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SELECTIVE NUCLEAR LITHIATION OF AROMATIC COMPOUNDS: FACILE SYNTHESIS OF METHOXYPHTHALIDE DERIVATIVES BY CARBOXYLATION OF THE LITHIO-COMPOUNDS

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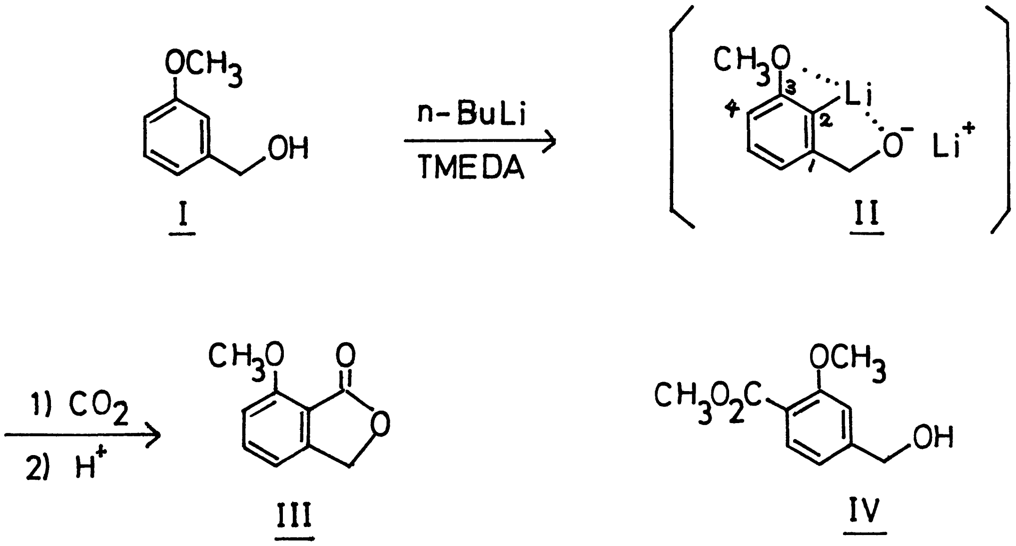
The aromatic compounds, which have both hydroxymethyl and methoxyl groups at 1,3-position, were lithiated mostly at 2-position with n-butyllithium. This reaction would provide a useful synthetic method of methoxyphthalide derivatives, in conjunction with carboxylation of the resulting lithio-compounds.

Aromatic compounds with such a substituent as methoxyl, methoxymethyl, dimethylamino, dimethylaminomethyl or alkylcarbamoyl group, have been known to undergo direct nuclear lithiation with n-butyllithium mainly at ortho-position of the substituent.[1), 2)] This metallation is presumably facilitated by initial coordination of the lithium atom with the hetero-atom on the substituent. Generally, when an appropriate aromatic substrate carries two of these groups at 1,3-position on the aromatic ring, the lithiation would be expected more easily and more selectively at 2-position,[3)] because the metal atom is coordinated with both substituents (Chart I). The lithio-compound thus formed may be derived to a variety of synthetic intermediate. This report concerns the studies along this consideration.

3-Methoxybenzyl alcohol <u>I</u> was treated in n-hexane with two molar amounts of n-butyllithium in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA). The reaction mixture was treated with a large excess of carbon dioxide. After treatment with diazomethane, two products were obtained. The main product was found to be 7-methoxyphthalide <u>III</u>, an expected 2-carboxylated product, in 53% yield. Methyl 4-hydroxymethyl-2-methoxybenzoate <u>IV</u> was obtained in 6% yield as a minor product. This means that the lithiation also proceeded at 4-position.

CHART I

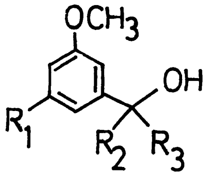
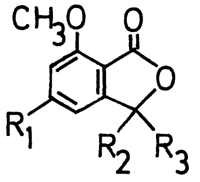
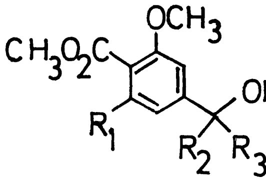
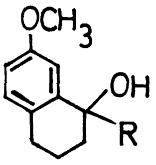
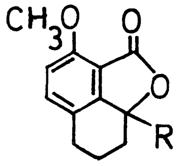
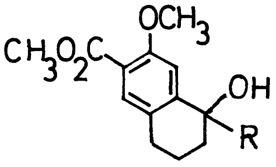
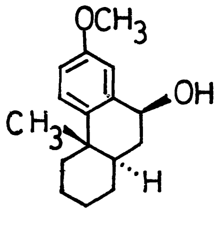
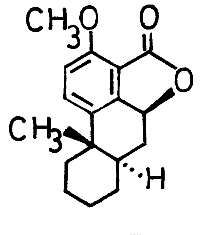


The reaction was carried out with a variety of derivatives of 3-methoxybenzyl alcohol in a similar procedure. The products in each experiment were analyzed by preparative TLC and by GLC. The results, summarized in Table I, reveal the following characteristics of the reaction: 1) Substitution with methyl group (or groups) at the benzylic position increased the yield of the methyl ester, in accordance with the increase of steric hindrance at 2-position (entries A, C, D, J and L). 2) Rigid conformation of the benzylic hydroxyl group stabilizes the intermediate 2-lithio compound of the type II, resulting in the preference of the phthalide formation to the methyl ester formation. Thus, a tetralol VI and a octahydrophenanthrol VIII(4) gave phthalides, VII and IX, respectively, in high yield without trace of by-products, such as corresponding methyl esters. These examples suggested the usefulness of this procedure in a synthesis of polycyclic complex molecules. 3) Additional methoxyl substitution on the benzene ring influenced the product ratio. In these cases, the phthalide formation was unfavorable (entries E$\sim$H). Interestingly, the compound V gave no carboxylated product, but only methoxy clevage was observed (entry I).

The use of TMEDA was not essential for lithiation, but the total yield of the carboxylated products improved markedly in the presence of the reagent (entries B and K).(5) Excess of n-butyllithium should be avoided, otherwise some quantity of bis-carboxylation product was formed (entry F).

Further investigations are in progress on the application of this method to

TABLE I LITHIATION AND SUBSEQUENT CARBOXYLATION OF METHOXYBENZYL ALCOHOL DERIVATIVES AND RELATED COMPOUNDS

Entry	Substrate	n-BuLi(eq),	TMEDA(eq)	Product and Yield(%)		
				Methoxyphthalide	Methyl ester	
						
A	$R_1=R_2=R_3=H$	2	2	53	6	
B	$R_1=R_2=R_3=H$	2	0	44	—	
C	$R_1=R_2=H$; $R_3=CH_3$	2	2	62	14	
D	$R_1=H$; $R_2=R_3=CH_3$	2	2	46	20	
E	$R_1=OCH_3$; $R_2=R_3=H$	2	2	—	10	
F	$R_1=OCH_3$; $R_2=R_3=H$	6	2	8	22	a)
G	$R_1=OCH_3$; $R_2=H$; $R_3=CH_3$	2	2	8	24	
H	$R_1=OCH_3$; $R_2=R_3=CH_3$	2	2	—	25	
I	3,4-Dimethoxybenzyl alcohol: V	2	2	—	—	b)
						
J	R=H: VI	2	2	VII; 80	—	
K	R=H: VI	2	0	VII; 62	—	
L	$R=CH_3$	2	2	42	23	
M	 VIII	2	2	 IX 80		

a) 5,7-Dimethoxy-6-methoxycarbonylphthalide was also obtained in 13% yield.

b) 3-Hydroxy-4-methoxybenzyl alcohol and 4-hydroxy-3-methoxybenzyl alcohol were obtained in 15% yield in each.

some natural product syntheses.

A representative of experimental procedure is as follows: To a hexane solution of 1 eq. of 3-methoxybenzyl alcohol and 2 eq. of TMEDA was added a hexane solution of 2 eq. of n-butyllithium (1.56M solution) under purified nitrogen at room temperature. The mixture was heated at 60° C for 5 hours. The resulting dark red solution, after cooling to –76° C, was treated with an excess of Dry-Ice (in small pieces). The reaction mixture was acidified (dil. HCl) and the product was extracted with ethyl acetate. After treatment with diazomethane, the crude product was purified by preparative TLC (Silica Gel G, benzene:hexane: ether=2:2:1). The exact ratio of the phthalide III to the methyl ester IV was determined by GLC analysis.

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