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The Lewis Acid-Promoted Reactions of *o*-Phthalaldehyde with Trialkyl Phosphites: Formation of 1-Dialkoxyphosphorylisobenzofuran

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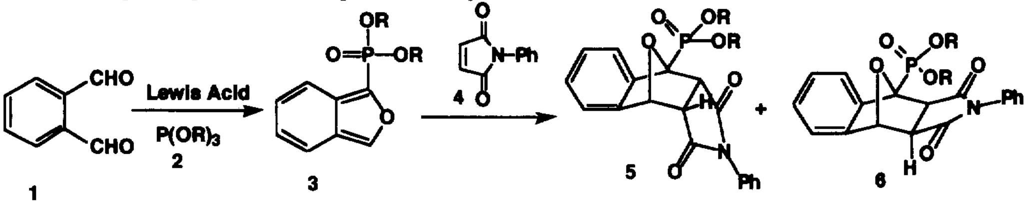
Abstract: The Lewis acid-promoted reaction of *o*-phthalaldehyde with trialkyl phosphites led to the formation of 1-dialkoxyphosphorylisobenzofurans, which underwent Diels-Alder reaction with dienophiles such as *N*-phenylmaleimide, maleic anhydride to give the corresponding adducts. Copyright © 1996 Elsevier Science Ltd

Recently, the chemistry of isobenzofuran[1] has attracted much attention from the synthetic and theoretical viewpoints and the formation of isobenzofuran has been investigated by many groups. Diels-Alder adducts of isobenzofuran derivatives have been used for synthesis of naphthalene derivatives and some kinds of natural products.[2] Haddadin *et al.*[3] reported that the reaction of *o*-phthalaldehyde with triethyl phosphite in the presence of *N*-phenylmaleimide gave *N*-phenyl-2,3-naphthalenecarboximide formed by the initial addition of triethyl phosphite to *N*-phenylmaleimide. The naphthalene derivative was not formed by deoxygenation reaction of the phosphite with the isobenzofuran-*N*-phenylmaleimide-adduct. In this letter, we demonstrate that the first Lewis acid-promoted reaction of *o*-phthalaldehyde with trialkyl phosphites led to the novel formation of 1-dialkoxyphosphorylisobenzofurans, which underwent Diels-Alder reaction with dienophiles to give the corresponding *endo*-adducts predominantly.



The aluminum trichloride (3 mmol)-catalyzed reaction of *o*-phthalaldehyde (**1**) (3 mmol) with trimethyl phosphite (**2a**) (3 mmol) in the presence of *N*-phenylmaleimide (**4**) (3 mmol) as a trapping agent in dichloromethane (20 mL) for 6 h at 25 °C gave *endo*- and *exo*-isobenzofuran-adducts **5a** and **6a** [4,5] in 24% and 1.6% yields, respectively. The ^{1}H NMR spectrum of **5a** showed the presence of a non-equivalent dimethoxyphosphoryl group at 3.89 and 4.11 ppm with phosphorous-coupling (d, $^3J_{HP}$= 11 Hz). Other spectroscopic data such as ^{13}C NMR, IR, and elemental analysis also indicated the presence of the dimethoxyphosphoryl group. The adduct of non-substituted isobenzofuran with *N*-phenylmaleimide was not detected in the reaction mixture by HPLC analysis comparing retention time with authentic sample.[6]

In order to investigate the effect of Lewis acid, we examined the catalytic efficiency of zinc(II) bromide, tin(IV) chloride, titanium(IV) chloride, and a boron trifluoride ethyl ether complex. In the case of zinc(II) chloride and zinc(II) bromide, no adduct was obtained, although in the case of the boron trifluoride ethyl ether complex, the adduct was obtained in moderate yield. In the reaction of *o*-phthalaldehyde with trimethyl phosphite, the best Lewis acid was the boron trifluoride ethyl ether complex and the reaction was completed within 8 h as shown in Table 1. Acetonitrile proved to be the best solvent (run 12, 15, and 16).

Table 2 indicates that the yields of **5** and **6** are affected by molar amounts of the boron trifluoride ethyl ether complex. The best yield was obtained in the case using 1 equivalent of the Lewis acid. These data indicate that the reaction does not proceed in the presence of a catalytic amount of Lewis acid on the other hand, excess Lewis acid inhibits the reaction.

Table. 1 Effect of Lewis Acid (1 equiv.) on the Yields of Diels-Alder Adducts **5** and **6**.

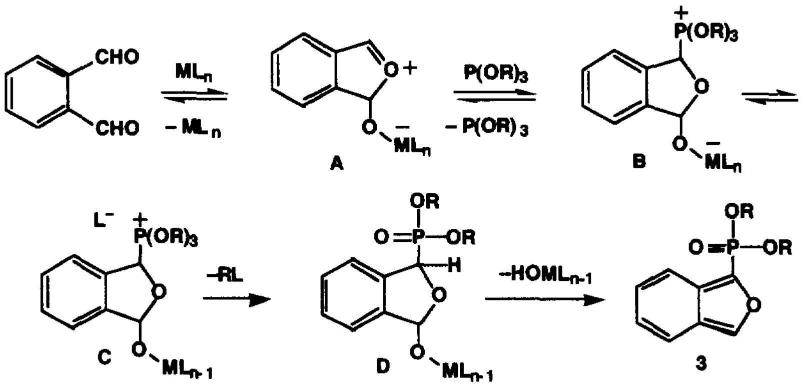
Run	Lewis Acid	Time/h	Solvent	Yields/%	
				endo-adduct **5**	*exo* -adduct **6**
1(7	none	8	CH_2Cl_2	–	–
2	$ZnBr_2$	6	CH_2Cl_2	–	–
3	$SnCl_4$	6	CH_2Cl_2	–	–
4	$TiCl_4$	6	CH_2Cl_2	30	0.4
5	$AlCl_3$	6	CH_2Cl_2	24	1.6
6	$BF_3\cdot OEt_2$	6	CH_2Cl_2	54	3.3
7	$BF_3\cdot OEt_2$	0.5	CH_2Cl_2	0.8	–
8	$BF_3\cdot OEt_2$	1	CH_2Cl_2	4.1	trace
9	$BF_3\cdot OEt_2$	2	CH_2Cl_2	22	1.0
10	$BF_3\cdot OEt_2$	3	CH_2Cl_2	41	1.8
11	$BF_3\cdot OEt_2$	6	CH_2Cl_2	54	2.6
12	$BF_3\cdot OEt_2$	8	CH_2Cl_2	60	3.1
13	$BF_3\cdot OEt_2$	24	CH_2Cl_2	61	3.2
14	$BF_3\cdot OEt_2$	48	CH_2Cl_2	64	3.6
15	$BF_3\cdot OEt_2$	8	$CH_3C_6H_5$	17	0.2
16	$BF_3\cdot OEt_2$	8	CH_3CN	67	2.0

Table 2. Yields of **5** and **6** with Varying Molar Amounts of a Boron Trifluoride Ethyl Ether Complex.

Run	$BF_3\cdot OEt_2$/equiv.	Time /h	Solvent	Yields/%	
				endo-adduct **5**	*exo* -adduct **6**
18	0.5	8	CH_3CN	40	1.7
16	1.0	8	CH_3CN	67	2.0
19	1.2	8	CH_3CN	57	2.5
20	2.0	8	CH_3CN	47	3.0

The formation of 1-dialkoxyphosphorylisobenzofuran is explained as follows. In the first step, the Lewis acid coordinates on an oxygen atom of the formyl group of **1**. In the second step, the other formyl oxygen attacks electrophilicaly on the Lewis acid-activated carbon atom to give the five-membered ring intermediate

A. Trialkyl phosphite as nucleophile adds to **A** to form **B**, which undergoes elimination of L to give **C**. The Arbuzov reaction[8] of **C** gives **D**. Then, the isobenzofuran **3** is formed by the elimination of HOML$_{n-1}$. Several attempts to isolate **3** were unsuccessful because of its high reactivity. The formation of **3** was deduced by the isolation of Diels-Alder adducts **5** and **6**.



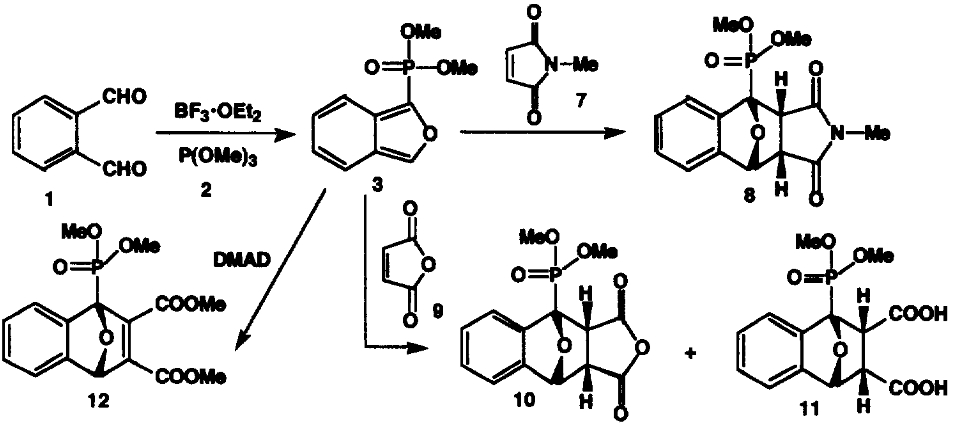
The Lewis acid-catalyzed reaction of *o*-phthalaldehyde with trimethyl phosphite in the presence of lithium iodide for 2 hours gave **5** in 33% yield (run 21) and in the presence of potassium iodide in 57% yield (run 23). Yield of **5** in the presence of KI for 8 hours (run 24) was the same as that of without KI (run 16). These results indicate that the additive acceralate only the rate of the reaction. The reactions of the other phosphites such as triethyl, tripropyl, triisopropyl phosphites in the presence of potassium iodide gave the corresponding adducts **5** and **6** in good yields, respectively, as shown in Table 3. In the absence of potassium iodide the reaction of triethyl phosphite gave the adducts in low yield.

Table. 3 Yields of Diels-Alder Adduct **5** and **6** in the Presence of Iodide.

Run	R	Time/h	Additive	Yields/%	
				endo-adduct **5**	*exo* -adduct **6**
17	Me **2a**	2	none	trace	–
21	Me **2a**	2	LiI	33	–
22	Me **2a**	2	NaI	trace	–
23	Me **2a**	2	KI	57	1.9
16	Me **2a**	8	none	67	2.0
24	Me **2a**	8	KI	66	2.2
25	Et **2b**	8	none	15	0.6
26	Et **2b**	8	KI	74	2.7
27	*n*-Pr **2c**	8	none	49	2.3
28	*n*-Pr **2c**	8	KI	61	3.5
29	*i*-Pr **2d**	8	none	46	3.4
30	*i*-Pr **2d**	8	KI	48	3.5

The BF$_3$-catalyzed reaction of *o*-phthalaldehyde (**1**) with trimethyl phosphite (**2a**) in the presence of *N*-

methylmaleimide (**7**) as a trapping agent gave an *endo*-adduct **8** in 73% yield after chromatographic separation. The reaction with maleic anhydride gave *endo*-adducts **10** and **11** in 24 and 16% yields, respectively. The dicarboxylic acid **11** is formed by the hydrolysis of acid anhydride **10** during work-up. The reaction with dimethyl acetylenedicarboxylate (DMAD) gave an adduct **12** in 13% yield. The adduct **12** was unstable presumably due to the retro-Diels-Alder reaction and gave a complex mixture on standing at room temperature.



In this letter we have demonstrated that the Lewis acid-promoted reaction of *o*-phthalaldehyde with trialkyl phosphites led to the formation of 1-dialkoxyphosphorylisobenzofurans, which underwent Diels-Alder reaction with dienophiles to give the corresponding adducts. The products can be used for synthesis of phosphorylnaphthalene derivatives and some kinds of natural product analogues. Further studies concerning this methodology are now in progress.

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3. Haddadin, M. J.; Agha, B. J.; Tabri, R. F. *J. Org. Chem.* **1979**, *44*, 494-497.
4. A solution of *endo*-adduct **5a** in tetrachloroethane at 140 °C for 60 h in the presence of *N*-phenylmaleimide gave a mixture of **5a** and **6a** (60:40).
5. **5a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ=3.89 (3H, d, J=11.0 Hz), 4.06 (1H, dd, J=8.4, 5.7 Hz), 4.11 (3H, d, J=11.0 Hz), 4.26 (1H, dd, J=9.1, 8.4 Hz), 5.91 (1H, dd, J=5.7, 1.7 Hz), 6.40-6.43 (2H, m), 7.24-7.27 (3H, m), 7.35-7.40 (3H, m), 7.56-7.58 (1H, m); **6a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ=3.23 (1H, d, J=6.7 Hz), 3.24 (1H, d, J=6.7 Hz), 3.85 (3H, d, J=11.0 Hz), 3.95 (3H, d, J=10.9 Hz), 5.95 (1H, d, J=1.0 Hz), 7.31-7.50 (7H, m), 7.63-7.65 (1H, m). The structure of **5a** was finally determined by single crystal X-ray analysis. The results will be reported in full paper.
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