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DEVELOPMENT OF AN EFFICIENT PROCESS FOR 3,6-DIHYDRO-2*H*-PYRAN-4-BORONIC ACID PINACOL ESTER

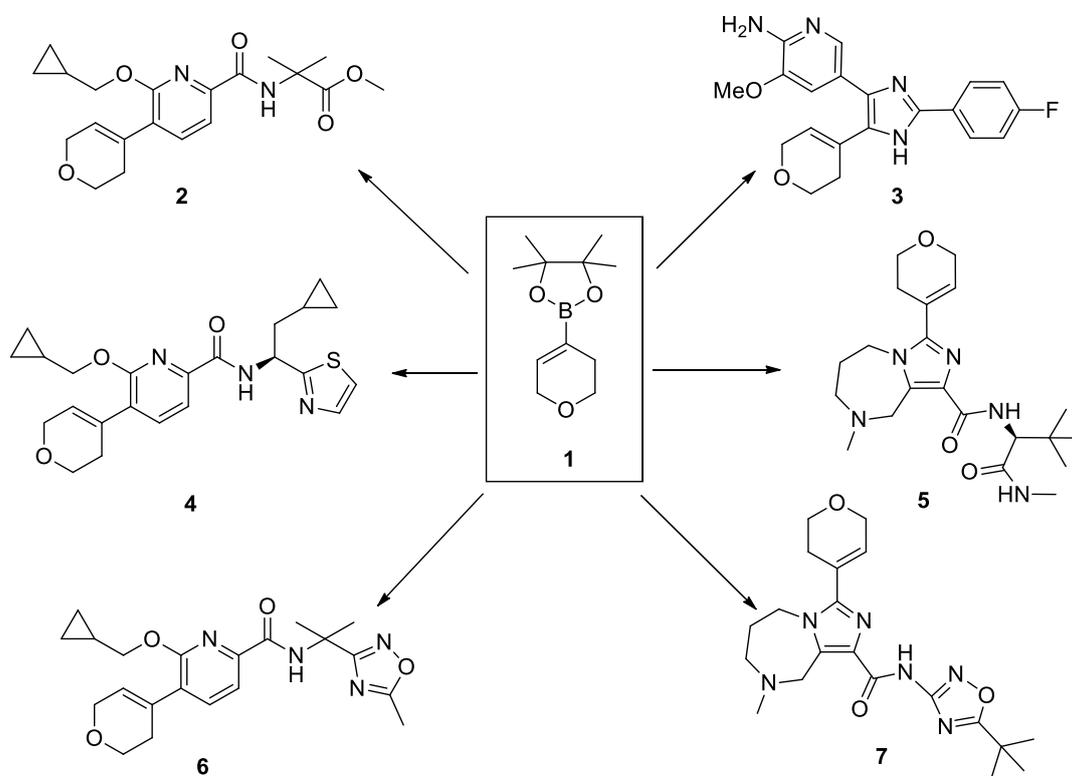
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Abstract – An efficient process for the synthesis of 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester has been developed in one-pot manner. Starting from the condensation of 4-tetrahydropyranone with hydrazine hydrate, the subsequent treatment of hydrazone with copper(II) bromide-triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) conveniently gave 4-bromo-3,6-dihydro-2*H*-pyran, which was then conducted through palladium-catalyzed borylation to afford the desired product using a low loading of a Pd catalyst.

In the search for biologically active compounds as potential drug candidates, the efficient synthesis of both libraries and individual heterocyclic small molecules is of major importance to the pharmaceutical industry. 1-Alkenylboron derivatives are an important class of compounds in synthetic organic chemistry,¹ the utility of which has been amply demonstrated in the synthesis of natural products, biologically active compounds, and functional organic materials by application of numerous carbon-carbon bond forming reactions, such as Pd-catalyzed cross-coupling with organic electrophiles,² Rh-catalyzed addition to carbonyl substrates,³ Matteson homologation,⁴ and Petasis reaction with amine and carbonyl compounds.⁵ Of a variety of such compounds, 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester is a versatile synthetic intermediate used in palladium-catalyzed Suzuki-Miyaura cross-coupling reaction for the preparation of a wide variety of natural products and biologically active compounds, such as pyridine-2-amide⁶ and polycyclic indazole derivatives⁷ (Scheme 1). These compounds exhibit various types of significant biological properties, such as anti-HIV, antituberculosis, anticancer, antimycobacterial.

For example, the pyridine-2-amide compounds are preferential agonists of the Cannabinoid Receptor 2 which are particularly useful in the treatment or prophylaxis of pain.

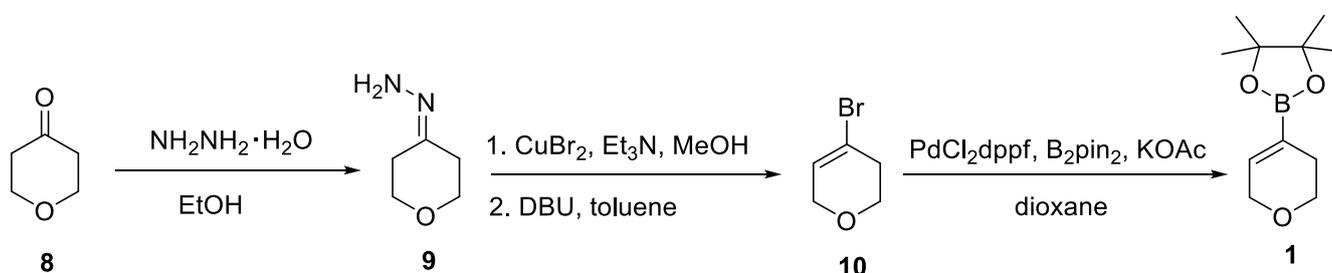


Scheme 1. Representative compounds based on 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester **1**

Up to now, some successes have been made in the preparation of 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester, typical examples included Masuda's palladium-catalyzed borylation of alkenyl triflates (or iodides) with pinacolborane,⁸ Scott's ruthenium-catalyzed olefin metathesis with the 2nd generation Grubbs' catalyst.⁹ Although these procedures have shown some practical applications in synthesis, their application has still been limited and deficient in view of laborious synthetic process, harsh reaction conditions and relatively expensive reagents. Considering that the great importance of 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester in synthesis, it is desired to find another efficient process to satisfy both laboratory and industrial operations. As an extension of our program dealing with the preparation of boric acid esters of biological interest,¹⁰ we herein described an efficient process for the preparation of 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester. With smooth and simple reaction procedures from 4-tetrahydropyranone, this method of synthesis provided easy access to the target compound.

During the investigation of palladium-catalyzed borylation of alkenyl triflate (or iodides) with pinacolborane by Masuda and co-workers,^{8,11} instead of a small amount of the expected pyranalkenylboronate **1**, the authors observed its isomeric allylic boronate as the major product. Another

method by Scott and co-workers,⁹ was, however, still problematic because it involved a multistep reaction route and hence the yield of terminal product was unsatisfactory. To develop more efficient method for the preparation of 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester **1** with advantage of simplicity, safety, and inexpensiveness, our attention was attracted to a report by Takeda and co-workers¹² on the transformation of ketones to *gem*-dihalides via hydrazones using copper(II) halides, the authors pointed out that the preparation of hydrazones by the treatment of carbonyl compounds with hydrazine hydrate using molecular sieves as a dehydrating agent was conducive to avoid the formation of the corresponding azines. But in the course of our study on the preparation of hydrazones, we found that almost quantitative relatively pure (dihydro-2*H*-pyran-4(3*H*)-ylidene)hydrazine **9** was easily achieved by the treatment of 4-tetrahydropyranone **8** with hydrazine hydrate without adding molecular sieves, thus bypassing the use of molecular sieves, which simplified the procedure without a decrease of the yield. On the other hand, when the oxidation of hydrazone **9** using copper(II) bromide-triethylamine in methanol to give *gem*-dibromide was completed, the subsequent intramolecular elimination reaction of *gem*-dibromide with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene could conveniently afford relatively pure 4-bromo-3,6-dihydro-2*H*-pyran **10** after simple aqueous work-up, which were removed of volatile materials and employed for the further cross-coupling reaction without any purification. It was reasonable to assume that the improved preparation of **10** from **8** without a relatively harsh process was more safe and efficient as compared with the previously reported procedure,¹³ thus making the reaction facile and easy to scale-up. In the final palladium-catalyzed borylation reaction of bis(pinacolato)diboron and **10**, Miyaura et al. mentioned that stronger base such as PhOK instead of KOAc, K₂CO₃ was beneficial to eliminate Heck product and the dimer product with toluene as solvent.¹⁴ Through exploration of reaction conditions, we found that a low loading of 1% mmol Pd catalyst was economical and satisfactory with KOAc as base additive in dioxane, and 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester **1** was smoothly obtained in 66% yield at 80 °C for 3 h.



Scheme 2. Synthesis of 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester **1**

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, B₂pin₂ = bis(pinacolato)diboron, PdCl₂dppf = 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride methylene chloride complex.

In conclusion, we report an improved and efficient process for the preparation of 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester with smooth and simplified reaction procedures. Preparation of 4-bromo-3,6-dihydro-2*H*-pyran through oxidation and subsequent elimination of (dihydro-2*H*-pyran-4(3*H*)-ylidene)hydrazine, which was easily prepared by the treatment of 4-tetrahydropyranone with hydrazine hydrate without molecular sieves 4Å, with copper(II) bromide-triethylamine and DBU was developed, and the next borylation by 1% mol Pd catalyst produced the target product in 66% yield. The advantages of this improved method are its preparative ease and its efficiency without laborious procedures. Compared with the reported procedures, the overall process is more economical as well as effective, which will satisfy both laboratory and industrial operations.

EXPERIMENTAL

Solvents and reagents were purchased and used without further purification. Melting points were determined on a Mettler FP5 melting point apparatus and are uncorrected. NMR spectra were recorded on Bruker DRX 400 MHz spectrometer using CDCl₃ as solvent, and tetramethylsilane (TMS) as internal standard. High resolution mass spectra were recorded on Applied Biosystems Mariner System 5303.

(Dihydro-2*H*-pyran-4(3*H*)-ylidene)hydrazine (9). 50 g of hydrazine hydrate, and 80 mL of anhydrous EtOH were added successively with stirring in a flask, After 10 min, EtOH (50 mL) solution of 4-tetrahydropyranone **8** (20 g, 0.2 mol) was added dropwise to the reaction mixture at rt and the mixture was stirred for additional 30 min. When the reaction was completed, the mixture was diluted with CH₂Cl₂ (150 mL), and transferred into a 500-mL separatory funnel, then rinsed with CH₂Cl₂ (3 × 50 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the corresponding crude hydrazone **9** as colorless liquid (22.1 g, 96% yield), which was suitable for use in the next step without further purification.

4-Bromo-3,6-dihydro-2*H*-pyran (10). Under an atmosphere of nitrogen, to MeOH (400 mL) solution of copper(II) bromide (134 mg, 0.6 mol) was added triethylamine (42 mL, 0.3 mol) at 20 °C and the reaction mixture was stirred for 10 min at the same temperature. The mixture was cooled to 0 °C, and MeOH (150 mL) solution of hydrazone **9** (11.4 g, 0.1 mol) was added dropwise over 10 min, and then stirring was continued for 1 h. The reaction was quenched by addition of 10% aqueous NH₃ solution, filtered over Celite, and organic materials were extracted with CH₂Cl₂, washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to give a pale yellow oily residue (24.0 g) which was dissolved in toluene (300 mL), and DBU (22.8 g, 0.15 mol) was added. Then the reaction mixture was stirred for further 1 h, and treated with 5% HCl until pH = 2 was reached, the resulted mixture was stirred for another 0.5 h, and the aqueous layer was separated and then extracted with CH₂Cl₂. The organics were combined, washed with brine, dried over Na₂SO₄, and then concentrated under reduced pressure to give

crude 4-bromo-3,6-dihydro-2*H*-pyran **10** as colourless oil (15.1 g, 93% yield), which was relatively pure enough to employ for the further reaction without any purification. ¹H NMR (400 MHz, CDCl₃): δ 6.07 (m, 1H), 4.20–4.13 (m, 2H), 3.86–3.82 (m, 2H), 2.56–2.49 (m, 2H).

3,6-Dihydro-2*H*-pyran-4-boronic acid pinacol ester (1). Under an atmosphere of nitrogen, a solution of 4-bromo-3,6-dihydro-2*H*-pyran **10** (24.5 g, 0.15 mol), bis(pinacolato)diboron (42.0 g, 0.15 mol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride methylene chloride complex (1.25 g, 1.5 mmol) and potassium acetate (44.5 g, 0.45 mol) in dioxane (350 mL) was heated to 80 °C for 3 h. Water (50 mL) was added to the reaction mixture which then was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was recrystallized in cold hexane to yield the title compound **1** (20.6 g, 0.098 mol, 66% yield) as white solid. mp 61–62 °C (lit.¹¹ 60–61 °C); ¹H NMR (400 MHz, CDCl₃): δ 6.53 (s, 1H), 4.20–4.18 (m, 2H), 3.77–3.74 (t, *J* = 6 Hz, 2H), 2.25–2.23 (m, 2H), 1.27 (s, 12H); HRMS calcd for C₁₁H₁₉BO₃ [M]⁺ 210.1427; found: 210.1429.

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