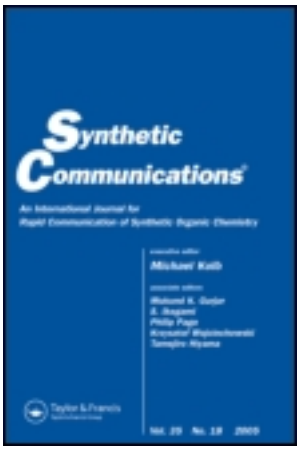

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Synthesis of 1-Bromo-3-butyn-2-one and 1,3-Dibromo-3-buten-2-one

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Abstract: Synthetic procedures for the preparation of 1-bromo-3-butyn-2-one and 1,3-dibromo-3-buten-2-one are given. These compounds are prepared from 2-bromomethyl-2-vinyl-1,3-dioxolane, which can readily be prepared from 2-ethyl-2-methyl-1,3-dioxolane. The synthetic routes are as follows: 2-bromomethyl-2-vinyl-1,3-dioxolane is converted to 2-(1,2-dibromoethyl)-2-bromomethyl-1,3-dioxolane. Double dehydrobromination with ^{t}BuOK affords 2-ethynyl-2-bromomethyl-1,3-dioxolane. Formolysis with formic acid gives 1-bromo-3-butyn-2-one. Deacetalized 2-bromoethyl-2-vinyl-1,3-dioxolane was treated with Br_2 and Li_2CO_3/12-crown-4 in tetrahydrofuran to give 1,3-dibrom-3-buten-2-one in moderate yield.

Keywords: Acetal deprotection, bromination, 2-bromomethyl-2-vinyl-1,3-dioxolane, dehydrobromination, formolysis

INTRODUCTION

1-Bromo-3-butyn-2-one, **5**, and 1,3-dibromo-3-buten-2-one, **9**, contain four functionalized carbons with three electrophilic sites (Fig. 1). The electrophilic sites are of different types and can be selectively attacked

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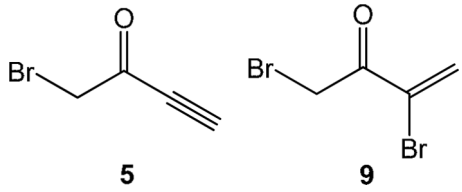

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Figure 1. Target compounds.

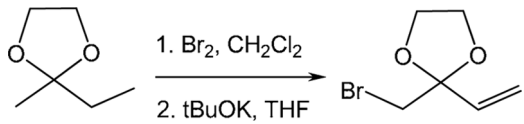
by nuclophiles to give regioselective functionalizations. The order of reactivity between the reactive sites can probably also be altered by adjusting the reactivity of the reagent used. For this reason, they may be highly versatile building blocks, particularly for diversity-oriented synthesis.[4] They may expand the possibilities for the synthesis of several carbocyclic and heterocyclic molecules by one-pot procedures.[1,2] However, the synthetic scope of these compounds remains to be established.

RESULTS AND DISCUSSION

In this article, we present novel procedures under mild and efficient reaction conditions for the syntheses of 1-bromo-3-butyn-2-one and 1,3-dibromo-3-buten-2-one. To the best of our knowledge, a synthetic procedure for 1-bromo-3-butyn-2-one has not previously been reported. 1,3-Dibromo-3-buten-2-one has previously been synthesized by a rather ineffective procedure starting from 2-trimethylsilyloxy-1,3-butadiene.[3] For the syntheses described, the precursor, 2-bromomethyl-2-vinyl-1,3-dioxolane **2**, was prepared from 2-ethyl-2-methyl-1,3-dioxolane **1** (Scheme 1). A procedure for the synthesis of 1-bromo-3-buten-2-one from **2** has been reported by our laboratory.[1,2]

Synthesis of 1-Bromo-3-butyn-2-one

The synthetic route to **5** is shown in Scheme 2. Addition of bromine to **2** is a smooth process and yielded **3** in quantitative amount. Several organic



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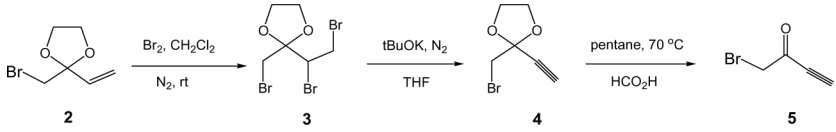
Scheme 1. Synthesis of key precursor.

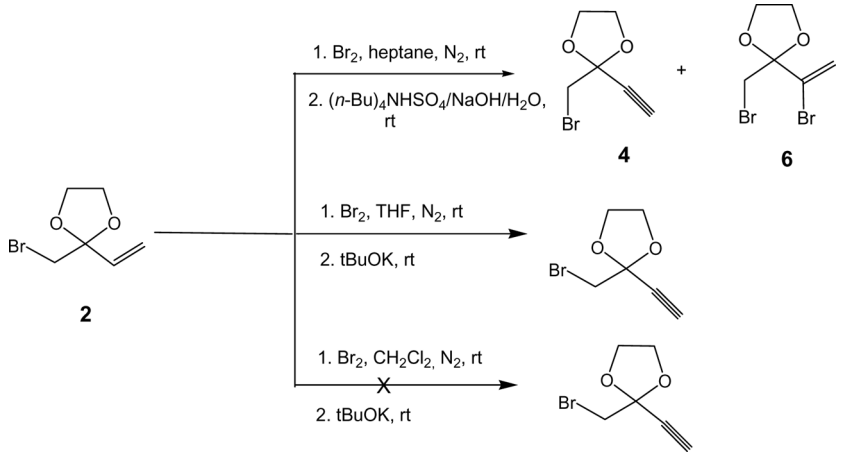


Scheme 2. Synthetic route from key precursor **2** to target **5**.

and inorganic bases and different solvents were examined for the subsequent elimination reaction. The efficiency and rate of dehydrobromination depend strongly on both the nature of the base and the solvent. It was found that ^{t}BuOK in tetrahydrofuran (THF) was the best combination for this transformation.

The dehydrobromination yields finely divided potassium bromide, which caused severe clogging upon attempted filtration through celite, silica, sintered glass filters, or filter paper. This was a known problem, and a method called Zebrazil filtration has been proposed to overcome this problem.[1,2] However, this method is unsuitable for large-scale synthesis. We have developed alternative procedures to remove potassium bromide from the reaction mixture. The most convenient one is to separate the product by steam distillation after evaporation of the solvent. Other methods that can be used, for example, adding dry silica to the reaction mixture, removing the solvent by evaporation, and packing a column with the dry reaction mixture on silica. The product can then be eluted from the column with diethyl ether. Another method involves removing THF by evaporation and adding water to dissolve the potassium bromide. The product can then be extracted with diethyl ether. However, fairly large volumes of water are necessary, and this makes extraction unsuitable for larger scale synthesis.

Cleavage of the acetal protective group in **4** with Lewis and Brønsted acids is a rather slow reaction.[1,4,5] For instance, aqueous boric acid alone did not work at all, but a mixture of aqueous hydrogen bromide and boric acid afforded hydrolysis. Unfortunately, it also gave some hydrogen bromide addition to the triple bond as a side reaction. Attempted transacetalisations[6,7] with a number of carbonyl compounds did not afford the desired product. It is difficult to displace the equilibrium to achieve complete conversion in favor of the deprotected product. Complete deprotection is essential, because separation of the final ketone from the acetal is difficult, both by distillation and by chromatography. We have found that formolysis of the acetal in the presence of pentane is a useful method for the deprotection of the acetal. The reaction mixture is a two-phase system. The bromoketone is dissolved in the pentane layer and thereby protected from the aggressive acid layer. After the reaction is complete, the layers are separated. The bis-formate

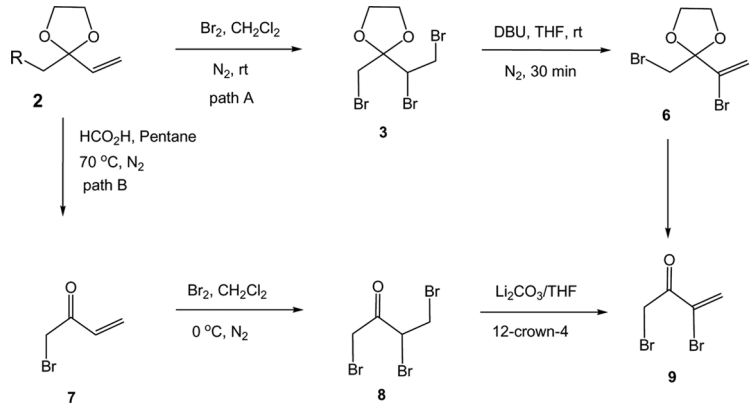


Scheme 3. Possible routes to the intermediary acetal **4**.

esters of diethylene glycol can easily be removed from the pentane layer by washing with water. This procedure totally avoids polymerization of the product during the workup procedure.

Attempts to develop a one-pot synthesis of compound **4** from **2** using different bases and phase-transfer agents such as $(n\text{-Bu})_4\text{NBr}/\text{NaOH}$, $(n\text{-hexyl})_4\text{NBr}/\text{NaOH}$, or $(n\text{-Bu})_4\text{NHSO}_4/\text{NaOH}$ were unsuccessful. For example, when the reaction mixture after the bromination step was treated with $(n\text{-Bu}_4)_2\text{NHSO}_4/\text{NaOH}$, both **4** and **6** were formed. Compound **6** was isolated in pure form only when 1 equivalent of $(n\text{-Bu})_4\text{NHSO}_4/\text{KOH}$ was used. This procedure can therefore be an alternative to the 1,4-diazabicyclo[5.4.0]undec-7-ene (DBU) procedure described below. Use of excess $(n\text{-Bu}_4)_2\text{NHSO}_4$ inevitably gave a mixtures of **4** and **6** (Scheme 3).

We have also attempted a one-pot procedure for the synthesis of **4** using tetrahydrofuran (THF) as solvent and ^{t}BuOK as base (see Scheme 3). Compared with the two-step procedure, the attempted one-pot procedure afforded poor yields of the desired product. THF is obviously an unsuitable solvent for the bromination reaction. In attempts to use CH_2Cl_2 instead of THF, only trace amounts of the expected product were detected. According to our observation, the formation of alkyne compound is favored only when the reaction solvent does not contain acidic protons. Solvents such as dichloromethane and chloroform could generate carbenes in the presence of ^{t}BuOK, and the carbene will immediately attack the target molecule as soon as it is formed.



Scheme 4. Possible routes to target **9**.

Synthesis of 1,3-Dibromo-3-buten-2-one

The attempted routes are summarized in Scheme 4. Compound **6** was obtained as the only product in quantitative amount when **3** was treated with DBU. However, all attempts to remove the acetal protection from **6** by acid hydrolysis were unsuccessful, and only trace amounts of **9** were obtained in attempted formolysis (Scheme 4).

Compound **7** is obtained from **2** by formolysis. When **7** was treated with Br_2 in CH_2Cl_2 at 0°C, **8** was obtained in good yield. Compound **8** was further treated with base in THF to achieve compound **9**. Several bases were tested. Strong bases (DBU, alkoxides, hydroxide) gave a mixture of several side products due to decomposition and Favorskii rearrangement reaction, whereas weak amine bases gave no conversion at all. The desired product could be obtained when compound **8** was treated with Li_2CO_3/12-crown-4/THF and **9** was isolated in moderate yield (31%) after 24 h (Scheme 4). The poor isolated yield was due to polymerization.

EXPERIMENTAL

General

All ^1H and ^{13}C NMR spectra were recorded on a Varian 400 Fourier transform (FT)–NMR system using $CDCl_3$ as a solvent at room temperature. Chemical shifts are given in parts per million (ppm), and *J*-values are given in hertz. Flash chromatography was carried out using matrix

silica (Si-60 A° 35–70 μm). Gas–liquid chromatographic (GLC) analyses were performed on a Varian 3300 chromatograph equipped with split injector, flame ionization detector (FID), and a Varian 4400 integrator. IR spectra were recorded on an FT-IR spectrometer and are reported as wave numbers. Gas chromatography (GC)–mass spectra (MS) were registered on a Hewlettz Packard 5890 series II CP Sil 5 CB column (25 m) followed by VG Quattro mass spectrometer. Finnigan-MAT-95XL mass spectrometer was used to obtain high-resolution electron impact mass spectroscopy (HREIMS) data, and the spectra were obtained at 250°C and 70 eV. All reagents and solvents except compounds **3** were obtained from commercial sources and, with the exception of THF, used as received without further purification. THF was distilled from potassium.

Synthesis of 2-(1,2-Dibromoethyl)-2-bromomethyl-1,3-dioxolane (3)

2-Bromomethyl-2-vinyl-1,3-dioxolane (10.0 mmol, 1.93 g) was dissolved in dichloromethane (5 mL) and placed in a round-bottomed flask equipped with a dropping funnel and a reflux condenser connected to a gas trap via a moisture-protecting $CaCl_2$ tube. Bromine (10.6 mmol, 1.70 g) was also dissolved in dichloromethane (5 mL) and placed in the dropping funnel. At the beginning, a small amount of bromine was added in one portion (the start of reaction was seen by decolorization of the reaction mixture), and then the rest of bromine was added dropwise (60 drops per minute). The temperature of the reaction mixture was maintained between 5 and 15°C throughout the addition of bromine. The reaction mixture remained reddish after all the bromine was added and was stirred at room temperature for 1 h. The solvent was removed on a rotary evaporator to yield 3.35 g (95%) of a dense reddish-brown liquid. This product was sufficiently pure for the next reaction. IR (neat, NaCl plates, ν_{max}, cm^{-1}): 2970, 2895; ^1H NMR: δ 4.50 (dd, 1H, $J = 9.3$, 3.5 Hz), 4.08–4.25 (m, 4H), 3.96 (dd, 1H, $J = 11.2$, 3.5 Hz), 3.85 (d, 1H, $J = 11.4$ Hz), 3.59 (d, 1H, $J = 11.4$ Hz), 3.58 (dd, 1H, $J = 11.2$, 9.3 Hz); ^{13}C NMR: δ 108.5, 67.1, 67.0, 55.5, 34.3, 32.7; HRMS: observed for $C_5H_7Br_2O_2$: 258.8788; calcd.: 258.8792.

Synthesis of 2-Bromomethyl-2-ethynyl-1,3-dioxolane (4)

A flame-dried, 500-mL, two-necked, round-bottomed flask was equipped with a reflux condenser and a magnetic stirring bar and was charged with **3** (10.0 mmol, 3.53 g) dissolved in dry THF (20 mL) at room temperature. The flask was kept under N_2 during the course of the reaction. Potassium

tert-butoxide (23.8 mmol, 2.62 g) was added, in several small portions via an addition funnel made for addition of solids. After all potassium *tert*-butoxide was added, the reaction mixture was stirred at 25°C for 30 min. A sample was taken from the reaction mixture, filtered, and analyzed by GC and NMR spectroscopy. After completion of the reaction, the resulting mixture was allowed to cool to room temperature. The solvent was removed by rotary evaporation. Water (300 mL) was then added to the residual mixture, which was steam distilled. Two layers were obtained in the receiver, and the layers were separated. The aqueous layer was extracted with diethyl ether (3×20 mL). The organic extracts were combined, dried over $MgSO_4$ (25 g), and concentrated by rotary evaporation to yield 1.74 g (91%) of a dark yellow liquid. IR (neat, NaCl plates, ν_{max}, cm^{-1}): 3275, 2115; ^1H NMR: δ 4.05–4.22 (m, 4H), 3.63 (s, 2H), 2.60 (s, 1H); ^{13}C NMR: δ 100.1, 79.2, 66.1, 35.8; HRMS: observed for $C_5H_5O_2$: 97.0286; calcd.: 97.0290.

Synthesis of 1-Bromo-3-butyn-2-one (5)

A mixture of **4** (10.0 mmol, 1.91 g) and formic acid (98%) (87 mmol, 4.0 g) in pentane (100 mL) were transferred into a one-necked, round-bottomed flask (500 mL) under nitrogen atmosphere and refluxed at 70°C for 6 h. After this time, GC analysis showed complete conversion of the starting material. The reaction mixture was allowed to cool to room temperature, and the layers were separated. The acid phase was extracted with pentane/ether (9:1) (2×15 mL). The pentane/ether layers were combined and carefully washed with water (2×10 mL) and saturated aqueous sodium chloride solution (3×15 mL), dried over anhydrous $MgSO_4$ for 3 h, and filtered. After filtration, the solvent was removed under vacuum followed by addition of magnesium oxide (100 mg) and hydroquinone (100 mg) to suppress polymerization. The yield was 1.09 g (74%) of dark red-brownish liquid. IR (neat, NaCl plates, ν_{max}, cm^{-1}): 3290, 2250, 2100, 1680; ^1H NMR: δ 4.05 (s, 2H), 3.41 (s, 1H); ^{13}C NMR: δ 177.6, 82.2, 79.1, 35.2; HRMS: observed for C_4H_3BrO: 147.9340; calcd.: 147.9347.

Synthesis of 2-Bromomethyl-2-(1-bromovinyl)-1,3-dioxolane (6)

Compound **3** (10.0 mmol, 3.53 g) was dissolved in dry THF under an N_2 atmosphere. DBU (17.1 mmol, 2.56 mL) was added dropwise via syringe. The reaction mixture was stirred at room temperature for 1 h. Then the reaction mixture was filtered through a plug of silica, which was washed with Et_2O. The solvent was removed in vacuum to give a brownish liquid

product. Yield (2.58 g, 95%); IR (neat, NaCl plates, v_{max}, cm^{-1}): 3100; ^1H NMR: δ 6.21 (d, 1H, $J = 1.8$ Hz), 5.74 (d, 1H, $J = 1.8$ Hz), 3.94–4.20 (m, 4H), 3.70 (s, 2H); ^{13}C NMR: δ 129.1, 120.8, 107.1, 66.2, 34.5; HRMS: observed for $C_5H_6BrO_2$: 178.9537; calcd.: 178.9531.

Synthesis of 1,3,4-Tribromobutan-2-one (8)

Compound **5** (1.0 mmol, 149 mg) was dissolved in CH_2Cl_2 (5 mL) and transferred into a three-necked, round-bottomed flask equipped with reflux condenser and magnetic stirrer. Br_2 (1.25 mmol, 200 mg) in CH_2C_2 (3 mL) was added dropwise until the bromine color persisted at 0°C. After complete addition of bromine, the reaction mixture was stirred for 5 min, and solvent was removed by rotary evaporation. A colorless oil was obtained (290 mg, 94%), which was sufficiently pure for the next reaction; IR (neat, NaCl plates, v_{max}, cm^{-1}): 2975, 2930, 1725; ^1H NMR δ 4.97 (dd, 1H, $J = 4.4$, 10.6 Hz), 4.28 (d, 1H, $J = 12.5$ Hz), 4.05 (d, 1H, $J = 12.5$ Hz), 3.97 (t, 1H, $J = 10.4$ Hz), 3.67 (dd, 1H, $J = 4.4$, 10.3 Hz); ^{13}C NMR: δ 192.2, 43.3, 31.0, 27.8; CC/MS m/z (relative intensity): 310 (M + 3), 308, 231 (13), 229 (27), 227, 217 (4), 215 (8), 213, 189 (7), 187 (14), 185, 135 (27), 133, 123 (100), 121, 108 (14), 107, 106, 105, 95 (40), 93, 81 (20), 79, 55 (45).

Synthesis of 1,3-Dibromo-3-buten-2-one (9)

Compound **8** (1.0 mmol, 309 mg), Li_2CO_3 (5 mol%, 3.4 mg), and a catalytic amount of 12-crown-4 (5 mol%, 8.81 mg) were placed in a two-necked, round-bottomed flask and dissolved in dry THF (5 mL) under N_2. The reaction mixture was stirred at 23°C for 24 h. The resulting mixture was filtered through a short plug of silica, washed with Et_2O, and concentrated using rotary evaporation to get the target compound in moderate yield (70.68 mg, 31%). ^1H NMR δ 6.92 (d, 1H, $J = 2.7$ Hz), 6.45 (d, 1H, $J = 2.7$ Hz), 4.33 (s, 2H); ^{13}C NMR: δ 186.1, 131.0, 127.1, 30.1; GC/MS m/z (relative intensity) 230 (15), 228 (28), 226, 135 (100), 133, 107 (41), 105, 95 (19), 93, 81 (12), 79.

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