Synthesis of Quinolines and Their Characterization by 2-D NMR Spectroscopy

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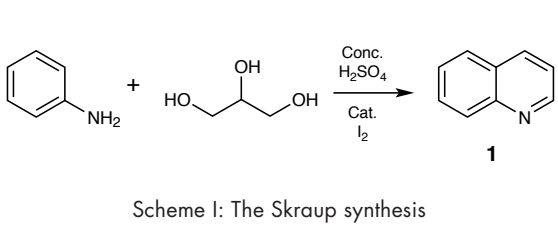
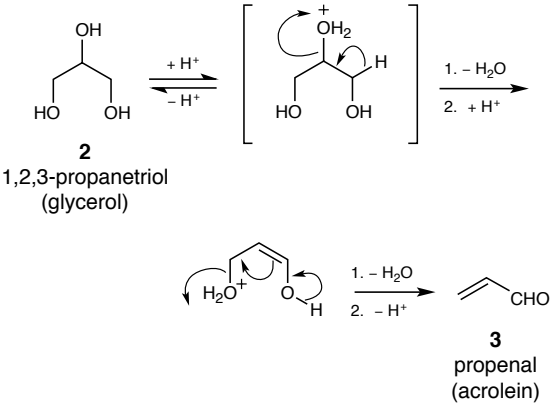
Substituted quinolines have interesting chemical and biological properties and thus have a wide variety of uses (*1–3*). Quinine (*4*) and quinidine, both of which contain the 6-methoxyquinoline moiety, have been employed extensively as antimalarial and antiarrhythmic drugs, respectively. The synthesis and ^{1}H NMR spectral characterization of simple quinoline derivatives is thus a valuable learning experience for advanced undergraduate organic chemistry students (*5*).

The well-known Skraup synthesis (*6, 7*) of quinoline (**1**) from aniline and glycerol (Scheme I) is an example of a simple heterocyclic synthesis and can be incorporated into the undergraduate organic chemistry laboratory curriculum, which has few examples of the synthesis of heterocyclic molecules (*5*). The chemistry involved in this synthesis is pedagogically very useful in terms of the overall transformation and the mechanism of the reaction. The isolation, purification, and spectral characterization of the product are additional learning experiences. Substituted anilines can be used in the Skraup synthesis to give substituted quinolines; for example, methyl anilines produce methylquinolines with a methyl substituent in the benzene ring of quinoline. In this paper we describe the synthesis of unknown methylquinolines and their characterization by one- and two-dimensional (1-D and 2-D) ^{1}H NMR spectroscopy (*9*).

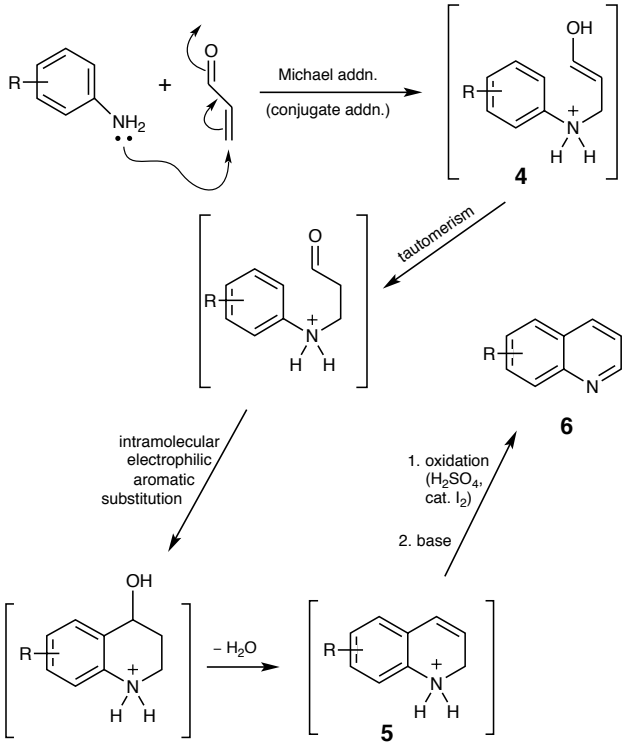
Most undergraduate lab courses use simple 1-D NMR spectroscopy for structure elucidation, but there are numerous compounds whose structure cannot be adequately defined from their 1-D ^{1}H NMR spectrum. Quinolines are an example of where 1-D ^{1}H NMR spectra are not adequate for complete structure elucidation and students must analyze both 1-D ^{1}H NMR and 2-D ^{1}H–^{1}H COSY (*CO*rrelation *S*pectroscop*Y*) spectra to characterize their product and confirm the position



Scheme I: The Skraup synthesis



Scheme II: Latent functionality, generation of propenal



Scheme III: Reactions in the Skraup synthesis

of the substituent (i.e., the CH_3 group) in the molecule. The COSY experiment is also known as the Jeener (*10*) experiment after its inventor, the Belgian physicist Jeener, and is considered one of the most important experiments of 2-D NMR spectroscopy. In this experiment both axes provide chemical shift values of the cross peaks of nuclei that are scalar spin–spin coupled.

The Synthesis

The Skraup synthesis involves (i) the concept of latent functionality, (ii) Michael (1,4) addition, (iii) cyclization via intramolecular electrophilic aromatic substitution, (iv) dehydration, and (v) oxidation. The 1,2,3-propanetriol (**2**), a three-carbon synthon (*11*) serves as the latent functionality for the propenal (**3**) and is obtained by the acid catalyzed tandem dehydration (Scheme II) of two molecules of water. Moderate yields from the Skraup synthesis may be attributed to the polymerization of propenal in the strong acidic medium, as evidenced by the direct reaction of aniline with propenal. α,β-Unsaturated aldehydes or ketones such as 2-butenal (crotonaldehyde) or 3-butene-2-one (methyl vinyl ketone), which do not polymerize as readily, can be used to give methylquinolines substituted in the pyridine ring in greater yields (*12*).

Michael (1,4) addition of the aniline nitrogen to the β carbon of propenal proceeds through an enol intermediate (**4**, Scheme III). Tautomerization followed by intramolecular electrophilic aromatic substitution and dehydration gives dihydroquinoline (**5**). Oxidation by sulfuric acid, catalyzed by iodine, then yields the methylquinoline (**6**).

The substituted aniline is the limiting reagent in this procedure but sometimes all of the aniline does not react and is extracted into the ether fraction along with the quinoline during workup of the reaction mixture. The presence of unreacted aniline is shown by TLC analysis. The unreacted aniline can be removed either by flash column chromatography (*13*) or by converting it to the neutral acetamide with acetic anhydride. The acetamide can then be separated from the unreactive quinoline by acid–base extraction. Polar impurities are removed in the final purification step by vacuum chromatography through silica gel. The product (60–80% yield) is pure enough for NMR spectroscopy.

Identification by 1-D and 2-D ^{1}H NMR Spectroscopy

Identification of the position of the methyl group in the quinoline ring requires a basic understanding of the 1-D spectrum of quinoline. The quinoline ring may be thought of as comprising a benzene and a pyridine ring. The H-2, H-3, and H-4 of pyridine are chemically and magnetically nonequivalent. The equivalent hydrogens of benzene become chemically and magnetically nonequivalent when joined with pyridine to give the quinoline ring system. The spectrum of quinoline thus shows signals corresponding to seven spin–spin-coupled hydrogen atoms that can be divided into two groups. One set corresponds to the protons in the benzene ring (H-5–H-8) and the second set corresponds to the protons in the pyridine ring (H-2–H-4). Literature chemical shift and coupling pattern differences between the protons of benzene and pyridine (*14*) rings of quinoline (Fig. 1) along with the COSY spectrum of quinoline provide necessary information for distinguishing and assigning the signals, and therefore for determining the position of the methyl group.

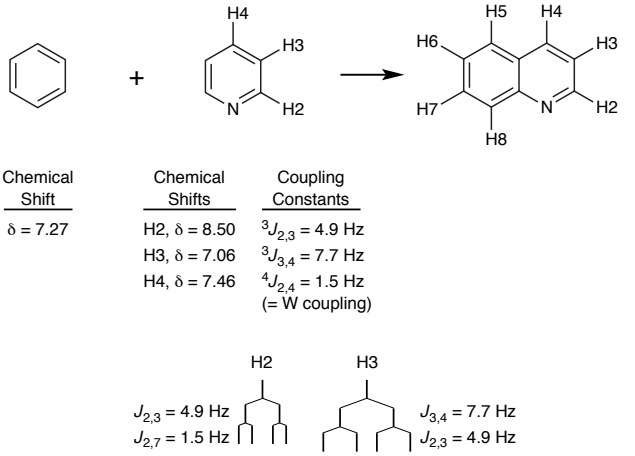


Figure 1. Chemical shifts and coupling constants of pyridine.

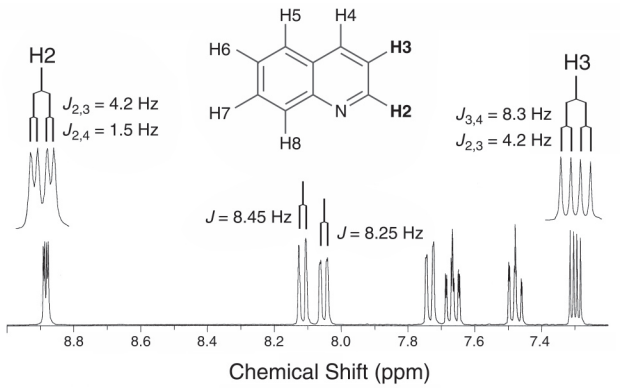


Figure 2. 1-D spectrum of quinoline with coupling trees.

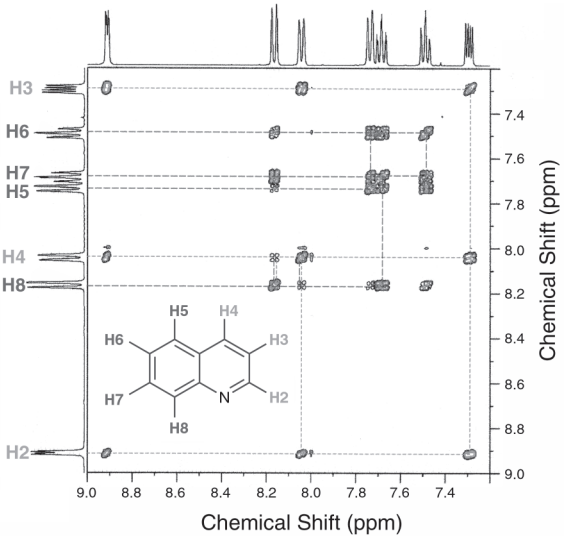


Figure 3. COSY spectrum of quinoline.

The H-2's of pyridine (δ = 8.50) and quinoline (δ = 8.88) have the highest chemical shifts, owing to deshielding by the proximal electronegative nitrogen, whereas the H-3's of pyridine (δ = 7.06) and quinoline (δ = 7.30) have the lowest chemical shifts. As in pyridine (*14*), the coupling constant differences between H-2 and H-3 ($J_{2,3}$ = 4.2 Hz) and H-3 and H-4 ($J_{3,4}$ = 8.3 Hz) of quinoline are very distinctive. The splitting patterns of H-2 and H-3 of quinoline provide further confirmation for the assignment of these protons in quinoline.

Assigning the remaining signals now requires analysis of their first-order splitting patterns and coupling constants (Fig. 2). Unfortunately, the splitting patterns of the various sets of protons are sometimes too complicated, owing to long-range couplings, to distinguish the protons. Assignment of H-2 and H-3, by comparison with the spectrum of pyridine, leaves three complex doublets[1] between δ = 7.7 and 8.2, which must correspond to H-4, H-5, and H-8. The two complex triplets[1] at δ = 7.3 and δ = 7.5 correspond to H-6 or H-7.

The complete assignment of all the quinoline protons thus requires a thorough analysis of its COSY spectrum, in addition to the 1-D spectrum. The COSY spectrum shows two sets of contours, one corresponding to the benzene ring and the other to the pyridine ring. Analysis of one of the sets (Fig. 3) immediately allows the student to assign H-4 using its connectivity with H-2 and H-3. This completes the assignment of H-2, H-3, and H-4 of the pyridine moiety.

Assigning the remaining four protons of the benzene ring requires some kind of a connectivity of these protons to the protons of the pyridine ring. A careful examination of the COSY spectrum at lower contour level shows a weak coupling between H-4 and H-8 (Fig. 3). The H-8 is coupled to H-4 via a long-range zigzag coupling (*15*). The H-4/H-8 coupling thus connects the two sets of protons of the benzene and pyridine rings. The H-8 (δ = 8.11) now serves as a marker for the assignment of the remaining signals of the benzene ring. The high chemical shift value due to the proximity of H-8 to the electronegative nitrogen further confirms the assignment. The contours between 7.7 and 8.2 ppm show the correlation between the four benzene ring protons. The doublet[1] at δ = 8.11, assigned as H-8, is coupled to the triplet[1] at δ = 7.66, which in turn is coupled to the triplet at δ = 7.48, which is further coupled to the doublet at δ = 7.73. Thus H-5 can be assigned to the remaining doublet at δ = 7.73. The COSY spectrum shows strong correlation between H-5 and the triplet at δ = 7.48, so that this triplet must be H-6, whereas H-8 shows strong correlation to the triplet at δ = 7.66, so that this signal can be assigned as H-7.

2-Methylaniline gives 8-methylquinoline, which has a doublet–triplet–doublet (dtd)[1] pattern for H-5, H-6, and H-7 (Fig. 4). 4-Methylaniline produces 6-methylquinoline, which has a double–doublet–singlet (dds)[1] pattern for H-5, H-7, and H-8 (Fig. 5). 3-Methylaniline produces a mixture of 5- and 7-methylquinoline and is not used for this laboratory, since the separation of the regioisomers is tedious.

The problems in assigning the protons of quinoline are also encountered in identifying the protons of the unknown methylquinoline. After the assignment of H-2 (the highest chemical shift value) and H-3 (the lowest chemical shift value) of the unknown methylquinoline, four signals remain, three

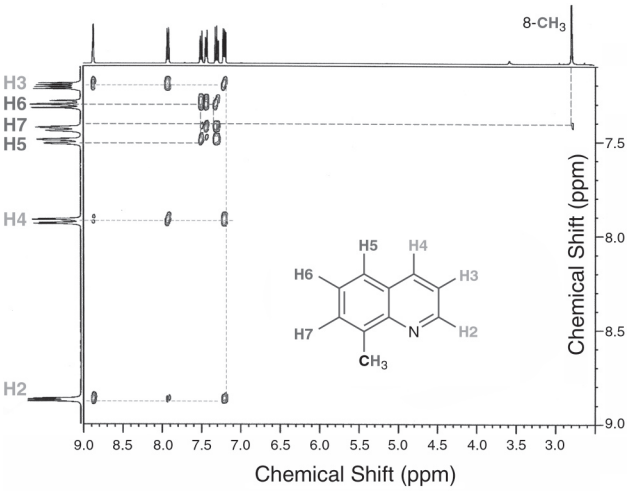


Figure 4. COSY spectrum of 8-methylquinoline.

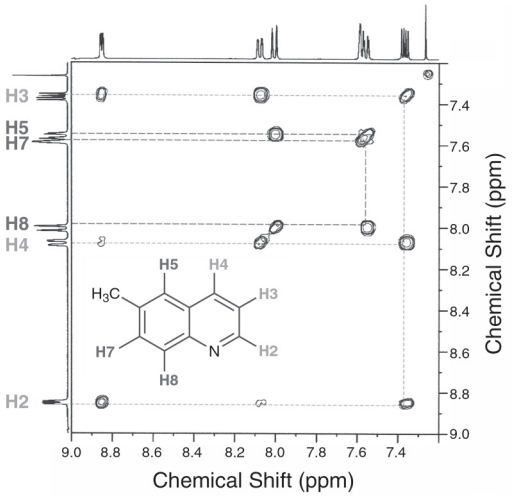


Figure 5. COSY spectrum of 6-methylquinoline.

of which are doublets[1] (one of them being H-4 [δ = 8.06] of the pyridine ring of quinoline. The doublet due to H-4 can be readily distinguished from the other two doublets of the benzene ring from its connectivity to H-2 and H-3 in the ^{1}H–^{1}H COSY spectrum. Evaluation of the coupling patterns of the remaining benzene ring protons leads to the assignment of the position of the methyl group.

Complete assignment of all proton signals still requires that the doublets[1] from protons H-5 and H-7 for 8-methylquinoline and H-7 and H-8 for 6-methylquinoline be distinguished. The NMR spectrum of quinoline has already been assigned and can be used as a reference for assigning the protons of methylquinolines. The H-8 of 6-methylquinoline (like that of quinoline) is distinctive enough, because of both its chemical shift and the zigzag coupling (*15*) with H-4, to distinguish between H-7 and H-8 of 6-methylquinoline.

However for 8-methylquinoline, H-5 and H-7 have relatively close chemical shifts. Nevertheless, weak long-range coupling between the 8-CH_3 and the doublet at $\delta = 7.55$ allows for assignment of that doublet to H-7 (Fig. 4). Alternatively, a valuable NMR technique that can readily provide information necessary to distinguish these signals is the NOE between hydrogens of the methyl group and the adjacent (ortho) ring proton.

Experimental Procedure (*5, 6*)

The unknown substituted aniline (0.75 g, 5.8 mmol), glycerol (2.0 mL, 27 mmol), and iodine (a few small crystals) are added to a 25-mL round-bottom flask fitted with a reflux condenser and a magnetic stir bar. While the mixture is gently stirred in an ice–water bath, concentrated H_2SO_4 (2 mL) is slowly added to the flask from a 6-in. disposable Pasteur pipet. The reaction mixture is then heated for an hour at 100–110 °C, with stirring. After cooling, 10 mL of ice-cold water is added to the flask and the "sludge" is transferred to a 125-mL Erlenmeyer flask. The round-bottom flask is rinsed with water (5 mL) and the rinse is transferred to the Erlenmeyer flask containing the reaction sludge. While the Erlenmeyer flask is cooling in an ice bath, 5 M NaOH is added until the solution is basic (by litmus). Ether (25 mL) is then added and the entire mixture is vacuum-filtered through a pad of diatomaceous earth (Celite) using a sintered glass Büchner funnel. The Erlenmeyer flask is rinsed twice with 20-mL portions of diethyl ether and these rinses are also passed through the filter pad. The filtrate is transferred to a separatory funnel; the bottom aqueous layer is drawn off and the remaining top organic layer is transferred to a clean Erlenmeyer flask. The aqueous layer is re-extracted with ether (20 mL) and the organic fractions are combined.

The ether solution is analyzed by TLC to check for the presence of any unreacted methylaniline. (For the synthesis of 8-methylquinoline, CH_2Cl_2–Et_2O [4:1, v/v] is the best TLC solvent system. For 6-methylquinoline, EtOAc–hexanes [1:4, v/v] is best for separation of the unreacted methylaniline from the methylquinoline.)

If TLC shows that unreacted methylaniline is present, the solution is dried over anhyd. $MgSO_4$, filtered, and concentrated under reduced pressure to provide an oil. Acetic anhydride (1 mL) is added to the oil and the mixture is allowed to react at room temperature for 30 min (or for a week in the refrigerator). After the reaction is complete, 1 M HCl (20 mL) is added and the reaction mixture and allowed to sit for ~15 min to hydrolyze the excess acetic anhydride. The solution is transferred to a separatory funnel and the reaction flask is rinsed with EtOAc (~20 mL). This rinse is transferred to the separatory funnel and the layers are mixed well and separated. The aqueous layer is re-extracted with EtOAc (~20 mL). (The combined EtOAc layers contain the methylacetanilide, which can be dried, concentrated, and purified by recrystallization in EtOAc–hexanes for further analysis.) The aqueous layer is then neutralized with 1 M NaOH and the methylquinoline is recovered by extraction with diethyl ether (2 × 20 mL). The product is purified by vacuum chromatography.

A vacuum chromatography column is prepared by filling a small (30-mL) sintered glass Büchner funnel with TLC-grade (2–25-μm) silica gel to a depth of about 1 in. The ether solution of quinoline is chromatographed through this column by suction (20–50 mmHg) and further eluted with 40 mL of ether. The combined eluants are transferred into a preweighed round-bottom flask and concentrated to an oil under reduced pressure. The flask is reweighed and the percent mass recovery of the methylquinoline is calculated.

For optimal resolution of the proton signals of 6-methylquinoline, solutions of <0.25 M are best (*16*). Thus, a 0.2 M solution is prepared by dissolving 30 μL (using a digital pipet or syringe) of the methylquinoline in 1 mL of $CDCl_3$. The solution is filtered through a small plug of Kimwipe or cotton wool in a Pasteur pipet into a 5-mm NMR tube. Either Wilmad 528-PP or the less expensive Wilmad 509-PP tubes may be used for acquiring 1-D and 2-D ^1H NMR spectra.

All NMR spectra were obtained on a Bruker AM 300-MHz or Bruker Avance 400-MHz spectrometer. The COSY spectra were taken using the COSY45 pulse program in the xwinnmr© (Bruker) or the COSY.AU pulse program in the winnmr© (Bruker).

Hazards

This experiment does not present any unusual hazards. Standard precautions should be used when handling and disposing of chemicals and solvents. The experiment should be carried out in a well-ventilated hood and gloves should be worn at all times. Sulfuric acid is a very strong acid; use special care when handling concentrated sulfuric acid.

Summary

In this experiment students taking the advanced organic chemistry laboratory learn a heterocyclic synthesis using synthons as latent functional groups. They also gain an understanding of acid–base extraction chemistry for the purification of the product. They learn to characterize and identify the product by 1-D and 2-D ^1H NMR spectroscopy. They learn to evaluate coupling patterns and calculate coupling constants and apply this information to the assignment of NMR signals of both quinoline and the product. Evaluation of their COSY spectrum guides the students in identification of their synthetic methyl quinoline and provides an excellent example of the power of 2-D NMR in structure elucidation.

Acknowledgments

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[W]Supplemental Material

Notes for the instructor, background information, experimental details, list of chemicals and spectra are available in this issue of *JCE Online*.

Note

1. In addition to ortho coupling, the doublets and triplets are further split into complex multiplets due to long range couplings.

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