Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Convenient Synthesis of 6-Bromo-1,2,3,4-tetrahydroisoquinoline and 3-Methoxy-1,2,3,4-tetrahydro-[2,7]-naphthyridine via Reductive Amination of Schiff's Bases

Pavol Zlatoidský [a] & Bálint Gábos [a]
[a] AstraZeneca AB, Discovery Lund, Lund, Sweden
Published online: 03 Aug 2009.

Synthetic Communications®, 39: 3060–3068, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902730911

Taylor & Francis
Taylor & Francis Group

Convenient Synthesis of 6-Bromo-1,2,3,4-tetrahydroisoquinoline and 3-Methoxy-1,2,3,4-tetrahydro-[2,7]-naphthyridine via Reductive Amination of Schiff's Bases

Pavol Zlatoidský and Bálint Gábos
AstraZeneca AB, Discovery Lund, Lund, Sweden

Abstract: Synthesis of 7-bromo-1,2,3,4-tetrahydroisoquinoline and 6-methoxy-1,2,3,4-tetrahydro-[2,7]-naphthyridine via lithiation of 2-methylarylidene-*tert*-butylamines, followed by formylation, reductive amination in one-pot, and removal of the *tert*-butyl group from the nitrogen, is described.

Keywords: Cyclization, formylation, lithiation, reductive amination

INTRODUCTION

Tetrahydroisoquinolines (THQs) are important structural motifs found in biologically active substances that have been used extensively in the synthesis of drug candidates.[1,2] The corresponding isoelectronic tetrahydronapthyridines (THNPs) are important bioisosteres of this fragment, providing a more polar structural alternative (clogP 1.59 was calculated for 1,2,3,4-tetrahydroisoquinoline and clogP −0.09 for 1,2,3,4-tetrahydro-[2,7]-naphthyridine) (Fig. 1).

Unfortunately, synthetic access to this structural class has proven cumbersome, and not surprisingly, there are consequently only a few examples in the literature that describes the synthesis of simple analogs.[3–8]

In the course of our studies, we decided to prepare compounds containing THQs, substituted in 6-position as a starting material for

Received October 1, 2008.
Address correspondence to Pavol Zlatoidský, AstroZeneca AB, Discovery Lund, S-221 87, Lund, Sweden. E-mail: Pavol.Zlatoidsky@astrazeneca.com

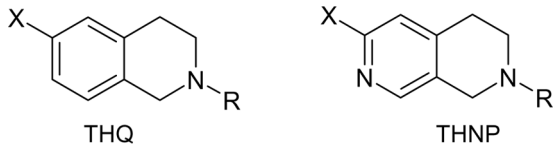


Figure 1. X = aryl, heteroaryl; R = acyl, alkyl, aryl/alkylsulfonyl.

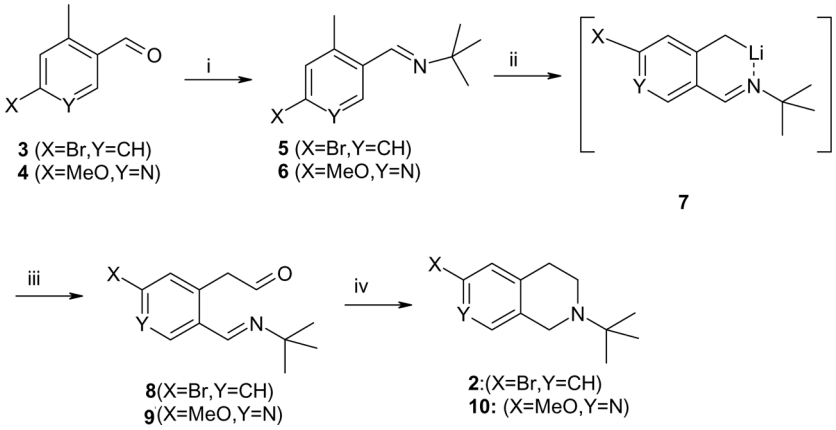
6-aryl (heteroaryl)–substituted THQs and 3-substituted THNPs.[1] Substitutions should optionally allow for the introduction of aryl or heteroaryl groups as well as for N-substitution of the heterocyclic nitrogen.

The syntheses of 6-methoxy-1,2,3,4-tetrahydroisoquinoline[3] as well as 6-nitro-3-alkyl-1,2,3,4-tetrahydroquinolines[4] have been described, but the reaction conditions are not generally applicable. For instance, when attempting to use selective hydrogenation of the pyridine ring of 3-methoxy-[2,7]-naphthyridine, this leads to a complicated mixture of products. Other approaches to this heterocyclic ring system have been described, for instance using the reduction of 6-bromo-4H-isoquinoline-1,3-dione[5,6] or approaches involving Diels–Alder reactions,[7] both including multistep syntheses with poor yield.

The most practical approach to the target heterocycles involves the benzylic lithiation of a Schiff base as described by Flippin et al.[8] The modified route described in this communication involves the use of dimethylformamide (DMF) as the electrophile instead of methyl iodide, followed by cyclization of the aldehyde via reductive amination.

CHEMISTRY

6-Bromo-THQ (**1**) and 2-*tert*-butyl-6-methoxy-1,2,3,4-tetrahydro-[2,7]-naphthyridine (**2**) are valuable intermediates for synthesis of libraries of compounds targeting metalloproteinases. We found that they could be readily accessible starting from 3-bromo-6-methylbenzaldehyde (**3**) for 6-bromo-1,2,3,4-tetrahydroisoquinoline (**1**) and for 2-*tert*-butyl-6-methoxy-1,2,3,4-terahydro-[2,7]-naphthyridine (**10**), and then 6-methoxy-4-methylpyridine-3-carbaldehyde (**4**) is the most available starting material, prepared via routine lithiation/formylation of the corresponding bromoderivative. As demonstrated in the article by Flippin et al.,[8] Schiff's bases **5** and **6**, prepared from these aldehydes, undergo smooth proton abstraction from the methyl group using lithium-2,2,6,6-tetramethylpiperidide, apparently facilitated by the neighboring imine function, forming a chelated lithium complex similar to **7**, which was smoothly alkylated with methyl iodide as electrophile.

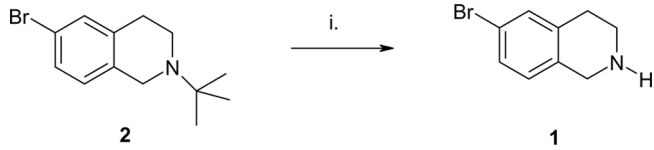


Scheme 1. (i) *tert*-Butylamine, mol. sieve 3 Å, (ii) LiTMP/THF, (iii) DMF, and (iv) $NaBH_3CN$/MeOH/AcOH.

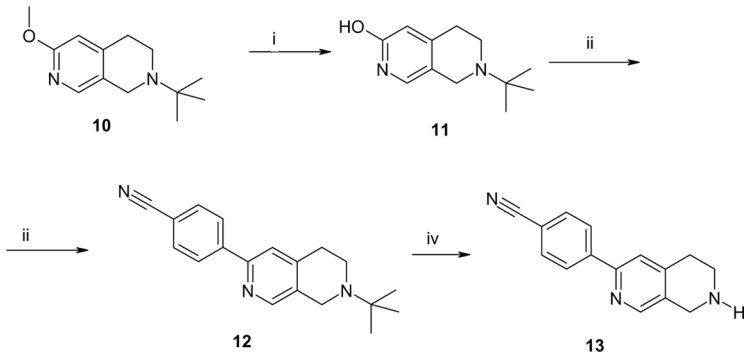
We subjected **7** to treatment with dimethylformamide (DMF) as an electrophile. The resulting aldehydes **8** and **9** were not isolated but immediately cyclized under reductive amination conditions, yielding the compounds **2** and **10** as required templates in their protected form. The reductive amination conditions chosen for the cyclization step included sodium cyanoborohydride in the presence of acetic acid and methanol, added directly to the reaction mixture. This was an efficient way to allow selective reduction of the carbon–nitrogen double bond prior to reductive amination and ring closure (Scheme 1).

Removal of the t-butyl group from (**2**) with 1-chloroethyl chloroformate generates the required **1** (Scheme 2). The removal of *tert*-butyl group, however, requires greater temperature and excess of chloroformate, compared to the conditions described for corresponding N-demethylations.[9]

One can further elaborate on this strategy in the THNP case. Deprotection of the methoxy group provides **11**, and transformation to its trifluoromethanesulfonic acid ester provides a suitable starting material for further transformation steps, as exemplified here: Coupling with



Scheme 2. (i) 1-Chloroethyl chloroformate, reflux; then MeOH, reflux.



Scheme 3. (i) HBr/AcOH/100°C, (ii) (a) triflic anhydride/pyridine/rt, (b) 4-cyanophenyl boronic acid, $Pd(dppf)Cl_2$, AcOK, dioxane, 90°C, (iii) 1-chloroethyl chlorformate (neat)/120°C.

4-cyanophenyl boronic acid under catalysis of dichloro[1,1-bis(diphenylphosphino)ferrocene] palladium (II) DCM complex $[Pd(dppf)Cl_2]$[10] provides the aryl-coupled derivative **12** in good yield. The 2-*tert*-butyl group can again be cleaved by 1-chloroethyl chloroformiate[9] to generate **13** (Scheme 3).

In conclusion, we have developed a convenient method for the preparation of THQ (**1**) and THNP (**2**), both versatile building blocks in medicinal chemistry. We have used a Schiff base–directed lithiation sequence followed by formylation of DMF. Reductive amination results in ring closure and heterocycle formation, yielding the required templates in a one-pot procedure.

EXPERIMENTAL

Melting points were measured on a Stuart MP3 capillary melting-point apparatus and are uncorrected. NMR spectra were measured at 300 MHz or 400 MHz on Varian 300 and Varian 400 instruments. Chemical shifts are reported in part per million (ppm) downfiled from tetramethylsilane (TMS) as internal standard. Mass spectra (MS) were measured on an HP 5890 GC-MS spectrometer and on an HP 1100 HPLC-MS spectrometer. Infrared (IR) spectra were measured on a Perkin-Elmer 10 PC-FTIR spectrometer as a film and are reported in cm^{-1}. Elemental analyses were performed by Belab AB, Norrköping. All chemicals and solvents were obtained from Sigma Aldrich or Fisher Scientific; silica gel 60 (230–400 mesh) used in flash chromatography was obtained from Merck Co. Preparative high-performance liquid chromatography (HPLC) was carried

out on a Gilson liquid chromatography preparative system using a Chirapack C-18 column (25 × 10 cm).

2-Methoxy-4-methylnicotinaldehyde (4)

To a stirred solution of 5-bromo-2-methoxy-4-methylpyridine (5 g, 24.75 mmol) in dry tetrahydrofuran (THF) (55 mL) under argon at −70°C, 2.5 M n-BuLi in hexanes were added (9.9 mL, 25 mmol) over 10 min. The mixture was stirred at −70°C for 30 min, and then anhydrous DMF (2.4 ml, 30.1 mmol) was added portionwise, maintaining the temperature at −70°C. The mixture was stirred at −70°C for 30 min and at rt overnight. The reaction was quenched with 1 M hydrochloric acid (60 mL) and then extracted three times with TBME. The combined organic phases were washed with brine, dried with magnesium sulfate, filtered, and evaporated to dryness. The compound was pure enough to be used in the next step. The Analytical sample was recrystallized from isohexane/tert.butyl methylether (TBME). Mp 90–91°C (lit.[11]. 91–92°C). Yield: 3.2 g, 86%. ^{1}H NMR ($CDCl_3$): 2.60 (s, 3H), 4.11 (s, 3H), 6.59 (s, 1H), 8.62 (s, 1H), 10.06 (s, 1H). ^{13}C NMR ($CDCl_3$): 21.88, 54.50, 112.15, 125.55, 148.10, 155.22, 170.10, 194.33.

(4-Bromo-2-methylbenzylidene)-*tert*-butylamine (5)

tert-butylamine (15 mL) and activated 4 Å mol.sieve (4 g) were added to the 3-bromo-6-methylbenzaldehyde (**3**) (2.55 g, 12.8 mmol). The vessel was sealed, and the mixture was stirred for 48 h at rt, filtered through a cellite pad, and eluted with 2 × 10 mL diethylether. The solution of the Schiff's base was evaporated to dryness, and the compound was used without purification immediately in the next step. Yield: 2.86 g, 88%. ^{1}H NMR ($CDCl_3$): 1.30 (s, 9H), 2.47 (s, 3H), 7.33 (d, 1H, $J = 1.8$ Hz) 7.35 (dd, $J = 8.4$ Hz,1.8 Hz, 1H), 7.89 (d, $J = 8.4$ Hz, 1H), 8.49 (s, 1H). ^{13}C NMR ($CDCl_3$): 20.19, 29.75, 57.55, 125.47, 128.97, 129.56, 130.56, 140.11, 156.22.

tert-Butyl-[(6-methoxy-4-methylpyridin-3-yl)methylene]-amine (6)

The compound was prepared according to the procedure described for **5**, starting from **4** (1.93 g, 12.8 mmol), and was used without purification in the next step. Yield: 2.26 g, 86%. ^{1}H NMR ($CDCl_3$): 1.32 (s, 9H), 2.49 (s, 3H), 3.94 (s, 3H), 6.53 (s, 1H), 8.52 (s, 1H), 8.53 (brs, 1H). ^{13}C NMR

($CDCl_3$): 19.78, 29.62, 53.37, 57.55, 111.51, 125.55, 147.85, 149.01, 151.78, 164.58.

6-Bromo-2-*tert*-butyl-1,2,3,4-tetrahydroisoquinoline (2)

n-BuLi solution in pentanes (11.3 mL of 1.7 M, 0.022 mol) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (3.45 mL, 0.022 mol) in 90 ml of dry THF at −40°C under argon. The mixture was stirred for 25 min at the same temperature, and then the Schiff's base (**5**) (0.011 mol) dissolved in dry THF (30 mL) was added portionwise, keeping the temperature at −40°C. The mixture was then stirred at −15 to −20°C for 1.5 h and recooled to −40°C, and DMF (2.5 mL, 0.03 mol) was injected through a septum in three portions. The mixture was stirred at rt for 2 h, and liquid chromatography–mass spectrometry (LC-MS) showed the presence of the expected aldehyde (**8**). A mixture of methanol (80 mL) and acetic acid (20 mL) was added at once, followed immediately with sodium cyanoborohydride (1.131 g, 0.018 mol), added in one portion. The mixture was stirred overnight, evaporated to dryness, partitioned between sat. potassium carbonate (300 mL) and ethyl acetate (100 mL), extracted twice with ethyl acetate, washed with brine, dried with magnesium sulfate, and evaporated to dryness. The residue was flashed on 110 g silica (eluted with TBME) to obtain a pale yellow solid, mp 72–74°C. Yield: 1.32 g, 43%. MS: $m/z = 269$ (MH^+), other fragments: 213 ($MH^+ - 56$). ^1H NMR ($CDCl_3$): 1.11 (s, 9H), 2.03 (m, 2H), 3.49 (t, $J = 13.9$ Hz, 1H), 3.77 (d, $J = 10.5$ Hz, 1H), 3.97 (d, $J = 14.4$ Hz, 1H), 4.57 (d, $J = 14.4$ Hz, 1H), 6.95 (d, $J = 8.1$ Hz, 1H), 7.27 (d, $J = 1.8$ Hz, 1H), 7.30 (dd, $J = 8.1$ Hz, $J = 1.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$): 26.46, 47.25, 47.23, 63.80, 122.17, 127.52, 128.73, 130.70, 131.40, 134.10. IR (film): 979, 1486, 1531,1626, 2358, 2782.

2-*tert*-Butyl-6-methoxy-1,2,3,4-tetrahydro-[2,7]-naphthyridine (10)

This compound was prepared according to the procedure described for **2**, starting from **6** (2.26 g, 0.011 mol). The compound was obtained as a colorless oil. Vacuum distillation gave 1.8 g (74.3%) (bp 105–106°C/0.5 torr). MS: $m/z = 221$ (MH^+), other fragments: 165 ($MH^+ - 56$). ^1H NMR (CD_3OD): 1.13 (s, 9H), 2.77 (t, 2H, $J = 4.7$ Hz), 2.81 (t, 2H, $J = 4.7$ Hz) (m, 3.85 (s, 3H), 6.6 (s, 1H), 7.9 (s, 1H). ^{13}C NMR (CD_3OD): 31.95, 39.81, 50.22, 53.02, 58.76, 68.95, 113.68, 122.87, 149.06, 149.91, 168.80. IR (cm^{-1}): 1180, 1401, 1665, 2604, 2981.

6-Bromo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (1)

1-Chloroethyl chloroformate (15 mL) was added to **2** (1.32 g, 0.0049 mol) at once, and the reaction mixture was refluxed overnight under a calcium chloride tube. The reaction mixture was evaporated to dryness, and the residue was refluxed for 4 h in methanol (15 mL) and evaporated to dryness. The crude product (0.9 g, 74%) was pure enough to be used in the next synthetic steps. Analytical sample was purified via preparative reverse-phase chromatography and recrystallized from ethanol. Mp 131–132°C. Element. anal. for $C_9H_{11}BrClN$: calcd. C, 43.49%; H, 4.46%; N, 5.64%. Found: C, 43.41%; H, 4.84%; N, 5.72%. MS: $m/z = 213$ (MH^+). ^1H NMR (CD_3OD): 3.12 (t, $J = 6.9$ Hz, 2H), 3.48 (t, $J = 6.9$ Hz, 2H), 4.44 (s, 2H), 7.1 (d, $J = 7.81$ Hz, 1H), 7.5 (d, $J = 7.81$ Hz, 1H), 7.46 (s, 1H). ^{13}C NMR (CD_3OD): 24.42, 40.25, 43.36, 120.31, 127.30, 128.91, 129.49, 131.35, 137.36. IR (film): 1071, 1186, 1393, 1592, 1641, 2978, 3395.

2-*tert*-Butyl-6-hydroxy-1,2,3,4-tetrahydro-[2,7]-naphthyridine (11)

A solution of 2-*tert*-butyl-6-methoxy-1,2,3,4-tetrahydro-[2,7]-naphthyridine (**10**) (0.5 g, 2.27 mmol) and 45% hydrobromic acid in acetic acid (20 mL) was heated in a sealed tube at 100°C for 1 h, cooled to rt, and concentrated by rotary evaporation. The residue was dissolved in 20% potassium carbonate solution (20 mL) and extracted four times with EtOAc. The combined organic phases were dried, filtered and concentrated. Recrystallization from TBME/hexanes gave 0.33 g (71%) of the title compound as a white solid, mp 126–127°C. MS: $m/z = 208$ (MH^+); other fragments: 152 ($MH^+ - 56$). ^1H NMR ($CDCl_3$): 1.34 (s, 9H), 2.88 (t, 2H, $J = 5.6$ Hz), 3.17 (t, 2H, $J = 5.6$ Hz), 4.72 (s, 2H), 6.39 (s, 1H), 7.17 (s, 1H). ^{13}C NMR ($CDCl_3$): 24.26, 25.85, 45.74, 54.25, 63.76, 116.68, 117.16, 130.93, 151.96, 164.40. IR (film): 1134, 1202, 1604, 1682, 1978, 2962.

2-*tert*-Butyl-6-(4-cyanophenyl)-1,2,3,4-tetrahydro-[2,7]-naphthyridine (12)

Trifluoromethane sulfonic acid anhydride (0.14 mL, 0.80 mmol) was slowly added to a stirred and cold (4°C) solution of 2-*tert*-butyl-6-hydroxy-1,2,3,4-tetrahydro-[2,7]-naphthyridine (**11**) (0.15 g, 0.73 mmol) in pyridine (5.0 mL). When the addition was complete, the mixture was stirred at 4°C for 30 min, quenched with 20% potassium carbonate solution (10 mL), and extracted four times with dichloromethane (DCM). The combined organic phases were dried, filtered, and concentrated to

give a crude product. Flash chromatography with EtOH-TBME (1:9) as eluent gave 0.30 g of the trifuoromethanesulfonic acid ester as an oil (containing solvent residues). MS: $m/z = 339$ (MH^+). The crude trifluoromethanesulfonic acid ester (0.30 g, 0.89 mmol) was dissolved in dioxane (10 mL), and then anhydrous potassium acetate (0.43 g, 4.5 mmol), 4-cyanophenylboronic acid (0.14 g, 0.89 mmol), and $PdCl_2$(dppf) (13 mg, 0.0178 mmol) were added. The mixture was degassed with argon, sealed, and stirred at 90°C overnight. After cooling, the solution was partitioned between water and ethyl acetate, and the water phase was extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried, filtered, and concentrated. The compound was subjected to silica-gel column chromatography and eluted with EtOH-TBME (1:9) and TBME-EtOH-TEA (20:2:1) to give 0.12 g (53% from two steps) of the title compound as a light brown solid. The analytical sample was precipitated from TBME as hydrochloride after addition of 4 N HCl in dioxane. Mp: decomp.220–230°C. MS: $m/z = 292$ (MH^+); other fragments: 236 ($MH^+ - 56$). ^{1}H NMR ($CDCl_3$): 1.04 (s, 9H), 3.25 (t, 2H, $J = 6.1$ Hz) 3.61 (t, 2H, $J = 6.1$ Hz) 3.86 (s, 2H), 7.44 (s, 1H), 7.84 (d, 1H, $J = 8.8$ Hz), 7.91 (s, 1H) 8.21 (d, 1H, $J = 8.8$ Hz). ^{13}C NMR ($CDCl_3$): 25.38, 25.46, 43.39, 45.93, 54.11, 109.11, 112.15, 118.85, 120.41, 127.27, 127.30, 132.48, 143.33, 148.57. IR (film): 884, 1130, 1202, 1603, 1681, 2217, 2596, 3412.

6-(4-Cyanophenyl)-1,2,3,4-tetrahydro-[2,7]-naphthyridine hydrochloride (13)

A mixture of 2-*tert*-butyl-6-(4-cyanophenyl)-1,2,3,4-tetrahydro-[2,7]-naphthyridine (**12**) (0.12 g, 0.41 mmol), 1-chloroethyl chloroformate (1.0 mL, 5.8 mmol), and dry toluene (5 mL) was refluxed for 4 h under a calcium chloride tube. After being concentrated in vacuo, the dark residue was dissolved in methanol (10 mL) and refluxed for 3 h more. Charcoal (1 g) was added and refluxed for additional 20 min. Then the mixture was filtered through a Cellite pad and washed with methanol, and the clear filtrate was concentrated to give the title compound as a solid, which was recrystallized from TBME/MeOH to give a white powder. Mp 232–234°C. Yield: 0.08 g, 72%. Element. anal. for $C_{15}H_{14}ClN_3$: calcd. C, 66.30%; H, 5.19%; N, 15.46%. Found: C, 66.20%; H, 5.36%; N, 15.56%. MS: $m/z = 236$ (MH^+). ^{1}H NMR (CD_3OD): 3.54 (d, 2H, $J = 5.9$ Hz), 3.58 (d, 2H, $J = 5.9$ Hz), 4.41 (s, 2H), 7.93 (d, 1H, $J = 7.9$ Hz), 8.26 (d, 1H, $J = 7.9$ Hz) 8.64 (s, 1H), 9.19 (bs, 2H). ^{13}C NMR (CD_3OD): 24.88, 43.77, 48.58, 114.05, 119.75, 122.36, 126.72, 133.98, 134.01, 143.98, 144.56, 149.39, 155.68. IR (film): 843, 1132, 1201, 1600, 1683, 2217, 2962, 3402.

ACKNOWLEDGMENT

The help of Dr. Klaus Uhrbans, Dr. Lena Börjesson, and Dave Chapman with the text is gratefully appreciated.

REFERENCES

1. Bálint, G.; Lundkvist, M.; Munck af Rosenschöld, M.; Shamovsky, I.; Zlatoidský, P. PCT *Int. Appl.* WO 2006065216, **2006**.
2. Gao, Y.; Han, B.; Xu, Y.; Caldwell, T. M.; Xie, L. PCT *Int. Appl.* WO 2007106349, **2007**.
3. Meagher, K. L.; Mewshaw, R. E.; Evrard, D. A.; Zhou, P.; Smith, D. L.; Scerni, R.; Spangler, T.; Abulhawa, S.; Shi, X.; Schechter, L. E.; Andree, T. H. Studies toward the next generation of antidepressants, part 1: Indolylcyclohexylamines as potent serotonin reuptake inhibitors. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1885–1888.
4. Bojarski, A. J.; Mokrosz, M. J.; Minol, C. S.; Koziol, A.; Wesolowska A.; Tatarczynska, E.; Klodzinska, A.; Chojnacka-Wojcik, E. The influence of substitution at aromatic part of 1,2,3,4-tetrahydroisoquinoline on in vitro and in vivo $5HT_{1A}/5HT_{2A}$ receptor activities of its 1-adamantoylaminoalkyl derivatives. *Bioorg. Med. Chem.* **2002**, *10*, 87–96.
5. Bodinell, W. E.; Chapin, F. W.; Girard, G. R.; Kaiser, C.; Krog, A. J.; Pavloff, A. M.; Schwartz, M. S.; Silvestri, J. S.; Vaidya, P. D.; Lam, B. L.; Wellman, G. R.; Pendelton, R. G. Inhibitors of phenylethylamine N-methyltransferase and epinephrine biosynthesis, 1: Chlorosubstituted 1,2,3,4-tetrahydroisoquinolines. *J. Med. Chem.* **1980**, *23*, 506–511.
6. Quiclet-Sire, B.; Zard, S. Z. An expedient synthesis of homophthalimides. *Chem. Commun.* **2002**, *20*, 2306–2307.
7. Finkelstein, J. A.; Perchonck, C. D. A Diels–Alder route to 7,8-substituted 1,2,3,4-tetrahydroisoquinolines. *Tetrahedron Lett.* **1980**, *21*, 3323–3326.
8. Flippin, L. A.; Muchowski, J. M.; Carter, D. S. Direct metallation of aromatic aldimines with lithium 2,2,6,6-tetramethylpiperidide. *J. Org. Chem.* **1993**, *58*, 2463–2467.
9. Sole, D.; Bosch, J.; Bonjoch, J. Synthesis of (±)-isofagonine and its stereoisomers from arecoline. *Tetrahedron* **1996**, *52*, 4013–4028.
10. Suzuki, A. Cross-coupling reactions via organoboranes. *J. Organomet. Chem.* **2002**, *653*, 83–90.
11. Commins, D. L.; Killpack, M. O. Lithiation of methoxypyridines directed by alpha-amino alkoxides. *J. Org. Chem.* **1990**, *55*, 69–73.