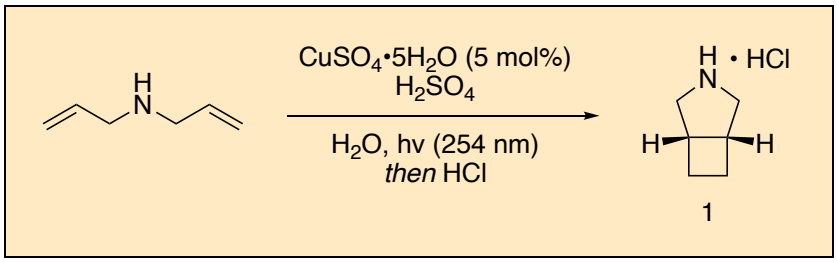
Organic Syntheses

Synthesis of 3-Azabicyclo[3.2.0]heptane hydrochloride

Carl M. F. Mansson and Noah Z. Burns*[1]

Department of Chemistry, Stanford University, Stanford, CA 94305

Checked by J. Andrew P. Maitland, Daniel J. Cox and Darren J. Dixon



Procedure (Note 1)

3-Azabicyclo[3.2.0]heptane hydrochloride (***1***). A 500-mL Erlenmeyer flask was charged with a Teflon-coated rod-shaped magnetic stir bar (45 mm) and aqueous 1 M H_2SO_4 (32.2 mL, 32.2 mmol, 1 equiv.) (Note 2). With stirring, diallylamine (3.13 g, 3.98 mL, 32.2 mmol, 1 equiv.) (Note 3) was steadily added by syringe over the course of 30 s (Note 4). The resulting solution was diluted with DI water (284 mL). $CuSO_4$•$5H_2O$ (402 mg, 1.61 mmol, 0.05 equiv.) (Note 5) was added in one portion and stirring was continued for 5 min to ensure complete dissolution of the salt. The resulting very pale blue solution was partitioned into four equal quartz test tubes (OD: 28 mm; ID: 25 mm; height: 20 cm) (Note 6) which were capped with rubber septa and degassed by bubbling through a long 18-gauge needle with a house N_2 line for 5 min each. The septa were covered in tin foil to avoid UV degradation, and the tubes placed in an appropriately sized test tube rack in a photoreactor (Note 7) such that the tubes are right up against the lamps (Figure 1A). The tubes were irradiated until full conversion, ca. 80 h (Notes 8 and 9). Upon completion, the reaction mixture has a pale pinkish red color (Figure 1B). The

DOI: 10.15227/orgsyn.101.0410

contents of the tubes were then combined in a 600-mL beaker (washing with 20 mL DI water) containing a rod-shaped magnetic stir bar (45 mm). The beaker is placed on a 200 °C hotplate and, with stirring and heating, the reaction solution was boiled to evaporate water until a final volume of ~ 100 mL remained (Note 10). The beaker was removed from the hotplate and let

Figure 1. (A) Quartz tubes containing reaction solution in photoreactor prior to irradiation. (B) Quartz tubes after irradiation

cool for 10 min, then placed in an ice bath (Figure 2A). When the internal temperature had reached 15–20 °C, Et_2O (300 mL) (Note 11) was added followed by NaOH pellets (Note 12) (6.58 g, 165 mmol) in a single portion (Note 13). The mixture was stirred for 10 min, or until full dissolution of the NaOH, during which time the aqueous layer turns from a pinkish red to a murky green (Figure 2B). The contents of the beaker were poured into a 1-L separatory funnel and shaken vigorously. The aqueous layer was drained back into the beaker and the colorless organic layer drained into a 1-L Erlenmeyer flask containing anhydrous Na_2SO_4 (~ 20 g) (Note 14). The aqueous layer was extracted once more with Et_2O (300 mL) in a similar manner (Note 15). The combined dried organic extracts were filtered (600-mL medium porosity sintered filter vacuum funnel) into a 2-L round bottom flask containing a Teflon-coated football-shaped magnetic stir bar (41 mm). The aqueous layer was extracted a final time with Et_2O (300 mL) which was then

used to rinse the Erlenmeyer flask, drying agent, and fritted funnel. The combined, colorless organic filtrate was stirred and aqueous concentrated hydrochloric acid (3.22 mL, 38.7 mmol, 1.2 equiv.) (Note 16) was added over the course of 15 s by graduated pipette. The solution immediately turned cloudy (Figure 3A) and was allowed to stir for an additional 5 min before the stir bar was removed and the Et_2O stripped by rotary evaporation (35 °C, 650 torr).

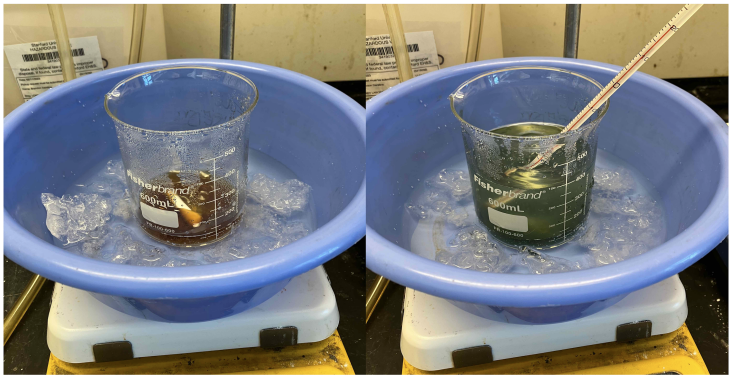


Figure 2. (A) Concentrated reaction in a cooling bath prior to basification. (B) Concentrated reaction with Et_2O after basification

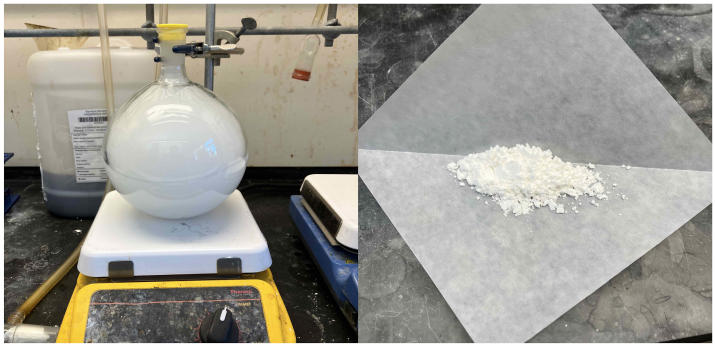


Figure 3. (A) Combined Et_2O extracts containing product 1 after acidification. (B) 2.34 g of final product 1

The water bath temperature was then increased to 50 °C and the residual contents of the flask were concentrated at full vacuum on the rotary evaporator (~ 1 torr) for 15 min (Note 17). DCM (150 mL) (Note 18) was added

to dissolve the contents of the flask. Anhydrous Na_2SO_4 (~ 10 g) was then added and briefly swirled to dry the organic layer which was subsequently filtered (120-mL medium porosity sintered filter vacuum funnel) into a 500-mL round-bottomed flask, washing both the 2-L round-bottomed flask and fritted funnel with additional DCM (75 mL). The combined colorless organic filtrates were concentrated in portions into a 250-mL round-bottomed flask (Note 19) to yield a white solid. Acetone (25 mL) (Note 20) and a Teflon-coated football-shaped magnetic stir bar (32 mm) were added, making sure to wash all crude product from the sides of the flask (Note 21). The resulting suspension was stirred for 1 h then filtered (30-mL medium porosity sintered filter vacuum funnel) washing both the 250-mL round-bottomed flask and fritted funnel with additional acetone (25 mL). The solid was briefly dried by suction on the filter then transferred to a pre-weighed 50-mL round-bottomed flask and further dried on a high vacuum line for 2 h at room temperature to obtain **1** as a white powder (2.41 g, 56%, 97.0 wt%) (Figure 3B) (Notes 22, 23 and 24).

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 diallylamine, copper(II) sulfate pentahydrate, sulfuric and hydrochloric acids, sodium hydroxide, sodium carbonate, diethyl ether, dichloromethane and acetone, as well as the proper procedures for working with UV-light

sources. UV-C light (254 nm) is especially damaging to the eyes and skin. The lamps should never be turned on while the door to the photoreactor is open. UVEX safety glasses should be worn while operating the photoreactor as an additional precaution.

2. Using a volumetric pipette, sulfuric acid (Sigma Aldrich, 95.0–98.0%, 258105) (5 mL) was slowly added to DI water (86 mL) to produce a 1 M stock solution.
3. Diallylamine (Sigma-Aldrich, 99%, D9603) was freshly distilled before use. A 250 mL boiling flask containing diallylamine was heated with stirring at ambient pressure in an oil bath set to 130 °C. The vapors (105 °C) were condensed using a water-cooled short path distillation head and collected in a 100 mL receiving flask (Figure 4).

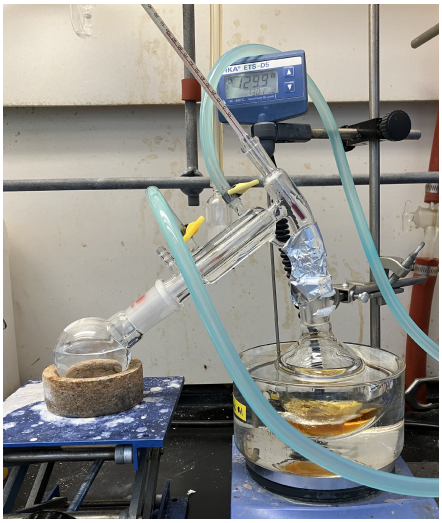


Figure 4. Diallylamine distillation set-up

4. The authors note only a minor exotherm, obviating the need for a cooling bath.
5. Copper (II) sulfate pentahydrate (Sigma Aldrich, 98%, C7631) was used as received.
6. The authors used TTL95 quartz tubes from Technical Glass Products: https://technicalglass.com/product/95cc-fused-quartz-test-tubes-w-lip/. The checkers used custom-made quartz tubes of identical specification, obtained from Robson Scientific.

7. A Luzchem photoreactor (LZC-5) equipped with four Philips TUV 8 W G8T5 bulbs (254 nm) was used. The authors observed that higher-wattage lamps afforded proportionally shorter reaction times.
8. The temperature of the reaction solution does not rise more than ~ 2 °C above room temperature.
9. Reaction times may vary, and the reaction progress can be monitored by temporarily stopping irradiation and removing a small aliquot (0.5 mL) which is placed into a 1 dram vial followed by $CDCl_3$ (1 mL) and aqueous saturated Na_2CO_3 (1 mL). The mixture is shaken and, after settling, the bottom layer is removed by pipette and analyzed by ^1H NMR; the absence of the characteristic diallylamine alkene NMR peaks is sufficient to indicate complete conversion.
10. Concentration of the aqueous layer was deemed efficacious in aiding subsequent extraction into the organic phase. It is possible to attain similar yields without concentrating the aqueous layer, by carrying out more ether extractions.
11. Diethyl ether (Sigma-Aldrich, >99.8%, 32203-M) was used as received.
12. Sodium hydroxide pellets (Sigma-Aldrich, 97%, 221465) was used as received.
13. The authors note that the internal temperature does not rise above 25 °C during NaOH dissolution. It is strongly basic pH ~ 14 indicated by a pH strip.
14. Sodium sulfate anhydrous (Sigma-Aldrich, granular, >99%, 239313) was used as received.
15. For each extraction, the Et_2O is first used to rinse the beaker used to transfer the aqueous layer.
16. Hydrochloric acid (VWR, 37% aq, 20252.335) was used as received. The authors note that new hydrochloric acid containers provided higher purity product.
17. At this point, the contents of the flask appeared mostly dry, see Figure 5. The flask may be placed on a high vacuum line if the rotary evaporation affords only an oily residue due to significant quantities of remaining water. The checkers emphasize that it is imperative that the material is fully dried at this stage, otherwise it will not readily dissolve upon the subsequent addition of DCM.

Figure 5. Almost dry (slightly sticky/oily) crude product after acidification and concentration of extracts

18. Methylene chloride (Sigma-Aldrich, >99.8%, 34856) was used as received.
19. The filtrates may be immediately concentrated in the 500-mL collection flask; however, subsequent trituration with acetone is best performed in smaller flasks to avoid material transfer loss.
20. Acetone (Sigma-Aldrich, >99.8%, 34850-M) was used as received.
21. This can be aided by briefly swirling the flask in a sonication bath.
22. Characterization data for product **1**; mp 200-201 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 2H), 3.46 - 3.35 (m, 2H), 3.22 - 3.02 (m, 4H), 2.31 - 2.15 (m, 2H), 2.10 - 1.93 (m, 2H). .^{13}C NMR (101 MHz, $CDCl_3$) δ 51.91, 36.80, 22.89. IR (neat) 2915, 2863, 2751, 2638, 2548, 1586, 646 cm^{-1}. HRMS-ES+ (*m*/z): $[M+H]^+$ calcd. for $C_6H_{11}N$, 98.0964; found 98.0965.
23. The purity of the product (**1**) was determined to be 97.0% wt. by quantitative ^{1}H NMR spectroscopy in $CDCl_3$ using 21.0 mg of the product and 19.0 mg of 1,3,5-trimethoxybenzene as an internal standard.
24. A duplicate reaction on an identical scale provided 2.19 g (51%) of the product (**1**). The purity of the duplicate run was determined to be 97.5% by qNMR using 41.4 mg of the product and 50.0 mg of 1,3,5-trimethoxybenzene as an internal standard.

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

Nitrogen heterocycles are paramount to the pharmaceutical industry, being present in almost 60% of all drugs.[2] Piperidines and pyrrolidines are particularly central as the first and fifth most prevalent heterocycle of any type. Accordingly, their analogues have garnered intense interest to modulate existing parent heterocycle properties and to access novel chemical space. The bicyclic pyrrolidines 3-azabicyclo[3.1.0]hexane and 3-azabicyclo[3.3.0]octane are two examples of pyrrolidine and piperidine analogues that have been successfully incorporated in a variety of biologically active scaffolds.[3] In contrast, their middle sibling, 3-azabicylo[3.2.0]heptane, has been explored to a lesser extent despite being featured in belaperidone, an anti-schizophrenia drug, and ecenofloxacin, a quinonolone antibiotic.[4a] A likely barrier to its further use is a lack of efficient synthetic access. Consequently, some methods have been devised for simple,

large-scale preparation of compounds containing the 3-azabicylo[3.2.0]heptane substructure.[4] While [2+2] cyclizations are arguably the most powerful methods for forging cyclobutanes, nearly all of the current methods rely on electronically activated olefins.[5] This activation requirement means that the resulting 3-azabicyclo[3.2.0]heptane scaffolds often contain undesired substitution that may be difficult or step-costly to remove.

The Kochi–Salomon reaction remains the only known photochemical [2+2] cycloaddition capable of engaging two unactivated olefins;[6] however, it is intolerant of basic amines, rendering a one-step synthesis of parent 3-azabicyclo[3.2.0]heptane from diallylamine unfeasible under classical conditions. Recently, our group devised an amine-tolerant version of this reaction, whereby in situ protonation with common acids effectively masks the basic properties of amine-containing substrates.[7] Additionally, this allowed the reaction to be run entirely in water with the most standard Cu(II) salts, representing a significant practical advantage to the dry organic solvents and sensitive Cu(I) catalysts previously used. The reaction is broadly applicable to other 1,6-heptadienes, the amine may be 1°, 2° or 3°, and the olefins may be variably substituted. Of the possible amines to choose from, we further detail the synthesis of 3-azabicyclo[3.2.0]heptane even though it is one of the lower-yielding substrates due to issues with isolation. It has fairly high aqueous solubility which makes extraction difficult without the use of large solvent quantities. Chlorinated solvents, although effective at solubilizing the product, form difficult emulsions in the extraction phase and are suboptimal from a safety perspective. Ethyl acetate is readily hydrolyzed by the basic aqueous layer during extraction, also forming emulsions. Despite this, we believe that **1** is likely the most attractive amine in our scope for an organic chemistry audience, being a small, unsubstituted building block ready for installment or further derivatization. Furthermore, it is an expensive product[8] that can now be accessed in one step from some of the most inexpensive precursors. We hope that the procedure detailed above will give synthetic chemists rapid and affordable access to this valuable pyrrolidine and piperidine surrogate.

References

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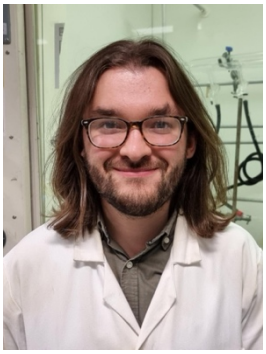
Appendix
Chemical Abstracts Nomenclature (Registry Number)

Diallylamine; (124-02-7)
Sulfuric acid; (7664-93-9)
Copper(II) sulfate pentahydrate; (7758-99-8)
Hydrochloric acid; (7647-01-0)

Carl Mansson was born in Stockholm, Sweden in 1995. He received his B.S. in chemistry from Yale University in 2018. He obtained his Ph.D. from Stanford University in 2023 under the guidance of Prof. Noah Burns. His research interests include new methodologies for cyclobutane formation, especially those involving photochemical [2+2] cycloadditions.

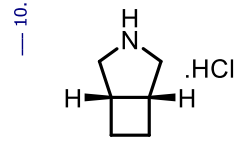
Noah Burns was born in Oakland, CA but grew up in south central Maine. He attended Columbia University in the city of New York where he was mentored by Professor James Leighton. He obtained his Ph.D. with Professor Phil Baran at the Scripps Research Institute in La Jolla, CA and was then an NIH postdoctoral fellow with Professor Eric Jacobsen at Harvard University. He joined the chemistry faculty at Stanford University in the fall of 2012 and was promoted to Associate Professor in 2019.

Andrew Maitland was born in Ayr, Scotland in 1995. He obtained his Master's in Chemistry from the University of St Andrews in 2018, incorporating an industrial placement at Syngenta. He recently completed his DPhil at the University of Oxford, under the supervision of Prof. Darren Dixon, where his research focused on the development of new photochemical methods.



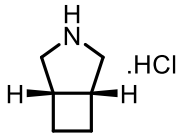
Daniel Cox was born in Buckinghamshire, UK in 1999. He obtained his Master's in Chemistry from the University of Oxford in 2022, having spent a year working under the supervision of Prof. Darren Dixon. Having returned to the same group, he is now a second year DPhil student, with his research centered on the total synthesis of complex natural products.

Darren Dixon studied Chemistry at the University of Oxford, where he received his Master's degree in 1993, and his DPhil in 1997 for work supervised by Prof Stephen G. Davies. After postdoctoral work with Professor Steven V. Ley CBE FRS, he joined the faculty at the Department of Chemistry in Cambridge in 2000. In 2004 he took a Senior Lecturership at The University of Manchester and in 2007 was promoted to Reader. In 2008 he moved to his current post at the University of Oxford where he is Professor of Chemistry and the Knowles-Williams Fellow in Organic Chemistry at Wadham College.



1

^{1}H NMR, 400 MHz, $CDCl_3$



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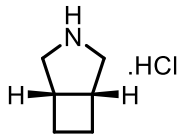
^{13}C NMR, 101 MHz, $CDCl_3$



1

^{1}H qNMR (**1** against 1,3,5-trimethoxybenzene),
400 MHz, $CDCl_3$

$$P(sample) = \frac{mg(stnd)}{mg(sample)} \times \frac{MW(sample)}{MW(stnd)} \times \frac{I(sample)}{I(stnd)} \times \frac{nH(stnd)}{nH(sample)}$$

$$= \frac{50.0}{41.4} \times \frac{133.62}{168.19} \times \frac{1.05}{1.55} \times \frac{3}{2} = 97.5\%$$