A Convenient Synthesis of 3-Phenacylidenephthalides

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(Received December 3, 1987)

Synopsis. 3-Phenacylidenephthalides were prepared by the dehydration of 2-(1,3-dioxo-3-phenylpropyl)benzoic acids, obtained in turn by the condensation of phthalic anhydride with acetophenones.

3-Phenacylidenephthalides (**4**) have attracted wide attention on account of their biological activities as plant growth regulants[1-5] and their reducing effects on the herbicidal injury to plants.[6] Several methods to prepare **4** have been developed.[2,7,8] However, these procedures need complex operations and the yields are often unsatisfactory. The Wittig reaction of phthalidylphosphonium bromide with phenylglyoxal has been reported to give *Z*-**4a** in 40% yield. We now report a convenient procedure for the synthesis of **4** by the dehydration of 2-(1,3-dioxo-3-phenylpropyl)benzoic acids (**3**).

The starting materials, 2-(1,3-dioxo-3-phenylpropyl)benzoic acids (**3**), were prepared in high yields by the reaction of acetophenones (**2**) with phthalic anhydride (**1**) in the presence of sodium methoxide[9] (Table 1). The dehydration was examined by several halogenating or dehydrating reagents (Table 2). Treatment of **3** with thionyl chloride in chloroform at reflux temperature gave **4** in excellent yields as a mixture of *E*- and *Z*-isomers, which was easily separated by silica-gel column chromatography. The stereochemistry of each isomer was determined by a consideration of the ^{1}H NMR spectrum.[8] Similar

Table 1. Preparation of 2-(1,3-Dioxo-3-phenylpropyl)benzoic Acids **3a—e**

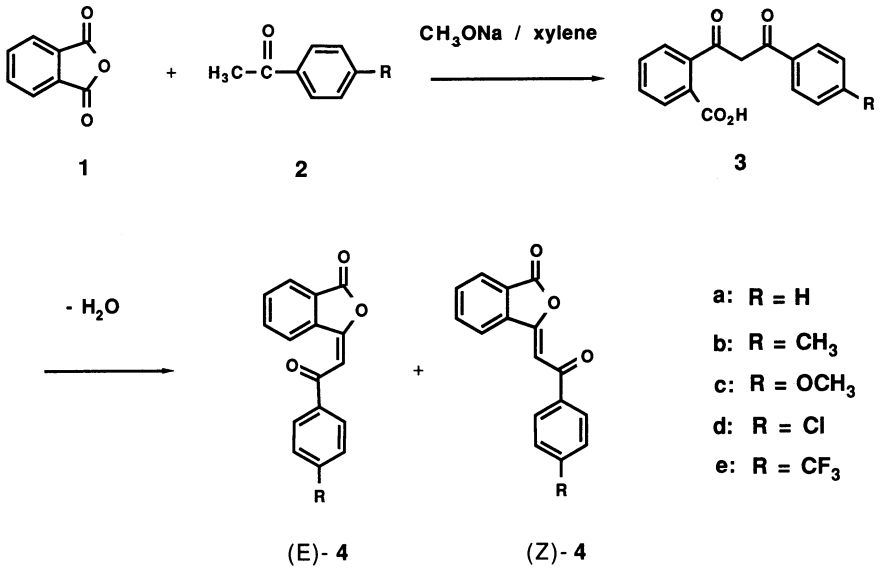
Entry	Product	R	Yield [%][a]
1	**3a**	H	85
2	**3b**	CH_3	82
3	**3c**	OCH_3	87
4	**3d**	Cl	81
5	**3e**	CF_3	80

a) Isolated yields.

Table 2. Preparation of 3-Phenacylidenephthalides **4a—e**

Reaction condition				Product	R	Yield [%][a]	*E* : *Z*[b]
Reagent	Solvent	Temp	Time/h				
$SOCl_2$	$CHCl_3$	Reflux	3	**4a**	H	92	50 : 50
$SOCl_2$	$CHCl_3$	Reflux	3	**4b**	CH_3	92	70 : 30
$SOCl_2$	$CHCl_3$	Reflux	3	**4c**	OCH_3	93	70 : 30
$SOCl_2$	$CHCl_3$	Reflux	3	**4d**	Cl	91	54 : 46
$SOCl_2$	$CHCl_3$	Reflux	3	**4e**	CF_3	91	57 : 43
MeCOCl	$CHCl_3$	Reflux	3	**4c**	OCH_3	94	63 : 37
p-TsOH[c]	C_6H_6	Reflux	3	**4c**	OCH_3	96	70 : 30
PPh_3	CCl_4	Reflux	24	**4c**	OCH_3	83	73 : 27
DCC[d]	AcOEt	r.t.	2	**4c**	OCH_3	90	0 : 100

a) Isolated yields. b) Ratios of the stereoisomers (*E* and *Z*) were determined by ^{1}H NMR spectrum. c) *p*-Toluenesulfonic acid. d) Dicyclohexylcarbodiimide.



1 2 3

(E)-4 (Z)-4

results were obtained by using acetyl chloride, *p*-toluenesulfonic acid or triphenylphosphine, while the use of dicyclohexylcarbodiimide (DCC) afforded the *Z*-isomer exclusively.

The advantages of this dehydration procedure for the large scale preparation of **4** over existing literature procedures are that the starting materials are readily available, and the procedure is simple, short, and requires only mild conditions.

Experimental

General. All melting points were uncorrected. IR spectra were taken on a Hitachi 270-30 spectrometer. ^{1}H NMR spectra (270 MHz) were taken on a JEOL JNM-GX270 spectrometer.

General Procedure for 2-(1,3-Dioxo-3-phenylpropyl)benzoic Acids (3). A stirred mixture of anhydrous xylene (700 ml) and 28% methanol solution of sodium methoxide (99.2 g, 0.51 mol) was heated at 110 °C until the distillation of methanol had ceased. The mixture was cooled to 60 °C, and then acetophenones (**2**) (0.2 mol) and phthalic anhydride (**1**) (35.0 g, 0.24 mol) were added successively. The reaction mixture was again heated at 110—120 °C for 2 h and cooled to room temperature. The mixture was poured into cooled 12% aqueous hydrochloric acid (160 ml) and extracted with methyl ethyl ketone (350 ml×2). The combined extracts were washed with water (300 ml) and dried over sodium sulfate. The crude product obtained after the evaporation of the solvent was purified by recrystallization from suitable solvents (Table 1).

2-(1,3-Dioxo-3-phenylpropyl)benzoic Acid (3a): Mp 110—112 °C (benzene) (lit,[2] 111—113 °C); IR (KBr) 3046, 1725, 1608, 1575, 1542, 1497, 1461, 1416, 1299, 1245, 1125, 1050, 891, 768 cm^{-1}.

2-[3-(4-Methylphenyl)-1,3-dioxopropyl]benzoic Acid (3b): Mp 154—156 °C (C_2H_5OH/benzene); IR (KBr) 3130, 1713, 1647, 1602, 1575, 1490, 1422, 1311, 1254, 1167, 990, 864, 759 cm^{-1}.

Found: C, 72.20; H, 4.95%. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00%.

2-[3-(4-Methoxyphenyl)-1,3-dioxopropyl]benzoic Acid (3c): Mp 152—154 °C (C_2H_5OH); IR (KBr) 3000, 1690, 1595, 1500, 1460, 1440, 1415, 1290, 1260, 1225, 1180, 1020, 930, 850, 805, 775 cm^{-1}.

Found: C, 68.42; H, 4.53%. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73%.

2-[3-(4-Chlorophenyl)-1,3-dioxopropyl]benzoic Acid (3d): Mp 150—152 °C (CH_3OH/CCl_4) (lit,[2] 149—153 °C); IR (KBr) 2992, 1713, 1653, 1587, 1575, 1492, 1425, 1407, 1317, 1296, 1254, 1167, 1089, 1010, 990, 870, 822, 768 cm^{-1}.

2-[1,3-Dioxo-3-(4-trifluoromethylphenyl)]benzoic Acid (3e): Mp 151—153 °C (benzene); IR (KBr) 3004, 1698, 1620, 1578, 1458, 1416, 1329, 1284, 1176, 1116, 1071, 1012, 921, 858, 804, 771 cm^{-1}.

Found: C, 60.80; H, 3.27%. Calcd for $C_{17}H_{11}F_3O_4$: C, 60.72; H, 3.30%.

General Procedure for 3-Phenacylidenephthalide (4). A stirred mixture of 2-(1,3-dioxo-3-phenylpropyl)benzoic acids (**3**) (0.34 mol) and thionyl chloride (60.94 g, 0.51 mol) in chloroform (400 ml) was heated under reflux for 3 h. Removal of solvent and excess thionyl chloride in vacuo left the crude product, which was chromatographed on silica-gel column using chloroform as eluent. The pure *E*- and *Z*-isomers of 3-phenacylidenephthalides (**4**) were obtained as slightly yellow crystals (Table 2).

(*E*)-3-Phenacylidenephthalide (*E*-4a): Mp 116—117 °C (lit,[8] 116—118 °C); IR (KBr) 1795, 1665, 1610, 1250, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.21 (s, 1H), 7.48—8.11 (m, 8H), 9.03 (d, 1H, J=8.1 Hz).

(*Z*)-3-Phenacylidenephthalide (*Z*-4a): Mp 165—167 °C (lit,[8] 165—167 °C); IR (KBr) 1795, 1685, 1650, 1225, 1090, 985 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=6.78 (s, 1H), 7.42—8.08 (m, 9H).

(*E*)-3-(4-Methylphenacylidene)phthalide (*E*-4b): Mp 205—207 °C; IR (KBr) 1795, 1675, 1630, 1235, 1215, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.45 (s, 3H), 7.20 (s, 1H), 7.33 (d, 2H, J=8.1 Hz), 7.66—8.09 (m, 5H), 9.02 (d, 1H, J=7.7 Hz).

Found: C, 77.44; H, 4.61%. Calcd for $C_{17}H_{12}O_3$: C, 77.26; H, 4.58%.

(*Z*)-3-(4-Methylphenacylidene)phthalide (*Z*-4b): Mp 205—207 °C IR (KBr) 1795, 1680, 1630, 1240, 1220, 975 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.43 (s, 3H), 6.76 (s, 1H), 7.29 (d, 2H, J=8.4 Hz), 7.60—8.06 (m, 6H).

Found: C, 77.22; H, 4.60%. Calcd for $C_{17}H_{12}O_3$: C, 77.26; H, 4.58%.

(*E*)-3-(4-Methoxyphenacylidene)phthalide (*E*-4c): Mp 163—164 °C (lit,[6] 145 °C); IR (KBr) 1795, 1660, 1605, 1255, 1180, 975 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.91 (s, 3H), 7.00 (d, 2H, J=8.5 Hz), 7.19 (s, 1H), 7.67—7.88 (m, 2H), 7.95—8.02 (m, 1H), 8.04 (d, 2H, J=8.5 Hz), 9.00 (d, 1H, J=8.1 Hz).

(*Z*)-3-(4-Methoxyphenacylidene)phthalide (*Z*-4c): Mp 172—173 °C (lit,[6] 170 °C); IR (KBr) 1795, 1670, 1615, 1220, 1165, 965 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.89 (s, 3H), 6.72 (s, 1H), 6.93—7.03 (m, 2H), 7.66—7.91 (m, 3H), 7.94—8.05 (m, 3H).

(*E*)-3-(4-Chlorophenacylidene)phthalide (*E*-4d): Mp 165—167 °C (lit,[6] 158—159 °C); IR (KBr) 1800, 1671, 1620, 1251, 1095, 975 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.15 (s, 1H), 7.38—8.05 (m, 7H), 9.04 (d, 1H, J=8.1 Hz).

(*Z*)-3-(4-Chlorophenacylidene)phthalide (*Z*-4d): Mp 202—203 °C (lit,[6] 204 °C); IR (KBr) 1776, 1671, 1626, 1221, 1083, 972 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=6.69 (s, 1H), 7.42—7.52 (m, 2H), 7.68—8.04 (m, 6H).

(*E*)-3-[4-(Trifluoromethyl)phenacylidene]phthalide (*E*-4e): Mp 156—158 °C; IR (KBr) 1791, 1674, 1620, 1251, 1065, 987 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.18 (s, 1H), 7.70—8.20 (m, 7H), 9.09 (d, 1H, J=8.1 Hz).

Found: C, 64.28; H, 2.84%. Calcd for $C_{17}H_9F_3O_3$: C, 64.16; H, 2.85%.

(*Z*)-3-[4-(Trifluoromethyl)phenacylidene]phthalide (*Z*-4e): Mp 212—214 °C; IR (KBr) 1788, 1677, 1632, 1218, 1065, 969 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=6.71 (s, 1H), 7.70—8.19 (m, 8H).

Found: C, 64.13; H, 2.81%. Calcd for $C_{17}H_9F_3O_3$: C, 64.16; H, 2.85%.

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