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A Reinvestigation of the Reaction of *α,β*-Unsaturated Acid Chlorides with Diazomethane

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With two equivalents of diazomethane, 3-(5-nitro-2-furyl)acryloyl chloride (Ia) gave 3-diazoacetyl-4-(5-nitro-2-furyl)-1-[3-(5-nitro-2-furyl)acryloyl]-2-pyrazoline (Va) in good yield, which was converted to the corresponding bromide (VIa (X=Br)), chloride (VIa (X=Cl)) and thiocyanate (VIIIa) in the usual methods.

To confirm the results described above, cinnamoyl chloride (Ib) was treated with various amounts of diazomethane. With excess, two equivalents of, and an equimolar amount of diazomethane Ib gave 3-diazoacetyl-4-phenyl-2-pyrazoline (IVb), 1-cinnamoyl-3-diazoacetyl-4-phenyl-2-pyrazoline (Vb) and the mixture of Vb and 3-chloroacetyl-1-cinnamoyl-4-phenyl-2-pyrazoline (VIb) respectively. Furthermore, the same mixture of Vb and VIb was obtained by the treatment of IVb with an equimolar amount of Ib.

Antimicrobial activities of nitrofuran derivatives are listed in the table.

Although the addition of diazomethane to *α,β*-unsaturated carbonyl compounds is well-known reaction, only a few studies on the same reaction with *α,β*-unsaturated acid chlorides are previously reported.[2–4] For example, it was reported that the reaction of cinnamoyl chloride with excess diazomethane gave first unstable 3-diazoacetyl-4-phenyl-1-pyrazoline, which was easily rearranged to more stable 2-pyrazoline derivative[3]; however, when the same

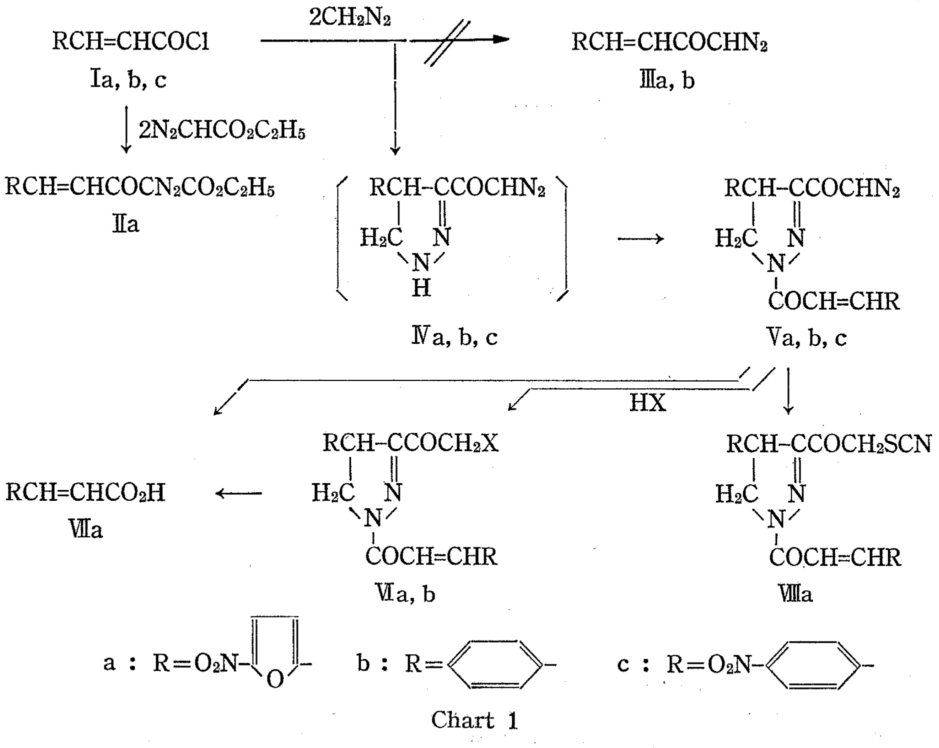

Chart 1

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[1] Location: *Kashima-cho, Higashiyodogawa-ku, Osaka.*

[2] C. Grundmann, F. Bär, and H. Trischmann, *Ann. Chem.*, 524, 31 (1936).

[3] J.A. Moore, *J. Org. Chem.*, 20, 1607 (1955).

reaction was carried out in highly diluted solution, 1-diazoacetyl-4-phenyl-3-buten-2-one (IIIb) was obtained without addition of diazomethane.[4]

In the present paper the reactions of α,β-unsaturated acid chlorides with various amounts of diazomethane are described. The reaction of 3-(5-nitro-2-furyl) acryloyl chloride (Ia) with two equivalents of ethyl diazoacetate[5] was first examined to give ethyl 2-[3-(5-nitro-2-furyl)acryloyl]-2-diazoacetate (IIa), which showed infrared (IR) absorption bands (Nujol, cm^{-1}) at 2140 (diazo), 1720 (ester carbonyl) and 1645 (diazo carbonyl). In this case, the addition of ethyl diazoacetate to the double bond was not observed because of its low reactivity.

Secondly, Ia was allowed to react with two equivalents of diazomethane at $-10°$ to give brownish yellow product of mp 189.5° (decomp.) in good yield, which was assigned to be 3-diazoacetyl-4-(5-nitro-2-furyl)-1-[3-(5-nitro-2-furyl)acryloyl]-2-pyrazoline (Va) on the basis of elemental analysis and the following data; IR (Nujol, cm^{-1}): 2110 (diazo), 1660 (amide) and 1615 (diazoacetyl, conjugated with C=N bond[3]), NMR[6] (δ (ppm), in dimethylformamide): 4.2—5.5 (3H, multiplet, pyrazoline ring protons), 6.80 (1H, singlet, $-COC\underline{H}N_2$), 6.90, 7.39, 7.66 and 7.87 (each 1H, doublet, $J=4$ cps, total 4H due to furan ring protons), 7.63 (2H, singlet, olefinic protons) and UV ($\lambda_{max}^{C_2H_4Cl_2}$ mμ, (log ε)): 328 (4.55) and 360 (4.42) suggesting the presence of 5-nitro-2-furyl and 3-(5-nitro-2-furyl)acryloyl groups.

Another chemical evidence for the presence of 3-(5-nitro-2-furyl)acryloyl group was provided by the acid-catalyzed hydrolysis of Va to give 3-(5-nitro-2-furyl)acrylic acid (VIIa).[7] Va was easily converted to 3-bromoacetyl-4-(5-nitro-2-furyl)-1-[3-(5-nitro-2-furyl)acryloyl]-2-pyrazoline (VIa, X=Br) and 3-chloroacetyl-4-(5-nitro-2-furyl)-1-[3-(5-nitro-2-furyl)acryloyl]-2-pyrazoline (VIa: X=Cl) by the hydrobromic and hydrochloric acid treatment in acetone suspension. VIa (X=Cl) was also prepared by the reaction of Ia with a half equivalent of diazomethane, but the synthesis of 3-diazoacetyl-4-(5-nitro-2-furyl)-2-pyrazoline (IVa) from Ia with excess diazomethane was failured. 4-(5-Nitro-2-furyl)-1-[3-(5-nitro-2-furyl)acryloyl]-3-thiocyanatoacetyl-2-pyrazoline (VIIIa) was also prepared from Va with KSCN and 10% H_2SO_4 in acetone or VIa with KSCN in acetone.

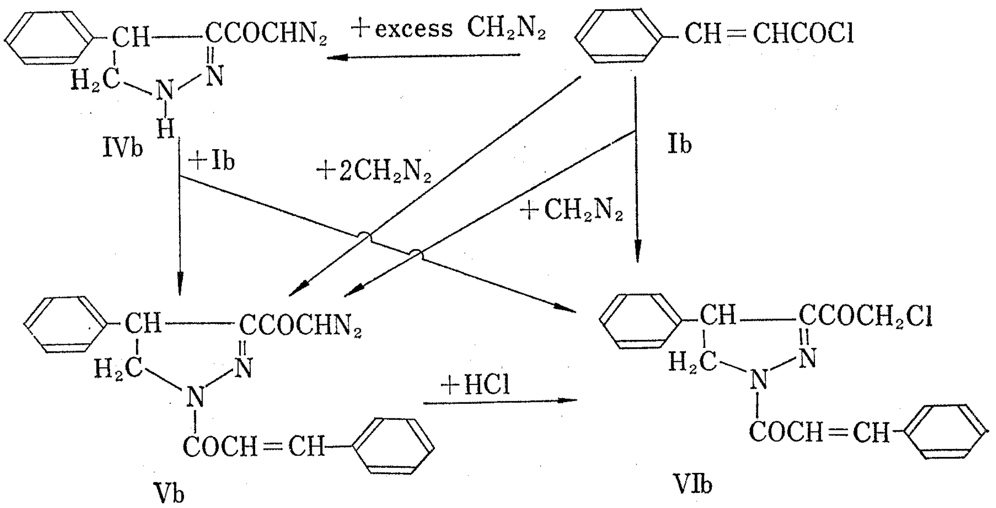

Chart 2

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[4] J.H. Wotiz and S.N. Buco, *J. Org. Chem.*, **20**, 210 (1955).

[5] E.B. Womack and A.B. Nelson, *Org. Synth.*, **24**, 56 (1944).

[6] The nuclear magnetic resonance (NMR) spectra were measured with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Those compounds prepared (Va, b, c and VIa, b) were only slightly soluble so that the complete assignment of ABC–type pyrazoline ring protons was impossible.

[7] H. Saikachi and A. Tanaka, *Yakugaku Zasshi*, **83**, 240 (1963).

Va is presumably formed by the diazoacetylation of acid chloride (Ia), addition of diazomethane to the double bond and subsequent acylation by the second acid chloride molecule.

To confirm the results described above, cinnamoyl chloride (Ib) was allowed to react with various amounts of diazomethane.

It was previously reported[3] that the reaction of Ib with excess diazomethane gave 3-diazoacetyl-4-phenyl-2-pyrazoline (IVb), but further study has not been achieved.

With an equimolar amount of diazomethane Ib gave about equal portion of 1-cinnamoyl-3-diazoacetyl-4-phenyl-2-pyrazoline (Vb) and 3-chloroacetyl-1-cinnamoyl-4-phenyl-2-pyrazoline (VIb). The same mixture was also prepared from the reaction of IVb with an equimolar amount of Ib and was converted to pure VIb by concentrated hydrochloric acid treatment in acetone at 60°. With two equivalents of diazomethane, Ib gave only pure Vb. The structure of Vb was confirmed by the following data; IR (Nujol, cm^{-1}): 2100 (diazo), 1660 (amide) and 1620 (diazoacetyl, conjugated with C=N bond), NMR[6] (δ (ppm), in deuterated acetone): 4.0—5.0 (3H, multiplet, pyrazoline protons), 4.72 (1H, singlet, $-COC\underline{H}N_2$), 7.3—7.9 (10H, multiplet, two phenyl protons), 7.63 and 7.87 (each 1H, doublet, two olefinic protons), and UV ($\lambda_{max}^{C_2H_4Cl_2}$ mμ, (logε)): 304 (4.40), 336 (4.35).

The reaction of *p*-nitrocinnamoyl chloride (Ic) with two equivalents of diazomethane gave similarly 3-diazoacetyl-1-*p*-nitrocinnamoyl-4-*p*-nitrophenyl-2-pyrazoline (Vc).

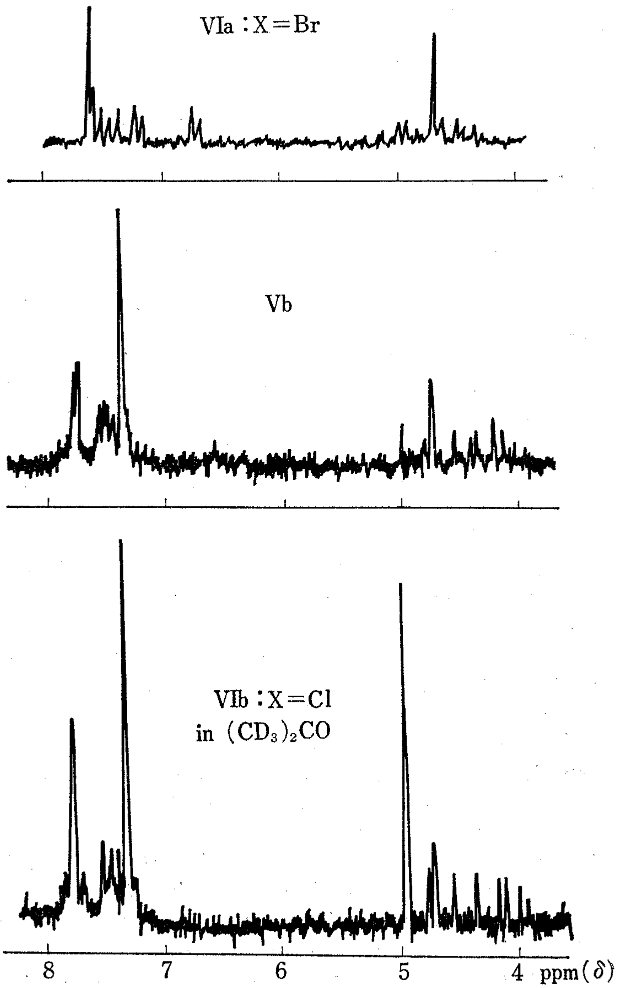

Fig. 1. NMR Spectra of VIa (X=Br), Vb and VIb (X=Cl) in Deuterated Acetone

Thus it was clarified that the reactions of the α,β-unsaturated acid chlorides with diazomethane might proceed through the intermediate IV to V or VI according to the amount of diazomethane.

Table I. Antimicrobial Activities of 5-Nitrofuran Derivatives (Minimum inhibitory concentration μg/ml)

Compound No.	*Escherichia coli* NIHJ[a)]	*Staphylococcus aureus* FDA209P[a)]	*Trichomonas vaginalis* 4FM[b)]
IIa	40	40	10
Va	2.5	40	2.5
VIa (X=Br)	40	40	10
VIa (X=Cl)	5	2.5	5
VIIIa	40	40	5

a) Incubated at 37° for 20 hr in neutral bouillon medium.
b) Incubated at 37° for 48 hr in V bouillon medium.

Antimicrobial activities of some nitrofuran derivatives are presented in Table I.

Experimental[8)]

Ethyl 3-(5-Nitro-2-furyl)acryloyldiazoacetate (IIa)——A solution of 3-(5-nitro-2-furyl)acryloyl chloride[9)] (Ia, 2.0 g) in dry benzene (30 ml) was added dropwise into a stirred solution of ethyl diazoacetate[5)] (2.0 g) in dry ether (35 ml) within 30 min at $-20°$, and the reaction mixture was allowed to stand overnight at room temperature. After removal of solvents under reduced pressure below 30°, the residue was extracted with ethanol to separate the product from insoluble tar. Recrystallization from ethanol gave 0.3 g of pale yellow flakes, mp 136—137°. *Anal.* Calcd. for $C_{11}H_9O_6N_3$: C, 47.32; H, 3.25; N, 15.05. Found: C, 47.25; H, 3.18; N, 15.04.

3-Diazoacetyl-4-(5-nitro-2-furyl)-1-[3-(5-nitro-2-furyl)acryloyl]-2-pyrazoline (Va)——A solution of diazomethane[10)] (4.0 g, 0.095 mole) in ether (200 mle) was added dropwise into a stirred solution of Ia (11.0 g, 0.054 mole) in a mixture of dry benzene (100 ml) and ether (75 ml) within 30 min at $-10°$, then the mixture was stirred for 1 hr at same temperature and allowed to stand overnight at room temperature. Precipitate was filtered and dried to give 8.0 g (70.9%) of brownish yellow powder, mp 167° (decomp.). Recrystallization from acetone–ethanol gave yellow crystalline powder, mp 189.5° (decomp.). *Anal.* Calcd. for $C_{16}H_{10}O_8N_6$: C, 46.27; H, 2.67; N, 20.24. Found: C, 46.63; H, 2.65; N, 19.98.

3-Bromoacetyl-4-(5-nitro-2-furyl)-1-[3-(5-nitro-2-furyl)acryloyl]-2-pyrazoline (VIa: X=Br)——47% HBr solution (5.0 g) was added dropwise into a stirred suspension of Va (1.0 g) in acetone (200 ml) at room temperature. Under evolution of nitrogen gas a clear solution was obtained. After the stirring for 1 hr, solvent was removed under reduced pressure and the residue was filtered with a small amount of ethanol to give 0.9 g of crystalline powder, mp 203° (decomp.). Recrystallization from acetone–ethanol gave yellow crystalline powder, mp 207° (decomp.). *Anal.* Calcd. for $C_{16}H_{11}O_8N_4Br$: C, 41.13; H, 2.37; N, 11.99; Br, 17.11. Found: C, 41.31; H, 2.60; N, 12.27; Br, 16.36. IR (Nujol, cm^{-1}): 1700, 1680 (α-bromoketone), 1660 (amide), NMR[6)] (δ(ppm), in deuterated acetone): 4.2—5.2 (3H, multiplet, pyrazoline ring protons), 4.67 (2H, singlet, $-CO\underline{C}\underline{H}_2Br$), 6.71, 7.20, 7.36 and 7.54 (each 1H, doublet, $J=3.5$ cps, total 4H due to furan ring protons), 7.59 (2H, singlet, olefinic protons). UV $\lambda_{max}^{C_2H_4Cl_2}$ mμ, (log ε): 238 (4.17), 316 (4.48), 360 (4.43).

3-Chloroacetyl-4-(5-nitro-2-furyl)-1-[3-(5-nitro-2-furyl)acryloyl]-2-pyrazoline (VIa; X=Cl)——Method A: A solution of Ia (31.0 g, 0.165 mol) in dry benzene (200 ml) was added into a stirred solution of diazomethane (3.4 g, 0.081 mol) in ether (170 ml) for 1 hr at $-15°$. After stirring for additional 1 hr, the mixture was allowed to stand overnight. Precipitate was filtered and dried to give 5.3 g (15.2%) of yellow crystals, mp 190—192° (decomp.). Recrystallization from acetone–ethanol gave yellow granular crystals, mp 201° (decomp.). *Anal.* Calcd. for $C_{16}H_{11}O_8N_4Cl$: C, 45.45; H, 2.53; N, 13.25. Found: C, 45.40; H, 2.86; N, 13.20. IR (Nujol, cm^{-1}): 1700 (α-chloroketone), 1660 (amide); NMR[6)] (δ(ppm), in deuterated acetone): 4.2—5.4 (3H, multiplet, pyrazoline ring protons), 4.93 (2H, singlet, $-COC\underline{H}_2Cl$), 6.73, 7.19, 7.39 and 7.54 (each 1H, doublet, $J=3.5$ cps, total 4H due to furan ring protons), 7.57 (2H, singlet, olefinic protons). Unreacted Ia was recovered from the mother liquor as ethyl 3-(5-nitro-2-furyl)acrylate (mp 124—125°, 24.1 g).

Method B: A suspension of Va (1.0 g) in acetone (200 ml) was treated with concentrated HCl (5 g) as described above to give 0.8 g of yellow granular crystals, mp 201°C (decomp.).

4-(5-Nitro-2-furyl)-1-[3-(5-nitro-2-furyl)acryloyl]-3-thiocyanatoacetyl-2-pyrazoline (VIIIa)——Method A: A solution of Va(1.0 g), KSCN (5.0 g) and 10% H_2SO_4 (50 ml) in acetone (100 ml) was refluxed for 30 min. After filtration, the filtrate was concentrated to dryness under reduced pressure to give 0.6 g of yellow powder. Recrystallization from acetone–ethanol gave 0.5 g of yellow fine needles, mp198°C (decomp.). *Anal.* Calcd. for $C_{17}H_{11}O_8N_5S$: C, 45.84; H, 2.49; N, 15.73; O, 28.74; S, 7.19. Found: C, 46.18; H, 2.92; N, 15.70; O, 28.39; S, 6.72. IR (Nujol, cm^{-1}): 2150 (thiocyanato), 1710, 1670 (ketone), 1660 (amide); UV $\lambda_{max}^{C_2H_4Cl_2}$ mμ, (log ε): 240 (4.20), 318(4.51), 360 (4.40, shoulder).

Method B: A solution of VIa (X=Br: 0.5 g) and KSCN (0.3 g) in a mixture of water (3 ml) and acetone (50 ml) was heated for 1 hr at 60°. After filtration, the filtrate was concentrated under reduced pressure. The residue was filtered with a small amount of ethanol. Recrystallization from acetone–ethanol gave 0.4 g of yellow fine needles, mp 191°C (decomp.). *Anal.* Calcd. for $C_{17}H_{11}O_8N_5S$: C, 45.84; H, 2.49; N, 15.73. Found: C, 46.24; H, 2.80; N, 15.64.

Acid-catalyzed Hydrolysis of Va and VIa (X=Br)——Va (200 mg) was refluxed with a mixture of each 4 ml of 5N HCl and acetic acid for 3 hr, then a small amount of water was added to separate dark brown tar. After filtration, the filtrate was concentrated under reduced pressure. The residue was filtered, washed with water and dried to give 70 mg of brown powder. Recrystallization from ethanol–water with charcoal gave crystalline powder of mp 235—236° (decomp.), which was identified with an authentic sample of

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8) All melting points are uncorrected. The infrared spectra were recorded on a Hitachi EPI S2.

9) T. Takahashi, H. Saikachi, T. Sasaki, K. Suzuki, and E. Moritani, *Yakugaku Zasshi*, **69**, 286 (1949).

10) F. Arndt, *Org. Synth.*, Coll. Vol. II, 165 (1943).

3-(5-nitro-2-furyl)acrylic acid (VIIa) by infrared spectrum. VIa (X=Br, 300 mg) was also treated in the similar manner and same result was obtained.

3-Diazoacetyl-4-phenyl-2-pyrazoline (IVb)——This material was prepared according to the description of Moore[3]; mp 113—114°C (decomp.), 66.7% yield.

1-Cinnamoyl-3-diazoacetyl-4-phenyl-2-pyrazoline (Vb)——A solution of cinnamoyl chloride (Ib, 3.8 g) in dry ether (20 ml) was added dropwise into a stirred solution of diazomethane (2.4 g) in ether (150 ml) at −10°. The reaction mixture was stirred for 1 hr at same temperature and allowed to stand overnight in refrigerator. Crystals formed were filtered and recrystallized from acetone–ethanol to give 1.2 g (30.6%) of pale yellow needles, mp 187° (decomp.).

The Reaction of Ib with an Equimolar Amount of Diazomethane——A solution of Ib (3.8 g) in dry ether (20 ml) was allowed to react with a solution of diazomethane (0.97 g) in ether (50 ml) as described above. Formed needles were recrystallized from acetone–ethanol to give 1.5 g of pale yellow fine needles, mp 182—183°C (decomp.). The product was confirmed to be the mixture of Vb and 3-chloroacetyl-1-cinnamoyl-4-phenyl-2-pyrazoline (VIb) by infrared spectrum. IR (Nujol, cm^{-1}): 2100 (diazo), 1700 (ketone), 1660 (amide).

The Reaction of IVb with Ib——A solution of Ib (0.8 g) in dry ether (5 ml) was added to a solution of IVb (1.0 g) in a mixture of ether (20 ml) and acetone (10 ml) at room temperature and allowed to stand overnight. Evolving the nitrogen gas, needles were gradually crystallized out, which were filtered and dried; mp 182—183°C (decomp.), 1.3 g. This material was identified to be the mixture of Vb and VIb by infrared spectrum.

3-Chloroacetyl-1-cinnamoyl-4-phenyl-2-pyrazoline (VIb)——The mixture of Vb and VIb (1.0 g), which was prepared from Ib with an equimolar amount of diazomethane or Ib with IVb, was suspended in acetone (40 ml) containing concentrated HCl (10 ml) and warmed for 1 hr at 60°. Evolving the nitrogen gas, crystals were disappeared gradually. After standing overnight, formed crystals were filtered and recrystallized from acetone–ethanol to give 0.8 g of white fine needles, mp 188—189°. *Anal.* Calcd. for $C_{20}H_{17}O_2N_2Cl$: C, 68.08; H, 4.86; N, 7.94; Cl, 10.05. Found: C, 68.17; H, 5.08; N, 8.02; Cl, 10.10. IR (Nujol, cm^{-1}): 1700 (ketone), 1660 (amide); NMR[6] (δ(ppm), in deuterated acetone): 3.9—4.8 (3H, multiplet, pyrazoline ring protons), 4.99 (2H, singlet, $-COC\underline{H}_2Cl$), 7.3—7.9 (10H, multiplet, phenyl protons), 7.80 (2H, singlet, olefinic protons). UV ($\lambda_{max}^{C_2H_4Cl_2}$ mμ, (log ε)): 280 (4.24), 328 (4.45).

3-Diazoacetyl-1-*p*-nitrocinnamoyl-4-*p*-nitrophenyl-2-pyrazoline (Vc)——A solution of diazomethane (0.67 g) in ether (22 ml) was added dropwise into a solution of *p*-nitrocinnamoyl chloride (Ic, 1.7 g) in a mixture of dry benzene (50 ml) and dry ether (50 ml) at −10°. After the stirring was continued for additional 1 hr at same temperature, the mixture was allowed to stand overnight. Formed crystals were filtered and recrystallized from dimethylformamide–ethanol–water to give 0.3 g (17.2%) of yellow crystals, mp 189—190° (decomp.). *Anal.* Calcd. for $C_{20}H_{14}O_6N_6$: C, 55.30; H, 3.25; N, 19.35. Found: C, 55.35; H, 3.38; N, 18.99. IR (Nujol, cm^{-1}): 2100 (diazo), 1655 (amide), 1615 (diazoacetyl, conjugated with C=N bond). UV ($\lambda_{max}^{C_2H_4Cl_2}$ mμ, (log ε)): 310 (4.45), 336 (4.36).

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