Stereoselective synthesis of 1,2-diamine containing indolines by a conjugate addition nitro-mannich reaction†

James C. Anderson,*a Ian B. Campbell,b Sebastien Campos,b Jonathan Shannona and Derek A. Tocher†a

A conjugate addition nitro-Mannich reaction followed by nitro reduction and intramolecular N-arylation gives diasteromERICALLY pure substituted 1,2-diamine containing indolines. Placing the N-arylation cyclisation handle on the imine precursor derived from an ortho-bromine substituted aromatic aldehyde gave the corresponding β-nitroamines in 55–72% yields as single diastereoisomers. Nitro reduction was effected with modified quantities of Zn/HCl and a subsequent Pd(0) catalysed Buchwald Hartwig cyclisation gave indoline products in 40–70% yields as single diastereoisomers.

Introduction

The nitro-Mannich (or aza-Henry) reaction has emerged as a reliable and predictable reaction for the synthesis of β-nitroamines in stereochemically pure form.1,2 These products have proven useful in the synthesis of many nitrogen containing functional groups including 1,2-diamines,3–10 α-amino carbonyls,11–13 peptidomimetics,14 natural products15–20 and many heterocyclic small molecules.21–32 Of importance to drug discovery. The anti-diastereoisomer dominates with higher homologues of nitromethane, with there being only a few methods for syn-selective nitro-Mannich reactions.26,33–35 We reported the enantioselective alkyl conjugate addition nitro-Mannich reaction of dialkyl zincs to nitroalkenes to synthesise complex β-nitroamines containing three contiguous stereo-centres (Scheme 1).36 The judicious choice of solvent determined whether the syn,anti- or syn,syn-diastereoisomer was formed and provided another method for the synthesis of syn-β-nitroamines. As part of an investigation into the nitro-Mannich reaction in diversity-oriented array synthesis, we were interested in the synthesis of arrays of stereochemically diverse fused heterocyclic ring systems. We have recently shown that the reductive nitro-Mannich reaction with aryl bromide nitrostyrenes can deliver stereodefined functionalised diamine building blocks that are precursors to either 3-aminotetrahydroquinolines or 2-aminomethylene indolines via N-arylation (Scheme 1).37

We detail here our investigation into the combination of the alkyl conjugate addition nitro-Mannich reaction with suitable aryl bromide containing coupling partners and their subsequent intramolecular cyclisation by palladium catalysed N-arylation to yield novel drug like heterocyclic ring systems (Scheme 2).

Results and discussion

Using conditions previously developed by us, the simplest 2-bromonitrostyrene (1a) underwent smooth Cu(OTf)2 catalysed (5 mol%) conjugate addition of ZnEt2 (1.1 equiv.) as judged by TLC. The resultant nitronate species was then reacted with PMP protected imine 2a (2.2 equiv.) and TFA (2.6 equiv.) with quenching at −78 °C. Crude 3aa was isolated in a 60:40 ratio of two of the possible four diastereoisomers, determined by 1H NMR (Scheme 3). Preliminary investigation of the reaction conditions varied the temperature after TFA addition and the time before quenching. The selectivity tended towards 1:1 and the crude product was unstable over time, reverting to starting materials.38 Usually formation of the corresponding trifluoroacetamide leads to an isolable product, but in this instance the instability of 3aa and the reluctance of similar syn,syn-diastereoisomers to be protected, led to the isolation of only 34% of the syn,anti-4aa diastereoisomer as a single diastereoisomer.36,§ This product was most likely the minor diastereoisomer in the mixture of 3aa.

§ β-Nitroamines without electron withdrawing protecting groups on nitrogen are known to be unstable to standard purification techniques and undergo retro-addition. See ref. 7 and 36.

† Electronic supplementary information (ESI) available: General experimental details, X-ray representations and copies of 1H and 13C NMR spectra. CCDC 1020679. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01793e

‡ Corresponding author for crystallographic results.

Department of Chemistry, University College London, 20 Gordon Street, London, WC1H 0AJ, UK. E-mail: j.c.anderson@ucl.ac.uk
GlaxoSmithKline, Medicines Research Centre, SG1 2NY Stevenage, UK
Electronic supplementary information (ESI) available: General experimental details, X-ray representations and copies of 1H and 13C NMR spectra. CCDC 1020679. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01793e
† Corresponding author for crystallographic results.

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A screen of different protecting groups of the imine partner \(2\) (\(\text{COPh, CO}_2\text{Bn, POPh}_2\)) along with various Lewis and Bronsted acid promoters in place of TFA (\(\text{AcOH, CF}_3\text{SO}_3\text{H, MeSO}_3\text{H, Yb(OTf)}_3, \text{AlCl}_3, \text{Zn(OTf)}_2, \text{BF}_3\cdot\text{Et}_2\text{O}\)) was undertaken. Disappointingly no conditions were found that gave either high conversion or a good level of diastereoselectivity with the 2-bromonitrostyrene (1a). These results were similar to what we had found in our earlier work with other ortho-substituted nitrostyrenes.\(^3\(6\)\)

An alternative cyclisation precursor was envisaged where the halide coupling partner was part of the aldehyde that the imine was derived from. This small change had a dramatic effect on the extent of diastereoselectivity, and stability of the nitro-Mannich product (Scheme 4). Complete consumption of 1b was verified by TLC and the reaction went to complete conversion as judged by \(^1\text{H NMR}\). The diastereoselectivity of the crude product did not change over reaction time or temperature after addition of TFA, indicating that the major stereoisomer was thermodynamically stable. We tentatively assigned the stereochemistry as the \(\text{syn, syn}\)-diastereoisomer by analogy to previous work where we found that this particular diastereoisomer was relatively stable and could be purified by column chromatography to give diastereomERICALLY pure material.\(^3\(6\)\)

With 2 equivalents of imine 2b the major diastereoisomer \(\text{syn, syn-3bb}\) could be isolated in 72% yield\(^4\) and the relative stereochemistry was confirmed by single crystal X-ray analysis (see 4).

\(^4\)A minor diastereoisomer was also isolated in 10% yield and is tentatively assigned \(\text{anti, syn-3bb}\), by analogy to other work (ref. 36), which has been more rigorously corroborated with single crystal X-ray crystallography. This is based upon the diastereoisomer being stable to purification, so most probably has the \(\text{syn}\)-relative stereochemistry across the nitro-amine bond.
ESI†). Reducing the quantity of imine 2b to 1.1 equivalents led to no change in crude diastereoselectivity (85 : 15), but the major compound was significantly easier to purify and was isolated in 68% yield.

A solvent screen (see ESI†) showed that Et₂O gave the highest diastereoselectivity followed by toluene (80 : 20), which contained more side products and unlike Et₂O was a homogenous solution. Other solvents which gave homogeneous reaction mixtures did not give as the major diastereoisomer the syn,anti-product which had been previously observed with very similar substrates. In most cases the syn,syn-diastereoisomer was the major compound to varying degrees and all attempts at protection of the amine as a trifluoroacetamide were unsuccessful, which is in agreement with our previous observations for this particular diastereoisomer.16

Intramolecular N-arylation required the reduction of the nitro function to an amine. Investigations commenced with 3bb and initial conditions we have developed for the reduction of β-nitroamines into 1,2-diamines using Zn/HCl (Scheme 5, conditions A). Although the nitro group was completely reduced, a 1 : 1 mixture of the desired amine 5bb and the debrominated material 6 were obtained. Optimisation studies found that reducing the amount of reductant zinc, but increasing the relative amount of HCl lead cleanly to the desired diamine. Normally β-nitroamines (like 3bb) would be isolated as their corresponding trifluoroacetamides and subsequent reduction is accompanied by migration of the trifluoroacetyl group to the primary nitrogen, giving a stable isolable product. However, as the syn,syn-diastereoisomers like 3bb are in general inert to trifluoroacetylation, the resultant 1,2-diamine reduction product 5bb was found to become less pure upon column chromatography. As a consequence intramolecular cyclisation using palladium catalysed N-arylation was attempted on the crude reduction material.

Treatment of 5bb under standard Pd[PPh₃]₄ Buchwald–Hartwig conditions that we have used to perform analogous cyclisations (Scheme 1), led cleanly to the indoline 7bb by ⁱH NMR of the crude cyclisation product (Scheme 6). Initial attempts at purification using silica gel chromatography led to degradation and isolation of the corresponding indole 8 (∼25%) as a mixture with p-anisidine. Indoline 7bb is unstable to acidic conditions, but using basic alumina chromatography we were able to isolate 7bb in a good 60% yield over two steps as a single diastereoisomer. Use solely of NaO'Bu as base led to 64% yield of indoline 7bb (Scheme 6).

The scope of this reaction sequence for the synthesis of the 1,2-diamine indolines was then investigated with a series of aldimines containing an ortho-bromine substituent and nitro styrenes under the optimised conditions described above (Scheme 7 and Table 1).

The conjugate addition nitro-Mannich reaction proceeds well with a range of imines 1 and nitrostyrenes 2 to give good diastereoselectivities of syn,syn-products and good isolated yields of diastereomerically pure β-nitroamines 3. The reductions proceeded smoothly except for the β-nitroamine derived from 2-bromo-3-pyridinylaldehyde (entry 6), which led to an inseparable mixture of unidentified products. Use of Sn/HCl gave similar results and Al/Hg amalgam, which we have used for the reduction of sensitive β-nitroamines, gave a complex mixture of products. No doubt the sensitivity of the pyridine function and the C-Br bond are both compounding this reduction. Cyclisations to give the indoline nucleus by standard Pd[PPh₃]₄ Buchwald–Hartwig conditions gave good yields in most cases. The β-nitroamine derived from 2-bromo-5-methoxy benzaldehyde (entry 3) cyclised using Pd[PPh₃]₄, albeit with a moderate yield of 40%. The congener derived from 2-bromo-4,5-dimethoxy benzaldehyde (entry 4) failed to cyclise and gradually led to decomposition of the β-nitroamine over longer reaction times. Changing to a Binap or X-Phos ligand system, which is known to coupling electron rich aryl bromides, also led to gradual decomposition.

With respect to the conjugate addition of other carbon nucleophiles, we have already shown that methyl and phenyl dialkylzinc species work in the conjugate addition nitro-Mannich reaction and led to syn,syn-β-nitroamines in high diastereoselectivity. There are a number of chiral metal catalysed systems that control the enantioselectivity of dialkyl zinc addition to nitro-alkenes and we have already shown that this is a good way of making the conjugate addition nitro-Mannich products enantioselectively, which would in turn lead to the heterocyclic products described here in enantiomerically pure form. This methodology is limited by the availability of dialkylzincs and although it is possible to add functionalised dialkylzincs that can be derived from the tandem hydroboration/boron-zinc exchange method developed by Knochel, it would
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Scheme 7  Scope of indoline formation.

Table 1  Scope of indoline formation

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<th>Entry</th>
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<th>Ar²</th>
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<th>Yield 3</th>
<th>Yield 2</th>
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<td>2-BrPh</td>
<td>85 : 15</td>
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<td>2</td>
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<td>4-FPh</td>
<td>2-BrPh</td>
<td>75 : 25</td>
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</table>

a Nitro-Mannich: 1 (3 mmol), Cu(Otf)², (5 mol%), ZnEt₂ (1.1 equiv.), Et₂O, −78 °C, 5 min, then RT 2 h; 2 (1.1 equiv.), Et₂O, −78 °C, 10 min; TFA (2.6 equiv.), Et₂O, −78 °C, 1 h then to RT 1 h. Nitro reduction: conc. HCl (10 mmol) added to crude 3 (0.50 mmol), Zinc (4.00 mmol), in EtOH (7.5 mL) at 0 °C, 5 min then RT. N-arylation: crude 2,1-diamine in PhMe (1.5 ml) added to NaOBu (1.00 mmol), Pd(PPh₃)₄ (0.025 mmol) in PhMe (1 ml) at RT then 90 °C, 16−24 h. Diastereoselectivities were calculated by comparison of the ¹H NMR signals for the CHNNO₂ protons (δ 3.1−3.6 ppm) of the crude reaction mixture. ² Isolated yield of pure syn,syn-diastereoisomer. ³ Reaction failed at cyclisation. ⁴ Reaction failed at reduction.

be better if more readily available carbon nucleophiles could be found. In an attempt to widen the scope of the reaction to include organozinc halides,42,43 test reactions revealed that benzylzinc bromide and allylzinc bromide both gave low diastereoselectivities and trace conversions (<10%) with benzylicnucleophiles to trigger this reaction and alternative cyclisation modes are being investigated to prepare alternate ring systems and will be reported in due course.

Conclusion

We have developed a diastereoselective synthesis of substituted 1,2-diamine containing indolines, that represent novel drug like heterocyclic ring systems, from a conjugate addition nitro-Mannich reaction followed by nitro reduction and intramolecular N-arylation. Attempts to make indoline precursors from nitro styrenes containing an ortho-bromine substituent were low yielding and poorly diastereoselective (Scheme 3). Placing the N-arylation cyclisation handle on the imine precursor derived from an ortho-bromine substituted aromatic aldehyde was much more successful giving the corresponding β-nitroamine in good yield and as a single diastereoisomer. Nitro reduction was effected with modified quantities of Zn/HCl and a subsequent Pd(0) catalysed Buchwald Hartwig cyclisation gave indoline products in good yields as single diastereoisomers (Table 1). Electron rich aryl bromides were found to be reluctant to cyclise. Despite exploring other more readily available organometallic carbon nucleophiles, especially organozinc halides, a limitation to the current methodology is that dialkyl zinc species are the most efficient for the initial conjugate addition to nitro styrene. We have previously modified literature protocols to enable the enantioselective synthesis of suitably functionalised β-nitroamines for cyclisation to functionalised heterocycles16,17,44 and this methodology could also be used in this case. We are investigating the use of other nucleophiles to trigger this reaction and alternative cyclisation modes are being investigated to prepare alternate ring systems and will be reported in due course.

[1] Allyl/aryl zinc halides have been shown to be useful in certain addition and conjugate addition reactions.

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**Experimental section**

**General procedure for the synthesis of syn,syn-β-nitroamines 3 (Table 1)**

To a stirred mixture of nitroalkene (3.00 mmol) and Cu(OTf)$_2$ (0.05 mmol) in Et$_2$O (5 mL) at −78 °C was added Et$_2$Zn (3.3 mmol, 1 M in hexanes) dropwise. The mixture was stirred at this temperature for 5 min then at RT until the reaction was complete by TLC analysis (approximately 2 h). The reaction mixture was cooled to −78 °C and a solution of imine (3.3 mmol) in dry Et$_2$O (5 mL) was added and the mixture stirred for 10 min. Then a solution of TFA (7.8 mmol) in Et$_2$O (0.2 mL) was added dropwise over 20 s and the reaction stirred for 1 h. The reaction was warmed to room temperature over 1 h to provide a suspension of white solid in a vivid yellow supernatant. The reaction was quenched by the addition of Et$_2$O and saturated aq. NaHCO$_3$. The layers were separated, and the aqueous phase was extracted with Et$_2$O. The organic layers were combined, and the solvent was removed in vacuo to provide crude β-nitroamine. Diastereoselectivities were calculated by comparison of the $^1$H NMR signals for the CHCHN$_2$O protons ($\delta$ 3.1–3.6 ppm). Purification by flash chromatography yielded diastereomERICally pure syn,syn-β-nitroamines 3.

**syn-,anti-4aa (1R*,2S*,3R*)-N -(1-(2-Bromomethyl)-2-nitro-3-phenylpentyl)-N-trifluoroacetyl-4-methoxybenzene.** Yellow solid (72%) m.p. 123–124 °C; $^1$H NMR (600 MHz, CDCl$_3$); $\delta$ 0.76 (3H, $t, J = 7.3$), 1.63 (1H, $dq, J = 13.4, 7.3, 3.5$), 1.80 (1H, $dq, J = 13.4, 11.6, 7.3$), 2.48 (1H, td, $J = 11.4, 3.5$), 2.73 (3H, s), 4.50 (1H, $dd, J = 10.2, 3.3$), 5.05 (1H, $dd, J = 11.4, 3.3$), 5.22 (1H, $d, J = 10.2$), 6.19–6.22 (2H, m), 6.62–6.65 (2H, m), 6.80 (1H, $dd, J = 8.6, 7.6, 3.0$), 7.16 (1H, $dd, J = 9.2, 3.0$), 7.24–7.30 (5H, m), 7.43 (1H, $dd, J = 8.6, 5.0$); $^{13}$C NMR (126 MHz, CDCl$_3$); $\delta$ 14.2 (CH$_2$), 25.1 (CH$_2$), 48.3 (CH), 55.7 (CH$_3$), 56.2 (CH), 95.2 (CH), 114.3 (2C, CH), 114.9 (2C, CH), 115.0 (d, $J_{CF} = 24.2$, CD), 116.9 (d, $J_{CF} = 2.7$, q), 117.2 (d, $J_{CF} = 22.9$, CH), 128.0 (CH), 128.9 (2C, CH), 129.0 (2C, CH), 134.5 (d, $J_{CF} = 7.7$, CH), 137.0 (q), 139.0 (q), 139.6 (d, $J_{CF} = 5.9$, q), 152.5 (q), 162.5 (d, $J_{CF} = 249.0$, q); IR $\nu_{max}$ (neat) 3417, 2966, 1550, 1242 cm$^{-1}$; HRMS (EI) calced for C$_2$H$_5$BrN$_2$O$_4^+$, [M$^+$] 486.0948 found 486.0934; Anal. calced for C$_2$H$_5$BrN$_2$O$_4$: C, 59.13; H, 4.96; N, 5.75; found: C, 59.09; H, 4.89; N, 5.78%.

**Entry 3 (1S*,2S*,3R*)-N -(1-(2-bromo-5-methoxyphenyl)-2-nitro-3-phenylpentyl)-4-methoxybenzene.** Yellow solid (63%) m.p. 148–150 °C; $^1$H NMR (400 MHz, CDCl$_3$); $\delta$ 0.75 (3H, $t, J = 7.3$), 1.63 (1H, $dq, J = 13.5, 7.3, 3.5$), 1.80 (1H, $dq, d, J = 13.5, 11.3, 7.3$), 3.56–3.66 (1H, m), 3.64 (3H, s), 3.66 (3H, s), 4.64 (1H, m), 5.06 (1H, $dd, J = 11.3, 5.5$), 5.20 (1H, br. s), 6.15–6.28 (2H, m), 6.56–6.69 (4H, m), 7.21–7.39 (6H, m); $^{13}$C NMR (101 MHz, CDCl$_3$); $\delta$ 11.6 (CH$_2$), 25.2 (CH$_2$), 55.3 (CH$_3$), 55.6 (CH$_3$), 56.2 (CH), 95.5 (CH), 113.1 (q), 113.6 (CH), 114.3 (2C, CH), 114.8 (2C, CH), 115.2 (CH), 127.8 (CH$_2$), 128.9 (2C, CH), 133.7 (CH), 137.1 (q), 138.0 (q), 139.5 (q), 152.3 (q), 159.5 (q); IR $\nu_{max}$ (neat) 3406, 2935, 1550, 1240 cm$^{-1}$; HRMS (ES) calced for C$_2$H$_5$BrN$_2$O$_4$: [M$^+$ + H$^+$] 499.1232 found 499.1236.

**Entry 4 (1S*,2S*,3R*)-N -(1-(2-bromo-4,5-dimethoxyphenyl)-2-nitro-3-phenylpentyl)-4-methoxybenzene.** Yellow solid (57%) m.p. 53–55 °C; $^1$H NMR (600 MHz, CDCl$_3$); $\delta$ 0.75 (3H, $t, J = 7.3$), 1.62 (1H, $dq, d, J = 13.5, 7.3, 3.5$), 1.79 (1H, $dd, d, J = 13.5, 11.7, 7.3$), 3.60 (1H, $td, d, J = 11.4, 3.5$), 3.67 (3H, s), 3.69 (3H, s), 3.80 (3H, s), 4.45 (1H, $dd, J = 10.0, 3.4$), 5.00 (1H, $dd, d, J = 11.4, 3.4$), 5.19 (1H, $d, J = 10.0$), 6.20–6.23 (2H, m), 6.55 (1H, $s$), 6.60–6.63 (2H, m), 6.90 (1H, s), 7.24–7.29 (5H, m); $^{13}$C NMR (126 MHz, CDCl$_3$); $\delta$ 11.7 (CH$_2$), 25.2 (CH$_3$), 48.3 (CH), 55.7 (CH$_3$), 56.1 (CH), 56.2 (CH$_3$), 95.9 (CH), 109.8 (CH), 114.4 (2C, CH), 114.9 (2C, CH), 115.6 (CH), 127.9 (CH), 128.8 (2C, CH), 128.9 (2C, CH), 134.5 (CH), 137.2 (q), 139.6 (q), 149.0
7.49 (1H, dd, J = 10.3, 3.0), 5.07 (1H, dd, J = 11.2, 3.3), 5.25 (1H, dd, J = 10.3), 6.19-6.29 (2H, m), 6.59-6.69 (2H, m), 7.04-7.21 (7H, m), 7.49 (1H, dd, J = 7.0, 1.8); 13 C NMR (101 MHz, CDCl3): δ 116.6 (CH3), 149.2 (q), 151.8 (q); IR νmax (neat) 3415, 2932, 1549, 1258 cm⁻¹; HRMS (ES) calcd for C25H28BrN2O3⁺ [M + H⁺] 483.2184 found 483.2181.

General procedure for the synthesis of indolines (Table 1)

To a stirred mixture of syn,syn-β-nitroamine 3 (0.50 mmol) and Zinc (4.00 mmol) in ETOH (7.5 mL) at 0 °C was added conc. hydrochloric acid (10 mmol). The mixture was stirred at this temperature for 5 min then at RT until the reaction was complete by TLC analysis (approximately 1 h). The reaction was quenched by the addition of ETOAc and saturated aq. NaHCO3. The layers were separated, and the aqueous phase was extracted with ETOAc. The organic layers were combined, and the solvent was removed in vacuo to provide crude 1,2-diamine.

To a stirred mixture of sodium tert-butoxide (1.00 mmol), palladium tetrakistriphenylphosphine (0.025 mmol) in toluene (1 mL) under nitrogen at RT was added a solution of crude 1,2-diamine in toluene (1.5 mL). The reaction vessel was heated at 90 °C until the reaction was complete by TLC analysis (approximately 16 to 24 h). Reaction cooled to RT and filtered thought celite and concentrated to give a brown oil. Purification by flash chromatography using basic Alumina or aminopropyl (NH2) silica yielded the indolines (Table 1).

7bb Entry 1 (15*S,25*S,1R*)-1-N-(4-methoxyphenyl)pyrrolidin-3-amine. Yellow oil (64%); 1 H NMR (500 MHz, CDCl3): δ 0.75 (3H, t, J = 7.3), 1.77 (1H, ddq, J = 12.7, 11.2, 7.3), 2.07 (1H, ddq, J = 12.7, 7.3, 4.0), 2.39 (3H, s), 3.71 (3H, s), 4.10 (1H, app. td, J = 11.1, 3.9), 5.28 (1H, dd, J = 11.1, 3.3), 5.30 (1H, dd, J = 10.2, 3.3), 5.50 (1H, dd, J = 10.2, 3.3), 6.54-6.58 (2H, m), 6.74-6.78 (2H, m), 7.10-7.15 (5H, m), 7.17-7.22 (2H, m), 7.23-7.27 (1H, m), 7.60 (1H, dd, J = 8.0); 13 C NMR (126 MHz, CDCl3): δ 11.2 (CH3), 19.9 (CH2) 25.2 (CH2), 42.0 (CH), 55.7 (CH3), 55.8 (CH3), 95.5 (CH3), 114.5 (2C, CH), 115.1 (2C, CH), 123.3 (q), 125.8 (CH), 126.6 (CH), 127.2 (CH), 127.5 (CH), 128.6 (CH), 130.0 (CH), 130.8 (CH), 133.3 (CH), 136.6 (q), 137.1 (q), 137.4 (q), 139.5 (q), 152.6 (q); IR νmax (neat) 3399, 2965, 1549, 1258 cm⁻¹; HRMS (ES) calcd for C25H25BrN2O3⁺ [M + H⁺] 482.1199 found 482.1185; Anal. calcd for C25H22BrN2O3: C 62.12; H, 5.63; N, 5.80; found: C, 62.09; H, 5.90; N, 5.63%.

9 Entry 9 (15*S,25*S,3R*)-1-(1-(2-bromophenyl)-3-(4-fluoro-phenylpropyl)indolin-3-amine. Yellow solid (55%) m.p. 143-145 °C; 1 H NMR (400 MHz, CDCl3): δ 0.77 (3H, t, J = 7.3), 1.63 (1H, ddq, J = 13.6, 7.3, 3.6), 1.79 (1H, ddq, J = 13.6, 11.7, 7.3), 2.35 (3H, s), 3.63 (1H, app. td, J = 11.3, 3.5), 3.68 (3H, s), 4.64 (1H, dd, J = 10.3, 3.3), 5.07 (1H, dd, J = 11.2, 3.3), 5.25 (1H, dd, J = 10.3); 13 C NMR (101 MHz, CDCl3): δ 116.6 (CH3), 25.2 (CH2), 48.1 (CH), 55.6 (CH3), 55.7 (CH3), 95.1 (CH3), 114.3 (2C, CH), 115.0 (2C, CH), 123.5 (CH), 128.0 (CH), 128.7 (2C, CH), 128.8 (2C, CH), 134.7 (q), 136.1 (CH3), 136.8 (q), 138.8 (q), 142.8 (q), 149.7 (CH); 152.6 (q); IR νmax (neat) 3415, 2934, 1548, 1241 cm⁻¹; HRMS (ES) calcd for C25H23F3BrN2O3⁺ [M + H⁺] 487.1027 found 487.1026.
Entry 2 (1S*,2S*,1'R*)-5-fluoro-N-(4-methoxyphenyl)-2-(1'-phenylpropyl)indolin-3-amine. Yellow oil (53%); 1H NMR (400 MHz, CDCl3): δ 0.72 (3H, t, J = 7.4), 1.66 (1H, ddq, J = 13.1, 11.5, 7.3), 1.83–1.92 (1H, m), 2.21 (3H, s), 2.93–3.09 (1H, m), 3.65 (3H, s), 3.83–4.02 (2H, m), 4.28 (1H, app. t, J = 8.2), 4.74 (1H, br. s), 6.23–6.32 (2H, m), 6.36 (1H, d, J = 7.5), 6.53 (1H, s), 6.56–6.67 (2H, m), 6.72–6.82 (1H, m), 7.10–7.28 (5H, m); 13C NMR (101 MHz, CDCl3): δ 10.8 (CH3), 25.6 (CH2), 46.7 (CH), 57.7 (CH2), 68.2 (CH), 110.1 (CH2), 113.1 (CH2), 114.1 (2C, CH), 115.0 (2C, CH), 125.7 (CH), 127.7 (2C, CH), 128.3 (2C, CH), 129.0 (q), 138.0 (q), 141.8 (q), 142.9 (q), 151.0 (q), 151.6 (q); IR ν max (neat) 3365, 2929, 1511 cm⁻¹; HRMS (EI) calecd for C23H25FN2O2, [M⁺] 388.2145 found 388.2151.

Entry 3 (1S*,2S*,1'R*)-5-methoxy-N-(4-methoxyphenyl)-2-(1'-phenylpropyl)indolin-3-amine. Light yellow oil (40%); 1H NMR (400 MHz, CDCl3): δ 0.70 (3H, t, J = 7.4), 1.66 (1H, ddq, J = 13.4, 11.5, 7.3), 1.83–1.92 (1H, m), 2.21 (3H, s), 2.93–3.09 (1H, m), 3.65 (3H, s), 3.83–4.02 (2H, m), 4.28 (1H, app. t, J = 8.2), 4.74 (1H, br. s), 6.23–6.32 (2H, m), 6.36 (1H, d, J = 7.5), 6.53 (1H, s), 6.56–6.67 (2H, m), 6.72–6.82 (1H, m), 7.10–7.28 (5H, m); 13C NMR (101 MHz, CDCl3): δ 10.8 (CH3), 25.6 (CH2), 46.7 (CH), 57.7 (CH2), 68.2 (CH), 110.1 (CH2), 113.1 (CH2), 114.1 (2C, CH), 115.0 (2C, CH), 125.7 (CH), 127.7 (2C, CH), 128.3 (2C, CH), 129.0 (q), 138.0 (q), 141.8 (q), 142.9 (q), 151.0 (q), 151.6 (q); IR ν max (neat) 3365, 2929, 1511 cm⁻¹; HRMS (EI) calecd for C23H25FN2O2, [M⁺] 388.2145 found 388.2151.

Entry 4 (1S*,2S*,1'R*)-5-methoxy-N-(4-methoxyphenyl)-6-methyl-2-(1'-phenylpropyl)indolin-3-amine. Light yellow oil (62%); 1H NMR (400 MHz, CDCl3): δ 0.70 (3H, t, J = 7.4), 1.66 (1H, ddq, J = 13.4, 11.5, 7.3), 1.83–1.92 (1H, m), 2.21 (3H, s), 2.93–3.09 (1H, m), 3.65 (3H, s), 3.83–4.02 (2H, m), 4.28 (1H, app. t, J = 8.2), 4.74 (1H, br. s), 6.23–6.32 (2H, m), 6.36 (1H, d, J = 7.5), 6.53 (1H, s), 6.56–6.67 (2H, m), 6.72–6.82 (1H, m), 7.10–7.28 (5H, m); 13C NMR (101 MHz, CDCl3): δ 10.8 (CH3), 20.4 (CH3), 25.5 (CH3), 46.7 (CH), 54.9 (CH2), 57.0 (CH2), 67.5 (CH), 110.3 (CH), 111.4 (2C, CH), 114.8 (2C, CH), 118.6 (2C, CH), 123.2 (CH), 125.7 (CH), 127.7 (2C, CH), 128.3 (2C, CH), 129.0 (q), 138.0 (q), 141.8 (q), 142.9 (q), 151.0 (q), 151.6 (q); IR ν max (neat) 3365, 2929, 1511, 1236 cm⁻¹; HRMS (EI) calecd for C23H25FN2O2, [M⁺] 388.2145 found 388.2151.

Entry 5 (1S*,2S*,1'R*)-N-(4-methoxyphenyl)propyl-N-(4-methoxyphenyl)indolin-3-amine. Prepared by the General Procedure for the synthesis of indole 7. Off white solid (75%), m.p. 83–85 °C; 1H NMR (600 MHz, CDCl3): δ 2.81 (1H, dd, J = 13.4, 9.4), 3.05 (1H, dd, J = 13.4, 4.8), 3.67 (1H, br. s), 3.80 (3H, s), 3.85 (1H, br. s), 3.87 (1H, app. dt, J = 9.3, 4.7), 4.77 (1H, dd, J = 4.4), 6.55 (2H, dd, J = 8.8), 6.65 (1H, dd, J = 7.7), 6.73–6.83 (3H, m), 7.16 (1H, t, J = 7.7), 7.22–7.34 (4H, m), 7.34–7.42 (2H, m); 13C NMR (151 MHz, CDCl3): δ 41.0 (CH2), 55.8 (CH3), 61.8 (CH3), 68.3 (CH3), 109.9 (CH), 115.0 (2C, CH), 115.0 (2C, CH), 118.8 (CH), 125.5 (CH), 133.8 (CH), 135.5 (CH), 136.1 (CH), 139.5 (CH), 140.7 (CH), 150.0 (CH), 152.4 (q); IR ν max (neat) 3408, 2928, 1510 cm⁻¹; HRMS (EI) calecd for C32H28N2O4, [M⁺] 572.2196 found 572.2203.
126.6 (CH), 128.7 (2C, CH), 129.2 (q), 129.3 (CH), 129.3 (2C, CH), 138.5 (q), 141.2 (q), 149.9 (q), 152.4 (q); IR ν_{max} (neat) 3373, 2932, 1510 cm\(^{-1}\); HRMS (El) calec for C\(_{25}\)H\(_{28}\)N\(_{2}\)O\(^+\), [M\(^+\)]: 330.1732 found 330.1741.

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References


