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Laboratory and Demonstration

Synthesis and NMR Analysis of *N*-Methyl-2-(4′-bromophenyl)morpholine: An Advanced Undergraduate Laboratory Experiment

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Through the advent of high-field FT-NMR…, undergraduates are increasingly able to gain experience with NMR spectroscopic techniques.

Nuclear magnetic resonance spectroscopy holds a premier position as a tool for structure elucidation in organic chemistry. With the increased availability of high-field Fourier-transform spectrometers in undergraduate laboratories, there is an increased need for good instructional experiments. We describe a reliable one-step synthesis of a moderately complex structure, and a straightforward ^{1}H NMR spectral assignment problem that illustrates the use of coupling constants for the determination of positional relationships, geminal coupling, and correlation spectroscopy (COSY) for the identification of coupled signals [1].

Introduction

Nuclear magnetic resonance spectroscopy is the organic chemist's most important tool for structure elucidation.

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Through the advent of high-field FT-NMR instruments and the support of programs such as the NSF ILI, undergraduates are increasingly able to gain experience with NMR spectroscopic techniques. These opportunities require well-planned educational experiences at both the introductory and advanced laboratory levels. Thus, a variety of NMR spectroscopy exercises for undergraduates have been reported [2, 3]. These include experiments with special features such as microscale preparation [4], photochemical equilibrium [5], proton exchange in a biochemically relevant compound [6], polymers [7], conformational analysis of an organometallic compound [8], ^{13}C NMR [9], and correlation spectroscopy [10].

We recently obtained an FT-NMR instrument and thus required a suitable exercise for advanced laboratory students that would reinforce basic concepts in ^{1}H NMR spectroscopy and extend these with some more advanced challenges in spectral interpretation. This synthesis and spectral interpretation problem thoroughly satisfies our needs.

The experiment consists of two parts: (1) the synthesis and purification of racemic *N*-methyl-2-(4′-bromophenyl)morpholine (MBPM), and (2) assignment of the signals in the ^{1}H NMR spectrum of this compound. In the first part of the experiment, students conduct an overnight reflux followed by an extractive workup and a vacuum distillation. The overall experiment can be shortened by having a laboratory assistant prepare a quantity of MPBM to be provided to the students. MBPM was found to be ideally suited for this experiment because it can be easily prepared and purified, and because the seven hydrogens on the morpholine ring generate nonoverlapping signals in the 200-MHz ^{1}H NMR spectrum. Although the appearance of the ^{1}H spectrum is initially complex, a systematic analysis of coupling constants and eventual consideration of the COSY spectrum lead to an unambiguous assignment of all of the signals.

Chemistry

The synthesis is based upon a procedure first described by Yordanova et al. [11] in which the morpholine ring is formed by treating an α-haloketone with an *N*-substituted ethanolamine in refluxing 90% formic acid.

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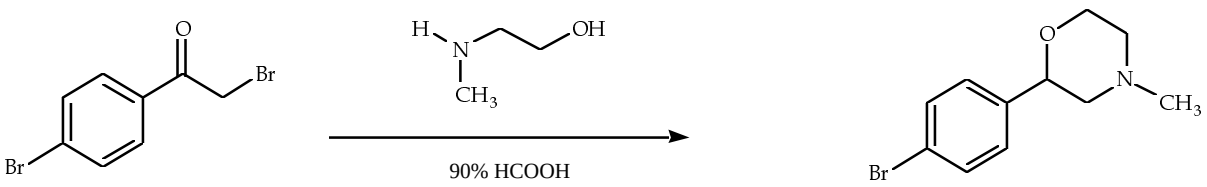
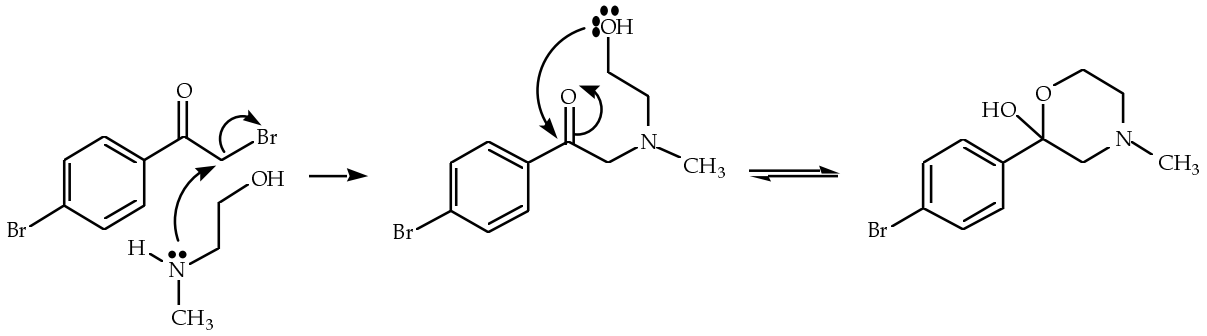
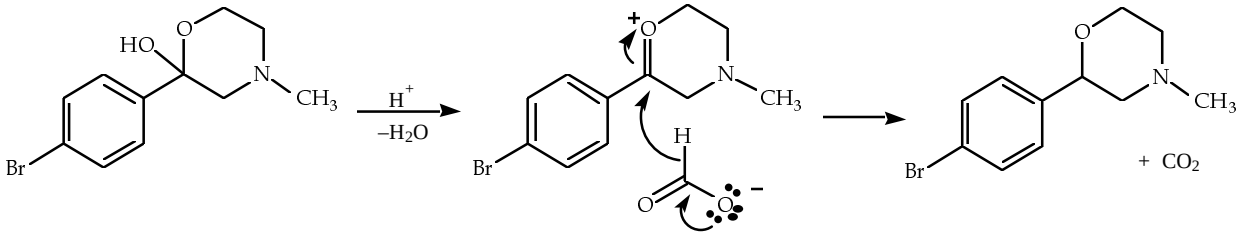


The reaction is thought to proceed via an initial S_N2 displacement of bromide from the α-haloketone, followed by hemiacetal formation.



The hemiacetal is then reduced in a Leuckart–Wallach-like reduction by formic acid, which is accompanied by the evolution of carbon dioxide.



NMR Analysis

Students begin the second part of the experiment by collecting a normal ^1H NMR spectrum of the product in $CDCl_3$ (Figure 1). Initially, the large singlet for the *N*-methyl group and the splitting pattern for the para-substituted aromatic ring are noted. Expansion of the 1.5–5.0-ppm region reveals the detail of the signals arising from the seven hydrogen atoms on the morpholine ring (Figure 2). The sample for which the spectra are shown is a typical student product (note the impurities at 2.3–2.5 and 2.8–3.6 ppm). Cleaner material can be obtained by collecting a narrower boiling fraction during the vacuum distillation.

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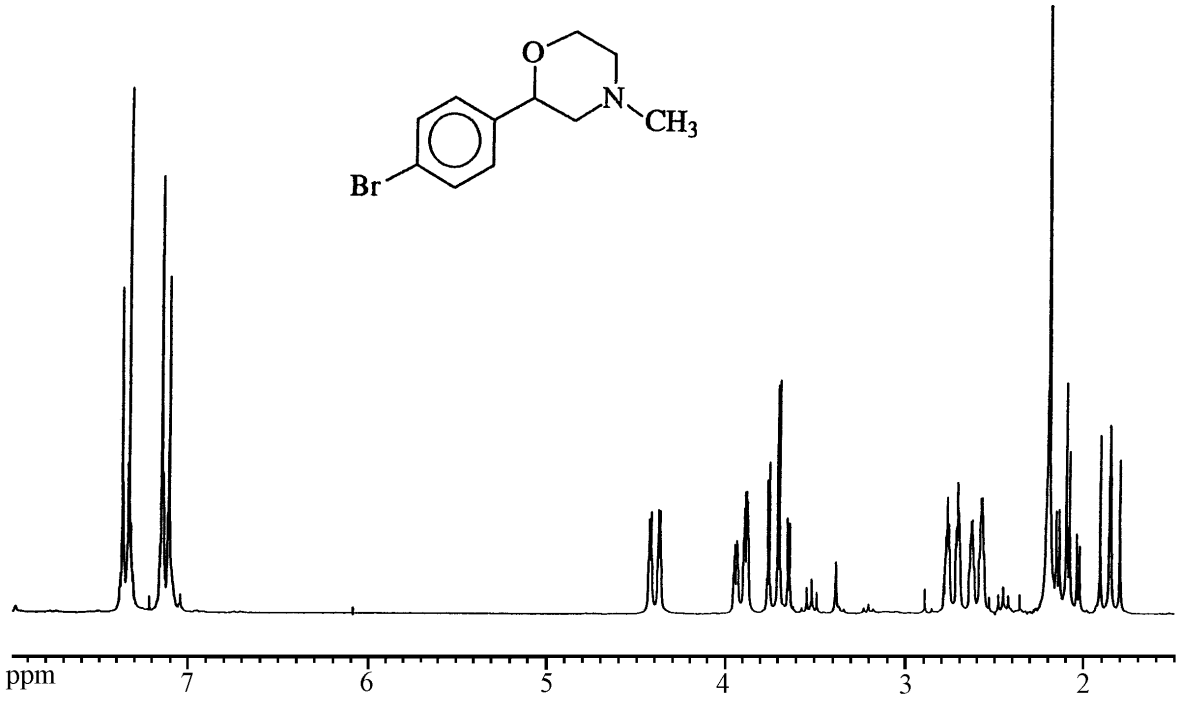

FIGURE 1. 200 MHz PROTON NMR SPECTRUM, 1.5–8.0 ppm.

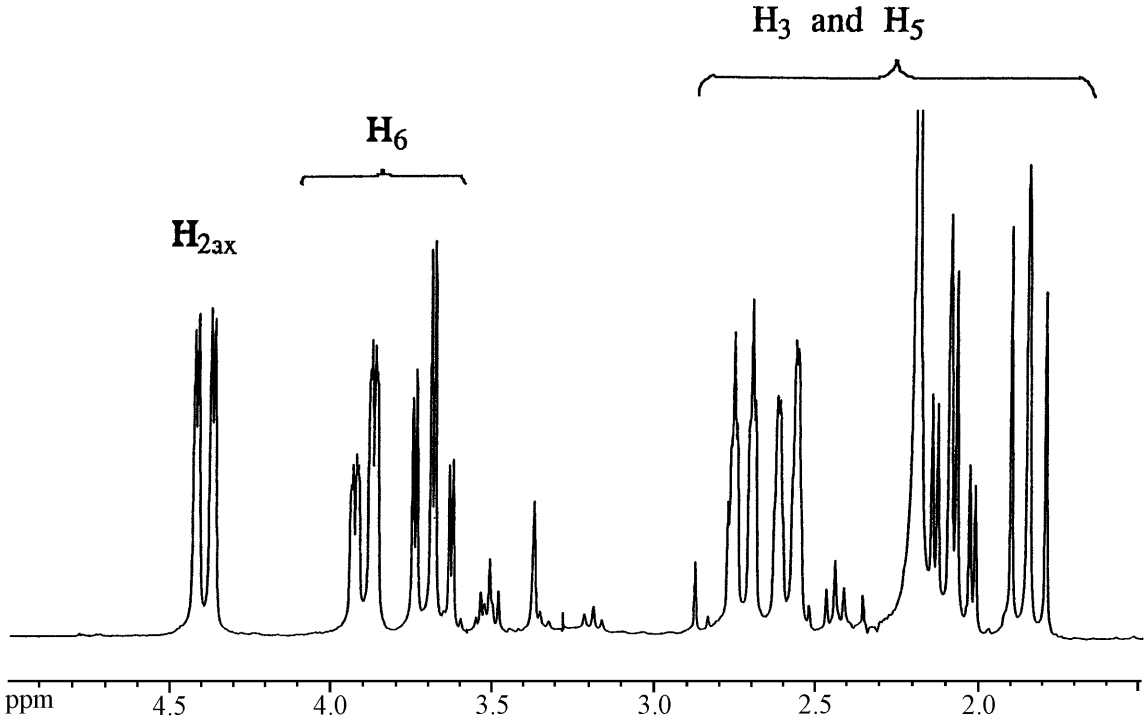

FIGURE 2. EXPANDED 200 MHz PROTON NMR SPECTURM, 1.5–3.0 ppm.

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Students begin their analysis by identifying the lone proton on C2 (See the numbering scheme for the morpholine ring in the Instructions for Students, or Supplemental Figures sections.) as the source of the most deshielded signal (4.4 ppm) of the morpholine ring protons. Examination of molecular models and consultation of the Karplus relationship [12] aid in deducing the expected splitting pattern for the C2 hydrogen. The signals from the C6 axial and equatorial hydrogens are found next in the 3.6–4.0 ppm region (Figure 3). Analysis of these signals requires consideration of the presence of geminal coupling. Students may recognize two general features of these signals which are exhibited also in the remaining signals: equatorial hydrogens are more deshielded than axial hydrogens on the same carbon, and an axial hydrogen signal generally appears as a triplet or a triplet of doublets.

At this point, assignment of the remaining signals is greatly facilitated by the availability of a COSY spectrum (Figure 4). Coupling of $H2_{ax}$ with $H3_{ax}$ and $H3_{eq}$, and coupling of the C6 hydrogens to $H5_{ax}$ and $H5_{eq}$ are easily identified. Identification of the axial and equatorial hydrogen signals for C3 and C5 then follows readily (Figure 5). With a higher field instrument (>200 MHz), long-range coupling between $H3_{eq}$ and $H5_{eq}$ may be observed.

Synthetic Procedure

In a 100-mL round-bottom flask containing a magnetic stirbar was placed 4.5g (0.060 mole) of *N*-methylethanolamine. With water cooling, 3.1 g (0.060 mole) of 90% formic acid solution was cautiously added. After mixing for several minutes, 8.34 g (0.030 mole) of 2,4′-dibromoacetophenone *(Caution: Lachrymator)* was added, a water-cooled condenser was attached, and the mixture was heated at reflux for 20 hours. The mixture was cooled, treated with 30 mL of 2M HCl, and extracted with $3 \times$ 50 mL of ether. The ether extracts were discarded and the aqueous phase was cooled and made basic with 4M NaOH. The mixture was extracted with 3×50 mL ether. The ether extracts were combined and dried over $MgSO_4$. After filtering, the ether was removed with a rotary evaporator and the crude product was transferred to a small flask and distilled under vacuum. Yield: 3.5 g (45%). (Lit. bp 136–7 °C at 5 torr; lit. mp 35–38 °C [11].)

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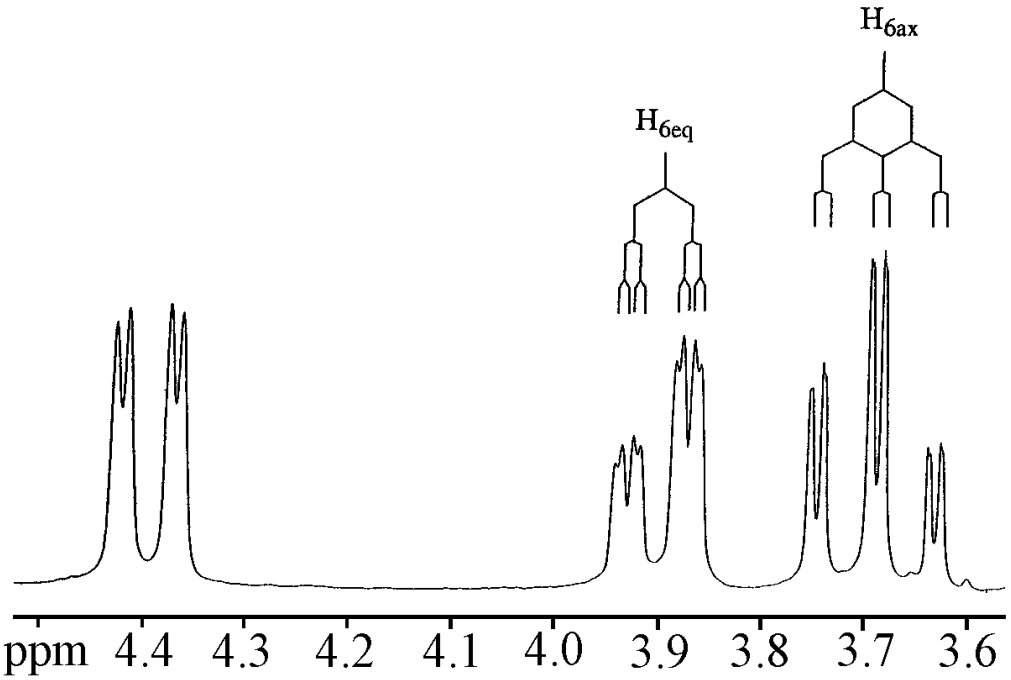

FIGURE 3. EXPANDED 200 MHz PROTON NMR SPECTURM, 3.5–4.5 ppm.

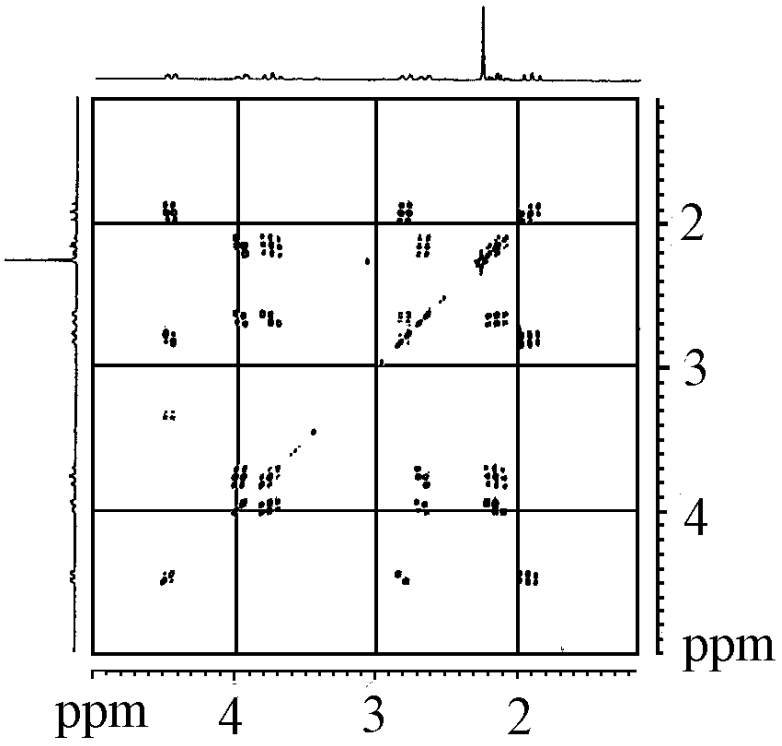

FIGURE 4. COSY SPECTURM, 1.0–5.0 ppm.

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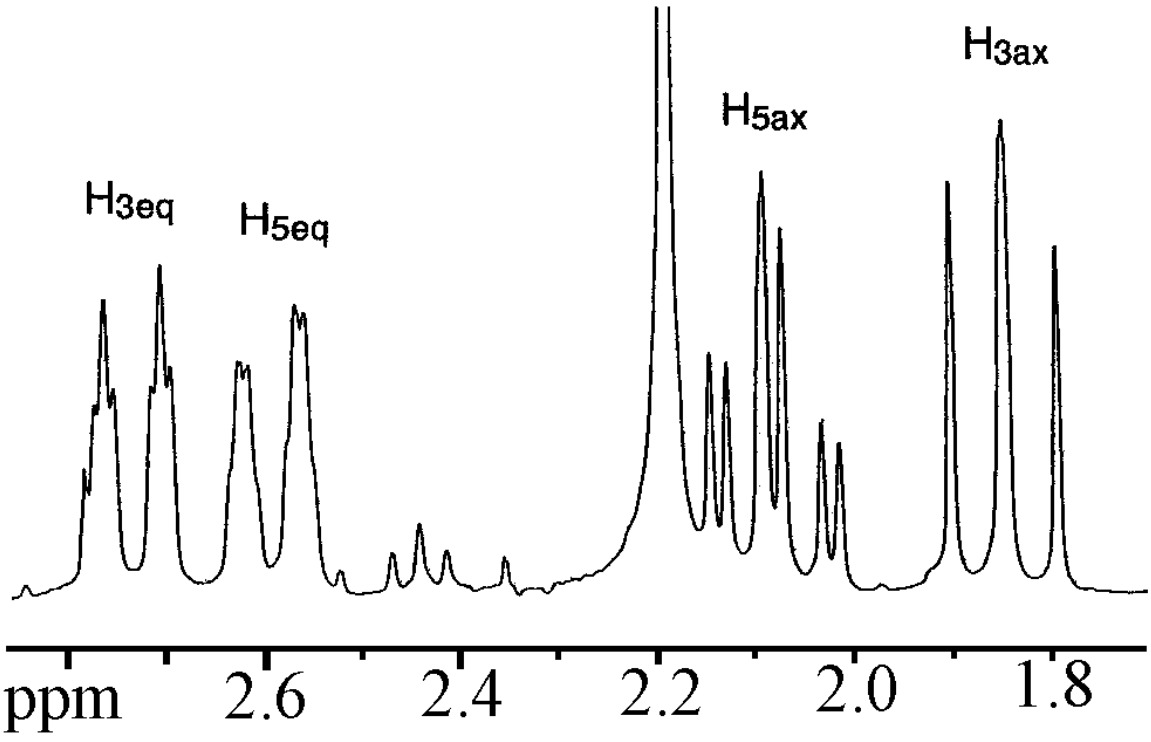

FIGURE 5. EXPANDED 200 MHz PROTON NMR SPECTURM, 1.7–2.8 ppm.

Instructions for Students

A handout which may be copied and distributed for student use is available in the document 21dr1897.pdf (43.0 Kbytes). The author would appreciate hearing from anybody who has enjoyed using this experiment or who would like to offer suggestions for its improvement.

Supplemental Figures

Figures showing the numbering system for the morpholine ring and showing typical coupling values found for $H2_{ax}$, $H6_{eq}$, and $H6_{ax}$ are available in the document 21dr2897.pdf (20.9 Kbytes).

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for the purchase of the Bruker DPX-200 FT-NMR instrument that was used to record the spectra described in this report.

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