Tetrahedron Letters,Vol.30,No.44,pp 6035-6038,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

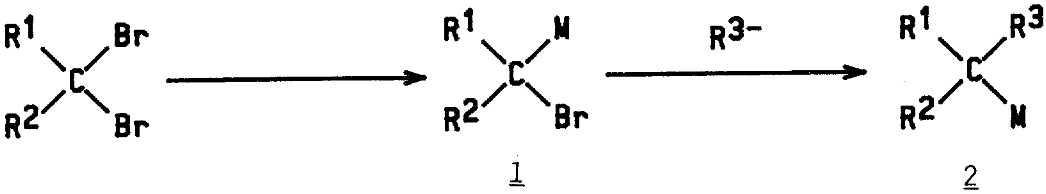
GENERATION AND ALKYLATION REACTION OF LITHIUM 1-HALOCYCLOPROPYLZINCATE

Toshiro Harada, Kazuhiro Hattori, Takeshi Katsuhira, and Akira Oku*
Department of Chemistry, Kyoto Institute of Technology,
Matusugasaki, Sakyo-ku, Kyoto 606, Japan

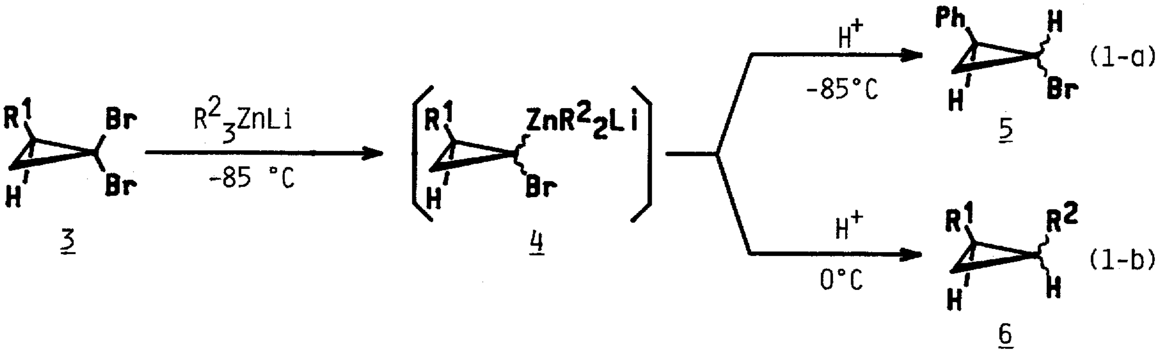
Summary: Lithium dialkyl(1-halocyclopropyl)zincates which are generated from 1,1-dibromocyclopropanes undergo intramolecular alkylation to give 1-alkylcyclopropanes stereoselectively.

α-Haloorganometallic compounds (so-called carbenoids) are versatile reagents which possess ambiphilic reactivity. Many useful reactions have been developed by utilizing carbenoids as α-halocarbanion equivalents.[1] In contrast to this, synthetic potential of carbenoids as α-metallated carbocation equivalents has not been fully demonstrated.[2] As shown in Scheme 1, substitution reactions of carbon nucleophilis at the carbenoid carbon provide us with a method for generating homologated organometallics. In this context, we recently disclosed that lithium (1-bromoalkenyl)zincate 1 (R^1, R^2 = alkylidene, X = Br, M = ZnR_2Li) which can be generated by a Br/Zn exchange reaction of 1,1-dibromoalkene with lithium trialkylzincate (R_3ZnLi) undergoes a facile intramolecular alkylation reaction to give the corresponding organozinc species 2.[3] We wish to report here an extention of the intramolecular alkylation reaction of zincate carbenoid to the stereoselective synthesis of 1,2-disubstituted cyclopropanes.

Scheme 1

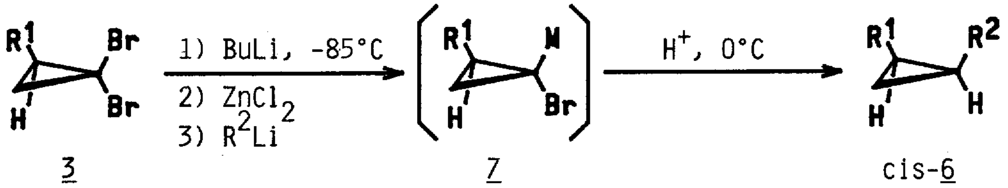


(1-Bromocyclopropyl)zincate **4** was readily prepared by the reaction of 1,1-dibromocyclopropane **3** with lithium trialkylzincate. Thus, treatment of 1,1-dibromo-2-phenylcyclopropane (**3b**; R^1 = Ph) with $(n\text{-Bu})_3ZnLi$[4] (1.3 equiv) in THF at -85 °C for 1 h followed by the addition of AcOH-THF gave the corresponding bromocyclopropane **5** (trans:cis = 1.8:1) in 82% yield (eq 1-a). The intermediate carbenoid **4** was stable at this temperature[5] but underwent alkylation reaction to give 1-butyl-2-phenylcyclopropane (**6b**) (86% yield) when the above reaction mixture was warmed to 0 °C before the addition of AcOH-THF (eq 1-b). More conveniently, alkylation product **6** (a mixture of trans and cis isomers)



was obtained in a high yield by simply adding dibromocyclopropane 3 to a solution of $(R^2)_3ZnLi$ (1.3 equiv) in THF at 0 °C followed by aqueous work-up after 0.5 h (Method A).[6] As shown in Table I, various lithium trialkylzincates can be employed in the present alkylation reaction whereas dibromocyclopropanes were unreactive to triaryl- or trialkenylzincates under these reaction conditions.

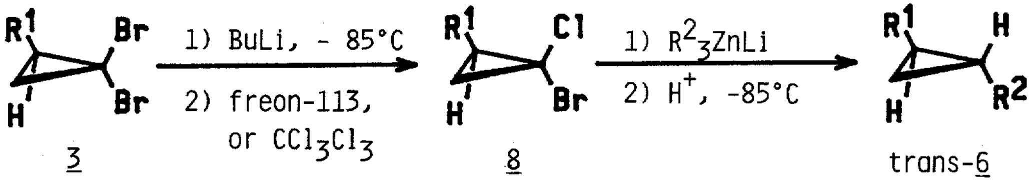
In order to improve the low stereoselectivity observed in Method A, we examined the generation of zincate carbenoid 4 from the corresponding lithium carbenoid which was prepared stereoselectively.[7,2a] Thus, trans-1-bromocyclopropyllithium 7 (M = Li) was prepared selectively by the reaction of 3 with n-BuLi in THF at -85 °C.[8] Successive treatment of 7 (M = Li) with $ZnCl_2$ (1 equiv) and R^2Li (2 equiv) followed by warming the resulting reaction mixture to 0 °C gave cis-6 with a high stereoselectivity (Method B[6] in Table I). Since the trans isomer of zincate carbenoid 7 (M = $Zn(R^2)_3$) is produced under these reaction conditions,[9] it is deduced that the intramolecular alkylation proceeds with inversion of configuration at the carbenoid carbon through a Matteson-Pasto-type rearrangement[10] to give trans alkylation product 6.



(2)

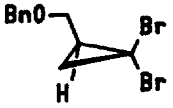
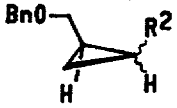
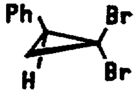
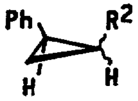
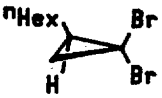
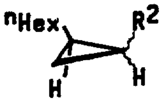
Chlorination of trans-bromocyclopropyllithium 7 (M = Li) with hexachloroethane or 1,1,2-trichloro-1,2,2-trifluoroethane (freon-113) gave trans-1-bromo-1-chlorocyclopropane 8 stereoselectively (eq 3). We anticipated that halogen/Zn exchange reaction of 8 proceeds preferentially on bromine atom and the resulting carbenoid undergoes alkylation reaction to afford the trans isomer of alkylation product 6. Indeed, the reaction of 8 (R^1 = Ph) with $(n\text{-}Bu)_3ZnLi$ in THF (-85 °C - room temperature, 3 h) gave trans-**6b** stereoselectively in 62% yield (trans:cis = 35:1).

It should be noted that the above reaction sequences can be performed in a single-flask operation without the isolation of bromochlorocyclopropane 8 (Method C[6] in Table I). Thus, for example, successive treatment of dibromo-



(3)

Table I Alkylation Reaction of 1,1-Dibromocyclopropanes via Zincate Carbenoid

Entry	Dibromocyclopropane	Method[6]	R^2	Product[a]	Yield[b]	trans:cis[c]
1	3a; 	A	n-Bu	6a; 	95%	1:2.0
2		B			85%	1:19
3		C			70%	15:1
4		A	sec-Bu		91%	1:1.4
5		B			56%	1:>10
6		C			63%	8.5:1
7		A	tert-Bu		76%	1.1:1
8		B			67%	1:13
9		C			50%	36:1
10		A	Me		78%	1:2.0
11		B			76%	1:8.0
12	3b; 	A	n-Bu	6b; 	88%	2.4:1
13		B			63%	1:33
14		C			60%	32:1
15	3c; 	A	n-Bu	6c; 	94%	1:1.6
16		B			43%	1:5.9

[a] All products were fully characterized by ^{1}H-NMR, IR, and high resolution MS.
[b] Isolated yield. [c] Ratios were determined by capillary GLC analysis.

cyclopropane **3b** with 1) n-BuLi (1.0 equiv, -85 °C, 15 min), 2) freon-113 (1.0 equiv, -85 °C, 30 min), and 3) (n-Bu)$_3$ZnLi (1.3 equiv, -85 °C - room temperature, 3 h) afforded trans-**6b** in 60% yield (trans:cis = 32:1).

We have shown here the alkylation reaction of 1,1-dibromocyclopropanes via zincate carbenoids. This endows us with a preparative method of trans or cis alkylation products stereoselectively. As shown in the following report, the synthetic potential of the present reaction is extended further to the gem-dialkylation reaction where the intermediately formed cyclopropylzinc was treated with various electrophiles in the presence of Pd(0) catalyst.[11]

References and Notes

(1) M. Fujita and T. Hiyama, J. Am. Chem. Soc., **107**, 4085 (1985), and references cited therein.

(2) (a) K. Kitatani, T. Hiyama, and H. Nozaki, Bull. Chem. Soc. Jpn., **50**, 1600 (1977). (b) K. Kitatani, H. Yamamoto, T. Hiyama, and H. Nozaki, ibid., **50**,

2158 (1977). (c) M. Duraisamy and H. M. Walborsky, *J. Am. Chem. Soc.*, **106**, 5035 (1984). (d) H. M. Walborsky and M. Duraisamy, *Tetrahedron Lett.*, **26**, 2743 (1985). (e) R. L. Danheiser, A. C. Savoca, *J. Org. Chem.*, **50**, 2401 (1985). (f) T. Harada, A. Karasawa, and A. Oku, *J. Org. Chem.* **51**, 842 (1986).

(3) T. Harada, D. Hara, K. Hattori, and A. Oku, *Tetrahedron Lett.*, **29**. 3821 (1988).

(4) Lithium trialkylzincate was prepared by the reaction of anhydrous $ZnCl_2$ with 3 equiv of alkyllithium in THF at 0 °C for 15 min; M. Isobe, S. Kondo, N. Nagasawa, and T. Goto, *Chem. Lett.*, 679 (1977).

(5) Hydrolysis of the reaction mixture of eq 1-a (R^1 = Ph, R^2 = n-Bu) after 24 h at -85 °C gave **5** (trans:cis = 1.6:1) in 95% yield.

(6) Method A; To a solution of $(R^2)_3ZnLi$ (1.0 mmol) in THF (3.5 mL) was added dibromocyclopropane **3a-c** (0.8 mmol) at 0 °C under a nitrogen atmosphere, and the resulting mixture was stirred for 0.5 h at 0 °C. After aqueous work-up (aq HCl-ether), product **6** was isolated by flash column chromatography. Method B; To a solution of **3a-c** (1.0 mmol) in THF (3.5 mL) was slowly added a hexane solution of n-BuLi (1.0 mmol) at -85 °C under a nitrogen atmosphere. After 15 min, a THF (1.5 mL) solution of $ZnCl_2$ was added successively to this solution and R^2Li (2.1 mmol) at -85 °C and the mixture was stirred at a room temperature for 0.5 h. Product **6** was isolated as described in Method A. Method C; To a THF solution of lithium carbenoid **7** (M = Li) prepared from **3a-c** as described in Method B was added freon-113 (1.0 mmol) and the mixture was stirred at -85 °C for 0.5 h. To this was added a THF (3.5 mL) solution of $(R^2)_3ZnLi$ (1.3 mmol) and the mixture was warmed from -85 °C to a room temperature during a period of 3 h and stirred further for 0.5 h at the same temperature. Product **6** was isolated as described in Method A.

(7) D. Seyferth, R. L. Lambert, Jr., and M. Massol, *J. Organomet. Chem.*, **88**, 255 (1975).

(8) We found that the addition of n-BuLi to a THF solution of dibromocyclopropane at -85 °C is more convenient to generate trans lithium carbenoid **7** (M = Li) stereoselectively in comparison with the previously reported procedures performed at -95°C or below.[7,2a] Reactions at -85 °C were performed by using Neslab Cryo Cool immersion cooler.

(9) Treatment of the reaction mixture of Method B (R^1 = Ph, R^2 = n-Bu) with AcOH-THF at -85 °C gave selectively trans-**5** (trans:cis = >40:1; 73% yield).

(10) (a) D. S. Matteson and R. W. H. Mah, *J. Am. Chem. Soc.*, **85**, 2599 (1963). (b) D. J. Pasto and J. L. Miesel, *ibid.*, **85**, 2118 (1963). (c) H. C. Brown, D. Basavaiah, S. U. Kulkarni, H. D. Lee, and E. Negishi, J-J. Katz, *J. Org. Chem.*, **51**, 5270 (1986).

(11) Acknowledgment: This work was supported by Grant-in-Aid for Special Project Research (No. 62215019) from Japan Ministry of Education, Science, and Culture.

(Received in Japan 15 June 1989)