Practical Preparation of Cyclopropenone 1,3-Propanediol Ketal

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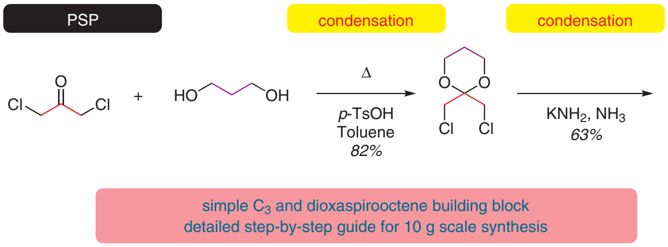

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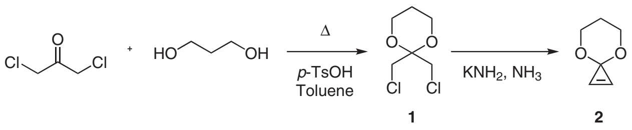
Abstract Cyclopropenone 1,3-propanediol ketal is an increasingly versatile building block for the introduction of various C_3 and dioxaspiro units due to the emergence of numerous methodologies for the application of strained hydrocarbons. This Practical Synthetic Procedure gives an updated synthesis for a basic ketal of cyclopropenone with lowered solvent toxicity and a detailed step-by-step guide for the safe production of potassium amide in liquid ammonia and for its application in the synthesis of the cyclopropene ring.

Key words acetals, bicyclic compounds, carbocycles, condensation, cyclization, elimination, ring closure

Early synthetic procedures for higher boiling ketals of cyclopropenone employ a stepwise procedure from ketals of 1-bromo-3-chloroacetone.[2] Potassium amide was used therein to generate the cyclopropene ring on the preformed ketal. Not long thereafter, in an article focusing on neopentyl glycol ketals, it was reported that the use of 1-bromo-3-chloroacetone is unnecessary.[3] 1,3-Dichloroacetone is obtained in the chemical industry by direct chlorination of acetone, together with monochloroacetone, 1,1-dichloroacetone, and higher chlorinated acetone derivatives such as 1,1,3-trichloroacetone.[4] On a molar basis, 1,3-dichloroacetone is 125 times less expensive as a reactant than 1 mole of 1-bromo-3-chloro-2,2-dimethoxypropane. For these reasons, we have established an updated procedure that avoids the use of the solvent carcinogen benzene without losses in performance in the Dean–Stark condensation to produce the ketal 2,2-bis(chloromethyl)-1,3-dioxane (**1**) in increased yield (79–84%). The dichloroacetone ketal can be easily purified by recrystallization from diethyl ether. We demonstrate a very inexpensive way to synthesize cyclopropenone 1,3-propanediol ketal (**2**, 54–71% yield) from **1** with freshly prepared potassium amide and deliver an easily reproducible step-by-step guide for this endeavour (Scheme 1).



Scheme 1 Updated synthetic route for cyclopropenone 1,3-propanediol ketal (**2**)

Due to aromatic stabilization via the zwitterionic mesomeric structure, cyclopropenones are surprisingly stable. Without further functionalization, they are, however, low-boiling and thus inconvenient for synthetic procedures. Their high-boiling ketal surrogates have attracted synthetic attention for their use as building blocks and for their appearance in natural products.

Cyclopropenone 1,3-propanediol ketal (**2**) is a versatile building block that has seen various applications in recent years due to ring-strain-release reactions emerging to become standard synthetic tools in preparative chemistry (Scheme 2). The π-system can be employed to induce cationic ring-opening analogues to the thermal generation of vinyl carbenes that cyclopropenes can undergo. This approach has been used to access allyl cationic vinylgold(I) species **3**.[5] Furthermore, the strain-induced CH acidity of the vinylic protons in cyclopropenone 1,3-propanediol ketal can be used to lithiate these positions with lithium diisopropylamide (LDA) granting access to a variety of functionalizations, as exemplary shown in the 1-aurated cyclopropenone complexes **4**.[6] These examples showcase the liberation of the cyclopropenone 3-oxo domain by hydrolysis of the ketal. Complexes **4** can also undergo cationic ring-opening reactions with gold(I) complexes.[7]

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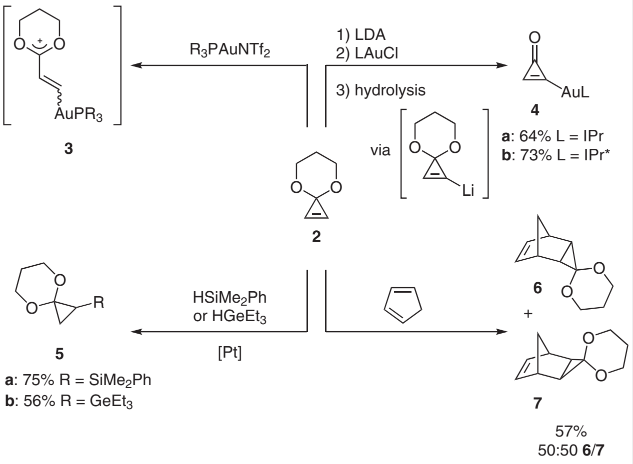

Scheme 2 Reaction with cationic gold complexes (**3**), substitution at a lithiated center (**4**), hydrometalation (**5**), and Diels–Alder reaction (**6**, **7**)

Group 10 metals can even be employed to catalyze reactions on cyclopropenone ketals, without decomposing the ring system. With $PtCl_2$, for example, hydrosilylation and hydrogermanation reactions give **5a** in 75% yield and **5b** in 56% yield, respectively.[8] Cyclopropenone ketals can also be employed in Diels–Alder reactions, to give a large variety of products, for example **6** and **7**.[9] The application of these reactions and, even more so, achieving a comprehensive understanding of them have not ceased to attract further investigation.[10]

1,3-Dichloroacetone (purity ≥95%) was purchased from Sigma-Aldrich. The brownish-gray solid was purified by dissolving it (50.0 g, 394 mmol) in dichloromethane (500 mL) and filtering the solution over Celite (50.0 g) on a porosity 3 glass filter frit. A black residue remained on the filter. Removal of the solvent under reduced pressure at 40 °C utilizing a rotary evaporator gave the colorless solid (48.0 g, 378 mmol, 96%). The following materials were employed as purchased from Sigma-Aldrich. Potassium in mineral oil: trace metals basis ≥98%, 1,3-propanediol: ≥98%, *p*-toluenesulfonic acid monohydrate: ≥98%, iron(III) chloride: ≥97%. The following materials were employed as purchased from Riedel-de Haën: toluene: ≥99.5%, diethyl ether: ≥99.5%, acetone: ≥99.5%, ammonium chloride: ≥99.5%. NMR spectra were recorded on a Bruker Avance III 300 spectrometer. FT-IR spectra were recorded on a Bruker Vector 22 FT-IR spectrophotometer with an ATR unit. Elemental analyses were performed on a vario MICRO cube analyzer.

2,2-Bis(chloryomethyl)-1,3-dioxane (1)

[CAS Reg. No. 69245-14-3]

The experimental setup is shown in Figure 1.

A 100 mL, one-necked, round-bottomed flask with a magnetic stirring bar (cylindric shape, 15 × 6 mm, PTFE covered) was charged with 1,3-dichloroacetone (25.0 g, 197 mmol, 1.00 equiv), toluene (50 mL), 1,3-propanediol (16.5 g, 217 mmol, 1.10 equiv), and *p*-toluenesulfonic acid monohydrate (749 mg, 3.94 mmol, 2.0 mol%). The flask was equipped with a 10 mL Dean–Stark apparatus and a condenser. The resulting solution was stirred and heated (bath temperature 150 °C) for 24 h.

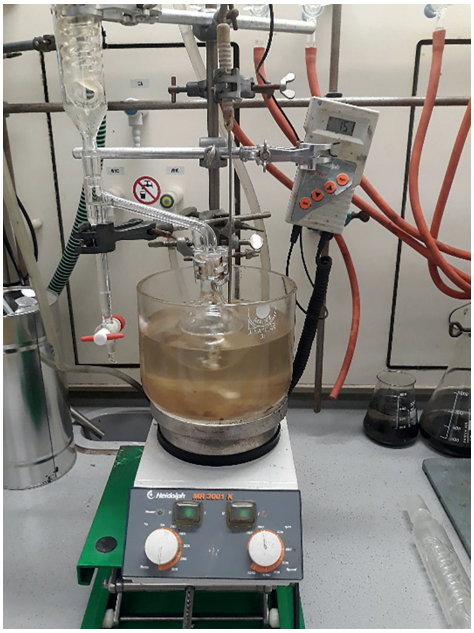

Figure 1 Experimental setup for the synthesis of 2,2-bis(chloromethyl)-1,3-dioxane (**1**)

The boiling point significantly rises over the course of the reaction. Lower temperatures do not ensure vigorous boiling until full conversion is reached. The reaction can be easily followed by observing the volume of the formed water in the Dean–Stark apparatus (3.62 mL of reaction water are expected).

The solution was allowed to cool to room temperature and the volatiles were removed under reduced pressure at 40 °C utilizing a rotary evaporator. The pressure was gradually reduced, until no further solvent was collected for 15 min at 15 mbar. The crude product was transferred to a 250 mL, one-necked, round-bottomed flask. The material was dissolved in diethyl ether (150 mL) at 40 °C and recrystallized by cooling to –21 °C for 24 h in a freezer. The mother liquor was collected in another 250 mL, one-necked, round-bottomed flask by decantation and recrystallized from diethyl ether (80 mL) following the same procedure as above. The crystals were combined in one of the two flasks. 2,2-Bis(chloromethyl)-1,3-dioxane was obtained as a colorless solid; yield: 28.8–30.6 g (79–84%).

Quantitative ^{1}H NMR purity (300 MHz, $CDCl_3$, *p*-dinitrobenzene): >99%.

IR (ATR): 2990, 2967, 2939, 2896, 2851, 1748, 1541, 1472, 1435, 1427, 1380, 1330, 1302, 1258, 1246, 1216, 1158, 1129, 1100, 1047, 1027, 950, 933, 889, 859, 821, 779, 762, 729, 650 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.96 (t, J = 1.78 Hz, 4 H, OCH_2), 3.79 (s, 4 H, $ClCH_2$), 1.79 (quin, J = 1.78 Hz, 2 H, $(CH_2)_2CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 97.7 (s, 1 C, O_2C), 60.7 (t, 2 C, OCH_2), 42.3 (t, 2 C, $ClCH_2$), 24.6 (t, 1 C, $(CH_2)_2CH_2$).

Anal. Calcd for $C_6H_{10}Cl_2O_2$: C, 38.95; H, 5.45; Cl, 38.32; O, 17.29. Found: C, 38.94; H, 5.43.

Analytical data match the literature.[3a]

Cyclopropenone 1,3-Propanediol Ketal (2)

[CAS Reg. No. 60935-21-9]

SAFETY: 1) We strongly encourage the use of an additional safety shield and full face, hand, arm, and body protection during work with liquid ammonia. While ignition or spontaneous evaporation of ammonia are not expected under the operating conditions, such risks can never fully be eliminated when working with condensed flammable gases. 2) Acetone will ignite on contact with potassium. Special care is advised.

The experimental setup is shown in Figure 2.

A 1000 mL, four-necked, round-bottomed flask (with a 400 mL filling height of the flask marked prior to the experiment) was equipped with a Quickfit joint with a low-temperature thermometer, a gas inlet connected to ammonia, an empty acetone–dry ice condenser, an empty 500 mL pressure-equalizing dropping funnel, and a magnetic stirring bar (dumbbell shape, 35 × 8 mm, PTFE covered). The procedure was most effective with the gas inlet tube pointing at the cooled flask surface. Alternatively, we also carried out the condensation by utilizing a septum and a cannula to connect the ammonia stream, and observed the same result. The top of the dropping funnel was equipped with a gas inlet connected to nitrogen. The outlet of the condenser was connected to a gas bubbler leading to the back of the fume hood through a wash bottle filled with potassium hydroxide pellets. The flask was purged with nitrogen for 30 min before the acetone–dry ice condenser was charged. The flask was cooled with an acetone–dry ice bath (–78 °C) and a low stream of dry ammonia was opened. Commercial dry ammonia (Air Liquide) was used (anhydrous, ≥99.98%) without further purification. The nitrogen stream was set to a very low stream. Nitrogen and ammonia can be switched off to check the corresponding gas streams with the gas bubbler. Ca. 400 mL of dry ammonia was condensed, measured by the filling height marking. The ammonia gas flow was switched off and a slow flow of nitrogen was switched on. The ammonia inlet was removed to charge the flask with pieces of potassium and with catalytic amounts of iron(III) chloride to catalyze the reduction of ammonia by potassium under hydrogen evolution. (ATTENTION: Acetone will ignite on contact with potassium. Special care is advised in the next step.) A piece of potassium (0.5 g) was added under vigorous stirring, and the solution turned dark blue. (Note: Potassium was employed due to potassium amide having 10^3 times better solubility in liquid ammonia over sodium amide, potentially avoiding stirring problems.) The neck was closed with a stopper in between addition steps. Iron(III) chloride (110 mg, 678 μmol, 0.5 mol%) was added, and the solution turned dark gray. The cooling bath was removed from the fume hood, replaced with a glass bowl, and the mixture was allowed to warm to reflux (ca. –33 °C). Over 30 min, the remainder of the potassium metal (total of 15.3 g, 391 mmol, 2.90 equiv) was added in 0.5 g pieces. After every piece, the solution turned dark blue for about 5 min.

A separate 250 mL, two-necked, round-bottomed flask was charged with 2,2-bis(chloromethyl)-1,3-dioxane (**1**; 25.0 g, 135 mmol, 1.00 equiv). The flask was then purged through a gas inlet with nitrogen for 30 min prior to the addition of anhydrous diethyl ether (200 mL) to dissolve the solid. The 500 mL dropping funnel on the 1000 mL flask was charged with the solution through a glass funnel. 20–30 min after the addition of potassium and iron(III) chloride, a dark gray suspension was observed. The acetone–dry ice cooling bath was allowed to warm and was then set to –50 °C by adding a sufficient amount of dry ice. The cooling bath was then placed under the flask again, replacing the glass bowl. The solution of 2,2-bis(chloromethyl)-1,3-dioxane was added to the freshly generated solution of potassium amide over 15 min while the bath temperature was maintained at –50 °C. The reaction mixture was stirred at –50 to –60 °C for 3 h. The solution turned olive over this period. Afterwards, the stopper was removed and ammonium chloride (30.0 g, 561 mmol, 4.16 equiv) was added with a spatula over 30 min. The dropping funnel was replaced with a new, clean, 500 mL scaled dropping funnel charged with anhydrous diethyl ether (350 mL) and the cooling bath was removed. The stopper on the 1000 mL flask was replaced with an internal thermometer. The condenser was not charged with dry ice anymore and the ammonia was allowed to evaporate overnight (8 h), while its volume was replaced with diethyl ether, maintaining a slow flow from the dropping funnel. The flow was observed for 10–15 min and adjusted with the scale of the dropping funnel to achieve a flow that would empty the 350 mL of diethyl ether within 90 min (~4 mL/min).

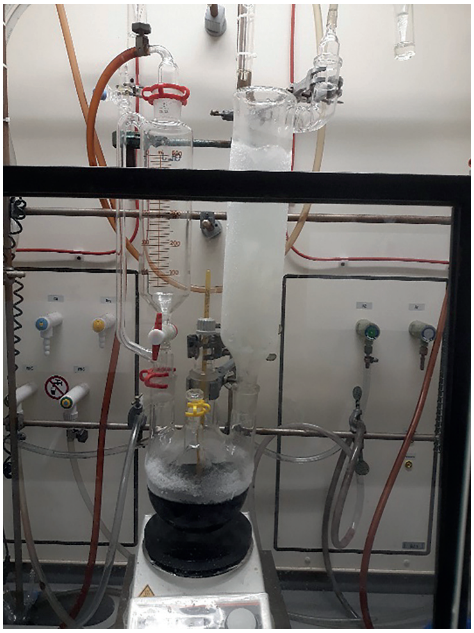

Figure 2 Experimental setup for the synthesis of cyclopropenone 1,3-propanediol ketal (**2**), after removal of the cooling bath (note the recommended safety shield).

The internal thermometer was used to monitor the reaction until it reached room temperature, before the reaction was left alone for the remaining time. The resulting brown suspension was filtered over a coarse glass frit (porosity 1) by suction. The inorganic remains on the filter were then washed with anhydrous diethyl ether (3 × 25 mL). The combined ethereal filtrate and washes were concentrated with a rotary evaporator under reduced pressure (80–100 mbar, 30 °C) until no more evaporation was visible on the condenser (1 h). The residue was then transferred to a 50 mL, round-bottomed flask with a pipet. Anhydrous diethyl ether (3 × 3 mL) can be used to dissolve the residue for transfer to the 50 mL flask. In this case, the solvent needs to be removed from the 50 mL flask under reduced pressure on a rotary evaporator (same conditions as before) for about 30 min.

The flask was fitted with a short-path distillation head with water-cooling, and the product was distilled (10^{-1} mbar, 30 °C) into 25 mL, one-necked, round-bottomed flask receivers, which were cooled to –78 °C with an acetone–dry ice cooling bath. The flask was exchanged with a clean, new flask when the desired fraction evaporated at >29 °C distillation head temperature. (Note: Careful temperature monitoring is advised. When present, impurities might show boiling points only separated by a few °C in both directions.) Cyclopropenone 1,3-propanediol ketal was obtained as a colorless liquid; yield: 8.2–10.7 g (73.1–96.5 mmol, 54–71%); bp 29–31 °C/10^{-1} mbar. The product is labile towards hydrolysis; storage under argon or nitrogen in a standard freezer is recommended.

Quantitative ^{1}H NMR purity (300 MHz, $CDCl_3$, 1,3,5-trimethoxybenzene): >96%.

IR (ATR): 3120, 3092, 2960, 2926, 2856, 2717, 1836, 1724, 1597, 1473, 1459, 1431, 1366, 1345, 1297, 1271, 1244, 1215, 1172, 1152, 1081, 1021, 960, 927, 906, 862, 733, 694, 648, 612 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (s, 2 H, CH), 4.02 (t, J = 5.5 Hz, 4 H, OCH_2), 1.85 (quin, J = 5.5 Hz, 2 H, $(CH_2)_2CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 125.8 (d, 2 C, CH), 81.3 (s, 1 C, O_2C), 66.5 (t, 2 C, OCH_2), 26.1 (t, 1 C, $(CH_2)_2CH_2$).

Analytical data match the literature.[2,3]

Note: Novel isolation procedures for the viscous and moisture-sensitive product promise to further increase the yield. Decomposition over the course of the careful evaporation of ammonia, rotary evaporation, and distillation cause fluctuations and losses in the isolated yield, alongside adhesion to the distillation apparatus.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690830.

Primary Data

for this article are available online at https://doi.org/10.1055/s-0039-1690830 and can be cited using the following DOI: 10.4125/pd0115th.

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