Pergamon

Tetrahedron Letters, Vol. 36, No. 14, pp. 2441-2444, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00311-8

Racemic and Diastereoselective Synthesis of Alkyl(1,3-butadien-2-yl)methanols *via* a Novel Homoallenylboration of Aldehydes with Diisopropyl 2,3-Butadien-1-ylboronate

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Abstract: *Diisopropyl 2,3-butadien-1-ylboronate has been prepared by a simple method and its utility as a novel homoallenylborating reagent has been demonstrated with a series of aldehydes. Also, a high diastereoselectivity of this reagent in its reaction with an α-chiral aldehyde has been established.*

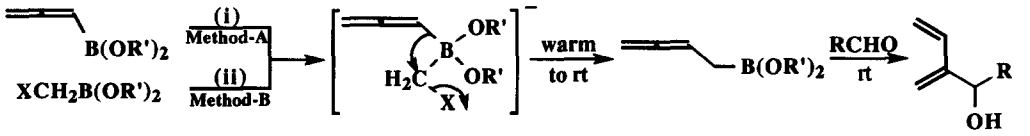
One-carbon homologation of boronic esters has emerged as a powerful tool for many valuable synthetic transformations.[1] We have recently examined several classes of boronic esters and compared their reactivities in homologation using *in situ* generated (halomethyl)lithiums ($LiCH_2X$).[2] Of these, α,β-unsaturated boronic esters, such as alkenyl-, alkynyl-, and allenylboronates are of special interest due to their considerable differences in reactivity. Earlier, we developed a stereospecific synthesis of 'higher' crotyl boronates *via* homologation of alkenylboronates and demonstrated their utility for enantioselective crotylboration.[3] Recently, alkynylboronates were successfully homologated to provide a general synthesis of 'higher' propargylboronates.[4] It was felt desirable to extend this study to the one-carbon homologation of allenylboronates. The ability of these homologated products to undergo further addition to carbonyl compounds, as had been amply demonstrated in many useful achiral and asymmetric syntheses, considerably enhances their importance.[5] It is our belief that a combination of these two methodologies would provide valuable advances in possible novel applications and greatly extend their utility.

In keeping with this strategy, the synthesis of alkyl(1,3-butadien-2-yl)methanols attracted our attention These are valuable starting materials for the synthesis of a variety of natural products, such as branched chain sugars.[6a] They also serve as potential intermediates for the stereoselective synthesis of polyfunctional cyclohexanes *via* the Diels-Alder reaction.[6b,c] However, the few currently available methodologies for their synthesis are far from ideal; they suffer from poor regiospecificity, producing mixtures of products in moderate to low yields.[7]

Accordingly, we envisaged a simple one-carbon homologation of allenylboronate and the subsequent addition of the product homoallenylboronate to aldehydes (homoallenylboration) as a route towards their synthesis. Herein, we report a simple general synthesis of alkyl (1,3-butadien-2-yl)methanols *via* homoallenylboration of aldehydes using diisopropyl 2,3-butadien-1-ylboronate (homoallenylboronate) reagent. The Scheme in the following page describes this novel tandem homologation - homoallenylboration strategy.

The starting diisopropyl 2,3-butadien-1-ylboronate can be prepared by either of two approaches; Method-A: one-carbon homologation of allenylboronate with *in situ* generated $LiCH_2X$, or Method-B: by

reaction of allenylmagnesium bromide with halomethylboronates.[8,9] Both procedures proved to be equally efficient, probably because they involve the same intermediate 'ate' complex.



(i) $LiCH_2X$; -78°C to rt (ii) $CH_2=C=CH_2MgBr$; -78°C to rt

X=Cl, Br, I $(OR')_2$= $(OiPr)_2$, $-O(CH_2)_3O-$

Table. Homoallenylboration of Various Aldehydes, RCHO, with Diisopropyl 2,3-Butadien-1-ylboronate[a]

No.	R	Solvent	Time	Yield(%)[b]
1	Et	$PhCH_3$	3 h	84
2	Et	neat	1 h	82
3	i-Pr	$PhCH_3$	8 h	80
4	t-Bu	$PhCH_3$	3 d	60
5	Chx	CH_2Cl_2	30 h	91
6	Chx	$PhCH_3$	4 h	91
7	Chx	neat	1 h	90
8	Ph	$PhCH_3$	0.5 h	85
9	(*E*)-PhCH=CH	CH_2Cl_2	5 h	95
10	$Ph_2CH_2OCH_2$	CH_2Cl_2	3 d	59
11		CH_2Cl_2	12 h	93[c,d]

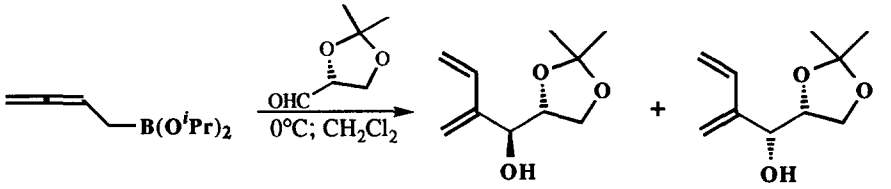
[a] 1.2 eq of the reagent was used; unless otherwise specified the reactions were carried out at rt. [b] Isolated yields of pure products; all compounds gave satisfactory spectral and analytical data. [c] anti : syn = 87:13 at rt; anti : syn = 92:8 at 0°C. [d] The anti : syn ratios were determined by GC analyses and by ^1H NMR.

In a direct comparison of various $LiCH_2X$ (X=Cl, Br, I) in Method-A, no significant rate differences were observed. Thus, diisopropyl 2,3-butadien-1-ylboronate was readily prepared in excellent isomeric purity. We have routinely employed Method-B (in ≥ 50 mmol scale) using diisopropyl iodomethylboronate and allenylmagnesium bromide to obtain the product in good (≈ 70%) yields.[10] The product, obtained as a clear liquid, is thermally stable and can be stored for extended periods of time with complete exclusion of air and moisture without noticeable deterioration in quality. Though, Suzuki *et. al.* in their recent publication report comparable yields of a similar intermediate, prepared by a different approach, the highly robust pinacol boronate esters realized in their procedure greatly diminishes the possibility for achieving subsequent transesterification with optically active diols.[11] Also, the reagent is obtained in only moderate yields by a tedious procedure . In contrast, our reagent, obtained as the diisopropyl boronate by a much simpler and more direct route, allows unrestricted transesterification with a large number of diols including pinacol, tartrates, etc.(*vide infra*), thus making it more versatile for further extensions and applications.[12]

This homoallenylboronate reagent readily reacts with aldehydes at rt *via* 1,3 rearrangement. The reaction can be conveniently monitored by observing ^{11}B NMR signals at regular intervals.[13] The product alkyl(1,3-butadien-2-yl)methanols are obtained exclusively in good to excellent yields. The results of the reactions with various aldehydes including n-, sec.-, tert. alkyl, cycloalkyl, aryl, alkenyl, and α-alkoxyalkyl

under different conditions are summarized in the Table. The reactivity of this homoallenylboronate reagent is considerably lower than that of the corresponding simple allylboronates. This is not so surprising considering the reduced electron density of the internal π-bond and the resultant diminished ability to undergo 1,3 rearrangement. As a result, the reaction times are longer in a given solvent, especially with reactions at lower temperatures. Among the solvents used, toluene proved to be the best solvent for enhancing the rate of the reaction. Also, the reaction is much faster under neat conditions. Sterically hindered aldehydes, such as isobutyraldehyde and pivalaldehyde, react significantly slower.

Later, we examined the diastereoselectivity of this reagent with an α-chiral aldehyde, *viz.* 2,3-O-isopropyliden-D-glyceraldehyde. At 0°C, the reagent exhibits 92% anti selectivity with excellent chemical yields.[14] The high anti selectivity exhibited by this reagent merit some discussion especially in the light of a related study by Takano *et. al.* using 2,3-butadien-1-yltrimethylsilane.[6a] The silicon reagent generally gives high syn selectivity with moderate yields in direct contrast to the very high anti selectivity obtained with our reagent. This may be rationalized on the basis of the chelating and non-chelating interactions of the reagents with the carbonyl oxygen. We must also add that the ability to exchange the isopropoxy group in our reagent with other alcohols of differing stereoelectronic environment should help to increase both the rate and the diastereoselectivity of this reaction.[12]



Preparation of the diisopropyl 2,3-butadien-1-ylboronate:

Freshly prepared allenylmagnesium bromide (1.54M, 50 mmol) in ether was slowly added with stirring to a solution of diisopropyl iodomethylboronate (13.60 g, 50 mmol) in THF (30 mL) while maintaining the temperature at -78°C. The resulting white suspension was stirred for 0.5 h at -78°C before removing the cold bath; the contents were then allowed to warm to rt and stirred for another 20 h. The solution was filtered under an inert atmosphere, concentrated in vacuo, and fractionally distilled to give pure diisopropyl 2,3-butadien-1-ylboronate. (6.56 g, 72 %; 58-60°C at 15 mm Hg)

Typical procedure for the preparation of the alkyl(1,3-butadien-2-yl)methanols:

Diisopropyl 2,3-butadien-2-ylboronate (0.393 g; 2.16 mmol) and cyclohexanecarboxaldehyde (0.202 g; 1.8 mmol) in dichloromethane (5 mL) was stirred at rt under a blanket of nitrogen. The reaction was monitored by ^{11}B NMR. After completion of the reaction, the mixture was diluted with dichloromethane (20 mL) followed by saturated NaCl (20 mL) and stirred for 0.5 h. The organic layer was then separated and the aqueous solution extracted with dichloromethane (2x20 mL). The combined organic layer was washed with water, dried over anhy. $MgSO_4$, and concentrated in vacuo. The residue was flash chromatographed on silica gel using dichloromethane as the eluent to afford the corresponding alcohol as a colorless oil (0.271 g; 91%).

Acknowledgments:

The financial support from the Borane Research Fund which made this study possible is gratefully acknowledged.

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10. Though $ICH_2B(O^iPr)_2$ was used in this preparation, other halomethylboronates are also equally efficient. (see text)
11. Gridnev, I.; Kanai, G.; Miyaura, N.; Suzuki, A. *J. Organometal. Chem.* **1994**, *481*, C 4. This limited study, published during our current investigation, describes a method using an entirely different approach for the preparation of a similar reagent.
12. Diisopropyl 2,3-butadien-1-ylboronate can readily be transesterified with pinacol in quantitative yield. The spectral characteristics of this pinacol derivative was identical with reported values.[11] Similarly, we have also successfully prepared corresponding D- and L-tartrate boronates and further work based on these derivatives for achieving enantioselective homoallenylboration is under active study.
13. ^{11}B NMR: starting boronate, δ 29 ppm; product borate, δ 18 ppm (relative to $BF_3.Et_2O$).
14. The reagent exhibits slightly lower selectivity (87% anti) at rt.

(*Received in USA* 19 *December* 1994; *revised* 9 *February* 1995; *accepted* 10 *February* 1995)