Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1137–1142

TETRAHEDRON: *ASYMMETRY*

Pd/Cu-catalyzed couplings of β-amino esters with aryl bromides. Synthesis of chiral 1,2,3,4-tetrahydro-4-oxo-2-alkyl-1-quinolines

Dawei Ma * and Jiqing Jiang

State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, PR China

Received 5 January 1998; accepted 16 February 1998

Abstract

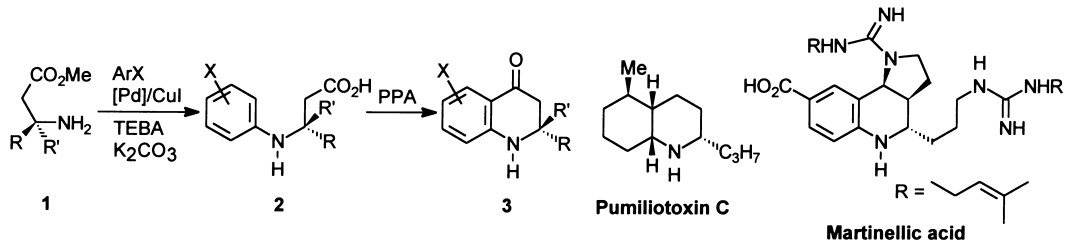
A new protocol to prepare chiral 1,2,3,4-tetrahydro-4-oxo-2-alkyl-1-quinolines has been developed. The key steps are Pd/Cu-catalyzed couplings of chiral β-amino esters and aryl bromides, and intramolecular acylation.

1. Introduction

The formation of a carbon–nitrogen bond by palladium-catalyzed coupling of aryl halides with amines has been realized in the past three years. These results represent a major advance in the development of aromatic amination methodology.[1,2] However, most studies were limited to broadening aryl halides and catalyst systems;[3] little attention has been directed to seeking more complex amines[4] that may expand the synthetic applications of this new manner of carbon–nitrogen bond formation. Recently, we reported a reasonably efficient method of coupling α-amino acids with aryl halides,[5] which gave enantiomerically pure *N*-aryl-α-amino acids in moderate to good yields. This is the first example of the preparation of chiral *N*-aryl amines using Pd-catalyzed aromatic amination.[4a] After several attempts, we have extended this method to β-amino esters. The coupling products could be further transformed to chiral 1,2,3,4-tetrahydro-4-oxo-2-alkyl-1-quinolines **3** through intramolecular Friedel–Crafts acylations. The products **3** were envisioned to be ideal building blocks for synthesizing biologically important molecules such as pumiliotoxin C,[6] L-689,560,[7] and martinellic acid[8] (Scheme 1). Herein we detail our results.

* Corresponding author. E-mail: madw@pub.sioc.ac.cn

0957-4166/98/$19.00
PII: S0957-4166(98)00078-0



Scheme 1.

2. Results and discussion

β-Amino esters could be obtained in enantiomerically pure form by stereoselective conjugate addition[9] of (S)- or (R)-lithium *N*-benzyl-*N*-α-methylbenzylamides to α,β-unsaturated esters followed by hydrogenation that provided a new class of chiral amines in a simple and efficient manner. Initially, we hydrolyzed the esters to the corresponding amino acid salts with potassium hydroxide; the salts were then subjected to our previously reported conditions.[5] It was found that the β-amino acid salt could couple with an aryl bromide under the catalysis of Pd/Cu to form the *N*-aryl-β-amino acid in moderate yields. After some experimentation, we found that the β-amino esters, which should hydrolyze quickly under the present reaction conditions, could be used directly in this reaction without the yield changing. As illustrated in Table 1, this coupling method provides a general route to a variety of chiral *N*-aryl-β-amino acids. Using bulky ligands gave higher yields (compare entries 3 and 4 and entries 5 and 6). These results are consistent with those reported by Buchward[3e] and Hartwig.[3f]

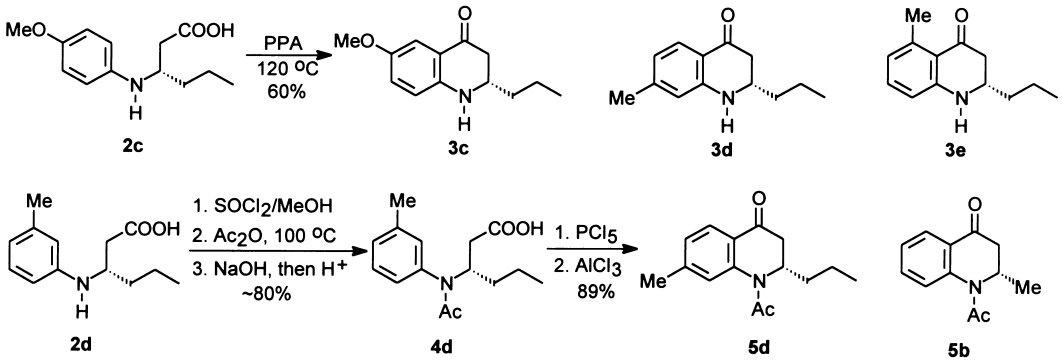
Table 1
Pd/Cu-catalyzed couplings of aryl bromides and chiral β-amino esters

Entry	R	R'	ArBr	[Pd][a]	product	Yield (%)[b]
1	H	n-Pr	4-$MeOC_6H_4Br$	A	**2a**	65
2	Me	H	C_6H_5Br	A	**2b**	66
3	n-Pr	H	4-$MeOC_6H_4Br$	A	**2c**	40
4	n-Pr	H	4-$MeOC_6H_4Br$	B	**2c**	70
5	n-Pr	H	3-MeC_6H_4Br	A	**2d**	45
6	n-Pr	H	3-MeC_6H_4Br	B	**2d**	55
7	H	n-Pr	3-MeC_6H_4Br	A	**2e**	40

[a]A: $Pd(PPh_3)_4$; B: $Pd(dba)_2$/tris(2,4,6-trimethylphenyl)phosphine. [b]Isolated yield.

As shown in the following scheme, the cyclization of **2** could be achieved under the action of PPA at 120°C.[10] Through this method we obtained **3c** in about 60% yield, while using **2d** as a starting material produced two regioisomers **3d** and **3e** in a ratio of 3:1. The product **3e** may serve as a suitable intermediate for the synthesis of pumiliotoxin C[6] by selective reduction. Alternatively, we could use $AlCl_3$-catalyzed acylation to obtain the *N*-protected cyclization product **5**. It is worth noting that we noticed that *N*-protection became very difficult to achieve after cyclization of **2** owing to the lower nucleophilicity of the NH group in **3**. Thus the latter cyclization method would give us more important synthetic intermediates. To convert the acids **2** to their corresponding acyl chlorides, the NH group should be protected first. Initially, we treated **2d** with acyl chloride or acetic anhydride directly but no desired product was obtained. Thus we first had to transform **2d** to its methyl ester. At this time we found the NH group

could be protected in high yield by using acetic anhydride as an acylating agent.[11] The protected product was then hydrolyzed to the corresponding acid **4d** in about 80% overall yield. Acid **4d** was converted to acyl chloride with PCl_5 and then treated with $AlCl_3$ to afford **5d** in 89% yield.[12] In a similar manner, **5b** was obtained from **2b** in 72% overall yield. In summary, we have established a new methodology to prepare chiral 1,2,3,4-tetrahydro-4-oxo-2-alkyl-1-quinolines or its *N*-acetyl derivatives by using Pd/Cu-catalyzed coupling and intramolecular acylation as key steps. The application of this methodology to the synthesis of biologically important molecules is under study in our laboratory and will be reported in due course.



3. Experimental section

3.1. General procedures

IR spectra were measured on a Schimadzu 440 spectrometer. ^{1}H NMR spectra were recorded with TMS as an internal standard on a Brucker AM-300 spectrometer. MS spectra were determined on a Finnigan 4201 spectrometer. Optical rotations were obtained on a Perkin–Elmer 241 Autopol polarimeter. THF was distilled from a deep blue ketyl prior to use. All reactions were run in flame-dried glassware under a nitrogen atmosphere unless stated otherwise.

3.2. Typical procedure for Pd/Cu-catalyzed couplings of aryl bromides and chiral β-amino esters

To a mixture of aryl bromide (4.1 mmol), β-amino esters (4.1 mmol), potassium carbonate (12 mmol), TEBA (0.25 mmol) in 0.1 mL of water, 5 mL of DMF were added 0.5 mL of triethylamine, CuI (0.25 mmol) and $Pd(PPh_3)_4$ (0.25 mmol). The resulting suspension was heated under argon at 110°C for 24 h. After cooling to room temperature, the reaction mixture was acidified with 1 N HCl to pH=2, and then extracted with ethyl acetate (4×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residual oil was chromatographed (silica gel, ethyl acetate:petroleum ether=1:2–1:1 as eluent) to afford the coupled product. The yield and analytical data for each compound were as follows.

3.3. (*R*)-N-(*4′-Methoxy*)*phenyl-3-aminohexanoic acid* ***2a***

65% Yield. $[\alpha]_D^{25}=-15.4$ (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 7.31 (br s, 1H), 6.90–6.74 (m, 4H), 3.75 (s, 3H), 3.61 (m, 1H), 2.54 (dd, *J*=16.5, 1.7 Hz, 1H), 2.47 (dd, *J*=16.5, 7.5 Hz, 1H), 1.74–1.46 (m, 2H), 1.43–1.37

(m, 2H), 0.91 (t, *J*=7.6 Hz, 3H); MS m/z 237 (M^+), 194, 178, 148; HRMS calcd for $C_{13}H_{19}NO_3$: 237.137, found: 237.136.

3.4. *(S)*-N-*Phenyl-3-aminobutanoic acid* ***2b***

66% Yield. $[\alpha]_D^{25}$=+1.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.21 (d, *J*=8.1 Hz, 2H), 6.78 (dd, *J*=8.1, 8.1 Hz, 1H), 6.68 (d, *J*=8.1 Hz, 2H), 6.13 (br s, 2H), 3.94 (m, 1H), 2.71 (dd, *J*=15.4, 5.68 Hz), 2.52 (dd, *J*=15.4, 6.5 Hz, 1H), 1.32 (d, *J*=7.2 Hz, 3H); MS m/z 179 (M^+), 164, 120; HRMS calcd for $C_{10}H_{13}NO_2$: 179.095, found: 179.094.

3.5. *(S)*-N-*(4′-Methoxy)phenyl-3-aminohexanoic acid* ***2c***

70% Yield. $[\alpha]_D^{25}$=+15.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 7.65 (br s, 2H), 6.93 (d, *J*=9.0 Hz, 2H), 6.79 (d, *J*=9.0 Hz, 2H), 3.75 (s, 3H), 3.61 (m, 1H), 2.54 (dd, *J*=16.5, 1.7 Hz, 1H), 2.47 (dd, *J*=16.5, 7.5 Hz, 1H), 1.74–1.46 (m, 2H), 1.43–1.37 (m, 2H), 0.91 (t, *J*=7.6 Hz, 3H); MS m/z 237 (M^+), 194, 178, 148; HRMS calcd for $C_{13}H_{19}NO_3$: 237.137, found: 237.138.

3.6. *(S)*-N-*(3′-Methyl)phenyl-3-aminohexanoic acid* ***2d***

55% Yield. $[\alpha]_D^{25}$=+3.8 (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 7.09 (dd, *J*=7.9, 7.9 Hz, 1H), 6.83 (br s, 2H), 6.57 (d, *J*=8.1 Hz, 1H), 6.51 (s, 1H), 6.50 (d, *J*=8.1 Hz, 1H), 3.82–3.67 (m, 1H), 2.59–2.50 (m, 2H), 2.28 (s, 3H), 1.57–1.49 (m, 2H), 1.44–1.35 (m, 2H), 0.95 (t, *J*=7.2 Hz, 3H); MS m/z 221 (M^+), 178, 162, 132, 119, 91, 77, 43; HRMS calcd for $C_{13}H_{19}NO_2$: 221.142, found: 221.142.

3.7. *(R)*-N-*(3′-Methyl)phenyl-3-aminohexanoic acid* ***2e***

40% Yield. $[\alpha]_D^{25}$=−3.6 (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 7.09 (dd, *J*=7.9, 7.9 Hz, 1H), 6.83 (br s, 2H), 6.57 (d, *J*=8.1 Hz, 1H), 6.51 (s, 1H), 6.50 (d, *J*=8.1 Hz, 1H), 3.82–3.67 (m, 1H), 2.59–2.50 (m, 2H), 2.28 (s, 3H), 1.57–1.49 (m, 2H), 1.44–1.35 (m, 2H), 0.95 (t, *J*=7.2 Hz, 3H); MS m/z 221 (M^+), 178, 162, 132, 119, 91, 77, 43; HRMS calcd for $C_{13}H_{19}NO_2$: 221.142, found: 221.141.

3.8. *(S)-6-Methoxy-1,2,3,4-tetrahydro-4-oxo-2-n-propyl-1-quinoline* ***3c***

A mixture of **2c** (510 mg, 2.2 mmol) and 7.5 g of PPA was stirred at 110–120°C for 2 h. The cooled solution was poured into 50 mL of ice–water and then the resulting solution was neutralized with $NaHCO_3$ to pH=8.5. After extraction with ethyl acetate (3×40 mL), the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed by rotavapor and the residue was loaded onto a column of silica gel. Eluting with ethyl acetate:petroleum ether (1:3) followed by evaporation of solvent afforded 283 mg (60% yield) of **3c**. $[\alpha]_D^{25}$=−157 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.29 (d, *J*=2.4 Hz, 1H), 7.00 (dd, *J*=8.1, 2.4 Hz, 1H), 6.71 (d, *J*=8.1 Hz, 1H), 3.78 (s, 3H), 3.59 (m, 1H), 2.68 (dd, *J*=16.2, 3.5 Hz, 1H), 2.46 (dd, *J*=16.2, 12.8 Hz, 1H), 1.59 (m, 2H), 1.41 (m, 2H), 0.99 (t, *J*=7.6 Hz, 3H); HRMS calcd for $C_{13}H_{17}NO_2$: 219.126, found: 219.125.

In a similar manner, **3d** (60% yield) and **3e** (20% yield) were obtained from the cyclization of **2d**. **3d**: $[\alpha]_D^{25}$=−209 (*c* 1.0, $CHCl_3$); IR (KBr) 3342, 1645, 1625, 1261, 796 cm^{-1}; ^{1}H NMR δ 7.72 (d, *J*=8.0 Hz, 1H), 6.50 (d, *J*=8.0 Hz, 1H), 6.47 (s, 1H), 3.67–3.56 (m, 1H), 2.65 (dd, *J*=16.0, 3.7 Hz, 1H), 2.46 (dd, *J*=16.0, 13.2 Hz, 1H), 2.38 (s, 3H), 1.57–1.50 (m, 2H), 1.47–1.36 (m, 2H), 0.98 (t, *J*=7.6 Hz, 3H);

MS m/z 203 (M^+), 160, 149, 137, 117, 99, 91, 85, 77, 44; HRMS calcd for $C_{13}H_{17}NO$: 203.131, found: 203.132. **3e**: $[\alpha]_D^{25}=-272.6$ (*c* 1.0, $CHCl_3$); IR (KBr) 3342, 1645, 1625, 1261, 796 cm^{-1}; ^1H NMR δ 7.12 (dd, *J*=7.8, 7.8 Hz, 1H), 6.56–6.49 (m, 2H), 3.67–3.56 (m, 1H), 2.63 (dd, *J*=15.6, 3.7 Hz, 1H), 2.58 (s, 3H), 2.47 (dd, *J*=15.6, 12.6 Hz, 1H), 1.63–1.54 (m, 2H), 1.47–1.38 (m, 2H), 0.97 (t, *J*=7.6 Hz, 3H); MS m/z 203 (M^+), 160, 137, 117, 99, 91, 85, 77, 44; HRMS calcd for $C_{13}H_{17}NO$: 203.131, found: 203.130.

3.9. (S)-N-*Acetyl*-N-*(3′-methyl)phenyl-3-aminohexanoic acid* ***4d***

To a solution of **2d** (480 mg, 2.2 mmol) in 20 mL of dry methanol was added $SOCl_2$ (0.8 mL, 10.9 mmol) dropwise at −40°C. After the addition the solution was allowed to warm gradually to room temperature and then the stirring was continued for 2 h. Triethylamine (2 mL) was added to neutralize the solution before it was concentrated at reduced pressure. The residue was diluted with 50 mL of ethyl acetate and the resulting solution was washed with brine and dried over Na_2SO_4. After removal of solvent, the crude ester was obtained, which was dissolved in 10 mL of acetic anhydride. The solution was heated at 100°C for 2 h and then acetic anhydride was evaporated via rotavapor. The residual oil was dissolved in 10 mL of methanol and 3 mL of aqueous 5% NaOH was introduced. After stirring for 5 h at room temperature, the solution was concentrated, acidified with 1 N HCl and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated to dryness, followed by chromatography (silica gel, ethyl acetate:petroleum ether=1:1 as eluent) to afford 440 mg (76% overall yield) of the crude **4d**. $[\alpha]_D^{25}=+17.8$ (*c* 1.0, $CHCl_3$); ^1H NMR δ 7.75 (br s, 1H), 7.28 (dd, *J*=7.8, 7.8 Hz, 1H), 7.17 (d, *J*=7.8 Hz), 7.06–6.90 (m, 2H), 5.19 (m, 1H), 2.45 (d, *J*=6.1 Hz, 2H), 2.41 (s, 3H), 1.80 (s, 3H), 1.47–1.30 (m, 4H), 0.96 (t, *J*=7.1 Hz, 3H); MS m/z 263 (M^+), 246, 220, 178, 162, 149, 118, 107, 91, 43; HRMS calcd for $C_{15}H_{21}NO_3$: 263.152, found: 263.152.

3.10. (S)-N-*Acetyl-7-methyl-1,2,3,4-tetrahydro-4-oxo-2-n-propyl-1-quinoline* ***5d***

To an ice-cooled solution of **4d** (121 mg, 0.46 mmol) in 10 mL of ether was added PCl_5 (115 mg, 0.55 mmol). After stirring for 1 h, the solvent was evaporated at reduced pressure and then 10 mL of methylene chloride was introduced. Anhydrous $AlCl_3$ (245 mg, 1.84 mmol) was added to the resulting solution before it was stirred for 3 h at room temperature. The mixture was poured onto 10 mL of ice–water to quench the reaction. The organic layer was separated and the aqueous layer was extracted with 20 mL of methylene chloride. The combined organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. The residue was chromatographed (silica gel, ethyl acetate:petroleum ether=1:3 as eluent) to afford 100 mg (89% yield) of **5d**. $[\alpha]_D^{25}=+201.5$ (*c* 1.0, $CHCl_3$); ^1H NMR δ 7.91 (d, *J*=8.0 Hz, 1H), 7.11 (s, 1H), 7.09 (d, *J*=8.0 Hz, 1H), 5.21 (m, 1H), 2.95 (dd, *J*=17.9, 5.7 Hz, 1H), 2.60 (dd, *J*=17.9, 1.9 Hz, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 1.51–1.20 (m, 4H), 0.83 (t, *J*=7.6 Hz, 3H); MS m/z 245 (M^+), 202, 160; HRMS calcd for $C_{15}H_{19}NO_2$: 245.141, found: 245.140.

Following the procedure for preparing **5d**, **5b** was obtained from **2b** in 74% overall yield. $[\alpha]_D^{25}=+349$ (*c* 1.0, $CHCl_3$); IR (KBr) 3030, 1693, 1665, 1484, 1319 cm^{-1}; ^1H NMR δ 8.01 (d, *J*=7.9 Hz, 1H), 7.56 (dd, *J*=7.9, 7.9 Hz, 1H), 7.36 (br s, 1H), 7.28 (dd, *J*=7.9, 7.9 Hz, 1H), 5.38 (br s, 1H), 3.03 (dd, *J*=17.9, 5.9 Hz, 1H), 2.61 (dd, *J*=17.9, 1.5 Hz, 1H), 2.36 (s, 3H), 1.20 (d, *J*=7.0 Hz, 3H); MS m/z 203 (M^+), 161, 146, 117, 91, 77, 43; HRMS calcd for $C_{12}H_{13}NO_2$: 203.095, found: 203.095.

Acknowledgements

The authors are grateful to the Chinese Academy of Sciences and the National Natural Science Foundation of China for their financial support.

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