



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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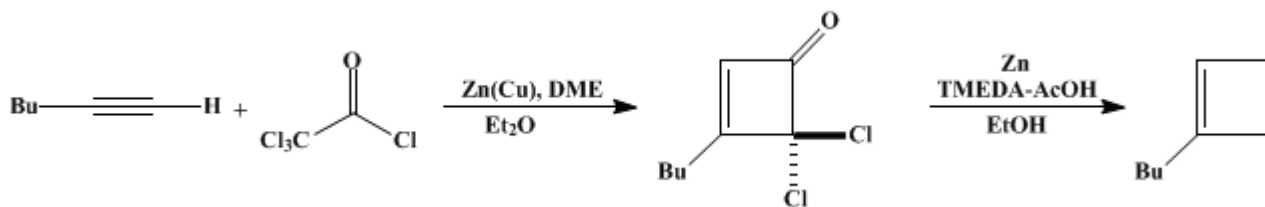
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 8, p.82 (1993); Vol. 68, p.32 (1990).

3-BUTYLCYCLOBUTENONE

[2-Cyclobuten-1-one, 3-butyl-]



Submitted by Rick L. Danheiser¹, Selvaraj Savariar, and Don D. Cha².

Checked by Reinhard Kratzberg and Ekkehard Winterfeldt.

1. Procedure

A. *3-Butyl-4,4-dichlorocyclobutenone*. A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, two glass stoppers, and a 250-mL pressure-equalizing addition funnel fitted with a nitrogen inlet adapter (Note 1). The flask is charged with 39.23 g (0.60 mol) of zinc-copper couple (Note 2), 400 mL of diethyl ether (Note 3), and 23.0 mL (0.20 mol) of 1-hexyne (Note 4). The dropping funnel is charged with a solution of 44.6 mL (0.40 mol) of trichloroacetyl chloride (Note 5) in 125 mL of dimethoxyethane (Note 6), and this solution is then added dropwise to the reaction mixture over 1 hr. After 18 hr, the resulting brown mixture is filtered through a sintered-glass Büchner funnel, and the black solid that is separated is thoroughly washed with 200 mL of hexane. The filtrate is washed successively with 200 mL each of ice-cold 0.5 N hydrochloric acid, ice-cooled 5% sodium hydroxide solution, and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and then concentrated at reduced pressure using a rotary evaporator. The residual brown oil is transferred to a 100-mL, round-bottomed flask and distilled through a 10-cm Vigreux column to afford 29.5–30.0 g (76–78%) of 3-butyl-4,4-dichlorocyclobutenone as a colorless liquid, bp 68.5–70°C (0.3 mm) (Note 7).

B. *3-Butylcyclobutenone*. A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, two glass stoppers, and a 125-mL pressure-equalizing dropping funnel fitted with a nitrogen inlet adapter (Note 1). The flask is charged with 52.6 g (0.805 mol) of zinc dust (Note 8), 121 mL of tetramethylethylenediamine (Note 9), and 270 mL of absolute ethanol, and cooled with an ice bath while 46 mL of glacial acetic acid is added dropwise over 5 min. The reaction mixture is maintained at 0°C while a solution of 26.59 g (0.138 mol) of 3-butyl-4,4-dichlorocyclobutenone in 27 mL of absolute ethanol is added over 10 min via the dropping funnel. After 15 min the ice bath is removed, and the reaction mixture is stirred for 2.5 hr and then filtered through a sintered-glass Büchner funnel with the aid of 1.5 L of a 1 : 1 mixture of diethyl ether and pentane. The filtrate is washed successively with 500 mL of 1 N hydrochloric acid, 500 mL of water, 800 mL of saturated sodium bicarbonate solution, and 500 mL of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator. The residual yellow oil is transferred to a 100-mL, round-bottomed flask fitted with a short-path distillation head (Note 10) and a pear-shaped receiver flask that is cooled below –75°C with a dry ice-acetone bath. Distillation at 0.001 mm (bath temperature 50–70°C) (Note 11) provides 3-butylcyclobutenone (13.4–16.2 g, 78–86% yield) as a clear, colorless liquid, bp 33°C (0.001 mm) (Note 12).

2. Notes

- The glass components of the apparatus are dried overnight in a 120°C oven and then assembled and maintained under an atmosphere of nitrogen during the course of the reaction.
- To a stirred mixture of 65.38 g (1.0 mol) of zinc dust (purchased from Mallinckrodt, Inc.) and 100 mL of water in a 1-L Erlenmeyer flask is added at 30-sec intervals two solutions of 7.6 g of copper sulfate, (CuSO₄·5H₂O) in 50 mL of water. After 1 min the mixture is filtered through a sintered-glass Büchner funnel and the zinc-copper couple is washed with two 50-mL portions of water, two 50-mL

portions of acetone, and 50 mL of diethyl ether. The resulting dark-gray powder is dried at 100°C at 1 mm for 4 hr and then stored under nitrogen.

3. Diethyl ether was distilled from sodium benzophenone ketyl immediately before use.

4. 1-Hexyne was obtained from Aldrich Chemical Company, Inc., and distilled from calcium hydride before use.

5. Trichloroacetyl chloride was purchased from Fluka Chemical Corporation and distilled before use.

6. Dimethoxyethane was obtained from Aldrich Chemical Company, Inc., and distilled from sodium benzophenone ketyl immediately before use.

7. The product exhibits the following spectral properties: IR (film) cm^{-1} : 2970, 2940, 2880, 1800, 1585, 1475, 1415, 1390, 1260, 1210, 1045, 850, and 630; UV (isooctane) nm max (ϵ): 306 (33) and 215 (9530); ^1H NMR (300 MHz, CDCl_3) δ : 0.96 (t, 3 H, $J = 7$), 1.45 (apparent sextet, 2 H, $J = 7$), 1.72 (apparent quintet, 2 H, $J = 7$), 2.69 (dt, 2 H, $J = 2, 7$), and 6.20 (t, 1 H, $J = 2$); ^{13}C NMR (75.4 MHz, CDCl_3) δ : 13.5, 22.3, 25.9, 27.6, 91.9, 135.6, 179.2, 186.1.

8. Zinc dust was purchased from Mallinckrodt, Inc. and used without further purification.

9. Tetramethylethylenediamine (TMEDA) was obtained from Aldrich Chemical Company, Inc., and distilled from calcium hydride before use.

10. The delivery tube of the short-path distillation head is fitted with a 5-cm length of Teflon tubing that extends nearly to the bottom of the receiving flask.

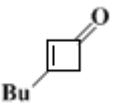
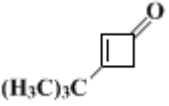
11. Substantial decomposition of the product was observed when the bath temperature was allowed to exceed 80°C or when distillation was attempted using a short Vigreux column.

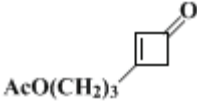
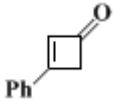
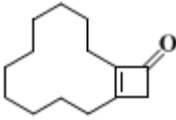
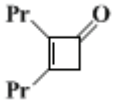
12. 3-Butylcyclobutenone displays the following spectral properties: IR (film) cm^{-1} : 2970, 2940, 2860, 1770, 1590, 1470, 1420, 1385, 1310, 1280, 1220, 1180, 1100, 1030, 990, 925, 850; UV (isooctane) nm max (ϵ): 306 (36) and 220 (6860); ^1H NMR (300 MHz, CDCl_3) δ : 0.93 (t, 3 H, $J = 7$), 1.38 (apparent sextet, 2 H, $J = 7$), 1.58 (apparent quintet, 2 H, $J = 7$), 2.54 (t, 2 H, $J = 7$), 3.12 (s, 2 H), and 5.86 (s, 1 H); ^{13}C NMR (75.4 MHz, CDCl_3) δ : 13.5, 22.2, 27.9, 31.6, 50.5, 133.8, 181.2, 187.6.

3. Discussion

The procedure described above illustrates a general two-step method for the preparation of 3-substituted and 2,3-disubstituted cyclobutenones.^{3,4} The first step in the procedure involves the [2+2] cycloaddition of an acetylene with dichloroacetylene, which is best carried out using a modification of the method originally reported by Hassner and Dillon.⁵ Under these conditions dichloroacetylene combines smoothly with a variety of alkyne derivatives in contrast to ketene itself which fails to add to unactivated acetylenes. The 4,4-dichlorocyclobutenone cycloadducts produced in the first step are then subjected to reductive dechlorination with zinc dust to afford the desired cyclobutenones. Although it has previously been reported that this reductive dechlorination reaction cannot be accomplished reliably,⁵ recent studies^{3,4} have shown that under carefully controlled conditions the desired transformation is in fact a feasible and efficient process. As summarized in Table I, this strategy is applicable to the synthesis of a variety of substituted cyclobutenones.

TABLE I
SYNTHESIS OF CYCLOBUTENONES FROM ALKYNES

Case	Alkyne	Cyclobutenone	Isolated Yield (%)
1	Bu-C \equiv CH		70
2	tBu-C \equiv CH		54
3	AcO(CH ₂) ₃ -C \equiv CH		56

			
4	Ph-C≡CH		66–77
5	Cyclododecyne		75
6	Pr-C≡C-Pr		73

The preparation of 3-butyl-4,4-dichlorocyclobutenone described here represents an optimized procedure for the [2+2] cycloaddition of dichloroketene with acetylenes. Previously there was some disagreement over the efficacy of phosphorus oxychloride (POCl₃) as a sequestering agent for the zinc chloride generated in the course of the reaction. Hassner and Dillon⁵ have reported that the inclusion of phosphorus oxychloride is crucial to the success of these reactions, and that in its absence tarry products are produced that are difficult to purify. Dreiding and co-workers,⁴ however, report that these conditions lead to the production of the desired cycloadducts contaminated with significant amounts of the corresponding 2,4-dichloro isomers. Dreiding consequently suggests that these cycloadditions are best carried out in the absence of phosphorus oxychloride employing short reaction times (< 15 min).

We have found that the method used to prepare the zinc–copper couple is an important variable in determining the efficiency and rate of these reactions. Optimal results are achieved using a couple prepared by brief (2 min) exposure of commercial zinc dust to twice the amount (0.06 equiv) of copper sulfate employed in the previous studies.^{4,5} We have also found that the cycloadditions proceed with equal efficiency and more conveniently by employing dimethoxyethane⁶ in place of phosphorus oxychloride as a zinc chloride sequestering agent. Under these optimized conditions a variety of terminal acetylenes are smoothly converted to 4,4-dichlorocyclobutenones in high yield. Although cycloadditions involving disubstituted acetylenes lead to the desired 4,4-dichlorocyclobutenones contaminated with varying amounts of isomeric 2,4-dichloro isomers, the formation of these by-products can be suppressed (to < 10%) simply by carrying out the cycloaddition at temperatures between 10 and 15°C.

Under conventional dechlorination conditions (20 equiv of zinc dust, acetic acid, 25 or 50°C) the reduction of 4,4-dichlorocyclobutenones affords complex mixtures of products that include the desired cyclobutenones as well as significant amounts of partially reduced by-products. We have found that the desired transformation can be accomplished cleanly provided that the reduction is carried out at room temperature in alcoholic solvents (preferably ethanol) in the presence of 5 equiv each of acetic acid and a tertiary amine (preferably tetramethylethylenediamine). Zinc dust has proved to be somewhat superior to zinc–copper couple for this reduction. The desired cyclobutenones are obtained in somewhat higher yield using this procedure as compared to the related conditions reported by Dreiding [Zn(Cu), 4 : 1 AcOH–pyridine, 50–60°C] for the same transformation.⁴

The most efficient synthetic route to 3-butylcyclobutenone reported previously^{7,8} involves the addition of butylmagnesium bromide⁹ or butyllithium¹⁰ to 3-ethoxycyclobutenone followed by acid hydrolysis. 3-Ethoxycyclobutenone is itself available in modest yield via the addition of ketene to ethoxyacetylene. This procedure provides 3-butylcyclobutenone in only 20% overall yield and requires the use of a ketene generator and the rather unstable ethoxyacetylene as starting material.

Cyclobutenones serve as versatile intermediates for the preparation of α,β-butenolides,¹¹

cyclopentenones,¹¹ and a variety of substituted [cyclobutane](#) derivatives. We have shown that cyclobutenones also function as four-carbon annulation components in routes to eight-membered carbocycles¹⁰ and highly substituted aromatic compounds.^{12 13}

References and Notes

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Appendix

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

amine

sodium benzophenone ketyl

Bu-C≡CH

tBu-C≡CH

AcO(CH₂)₃-C≡CH

Ph-C≡CH

Pr-C≡C-Pr

phosphorus oxychloride (POCl₃)

[ethanol](#) (64-17-5)

[hydrochloric acid](#) (7647-01-0)

[acetic acid](#) (64-19-7)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

copper sulfate (7758-98-7)

copper (7440-50-8)

acetone (67-64-1)

Phosphorus Oxychloride (21295-50-1)

zinc (7440-66-6)

zinc chloride (7646-85-7)

Pentane (109-66-0)

Butylmagnesium bromide (693-03-8)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

hexane (110-54-3)

1-Hexyne (693-02-7)

Ethoxyacetylene (927-80-0)

calcium hydride (7789-78-8)

dimethoxyethane (534-15-6)

cyclobutane (287-23-0)

cyclododecyne (1129-90-4)

trichloroacetyl chloride (76-02-8)

tetramethylethylenediamine (20485-44-3)

3-Butylcyclobutenone,
2-Cyclobuten-1-one, 3-butyl- (38425-48-8)

3-butyl-4,4-dichlorocyclobutenone (72284-70-9)

4,4-dichlorocyclobutenone

Cyclobutenone

3-ethoxycyclobutenone

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