9.27. Found: C, 73.92; H, 5.92; N, 9.22.

2,2-Diphenylpropionaldehyde. To a stirred solution of 41.4 g (0.2 mol) of 2,2-diphenylpropionitrile in 200 mL of dry ether was added dropwise 41 mL of a 1.5 M $LiAlH_4$ dry ether solution over 1 h. After the solution was refluxed for 1 h, it was cooled to room temperature, and 24 mL of water was added to decompose the rest of the $LiAlH_4$. The ether layer was separated, dried over Na_2SO_4, and evaporated to get the residue, which was subjected to chromatography on silica gel to yield 30.2 g (72%) of 2,2-diphenylpropionaldehyde as pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3 H), 7.1–7.5 (10 H, Ph), 9.92 (s, 1 H, aldehyde H).

Preparation of (*E*)-3c from 2,2-Diphenylpropionaldehyde by the Cope–Knoevenagel Condensation. In a round-bottomed flask equipped with a water separator, a mixture of 23.1 g (0.11 mol) of 2,2-diphenylpropionaldehyde, 50 g (0.5 mol) of methyl cyanoacetate, 30 g (0.5 mol) of acetic acid, 10 g (0.13 mol) of ammonium acetate, and 150 mL of benzene was refluxed for 17 h at 130 °C bath temperature. The reaction mixture, after being cooled to room temperature, was neutralized with 1 N Na_2CO_3. The benzene layer was separated and dried over Na_2SO_4, and the solvent was distilled at reduced pressure to give 49.2 g of a crude product. The product was chromatographed on silica gel with a $CHCl_3$–CCl_4 mixture as eluant, and a solid was obtained. The solid was recrystallized from 95% ethanol to give 17.7 g (yield 55%) of crystals, mp 74–75 °C. ^{1}H NMR spectrum ($CDCl_3$) of the crystal agreed with that of (*E*)-**3c**, which was produced by the reaction compound **2c** with compound 1: IR (Nujol) 2228 (C≡N), 1738 cm^{-1} (C=O). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.35; H, 5.84; N, 4.81. Found: C, 78.07; H, 5.69; N, 4.52.

Independent Syntheses of Pyrazolines 5. 4-Cyano-5-[1-phenyl-1-(*p*-nitrophenyl)ethyl]-4-(methoxycarbonyl)-3-methyl-3-phenyl-1-pyrazoline (5a). A reaction of 0.67 g (0.002 mol) of (*E*)-**3a** (which was prepared from compound (*E*)-**2a** with compound **1**) and compound 1, prepared from 0.4 g (0.003 mol) of acetophenone hydrazone, gave 1.2 g of a crude product. The product was chromatographed on silica gel with a $CHCl_3$–CCl_4 mixture and recrystallized from ethanol to give 0.14 g (yield 15%) of *cis*-**5a**: mp 131–132 °C; ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3 H), 2.05 (s, 3 H), 3.16 (s, 3 H, OMe), 6.34 (s, 1 H), 7.0–7.5 (10 H, Ph), 7.6 and 8.1 (A_2B_2, 4 H); IR (Nujol) 2250 (C≡N), 1742 (C=O), 1580 cm^{-1} (N=N). Anal. Calcd for $C_{27}H_{24}N_4O_4$: C, 69.23; H, 5.13; N, 11.97. Found: C, 68.98; H, 5.08; N, 11.69.

***cis*- and *trans*-4-Cyano-5-(1,1-diphenylethyl)-4-(methoxycarbonyl)-3-methyl-3-phenyl-1-pyrazoline (5c).** A reaction of 8.4 g (0.03 mol) of (*E*)-**3c**, which was prepared from 2,2-diphenylpropionaldehyde, and **1** gave 8.2 g of crystals. The crystals were recrystallized from ethanol to give *cis*- and *trans*-**5c**.

***cis*-5c** (6.0 g; 47%): mp 131–132 °C; ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3 H), 2.02 (s, 3 H), 3.10 (s, 3 H, OMe), 6.30 (s, 1 H), 7.0–7.6 (15 H, Ph); (C_6D_6) 1.88 (s, 3 H), 2.03 (s, 3 H), 2.66 (s, 3 H, OMe), 6.60 (s, 1 H), 6.95 (10 H, Ph), 7.2–7.8 (5 H, Ph).

***trans*-5c** (0.11 g; 0.9%): mp 155–156 °C; ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 3 H), 2.03 (s, 3 H), 3.55 (s, 3 H, OMe), 6.24 (s, 1 H), 7.3–7.4 (15 H, Ph); (C_6D_6) 1.34 (s, 3 H), 2.13 (s, 3 H), 2.92 (s, 3 H, OMe), 6.38 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.37, 49.20, 54.25, 57.78, 97.69, 99.16, 114.78, 139.97, 142.90, 149.77, 166.67; IR (Nujol) 2250 (C≡N), 1748 (C=O), 1580 cm^{-1} (N=N). Anal. Calcd for $C_{27}H_{25}N_3O_2$: C, 76.60; H, 5.91; N, 9.93. Found: C, 77.10; H, 5.74; N, 9.97.

***cis*-4-Cyano-5-(1,1-diphenylethyl)-4-(methoxycarbonyl)-3-methyl-3-(*p*-chlorophenyl)-1-pyrazoline (5f)**: A reaction of 5.8 g (0.02 mol) of (*E*)-**3c**, which was prepared from 2,2-diphenylpropionaldehyde, and 1 (Y = Cl),[28] prepared from 4.0 g (0.02 mol) of *p*-chloroacetophenone hydrazone, produced 3.2 g of crystals. From ethanol, recrystallization afforded *cis*-**5f** (2.9 g; 32%): mp 143–144 °C; ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 3 H), 2.02 (s, 3 H), 3.24 (s, 3 H, OMe), 6.33 (s, 1 H), 6.98 and 7.18 (A_2B_2, 4 H), 7.3–7.4 (10, Ph); ^{13}C NMR ($CDCl_3$) δ 25.19, 49.49, 53.90, 55.77, 100.45, 100.92, 114.89, 134.98, 135.15, 144.08, 146.66, 166.56; MS, *m/e* (relative intensity) 457 (100, M^+), 442 (0.1), 424 (0.1); IR (Nujol) 2230 (C≡N), 1745 (C=O), 1538 cm^{-1} (N=N); UV (EtOH) λ_{max} (log ε) 213 (4.34) 260 nm (sh) (3.22). Anal. Calcd for $C_{27}H_{24}N_3O_2Cl$: C, 70.90; H, 5.27; N, 9.19; Cl, 7.66. Found: C, 71.03; H, 5.16; N, 9.37; Cl, 8.00.

***cis*-4-Cyano-5-(1,1-diphenylethyl)-4-(methoxycarbonyl)-3-methyl-3-(*p*-methylphenyl)-1-pyrazoline (5g).** By the same method as described for *cis*-**5f**, 9.0 g (0.03 mol) of (*E*)-**3** and compound 1 (Y = CH_3),[28] prepared from 6.0 g (0.04 mol) of *p*-methylacetophenone hydrazone, gave 6.0 g of crude products. Recrystallization from ethanol gave *cis*-**5g** (4.4 g; 34%): mp 136.5–137.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3 H), 2.00 (s, 3 H), 2.30 (s, 3 H), 3.10 (s, 3 H, OMe), 6.24 (s, 1 H), 6.9 and 7.0 (A_2B_2, 4 H), 7.2–7.3 (Ph); ^{13}C NMR ($CDCl_3$) δ 24.36, 49.26, 53.65, 55.95, 99.69, 100.57, 115.07, 132.80, 138.85, 144.13, 147.07, 166.32; MS, *m/e* (relative intensity) 437 (2.7, M^+), 301 (77), 259 (98), 199 (100); IR (Nujol) 2248 (C≡N), 1750 (C=O), 1590 cm^{-1} (N=N); UV (EtOH) λ_{max} (log ε), 215 (4.35), 265 nm (sh) (3.09). Anal. Calcd for $C_{28}H_{27}N_3O_2$: C, 76.89; H, 6.18; N, 9.61. Found: C, 76.96; H, 6.09; N, 9.54.

Photolysis of *cis*-5c. In a quartz tube for NMR measurement, a solution of 34.5 mg of *cis*-**5c** in 0.4 mL of benzene-d_6 was irradiated with a high-pressure mercury lamp (10 A, 100 W)[29] for 8 h, and then the solution was subjected to ^{1}H NMR spectral measurement. It was found that *cis*-**5c** was decomposed into (*E*)-**3c** and acetophenonazine,[15] which might been formed from the releasing diazo compound. The ratio of the products was *cis*-**5c**:(*E*)-**3c** = 1:4. Acetophenonazine was a very small amount of the products: ^{1}H NMR (C_6D_6) δ (*cis*-**5c**) 1.88 (s, 3 H), 2.03 (s, 3 H), 2.66 (s, 3 H, OMe), 6.60 (s, 1 H); ((*E*)-**3c**) 1.89 (s, 3 H), 3.25 (s, 3 H, OMe), 7.0 (s, 10 H), 8.27 (s, 1 H, vinyl); (acetophenonazine) 2.02 (very small).

Thermolysis of *cis*-5c. In a quartz tube for NMR measurement, a solution of 33 mg of *cis*-**5c** in 0.5 mL of benzene-d_6 was sealed and heated at 90 °C in an oil bath for 9 h. It was cooled to room temperature, and the ^{1}H NMR and MS spectra were measured. As a result, it was found that *cis*-**5c** also was decomposed into (*E*)-**3c** and acetophenonazine by heating. The ratio of the produced and remaining compounds in the tube was *cis*-**5c**:(*E*)-**3c**:acetophenonazine = 1:3.5:0.5. MS spectra of the mixture: *m/e* (relative intensity) 291 (10, M^+ of **3c**), 259 (22, M^+ of **3c** minus MeOH), 235 (5, M^+ of acetophenonazine).

Photolysis of *cis*-5f. In a quartz tube for NMR measurement, a solution of 30 mg of *cis*-**5f** in 0.35 mL of benzene-d_6 was irradiated with a high-pressure mercury lamp for 20 h, and the ^{1}H NMR spectrum was measured. By the irradiation, *cis*-**5f** also was decomposed into (*E*)-**3c** and *p*-chloroacetophenonazine; the ratio of the products was *cis*-**5f**:(*E*)-**3c**:*p*-chloroacetophenonazine = 2:2:1. ^{1}H NMR (C_6D_6): δ (cis 5f) 1.75 (s, 3 H), 2.02 (s, 3 H), 2.64 (s, 3 H, OMe), 6.57 (s, 1 H); ((*E*)-**3c**) 1.88 (s, 3 H), 3.24 (s, 3 H, OMe), 7.0 (s, 10 H), 8.26 (s, 1 H, vinyl); (*p*-chloroacetophenonazine) 2.02 (s, 6 H).

Thermolysis of *cis*-5f. In a quartz tube for NMR measurement, a solution of 33.0 mg of *cis*-**5f** in 0.5 mL of benzene-d_6 was sealed, heated at 90 °C for 9 h, and cooled to room temperature, and the ^{1}H NMR and MS spectra were measured. The ratio of the compounds in the tube was *cis*-**5f**:(*E*)-**3c**:*p*-chloroacetophenazine = 1:3:2.5. MS spectra of the mixture: *m/e* (relative intensity) 291 (52, M^+ of **3c**, without chlorine), 259 (100, M^+ of **3c** minus MeOH, without chlorine), 138 and 140 (84 and 27, corresponding to the peaks of CH_3–C–C_6H_4–^{35}Cl and CH_3–C–C_6H_4–^{37}Cl).

Registry No. 1 (Y = H), 22293-10-3; 1 (Y = Cl), 61185-76-0; 1 (Y = CH_3), 64252-52-4; **2a**, 42348-04-9; **2b**, 49678-54-8; **2c**, 14533-86-9; **2d**, 13432-70-7; **2e**, 14479-58-4; (*E*)-**3a**, 117918-86-2;

(28) "Y" shows the substituent at the para position of a phenyl group in compound 1. For example, Y = Cl, that is 1-(*p*-chlorophenyl)diazoethane.

(29) A quartz high-voltage mercury lamp HL-100 (10 A, 100 W), (Fuji Glasses Manufacture Co., Osaka, Japan), was covered with a Pyrex tube to cut the wavelengths shorter than 325 nm, and the pyrex tube was cooled with water.

(*E*)-**3b**, 117918-88-4; (*E*)-**3c**, 117918-91-9; (*E*)-**3d**, 117918-94-2; (*E*)-**3e**, 117918-97-5; *trans*-**4a**, 117918-87-3; *cis*-**4a**, 118013-65-3; *trans*-**4b**, 117918-89-5; *trans*-**4c**, 117918-92-0; *trans*-**4d**, 117918-95-3; *trans*-**4e**, 117918-98-6; **5a**, 117919-00-3; **5b**, 117918-90-8; **5c**, 117918-93-1; **5d**, 117918-96-4; **5e**, 117918-99-7; **5f**, 117919-01-4; **5g**, 117919-02-5; acetophenone hydrazone, 13466-30-3; 2,2-diphenylpropionaldehyde, 22875-82-7; diphenylpropionitrile, 5558-67-8; methyl cyanoacetate, 105-34-0; acetophenonazine, 729-43-1; *p*-chloroacetophenone hydrazone, 5326-15-8; *p*-chloroacetophenonazine, 5326-15-8.

Substituent-Directing Effects in the Homolytic Acylation of Pyrazine Derivatives

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The homolytic acylation of various monosubstituted pyrazines was studied for a wide spectrum of substituents. Methoxy and chloro substituents were found to direct ortho substitution, thus giving the corresponding 2,3-disubstituted pyrazines. Acetyl, carbethoxy, and carboxamide groups were found to direct para substitution, thus leading to the corresponding 2,5-disubstituted pyrazines. These selectivities result from the combination of the inductive and resonance effects of the substituents. The synthetic potential of the acylation reaction is demonstrated in the preparation of some novel pyrazine flavorants.

In a previous study[1] we described a simple method for the homolytic acylation of pyrazines. Thus, a mixture of a pyrazine and an aldehyde in water containing sulfuric acid, *tert*-butyl hydroperoxide, and ferrous sulfate reacted to form the corresponding monoacylpyrazine derivative as the major product.[1] Under these conditions the aldehyde is converted to an acyl radical, which behaves as a nucleophile and undergoes addition to the pyrazine ring followed by rearomatization.

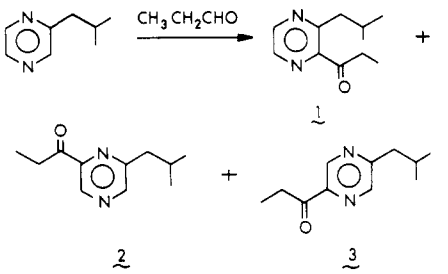
Most of our previous work was carried out on either pyrazine itself or various alkylpyrazines.[1] For example, acylation of isobutylpyrazine with propionaldehyde gave a mixture of all three possible isomers, **1**, **2**, and **3**, in a 3:4:3 ratio (Scheme I).

A study by Caronna et al.[2] describes a similar procedure, which leads to diacylation products. Thus, treatment of pyrazine with the above reagents led to the formation of 2,5-diacylpyrazine (Scheme II). It was suggested that the first acyl group directs the second group into the 5-position.[2]

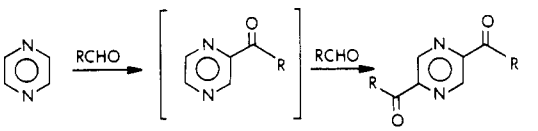
The above observations indicate significant differences in the directing effects of an acyl and an alkyl group in the homolytic acylation process. The aim of the present investigation was to establish the generality of this phenomenon. In particular we were interested to see whether other functional groups show specific directing patterns.

Different substituted pyrazines were selected to cover a wide spectrum of electronic effects. Some substituents, in particular chlorine, were selected because their reaction products can be used as intermediates in the preparation of a variety of new pyrazine derivatives (see below). Aldehydes of different sizes were chosen in order to determine the importance of steric effects in the acylation process. Reactions were carried out as described in our earlier study,[1] and the results are summarized in Table I. Each reaction mixture was analyzed by GC and showed two major peaks, which were identified as the corresponding acyl product and unreacted starting material.

Scheme I



Scheme II



Small amounts of the diacyl product as well as methylated and alkylated products were observed. The latter arise from decomposition of *tert*-butyl hydroperoxide to acetone and a methyl radical and by decarbonylation of the acyl radical to the corresponding alkyl radical, respectively.

Methoxy and chloro substituents were found to direct predominantly ortho substitution, thus giving the 2,3-disubstituted pyrazines, **4–6** and **7–8**, respectively.[3] Acetyl, carbethoxy, and carboxamide groups were found to direct predominantly para substitution, thus giving the 2,5-disubstituted pyrazines, **9**, **10**, and **11**, respectively.[3] Further examination of GC chromatograms of the above reaction mixtures indicated the presence of other minor components. The possibility that these minor components are other structural isomers was investigated in detail in the case of the reaction of chloropyrazine with propionaldehyde. The following reaction mixture composition was obtained (GC yields): unreacted chloropyrazine (26%); **7** (42%); 1-(2-chloro-5-pyrazinyl)-1-propanone (6%), and trace amounts of chloromethylpyrazine, chloroethyl-

(1) Houminer, Y.; Southwick, E. W.; Williams, D. L. *J. Heterocycl. Chem.* **1986**, *23*, 497.

(2) Caronna, T.; Fronza, G.; Minisci, F.; Porta, O. *J. Chem. Soc., Perkin Trans. 2* **1972**, 2035.

(3) In each of the reactions the composition of the crude product was carefully analyzed by GC. The limit of detection was about 2%. Therefore, it is possible that other isomers were formed in amounts smaller than 2%.

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