

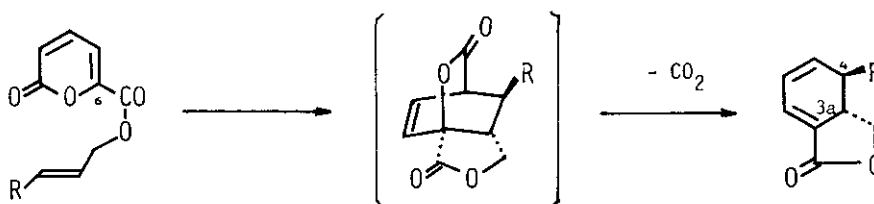
REGIOSELECTIVE SYNTHESIS OF SUBSTITUTED PHTHALIDES VIA INTRAMOLECULAR
 "DIENE-REGENERATIVE" DIELS-ALDER REACTION OF 2-PYRONES¹

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Abstract — Some 2-pyrone-6-carboxylates bearing appropriate dienophiles in ester moieties underwent "diene-regenerative" Diels-Alder reaction to afford the dihydrophthalides, which were aromatized to phthalide derivatives in the presence of palladium-charcoal. In these reactions the substituents at 4 or 7-position of phthalides arose from those on the dienophile moieties in the starting 2-pyrones.

Although phthalide is one of the simplest and most familiar heterocycles, the scope for the preparations of phthalide and its derivatives has been considerably limited, e.g., mostly via the lactonization of 2-(hydroxymethyl)benzoic acids or related compounds.² Now, among some recent improvements on phthalide formation,^{3a-3d} a novel synthetic route reported by Pelter and his co-worker⁴ was much fascinating, in which an intramolecular Diels-Alder reaction of furan derivatives followed by the base-induced aromatization was involved. However, according to Pelter's method the 4, 5, and 6-positions in phthalide arose from the 3, 4, and 5-positions in furfuryl alcohol as a starting material, respectively, and thus the introduction of substituents into these positions seems to be also limited.

We recently reported that 2-pyrone-6-carboxylic acid esters bearing dienophiles at ester moieties underwent "diene-regenerative" Diels-Alder reaction intramolecularly to give the 3a,4-dihydrophthalides.⁵



Now, we wish to communicate here the regioselective preparation of some phthalide derivatives. Therein, 2-pyrones having the appropriate dienophiles at 6-position were cyclized to the corresponding dihydrophthalides, which were subsequently converted to phthalide derivatives substituted at 4 or 7-position by dehydrogenation in good yields.

The results of the preliminary experiments on the aromatization of 3a,4-dihydro-4-phenylphthalide to 4-phenylphthalide with various oxidants showed that palladium-charcoal was most suitable for the dehydrogenation.

In a typical experiment; allyl 2-pyrone-6-carboxylate (1a)⁶ (0.5 g, 2.8 mM) in dry *o*-dichlorobenzene (30 ml) was heated in the presence of 0.25 g of 5% palladium-charcoal under reflux for 1.5 days, the palladium-charcoal was filtered, then the filtrate was evaporated *in vacuo* to give the oily residue. The residue was purified by short column chromatography on silica gel to afford 0.32g (86 %) of phthalide (2a). Similarly, 4-methyl- (2b), 4-phenyl- (2c), 4-methoxycarbonyl- (2d), and 4-ethoxycarbonylphthalide (2e) were obtained from the corresponding 2-pyrone-6-carboxylic acid esters (1b-1e) in good yields. The structural assignments of these phthalides were accomplished by comparing the physical or spectral data with those of authentic samples or related systems. These results are summarized in Table 1.

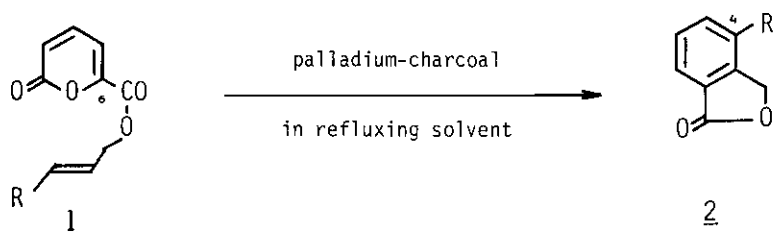


Table 1. Preparation of 4-Substituted Phthalide Derivatives 2.

Compds	R	Conditions		Yield	Mp	IR (cm ⁻¹)	PMR ^d δ	MS (m/e)
		solvent, ^{c)}	time	%	°C	ν_{CO}	-CH ₂ -	M ⁺
<u>2a</u> ^{a)}	H	A,	1.5 d	86	72-74	1760	5.30	—
<u>2b</u> ^{a)}	Me	A,	1.5 d	72	71-73	1770	5.18	—
<u>2c</u> ^{b)}	Ph	A,	1 d	85	120-121	1770	5.34	—
<u>2d</u>	CO ₂ Me	A,	1 d	85	177-179	1780, 1710	5.55	192
<u>2e</u>	CO ₂ Et	B,	1 d	87	140-141	1760, 1710	5.56	206

a) Known compounds. Identified with authentic samples.

b) Known compound (lit.⁷ mp 119-120 °C). c) A: *o*-Dichlorobenzene; B: xylene.

d) Measured in CDCl₃.

The introduction of substituents into 7-position in phthalide was also examined, i.e., (4-methyl-2-oxo-2H-pyran-6-yl)methyl acrylate (3a)⁸ was cyclized to 5-methylphthalide (4a) in 71% yield. Similarly, in the reaction of (4-methyl-2-oxo-2H-pyran-6-yl)methyl crotonate (3b), cinnamate (3c), 3-(2-furyl)acrylate (3d), and 3-(3-pyridyl)acrylate (3e), the corresponding 5-methyl-7-substituted phthalides (4b-4e) were obtained. Furthermore, ethyl (4-methyl-2-oxo-2H-pyran-6-yl)methyl fumarate (3f) gave 7-ethoxycarbonyl-5-methylphthalide (4f). These results are summarized in Table 2.

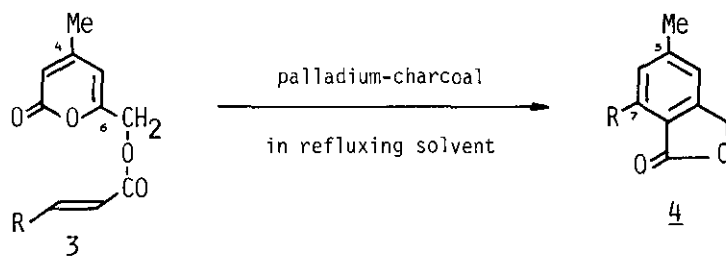


Table 2. Preparation of 5-Methyl-7-substituted Phthalide Derivatives 4.

Compds	R	Conditions		Yield %	Mp °C	IR(cm ⁻¹) ν _{CO}	PMR ^{b)} δ(ppm)		MS(m/e) M ⁺
		solvent, ^{a)}	time				-CH ₂ -	-CH ₃	
<u>4a</u>	H	A,	2 d	71	116-117	1730 - 1760	5.21	2.46	148
<u>4b</u>	Me	A,	7 d	86	94-96	1740	5.13	2.40, 2.60	162
<u>4c</u>	Ph	A,	3 d	95	115-116	1760	5.17	2.46	224
<u>4d</u>	2-furyl	A,	1 d	87	138-140	1730	5.14	2.23	214
<u>4e</u>	3-pyridyl	A,	1 d	77	184-186	1750	5.24	2.52	225
<u>4f</u>	CO ₂ Et	B,	1 d	100	110-111	1760, 1700	5.22	1.40, 2.49	220

a) A: *o*-Dichlorobenzene; B: xylene. b) Measured in CDCl₃.

As mentioned above, in these preparations, the substituents at 4-position in phthalides 2 stemmed from those at 3-position of allyl halides used in the preparation of esters 1 and , on the other hand, the substituents at 7-position in 4 from those at β-position of acrylic acids used. Thus, our method seems to be versatile for the regioselective synthesis of the substituted phthalides.

Further investigations on similar systems are under progress.

ACKNOWLEDGEMENT

We would like to express our thanks to Prof. Masashi Tashiro, Research Institute of Industrial Science, Kyushu University, for the elemental analyses and the measurements of high mass spectra.

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6. Esters 1 were prepared from the reaction of 2-pyrone-6-carboxylic acid and the corresponding allyl halides in the presence of DBU according to the reported method.⁹ 1a: Yield 93%; mp 85-86 °C. 1b: Yield 55%; mp 49-51 °C. 1c: Yield 93%; mp 85-87 °C. 1d: Yield 63%; mp 105-107 °C. 1e: Yield 88%; mp 81-83 °C. All new compounds in this paper gave satisfactory elemental analyses.
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8. Esters 3 were prepared similarly to esters 1 from 6-chloromethyl-4-methyl-2-pyrone and the corresponding α,β -unsaturated carboxylic acids. 3a: Yield 90%; bp 190 °C. 3b: Yield 90%; bp 220 °C. 3c: Yield 87%; mp 99-100 °C. 3d: Yield 98%; mp 91-93 °C. 3e: Yield 76%; mp 110-112 °C. 3f: Yield 91%; mp 49-50 °C.
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Received, 18th January, 1985