Substitution on Carbenoid Carbon of α-Halocyclopropyllithium. A Novel Stereoselective Synthesis of Geminally Substituted Cyclopropanes

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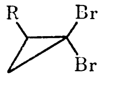
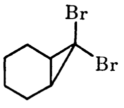
The halogen atom of the title carbenoids is susceptible to displacement by butyllithium. 1-Butyl-1-lithiocyclopropanes are formed, in which the butyl group occupies the less hindered site (*trans* or *exo* position). The new reaction provides a means for the preparation of geminally disubstituted cyclopropanes with high degree of stereoselectivity.

In contrast to the view that the halogen atom on cyclopropane carbon is not easily displaced by nucleophiles,[1] it was found that the halogen atom of α-halocyclopropyllithium undergoes a displacement reaction, the process being applicable to the synthesis of *gem*-disubstituted cyclopropanes.

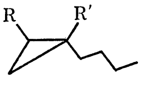
Addition of 1,1-dibromo-2-phenylcyclopropane (**1a**) to excess butyllithium at −95 °C, followed by aqueous work-up, afforded 1-butyl-2-phenylcyclopropane (**2a** and **3a**, 90: 10). The product distribution changes with reaction time, as shown in Fig. 1, according to Scheme 1. Apparently the decrease of the initially predominant *trans*-lithiocarbenoid **4**[2,3] is accompained by an increase of the *trans*-alkylated cyclopropyllithium **6**, whereas the concentration of the thermodynamically favored carbenoid **5** remains almost constant. The bulky phenyl substituent probably prevents the conversion of **5** into **7**. When the temperature is raised, however, the conversion occurs along with partial isomerization to **4** which would account for **6** to some extent.



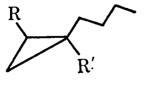
1a: R=Ph
1b: R=$PhCH_2OCH_2$



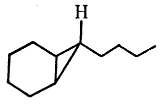
1c



2a: R=Ph, R′=H
2b: R=Ph, R′=D
2c: R=Ph, R′=Me_3Si
2d: R=Ph, R′=PhCO
2e: R=Ph, R′=MeS
2f: R=Ph, R′=I
2g: R=Ph, R′=Me
2h: R=$PhCH_2OCH_2$, R′=Me



3a: R=Ph, R′=H
3b: R=Ph, R′=D
3c: R=Ph, R′=Me_3Si
3d: R=Ph, R′=PhCO
3e: R=Ph, R′=MeS
3f: R=Ph, R′=I
3g: R=Ph, R′=Me
3h: R=$PhCH_2OCH_2$, R′=Me



2i

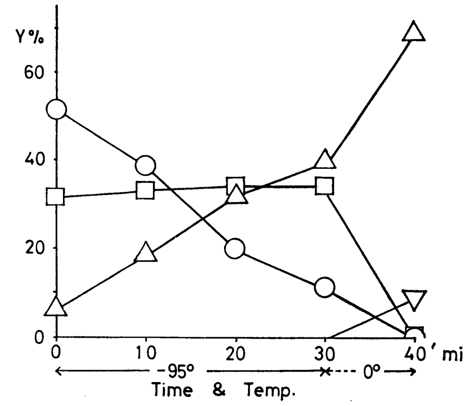
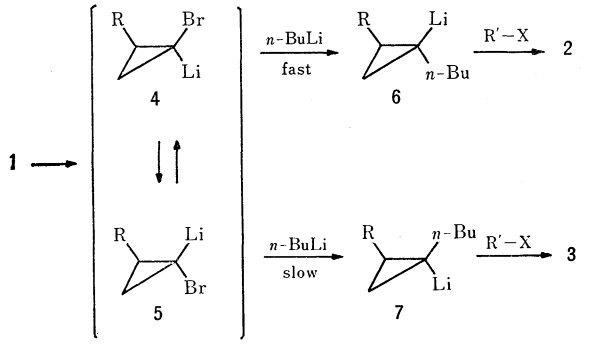


Fig. 1. Products distribution *vs.* reaction time in the reaction of **1a** with 3.3 molar eq of *n*-BuLi (as determined by GLC after methanol quenching). The reaction time was counted after completion of the addition of **1a** which required 5 min. ○: *cis*-1-Bromo-2-phenylcyclopropane corresponding to **4a**; □: *trans*-1-Bromo-2-phenylcyclopropane corresponding to **5a**; △: **2a** which corresponds to **6a**; ▽; **3a** which corresponds to **7a**.



Scheme 1.

Synthetic utility of cyclopropyllithium (**6**) and (**7**) was subsequently found in the reaction with several electrophiles. The results are summarized in Table 1. Stereoselectivity (91—100%) was excellent as compared with that (86%) obtained in the dibutylcuprate reaction.[1d] The reaction of the cyclopropyllithium with methyl iodide resulted in the formation of an iodocyclopropane **2f** in sharp contrast to the reaction of cyclopropylcopper species[1d] which afforded methylated cyclopropanes **2g** and **3g**. They were obtained by the reaction of **6** and **7** with dimethyl sulfate. Similarly **1b** afforded **2h** as the sole product.

More hindered 7,7-dibromonorcarane (**1c**) gave a mixture of *exo*-7-butylnorcarane (**2i**) and *exo*-7-bromo-

Table 1. Preparation of *gem*-disubstituted cyclopropanes

Dihalo-cyclopropane	R′–X	Products	Yield (%) of **2** and **3**	**2**: **3**
1a	H_2O	**2a** and **3a**	80	90: 10
1a	D_2O	**2b** and **3b**	76	91: 9
1a	Me_3SiCl	**2c**	46	100: 0[a]
1a	PhCOCl	**2d**	45	100: 0[a]
1a	MeSSMe	**2e** and **3e**	55	94: 6
1a	I_2	**2f**	59	100: 0[b]
1a	MeI	**2f**	58	100: 0[b]
1a	$(MeO)_2SO_2$	**2g** and **3g**	53	96: 4
1b	$(MeO)_2SO_2$	**2h**	40	100: 0
1c	MeOH	**2i**	24	100: 0[c]

a) By-products **2a** and **3a** were obtained (see Experimental). Complete absence of **3c** isomer is attributed to the preferential protonolysis of **7** to **3a**. The proton source is still obscure. b) 1,1-Dibutyl-2-phenylcyclopropane (**8**) was also obtained. c) *exo*-7-Bromonorcarane formed as a by-product.

norcarane. The stereochemical outcome strongly suggests the large steric hindrance of the tetramethylene chain prohibiting the attack of butyl anion to the carbenoid of type **5** and the large barrier in the configurational isomerization of carbenoid **5** to **4**.

Extension of the reaction of **4** and **5** with anionic species other than butyl anion was not successful with the exception of that of lithium phenylthiolate complexed with tetramethylethylenediamine which afforded *trans*-1-phenyl-2-phenylthiocyclopropane (**9**) in 25% yield.

Experimental

All the temperatures are uncorrected. The IR spectra were obtained on a Shimadzu spectrometer 27-G, MS on a Hitachi RMU-6L, and PMR on JEOL JNM-PMX 60, Varian EM-360, or Varian HA-100D spectrometer. Butyllithium from Aldrich Chemical Co. Ltd. was used. Tetrahydrofuran (THF) was dried on benzophenone ketyl and freshly distilled before use. Tetramethylethylenediamine was dried on KOH and distilled. All the reactions were performed under nitrogen atmosphere. The cold bath was prepared by mixing liquid nitrogen with a solvent (−95 °C: toluene; −126 °C: methylcyclohexane).

1-Butyl-2-phenylcyclopropanes (2a and 3a).[3] *A Standard Procedure*: A solution of **1a** (0.40 g, 1.5 mmol) in THF (3 ml) was cooled to −78 °C and added to a stirred solution of *n*-BuLi (3.7 ml of 1.33 M in hexane, 5.0 mmol) in THF (30 ml) at −95 °C during 5 min. After 30 min the cold bath was removed and the reaction mixture was rapidly warmed to 0 °C in 10 min. This procedure is pertinent to the preparation of **2a**—**g** and their isomers if any. Work-up followed by preparative TLC (silica gel, hexane, R_f 0.7—0.8) afforded a mixture of **2a** and **3a** (0.20 g, 80% yield). Each isomer was identified by comparison of spectral data with those of authentic sample.

1-Butyl-1-deuterio-2-phenylcyclopropanes (2b and 3b). Addition of deuterium oxide (0.1 ml) to cyclopropyllithium (**6**) and (**7**) followed by work-up and preparative TLC (silica gel, hexane, R_f 0.7—0.8) afforded a mixture of **2b** and **3b** (0.20 g, 76% yield, 73% deuterium content). Bp 65—68 °C (bath temp)/15 Torr; IR (neat): 1605, 1495, 1455, 1370, 1025, 745, 695 cm^{-1}; MS: *m/e* (%), 175 (M^+, 16), 174 (M^+-1, 8), 119 (68), 117 (100), 104 (93), 91 (38); PMR (CCl_4): δ 0.5—2.0 (m, 12H), 6.7—7.5 (m, 5H, Ph).

*1-Butyl-*r*-1-trimethylsilyl-*c*-2-phenylcyclopropane (2c).* Addition of Me_3SiCl (0.24 g, 2.3 mmol) to the reaction mixture obtained from **1a** (0.42 g, 1.5 mmol) and 5.0 mmol of *n*-BuLi, followed by work-up and preparative TLC (silica gel, hexane, R_f 0.7—0.8), afforded **2c** (0.17 g, 46%). Bp 106—111 °C (bath temp)/3 Torr; IR (neat): 1600, 1490, 1245, 1030, 835, 780, 755, 730, 700 cm^{-1}; MS: *m/e* (%), 246 (M^+, 5), 172 (49), 129 (35), 117 (60), 104 (69), 73 (100); PMR (CCl_4): δ −0.30 (s, 9H, Me_3Si), 0.5—1.8 (m, 11H), 1.97 (dd, J=6, 8 Hz, 1H, PhC$\underline{H}$), 7.1—7.3 (m, 5H, Ph). Found: C, 78.1; H, 10.9%. Calcd for $C_{16}H_{26}Si$: C, 78.0; H, 10.6%. By-products **2a** (7%) and **3a** (7%) were also obtained.

r*-1-Benzoyl-1-butyl-*c*-2-phenylcyclopropane (2d).* Dibromocyclopropane (**1a**) (0.41 g, 1.5 mmol) was subjected to the reaction with *n*-BuLi as above. Benzoyl chloride (0.35 g, 2.5 mmol) was then added. Work-up and preparative TLC (silica gel, hexane–ether 20: 3, R_f 0.5—0.6) afforded **2d** (0.19 g, 45%). Mp 69.5—70.5 °C (hexane); IR (Nujol): 1660, 1455, 1064, 785, 770, 715, 690 cm^{-1}; MS: *m/e* (%), 278 (M^+, 17), 235 (36), 105 (100), 91 (18), 77 (47); PMR (CCl_4): δ 0.5—2.6 (m, 12H), 6.7—7.7 (m, 10H). Found: C, 86.6; H, 8.2%. Calcd for $C_{20}H_{22}O$: C, 86.3; H, 8.0%. By-products were **2a** (7%) and **3a** (6%).

*1-Butyl-*r*-1-methylthio-*c*-2-phenylcyclopropane (2e).* Quenching the cyclopropyllithium (**6** and **7**) with dimethyl disulfide (0.21 g, 2.3 mmol) and work-up afforded **2e** (0.18 g, 55% yield). A small amount of its stereoisomer **3e** was detected by GLC and identified by MS. Physical properties of **2e**: bp 120—124 °C (bath temp)/3 Torr; IR (neat): 1600, 1495, 1030, 770, 700 cm^{-1}; MS: *m/e* (%), 222 (M^++2, 1.5), 220 (M^+, 21), 205 (30), 173 (100), 129 (71), 115 (79); PMR (CCl_4): δ 0.7—1.7 (m, 11H), 1.66 (s, 3H, SMe), 2.13 (dd, J=6, 7 Hz, 1H, PhC$\underline{H}$), 7.0—7.3 (m, 5H, Ph). Found: C, 75.7; H, 9.4%. Calcd for $C_{14}H_{20}S$: C, 76.0; H, 9.6%.

*1-Butyl-*r*-1-iodo-*c*-2-phenylcyclopropane (2f).*[3] Iodine (0.46 g, 1.8 mmol) in THF (2 ml) was added to the cyclopropyllithium prepared as above, and the resulting mixture was stirred at 0 °C for 1 h and subjected to work-up. Preparative TLC (silica gel, hexane, R_f 0.5—0.6) of the crude product afforded **2f** (0.26 g, 59% yield) besides 2,2-dibutyl-1-phenylcyclopropane (**8**) (38 mg, 10%).

Treatment of the cyclopropyllithium with excess methyl iodide (1 ml) at 0 °C gave **2f** (58%) and **8** (14%).

1-Butyl-1-methyl-2-phenylcyclopropanes (2g and 3g).[3] Dibromocyclopropane **1a** (0.28 g, 1.0 mmol) was treated with 3.3 mmol of *n*-BuLi and then dimethyl sulfate (0.20 g, 1.5 mmol). Work-up and preparative TLC (silica gel, hexane, R_f 0.7—0.8) afforded an oil (0.15 g). The ratio of **2g** to **3g** was estimated by GLC assay (10% HVSG on Celite 545, 122 °C, 0.8 kg/cm^2, naphthalene as an internal standard).

c*-2-Benzyloxymethyl-*r*-1-butyl-1-methylcyclopropane (2h).*[3] To *n*-BuLi (2.5 ml of 1.98 M hexane solution, 5.0 mmol) in THF (20 ml) was added a cooled solution of **1b** (0.48 g, 1.5 mmol) in THF (2 ml) at −95 °C. After 30 min the reaction mixture was warmed rapidly to 0 °C. Dimethyl sulfate (0.21 ml, 2.3 mmol) was then added. Work-up and preparative TLC afforded **2h** (0.14 g, 40%).

exo*-7-Butylnorcarane (2i).*[4] A cooled solution (−78 °C) of **1c** (0.25 g, 0.99 mmol) in a mixture[5] of THF–ether–hexane (50: 5: 18, 3 ml) was added to a solution of *n*-BuLi (1.7 ml, of 1.92 M in hexane, 3.2 mmol) in the same solvent mixture (22 ml) at −126 °C. After 7 h the reaction mixture was quenched with methanol and subjected to work-up affording

2i (24% yield by GLC, R_f (hexane) 0.8—0.9); bp 90—100 °C (bath temp)/20 Torr; IR (neat): 1450, 1370, 1112, 1064 cm^{-1}; MS: *m/e* (%), 152 (M$^+$, 12), 109 (24), 95 (51), 81 (65), 67 (100), 55 (46), 41 (51); PMR (CCl$_4$): δ 0.4—0.6 (m, 3H), 0.6—2.1 (m, 17H). By-product, *exo*-7-bromonorcarane,⁶⁾ was also obtained (53% yield by GLC, R_f (hexane) on silica gel TLC 0.7—0.8).

trans-*1-Phenyl-2-phenylthiocyclopropane (9).* The dibromocyclopropane **1a** (0.41 g, 1.5 mmol) in THF (3 ml) was added to a THF (15 ml) solution of *n*-BuLi (0.82 ml of 1.95 M hexane solution, 1.6 mmol) and tetramethylethylenediamine (0.19 g, 1.6 mmol) cooled to *ca.* −95 °C Subsequently a THF (10 ml) solution of PhSLi (3.3 mmol, prepared from thiophenol and *n*-BuLi)⁷⁾ and tetramethylethylenediamine (0.42 g, 3.6 mmol) which had been cooled to −78 °C was added dropwise in a period of 8 min. After 30 min the whole was allowed to warm to 0 °C and then worked up. Preparative TLC (silica gel, hexane, R_f 0.3—0.4) of the crude product afforded **9** (85 mg, 25%). Bp 100—105 °C (bath temp)/1 Torr; IR (neat): 1603, 1582, 1493, 1480, 1085, 1020, 733, 685 cm^{-1}; MS: *m/e* (%), 228 (M$^+$+2, 1.8), 226 (M$^+$, 30), 115 (100), 109 (8), 91 (49), 77 (98); PMR (CCl$_4$): δ 1.1—1.6 (m, 2H), 2.0—2.4 (m, 2H,) 6.9—7.3 (m, 10H). Found: C, 79.4; H, 6.2%. Calcd for $C_{15}H_{14}S$: C, 79.6; H, 6.2%.

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