BENZ-FUSED LACTONES I. SYNTHESIS OF 3-METHYL-1(3H)-ISOBENZOFURANONES [PHTHALIDES]

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Abstract-Unsubstituted and 3-alkyl substituted 1(3H)-isobenzofuranones [phthalides] are readily prepared in good yields via ortho-metallation of appropriate aromatics.

1(3H)-Isobenzofuranones, commonly referred to as phthalides, have found considerable utility as intermediates in the synthesis of more complex heterocycles such as phthalideisoquinoline[1], phenanthroindolizidine[2], and phenanthroquinolizidine[2] alkaloids, and naturally occurring anthraquinones[3] and benzanthracenes[4]. Phthalides are found in Nature, including, for example, iso-ochracinic acid and a variety of simple phthalides[5]. In the former cases, the 3-position normally bears an aromatic or heteroaromatic substituent, while the natural products are unsubstituted or bear a functionalized alkyl group. During our study of other naturally occurring benz-fused lactones having fungicidal activity, we required an homologous series of 1(3H)-isobenzofuranones bearing simple alkyl substituents at C_3 (e.g. methyl). These are not available by routes previously described in the literature, and we hereby report a simple, efficient route to 3-methyl-1(3H)-isobenzofuranones.†

The utility of ortho-metallation in the regiospecific synthesis of aromatic compounds has been the subject of a number of reviews[6-8], and a number of reports have described the preparation of phthalides utilizing a variety of directed metallation groups (DMG). Beak and Brown used the diethylamido group for the preparation of a series of 5-substituted 3,3-diphenylphthalides[9] and 3,3-dimethyl or 3-phenyl analogues[10]. Snieckus and co-workers[11] employed the 4,4-dimethyloxazoline DMG to generate an ortho-lithiated species which was condensed with a variety of electrophiles to yield C_3 carboxylate substituted or unsubstituted phthalides. Similarly, Meyers and Avila[12] described the preparation of a 3-unsubstituted phthalide utilizing an oxazolinyl DMG in which the ortho-lithiated species is alkylated with methyl iodide, the methyl group brominated, and the phthalide ring subsequently being produced by hydrolysis and lactonization. Newman and Kumar[4] condensed a similar ortho-lithiooxazoline with β-acetylnaphthalene to produce a 3,3-disubstituted phthalide.

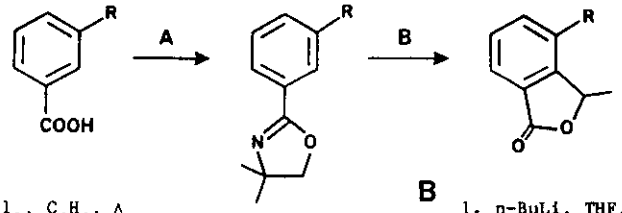
The route utilized by Uemura and co-workers[13] follows a reverse methodology in which the carbonyl

† Initial presentation of this material was made at the Chemical Institute of Canada Annual Meeting, Kingston, Ont. (June 1985) and at the 10th International Congress of Heterocyclic Chemistry, Waterloo, Ont. (August 1985).

functionality of the phthalide is introduced by the ortho-metallation: lithiation between the methoxy and hydroxymethyl DMGs followed by carboxylation (CO_2 attack) produced a series of phthalides in modest yields (44-62%); introduction of a second methoxy group on the aromatic ring led to extremely low yields (8%) or failure of this route. Better yields were subsequently reported by Trost et al.[14] for 7-methoxy- and 5,7-dimethoxyphthalide, and by Hung et al.[15] for 3-aminomethylphthalide derivatives. The most recent report[16] again utilizes the oxazoline DMG for the introduction of a carboxylate group in the preparation of 3-hydroxyphthalides.

Synthesis of C_3 substituted phthalides via a condensation of an ortho-lithiated aromatic with simple aldehydes is not well known in the literature. Indeed, the use of formaldehyde is reported in only one instance[12] and the use of acetaldehyde has not been reported.

The starting methoxy substituted phenyloxazolines were readily prepared from the benzoyl chlorides in excellent yields. Condensation of the intermediate ortho-lithiated oxazolines with the low

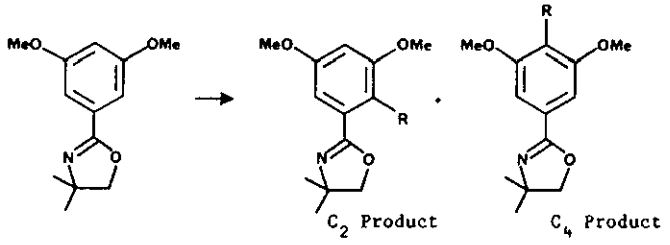


A
1. $SOCl_2$, C_6H_6, Δ
2. 2-amino-2-methyl-1-propanol, CH_2Cl_2
3. $SOCl_2$

B
1. n-BuLi, THF, 0°C
2. $MgBr_2$ $2Et_2O$
3. CH_3CHO, r.t.
4. 4.5N HCl

molecular weight aldehydes (HCHO, CH_3CHO) however did not occur. Formation of the ortho-lithiated species with n-butyllithium at 0°C was confirmed by quenching of the anion with deuterium oxide. Successful condensation with acetaldehyde was achieved after trans-metallation of the ortho-lithiated species with magnesium dibromide etherate[17]; treatment of the ortho-lithio species with three equivalents of $MgBr_2$ $2Et_2O$ at 0°C and quenching with excess aldehyde gave, after hydrolysis of the oxazoline with 4.5N HCl, good yields of the 3-methylphthalides.

These conditions gave exclusive functionalization ortho- to the oxazoline. Examination of the nmr spectra of the crude product mixture after condensation with the aldehyde showed only the C_2 functionalized products. Previously, Meyers and Avila[18] had shown that the ortho-directing ability of DMGs was additive and that both C_2 and C_4 functionalization of 3,5-dimethoxyphenyloxazoline occurred. The position of alkylation is sensitive to reaction conditions, and the conditions employed in our study allowed for exclusive C_2 alkylation, possibly as a consequence of the higher temperatures employed.



In conclusion, we report the efficient and highly regiospecific synthesis of a number of novel 3-methyl substituted phthalides and conditions for the efficient ortho-metallation and condensation of the phenyloxazolines with simple aldehydes.

EXPERIMENTAL

General.

Melting points were determined on a Kofler hot stage and are uncorrected. Proton nmr spectra were determined on a Perkin-Elmer R32 spectrometer at 90 MHz or on a Bruker WM250 spectrometer at 250 MHz with reference to internal TMS. Infrared spectra were obtained on the Perkin Elmer 283 spectrophotometer (KBr discs for solid samples, thin film samples for liquids), ultraviolet spectra on the Beckman DU8 spectrophotometer, and mass spectra on the Finnigan 3300 gas chromatograph/mass spectrometer using methane CI or electron impact (70eV) ionization. Solvents were distilled immediately prior to use, and dried by standard methods. Ether refers to diethyl ether. Reactions were carried out under a positive pressure of dry nitrogen. All organic extracts were dried using anhydrous $MgSO_4$, and were evaporated to dryness by concentration in a rotary evaporator. Column chromatography was carried out on E. Merck silica gel (70–230 mesh), thin layer chromatography on Kodak precoated silica gel sheets (Chromatogram®, with fluorescent indicator).

Preparation of oxazolines

General procedure

p-Methoxybenzoic acid (0.17 mole, 30.4 g) and thionyl chloride (0.4 mole, 29 ml) in benzene (100 ml) was heated to reflux under dry N_2 for 4 h. Excess thionyl chloride was removed by distillation. The crude benzoyl chloride was dissolved in CH_2Cl_2 (100 ml) and added dropwise under dry N_2 to 2-amino-2-methyl-1-propanol (0.41 mole, 39 ml) in dichloromethane (100 ml) at 0°C. The mixture was stirred for 2 h, after which the precipitate was removed by filtration. The filtrate was washed with water (2 x 50 ml) and the organic layer dried and concentrated *in vacuo* to give crude N-(1,1-dimethyl-2-hydroxyethyl)-p-methoxybenzamide which was used directly in the next reaction without purification.

Thionyl chloride (0.6 mole, 71 g) was added dropwise to the stirred crude amide. After the vigorous reaction has subsided, the yellow oil was washed with ether (200 ml) to remove excess thionyl chloride, and the salt neutralized with cold 30% potassium hydroxide solution. Extraction with ether (3 x 200 ml), followed by drying and *in vacuo* concentration of the combined ether extracts afforded the crude product which was distilled to yield 2-(4-methoxyphenyl)-4,4-dimethyl-2-oxazoline, 34.6 g, 83%. Physical and spectroscopic data for all aryldimethyloxazolines are presented in Table I.

Compounds prepared

2-Phenyl-4,4-dimethyl-2-oxazoline, 24.3 g, 46%, from benzoyl chloride (0.3 mole, 35 ml) as described above.

2-(3-Methoxyphenyl)-4,4-dimethyl-2-oxazoline, 8.7 g, 84%, from m-methoxybenzoyl chloride (0.05 mole, 7.6 g) as described above.

2-(3,4-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline, 5.0 g, 84%, from 3,4-dimethoxybenzoyl chloride (0.025 mole, 4.6 g) as described above.

2-(3,5-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline, 10.0 g, 85%, from 3,5-dimethoxybenzoyl chloride (0.05 mole, 9.1 g) as described above.

Table I. Physical and Spectroscopic Data of 2-Aryl-4,4-dimethyl-2-oxazolines.

Aryl Substituent	bp, °C (mm Hg)	ν_{max} (cm^{-1})	δ ($CDCl_3$) ppm
None	64-70 (3.8)	1650	1.37 (s, 6H) 4.09 (s, 2H) 7.36-7.50 (m, 3H) 7.89-8.03 (m, 2H)
3-Methoxy	114-118 (1.0)	1650, 1590 1312, 1249	1.34 (s, 6H) 3.80 (s, 3H) 4.05 (s, 2H) 6.90-7.60 (m, 4H)
4-Methoxy	110-111 (3.0)	1650, 1518 1269	1.33 (s, 6H) 3.80 (s, 3H) 4.03 (s, 2H) 6.87 (d, 2H, J = 9Hz) 7.88 (d, 2H, J = 9Hz)
3,4-Dimethoxy	138-145 (4.7)	1650, 1518 1277	1.33 (s, 6H) 3.85 (s, 3H) 3.87 (s, 3H) 4.03 (s, 2H) 6.84 (d, 1H, J = 9Hz) 7.50 (m, 2H)
3,5-Dimethoxy	mp 62-64	1640, 1590 1350, 1194	1.33 (s, 6H) 3.78 (s, 6H) 4.04 (s, 2H) 6.54 (d, 1H, J = 2Hz) 7.08 (d, 2H, J = 2Hz)

Preparation of 3-Methyl-1(3H)-isobenzofuranones

General procedure

ortho-Lithiations and transmetallations were performed as one-pot procedures in three-necked round bottomed flasks equipped with an inlet for dry N_2 and with serum caps. All glassware was baked at 125°C prior to use and solutions were transferred by inert atmosphere syringe techniques. The solutions were magnetically stirred and cooled in an ice/salt water bath. Stock solutions of magnesium dibromide dietherate in ether (0.0338 M) were prepared according to literature procedures.

To 2-phenyl-4,4-dimethyl-2-oxazoline (5.6 mmole, 0.98 g) dissolved in tetrahydrofuran (20 ml) at 0°C was added n-butyllithium in hexane (6.7 mmole, 2.7 ml stock solution, Aldrich) dropwise over

ten minutes. The solution was allowed to stir for 2 h at 0°C. Three equivalents of magnesium bromide dietherate (17 mmole, 6.4 ml) were added and the solution allowed to stir for a further 2 h. A large excess of acetaldehyde (approx. 6 ml) was then added and the mixture allowed to warm to room temperature.

After 1 h, excess reagent was quenched with water (10 ml) and the product extracted with ether (3 x 300 ml). The combined ether extracts were concentrated in vacuo to give the crude alcohol which was hydrolyzed and lactonized directly by refluxing the crude product for 2 h with 4.5 M HCl (50 ml). The aqueous solution was diluted further with water (100 ml), extracted with ether (3 x 100 ml), the combined ether extracts dried and concentrated in vacuo to yield the crude product. Chromatography on silica gel with dichloromethane as eluant gave 3-methyl-1(3H)-isobenzofuranone (3-methylphthalide), 0.60 g, 74%. Physical and spectroscopic data are given in Table II for all isobenzofuranones.

Compounds prepared

4-Methoxy-3-methyl-1-(3H)-isobenzofuranone, 1.17g, 66%, from 2-(3-methoxyphenyl)-4,4-dimethyl-2-oxazoline (10.0 mmole, 2.05 g) as described above, with the product purified by crystallization from ether. Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.54, H, 5.73%.

5-Methoxy-3-methyl-1-(3H)-isobenzofuranone, 0.98g, 77%, from 2-(4-methoxyphenyl)-4,4-dimethyl-2-oxazoline (5.1 mmole, 1.05 g) as described above, with elution using dichloromethane/ethyl acetate (90/8, v/v). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 66.91, H, 5.62%.

4,5-Dimethoxy-3-methyl-1-(3H)-isobenzofuranone, 1.05g, 51%, from 2-(3,4-dimethoxyphenyl)-4,4-dimethyl-2-oxazoline (10.0 mmole, 2.35 g) as described above, with the product purified by crystallization from ether. Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.46; H, 5.81. Found: C, 63.58, H, 5.81%.

4,6-Dimethoxy-3-methyl-1-(3H)-isobenzofuranone, 0.98g, 47%, from 2-(3,5-dimethoxyphenyl)-4,4-dimethyl-2-oxazoline (10.0 mmole, 2.40 g) as described above, with the product purified by crystallization from ether. Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.46; H, 5.81. Found: C, 63.18, H, 5.59%.

Table II. Physical and Spectroscopic Data of 3-Methyl-1(3H)-isobenzofuranones.

Aryl Substituent	mp, °C	ν_{max} cm^{-1}	δ ($CDCl_3$) ppm
None	oil	1765	1.67 (d, 3H, J = 6.5Hz) 5.61 (q, 1H, J = 6.5Hz) 7.3-7.9 (m, 4H)
4-Methoxy	108-110	1755	1.59 (d, 3H, J = 7Hz) 3.87 (s, 3H) 5.51 (q, 1H, J = 7Hz) 7.09 (t, 1H, J = 6Hz) 7.46 (d, 2H, J = 6Hz)

Table II Continued

Aryl Substituent	mp, °C	ν_{max} cm^{-1}	δ ($CDCl_3$) ppm
5-Methoxy	152-154	1760	1.64 (d, 3H, J = 7Hz) 3.92 (s, 3H) 5.51 (q, 1H, J = 7Hz) 6.90 (d, 1H, J = 2Hz) 7.07 (dd, 1H, J = 9, 2Hz) 7.84 (d, 1H, J = 9Hz)
4,5-Dimethoxy	87-88	1760	1.62 (d, 3H, J = 7Hz) 3.79 (s, 3H) 3.89 (s, 3H) 5.53 (q, 1H, J = 7Hz) 7.04 (d, 1H, J = 6.4Hz) 7.56 (d, 1H, J = 6.4Hz)
4,6-Dimethoxy	144-146	1754	1.64 (d, 3H, J = 7Hz) 3.89 (s, 6H) 5.53 (q, 1H, J = 7Hz) 6.72 (d, 1H, J = 2Hz) 6.95 (d, 1H, J = 2Hz)

REFERENCES

1. S.O. de Silva, I. Ahmad, and V. Snieckus, Can. J. Chem., 1979, 57, 1598.
2. M. Iwao, M. Watanabe, S.O. de Silva, and V. Snieckus, Tetrahedron Lett., 1981, 22, 2349.
3. S.O. de Silva, M. Watanabe, and V. Snieckus, J. Org. Chem., 1979, 44, 4802.
4. M.S. Newman and S. Kumar, J. Org. Chem., 1978, 43, 370.
5. T.K. Devon and A.I. Scott, 'Handbook of Naturally Occurring Compounds,' Vol. 1, Academic Press, Inc., New York, 1975, pp. 249-250.
6. V. Snieckus, Heterocycles, 1980, 14, 1649.
7. P. Beak and V. Snieckus, Acc. Chem. Res., 1982, 15, 306.
8. M. Reuman and A.I. Meyers, Tetrahedron, 1985, 41, 837.
9. P. Beak and R.A. Brown, J. Org. Chem., 1979, 44, 4463.
10. idem, ibid., 1982, 47, 34.
11. S.O. de Silva, J.N. Reed, and V. Snieckus, Tetrahedron Lett., 1978, 5099.
12. A.I. Meyers and W.B. Avila, J. Org. Chem., 1981, 46, 3881.
13. M. Uemura, S. Tokuyama, and T. Sakan, Chem. Lett., 1975, 1195.
14. B.M. Trost, G.T. Rivers, and J.M. Gold, J. Org. Chem., 1980, 45, 1835.
15. T.V. Hung, B.A. Mooney, R.H. Prager, and J.M. Tippett, Aust. J. Chem., 1981, 34, 383.
16. A.M. Becker, R.W. Irvine, A.S. McCormick, R.A. Russell, and R.N. Warrener, Tetrahedron Lett. 1986, 27, 3431.
17. M.P. Sibi, M.A.J. Mian, and V. Snieckus, J. Org. Chem., 1984, 49, 737.
18. A.I. Meyers and W.B. Avila, Tetrahedron Lett., 1980, 21, 3335.

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