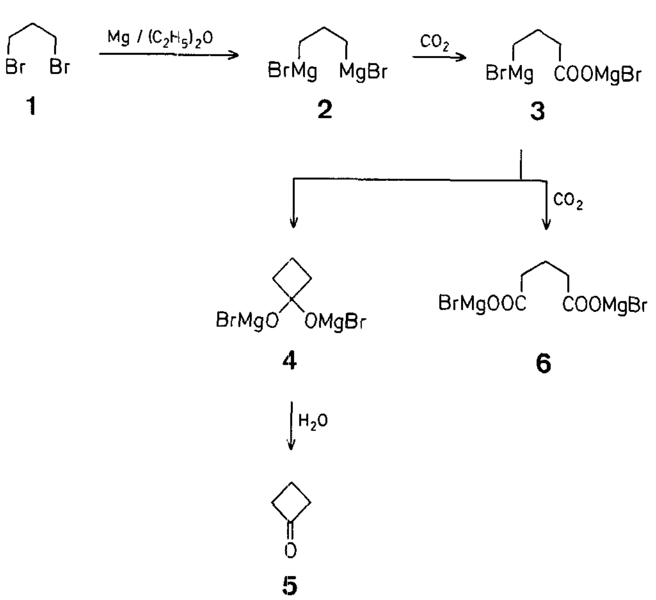
A Convenient Synthesis of Cyclobutanone

J. W. F. L. SEETZ, R. TOL, O. S. AKKERMAN, F. BICKELHAUPT*

Vakgroep Organische Chemie, Vrije Universiteit, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands

Cyclobutanone (**5**), a "potentially very valuable basic building block"[1], has been, and continues to be, the object of a remarkable synthetic activity[1,2,3]; about thirty syntheses have been reported. We now report a novel approach to **5** which permits its preparation on a 10 g laboratory scale. The synthesis requires only simple, readily available chemicals [1,3-dibromopropane (**1**), magnesium, dry diethyl ether, carbon dioxide] and compares favourably with the known methods in price/mol **5** and in working time.

The new approach is based on the preparation of 1,3-bis[bromomagnesio]propane (**2**) from **1** and magnesium in diethyl ether in a direct Grignard reaction[4]. The yield of **2** is moderate (40%), and it is accompanied by small amounts of organometallic impurities such as 1,6-bis[bromomagnesio]hexane, allylmagnesium bromide, and *n*-propylmagnesium bromide. However, removal of these impurities, though possible[4], is not required for the successful preparation of **5**, and even though the yield of product isolated (~13% from **1**) may seem low at first sight, the new method is competitive because of the cheap starting materials.



The Grignard reagent **2** is reacted with gaseous carbon dioxide/nitrogen (1 : 2) which is conducted in a slow stream over the solution at room temperature. If the carbon dioxide is added too rapidly, glutaric acid is the main product; slow addition of carbon dioxide facilitates the attack of the second Grignard function in **3** on the carboxylate, yielding **4** which, on hydrolysis, furnishes **5**. Similar formation of cyclopentanone and cyclohexanone has been observed from the corresponding 1,4- and 1,5-di-Grignard reagents[5]. Apparently, two factors cooperate to make the synthesis of cyclic ketones by the Grignard approach practicable. In the first place, the inherently reduced reactivity of the carboxylate group as in **3** is compensated by the intramolecularity of transformations such as **3**→**4**; in the monovalent, acyclic series, the reactions are more prone to stop at the carboxylate stage[6]. It is, however, remarkable that in spite of the high strain introduced in the formation of the four-membered ring, the reaction still proceeds in reasonable yield *(vide infra)*. A second feature which normally lowers the yield of ketones in the acyclic series is the elimination of BrMgOMgBr (or its equivalent) from the diadducts corresponding to **4**; the ketone is thus liberated prematurely and is consumed by excess Grignard reagent still present. Such spontaneous conversion of **4** to **5** is only a minor side reaction; this follows from the low yield of cyclobutanol (2%) which must be the reaction product of **5**, liberated *in situ*, with **2**, because **2** has been shown to react with ketones exclusively by reduction and not by addition[7].

Another agreeable property of **4** is that it precipitates relatively pure from the rather complex reaction mixture, thus simplifying the purification procedure: the ethereal solution containing most impurities is decanted and the solid residue is hydrolyzed with water and hydrochloric acid; after continuous extraction with pentane (41% spectroscopically determined yield of **5**, relative to **2**), spinning band distillation afforded pure **5** (33% from **2**, 13% from **1**).

Cyclobutanone (5):
A 4-l, three-necked, round-bottomed flask, equipped with a nitrogen inlet, a reflux condenser, a mechanical stirrer, and a pressure-equalizing dropping funnel is dried by heating with a flame under evacuation. Under nitrogen, it is charged with magnesium (264 g, 11 mol) and anhydrous diethyl ether (1.5 l). Under rapid stirring, the solution of 1,3-dibromopropane (**1**; 212 g, 1.05 mol) in diethyl ether (1.5 l) is added during 15 h. Afterwards, the reaction mixture is transferred by nitrogen pressure through a glass tube plugged with glass wool into another dry 4-l, three-necked, round-bottomed flask equipped with a gas inlet, a reflux condenser, and a mechanical stirrer. At room temperature, a gaseous mixture (2 : 1) of nitrogen and carbon dioxide (30.2 l carbon dioxide from Dry Ice, dried by leading the gas through a tube filled with a mixture of calcium chloride and phosphorus pentoxide) is introduced above the surface of the rapidly stirred solution during 3 h. Then, the supernatant solution is decanted; to the white, solid residue, water (150 ml) is added dropwise, followed by 4 normal hydrochloric acid (250 ml). The mixture was extracted with pentane (400 ml) by continuous extraction (14 h); G.L.C. analysis (Carbowax 20 M, isothermal, 90 °C) of the pentane solution and comparison with authentic samples reveal the presence of **5** (41%), and cyclobutanol (2%); according to ^{1}H-N.M.R. spectroscopy, glutaric acid (17%) is also present. The pentane solution is subjected to distillation on a spinning band column (0.65 m) at normal pressure; after removal of the pentane, cyclobutanone (**5**) is obtained by vacuum distillation; yield: 9.7 g (13% relative to **1**); b.p. 44 °C/140 mbar; purity $\geq$98% by G.L.C. as above and ^{1}H-N.M.R. spectroscopy[8].

^{1}H-N.M.R. ($CDCl_3$/TMS, 90 MHz): $\delta = 1.93$ (m, 2 H); 3.02 ppm (m, 4 H).

Received: April 18, 1983

---

[1] B. M. Trost, W. C. Vladuchick, *Synthesis* **1978,** 821, and references cited.

[2] D. van Leusen, A. M. van Leusen, *Synthesis* **1980,** 325.

[3] M. Krumpolc, J. Rocek, *Org. Synth.* **60,** 20 (1981), and references cited.

[4] J. W. F. L. Seetz, F. A. Hartog, H. P. Böhm, C. Blomberg, O. S. Akkerman, F. Bickelhaupt, *Tetrahedron Lett.* **23,** 1497 (1982).

[5] V. Grignard, G. Vignon, *Compt. rend.* **144,** 1358 (1907).
J. von Braun, W. Sobecki, *Ber. Dtsch. Chem. Ges.* **44,** 1918 (1911).

[6] K. Nützel in Houben-Weyl: *Methoden der Organischen Chemie*, 4th Edn., E. Müller, Ed., Vol. XIII/2a, Georg Thieme Verlag, Stuttgart, 1973, p. 247, 251.

[7] J. W. F. L. Seetz, *Thesis*, Amsterdam, 1983.

[8] B. Braillon, *J. Mol. Spectrosc.* **27,** 313 (1968).