Introducing Environmentally Benign Synthesis into the Introductory Organic Lab—A Greener Friedel–Crafts Acylation

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Abstract: An example of a more environmentally benign Friedel–Crafts acylation reaction constitutes the first step of a two step synthesis of p-anisic acid. The greener Friedel–Crafts acylation involves reaction, on acidic alumina in the absence of solvent, of anisole with a mixed anhydride derived from acetic acid and trifluoroacetic anhydride. The acylated anisole is then oxidized, employing the haloform reaction to produce p-anisic acid. Students identify the anisic acid isomer obtained through spectral analysis and/or melting-point determination and then infer the regioselectivity of the initial acylation. The experiment offers opportunities for instruction in the tenets of green chemistry and reinforcement of the theory of electrophilic aromatic substitution presented in lecture.

Background and Introduction

The most recent revolution in the pedagogy of the introductory organic chemistry lab has involved the widespread adoption of the microscale approach. Although hugely successful at reducing the detrimental local environmental impacts associated with experimental work in the teaching laboratory, reduction of scale obviously does not represent a solution transferable to the real world of chemical production. Students recognize this. The new paradigms of green chemistry are stimulating great interest in industrial, governmental, and academic research circles.

Green chemistry [1] involves a shift in emphasis on how to most effectively mitigate collateral environmental damage accompanying chemical manufacture and use, from remediation to prevention—from “end of the pipe” to “front of the pipe” solutions. The analogy with modern medicine’s focus on prevention as the smarter, and economically superior, strategy for managing healthcare is particularly apt. Representative areas of exploration within the domain of green chemistry include: 1) alternate solvents for organic transformations, including design of methodology compatible with aqueous reaction media, 2) solventless transformations, 3) atom economy, 4) renewable feedstocks as sources for starting materials, 5) biocatalysis, 6) development of more robust catalytic processes, and 7) design of safer, less toxic reagents.

The goal of integrating green chemistry as a central concept in the undergraduate curriculum has prompted us to undertake a program to identify appropriate examples of green chemical methodology in the literature and adapt them for transfer to the undergraduate laboratory. To attract a new generation of highly environmentally conscious students into chemical careers, opportunities to showcase how chemists are proactively addressing the environmental consequences of their work should be seized upon.

The traditional Friedel–Crafts acylation [2], a mainstay in industrial organic chemistry, falls short when judged according to green chemical criteria for evaluating methodology. Hazardous solvents such as methylene chloride and carbon disulfide are often required, and aluminum trichloride must be employed in greater-than-stoichiometric quantities, rather than in catalytic quantities. The use of excess Lewis acid “catalyst” necessitates cumbersome workup and separation protocols, processes that generate large volumes of acidic aqueous waste and aluminum salts. The acid chloride/aluminum trichloride methodology also suffers from poor atom economy. The commercial importance of the reaction, in conjunction with its environmental deficiencies, has generated substantial research activity seeking greener alternatives.

Friedel–Crafts acylation has similarly long been a centerpiece in the introductory organic chemistry laboratory [3]. This testifies both to the commercial significance of the process and to the attention devoted to the theory and mechanism of electrophilic aromatic substitution in lecture. Representative examples encountered recently in laboratory textbooks include the acylation of toluene with acetyl chloride and stoichiometric $AlCl_3$ [4], reaction of ferrocene with acetic anhydride and two equivalents of $AlCl_3$ [5], and reactions of toluene and xylenes with phthalic anhydride mediated by $AlCl_3$ [6]. Additional experiments that have appeared in the chemical education literature include acylation of variously substituted alkyl benzenes [7] and biphenyl [8] with $AcCl/AlCl_3$, and the use of $FeCl_3$ as the Lewis acid for propanoylation of anisole [9].

For several years we had run the toluene acylation reaction essentially as detailed in Pavia [4], incorporating the reaction into a two-step sequence for the production of *p*-toluic acid. Friedel–Crafts acylation was followed by hypochlorite (haloform) oxidation to afford a solid carboxylic acid product for characterization. The product of the laboratory exercise was presented as an unknown; students utilized the melting point of the carboxylic acid ultimately obtained to determine the regioselectivity of the initial aromatic substitution. We found that the standard Friedel–Crafts (FC) chemistry with moisture-labile $AlCl_3$, acetyl chloride, and a multiple-wash workup did not transfer very well to the realm of microscale. Yields of distilled *p*-methylacetophenone were almost always

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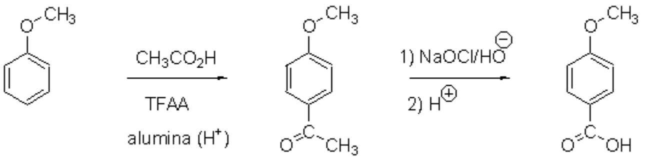

Figure 1. Friedel–Crafts acylation of anisole with the acetic-acid-derived mixed anhydride on acidic alumina and subsequent bleach oxidation

insufficient to carry to the next step, and supplementation with commercially available material was the norm.

Our interest in green chemistry, in concert with the problems encountered in the aforementioned laboratory exercise, led us to review the recent FC-acylation literature with the aim of identifying and adapting a more environmentally friendly replacement for this laboratory exercise. A number of potentially greener FC methodologies have been reported. These include the use of lanthanide triflates as catalysts with acetic anhydride as the electrophile [10], use of mixed anhydrides derived from carboxylic acids and trifluoroacetic anhydride in phosphoric acid [11], acyl triflate acylating agents [12], and solid-acid catalysis (with Nafion-H) employing acid chlorides [13]. The mixed anhydride method of Ranu et. al. [14] appeared particularly well-suited for our purposes. The reaction involves in situ formation of the acylating agent from a carboxylic acid and trifluoroacetic anhydride, and takes place on the surface of acidic alumina in the absence of solvent. The scope of the reaction is reported to be limited to highly activated aromatic substrates.

Results and Discussion:

We have successfully adapted the Ranu procedure, and replaced the toluic acid preparation and identification laboratory exercise with a parallel synthesis of *p*-anisic acid via the solventless Friedel–Crafts acylation of anisole with the acetic-acid-derived mixed anhydride on acidic alumina and subsequent bleach oxidation (Figure 1). Yields for the electrophilic aromatic substitution typically range between 60 and 70%, and afford the low-melting *p*-methoxyacetophenone as a light yellow oil shown by capillary GC–MS and ^{1}H NMR to normally contain 3–5% unreacted anisole starting material. The crude product is easily carried through the oxidation step, and the final workup effectively removes the residual anisole. The hypochlorite oxidation is normally conducted during the following laboratory session, and proceeds in very high yield. Students identify the anisic acid regioisomer obtained via melting-point analysis, and then infer the positional selectivity of the Friedel–Crafts reaction (*p*-anisic acid, mp 182–185 °C; *m*-anisic acid, mp 106–108 °C; and *o*-anisic acid, mp 98–100 °C).

This laboratory exercise provides an opportunity to discuss aspects of benign-by-design organic synthesis, and can be a stimulus for discussion concerning what does and does not constitute “green chemistry.” It is indeed a complex analysis that must take all aspects of product lifecycle and energy costs into account. Tradeoffs in making one part of the scheme more environmentally benign certainly must be considered in light of other, perhaps detrimental, changes in the overall process. It is particularly instructive to contrast the Friedel–Crafts acylation, which can be conducted with subsequent recovery and recycling of trifluoroacetic acid, with the methodology of the oxidation step (chlorine-based and wasteful from the atom-economy standpoint). At the microscale level, recapturing and recycling the spent TFAA/TFA mixture would not be viable, nor do we believe it would substantially add to the pedagogical value of the experience. However, a procedure for effectively doing so has been demonstrated on a 4-mole scale [11a]. The exercise also provides an opportunity to carry out a two-step synthesis and offers an opportunity to apply the theory of electrophilic aromatic substitution to predict and then ascertain the regioselectivity of substitution. Although we have relied on melting-point determination to identify the anisic acid isomer obtained, ^{1}H NMR and IR could also be utilized at either point in the synthetic route as well.

Experimental Procedures

Safety. Caution: Trifluoroacetic anhydride is highly volatile, corrosive, and it reacts violently with water. This reagent should be dispensed into a dry, septum-capped, conical vial in the hood.

Procedure. Part 1: Acylation of Anisole. To a clean and dry 25-mL round-bottom flask equipped with a spin bar is added acidic alumina (Brockmann 1, 150-mesh, 3.0 g). The flask is capped with a septum, and anisole (0.33 mL, 3.0 mmol) is added dropwise from a disposable syringe with efficient stirring so as to achieve a uniform distribution of the substrate over the catalyst surface. To a 3- or 5-mL conical vial equipped with a spin vane is added trifluoroacetic anhydride (1.25 mL, 8.85 mmol), the vial is capped with a septum, and glacial acetic acid (0.35 mL, 6.0 mmol) is added dropwise via syringe with stirring (mixed anhydride formation is somewhat exothermic, and carrying out the reaction in a closed vessel prevents evaporation losses). Once the addition is complete and the reaction mixture has cooled, the mixed anhydride is taken up in a disposable syringe. The mixture is delivered dropwise through the septum into the flask containing the substrate-coated alumina. Again, uniform distribution of the reagent, rather than clumping of the solid acid catalyst, is the goal as this improves reaction rate. Agitation by magnetic stirring or by intermittent application of a vortex shaker will assist in this process. The reaction mixture is periodically shaken or stirred over a period of about 40 minutes. The mixture will take on a pink color, which gradually intensifies to a deep purple over the course of reaction. The solid is extracted with ether (2 x 15 mL) and the combined ether layers washed with saturated sodium bicarbonate (30 mL) (*be careful of foaming)* and brine (30 mL), and then dried over anhydrous sodium sulfate. Evaporation of ether on a steam bath in the hood provides the crude acylated anisole as an oil typically containing 2–5% of unreacted anisole. Yields normally range between 55 and 70%. The crude oil is suitable for the next step.

p-Methoxyacetophenone is a low-melting (36–38 °C) colorless solid. ^{1}H NMR ($CDCl_3$, δ): 8.0 (d, $J = 9$ Hz, 2H), 7.0 (d, $J = 9$ Hz, 2H), 3.9 (s, 3H), 2.6 (s, 3H). IR (film): 1670, 1260 cm^{-1}. LRMS (70 eV) m/z (relative intensity): 150 (M^+, 33), 135 (100), 107 (13), 92 (16), 77 (20).

Part 2: Oxidation of *p*-methoxyacetophenone. Product from Part 1 is added to a 25- or 50-mL Erlenmeyer flask. For every 100 mg of crude *p*-methoxyacetophenone, 4 mL of 5% NaOCl (aq) (commercial bleach) and approximately 0.25 mL of 10% NaOH are added. The biphasic mixture is heated with stirring on a steam bath, or in a warm water bath, for 20 or 30 minutes or until all of the organic material dissolves. If at the end of this time material remains undissolved, an additional 4 mL of bleach and 0.25 mL of 10% NaOH are added and heating is continued for 10 more minutes. At this time, any undissolved material is likely unreacted anisole carried over from Part 1 and decantation of the hot solution will be required. When the reaction is complete, acetone (0.5 mL) is added dropwise to destroy excess hypochlorite. To the cooled solution is slowly added concentrated HCl until pH paper indicates a pH of 2–3. A voluminous white precipitate of *p*-anisic acid will be deposited. The mixture is cooled in an ice bath and the product collected via suction filtration.

The crude product, obtained in 70–80% yield, is highly pure, and when dry has a mp range of 180–184 °C (lit. 182–185 °C). If desired, recrystallization from 95% ethanol yields colorless needles (mp 182–85 °C). ^{1}H NMR (DMSO-d_6, δ): 13 .0 (br, s 1H), 7.95 (d, J = 8 Hz, 2H), 7.1 (d, J = 8 Hz, 2H), 3.75 (s, 3H).

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Supporting Material. The student laboratory handout is available as 610025lfs1.pdf (http://dx.doi.org/10.1007/s00897000451b).

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