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An Efficient Method for Preparing *gem*-Dimethylcyclopropanes from *gem*-Dibromocyclopropanes

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Reaction of *gem*-dibromocyclopropanes (**1**) with a higher-order organocuprate prepared from cuprous thiocyanate and methyllithium, followed by the addition of methyl iodide *in situ*, readily afforded dimethylcyclopropanes (**2**) in good to excellent yields regardless of the functional group in **1**

Keywords—higher-order organocuprate, dibromocyclopropane, dimethylcyclopropane, substitution reaction, dibromocarbene

In connection with studies of the total synthesis of a class of natural products that contain the *gem*-dimethylcyclopropane ring system,¹⁾ several methods for preparing *gem*-dimethylcyclopropanes have been developed, *e.g.* substitution of *gem*-dihalocyclopropanes with dimethylcopper lithium (Gilman's reagent),²⁾ addition of dimethylcarbene to olefins,³⁾ reaction of diphenylsulfonium isopropylide with conjugated carbonyl compounds,⁴⁾ and thermolysis of a pyrazolidine prepared by cycloaddition of dimethyldiazomethane to an olefin.⁵⁾ Although dimethylcopper lithium has usually been used for this purpose, the reaction is occasionally sluggish, requiring a long reaction time.^{6–8)} Recently, Lipshurtz *et al.* have reported that the higher-order organocuprates react readily and efficiently with inactive alkyl iodides and bromides, affording substitution products.^{9–11)} An application of the Lipshurtz method to *gem*-dibromocyclopropane was attempted in order to develop an efficient method for preparing *gem*-dimethylcyclopropane, and we have already reported that reaction of the higher-order organocuprates with 8,8-dibromobicyclo[5.1.0]octane, followed by the addition of methyl iodide *in situ*, afforded the desired dimethylated compound in good yield.¹²⁾ Subsequently, we attempted an application of the present method to other *gem*-dibromocyclopropanes in order to examine its generality and usefulness. We describe here the results of this substitution reaction.¹³⁾

gem-Dibromocyclopropanes (**1**) except **1c** were synthesized directly by reactions of the respective olefins with dibromocarbene prepared from bromoform and 40% sodium hydroxide solution in methylene chloride (method A) or from bromoform and potassium *tert*-butoxide in pentane (method B). The dibromo-silyl ether (**1c**) was synthesized by reaction of 1-cyclohexene-1-methanol with dibromocarbene (method A), followed by silylation with *tert*-butyldimethylsilyl (TBDMS) chloride. The yields are indicated in Table I. The structures of **1** were elucidated on the basis of their spectral data, and the stereostructure of **1b** will be discussed later. In a previous paper,¹²⁾ we reported that Me₂Cu(CN)Li₂ was more reactive than Me₂Cu(SCN)Li₂ in the reaction with dibromobicyclo[5.1.0]octane, yielding overalkylated by-products. Therefore, the reactions of **1** with Me₂Cu(SCN)Li₂–MeI were examined. The results are listed in Table I, showing that reactions proceed smoothly to afford

Chart 1

TABLE I. Yields of *gem*-Dibromocyclopropanes (1) and *gem*-Dimethylcyclopropanes (2)^{a)}

Products (Yield, %)		Method	Products (Yield, %)	
1a	(62)	A	2a	(91)
1b	(34)		2b	(76)
1c^{c)}			2c	(75)
1d	(91)		2d	(44) ^{d)}
1e^{b)}	(80)	B	2e^{b)}	(71)
1f^{b)}	(51)	A	2f^{b)}	(73)
1g^{b)}	(80)	A	2g^{b)}	(71)
1h^{b)}	(40)	A	2h^{b)}	(85)
1i^{b)}	(86)	A	2i^{b)}	(80)
			2h^{b)}	(12)

^{a)} Isolated yields. The compounds indicated by ^{b)} were inseparable mixtures (about 1 to 1.5 ratio). ^{c)} See Experimental. ^{d)} The low yield was assumed to be because of the high volatility of **2d**.

2 in a good yield regardless of the functional group, such as ester, acetate, alkyl ether, silyl ether, acetal, or hydroxy group. The structures of products were elucidated on the basis of their spectral data. Dimethylation of **1b** gave a small amount of the tricyclic ketone (**3**) produced *via* the metalated intermediate (**A**) along with the desired dimethylated compound (**2b**), indicating that **1b** is a *cis*-dibromide.¹²⁾

In conclusion, the present method using $\text{Me}_2\text{Cu}(\text{SCN})\text{Li}_2\text{-MeI}$ is efficient for preparing the dimethyl compound (**2**) from the dibromo compound (**1**).

Experimental

The melting point of **1c** was determined with a Yanagimoto micro melting point apparatus, and is uncorrected. Compounds for which no melting point is given are oily. The infrared (IR) spectra ($\text{IR } \nu_{\text{max}}$) were determined on a Shimadzu IR-400 spectrometer in chloroform. The proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra were obtained in chloroform-*d* at 200 MHz on a JEOL FX 200 instrument with chemical shifts being reported in parts per million downfield from tetramethylsilane as an internal standard (δ 0.0), and coupling constants in Hertz. Mass spectra (MS) were taken on a JEOL JMS 01SG-2 instrument (direct inlet) at 70 eV. All reactions were carried out under an atmosphere of argon. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with brine, dried over MgSO_4 , and filtered, then the filtrate was concentrated to dryness *in vacuo*. Column chromatography was carried out on silica gel (Wakogel C-200) or Aluminum oxide 90 (Merck, activity II—III). Preparative thin layer chromatography (pTLC) was run on 20×20 cm plates coated with a 0.25 mm layer of Merck Silica gel GF₂₅₄.

General Procedure for Preparation of the Dibromides (1)—Method A: Bromoform (17 mmol), tributylamine (0.2 ml), and 40% aqueous sodium hydroxide (8 ml) were added successively to a solution of an olefinic compound

(3 mmol) in methylene dichloride (4 ml). The mixture was vigorously stirred under reflux for 2–6 h.

Method B: Bromoform (9 mmol) in pentane (5 ml) was added to a suspension of *tert*-BuOK (20 mmol) and an electron-rich olefin (5 mmol) in pentane (50 ml) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. Yields are given in Table I.

Methyl (1*RS*,3*SR*,6*SR*)-7,7-Dibromobicyclo[4.2.0]heptane-3-carboxylate (1a) and Methyl (1*RS*,3*RS*,6*SR*)-7,7-Dibromobicyclo[4.2.0]heptane-3-carboxylate (1b)—The residue in hexane was chromatographed on silica gel. Elution with hexane gave **1a**. IR: 1720 cm⁻¹. ¹H-NMR: 3.67 (3H, s, COOMe). MS Calcd for C₉H₁₂Br₂O₂: 309.9205 (M⁺). Found: 309.9212. Successive elution with the same solvent gave **1b**. IR: 1720 cm⁻¹. ¹H-NMR: 2.48 (1H, dddd, *J* = 14.4, 10.3, 4.4, 1.9 Hz, CH), 3.67 (3H, s, COOMe). MS Calcd for C₉H₁₂Br₂O₂: 309.9205 (M⁺). Found: 309.9199.

(1*RS*,6*RS*)-(7,7-Dibromobicyclo[4.1.0]hept-1-yl)methoxy-*tert*-butyldimethylsilane (1c)—(7,7-Dibromobicyclo[4.1.0]hept-1-yl)methanol was synthesized from 1-cyclohexene-1-methanol in 50% yield according to method A. mp 104–105 °C (colorless plates from hexane). IR: 3580, 3430 cm⁻¹. ¹H-NMR: 3.67 (1H, d, *J* = 11.7 Hz, CH_AH_BO), 3.86 (1H, d, *J* = 11.7 Hz, CH_AH_BO). *Anal.* Calcd for C₈H₁₂Br₂O: C, 34.00; H, 4.28. Found: C, 33.83; H, 4.26. A mixture of the above dibromide (142 mg, 0.5 mmol), imidazole (102 mg, 1.5 mmol), and TBDMS chloride (91 mg, 0.6 mmol) in dimethylformamide (1 ml) was stirred at room temperature overnight. The residue in hexane was chromatographed on silica gel. Elution with hexane afforded **1c** (190 mg, 95% yield). IR: 1095, 840 cm⁻¹. ¹H-NMR: 0.06 (3H, s, Me), 0.08 (3H, s, Me), 0.91 (9H, s, *tert*-Bu), 3.67 (1H, d, *J* = 10.1 Hz, CH_AH_BO), 3.75 (1H, d, *J* = 10.1 Hz, CH_AH_BO). MS Calcd for C₁₄H₂₆Br₂OSi: 396.0120 (M⁺). Found: 396.0122.

(1*RS*,6*RS*)-7,7-Dibromo-1-methoxybicyclo[4.1.0]heptane (1d)—The residue in hexane was chromatographed on silica gel and elution with hexane provided **1d**. IR: 1110–1070 cm⁻¹. ¹H-NMR: 3.47 (3H, s, OMe). MS Calcd for C₈H₁₂Br₂O: 281.9264 (M⁺). Found: 281.9265.

7,7-Dibromo-4-*tert*-butyl-1-methoxybicyclo[4.1.0]heptane (1e)—The residue in hexane was chromatographed on aluminum oxide, and elution with hexane provided **1e**. IR: 1120–1080 cm⁻¹. ¹H-NMR: 0.82, 0.84 (total 9H, each s, *tert*-Bu), 3.46, 3.47 (total 3H, each s, OMe). MS Calcd for C₁₂H₂₀Br₂O: 337.9863 (M⁺). Found: 337.9865.

Methyl 9,9-Dibromobicyclo[6.1.0]decane-4-carboxylate (1f)—The residue in hexane was chromatographed on silica gel. Elution with hexane afforded **1f**. IR: 1720 cm⁻¹. ¹H-NMR: 3.66, 3.67 (total 3H, each s, COOMe). MS Calcd for C₁₁H₁₆Br₂O₂: 337.9518 (M⁺). Found: 337.9519.

2-(7,7-Dibromobicyclo[4.1.0]hept-3-yl)-1,3-dioxolane (1g)—The residue in hexane was chromatographed on aluminum oxide. Elution with hexane and 5% ether in hexane gave **1g**. IR: 1150–1120 cm⁻¹. ¹H-NMR: 3.84–3.94 (4H, m, OCH₂CH₂O), 4.58 (1H, d, *J* = 4.4 Hz, CH). MS Calcd for C₁₀H₁₄Br₂O₂: 323.9363 (M⁺). Found: 323.9378.

7,7-Dibromobicyclo[4.1.0]heptane-3-methanol (1h)—The residue in hexane was chromatographed on aluminum oxide. Elution with 20–50% ether in hexane gave **1h**. IR: 3600, 3430 cm⁻¹. ¹H-NMR: 3.32–3.52 (2H, m, CH₂O). MS Calcd for C₈H₁₂Br₂O: 281.9264 (M⁺). Found: 281.9263.

3-Acetoxymethyl-7,7-dibromobicyclo[4.1.0]heptane (1i)—The residue in hexane was chromatographed on aluminum oxide. Elution with hexane and 10% ether in hexane provided **1i**. IR: 1730 cm⁻¹. ¹H-NMR: 2.04 (3H, s, COMe), 3.76–3.95 (2H, m, CH₂OAc). MS Calcd for C₁₀H₁₄Br₂O₂: 323.9363 (M⁺). Found: 323.9363.

General Procedure for Reaction of Dibromides (1) with Me₂Cu(SCN)Li₂-MeI—Cuprous thiocyanate (345 mg, 2.84 mmol) dried under vacuum at 50 °C for 2 d was placed in a flamed-dried 30 ml two-necked flask, and dry ether (2 ml) was added. Methylolithium (5 ml of 1.1 M ether solution, 5.5 mmol) was added to the suspension at –78 °C and the mixture was gradually warmed to –10 °C over 30 min. Then, the mixture was cooled to –20 °C and a solution of a bromide (**1**) in dry ether (2.5 ml) and hexamethylphosphoric triamide (0.11 ml) was added to the mixture at the same temperature. The reaction mixture was stirred for 1–2 h and methyl iodide (1 ml) was added at –50 °C. After 10 min, the reaction mixture was quenched with saturated aqueous ammonium chloride at –50 °C and precipitates were filtrated off on a celite bed. The filtrate was extracted with ether and the organic layer was washed with 5% aqueous ammonia. Yields are given in Table I.

Methyl (1*RS*,3*SR*,6*SR*)-7,7-Dimethylbicyclo[4.1.0]heptane-3-carboxylate (2a)—Purification of the residue by pTLC (hexane: AcOEt = 6:1) gave **2a**. IR: 1725 cm⁻¹. ¹H-NMR: 0.65 (2H, m, 2 × CH), 0.93 (3H, s, Me), 0.98 (3H, s, Me), 3.66 (3H, s, COOMe). MS Calcd for C₁₁H₁₈O₂: 182.1308 (M⁺). Found: 182.1309.

Methyl (1*RS*,3*RS*,6*SR*)-7,7-Dimethylbicyclo[4.1.0]heptane-3-carboxylate (2b) and (1*RS*,2*SR*,5*RS*,7*SR*)-7-Methyltricyclo[3.2.1.0^{2,7}]octan-6-one (3)—The residue was subjected to pTLC (hexane: AcOEt = 7:1). The upper zone gave **2b**. IR: 1725 cm⁻¹. ¹H-NMR: 0.46 (1H, ddd, *J* = 9.2, 6.5, 2.4 Hz, CH), 0.75 (1H, ddd, *J* = 9.2, 9.2, 5.5 Hz, CH), 0.96 (3H, s, Me), 0.99 (3H, s, Me), 3.65 (3H, s, COOMe). MS Calcd for C₁₁H₁₈O₂: 182.1307 (M⁺). Found: 182.1310. The lower zone gave **3**. IR: 1725 cm⁻¹. ¹H-NMR: 1.21 (3H, s, Me). MS Calcd for C₉H₁₂O: 136.0888 (M⁺). Found: 136.0887.

(1*RS*,6*RS*)-(7,7-Dimethylbicyclo[4.1.0]hept-1-yl)methoxy-*tert*-butyldimethylsilane (2c)—The residue in hexane was chromatographed on aluminum oxide. Elution with hexane afforded **2c**. IR: 1080, 840 cm⁻¹. ¹H-NMR: 0.01 (3H, s, Me), 0.02 (3H, s, Me), 0.38 (1H, dd, *J* = 8.5, 2.0 Hz, CH), 0.89 (9H, s, *tert*-Bu), 0.99 (3H, s, Me), 1.08 (3H, s, Me), 3.41 (1H, d, *J* = 10.0 Hz, CH_AH_BO), 3.58 (1H, d, *J* = 10.0 Hz, CH_AH_BO). MS Calcd for C₁₆H₃₂OSi: 268.2222 (M⁺). Found: 268.2206.

(1*RS*,6*RS*)-1-Methoxybicyclo[4.1.0]heptane (2d)—The residue in hexane was chromatographed on silica gel.

Elution with hexane gave **2d**. IR: 1140 cm^{-1} . $^1\text{H-NMR}$: 0.68 (1H, dd, $J=8.9, 2.0\text{ Hz}$, CH), 0.99 (3H, s, Me), 1.16 (3H, s, Me), 3.24 (3H, s, OMe). MS Calcd for $\text{C}_{10}\text{H}_{18}\text{O}$: 154.1358 (M^+). Found: 154.1358.

4-tert-Butyl-1-methoxy-7,7-dimethylbicyclo[4.1.0]heptane (2e)—The residue in hexane was chromatographed on silica gel. Elution with hexane **2e**. IR: 1080 cm^{-1} . $^1\text{H-NMR}$: 0.80, 0.82 (total 9H, each s, *tert*-Bu), 0.98, 0.99 (total 3H, each s, Me), 1.16, 1.17 (total 3H, each s, Me), 3.23, 3.25 (total 3H, each s, OMe). MS Calcd for $\text{C}_{14}\text{H}_{26}\text{O}$: 210.1984 (M^+). Found: 210.1978.

Methyl 9,9-Dimethylbicyclo[6.1.0]decane-4-carboxylate (2f)—Purification of the residue by pTLC (hexane: AcOEt = 10:1) gave **2f**. IR: 1720 cm^{-1} . $^1\text{H-NMR}$: 0.20–0.51 (2H, m, $2\times\text{CH}$), 0.93 (3H, s, Me), 1.01 (3H, s, Me), 3.65, 3.66 (total 3H, each s, COOMe). MS Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_2$: 210.1620 (M^+). Found: 210.1627.

2-(7,7-Dimethylbicyclo[4.1.0]hept-3-yl)-1,3-dioxolane (2g)—The residue in hexane was chromatographed on aluminum oxide and elution with hexane afforded **2g**. IR: 1150 cm^{-1} . $^1\text{H-NMR}$: 0.41–0.90 (2H, m, $2\times\text{CH}$), 0.93, 0.95 (total 3H, each s, Me), 0.98 (3H, s, Me), 3.79–4.00 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 4.57 (1H, d, $J=4.9\text{ Hz}$, CH). MS Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2$: 196.1463 (M^+). Found: 196.1469.

7,7-Dimethylbicyclo[4.1.0]heptane-3-methanol (2h)—The residue in hexane was chromatographed on silica gel. Elution with 5% ether in hexane provided **2h**. IR: $3620, 3440\text{ cm}^{-1}$. $^1\text{H-NMR}$: 0.42–0.91 (2H, m, $2\times\text{CH}$), 0.93, 0.94 (total 3H, each s, Me), 0.99 (3H, s, Me), 3.22–3.52 (2H, m, CH_2O). MS Calcd for $\text{C}_{10}\text{H}_{18}\text{O}$: 154.1358 (M^+). Found: 154.1355.

3-Acetoxymethyl-7,7-dimethylbicyclo[4.1.0]heptane (2i) and 2h—The residue in hexane was chromatographed on silica gel. Elution with 5% ether in hexane gave **2i**. IR: 1720 cm^{-1} . $^1\text{H-NMR}$: 0.42–0.85 (2H, m, $2\times\text{CH}$), 0.93, 0.94 (total 3H, each s, Me), 0.98 (3H, s, Me), 2.05 (3H, s, COMe), 3.78–3.98 (2H, m, CH_2OAc). MS Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2$: 196.1463 (M^+). Found: 196.1467. Elution with 40% ether in hexane gave **2h**. This compound was identical with the alcohol (**2h**) on the basis of IR and $^1\text{H-NMR}$ spectral comparisons.

References and Notes

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