A Convenient Synthesis of (*E*)-$\Delta^{3,3'}$-Biphthalides

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Our need for a variety of substituted biphthalides **3** as precursors to potential analogues of the convulsant alkaloid bicuculline[1,2] revealed that no detailed investigation into their synthesis has been made recently. Although Graebe and Guye[3] made several

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Table. $\Delta^{3,3'}$-Biphthalides 3 prepared

Product No.	R^2	R^3	R^4	R^5	R^6	Y	Yield [%]	m.p. [°C]	Molecular formula[a] or Lit. m.p. [°C]	
3a	H	H	H	H	H	O	85[b]	350–352°	352–354°[7]	
3b	H	H	H	H	H	S	90	317–319°	$C_{16}H_8O_3S$	(280.2)
3c[c]	H	H	H	H	H	NH	85	350–352°	>360°[3]	
3d[d]	H	H	OCH_3	OCH_3	H	O	90	289–290°	$C_{18}H_{12}O_6$	(324.3)
3e	H	H	H	NO_2	H	O	90	251–253°	$C_{16}H_7NO_6$	(309.2)
3f[d]	H	H	H	O—CH_2—O		O	95	>350°	$C_{17}H_8O_6$	(308.2)
3g[e]	H	H	CH_3	H	H	O	76	260–267°	$C_{17}H_{10}O_4$	(278.3)
3h[e]	H	H	Cl	H	H	O	91	268–275°	$C_{16}H_7ClO_4$	(298.7)
3i[d]	OCH_3	OCH_3	OCH_3	OCH_3	H	O	70	>350°	$C_{20}H_{16}O_8$	(384.3)
3j[d]	OCH_3	OCH_3	H	O—CH_2—O		O	94	>350°	$C_{19}H_{12}O_8$	(368.3)
3k[d]	OCH_3	OCH_3	H	OCH_3	OCH_3	O	85	>350°	$C_{20}H_{16}O_8$	(384.3)

[a] The biphthalides tended to retain solvent tenaciously on recrystallisation: all compounds obtained had either satisfactory microanalytical data (C ±0.38, H ±0.48, N ±0.13, S ±0.1) or the correct high resolution mass spectrum molecular weight (**3b, 3h, 3k**: ±0.0005 mass units).

[b] A yield of 92% was obtained when the tributylphosphonium salt was used. All yields recorded refer to those obtained using the triphenylphosphonium salt.

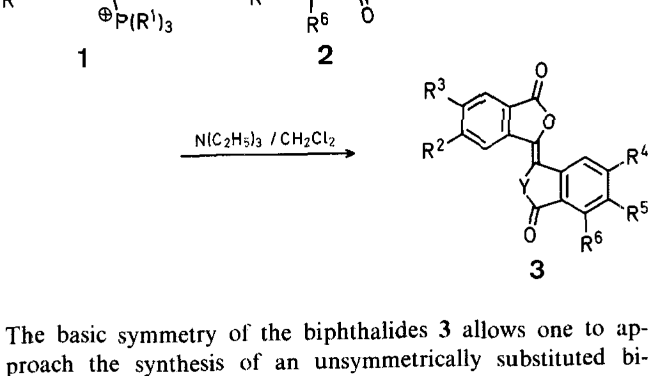
[c] The reactant was *N*-trifluoroacetylphthalimide.

[d] Reflux temperature was necessary.

[e] The product was an inseparable 1:1 mixture of isomers about R^4 and R^5.

biphthalides by fusing phthalides and phthalic anhydrides in the presence of sodium acetate, we have found that this procedure proceeds very poorly when applied to alkoxyphthalides. Low yields of biphthalides were obtained when Becker[4] treated 3-alkoxyphthalides with strong base and similarly Chatterjea et al.[5] isolated small amounts of biphthalide when methyl 2-formylbenzoate was warmed with ethanolic potassium cyanide, an observation similar to that made earlier by Graebe and Juillard[6]. Finally, we have found the method of Ramirez et al.[7,8] in which phthalic anhydride is heated with triethyl phosphite, is applicable only when the anhydride possesses electron-withdrawing substituents.

The phosphonium salts **1** are generally readily available from the corresponding 3-bromo- or 3-chlorophthalides or phthalaldehydic acids[9] and react smoothly with a variety of phthalic anhydrides **2** at room temperature or in refluxing dichloromethane solution, containing triethylamine, to afford **3** in 70–95% yields.



The basic symmetry of the biphthalides **3** allows one to approach the synthesis of an unsymmetrically substituted biphthalide by two general methods. For example, 3-bromo-6,7-dimethoxy- and 3-chloro-6,7-methylenedioxyphthalide could not be converted to either the triphenyl- or tributylphosphonium salt **1**, but synthesis of the required biphthalide was achieved when 5,6-dimethoxy- or 5,6-methylenedioxyphthalic anhydride were reacted with the appropriate phosphorane. The phosphoranes also reacted very rapidly with thiophthalic anhydride. Although no apparent reaction occurred with phthalimide, *N*-methyl- or *N*-phenylphthalimide, the desired imide **3c** was formed when *N*-trifluoroacetylphthalimide, prepared from potassium phthalimide and trifluoroacetic anhydride in dimethylformamide, was used.

Except for the case of **3c**, which was isolated as a 1:4 mixture of isomers and separated by T.L.C. to give a yellow solid of m.p. 308–311 °C, [(*Z*)-isomer] and an orange solid of m.p. 350–352 °C [(*E*)-isomer], the biphthalides **3** all appeared as a single isomer and the (*E*)-configuration was assigned to each on the basis of its strong yellow colour and infrared spectrum which exhibited one carbonyl peak around 1780 cm⁻¹; the corresponding colourless (*Z*)-isomers were reported[4] to show two carbonyl absorptions at 1720 and 1740 cm⁻¹, but the structure of these compounds was subsequently revised[10].

5,6-Dimethoxybiphthalide (3d); Typical Procedure:

To a solution of 4,5-dimethoxyphthalic anhydride (2.0 g, 9.6 mmol) and triphenyl-(3-phthalidyl)-phosphonium bromide[9] (4.95 g, 9.6 mmol) in dichloromethane (100 ml) is added triethylamine (0.97 g, 9.6 mmol) and the resultant bright yellow solution is further stirred under a blanket of nitrogen for 10 h. The mixture is then diluted with dichloromethane (200 ml) and washed with brine (2 × 50 ml). The brine is extracted with dichloromethane until no colour remains in the aqueous phase. The combined organic extracts are dried with magnesium sulphate and the solvent is removed to afford a yellow solid which is boiled in ether (20 ml) and filtered whilst hot. The residual solid is recrystallised from xylene to yield bright yellow needles; *yield*: 2.8 g (90%); *m.p.* 289–290 °C.

$C_{18}H_{12}O_6$	calc.	C 66.67	H 3.73
(324.3)	found	66.76	3.82

I.R. (nujol): $\nu = 1780$; 1600 cm⁻¹.

¹H-N.M.R. (CF₃COOD): $\delta = 4.11$ (s, 3H); 4.21 (s, 3H); 7.5–8.4 ppm (m, 6 H_{arom}).

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[1] D. R. Curtis, A. W. Duggan, D. Felix, G. A. R. Johnston, *Brain Res* **32**, 69 (1971).

[2] P. A. Marshall, B. A. Mooney, R. H. Prager, A. D. Ward, *Aust. J Chem.* **34**, accepted for publication.

[3] C. Graebe, P. Guye, *Justus Liebigs Ann. Chem.* **233**, 241 (1886).

[4] H. D. Becker, *J. Org. Chem.* **29**, 3070 (1964).

[5] J. N. Chatterjea, B. K. Banerjee, N. Prasad, *J. Ind. Chem. Soc.* **42**, 283 (1965).

[6] C. Graebe, P. Juillard, *Justus Liebigs Ann. Chem.* **242**, 214 (1887).

[7] F. Ramirez, H. Yamanaka, O. H. Basedow, *J. Am. Chem. Soc.* **83**, 173 (1961).

[8] F. Ramirez, J. S. Ricci, H. Tsuboi, J. F. Marecek, H. Yamanaka, *J. Org. Chem.* **41**, 3910 (1976).

[9] R. K. Howe, *J. Org. Chem.* **38**, 4164 (1973).

[10] H. A. Staab, J. Ipaktschi, *Chem. Ber.* **101**, 1457 (1968).