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General Synthesis of 2-Alkyn-1-ylboronates in Excellent Isomeric Purity

Raman Soundararajan, Guisheng Li and Herbert C. Brown*

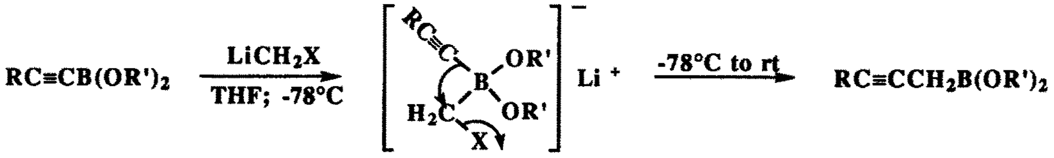
H. C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University,
West Lafayette, Indiana 47907 USA

Abstract: *2-Alkyn-1-ylboronates have been synthesized successfully, in excellent isomeric purity, via the in situ homologation of alkyn-1-ylboronates with $LiCH_2I$. The relative reactivities exhibited by various $LiCH_2X$ reagents (X=Cl; Br; I) are described.*

Allyl, allenyl and propargylboranes have emerged as highly useful reagents in asymmetric organic synthesis.[1] The high stereoselectivities offered by these reagents in their reactions with carbonyl compounds have contributed to their popularity, and consequently several modifications and improvements have been appearing regularly. Among these reagents, the propargylboronates have been less studied mainly due to the lack of a convenient general synthesis for these compounds.[2] Direct methods such as the reaction of Grignard reagents obtained from 2-alkynylbromides with methyl borate are beset with problems due to the formation of an isomeric mixture of allenyl- and propargylboronates, except in the case of phenyl substituted propargyl bromides.[3] This is due to the rapid equilibration that occurs between the allenic and propargylic magnesium species even at -78°C.[4] The preparation of the simplest propargyl boron reagent by this method has been unsuccessful since the Grignard reagent from propargyl bromide gives only the allenic isomer, captured by the boron without rearrangement.[3a,5] Corey *et.al* have reported the preparation of a simple propargylboron reagent using an organotin intermediate.[1g] Apart from these reports, no systematic effort has been described for the preparation of title compounds in good isomeric purity.

Both (chloromethyl)- and (bromomethyl)lithiums have been used for the one-carbon homologation of boronic esters.[6,7] More recently, Wallace *et.al* have reported successful homologations with $LiCH_2I$ for cases where both $LiCH_2Br$ and $LiCH_2Cl$ gave poor results.[8] In our recent paper regarding a comparative study of homologation reactions of different classes of boronic esters with *in situ* generated $LiCH_2X$ (X=Cl; Br; I), we have delineated the effects of the nature of the boronic ester and the halogen atom in these reactions.[9] Earlier, we had developed a convenient synthesis of "higher" crotylboronates, *via* homologation of stereodefined alken-1-ylboronates, using $LiCH_2Cl$.[10] In the light of the foregoing observations, we envisaged a similar methodology for a general synthesis of higher homologues of propargylboronates.

We now report a simple, general synthesis of higher propargylboronates in excellent isomeric purity from readily available alkyn-1-ylboronates *via* one-carbon homologation using LiCH$_2$X. The starting boronates and the various LiCH$_2$X reagents are prepared according to previously published procedures.[11,12]



Alkyn-1-ylboronates (B^{11} NMR at δ 21 ppm) are treated with *in situ* generated LiCH$_2$X (1.2 eq.) at -78°C in THF. The instantaneous capture of the carbenoid species gives rise to the intermediate 'ate' complex (δ 0 ppm) which undergoes slow rearrangement to the product boronate. The reaction can be monitored, using ^{11}B NMR, by the appearance of the product peak at δ 27 ppm and the disappearance of the 'ate' complex at δ 0 ppm. The results obtained with representative boronates and the effects of the halogen atom in LiCH$_2$X are summarized in the Table.

Unfortunately, our initial attempts for the homologation of heptyn-1-ylboronate with LiCH$_2$Cl gave very poor results. Though the 'ate' complex was formed quantitatively, the desired rearrangement was sluggish. Even the small amount of product formed (δ 27 ppm) was undergoing decomposition rapidly, even at rt, as evidenced by the ^{11}B NMR spectrum. On the other hand, the formation of the side product as well as the rearrangement of the 'ate' complex was very slow at 0°C.[13] Consequently, only a 43% yield of the desired product was realized after all the 'ate' complex had disappeared, the rest being the decomposition product (δ 17.5 ppm). The impurity persisted even after hydrolysis, thus ruling out presence of any tricoordinated borates. Oxidation with alkaline hydrogen peroxide gave only the propargylic alcohol and no carbonyl compound was formed indicating absence of any allenic intermediates, from possible 1,3 rearrangement of the initially formed 2-alkyn-1-ylboronates.[14] Also, an IR spectrum of the product revealed the complete absence (at $\nu_{C=C=C} \approx 1930$ cm^{-1}) of any allenyl group.[15]

The yield of the desired product increased from 43% to 83% when the above homologation was attempted with LiCH$_2$Br instead of LiCH$_2$Cl. Formation of the side product was less severe, though still present. Prompted by earlier reports of the success of LiCH$_2$I in cases where both LiCH$_2$Cl and LiCH$_2$Br were less effective,[8] we attempted the homologation of the same boronate with *in situ* generated LiCH$_2$I. In this case, we were pleased to find that the rate of rearrangement was much faster than those with LiCH$_2$Cl and LiCH$_2$Br and the yields obtained were nearly quantitative. The reaction was complete in half the time as compared to the reaction with LiCH$_2$Br. The reactivity is in the order $\text{Cl} \ll \text{Br} < \text{I}$. This is unlike our earlier findings with other classes of boronates, such as, alkyl-, alken-1-yl and arylboronates. This unique reactivity of alkyn-1-ylboronates is not surprising given the nature of alkynyl-boron bonds in the 'ate' complex.[16] To our knowledge this is the first report of a successful homologation of alkyn-1-ylboronates, providing an efficient and highly general synthesis of "higher" propargylboronates in excellent isomeric purity.[17]

In order to demonstrate the generality of the reaction we have studied a series of representative alkyn-1-ylboronates with various $LiCH_2X$ (see Table). As pointed out earlier, the rate of conversion to the desired product was considerably higher with $LiCH_2I$ with little side product formed. Though the yields obtained with $LiCH_2Br$ were generally comparable, the rate was much slower giving rise to occasional problems of competing decomposition of the product. Among the three reagents, $LiCH_2Cl$ gave the poorest yields, attributed to its lesser reactivity and the concomitant transformation of the desired product to some material not yet identified.

Table. Homologation of Representative $RC{\equiv}CB(OR')_2$ Using *in situ* Generated $LiCH_2X^a$ (X=Cl; Br; I)

No.	R	$(OR')_2$	Yield(%)^b		
			Cl	Br	I
1	n-Pen^c	$(O^iPr)_2$	43	83	91
2	n-Pen^c	$(OCH_2)_2CH_2$	43	87	81
3	$Cl(CH_2)_3{}^d$	$(O^iPr)_2$	29	50	78
4	t-Bu^d	$(O^iPr)_2$	--	69	72
5	$CH_2{=}C(CH_3)^d$	$(O^iPr)_2$	13	68	85
6	Ph	$(O^iPr)_2$	7^d	42^d	71^e

[a] 1.2 eq of the reagent is used; the reaction time is 0.5 - 4.0 h. [b] Yields based on the analyses of the alcohol produced by oxidation of the homologated product with alkaline hydrogen peroxide. [c] GC analyses using tridecane as an internal standard. [d] NMR analyses using biphenyl as the internal standard. [e] Isolated yields.

The following is a representative procedure for homologation of diisopropyl heptyn-1-ylboronate with (iodomethyl)lithium: n-BuLi (4.50 mmol) was added slowly along the cold inner surface of the flask to a solution of diisopropylheptyn-1-ylboronate (0.84 g; 3.75 mmol) and diiodomethane (0.36 mL; 4.50 mmol) in THF (5 mL), cooled to -78°C under an inert atmosphere. The mixture was stirred at -78°C for 0.5 h; the cold bath was then removed and the contents were allowed to warm to rt and stirred for another 1.5 h. The boronate was then oxidized with alkaline hydrogen peroxide according to the usual procedure.[18] The product alcohol was extracted with diethyl ether, washed with water and dried over anhy. K_2CO_3. This crude product was analyzed by GC (10% Carbowax on Chromosorb W; 20 m) using tridecane as an internal standard.

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12 $LiCH_2Cl$: ref. 6a or ref. 6c; $LiCH_2Br$: ref. 7 and $LiCH_2I$: ref. 8 (n-BuLi was used instead of MeLi).

13 The product undergoes complete decomposition in < 2 days at rt. A sample kept at 0°C for several days showed little decomposition of the desired product. On the other hand, the pure 2-alkyn-1-ylboronate when heated to 65°C for few hours, completely converts to the compound at δ 17.5 ppm (^{11}B NMR).

14 A pure sample of 2-heptyn-1-ylboronate obtained *via* homologation with $LiCH_2I$ was converted to the compound at δ 17.5 ppm by heating to 65°C in THF, under a nitrogen atmosphere, for few hours. This when subjected to alkaline hydrogen peroxide oxidation gave an unidentified sticky polymeric residue that had no hydroxyl or carbonyl group present.

15 IR absorption for propargyl- and allenylboronates: $\nu_{C\equiv C} = 2220\ cm^{-1}$; $\nu_{C=C=C} = 1925\ cm^{-1}$. (*cf* ref. 3(b))

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