What is X? A Classroom Exercise

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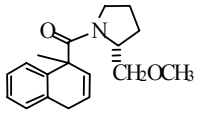
Abstract: The last stage of three-step synthetic sequence to obtain an alkylated Birch product gave an unexpected and undesired product. From the discussion of all the reactions involved rather than from the interpretation of NMR spectra, the structure of the product **X** is elucidated.

Introduction

This example proposes an interplay between organic synthesis and chemical and spectroscopic properties so as to arrive at the solution of an unknown product structure. From the pedagogical point of view, we consider it valuable for the cultivation of an open-mind when dealing with chemical procedures and also for the utilization of critical judgment, which we hope our students have acquired during their courses in organic chemistry. Experience with advanced students of organic chemistry has confirmed that examples of this type have the added advantage of communicating the excitement of scientific discovery. It is with this purpose in mind that we have selected the following example.

The use of enantioselective methods in reductive alkylation of monoaromatic systems for producing chiral amides from benzoic acid and L-proline is well-known. It has been widely studied by A. J. Schultz [1, 2]. With that knowledge as a basis, we set out to obtain chiral amides of biarylic systems such as **1** derived from 1-naphthoic acid **2** [3], and eventually we carried out the functional group transformations shown in Scheme 1.



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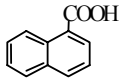

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To our surprise, the last reaction in this sequence, the Birch alkylation between the amide **4** and methyl iodide as alkylating reagent, did not give the desired monoalkylated product **1** but, after chromatographic purification, a yellow oil **X** was obtained instead.

Using all the NMR data for the sequence **2** → **X**, students have the opportunity to use their chemical reasoning to interpret the results, and they are able to answer the following questions:

(a) Identify each **2** → **4** reaction.
(b) Assign the NMR signals for **2**, **3** and **4**. (Even when some compounds are known, such as benzoic acid, we show students the spectroscopic data for comparative proposals of the complete sequence of reactions.) The spectra are available in the supporting material.
(c) Determine the structure of **X** on the basis of the NMR spectra.
(d) Suggest a reasonable explanation for the outcome of the Birch reaction and for the relative stereochemistry of all the functional groups as well.

Data

1-Naphthoic Acid (2, $C_{11}H_8O_2$)**.** White solid, mp 159–161 °C (lit 160–162 °C).^{1}H NMR ($CDCl_3$, 200 MHz, δ) 9.06 (d, *J* = 8.8 Hz, 1H), 8.40 (dd, *J* = 7.3 and 1.3 Hz, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 7.92 (dd, *J*= 8.8 and 1.5 Hz, 1H), 7.51–7.66 (m, 3H), 11.0 (s, 1H).

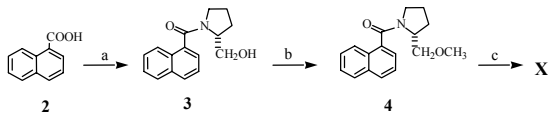
1-(2-(*R*)-Hydroxymethyl-pyrrolidinyl carbonyl)naphthalene (3, $C_{16}H_{17}O_2N$**).** Yellow oil, 98%. ^{1}H NMR ($CDCl_3$, 200 MHz, δ) 7.91–7.86 (m, 3H), 7.56–7.46 (m, 4H), 4.60 (m, 1H), 3.87 (m, 2H), 3.21–3.12 (m, 3H), 2.20 (m, 1H), 1.75 (m, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, δ) 170.2, 134.5, 132.7, 128.6, 128.2, 127.7, 126.4, 125.7, 124.5, 123.9, 123.0, 64.6, 59.7, 49.1, 27.4, 23.6.

1-(2-(*R*)-Methoxymethyl-pyrrolidinylcarbonyl)naphthalene (**4**, $C_{17}H_{19}O_2N$**).** Yellow oil, 72%. ^{1}H NMR (200 MHz, $CDCl_3$, δ) 7.86–7.82 (m, 3H), 7.52–7.43 (m, 4H), 4.55 (m, 1H), 3.76 (m, 2H), 3.47 (s, 3H), 3.09 (m, 2H), 2.69 (sa, 1H), 2.04 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ) 168.9, 135.7, 133.2, 128.9, 128.8, 128.1, 126.6, 126.0, 124.9, 124.6, 123.5, 72.1, 58.8, 56.3, 49.9, 27.6, 24.2.

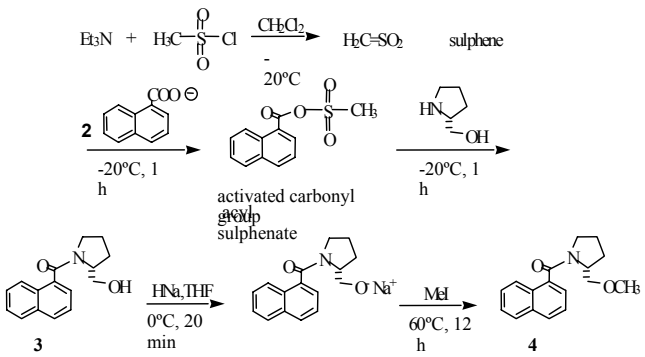
Compound X ($C_{19}H_{25}O_2N$**).** Yellow oil, 85%. ^{1}H NMR (200 MHz, $CDCl_3$, δ) 7.27–7.12 (m, 4H), 5.91 (dd, *J* = 6 and 12 Hz, 1H), 5.74 (dd, *J*= 1.2 and 12 Hz, 1H), 4.30 (m, 1H), 3.60 (m, 1H), 3.45 (m, 1H), 3.36, 3.37 (duplicated signal, s, 3H), 3.15 (m, 1H), 2.20 (m, 1H), 1.70 (m, 4H), 1.54, 1.55 (duplicated signal, s, 3H), 1.36 (d, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, δ) 172.8, 137.89, 137.56, 129.7, 128.6, 128.0, 127.9, 126.6, 126.5, 126.4, 126.3, 125.8, 72.0, 71.6, 58.7, 58.6, 57.5, 57.4, 48.1, 46.7, 46.3, 33.9, 31.4, 31.2, 26.4, 24.6, 24.3.

Solution

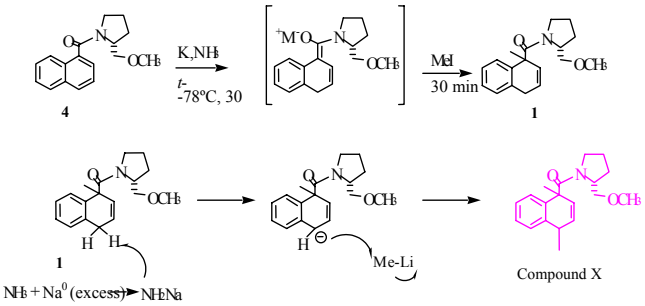
The chiral amide **3** was obtained from a solution of 1-naphthoic acid in dichloromethane, triethylamine, mesyl chloride, and (*R*)-prolinol [4]. The reaction involving triethylamine and mesyl chloride forms a sulphene species that reacts with the carboxylic acid to create a good leaving group on the acid [5]. Then, the hydroxyamide is ortho methylated with sodium hydride and methyl iodide to afford **4** (Scheme 2) and finally the treatment of **4** under Birch-alkylation protocol gave **X**. This finding suggested the existence of another pathway via compound **1** as we show in Scheme 3 and finally the treatment of **4** under Birch-alkylation protocol gave **X**.



Scheme 1. Reagents: (a) CH_2Cl_2, Et_3N, –20 °C; 2. MsCl, 1 hr; (*R*)-prolinol (98%). (b) 1. THF, NaH, 0 °C; 2. CH_3I, 60 °C, 12 hr (70%). (c) 1. Amide (0.71 mmol), NH_3, K (1.56 mmol), *tert*-BuOH (0.71 mmol), –78 °C; 2. CH_3I (1.42 mmol).



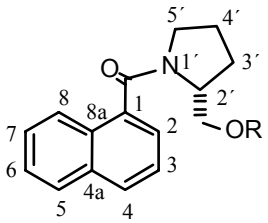
Scheme 2. Mechanism of the reaction for the transformation of 2 into 4.



Scheme 3. The alkylation Birch reaction.

Analysis of the NMR Spectra

The numbering system for the NMR spectra is shown below.

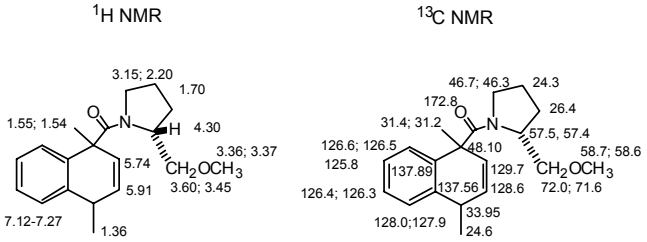


1-Naphthoic acid (2, $C_{11}H_8O_2$). White solid, mp 159–161 °C (lit 160–162 °C).[1]H NMR (200 MHz, $CDCl_3$ δ) 9.06 (d, *J* = 8.8 Hz, 1H, H-8), 8.40 (dd, *J* = 7.3 and 1.3 Hz, 1H, H-2), 8.09 (d, *J* = 8.1 Hz, 1H, H-4), 7.92 (dd, *J* = 8.8 and 1.5 Hz, 1H, H-5), 7.51–7.66 (m, 3H, H-3, H-6, and H-7), 11.0 (s, 1H, COO**H**).

1-(2-(*R*)-Hydroxymethylpyrrolidinylcarbonyl)napthalene (3, $C_{16}H_{17}O_2N$). Yellow oil, 98%. [1]H NMR (200 MHz, $CDCl_3$, δ) 7.91–7.86 (m, 3H, aromatics), 7.56–7.46 (m, 4H, aromatics), 4.60 (m, 1H, H-2′), 3.87 (m, 2H, C**H**$_2$OH), 3.21–3.12 (m, 3H, H-5′ and OH), 2.20 (m, 1H, H-4′), 1.75 (m, 3H, H-4′ and H-3′). ^{13}C NMR (50 MHz, $CDCl_3$, δ) 170.2 (C=O), 134.5 (C-1), 132.7 (C-8a), 128.6 (C-4), 128.2 (C-4a), 127.7 (C-3), 126.4 (C-5), 125.7 (C-7), 124.5 (C-2), 123.9 (C-6), 123.0 (C-8), 64.6 (CH_2OH), 59.7 (C-2′), 49.1 (C-5′), 27.4 (C-3′), 23.6 (C-4′).

1-(2-(R)-methoxymethylpyrrolidinylcarbonyl) naphthalene (4, $C_{17}H_{19}O_2N$). Yellow oil, 72%. [1]H NMR (200 MHz, $CDCl_3$, δ) 7.86–7.82 (m, 3H, aromatics), 7.52–7.43 (m, 4H, aromatics), 4.55 (m, 1H, H-2′), 3.76 (m, 2H, CH_2OR), 3.47 (s, 3H, -OCH_3), 3.09 (m, 2H, H-5′), 2.69 (sa, 1H, H-4′), 2.04 (m, 3H, H-4′ and H-3′). ^{13}C NMR (50 MHz, $CDCl_3$, δ) 168.9 (C=O), 135.7 (C-1), 133.2 (C-8a), 128.9 (C-4a), 128.8 (C-4), 128.1 (C-3), 126.6 (C-5), 126.0 (C-7), 124.9 (C-2), 124.6 (C-6), 123.5 (C-8), 72.1 (**C**H_2OCH$_3$), 58.8 (C-2′), 56.3 (-OCH_3), 49.9 (C-C-5′), 27.6 (C-3′), 24.2 (C-4′).

Compound X. In accordance with the NMR spectrum [6], we first came to believe that **X** might be a mixture of four diastereoisomers [(1*R*,4*S*), (1*R*,4*R*), (1*S*,4*S*), (1*S*,4*R*)] with two new stereogenic centers at C1 and C4, a dimethylated product [7] (*syn*- and *anti*-1,4-dimethyl).



Several signals appear duplicated in the [1]H NMR spectra, in particular, those singlets corresponding to the angular C1 methyl group at 1.54 and 1.55 ppm and to the methoxyl group at 3.36 and 3.37 ppm. The presence of the second methyl group bonded at C4 is corroborated by a sole signal appearing at 1.36 ppm as a doublet. In the ^{13}C NMR, the signals at 58.62 and 31.38 are duplicated for the methoxyl and C1 methyl groups, respectively, whereas the C4 methyl group exhibits a signal at 24.56. This duplicity in the signal points to the formation of only two diastereomers (*syn*-1,4-dimethyl), and based on the difference of the relative intensities of the methyl groups in the ^{13}CNMR spectra, it shows that one of the diastereomers predominates. Is the alkylation of the amide enolate produced exclusively by one face? Also, is the second methyl group selectively introduced yielding the two diastereoisomers?

We think that the entry of the second methyl group has been introduced from the same face as that of the first methyl group because of minor steric hindrance with respect to the prolinol moiety. On the other hand, if **X** is a *syn*-dimethylated product, the chemical shifts of the C4 methyl groups are identical in both diastereoisomers. Finally, to make this compatible with the spectral analysis previously shown, molecular modeling of the anions generated by C4 deprotonation for two diastereoisomers (Figure 1) shows that in both the **1** and **3** anions, the prolinol ring hinders the anionic center, restricting the approach of methyl iodide at the same face; therefore the entrance of the second methyl group occurs exclusively from the opposite face in respect to that of the amide group.

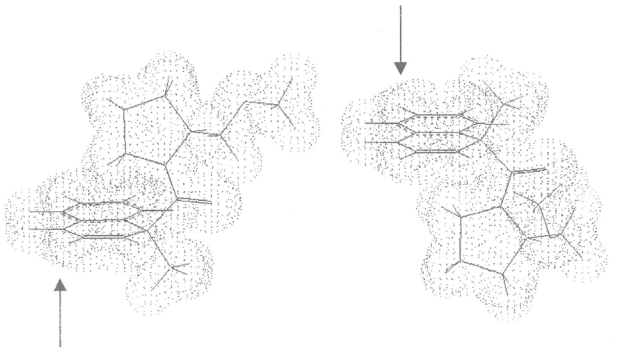


Figure 1. Structures of the anions obtained from C4 deprotonation using semiempirical calculations [8]; left: 1(*S*)-diastereoisomer, right: 1(*R*)-diastereoisomer. The arrow indicates the attack orientation of methyl iodide reagent.

Conclusions

For many years we have been working on the organic synthesis of natural products and often the products are not the desired ones. These unexpected results can be used as examples to teach chemistry students to interpret experimental findings and seek relationships between variables rather than simply verifying what they have learned in the past [9, 10].

In most cases, it is not the absence of theoretical knowledge that makes students fail in tasks, but it is difficulty with the utilization of this knowledge to reach an answer.

Acknowledgment. We acknowledge the financial support of UNR (Universidad Nacional de Rosario) and CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas).

Supporting Materials. Supporting material, consisting of the NMR spectra for compounds **3**, **4**, and **X** is available for in a zip file (http://dx.doi.org/10.1007/s008970020597b).

References and Notes

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