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SYNTHESIS OF 7-HYDROXYPHTHALIDES STARTING FROM UNSATURATED LACTONES VIA 2-TRIALKYLSILOXYFURANS

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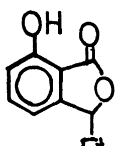
Diels-Alder adducts of maleic anhydride and 2-trialkylsiloxy furans, prepared from unsaturated lactones and trialkylchlorosilane in high yields, afforded 3-hydroxyphthalic anhydrides on treatment with hydrobromic acid. The anhydrides were regiospecifically reduced to 7-hydroxyphthalides in high yields by means of excess sodium borohydride in alcohol.

7-Hydroxyphthalide derivatives(**1**-**3**) are found in nature as metabolites of microorganisms.[1)]



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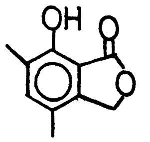

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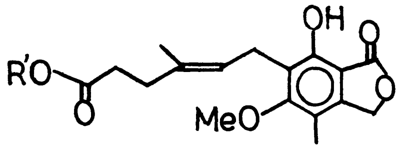

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Several synthetic methods of 3-hydroxyphthalic acids or 3-hydroxyphthalic anhydrides, the intermediates to 7-hydroxyphthalides, using heterocycles or butadiene derivatives were reported.[2)] However, these methods seem to be of limited scope because of following disadvantages; 1) migration of alkyl group is involved, 2) introduction of suitable substituents to starting materials is somewhat difficult, and 3) starting materials are labile in some cases. But the benzenoid ring constructive methods from heterocyclic precursors, such as pyrylium salts,[3)] thiapyrylium salts,[4)] pyridinium salts,[5)] 2-pyrones,[6)] thiophenes,[7)] furans,[2)] and pyrroles,[8)] have some advantages. The major advantage of these synthetic methods lies in the fact that substituents originally present in the heterocycles are incorporated into the aromatic products in a regiospecific manner. In this communication we wish to report the synthesis and the reaction of new stable furan **4**, which will provide a useful intermediate for the synthesis of highly substituted benzenes.

2-Trialkylsiloxyfuran derivatives **4** were synthesized from unsaturated lactones in high yields.

A typical procedure is shown as follows; a mixture of triethylamine (205 mmol) and trimethylchlorosilane (202.5 mmol) was added to precooled (0°C) 3-penten-4-olide (200 mmol). After standing at room temperature for 5 hours, distillation under reduced pressure gave 5-methyl-2-trimethylsiloxyfuran 4c in 98% yield. This material is sufficiently pure to use for the next step, though it contained a small amount of triethylammonium chloride, which can be removed by redistillation. The yields and boiling points of various 2-trialkylsiloxyfuran derivatives[9)] are listed in Table 1.

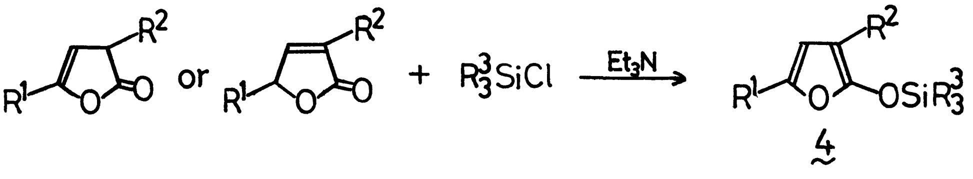

Table 1. Synthesis of 2-Trialkylsiloxyfurans

	R^1	R^2	R^3	Bp (°C/mm Hg)	Yield 4 (%)
4a	H	H	Me	34-35/9-10	90
4b	H	H	Et	108-109/26	95
4c	Me	H	Me	37-38/2-3	98
4d	Me	Me	Me	43-44/4-5	95
4e	Et	H	Me	43-45/2	91

5-Methyl-2-trimethylsiloxyfuran 4c reacted exothermically with maleic anhydride in THF solution at room temperature, and the resulted Diels-Alder adduct afforded 5-methyl-3-hydroxyphthalic anhydride 6 (R^1=Me, R^2=H) only in 28% yield on treatment with hydrobromic acid. After several experiments, the yield could be increased to 67% (see Table 2).

Under similar conditions, various 3-hydroxyphthalic anhydrides were successfully synthesized and these results are summarized in Table 2. When 2-trimethylsiloxyfuran 4a, which exhibited higher reactivity than 4c, was used, complex side reaction took place and corresponding 3-hydroxyphthalic anhydride 6 (R^1, R^2=H) was obtained only in a poor yield. But less reactive 2-triethylsiloxyfuran 4b was used, 6 (R^1, R^2=H) was obtained in 65% yield.

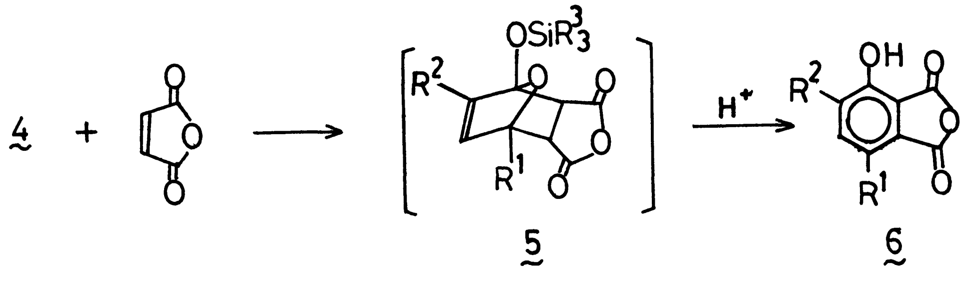

Table 2. Synthesis of 3-Hydroxyphthalic Anhydrides[12)]

Furan Deriv.	Solvent	Temp. (°C)	Time (h)	R^1	R^2	Yield **6** (%)	Mp (°C)
4c	THF	-78∿10	18	Me	H	10	157.5-158.5
4c	THF	0∿r.t.	1	Me	H	53	
4c	THF	55∿60	0.5	Me	H	trace	
4c	THF	r.t.	2	Me	H	28	
4c	Et_2O	0	1.5	Me	H	40	
4c	CH_2Cl_2	0∿5	1	Me	H	37	
4c	Pentane	r.t.	1	Me	H	62	
4c	None	r.t.	0.25	Me	H	53	
4c	None	-20∿0	0.5	Me	H	67	
4a	None	-20∿0	0.5	H	H	5	196-198
4b	None	-20∿r.t.	2	H	H	65	
4d	None	0∿r.t.	2	Me	Me	95	175.5-177
4e	None	0∿40	5	Et	H	90	134.5-135.5

The regiospecific reduction of 3-hydroxyphthalic anhydrides was achieved using excess of sodium borohydride in alcoholic solvent.[11)] For example, when **6** (R^1, R^2=Me) was subjected to the reduction, 4,6-dimethyl-7-hydroxyphthalide was obtained as a sole product. Its melting point and characteristic bands of IR were essentially identical with the reported values of the natural product isolated from the metabolites of p-gladioli.[10)] This regiospecificity can be explained by the formation of chelate complex **7**, which causes the difference in reactivity of the two carbonyl groups against the nucleophilic attack of hydride. The yields and melting points of 7-hydroxyphthalide derivatives are listed in Table 3.

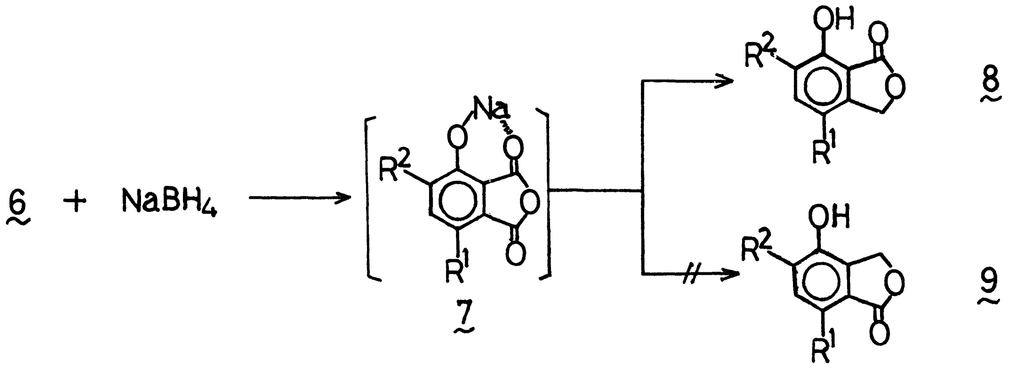

Table 3. Synthesis of 7-Hydroxyphthalides[12)]

R^1	R^2	Mp (°C) (lit)	Yield 8 (%)
H	H	136-137 (135-136.5)[11a)]	94
Me	H	167	90
Me	Me	158-159 (156-158)[10)]	94
Et	H	114.5-116.5	95

Further studies using 2-siloxyfurans which have various substituents, are now in progress.

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