

Short Communication

A New and Simple Synthesis of Cyclonon-2-ynone

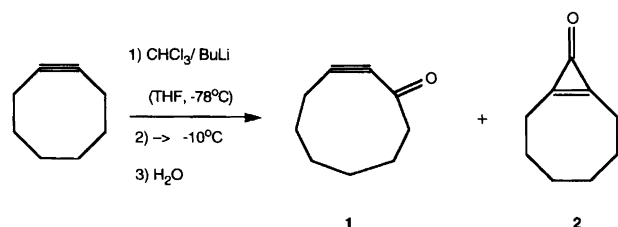
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Dedicated to Professor Lars Skattebøl on the occasion of his 70th birthday

Recently Gleiter and Merger reported the synthesis of cyclonon-2-ynone (**1**), the smallest cyclic 2-ynone stable at ambient temperature.¹ By addition of a hexane solution of butyllithium to a mixture of cyclooctyne and chloroform in tetrahydrofuran kept at -78°C , **1** and bicyclo[6.1.0]non-1(8)-en-9-one (**2**) were obtained in a 2:1 ratio in 50% total yield.¹ Chromatographic separation on neutral alumina afforded **1** in 33% yield.

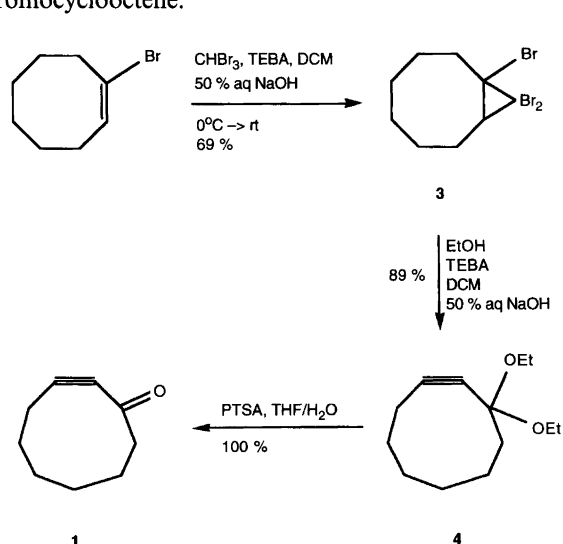


An alternative synthesis of **1** can be envisaged on the basis of the observation that 1,1,2-trihalocyclopropanes undergo ring opening and furnish acetylenic ketals in good yields when treated with 50% aqueous sodium hydroxide in the presence of ethanol, dichloromethane and triethylbenzylammonium chloride (phase-transfer conditions = PTC).² Applying this transformation to 1,9,9-tribromobicyclo[6.1.0]nonane (**3**) the likely product will be cyclonon-2-ynone diethyl ketal (**4**), which should give **1** upon deketalization.

Application of this strategy turned out to be a success. Cyclopropane **3** was obtained as colourless crystals in 69% yield when 1-bromocyclooctene^{3,4} reacted with dibromocarbene as described by Makosza and Wawrzyniewicz.^{2,5} Subsequent exposure of **3** to PTC gave ketal **4** which was isolated as a colourless oil in 89% yield by flash chromatography on silica gel; no allene was detected. The final step was deketalization of

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4 to cyclonon-2-ynone, which proved to be a minor challenge. Several of the standard conditions employed to perform such reactions⁶ gave complex mixtures and only minor amounts of **1** at best. However, when **4** was stirred in a 1:1 mixture of tetrahydrofuran and water containing a small amount of *p*-toluenesulfonic acid essentially pure **1** was obtained in quantitative yield. Thus, **1** is obtained in 61% total isolated yield from 1-bromocyclooctene.



The strategy outlined above is currently being used to prepare other α,β -unsaturated ynones.

Experimental

General. IR spectra were recorded on a Perkin-Elmer 1310 infrared spectrophotometer. NMR spectra were run on a Bruker Spectrospin 400 (400 MHz for ^1H) or a Bruker Spectrospin AC 200 F spectrometer (200 MHz

for ^1H and 50 MHz for ^{13}C) with CDCl_3 as the solvent and tetramethylsilane (TMS) as an internal reference. Chemical shifts are reported in ppm downfield from TMS. GC analyses were performed on a Hewlett Packard 5720 A gas chromatograph equipped with FID and a 15% SP2100 fused silica column. TLC analysis of the reaction mixtures was carried out with silica gel (60 F₂₅₄) on aluminium sheets (Merck 5554) with hexane or hexane–EtOAc as the solvent. Flash chromatography was carried out on a column (2 cm \times 70 cm) with silica gel (Merck 9385) with hexane–EtOAc as the solvent. The melting point was determined on a Gallenkamp apparatus and is uncorrected.

1,9,9-Tribromobicyclo[6.1.0]nonane (3). To a vigorously stirred solution of 1-bromocyclooctene⁴ (18.9 g, 0.10 mol), bromoform (ethanol free) (50.6 g, 0.20 mol), triethylbenzylammonium chloride (TEBA, ca. 0.2 g) and dichloromethane (DCM) (15 ml), kept at 0 °C, a 50% aqueous solution of NaOH (24.0 g, 0.30 mol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h and after that at RT overnight. Water (150 ml) was added followed by hydrochloric acid (6 M) until acidic reaction. The product was extracted with DCM (4 \times 75 ml) and the combined extracts were dried (MgSO_4). Filtration and evaporation of the solvent left a residue, from which excess bromoform and a small amount of unchanged starting material were removed by distillation under vacuum (20 Torr). The product was isolated by flash chromatography (hexane) and subsequently recrystallized from hexane to give colourless crystals; m.p. 41–43 °C; yield: 24.9 g (69%). IR (CHCl_3): 2920 (s), 2840 (s), 1455 (s), 1440 (s), 1360 (w), 1240 (w), 1200 (w), 1140 (m), 1090 (w), 1060 (w), 1020 (w), 895 (m), 870 (w), 830 (m) cm^{-1} ; ^1H NMR (400 MHz): δ 1.14–1.41 (2 H, m), 1.45–1.95 (9 H, m), 2.01–2.13 (1 H, m), 2.18–2.32 (1 H, m); ^{13}C NMR (50 MHz): δ 25.3 (CH_2), 25.6 (CH_2), 26.9 (CH_2), 27.0 (CH_2), 27.9 (CH_2), 34.9 (CH_2), 41.3 (CBr_2), 43.5 (CH), 49.4 (CBr). Anal. $\text{C}_9\text{H}_{13}\text{Br}_3$: C, H.

Cyclonon-2-ynone diethyl ketal (4). To a vigorously stirred solution of 1,9,9-tribromobicyclo[6.1.0]nonane (9.02 g, 25 mmol), ethanol (4.61 g, 100 mmol), triethylbenzylammonium chloride (TEBA, ca. 0.2 g) and DCM (50 ml), kept at RT, a 50% aqueous solution of NaOH (16 g of the solution, 8.0 g NaOH, 0.20 mol) was added dropwise. The resulting mixture was stirred at RT until all of the starting material had been consumed as shown by GC and TLC (hexane–EtOAc 90:10) analyses. Water

(100 ml) was added, the product was extracted with Et_2O (5 \times 50 ml), and the combined extracts were dried (MgSO_4). Filtration and evaporation of the solvent left a residue, from which the product was isolated as a colourless oil by flash chromatography (hexane–EtOAc 97.5:2.5); yield: 4.7 g (89%). IR (film): 2920 (s), 2895 (s), 2195 (m), 1690 (w), 1655 (w), 1445 (s), 1370 (m), 1300 (m), 1250 (m), 1110 (s), 1035 (s), 985 (s), 960 (s), 870 (w), 720 (w) cm^{-1} ; ^1H NMR (200 MHz): δ 1.20 (6 H, t, J 4 Hz), 1.44–1.80 (8 H, m), 1.91–1.98 (2 H, m), 2.15–2.25 (2 H, m), 3.35–3.75 (4 H, m); ^{13}C NMR (50 MHz): δ 14.9 (2 \times CH_3), 18.8 (CH_2), 21.0 (CH_2), 24.7 (CH_2), 26.1 (CH_2), 29.4 (CH_2), 38.2 (CH_2), 57.8 (OCH_2), 84.2 (C), 93.2 (C), 101.0 [$\text{C}(\text{OEt})_2$].

Cyclonon-2-ynone (1). To a vigorously stirred solution of cyclonon-2-ynone diethyl ketal (1.05 g, 5 mmol) in a 1:1 mixture of THF– H_2O (50 ml), *p*-toluenesulfonic acid (100 mg) was added. The resulting mixture was stirred at RT, and the reaction was monitored by TLC (hexane–EtOAc 90:10), which showed that all starting material had been consumed after 1 h. Water (50 ml) was added, the product was extracted with Et_2O (5 \times 50 ml), and the combined extracts were dried (MgSO_4). Filtration and evaporation of the solvent left a residue of essentially pure cyclonon-2-ynone as a colourless oil; yield: 0.68 g (100%). The product gave IR and ^{13}C NMR (CDCl_3) spectra identical with those reported in the literature.¹ The ^1H NMR spectrum using CDCl_3 as the solvent differed from that obtained from a C_6D_6 solution of **1**.¹ ^1H NMR (200 MHz): δ 1.63–2.06 (8 H, m), 2.33–2.45 (2 H, m), 2.45–2.55 (2 H, m).

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