A Convenient Synthesis of Hydroxyphthalides

John Freskos, Tadeusz Cynkowski, and John S. Swenton*

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210, U.S.A.

The Diels–Alder reaction of *in situ* generated cyclohexa-1,3-dienes with methyl 4,4-diethoxybut-2-ynoate (**1**) followed by reverse Diels–Alder and hydrolysis affords substituted hydroxyphthalides in good yield.

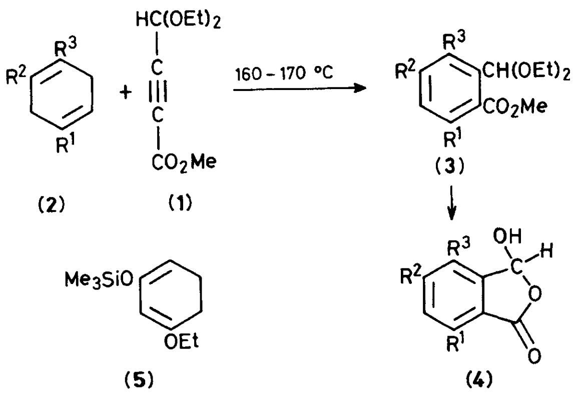
Hydroxyphthalides are key intermediates in synthetic strategies to a number of naturally occurring systems.[1,2] Methods for their synthesis are limited to functional group interconversions of phthalic anhydrides,[2a,3] phthalides,[2b,2c] and *o*-toluic acid derivatives[1a] and recently developed metallation procedures.[1a,4] We report here a Diels–Alder sequence which complements the above routes and affords excellent overall yields of hydroxyphthalides from readily available starting materials.

Since a regiospecific synthesis of hydroxyphthalides was of

Table 1. Preparation of hydroxyphthalides from (**1**).

Diene	Acetal ester[a] (yield %)	Hydroxyphthalide[b] (yield %)
(**2a**)	(**3a**) (80)	(**4a**) (77)
(**2b**)	(**3b**) (81)	(**4b**) (75)
(**2c**)	(**3c**) (79)	(**4c**) (79)
(**5**)	(**3d**) (89)	(**4e**) (85)

[a] (**3a**) B.p. 112—115 °C at 0.06 mmHg; (**3b**) b.p. 125—130 °C at 0.07 mmHg; (**3c**) b.p. 126—131 °C at 1×10^{-4} mmHg; (**3d**) b.p. 140—142 °C at 5×10^{-4} mmHg. [b] (**4a**) M.p. 149—151 °C; (**4b**) m.p. 98—100 °C; (**4c**) m.p. 192—193 °C; (**4e**) m.p. 220—221 °C.



	R^1	R^2	R^3
a	OMe	H	H
b	OBu^n	H	H
c	OMe	H	OMe
d	OEt	$OSiMe_3$	H
e	OEt	OH	H

prime interest, we focused on the Diels–Alder reaction of the unsymmetrical acetylene (**1**).[5†] Not only did the compound possess the correct oxidation state of the hydroxyphthalide at the carbonyl groups, but also both electronic and steric effects present in (**1**) should favour regioselectivity in its Diels–Alder chemistry. Since cyclohexa-1,4-dienes (**2**) are available in one step from the corresponding aromatic compound *via* Birch reduction, and an *in situ* thermally induced isomerization of the 1,4- to the 1,3-diene would not be unreasonable, the direct reaction of (**1**) and (**2**) was studied. Reaction of the dienes (**2a—c**) (1.3—1.8 equiv.) with (**1**) at 160—170 °C gave the acetal esters (**3a—c**) in good yield after simple distillation (pure by ^{1}H and ^{13}C n.m.r.). However, the reaction of (**1**) and 1,5-dimethoxycyclohexa-1,4-diene gave a complex mixture of products. Surmising that this might be due to a slow isomerization of the 1,4- to the 1,3-diene, the reaction of (**1**) with 1-ethoxy-3-(trimethylsiloxy)cyclohexa-1,3-diene (**5**) was examined.‡ This reaction afforded (**3d**) in excellent yield after distillation.

Acid hydrolysis[1a] of the acetal esters (**3a,b,d**) cleanly afforded the hydroxyphthalides (**4a,b,e**) (Table 1). Under these conditions (**3c**) gave several additional products. However, the (**3c**) → (**4c**) conversion could be effected by shaking an ethereal solution of (**3c**) with 5% aqueous hydrochloric acid, concentration *in vacuo*, and trituration of the solid, followed by overnight stirring with 20% aqueous potassium hydroxide at room temperature and then acidification.

This two-step conversion of the cyclohexa-1,4-dienes and methyl 4,4-diethoxybut-2-ynoate into hydroxyphthalides makes these compounds available in quantity from convenient starting materials. The use of the readily available (**1**) in other Diels–Alder reactions may prove especially useful since the two carbonyl groups in the product are easily differentiated chemically.§

We thank the National Cancer Institute and the National Science Foundation for partial support.

Received, 21st March 1984; Com. 386

References

1 For leading references using hydroxyphthalides as starting materials in the synthesis of quinone annelating reagents, see: (a) B. L. Chenard, M. G. Dolson, A. S. Sercel, and J. S. Swenton, *J. Org. Chem.*, 1984, **49**, 318; (b) G. A. Kraus, H. Cho, S. Crowley, B. Roth, H. Sugimoto, and S. Prugh, *J. Org. Chem.*, 1983, **48**, 3439; (c) F. M. Hauser and B. J. Mal, *J. Am. Chem. Soc.*, 1983, **105**, 5688.

2 (a) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Tetrahedron*, 1968, **24**, 2443; (b) M. Uemura, S. Tokuyama, and T. Sakan, *Chem. Lett.*, 1975, 1195; (c) B. M. Trost, G. T. Rivers, and J. M. Gold, *J. Org. Chem.*, 1980, **45**, 1835.

3 Reduction of phthalic and other cyclic anhydrides with a variety of reducing agents usually affords the corresponding phthalides: (a) D. M. Bailey and R. E. Johnson, *J. Org. Chem.*, 1970, **35**, 3574; (b) P. G. Sammes and S. M. Mellows, *Chem. Commun.*, 1971, 21; (c) A. J. Birch and R. A. Russell, *Aust. J. Chem.*, 1971, **24**, 1975; (d) D. E. Burke and P. W. LeQuesne, *J. Org. Chem.*, 1971, **36**, 2397; (e) C. C. Shroff, W. S. Stewart, S. J. Uhm, and J. W. Wheeler, *ibid.*, 1971, **36**, 3356; (f) T. Koizumi, N. Yamamoto, and E. Yoshii, *Chem. Pharm. Bull.*, 1973, **21**, 312; (g) B. C. Subba Rao, *Curr. Sci.*, 1961, **30**, 218; (h) A. J. McAlles, R. McCrindle, and D. W. Sneddon, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2037.

4 (a) S. O. DeSilva, J. N. Reed, and V. Snieckus, *Tetrahedron Lett.*, 1978, 5099; (b) H. P. Plauman, B. A. Keay, and R. Rodrigo, *Tetrahedron Lett.*, 1979, 4921; (c) F. E. Zielger and K. W. Fowler, *J. Org. Chem.*, 1976, **41**, 1564; (d) D. L. Commins, J. D. Brown, and N. B. Mantlo, *Tetrahedron Lett.*, 1982, **23**, 3979; (e) A. K. Sinhababu and R. T. Borchardt, *J. Org. Chem.*, 1983, **48**, 2357.

5 The 1,3-dipolar cycloadditions of (**1**) have been studied. (a) F. Farina, M. V. Martin, and F. Sanchez, *An. Quim.*, 1982, **78**, 332; (b) F. Farina, P. Fernadez, M. R. Martin, M. V. Martin, and F. Sanchez, *ibid.*, 1983, **79**, 333; (c) see also A. Gorgues, A. Simon, A. LeCoq, and F. Corre, *Tetrahedron Lett.*, 1981, **22**, 625.

---

† The acetylene (**1**) was prepared by reaction of 3,3-diethoxypropyne [prepared in a one-pot 40% yield from acrolein (O. H. Johnson, *J. Org. Chem.*, 1958, **23**, 738)] in tetrahydrofuran with methyl-lithium (1 equiv.) followed by addition of this lithium salt to a solution of methyl chloroformate at −78 °C. Distillation afforded 82% of (**1**). The procedure is a substantial improvement over that reported for an analogous system which afforded the acetylene ester in 45% yield (R. N. Warrener and E. N. Cain, *Aust. J. Chem.*, 1977, **24**, 785).

‡ Diene (**5**) was prepared by reaction of 3-ethoxycyclohex-2-enone (W. Gannon and H. O. House, *Org. Synth.*, **40**, 41) with 1.1 equiv. of lithium di-isopropylamide at −78 °C followed by addition of trimethylsilyl chloride.

§ Professor F. Farina has informed us that he has studied the Diels–Alder reaction of (**1**) with simple dienes.