



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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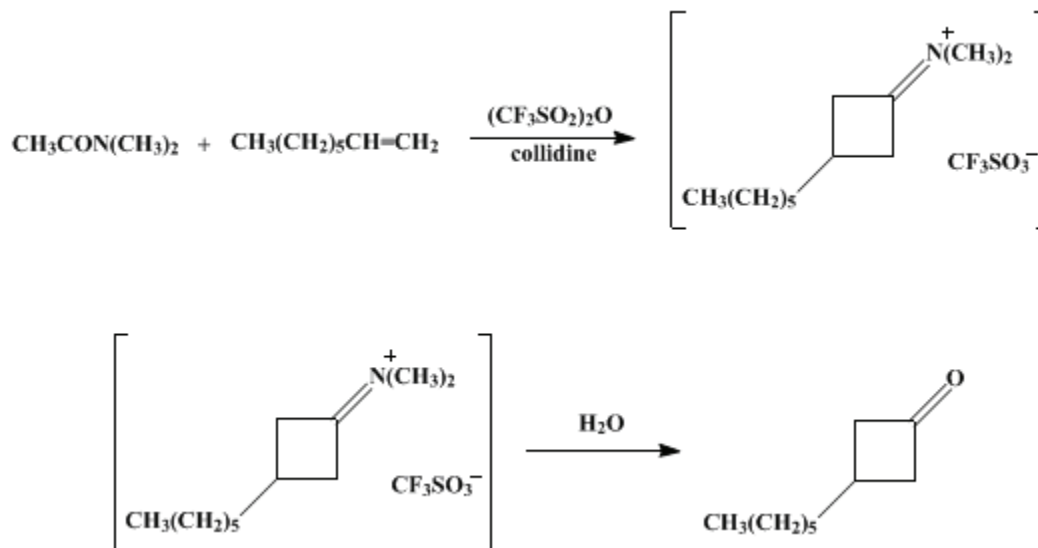
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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A GENERAL SYNTHESIS OF CYCLOBUTANONES FROM OLEFINS AND TERTIARY AMIDES: 3- HEXYLCYCLOBUTANONE



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Checked by Thomas J. Sowin and Albert I. Meyers.

1. Procedure

A 500-mL, three-necked flask is equipped with a rubber septum, a magnetic stirring bar, a gas inlet, and a reflux condenser. The top of the condenser is connected to a pressure-equalizing dropping funnel isolated from moisture by a sulfuric acid trap (Note 1). The flask is cooled to -15°C and charged with *N,N*-dimethylacetamide (3.26 g, 37.5 mmol) (Note 2) in 100 mL of 1,2-dichloroethane (Note 3). The dropping funnel is charged with 1-octene (16.8 g, 150 mmol) (Note 4) and 2,4,6-collidine (5.44 g, 45 mmol) (Note 5) in 50 mL of 1,2-dichloroethane. A slightly positive pressure of argon is maintained in the apparatus throughout the course of the reaction. Trifluoromethanesulfonic anhydride (12.69 g, 45 mmol) (Note 6) is added through the rubber septum into the solution of *N,N*-dimethylacetamide by means of a syringe. A precipitate is formed. The olefin-collidine solution is then added dropwise over a 20-min period. During these operations rapid stirring and cooling are maintained. The resulting mixture is refluxed for 17 hr (Note 7). The solvent is removed by rotary evaporation. The oily residue is washed with dry ether (3×20 mL) (Note 8). Then 20 mL of carbon tetrachloride (Note 9) and 20 mL of water are added to the crude cyclobutaniminium salt. The mixture is refluxed for 6 hr (Note 10). The organic phase is separated and the aqueous phase is extracted with carbon tetrachloride (3×20 mL). The combined organic phases are dried over anhydrous magnesium sulfate. The solvent is removed by distillation at atmospheric pressure (Note 11). Bulb-to-bulb distillation (bath temperature 100 – 110°C , water pump) gives 3.3 g (59%) of 3-hexylcyclobutanone (Note 12) and (Note 13).

2. Notes

1. The assembled apparatus is flame-dried under a slight pressure of argon.
2. *N,N*-Dimethylacetamide (Janssen Chimica, Beerse, Belgium) is distilled before use. The checkers used it as obtained from Aldrich Chemical Company, Inc.
3. 1,2-Dichloroethane (99%) is obtained from Janssen Chimica or Aldrich Chemical Company, Inc. It is distilled from calcium hydride.
4. 1-Octene (97%) is purchased from Janssen Chimica or Aldrich Chemical Company, Inc. and distilled.
5. 2,4,6-Collidine (99%, Janssen Chimica or Aldrich Chemical Company, Inc.) is distilled from calcium

hydride and stored under argon in a brown bottle.

6. Trifluoromethanesulfonic anhydride is prepared just prior to use according to the procedure of Stang and Dueber.² The checkers obtained it from Aldrich Chemical Company, Inc.

7. During this period the solution turns dark brown and, after rotary evaporation, the residue is a thick, black oil. The progress of the reaction can be followed by IR (



) cm^{-1} : 1730–1735, but the checkers found that it was complete in this 17-hr period.

8. Technical ether is dried over potassium hydroxide.

9. Technical carbon tetrachloride is used. Dichloromethane is preferred only when the cyclobutanone is too volatile.

10. The progress of the hydrolysis can be followed by IR, but the checkers found that it was complete in 6 hr.

11. Rotary evaporation or vacuum distillation can lead to a substantial loss of cyclobutanone.

12. The spectral properties of the compound are as follows: IR (CCl_4 , $\nu_{\text{C=O}}$) cm^{-1} 1785; ^1H NMR (270 MHz, CDCl_3) δ : 0.840 (t, 3 H, CH_3), 1.226–1.243–1.302 (m, 8 H, CH_2), 1.513 (m, 2 H, CH), 2.300 (m, 1 H, CH), 2.610 (m, 2 H, CH), 3.079 (m, 2 H, CH); ^{13}C NMR (75.5 MHz, CDCl_3) δ : 13.98, 22.53, 23.78, 28.16, 29.02, 31.71, 36.29, 52.43, 208.61.

13. The physical properties of the semicarbazone are as follows: mp 148.5°C; Anal. calcd. for $\text{C}_{11}\text{H}_{21}\text{N}_3\text{O}$: C, 62.53; H, 10.02; N, 19.88; O, 7.57. Found: C, 62.63; H, 10.05; N, 19.95; O, 7.50.

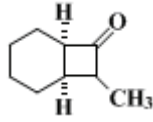
3. Discussion

Cyclobutanones are important synthetic intermediates. A common synthetic method for their preparation is the [2+2] cycloaddition of olefins with ketenes often generated in situ from acid chlorides. However, that method suffers limitations especially when aldoketenes and unreactive olefins are used.

Keteniminium salts are more electrophilic than ketenes and are thus able to react with less nucleophilic olefins. Ketoketeniminium salts can be conveniently prepared from the corresponding α -chloroanilines and Lewis acids.^{3 4 5 6} However, the method cannot be applied well to the preparation of the less stable aldoketeniminium salts.

The method described here which involves the in situ generation of keteniminium triflates is practical and more general. The best results were obtained with 2,4,6-collidine, but occasionally the more expensive 2,6-di-*t*-butyl-4-methylpyridine was superior. Pyridine gave satisfactory results in few cases only. Triethylamine always gave poor results. With the more reactive olefins (e.g., styrene), reactions can be run in refluxing dichloromethane. The procedure described here usually gives better yields than that previously reported in a preliminary communication.¹⁰ It has been used to prepare cyclobutanones as well as cyclobutenones^{7,8 9} from a wide variety of olefins or acetylenes. A few examples are shown in Table I. The method works well for olefins or acetylenes bearing alkyl, alkenyl or aryl groups. It does not apply to enol ethers or enamines.

TABLE I
SYNTHESIS OF CYCLOBUTANONES FROM TERTIARY AMIDES AND OLEFINS

Amide	Olefin	Cyclobutanone	Yield (%)
$\text{CH}_3\text{CH}_2\text{CON}(\text{CH}_3)_2$	Cyclohexene		89 ^a
$\text{CH}_3\text{CH}_2\text{CON}(\text{CH}_3)_2$	α -		79 ^a

	Methylstyrene		
$\text{CH}_3\text{CH}_2\text{CON}(\text{CH}_3)_2$	Allyl ethyl ether		56 ^a
$\text{CH}_3\text{CON}(\text{CH}_3)_2$	Cyclohexene		46
$\text{CH}_3\text{CON}(\text{CH}_3)_2$	Styrene		71
$(\text{H}_3\text{C})_2\text{NCO}-\underset{\text{CH}_3}{\text{CH}}(\text{CH}_2)_3\text{CH}=\text{CH}_2$			87 ^b
$(\text{H}_3\text{C})_2\text{NCO}(\text{CH}_2)_6\text{CH}=\text{CH}_2$			71 ^b

^a Mixture of *endo* + *exo* isomers.

^b These reactions were performed under slightly different conditions.¹⁰

References and Notes

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(Registry Number)



ether (60-29-7)

Cyclohexene (110-83-8)

carbon tetrachloride (56-23-5)

1,2-dichloroethane (107-06-2)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

dichloromethane (75-09-2)

styrene (100-42-5)

magnesium sulfate (7487-88-9)

2,4,6-collidine (108-75-8)

triethylamine (121-44-8)

argon (7440-37-1)

calcium hydride (7789-78-8)

α -methylstyrene (98-83-9)

Cyclobutanone (1191-95-3)

N,N-dimethylacetamide (127-19-5)

1-octene (111-66-0)

Trifluoromethanesulfonic anhydride (358-23-6)

3-Hexylcyclobutanone (138173-74-7)

Allyl ethyl ether (557-31-3)

2,6-di-t-butyl-4-methylpyridine (38222-83-2)