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Short Note

Potassium {4-[(3S,6S,9S)-3,6-dibenzyl-9-isopropyl-4,7,10-trioxo-11–oxa-2,5,8-triazadodecyl]phenyl}trifluoroborate

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Abstract: The reported compound **4** was synthesized and fully characterized by ^{1}H NMR, ^{13}C NMR, ^{11}B NMR, ^{19}F NMR, and high resolution mass spectrometry.

Keywords: peptide; organotrifluoroborate; potassium trifluoroborate

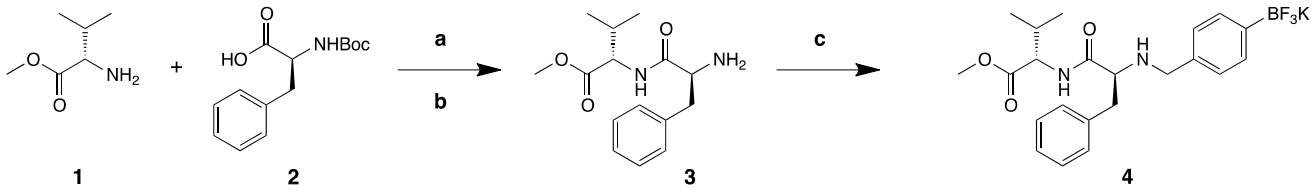
Of the boron-containing compounds that are currently in pharmaceutical development programs, boronic acids [1,2], boronate esters [3,4], benzoxaboroles [5,6], and oxazaborolidines [7,8] are frequently used boron functional groups. Having an empty *p*-orbital on the trivalent boron atom, these analogs interact with their targets to form tetrahedral intermediates. Organotrifluoroborates, on the other hand, are seldom considered in biological applications due to their lack of an empty *p*-orbital. Srebnik and coworkers, the first group to investigate the biological activity of a series of aryl organotrifluoroborates in enzyme-inhibition assays, reported that aryl potassium trifluoroborates were much more potent than the corresponding boronic acids against α-chymotrypsin and trypsin [9,10]. The toxicological profile of organotrifluoroborates were also investigated by Oliveira and co-workers, who showed that thiophene-3-trifluoroborate exhibits minimal toxicity in a mouse model, and concluded that this class of compounds is suitable for further development as pharmacologically active agents [11]. Despite their promising biological studies, the reported studies of organotrifluoroborates

have focused mainly on simple aryl/heteroaryl structures. Herein, we report the synthesis of the dipeptidyl organotrifluroborate, which should possess additional hydrophilic elements and hydrophobic moieties, which are vital factors for ligand/receptor binding.

Result and Discussion

The desired product was prepared as follows. H-L-valine-methyl ester (**1**) was first coupled with Boc-L-phenylalanine-OH (**2**) by general peptide coupling protocol [12] followed by removal of *t*-butyloxycarbonyl (Boc) protecting group to afford dipeptide **3** (Scheme 1). Then, compound **3** was condensed with potassium 4-formylphenyltrifluoroborate to give the corresponding imine intermediate. Finally, the resulting intermediate was directly reduced by 5-ethyl-2-methylpyridine borane complex (PEMB) [13] to give the final product **4** in 64% yield.

Scheme 1. (**a**) TBTU (1.3 equiv), DIPEA (4.0 equiv), CH_2Cl_2 (0.1 M); (**b**) TFA (20%), CH_2Cl_2 (0.1 M); (**c**) 4-formylphenyltrifluoroborate (1.0 equiv), PEMB (0.5 equiv), MeOH (0.5 M).



Experimental

To a vial containing potassium 4-formylphenyltrifluoroborate (118 mg, 0.55 mmol) in MeOH was added **3** (411 mg, 0.83 mmol) to generate a 0.5 M solution. The reaction mixture was stirred for 3 h at room temperature. PEMB (0.042 mL, 0.28 mmol) was then added, and stirring was continued for 5 h. The solvent was then removed *in vacuo*, and the resulting crude material was washed with hexane. The crude solid was purified by continuous Soxhlet extraction (3 h) with acetone. The collected solvent was concentrated and then precipitated with acetone/ hexane to afford the desired pure product **4** as a white solid (167 mg, 64% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 7.58 (d, J = 7.8 Hz, 2H), 7.36–7.29 (m, 3H), 7.28–7.18 (m, 2H), 4.34 (d, J = 9.9 Hz, 1H), 4.11–3.97 (m, 3H), 3.68 (s, 3H), 3.14 (d, J = 7.2 Hz, 2H), 2.09 (oct, J = 6.6 Hz, 1H), 0.95 (dd, J = 6.6, 3.9 Hz, 6H). ^{13}C NMR (75.5 MHz, CD_3OD) δ 172.4, 168.8, 135.2, 133.6, 130.7, 130.1, 129.5, 128.9, 128.8, 61.4, 59.7, 52.7, 51.8, 37.9, 32.1, 19.5, 18.8. ^{11}B NMR (192.5 MHz, acetone-d_6) δ 4.0. ^{19}F NMR (564.6 MHz, CD_3OD) δ 144.8. M.p. 207 °C. HRMS (ESI, negative ion) *m/z* calcd for $[M\text{-}K]^-$ = 435.2069, *m/z* found 435.2088.

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Author Contributions

Chia-Hua Tsai, Chia-Hung Lin, and Ching-Tien Hsieh are responsible for developing an optimal peptide coupling condition. Chih-Cheng Cai, Ting-Ju Lin, and Pin-Yi Liu are responsible for developing an optimal Boc removal condition. Meng-Hsuan Lin, Meng-Ju Wu, and Chia-Chieh Fu are responsible for developing an optimal imine formation and reduction conditions. Yang-Chang Wu, Fang-Rong Chang and Po-Shen Pan are responsible for designing the synthetic strategy as well as collaborative manuscript preparation.

Conflicts of Interest

The author declares no conflict of interest.

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