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Preparation of 13-Substituted 8*H*-Dibenzo[*a*,*g*]quinolizin-8-ones by Intramolecular Wittig-Horner Reaction of Dialkyl 2-(*o*-Acylbenzoyl)-1,2-dihydro-1-isoquinolylphosphonates

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Dialkyl 2-(*o*-acylbenzoyl)-1,2-dihydro-1-isoquinolyl-phosphonates (**1**) were prepared by reactions of isoquinoline, *o*-acylbenzoyl chloride, and trialkyl phosphites. Treatment of **1** with lithium diisopropylamide gave 13-substituted 8*H*-dibenzo[*a*,*g*]quinolizin-8-ones by intramolecular Wittig-Horner reaction. Especially, 13-alkoxy and dimethylamino derivatives were obtained in good yields. A similar reaction of dimethyl 1-[*o*-(methoxycarbonyl)benzoyl]-1,2-dihydro-2-quinolylphosphonate was also described.

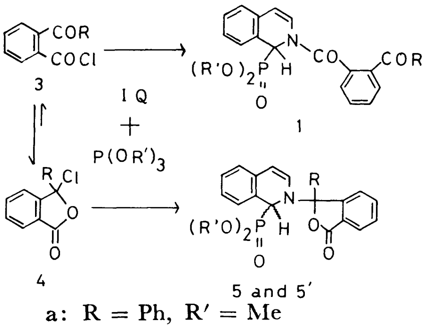
As a general method to introduce substituents into heteroaromatics, we recently reported preparation of a variety of heterocyclic phosphonates from the corresponding heteroaromatic cations and their use for carbonyl olefination to afford heterocycles containing *exo*-methylene groups.[1]

This method was extended to isoquinolinium salts, and it was found that dimethyl 2-isopropoxycarbonyl-1,2-dihydro-1-isoquinolylphosphonate, prepared from isoquinoline, isopropyl chloroformate, and trimethyl phosphite, afforded the corresponding 1-*exo*-methylene compounds by the Wittig-Horner reaction with various aldehydes, and the *exo*-methylene compounds thus obtained were readily converted to 1-substituted isoquinolines with hydrogen chloride.[2]

This paper describes on preparation of dialkyl 2-(*o*-acylbenzoyl)-1,2-dihydro-1-isoquinolylphosphonates (**1**) and their intramolecular Wittig-Horner reaction to afford 13-substituted 8*H*-dibenzo[*a*,*g*]quinolizin-8-ones (**2**).[3]

Results and Discussion

Synthesis of Dialkyl 2-(o-Acylbenzoyl)-1,2-dihydro-1-isoquinolylphosphonates (1). *o*-Aroylbenzoyl chlorides were used as acylating reagent of isoquinoline, but it is known that *o*-benzoylbenzoyl chloride (**3a**) exists as the tautomeric form, 3-chloro-3-phenylphthalide (**4a**)[4] which is unsuitable for the synthesis of **1a**.



a: R = Ph, R′ = Me
b: R = p-MeC$_6$H$_4$, R′ = Me
c: R = MeO, R′ = Me
d: R = EtO, R′ = Me
c′: R = MeO, R′ = Et
d′: R = EtO, R′ = Et
e: R = Me$_2$N, R′ = Me
f: R = PhCH$_2$S, R′ = Me

Therefore, in order to increase the contribution of **3a** and to obtain **1a** as much as possible, a solution of isoquinoline (IQ) was added dropwise to a heated solution of **4a**, followed by addition of trimethyl phosphite. The results are shown in Table 1.

As seen in Table 1, the products were a mixture of the expected phosphonate (**1a**) and undesirable diastereomeric phosphonates (**5a** and **5′a**), 3-phenyl-3-(1-dimethoxyphosphinyl-1,2-dihydro-2-isoquinolyl)-phthalides, derived directly from **4a**.

It was found that the best yield of **1a** was obtained by use of a more dilute solution in propiononitrile as solvent. Under similar conditions **1b** was also prepared in good yield (see Table 1).

Although **5′b** could not be isolated in a pure state, the isomer which has higher melting point and larger J_{PCH} value was regarded as **5** and the other as **5′**.

On the other hand, since phthalic monoesters, monoamides, or monothioester gave only the corresponding chlorides **3c—f**, **1c—f** were prepared by usual method[5] in the absence of sodium iodide in 64—87% yields, except for **1f** (8.2% yield).

Dimethyl 1-[*o*-(methoxycarbonyl)benzoyl]-1,2-dihydro-2-quinolylphosphonate (**6**) was prepared by a similar method in 60% yield.

Intramolecular Wittig-Horner Reactions. Reactions of the phosphonates **1a**, **b** with lithium diisopropylamide (LDA) geve not only the expected 13-aryl-8*H*-dibenzo[*a*,*g*]quinolizin-8-ones (**2a**, **b**) but also phthalides (**7**) and a considerable amount of IQ.

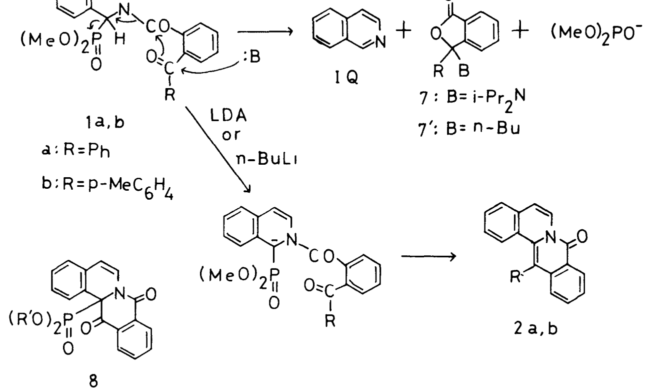


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TABLE 1. PREPARATION OF **1a** AND **1b**

Solvent	Temp/°C	Concn/M[a)]		Total yield/%	Ratio of **1**:**5**:**5′**[b)]
		4	IQ		
MeCN	82 (refl)	**a** 1.1	3.8	86	48:22:30
PhMe	111 (refl)	**a** 0.7	0.34	6.6	55:0:45
PhCN	120—130	**a** 0.3	0.36	20	80:5:15
EtCN	98 (refl)	**a** 0.3	0.33	81	76:9:15
EtCN	98 (refl)	**b** 0.6	1.48	65	42:23:35
EtCN	98 (refl)	**b** 0.15	0.24	93	68:16:16

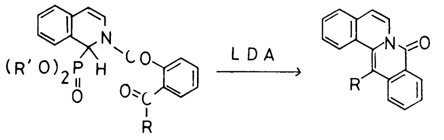
a) 1 M=1 mol dm^{-3}. b) The ratios were determined from the peak areas of the following signals (each is doublet) in the NMR spectra of the mixtures using simultaneous equations: δ 3.56 and 3.66 for **1a**, 3.56 and 3.59 for **5a**, 3.50 for **5′a**, 3.54 and 3.66 for **1b**, 3.57 and 3.59 for **5b**, and 3.50 for **5′b**.

TABLE 2. REACTION PRODUCTS FROM **1** AFTER QUENCHING WITH METHANOL

1	Base	Yield/%		
		2	**7** or **7′**	IQ
1a	LDA	**2a** (31)	**7a** (7)	40
1a	*n*-BuLi	**2a** (9.4)	**7′a** (22)	53
1b	LDA	**2b** (4.5)	**7b** (6)	46
1c	LDA[a)]	**2c** (76)		
1c′	LDA[a)]	**2c** (66)		
1d	LDA	**2d** (67)		
1d′	LDA[a)]	**2d** (75)		
1e	LDA	**2e** (67)		
1f	LDA	**2f** (3.0)		

a) Quenched with ethanol.

Formation of **7** and IQ is attributed to a nucleophilic attack of diisopropylamide anion toward the aroyl carbonyl group of **1a**, **b**. In fact, use of more nucleophilic butyllithium as base resulted in a low yield of **2** and a higher yield of **7′** (see Table 2).



1c-f 2c-f

On the other hand, *o*-(alkoxycarbonyl)benzoyl phosphonates (**1c**, **d**, **c′**, **d′**) gave the corresponding **2c**, **d** in good yields (see Table 2), through the intramolecular Wittig-Horner reaction at the esteric carbonyl group. Formation of **2c**, **d** irrespective of kinds of the phosphonate esters or alcohols as quencher indicates no contribution of a β-keto phosphonate (**8**), which is formed by usual acylation of carbanion with ester. No formation of **8** is attributed to a relief of steric congestion and formation of an extended conjugate system in **2**.

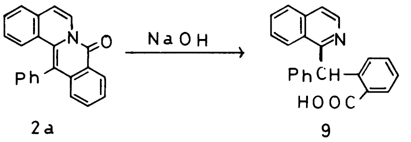
There are a few reports on the intermolecular or intramolecular Wittig reaction at esteric carbonyl group of formate,[6)] oxalate,[6)] acetate,[7,8)] benzoate,[8)] oxomalonate (methylenemalonate),[9)] and carbonate.[10)]

Furthermore, *o*-(dimethylcarbamoyl)benzoyl phosphonate (**1e**) gave 13-dimethylamino derivative (**2e**) in 67% yield, through the intramolecular Wittig-Horner reaction at amidic carbonyl group. Recently, a similar intramolecular Wittig reaction at amidic carbonyl in *o*-(acylamino)benzylidenetriphenylphosphorane has been reported.[11)]

Good yields of **2c**—**e** from **1c**—**e** are attributed to a prevention of side reactions by electron-donating effect of alkoxyl and dimethylamino groups.

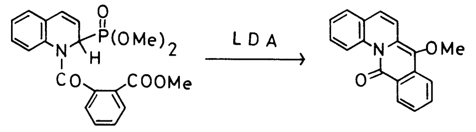
In the case of **1f**, yield of **2f** was very poor (3%), probably because benzylthio group is a good leaving group as indicated by formation of benzyl methyl sulfide (42%), which is probably formed *via* reaction between two leaving groups, α-toluenethiolate and dimethyl phosphate anions.

The structures of **2** were determined by comparison of the spectral data with analogous compounds,[12—14)] and by alkaline hydrolysis of **2a** to 1-[α-(*o*-carboxyphenyl)benzyl]isoquinoline (**9**).



2a 9

A similar reaction of **6** with LDA gave 7-methoxy-12*H*-dibenzo[*b*,*f*]quinolizin-12-one (**10**) in 54% yield.



6 10

Experimental

All the melting points are uncorrected. IR spectra were measured with a Hitachi 260-30 spectrophotometer, ^{1}H NMR spectra with a Hitachi R-20B spectrometer using TMS as an internal standard and MS with a Hitachi RMU-6L mass spectrometer at 70 eV.

*Synthesis of Dimethyl 2-(*o*-Benzoylbenzoyl)-1,2-dihydro-1-isoquinolylphosphonate (**1a**).* A mixture of anhyd *o*-benzoylbenzoic acid[15)] (1.04 g, 4.6 mmol) and $SOCl_2$ (0.87 ml, 12 mmol) was stirred at room temp until the reaction mixture became clear, and excess $SOCl_2$ was removed *in vacuo*. The residue (**4a**) in dry EtCN (10 ml) was refluxed under nitrogen. IQ (0.59 g, 4.6 mmol) in dry EtCN (13 ml) and then trimethyl phosphite (0.54 ml, 4.6 mmol) were added dropwise to the above refluxing soln, and the refluxing was continued for 1 h. After removal of the solvent, 4% aq $NaHCO_3$ (100 ml) was added to the residue and the mixture was extracted with CH_2Cl_2. The extract was washed with aq NaCl and dried ($MgSO_4$). Removal of the solvent gave a colorless mixture of **1a**, **5a**, and **5′a** (16:2:3; 1.64 g, 81% in total). Only **5a** was isolated by column chromatography (Al_2O_3, Et_2O). The residual mixture was separated by recrystallization. **1a**: Mp

157.1—157.9 °C (from EtOAc-hexane); IR (KBr) 1670, 1620, and 1255 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.56, 3.66 (6H, 2d, J_{POCH}=10.2 Hz), 5.85 (1H, d, J=7.8 Hz), 6.07 (1H, d, J_{PCH}=18 Hz), 6.40 (1H, d, J=7.8 Hz), and 6.9—7.8 (13H, m); MS m/z (rel intensity) 447 (M^+; 0.3) and 209 (100). Found: C, 67.21; H, 4.96; N, 3.00%. Calcd for $C_{25}H_{22}NO_5P$: C, 67.11; H, 4.96; N, 3.13%. **5a**: Mp 185.2—185.7 °C (from EtOAc); IR (KBr) 1765, 1630, and 1255 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=3.56, 3.59 (6H, 2d, J_{POCH}=10.5 Hz), 4.65 (1H, dd, J_{PCH}=19.2 Hz, J=1.5 Hz), 5.97 (1H, d, J=7.2 Hz), 6.09 (1H, dd, J=7.2 Hz, 1.5 Hz), and 6.7—8.1 (13H, m); MS m/z (rel intensity) 447 (M^+; 0.2) and 209 (100). Found: C, 67.26; H, 5.11; N, 3.05%. **5′a**: Mp 164.2—165.0 °C (from EtOAc-hexane); IR (KBr) 1760, 1630, 1260, and 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.50 (6H, d, J_{POCH}=10.2 Hz), 4.82 (1H, dd, J_{PCH}=16.8 Hz, J=1.5 Hz), 5.93 (1H, d, J=7.8 Hz), 6.07 (1H, dd, J=7.8 Hz, 1.5 Hz), and 6.9—8.0 (13H, m); MS m/z (rel intensity) 447 (M^+; 0.2) and 209 (100). Found: C, 67.40; H, 4.97; N, 3.00%.

*Synthesis of Dimethyl 2-[o-(p-Toluoyl)benzoyl]-1,2-dihydro-1-isoquinolylphosphonate (**1b**).* *o*-(*p*-Toluoyl)benzoic acid[16] was dried at 90 °C overnight. A mixture of the anhyd acid (1.12 g, 4.7 mmol) and $SOCl_2$ (1.0 ml, 14 mmol) was treated similarly to that of **1a**. Then dry EtCN (30 ml), IQ (0.60 g, 4.7 mmol) in EtCN (15 ml), and trimethyl phosphite (0.55 ml, 4.7 mmol) were successively added. A similar treatment gave a colorless mixture of **1b**, **5b**, and **5′b** (9:2:2; 1.99 g, 93% in total). **5b** was isolated by column chromatography (Al_2O_3, Et_2O). **1b** was isolated by crystallization from the mixture of **1b** and **5′b**, the latter of which could not be isolated in pure state. **1b**: Mp 157.1—157.8 °C (from EtOAc-hexane); IR (KBr) 1660, 1625, and 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.32 (3H, s), 3.54, 3.66 (6H, 2d, J_{POCH}=10.5 Hz), 5.84 (1H, d, J=7.8 Hz), 6.05 (1H, d, J_{PCH}=18.6 Hz), 6.40 (1H, d, J=7.8 Hz), 7.0—7.3 (6H, m), and 7.45—7.7 (6H, m); MS m/z (rel intensity) 461 (M^+; 0.3) and 233 (100). Found: C, 67.46; H, 5.05; N, 3.14%. Calcd for $C_{26}H_{24}NO_5P$: C, 67.67; H, 5.24; N, 3.04%. **5b**: Mp 176.0—176.8 °C (from EtOAc); IR (KBr) 1770, 1635, and 1260 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ=2.33 (3H, s), 3.57, 3.59 (6H, 2d, J=10.5 Hz), 4.67 (1H, dd, J_{PCH}=19.8 Hz, J=0.9 Hz), 5.92 (1H, d, J=7.8 Hz), 6.11 (1H, dd, J=7.8 Hz, 0.9 Hz), 6.7—7.3 (6H, m), and 7.5—8.1 (6H, m); MS m/z (rel intensity) 461 (M^+; 0.2) and 223 (100). Found: C, 67.73; H, 5.26; N, 3.14%. **5′b**: ^{1}H NMR (partly) ($CDCl_3$) δ=3.50 (6H, d, J=10.5 Hz), 4.84 (1H, dd, J_{PCH}=16.2 Hz, J=0.9 Hz), 5.89 (1H, d, J=7.8 Hz), and 6.11 (1H, dd, J=7.8 Hz, 0.9 Hz).

*Synthesis of Dimethyl 2-[o-(Methoxycarbonyl)benzoyl]-1,2-dihydro-1-isoquinolylphosphonate (**1c**).* A mixture of methyl hydrogen phthalate[17] (1.78 g, 9.9 mmol) and $SOCl_2$ (5.0 ml, 69 mmol) was refluxed for 1 h. Excess $SOCl_2$ was evaporated and completely removed by repeating three times addition of dry benzene (2.5 ml each) and distillation. To the resulting chloride (**3c**) in an ice bath, MeCN (5 ml), IQ (1.28 g, 9.9 mmol) in MeCN (7 ml) and trimethyl phosphite (1.17 ml, 9.9 mmol) were added successively and the mixture was refluxed for 10 min. After removal of the solvent, 2% 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 and dried ($MgSO_4$). Removal of the solvent gave **1c** (3.3 g, 8.21 mmol) in 83% yield as colorless crystals, mp 154.1—154.6 °C (from EtOAc); IR (neat) 1725, 1665, 1630, and 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.59 (3H, s), 3.63, 3.75 (6H, 2d, J_{POCH} =10.5 Hz), 5.83 (1H, d, J=7.8 Hz), 6.15 (1H, d, J=7.8 Hz), 6.51 (1H, d, J_{PCH}=17.4 Hz), 7.0—7.8 (7H, m), and 8.0—8.3 (1H, m); MS m/z (rel intensity) 401 (M^+; 0.3) and 163 (100). Found: C, 59.99; H, 5.08; N, 3.59%. Calcd for $C_{20}H_{20}NO_6P$: C, 59.85; H, 5.02; N, 3.49%.

*Synthesis of Diethyl 2-[o-(Methoxycarbonyl)benzoyl]-1,2-dihydro-1-isoquinolylphosphonate (**1c′**).* This compd was prepared by a similar method to that of **1c** in 87% yield as colorless crystals, mp 91.9—92.6 °C (from Et_2O-hexane); IR (KBr) 1720, 1660, 1620, and 1255 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.20, 1.25 (6H, 2t, J=6.6 Hz), 3.52 (3H, s), 3.7—4.5 (4H, m), 5.76 (1H, d, J=7.5 Hz), 6.12 (1H, d, J=7.5 Hz), 6.45 (1H, d, J_{PCH}=18.0 Hz), 6.9—7.7 (7H, m), and 7.95—8.15 (1H, m); MS m/z (rel intensity) 429 (M^+; 0.3) and 163 (100). Found: C, 61.41; H, 5.51; N, 3.26%. Calcd for $C_{22}H_{24}NO_6P$: C, 61.54; H, 5.63; N, 3.26%.

*Synthesis of Dimethyl 2-[o-(Ethoxycarbonyl)benzoyl]-1,2-dihydro-1-isoquinolylphosphonate (**1d**).* This compd was prepared by a similar method to that of **1c** in 80% yield as colorless crystals, mp 113.9—114.4 °C (from Et_2O-hexane); IR (KBr) 1720, 1675, 1630, and 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.02 (3H, t, J=6.9 Hz), 3.60, 3.73 (6H, 2d, J_{POCH}=10.8 Hz), 4.04, 4.07 (2H, 2q, J=6.9 Hz), 5.77 (1H, d, J=7.8 Hz), 6.13 (1H, d, J=7.8 Hz), 6.49 (1H, d, J_{PCH}=17.4 Hz), 6.9—7.7 (7H, m), and 8.0—8.15 (1H, m); MS m/z (rel intensity) 415 (M^+; 0.5), 177 (86), and 149 (100). Found: C, 60.68; H, 5.22; N, 3.46%. Calcd for $C_{21}H_{22}NO_6P$: C, 60.72; H, 5.34; N, 3.37%.

*Synthesis of Diethyl 2-[o-(Ethoxycarbonyl)benzoyl]-1,2-dihydro-1-isoquinolylphosphonate (**1d′**).* This compd was prepared by a similar method to that of **1c** in 64% yield as colorless crystals, mp 96.4—97.1 °C (from EtOAc); IR (KBr) 1720, 1665, 1630, and 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.00 (3H, t, J=6.6 Hz), 1.20, 1.26 (6H, t, J=6.6 Hz), 4.03 (2H, q, J=6.6 Hz), 3.6—4.5 (4H, m), 5.75 (1H, d, J=7.8 Hz), 6.14 (1H, d, J=7.8 Hz), 6.47 (1H, d, J_{PCH}=17.4 Hz), 6.9—7.8 (7H, m), and 8.0—8.15 (1H, m); MS m/z 443 (M^+; 0.5), 177 (100), and 149 (94). Found: C, 62.22; H, 6.00; N, 3.20%. Calcd for $C_{23}H_{26}NO_6P$: C, 62.30; H, 5.91; N, 3.16%.

*Synthesis of Dimethyl 2-[o-(Dimethylcarbamoyl)benzoyl]-1,2-dihydro-1-isoquinolylphosphonate (**1e**).* A mixture of *N*,*N*-dimethylphthalamic acid[18] (1.90 g, 9.8 mmol) and $SOCl_2$ (5.0 ml, 69 mmol) was refluxed for 1 h, and excess $SOCl_2$ was evaporated. After addition of dry benzene (5 ml) and evaporation, MeCN (10 ml) was added to the chloride (**3e**). IQ (1.28 g, 9.9 mmol) in MeCN (2 ml) was added to the refluxing suspension and after 10 min trimethyl phosphite (1.16 ml, 9.8 mmol) was added. The refluxing was continued for 10 min. After usual work-up, **1e** was obtained in 78% yield (3.2 g, 7.72 mmol) as colorless crystals, mp 131.7—132.5 °C (from EtOAc-hexane (1:1)); IR (KBr) 1660, 1650, 1625, and 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.92 (6H, br s), 3.55, 3.71 (6H, 2d, J_{POCH}=10.8 Hz), 5.84 (1H, d, J=7.8 Hz), 6.30 (1H, d, J_{PCH}=16.8 Hz), 6.47 (1H, d, J=7.8 Hz), and 7.0—7.6 (8H, m); MS m/z (rel intensity) 414 (M^+; 0.75) and 176 (100). Found: C, 60.64; H, 5.60; N, 6.83%. Calcd for $C_{21}H_{23}N_2O_5P$: C, 60.87; H, 5.59; N, 6.76%.

*Synthesis of Dimethyl 2-[o-(Benzylthio)carbonylbenzoyl]-1,2-dihydro-1-isoquinolylphosphonate (**1f**).* A mixture of *S*-benzyl o-carboxythiobenzoate[19] (3.72 g, 13.7 mmol) and $SOCl_2$ (7 ml) was refluxed for 1 h and excess $SOCl_2$ was removed *in vacuo*. To the residue was added dry benzene (3.5 ml) and the mixture was evaporated. This treatment was repeated twice. To the residue were added MeCN (10 ml), IQ (1.77 g, 13.7 mmol) in MeCN (5 ml), and trimethyl phosphite (1.62 ml, 13.7 mmol) successively. After refluxing for 10 min, MeCN was removed *in vacuo*, to the residue were added a small amount of ether and a trace of EtOAc, and ppt thus obtained (phthalic anhydride, 0.564 g) was filtered off. To the filtrate was added 3% aq $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The extract was washed with aq NaCl, dried ($MgSO_4$), and evaporated. The residue (5.12 g) was dissolved in CH_2Cl_2 (50 ml), successively washed with 2M aq HCl, 5% aq Na_2CO_3, and aq NaCl, dried ($MgSO_4$), and evaporated. The residue (2.83 g) was subjected to dry column chromatography (DCC; Al_2O_3, Et_2O) to afford **1f** (0.55 g, 1.12 mmol, 8.2%) as colorless crystals, mp 152—154 °C (from EtOAc-hexane (1:1));

IR (KBr) 1660, 1620, and 1245 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ= 3.55, 3.67 (6H, 2d, J_{POCH}=10.8 Hz), 4.05 (2H, s), 5.70 (1H, d, J=7.8 Hz), 6.10 (1H, d, J=7.8 Hz), 6.41 (1H, d, J_{PCH}=16.2 Hz), 6.9—7.7 (12H, m), and 7.8—8.3 (1H, m); MS *m/z* (rel intensity) 493 (M$^+$; 0.0008) and 91 (100). Found: C, 63.41; H, 4.74; N, 3.02%. Calcd for $C_{26}H_{24}NO_5PS$: C, 63.28; H, 4.90; N, 2.84%.

Synthesis of Dimethyl 1-[o-(Methoxycarbonyl)benzoyl]-1,2-dihydro-2-quinolylphosphonate (6). MeCN (2 ml) was added to acid chloride prepared from methyl hydrogen phthalate (1.81 g, 10.0 mmol) and SOCl$_2$ (5 ml) similarly to preparation of **1c**. To the above soln, quinoline (1.30 g, 10.1 mmol) in MeCN (7 ml), trimethyl phosphite (1.18 ml, 10.0 mmol), and NaI (2 g, 13 mmol) were successively added at 0°C with stirring, and the mixture was heated at 50°C with stirring for 10 min. After removal of the solvent, 2% aq NaHCO$_3$ (50 ml) was added to the residue, the mixture was extracted with CH$_2$Cl$_2$, the extract was washed with aq NaCl, dried (MgSO$_4$), and evaporated. The residue (3.05 g) was subjected to DCC (Al$_2$O$_3$, Et$_2$O) to give **6** (2.40 g, 5.98 mmol, 60% yield) as pale yellow oil; IR (neat) 1730, 1660, and 1300—1265 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=3.53, 3.75 (6H, 2d, J_{POCH}= 10.2 Hz), 3.83 (3H, s), and 5.8—8.2 (10H, m). Analytically pure sample could not be obtained because of a difficulty of purification. Therefore, crude material was used in the reaction.

Intramolecular Wittig-Horner Reaction. General Procedure Using LDA: The reaction was performed under nitrogen atmosphere. To phosphonate (**1**; 3.0 mmol) in tetrahydrofuran (THF) (20 ml) was added a LDA soln (3.5 mmol) in THF (5 ml) at −70°C. After stirred for 0.5 h, the temperature was gradually raised to room temp and kept at about 40°C for 0.5 h. After addition of methanol (3—6 ml), the solvent was removed and water (70 ml) was added to the residue. After usual work-up, the residue was separated or purified by column chromatography (SiO$_2$, Et$_2$O).

Reaction of 1a: **2a** (31%), IQ (41%), and **7a** (6%) were isolated. **2a**: Yellow crystals, mp 211.1—211.7°C (from CH$_2$Cl$_2$-Et$_2$O); IR (KBr) 1660 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=6.70 (1H, d, J= 8.1 Hz), 6.8—7.6 (12H, m), 8.6—8.7 (1H, m), and 8.67 (1H, d, J=8.1 Hz); MS *m/z* (rel intensity) 321 (M$^+$; 100). Found: C, 86.01; H, 4.69; N, 4.34%. Calcd for $C_{23}H_{15}NO$: C, 85.96; H, 4.70; N, 4.36%. **7a**: Colorless crystals, mp 126—128°C; IR (neat) 1750 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.03, 1.11 (12H, 2d, J=6.6 Hz), 3.27 (2H, sept, J=6.6 Hz), and 70—7.7 (9H, m). Found: *m/z* 309.1718. Calcd for $C_{20}H_{23}NO_2$: M, 309.1728.

The reaction of **1a** with *n*-BuLi gave IQ (53%) and a mixture of **2a** (isolated yield 9.4%) and **7′a** (could not be purified, 22% yield; IR (neat) 1760 cm^{-1}).

Reaction of 1b: A mixture of **2b** and an unidentified compd, IQ (46%), and **7b** (6%) (^{1}H NMR (CDCl$_3$) (partly) δ=1.02, 1.09 (12H, 2d, J=6.6 Hz), 2.21 (3H, s), 3.36 (2H, sept, J=6.6 Hz)) were obtained. Twice recrystallizations gave **2b** (4.5%) as yellow crystals, mp 215.2—215.9°C (from CH$_2$Cl$_2$-Et$_2$O); IR (KBr) 1660 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=2.50 (3H, s), 6.74 (1H, d, J=7.8 Hz), 6.9—7.7 (1H, m), 8.5—8.8 (1H, m), and 8.70 (1H, d, J=7.8 Hz); MS *m/z* (rel intensity) 335 (M$^+$; 100). Found: C, 85.66; H, 5.03; N, 4.21%. Calcd for $C_{24}H_{17}NO$: C, 85.95; H, 5.11; N, 4.18%.

Reaction of 1c: **2c** was obtained in 76% yield as yellow crystals, mp 143.8—144.7°C (from CH$_2$Cl$_2$-Et$_2$O); IR (KBr) 1650 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=3.83 (3H, s), 6.72 (1H, d,) J= 7.8 Hz), 7.3—8.2 (6H, m), 8.65 (1H, d, J=7.8 Hz), 8.55—8.80 (1H, dm, J=8 Hz), and 9.10—9.40 (1H, m); MS *m/z* (rel intensity) 275 (M$^+$; 19) and 260 (100). Found: C, 78.82; H, 4.48; N, 5.11%. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09%.

Reaction of **1c′** also gave **2c** in 66% yield.

Reaction of 1d: **2d** was obtained in 67% yield as yellow crystals, mp 181.7—182.3°C (from CH$_2$Cl$_2$-Et$_2$O); IR (KBr) 1650 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.50 (3H, t, J=6.9 Hz), 3.87 (2H, q, J=6.9 Hz), 6.63 (1H, d, J=7.8 Hz), 7.3—8.1 (6H, m), 8.55 (1H, d, J=7.8 Hz), 8.5—8.65 (1H, dm, J=8 Hz), and 9.0—9.3 (1H, m); MS *m/z* (rel intensity) 289 (M$^+$; 15) and 260 (100). Found: C, 78.58; H, 4.98; N, 4.82%. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84%.

Reaction of **1d′** also gave **2d** in 75% yield.

Reaction of 1e: **2e** was obtained in 67% yield as yellow crystals, mp 144.4—145.7°C (from CH$_2$Cl$_2$-Et$_2$O); IR (KBr) 1655 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=3.00 (6H, s), 6.67 (1H, d, J= 7.8 Hz), 7.35—7.65 (4H, m), 7.7—7.95 (2H, m), 8.60 (1H, d, J= 7.8 Hz), 8.55—8.75 (1H, dm, J=8 Hz), and 8.85—9.15 (1H, m); MS *m/z* (rel intensity) 288 (M$^+$; 100) and 273 (84). Found: C, 79.41; H, 5.29; N, 9.67%. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72%.

Reaction of 1f: The residue (234 mg) from reaction of **1f** (0.435 g, 0.882 mmol) was subjected to column chromatography (Al$_2$O$_3$, Et$_2$O-hexane (1:2)) to separate benzyl methyl sulfide (51 mg, 0.37 mmol, 42% yield) and crude **2f**. Pure **2f** was isolated by treatment with ether, 9.7 mg (0.026 mmol, 3.0%), yellow crystals, mp 115—118°C (from EtOAc-hexane); IR (KBr) 1660 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=3.68 (2H, s), 6.68 (1H, d, J= 7.8 Hz), 6.6—7.0 (4H, m), 7.2—7.7 (5H, m), 7.87 (1H, td, J=7.7 Hz, 1.7 Hz), 8.47 (1H, d, J=7.8 Hz), 8.61 (1H, d, J=10 Hz), 8.71 (1H, d, J=9.3 Hz), and 9.05—9.2 (1H, m); MS *m/z* (rel intensity) 367 (M$^+$; 0.9) and 276 (100). Found: C, 78.21; H, 4.92; N, 3.55%. Calcd for $C_{24}H_{17}NOS$: C, 78.45; H, 4.66; N, 3.81%.

Reaction of 6: **10** was obtained in 54% yield as yellow crystals (gradually decompose in soln), mp 299.5—301.2°C (decomp) (from CH$_2$Cl$_2$-Et$_2$O); IR (KBr) 1660 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=3.86 (3H, s), 6.94 (1H, s), 7.05—8.05 (7H, m), 8.6—8.8 (1H, m), and 9.35—9.65 (1H, m), MS *m/z* (rel intensity) 275 (M$^+$; 17), 260 (88), and 49 (100). Found: C, 78.73; H, 4.99; N, 5.34%. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09%.

Hydrolysis of 2a: A mixture of aq NaOH (20%; 2.4 ml) and **2a** (42.4 mg, 0.132 mmol) in EtOH (22 ml) was refluxed under nitrogen for 8 h. The reaction mixture was neutralized with dilute HCl and EtOH was evaporated. After addition of water (30 ml) to the residue, the mixture was extracted with CH$_2$Cl$_2$. The extract was dried (MgSO$_4$) and evaporated to give 1-[α-(*o*-carboxyphenyl)benzyl]isoquinoline (**9**) (37.1 mg, 83% yield), colorless crystals, mp 191—193°C (decomp) (from CH$_2$Cl$_2$-CCl$_4$); IR (KBr) 3100—2300 and 1705 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=6.9—7.4 (10H, m), 7.6—7.9 (1H, m), 8.3—8.45 (1H, m), and 8.35 (1H, d, J=5.7 Hz); MS *m/z* (rel intensity) 339 (M$^+$; 30), 321 (100), and 294 (66). Found: C, 81.43; H, 4.82; N, 4.21%. Calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13%.

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