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

Masatomo IWAO,\* Hisao INOUE, and Tsukasa KURAISHI Department of Chemistry, Faculty of Liberal Arts, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852

1-t-Butyldimethylsiloxy-3-arylisobenzofurans, a new type of isobenzofurans, were generated from 3-arylphthalides by sequential treatment with LDA and TBDMSC1. 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.<sup>1)</sup> Since the recent discovery<sup>2)</sup> of the generation of isobenzofurans from 1-alkoxyphthalans or their equivalents under mild conditions, their utility in organic synthesis, particularly in natural products synthesis,<sup>3)</sup> 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.<sup>4)</sup>

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



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

Phthalide	Adduct		х	Y	<u>3</u> Yield/%	Mp/°C	4 Yield/%	Mp/°C
<u>1a</u>	<u>3a</u>	<u>4a</u>	С-н	Н	87	93.5-94	≈0	
<u>1b</u>	<u>3b</u>	<u>4b</u>	С-Н	OMe	78	138-139	12	oil
<u>1c</u>	<u>3c</u>	<u>4c</u>	C-OMe	н	80	118	10	oil
<u>1d</u>	<u>3d</u>	<u>4d</u>	N	OMe	38	139-140.5	8	oil

We employed 3-arylphthalides <u>la-d</u> as isobenzofuran precursors, t-butyldimethylsilyl chloride(TBDMSCl) as a silylating agent and dimethyl fumarate<sup>7)</sup> 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, TBDMSC1(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 <sup>1</sup>H-NMR spectra<sup>8)</sup> of both adducts with those of closely related systems<sup>9)</sup> having unambiguous configurations. The adducts 3a,c,d and 4c,d were obtained similarly from the corresponding phthalides <u>la,c,d</u>. 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 <u>1d</u> as an isobenzofuran precursor. The low yield may be attributable to the instability of the pyridine ring<sup>10)</sup> 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 <u>3a-c</u> were converted into the 1-naphthol derivatives <u>5a-c</u> in over 80% yields upon brief treatment with trifluoroacetic acid(TFA) at room temperature. Although the pyridine derivative <u>3d</u> resisted this set of conditions for aromatization, it was readily converted into the desired compound <u>5d</u> by heating with *p*-toluenesulfonic acid(TSOH) in refluxing benzene.

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



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



## References

- For recent reviews of isobenzofuran chemistry, see: M. J. Haddadin, Heterocycles, <u>9</u>, 865(1978); W. Friedrichsen, Adv. Heterocycl. Chem., <u>26</u>, 135 (1980); U. E. Wiersum, Aldrichimica Acta, 14, 53(1981).
- 2) K. Naito and B. Rickborn, J. Org. Chem., <u>45</u>, 4061(1980); J. G. Smith, S. S. Welankiwar, B. S. Schantz, E. H. Lai, and N. G. Chu, *ibid.*, <u>45</u>, 1817(1980);
  B. A. Keay, D. K. W. Lee, and R. Rodrigo, *Tetrahedron Lett.*, <u>21</u>, 3633(1980);
  M. A. Makhlouf and B. Rickborn, J. Org. Chem., <u>46</u>, 2734(1981).
- 3) D. Rajapaksa and R. Rodrigo, J. Am. Chem. Soc., <u>103</u>, 6203(1981); B. A. Keay and R. Rodrigo, *ibid.*, <u>104</u>, 4725(1982); *idem.*, Can. J. Chem., <u>61</u>, 637(1983).
- 4) For a review of directed lithiation of tertiary aromatic amides, see: V. Snieckus and P. Beak, Acc. Chem. Res., <u>10</u>, 306(1982); synthesis of phthalides: S. O. de Silva, M. Watanabe, and V. Snieckus, J. Org. Chem., <u>44</u>, 4802(1979); M. Iwao, K. K. Mahalanabis, M. Watanabe, S. O. de Silva, and V. Snieckus, *Tetrahedron*, <u>39</u>, 1955(1983).
- 5) N. J. P. Broom and P. G. Sammes, J. Chem. Soc., Perkin Trans. 1, <u>1981</u>, 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 <u>3b</u>:  $\delta$  (CDCl<sub>3</sub>): 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<sub>3</sub>, J=4.5 Hz), 3.55(s, 3H, 3-COOMe), 3.74 (d, 1H, H<sub>2</sub>, 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 <u>4b</u>:  $\delta$  (CDCl<sub>3</sub>): 0.04(s, 3H, SiMe), 0.09(s, 3H, SiMe), 1.00(s, 9H, *t*-Bu), 3.27(d, 1H, H<sub>2</sub>, 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<sub>3</sub>, 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., <u>1980</u>, 995; R. Rodrigo, J. Org. Chem., <u>45</u>, 4538(1980).
- 10) For example, pyridines easily form their radical-anions by LDA, see: G. R. Newkome and D. C. Hager, J. Org. Chem., <u>47</u>, 599(1982); J. Epsztajn, A. Bieniek, J. Z. Brzezinski, and A. Jozwiak, *Tetrahedron Lett.*, <u>24</u>, 4735(1983).
- 11) Recent synthetic approaches to this type of lignans, see: T. Momose, K. Kanai, and K. Higashi, Chem. Pharm. Bull., <u>26</u>, 3195(1978); H. Plaumann, J. G. Smith, and R. Rodrigo, J. Chem. Soc., Chem. Commun., <u>1980</u>, 354; A. I. Meyers and W. B. Avila, J. Org. Chem., <u>46</u>, 3881(1981); A. Pelter, R. S. Ward, P. Satyajan, and P. Collins, J. Chem. Soc., Perkin Trans. 1, <u>1983</u>, 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.
- 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*, <u>26</u>, 4301(1970). We thank Professor N. Kawano, this University, for providing us a sample of natural diphyllin.

(Received May 31, 1984)