**Studies on Heterocyclic Compounds. XIV.¹⁾ 1,3-Dipolar Cycloaddition
Reaction of Dimethyl Acetylenedicarboxylate with Phenylhydrazones²⁾**

HARUO OGURA, KAZUO KUBO, YUMIKO WATANABE, and TSUNEO ITOH

School of Pharmaceutical Sciences, Kitasato University³⁾

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1,3-Dipolar cycloaddition of aldehyde hydrazones with dimethyl acetylenedicarboxylate without solvent gives rise to dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate, and in some cases trimethyl 1-phenylpyrazole-3,4,5-tricarboxylate as a by-product. In case of *p*-chloro- and *p*-methoxy-benzaldehyde phenylhydrazone, dimethyl 1-phenyl-3-(*p*-substitutedphenyl)pyrazoline-4,5-dicarboxylate is formed. In dimethylformamide as a solvent, the reaction gives the same product in a similar yield. Although, when ethanol is used as a solvent, a small amount of the product is formed.

Huisgen, *et al.*^{4,5)} reported the formation of pyrazole derivatives by the 1,3-dipolar cycloaddition of nitrilimide and dimethyl acetylenedicarboxylate. A photochemical formation of pyrazole derivatives from the 1,3-dipolar cycloaddition of sydnone or tetrazole with dimethyl acetylenedicarboxylate was reported by Angadiyavar and George.⁶⁾ Brown⁷⁾ also reported that reaction of phosphorus ylides with dimethyl acetylenedicarboxylate yield a pyrazole derivatives. Other reports^{8,9)} also suggested the pyrazole ring formation from hydrazone derivatives.

In this report we describe the direct reaction of benzaldehyde phenylhydrazone and its derivatives (Ia—l) with dimethyl acetylenedicarboxylate to form pyrazole derivatives (IIa—c, e—l; III).

Fusion of Ia with 1.5 equivalent of dimethyl acetylenedicarboxylate under nitrogen gave dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate (IIa; 8%) and trimethyl 1-phenylpyrazole-3,4,5-tricarboxylate (III; 35%). This compound showed mp 88°, $\nu_{C=O}$ 1730 cm⁻¹ (ester), λ_{max}^{EtOH} 250 nm (ϵ 5400); NMR: δ 3.80 (ester), 3.98 (ester), 7.46 (aromatic protons), and M⁺ 318.¹⁰⁾ These values are different from those reported for trimethyl 1-phenylpyrazole-3,4,5-tricarboxylate; mp 194°, $\nu_{C=O}$ 1735, 1705, and 1645 cm⁻¹, λ_{max}^{EtOH} 294 nm (ϵ 16,700). III was obtained by the use of phenylhydrazone (R³=H) in rather a small yield. In the case of Ib, Ic, and Id, yield of III was 0.2%, 10%, and 10%, respectively. This reaction was attempted in ethanol and the yield of the pyrazole (IIa) was reduced to 4%. IIa had already been obtained from diphenylnitrilimine with dimethyl acetylenedicarboxylate by thermal⁴⁾ or by photochemical⁶⁾ 1,3-dipolar cycloaddition reaction of 2,5-diphenyltetrazole with dimethyl acetylenedicarboxylate.

- 1) Part XIII: H. Ogura, M. Kawano, and T. Itoh, *Chem. Pharm. Bull.* (Tokyo), **21**, 2019 (1973).
- 2) In preparation of this manuscript, M.K. Saxena, M.N. Gudi, and M.V. George [*Tetrahedron*, **29**, 101 (1973)] have published the similar report.
- 3) Location: *Shirokane, Minato-ku, Tokyo, 108, Japan.*
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- 10) Saxena, *et al.*²⁾ reported that the compound III obtained in a 5% yield, mp 89°, ν_{CO} 1730 cm⁻¹, and λ_{max}^{MeOH} 250 nm (ϵ 6800).

In the case of *p*-nitrobenzaldehyde phenylhydrazone, methyl *cis*-*p*-nitrocinnamate¹¹⁾ (IV) was formed in a small amount with a moderate yield of the main product (IIb; 32%). This reaction was attempted in dimethylformamide and IIb was obtained in 16% yield without any by-products. In the case of *p*-chloro- and *p*-methoxybenzaldehyde phenylhydrazone, the desired pyrazole (IIc, IId) was obtained in a poor yield (6%, 0%). Instead of pyrazole, there was obtained dimethyl 1-phenyl-3-(*p*-substituted phenyl)pyrazoline-*trans*-4,5-dicarboxylate (Vc, d). The configuration at the 4- and 5-positions was confirmed from their *J* value (5 Hz) in nuclear magnetic resonance (NMR) spectra.¹²⁾

In the case of *p*-nitrophenylhydrazone (Ie-1), the pyrazole derivatives (IIe-1) were obtained in a moderate yield without any by-products (III, IV, and V) (Table).

These reaction mechanisms may be represented by the sequence shown in Chart 2. The first step of the reaction may be represented by two ways a and b. The route a is the oxidation of hydrazone by dimethyl acetylenedicarboxylate to form 1,3-dipole (A).^{13,14)} This was supported by the fact that pyrazoline (Vc, d) was remained in the reaction mixture with excess dimethyl acetylenedicarboxylate. The second step of the cyclization of A went with dimethyl acetylenedicarboxylate to form the pyrazole ring (II). When R¹ group is an electron-donating substituent (OCH₃, Cl), the proton elimination of the hydrazone was difficult and a pyrazoline (Vc, d) was formed. In this case, cyclization occurred by the intermolecular electron transfer between I and dimethyl acetylenedicarboxylate to form the pyrazoline (Vc, d) through the route b *via* an intermediate B. A retro Diels-Alder reaction of the intermediate B and

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Chart 2

dimethyl acetylenedicarboxylate lead through an intermediate C to trimethyl 1-phenylpyrazole-3,4,5-tricarboxylate (III) and methyl cinnamate (IV).

Experimental

Temperatures are uncorrected. NMR spectra were measured in CDCl_3 with a Varian T-60 spectrometer with Me_4Si as an internal standard. Mass spectra were measured with JEOL-OIS spectrometer by a direct inlet system at 75 eV.

Reaction of Benzaldehyde Phenylhydrazone (Ia) with Dimethyl Acetylenedicarboxylate—a) Without Solvent: A mixture of Ia (1.0 g) and dimethyl acetylenedicarboxylate (1.06 g) was heated at 120–140° for 3 hr under nitrogen atmosphere. The red-brown colored mass was dissolved in benzene and chromatographed on silica gel with a mixture (4:1) of petr. ether and benzene. From the first eluate, there was obtained 0.14 g (8%) of dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate (IIa) as colorless needles, mp 154.5–155° (EtOH). Reported mp 153–154°, 156°. ⁶⁾ Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{O}_4\text{N}_2$: C, 67.85; H, 4.80; N, 8.33. Found: C, 67.92; H, 4.79; N, 8.26. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1730 (CO), 1590 (phenyl). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 238 (8500). NMR δ (ppm): 3.82 (3H, singlet, COOCH_3), 3.85 (3H, singlet, COOCH_3), 7.20–7.97 (10H, broad, aromatic protons). Mass Spectrum m/e : 336 (M^+).

Subsequent elution of the column with petr. ether and benzene (7:3) gave 0.54 g (35%) of trimethyl 1-phenylpyrazole-3,4,5-tricarboxylate (III) as colorless fine needles, mp 88°. Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{O}_6\text{N}_2$: C, 56.60; H, 4.43; N, 8.80. Found: C, 56.62; H, 4.40; N, 8.67. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1730 (CO), 1595 (phenyl).

TABLE I. Dimethyl 1-(3,4-Substitutedphenyl)-3-(4-nitrophenyl)-pyrazole-4,5-dicarboxylate (IIe—1)

Compound No.	R ¹	R ²	R ³	mp °C	Yield (%) (recovery of the starting material)	IR CO	$\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹ phenyl	UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ)
IIe	H	H	NO ₂	115	6(43) (colorless fine needles)	1735 1715	1605 1595	224(25400) 306(15500)
IIf	NO ₂	H	NO ₂	207—208	16(47) (yellow fine needles)	1730	1590	301(16600)
IIg	Cl	H	NO ₂	146	14(36) (colorless fine needles)	1730 1720	1595	226(24400) 246(2440) 306(16100)
IIh	CH ₃	H	NO ₂	125—127	12(17) (colorless fine needles)	1725	1595	243(10500) 312(6400)
IIi	CH(CH ₃) ₂	H	NO ₂	134—135	12(35) (pale yellow prisms)	1725	1600	244(14200) 312(8200)
IIj	OCH ₃	H	NO ₂	162	7(30) (colorless fine needles)	1725 1720	1600	258(11100) 323(5000)
IIk	OC ₂ H ₅	H	NO ₂	135—136	4(29) (pale yellow fine needles)	1735 1720	1590	258(11500) 323(5100)
III	OCH ₃	OCH ₃	NO ₂	155	12(15) (pale yellow needles)	1725	1605 1595	264(9100) 317(4000)

Compound No.	Formula Mass Spectrum m/e (M^+)	Analysis (%)						NMR δ ppm ($CDCl_3$)
		Calcd.			Found			
		C	H	N	C	H	N	
IIe	C ₁₉ H ₁₅ O ₆ N ₃ (381)	59.84	3.96	11.02	59.72	3.97	11.18	3.85 (3H, s, COOCH ₃), 3.95 (3H, s, COOCH ₃), 7.30—8.50 (9H, br, aromatic protons)
IIf	C ₁₉ H ₁₄ O ₈ N ₄ (426)	53.53	3.31	13.14	53.42	3.20	12.96	3.90 (3H, s, COOCH ₃), 3.95 (3H, s, COOCH ₃), 7.70—8.60 (8H, m, aromatic protons)
IIg	C ₁₉ H ₁₄ O ₆ N ₃ Cl (415)	54.89	3.39	10.11	54.90	3.35	10.09	3.90 (3H, s, COOCH ₃), 3.97 (3H, s, COOCH ₃), 7.31—8.58 (8H, m, aromatic protons)
IIh	C ₂₀ H ₁₇ O ₆ N ₃ (395)	60.76	4.33	10.63	60.99	4.35	10.79	2.40 (3H, s, CH ₃), 3.83, 3.92 (6H, s, (COOCH ₃) ₂), 7.25 (2H, d, $J=8$ Hz), 7.60 (2H, d, $J=8$ Hz), 7.70 (2H, d, $J=9$ Hz), 8.33 (2H, d, $J=9$ Hz)
IIi	C ₂₂ H ₂₁ O ₆ N ₃ (423)	62.41	5.00	9.92	62.35	4.97	9.99	1.23 (3H, s, CH ₃), 1.36 (3H, s, CH ₃), 2.98 (1H, q, —CH—), 3.85 (3H, s, COOCH ₃), 3.92 (3H, s, COOCH ₃), 7.30 (2H, d, $J=7$ Hz), 7.70 (2H, d, $J=7$ Hz), 7.72, 8.35 (4H, d-d, $J=9$ Hz)
IIj	C ₂₀ H ₁₇ O ₇ N ₃ (411)	58.40	4.17	10.21	58.15	4.23	10.32	3.90 (9H, s, OCH ₃), (COOCH ₃) ₂ , 6.97 (2H, d, $J=9$ Hz), 7.64 (2H, d, $J=2$ Hz), 7.80 (2H, d, $J=2$ Hz), 8.37 (2H, d, $J=9$ Hz)
IIk	C ₂₁ H ₁₉ O ₇ N ₂ (425)	59.29	4.50	9.88	59.00	4.41	10.01	1.45 (3H, t, OCH ₂ CH ₃), 3.88 (3H, s, COOCH ₃), 3.92 (3H, s, COOCH ₃), 3.98 (2H, q, OCH ₂ CH ₃), 6.97 (2H, d, $J=9$ Hz), 7.65 (2H, d, $J=2$ Hz), 7.80 (2H, d, $J=2$ Hz), 8.36 (2H, d, $J=9$ Hz)
III	C ₂₁ H ₁₉ O ₈ N ₃ (441)	57.14	4.34	9.52	56.86	4.34	9.65	3.91 (12H, s, (OCH ₃) ₂ , (COOCH ₃) ₂), 6.90 (1H, d, $J=9$ Hz), 7.30 (2H), 7.70 (2H, d, $J=9$ Hz), 8.32 (2H, d, $J=9$ Hz)

UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 250 (5400). NMR δ (ppm): 3.80 (3H, singlet, COOCH₃), 3.98 (6H, singlet, (COOCH₃)₂), 7.46 (5H, singlet, aromatic protons). Mass Spectrum m/e : 318 (M⁺).

b) In Ethanol: A mixture of Ia (5.0 g) and dimethyl acetylenedicarboxylate (5.5 g) in ethanol (30 ml) was heated under reflux for 4 hr. After evaporation of the solvent, the residue was chromatographed on silica gel to obtain 0.32 g (4%) of IIa, mp and mixed mp 155°.

Reaction of *p*-Nitrobenzaldehyde Phenylhydrazone (Ib) with Dimethyl Acetylenedicarboxylate—a) Without Solvent: A mixture of Ib (6.0 g) and dimethyl acetylenedicarboxylate (7.0 g) was heated at 140–150° for 3 hr under nitrogen. Resulted brown mass was chromatographed on silica gel with petr. ether and benzene. From the first eluate (9:1) 0.14 g of methyl *cis*-*p*-nitrocinnamate (IV) was obtained. mp 91°. Anal. Calcd. for C₁₀H₉O₄N: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.76; H, 4.33; N, 6.64. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1723 (CO), 1640 (C=C), 1600 (phenyl). NMR δ (ppm): 3.72 (3H, singlet, COOCH₃), 6.12 (1H, doublet, $J=12.5$ Hz, $=\text{CHCOOCH}_3$), 7.05 (1H, doublet, $J=12.5$ Hz, C_6H_5), 7.67, 8.24 (4H, d-doublet, $J=9$ Hz, aromatic protons). Mass Spectrum m/e : 207 (M⁺).

From the second eluate (4:1), there was obtained 3.0 g (32%) of dimethyl 1-phenyl-3-(4-nitrophenyl)pyrazole-4,5-dicarboxylate (IIb) as colorless fine needles, mp 124°. Anal. Calcd. for C₁₉H₁₅O₆N₃: C, 59.84; H, 3.96; N, 11.02. Found: C, 60.38; H, 3.98; N, 10.99. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1730 (CO), 1600 (phenyl). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 218 (14500), 294 (10100). NMR δ (ppm): 3.87 (3H, singlet, COOCH₃), 3.90 (3H, singlet, COOCH₃), 7.55 (5H, singlet, aromatic protons), 8.00 (2H, doublet, $J=9$ Hz), 8.34 (2H, doublet, $J=9$ Hz). Mass Spectrum m/e : 381 (M⁺).

Further elution of the column with a mixture (7:3) of petr. ether and benzene yielded 0.03 g (0.2%) of III, mp and mixed mp 88°.

b) In Dimethylformamide: A mixture of Ib (1.2 g) and dimethyl acetylenedicarboxylate (1.06 g) in dimethylformamide (10 ml) was heated under reflux for 3 hr. After evaporation of the solvent, the residue was chromatographed on silica gel to obtain 0.3 g (16%) of IIb, mp and mixed mp 124°.

Reaction of *p*-Chlorobenzaldehyde Phenylhydrazone (Ic) with Dimethyl Acetylenedicarboxylate—A mixture of Ic (2.3 g) and dimethyl acetylenedicarboxylate (2.13 g) was heated at 150–160° for 3 hr under nitrogen. Resulted brown mass was chromatographed on silica gel with a mixture (4:1) of petr. ether and benzene. From the first eluate, there was obtained 0.22 g (6%) of dimethyl 1-phenyl-3-(4-chlorophenyl)pyrazole-4,5-dicarboxylate (IIc) as colorless fine needles, mp 73°. Anal. Calcd. for C₁₉H₁₅O₄N₂Cl: C, 61.55; H, 4.08; N, 7.56. Found: C, 61.58; H, 4.13; N, 7.40. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1730, 1710 (CO), 1595 (phenyl). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 247 (12600). NMR δ (ppm): 3.75 (3H, singlet, COOCH₃), 3.80 (3H, singlet, COOCH₃), 7.35 (2H, doublet, $J=9$ Hz), 7.50 (5H, singlet, aromatic protons), 7.75 (2H, doublet, $J=9$ Hz). Mass Spectrum m/e : 370 (M⁺).

After repeated recrystallization and mechanical separation of IIc, there was obtained 0.39 g (11%) of dimethyl 1-phenyl-3-(4-chlorophenyl)pyrazoline-*trans*-4,5-dicarboxylate (Vc) as yellow prisms, mp 186°. Anal. Calcd. for C₁₉H₁₇O₄N₂Cl: C, 61.21; H, 4.60; N, 7.51. Found: C, 61.21; H, 4.65; N, 7.35. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1735 (CO), 1600 (phenyl). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 246 (27400), 297 (11000), 363 (25300). NMR δ (ppm): 3.70 (3H, singlet, COOCH₃), 3.75 (3H, singlet, COOCH₃), 4.50 (1H, doublet, $J=5$ Hz, 4-H), 5.20 (1H, doublet, $J=5$ Hz, 5-H), 6.70–7.90 (9H, broad, aromatic protons).

From the further eluate (7:3), 0.3 g (10%) of III was obtained, mp and mixed mp 88°.

Reaction of *p*-Methoxybenzaldehyde Phenylhydrazone (Id) with Dimethyl Acetylenedicarboxylate—A mixture of Id (2.26 g) and dimethyl acetylenedicarboxylate (2.13 g) was heated at 150–160° for 3 hr under nitrogen. Resulted brown mass was chromatographed on silica gel with a mixture (4:1) of petr. ether and benzene. From the first eluate, there was obtained small amount of dimethyl 1-phenyl-3-(4-methoxyphenyl)pyrazoline-4,5-dicarboxylate (Vd) as colorless prisms, mp 152–153°. Anal. Calcd. for C₂₀H₂₀O₅N₂: C, 65.21; H, 5.47; N, 7.60. Found: C, 64.81; H, 5.43; N, 7.81. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1730 (CO), 1595 (phenyl). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 248 (12900), 304 (8700), 355 (15900). NMR δ (ppm): 3.70 (3H, singlet, COOCH₃), 3.75 (3H, singlet, COOCH₃), 3.85 (3H, singlet, OCH₃), 4.50 (1H, doublet, $J=5$ Hz, 4-H), 5.15 (1H, doublet, $J=5$ Hz, 5-H), 6.70–7.95 (9H, broad, aromatic protons). Mass Spectrum m/e : 368 (M⁺).

Further elution of the column yielded 0.29 g (10%) of III, mp and mixed mp 88°.

General Procedure for Dimethyl 1-(3,4-Substituted)-3-(4-nitrophenyl)pyrazole-4,5-dicarboxylate (IIe–I) (Table)—A mixture of Ie–I and 1.5 molar equivalent of dimethyl acetylenedicarboxylate was heated at 140–220° for 3 hr under nitrogen. Resulted brown mass was treated with benzene to separate a starting material as a precipitate, and the filtrate was chromatographed on silica gel to yield pyrazole derivatives (IIe–I).

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