A New Method for Preparing Benzylzinc Reagents via Homologation of Triorganozincates

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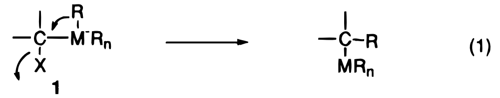
Homologation of organometallics is becoming of increasing importance in organic syntheses because the reaction allows the efficient assembly of complex molecular structures through additional bond formation of the resulting homologated organometallics.[1] Organoboronate complexes **1** and **2** (M = B, n = 2) bearing a leaving group at the α-position and the γ-position with α,β-unsaturation, respectively, undergo 1,2-migration of a ligand (R) to give homologated organoboron compounds (eqs 1 and 2).[2,3] Recent reports from this laboratory revealed that related organozincates **1** and **2** (M = Zn, n = 1), readily generated by halogen/zinc exchange and zincation with triorganozincates (R_3ZnM', M′ = Li, MgX), undergo facile 1,2-migration at lower temperatures to give synthetically versatile organozinc reagents with carbon−carbon bond formation.[4]



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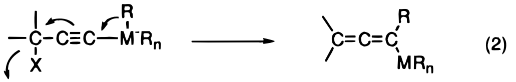
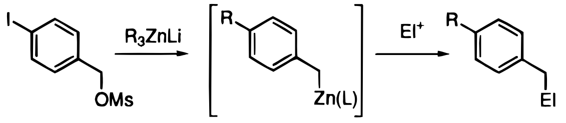


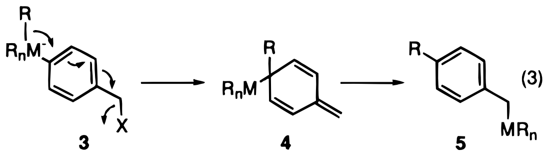
2

Ate complexes **3** bearing a leaving at the remote benzylic position would rearrange with carbon−carbon bond formation to give benzylmetal **5** via (4-methylene-2,5-cyclohexadienyl)metal **4** (eq 3). Coexistence of the negatively charged metal atom center and the potential cationic center in **1** and **2** must be a major driving force of the 1,2-migration. However, for **3**, not only are these two reactive centers separated by the longer aromatic π-system but also 1,2-migration leading to cross-conjugated **4** would suffer from a considerable loss of aromatic stabilization. We wish to report herein that arylzincates **3** (M = Zn, n = 1), generated by the reaction of p-iodobenzyl mesylate (**6**) and organozincates, undergo facile 1,2-migration even at low temperatures (<−40 °C) to give benzylzinc **5a**, which can be utilized in the reaction with a variety of electrophiles (Scheme 1).

Scheme 1

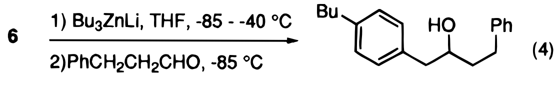


6 **5a**



3 **4** **5**

Treatment of mesylte **6** with Bu_3ZnLi (1.2 equiv) in THF at −85 °C and hydrolysis of the mixture after being warmed to −40 °C afforded p-butyltoluene (**7**) in 61% yield.[5,6] The yield of **7** was improved to 90% by using 2.0 equiv of Bu_3ZnLi under similar conditions. Generation of benzylzinc **5a** (R = Bu) under these conditions was verified by the formation of alcohol **8** (80% yield) in subsequent treatment of the reaction mixture with 2-phenylpropanal (1.2 equiv) at −85 °C (eq 4). Although an excess amount of Bu_3ZnLi was employed in this reaction, formation of the butylation product, 1-phenyl-3-heptanol, was not detected, indicating the higher reactivity of the benzyl moiety in zinc reagent **5a**.[7]



8

Treatment of **6** with Bu_3ZnLi (2.0 equiv) at −85 °C for 20 min and the hydrolysis of the mixture at this temperature gave benzyl mesylate in 84% yield. The result shows that the iodine/zinc exchange reaction[9] proceeds smoothly at −85 °C, giving rise to arylzincate intermediate **3** (M = Zn, n = 1, R = Bu), which is stable at this temperature. Upon warming to −40 °C, the arylzincate may undergo 1,2-migration to give benzylzinc **5a** (R = Bu) via intermediate **4** (M = Zn, n = 1, R = Bu). When the reaction mixture was allowed to warm to rt, **5a** (R =

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[1] (a) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 865−911. (b) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718. (c) Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 11689. (d) Marek, I.; Normant, J.-F. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 3241.

[2] (a) Matteson, D. S.; Mah, R. W. H. *J. Am. Chem. Soc.* **1963**, *85*, 2599. (b) Leung, T.; Zweifel, G. *J. Am. Chem. Soc.* **1974**, *96*, 5620. (c) Brown, H. C. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975. (d) Negishi, E. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 5, p 255. (e) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: London, 1988. (f) Matteson D. S. *Pure Appl. Chem.* **1991**, *63*, 339. (g) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1994**, *66*, 201. (h) Jadhav, P. K.; Man, H.-W. *J. Am. Chem. Soc.* **1997**, *119*, 846.

[3] For 1,2-migration of other ate complexes see: (a) Negishi, E.; Akiyoshi, K. *J. Am. Chem. Soc.* **1988**, *110*, 646. (b) Negishi, E.; Akiyoshi, K.; O'Connor, B.; Takagi, K.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 3089. (c) Kitatani, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1600 and 2158. (d) Kocienski, P.; Wadman. S.; Cooper, K. *J. Am. Chem. Soc.* **1989**, *111*, 2363. (e) Stocks, M.; Kocienski, P.; Donald, K. K. *Tetrahedron Lett.* **1990**, *31*, 1637. (f) Knochel, P.; Jeong, N.; Rozema, M. J.; Yeh, M. C. P. *J. Am. Chem. Soc.* **1989**, *111*, 6474. (g) AchyuthaRao, S.; Rosema, M. J.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 2694. (h) Miller, J. A. *J. Org. Chem.* **1989**, *54*, 998. (i) Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1997**, *38*, 3275.

[4] (a) Harada, T.; Hara, D.; Hattori, K.; Oku, A. *Tetrahedron Lett.* **1988**, *29*, 3821−3824. (b) Harada, T.; Katsuhira, T.; Osada, A.; Iwazaki, K.; Maejima, R.; Oku, A. *J. Am. Chem. Soc.* **1996**, *118*, 11377 and references therein.

[5] Lithium trialkylzincates R_3ZnLi were prepared by treatment of RLi (3 equiv) with anhydrous $ZnCl_2$ in THF at 0 °C.[4b]

[6] The temperature −85 °C is not critical. A similar result was obtained at −78 °C. Authors use a Neslab Cryocool CC-100 immersion cooler in performing low-temperature reactions.

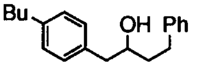
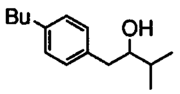
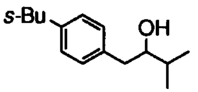
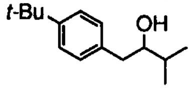
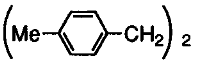
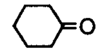
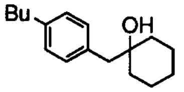
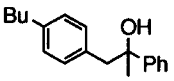
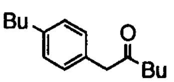
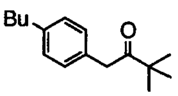
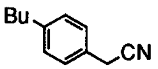
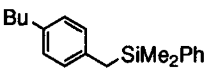
[7] Assuming a rapid ligand transfer,[8] the initially formed benzylzinc (L = Bu) should react reversibly with Bu_3ZnLi to form the corresponding benzylzincate (Zn(L) = $Zn(Bu)_2Li$).

[8] (a) Seitz, L. M.; Brown, T. L. *J. Am. Chem. Soc.* **1966**, *88*, 4140. (b) Seitz, L. M.; Brown, T. L. *J. Am. Chem. Soc.* **1967**, *89*, 1602. (c) Seitz, L. M.; Little, B. F. *J. Organomet. Chem.* **1969**, *18*, 227.

[9] Y. Kondo, N. Takezawa, C. Yamazaki, and T. Sakamoto, *J. Org. Chem.* **1995**, *59*, 4717.

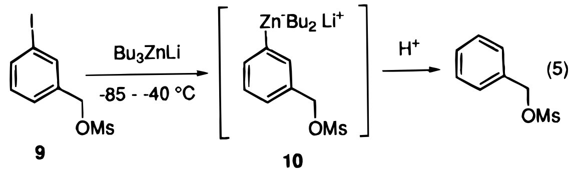
S0022-3263(97)01615-0 CCC: $14.00

Table 1. Generation and Reaction of Benzylzinc Reagents[a]

entry	zincate	electrophile	product	yield (%)
1	Bu_3ZnLi	$Ph(CH_2)_2CHO$		80
2	Bu_3ZnLi	*i*-PrCHO		72
3	$Bu_3ZnMgCl$			45
4	*s*-Bu_3ZnLi	*i*-PrCHO		62
5	*t*-Bu_3ZnLi	*i*-PrCHO		56
6	Me_3ZnLi	*i*-PrCHO		55
7	Bu_3ZnLi			63
8	Bu_3ZnLi	$PhCOCH_3$		48
9	Bu_3ZnLi	BuCOCl		61
10	Bu_3ZnLi	*t*-BuCOCl		48
11	Bu_3ZnLi	TsCN		58
12	Bu_3ZnLi	$PhMe_2SiCl$		62

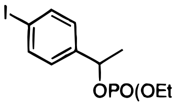
[a] Reactions were carried out by mixing mesylate **6** and zincates (2.0 equiv) at -85 °C, warming the mixture to -40 °C, and treating with electrophiles (1.2 equiv) for 3 h at -85 °C.

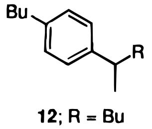
Bu) reacted with iodobutane, generated in situ by iodine/zinc exchange, to give *p*-butylpentylbenzene in 57% yield. Support for the 1,2-migration mechanism was obtained in the reaction of *m*-iodobenzyl mesylate (**9**) with Bu_3ZnLi at temperatures from −85 to −40 °C (eq 5). Formation of benzyl mesylate (71%) shows the stability of *m*-substituted arylzincate **10** at higher temperatures.

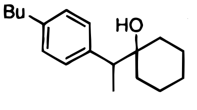


Tributylzincate prepared from BuMgBr (3 equiv) and $ZnCl_2$ can also be used albeit with lower efficiency (Table 1, entry 3). The reaction of *s*-Bu_3ZnLi and *t*-Bu_3ZnLi afforded the corresponding *p*-substituted benzylzinc reagents, which further reacted with isobutyraldehyde to give the corresponding adducts (entries 4 and 5). The reaction of Me_3ZnLi, however, gave 4,4′-dimethylbibenzyl as a major product but not the corresponding product (entry 6).[10] The benzylzinc reagents reacted successfully not only with aldehydes but also with ketones, acyl chlorides, tosyl cyanide,[12,13] and chlorodimethylphenylsilane (entries 7−12). It should be noted that, in acylation, the formation of *tert*-alcohols derived from further reaction of the benzylzinc to the product ketones was not detected.

Because secondary benzyl mesylates are unstable and difficult to handle, the reaction of stable phosphate **11** was examined. The reaction with Bu_3ZnLi at temperatures from −85 to 0 °C gave dibutylation products **12** in 85% yield. The secondary benzylzinc reagent is more reactive, and the formation of **12** was not completely retarded even at −40 °C. Nevertheless, the secondary zinc can be used in the reaction with other electrophiles under Barbier conditions. Thus, the reaction of phosphate **11** and Bu_3ZnLi in the presence of allyl bromide (3 equiv) at temperatures from −85 to 0 °C afforded the corresponding adducts **13** (74%) and **14** (65%), respectively.


11


12; R = Bu
13; R = $CH_2{=}CHCH_2$


14

In summary, we have shown that arylzincates bearing a remote leaving group at the benzylic position undergo a facile 1,2-migration to give homologated benzylzinc reagents. The zinc reagents reacted efficiently with a variety of electrophiles. The overall reaction serves as a useful one-pot method for the synthesis of *p*-substituted benzene derivatives.

Supporting Information Available: Experimental procedure including synthesis and characterization of new compounds (17 pages).

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[10] Me_3ZnLi did not react with **6** at −85 °C. Owing to the lower reactivity,[11] iodine/zinc exchange and subsequent 1,2-migration took place simultaneously at higher temperatures. The dimeric product was most probably produced by the coupling reaction of 4-methylbenzylzinc reagent with 4-methylbenzyl iodide, which is formed in situ by iodine/zinc exchange of **6** with the benzylzinc reagent.

[11] Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993**, *58*, 4897.

[12] It was reported that benzylzinc bromide reacts with tosyl cyanide exclusively at the ortho position to give 2-methylbenzonitrile.[13] Formation of this regioisomeric product was not observed in the present reaction.

[13] Klement, I.; Lennick, K.; Tucker, C. E.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 4623.