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USE OF THE SUZUKI CROSS-COUPLING REACTION TO SYNTHESIZE 5-(METHOXYMETHOXY)-2-METHYLIDENEPENTANOL

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Abstract

Synthesis of silanediol inhibitor **1** for human heart chymase (HHC) depends on synthesis of 5-(methoxymethoxy)-2-methylidenepentanol (**2**). A four step sequence was successful using the Csp^3-Csp^2 Suzuki cross coupling reaction between 2-[3-(methoxymethoxy)propyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**8**) and 2-iodoprop-2-en-1-ol (**9**) to produce the allyl ancohol **2** in 38 % yield. The $PdCl_2$(dppf) (5 mol%), TlOH (5 equiv) in THF/water at 50 °C was found to be the best condition for this reaction.

Keywords. Allyl alcohol, pentan-1-ol, Suzuki reaction, $PdCl_2$(dppf), TlOH.

1. INTRODUCTION

Silanediol inhibitor **1** has been designed for inhibiting human heart chymase (HCC). It could be synthesized from allyl alcohol **2** as a middle part of the inhibitor structure containing silicon [1, 2].

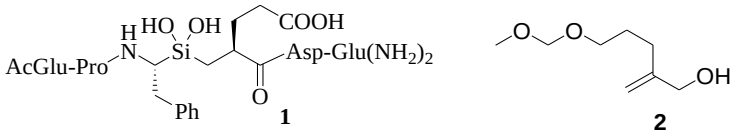
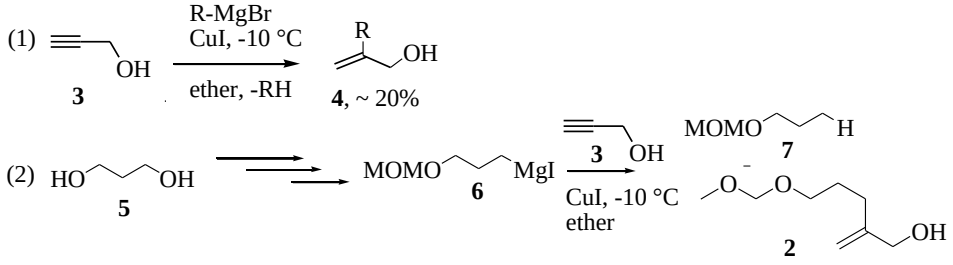


Figure 1: Structures of the HCC silanediol inhibitor **1** and allyl alcohol **2**

The synthesis of the allyl alcohol **2** was carried out in 7 steps from propan-1,3-diol (**5**) [2] using an expensive chemical (DIBAL) and a toxic chemical (MOMCl). On the other hand, the similar allyl alcohols (**4**) can be obtained by organocuprate addition to propargyl alcohol at -10 ºC in ether, scheme 1, equation 1 [3]; however, it gives low yield (~ 20 %). In addition, the Grignard agent is added in excess of 2.5 times.



Scheme 1: Synthesis of allyl alcohols using Grignard reagent

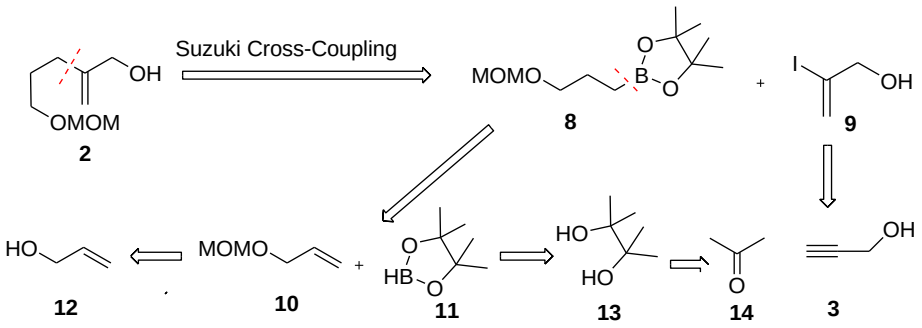
However, in our case, it takes several steps to obtain a Grignard reagent **6** from propan-1,3-diol (**5**). Unfortunately, the Grignard reagent **6** was treated with propargyl alcohol (**3**) producing compound **7** as a major product and trace of the expected allyl alcohol **2**, Scheme 1, equation 2. It is notable to know that compound **7** cannot be recycled for any purpose in my synthesis. Hence, it is not good method to produce the allyl alcohol **2** for a long synthesis.

To cover these disadvantages of these methods above and take advantages of the Suzuki reaction such as simple procedure, ease of removing the inorganic by-products from reaction mixture, the allyl alcohol **2** was synthesized in four steps from inexpensively commercial chemicals such as propargyl alcohol **3**, allylic alcohol (**12**), and pinacol borane **11**. The retrosynthesis is given in Scheme 2. Simply, allyl alcohol **2** can be obtained from alkyl boronic ester **8** and iodo compound **9**. The alkyl boronic ester **8** is easily produced from allylic alcohol (**12**) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**11**). The iodo compound **9** can be made by one step from propargyl alcohol. In addition, the 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**11**) is made from acetone (**14**) in macro-scale.

2. EXPERIMENTAL

2.1. Chemicals and equipment

Solvents and other chemicals were purchased from Sigma-Aldrich, Gelest or TCI and were used as received unless otherwise indicated. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer in $CDCl_3$. Chemical-shift data for each signal was reported in ppm units. IR spectra were recorded on a Mattson 4020 GALAXY Series FT-IR. Mass spectra were obtained from Mass Spectrometry Facility of University of California at Riverside on an Agilent 6210 TOF mass spectrometer.



Scheme 2: Retrosynthesis of 5-(methoxymethoxy)-2-methylidenepentanol (**2**)

2.2. Synthetic procedure

*2.2.1. Synthesis of 2-iodoprop-2-en-1-ol (**9**)*

To a solution of NaI (0.1 mol, 15 g) in acetonitrile (160 mL) was added $(CH_3)_3SiCl$ (12.6 mL, 0.1 mol) followed by water (0.9 mL, 0.05 mol). After 10 min, the solution was added propagyl alcohol (**3**, 4.7 mL, 0.085 mol), the resulting solution was stirred for 1 h at rt. The reaction was quenched with water (90 mL). The title product **9** was extracted with diethyl ether (3 x 50 mL). The organic layers were washed with water (5 x 50 mL), brine (2 x 20 mL), then dried over $MgSO_4$ followed by evaporated to give 2-iodoprop-2-en-1-ol (**9**) in 92% yield. The product is pure enough for next steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.37 (dd, J = 1.7, 1.6 Hz, 1H), 5.84 (dd, J = 1.6, 1.4 Hz, 1H), 4.17 (s, 2H), 2.98 (bs, 1H).

*2.2.2. Synthesis of 2,3-dimethylbutane-2,3-diol (**13**)*

To a mixture of magnesium turnings (10 g, 0.42 mol) and dry benzene (300 mL) was added slowly through the dropping funnel the solution of mercuric chloride (9.0 g, 0.033 mol) and acetone (**14**, 50 mL, 0.69 mol), carefully at first and then more rapidly after the reaction starts. Then a mixture of acetone (**14**, 25.8 mL, 0.35 mol) and benzene (20 mL) was added. When the reaction slows down, the flask was heated in a water bath for about 2 h. The reaction mixture was then added water (20 mL) through the separatory funnel, and heated for another hour. When the reaction was completed, it was cooled to about 50 °C and filtered. Remaining pinacol was rinsed with a portion of benzene (20 mL). The organic liquid was distilled to one-half the original volume in order to remove the acetone. The pinacol hydrate was filtered, and transferred to a Dean-Stark apparatus to remove water to give anhydrous 2,3-dimethylbutane-2,3-diol (**13**, 33.7 g, 68 % yield) as pale yellow oil.

*2.2.3. Synthesis of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**11**)*

To a solution of pinacol (**13**, 5.2 g, 44 mmol) in dry CH_2Cl_2 (40 mL) was slowly added, at 0 °C under a dry nitrogen atmosphere, borane dimethylsulfide complex (4.4 mL, 46.4 mmol). The mixture was stirred at room temperature for 16 h. The solution was distilled directly under reduced

pressure (100 mmHg, 40 °C) to afford 4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (**11**) as oil (4.6 g, 81 % yield).

*2.2.4. Synthesis of 3-(methoxymethoxy)propene (**10**)*

Dimethoxymethane (32 mL, 0.36 mol) and allylic alcohol (**12**, 5.0 mL, 0.073 mol) were added to lithium bromide (0.64 g, 7.37 mmol) and *p*-toluenesulfonic acid monohydrate (0.7 g, 3.68 mmol). The mixture was stirred at room temperature for 1 d. The solution was washed with H_2O (5 × 10 mL), brine (50 mL), dried over $MgSO_4$. Fractional distillation of the organic phase gave 3-methoxymethoxypropene (**10**) as clear oil (4.36 g, 0.043 mmol, 58 % yield).

*2.2.5. Synthesis of 2-[3-(methoxymethoxy)propyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**8**)*

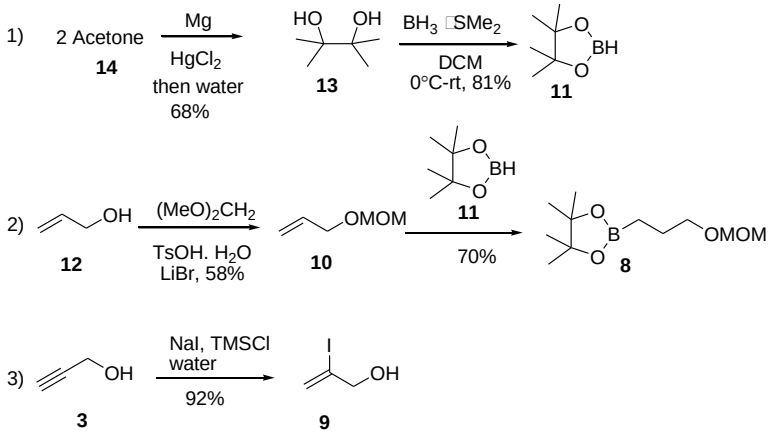
To a solution of 3-(methoxymethoxy)propene (**10,** 3.0 g, 29.4 mmol) in DCM (20 mL) was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**11**) at 0 °C. The solution was stirred at 0 °C for 1 h and at rt for 20 h. The solution was cooled to 0 °C, methanol (3 mL) was added, after stirring for 30 min, concentrated *in vacuo*. Column chromatography purification gave compound alkyl boronic ester **8** as colorless oil (4.6 g, 70% yield), R_f = 0.4 (hexane/ethyl acetate: 9/1), IR: 2977, 2933, 2885, 1517, 1446, 1373, 1147, 1045, 846, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.5 (s, 2H), 3.44-3.40 (t, J = 7.4 Hz, 2H), 3.28 (s, 3H), 1.66-1.60 (m, 2H), 1.17 (s, 12H), 0.77-0.73 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 96.4, 83.2, 69.6, 55.2, 25.0, 24.3, 8.1.

*2.2.6. Synthesis of 5-(methoxymethoxy)-2-methylidenepentanol (**2**)*

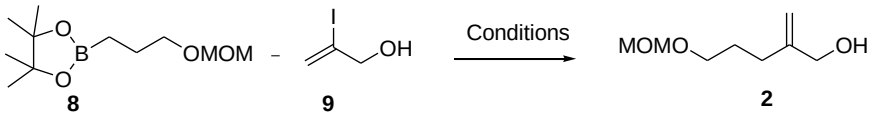
To a solution of 2-[3-(methoxy methoxy)propyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**8**, 1 g , 4.3 mmol) and 2-Iodoprop-2-en-1-ol (**9**, 0.8 g, 4.0 mmol) in THF/water (9/1, 10 mL) was added TlOH (5 g, 22.5 mmol, 5 equiv.) followed by $PdCl_2$(dppf) (0.31 g, 0.43 mmol, 10 mol%). The resulting mixture was heated at 50 °C for 16 h. The progress of reaction was monitored by TLC. The solution was extracted with DCM (3 x 10 mL). The organic layers were dried over $MgSO_4$, concentrated *in vacuo*. The title product **2** was purified by column chromatography with eluent ethyl acetate/*n*-hexane: (1/1), 0.24 g (38 % yield, R_f = 0.62 (ethyl acetate/ *n*-hexane:1/1). IR: 3415 (broad), 2933, 2879, 1652, 1558, 1452, 1386, 1213, 1147, 1039, 917, 790 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$): δ 5.03-5.02 (m, 1H), 4.88 -4.87 (m, 1H), 4.6 (s, 2H), 4.06 (d, J = 4.9 Hz, 2H), 3.5 (t, J = 6.4 Hz, 2H), 3.3 (s, 3H), 2.1 (t, J = 7.8 Hz, 2H), 1.79-1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 110.0, 96.7, 67.7, 66.2, 55.5, 29.8, 28.1; Exact mass (FAB) MH^+ calcd. for $[C_8H_{17}O_3]^+$ 161.1171, found 161.1172.

3. RESULTS AND DISCUSSION

Synthesis of starting materials for Suzuki reaction is shown in Scheme 3. Pinacol **13** is a commercial product; however it was made easily from acetone in the classic method [4] (careful with Hg waste), which was then converted directly to 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**11**), Scheme 3, equation 1 [5]. Allyl alcohol **12** was protected with a MOM group using a catalytic amount of $TsOH_{\bullet}H_2O$ and LiBr. After fractional distillation at 85 - 88 °C compound **10** was isolated in 58% yield [6]. This procedure is non-toxic, not moisture sensitive, and simple. Alkene **10** was treated with anhydrous 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**11**) to give a new alkyl borane **8** in a clean reaction, Scheme 3, equation 2 [7]. Vinyl iodide **9** was made in 92% yield from propargyl alcohol, Scheme 3, equation 3 [8].



Scheme 3: Starting material synthesis



Scheme 4: Csp^3-Csp^2 Suzuki Cross coupling reaction

In order to optimize the coupling reaction conditions (scheme 4) many entries were screened in constant of temperature at 50 °C. The results were shown in table 1. Both entries 1 and 2 did not give any products at all [9]. It was not surprised, since these conditions worked well for Csp^2-Csp^2 coupling reaction but Csp^3-Csp^2 case. In our case, transmetallation between alkyl boronic ester **8**, a poor nucleophilicity, and RPdX might cause this issue. Suzuki *et al*. [10] reported that $PdCl_2$(dppf) and TlOH could solve this problem. Therefore, $PdCl_2$(dppf) (3 mol%) and TlOH (3 equiv) in THF were tried. It was found that this reagent gave only trace of product on TLC. It might need water to hydrolyze TlOH better. Therefore, solvent was changed in THF/water: (9/1) for the reaction. Interestingly, after a flash column chromatography, the expected product was isolated in 15 yield %. It seems that THF/water is better solvent than THF. Consequently, THF/water was kept constantly, but amount of $PdCl_2$(dppf) was increased up to 5 mol%, and TlOH was used 5 equivalent of vinyl iodide **9**. The change gave the best yield (38 %). Unfortunately, $PdCl_2$(dppf) (10 mol%) and TlOH (5 equiv), entry 6 gave lower yield (28 %), table 1.

Table 1: Optimization of the Suzuki reaction

Entry	Reagent	Solvent	Yield % (Isolated **2**)
1	$Pd(PPh_3)_4$ (10 mol%), $CsCO_3$ (5 equiv)	THF/water	No Reaction
2	$Pd(PPh_3)_4$(10 mol%), MeOK (5 equiv)	THF/water	No Reaction
3	$PdCl_2$(dppf) (3 mol%), TlOH (3 equiv)	THF	Trace
4	$PdCl_2$(dppf) (3mol%), TlOH (3 equiv)	THF/water	15
5	$PdCl_2$(dppf) (5 mol%), TlOH (5 equiv)	THF/water	38
6	$PdCl_2$(dppf) (10 mol%), TlOH (5 equiv)	THF/water	28

4. CONCLUSION

The first use of the Suzuki cross coupling reaction was successful to synthesize 5-(methoxymethoxy)-2-methylidenepentanol (**2**) in a four step sequence. All starting materials are commercially available or synthesized from inexpensive chemicals such as acetone, allylic alcohol. The classic conditions like $Pd(PPh_3)_4$ (10 mol%) $CsCO_3$ (5 equiv) did not form the expected product. However, the $PdCl_2$(dppf) (5 mol%), TlOH (5 equiv) in THF/water at 50 °C was found to be the best condition to give in moderate yield (38 %). Structures of the new alkylborane **8** and the allylic alcohol **2** were proved by IR, NMR spectra. Compound **2** was measured for MS spectrum as well.

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