Preparation of Tetraalkyl 2,2'-Phthaloylbis[1,2-dihydro-1-isoquinolylphosphonate]s and their Reactions with Base

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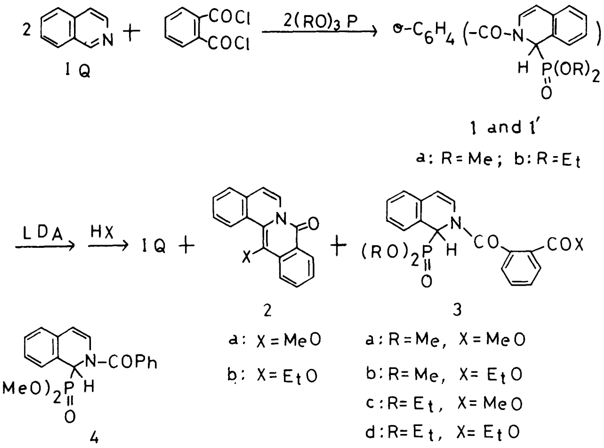
Synopsis. The titled compounds were prepared and the reaction with lithium diisopropylamide followed by quenching with alcohol gave isoquinoline, 13-alkoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-ones, and dialkyl 2-(*o*-alkoxycarbonylbenzoyl)-1,2-dihydro-1-isoquinolylphosphonates.

We reported previously preparation of 13-substituted 8*H*-dibenzo [*a*,*g*]quinolizin-8-ones (**2**) by the intramolecular Wittig-Horner reaction of dialkyl 2-(*o*-acylbenzoyl)-1,2-dihydro-1-isoquinolylphosphonates (**3**).[1)]

If the bis(phosphonate)s such as **1** are allowed to react with diketones under reaction conditions of the Wittig-Horner reaction, formation of the large-membered rings would be expected. Thus, a possibility of this type of reaction was examined.

Tetraalkyl 2,2'-Phthaloylbis [1,2-dihydro-1-isoquinolylphosphonate]s were prepared from isoquinoline (IQ), phthaloyl dichloride, and trialkyl phosphites in good yields as a diastereomeric mixtures of **1** and **1'**, where the isomers having lower melting points were regarded as **1**.

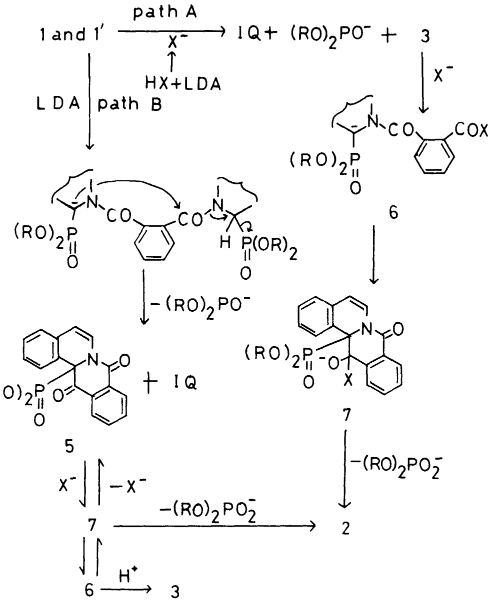


The reaction of a 1:1 mixture of **1a** and **1'a** with phthalaldehyde using two molar amounts of lithium diisopropylamide (LDA), followed by quenching with methanol, gave IQ (76%), **2a** (24%), and dimethyl 2-(*o*-methoxycarbonylbenzoyl)-1,2-dihydro-1-isoquinolylphosphonate (**3a**) (43%), indicating that phthalaldehyde did not take part in the reaction. Use of sodium methoxide (2 equiv) as a base gave mainly IQ and dimethyl phthalate.

In order to clarify the mechanism for the reaction, **1a** and **1b** were treated with LDA (1.3 equiv) at −70°C, then the reaction mixtures were quenched with alcohols, and allowed to stand at room temperature overnight. The results are summarized in Table 1, indicating that the 13-substituents in **2** are derived from the alcohols as quencher. However, the reaction of **1b** with LDA, followed by quenching with acetic acid, resulted in a quantitative recovery of a mixture of **1b** and **1'b** (5:8).

A similar reaction of dimethyl 2-benzoyl-1,2-dihydro-1-isoquinolylphosphonate (**4**)[2)] as model with LDA, followed by quenching with methanol, gave a 1:1 mixture of IQ and methyl benzoate quantitatively.

From the above results, two mechanisms for formation of **2** and **3** are possible (see Scheme 1). Absence of a keto phosphonate (**5**) by quenching with acetic acid and the model experiment using **4** seem to support path A, though path B can not be ruled out completely.



Scheme 1.

Experimental

Preparation of 1a. A mixture of phthaloyl dichloride (0.44 ml, 3.06 mmol) and IQ (0.79 g, 6.12 mmol) in MeCN (5 ml) was heated at 50—60°C for 10 min. To the above soln was added trimethyl phosphite (1.08 ml, 9.14 mmol) at 0°C and the mixture was refluxed for 10 min. After addition of aq $NaHCO_3$ (3%, 50 ml), the mixture was extracted with CH_2Cl_2. The extract was washed with aq NaCl and dried ($MgSO_4$). After removel of the solvent, the residue (2.2 g) was

Table 1. Reaction products from **1** and LDA (1.3 equiv)

1	R	X	Yield/%		
			IQ	**2**	**3**
1a	Me	MeO	87	**2a** 18	**3a** 62
1a	Me	EtO	84	**2b** 43	**3b** trace
1b	Et	MeO[a)]	84	**2a** 12	**3c** 56
1b	Et	EtO	74	**2b** 26	**3d** 55

a) Dimethyl phthalate was also produced in 4% yield.

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crystallized with ether to give a colorless mixture of **1a** and **1′a** (1.4:1; 1.55 g, 83%), which were separated by fractional recrystallization. **1a**: mp 208—209°C (from EtOAc-Et_2O); ^1H NMR ($CDCl_3$) δ=3.54, 3.59 (12H, 2d, J_{POCH}=10.8 Hz), 5.79 (2H, d, J=7.8 Hz), 6.25 (2H, d, J_{PCH}=17.7 Hz), 6.52 (2H, d, J=7.8 Hz), 6.8—7.0 (2H, m), 7.2—7.3 (6H, m), and 7.55 (4H, s); MS (70 eV) *m/z* (rel intensity) 608 (M^+; 0.5), 222 (48), and 93 (100). Found: C, 59.40; H, 4.95; N, 4.66%. Calcd for $C_{30}H_{30}N_2O_8P_2$: C, 59.21; H, 4.97; N, 4.60%. **1′a**: mp 224.9—225.8°C (from EtOAc-Et_2O); ^1H NMR ($CDCl_3$) δ=3.49, 3.67 (12H, 2d, J_{POCH}=10.8 Hz), 5.87 (2H, d, J=7.8 Hz), 6.09 (2H, d, J_{PCH}=17.7 Hz), 6.41 (2H, d, J=7.8 Hz), 7.0—7.2 (8H, m), and 7.55 (4H, s); MS (70 eV) *m/z* (rel intensity) 608 (M^+; 0.6), 222 (59), and 93 (100). Found: C, 59.48; H, 4.86; N, 4.70%.

*Preparation of **1b**.* Similarly to that of **1a**, phthaloyl dichloride (1.35 ml, 9.4 mmol), IQ (2.43 g, 18.8 mmol) in MeCN (13 ml), and triethyl phosphite (3.2 ml, 18.5 mmol) were allowed to react. On cooling the reaction mixture with ice, **1′b** precipitated (1.58 g, 25% yield). The filtrate was evaporated *in vacuo* and 3% aq $NaHCO_3$ (50 ml) was added to the residue and the mixture was extracted with CH_2Cl_2. The extract was washed with aq NaCl, dried ($MgSO_4$), and evaporated to give **1b** (4.00 g, 64% yield). **1b**: mp 168.2—169.2°C (from EtOAc-Et_2O); ^1H NMR ($CDCl_3$) δ=1.12 (6H, t, J=7.2 Hz), 1.15 (6H, t, J=7.2 Hz), 3.5—4.3 (8H, m), 5.72 (2H, d, J=7.8 Hz), 6.18 (2H, d, J_{PCH}=17.4 Hz), 6.47 (2H, d, J=7.8 Hz), 6.7—6.9 (2H, m), 7.0—7.3 (6H, m), and 7.51 (4H, m); MS (70 eV) *m/z* (rel intensity) 664 (M^+; 1.1), 398 (41), 250 (73), and 121 (100). Found: C, 61.29; H, 5.90; N, 4.19%. Calcd for $C_{34}H_{38}N_2O_8P_2$: C, 61.44; H, 5.76; N, 4.21%. **1′b**: mp 221.7—222.7°C (from EtOAc-Et_2O); ^1H NMR ($CDCl_3$) δ=1.09 (6H, t, J=6.9 Hz), 1.18 (6H, t, J=6.9 Hz), 3.5—4.3 (8H, m), 5.76 (2H, d, J=7.8 Hz), 5.95 (2H, d, J_{PCH}=16.8 Hz), 6.32 (2H, d, J=7.8 Hz), 6.8—7.2 (8H, m), and 7.56 (4H, s); MS (70 eV) *m/z* (rel intensity) 664 (M^+; 0.8), 398 (57), 250 (89), and 121 (100). Found: C, 61.14; H, 5.70; N, 4.26%.

*Reaction of **1a** and **1′a** in the Presence of Phthalaldehyde.* To a soln of LDA (2.38 mmol) in THF (50 ml) was added a mixture of **1a** and **1′a** (1:1) (604 mg, 0.99 mmol) at −50—−60°C and after 40 min phthalaldehyde (133 mg, 0.99 mmol) in THF (21.2 ml) was added dropwise at −65°C. After 0.5 h, the mixture was stirred at 40°C for 0.5 h and quenched with MeOH (2 ml). After filtration, the filtrate was evaporated and aq $NaHCO_3$ (2%, 50 ml) was added to the residue. The mixture was extracted with ether and then the aq layer was extracted with CH_2Cl_2. The combined extracts were washed with aq NaCl (50 ml), dried ($MgSO_4$), and evaporated. The residue (392 mg) was subjected to dry column chromatography (DCC) (SiO_2, Et_2O-hexane (1:1)) to give **2a**(1) (65 mg, 24%). IQ (97 mg, 76%), and **3a**(1) (171 mg, 43%).

*Reaction of Bis(phosphonate)s (**1**) and LDA. General Method*: To a soln of **1** (*ca.* 1 mmol) in THF (30 ml) was added at −70°C LDA (1.3 mmol) in THF (5 ml) under nitrogen atmosphere with stirring. After stirring for 0.5 h, alcohol (2 ml) was added at −70°C and the mixture was allowed to stand at room temp overnight. After removal of solvent *in vacuo*, 2% aq $NaHCO_3$ (50 ml) was added to the residue, the mixture was extracted with CH_2Cl_2, the extract was dried ($MgSO_4$), and evaporated to be subjected to DCC (SiO_2, Et_2O). The results were shown in Table 1. The products **2** and **3** were identified by the mps and spectral data.(1)

References

1) K. Akiba, Y. Negishi, and N. Inamoto, *Bull. Chem. Soc. Jpn.*, **57**, 2188 (1984).

2) K. Akiba, Y. Negishi, and N. Inamoto, *Synthesis*, **1979**, 55.