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ARTICLE

Novel Synthesis of β-Keto Cycloacetals *via* Organoboranes

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ABSTRACT

(*Z*)-1-Bromo-1-alkenylboronate esters were easily synthesized from the hydroboration of terminal alkynes with dibromoborane dimethyl complex under nitrogen atmosphere followed by treatment with propne-1,3-diol. These boronate esters are readily reacted with 1,3-dioxan-2-ylethyl)magnesium bromide in ether and tetrahydrofuran at -78 ºC for 1 h. The resulting "ate" complex upon addition of sodium methoxide in methanol undergo intramolecular nucleophilic substitution reactions to produce the corresponding (*E*)-alkenylboronate esters containing (1,3-dioxan-2-ylethyl) moiety in 70-82% isolated yields. The resulting intermediates are oxidized with sodium acetate and hydrogen peroxide to provide the corresponding β-keto cycloacetals in good yields (68-84%).

KEYWORDS

Organoboranes, Hydroboration, Terminal alkynes, β-keto cycloacetals.

INTRODUCTION

β-Keto cycloacetals are the important intermediates in organic synthesis since they serve as precursors to keto-aldehydes. In the reaction of a ketoaldehyde with a nucleophile such as a Grignard reagent, nucleophile will not discriminate between the two carbonyl groups [1]. Transforming the aldehyde into a cyclic acetal protects the aldehyde from nucleophilic attack, leaving only ketone to react with nucleophile. The cycloacetal can then be returned to its aldehyde state by the addition of hydronium ion. Because of the utility of β-keto cycloacetals, it is advantageous to have an efficient and simple method of synthesizing these compounds.

A stereoselective synthesis of (*Z*)-1-bromo-1-alkenylboronate esters by hydroboration of 1-bromo-1-alkynes with dibromoborane-dimethyl sulfide complex followed by addition of propane-1,3-diol is reported [2]. The reaction of these (Z)-1-bromo-1-alkenylboronate esters with different nucleophiles, including Grignard reagents, hydrides and organolithium reagents is well documented in literature [3-10].

EXPERIMENTAL

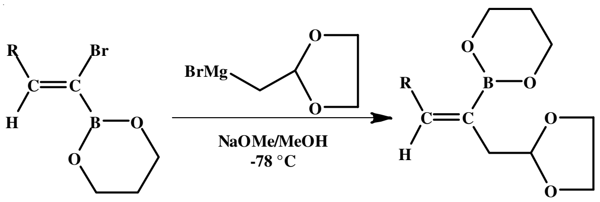
All experiments were carried out under an inert atmosphere and all the glassware were dried at 160 ºC for at least 4 h. Tetrahydrofuran, (1,3-dioxan-2-ylethyl)magnesium bromide and ether were purchased from Aldridge Chemical Company.

The starting Z-α-bromo-1-alkenylboronate esters were synthesized using literature methods. All β-keto cycloacetals were purified using column chromatography. In column chromatography, neutral alumina was used as an adsorbent and pentane and 20% acetone in pentane were used as eluents.

Synthesis of β-keto cycloacetal using Z-α-bromo-1-octynylboronate ester: In an oven-dried two-necked flask with a septum inlet were placed with *Z*-α-bromo-1-octynylboronate ester (2 mmol, 0.45 mL) and ether (2 mL) under a nitrogen atmosphere. The solution was cooled to -78 ºC using a dry ice-acetone mixture and (1,3-dioxan-2-ylethyl)magnesium bromide (4 mL, 0.5 M solution in THF) was added. The reaction mixture was allowed to stir for 1 h at -78 ºC to allow the formation of the 'ate' complex. Sodium methoxide in methanol (4 mmol, 1 mL) was added at -78 ºC and the stirring was continued for 2 h at -78 ºC, followed by stirring at room temperature overnight. The reaction mixture was diluted with water (30 mL) and extracted with ether (2 × 30 mL). The ether extract was dried over sodium sulfate (5 g). The removal of ether followed by esterification with propane-1,3-diol (2 mmol, 0.2 mL) provided the corresponding trisubstituted alkene containing (1,3-dioxan-2-ylethyl) moiety in 76% isolated yield. It was then oxidized with sodium acetate (2 mL, 3 M solution in water) and 30% H_2O_2 (1 mL) for 4 h at room temperature. Work-up followed by purification over column chromatography provided the corresponding β-keto cycloacetal in 82% isolated yield.

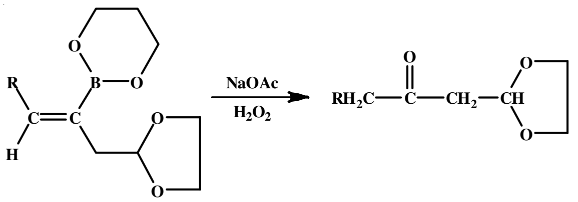
RESULTS AND DISCUSSION

In this investigation, a new nucleophilic reagent such as (1,3-dioxan-2-ylethyl)magnesium bromide was utilized and reacted with (*Z*)-1-bromo-1-alkenylboronate esters in the presence of sodium methoxide in methanol (eqn. 1).



(1)

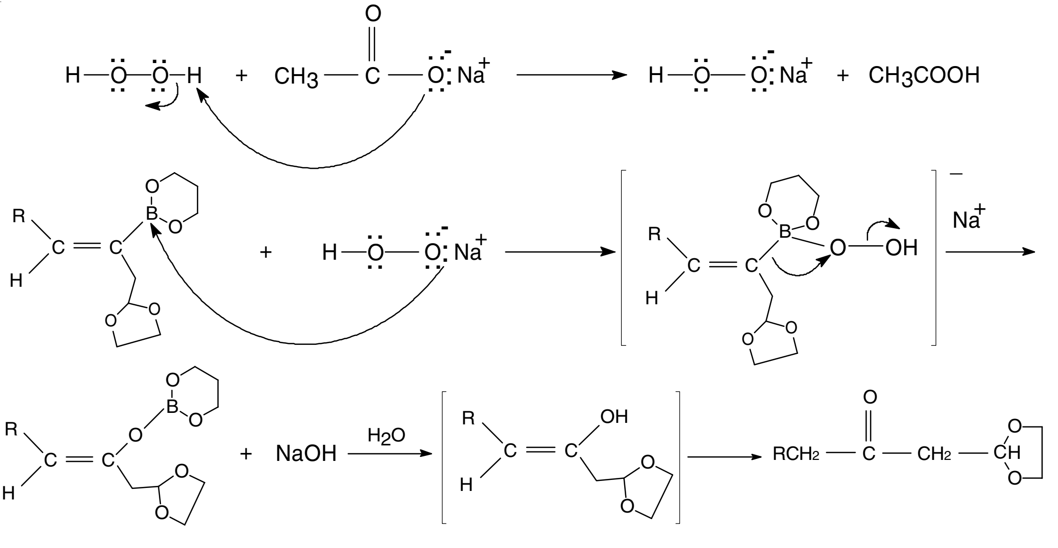
After work-up followed by esterification with propane-1,3-diol, the corresponding (*E*)-1-alkenyl-boronate esters were isolated and then oxidized with sodium acetate and hydrogen peroxide (eqn. 2). Thus, a general convenient synthesis of β-keto cycloacetals based on (*Z*)-1-bromo-1-alkenylboronate ester intermediate is described.



(2)

The required starting compounds, 1-bromo-1-alkynes and (*Z*)-1-bromo-1-alkenylboronate esters, were synthesized using reported procedures [2]. In brief, (*Z*)-1-bromo-1-hexenylboronate ester in ether reacted with (1,3-dioxan-2-ylethyl)magnesium bromide in THF at -78 ºC in an inert atmosphere. The reaction was stirred for 1 h under these conditions. Two equivalents of sodium methoxide in methanol were added at -78 ºC and the reaction mixture was allowed to stir overnight at room temperature. After aqueous workup of the mixture, the resulting boronic acid was esterified with propane-1,3-diol. The solvents were then pumped off and the resulting product was isolated by distillation to provide the corresponding (*E*)-1-hexenylboronate ester containing (1,3-dioxan-2-ylethyl) moiety in 82% yield. This was then oxidized with sodium acetate and H_2O_2 in THF at room temperature for 4 h. After purification, the corresponding β-keto cycloacetal was isolated in 84% yield. Using this procedure, representative (*E*)-1-alkenylboronate esters containing the (1,3-dioxan-2-ylethyl) moiety were synthesized (Table-1) and β-keto cycloacetals were synthesized (Table-2). The proposed mechanism for the oxidation of (*E*)-1-alkenylboronate ester containing (1,3-dioxan-2-ylethyl) moiety is shown in eqn. 3).

Mechamism: Presumably, starting compound, (*Z*)-1-bromo-1-alkenyl-boronate ester, could react with (1,3-dioxan-2-ylethyl)-magnesium bromide and form an 'ate' complex. This complex would then undergo anionotropic rearrangement in which the (1,3-dioxan-2-ylethyl) moiety would migrate from boron to the adjacent alkenyl carbon, resulting in inversion of configuration. This would provide (*E*)-trisubstituted boron intermediate containing (1,3-dioxan-2-ylethyl) moiety, which would



(3)

TABLE-1
DIASTEREOSELECTIVE SYNTHESIS OF (*E*)-1-ALKENYLBORONATE ESTERS CONTAINING (1,3-DIOXAN-2-YLETHYL) MOIETY (eqn. 1)

Entry	R =	Isolated yield[a,b] (%)
1	n-C_4H_9	82
2	n-C_5H_{11}	78
3	n-C_6H_{13}	76
4	$-(CH_2)_3Cl$	70
5	$-CH_2CH_2(C_6H_5)$	76
6	$-CH_2CH_2CH(CH_3)_2$	74

[a]All of the reactions were carried out on a 2 mmol scale. The yields were based on the corresponding (*Z*)-1-bromo-1-alkenylboronate esters; [b]All of the compounds were purified by vacuum distillation.

TABLE-2
SYNTHESIS OF β-KETO CYCLOACETALS *via* ORGANOBORANES (eqn. 2)

Entry	R =	Isolated yield (%)[a,b]
1	n-C_4H_9	84
2	n-C_5H_{11}	80
3	n-C_6H_{13}	82
4	$-(CH_2)_3Cl$	68
5	$-CH_2CH_2(C_6H_5)$	72
6	$-CH_2CH_2CH(CH_3)_2$	70

[a]All of the reactions were carried out on a 2 mmol scale. The yields were based on the corresponding (*Z*)-1-bromo-1-alkenylboronate esters; [b]All of the compounds were isolated by column chromatography over alumina.

then be oxidized to provide the β-keto cycloacetal. It is worth to mention that nucleophilic substitution reactions on sp^2 carbon is difficult to achieve. In the present report, nucleophilic substitution has been made easy by boron induced reaction.

Conclusion

In summation, a novel synthetic method is developed for the preparation of β-keto cycloacetals based on the reactions of (1,3-dioxan-2-ylethyl)magnesium bromide with (*Z*)-1-bromo-1-alkenylboronate esters followed by oxidation.The potential organoborane intermediate precursors to β-keto cycloacetals were successfully isolated.

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