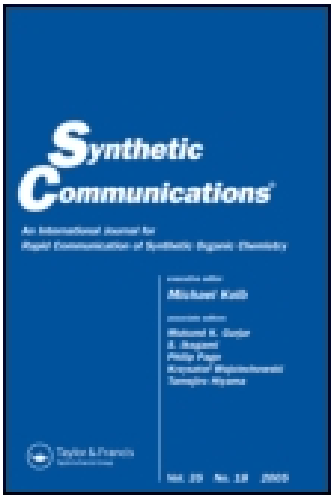

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A Convenient Synthesis of 1-Amino-7-(Piperidin-4-yl)Isoquinoline

Sergey Shkavrov [a], Sergey Popov [a], Dmitry Kravchenko [a] & Mikhail Krasavin [a]

[a] Chemical Diversity Research Institute, Khimki, Moscow Reg., Russia

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A Convenient Synthesis of 1-Amino-7-(Piperidin-4-yl)Isoquinoline

Sergey Shkavrov, Sergey Popov, Dmitry Kravchenko, and Mikhail Krasavin
Chemical Diversity Research Institute, Khimki
Moscow Reg., Russia

Abstract: An optimized synthesis of 2-amino-7-(piperidin-4-yl)isoquinoline, starting from 4-bromocinnamic acid, was developed.

Keywords: Isoquinoline, lithium-halogen exchange, microwave irradiation

INTRODUCTION

7-Substituted 1-aminoisoquinolines have been reported to possess various biological activities. For instance, a recent report on factor Xa inhibitors[1] revealed that incorporation of 1-aminoisoquinol-7-yl moiety resulted in the best inhibitory potency in the series.

In our continuing search for novel combinatorial library scaffolds with a high degree of medicinal relevance, we required multigram quantities of 1-amino-7-(piperidin-4-yl)isoquinoline (**1**).

We chose known 7-bromo-1-chloroisoquinoline (**2**) as the key intermediate in the synthesis. Reported methods for preparation of (**2**) employed Pomerantz-Fritsch isoquinoline synthesis resulting in mixture of regioisomers.[2] Thus, our

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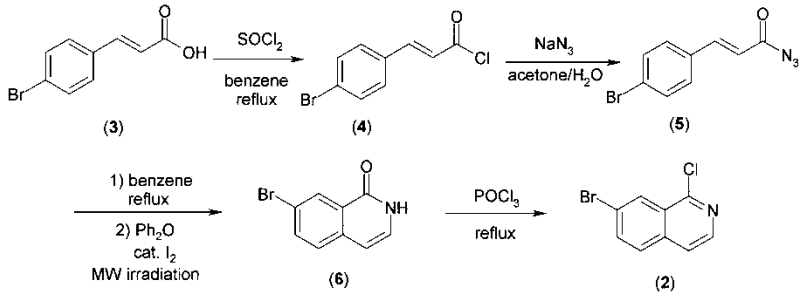
Address correspondence to Mikhail Krasavin, Chemical Diversity Research Institute, 2a Rabochaya St., KhimkiMoscow Reg. 114401, Russia. Fax: +7(095)926-9780; E-mail: myk@chemdiv.com

immediate goal was to elaborate a synthetic protocol that would not include tedious separation of isomeric products (Scheme 1).

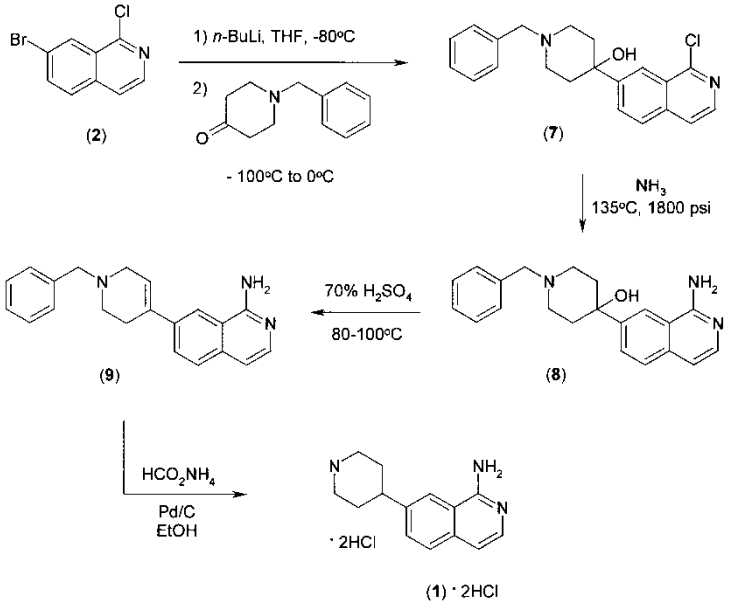
4-Bromocinnamyl azide (**5**) was prepared from 4-bromocinnamic acid (**3**) and subjected to thermal Curtius rearrangement into an intermediate isocyanate, which, after replacement of reaction solvent, underwent intramolecular electrophilic cyclization into 7-bromoisoquinolone (**6**), the process driven by catalytic iodine and microwave irradiation. Notably, conventional heating of the above isocyanate in the same reaction medium resulted only in extensive decomposition and no appreciable formation of the desired cyclization product. Subsequent treatment with phosphorus oxychloride gave the 7-bromo-1-chloroisoquinoline (**2**). No chromatographic purification was required at any stage of the described four-step synthetic sequence.

The reaction sequence leading to the final product (**1**) is outlined in Scheme 2. Lithium-halogen exchange proceeded selectively at C-Br and the resultant aryl anion was intercepted by 1-benzyl-4-piperidone at carefully controlled low temperature. Higher reaction temperatures resulted in lower yields and by-product formation, presumably due to enolization and self-condensation of the ketone electrophile.

The isolated tertiary alcohol (**7**) was treated with ammonia at high temperature and pressure in an autoclave. This 1-chloroisoquinoline proved to be surprisingly resistant toward ammonolysis conditions and the full conversion was achieved only upon prolonged treatment for seven days. Without further purification, compound **8** was dehydrated in hot 70% sulfuric acid and the isolated N-benzyl-1,2,5,6-tetrahydropyridine (**9**) was boiled in an ethanolic solution of ammonium formate in presence of 10% palladium on charcoal. This process resulted in fast (over 3 hours) reduction of the olefinic portion and much slower N-debenzylation due to poisoning of the Palladium (Pd) catalyst by the secondary amine formed (the poisoned catalyst was replaced by a fresh batch once during the reaction). The target isoquinoline (**1**) was isolated as a dihydrochloride salt of 95% purity.



Scheme 1.



Scheme 2.

EXPERIMENTAL

All reactions were run in oven-dried glassware in a nitrogen atmosphere. Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected. Analytical thin-layer chromatography (TLC) was carried out on EM Separations Technology F_{254} silica gel plates. Compounds were visualized with short-wavelength ultraviolet (UV) light. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Gemini-300 and Bruker DRX-500 spectrometers in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. Mass-spectral analyses were obtained on a PE SCIEX API 150EX mass spectrometer. All solvents and reagents were obtained from commercial sources and used without purification.

4-Bromocinnamyl Azide (5)

To a suspension of 4-bromocinnamic acid (**3**, 150 g, 0.66 mol) in benzene (750 mL), thionyl chloride (96 mL, 1.32 mol) was added and the mixture was refluxed for 2 hrs (or until full dissolution of solids) and for an additional 1 hr to ensure completeness of the conversion. The excess thionyl chloride was distilled off and the crystalline residue (160 g, 89%) was taken on to the next step as sufficient purity (>90%) was established by liquid crystal-mass spectrometry (LC-MS) analysis.

One mole (67 g) of sodium azide was suspended in a mixture of water and acetone (1:1, 300 mL). The mixture was cooled down to 0°C and a solution of 4-bromocinnamyl chloride (**4**, 125 g, ca. 0.5 mol) in dry acetone (400 mL) was added at such a rate as to maintain the temperature below 5°C. The resulting mixture was stirred at 0–6°C for 4 hrs and then poured into water (1.5 L). The precipitate was filtered off, washed with copious amounts of water, and air dried. Additional drying in vacuo over P_2O_5 afforded 124 g (0.48 mol, 96%) of the solid (**5**). ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.68 (AA'BB', $J = 8.6$ Hz, 4H), 6.73 (d, $J = 15$ Hz, *trans*-CH=CH, 2H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 167.3, 142.5, 131.8, 130.1, 123.5, 117.7, 120.1; MS $MH^+ = 227$.

7-Bromo-1(2H)-isoquinolone (6)

A 500 mL flask was charged with 4-bromocinnamyl azide (**5**, 54.2 g, 0.24 mol) and anhydrous benzene (300 mL) and the mixture was brought to moderate reflux with quiet evolution of N_2. The reflux was continued for 7 hrs until gas evolution ceased. The solvent was removed in vacuo and the residue with added catalytic amount (1.4 g) of finely ground iodine were dissolved in molten diphenyl ether (125 mL). The bulk solution was split into 5 mL microwave vials with septa and heated at 220°C for 30 min using Personal Chemistry Emrys Optimizer® microwave reactor. After cooling down, the gummy solid was transferred into a 1 L beaker, triturated with ether, filtered, thoroughly washed with ether, and air-dried. The brown powdered residue (ca. 20 g) was dissolved at 50–60°C in DMF (150 mL). The solution was slowly added to thoroughly stirred 2% aqueous NaOH (900 mL). A black sticky precipitate was removed by filtration and the light-yellow filtrate was diluted with water up to a volume of 2.1 L and allowed to stand for 1 hr. The precipitated material was filtered off, washed with water, and dried at 100–110°C to provide 10.5 g (20%) of solid isoquinolone (**6**): mp 230°C (decomp). ^{1}H NMR (300 MHz, d_6-DMSO): δ 11.38 (br s, N-H, 1H), 8.26 (d, $J = 2.2$ Hz, 1H), 7.84 (dd, $J = 8.1$, 2.2 Hz, 1H), 7.63 (d, NH-CH, $J = 8.1$ Hz, 1H), 7.22 (dd, $J = 6.6$, 5.1 Hz, 1H), 6.56 (d, NHCH = CH, $J = 8.1$ Hz, 1H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 160.6, 136.8, 135.1, 130.8, 129.7, 128.8, 128.6, 119.0, 118.6; MS $MH^+ = 225$.

7-Bromo-1-chloroisoquinoline (2)

To solid 7-bromo-1(2H)-isoquinolone (**6**, 10 g, 44.6 mmol) $POCl_3$ (40 mL) was added and the mixture was heated at reflux for 1 hr, at which point the reaction was complete by TLC analysis. The cooled solution was poured over crushed ice. Exothermic hydrolysis of the remaining $POCl_3$ occured after 5–10 min and the temperature rose up to 70–80°C. Most of the material was in solution except for black tar, which was removed by filtration.

The filtrate was diluted with water up to a volume of 1 L and the resulting white precipitate was collected, washed with water, air-dried, and crystallized from butan-1-ol and then from heptane to afford (**2**) as white solid (7.5 g, 31 mmol, 70%): mp 123–125°C. ^{1}H NMR (300 MHz, d_6-DMSO): δ 8.41 (s, 1H), 8.37 (d, $J = 5.9$ Hz, 1H), 8.02–8.09 (m, 2H), 7.94 (d, $J = 5.1$ Hz, 1H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 148.9, 142.1, 136.1, 134.8, 129.7, 127.3, 126.9, 122.2, 121.2; MS $MH^+ = 244$.

1-Benzyl-4-(1-chloro-7-isoquinolyl)-4-piperidinol (7)

A suspension of 7-bromo-1-chloroisoquinoline (48.5 g, 0.20 mol) in anhydrous THF (1 L) was treated at −78°C at with 1.6 M solution of *n*-BuLi in hexane (145 mL, 0.23 mol). The resulting clear red solution was stirred for 20 min, then cooled to −100°C (ethanol-dry ice), and solution of N-benzylpiperidone (41.6 g, 0.22 mol) in THF (50 mL) was added dropwise to maintain temperature below −60°C. After the addition was completed, the reaction mixture was stirred for 2–3 hrs while the temperature rose up to 0°C. Water (300 mL) was added and the biphasic mixture was transferred into a separatory funnel. Organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 150 mL). Combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The oily residue was boiled with heptane for 15 min and the resulting solution was left to stand overnight. The light crystalline product was collected by filtration, washed with heptane, and air dried to provide 56.5 g (80%) of the piperidinol **7**: mp 141–142°C. ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.39 (s, 1H), 8.26 (d, $J = 5.5$ Hz, 1H), 8.03 (s, 2H), 7.86 (d, $J = 5.5$ Hz, 1H), 7.32–7.38 (m, 4H), 7.25 (dd, $J = 6.8$, 7.3 Hz, 1H), 5.13 (s, O<u>H</u>, 1H), 3.55 (s, PhC<u>H</u>$_2$, 2H), 2.68 (d, C<u>H</u>-N-C<u>H</u>, $J = 11.0$ Hz, 2H), 2.52 (d, C<u>H</u>-N-C<u>H</u>, $J = 11.0$ Hz, 2H), 2.08 (td, $J_t = 12.8$ Hz, $J_d = 3.7$ Hz, 2H), 1.68 (d, $J = 13.5$ Hz, 2H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 151.4, 150.3, 141.1, 138.6, 136.3, 129.8, 128.8, 128.1, 127.1, 126.8, 125.8, 121.0, 120.5, 70.1, 62.4, 49.1, 37.7; MS $MH^+ = 354$.

1-Amino-7-(piperidin-4-yl)isoquinoline Dihydrochloride (1)

An autoclave chamber cooled to −78°C was charged with piperidinol (**7**) (50 g, 0.14 mol) and liquid ammonia (800 mL), sealed, and heated at 135°C and 1.8 kpsi for seven days. The chamber was cooled to room temperature, the gaseous ammonia was let out, the chamber contents were washed out with ethanol. The solution was concentrated in vacuo and the residue was partitioned between dichloromethane (500 mL) and water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo.

The resulting brown oil (containing over 90% of 4-(1-amino-7-isoquinolyl)-1-benzyl-4-piperidinol (**8**) by LC-MS analysis: MS $MH^+ = 334$, 99% yield) was dissolved in hot 70% sulfuric acid (400 mL) and heated at 80–100°C for 48 hours. The completeness of the conversion was determined by liquid chromatography-mass spectrometry (LC-MS) analysis of reaction mixture aliquots (after neutralization and extraction with ethyl acetate). The reaction mixture was cooled down and poured into ice-cold 40% aqueous KOH (1 L). The mixture was extracted with ethyl acetate (3 × 250 mL), organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to provide brown oil. The latter was analyzed by LC-MS (to reveal that it contains at least 80% of the desired olefin **9**: MS $MH^+ = 316$) and taken on to the last step without further purification.

The crude olefin (**9**) was dissolved in ethanol (1 L) along with ammonium formate (50 g). Pd on charcoal (10%, 8 g) was added and the reaction mixture was heated at reflux for 3 hrs. Then it was cooled down and filtered. The fresh Pd catalyst (5 g) and ammonium formate (10 g) were added and the mixture was brought to reflux again. After additional 3 hrs, the reaction was cooled down, filtered, and concentrated in vacuo. Toluene (150 mL) was added and the volatiles were removed again. The residue was redissolved in isopropyl alcohol (200 mL), concentrated hydrochloric acid (50 mL) was added, and the mixture was left at −20°C for 48 hrs to ensure complete precipitation of the dihydrochloride salt. The latter was isolated by filtration, washed with cold isopropanol, and air dried to provide (**1**). 2HCl as white crystals (15.6 g, 37% for three steps): mp > 200°C (decomp). ^{1}H NMR (500 MHz, d_6-DMSO): δ 13.50 (br s, isoquinoline-bound HCl, 1H), 9.22 (unresolved d, protonated $CH_2N\underline{H}_2CH_2$, 2H), 9.12 (unresolved d, $N\underline{H}_2$, 2H), 8.48 (s, 1H), 7.93 (d, $J = 8.5$ Hz, 1H), 7.88 (dd, $J = 8.5$, 1.3 Hz, 1H), 7.67 (d, $J = 7.3$ Hz, 1H), 7.20 (d, $J = 7.3$ Hz, 1H), 3.39 (d, $C\underline{H}$-$^+NH_2$-$C\underline{H}$, $J = 12.8$ Hz, 2H), 3.01–3.08 (overlapped d $C\underline{H}$-$^+NH_2$-$C\underline{H}$ and m Ar-$C\underline{H}$, 3H), 2.08 (m, 2H), 1.98 (m, 2H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 154.1, 145.3, 135.6, 134.0, 127.9, 127.1, 122.7, 117.7, 110.8, 43.1, 38.8, 28.8; MS $MH^+ = 228$; HRMS (EI) m/z calcd. for $C_{14}H_{18}N_3$ (MH^+) 228.3197, found 228.3201

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