Preparative-Scale Syntheses of Bicyclobutylidene, Methylenecyclobutane and Cyclobutanone

Lutz Fitjer,* Ulrike Quabeck

Institut für Organische Chemie der Universität Göttingen,
Tammannstraße 2, D-3400 Göttingen, West Germany

One-pot syntheses of bicyclobutylidene (**3**) and methylenecyclobutane (**4**) are described. Both **3** and **4** are valuable precursors of cyclobutanone (**5**).

In connection with studies directed toward the synthesis of triquinanes by rearrangement routes,[1] we needed large quantities of bicyclobutylidene (**3**). The known syntheses of **3**[2,3] are all based on methylenecyclobutane (**4**)[4] or cyclobutanone (**5**)[5] and are thus hampered by the fact that both compounds are not easily prepared. We therefore thought it valuable (a) to apply the known[6] ylide autoxidation to cyclobutylidenetriphenylphosphorane (**2**) in order to obtain direct access to **5** and/or **3**, and (b) to react the same phosphorane **2** with formaldehyde in order to shorten the synthesis of **4**.[4]

Treatment of the readily available 4-bromobutyltriphenylphosphonium bromide (**1**)[7] with two equivalents of potassium *t*-butoxide in benzene followed by autoxidation of the resulting phosphorane **2** with molecular oxygen resulted in an efficient formation of cyclobutanone (**5**) and its trapping with unreacted **2**, as evidenced by a 75 % yield of isolated bicyclobutylidene (**3**).[8] Typically, **3** was obtained in batches of 60 g. The cyclobutylidenation of formaldehyde proved equally effective and yielded methylenecyclobutane (**4**) in batches of 70 g.

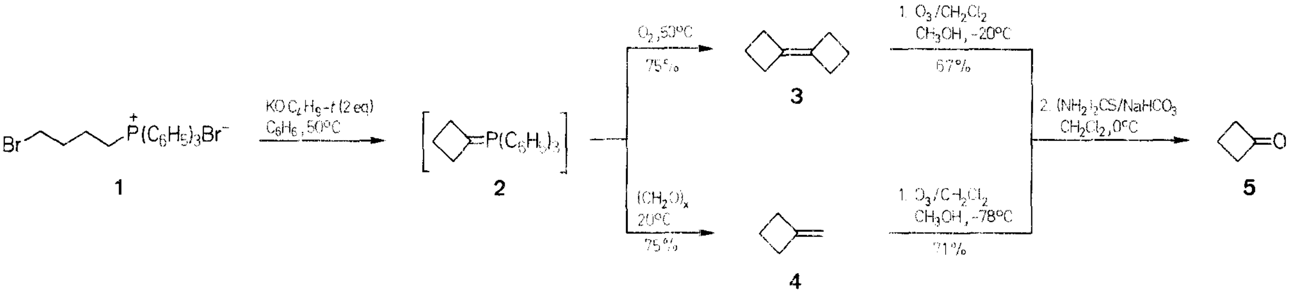
Having large quantities of **3** and **4** at our disposal we investigated their ozonolysis to cyclobutanone (**5**). The best yields of **5** were obtained by ozonolysis in dichloromethane/methanol[10] followed by treatment with thiourea[11] (67% from **3** and 71% from **4**). Less satisfactory results were obtained by ozonolysis of **3** in dichloromethane/methanol and dimethyl sulphide work-up[12] (60 %), and by ozonolysis of **3** in dichloromethane/pyridine and hydrochloric acid work-up (51 %) as described[13] for **4**. For preparative scale work, we recommend the ozonolysis of **3** by the first method described above. Depending on the flow rate of the ozone-oxygen mixture used (1.5% w/w O_3 in O_2), up to 20 g of cyclobutanone (**5**) may be produced within a 6 h period.

In summary, short and efficient syntheses of bicyclobutylidene (**3**), methylenecyclobutane (**4**) and cyclobutanone (**5**) have been described, which compare favourably with published procedures.[2-5] If no ozonisator is available, methylenecyclobutane (**4**) may be transformed to cyclobutanone (**5**) by the two-step procedure of Roberts.[4]

Reagents. 4-Bromobutyltriphenylphosphonium bromide (**1**)[7] is prepared by heating triphenylphosphine (1049 g, 4.00 mol) and 1,4-dibromobutane (864 g, 4.00 mol) in dry xylene (1.5 l of a mixture of isomers) for 12 h at reflux. The crude material (95 % yield) is washed with ether and dried at 100°C/8 torr prior to use. Benzene and dichloromethane are refluxed over sodium wire and calcium chloride, respectively, and distilled. Commercial grade (Merck) potassium *t*-butoxide and paraformaldehyde are used. Paraformaldehyde is dried over phosphorus pentoxide for 48 h at 8 torr prior to use.

Bicyclobutylidene (3):

To a vigorously stirred suspension of 4-bromobutyltriphenylposphonium bromide (**1**) (717 g, 1.50 mol) in dry benzene (1.50 l) under nitrogen are added three portions of potassium *t*-butoxide (3 × 112 g, 3.00 mol) in 15 min intervals, and the mixture is then heated to 50°C. After 3 h the heating is stopped, and a stream of oxygen is passed over the surface of the still warm and vigorously stirred suspension, causing an exothermic reaction and a gentle to strong reflux. After 30–45 min



the exothermic reaction has subsided and the colour has changed from the original brown-red to pale yellow. Water (75 ml) is added, the organic layer decanted, the heterogeneous residue extracted with pentane (3 × 150 ml), and combined organic layers concentrated through a 60 cm Vigreux column equipped with a variable take-off head (bath temperature up to 125°C). The residue is distilled to dryness (bath temperature 180°C/20 torr), and the distillate redistilled through a 40 cm Vigreux column and then through a microdistillation apparatus to give **3** as a colourless liquid; yield: 60.9 g (75%); b.p. 145–148°C (Lit.[3], b.p. 85°C/100 torr).

According to GLC (25 m × 0.25 mm fused silica capillary column coated with SE 52) **3** is 94% pure and contains 2% of xylenes (which originate from the preparation of **1** and may be avoided) and 4% of an unknown impurity. ^{1}H-NMR and ^{13}C-NMR data are in accord with literature data.[3,14]

Methylenecyclobutane (4):

Phosphorane **2** is prepared from **1** (717 g, 1.50 mol) and potassium *t*-butoxide (3 × 112 g, 3.00 mol) in dry benzene (1.50 l) as described for **3**. The brown-red suspension is cooled with an ice bath and paraformaldehyde (5 × 8.41 g, corresponding to 1.40 moles of formaldehyde) is added with stirring under nitrogen in five portions such that the reaction temperature does not exceed 20°C. Thereafter the mixture is distilled through an efficient condensor into an ice-cooled trap until the head temperature reaches 78°C. The distillate is fractionated twice through an efficient Vigreux column equipped with a variable take-off head to give **4** as a colourless liquid; yield: 71.5 g (75%); b.p. 39–42°C (Lit.[4], b.p. 41.5–42°C).

According to GLC (3 m × 1/4" all glass system, 15% SE 30 on chromosorb W AW/DMCS 60/80 mesh, 30°C) **4** is 95% pure and contains methyl formate (2%) and *t*-butanol (2%) as the main impurities. ^{1}H-NMR and ^{13}C-NMR data are in accord with literature data.[15,16]

Cyclobutanone (5):

Ozonolysis of 3: An ozone-oxygen mixture (1.5% w/w O_3 in O_2) is bubbled through a solution of **3** (21.9 g, 94%, 0.19 mol) in anhydrous dichloromethane/methanol (200 ml, 5:1 v/v) with addition of sodium hydrogencarbonate (5 g) at −20°C. According to GLC (3 m × 1/4" all glass system, 15% OV 101 on chromosorb W AW/DMCS 60/80 mesh, 70–110°C) **3** is completely consumed within 5 h. Excess ozone is displaced by nitrogen, and then the still cold solution is transferred *via* a Teflon cannula into a well stirred suspension of thiourea (7.6 g, 0.10 mol) and sodium hydrogencarbonate (5 g) in anhydrous dichloromethane (30 ml) precooled to 0°C such that the temperature did not exceed 10°C (15 min). Stirring is continued for 1 h at 0°C; the mixture is then filtered and immediately extracted with a saturated solution of sodium hydrogencarbonate (2 × 40 ml). The aqueous phases are combined and extracted with dichloromethane (5 × 20 ml). The combined organic phases are dried over 4 A molecular sieves, and then most of the solvent is distilled through a 40 cm Vigreux column equipped with a variable take-off head. The residue is distilled to dryness (bath temperature 120°C/20 torr) and redistilled through a 20 cm Vigreux column to give **5** as a colourless liquid; yield: 17.7 g (67%); b.p. 99–100°C (Lit.[4], b.p. 98–100°C).

According to GLC **5** is 97% pure. ^{1}H-NMR and ^{13}C-NMR data are in accord with literature data.[17,18]

Ozonolysis of 4: An ozone-oxygen mixture (1.5% w/w O_3 in O_2) is bubbled through a solution of **4** (14.3 g, 95%, 0.20 mol) in anhydrous dichloromethane/methanol (200 ml, 5:1 v/v), containing sodium hydrogencarbonate (5 g), at −78°C until the solution turned deep blue (6 h). Work-up as described above gives **5** in 97% purity (GLC); yield: 10.0 g (71%).

Caution: To prevent ketalization of the cyclobutanone formed, it is essential that all operations, including drying and distillation, are carried out in the presence of sodium hydrogencarbonate.

Financial support of the Deutsche Forschungsgemeinschaft (project Fi 191/8–1) and the Fonds der Chemischen Industrie is gratefully acknowledged.

Received: 23 September 1986

(1) Fitjer, L., Kanschik, A., Majewski, M. *Tetrahedron Lett.* **1985**, *26*, 5277.
Fitjer, L., Majewski, M., Kanschik, A., Egert, E., Sheldrick, G.M. *Tetrahedron Lett.* **1986**, *27*, 3603.
(2) Synthesis based on methylenecyclobutane: Popov, A.M., Fridman, R.A., Finkel'shtein, E.Sh., Nametkin, N.S., Vdovin, V.M., Bashkirov, A.N., Kryukov, Yu.B., Liberov, L.G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1973**, 1429; *C. A.* **1973**, *79*, 91638.
(3) Syntheses based on cyclobutanone:
Everett, J.W., Garrat, P.J. *J. Chem. Soc. Chem. Commun.* **1972**, 642.
Krapcho, A.P., Jahngen, E.G.E., Jr. *J. Org. Chem.* **1974**, *39*, 1650.
Bee, L.K., Beeby, J., Everett, J.W., Garrat, P.J. *J. Org. Chem.* **1975**, *40*, 2212.
(4) Roberts, J.D., Sauer, C.W. *J. Am. Chem. Soc.* **1949**, *71*, 3925.
(5) Trost, B.M., Vladuchik, W.C. *Synthesis* **1978**, 821, and references cited therein.
Van Leusen, D., van Leusen, A.M. *Synthesis* **1980**, 325.
Seetz, J.W.F.L., Tol, R., Akkerman, O.S., Bickelhaupt, F. *Synthesis* **1983**, 721.
Krumpolc, M., Rocek, *Org. Synth.* **1981**, *60*, 20, and references cited therein.
(6) Bestmann, H.J., Kratzer, O. *Chem. Ber.* **1963**, *96*, 1899.
(7) Mondon, A. *Justus Liebigs Ann. Chem.* **1957**, 115.
(8) An attempt to slow down the Wittig reaction as compared to the autoxidation by use of phenyllithium instead of potassium *t*-butoxide[9] while lowering the temperature to −10°C resulted in the survival of less than 10% of the cyclobutanone formed and was not further pursued.
(9) Potassium *t*-butoxide generates more reactive ylides than phenyllithium: Fitjer, L., Quabeck, U. *Synth. Commun.* **1985**, *15*, 855.
(10) Schreiber, S.L., Claus, R.E., Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.
(11) Gupta, D., Soman, R., Dev, S. *Tetrahedron* **1982**, *38*, 3013.
(12) Pappas, J.J., Keaveney, W.P., Gancher, E., Berger, M. *Tetrahedron Lett.* **1966**, *7*, 4273.
(13) Conia, J.M., Leriverend, P., Ripoli, J.L. *Bull. Soc. Chim. Fr.* **1961**, 1803.
For a recent investigation of the mechanism of the ozonolysis of **4** see: van Velzen, J.C., van Tunen, W.C.J., de Boer, Th.J. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 225.
(14) Knothe, L., Werp, J., Babsch, H., Prinzbach, H., Fritz, H. *Justus Liebigs Ann. Chem.* **1977**, 709.
(15) Bhacca, N.S., Johnson, L.F., Shoolery, J.N. *NMR Spectra Catalog*, Varian Associates, Palo Alto, 1962, No. 109.
(16) Thummel, R.P., Nutakul, W. *J. Org. Chem.* **1978**, *43*, 3170.
(17) Pouchert, C.J., Campbell, J.R. *The Aldrich Library of NMR Spectra*, Vol. 2, Aldrich Chemical Company, Milwaukee, 1974, 125 B.
(18) Pretsch, E., Seibl, J., Simon, W. *Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Methoden*, 2nd ed., Springer Verlag, Berlin, 1981, p. C175.