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Studies on Carboxylation of Alkoxy-Substituted Benzyl Alcohols *via* Direct Lithiation and Bromine-Lithium Exchange: Synthesis of Phthalides and Phthalideisoquinoline Alkaloids

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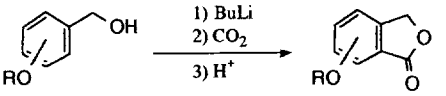
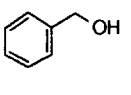
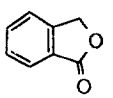
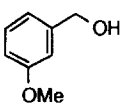
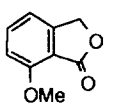
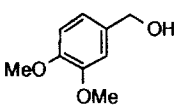
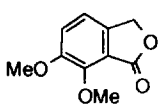
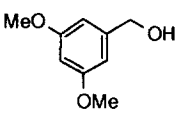
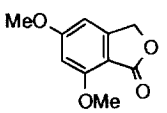
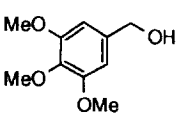
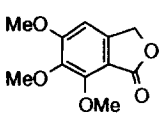
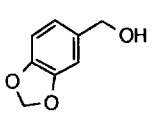
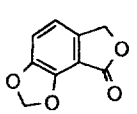
Abstract: Conversion of alkoxy-substituted benzyl alcohols to the corresponding phthalides by carboxylation *via ortho* lithiation and bromine-lithium exchange was studied. The method was applied to the key step in the synthesis of phthalideisoquinoline alkaloids.

Halogen-lithium exchange has permitted the preparation of many aromatic organolithium reagents.[1,2] The reagents bearing electron withdrawing substituents are generated by direct lithiation with *ortho* specificity.[3,4] Hydroxyalkyl- and aminoalkyl-substituents are also effective for inducing a similar lithiation at the *ortho* position, and subsequent treatments of the resultant lithium salts with proper electrophiles produce a variety of heterocycles[5] having isobenzofuran,[6-14] isochroman[11,15-18] and isoquinoline skeletones.[19-23]

Phthalides have been utilized as key intermediates in the synthesis of some classes of natural products[6] and anthraquinones.[12] *Ortho* lithiation of benzyl alcohols followed by carboxylation provided a useful method for the preparation of phthalides.[6-13] A *m*-alkoxy substituent of benzyl alcohols render *ortho* lithiation more easily because of the enhanced stability of the anion by their inductive effect and chelation,[8,24] but may cause steric hindrance at the same time. In order to clarify the effects of alkoxyl groups we first searched literature on lithiation of alkoxy-substituted benzyl alcohols for their lactonizations. According to a study on direct lithiation of anisole derivatives by Shirley,[3] the steric requirement of the lithiation is related to the origomer size of alkyl lithium.[25] Trost reported that lithiation of *m*-methoxybenzyl alcohol with hexameric BuLi (BuLi in hexane at 0°C for 1.5h) followed by carboxylation with Dry Ice at -78 °C afforded 7-methoxyphthalide in 65% yield and identical conversion of 3,5-dimethoxybenzyl alcohol gave 5,7-dimethoxyphthalide in a lower yield (24%),[9] as shown in column 1 of Table 1. Uemura reported that 7-methoxyphthalide was obtained from 3-methoxybenzyl alcohol in 53% yield by using monomeric BuLi (with TMEDA in hexane at 60°C for 5h), but 3,4- and 3,5-dimethoxybenzyl alcohol gave no phthalide (column 2).[8] Phthalide itself is prepared from benzyl alcohol by similar carboxylations. Seebach produced phthalide (59%) by using monomeric BuLi (with TMEDA in boiling petroleum ether for 11 h)[7] in a similar manner to that reported by Uemura[8] as noted above. In contrast, Dodsworth reported that tetrameric BuLi (in boiling ether for 24 h) gave phthalide in 15% yield and 7-methoxyphthalide in 45% yield, respectively[12] (column 3). Thus, these numerical values appear to be somehow dissonant with each other. This encouraged us to reexamine the effects of alkoxy-substituents on carboxylation *via ortho* lithiation of benzyl alcohols. Our experiments were carried out under the following conditions. Each

Table 1. Carboxylation of Benzyl Alcohols *via ortho* Lithiation: Conditions for Lithiation with BuLi and Yields of Phthalides.

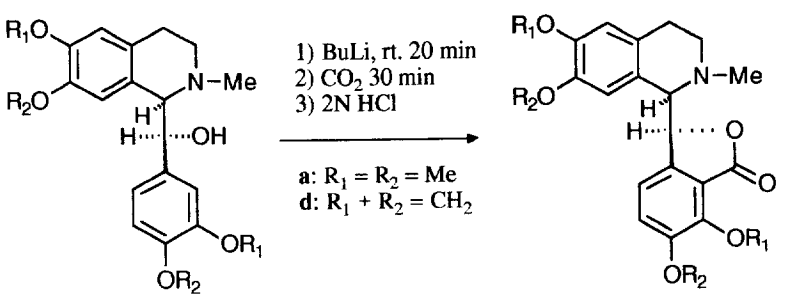


substrate: benzyl alcohol	product: phthalide	yield			
		reported works			present work
		hexane 0°C 1.5 h (ref.9)	hexane TMEDA 60°C 5h (ref.8)	ether reflux 24h (ref.12)	THF r.t. 20min[b]
			59%[a]	15%	0.7%
		65%	53%	45%	15%
		24%	0%		27%
			0%		25%
					19%
					83%

a. Petroleum ether, reflux 11 h / CO_2 (ref.7)
b. 2.4 M BuLi in THF, r.t., 20 min / CO_2 gas, 10 min / 2N HCl, 3 h.

benzyl alcohol was treated with BuLi (2.4 M) in dry THF (tetrameric BuLi) at 20°C for 20 min in an atmosphere of nitrogen, and the resultant aryl lithium was quenched by bubbling CO_2 gas for 10 min at the same temperature. This carboxylation was completed by acidification of the resultant pasty reaction mixture with aq. 2N HCl solution for 3 h. The results are summarized in column 4 of Table 1. 3,4-Methylenedioxybenzyl alcohol was the most reactive among the tested benzyl alcohols, and gave 6,7-methylenedioxyphthalide in 83% yield accompanied by the unchanged benzyl alcohol (17%). Other benzyl alcohols gave the corresponding phthalides in yields less than 27%. Lactonization of 3,4-dimethoxybenzyl alcohol gave only 25% of 6,7-dimethoxyphthalide and the unchanged alcohol (75%). This is probably due to steric bulk of a dimethoxy group, compared with a methylenedioxy group. However even so, the *m*-methoxy group is very effective for stabilizing *ortho* lithium salt, since carboxylation of benzyl alcohol itself occurred only in an 0.7% yield. Results of these tests probably reflect electronic and steric factors.

Introduction of an additional hetero atom, such as an amino group, to this system may increase the stability of the anion by a chelation. However, when amino alcohol **1a** was subjected to lactonization by a similar treatment with BuLi (4 M) at 20°C for 20 min followed by the introduction of CO_2 for 10 min, most of amino-alcohol **1a** was recovered, and the desired phthalide, (±)-cordrastine II (**2a**), was formed in only 6% yield. Lactonization of methylenedioxy derivative **1d** was also not very successful and gave (±)-bicuculline (**2d**) in 36 % yield.[26]



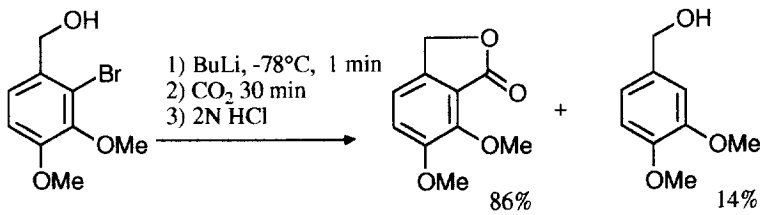
1a
1d

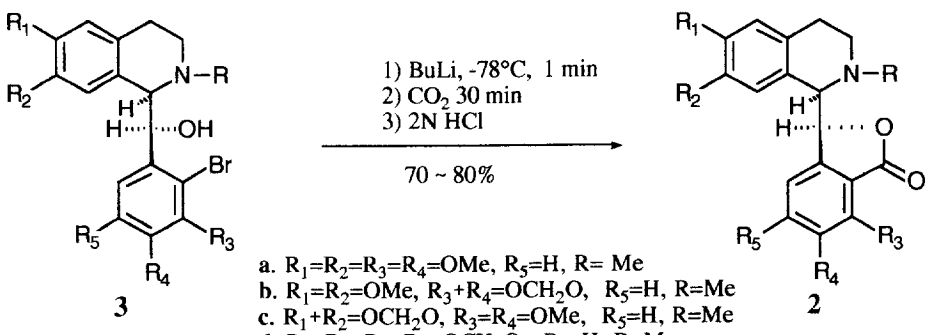
2a (±)-cordrastine II, 6%
2d (±)-bicuculline, 36%

So we turned our attention to a halogen-lithium exchange of *o*-bromobenzyl alcohol. In this case, lithiation of 2-bromo-3,4-dimethoxybenzyl alcohol[27] occurred much faster [BuLi (2.5 M) at -78°C for less than 1 min], and subsequent treatment for the carboxylation procedure described above gave 6,7-dimethoxyphthalide (86%), accompanied by a debromination product, 3,4-dimethoxybenzyl alcohol (14%). Under these low temperature conditions 3,4-dimethoxybenzyl alcohol gave no phthalide.

This one pot operation was applied to lactonization of *erythro* amino-alcohols **3**. A THF solution of **3a** was exposed to BuLi (4 M) at -78°C for 5 min and CO_2 gas was then introduced (10 min). Subsequent acidic work-up gave **2a** (95%) accompanied by β-hydroxylaudanosine **1a** (5%). Longer treatment with BuLi (30 min) increased the amount of this undesired compound **1a** (36%),[28] as shown in Table 2. When the deuterated alcohol (**3a-OD**), prepared by recrystallizations of **3a** from 99% CH_3OD, was taken up to the latter conditions involving 30 min treatment with BuLi, a deuterium atom was incorporated in one half of the formed β-hydroxylaudanosine **1a** at the 2' position. These results suggest that the 2'-lithio compound is initially formed by a rapid halogen-lithium exchange, and then reacts with an acidic hydrogen of the benzylic OH group.[29]

Australian pioneers in the synthetic studies of these alkaloids described a similar halogen-lithium exchange by a prolonged reaction period, which gave phthalides in low yields.[30] Thus, lactonization of **3a** was undertaken, commencing with a one minute treatment with BuLi to lead to the almost quantitative formation of **2a**, accompanied by a very trace amount of β-hydroxylaudanosine **1a**.





a. R_1=R_2=R_3=R_4=OMe, R_5=H, R= Me
b. R_1=R_2=OMe, R_3+R_4=OCH_2O, R_5=H, R=Me
c. R_1+R_2=OCH_2O, R_3=R_4=OMe, R_5=H, R=Me
d. R_1+R_2=R_3+R_4=OCH_2O, R_5=H, R=Me
e. R_1=R_2=R_3=R_4=OMe, R_5=H, R=CH_2Ph
f. R_1+R_2=R_3+R_4=OCH_2O, R_5=H, R=CH_2Ph
g. R_1=R_2=R_4=R_5=OMe, R_3=H, R=Me

Table 2. Carboxylation of 3a[a]

reaction time of **3a** with BuLi	product (%) **2a** : **1a**
1 min	99 : trace
5 min	95 : 5
30 min	64 : 36

a. 4M BuLi in THF, -78°C / CO_2 gas, 10 min / 2N HCl, 3 h

One recrystallization gave 70 ~ 80 % of the alkaloids **2a-d** even in such a small scale as 0.04 mmol. Lactonization of **3e,f** having N-benzyl group proceeded smoothly to give N-benzyl phthalide **2e,f**. Compound **2e** has previously been converted by hydrogenolysis to norcordrastine II.[27,31] In addition *erythro* alcohol **3g** bearing no alkoxyl group at the 3' position was also carboxylated *via* a short time lithiation to give isocordrastine II **2g** in 78 % yield.

Thus, the present study on carboxylation of benzyl alcohols *via ortho*-lithiation and halogen-lithium exchange provided a useful alternative methodology for the synthesis of phthalides and phthalideisoquinoline alkaloids.

EXPERIMENTAL

Melting points were measured with a Yanagimoto micro melting point apparatus, and were uncorrected. ^{1}H NMR spectra were recorded on either a JEOL JNM-JX270 or a Bruker MSL 400 spectrometer. IR spectrum was recorded on a JASCO IR-810 infrared spectrophotometer. ^{1}NMR samples were prepared using $CDCl_3$ (99.8 atom % D, containing 0.03 % v/v TMS, Aldrich). β-Hydroxylaudanosine **1a**[32] and its methylenedioxy derivative **1d**,[33] as well as bromides **3a**,[27] **3b** [mp 133-134°C], **3c** [mp 138-139°C], **3d** [mp 187-189°C], **3e**,[27] **3f** [mp 77-79°C] and **3g** [mp 137-138°C], were prepared by stereoselective reduction of the corresponding 1-benzoyl-3,4-dihydroisoquinoline methiodides and benzyl bromides with $NaBH_4$.[27] Details for the preparation of these *erythro* amino alcohols having a bromine atom at 2' position will be reported later.

General Procedure for Carboxylation of Benzyl Alcohols *via ortho* Lithiation. BuLi-hexane solution (1.58 M, 0.76 ml, 1.2 mmol, Ardrich) was added to a stirred solution of benzyl alcohol (0.5 mmol) in dry THF (10 ml) at room temperature in an atmosphere of nitrogen. After the mixture was stirred for 20 min., CO_2 gas was introduced for 10 min. 2N HCl solution (3 ml) was added to the mixture. After stirring for 30 min, THF was evoporated. The residue was extracted with CH_2Cl_2 (3 ml × 3), and the combined extracts were washed with H_2O (5 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave an oil which was subjected to ^{1}H NMR analysis. The results are summarized in column 4 of Table 1.

Synthesis of (±)-Cordrastine II (2a) and (±)-Bicuculline (2d) *via ortho* Lithiation. In a similar manner to the procedure for carboxylation described above, β-hydroxylaudanosine (**1a**, 93 mg, 0.25 mmol) in dry THF (10 ml) was treated with BuLi (1.58 M, 0.63 ml, 1.0 mmol) and CO_2 gas. The reaction mixture was then evaporated. Water (5 ml) and aq. 2N NaOH (0.5 ml) was added to the residue. The mixture was extracted with CH_2Cl_2 (5 ml × 2). The extracts were washed with water (5 ml), dried over anhydrous Na_2SO_4. and evaporated to give the unchanged amino-alcohol **1a** (81 mg) as a solid. The alkaline water layer was worked up according to the procedure described below for (±)-cordrastine II to give a crystalline solid of (±)-cordrastine II (**2a**, 3 mg), mp 117-119°C (MeOH).

Similar treatment of amino-alcohol **1d** (34 mg, 0.1 mmol) with BuLi (1.58 M, 0.25 ml, 0.4 mmol) followed by bubbling CO_2 gas and acidification gave (±)-bicuculline (**2d**,13 mg, 36%), mp 227-229°C (MeOH-ether), and 19 mg of **1d** was recovered.

Carboxylaion of 2-Bromo-3,4-dimethoxybenzyl Alcohol. BuLi (1.58 M, 0.39 ml, 0.625 mmol) was added to a stirred solution of 2-bromo-3,4-dimethoxybenzyl alcohol[27] (62 mg, 0.25 mmol) in dry THF (5 ml) cooled in Dry Ice acetone bath at -78 °C in an atmosphere of nitrogen. After 1 min, the cooling bath was removed and CO_2 gas was introduced into the solution for 10 min. 2N HCl solution (3 ml) was then added to the mixture. After stirring for 3 h, THF was evoporated. The residue was worked up in the same manner as noted above for carboxylation of benzyl alcohols to give a crude product (52 mg), which was found to be a mixture of 6,7-dimethoxyphthalide (86%) and 3,4-dimethoxybenzyl alcohol (14%) by ^{1}H NMR analysis.

General Procedure for the Synthesis of Phthalideisoquinoline Alkaloids *via* Bromine-Lithium Exchange. (±)-Cordrastine II (2a). BuLi (1.58 M, 0.32 mL, 0.5 mmol) was added to a stirred solution of

erythro-1-(β-hydroxy-2-bromo-3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **3a** (57 mg, 0.125 mmol) in dry THF (5 ml) cooled at -78 °C in an atmosphere of nitrogen. After 1 min, the cooling bath was removed and CO_2 gas was introduced into the solution for 10 min. The mixture was further stirred at room temperature for 1 h, and then evoporated [Results shown in Table 2 were obtained by acidication with 2N HCl (2 ml) for 3 h before THF was evoporated, followed by careful treatment with aq. 2N NaOH for adjusting to pH 9, extraction with CH_2Cl_2 (7 ml × 3) and ^1H NMR analysis of crude products]. Water (5 ml) and aq. 2N NaOH (0.5 ml) were added to the residue, which was washed with CH_2Cl_2 (5 ml × 2). The water layer, after addition of aq. 2N HCl (2 ml), was allowed to stand at room temperature for 3 h, then basified with aq. 2N NaOH (about 1.2 ml) adjusting to pH 9 and extracted with CH_2Cl_2 (7 ml × 3). The combined CH_2Cl_2 layers were washed with water (15 ml), and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave an oil (43 mg), which was crystallized from MeOH to give (±)-cordrastine II (**2a**, 35 mg, 70%), as colorless crystals, mp 117-119 °C (lit.[34] mp 118-119°C).

(±)-Corlumine (2b). Similarly, **3b** (22 mg, 0.05 mmol) in THF (3 ml) was treated with BuLi (1.56 M, 0.128 ml, 0.2 mol) for 1 min at -78 °C and CO_2 gas was introduced for 30 min. A crude oily product (14 mg) was treated with MeOH to give (±)-corlumine **2b** (12 mg, 80%), as colorless crystals, mp 178-181°C (MeOH) (lit.[35] mp 178-181°C, lit.[36] mp 193.5-195°C).

(±)-β-Hydrastine (2c). Similar treatment of **3c** (17.5 mg, 0.04 mmol) afforded a crude product (14 mg), which was crystallyzed from MeOH to give **2c** (12 mg, 80%), as colorless crystals, mp 150-151°C (lit.[32] mp 136-140°C, lit.[37] mp 138-139°C, lit.[38] mp 135-137°C).

(±)-Bicuculline (2d) Similar treatment of **3d** (52 mg, 0.125 mol) afforded an oil (35 mg), which was crystallized from MeOH-ether to give **2d** (33 mg, 72%), as colorless crystals, mp 227-229 °C. Recrystallization from $CHCl_3$-MeOH gave a sample which melted at 217-220°C (lit.[35] mp 217-220°C).

N-Benzyl phthalide (2e). Similar treatment of N-benzyl *erythro* alcohol **3e** (53 mg, 0.10 mmol) gave an oily product (45 mg), which was crystallized from MeOH-Et_2O to give N-benzyl phthalide **2e**, (36 mg, 76%), as colorless crystals, mp 119-120 °C.[27]

N-Benzyl phthalide (2f). Similar treatment of N-benzyl *erythro* alcohol **3f** (50 mg, 0.10 mmol) gave an oily product (39 mg), which was crystallized from MeOH-Et_2O to give N-benzyl phthalide **2f** (33 mg, 75%), as colorless crystals, mp 194-196 °C. IR (Nujol) 1765, 1618, 1596 cm^{-1}; ^1H NMR (270 MHz) δ 2.28-2.39 (1H, m, 4-H), 2.63-2.80 (2H, m, 4- and 3-H), 2.83-2.94 (1H, m, 3-H), 3.78, 3.92 (each 1H, AB type, J = 3.9 Hz, benzylic H), 5.92 (2H, s, 6,7-OCH_2O), 6.16, 6.18 (each 1H, AB type, J = 1.4 Hz, 6',7'-OCH_2O), 6.33 (1H, s, 8-H), 6.36 (1H, AB type J = 8.3 Hz, 4'-H), 6.60 (1H, s, 5-H), 6.95 (1H, AB type J = 8.3 Hz, 5'-H), 7.29 (5H, br. s, aromatic H). Anal. Calcd for $C_{26}H_{21}NO_6$: C, 70.42; H, 4.77; N, 3.16. Found: C, 70.55; H, 4.73; N, 3.12.

(±)-Isocordrastine II (2g). *erythro*-1-(β-Hydroxy-2-bromo-4,5-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **3g** (45 mg, 0.1 mmol) gave a crude oily product (39 mg). Recrystallization of a crude product from EtOH gave isocordrastine II **2g** (31 mg, 78%), as colorless crystals, mp 167-169°C (lit.[34] mp 169-170°C, lit.[39] mp 157-159°C, lit.[40] mp 166-167°C).

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