Synthesis of a chiral β-amino acid derivative by a cobalt-catalysed coupling reaction

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A chiral β-amino acid derivative was synthesised by a cobalt-catalysed alkylation of 2,4,5-trifluorophenyl magnesium bromide with the alkyl halide derivative of L-aspartic acid, using an efficient catalytic reagent: $CoCl_2$/TMEDA. The halide derivative was synthesised from protected L-aspartic acid β-methyl ester and the Grignard reagent was made by bromine- magnesium exchange. The stereo-structure was well preserved from L-aspartic acid.

Keywords: β-amino acid, aspartic acid, cobalt-catalysed, coupling reaction

The synthesis of chiral β-amino acids and derivatives has attracted attention due to their importance in biologically active peptides and small molecule pharmaceuticals.[1] Much effort has been put into developing satisfactory synthetic routes for the preparation of β-amino acids and derivatives. Many methods have been reported, such as catalytic asymmetric hydrogenation of enamino derivatives,[2] Arndt–Eistert homologation of the α-amino acids,[3] asymmetric Michael addition of the chiral amino-group to α, β-unsaturated esters,[4] β-lactams ring opening[5,6] and others.[7,8]

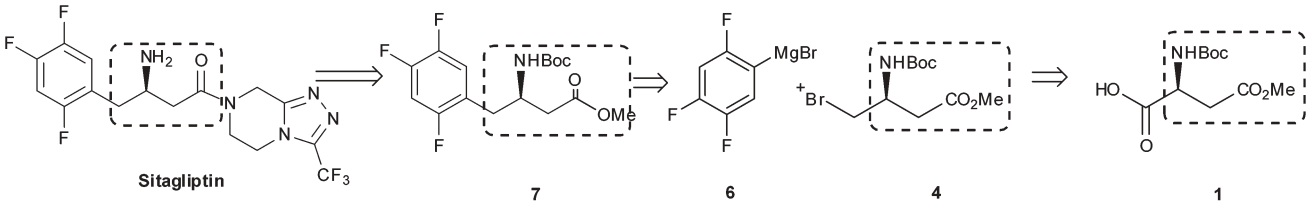
Transition metal-catalysed cross-coupling reactions of unactivated alkyl halides have permitted many transformations in organic synthesis.[9–14] Among all the transition metal catalysed systems, cobalt salts are not as convenient as manganese salts or iron salts, from both an environmental or economical point of view.[15] However, they compare favourably to nickel or palladium salts and deserve to be considered when iron or manganese salts are not efficient enough.[16] In 2009, Cahiez described the cobalt-catalysed cross-coupling of aryl Grignard reagents with primary and secondary alkyl halides. Note that not only alkyl iodides but also the non-activated alkyl bromides reacted in satisfactory yields by using an efficient and simple catalytic system: $CoCl_2$/TMEDA(1:1).[17]

As a part of our interest in developing practical and simple approaches to the synthesis of Sitagliptin, a new dipeptidyl peptidase IV(DPP-IV) inhibitor for the treatment of type 2 diabetes mellitus(T2DM),[4,18] we report here a novel synthetic route for the preparation of the enantiopure β-amino acid derivative, 3-R-Boc-amino-4-(2,4,5-trifluoro-phenyl)butyric acid methyl ester, a key synthetic intermediate of Sitagliptin, by a cobalt-catalysed cross-coupling reaction between an aryl Grignard reagent and a halide. In this approach, the stereochemistry of the chiral amine is retained from the aspartic acid equivalent, which was converted from the protected L-aspartic acid β-methyl ester **1** through several steps (Scheme 1).

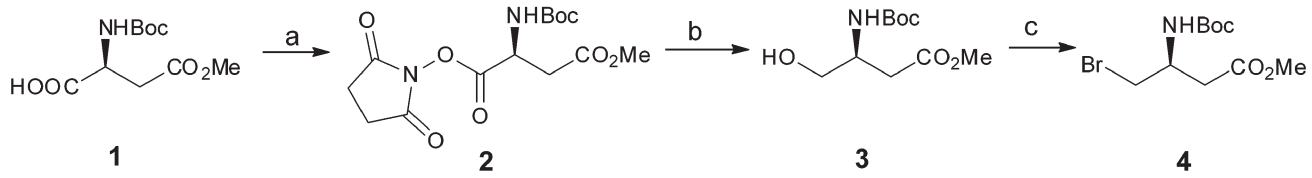
A bromide precursor, containing the necessary β-amino acid moiety, was synthesised from protected L-aspartic acid β-methyl ester **1**[18] (Scheme 2). After condensation with N-hydroxysuccinimide, the product succinimide ester **2** was reduced with $NaBH_4$ at a low temperature to give the compound **3**.[19] Converting the alcohol **3** to bromide **4** was accomplished by using bromine, triphenylphosphine and imidazoline.[20]

With the alkyl bromide **4** in hand, we attempted to examine the cobalt-catalysed Grignard reaction. The 1-bromo-2,4,5- trifluoro-benzene Grignard reagent was synthesised by the bromine- magnesium- exchange protocol. [21] The Br–Mg-exchange was accomplished with *n*-BuMgBr at –20 °C, which was monitored by GC (Scheme **3**). As the bromide **4** contained an exchangeable amino proton, excessive Grignard reagent was used. The pre-deprotonation was achieved by adding 1.0 equivalent of *n*-BuMgBr and the by-product butane could be removed easily. This was followed by the addition of 1.1 equiv. of the nucleophile **6** at –20 °C. Then, the β-amino acid derivative **7** was obtained in moderate yield by catalysis using $CoCl_2$/TMEDA(1:1). The configuration of compound **7** was identified by comparison with the literature.[22]

In conclusion, we have disclosed a novel and simple synthetic route to the chiral β-amino acid derivative, 3-R-Boc-amino-4-(2,4,5-trifluoro-phenyl)butyric acid methyl ester, by



Scheme 1 Synthetic strategy for a β-amino acid derivative.



a)NHS, DCC, E.A.,0 ºC-r.t. b) $NaBH_4$, THF, 0 ºC . 84 % for two steps. C) Br_2, PPh_3, imidazoline, CH_2Cl_2, 0 ºC, 90 %.

Scheme 2

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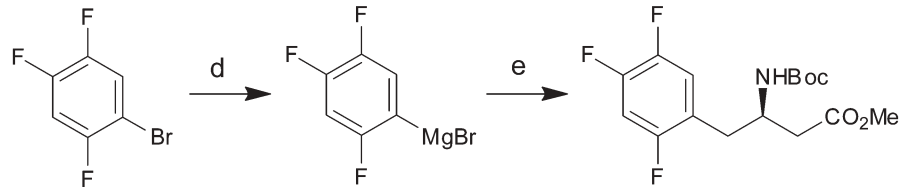

d) n-BuMgBr, THF, -10 °C. e) **4,** $CoCl_2$, TMEDA, THF, 0 °C, 72 %.

Scheme 3

a cobalt- catalysed coupling reaction, using an efficient catalytic reagent, $CoCl_2$/TMEDA. This simple protocol will be very attractive for large scale production. Further studies are currently underway in our laboratory.

Experimental

Melting points were determined with a SGW X-4 micro melting point apparatus. IR spectra were determined on a Bruker Vertex 70 spectrophotometer. ^{1}H NMR spectra were recorded using an Avance 400 MHz spectrometer. ESI-MS were recorded on a Dionex MSO-Plus Mass Spectrometer. High resolution mass spectra were recorded on a Finnigan MAT XL95 mass spectrometer. GC were determined on a Fuli GC-9790 system. Optical rotations were obtained on a Perkin-Elmer 241 Autopol polarimeter.

*(S)-Methyl [3-(*tert*-butoxycarbonyl)-amino]-4-hydroxybutanoate* (**3**): To a mixture of **1** (26.1 g, 0.1 mol) and 1-hydroxypyrrolidine-2, 5-dione (12.7g., 0.11 mol) in ethyl acetate (200 mL), a solution of DCC (22.7 g, 0.11 mol) in ethyl acetate (50 mL) was added dropwise at 0 °C. The mixture was then stirred at r.t. for 8 h and the solvent was removed under vacuum after being filtered. The formed white solid and $NaBH_4$ (3.8 g, 0.1 mol) were suspended in THF (200 mL), methanol (20 mL) was added dropwise at 0 °C. After 0.5 h, sat. NH_4Cl (100 mL) was added, the mixture was stirred for 0.5 h and then extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried, filtered and concentrated to give the colourless oil **3** (19.6 g, 0.084 mol) in 84% yield over the two steps. $[\alpha]_D^{20}$ = + 5.9 (c 0.5, $CHCl_3$). {lit^{23}. $[\alpha]_D^{23}$ = + 6.3 (c 0.5, $CHCl_3$).} IR(cm^{-1}): 3373, 1717, 1692, 1523, 1048, 777. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (d, *J* = 7.8 Hz, 1H), 3.95 (s, 1H), 3.63 (s, 3H), 3.62 (s, 2H), 3.50–3.16 (m,1H), 2.56 (t, *J* = 13.3 Hz, 2H), 1.38 (s, 9H). ESI-MS *m/z* 234.2 $(M + 1)^+$.

*(S)-Methyl 4-bromo-3-[(*tert*-butoxycarbonyl)-amino]butanoate* (**4**): Br_2 (17.6 g, 0.11 mol) was added dropwise at 0 °C to a solution of **3** (23.3 g., 0.1 mol), PPh_3 (28.2 g, 0.1 mol) and imidazole (7.5 g, 0.11 mol) in dichloromethane (200 mL). The mixture was stirred at 0 °C for 15 min and then at room temperature for 1 h. After completion of the reaction, sat. sodium hyposulfite (100 mL) was added, the phases were separated and the organic phase was dried with $MgSO_4$, filtered and concentrated. Flash chromatography with petroleum ether/ethyl acetate (3:l) gave **4** as a colourless oil (26.6 g, 0.09 mol, 90%). $[\alpha]_D^{20}$ = −1.3 (c 1.0, $CHCl_3$). IR (cm^{-1}): 3355, 1728, 1682, 1523. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31–5.12 (m, 1H), 4.16 (s, 1H), 3.63 (s, 3H), 3.53 (dt, *J* = 15.8, 8.5 Hz, 2H), 2.75–2.52 (m, 2H), 1.37 (s, 9H). ESI-MS: 297.2 $(M + 1)^+$. HRMS Calcd for: $C_{10}H_{18}BrO_4Na$ $(M + Na)^+$ requires: 318.0317; found: 318.0325.

3-R-Boc-amino-4-(2,4,5-trifluoro-phenyl)butyric acid methyl ester (**7**): A dry three-necked flask equipped with a magnetic stirring bar and a N_2 balloon was charged with 1-bromo-2,4,5-trifluorobenzene (4.62 g, 22 mmol) in THF (50 mL) and cooled to –20 °C, n-C_4H_9MgBr (22 mL, 22 mmol, 1 M in THF) was added dropwise and the reaction mixture was stirred at –20 °C for 1 h. At the point GC assay indicated disappearance of the bromobenzene, the Grignard reagent **6** was stored as a THF solution in an inert gas atmosphere. To another dry and nitrogen flushed three-necked flask, equipped with a magnetic stirring bar, a N_2 balloon and a dropping funnel, compound **4** (5.9 g, 20 mmol), $CoCl_2$ (258 mg, 2 mmol) and TMEDA (344 mg, 2 mmol) and dry THF (50 mL) were added. The solution was cooled to –20 °C and to the resulting slurry was added 1.0 M n-C_4H_9MgBr (20 mL, 20 mmol) dropwise at –15 to –5 °C to afford a clear solution. After cooling to –20 °C again, the Grignard reagent **6** was exchanged above and added dropwise at 0 °C over 0.5 h.

After the completion of the addition, the reaction mixture was allowed to warm to room temperature over 30 min. and then quenched with aqueous HCl (1 M, 100 mL). The aqueous layer was extracted with EtOAc (50 mL × 2), the combined organic layers were washed with water (100 mL) and dried with $MgSO_4$. Evaporation of the solvent, then flash chromatography with petroleum ether/ethyl acetate (5:l) gave **7** as a pale yellow solid (5 g, 14.4 mmol, 72% yield).

$[\alpha]_D^{22}$ = + 14.5 (c 1.0, MeOH). M.p. 76–78 °C. {lit.^{22} $[\alpha]_D^{20}$ = + 15.2 (c 1.0, MeOH). M.p. 88–88.5 °C.} IR (cm^{-1}): 3360, 2983, 1729, 1688, 1424, 1335, 1250,1029,. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–6.70 (m, 2H), 5.19 (br, 1H), 4.20–4.00 (m, 1H), 3.71 (s, 3H), 2.90–2.81 (m, 2H), 2.58–2.47 (m, 2H), 1.37 (s, 9H). ESI-MS: 348.2 $(M + 1)^+$

The authors are grateful to Zhejiang Hisoar Pharmaceutical Co., Ltd. for financial support.

Received 14 July 2011; accepted 15 September 2011
Paper 1100795 doi: 10.3184/174751911X13155906432537
Published online: 30 September 2011

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