Preparation of 1-Bromo-1-chloro-, 1,1-Dibromo- or 1,1-Dichloroalk-1-enes from Ketones

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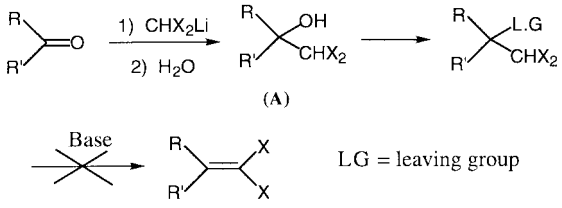
Abstract. An efficient three steps process for converting aliphatic ketones to the homologous gem-bromochloro, or gem-dibromo alkenes is presented.

Key words: ketones, trihalomethyl carbenoids, eliminations, gem-dihaloalkenes, halides, halogens

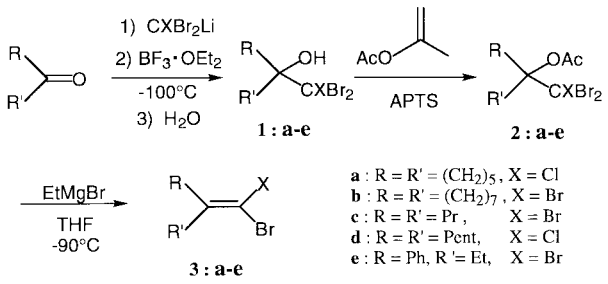
The MacKelvie,[1] Corey, Fuchs[2] conversion of aldehydes to homologous alkynes is a commonly used straightforward process, which relies upon an initial preparation of the gem-dibromoalkenes. The corresponding one-carbon homologation starting from a ketone, however, is much more troublesome and has been scarcely reported, generally with low yields, except for cycloalkanones. Olah and Wu[3] converted polycycloalkanones to the gem-dibromomethylene derivatives via PPh_3/CBr_4. Savignac and Coutrot[4] used the anion of diethyl dibromomethylphosphonate to convert the cycloalkanones to gem-dibromoalkenes in yields of 45−70%, but no example of a linear aliphatic ketone was reported. More recently, Oku et al.[5] disclosed one example of a dibromo and a bromochloroalkene bearing two geminal alkyl moieties. In a first approach, we treated linear or cyclic ketones by dihalomethyllithiums[6] according to Scheme 1.



Scheme 1

However, transformation of tertiary alcohols (**A**) into the corresponding chlorides (or bromides) via $SOCl_2$ or PPh_3/Br_2 under various conditions uniformly failed, as did their attempted transformations to phosphates via $(RO)_2POCl$, mesylates, or esters (via MeCOCl, MeCOBr, PhCOCl) except for the trichloroacetylation. The Burgess reagent[7] did operate, but the subsequent elimination was not regioselective and led to allylic dihalides instead. The silyl ethers could be obtained (from TMSOTf/lutidine) but were of no avail for the next step, since we knew from previous studies that β-silyloxy carbenoids undergo α- rather than β-elimination.[8]

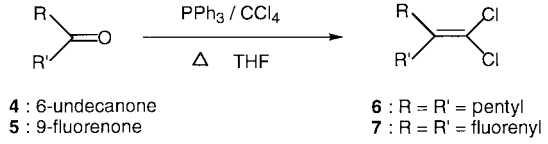
We then turned to a process where gem-trihalo substrates are first formed (Scheme 2, Table). The addition of ketones to $LiCBr_2X$ is straightforward at −90°C in the presence of $BF_3{\bullet}OEt_2$, whatever the nature (cyclic or not) of the ketone and of the carbenoid (X = Br or Cl). Transformations of the hydroxy group of **1** into various leaving groups uniformly failed as they did for **A** except for the ester formation, when we added an enol ether under acidic catalysis to these hindered alcohols. Finally, the trihaloesters **2** were converted to the desired alkenes by treatment with ethyl magnesium bromide[9] in THF at −90°C.



Scheme 2

In conclusion, the three steps sequence presented here allows an efficient conversion of ketones to the homologous geminal bromochloro or dibromo alkenes.

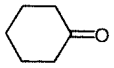
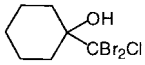
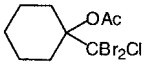
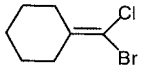
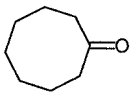
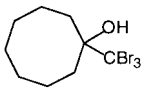
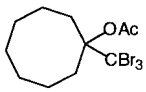
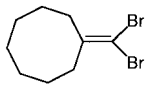
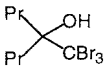
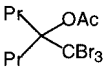
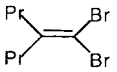
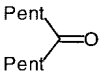
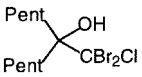
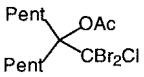
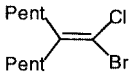
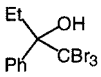
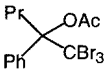
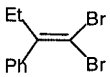
We also prepared 1,1-dichloroalkenes **6** and **7**[10] from ketones, with good yields (Scheme 3) only if a procedure described for lactones[11] (PPh_3/CCl_4, THF, reflux) is used, instead of the classical analogous reaction in CCl_4 alone.



Scheme 3

Experiments involving organometallics were carried out under a positive pressure of dry N_2. Liquid N_2 was used as a cryoscopic fluid. A four-necked round bottom flask was equipped with an internal

Table Preparation of 1-Bromo-1-Chloro- or 1,1-Dibromoalk-1-enes from Ketones

Entry	Ketone	$LiCBr_2X$ (X), Equiv	Product **1**	Product **2**	Product **3**	Yield (%)[a]
a		1.2 (Cl)				89
b		1.2 (Br)				95
c		1.2 (Br)				84
d		1.2 (Cl)				81
e		2 (Br)				60

[a] Total yield of the product via 3 steps starting from the ketone.

thermometer, a septum cap, a N_2 inlet, and a mechanical stirrer was used. Et_2O and THF were distilled from sodium-benzophenone ketyl. IR spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. NMR spectra were recorded on either a Bruker ARX 400 or a Bruker AC 200 in $CDCl_3$ as solvent. Chemical shifts are reported in ppm relative to TMS.

Trihalomethyl Alkanols 1; General Procedure

A 100 mL four-necked round bottom flask equipped with a mechanical stirrer was charged with a solution of diisopropylamine (12 mmol, 1.7 mL) in anhyd THF (20 mL). To this solution was added BuLi (1.6 M in hexanes, 12 mmol, 7.5 mL) at −30°C. The mixture was warmed to 0°C for 10 min and then cooled down to −100°C and $CHBr_2X$ (X = Br or Cl) (12mmol) was added dropwise. After 10 min at -100°C, a solution of ketone (10 mmol) in anhyd Et_2O (5 mL) was slowly added, followed by the addition of $BF_3{\bullet}OEt_2$ (10 mmol, 1.2 mL). After 4 h at −90°C aq 1M HCl (20 mL) was added at −100°C and the mixture was warmed to r.t. The aqueous layer was extracted with Et_2O (3 × 20 mL) the combined organic layers were washed with aq 0.5 M HCl (15 mL), then with satd $NaHCO_3$ solution (15 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to provide the crude product which can be used directly in the next step.

1-(Dibromochloromethyl)cyclohexan-1-ol (1a)

Yield: 3.1 g (~100%); colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.01−2.07 (m, 10 H), 2.23 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.47, 24.19, 19.27, 27.68, 32.04, 68.26, 83.36.

IR (neat): ν = 3560, 3400, 2940, 2875, 1450, 1160, 990, 710 cm^{-1}.

Anal. Calcd for $C_7H_{11}Br_2ClO$ (306.4): C, 27.44; H, 3.62. Found: C, 27.31; H, 3.65.

1-(Tribromomethyl)cyclooctan-1-ol (1b)

Yield: 3.78 g (~100%); yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45−1.85 (m, 10 H), 2.24−2.30 (m, 4 H), 2.61 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 22.47, 24.19, 27.68, 32.04, 68.26, 83.36.

IR (neat): ν = 3550, 3350, 2910, 2880, 1450, 1140, 1050, 700 cm^{-1}.

4-(Tribromomethyl)heptan-4-ol (1c)

Yield: 3.68 g (~100%); yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.96 (t, 6 H, *J* = 7.3 Hz), 1.56 (sext, 4 H, *J* = 9.21 Hz), 1.96−2.08 (m, 4 H), 2.40 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.89, 18.88, 38.27, 66.45, 83.07.

IR (neat): ν = 3575, 3495, 2980, 2885, 1515, 1140, 740, 710 cm^{-1}.

Anal. Calcd for $C_8H_{15}Br_3O$ (366.9): C, 26.19; H, 4.12. Found: C, 26.06; H, 4.03.

6-(Dibromochloromethyl)undecan-6-ol (1d)

Yield: 3.75 g (~100%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, 6 H, *J* = 7.2 Hz), 1.29−1.55 (m, 12 H), 1.96−2.05 (m, 4 H), 2.34 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 14.10, 22.57, 24.81, 32.48, 35.68, 82.99, 83.45.

1,1,1-Tribromo-2-phenylbutan-2-ol (1e)

Yield: 3.85 g (~100%); yellow crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, 3 H, *J* = 7.5 Hz), 2.37 (sext, 1 H, *J* = 7.2 Hz), 2.88 (sext, 1 H, *J* = 7.2 Hz), 2.94 (s, 1 H), 7.38 (m, 3 H), 7.81 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.37, 29.36, 64.63, 85.75, 127.30, 128.35, 129.72, 135.47.

Acetylation of Tertiary Alcohols 1 to Acetates 2; General Procedure

A 100 mL round bottom flask equipped with a magnetic stirrer was charged with a solution of alcohol **1** (5 mmol) in isopropenyl acetate (45 mL) under N_2. To this solution was added TsOH (5.5 g, 29

mmol) at 30°C. After 5 min an exothermic reaction was observed and the solution became dark. The mixture was stirred at 30°C until TLC showed the absence of starting material (4 to 24 h). A large part of isopropenyl acetate was evaporated under vacuum, then Et_2O (30 mL) was added and under stirring at 0°C aq satd Na_2CO_3 solution (~40 mL) was added slowly until no more gas evolution was observed . After 30 min at r.t., the aqueous layer was extracted with Et_2O (3 × 30 mL). The organic layers were washed with aq satd $NaHCO_3$ solution (15 mL) and dried ($MgSO_4$). The residue was purified by filtration on silica gel using petroleum ether/Et_2O/CH_2Cl_2 (90:5:5).

1-(Dibromochloromethyl)-1-acetoxycyclohexane (2a)
Yield: 1.65 g (96%); colourless crystals; mp 56−57°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19−1.27 (m, 2 H), 1.44−1.99 (m, 8 H), 2.14 (s, 3 H), 1.13−2.18 (m, 2 H), 2.84 (d, 1 H, *J* = 1.2 Hz), 2.87 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.81, 22.97, 24.48, 31.54, 75.11, 91.92, 169.17.

IR (neat): ν = 2950, 2880, 1750, 1450, 1205, 1020 cm^{-1}.

1-(Tribromomethyl)-1-acetoxycyclooctane (2b)
Yield: 2.1 g (~100%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55−1.95 (m, 10 H), 2.12 (s, 3 H), 2.28−2.34 (m, 2 H), 2.96−3.03 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.58, 23.02, 23.62, 27.68, 31.13, 57.77, 93.30, 168.78.

IR (neat): ν = 2940, 2875, 1750, 1470, 1440, 1360, 1210, 1025 cm^{-1}.

4-(Tribromomethyl)-4-acetoxyheptane (2c)
Yield: 1.94 g (95%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, 6 H, *J* = 7.2 Hz), 1.52−1.73 (m, 4 H), 2.12 (s, 3 H), 2.24−2.32 (m, 2 H), 2.43−2.51 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.81, 19.23, 22.59, 38.46, 55.71, 92.11, 168.71.

6-(Dibromochloromethyl)-6-acetoxyundecane (2d)
Yield: 1.89 g (90%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, 6 H, *J* = 6.8 Hz), 1.25−1.55 (m, 12 H), 2.12 (s, 3 H), 2.29−2.34 (m, 2 H), 2.41−2.51 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.14, 22.51, 22.59, 25.24, 36.04, 74.46, 92.76, 168.82.

IR (neat): ν = 2980, 2885, 1750, 1465, 1230, 1010, 735 cm^{-1}.

1,1,1-Tribromo-2-phenyl-2-acetoxybutane (2e)
Yield: 1.71 g (80%); colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, 3 H, *J* = 7.2 Hz), 2.31 (s, 3H), 2.92 (sext, 1 H, *J* = 7.6 Hz), 3.24 (sext, 1 H, *J* = 7.6 Hz), 7.34 (m, 3 H), 7.61 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.17, 22.31, 28.47, 55.36, 91.75, 126.99, 128.67, 129.79, 136.52, 168.03.

IR (neat): ν = 3180, 2970, 1760, 1495, 1445, 1370, 1220, 1020, 710 cm^{-1}.

1,1-Dihalo-2,2-dialkylethylenes 3; General Procedure
A 100 mL four-necked round bottom flask equipped with mechanical stirrer was charged with a solution of ethylmagnesium bromide [1.2 M in THF] (6.7 mL, 8 mmol) in THF (10 mL). To this solution at −95°C was added dropwise a THF solution of the acetate **2** (2 mmol). The mixture was then stirred at −90°C for 30 min, cooled to −100°C and hydrolysed with aq 1 M HCl (15 mL). The mixture was then warmed to r.t. and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with aq satd $NaHCO_3$ solution (15 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to provide the crude product which was purified by flash chromatography on silica gel using petroleum ether to give the alkenes **3**.

(Bromochloromethylene)cyclohexane (3a)
Yield: 390 mg (93%); colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79 (m, 6 H), 2.58−2.63 (m, 4 H).
^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.95, 26.82, 26.92, 32.04, 34.61, 97.54, 141.67.

IR (neat): ν = 2970, 2875, 1450, 1230, 790 cm^{-1}.

Anal. Calcd for $C_7H_{10}BrCl$ (209.5): C, 40.13; H, 4.81. Found: C, 40.17; H, 4.77.

(Dibromomethylene)cyclooctane (3b)
Yield: 536 mg (95%); colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45−1.54 (m, 6 H), 1.73−1.78 (m, 4 H), 2.39−2.42 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.29, 25.70, 27.50, 35.56, 84.47, 147.10.

1,1-Dibromo-2-propylpent-1-ene (3c)
Yield: 502 mg (93%); colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.94 (t, 6 H, *J* = 7.3 Hz), 1.48 (sext, 4 H, *J* = 7.6 Hz), 2.22 (t, 4 H, *J* = 7.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.06, 20.67, 38.20, 85.66, 143.31.

IR (neat): ν = 2980, 2875, 1470, 810 cm^{-1}.

Anal. Calcd for $C_8H_{14}Br_2$ (270.0) : C, 35.59; H, 5.23. Found: C, 35.73; H, 5.31.

1-Bromo-1-chloro-2-pentylhept-1-ene (3d)
Yield: 507 mg (90%); colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, 6 H, *J* = 7.0 Hz), 1.28−1.45 (m, 12 H), 2.18−2.26 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.20, 22.66, 27.08, 31.82, 33.78, 36.13, 100.99, 143.52.

1,1-Dibromo-2-phenylbut-1-ene (3e)[5]
Yield: 430 mg (75%); colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.98 (t, 3 H, *J* = 7.5 Hz), 2.65 (q, 2 H, *J* = 7.5 Hz), 7.18 (m, 2 H), 7.32−7.35 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.47, 32.85, 87.65, 127.64, 127.95, 128.36, 140.85, 148.92.

1,1-Dichloroalkenes 6 and 7; General Procedure
A 100 mL two-necked round bottom flask equipped with magnetic stirrer and a condenser, under N_2, was charged with a solution of ketone **4** or **5** (10 mmol) in THF (30 mL). Ph_3P (40 mmol, 10.5 g) was added and the mixture was brought to reflux. CCl_4 (25 mL, 240 mmol) was added dropwise in 2 h (the solution turned dark). When TLC (2−3 h) showed the absence of starting material, the mixture was cooled to 0°C and hydrolysed with H_2O (30 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL) the combined organic layers were washed with aq satd $NaHCO_3$ solution (20 mL), and then with brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to provide a solid mixture of product and Ph_3PO. The solid was washed several times with pentane and filtered. After the evaporation of pentane the crude product was purified by flash chromatography on silica gel using petroleum ether to give the dichloroethylenes **6** or **7**.

1,1-Dichloro-2-propylpent-1-ene (6)
Yield: 2.1g (88%); colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, 6 H, *J* = 7.0 Hz), 1.30−1.49 (m, 12 H), 2.23 (t, 4 H, *J* = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.06, 22.57, 26.98, 31.74, 33.55, 114.69, 139.79.

IR (neat): ν = 2985, 2875, 1475 cm $^{-1}$.

9-Dichloromethylene-9-fluorene (7)
Yield: 2.21g (89%); yellow solid; mp 131−133 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33−7.37 (m, 2 H), 7.40−7.44 (m, 2 H), 7.71 (d, 2 H, *J* = 7.2 Hz), 8.34 (d, 2 H, *J* = 7.7 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.45, 120.03, 126.19, 127.94, 239.54, 134.62, 136.92, 140.60.

IR (KBr): ν = 3080, 1610, 1575, 910, 720 cm^{-1}.

Anal. Calcd for $C_{14}H_8Cl_2$ (247.1): C, 68.04; H, 3.26. Found: C, 67.92; H, 3.16.

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