Pergamon

*Tetrahedron Letters*, Vol. 35, No. 48, pp. 8957-8960, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01990-8

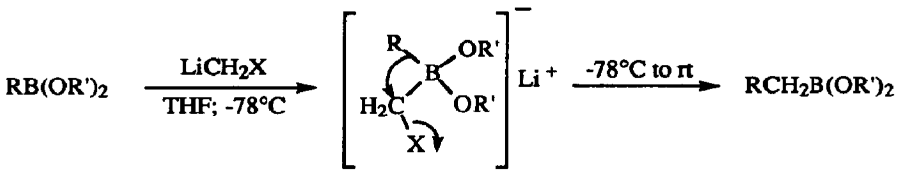
# Homologation of Representative Boronic Esters Using *in situ* Generated (Halomethyl)lithiums: A Comparative Study

Raman Soundararajan, Guisheng Li and Herbert C. Brown*

*H.C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University,*
*West Lafayette, Indiana 47907 USA*

**Abstract:** *A comparative study of the homologation of representative boronic esters with in situ generated* $LiCH_2X$ *(X= Cl; Br; I) is presented wherein the reactivity differences arising out of the steric and electronic effects of the migrating groups, and the nature of the ester groups are determined and discussed.*

*In situ* generation and capture of (halomethyl)lithiums in the presence of boronic esters is an efficient process for the insertion of the $CH_2$ group into the C-B bond.[1-5] Instantaneous capture of the highly reactive carbenoid by boronic esters gives rise to the intermediate 'ate' complex which then undergoes rearrangement with stereoretention at the migrating center.[1,2] Matteson *et.al*, in their pioneering work, showed that (chloromethyl)lithium generated from $ICH_2Cl$ and n-BuLi at -78°C in the presence of boronic ester is an effective reagent for this process.[1a] Later, as part of a detailed study, an alternative route was developed by us using $BrCH_2Cl$ instead of $ICH_2Cl$ with essentially similar results.[2] However, in view of the significance of this process in asymmetric organic syntheses, occasional problems arising from B-O elimination or from oxygen migration made it desirable to find new and improved procedures.[6-8]



R = *n*-, *sec*-, *tert*- alkyl; cycloalkyl; aryl; alken-1-yl. X= Cl; Br; I
$(OR')_2 = (O^iPr)_2$; $(OCH_2)_2$; $(OCH_2)_2CH_2$; $(OCH_2)_2CMe_2$; $(OCMe_2)_2$

Matteson and Michnik demonstrated that even $LiCH_2Br$ can be used as an efficient reagent for the homologation with similar or higher yield as compared to $LiCH_2Cl$.[3] Though this reagent was efficient in many cases, only moderate yields were reported for functionalised boronic esters, such as alkoxymethyl boronates. Moreover, recently Wallace *et.al* reported that both $LiCH_2Cl$ and $LiCH_2Br$ failed to give satisfactory results in the homologation of $\Delta^2$ isooxazolinylboronic esters.[4] Interestingly, they showed for the first time that even the highly labile (iodomethyl)lithium can be effectively captured *in situ* by the boronic esters followed by efficient homologation.

With the appearance of their report, it is now established that all three (halomethyl)lithiums are highly useful reagents for homologation despite their proclivity towards fast decomposition. Besides these sporadic reports of the problems and solutions, no detailed report has appeared to establish the scope and limitations of each of these reagents. In the light of the synthetic importance of this homologation process in asymmetric syntheses, zealously developed by Matteson *et. al.*[7] and subsequently by our group,[6] we decided to undertake a systematic study for direct comparison of these reagents in the homologation of different classes of representative boronic esters, to explore the effects of the changes in the steric and electronic requirements of the migrating group and the nature of the ester moiety.

The (halomethyl)lithiums were generated *in situ* according to the previously published procedures.[9] The reactions were monitored by $^{11}$B NMR and the yields determined by GC analyses of the corresponding alcohols obtained from oxidation of the homologated products with alkaline hydrogen peroxide.[2] The results of the homologation of representative *n*-, *sec*-, *tert*- alkyl, cycloalkyl, aryl and alken-1-yl boronic esters with each of $LiCH_2X$ (X= Cl; Br; I) under otherwise identical conditions are reported in Table I. A similar study of the effects of ester groups on the homologation of *n*-butyl- and phenylboronates, containing representative ester groups, is summarized in Table II.

**Table I. Homologation of Representative Boronic Esters, $RB(OCH_2)_2CH_2$, Using *in situ* Generated $LiCH_2X^a$ (X=Cl; Br; I)**

| No. | R | Yield(%)$^b$ | | |
|---|---|---|---|---|
| | | Cl | Br | I |
| 1 | *n*-Bu | 96 | 89 | 68 |
| 2 | *sec*-Bu | 92 | 87 | 63 |
| 3 | *tert*-Bu | 41 | 66 | 51 |
| 4 | Chx | 91 | 93 | 88 |
| 5 | Ph | 92 | 92 | 82 |
| 6 | $^nC_5H_{11}CH{=}CH$ (*E*) | 93 | 95 | 81 |

[a] 1.2 eq of the reagent was used. [b] Yields based on gc analyses of the alcohol produced by oxidation of the homologated product with alkaline hydrogen peroxide.

A perusal of Table I reveals that best yields are generally obtained with $LiCH_2Cl$ and $LiCH_2Br$ in all the cases examined except *tert*-butylboronate. In the case of this sterically bulky alkyl group optimum yields are obtained with $LiCH_2Br$. As one would normally expect with aryl and alken-1-yl boronates, due to the electronic effect and the resultant higher reactivity, any rate differences between the three carbenoid reagents are attenuated.[10] Among the (halomethyl)lithiums, the iodo derivative gives poorer results presumably due to inherent instability of the intermediate 'ate' complex as can be seen by the appearance in the $^{11}B$ NMR of unrearranged starting material. Interestingly, in the case of *tert*-butylboronate, the lower yield with $LiCH_2Cl$ reflects a considerable amount of ring expansion product (20%) as a result of concomitant oxygen migration (identified in the $^{11}B$ NMR as the corresponding borinate peak at $\delta$ 53 ppm), competing with the relatively sluggish rearrangement of the bulky alkyl group.

On the other hand, with $LiCH_2I$ the lower yield is attributable to either the incomplete capture of the reactive carbenoid, as was pointed out by Matteson *et.al.* in the case of $LiCH_2Br$,[4] or poorer stability of the 'ate' complex. $^{11}B$ NMR analyses of the reactions generally support the latter reasoning though the intermediate 'ate' complex disappears quite rapidly at rt in almost all cases, making an unequivocal conclusion difficult.[11] However, in the case of cyclohexyl-, phenyl- and hepten-1-ylboronates, the higher yields (entries 4-6, Table I) indicate efficient capture of the reactive species. Also, a similar reaction with alkyn-1-ylboronates shows a complete capture even in the case (iodomethyl)lithium as the more stable intermediate 'ate' complex (100 %) can be clearly seen ($^{11}B$ NMR; $\delta$ 0-3 ppm) even at rt before rearranging slowly to the homologated product.[12] As aforementioned, all three (halomethyl)lithiums react equally efficiently when the rearranging group is reactive enough to offset any instability of the corresponding 'ate' complexes.

**Table II. Homologation of Selected Boronic Esters, n-BuB(OR')$_2$ and PhB(OR')$_2$ with *in situ* Generated $LiCH_2X$[a]**

| No. | B(OR')$_2$ | Yield(%)[b] | | | | | |
|---|---|---|---|---|---|---|---|
| | | n-Bu | | | Ph | | |
| | | Cl | Br | I | Cl | Br | I |
| 1 | $B(O^iPr)_2$ | 86 | 91 | 83 | 94 | 95 | 89 |
| 2 | $B(OCH_2)_2$ | 68 | 83 | 73 | 72 | 68 | 76 |
| 3 | $B(OCH_2)_2CH_2$ | 96 | 89 | 68 | 92 | 92 | 82 |
| 4 | $B(OCH_2)_2CMe_2$ | -- | -- | -- | 97 | 87 | 49 |
| 5 | $B(OCMe_2)_2$ | 87 | 73 | 48 | 79 | 64 | 41 |

[a] 1.2 eq of the reagent was used. [b] Yields based on gc analyses of the alcohol produced by oxidation of the homologated product with alkaline hydrogen peroxide.

Among the cyclic boronates, the five-membered ethyleneglycol boronates (entry 2, Table II) seem to give slightly lower yields due to the formation of a small quantity of borinates (≥ 8%) from a ring expansion reaction. However, the problem of ring expansion was negligible or absent in all other cases, including the other five-membered pinacol boronate for both the *n*-butyl- and phenylboronates. It is noteworthy that when the phenylboronate of neopentylglycol was homologated with $LiCH_2I$, the yields drop considerably to 49% as compared to 82% for the corresponding 1,3-propanediol ester, indicating a steric effect of the methyl groups in the neopentyl moiety.

Based on the above discussions, we conclude that in general, for acyclic and relatively unhindered cyclic boronates both $LiCH_2Br$ and $LiCH_2Cl$ give very high conversions, while for hindered alkyl boronates $LiCH_2Br$ seems to be the reagent of choice for optimum results. Though $LiCH_2I$ is equally effective in the case of more reactive boronates (aryl and alken-1-yl), the relative instability of the species probably accounts for the overall drop in yield. Finally, the bulkier the ester group, the better the conversion with $LiCH_2Cl$ compared to the conversions with $LiCH_2Br$ and $LiCH_2I$.

**Acknowledgments:**

This study was initiated with support from National Science Foundation grant (CHE 9012236) and completed with support from the Borane Research Fund. This financial support which made this study possible is gratefully acknowledged.

**References and Notes:**

1. (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687.
   (b) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795.
2. Brown, H. C.; Singh, S. M.; Rangaishenvi, M. V. *J. Org. Chem.* **1986**, *51*, 3150.
3 Michnik, T. J.; Matteson, D. S. *Synlett* **1991**, 631.
4. Wallace II, R.; Zong, K. K. *Tetrahedron Lett.* **1992**, *33*, 6941.
5. Brown, H. C.; Phadke, A. S.; Rangaishenvi, M. V. *J. Am. Chem. Soc.* **1988**, *110*, 6263.
6. (a) Brown, H. C.; Phadke, A. S.; Bhat, N. G. *Tetrahedron Lett.* **1993**, *34*, 7845.
   (b) Brown, H. C.; Phadke, A. S. *Synlett* **1991**, 631.
7. Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859.
8. (a) Matteson, D. S.; Peterson, M. L. *J. Org. Chem.* **1987**, *52*, 5116.
   (b) For a related problem see Matteson, D. S. *Pure & Appl. Chem.* **1991**, *63*, 339.
9. $LiCH_2Cl$: see ref. 1a or ref. 2; $LiCH_2Br$: see ref. 3 and $LiCH_2I$: see ref. 4 (n-BuLi was used instead of MeLi). Conditions identical to the one described in reference 2 was used for the *in situ* capture and homologation with various boronic esters except for the temperature (65°C). Instead, the contents were rapidly warmed to rt and stirred for an additional 1.5 h , by which time the 'ate' complex had completely disappeared in most cases.
10. In the case of aryl and alken-1-ylboronates the rearrangement was complete by the time the $^{11}B$ NMR was recorded at rt at the end of 30 min, at -78°C, after the addition of n-BuLi was completed.
11. Low temperature $^{11}B$ NMR analysis of the reaction probably could help identify the source of the problem more conclusively.
12. See the following paper in this issue.

(*Received in USA* 18 *August* 1994; *revised* 30 *September* 1994; *accepted* 7 *October* 1994)