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The Birch reduction–dialkylation reaction. Scope and limitations

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Abstract—The Birch reduction–dialkylation reaction has been studied with different aromatic carboxylic acids and primary and secondary bromides. From these results it can be concluded that it is a reasonably general reaction. However, we found important exceptions with the primary bromides: allyl bromide, β-phenethyl bromide, and 5-bromo-2-methyl-2-pentene. The unusual behavior of allyl bromide is briefly discussed.

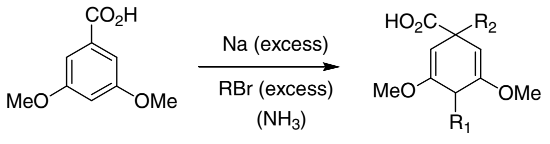
1. Introduction

The Birch reduction–dialkylation of aromatic carboxylic acids is a potentially useful reaction since after the usual Birch reduction of the aromatic ring, two C–C bonds are formed sequentially at the C-1 and C-4 positions of the intermediate 1,4-dihydrobenzoic acid.[1] The reaction was first observed with 3,5-dimethoxybenzoic acid and excesses of Na and ethyl bromide in liquid NH_3 although Li but not K, also gives similar results (Scheme 1).[2] We have now extended our studies to other aromatic carboxylic acids and alkyl bromides with the purpose to determine its generality.

2. Birch reduction–dialkylation of 3,5-dimethoxybenzoic acid with alkyl bromides

Following the general procedure described in Ref. 1, in the first group of experiments 3,5-dimethoxybenzoic acid **1** was submitted to the Birch reduction–dialkylation reaction with different primary and secondary alkyl bromides.[3] Sodium was used as the reducing alkali metal and analysis of the crude reaction mixtures were done by ^1H NMR spectroscopy of the crude methyl esters as reported previously for the ethyl case **2a**.[4] Results are presented in Table 1.

With 6.2 molar equiv of Na, dialkylation with primary alkyl bromides (entries 1 and 2) proceeded smoothly to give high yields of products, whilst the secondary isopropyl bromide afforded the dialkylated products contaminated with 20% of monoalkylated product. Since dehydrobromination of secondary alkyl bromides was expected to be a competitive base-consuming side reaction, in experiments with these bromides the molar equivalent of Na and alkyl bromides were increased up to 10.2, but even so some monoalkylated compound still remained in the product (10% for isopropyl bromide, entry 3 and 12% for cyclohexyl bromide, entry 5).



1

2a, $R_1=R_2=C_2H_5$
2b, $R_1=R_2=n\text{-}C_3H_7$
2c, $R_1=R_2=n\text{-}C_5H_{11}$
2d, $R_1=R_2=i\text{-}C_3H_7$
2e, $R_1=R_2=(CH_2)_4CH$
2f, $R_1=R_2=(CH_2)_5CH$
2g, $R_1=H$, $R_2=Me_2C{=}CH(CH_2)_2$
2h, $R_1=H$, $R_2=Ph(CH_2)_2$
2i, $R_1=H$, $R_2=CH_2CH{=}CH_2$

Scheme 1.

Keywords: Birch reduction; Dialkylation; Primary and secondary alkyl bromides; Substituted benzoic acids.

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Table 1. Birch reduction–dialkylation of 3,5-dimethoxybenzoic acid

Entry	RBr (molar equiv)	Na (molar equiv)	Main product (see text)	Yield (%)
1	$n\text{-}C_3H_7\text{–}$ (8.2)	6.2	**2b**	95
2	$n\text{-}C_5H_{11}\text{–}$ (8.2)	6.2	**2c**	84
3	$i\text{-}C_3H_7\text{–}$ (8.2)	10.2	**2d**	98[a]
4	$(CH_2)_4CH\text{–}$ (10.2)	10.2	**2e**	91
5	$(CH_2)_5CH\text{–}$ (10.2)	10.2	**2f**	76[b]
6	$Me_2C{=}CH(CH_2)_2\text{–}$ (8.2)	8.2	**2g**	55
7	$Ph(CH_2)_2\text{–}$ (8.2)	8.2	**2h**	75
8	$CH_2{=}CHCH_2\text{–}$ (8.2)	8.2	**2i**	81[c]

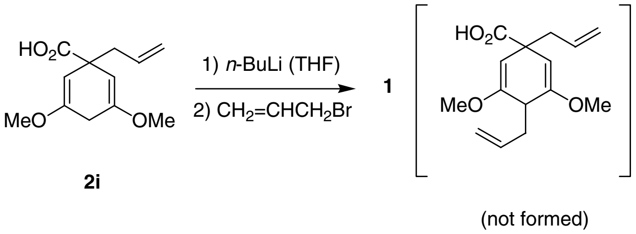
[a] The product contained 12% of mono *iso*-propyl compound.
[b] The product contained 10% of monocyclohexyl compound.
[c] The product contained 40% of starting material (see text).

Surprisingly, cyclopentyl bromide (entry 4) gave cleanly only dialkylated products in high yield and it is also noteworthy that a reasonably good yield was obtained with the easily dehydrohalogenated cyclohexyl bromide (entry 5).

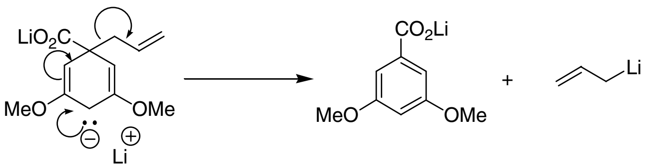
Even more easily dehydrohalogenated primary alkyl bromides such as the homoprenyl and homobenzyl bromides failed to give the dialkylation reaction and afforded only monoalkylated products in fair yields (entries 6 and 7). Probably, after alkylation at C-1 $NaNH_2$ and/or the sodium carbanion at C-4 are too basic and dehydrohalogenate the excess alkyl bromide before alkylation at C-4 takes place. Fortunately, in these and other related cases dialkylated products can be obtained successfully in separate experiments by C-4 metalation (*n*-BuLi, THF, −78 °C)–alkylation of the corresponding monoalkylated dihydrobenzoic acids (Scheme 2).[5] Incidentally, we have used this two-step method for the synthesis of several 1,4-dialkyl-2,5-cyclohexadiene carboxylic acids containing two different groups at C-1 and C-4.

Finally, our reaction conditions were also tested with the highly reactive allyl bromide but unexpectedly, the 1,4-diallyl compound was not obtained. A 3:2 mixture of monoallyl compound **2i** and 3,5-dimethoxybenzoic acid **1** were produced instead. We could demonstrate that the 3,5-dimethoxybenzoic acid present in the crude product was not due to an incomplete Birch reduction when we attempted to prepare 1,4-diallyl compound from **2i** by the two-step method cited before (*n*-BuLi, THF, −78 °C; then allyl bromide). The starting material was totally consumed and a quantitative yield of crude 3,5-dimethoxybenzoic acid was obtained (Scheme 3).

Presumably, the intermediate lithium carbanion at C-4 aromatizes by expulsion of the allyl anion (Scheme 4).



Scheme 3.

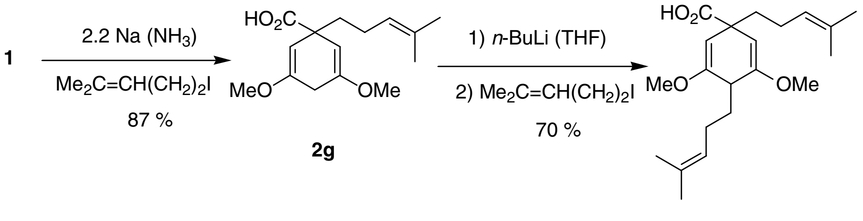


Scheme 4.

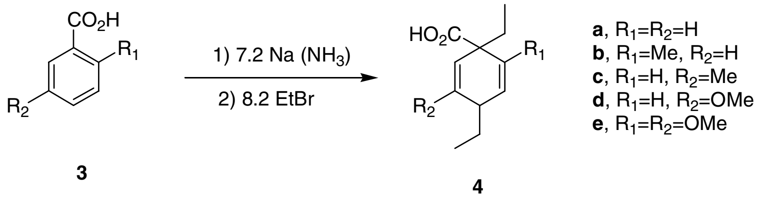
This unusual aromatization, which involves elimination of a poor leaving group has been previously observed with the somewhat related benzyl anion.[6]

3. Birch reduction–diethylation of substituted benzoic acids

The second group of experiments we performed involved the use of different benzoic acids as substrates in the Birch reduction–diethylation reaction. Ethyl bromide (8.2 molar equiv) was used both as the ethylating agent as well as reagent for $NaNH_2$ formation. The experiments were carried out following the procedure reported for the Birch reduction–diethylation of 3,5-dimethoxybenzoic acid with 7.2 molar equiv of Na.[3] The crude products were analyzed as the methyl esters by ^1H NMR spectroscopy and results are presented in Scheme 5 and Table 2.



Scheme 2.



Scheme 5.

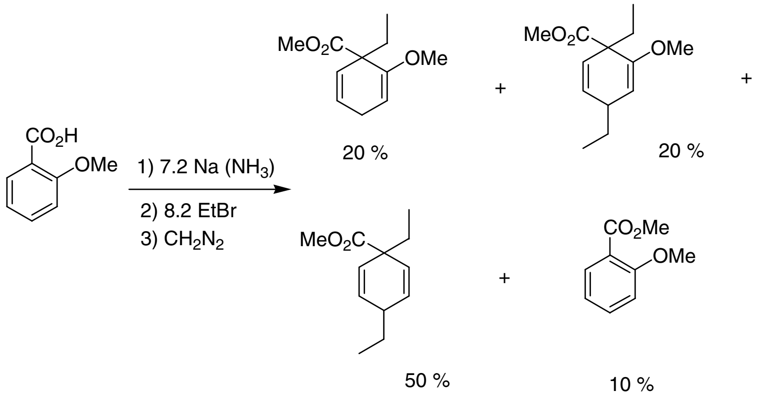
Table 2. Birch reduction–diethylation of substituted benzoic acids

Entry	Benzoic acid	Diethylated product	Yield (%)
1	$R_1 = R_2 = H$	$R_1 = R_2 = H$	85
2	$R_1 = CH_3$, $R_2 = H$	$R_1 = CH_3$, $R_2 = H$	86
3	$R_1 = H$, $R_2 = CH_3$	$R_1 = H$, $R_2 = CH_3$	91
4	$R_1 = H$, $R_2 = OCH_3$	$R_1 = H$, $R_2 = OCH_3$	89
5	$R_1 = R_2 = OCH_3$	$R_1 = R_2 = OCH_3$	91

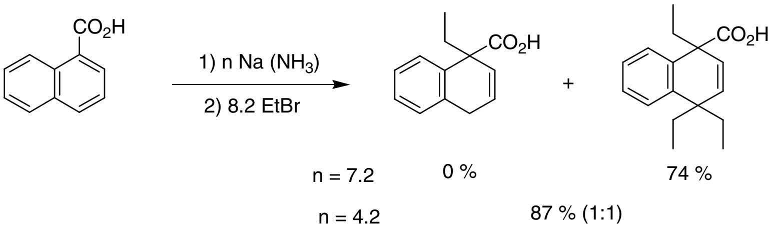
Very high yields of diethylated products were obtained with the five benzoic acids listed in Table 2. The only substituted benzoic acid tested, which failed to give a clean reaction was *o*-anisic acid (not included in the Table). In this case, a complex mixture of starting material (10%), mono- (20%) and diethylated (20%) products, and diethylated 1,4-dihydrobenzoic acid (50%) was obtained in 86% yield (Scheme 6). Loss of the *o*-methoxy group during the Birch reduction of this acid has been previously observed.[7]

We have also submitted 1-naphthoic acid to the Birch reduction–diethylation reaction but triethylated product was exclusively formed in 74% yield. Interestingly, with reduced amounts of Na (4.2 molar equiv) a 1:1 mixture of mono- and triethylated products were obtained, but diethylated products were not detected (Scheme 7).[8]

In conclusion, the results presented in this letter show that the Birch reduction–dialkylation reaction is a quite general transformation with benzoic acids and primary and secondary bromides. Easily dehydrohalogenated alkyl bromides (e.g., homoallyl and homobenzyl bromides) and the highly reactive allyl bromide are important exceptions in this reaction.



Scheme 6.



Scheme 7.

Acknowledgement

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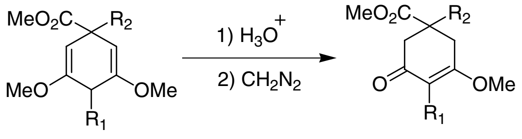
References and notes

1. Guzmán, J. A.; Castanedo, R.; Maldonado, L. A. *Synth. Commun.* **1991**, *21*, 1001–1012.
2. Unpublished results.
3. General procedure: In a two-necked 250 mL round bottom flask, fitted with a dry ice condenser and a stopper, were placed 1 g (5–8 mmol) of the appropriate benzoic acid and a stirring bar. Dry liquid NH_3 (125 mL, from Na) was condensed in the flask, and with stirring, the required molar equivalent of Na (6.2–10.2) was added in small pieces (10–15 min depending of the amount of metal). The initial almost colorless solution gradually turns yellow, orange, and deep red with the first 2 equiv of metal and beyond this number, the solution becomes deep blue. After 15 min, the stopper was replaced by an addition funnel containing cold, neat alkyl bromide (8.2–10.2 molar equiv) and added dropwise in about 10 min (CAUTION! Exothermic reaction). The sequence of colors in the solution reverses, changing from deep blue to deep red, orange, and finally pale yellow. NH_3 was left to evaporate overnight, the residue dissolved in H_2O (30 mL) and washed with Et_2O to remove any neutral material. The aqueous layer was covered with fresh Et_2O (20 mL) and carefully acidified (pH 5) with small portions of cold 5% aqueous HCl, shaking vigorously after each addition. The aqueous solution was extracted again with 20 mL of fresh Et_2O and the combined organic extracts rapidly washed with H_2O (2×10 mL) and dried over anhydrous Na_2SO_4. Removal of solvent gave the crude product as a white or yellow crystalline mass in the indicated yields. About 100 mg of the crude acids were quantitatively esterified with ethereal CH_2N_2 and the crude methyl esters were analyzed by ^1H NMR and/or GC.

   Note: In the case of methoxy substituted benzoic acids, careful acidification with cold acid and rapid extraction is crucial to avoid hydrolysis of the acid sensitive methoxy enol ethers present in the products. For alkyl substituted benzoic acids, the usual acidification and workup can be followed.
4. Furthermore, values thus obtained were checked in every case by an alternative method involving the two-step conversion (acid-catalyzed hydrolysis and ethereal CH_2N_2) of the alkylated dihydrobenzoic acid methyl esters into the corresponding cyclic vinylogous methyl esters **5**, which were separated and purified by preparative TLC. If present, the more polar 2-unsubstituted vinylogous methyl ester **5a** (from monoalkylated product) was easily identified by the olefin broad singlet signal at $\approx\delta$ 5.20 in its ^1H NMR spectrum. This second method of analysis was especially useful when important amounts of monoalkylated product were obtained.



5a, $R_1 = H$
5b, $R_1 = R_2$

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