CHEMISTRY LETTERS, pp. 1263 - 1266, 1984.

GENERATION AND DIELS-ALDER REACTION OF 1-SILOXY-3-ARYLISOBENZOFURANS FROM 3-ARYLPHTHALIDES

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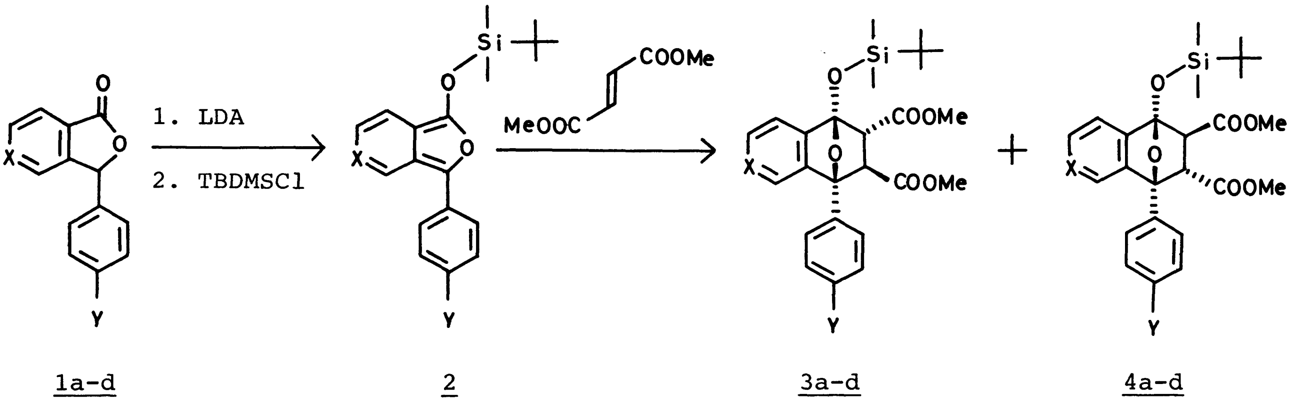
1-*t*-Butyldimethylsiloxy-3-arylisobenzofurans, a new type of isobenzofurans, were generated from 3-arylphthalides by sequential treatment with LDA and TBDMSCl. The isobenzofurans, thus formed, were intercepted *in situ* by dimethyl fumarate to give stable Diels-Alder adducts in good yields. These adducts were converted into 4-aryl-1-naphthols by acid treatment. This new route for the preparation of naphthols was applied to the synthesis of natural arylnaphthalide lignan, diphyllin.

The Diels-Alder reactivity of isobenzofuran derivatives has played a prominent role in the construction of polycyclic compounds.1) Since the recent discovery2) of the generation of isobenzofurans from 1-alkoxyphthalans or their equivalents under mild conditions, their utility in organic synthesis, particularly in natural products synthesis,3) has expanded significantly. In this Letter, we report a new approach to the facile generation of the reactive isobenzofuran derivatives from substituted phthalides. The advantage of the use of phthalides as isobenzofuran precursors is their ready accessibility from a variety of substituted benzamides and aldehydes *via* directed lithiation strategy.4)

The C-3 deprotonation of phthalides by LDA to generate 3-lithiophthalides has been reported previously.5) We envisaged that silylation of the resulting ambident anions would afford 1-siloxyisobenzofurans, because silicon has much stronger affinity to oxygen rather than carbon.6) Based on this assumption, the following experiments were carried out.

Table 1. Diels-Alder Reaction of 1-*t*-Butyldimethylsiloxy-3-arylisobenzofurans 2 with Dimethyl Fumarate

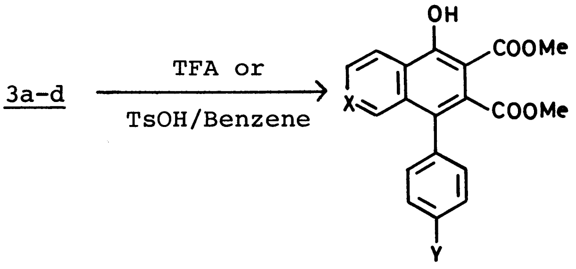


Phthalide	Adduct		X	Y	3 Yield/%	Mp/°C	4 Yield/%	Mp/°C
1a	3a	4a	C-H	H	87	93.5-94	≈0	—
1b	3b	4b	C-H	OMe	78	138-139	12	oil
1c	3c	4c	C-OMe	H	80	118	10	oil
1d	3d	4d	N	OMe	38	139-140.5	8	oil

We employed 3-arylphthalides 1a-d as isobenzofuran precursors, *t*-butyldimethylsilyl chloride(TBDMSCl) as a silylating agent and dimethyl fumarate[7)] as a dienophile. The reactions were performed as described in the following example. Under an atmosphere of nitrogen, a THF solution of 3-(*p*-methoxyphenyl)phthalide 1b (481 mg, 2.0 mmol) was injected into a stirred solution of LDA(2.2 mmol) in 50 ml of THF at -78 °C. After one hour, TBDMSCl(332 mg, 2.2 mmol) in THF was injected and the temperature was gradually warmed to 0 °C. The deep-red color of the lithiophthalide slowly changed to light-orange at this temperature. After standing for two hours at 0 °C, *t*-BuOH(0.2 ml) was added in order to quench unreacted LDA, followed by dimethyl fumarate(317 mg, 2.2 mmol) in THF. The light-orange color disappeared instantaneously upon the addition of the dienophile. The reaction mixture was stirred overnight and worked up in a usual manner to give crude material which upon recrystallization and chromatography gave 780 mg(78%) of adduct 3b and 120 mg(12%) of adduct 4b. The stereochemical assignments were derived by comparing ^{1}H-NMR spectra[8)] of both adducts with those of closely related systems[9)] having unambiguous configurations. The adducts 3a,c,d and 4c,d were obtained similarly from the corresponding phthalides 1a,c,d. As is shown in Table 1, these reactions proceed with high stereoselectivity affording adducts 3 as major products. The chemical yields are also high except for the reaction which used pyridine-phthalide 1d as an isobenzofuran precursor. The low yield may be attributable to the instability of the pyridine ring[10] to the strongly basic conditions employed for the anion formation.

Desilylation and aromatization of the Diels-Alder adducts proceeded cleanly under acidic conditions. For example, the major adducts 3a-c were converted into the 1-naphthol derivatives 5a-c in over 80% yields upon brief treatment with trifluoroacetic acid(TFA) at room temperature. Although the pyridine derivative 3d resisted this set of conditions for aromatization, it was readily converted into the desired compound 5d by heating with *p*-toluenesulfonic acid(TsOH) in refluxing benzene.

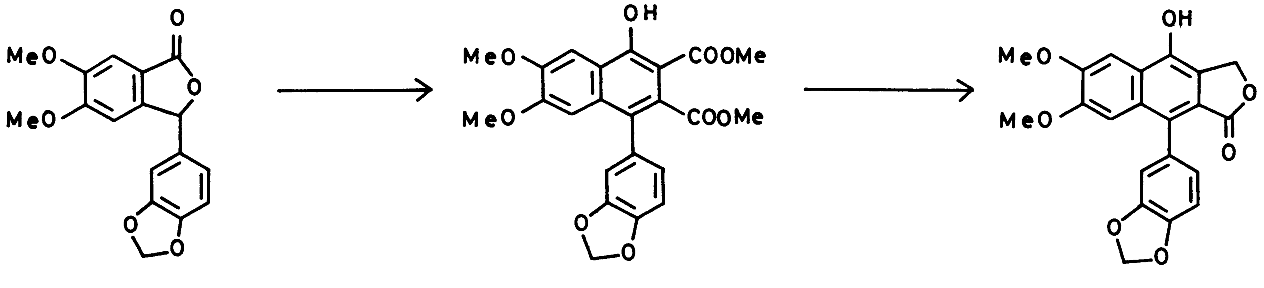
Table 2. Conversion of the Diels-Alder Adducts 3a-d to 4-Aryl-1-naphthols 5a-d



5a-d

Naphthol	X	Y	Yield/%	Mp/°C
5a	C-H	H	84	149-150
5b	C-H	OMe	81	147-148.5
5c	C-OMe	H	85	184-185
5d	N	OMe	80	>300

This overall transformation of 3-arylphthalides to 4-aryl-1-naphthols was applied to the synthesis of arylnaphthalide lignan,[11] diphyllin. Thus, the phthalide 6[12] was converted into a mixture of the Diels-Alder adducts, which without separation, was transformed into the naphthol 7, mp 234-236 °C, using the conditions mentioned above in 70% overall yield. The C-2 methoxycarbonyl group of 7 was selectively reduced by a large excess of $NaBH_4$ in methanol[13] to afford the lactone 8, mp 283-285 °C(decomp) in 85% yield after acidic work-up. This compound was shown to be identical with natural diphyllin[14] by TLC and IR comparisons.



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References

1) For recent reviews of isobenzofuran chemistry, see: M. J. Haddadin, *Heterocycles*, 9, 865(1978); W. Friedrichsen, *Adv. Heterocycl. Chem.*, 26, 135 (1980); U. E. Wiersum, *Aldrichimica Acta*, 14, 53(1981).

2) K. Naito and B. Rickborn, *J. Org. Chem.*, 45, 4061(1980); J. G. Smith, S. S. Welankiwar, B. S. Schantz, E. H. Lai, and N. G. Chu, *ibid.*, 45, 1817(1980); B. A. Keay, D. K. W. Lee, and R. Rodrigo, *Tetrahedron Lett.*, 21, 3633(1980); M. A. Makhlouf and B. Rickborn, *J. Org. Chem.*, 46, 2734(1981).

3) D. Rajapaksa and R. Rodrigo, *J. Am. Chem. Soc.*, 103, 6203(1981); B. A. Keay and R. Rodrigo, *ibid.*, 104, 4725(1982); *idem.*, *Can. J. Chem.*, 61, 637(1983).

4) For a review of directed lithiation of tertiary aromatic amides, see: V. Snieckus and P. Beak, *Acc. Chem. Res.*, 10, 306(1982); synthesis of phthalides: S. O. de Silva, M. Watanabe, and V. Snieckus, *J. Org. Chem.*, 44, 4802(1979); M. Iwao, K. K. Mahalanabis, M. Watanabe, S. O. de Silva, and V. Snieckus, *Tetrahedron*, 39, 1955(1983).

5) N. J. P. Broom and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1981, 465.

6) E. Colvin, "*Silicon in Organic Synthesis*," Butterworths, London(1981), p. 4.

7) *N*-Phenylmaleimide, Dimethyl acetylendicarboxylate and methyl acrylate also worked very well as dienophiles.

8) Adduct 3b: δ($CDCl_3$): 0.22(s, 3H, SiMe), 0.37(s, 3H, SiMe), 1.05(s, 9H, *t*-Bu), 3.30(s, 3H, 2-COOMe), 3.44(d, 1H, H_3, J=4.5 Hz), 3.55(s, 3H, 3-COOMe), 3.74 (d, 1H, H_2, J=4.5 Hz), 3.81(s, 3H, OMe), 6.92(d, 2H, ArH, J=9 Hz), 7.18(near s, 4H, ArH), 7.44(d, 2H, ArH, J=9 Hz); Adduct 4b: δ($CDCl_3$): 0.04(s, 3H, SiMe), 0.09(s, 3H, SiMe), 1.00(s, 9H, *t*-Bu), 3.27(d, 1H, H_2, J=4.5 Hz), 3.44(s, 3H, 3-COOMe), 3.78(s, 3H, 2-COOMe), 3.83(s, 3H, OMe), 4.27(d, 1H, H_3, J=4.5 Hz), 6.95(d, 2H, ArH, J=9 Hz), 6.9-7.5(m, 4H, ArH), 7.65(d, 2H, ArH, J=9 Hz).

9) S. O. de Silva, C. R. Denis, and R. Rodrigo, *J. Chem. Soc., Chem. Commun.*, 1980, 995; R. Rodrigo, *J. Org. Chem.*, 45, 4538(1980).

10) For example, pyridines easily form their radical-anions by LDA, see: G. R. Newkome and D. C. Hager, *J. Org. Chem.*, 47, 599(1982); J. Epsztajn, A. Bieniek, J. Z. Brzezinski, and A. Jozwiak, *Tetrahedron Lett.*, 24, 4735(1983).

11) Recent synthetic approaches to this type of lignans, see: T. Momose, K. Kanai, and K. Higashi, *Chem. Pharm. Bull.*, 26, 3195(1978); H. Plaumann, J. G. Smith, and R. Rodrigo, *J. Chem. Soc., Chem. Commun.*, 1980, 354; A. I. Meyers and W. B. Avila, *J. Org. Chem.*, 46, 3881(1981); A. Pelter, R. S. Ward, P. Satyajan, and P. Collins, *J. Chem. Soc., Perkin Trans. 1*, 1983, 645.

12) This compound was prepared by condensation of *N*,*N*-diethyl-2-lithio-4,5-dimethoxybenzamide, which was generated from the corresponding bromide and *t*-BuLi in ether at -78 °C, with piperonal followed by TsOH-catalyzed lactonization in refluxing toluene, 34% yield, mp 157.5-158 °C.

13) B. J. Arnold, S. Mellows, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1266.

14) M. Okigawa, T. Maeda, and N. Kawano, *Tetrahedron*, 26, 4301(1970). We thank Professor N. Kawano, this University, for providing us a sample of natural diphyllin.

(Received May 31, 1984)