Wittig–Horner Reaction of Dimethyl Phthalide-3-phosphonates with Ketones: Synthesis of 3-Ylidenephthalides and Their Conversion to 2,2-Disubstituted Indan-1,3-diones Including Spirocyclic Compounds

Mitsuaki Watanabe,*[a] Hitoshi Morimoto,[b] Maya Tomoda,[b] Umeka Iwanaga[b]

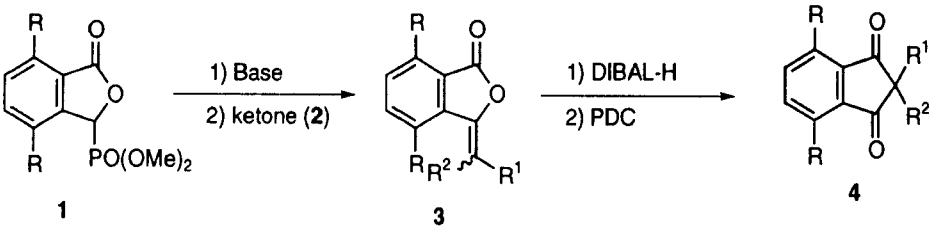
[a] Center for Instrumental Analysis, Nagasaki University, 1–14 Bunkyo-machi, Nagasaki 852, Japan
[b] School of Pharmaceutical Sciences, Nagasaki University, 1–14 Bunkyo-machi, Nagasaki 852, Japan

Received 1 April 1994; revised 13 May 1994

The Wittig–Horner reaction of dimethyl phthalide-3-phosphonates with various ketones was investigated under the conditions: lithium bis(trimethylsilyl)amide (LHMDS) or sodium hydride in tetrahydrofuran, and cesium carbonate in isopropyl alcohol. The sequential treatment of the 3-ylidenephthalides with diisobutylaluminium hydride (DIBAL-H) and pyridinium dichromate (PDC) afforded 2,2-disubstituted indan-1,3-dione derivatives in modest to high overall yields.

3-Ylidenephthalides are versatile starting materials for the preparation of heterocycles and alkaloids.[1] We have previously investigated the Wittig–Horner reaction of dimethyl phthalide-3-phosphonates[2] with various aldehydes leading to 3-ylidenephthalides.[3] In this paper, we report the reaction of phthalide-3-phosphonates with ketones to prepare 3-ylidenephthalides and their transformation to the 2,2-disubstituted indan-1,3-diones, including spirocyclic compounds[4] related to the core of the antitumor antibiotic fredericamycin A.[5]

Applying the Wittig–Horner reaction conditions as previously used with aldehydes,[3] dimethyl phthalide-3-phosphonate **(1a)** was treated with acetone **(2a)** under the conditions (LHMDS/THF/−78 °C to r.t.: Method A, and NaH/THF/0 °C to r.t.: Method B) and the expected product, 3-isopropylidenephthalide **(3aa)**, was obtained in 92 and 46% yields, respectively. The reaction also



1 3 4

1	R	2	3, 4	R	R^1	R^2
a	H	a	aa	H	Me	Me
b	OMe		ab	H	Ph	Ph
		b	ac	H	$-(CH_2)_4-$	
		c	ad	H	$-(CH_2)_5-$	
		d	ae	H	CH_2, CH_2	
		e	af	H		
		f	ag	H	$(CH_2)_3$	
		g	bc	OMe	$-(CH_2)_4-$	

Scheme

proceeded well to give **3aa** (85% yield) under the conditions (Cs_2CO_3/*i*-PrOH/0°C to r.t.: Method C) which have been found to be effective in solid-liquid interfacial Wittig–Horner reaction of dimethyl 2,3-*O*-isopropylidene-D-glyceroylmethylposphonate[6] or diethyl (ethoxycarbonyl)methylphosphonate[7] with aldehydes. These reaction conditions were consequently employed in the reaction of **1a,b** with various ketones **2b–g** and the corresponding 3-ylidenephthalides **3** were obtained in modest to good yields (Scheme). In contrast to its reaction with acetone, the reaction of **1a** with benzophenone **(2b)** in Method A gave the product **3ab** in 90% yield while the reaction in Method C resulted in the recovery of starting material in quantitative yield. Similar results were also observed when fluoren-9-one **(2f)** was used; **3af** was obtained in 90% yield (Method A) and in trace amounts (Method C). The low yields of **3ab** and **3af** under the conditions of Method C might be rationalized by the poor solubility of ketones **2b** and **2f** in isopropyl alcohol. When the unsymmetrical cyclic ketone **2g** was reacted with **1a**, **3ag** was obtained in 53% (Method A) and 21% (Method C) yields as a mixture of *E* and *Z* isomers in 1.5:1 and 3:1 ratios,[3] respectively. The stereochemistry of the isomers **3ag** were determined by nuclear Overhauser effect (NOE) experiments.[8] The preferential formation of the *E* isomer (*E*)-**3ag** was similar to the Wittig–Horner reaction of **1a** with aldehydes previously reported.[3] In general, LHMDS (Method A) was the most effective base in the Wittig–Horner reaction of **1** with ketones **2**, affording the corresponding 3-ylidenephthalides **3** in satisfactory yields.

Conversion of the 3-ylidenephthalides **3** to the 2,2-disubstituted indan-1,3-diones **4** were achieved by sequential DIBAL-H reduction and PDC oxidation.[4,9] Among the spirocyclic compounds **4** synthesized, **4ac** and **4bc** constitute the BCD ring skeleton, benzo-1,4-dioxospiro[4.4]nonanes, of structurally unique fredericamycin A.[5]

The structures of **3** and **4** were identified by IR, UV, ^1H and ^{13}C NMR, MS data and elemental analyses. Physical properties and spectral data of **3** and **4** are listed in Tables 1 and 2, respectively.

In conclusion, we have examined the Wittig–Horner reaction of dimethyl phthalide-3-phosphonates **1** with ketones **2** under various conditions. As a result of our expe-

Table 1. Physical Properties and Spectral Data of 3-Ylidenephthalides **3** Prepared

Product[a]	Yield[b] (%)	mp (°C)[c] (solvent)	IR (KBr) $\nu_{C=O}$ (cm^{-1})	UV (EtOH) λ_{max} (nm) (log ε)	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	MS, *m/z* (M^+)
3aa	92 (A) 46 (B) 85 (C)	84–85 (Et_2O/ hexane)	1760	203 (3.84), 209 (3.87), 216 (3.82), 236 (3.89), 263 (3.93), 273 (3.82), 315 (3.54)	2.13 (3H, s), 2.20 (3H, s), 7.49 (1H, t, *J* = 7.3), 7.80 (1H, d, *J* = 8.1), 7.93 (1H, d, *J* = 7.7)	174
3ab	90 (A)	152–153 (EtOAc/ hexane)	1770	206 (4.53), 240 (4.27), 294 (4.14), 306 (4.14), 338 (4.27)	6.25–6.35 (1H, m), 7.24–7.61 (12H, m), 7.85–7.96 (1H, m)	298
3ac	76 (A) 47 (B) 65 (C)	75–76 (Et_2O)	1770	203 (4.07), 210 (s, 4.07), 217 (s, 4.06), 233 (3.96), 265 (3.91), 275 (3.82), 317 (3.52)	1.75–1.83 (2H, m), 1.87–1.96 (2H, m), 2.71–2.78 (2H, m), 7.47 (1H, t, *J* = 7.7), 7.62 (1H, d, *J* = 7.7), 7.69 (1H, dt, *J* = 1.1, 8.1), 7.91 (1H, dt, *J* = 1.1, 7.7)	200
3ad	72 (A) 21 (B) 40 (C)	85–86 (Et_2O/ hexane)	1770	210 (4.11), 216 (s, 4.08), 238 (4.14), 266 (4.24), 275 (s, 4.14), 317 (3.90)	1.64–1.77 (6H, m), 2.61–2.64 (2H, m), 2.69–2.72 (2H, m), 7.46 (1H, t, *J* = 7.7), 7.66 (1H, dt, *J* = 1.1, 8.4), 7.86 (1H, d, *J* = 8.1), 7.91 (1H, d, *J* = 7.7)	214
3ae	46 (A) 10 (B) 39 (C)	182–184 (EtOAc)	1780	207 (4.36), 237 (4.22), 263 (4.28), 273 (s, 4.04), 279 (3.99), 320 (4.03)	4.15 (4H, s), 7.24–7.27 (2H, m), 7.30–7.36 (2H, m), 7.53 (1H, t, *J* = 7.7), 7.70 (1H, d, *J* = 7.7), 7.75 (1H, dt, *J* = 1.1, 8.1), 7.95 (1H, d, *J* = 7.7)	248
3af	90 (A)	208–209 (CH_2Cl_2/ EtOAc)	1790	210 (4.56), 227 (4.57), 235 (s, 4.48), 260 (4.46), 270 (4.52), 298 (s, 3.88), 375 (4.77)	7.31–7.41 (4H, m), 7.63 (1H, t, *J* = 7.7), 7.67–7.71 (1H, m), 7.75 (1H, d, *J* = 7.3), 7.80 (1H, dt, *J* = 0.7, 8.0), 8.05 (1H, d, *J* = 8.0), 8.22 (1H, d, *J* = 7.7), 8.47–8.49 (1H, m), 8.58 (1H, d, *J* = 8.0)	296
(*E*)-**3ag**	40 (A) 13 (C)	120–123 (Et_2O)	1780	216 (4.32), 247 (s, 3.94), 300 (s, 4.06), 340 (4.23)	1.83–1.89 (2H, m), 2.72 (2H, t, *J* = 7.0), 2.94 (2H, t, *J* = 7.0), 7.25–7.27 (2H, m), 7.32–7.35 (1H, m), 7.44–7.50 (2H, m), 7.69 (1H, dd, *J* = 1.5, 7.0), 7.87–7.91 (2H, m)	262
(*Z*)-**3ag**	13 (A) 8 (C)	146–147 (Et_2O)	1770	210 (4.35), 233 (4.06), 245 (s, 4.02), 297 (4.19), 310 (s, 4.16), 345 (4.24)	1.95–2.01 (2H, m), 2.77 (2H, t, *J* = 7.0), 3.05 (2H, t, *J* = 7.0), 7.18 (1H, d, *J* = 7.3), 7.25 (1H, dt, *J* = 1.5, 7.3), 7.31 (1H, dt, *J* = 1.5, 7.3), 7.55 (1H, t, *J* = 7.7), 7.75 (1H, dt, *J* = 1.5, 8.4), 7.94 (1H, d, *J* = 8.1), 8.00 (1H, d, *J* = 7.7), 8.24 (1H, d, *J* = 8.1)	262
3bc	80 (A)	136–137 (CH_2Cl_2/ Et_2O)	1760	228 (4.48), 275 (4.13), 284 (4.12), 365 (4.12)	1.70–1.79 (4H, m), 2.75 (2H, t, *J* = 6.9), 2.95 (2H, t, *J* = 6.9), 3.84 (3H, s), 3.93 (3H, s), 6.82 (1H, d, *J* = 8.7), 7.01 (1H, d, *J* = 8.7)	260

[a] Satisfactory microanalyses obtained: C ± 0.30, H ± 0.23.
[b] A: Method A, B: Method B, C: Method C.
[c] Uncorrected, measured with a Yanagimoto micromelting point apparatus.

Table 2. Physical Properties and Spectral Data of 2,2-Disubstituted Indan-1,3-diones **4** Prepared

Product[a]	Yield (%)	mp (°C)[b] (solvent)	IR (KBr) $\nu_{C=O}$ (cm^{-1})	UV (EtOH) λ_{max} (nm) (log ε)	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS), δ	MS, m/z (M^+)
4aa	44	99–103 (Et_2O)	1700, 1740	221 (4.57), 244 (4.01), 289 (3.49), 299 (3.46)	1.31 (6H, s), 7.86–7.88 (2H, m), 7.98–8.00 (2H, m)	20.32, 49.90, 123.65, 135.87, 140.43, 204.49	174
4ab	66	121–123 (CH_2Cl_2/hexane)	1700, 1720	226 (4.82), 303 (3.12), 332 (2.79), 343 (2.80), 403 (2.10)	7.28 (10H, s), 7.85–7.88 (2H, m), 8.06–8.08 (2H, m)	–	298
4ac	68	78–79 (Et_2O/pentane)	1700, 1740	223 (4.35), 245 (3.98), 300 (2.37)	1.97 (8H, s), 7.82–7.84 (2H, m), 7.95–7.97 (2H, m)	27.57, 35.42, 59.98, 123.31, 135.52, 141.59, 204.96	200
4ad	75	56–57 (pentane)	1700, 1740	223 (4.35), 246 (3.99), 300 (s, 2.77)	1.58–1.64 (2H, m), 1.70–1.73 (4H, m), 1.80–1.86 (4H, m), 7.82–7.85 (2H, m), 7.94–7.96 (2H, m)	21.13, 25.11, 29.66, 52.62, 123.42, 135.60, 140.35, 204.26	214
4ae	67	204 (CH_2Cl_2)	1700, 1740	223 (4.64), 245 (s, 4.10), 273 (s, 3.38)	3.36 (4H, s), 7.22 (4H, s), 7.87–7.90 (2H, m), 8.01–8.03 (2H, m)	40.75, 58.81, 123.69, 124.20, 127.19, 135.83, 140.31, 141.55, 202.89	248
4af	70	230–235 (CH_2Cl_2)	1710, 1740	207 (4.59), 226 (4.79), 253 (4.37), 265 (s, 4.32), 275 (s, 4.14), 287 (s, 3.97), 299 (3.60)	7.82–7.84 (6H, m), 7.95–7.97 (6H, m)	27.56, 35.42, 59.98, 123.30, 135.52, 141.59, 204.96	296
4ag	80	160–165 (Et_2O)	1710, 1740	226 (4.76), 248 (s, 4.08), 289 (s, 2.97)	2.08–2.11 (2H, m), 2.13–2.19 (2H, m), 2.95 (2H, t, J = 6.2), 6.53 (1H, d, J = 7.7), 6.99 (1H, dt, J = 1.1, 7.7), 7.15–7.21 (2H, m), 7.89–7.91 (2H, m), 8.06–8.08 (2H, m)	18.92, 29.11, 30.63, 57.91, 124.00, 126.34, 127.50, 130.03, 132.72, 135.87, 138.91, 142.06, 202.82	262
4bc	50	198–202 (CH_2Cl_2/Et_2O)	1700, 1730	227 (4.49), 283 (3.22), 371 (3.82)	1.93 (8H, s), 3.97 (6H, s), 7.23 (2H, s)	27.36, 35.49, 56.51, 60.52, 119.75, 129.21, 151.05, 203.08	260

[a] Satisfactory microanalyses obtained: C ± 0.29, H ± 0.20.
[b] Uncorrected, measured with a Yanagimoto micromelting point apparatus.

riments, the use of LHMDS (Method A) was revealed to be an effective base to afford 3-ylidenephthalides **3**. The utility of **3** in organic synthesis was demonstrated in the transformation to the 2,2-disubstituted indan-1,3-diones **4** related to fredericamycin A.

The IR spectra were measured in a KBr disk with a JASCO 810 spectrophotometer. The UV spectra were recorded in 95% EtOH on a Shimadzu UV 3100PC spectrophotometer. The NMR spectra were obtained on a JEOL GX-400 spectrometer operating at 399.65 MHz for ^1H and 100.40 MHz for ^{13}C nuclei using $CDCl_3$ as a solvent and TMS as an internal reference. The MS were determined on a JEOL DX-303 mass spectrometer. Elemental analyses were performed at the Microanalytical Laboratory of the Center for Instrumental Analysis in Nagasaki University. Flash column chromatography was carried out on a column of FL60D.

3-Ylidenephthalides 3; General Procedure:

Method A.[3] A solution of LHMDS (2.2 mmol, 1.0 M solution of hexane) was injected via a syringe into a stirred solution of **1** (2.2 mmol) in THF (60 mL) at −78 °C under an Ar atmosphere. The mixture was stirred at −78 °C for 1 h. To the greenish yellow solution was added via a syringe a solution of **2** (2.0 mmol) in THF (5 mL) at −78 °C and stirring was continued for an additional 1 h at −78 °C and 12 h at r.t. Standard workup and chromatographic purification gave **3**.

Method B. A mixture of NaH (60%, 0.09 g, 2.2 mmol) and **1** (2.2 mmol) in THF (80 mL) was stirred at 0 °C for 10 min under an Ar atmosphere. A solution of ketone **2** (2.0 mmol) in THF (5 mL) was added at 0 °C and the resulting mixture was stirred at 0 °C for 1 h, and 12 h at r.t. Standard workup and chromatographic purification gave **3**.

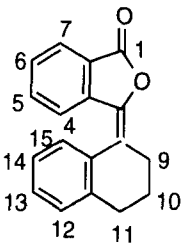
Method C. A modification of the literature procedure[6] was employed. A mixture of Cs_2CO_3 (1.4 g, 4.4 mmol) and **1** (4.0 mmol) in *i*-PrOH (10 mL) was stirred at 0 °C for 10 min under an Ar atmosphere. To this yellowish suspension was added a solution of **2** (4.4 mmol) in *i*-PrOH (5 mL) at 0 °C. The mixture was stirred for an additional 1 h. The resulting mixture was allowed to reach r.t. over 12 h with stirring, then quenched with 5% HCl solution, and evaporated. The residue was extracted with CH_2Cl_2, the extract was dried (Na_2SO_4) and evaporated. The crude product was chromatographed using EtOAc as eluent to give the corresponding product **3**. For the separation of *E* and *Z* isomers of **3ag**, several chromatographic purifications using benzene as eluent were neccessary (Table 1).

2,2-Disubstituted Indan-1,3-diones 4; General Procedure:

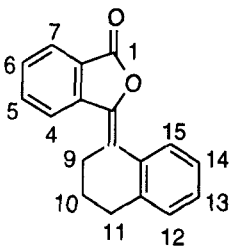
A solution of DIBAL-H (2.0 mmol, 1.0 M in CH_2Cl_2) was injected via a syringe into a stirred solution of **3** (1.0 mmol) in CH_2Cl_2 (50 mL) at −78 °C under an Ar atmosphere. After stirring at −78 °C for 1 h, a catalytic amount of NaOMe was added to the mixture and the solution was allowed to warm to r.t. for 3 h. The mixture was poured into sat. NH_4Cl solution and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated to give a keto alcohol intermediate which without isolation was used in the next step. To a solution of the keto alcohol in CH_2Cl_2 (30 mL) was added PDC (2 equiv) at r.t. and the mixture was stirred for 12 h. Standard workup and chromatography purification using CH_2Cl_2 as eluent gave the corresponding product **4** (Table 2).

We thank the Ministry of Education, Science and Culture, for financial support (Grant-in Aid No. 05671757).

(1) Scartoni, V.; Fiaschi, R.; Catalano, S.; Morelli, I.; Marsili, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1547.
Cundasawmy, N.E.; MacLean, D.B. *Can. J. Chem.* **1972**, *50*, 3028.
Barili, P.L.; Fiaschi, R.; Napolitano, E.; Pistelli, L.; Scartoni, V.; Marsili, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1654.
(2) Watanabe, M.; Furukawa, S. *Synlett* **1991**, 481.
Watanabe, M.; Ijichi, S.; Furukawa, S. *Synthesis* **1993**, 94.
(3) Watanabe, M.; Ijichi, S.; Morimoto, H.; Nogami, K.; Furukawa, S. *Heterocycles* **1993**, *36*, 553.
(4) Watanabe, M.; Morimoto, H.; Furukawa, S. *Heterocycles* **1993**, *36*, 2681.
(5) Total synthesis, see: Kelly, T.R.; Ohashi, N.; Armstrong-Chong, R.J.; Bell, S.H. *J. Am. Chem. Soc.* **1986**, *108*, 7100.
Kelly, T.R.; Bell, S.H.; Ohashi, N.; Armstrong-Chong, R.J. *Ibid.* **1988**, *110*, 6471.
Clive, D.L.J.; Tao, Y.; Khodabocus, A.; Wu, Y-J.; Angoh, A.G.; Bennett, S.M.; Boddy, C.N.; Bordeleau, L.; Kellner, D.; Kleiner, G.; Middleton, D.S.; Nichols, C.J.; Richardson, S.R.; Vernon, P.G. *J. Chem. Soc., Chem. Commun.* **1992**, 1489.
Rama Rao, A.V.; Singh, A.K.; Rao, B.V.; Reddy, K.M. *Tetrahedron Lett.* **1993**, *34*, 2665.
(6) Yamanoi, T.; Akiyama, T.; Ishida, E.; Abe, H.; Amemiya, M.; Inazu, T. *Chem. Lett.* **1989**, 335.
(7) Sinisterra, J.V.; Barrios, J.; Moulougui, Z.; Delmas, M.; Gaset, A. *Bull. Soc. Chim. Belg.* **1991**, *100*, 267.
(8) The irradiation of C-15 proton (δ = 7.69, dd, J = 1.5, 7.0 Hz) of (*E*)-**3ag** produced NOE enhancement at the signals of C-4 proton (δ = 7.87 ~ 7.91, m, with C-7 proton) and C-14 proton (δ = 7.25 ~ 7.27, m, with C-12 proton). On the other hand, in the case of (*Z*)-**3ag**, the irradiation of C-4 proton (δ = 7.94, d, J = 8.1 Hz) produced NOE enhancement at the signals of C-5 proton (δ = 7.75, dd, J = 1.5, 8.4 Hz) and C-9 protons (δ = 2.94, t, J = 7.0 Hz).



E-**3ag**



Z-**3ag**

(9) Holland, H.L.; MacLean, D.B.; Rodrigo, R.G.A.; Manske, R.F.H. *Tetrahedron Lett.* **1975**, 4323.