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Laboratory Experiment

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Reaction of Orthoesters with Amine Hydrochlorides: An Introductory Organic Lab Experiment Combining Synthesis, Spectral Analysis, and Mechanistic Discovery

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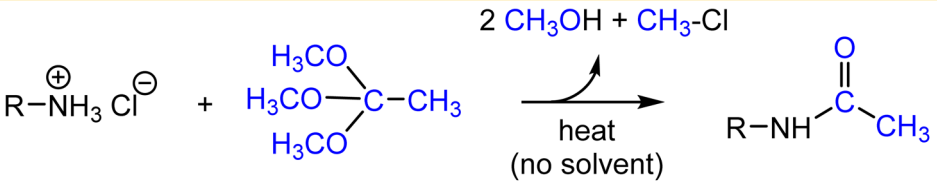
Supporting Information



ABSTRACT: While orthoesters are often used by chemists as alkylating, acylating, and formylating agents, they are rarely encountered in introductory organic chemistry curricula. We describe a second-semester organic chemistry laboratory experiment in which students acetylate unknown amine hydrochloride salts with trimethyl orthoacetate (TMOA) in the absence of solvent, monitor the progress of the reaction chromatographically, identify the amide product spectroscopically, and propose a mechanism supported by spectral detection of a transient imidate intermediate in an aliquot removed from the reaction mixture. This operationally straightforward experiment combines synthesis with spectral analysis as part of a mechanistic investigation.

KEYWORDS: *Second-Year Undergraduate, Laboratory Instruction, Organic Chemistry, Hands-On Learning/Manipulatives, Amides, Gas Chromatography, Mass Spectrometry, Mechanisms of Reactions, NMR Spectroscopy, Thin-Layer Chromatography*

Orthoesters [$RC(OR)_3$] are useful reactants in organic chemistry, e.g., the Bodroux–Chichibabin synthesis of aldehydes by treatment of an orthoformate with a Grignard reagent,[1] and the Johnson–Claisen rearrangement where an allylic alcohol is heated with a trialkyl orthoacetate to afford a γ,δ-unsaturated ester.[2] The preeminent synthetic chemist W. S. Johnson commented that the latter was "probably the most useful chemistry to emanate from our laboratories",[3] and it continues to serve as a key reaction in the synthesis of desirable targets.[4] Orthoesters also serve as effective protective groups for carboxylic acids and esters in basic and nucleophilic reaction media.[5] Despite their continued use as versatile synthetic reagents, orthoesters are rarely encountered in introductory organic chemistry curricula and, as far as we know, there are no reports of undergraduate experiments that employ this structurally simple class of compounds in chemical synthesis.

Given the sustained interest in experiments involving spectral identification of unknown compounds,[6] the steady increase in experiments aimed at discovering features associated with chemical reactions,[7] and that many instructors consider reaction mechanisms as a key fundamental concept in undergraduate organic chemistry,[8] we developed a second-semester organic chemistry laboratory experiment in which students acetylate *unknown* amine hydrochloride salts (Figure 1) with trimethyl orthoacetate (TMOA) in the absence of solvent, monitor reaction progress chromatographically (TLC and GC–MS), identify the amide product spectroscopically (MS, ^{1}H and ^{13}C NMR spectroscopy), and propose a mechanism for the reaction supported by mass spectral detection of a transient imidate (imino ether) intermediate in an aliquot removed from the reaction mixture and a literature report on related orthoester chemistry (Scheme 1).[9]

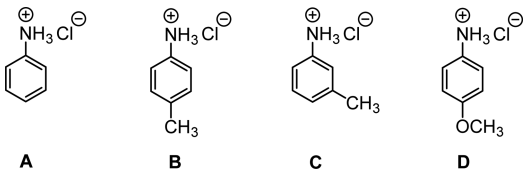


Figure 1. Commercially available arylamine hydrochloride salts assigned to students as unknowns.

The rapid and solvent-free acetylation of easily handled solid amine hydrochloride salts with TMOA serves as a safer alternative to more traditional acetylation methods that employ liquid amine free bases and acetic anhydride[10] or acetyl chloride.[11] It also serves as an excellent reaction for students to elucidate the mechanism since, although all students are made familiar with the acyl substitution mechanism by which amines are acetylated with acetic anhydride, few if any are familiar with orthoester chemistry, and they must rely on their experimental results and literature precedence to propose a reasonable mechanism.

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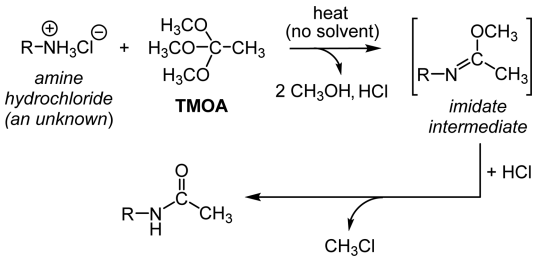
Scheme 1. Solvent-Free Acetylation of Amine Hydrochlorides with Trimethyl Orthoacetate (TMOA)



Beyond learning common lab techniques that include monitoring the progress of a chemical reaction chromatographically, the main pedagogical goals for students are similar to what might be those of a chemical researcher studying this reaction: interpreting spectral data of reaction mixture components obtained during and at the completion of the reaction, and using that information in the context of relevant chemistry reported in the literature to propose a reasonable mechanism for the reaction. The exercise also highlights in a general way how chemists can use experimentation and spectral analysis to obtain evidence in support of the mechanisms they propose for organic reactions; i.e., a rigorous approach to confirming the presence of mechanistic intermediates is by detecting or isolating them during the course of a reaction.

EXPERIMENTAL OVERVIEW

This experiment was performed by students enrolled in multiple sections (≤22 students per section) of a second-semester introductory organic chemistry laboratory course. After a thorough prelab discussion of the mechanism proposed for acid-catalyzed reaction of orthoesters with alcohols at room temperature,[12] each student was asked to work individually during a single 4 h lab period to perform the reaction of an assigned unknown arylamine hydrochloride with TMOA, monitor its progress, and isolate the product. The experimental procedure is straightforward: TMOA (6.0 mmol) was weighed into a 25 mL round-bottom flask to which was added 5.0 mmol of one of the four commercially available arylamine hydrochloride salts shown in Figure 1, and the resulting mixture was gently heated for 5 min while being magnetically stirred. Heating was stopped momentarily, a small sample of reaction mixture was removed for TLC and/or GC–MS analysis, the mixture was heated for an additional 45 min, and the reaction products were purified by recrystallization from ethanol/water (with the exception of the *N*-acetyl derivative of *m*-toluidine). Students determined the weights and melting point ranges of their air-dried products during the following lab period.

TLC Analysis of the Reaction's Progress after 5 min

All students monitored the progress of their reaction by TLC. A small sample of the reaction was transferred to a 10 × 75 mm test tube and dissolved in 20–30 drops of CH_2Cl_2. Using a microcapillary tube, students spotted the CH_2Cl_2 solution of reaction mixture on a 2.5 × 10 cm TLC plate, which was then eluted with 5:1 (v/v) petroleum ether–ethyl acetate. TLC spots were visualized by UV (two major spots were visible) and circled with a pencil.

GC–MS Analysis of Major TLC Spots after 5 min

To unambiguously correlate TLC spots with GC peaks, for each assigned unknown one student on each lab day obtained GC–MS data on the reaction mixture at 5 min, and then performed separate analyses on major TLC spots as described below. Their data was shared with the class. A 2.5 × 10 cm glass-backed analytical TLC plate was spotted heavily along the origin with a CH_2Cl_2 solution of a sample taken from the reaction mixture. After elution and visualization under UV light, horizontal lines were drawn with a pencil above and below the two major spots. Using a spatula, the silica gel between the lines was scraped off the plate's surface and transferred to separate small test tubes. CH_2Cl_2 (20–25 drops) was added to each test tube to extract the organic compounds from the surface of the silica gel. The CH_2Cl_2 solutions were analyzed by GC–MS.

NMR Analysis of Products

For each assigned unknown, one student on each lab day recorded NMR spectra, and the data were shared with the class.

Student handouts, TLC and GC–MS results, and full-scale spectral data for the products of each unknown are provided in the Supporting Information.

HAZARDS

Eye protection, lab coats, and gloves are required as all materials used in this experiment, including the amine hydrochloride salts and their corresponding *N*-acetyl products, are irritants or harmful if inhaled or swallowed. Students should perform their reactions in a well-ventilated fume hood. TMOA, petroleum ether, ethyl acetate, and ethanol are flammable. Dichloromethane, chloroform-*d*, and chloromethane are inhalation hazards and suspected carcinogens. Exposure of skin or eyes to UV light should be avoided. A detailed list of hazardous substances is available in the Supporting Information.

RESULTS AND DISCUSSION

TMOA reacts relatively quickly with arylamine salts upon heating in the absence of solvent to cleanly afford the corresponding *N*-aryl acetamides, but slowly enough for the imidate intermediate **3** to be captured and detected by TLC and GC–MS (Scheme 2).

Students encountered no difficulties in running and monitoring their reactions by TLC. All but one of the 100 students who performed the reaction obtained an acceptable yield of product; e.g., in 2015, students in 8 lab sections obtained an average product yield of 59% after recrystallization. All students observed two major UV–visible TLC spots: one at high R_f (imidate) and one at very low R_f (amide); correspondingly, the GC traces obtained by four students per lab day showed two major peaks (with the imidate eluting several minutes ahead of the amide in each case). To unambiguously correlate the two major TLC spots observed at a reaction time of 5 min with the two major peaks observed in the corresponding GC trace, four students per lab day also performed a small-scale isolation of the two major TLC spots as described above, and analyzed them by GC–MS (Figure 2). This "TLC–GC–MS" approach worked very well and provided valuable MS data to those students who only performed TLC analysis. Since each GC peak was experimentally correlated with a TLC spot, students readily identified the low R_f spot as product and the high R_f spot as intermediate.

After the experiment, student-generated NMR spectra of the products from each unknown and GC–MS data for both major TLC spots were made available to the entire class, along with a

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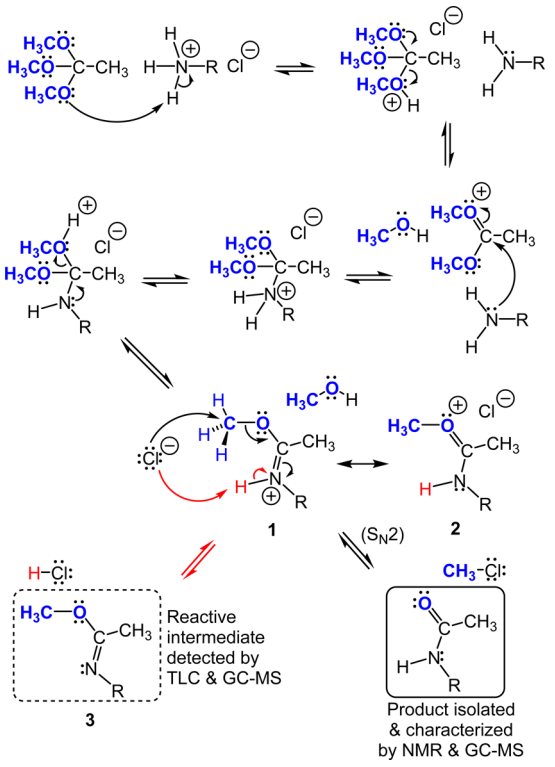
Scheme 2. Mechanism Proposed for the Reaction of Amine Hydrochlorides with TMOA Affording *N*-Substituted Acetamides via a Transient Imidate Intermediate



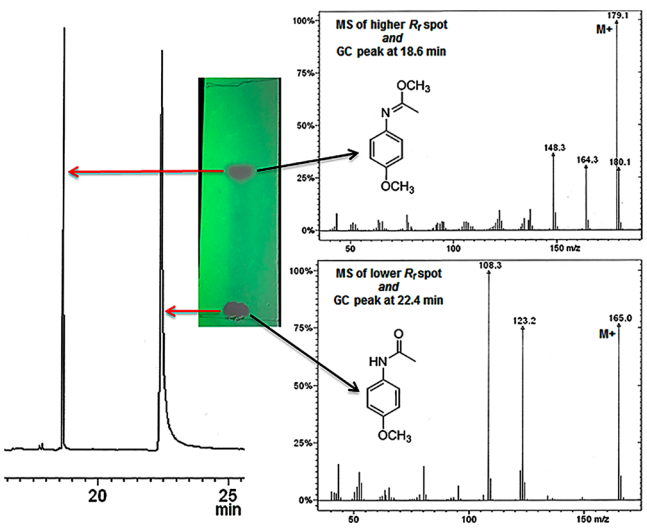


Figure 2. GC trace, UV−visualized TLC plate, and MS results for the reaction of arylamine hydrochloride **D** with TMOA after 5 min.

set of questions (Supporting Information) asking students to independently assign a structure to their *N*-aryl acetamide product, to propose a reasonable mechanism for the reaction of TMOA with their assigned amine hydrochloride, and to find support for their mechanism by identifying the transient species detected by TLC and GC−MS. The products obtained from amine salts **B**−**D** displayed the expected ^{1}H NMR peak patterns in the aromatic region for 1,3- and 1,4-disubstituted benzenes bearing different groups, ^{13}C peaks for all products were widely separated, and each product displayed a prominent molecular ion in its mass spectrum along with identifiable fragment losses (e.g., $[M - CH_3]^+$, $[M - OCH_3]^+$, and $[M - C(O)CH_3]^+$). With a basic knowledge of mass spectrometry and NMR spectroscopy from their lecture course all students correctly identified the structures of their *N*-aryl acetamide products, and thereby their amine hydrochloride unknowns. All students correctly assigned TLC spots and GC peaks to intermediate and product, and although 90% of students proposed correct or nearly correct mechanisms similar to that shown in Scheme 2, a number had difficulty in correctly identifying the intermediate detected by TLC and GC−MS as imidate **3**; e.g., in one lab section 19 of 22 students proposed the correct mechanism, but only 7 of 19 identified the isolated intermediate as **3**. Interestingly, 10 of the other 12 students identified the intermediate as structure **2** (despite it being an ionic species with a mass higher than that indicated by the molecular ion in the mass spectrum), even if they included both resonance structures **1** and **2** in their proposed mechanisms.

The successful results of virtually all students at the bench—from performing and monitoring the reaction by TLC and/or GC−MS to isolation and purification of product in good yield—and their success at structure elucidation, interpretation of chromatographic data, and mechanistic analysis of their reaction demonstrates that most of the learning goals were met for this exercise.

CONCLUSION

We have developed an operationally straightforward experiment suitable for the introductory organic teaching lab that combines synthesis with spectral analysis as part of a mechanistic investigation. Students are introduced to a useful class of organic compounds, not normally encountered in introductory organic chemistry courses, as a key reactant in a safer alternative to more standard methods for amide bond formation. This experiment emphasizes the methods and usefulness of monitoring the progress of a chemical reaction while reinforcing the importance of experimentation in elucidating organic reaction mechanisms. This "mechanistic investigation" is suitable for laboratory courses with relatively large enrollments since reactions are run on a fairly small scale using commercial reactants/reagents (reducing costs and enhancing safety), reaction times are relatively short, and products are isolated in good yield. Plausible variations or extensions of this experiment include the use of other commercial orthoesters or arylamine (or alkylamine) salts and ^{1}H NMR analysis of the imidate intermediate isolated from the TLC plate. For teaching laboratories without access to NMR or GC−MS instruments, spectral data could be provided to students or the experiment could be easily modified into a meaningful exercise in which students are introduced to orthoester chemistry by reacting TMOA with unknown arylamine hydrochlorides and identifying their *N*-aryl acetamide products by mp analysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00782.

Student handouts and notes to the instructor (PDF, DOC)

Representative spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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