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J. A. Guzmán [a], R. Castanedo [a] & L. A. Maldonado [a]
[a] División de Estudios de Posgrado, Facultad de Química, UNAM, 04512, México, D.F., México

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THE BIRCH REDUCTION - DIALKYLATION REACTION OF AROMATIC CARBOXYLIC ACIDS. IDENTIFICATION OF $NaNH_2$ AS THE BASE RESPONSIBLE FOR THE SECOND ALKYLATION

J.A. Guzmān, R. Castanedo and L.A. Maldonado*

Divisiōn de Estudios de Posgrado, Facultad de Quīmica,
UNAM, 04510 Mēxico D.F., Mēxico.

ABSTRACT : The Birch reduction-alkylation of 3,5-dimethoxybenzoic acid with excesses Na and EtBr gives 1,4-diethyl-3,5-dimethoxy-2,5-cyclohexadiene carboxylic acid, **3**. The base responsible for the alkylation at C-4 has been identified as $NaNH_2$, generated in situ.

The alkaline metal-NH_3 reduction of aromatic systems (the Birch reduction) stands as an important reaction in synthetic organic chemistry[1]. The reaction has been further extended to include C-C bond forming reactions, either by trapping in situ the dianion species generated by the reduction of aromatic carboxylic acids[2] (reaction 1) or by metalation-alkylation of the 1,4-dihydroaromatic systems isolated from such reductions[3] (reaction 2).

In an earlier paper[4], we briefly described the previously unreported observation that the Birch reduction-alkylation of 3,5-

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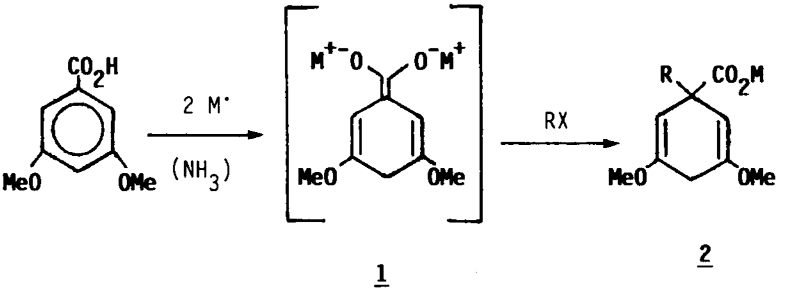
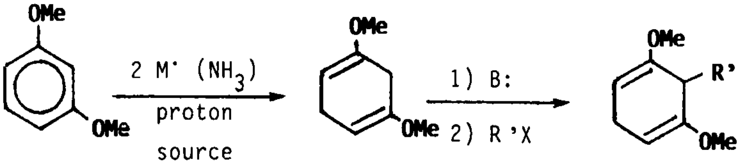
* To whom correspondence should be addressed.

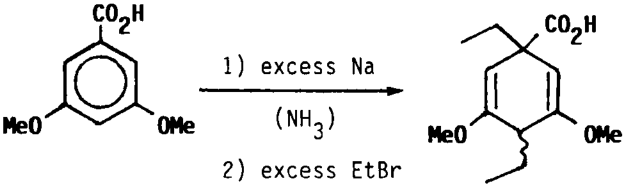


(1)



(2)

dimethoxybenzoic acid with excesses Na and EtBr (8-9 equivalents each) gave the reduced 1,4-diethyl compound **3** as a crystalline mixture of diastereoisomers in a 3 : 2 ratio :



3

The obvious utility of this conversion which includes reactions (1) and (2) in tandem, prompted us to examine further this transformation and it is the purpose of this paper to present our initial studies concerning the mechanism of this reaction[5].

Taking into account our initial observation that the diethyl product is obtained with 8-9 equivalents of Na and EtBr, our first goal was to find the lower limit of the Na concentration in order to observe exclusive diethylation. Toward this end a series of experiments were carried out in which the 3,5-dimethoxybenzoic acid (2 g, 11 mmol), dry liquid NH_3 (250 ml) and the equivalents of EtBr (9.5 g, 87 mmol) were kept constant and the amount of Na was steady increased from one experiment to another. All these reactions were remarkably clean; the crude acids being obtained in yields up to 90 %. The crude methyl esters, obtained quantitatively by esterification with ethereal CH_2N_2, were analyzed by pmr spectroscopy integrating the peak areas at δ 4.55 (monoethyl product and the minor diethyl diastereoisomer) and δ 4.70 (major diethyl diastereoisomer). Based on the reasonable assumption that the ratio of diastereoisomers is kept constant in all these experiments, one can calculate the ratio of mono- and diethyl products easily[6]. The results are shown in table 1.

Mechanistically, the Birch reduction of an aromatic carboxylic acid in the absence of proton source requires about 2 equivalents of the alkaline metal and proceeds through dianion <u>1</u> (reaction 1)[7]; alkylation of this intermediate then gives the 1-alkyl-1,4-dihydroaromatic acid. We have confirmed this result (entry 1) and have also carried out experiments with larger amounts of Na. As is seen from table 1, the experiments beyond 2.2 equivalents of Na (entries 2-6) showed an almost linear dependence between the amounts of Na used and diethylated product obtained. Experimentally, excess Na gave the usual deep blue colored solutions of alkaline metals in liquid NH_3, a highly exothermic reaction ensues on addition of the EtBr. This contrasting behaviour, as compared with the relative mildness of experiments with 2.2 equivalents of Na, thus

TABLE 1. Ratio of mono- and diethyl products from 3,5-dimethoxybenzoic acid and increasing amounts of Na*.

Entry	Equivalents of Na, n**		Ethylated products	
			mono	di
1	2.2	(0.0)	100	0
2	3.2	(0.5)	85	15
3	4.2	(1.0)	60	40
4	5.2	(1.5)	35	65
5	6.2	(2.0)	15	85
6***	7.2	(2.5)	0	100

*Average ratio of two experiments.

**Numbers in parenthesis refer to the equivalents of generated $NaNH_2$ (see text).

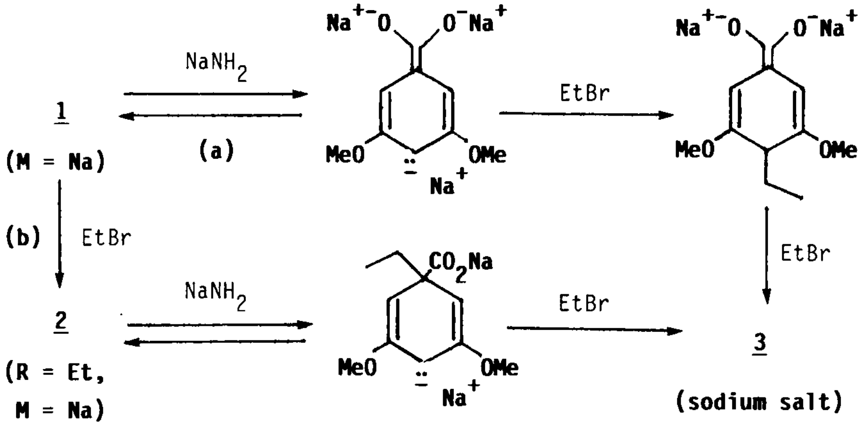
***Some triethyl product has been identified in these experiments.

suggesting that the known[8] reaction of alkyl halides with Na in liquid NH_3 to give $NaNH_2$ was operating here :

$$R{-}X \quad + \quad 2\ Na \quad + \quad NH_3 \longrightarrow R{-}H \quad + \quad NaX \quad + \quad NaNH_2 \qquad (3)$$

In view of the fact that 2.2 equivalents of Na are consumed in the Birch reduction step and 2 equivalents of Na are required for each equivalent of EtBr according to reaction (3), it follows that the number of equivalents of generated $NaNH_2$ is given by $\frac{n - 2.2}{2}$; where n = total equivalents of Na. These values are also given in parenthesis for each experiment in table 1. In addition, since the reaction was started with 8 equivalents of EtBr, it is also clear that even in the experiments with large amounts of Na (e.g. entry 6) enough EtBr should remain after the total consumption of Na and alkylate whatever carbanion species are present in the reaction medium.

Therefore, our proposal to explain the formation of the diethyl product 3 is that $NaNH_2$, generated by excesses Na and EtBr, metalates reversibly at C-4 dianion 1 and/or monoethyl carboxylate 2 **(R = Et)** thus affording new polyanions which are ethylated by the remaining EtBr. Both pathways are shown in the following scheme :



The reversible nature of the deprotonation step at C-4 is demonstrated by the fact that $NaNH_2$ in excess of 1 equivalent (2.5 equivalents, entry 6) is required to observe complete diethylation. This is undoubtedly due to the relatively low acidity of the double allylic CH_2 protons.

In order to prove that $NaNH_2$ is the base responsible for the C-4 ethylation reaction, a new sequence of experiments were car-

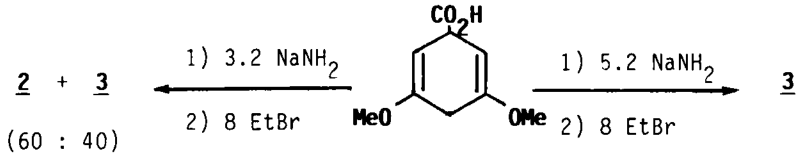
TABLE 2. Birch reduction-ethylation of 3,5-dimethoxybenzoic acid in the presence of $NaNH_2$ formed by Fe(III) catalysis.

Entry	Equivalents of $NaNH_2$*	Ethylated products	
		mono	di
1	1.2	50	50
2	2.2	15	85
3	2.6	0	100

*Generated after the Birch reduction step.

ried out but now in the presence of Fe (III)-generated $NaNH_2$. Thus, 3,5-dimethoxybenzoic acid was first reduced to the dianion stage with 2.2 equivalents of Na (blue color as end point indicator) and then the appropriate amount of Na was added in the presence of $Fe(NO_3)_3$ for generating $NaNH_2$. Addition of excess EtBr (8 equivalents) afforded the mixture of mono- and diethyl products in ratios close to that obtained in the first group of experiments (compare tables 1 and 2).

An additional confirmation for the need of $NaNH_2$ in this C-4 alkylation reaction was obtained in the following way. We reasoned that if dianions of carboxylic acids can be prepared by the double deprotonation of carboxylic acids with strong bases such as $NaNH_2$[9], then treatment of 1,4-dihydro-3,5-dimethoxybenzoic acid **4** with an appropriate excess of $NaNH_2$ would give reaction conditions (and intermediates) closely similar to that obtained by the Birch reduction method. Thus, the reaction of **4**[7] with 5.2 equivalents of $NaNH_2$ in liquid NH_3 gave a deep red wine colored solution, which was alkylated with 8 equivalents of EtBr affording exclusively the diethyl compound **3**. Similarly, if the deprotonation-alkylation of **4** is carried out under the same reaction conditions, but now with only 3.2 equivalents of $NaNH_2$, a 60 : 40 mixture of mono- and diethyl products is obtained in excellent agreement with the results of entries 3 (table 1) and 1 (table 2) :



The above experiments conclusively demonstrate the important role that $NaNH_2$ plays for the succesful alkylation at C-4 and although we feel that the reaction conditions point toward pathway (a)[4], we hope to be able to design in the near future appropriate experiments to rule out definitively, pathway (b).

EXPERIMENTAL SECTION

Melting points and boiling points are uncorrected. I.r. spectra were run on a Perkin-Elmer 599B instrument. P.m.r. spectra were recorded with a Varian EM-390 instrument and chemical shifts are given in p.p.m. (δ) downfield from tetramethylsilane. V.p.c. was carried out on a Perkin-Elmer 3920 instrument equipped with a flame-ionization detector, using nitrogen at 30 ml/min as carrier gas. Microanalysis were performed by Galbraith Laboratories Inc..

Birch reduction-diethylation of 3,5-dimethoxybenzoic acid

a) $NaNH_2$ generated from excess Na and ethyl bromide : In a two-necked 500 ml round bottom flask, fitted with a dry ice condenser and a stopper, were placed 2 g (11 mmol) of 3,5-dimethoxybenzoic acid (Aldrich) and a stirring bar. Dry liquid NH_3 (about 250 ml, from Na) was condensed in the flask, and with stirring the required equivalents of Na were added in small pieces (20-30 min depending of the amount of Na). The initial almost colorless solution gradually turns yellow, orange and deep red with the first 2 equivalents of Na. Beyond this number the solution turns deep blue and becomes dense, especially with the larger amounts of Na. After 15 min the stopper was replaced by an addition funnel containing 9.5 g (6.5 ml, 87 mmol) of cold EtBr 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. The NH_3 was left to evaporate overnight, the residue dissolved in H_2O (about 50 ml) and washed with Et_2O to remove any neutral material. The aqueous layer was covered with fresh Et_2O (30 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 x 10 ml) and dried over anhydrous Na_2SO_4. Removal of solvent gave the crude product as a white or faint yellowish crystalline mass in yields of about 90 %.

A small portion (100 mg) of the crude acids was quantitatively esterified with ethereal CH_2N_2 and after removal of solvent, the crude methyl esters were analyzed by pmr and vpc (2 columns of 3 ft x 1/8 in. each, packed with 10 % and 3 % OV-17 on Chromosorb W respectively, at 200°). Retention times : monoethylated methyl ester, 9.52 min; minor diethylated diastereoisomer methyl ester, 10.40 min; major diethylated diastereoisomer methyl ester, 12.36 min.

From the experiment with 2.2 equivalents of Na, pure monoethylated acid was obtained, mp 149-150° (prisms from Et_2O-hexane); ir (KBr) ν_{max} 3100-2500 and 1695 (CO_2H), 1660 (CH=C-), 1270, 1200 and 1150 cm^{-1} (C-O); pmr ($CDCl_3$) 11.30 (broad s, exchanges with D_2O, CO_2H), 4.60 (s, CH=C-), 3.60 (s, 2 OCH_3), 2.70 (s, double allylic CH_2), 1.75 (q, J = 6.5 Hz, $\underline{CH_2}CH_3$), 0.80 (t, J = 6.5 Hz, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.26; H, 7.54. Found : C, 61.91; H, 7.52.

The methyl ester is a low melting solid, mp 34° which can be distilled at reduced pressure, bp 70°/0.3 (kugelrohr); ir (film) ν_{max} 1730 (C=O), 1660 (CH=C-), 1200 and 1150 cm^{-1} (C-O); pmr (CCl_4) 4.55 (s, CH=C-), 3.60 (s, CO_2CH_3), 3.55 (s, 2 OCH_3), 2.65 (s, double allylic CH_2), 1.65 (q, J = 6.5 Hz, $\underline{CH_2}CH_3$), 0.75 (t, J = 6.5 Hz, $CH_2\underline{CH_3}$).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.72; H, 7.96. Found : C, 63.89; H, 7.75.

From the experiment with 7.2 equivalents of Na, the mixture of diastereoisomeric diethylated acids were obtained. Fractional crystallization of the mixture from Et_2O-hexane afforded the less soluble, more abundant isomer, mp 140-141° (prisms); ir (KBr) ν_{max} 3100-2500 and 1700 (CO_2H), 1660 (CH=C-), 1200 and 1150 cm^{-1} (C-O); pmr ($CDCl_3$) 10.60 (broad s, exchanges with D_2O, CO_2H), 4.75 (s, CH=C-), 3.60 (s, 2 OCH_3), 2.90 (t, J = 4.5 Hz, double allylic CH), 1.60-1.90 (complex, 2 $\underline{CH_2}CH_3$), 0.85 and 0.65 (2 t, J = 6.5 Hz, 2 $CH_2\underline{CH_3}$).

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found : C, 65.11; H, 8.47.

The methyl ester of this diastereoisomer was obtained as a low melting solid (mp 30-31°), after distilling at reduced pressure, bp 80-85°/0.3 (kugelrohr); ir (film) ν_{max} 1730 (C=O), 1650 (CH=C-), 1200 and 1150 cm^{-1} (C-O); pmr (CCl_4) 4.70 (s, CH=C-), 3.60 (s, CO_2CH_3), 3.55 (s, 2 OCH_3), 2.80 (t, J = 4.5 Hz, double allylic CH), 1.50-1.85 (complex, 2 $\underline{CH_2}CH_3$), 0.80 and 0.65 (2 t, J = 6.5 Hz, 2 $CH_2\underline{CH_3}$).

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found : C, 66.24; H, 8.57.

b) $NaNH_2$ generated by excess Na and $Fe(NO_3)_3$: Liquid NH_3 (250 ml, from Na) was condensed in a two-necked 500 ml round bottom flask containing 2 g (11 mmol) of 3,5-dimethoxybenzoic acid and a stirring bar. To the clear solution 0.56 g (24.3 mmol) of Na was added in small pieces; a blue solution being obtained at the end of the addition. A small amount of solid $Fe(NO_3)_3.6H_2O$ was added to discharge the blue color and then, additional Na was introduced to generate the required equivalents of $NaNH_2$. After 15 min, 9.5 g

(6.5 ml, 87 mmol) of cold EtBr was added dropwise in about 10 min and the experiment was completed as in method (a). Although yields were comparable in both experiments, the solid material now obtained was yellow-brown. The crude methyl esters were prepared and analyzed as above (table 2).

Diethylation of 1,4-dihydro-3,5-dimethoxybenzoic acid

To a solution of 2 g (11 mmol) of acid **4**[7] in 250 ml of freshly distilled liquid NH_3 (from Na), a small amount of $Fe(NO_3)_3 \cdot 6\ H_2O$ was added. Small pieces of Na (experiments with 1.3 and 0.8 g (56.5 and 34.7 mmol, respectively) were carried out) were then introduced as rapidly as the blue color was discharged. The red wine colored solution was then treated with 9.5 g (6.5 ml, 87 mmol) of cold EtBr and worked up and analyzed as in the previous methods.

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5. In this paper we will refer only to the identification of the base responsible for the alkylation at C-4 and hope to submit in other paper our experiments leading to the identification of the polyanion species involved.

6. Peak area at δ 4.70 (A) = 3/5 diethyl product (**3**); therefore, (**3**) = 5/3 A. Peak area at δ 4.55 (B) = monoethyl product (**2**) + 2/5 diethyl product (**3**); therefore, (**2**) = B - 2/5(5/3) A = B - 2/3 A.

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