An Improved Synthesis of Cyclooctyne

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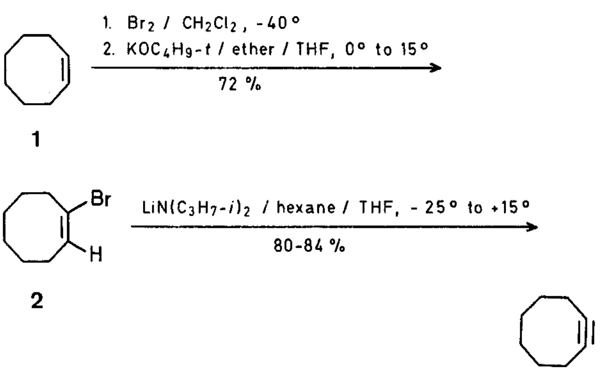
Cyclooctyne has been synthesised by a number of methods, which either start from cyclooctene or from cyclooctanone[1-4]. Wittig and Dorsch[2] added bromine to cyclooctene and prepared 1-bromocyclooctene from the adduct in 47% yield by heating it with morpholine. Further dehydrobromination with sodamide at about 200° gave a mixture of cyclooctyne, cyclooctene, and 1,3-cyclooctadiene, from which the pure cycloalkyne was obtained via purification of the silver nitrate complex in 17% yield.

In a recent method giving cyclooctyne in 34% overall from cyclooctanone, cyclooctaselenadiazole was decomposed photochemically[3]. We wish to present the following improved synthesis of reasonably (~97% by G.L.C. and N.M.R.) pure cyclooctyne in yields up to about 60% overall.



The dehydrobromination of 1,2-dibromocyclooctane with uncomplexed KO-*t*-C_4H_9 gave the 1-bromocompound **2** (the same procedure with the seven-membered ring gave also 1-bromocycloalkene, yield 87%, but starting from cyclopentene and cyclohexene only 3-bromocycloalkene and 1,3-cycloalkadienes were formed by *trans*-anti-coplanar elimination). The second dehydrobromination gave the best results when a 100% excess of **2** was used. In the case of a 1:1 mixture of **2** and base lower yields (55–60%) were obtained, probably due to base-catalysed isomerisation of **3** into the cyclic allene which dimerised giving high-boiling residues after the distillation. The use of hexamethylphosphoric triamide as cosolvent also caused an increase of the amount of high-boiling material.

Preparation of Cyclooctyne (3):

1-Bromocyclooctene (**2**): To a solution of cyclooctene (**1**; 110.2g, 1 mol) in dichloromethane (350 ml) is added with cooling at about −40° bromine (1 mol) until the brown colour persists. After removal of the solvent in a water pump vacuum (rotary evaporator) the residue is dissolved in dry ether (400 ml) and a solution of potassium *t*-butoxide (1.5 mol; commercially available from Nobel-Dynamit, West Germany) in tetrahydrofuran (150 ml) is added in 20 minutes to the vigorously stirred mixture, keeping its temperature at about 0°. After the addition, stirring is continued for 1 h at 15°. The mixture is then poured into ice/water (500 ml) and the organic products are extracted with ether. After drying of the extracts the solvents are removed in vacuo. Distillation of the residue gives 1-bromocyclooctene (**2**); b.p. 90–95°/20 torr; n_D^{20}: 1.5187; Lit.[2], b.p. 87°/15 torr.

Cyclooctyne (**3**): A portion of the above product (113.4 g, 0.60 mol) is added at once to a solution of lithium diisopropylamide, cooled at −25°. This solution is obtained by adding at −25° butyllithium (0.30 mol) in hexane (190 ml) to a mixture of dry diisopropylamine (32.3 g, 0.32 mol) and dry tetrahydrofuran (125 ml). The temperature of the reaction mixture is allowed to rise gradually over a period of 45 min to 15° and is kept at this level for another 90 min. It is then poured into a cold solution of ~3 normal hydrochloric acid (just enough to neutralise the amine). Five extractions with pentane (5 × 40 ml) are carried out. The combined extracts are washed several times with water in order to remove the tetrahydrofuran and are then dried with magnesium sulfate. The solvents are removed in a water pump vacuum, keeping the bath temperature at 0°. Careful distillation of the residue through a 30 cm Widmer column gives cyclooctyne (**3**); yield: 25.9 g (80%); b.p. 50–55°/20 torr; n_D^{20}: 1.4876; Lit.[2] b.p. 51–52°/22 torr; Lit.[2] n_D^{20}: 1.4888; and 1-bromocyclooctene (recovery about 0.3 mol).

Received: November 24, 1977

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[1] A. T Blomquist, L. H. Liu, *J. Am. Chem. Soc.* **75**, 2153 (1953).

[2] G. Wittig, H. L. Dorsch, *Justus Liebigs Ann. Chem.* **74**, 46 (1968).

[3] H. Meier, I. Menzel, *J. Chem. Soc.* [D] **1971**, 1059.

[4] P. Caubere, G. Coudert, *Bull. Soc. Chim. Fr.* **1973**, 3067.

0039-7881/78/0432-0290 $ 03.00