Communications to the Editor

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AN EFFICIENT METHOD FOR PREPARING *GEM*-DIMETHYLCYCLOPLOPANES FROM *GEM*-DIBROMOCYCLOPROPANES

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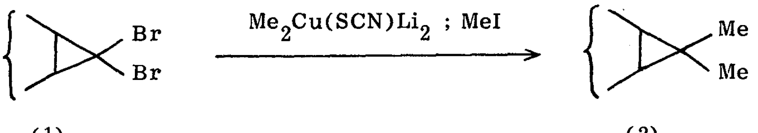
Treatment of *gem*-dibromocyclopropanes (1) with a higher order organocuprate prepared from cuprous thiocyanate and methyllithium, followed by the addition of methyl iodide *in situ*, readily afforded dimethylcyclopropanes (2) in good to excellent yields as listed in Table I.

KEYWORDS——dobromocarbene; dimethylcyclopropane ring; dibromocyclopropane ring; substitution reaction; higher order organocuprate

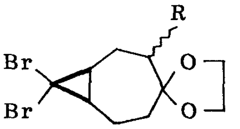
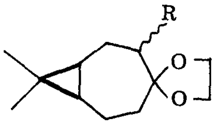
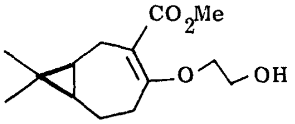
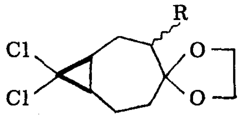
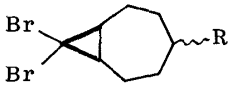
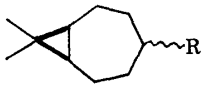
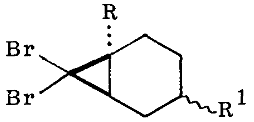
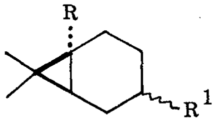
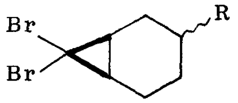
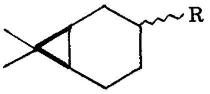
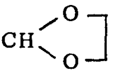
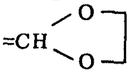
In connection with studies of the synthesis of a class of natural products having a *gem*-dimethylcyclopropane ring,[1] several methods for preparation of *gem*-dimethylcyclopropane derivatives (2) have been explored, *e.g.* substitution of *gem*-dihalocyclopropanes with dimethylcopper lithium (Gilman reagent),[2] addition of dimethylcarbene to olefins,[3] and reaction of diphenylsulfonium isopropylide with conjugated carbonyl compounds.[4] The ordinary substitution reaction with dimethylcopper lithium is occasionally sluggish requiring a long reaction time.[5-7] Recently, Lipshutz *et al.* have reported that the higher order organocuprates [$R_2Cu(SCN)Li_2$] prepared from cuprous thiocyanate and organolithium reagents react readily and efficiently with alkyl iodides and bromides affording products of substitution.[8,9] An application of the Lipshutz method to *gem*-dibromocyclopropanes (1) has been attempted in order to develop an efficient method for preparing dimethylcyclopropanes (2). The reaction of the higher order organocuprate with (1), followed by the addition of methyl iodide *in situ*, produced the desired dimethylated compound (2) in good to excellent yield regardless of the functional group(s) in (1). In this communication, we describe the results of the substitution reactions under such conditions.



(1) (2)

Dibromocyclopropanes (1)[10] were synthesized by adding dibromocarbene to olefins under the reaction conditions indicated in Table I. Then, dimethylation of (1) was examined. Treatment of (1a) with 4 eq of dimethylcopper lithium (Me_2CuLi) at -20°C for 6 days afforded (2a) in only 5% yield along with 80% recovery of (1a). Next, treatment of (1a) with 4 eq of the higher order organocuprate [$Me_2Cu(SCN)Li_2$] at -20°C for 1 hour, followed by quenching with aq. NH_4Cl gave a mixture of (2a) and two compounds containing a secondary methyl group without recovery of (1a). From the formation of the above monomethylated compounds, it was anticipated that addition of methyl iodide at the end of the reactions would cause further methylation of the intermediary monomethylcyclopropane anion equivalent to afford the desired dimethylated compound (2a) exclusively.

Table I. Yields of Preparations of *gem*-Dibromocyclopropanes (1) and *gem*-Dimethylcyclopropanes (2)

Dibromocyclopropane				Dimethylcyclopropane				
								
(1a)	R=α-CO_2Me	64%	(A)[b]	(2a)	R=α-CO_2Me	63%	(3)	20%
(1b)[12]	R=β-CO_2Me	35%		(2b)	R=β-CO_2Me	69%	(3)	Trace
								
(1c)	R=α-CO_2Me	60%	(A)	-----			-----	
(1d)[12]	R=β-CO_2Me	35%		-----			-----	
								
(1e)	R=α-OAc	59%	(A)	(2e)	R=α-OAc	75%	(4) R=α-OH	16%
(1f)	R=β-OAc	35%		(2f)	R=β-OAc	67%	(5) R=β-OH	Trace
								
(1g)	R=$CH_2OSiBu^tMe_2$ R^1=H	95%	(A)	(2g)	R=$CH_2OSiBu^tMe_2$ R^1=H	75%		
(1h)	R=OMe, R^1=H	91%	(B)[b]	(2h)	R=OMe, R^1=H	>44%[c]		
(1i)*	R=OMe, R^1=Bu^t	80%	(B)	(2i)*	R=OMe, R^1=Bu^t	71%		
								
(1j)*	R=CH_2OH	40%	(A)	(2j)*	R=CH_2OH	73%[d]		
(1k)*	R=CH_2OAc	86%	(A)	(2k)*	R=CH_2OAc	80%	(2j)*R=CH_2OH	12%
(1l)*	R=CH 	80%	(A)	(2l)*	R=CH 	71%		

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[a] Isolated yields. The compounds indicated by an asterisk(*) were unseparable mixtures (about 1 to 1.2 ratio).

[b] (A): $CHBr_3$, Bu_3N, and 40% NaOH in CH_2Cl_2 under reflux for 2-6 h.
(B): $CHBr_3$ and *tert*-BuOK in pentane at 0°C for 2 h.

[c] Low yield assumed to be because of the easy volatility of (2h).

[d] 24% recovery of the starting material (1j).

In fact, addition of methyl iodide provided (2a) and (3) in 63% and 20% yields, respectively. However, neither (1c) nor (1d) gave the dimethylated compound (2a) or (2b) by this method. A similar treatment of (1e) with $Me_2Cu(SCN)Li_2$ for one hour, followed by the addition of methyl iodide *in situ*, afforded the dimethylated compounds (2e) and (4) in 75% and 16% yields, respectively.[11] These results suggest that the present method for dimethylation of *gem*-dibromocyclopropane is more efficient than the commonly used dimethylcopper lithium method. The reactions of (1) under with the present method are listed in Table I. A representative experimental procedure is as follows.

Reaction of (1a) with $Me_2Cu(SCN)Li_2$——Cuprous thiocyanate (640 mg, 5.28 mmol) dried under vacuum at 50° C overnight was placed in flame-dried 30 ml two-necked flask, and dry ether (5 ml) was added. Methyllithium (10.7 ml of 0.9 M ether solution, 9.6 mmol) was added to the suspension at -78° C under argon atmosphere and the mixture was gradually warmed up to 0° C in 30 min. Then the mixture was cooled to -20° C and a solution of (1a) (186 mg, 0.48 mmol) in dry ether (1 ml) and HMPA (216 mg, 1.2 mmol) was added dropwise to the mixture at -20° C. The reaction mixture was stirred for 1 h and much excess of methyl iodide was added at -50° C. After 10 min, the reaction mixture was quenched with aq. NH_4Cl at -78°C and extracted with ether. The ether extracts were washed with dil. NH_4OH and brine, dried over K_2CO_3 and concentrated *in vacuo*. Chromatography on Al_2O_3 gave (2a) (76 mg, 63%) and (3) (24 mg, 20%).

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10) All new compounds gave satisfactory elemental analyses and/or mass spectra, and other spectral data (200 MHz ^1H-NMR and IR).

11) In contrast to this result, reaction of a mixture of (1e) and (1f) with Me_2CuLi for nine days afforded a mixture of (2e) and (2f) in comparable yield.[5]

12) The stereostructure of (1b) was unambiguously determined by X-ray analysis. *Crystal data* for (1b) : $C_{12}H_{16}Br_2O_4$, M=384, monoclinic, space group *A*2/*a*, *a*=10.799(1), *b*=10.464(1), *c*=25.964(3) Å, β=103.18°, *U*=2851 Å^3, *Z*=8, and D_c=1.789 gcm^{-3}. The reflection data were collected on a Rigaku AFC-5 diffractometer for $0<\theta<60°$ using monochromated Cu*K*α radiation and ω-2θ scan technique. The structure was solved by the direct method and refined by the full-matrix least-squares method. The final *R* value was 0.055 for 1925 independent reflections [$F>3\sigma(F)$]. The stereostructure of (1d) was elucidated by comparison of its spectral data with those of (1b).

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