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Synthesis of (*S*)-3-Aminoethyl-1,2,3,4-Tetrahydroisoquinoline (TIQ-Diamine) *via* the Mitsunobu Protocol†

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ABSTRACT

The synthesis of (*S*)-3-Aminoethyl-1, 2, 3, 4-tetrahydroisoquinoline (TIQ-diamine) was successfully achieved *via* the Mitsunobu protocol. The method from earlier reports utilizing aminolysis of commercially available TIQ-amino methyl ester, and reduction of the amide, proved to be inadequate for preparation of TIQ-diamines. The modified route requires three additional steps and consequently rendered three novel intermediates, which were furnished under mild conditions.

KEYWORDS

Tetrahydroisoquinoline, TIQ-diamine, Mitsunobu reaction.

1. Introduction

The potent biological activity of tetrahydroisoquinoline derivatives (TIQ) has been shown in β_3-adrenergic receptor[1] stimulation as well as δ opioid[2] and $5HT_{1A}$ receptor antagonism. This particular heterocycle is a common key intermediate in many biosynthetic pathways, contributing further to the level of interest in it. Among the biologically important TIQ compounds is (*S*)-3-aminoethyl-1,2,3,4-tetrahydroisquinoline which has demonstrated remarkable activity.[4,5] Generally, the diamine is synthesized *via* a two-step protocol; aminolysis of the TIQ-amino methyl ester **1** and amide **2** reduction with $LiAlH_4$ to produce the amine **3**.[6] Unfortunately, this method proved to be inadequate, requiring rigorous purification of intermediates and giving low overall yields, especially for slightly larger quantities (over 100 mg of the TIQ starting material). This was inferred to be as a result of the intense reaction conditions, i.e. high temperatures and long periods needed for the $LiAlH_4$ reduction.[7]

In recent years, the Mitsunobu reaction has been the subject of numerous investigations and a number of modifications have been reported, extending the applications far beyond its initial use.[8–10] The use of phthalimide in the reaction has become a popular method for the preparation of amines from alcohols.[7] This approach was found to be successful for our system and it is believed that this synthetic procedure can be applied to the synthesis of other TIQ-diamine derivatives.[11–14]

2. Results and Discussion

A representative synthesis of the TIQ-diamine **3** is outlined in Scheme 1.[6] The synthesis starts with methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **1**, which is then converted to (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide **2** in good yield through aminolysis of the ester. Reduction of the amide **2** with $LiAlH_4$ in dry THF, under reflux yields **3** in 30 % yield, providing an overall yield of 22 % for compound **3**. However, this is unsatisfactory and a marked increase in side products upon scaling up the reaction makes purification of the final product **3** more difficult.

Our alternative approach was based on a method in literature[15] and involves reduction of the methyl ester **1** to give the amino alcohol **4** in quantitative yield (Scheme 2). This was followed by amine protection using benzyl chloroformate to produce **5** in 74 % yield. The alcohol group of compound **5** was substituted with a phthalimide group using triphenylphosphine (PPh_3) and diethyl azodicarboxylate (DEAD) for a Mitsunobu conversion into **6** in 85 % yield. Removal of the phthalimide group by treatment with hydrazine hydrate in ethanol (EtOH) gave compound **7** in a 72 % yield.[10] Final deprotection of the Cbz group with 10 % palladium on carbon and 1 atmosphere of hydrogen gas afforded the desired diamine compound **3**. Purification of **3** was achieved by converting the compound into the crystalline dihydrochloride salt upon treatment with a solution of HCl bubbled through diethylether. The final overall yield using this protocol was 28 %. Although this method has more steps with essentially the same yield as before, it does offer improved consistency during scale up over 100 mg TIQ starting material (up to 1.5 g of TIQ starting material).

All the compounds were characterized by IR, NMR and high resolution mass spectroscopy. The ^{13}C NMR spectrum provides a peak at 156 ppm confirming the presence of the carbonyl group of the benzyl carbamate (Cbz) group in **5**. The disappearance of the OH signal from the IR spectrum of compound **6** and the appearance of an additional carbonyl signal at 1771 cm^{-1} suggests that the introduction of the phthalimide unit *via* the Mitsunobu reaction was successful. Similarly, the ^{13}C resonances appearing at 156 ppm and 171 ppm provide further evidence for the presence of the carbonyl groups from the benzyl carbamate

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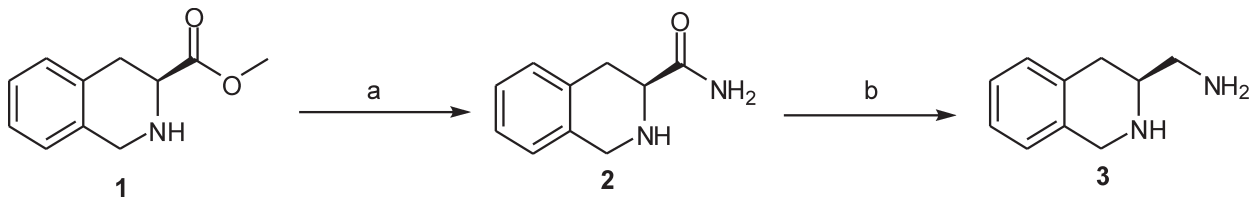
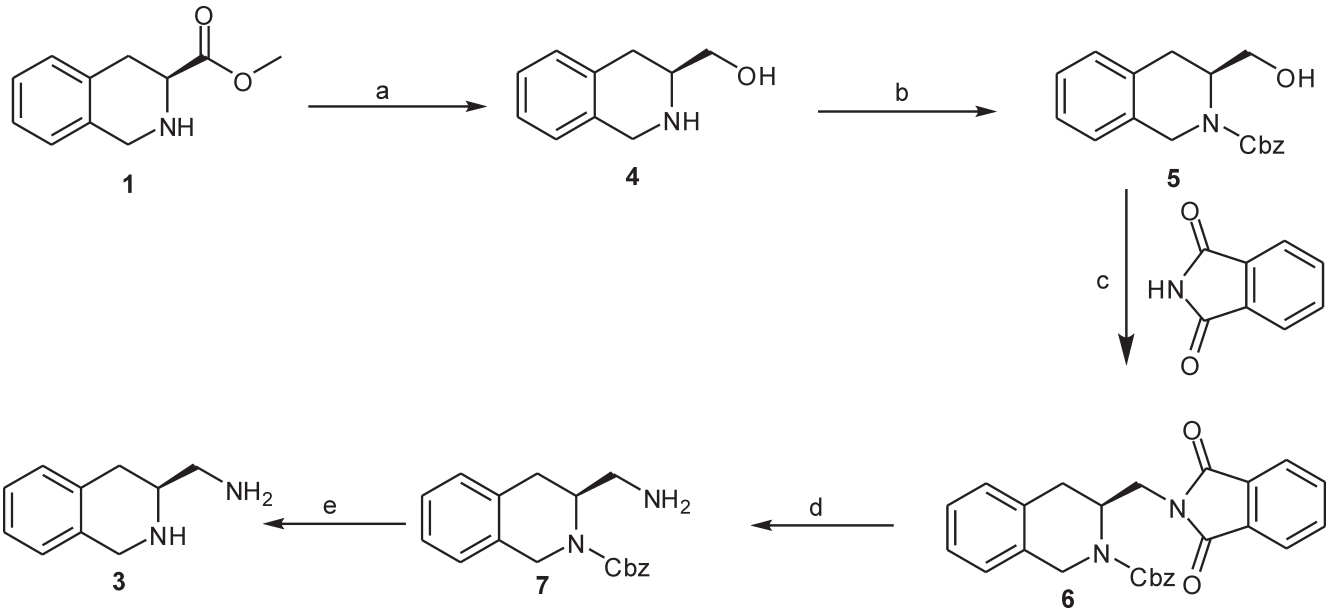


Scheme 1
Synthesis reagents and conditions: (**a**) aq. NH_3, 12 h, 75 %; (**b**) $LiAlH_4$, Dry THF, reflux, 16 h, 30 % yield.



Scheme 2
Reagents and conditions: (**a**) $LiAlH_4$, Dry THF, 0 °C, 3 h, 98 %; (**b**) CbzCl, dioxane/H_2O, 0 °C → r.t., 3 h, 74 %;(**c**) PPh_3, DEAD, DCM, 0 °C → r.t., 4 h, 85 %; (**d**) $H_2NNH_2 \cdot H_2O$, EtOH, reflux, 6 h, 75 %; (**e**) Pd/C, H_2, MeOH, 6 h, 60 %.

and phthalimide functionalities respectively. The TIQ-diamine compound **3** was identified by the presence of a NH stretch at 2879 cm^{-1} in the IR spectrum. Finally, the expected masses of these four compounds (**3**, **5**, **6** and **7**) were obtained with HRMS techniques.

Another approach and shorter synthetic route was also considered for the preparation of **3**, namely a borane reduction in tetrahydrofuran (BH_3 THF). However, this method proved unsuccessful in yielding the desired product. Some byproducts were observed which were not analysed further. This was reported before in literature.[16–18]

Our group is currently investigating the potential of the TIQ-diamine backbone in enantioselective catalytic applications.

3. Conclusions

The Mitsunobu protocol was successfully used to prepare the TIQ-diamine **3** with preservation of absolute stereochemistry in an overall yield of 28 %. This communication is the first to our knowledge in which a TIQ-diamine derivative has been synthesized using the Mitsunobu reaction. This protocol could be used for the preparation of other TIQ-diamine compounds, being insensitive to the scale of the reaction.

4. Experimental

4.1. General

All reagents and solvents were purchased from Aldrich, Merck or Fluka unless stated otherwise. All NMR analysis was carried out on a Bruker AVANCE III 400 MHz instrument. Chemical shifts are expressed in ppm and referenced to the TMS signal. Coupling constants are reported in Hz. NMR spectrum were obtained at room temperature, except if stated differently. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254. Products were purified *via* column chromatography using silica gel (60–200 mesh unless otherwise stated). All solvents were dried using standard procedures, *e.g.* Vogel.[19] All IR spectrum were recorded on a Perkin Elmer spectrum 100 instrument with a universal ATR attachment. Optical rotations were measured on a Perkin Elmer Polarimeter Model 341. All melting points are uncorrected. High resolution mass spectrometric data was obtained using a Bruker micrOTOF-Q II instrument, using a sample concentration of approximately 1 ppm.

4.2. 3-Aminomethyl-1,2,3,4-tetrahydroisoquinoline dihydrochloride (3)

The experimental procedure used for this reaction was adapted from literature.[6,7] A solution of amino ester **1** (1.00 g, 5.20 mmol) in methanol was added to an ammonia solution (30 mL). The mixture was allowed to stand in a closed flask at ambient temperature for 24 h, and the solvent was then evaporated. The crystalline product **2** was collected and dried. Yield 0.75 g (82 %, mp 157–160 °C). The ^{1}H NMR data of the product corresponded to the literature data.[7]

The carboxamide **2** (0.75 g, 42 mmol) was added in small portions to a cooled, stirring suspension of $LiAlH_4$ (0.64 g, 170 mmol) in dry THF (100 mL). The mixture was refluxed with stirring for 3 days. The reaction was monitored by TLC (methanol : DCM, 20:80, R_f = 0.32). Excess $LiAlH_4$ was decomposed by the addition

of a mixture of water (6 mL) in THF (40 mL) and the resulting inorganic solid was filtered. The combined organic filtrate and washings were dried (Na_2SO_4) and the solvent removed under reduced pressure to give the crude oily diamine **3**. Purification was carried out by precipitation of **3** as a crystalline dihydrochloride salt by means of stirring in a solution of HCl in diethyl ether. Yield 0.21 g (30 %, mp 224–226 °C); ^{1}H NMR data and the optical rotation $[\alpha]_D^{20}$ (c = 0.17, in 1N HCl) of the product correspond to literature data.[7]

4.3. (*S*)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (4)

The experimental procedure used for this reaction was adapted from literature.[6] To a stirred and cooled suspension of $LiAlH_4$ (1.98 g, 52.0 mmol) in dry THF (100 mL) under a N_2 atmosphere, was added dropwise a solution of (*S*)-methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate **1** (2.50 g, 13.0 mmol) in THF. The mixture was stirred at 0 °C for 3 h, completion of the reaction was monitored by TLC using hexane:ethyl acetate (70:30, R_f = 0.43). Excess $LiAlH_4$ was decomposed by the addition of a saturated sodium sulfate solution (4 mL) and THF (20 mL) at 0 °C. The inorganic solids were filtered and washed with EtOAc (3 × 30 mL). The combined organic washings were dried (Na_2SO_4) and removed under reduced pressure to give (*S*)-3-hydroxymethyl-1, 2, 3, 4-tetrahydroisoquinoline **4** as a crystalline yellow solid: Yield 2.09 g (98%, mp 95–97 °C). Optical rotation as reported in literature.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.57 (dd, 1H, J = 10.8, 11.2 Hz), 2.70 (dd, 1H, J = 4.34, 16.42 Hz), 3.05–3.10 (m, 1H), 3.49 (dd, 1H, J = 8.17, 10.82 Hz), 3.78 (dd, 1H, J = 3.98, 10.60 Hz), 4.05 (s, 2H) and 7.01–7.15 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 135.6, 133.9, 129.3, 126.3, 126.0, 125.9, 65.8, 55.0, 47.83 and 30.9.

4.4. (*S*)-benzyl 3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (5)

The experimental procedure used for this reaction was adapted from the literature.[15] To a solution of (*S*)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline **4** (1.42 g, 8.70 mmol) in dioxane (20 mL) and water (10 mL) at 0 °C, was added dropwise a solution of potassium hydrogen carbonate (4.30 g, 41.0 mmol) in water (10 mL) over 15 min followed by addition of CbzCl (1.63 g, 9.50 mmol). The mixture was stirred for 1.5 h at 0 °C and then at ambient temperature for a further 1.5 hours. Completion of the reaction was monitored by TLC in hexane:ethyl acetate (60:40, R_f = 0.32). The solvent was removed under reduced pressure to afford the crude compound (*S*)-benzyl 3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate **5**, which was purified by column chromatography using 0–40% ethyl acetate in hexane as the eluent to yield pure compound **5** as an oil. Yield 1.85 g (74%). $[\alpha]_D^{20}$ (c = 0.35, in CH_2Cl_2). IR ν_{max}/cm^{-1} = 3418, 3030, 2945, 1676, 1415, 1345, 1219, 1119, 1027 and 741. NMR spectrum are reported for a mixture of two rotamers.[20,21] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.83 (brd, 1H, J = 15.15 Hz), 3.04 (dd, 1H, J = 6.08, 15.95 Hz) , 3.36–3.63 (m, 2H), 4.29–4.47 (m, 1H), 4.48–4.64 (m, 1H), 4.70–4.95 (m, 1H), 5.19 (s, 2H) and 7.01–7.43 (m, 9H). The OH proton was not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.9, 136.4, 132.8, 132.5, 129.8, 128.8, 128.5, 128.0, 127.9, 127.8, 127.0, 126.4, 126.0, 125.9, 67.4, 63.3, 52.3, 43.7 and 29.8. HR ESI MS: m/z = 320.2159 [M+ Na]$^+$ (calcd. for $C_{18}H_{19}NNaO_3$ = 320.1257).

4.5. (*S*)-benzyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (6)

The experimental procedure used for this reaction was adapted from the literature.[11] Phthalimide (0.79 g, 5.9 mmol) and triphenylphosphine (3.19 g, 12.0 mmol) were added to a solution of **5** (1.45 g, 4.80 mmol) in dry dichloromethane (70 mL). The reaction mixture was cooled in an ice bath and diethyl azodicarboxylate (2.12 g, 12.0 mmol) in dichloromethane was added dropwise. The reaction was allowed to return to room temperature and stirring was continued for a further 4 hours. The reaction was monitored with TLC in hexane:ethyl acetate (70:30, R_f = 0.40). Removal of the solvent *in vacuo* provided a residue which was purified by column chromatography using 0–30 % hexane: ethyl acetate as the eluent to afford a white solid, compound **6** ((*S*)-benzyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate). Yield 1.81 g (85 %, mp 58–60 °C). $[\alpha]_D^{20}$ (c = 0.30, in CH_2Cl_2). IR ν_{max}/cm^{-1} = 3030, 2932, 1771, 1676, 1391, 1304, 1218, 1019, 964 and 712. NMR spectrum are reported for a mixture of two rotamers.[20–21] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.82 (m, 1H) 3.15–3.20 (dd, 1H, J = 4.4, 11.2 Hz) 3.51–3.63 (m, 1H), 3.75–3.83 (m, 1H), 4.56–4.59 (m, 5H), 7.15–7.29 (m, 9H) and 7.65–7.77 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.1, 168.2, 167.9, 156.0, 155.3, 136.5, 136.0, 133.8, 133.7, 132.3, 132.0, 131.9, 131.7, 131.3, 131.0, 129.0, 128.9, 128.4, 128.3, 128.3, 127.8, 127.8, 127.7, 127.6, 126.7, 126.5, 126.5, 126.3, 123.2, 123.1, 67.2, 67.0, 60.3, 48.6, 48.4, 43.3, 39.5, 31.8, 31.6, 21.0, 14.1 and 14.1. HR ESI MS: m/z = 427.1252 [M+ H]$^+$ (calcd. for $C_{26}H_{23}N_2O_2$ = 427.1653).

4.6. (S)-benzyl 3-(aminomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (7)

The experimental procedure used for this reaction was adapted from literature.[11] Hydrazine hydrate (1.26 g, 5.00 mmol) was added to a solution of **6** (1.8 g, 1.0 mmol) in absolute EtOH (20 mL). The mixture was stirred whilst refluxing for 6 hours. The reaction mixture was concentrated in *vacuo,* giving a semi crystalline slurry. The slurry was dissolved in dichloromethane (25 mL) and the precipitate of phthalalhydrazide was filtered and washed with dichloromethane (2 × 10 mL). The filtrate was concentrated in *vacuo* to give a pale yellow oil, compound **7** (0.90 g, 75%): $[\alpha]_D^{20}$ (c = 0.25, in CH_2Cl_2). IR ν_{max}/cm^{-1} = 2962, 1693, 1419, 1329, 1248, 1219, 1117, 745 and 698. NMR spectrum are reported for a mixture of two rotamers.[20.21] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.17–1.27 (m, 2H), 2.03–2.80 (m, 3H), 3.0 (d, 1H), 4.16–5.20 (m, 3H), 5.23 (s, 2H) and 7.08–7.38 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.2, 126.8, 136.6, 135.5, 133.9, 132.6, 132.3, 129.3, 129.1, 128.9, 128.5, 128.5, 128.3, 128.0, 127.9, 126.7, 126.3, 126.1, 126.0, 125.9, 67.3, 53.3, 52.7, 52.4, 45.9, 43.3, 43.1, 32.5, 30.8, 30.6 and 14.4. HR ESI MS: m/z = 297.1598 [M+ H]$^+$ (calcd. for $C_{18}H_{21}N_2O_2$ = 297.1585).

4.7. (*S*)-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanamine (3)

The experimental procedure used for this reaction was adapted from literature.[7] A solution of amine **7** (0.30 g, 0.7 mmol) in methanol (10 mL) was added to a suspension of 10 wt.% Pd/C (0.20 g) in methanol (10 mL). The reaction mixture was exposed to hydrogen gas *via* a balloon (~ 1 atm) and stirred at room temperature for 6 h. The Pd/C was filtered through a plug of celite. The filtrate was concentrated under reduced pressure to afford the crude TIQ-diamine **3** as an oil, which was converted to the crystalline dihydrochloride salt by treatment with a solution of HCl in Et_2O. Yield 0.10 g (52%, mp 224–226 °C); $[\alpha]_D^{20}$ (c = 0.17, at 1N HCl). IR ν_{max}/cm^{-1} = 2879, 1582, 1528, 1496, 1453, 1102 and 764. ^{1}H NMR (400 MHz, D_2O) δ = 2.75 (dd, 1H, J = 10.8, 10.4 Hz), 3.05 (dd, 1H, J = 4.91, 16.91 Hz), 3.15 (d, 2H, J = 6.00 Hz), 3.46–3.50 (m, 1H) 4.15 (s, 2H) and 7.09–7.20 (m, 4H). The amine protons were not observed. ^{13}C NMR (100 MHz, D_2O) δ = 131.1, 130.4, 129.1, 127.5, 126.9, 126.3, 51.4, 45.4, 42.0 and 29.7. HR ESI MS: m/z = 163.1192 [M+ H]$^+$ (calcd. for $C_{10}H_{15}N_2$ = 163.1230).

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