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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 heterocycles⁵ 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 products⁶ 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 3,5dimethoxybenzyl 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 Uemura⁸ as noted above. In contrast, Dodsworth reported that tetrameric BuLi (in boiling ether for 24 h) gave phthalide in 15% yield and 7methoxyphthalide in 45% yield, respectively¹² (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 1) BuLi 2) CO₂

RO

3) H⁺

substrate: benzyl alcohol	product: phthalide	yield			
		re hexane 0°C 1.5 h (ref.9)	ported wor hexane TMEDA 60°C 5h	tks ether reflux 24h	present work THF r.t. 20min ^b
		· ···· · · · · · · · · · · · · · · · ·	(ref.8)	(ref.12)	<u></u>
ОЧ	\bigcup_{o}^{o}		59% *	15%	0.7%
ОМе	OMe O	65%	53%	45%	15%
MeO OMe Med		24%	0%		27%
MeO OH Med			0%		25%
MeO OMe MeO					19%
ОН	Ω.				83%

 Table 1. Carboxylation of Benzyl Alcohols via ortho Lithiation:

 Conditions for Lithiation with BuLi and Yields of Phthalides.

ОН

RO

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 CO₂ 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 CO₂ for 10 min, most of amino-alcohol 1a was recovered, and the desired phthalide, (\pm)-cordrastine II (2a), was formed in only 6% yield. Lactonization of methylenedioxy derivative 1d was also not very successful and gave (\pm)-bicuculline (2d) in 36 % yield.²⁶



So we turned our attention to a halogen-lithium exchange of *o*-bromobenzyl alcohol. In this case, lithiation of 2-bromo-3,4-dimethoxybenzyl alcohol²⁷ 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 CO₂ 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% CH₃OD, 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**.



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 / CO₂ gas, 10 min / 2N HCl, 3 h

One recrystallization gave 70 \sim 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. ¹H 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. ¹NMR samples were prepared using CDCl₃ (99.8 atom % D, containing 0.03 % v/v TMS, Aldrich). β -Hydroxylaudanosine 1a³² 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 NaBH₄.²⁷ 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., CO₂ 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 CH₂Cl₂ (3 ml × 3), and the combined extracts were washed with H₂O (5 ml) and dried over anhydrous Na₂SO₄. Evaporation of the solvent gave an oil which was subjected to ¹H NMR analysis. The results are summarized in column 4 of Table 1.

Synthesis of (\pm)-Cordrastine II (2a) and (\pm)-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 CO₂ 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 CH₂Cl₂ (5 ml × 2). The extracts were washed with water (5 ml), dried over anhydrous Na₂SO₄. 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 (\pm)-cordrastine II to give a crystalline solid of (\pm)-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 CO₂ gas and acidification gave (\pm)-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 alcohol²⁷ (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 CO₂ 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 ¹H 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 CO₂ 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 CH₂Cl₂ (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 CH₂Cl₂ (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 CH₂Cl₂ (7 ml × 3). The combined CH₂Cl₂ layers were washed with water (15 ml), and dried over anhydrous Na₂SO₄. 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 CO₂ 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 CHCl₃-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-Et₂O 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-Et₂O 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-OCH₂O), 6.16, 6.18 (each 1H, AB type, J = 1.4 Hz, 6',7'-OCH₂O), 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 C₂₆H₂₁NO₆: 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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