Synthesis of Dimethyl Phthalide-3-phosphonates and Their Use in the Regiospecific Synthesis of 3-Ylidenephthalides

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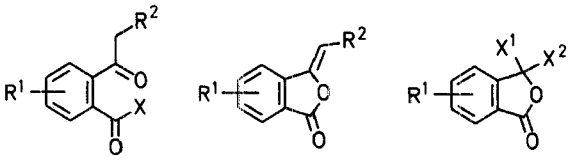
Aromatic 1,4-dicarbonyl compounds of general structure **1** are not easily obtained by direct substitution of the benzene ring, except in special cases[1]. Major sources of this class of compounds are 3-ylidenephthalides **2**, whose lactone ring is easily opened by nucleophilic bases. As equivalents of **1**, 3-benzylidenephthalides (**2**, $R^2 = C_6H_5$) have been used as starting material for the synthesis of polycondensed nitrogen heterocycles[2], in the preparation of biologically active substances[3,4], in the total synthesis of phthalideisoquinoline alkaloids[5], and in a new approach to synthesize protopine and protoberberine alkaloids[6]. Moreover, 3-alkylidenephthalides (**2**, R^2 = alkyl) are also found in nature as components of the essential oils of some umbelliferous plants[7].



1 **2** **3**

A general and extensively used method of preparation of 3-ylidenephthalides is the Perkin reaction between phthalic anhydrides (**3**, $X^1 - X^2 = O$) and carboxylic acid anhydrides[3,5,7]. A recent method involves Wittig reaction of phthalic anhydrides with a stabilized phophorane[8]. However, starting from unsymmetrically substituted phthalic anhydrides, these methods lead to mixtures of regioisomers. Thus, in contrast to a published report[5] concerning the preparation of pure 3-(3,4-methylenedioxybenzylidene)-6,7-methylenedioxyphthalide [(*Z*)-**7bb**] by Perkin reaction between 3,4-methylenedioxyphenylacetic acid and 3,4-methylenedioxyphthalic anhydride, we have found that the analogous reaction between the corresponding methoxy-substituted reagents affords a mixture of 3-(3,4-dimethoxybenzylidene)-4,5-dimethoxyphthalide and 3-(3,4-dimethoxybenzylidene)-6,7-dimethoxyphthalide in the ratio 70:30.

To the best of our knowledge, the only reported regiospecific synthesis of 3-ylidenephthalides is the Wittig-Horner-type condensation of aromatic aldehydes and diphenyl 6-nitrophthalide-3-phosphonate [**3**, $R^1 = 6\text{-}NO_2$, $X^1 = H$, $X^2 = PO(OC_6H_5)_2$] obtained by thermal condensation of 5-nitrophthalaldehydic acid and diphenyl phosphite[9]. However, the formation of the phosphonate reagent, as well as the generation of the α-phosphonate anion for subsequent nucleophilic reaction with the aldehyde carbonyl, appear to be limited to phthalaldehydic acids bearing a strong electron-withdrawing group. Furthermore, only the condensation with aromatic aldehydes has been reported. Indeed, attempts to achieve the thermal condensation between diphenyl phosphite and phthalaldehydic acids (**4a–c**) lacking an electron-withdrawing substituent have been unsuccessful in our hands.

We now report an efficient procedure for the preparation of phosphonate reagents **5a–c** and their use in Wittig-Horner-type condensations with aromatic aldehydes. Furthermore, one example for the condensation with an aliphatic aldehyde leading to the natural product **7cc** is given.

Compounds **4a–c** give good yields of the phosphonates **5a–c** on short exposure to an excess of 30% sodium dimethyl phosphite in methanol followed by acidification of the mixture. Hydroxyphosphonate esters are probable reaction intermediates which lactonize upon acidification. Condensation of **5a–c** with aromatic aldehydes **6a, b** to form the benzylidenephthalides **7** is achieved by stirring of the reactants in the presence of sodium hydride in dry tetrahydrofuran for 3 days. Use of alternative conditions such as stirr-

Table 1. Dimethyl Phthalide-3-phosphonates **5a–c** prepared

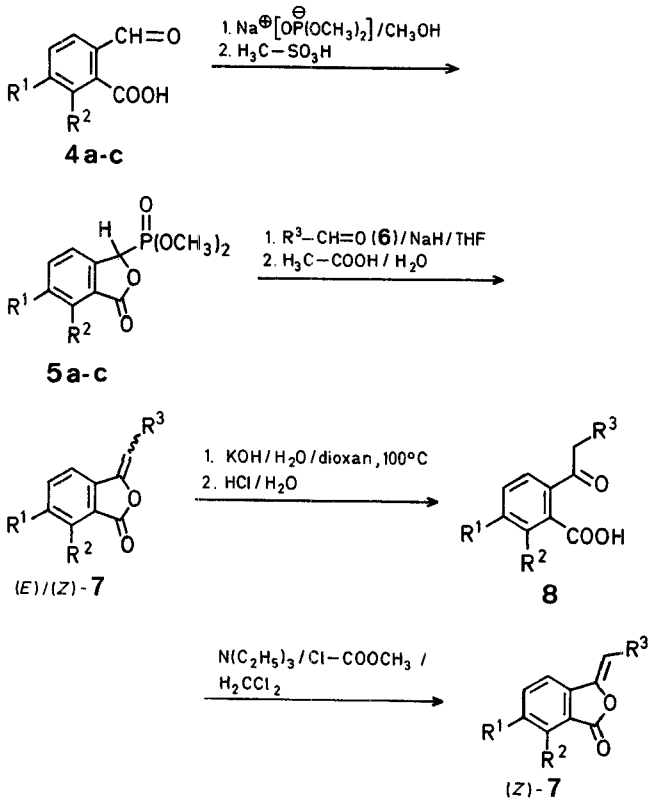
Product	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (Nujol) $\nu_{C=O}$[cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ[ppm]
5a	76	84–87°	$C_{12}H_{15}PO_7$ (302.2)	1760	3.62, 3.94 (2d, 6H, J_{HP} = 11 Hz, OCH_3); 3.95, 4.11 (2s, 6H, OCH_3); 5.62 (d, 1H, J_{HP} = 11 Hz, P—CH); 7.35 (br. s, 2H_{arom})
5b	77	154–156°	$C_{11}H_{11}PO_7$ (286.2)	1750	3.69, 3.94 (2d, 6H, J_{HP} = 11 Hz, OCH_3); 5.70 (d, 1H, J_{HP} = 11 Hz, P—CH); 6.26 (s, 2H, CH_2); 7.17 (br. s, 2H_{arom})
5c	74	97–99°	$C_{10}H_{11}PO_5$ (242.2)	1760	3.62, 3.92 (2d, 6H, J_{HP} = 11 Hz, OCH_3); 5.75 (d, 1H, J_{HP} = 11 Hz, P—CH); 7.34–8.10 (m, 4H_{arom})

[a] Satisfactory microanalyses obtained: C ±0.41, H ±0.07.

Table 2. (*E*)/(*Z*)-Benzylidenephthalides (*E*)/(*Z*)-**7** and Pure Stereoisomers (*Z*)-**7** prepared

Educts	Product	(*E*)/*Z*-Mixture		(*Z*)-**7**				
		Yield[a] [%]	(*E*/*Z*)-Ratio	Yield[b] [%]	m.p. [°C]	Molecular formula[c] or Lit. m.p. [°C]	I.R. (Nujol) ν[cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6/TMS) δ[ppm]
5a + **6a**	**7aa**	89	50/50	98	165–167°	170–172°[1]	see Ref.[1]	
5a + **6b**	**7ab**	91	60/40	97	179–180°	$C_{18}H_{14}O_6$ (326.3)	1750	3.91, 3.98 (2s, 6H, OCH_3); 6.05 (s, 2H, CH_2); 6.63 (s, 1H, —CH=); 6.89–8.25 (m, 5H_{arom})
5b + **6a**	**7ba**	94	60/40	95	218–219°	$C_{18}H_{14}O_6$ (326.3)	1760	3.81 (s, 6H, OCH_3); 6.30 (s, 2H, CH_2); 6.65 (s, 1H, —CH=); 6.95–7.55 (m, 5H_{arom})
5b + **6b**	**7bb**	96	50/50	94	298–299°[d]	$C_{17}H_{16}O_6$ (310.3)	1760	6.06, 6.30 (2s, 4H, CH_2); 6.67 (s, 1H, =CH—); 6.91–7.57 (m, 5H_{arom})
5c + **6b**	**7bc**	93	50/50	94	201–203°	202.5–204°[3]	see Ref.[3]	

[a] Yield based on **5**.
[b] Yield based on (*E*)/(*Z*)-**7**.
[c] Satisfactory microanalyses obtained: C ±0.29, H ±0.07.
[d] Ref.[5], m.p. 259–261°C.



4,5	R¹	R²
a	OCH_3	OCH_3
b	$-O-CH_2-O-$	
c	H	H

6	a	b	c
R³	H_3CO, H_3CO	O, O	n-C_3H_7

ing with sodium hydride in dimethylformamide for 15 min or with potassium *t*-butoxide in tetrahydrofuran for 60 min, although permitting shorter reaction times, result in lower yields of **7** as a result of substantial contamination with 2-phenyl-1,3-indanediones. However, such conditions were used for the condensation of **5c** with butanal.

As shown by T.L.C. and ^{1}H-N.M.R. analysis, the double bond formation in the Wittig reaction results in mixtures of (*E*)/(*Z*)-isomers. No attempt has been made to separate the geometrical isomers of the benzylidenephthalides. The (*E*)/(*Z*)-mixtures of **7** may be used directly for all reactions involving opening of the lactone ring. Furthermore, the isomeric mixtures are converted quantitatively to the more stable (*Z*)-isomers by opening of the lactone ring with potassium hydroxide in aqueous dioxan followed by recyclization of the intermediate deoxybenzoin-2-carboxylic acid **8** with triethylamine/methyl carbonochloridate in dichloromethane.

Melting points are uncorrected. I.R. spectra were recorded on a Perkin Elmer 195 spectrophotometer and ^{1}H-N.M.R. spectra on a Varian EM 360 A or on a Varian CFT20 spectrometer. Compounds **4a** and **4b** were prepared according to reported procedures[1]. Dry tetrahydrofuran was distilled from sodium/benzophenone under nitrogen.

Dimethyl Phthalide-3-phosphonates 5a–c; General Procedure:
Dimethyl phosphite (11.0 g, 0.1 mol) and the appropriate phthalaldehydic acid **4** (0.07 mol) are successively added under nitrogen at 0°C to a stirred solution of sodium (2.3 g, 0.1 mol) in methanol (80 ml). After stirring for 30 min at room temperature, methanesulphonic acid (11.0 g, 0.11 mol) is added. Most of the solvent is evaporated under reduced pressure with gentle heating and the residue is partitioned between dichloromethane (200 ml) and cold

water (50 ml). The organic layer is washed with water (2 × 50 ml), dried with magnesium sulphate, and evaporated to give crude **5**, which is recrystallized from dichloromethane/ether (Table 1).

(*E*)/(*Z*)-3-Benzylidenephthalides [(*E*)/(*Z*)-7; General Procedure:
To a solution of **5** (5 mmol) and aldehyde **6** (6 mmol) in dry tetrahydrofuran (50 ml), sodium hydride (350 mg of a 50% dispersion in mineral oil, 7.7 mmol) is added and the mixture stirred under nitrogen at room temperature. Stirring is continued until T.L.C. analysis (silica gel plates, ether) indicates the disappearance of starting material 5 (3–4 days). Acetic acid (1 ml) and water (30 ml) are cautiously added to decompose excess sodium hydride and to dissolve inorganic materials. The reaction product may in part precipitate during this operation. The solid is collected by suction and the organic layer evaporated at reduced pressure to give a residue which, together with the solid, is taken up in dichloromethane (150 ml). The resulting solution is washed with water (2 × 50 ml), dried with magnesium sulphate, and evaporated. The bright yellow residue is collected after trituration with ether. Due to the low solubility of the (*E*)/(*Z*)-mixtures of **7bb** in all common solvents, the precipitate obtained is used as such without further purification.

Preparation of Pure Stereoisomers (*Z*)-7; General Procedure:
The mixture of (*E*)- and (*Z*)-**7** (2 mmol), 10 molar aqueous potassium hydroxide (0.25 ml, 2.5 mmol), and dioxan (6 ml) is heated to 100°C in a sealed tube with occasional shaking for 1 h. The homogeneous solution thus formed is evaporated at reduced pressure, the residue is dissolved in water and the filtered solution, after acidification with dilute hydrochloric acid, extracted with dichloromethane (3 × 50 ml). The volume of the dried organic extract is adjusted to ~ 50 ml and the solution, containing the crude deoxybenzoin-2-carboxylic acid (**8**), is treated with triethylamine (1 ml) and methyl chloroformate (1 ml); a strong gas evolution occurs and the solution becomes bright yellow. Pure (*Z*)-**7** is obtained as a bright yellow solid by evaporation of the dichloromethane solution after washing with water (2 × 20 ml), and dilute hydrochloric acid (20 ml). An analytical sample is recrystallized from dichloromethane/ether (Table 2). Compound (*Z*)-**7bb** precipitates as a solid from the reaction mixture, and is collected by suction; the analytical sample is obtained by recrystallization from a large amount of dichloromethane.

***(E)/(Z)*-3-*n*-Butylphthalide[(*E*)/(*Z*)-7cc]:**
Compound **5c** (2.4 g, 10 mmol) is dissolved in dry tetrahydrofuran (50 ml) and to the chilled solution potassium *t*-butoxide (1.12 g, 10 mmol) is added with stirring under nitrogen. After 30 min *n*-butanal (**6c**; 0.8 g, 11 mmol) is added. The resulting mixture is stirred for 30 min at room temperature, then diluted with an equal volume of hexane and treated with acetic acid (1 ml). Water (30 ml) is slowly added until two homogeneous phases are obtained. The organic layer is washed with water (50 ml), saturated sodium hydrogen carbonate solution (20 ml), brine (50 ml), and dried with magnesium sulphate. The oily residue obtained by evaporation is bulb to bulb distilled (120°C/0.01 torr) to obtain a mixture of (*E*)- and (*Z*)-**7cc**; yield: 1.5 g (79%). The (*E*)/(*Z*)-ratio is determined as 20:50 on the basis of the reported ^{1}H-N.M.R. data[7]. The 2 isomers can be separated by flash chromatography[10] using dichloromethane as eluent.

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