Organic Syntheses

From 5-Hydroxynicotinic Acid to Nitrogenous (4+3)-Cycloadducts

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Procedure (Note 1)

A. *Ethyl 5-hydroxynicotinate (***2***).* A 200 mL, single-necked recovery flask is equipped with a Teflon-coated magnetic stir bar (20 x 6 mm, cylindrical). 5-Hydroxynicotinic acid (5.01 g, 36.0 mmol, 1.0 equiv) (Note 2) is added through a powder addition funnel, which is rinsed with absolute ethanol (20 mL, 343 mmol, 9.5 equiv) (Note 3). Upon stirring, this gives a white suspension. Sulfuric acid (2.0 mL, 37.5 mmol, 1.0 equiv) (Note 4) is added in a single portion via pipette (Note 5). The flask is immediately equipped with a condenser topped with a drying tube filled with Drierite (Note 6) and placed in an oil bath at 95-100 °C. Upon heating, the solids largely dissolve to produce a yellow solution. The mixture is refluxed for 12 hours (Note 7). The solution is allowed to cool to room temperature and is made basic by the careful addition over 10 minutes of saturated sodium bicarbonate solution (125 mL) (Note 8). The mixture is transferred to a 500 mL separatory funnel and extracted with ethyl acetate (4 x 50 mL) (Note 9). The organic extracts are combined and dried over sodium sulfate (20 g) (Note 10) and vacuum filtered into a pre-weighed 500 mL recovery flask through a fritted funnel. The sodium sulfate is washed with ethyl acetate (50

mL). The solvent is removed by rotary evaporation at 50 °C (150 to 75 mmHg) followed by evaporation at 23 °C under high vacuum (<1 mmHg) to give a white solid (4.46 g, 74.1%) (Notes 11 and 12).

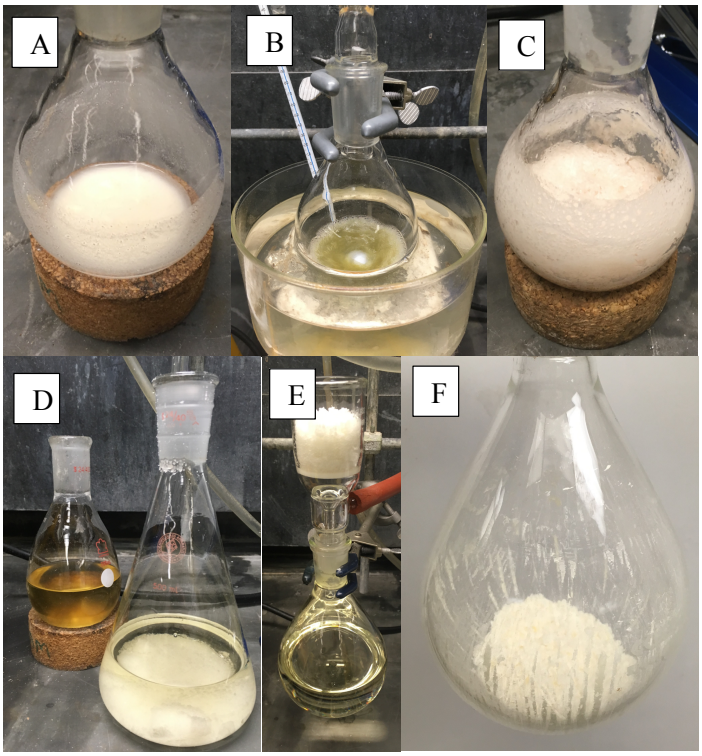

Figure 1. A) Suspension of 1 in ethanol; B) Refluxing reaction mixture; C) Precipitation during quenching with sodium bicarbonate solution; D) Aqueous phase (left) and organic phase (right) after extraction; E) Filtration of sodium sulfate from aqueous phase; F) Solid 2 after evaporation of ethyl acetate

B. *3-(Ethoxycarbonyl)-5-hydroxy-1-methylpyridin-1-ium trifluoromethanesulfonate (**3**)*. A 500 mL, single-necked recovery flask is equipped with a Teflon-coated magnetic stir bar (20 x 6 mm, cylindrical) and **2** (4.44 g, 26.6 mmol, 1.0 equiv) is added via powder addition funnel. The funnel is equipped with a rubber septum and put under argon (Note

13). Dichloromethane (100 mL) (Note 14) is added via syringe. Stirring at 500 r.p.m. gives a yellow suspension. Methyl trifluoromethanesulfonate (3.00 mL, 26.5 mmol, 1.0 equiv) (Note 15) is added in one portion via syringe (Note 16), leading to the formation of a yellow solution within one minute of addition. A white solid precipitates from the solution within 10 minutes of addition and stirring becomes labored.

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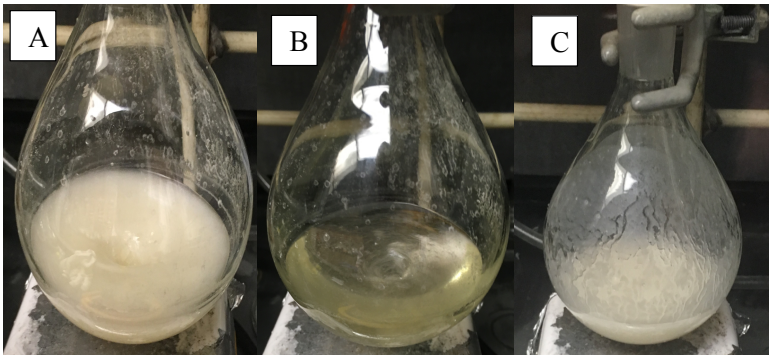

Figure 2. A) Suspension of 2 in dichloromethane; B) Homogeneous solution following addition of methyl trifluoromethanesulfonate; C) Precipitation of 3

The mixture is stirred for 4 hours at 23 °C (Note 17). The septum is removed and pentane (50 mL) (Note 18) is added. The flask is placed in an ice bath and cooled for 30 minutes. The suspension is filtered within the same hood through a sintered glass funnel. The precipitate is washed once with pentane (50 mL) (Note 19). The filtered product is transferred to a pre-weighed 250 mL round-bottom flask and further dried at 23 °C under high vacuum (<1 mmHg) to give a white solid (8.37 g, 95.1%) (Notes 20 and 21).

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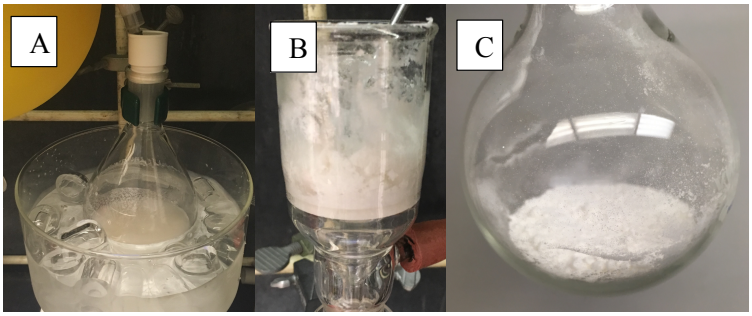


Figure 3. A) Cooling mixture in ice bath; B) Filtration of 2; C) Solid 2 after drying under high vacuum

C. *Ethyl 3,4,7-trimethyl-10-oxo-7-azabicyclo[4.3.1]deca-3,8-diene-9-carboxylate (**4**).* A 350 mL pressure tube (Note 22) is equipped with a Teflon-coated magnetic stir bar (20 x 6 mm, cylindrical). Using a powder addition funnel, **3** (6.66 g, 20.1 mmol, 1.0 equiv) is added to the tube and the funnel is rinsed with acetonitrile (100 mL) (Note 23). To the mixture is added 2,3-dimethyl-1,3-butadiene (11.4 mL, 100 mmol, 5.0 equiv) (Note 24) in one portion via syringe. Triethylamine (8.4 mL, 60 mmol, 3.0 equiv) (Note 25) is then added in one portion via syringe. Upon the addition of triethylamine, the solution becomes yellow. The tube is immediately tightly sealed under air. The reaction vessel is placed behind a blast shield and placed in a silicone oil bath at 85-90 °C such that the level of the oil in the bath is the same as the level of solvent in the tube.

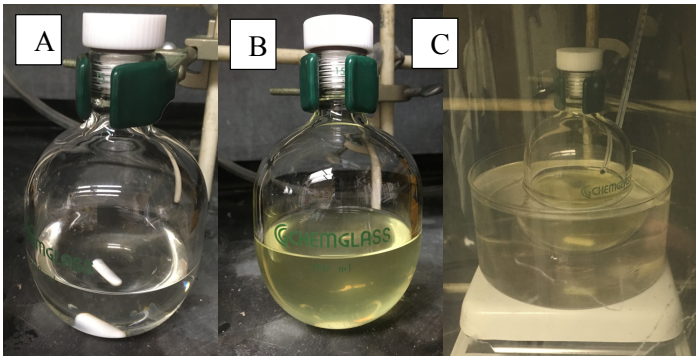
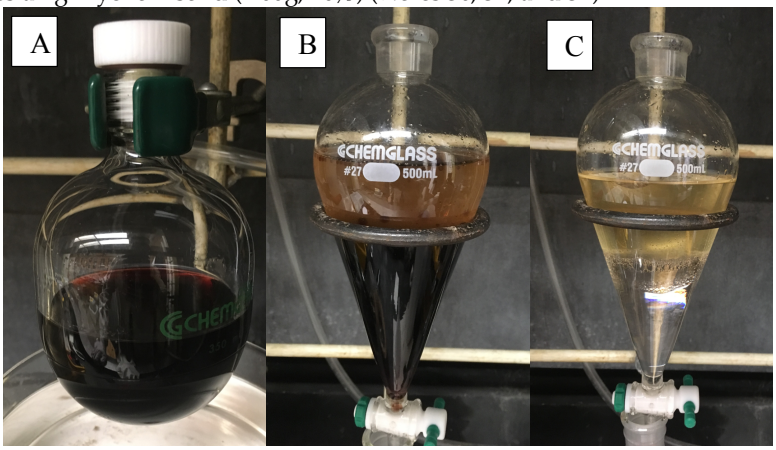


Figure 4. A) Solution of 3 and 2,3-dimethyl-1,3-butadiene in acetonitrile; B) Mixture after addition of triethylamine; C) Tube immediately after inserting into oil bath

The mixture is heated for 7 hours (Note 26). The reaction mixture is allowed to cool to room temperature and is diluted with 0.5 M HCl (200 mL) (Note 27). The aqueous layer is extracted with dichloromethane (3 x 100 mL) and dried over sodium sulfate (40 g). The liquid is decanted from the sodium sulfate followed by a rinse with dichloromethane (50 mL) onto a plug of silica gel (160 g, 18 cm x 5 cm) (Note 28) equilibrated with dichloromethane (Note 29). The liquid is passed through the plug with positive pressure until the solvent level is at the height of the plug. The plug is rinsed with dichloromethane (700 mL). The combined filtrate is concentrated by rotary evaporation at 40 °C (400-200 mmHg) to remove the majority of the dichloromethane followed by rotary evaporation at 50 °C (200 to 75 mmHg). Further drying at 23 °C under high vacuum (<1 mmHg) gives a light yellow solid (4.00g, 76%) (Notes 30, 31, and 32).



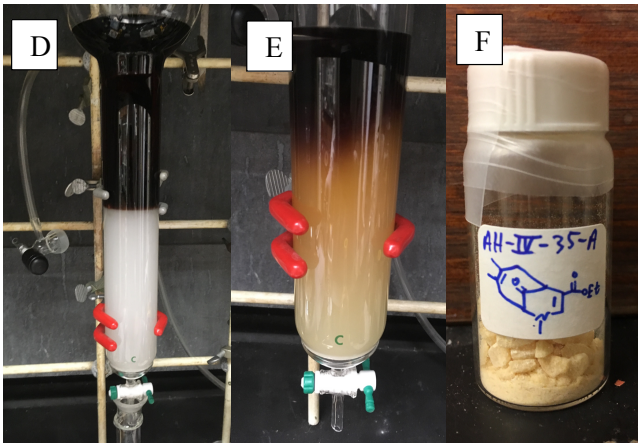


Figure 5. A) Reaction vessel after cooling; B) First extraction with dichloromethane; C) Third extraction with dichloromethane; D) Silica plug before elution; E) Silica plug after elution; F) Solid 3 after evaporation of solvent under vacuum

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with (*enter list of chemicals here*), as well as the proper procedures for (*list any unusual experimental*

operations here). (*Provide additional cautions with regard to exceptional hazards here).*

2. 5-Hydroxynicotinic acid (97%) was purchased from Ambeed, Inc. and used as received.
3. Ethanol (200 proof) was purchased from Decon Labs, Inc. and used as received.
4. Sulfuric Acid (96.4% w/w) was purchased from Fisher Scientific and used as received.
5. Addition of sulfuric acid is exothermic and addition in one portion may be inappropriate on larger scales than that described.
6. Drierite (10-20 mesh) was purchased from W.A. Hammond Drierite Company, Ltd. and used as received.
7. TLC monitoring JAZZ
8. Sodium bicarbonate (100%) was purchased from Fischer Chemical and was shaken with less than 8 mL of deionized water per gram. After settling for several days, the supernatant was decanted to give a saturated solution of sodium bicarbonate.
9. Ethyl acetate (99.9%) was purchased from Fisher Chemical and used as received.
10. Sodium sulfate (99.32%) was purchased from Chem-Impex International and used as received.
11. A second run on 5.01 g scale gave 4.60 g (76.4%) of compound **2** as a white solid. The product has been characterized as follows: mp 66–68 °C; 1 H NMR (500 MHz, CDCl) d: 2.65 (m, 2H), 2.89 (m, 2H), 3.91 (s, 3H); 13C NMR (125 MHz) d: 28.4, 32.7, 52.8, 131.1, 157.7, 163.9, 201.6; FTIR (cm^{-1}) 2954, 1725, 1436, 1282, 1202, 1178; ESI [M + H] m/z calcd for C7H8BrO3: 218.9651. Found: 218.9651.
12. Quantitative nmr for ester
13. Balloon containing a total of 5 liters of argon were used to displace the air in the flask and the flask was maintained under an argon atmosphere with a balloon.
14. Dichloromethane (99.9%) was purchased from Fisher Chemical and distilled from calcium hydride before use.
15. Methyl trifluoromethanesulfonate (98%) was purchased from CombiBlocks and used as received.
16. Addition of methyl trifluoromethanesulfonate is exothermic and addition in one portion may be inappropriate on larger scales than that described.
17. TLC monitoring JAZZ

18. Pentane (98%) was purchased from Fisher Chemical and used as received.
19. The filtrate was treated with triethylamine (1 mL) to quench any unreacted methyl trifluoromethanesulfonate.
20. A second run on 4.58 g scale gave 8.51 g (93.8%) of compound **3** as a white powder. The product has been characterized as follows: mp 66–68 °C; 1 H NMR (500 MHz, CDCl) d: 2.65 (m, 2H), 2.89 (m, 2H), 3.91 (s, 3H); 13C NMR (125 MHz) d: 28.4, 32.7, 52.8, 131.1, 157.7, 163.9, 201.6; FTIR (cm) 2954, 1725, 1436, 1282, 1202, 1178; ESI [M + H] m/z calcd for C7H8BrO3: 218.9651. Found: 218.9651.
21. Quantitative nmr for ester
22. The heavy wall pressure vessel was purchased from Chemglass (item number CG-1880-45).
23. Acetonitrile was purchased from Fisher Chemical and distilled from calcium hydride before use.
24. 2,3-Dimethyl-1,3-butadiene (98% containing 100ppm BHT as stabilizer) was purchased form Alfa Aesar and used as received.
25. Triethylamine (99.5%) was purchased from Sigma-Aldrich and distilled under argon from calcium hydride before use.
26. TLC monitoring JAZZ
27. Concentrated hydrochloric acid (36.5-38% w/w) was purchased from Fisher Chemical and diluted with deionized water to a concentration of 0.5 M.
28. Silica gel (40-63 micron) was purchased from Zeochem and used as received.
29. Dichloromethane (99.9%) was purchased from Fischer Chemical and used as received.
30. If evaporation provides a thick oil, scratching of the oil with a glass rod or several hours in a -20 °C freezer can lead to nucleation and the isolation of the product as a solid.
31. A second run on 6.66 g scale gave 3.97 g (75.0%) of compound **4** as a light yellow solid. The product has been characterized as follows: mp 66–68 °C; 1 H NMR (500 MHz, CDCl) d: 2.65 (m, 2H), 2.89 (m, 2H), 3.91 (s, 3H); 13C NMR (125 MHz) d: 28.4, 32.7, 52.8, 131.1, 157.7, 163.9, 201.6; FTIR (cm) 2954, 1725, 1436, 1282, 1202, 1178; ESI [M + H] m/z calcd for C7H8BrO3: 218.9651. Found: 218.9651.
32. Quantitative NMR for cycloadduct

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

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Tables should be numbered and use 10 point Palatino Bold font for the titles, which is placed just above the table. Titles are recommended for schemes but are not required.

References

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Appendix

Chemical Abstracts Nomenclature (Registry Number)

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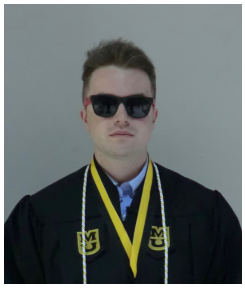

Alexander Harmata was born in Columbia, Missouri. He received his bachelor's degree in chemistry from the University of Missouri in the spring of 2019. He began graduate studies in chemistry at the University of Michigan in the fall of 2019.

Michael Harmata was born in Chicago, Illinois and lived on the south side of Chicago for the first 20 years of his life. He received a bachelor's degree from the University of Illinois-Chicago and earned his Ph.D. with Scott E. Denmark at UIUC. He then headed west to do an NIH postdoctoral fellowship with Paul A. Wender at Stanford University. He began his independent career in 1986 at the University of Missouri Columbia, where he is now the Norman Rabjohn Distinguished Professor of Chemistry.

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