Pergamon

Tetrahedron Letters 39 (1998) 555–556

TETRAHEDRON LETTERS

A New Access to α-Hydroxy Boronic Esters from α-Alkoxyorganolithium Reagents

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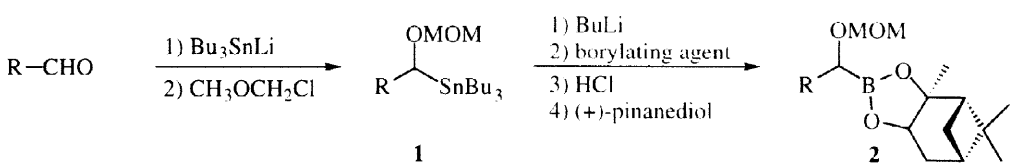
Received 9 October 1997; accepted 17 November 1997

Abstract: Various α-alkoxy boronic esters have been synthetized by borylation of α-alkoxyorganolithium reagents generated *via* tin/lithium exchange. This reaction occured with retention of configuration and gave access to α-hydroxy and α-amino boronic esters.

This last decade has witnessed an increased interest in the chemistry of boronic acid and esters, especially as boron analogues of biomolecules.[1] Methods available for the preparation of these compounds include the addition of organometallic reagents to trialkoxyborane. Hovewer, although α-oxygen alkyl carbanions have received considerable attention,[2] their reactions with borylating agents have been rarely examined. To our knowledge, only one example was reported by Schlosser *et al.*[3] in a synthesis of α-alkoxyallyl boronic esters. In connection with our ongoing program related to the synthesis of boronic acid derivatives, we here report our preliminary investigation concerning the preparation of α-alkoxy boronic esters from the corresponding α-alkoxyorganolithium reagents.

A series of α-alkoxyorganostannanes were readily prepared from the corresponding aldehyde by condensation of lithium tributylstannylate followed by protection of the alcohol using chloromethyl methyl ether and Hünig's base according to the method described by Still.[4] Preliminary investigations examined the transmetallation of **1a** (R=iPr) with BuLi in THF at -78°C followed by the addition of various borylating agents. In order to form a stable derivative, the boronic acid was then esterified with (+)-pinanediol to yield the corresponding α-alkoxy boronic ester **2a** (R=iPr). Best results were obtained with triisopropoxyborane ($B(OiPr)_3$, 75% ; $B(OMe)_3$, 60% ; $ClB(NiPr_2)_2$, 5%) which was therefore chosen later.



Using the same procedure, we extended this borylation reaction to other α-alkoxyorganostannanes (Table 1). As expected, best yields were obtained from secondary α-alkoxyorganostannanes (entries a-e) in accordance with the stability of the intermediate organolithium reagents.[5] Condensation with triisopropoxyborane was found to proceed cleanly with no loss of configurational integrity at the tertiary stereocenter (entries f, g) as indicated by their distinctive ^1H NMR and ^{13}C NMR.

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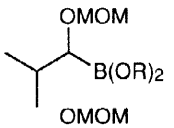
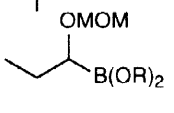
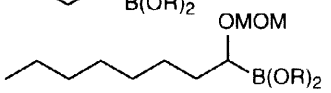
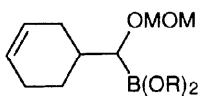
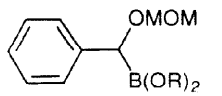
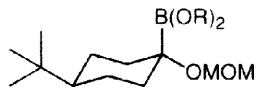
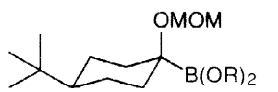
0040-4039/98/$19.00
PII: S0040-4039(97)10682-7

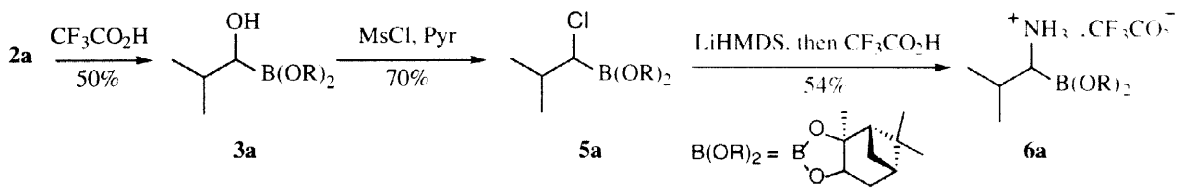
Table 1. Synthesis of α-alkoxy boronic esters **2**

Entry	Product	Yield [a] (%)
a		75
b		70
c		58
d		73
e		55
f		30[b,d]
g		45[c,d]

[a] Yields after chromatographic purification. All new compounds exhibited correct spectral and elemental analyses.

[b] Reaction run in THF at -45°C. [c] Reaction run in Et_2O at -30°C. [d] After hydrolysis, a substantial amount of the product resulting of protonation of the organolithium was observed

α-Chloro boronic esters, prepared by the two-step homologation technology, have found valuable applications in the preparation of various boron- containing mimics of α-amino carboxylic acids.[6] To illustrate the synthetic utility of our different approach in the preparation of α-amino boronic acid, a short synthesis of the boron analogue[7] of valine was carried out as shown below.



Removal of the MOM ether protecting group of **2a** with trifluoroacetic acid provided the stable α hydroxyalkylboronate **3a**. It is noteworthy that this compound cannot be directly obtained from 1-chloro-2 methylpropyl boronic ester by displacement of chloride using sodium hydroxide.[8] **3a** is converted to α-chloro boronic ester **5a** by treatment with methanesulfonyl chloride and pyridine.[8] Displacement of chloride with lithium hexamethyldisilamide followed by acidic hydrolysis afforded the inhibitor of aminopeptidases **6a**.[7]

Synthesis of optically active α-hydroxy and α-amino boronic esters are currently in progress in our laboratory.

References and Notes

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