



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## 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](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.

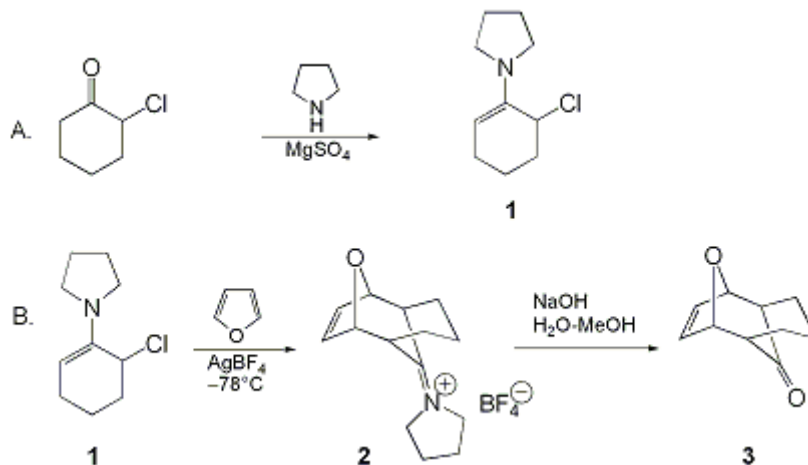
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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## [4 + 3] CYCLOADDITION OF AMINOALLYL CATIONS WITH 1,3-DIENES: 11-OXATRICYCLO[4.3.1.1<sup>2,5</sup>]UNDEC-3-EN-10-ONE

[ 11-Oxatricyclo[4.3.1.1<sup>2,5</sup>]undec-3-en-10-one, (1 $\alpha$ ,2 $\beta$ ,5 $\beta$ ,6 $\alpha$ )- ]



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Checked by Matthew Surman and Marvin J. Miller.

### 1. Procedure

*A. 6-Chloro-1-pyrrolidinocyclohexene (1).*<sup>3</sup> A 500-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with 15 g (0.11 mol) of 2-chlorocyclohexanone (Note 1) and 170 mL of cyclohexane (Note 2). To the stirred solution under a nitrogen atmosphere is added 60 g of anhydrous magnesium sulfate in one portion. The mixture is cooled to 0°C with an ice bath, and 48 mL of pyrrolidine (0.57 mol, 5 equiv) is added dropwise via a syringe over a 15-min period. After the reaction mixture has been stirred for an additional 30 min at 0°C, the ice bath is removed and the mixture is stirred overnight at room temperature. Magnesium sulfate is removed by filtration and rinsed thoroughly with hexane (3 × 50 mL). The combined filtrate and rinsings are concentrated under reduced pressure without heating to give crude 6-chloro-1-pyrrolidinocyclohexene (1) as an orange oil (20.76 g, 0.11 mol, 99%), which is sufficiently pure for the next step (Note 3).

*B. 11-Oxatricyclo[4.3.1.1<sup>2,5</sup>]undec-3-en-10-one (3).*<sup>2, 4,5</sup> A 500-mL, two-necked, round-bottomed flask is equipped with a magnetic stirring bar and a rubber septum. The flask is quickly charged with 30.8 g (0.158 mol) of silver tetrafluoroborate (Note 4) and wrapped in aluminum foil to exclude room light. After the system has been dried under vacuum pump and purged with nitrogen, 150 mL of anhydrous methylene chloride (Note 5) is added, followed by furan (80 mL, 1.1 mol) (Note 6). The reaction mixture is cooled to -78°C with an acetone-dry ice bath and stirred under a nitrogen atmosphere. To this cooled solution is added dropwise over a period of 1 hr via cannula (using positive nitrogen pressure) a solution of crude 1 in 120 mL of methylene chloride. After the addition is completed, the cooling bath is removed, and the mixture is allowed to warm slowly to room temperature, and then stirred for an additional 12 hr. The reaction mixture is filtered through Celite, insoluble material is rinsed with methylene chloride (3 × 70 mL), and the combined filtrate and rinsings are concentrated under reduced pressure to afford the immonium salt 2 as a dark brown oil (47.4 g, 0.16 mol).

To this crude concentrate 2, which is placed in a 1-L, one-necked, round-bottomed flask, are added 300 mL of deionized water and 250 mL of methanol, followed by 18 g (0.45 mol) of sodium hydroxide. The reaction mixture is stirred for 10 hr at room temperature and extracted with ether (300 mL, then 7 × 200 mL). The combined organic layers are washed with brine, dried over magnesium

sulfate, filtered, and concentrated under reduced pressure to a dark orange oil. The crude product is purified by chromatography on silica gel (400 g) with 1:4 ethyl acetate/hexane as eluant to afford 13.0 g (72% overall from 2-chlorocyclohexanone) of the cycloadduct **3** as a white solid, mp 46-47.5°C (Note 7).

## 2. Notes

- (a) 2-Chlorocyclohexanone (98%) was purchased from Aldrich Chemical Company, Inc., and used without further purification. All glassware was oven-dried (>100°C) and quickly assembled prior to use. (b) Newman, M. S.; Farbman, M. D.; Hipsher, H. *Org. Synth., Coll. Vol. III* **1955**, 188.
- Cyclohexane was dried by distillation from calcium hydride and stored over 4Å molecular sieves. Unless stated otherwise, all solvents and reagents in this procedure were obtained commercially and used as received.
- Most conveniently, the crude  $\alpha'$ -chloroamine was used immediately without further purification for the next step. Although it can be distilled under high vacuum with some loss (bp 93-94°C/0.5 mm),<sup>3</sup> there is little advantage to be gained from purification. Spectral data are as follows: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.62-2.22 (m, 10 H), 2.96-3.22 (m, 4 H), 4.40 (m, 1 H), 4.68 (m, 1 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ : 17.0, 24.2, 24.6, 32.9, 47.1, 56.3, 97.7, 142.0.
- Silver tetrafluoroborate (98%) was purchased from Aldrich Chemical Company, Inc.
- Methylene chloride was dried by distillation from calcium hydride.
- Immediately before use, furan was shaken with aqueous 5% sodium hydroxide twice, dried over sodium sulfate, filtered, and distilled from sodium hydroxide pellets under a nitrogen atmosphere.
- Overall yields in several runs were obtained in the range of 73-86% by the submitters, and 50-72% by the checkers. Previous literature reported mp 45.5-46°C.<sup>5a</sup> Spectral data for **3** (R<sub>f</sub> = 0.44 (1:4 ethyl acetate-hexane)) are as follows: IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 1725; <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.49-1.56 (m, 1 H), 2.04-2.13 (m, 2 H), 2.27-2.33 (m, 2 H), 2.35-2.36 (m, 2 H), 2.52-2.62 (m, 1 H), 4.94 (d, 2 H, J = 1.9), 6.37 (s, 2 H); <sup>13</sup>C NMR (90 MHz, CDCl<sub>3</sub>)  $\delta$ : 20.8, 31.0, 53.1, 83.5, 135.4, 214.8; Mass spectrum: m/z 164 (M<sup>+</sup>, 42), 136 (33), 107 (64), 96 (62), 81 (37), 79 (40), 68 (58), 67 (32), 55 (72), 41 (60), 39 (100). The spectral data are identical to those reported in the literature.<sup>2, 4, 5</sup>

## Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press: Washington, DC, 1995.

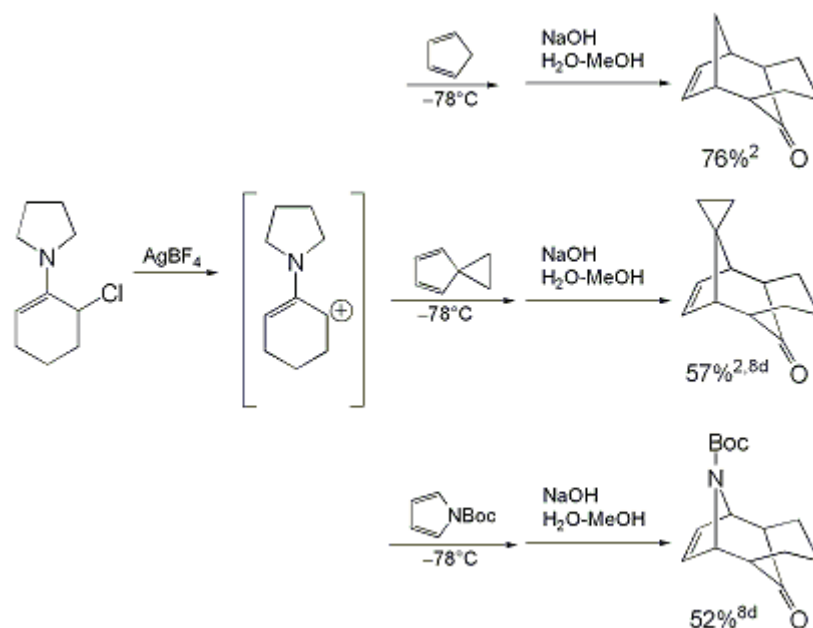
## 3. Discussion

The [4 + 3] cycloaddition reactions of oxyallyls and related allyl cations to 1,3-dienes are general methods for the synthesis of seven-membered ring ketones and have been the subject of several excellent reviews.<sup>6</sup> A representative experimental procedure using acyclic oxyallyls was described by Hoffmann for the preparation of 2 $\alpha$ ,4 $\alpha$ -dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one.<sup>7</sup> Subsequent elaboration of the resulting cycloadducts provides facile preparation of seven-membered carbocycles, tetrahydrofurans, and tetrahydropyrans; these earlier investigations focused on acyclic oxyallyls. More recently, a key variant of using cyclic oxyallyls, (i.e., the oxyallyl functionality is embedded within a ring) has been developed as a convenient route to functionalized medium-sized carbocycles and heterocycles: By virtue of the spectator ring skeleton, this formal [n + 4] cycloaddition allows rapid assembly of these challenging ring systems in addition to providing a seven-membered ring.<sup>8,9</sup> Other key advantages of cyclic oxyallyls include (1) the geometrically constrained, rigid conformation of the oxyallyl function (especially compared to conformationally flexible acyclic oxyallyls), which results in highly diastereoselective formation of the cycloadducts via a "compact" transition state; (2) facile generation of the requisite oxyallyls, which can be attributed to the stabilizing influence of alkyl substituents (i.e., the ring carbons); and (3) well-defined diastereofacial bias present in the resulting tricyclic or tetracyclic cycloadducts made rigid by the keto bridge, which is useful for subsequent elaboration.

Among the known [4 + 3] cycloaddition protocols examined, only the Schmid<sup>2a,2b</sup> and Föhlisch<sup>4, 10</sup> procedures were found to afford the [4 + 3] cycloadducts in synthetically useful yields. Schmid's rarely-

used "aminoallyl" reaction appears to be most effective, particularly when sterically demanding 1,3-dienes [e.g., [spiro\[2.4\]hepta-4,6-diene](#) ] or otherwise recalcitrant N-acylpyrroles are required for the cycloadditions. On the other hand, with sterically unencumbered 1,3-dienes and also with furans, the Föhlisch reaction has emerged as the method of choice in view of the practical aspects of simple and convenient execution.

The method described here is the direct adaptation of the original procedure developed by the late Professor Hans Schmid. As summarized in Scheme 1, the Schmid reaction has been successfully applied to [4 + 3] cycloadditions with [cyclopentadiene](#) , [spiro\[2.4\]hepta-4,6-diene](#) , and [N-Boc-pyrrole](#) . Additional examples can be found in references 8 and 9. Use of functionalized six-membered oxyallyls and synthetic applications of the [4 + 3] cycloadducts have also been described.<sup>8a,8b,8c,8d,8e,8f</sup>



## References and Notes

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- This present method is an adaptation of the original procedure of the late Professor Hans Schmid: (a) Schmid, R.; Schmid, H. *Helv. Chim. Acta* **1974**, *57*, 1883; (b) Schmid, R. Ph. D. Dissertation, University of Zürich, 1978. The submitters thank Professor Manfred Hesse for providing a copy of the Ph.D. dissertation.
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- For other recent developments, see also: (a) Ref. 6e; (b) Harmata, M. In "Advances in Cycloaddition"; Lautens, M., Ed.; JAI Press: Greenwich, CT, 1997; Vol 4, pp 41-86; (c) West, F.

- G. In "Advances in Cycloaddition"; Lautens, M., Ed.; JAI Press: Greenwich, CT, 1997; Vol 4, pp 1-40.
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**Appendix**  
**Chemical Abstracts Nomenclature (Collective Index Number);**  
**(Registry Number)**

11-Oxatricyclo[4.3.1.1<sup>2,5</sup>]undec-3-en-10-one, (1 $\alpha$ ,2 $\beta$ ,5 $\beta$ ,6 $\alpha$ )- (9); (42768-72-9)

6-Chloro-1-pyrrolidinocyclohexene:  
Pyrrolidine,  
1-(6-chloro-1-cyclohexen-1-yl)- (9); (35307-20-1)

2-Chlorocyclohexanone:  
Cyclohexanone, 2-chloro- (8,9); (822-87-7)

Furan (8,9); (110-00-9)

Pyrrolidine (8,9); (123-75-1)

Silver tetrafluoroborate:  
Borate (1-), tetrafluoro-, silver (1+) (9); (14104-20-2)