A New Synthesis of 1,3-Diarylisobenzofurans

Tatsuo OIDA, Shigeo TANIMOTO, Toyonari SUGIMOTO, Masaya OKANO

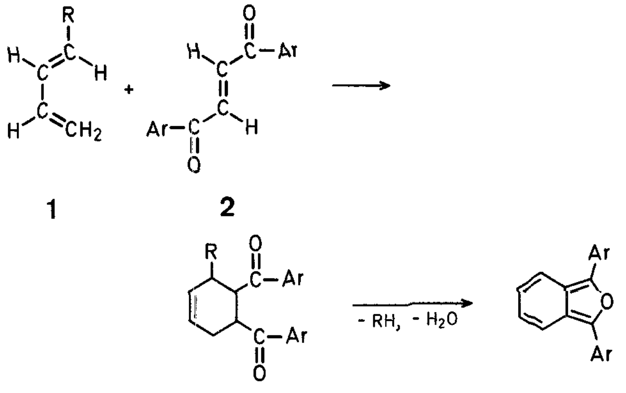
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan

Although the isolation of the parent isobenzofuran has not been achieved, its presence has been inferred from trapping experiments with some dienophiles[1]. In contrast, many stable isobenzofuran derivatives, such as 1,3-diarylisobenzofurans **4**, have been known for a fairly long time, and considerable efforts have been devoted towards the discovery of useful synthetic methods for these compounds. These include the addition of phenylmagnesium bromide or mesitylmagnesium bromide to 2-phenyl phthalide[2], the reaction of *o*-dibenzoylbenzene with excess sodium borohydride followed by treatment with hot acetic anhydride[3], the thermolysis of 1,2-diphenylbenzocyclobutene-1,2-diol[4], and the photolysis of 1,4-diphenylphthalazine *N*-oxide in acetone[5], as well as the Diels-Alder addition of dibenzoylacetylene to substituted 1,3-butadienes and subsequent dehydration of the adducts[6,7].

In a search for a more versatile synthesis of isobenzofuran derivatives, we have found that 3-substituted 4,5-diaroylcyclohexenes **3**, prepared by Diels-Alder addition of easily

0039-7881/80/0232-0131 $ 03.00

available *trans*-diaroylethenes **2** to 1-substituted 1,3-butadienes **1**[8], afford the corresponding **4** upon treatment with polyphosphoric acid. It is evident that the substituent R in **1** is easily eliminated to form the isobenzofuran moiety with simultaneous dehydration by heating the Diels-Alder adducts **3** in polyphosphoric acid.



1 **2**

3 **4**

It is also definite that **3** is composed of diastereoisomers and, in fact, they could be separated easily by high-pressure liquid chromatography (μ-Porasil, 80% hexane/20% chloroform as eluent) to give the respective *exo*- and *endo*-adducts. For example, 3-trimethylsiloxy-4,5-dibenzoylcyclohexene [**3**, R = $OSi(CH_3)_3$, Ar = C_6H_5] was a mixture of 58% *exo*- and 42% *endo*-adducts. However, when the *exo*- and *endo*-adduct were separately converted into 1,3-diphenylisobenzofuran (**4**, Ar = C_6H_5), the yields were almost the same. Since similar results can be anticipated for the other Diels-Alder adducts, it was judged to be expedient to use **3** without a prior separation of the respective *exo*- and *endo*-adducts.

The formation of **4** was realized smoothly by heating of **3** in polyphosphoric acid. The reaction was complete within 10 min. The results obtained by this new process are summarized in the Table.

Table. 4,5-Diaroylcyclohexenes **3** and 1,3-Diarylisobenzofurans **4**

R	Ar	Yield [%] of **3** (Method)	m.p. or b.p./torr	Molecular formula[a]	Yield [%] of **4**[b]	m.p. (solvent)	Molecular formula[a] or Lit. m.p.
$(C_2H_5)_2N$	C_6H_5	100 (A)	94–95 °C	$C_{24}H_{27}NO_2$ (361.5)	66[c]	130–131 °C (C_2H_5OH)	130–131 °C[2]
morpholino	C_6H_5	92 (A)	168–170 °C	$C_{24}H_{25}NO_3$ (375.5)	18[d]	—	—
piperidino	C_6H_5	99 (A)	114–115 °C	$C_{25}H_{27}NO_2$ (313.5)	33[d]	—	—
$(H_3C)_3SiO$	C_6H_5	93 (B)	102 °C	$C_{23}H_{26}O_3Si$ (318.5)	32[d]	—	—
C_2H_5O	C_6H_5	91 (B)	203–205 °C/ 0.1 torr	$C_{22}H_{22}O_3$ (334.4)	35[d]	—	—
C_6H_5COO	C_6H_5	88 (B)	119–121 °C	$C_{24}H_{22}O_4$ (374.4)	16[d]	—	—
H_3CCOO	C_6H_5	93 (B)	107–109 °C	$C_{19}H_{20}O_4$ (312.4)	44[d]	—	—
$(C_2H_5)_2N$	4-H_3C—C_6H_4	100 (A)	127–128 °C	$C_{26}H_{31}NO_2$ (389.5)	63[c]	124–125 °C (C_2H_5OH)	125 °C[9]
$(C_2H_5)_2N$	4-H_3CO—C_6H_4	92 (A)	110–111 °C	$C_{26}H_{31}NO_4$ (421.5)	30[d]	124–126 °C (C_2H_5OAc/C_6H_{14})	125–126 °C[10]
$(C_2H_5)_2N$	4-Cl—C_6H_4	61 (A)	118–119 °C	$C_{24}H_{25}Cl_2NO_2$ (430.4)	58[c]	198–199 °C (C_2H_5OAc/C_6H_{14})	199–200 °C[9]
$(C_2H_5)_2N$	4-Br—C_6H_4	56 (A)	114–115 °C	$C_{24}H_{25}Br_2NO_2$ (519.3)	84[c]	190 °C dec. (C_2H_5OAc)	$C_{20}H_{12}Br_2O$ (428.1)

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.25, H ±0.15); spectral data were in accord with the proposed structures.

[b] Yield of isolated product based on **3**.

[c] Isolated by filtration.

[d] Isolated by column chromatography.

The results starting with *N*,*N*-diethyl-1,3-butadienylamine [**1**, R = $N(C_2H_5)_2$] were satisfactory in view of the yield and purity of the final products, together with the fact that the isolation was extremely simple. Considering that *N*,*N*-diethyl-1,3-butadienylamine is readily formed from crotonaldehyde and diethylamine, the present method using this diene provides one of the most convenient routes for the preparation of **4**.

3-Diethylamino-4,5-dibenzoylcyclohexene [3, R = $N(C_2H_5)_2$, Ar = C_6H_5]; Illustrative Example of Procedure A:

N,*N*-Diethyl-1,3-butadienylamine (0.80 g, 6.4 mmol) is added over period of 10 min to a stirred solution of *trans*-dibenzoylethene (1.18 g, 5.0 mmol) in dry ether (70 ml) at room temperature. After stirring for an additional 2 h, the reaction mixture is poured into an excess of dilute hydrochloric acid. The aqueous layer is separated, basified with an aqueous solution of sodium carbonate, and extracted twice with ether. The ether solution is dried with anhydrous magnesium sulfate, and the ether removed to leave 3-diethylamino-4,5-dibenzoylcyclohexene; yield: 1.80 g (100%).

3-Trimethylsiloxy-4,5-dibenzoylcyclohexene [3, R = $OSi(CH_3)_3$, Ar = C_6H_5]; Illustrative Example of Procedure B:

A mixture of 1-trimethylsiloxy-1,3-butadiene (0.90 g, 6.3 mmol) and *trans*-dibenzoylethene (1.18 g, 5.0 mmol) in dry benzene (70 ml) is heated under reflux for 5 h. Evaporation of the benzene gives a residue which, after purification by column chromatography on silica gel (75% hexane/25% chloroform as eluent), affords 3-trimethylsiloxy-4,5-dibenzoylcyclohexene; yield: 1.75 g (93%).

1,3-Diarylisobenzofurans 4:

A stirred mixture of **3** (1.4 mmol) and polyphosphoric acid (5 ml) is heated at 110 °C for 10 min. After cooling, the reaction mixture is poured into water, the precipitate filtered, washed with water, and purified by recrystallization. When precipitation is not observed on addition of the reaction mixture to water, the reaction product is extracted into benzene and subjected to a preliminary purification by column chromatography on silica gel (85% hexane/15% chloroform as eluent).

Received: October 5, 1979

---

[1] R. Kreher, J. Seubert, Z. *Naturforsch.* **20**, 75 (1966).

[2] M. S. Newman, *J. Org. Chem.* **26**, 2630 (1961).

[3] K. T. Potts, A. J. Elliot, *Org. Prep. Proc. Int.* **4**, 269 (1972).

[4] J. Hambrecht, *Synthesis* **1977**, 280.

[5] O. Buchardt, *Tetrahedron Lett.* **1968**, 1911.

[6] W. Ried, K. N. Bönninghausen, *Justus Liebigs Ann. Chem.* **639**, 61 (1961).

[7] J. D. White, M. E. Mann, H. D. Kirshenbaum, A. Mitra, *J. Org. Chem.* **36**, 1048 (1978).

[8] All 1-substituted 1,3-butadienes (**1**) employed in this work exist in the *trans*-form.

[9] R. Adams, R. B. Wearn, *J. Am. Chem. Soc.* **62**, 1233 (1940).

[10] F. F. Blicke, R. A. Potelski, *J. Am. Chem. Soc.* **58**, 559 (1936).

0039-7881/80/0232-0133 $ 03.00