



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

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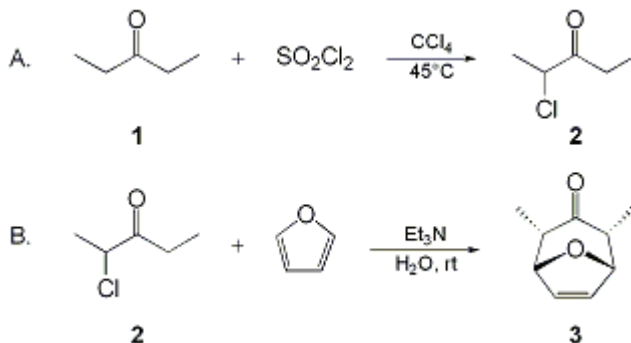
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

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## [4+3] CYCLOADDITION IN WATER. SYNTHESIS OF 2,4- endo,endo-DIMETHYL-8-OXABICYCLO[3.2.1]OCT-6-EN-3-ONE

[ 8-Oxabicyclo[3.2.1]oct-6-en-3-one, 2,4-dimethyl-, (endo,endo)- ]



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### 1. Procedure

*A. 2-Chloropentan-3-one*, **2**. A 500-mL, two-necked, round-bottomed flask, containing a magnetic stirring bar, is equipped with a 100-mL pressure-equalizing addition funnel and a reflux condenser fitted with a calcium chloride trap. The flask is charged with 85 mL (69.40 g, 0.80 mol) of *pentan-3-one* **1** (Note 1) and 200 mL of *carbon tetrachloride* and the mixture is heated to 45°C in an oil bath. The addition funnel is charged with 71 mL (0.88 mol, 1.1 mol equiv) of *sulfonyl chloride* that is added dropwise over a period of 2 hr. The resulting mixture is stirred for 3 hr at 45°C, *carbon tetrachloride* is removed by distillation under atmospheric pressure at 85°C (Note 2) and the residue is purified by distillation under reduced pressure (Note 3). After a forerun at 65–80°C (62 mm) containing mainly *3-pentanone*, *2-chloropentan-3-one* **2** is collected (bp 80–102°C, 62 mm) as a pale yellow liquid (77.0 g, 80%) (Notes 4, 5).

*B. 2,4-endo,endo-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one*, **3**. A 500-mL round-bottomed flask is equipped with a magnetic stirring bar and a 50-mL pressure-equalizing addition funnel. The flask is charged with 15.0 g (0.12 mol) of **2** (Note 6), 36.1 mL (0.50 mol, 4 mol equiv) of *furan* and 125 mL of distilled water. The mixture is stirred vigorously at room temperature and *triethylamine* (18.05 mL, 0.13 mol, 1.05 mol equiv) is placed in the addition funnel and added dropwise to the reaction over a period of 30 min (Note 7). The reaction mixture is stirred for 12 hr and quenched by adding a saturated solution of *ammonium chloride* (50 mL). The mixture is poured into a 500-mL separatory funnel. The layers are separated and the aqueous layer is extracted with *dichloromethane* (3 × 50 mL). The combined organic layers are washed with brine, dried over anhydrous *magnesium sulfate*, and the organic layer is filtered and concentrated under reduced pressure. The crude reaction mixture is resubjected to the reaction conditions by adding additional *furan* and *triethylamine* (1.05 mol equiv based on the amount of unreacted starting material as determined by <sup>1</sup>H NMR), (Notes 8, 9). After 5 hr of vigorous stirring at room temperature, the reaction is quenched by adding a saturated solution of *ammonium chloride* (50 mL). The layers are separated, the aqueous layer is extracted with *dichloromethane* (3 × 25 mL) and the combined organic layers are washed with brine and dried over anhydrous *magnesium sulfate*. After filtration, the solvent is removed with a rotatory evaporator and the crude reaction mixture is dried for 2 hr on a high vacuum pump. The oil is cooled to –20°C in the freezer overnight and pale yellow crystals are filtered on a Buchner funnel and washed with cold *pentane*. The mother liquors are concentrated, placed on a high vacuum pump for 5 hr, and cooled in the freezer. The procedure is repeated once more so that a total of 6.10 g (33%) of pure **3** (Note 10) is obtained.

The filtrate is concentrated under reduced pressure and the residue is purified by flash column

chromatography on silica gel [500 mL, 230-400 mesh, eluted sequentially with hexane/ethyl acetate (90% to 70%)] to afford the cycloadduct **3** as a white powder (2.25 g, 12%); total 8.35 g (45%) (Note 11).

## 2. Notes

1. Pentan-3-one, furan and sulfonyl chloride were purchased from Aldrich Chemical Company, Inc. , and used without further purification.
2. The condenser and the addition funnel are removed and replaced by a simple distillation head and a condenser.
3. The residue is cooled to room temperature and transferred into a 200-mL round-bottomed flask equipped with a 6"-Vigreux column, distillation head, condenser and a cow receiver to be purified by distillation under reduced pressure.
4. A small quantity of 2,4-dichloropentan-3-one (5%) is obtained with the  $\alpha$ -monochloropentanone **2** during the distillation. The NMR analysis for 2-chloropentan-3-one **2** is described by Wyman and Kaufman<sup>2</sup>.
5. The monochloroketone must be stored in a refrigerator.
6. Trace amounts of dichloroketone do not interfere with the [4+3] cycloaddition.
7. The mixture becomes a pale orange, biphasic solution. This mixture becomes red if the addition of triethylamine is too fast.
8. The reaction cannot be monitored by TLC because the monochloro ketone cannot be visualized.
9. The starting material remaining is usually about 40% of the crude weight.
10. Spectral data for the  $\alpha,\alpha$ -cycloadduct **3** are identical to that reported by Hoffmann and coworkers<sup>3</sup>.
11. The submitters report the isolation of 0.75 g (4%) of the corresponding exo-exo isomer; the checkers could not isolate this material in pure form.

## Waste Disposal Information

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

## 3. Discussion

Seven membered ring heterocycles are valuable synthetic intermediates for various natural products. The uses and synthesis of [4+3] cycloadducts have been the subject of extensive reviews.<sup>4</sup> The usual method to prepare these compounds is the [4+3] cycloaddition between an oxyallylic cation and various dienes. The procedure described here provides a simple and efficient method for the construction of 8-oxabicyclo[3.2.1]oct-6-ene on a large scale in water using common reagents and mild conditions. To date, the two main routes reported in the literature involve the generation of oxyallylic cations starting from  $\alpha,\alpha'$ -dihalo ketones<sup>5</sup> or  $\alpha$ -monohalo ketones.<sup>6</sup> All these reactions were carried out using sophisticated promoters [Zn-B(OEt)<sub>3</sub>,<sup>7</sup> CeCl<sub>3</sub>-SnCl<sub>2</sub>,<sup>8</sup> etc.] or an expensive and highly toxic reductive agent [Fe<sub>2</sub>(CO)<sub>9</sub>],<sup>9</sup> under nitrogen in anhydrous solvents. Lubineau and Bouchain<sup>10</sup> reported the [4+3] cycloaddition in water using  $\alpha,\alpha'$ -dibromo ketones or  $\alpha$ -monochloro ketones to provide [3.2.1] oxabicyclic compounds in good yields. Moreover, these conditions afford a good to excellent stereoselectivity in favor of the  $\alpha,\alpha$ -cis isomers. By using the monochloro ketone in excess (2 equiv), the yield of the [4+3] cycloadduct is 88% based on furan , but this procedure, which uses furan in excess, is less cost effective. In order to optimize the yield, after a cycloaddition reaction, the crude mixture containing some starting monochloropentan-3-one was worked-up and resubjected to the same conditions without any intermediate purification. Moreover the pure  $\alpha,\alpha$ -cycloadduct is easily obtained by crystallization.

In conclusion, this is the most practical and least expensive method available for the synthesis of [3.2.1]oxabicyclic compounds.

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## References and Notes

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**Appendix**  
**Chemical Abstracts Nomenclature (Collective Index Number);**  
**(Registry Number)**

2,4-endo,endo-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one:  
8-Oxabicyclo[3.2.1]oct-6-en-3-one, 2,4-dimethyl-, (endo,endo)- (9); (37081-58-6)

2-Chloropentan-3-one:  
3-Pentanone, 2-chloro- (8,9); (17042-21-6)

Carbon tetrachloride: CANCER SUSPECT AGENT (8);  
Methane, tetrachloro- (9); (56-23-5)

Sulfuryl chloride (8,9); (7791-25-5)

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

Triethylamine (8);  
Ethanamine, N,N-diethyl- (9); (121-44-8)