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Preparation of (1-Cyclopropylidenealkyl)zinc Reagents by the Reaction of Homopropargylic Sulfonates with Triorganozincates

Toshiro Harada,* Hiroki Wada, and Akira Oku*

Department of Chemistry, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606, Japan

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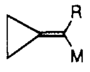
Methylenecyclopropanes, which are cumulated combination of a cyclopropane and a double bond,[1] exhibit unique reactivity in ring-opening reactions, cycloadditions, and transformations to cyclopropanes.[2] Considerable attention has been focused on their use as synthetic building blocks.[1,3-5] (1-Cyclopropylidenealkyl)metals **1** may serve as useful reagents for the preparation of functionalized alkylidenecyclopropanes.[6] However, little effort has been expended on their generation and synthetic applications. Previously, Merril and Negishi reported the generation of organoboron derivatives **1** (M = BR_2) via a 1,2-migration reaction of alkynylborate $LiB(R)_3C{\equiv}CCH_2CHOTs$.[7] The organoboron derivatives were not used in the preparation of functionalized alkylidenecyclopropanes but converted oxidatively into cyclopropyl ketones.[8]



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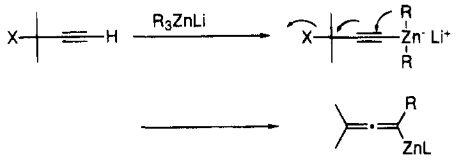
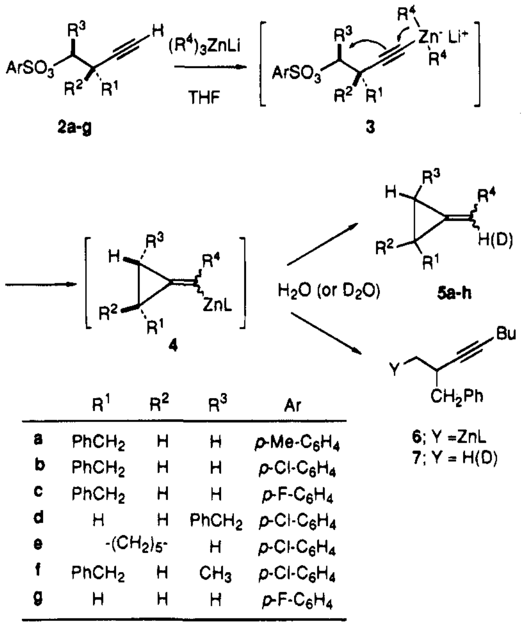
We reported recently that the reaction of propargylic substrates with triorganozincates affords homologated allenic zinc reagents through a mechanism involving an initial metalation of the acetylenic proton and a 1,2-migration of the resulting alkynylzincates (eq 1).[9-11] The facile migration observed for the alkynylzincates derived from propargylic substrates prompted us to investigate the reaction of those derived from homopropargylic sulfonates **2** with the hope of developing a method for the preparation of (1-cyclopropylidenealkyl)zinc reagents **4** (Scheme 1).



(1)

Scheme 1



	R^1	R^2	R^3	Ar
a	$PhCH_2$	H	H	*p*-Me-C_6H_4
b	$PhCH_2$	H	H	*p*-Cl-C_6H_4
c	$PhCH_2$	H	H	*p*-F-C_6H_4
d	H	H	$PhCH_2$	*p*-Cl-C_6H_4
e	-$(CH_2)_5$-		H	*p*-Cl-C_6H_4
f	$PhCH_2$	H	CH_3	*p*-Cl-C_6H_4
g	H	H	H	*p*-F-C_6H_4

Treatment of tosylate **2a** with $(Bu)_3ZnLi$ (2.0 equiv) in THF at 0 °C for 1 h and quenching of the mixture with D_2O gave methylenecyclopropane **5a** (R^4 = Bu) (*E*:*Z* = 1.9:1)[12] and alkyne **7** in 75% and 8% yields, respectively. ^{1}H NMR analysis of the major product showed incorporation of deuterium (98%-*d*) at the olefinic carbon, demonstrating generation of (1-cyclopropylidenepentyl)zinc (**4a**). The yield of **7** increased to 42% when a similar reaction was carried out at 0 °C for 6 h,[13] suggesting that **4a** underwent a ring-opening reaction leading to homopropargylic zinc **6**. The ring-opening reaction was retarded completely at −20 °C, but the starting material was not

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(12) Configurations of (*E*)- and (*Z*)-**5** were determined by NOESY experiments (for **5f,g**) and by the observation of large differences ($\Delta\delta$ 0.2−1.1 ppm) in the ^{1}H chemical shifts of the nonequivalent benzylic methylene protons of (*Z*)-**5a−f,h**.

(13) Methylenecyclopropane **5a** (*E*:*Z* = 1:1.6) was obtained in 53% yield.

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Table 1. Preparation of (1-Cyclopropylidenealkyl)zinc Reagents 4[a]

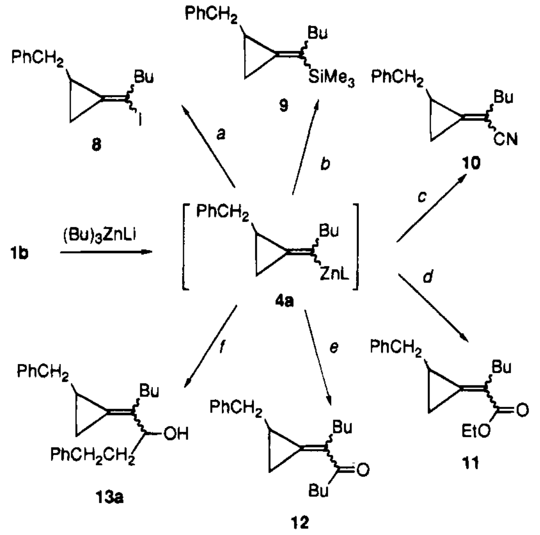
entry	substrate	zincate R^4	condns[b]	product	yield,[c] % (*d*-cont. %)[d]	E:Z[e]
1	**2b**	Bu	A	**5a**	93 (95)	2.4:1
2[f]	**2b**	Bu	A	**5a**	91 (88)	2.2:1
3	**2c**	Bu	A	**5a**	88 (97)	2.2:1
4	**2b**	^{s}Bu	A	**5b**	81 (92)	3.8:1[g]
5	**2b**	^{t}Bu	B	**5c**	71 (91)	5.3:1
6	**2b**	Me	B	**5d**	65 (75)	1.6:1[g]
7	**2c**	$TMSCH_2$	B	**5e**	59	1.2:1
8	**2b**	Ph	C	**5f**	76 (92)	1:2.4
9	**2d**	Bu	C	**5a**	78 (93)	1:1.9
10	**2e**	Bu	A	**5g**	93	9.5:1
11	**2f**	Bu	C	**5h**	99	3.4:1

[a] Unless otherwise noted, reactions were carried out by using 2.0 equiv of zincates in THF. [b] A: −20 °C, 6 h. B: −10 °C, 6 h. C: 0 °C, 6 h. [c] Isolated yield. [d] Mean values of (*E*)- and (*Z*)-**5** determined by ^{1}H NMR analyses. [e] Unless otherwise noted, ratios were determined by a capillary GC analyses. [f] The reaction was carried out by using 1.5 equiv of the zincate. [g] Determined by ^{1}H NMR analyses.

fully consumed after 6 h.[14] Finally, efficient generation of **4a** was realized by using more reactive *p*-chloro- and *p*-fluorobenzenesulfonates **2b,c** as substrates. Thus, the reactions of **2b** and **2c** at −20 °C for 6 h gave **5a** of high deuterium content in 93% and 88% yields, respectively (entries 1 and 3 in Table 1).

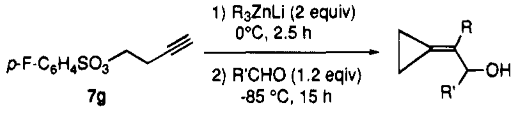
A variety of triorganozincates were used successfully in the preparation of the corresponding (1-cyclopropylidenealkyl)zinc reagents (entries 1−8). Temperatures above −20 °C were required in the reactions of the less reactive zincates, such as Me_3ZnLi, Ph_3ZnLi, and $(TMSCH_2)_3ZnLi$. However, no ring-opening reactions occurred for the resulting organozinc species under these conditions. Not only primary but also secondary sulfonates **2d,f** underwent the 1,2-migration/cyclization efficiently (entries 9 and 11). Formation of 2′,3′-*cis* product **5h**[15] in the reaction of *anti* homopropargylic sulfonate **2f** demonstrated that the cyclization proceeded with inversion of stereochemistry at the electrophilic carbon. Except for the reaction of $(Ph)_3ZnLi$, 1,2-migration and cyclization of alkynylzincates **3** took place preferentially at the same face of the triple bond. Thus, for example, in the reaction with $(Bu)_3ZnLi$, both **2b** and **2d** afforded the same product **5a**, but with opposite stereoselectivity (entries 1 and 9). Higher selectivities were observed when an alternative *anti* mode of 1,2-migration/cyclization was sterically unfavorable (entries 5 and 10). The starting homopropargylic sulfonates are readily available,[16,17] so their reactions with triorganozincates can be easily used in the preparation of a variey of (1-cyclopropylidenealkyl)zinc reagents.

Scheme 2



[a] I_2 (5 equiv), −85 °C, 77%, *E*:*Z* = 1:2.3. [b] TMSCl (7 equiv), −85 to 0 °C, 56%, *E*:*Z* = 1:1.3. [c] TsCN (2 equiv), −85 °C, 73%, *E*:*Z* = 1:2.1. [d] $ClCO_2Et$ (4.5 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), −20 °C to rt, 65%, *E*:*Z* = 1:3.4. [e] BuCOCl (4.5 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), −20 °C to rt, 61%. [f] $PhCH_2CH_2CHO$ (1.0 equiv), −85 °C, 65%.

Organozinc reagents **4**, thus generated, underwent a coupling reaction with a variety of electrophiles (I_2, TMSCl, TsCN,[18] $ClCO_2Et$, BuCOCl,[19] and aldehydes) to furnish functionalized methylenecyclopropanes **8**−**13** (Scheme 2 and eq 2). It should be noted that, in the reaction with aldehydes and TsCN, organozinc reagents **4** underwent a transfer of the 1-(cyclopropylidene)alkyl group in preference to the alkyl group.[20] Thus, for example, reaction of **4b** with 1 equiv of 3-phenylpropanal at −85 °C for 15 h afforded adduct **13a** in 65% yield with minor formation of the butyl adduct (6%).[21]



(2)

13b; R = Me, R′ = $PhCH_2CH_2$ 57%
13c; R = Bu, R′ = ^{i}Pr 52%

Elucidation of the full scope of the reaction as well as utilization of homopropargylic zinc species produced by the ring-opening of **4** are currently underway in our laboratories.

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Supporting Information Available: Spectral data (^{1}H NMR, ^{13}C NMR, IR, MS, and/or HRMS) for new products (4 pages).

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(14) The reaction afforded **5a** in 55% yield (*E*:*Z* = 2.3:1) with the recovery of **2a** (32%).

(15) The *cis* stereochemistry of (*E*)-**5h** was determined by a NOESY experiment in which NOE was observed between the methyl and the benzylic methylene protons.

(16) Sulfonates **2a**−**f** were prepared by the reaction of allenic zinc reagents with aldehydes[9,15] and the subsequent sulfonylation of the resulting homopropargylic alcohols.

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(20) It is probable that initially formed organozinc **4** (L = R^4) reacts reversibly with excess $(R^4)_3ZnLi$ to be converted partly to the more reactive zincate **4** (ZnL = $Zn(R^4)_2Li$), from which the reaction with aldehydes may proceed.

(21) Typical procedure: Preparation of methylenecyclopropane derivative **10**: To a solution of $ZnCl_2$ (106 mg, 0.78 mmol) in THF (2.4 mL) was added BuLi (1.62 M in hexane, 1.4 mL, 2.3 mmol) at 0 °C, and the mixture was stirred for 15 min. After addition of a THF (2 mL) solution of **2b** (131 mg, 0.39 mmol) to the resulting solution of $(Bu)_3ZnLi$ at −85 °C, the mixture was stirred at −20 °C for 6 h. The mixture was then allowed to cool back to −85 °C, and then a THF (1 mL) solution of TsCN (142 mg, 0.78 mmol) was added. After being stirred for 15 h at −85 °C, the mixture was poured into 1 N HCl and extracted twice with ether. The combined organic layers were washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (SiO_2, eluting with 4% ethyl acetate in hexane) afforded, in the order of elution, 15.2 mg (19%) of **5a** and 64.2 mg (73%) of **10a** (*Z*:*E* = 2.1:1).