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Studies on Ketene and Its Derivatives. LXIX.[1] Reaction of Diketene with Hydrazobenzenes

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Reaction of hydrazobenzene (Ia) with diketene in the presence of triethylamine gave 1,2-diphenyl-5-methyl-3-pyrazolone (IIIa) in 80% yield. Similarly, twelve kinds of symmetrical substituted hydrazobenzene derivatives, such as dimethylhydrazobenzenes (Ib,c,d), dichlorohydrazobenzenes (Ie,f,g), dimethoxyhydrazobenzenes (Ih,i,j), and diethoxyhydrazobenzenes (Ik,l,m) afforded the corresponding 1,2-diaryl-5-methyl-3-pyrazolone derivatives (IIIb—m).

It is well known that diketene reacts with phenylhydrazines to give pyrazolone derivatives.[3] However, the reaction of diketene with hydrazobenzene derivatives has not ever been reported yet. The present paper reports the reaction of diketene with hydrazobenzene derivatives to give 1,2-diaryl-5-methyl-3-pyrazolone derivatives in good yields.

When hydrazobenzene (Ia) was allowed to react with diketene in the presence of triethylamine, 1,2-diphenyl-5-methyl-3-pyrazolone (IIIa) was obtained as colorless needles in about 80% yield. The product was unequivocally identified by the comparison of the infrared (IR) spectrum, and mixed melting point with an authentic sample prepared from Ia and ethyl acetoacetate according to the method reported in the literature.[4]

Similarly, twelve kinds of symmetrical substituted hydrazobenzene derivatives (Ib-m), prepared from the corresponding substituted nitrobenzenes, were allowed to react with diketene to give 1,2-diaryl-5-methyl-3-pyrazolone derivatives (IIIb-m) in reasonable yields. In case of 2,2′-dichloro-, 2,2′-dimethoxy-, 2,2′-diethoxy-, and 3,3′-dichlorohydrazobenzene, a considerable amount of N-acetoacetyl hydrazobenzene derivatives (II) were obtained as intermediates together with III.

Acetoacetyl derivatives (II) were fairly unstable and cyclized to some extent to pyrazolone derivatives even by recrystallization or chromatography over silica gel. The IR spectrum of crude II showed absorptions at about 3360 cm^{-1} (NH), 1720 cm^{-1} (keto carbonyl), and 1685 cm^{-1} (amide). The nuclear magnetic resonance (NMR) spectrum of II showed three characteristic signals at about 2.3 ppm (singlet, 3H), 3.8 ppm (singlet, 2H) and 7.50—7.65 (1H), which were assigned to acetyl methyl, active methylene and NH protons, respectively. These data suggested the intermediate II being N-acetoacetate.

When refluxing of the reaction mixture was continued for additional hours, the N-acetoacetate was completely cyclized to the pyrazolone derivative (III).

IR spectrum of III showed its carbonyl stretching band at about 1660 cm^{-1}, and NMR spectrum showed the characteristic signals at about 2.0 ppm (singlet, 3H), and about 5.5 ppm (singlet, 1H), assignable to methyl protons and olefinic proton of 4-position of pyrazolone ring, respectively.

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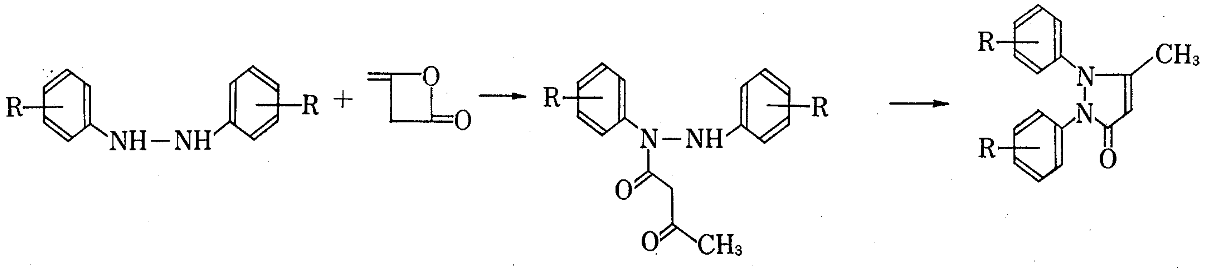
In the present reactions, the yields of 3-pyrazolone derivatives were improved to several percents by refluxing the mixture under nitrogen atomosphere, because the oxidation of hydrazobenzenes to azo compounds was suppressed.



I II III

a : R=H
b : R=*o*-CH_3
c : R=*m*-CH_3
d : R=*p*-CH_3
e : R=*o*-Cl
f : R=*m*-Cl
g : R=*p*-Cl
h : R=*o*-OCH_3
i : R=*m*-OCH_3
j : R=*p*-OCH_3
k : R=*o*-OC_2H_5
l : R=*m*-OC_2H_5
m : R=*p*-OC_2H_5

Chart 1

Experimental

All melting points were determined by a calibrated Yanagimoto melting point apparatus. IR spectra were measured by a Hitachi Model 215 spectrometer in a $CHCl_3$ solution. The NMR spectra were taken at 60 MHz, with TMS as an internal standard, by a Varian A-60 spectrometer in a deuteriochloroform solution, and the chemical shifts are given in part per million. Abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad. The mass spectra were measured by a Hitachi Double Focusing Mass Spectrometer Model RMU-7L.

Materials——Hydrazobenzenes were prepared by the reduction of the corresponding nitrobenzenes with zinc and alkali or by Drynap reduction in methanol.[5] Materials were purified by recrystallization from ethanol.

1,2-Diphenyl-5-methyl-3-pyrazolone (IIIa)——A solution of 3.68 g of hydrazobenzene (Ia), 2 g of diketene and three drops of triethylamine in 50 ml of $CHCl_3$ was refluxed for 4 hr on a steam bath. After removal of the solvent and excess diketene by vacuum distillation, the resulting oily residue was dissolved in 150 ml of benzene. The benzene solution was extracted with 10% HCl. The HCl layer was made alkaline with 10% NaOH, and extracted with benzene. The benzene solution was washed with H_2O, dried over Na_2SO_4, and filtered. The filtrate was condensed to give a crystalline solid, which was purified by recrystallization from AcOEt to colorless needles of mp 131° (lit. mp 120°,[6] 122°,[4] 130°[7]). Yield, 4.1 g (80%). *Anal.* Calcd. for $C_{16}H_{14}ON_2$ (IIIa): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.95; H, 5.67; N, 11.46. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1665. NMR: 2.09 (3H, s, 5-CH_3), 5.56 (1H, s, 4-H), 7.30 (10H, m, arom. H). Mass Spectrum *m/e*: 250 (M^+).

1,2-Di(*o*-tolyl)-5-methyl-3-pyrazolone (IIIb)——A solution of 1.8 g of 2,2′-dimethylhydrazobenzene (Ib), 1 g of diketene in 50 ml of benzene was refluxed in the presence of a catalytic amount of triethylamine. After 4 hr, the reaction mixture was treated similarly as described above to give colorless prisms of mp 141° (benzene–hexane). Yield, 1.54 g (68%). *Anal.* Calcd. for $C_{18}H_{18}ON_2$ (IIIb): C, 77.67; H, 6.52; N, 10.07. Found: C, 77.55; H, 6.28; N, 10.16. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1654. NMR: 1.96 (3H, s, 5-CH_3), 2.27 (6H, s, tolyl-CH_3), 5.57 (1H, s, 4-H), 6.95—7.18 (8H, m, arom. H). Mass Spectrum *m/e*: 278 (M^+).

1,2-Di(*m*-tolyl)-5-methyl-3-pyrazolone (IIIc)——Employing the similar fashion given for IIIa, 3,3′-dimethylhydrazobenzene (Ic) (4.3 g) was allowed to react with diketene (1.9 g) in benzene (50 ml) in the presence of triethylamine, giving colorless prisms (benzene) of mp 144° (lit.[4] mp 143°). Yield, 3.85 g (68%). *Anal.* Calcd. for $C_{18}H_{18}ON_2$ (IIIc): C, 77.67; H, 6.52; N, 10.07. Found: C, 77.48; H, 6.59; N, 10.02. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660. NMR: 2.03 (3H, s, 5-CH_3), 2.26 (6H, s, tolyl-CH_3), 5.50 (1H, s, 4-H), 6.87—7.30 (8H, m, arom. H). Mass Spectrum *m/e*: 278 (M^+).

1,2-Di(*p*-tolyl)-5-methyl-3-pyrazolone (IIId)——Following the similar procedure given for IIIa, 4,4′-dimethylhydrazobenzene (Id) (4.1 g) was allowed to react with diketene (2 g) to give colorless needles (AcOEt)

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[6] A. Müller, *Chem. Ber.*, **19**, 1771 (1866).
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of mp 143°. Yield, 4.7 g (89%). *Anal.* Calcd. for $C_{18}H_{18}ON_2$ (IIId): C, 77.67; H, 6.52; N, 10.07. Found: C, 77.73; H, 6.45; N, 10.04. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1663. NMR: 2.08 (3H, s, 5-CH_3), 2.26 (3H, s, tolyl-CH_3), 2.33 (3H, s, tolyl-CH_3), 5.57 (1H, s, 4-H), 7.20 (8H, m, arom. H). Mass Spectrum *m/e*: 278 (M^+).

1,2-Di(*o*-chlorophenyl)-5-methyl-3-pyrazolone (IIIe) and N-Acetoacetyl-2,2′-dichlorohydrazobenzene (IIe)——A solution of 4.9 g of 2,2′-dichlorohydrazobenzene (Ie) and 1.5 g of diketene in 50 ml of $CHCl_3$ was refluxed for 3 hr in the presence of a catalytic amount of triethylamine. The reaction mixture was condensed *in vacuo*, and the residue was dissolved in 150 ml of benzene. The benzene solution was extracted with 5% HCl. The HCl solution was made alkaline with 10% NaOH, and extracted with benzene. The benzene solution was condensed *in vacuo* to give crude crystals. Recrystallization from AcOEt gave colorless prisms of mp 159°. Yield, 2.1 g (34%). *Anal.* Calcd. for $C_{16}H_{12}ON_2Cl_2$ (IIIe): C, 60.18; H, 3.76; N, 8.78. Found: C, 60.21; H, 3.69; N, 8.99. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1655. NMR: 2.03 (3H, s, 5-CH_3), 5.55 (1H, s, 4-H), 7.10—7.40 (8H, m, arom. H). Mass Spectrum *m/e*: 318 (M^+).

After washing with benzene, the alkaline solution was neutralized with 5% HCl and extracted with benzene. The benzene solution was washed with H_2O, dried over Na_2SO_4 and condensed *in vacuo* to give a crystalline residue, which was crystallized from benzene–hexane to colorless prisms of mp 146—149° (IIe). Yield, 1.28 g (19%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1720 (acetyl), 1680 (amide). NMR: 2.23 (3H, s, CH_3CO), 3.74 (2H, s, CH_2), 7.62 (1H, b, NH), 7.10—7.58 (8H, m, arom. H). On further purification by recrystallization, IIe cyclized to give IIIe.

1,2-Di(*m*-chlorophenyl)-5-methyl-3-pyrazolone (IIIf) and N-Acetoacetyl-3,3′-dichlorohydrazobenzene (IIf)——Following the procedure given for IIe, 3,3′-dichlorohydrazobenzene (If) (5 g) was allowed to react with diketene (1.7 g) for 3 hr. From the 10% NaOH soluble fraction N-acetoacetyl-3,3′-dichlorohydrazobenzene (IIf) was obtained, colorless prisms of mp 91° (benzene–hexane). Yield, 3.82 g (56%). *Anal.* Calcd. for $C_{16}H_{14}O_2N_2Cl_2$ (IIf): C, 56.99; H, 4.19; N, 8.38. Found: C, 57.22; H, 4.42; N, 8.13. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1720, 1682. NMR: 2.23 (3H, s, CH_3CO), 3.74 (2H, s, CH_2), 6.80—7.40 (8H, m, arom. H), 7.65 (1H, b, NH). Mass Spectrum *m/e*: 334 (M^+).

When the above reaction mixture was refluxed for 6 hr, IIf could not be isolated. Instead, the similar treatment given for IIIa afforded the cyclic product IIIf as colorless needles of mp 128° (AcOEt). Yield, 4.8 g (75%). *Anal.* Calcd. for $C_{16}H_{12}ON_2Cl_2$ (IIIf): C, 60.18; H, 3.76; N, 8.78. Found: C, 60.10; H, 3.57; N, 8.79. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1660. NMR: 2.07 (3H, s, 5-CH_3), 5.55 (1H, s, 4-H), 7.15—7.50 (8H, m, arom. H). Mass Spectrum *m/e*: 318 (M^+).

1,2-Di(*p*-chlorophenyl)-5-methyl-3-pyrazolone (IIIg)——Following the procedure given for IIIa, 4,4′-dichlorohydrazobenzene (Ig) (4.8 g) was allowed to react with diketene (2 g) to give colorless needles of mp 142° (benzene). Yield, 4.7 g (78%). *Anal.* Calcd. for $C_{16}H_{12}ON_2Cl_2$ (IIIg): C, 60.18; H, 3.76; N, 8.78. Found: C, 60.24; H, 3.60; N, 8.77. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1662. NMR: 2.11 (3H, s, 5-CH_3), 5.60 (1H, s, 4-H), 7.35 (8H, m, arom. H). Mass Spectrum *m/e*: 318 (M^+).

1,2-Di(*o*-methoxyphenyl)-5-methyl-3-pyrazolone (IIIh) and N-Acetoacetyl-2,2′-dimethoxyhydrazobenzene (IIh)——Following the procedure given for IIe, 2,2′-dimethoxyhydrazobenzene (Ih) (4.2 g) was allowed to react with diketene (1.9 g) to give the N-acetoacetate (IIh) as colorless prisms of mp 148—151°. Yield, 3.4 g (60%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1720, 1680. NMR: 2.35 (3H, s, $COCH_3$), 3.24 (6H, s, OCH_3), 3.92 (2H, s, CH_2), 6.70—7.25 (8H, m, arom. H).

When the reaction was carried out according to the procedure given for IIIf, IIIh was obtained in 70% yield (3.7 g) as colorless needles of mp 127° (AcOEt). *Anal.* Calcd. for $C_{18}H_{18}O_3N_2$ (IIIh): C, 69.66; H, 5.85; N, 9.03. Found: C, 69.76; H, 5.89; N, 9.30. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1640. NMR: 2.01 (3H, s, 5-CH_3), 3.82 (6H, s, OCH_3), 5.42 (1H, s, 4-H), 6.80—7.30 (8H, m, arom. H). Mass Spectrum *m/e*: 310 (M^+).

1,2-Di(*m*-methoxyphenyl)-5-methyl-3-pyrazolone (IIIi)——Following the procedure given for IIIa, 3,3′-dimethoxyhydrazobenzene (Ii) (4.2 g) was allowed to react with diketene (1.9 g) to give colorless prisms of mp 134° (AcOEt). Yield, 5.5 g (87%). *Anal.* Calcd. for $C_{18}H_{18}O_3N_2$ (IIIi): C, 69.66; H, 5.85; N, 9.03. Found: C, 69.69; H, 5.67; N, 8.91. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1660. NMR: 2.05 (3H, s, 5-CH_3), 3.69 (6H, s, OCH_3), 5.50 (1H, s, 4-H), 6.60—7.20 (8H, m, arom. H). Mass Spectrum *m/e*: 310 (M^+).

1,2-Di(*p*-methoxyphenyl)-5-methyl-3-pyrazolone (IIIj)——Employing the same fashion given for IIIa, 4,4′-dimethoxyhydrazobenzene (Ij) (4.8 g) was allowed to react with diketene (2 g) to afford colorless needles of mp 115° (AcOEt). Yield, 5.3 g (86%). *Anal.* Calcd. for $C_{18}H_{18}O_3N_2$ (IIIj): C, 69.66; H, 5.85; N, 9.03. Found: C, 69.72; H, 5.90; N, 9.31. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1650. NMR: 2.02 (3H, s, 5-CH_3), 3.77 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 5.51 (1H, s, 4-H), 6.70—7.30 (8H, m, arom. H). Mass Spectrum *m/e*: 310 (M^+).

1,2-Di(*o*-ethoxyphenyl)-5-methyl-3-pyrazolone (IIIk) and N-Acetoacetyl-2,2′-diethoxyhydrazobenzene (IIk)——Following the procedure given for IIe and IIIe, 2,2′-diethoxyhydrazobenzene (Ik) (2.7 g) was allowed to react with diketene (1 g) in $CHCl_3$ (40 ml) for 3 hr to give IIIk as colorless needles of mp 89° (AcOEt). Yield, 1 g (31%). *Anal.* Calcd. for $C_{20}H_{22}O_3N_2$ (IIIk): C, 70.98; H, 6.55; N, 8.28. Found: C, 70.78; H, 6.45; N, 8.12. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1634. NMR: 1.35 (6H, t, $J=7$ Hz, $C\underline{H}_3\cdot CH_2O$), 2.01 (3H, s, 5-$CH_3$), 3.95 (2H, q, $J=7$ Hz, $CH_3\cdot C\underline{H}_2O$), 3.96 (2H, q, $J=7$ Hz, $CH_3\cdot C\underline{H}_2O$), 5.49 (1H, s, 4-H), 6.80—7.30 (8H, m, arom. H). Mass Spectrum *m/e*: 338 (M^+).

From the NaOH soluble fraction, IIk was obtained in 24% yield (0.87 g) as colorless prisms of mp 98—100° (benzene–hexane). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1720, 1685. NMR: 1.4 (6H, t, $J=8$ Hz, ethoxy CH_3), 2.28 (3H, s, $COCH_3$), 3.79 (2H, s, $-CH_2-$), 4.02 (4H, q, $J=8$ Hz, ethoxy CH_2), 7.50 (1H, s, NH), 6.70—7.30 (8H, m, arom. H). Mass Spectrum *m/e*: 356 (M^+).

When the reaction was carried out under the same procedure given for IIIf, IIIk was obtained in 82% yield (2.75 g).

1,2-Di(*m*-ethoxyphenyl)-5-methyl-3-pyrazolone (IIIl)——Following the similar procedure given for IIIa, 3,3′-diethoxyhydrazobenzene (Il) (5 g) was allowed to react with diketene (2 g) to give colorless prisms of mp 134.5° (AcOEt). Yield, 2.98 g (50%). *Anal.* Calcd. for $C_{20}H_{22}O_3N_2$ (IIIl): C, 70.98; H, 6.55; N, 8.28. Found: C, 71.12; H, 6.58; N, 8.17. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1648. NMR: 1.31 (6H, t, $J=6$ Hz, ethoxy CH_3), 2.04 (3H, s, 5-CH_3), 3.88 (2H, q, $J=6$ Hz, ethoxy CH_2), 3.90 (2H, q, $J=6$ Hz, ethoxy CH_2), 5.50 (1H, s, 4-H), 6.60—7.25 (8H, m, arom. H). Mass Spectrum *m/e*: 338 (M^+).

1,2-Di(*p*-ethoxyphenyl)-5-methyl-3-pyrazolone (IIIm)——Following the procedure given for IIIa, 4,4′-diethoxyhydrazobenzene (Im) (5.4 g) was allowed to react with diketene (1.9 g) to give colorless needles of mp 124° (AcOEt). Yield, 5.7 g (85%). *Anal.* Calcd. for $C_{20}H_{22}O_3N_2$ (IIIm): C, 70.98; H, 6.55; N, 8.28. Found: C, 71.13; H, 6.62; N, 8.38. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1670. NMR: 1.37 (3H, t, $J=6$Hz, ethoxy CH_3), 1.40 (3H, t, $J=6$Hz, ethoxy CH_3), 2.05 (3H, s, 5-CH_3), 3.96 (4H, q, $J=6$ Hz, ethoxy CH_2), 6.70—7.35 (8H, m, arom. H). Mass Spectrum *m/e*: 338 (M^+).

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