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SYNTHESIS OF 3,4-DIHYDROISOQUINOLINES BY CYCLIZATION OF 1-BROMO-2-(2-ISOCYANOALKYL)BENZENES WITH BUTYLLITHIUM

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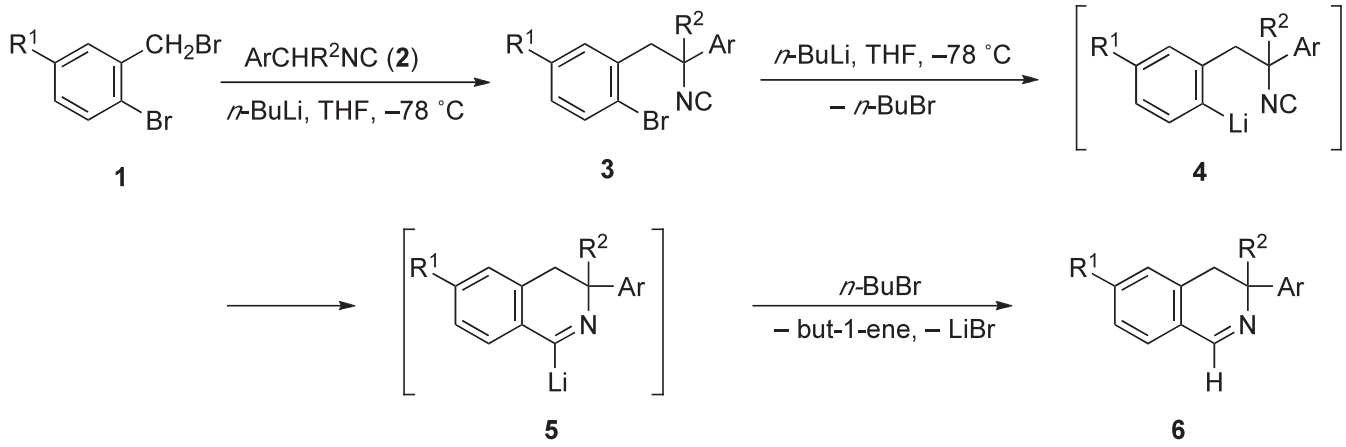
Abstract – A new and convenient method for the preparation of 3,3-disubstituted 3,4-dihydroisoquinolines has been developed. Thus, the reaction of 1-bromo-2-(bromomethyl)benzenes with (1-isocyano-1-lithioalkyl)benzenes, generated by the treatment of (1-isocyanoalkyl)benzenes with butyllithium, in THF at –78 ˚C gave the corresponding 1-(2-aryl-2-isocyanoalkyl)-2-bromobenzenes, which in turn were transformed into the desired products on treatment with butyllithium in THF at –78 ˚C.

3,4-Dihydroisoquinoline derivatives are receiving considerable attention in relation to their biological activities[1,2] and their uses in the preparation of more structurally complex and useful polycyclic compounds,[3] such as 3,4-dihydro-7a*H*,15*H*-naphtho[1',2':5,6][1,3]oxazino[2,3-*a*]isoquinolines[3m] and 8,9-dihydro-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-*a*]isoquinolines.[3n] Most of the methods for the preparation of 3,4-dihydroisoquinolines have been relied upon Bischler-Napieralski-type reactions of *N*-(2-arylethyl)carboxamides with various dehydrating agents, such as phosphoryl chloride and polyphosphoric acid,[4] though several efficient methods based on other reactions have recently been reported.[5] Therefore, there have been few reports on the synthesis of 3,3-disubstituted derivatives.[6] Herein we describe a convenient synthetic route to 3,3-disubstituted 3,4-dihydroisoquinolines. We have found that this type of 3,4-dihydroisoquinolines (**6**) could be obtained by cyclization of 1-(2-aryl-2-isocyanoalkyl)-2-bromobenzenes (**3**), which could be easily prepared from 1-bromo-2-(bromomethyl)benzenes (**1**) and (1-isocyanoalkyl)benzenes (**2**), on treatment with butyllithium.

Our synthesis of 3,3-disubstituted 3,4-dihydroisoquinolines (**6**) from 1-bromo-2-(bromomethyl)benzenes (**1**) and (1-isocyanoalkayl)benzenes (**2**) was conducted according to the procedure illustrated in Scheme 1. Thus, the reaction of **1** with (1-isocyano-1-lithioalkyl)benzenes, generated by the treatment of **2** with

butyllithium, in THF at –78 ˚C afforded 1-(2-aryl-2-isocyanoalkyl)-2-bromobenzenes (**3**) in good yields as listed in Table 1. These precursors (**3**) were then allowed to react with butyllithium in THF at –78 ˚C to generate 1-(2-aryl-2-isocyanoalkyl)-2-lithiobenzene intermediates (**4**), which cyclized by intramolecular attack of the carbanion on the isocyano carbon to give 1-lithio-3,4-dihydroisoquinoline intermediates (**5**). After aqueous workup followed by purification of the crude products by column chromatography on silica gel, the desired products (**6**) were obtained in moderate-to-fair yields as listed in Table 1 as well.



Scheme 1

Table 1. Preparation of 3-alkyl-3-aryl-3,4-dihydroisoquinolines (**6**)

Entry	**1**	**2**	**3**	Yield/%[a]	**6**	Yield/%[a]
1	**1a** (R^1 = H)	**2a** (Ar = Ph, R^2 = Me)	**3a**	88	**6a**	58
2	**1a**	**2b** (Ar = 3-$MeOC_6H_4$, R^2 = Me)	**3b**	85	**6b**	50
3	**1a**	**2c** (Ar = 4-ClC_6H_4, R^2 = Me)	**3c**	72	**6c**	43
4	**1a**	**2d** (Ar = Ph, R^2 = Et)	**3d**	87	**6d**	56
5	**1a**	**2e** (Ar = R^2 = Ph)	**3e**	89	**6e**	56
6	**1b** (R^1 = Cl)	**2a**	**3f**	90	**6f**	47
7	**1b**	**2b**	**3g**	78	**6g**	47
8	**1b**	**2d**	**3h**	79	**6h**	58
9	**1c** (R^1 = OMe)	**2a**	**3i**	84	**6i**	58
10	**1c**	**2d**	**3j**	92	**6j**	57

[a] Yields of isolated products.

Unfortunately, however, it should be noted that attempted trapping reactions of 1-lithio-3,4-dihydroisoquinoline intermediates (**5**) with various electrophiles, such as iodomethane, benzaldehyde, benzoyl chloride, dimethyl disulfide and chlorotrimethylsilane, which enable us to introduce various substituents at the 1-position of 3,4-dihydroisoquinolines, all resulted in failure. In each case, the expected substitution product was not observed in the reaction mixture at all. Probably, the intermediates (**5**) abstract a proton quickly from 1-bromobutane, which was produced by the

lithium-bromine exchange between butyllithium and **3**, to lead to the formation of **6**, as depicted in Scheme 1 as well.

In conclusion, we have synthesized 3,3-disubstituted 3,4-dihydroisoquinolines *via* a two-step sequence from 1-bromo-2-(bromomethyl)benzenes and (1-isocyanoalkayl)benzenes. The present method may be of value in organic synthesis, because starting materials are readily available and manipulations are very simple. Further investigations toward syntheses of related heterocycles utilizing methodologies similar to that described here are now in progress in our laboratory.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum65 FTIR spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or a JEOL LA400FT NMR spectrometer operating at 400 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. High-resolution MS spectra (DART, positive) were measured by a Thermo Scientific Exactive spectrometer. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. 1-Bromo-2-(bromomethyl)-4-chlorobenzene (**1b**) and 1-bromo-2-(bromomethyl)-4-methoxybenzene (**1c**) were prepared by the procedure reported by Hirashima *et al*.[7] *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

***N*-(1-Arylalkyl)formamides**. *N*-(1-Phenylethyl)formamide was prepared by *N*-formylation of 1-phenylethanamine by the procedure reported by Chantrapromma *et al*.[8] *N*-(1-Phenylpropyl)formamide was prepared by the method reported by Musatov *et al*.[9] The others were prepared from the respective 1-arylalkan-1-ones under the conditions reported for the preparation of 1-arylethanamines by Ho *et al*.[10] by omitting the last acidic hydrolysis procedure.

***N*-[1-(3-Methoxyphenyl)ethyl]formamide:** yield: 71%; a beige oil; R_f 0.12 (AcOEt–hexane 1:2); IR (neat) 3272, 1661, 1601 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.50 and 1.55 (2d, J = 6.8 Hz each, combined 3H), 3.80 and 3.81 (2s, combined 3H), 5.15–5.22 (m, 1H), 5.96 (br s, 1H), 6.80–6.92 (m, 3H), 7.24–7.28 (m, 1H), 8.12 and 8.16 (2s, combined 1H). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.92; H, 7.40; N, 7.80.

***N*-[1-(4-Chlorophenyl)ethyl]formamide:** yield: 66%; a white solid; mp 81–83 ˚C (hexane–CH_2Cl_2); IR (KBr) 3277, 1662 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.50 and 1.55 (2d, J = 6.9 Hz each, combined 3H),

5.16–5.22 (m, 1H), 5.80 (br 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 8.18 (s, 1H). Anal. Calcd for $C_9H_{10}ClNO$: C, 58.86; H, 5.49; N, 7.63. Found: C, 58.88; H, 5.52; N, 7.69.

***N*-(Diphenylmethyl)formamide:** yield: 85%; colorless needles; mp 131–132 ˚C (hexane–CH_2Cl_2) (lit.,[11] mp 132–133 ˚C); IR (KBr) 3229, 3193, 1682, 1652 cm^{-1}; ^1H NMR (400 MHz) δ 5.74–6.36 (m, 2H), 7.21–8.25 (m, 11H). Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.58; H, 6.40; N, 6.50.

(1-Isocyanoalkyl)benzenes 2. These compounds were prepared by the dehydration of the respective *N*-(1-arylalkyl)formamides with $POCl_3/Et_3N$ under the conditions reported previously by us.[12]

(1-Isocyanoethyl)benzene (2a): yield: 77%; a pale-yellow liquid; R_f 0.68 (AcOEt–hexane 1:5). The spectral data (IR and ^1H NMR) were identical to those reported previously.[13]

1-(1-Isocyanoethyl)-3-methoxybenzene (2b): yield: 77%; a pale-yellow liquid; R_f 0.60 (AcOEt–hexane 1:2); IR (neat) 2140, 1604 cm^{-1}; ^1H NMR (400 MHz) δ 1.66–1.69 (m, 3H), 3.83 (s, 3H), 4.79 (q, *J* = 6.8 Hz, 1H), 6.87 (dd, *J* = 7.8, 2.0 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H). HR MS. Calcd for $C_{10}H_{12}NO$ (M+H): 162.0920. Found: *m/z* 162.0909.

1-Chloro-3-(1-Isocyanoethyl)benzene (2c): yield: 76%; a yellow liquid; R_f 0.36 (Et_2O–hexane 1:5); IR (neat) 2140 cm^{-1}; ^1H NMR (400 MHz) δ 1.66–1.69 (m, 3H), 4.80 (q, *J* = 6.9 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H). HR MS. Calcd for C_9H_9ClN (M+H): 166.0424. Found: *m/z* 166.0423.

(1-Isocyanopropyl)benzene (2d):[14] yield: 87%; a yellow liquid; R_f 0.34 (Et_2O–hexane 1:5); IR (neat) 2140 cm^{-1}; ^1H NMR (500 MHz) δ 1.05 (t, *J* = 7.4 Hz, 3H), 1.91–1.94 (m, 2H), 4.64 (t, *J* = 5.7 Hz, 1H), 7.33–7.41 (m, 5H).

[Isocyano(phenyl)methyl]benzene (2e): yield; 90%: a white solid; mp 33–35 ˚C (hexane–Et_2O) (lit.,[15] 35–36 ˚C); IR (KBr) 2144 cm^{-1}; ^1H NMR (500 MHz) δ 5.91 (s, 1H), 7.31–7.40 (m, 10H).

Typical Procedure for the Preparation of 1-(2-Aryl-2-isocyanoalkyl)-2-bromobenzenes (3). 1-Bromo-2-(2-isocyano-2-phenylpropyl)benzene (3a). To a stirred solution of **2a** (0.47 g, 3.5 mmol) in THF (10 mL) at –78 ˚C was added *n*-BuLi (1.6 M in hexane; 3.5 mmol) dropwise. After 5 min, a solution of **1a** (0.88 g, 3.5 mmol) in THF (2 mL) was added and stirring was continued for an additional 10 min before saturated aqueous NH_4Cl (20 mL) was added. The mixture was warmed to room temperature and extracted with Et_2O (3 × 15 mL). The combined extracts were washed with brine (15 mL), dried (anhydrous Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel to give **3a** (0.92 g, 88%); a colorless oil; R_f 0.32 (Et_2O–hexane 1:10); IR (neat) 2130, 1602 cm^{-1}; ^1H NMR (500 MHz) δ 1.86 (s, 3H), 3.26 (d, *J* = 14.3 Hz, 1H), 3.54 (d, *J* = 14.3 Hz, 1H), 7.12–7.16 (m, 1H), 7.23 –7.25 (m, 2H), 7.35 (t, *J* = 6.8 Hz, 1H), 7.40 (dd, *J* = 8.0, 6.8 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 1H). HR MS. Calcd for $C_{16}H_{15}BrN$ (M+H): 300.0389. Found: *m/z* 300.0375.

1-Bromo-2-[2-isocyano-2-(3-methoxyphenyl)propyl]benzene (3b): a colorless oil; R_f 0.37 (Et_2O–hexane 1:10); IR (neat) 2132, 1603 cm^{-1}; ^1H NMR (400 MHz) δ 1.79 (s, 3H), 3.25 (d, *J* = 14.2 Hz, 1H), 3.53 (d, *J* = 14.2 Hz, 1H), 3.82 (s, 3H), 6.88 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.01 (t, *J* = 2.4 Hz, 1H), 7.05 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.14 (ddd, *J* = 7.8, 6.9, 1.4 Hz, 1H), 7.23–7.34 (m, 3H), 7.57 (d, *J* = 7.8 Hz, 1H). HR MS. Calcd for $C_{17}H_{17}BrNO$ (M+H): 330.0494. Found: *m/z* 330.0491.

1-Bromo-2-[2-(4-chlorophenyl)-2-isocyanopropyl]benzene (3c): a colorless oil; R_f 0.43 (Et_2O–hexane 1:20); IR (neat) 2130 cm^{-1}; ^1H NMR (400 MHz) δ 1.80 (s, 3H), 3.25 (d, *J* = 13.7 Hz, 1H), 3.49 (d, *J* = 13.7 Hz, 1H), 7.13–7.17 (m, 1H), 7.25–7.26 (m, 2H), 7.37 (s, 4H), 7.56 (d, *J* = 7.8 Hz, 1H). HR MS. Calcd for $C_{16}H_{14}BrClN$ (M+H): 333.9999. Found: *m/z* 333.9987.

1-Bromo-2-(2-isocyano-2-phenylbutyl)benzene (3d): a pale-yellow oil; R_f 0.33 (Et_2O–hexane 1:30); IR (neat) 2131 cm^{-1}; ^1H NMR (400 MHz) δ 0.81 (t, *J* = 7.4 Hz, 3H), 1.95–2.03 (m, 1H), 2.21–2.28 (m, 1H), 3.23 (d, *J* = 14.6 Hz, 1H), 3.62 (d, *J* = 14.6 Hz, 1H), 7.09–7.22 (m, 3H), 7.31–7.44 (m, 5H), 7.55 (d, *J* = 7.8 Hz, 1H). HR MS. Calcd for $C_{17}H_{17}BrN$ (M+H): 314.0545. Found: *m/z* 314.0528.

1-Bromo-2-(2-isocyano-2,2-diphenylethyl)benzene (3e): colorless crystals; mp 101–104 °C (hexane–Et_2O); IR (KBr) 2129 cm^{-1}; ^1H NMR (500 MHz) δ 3.93 (s, 2H), 6.90 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.06–7.12 (m, 2H), 7.34–7.36 (m, 10H), 7.50 (dd, *J* = 7.8, 2.0 Hz, 1H). Anal. Calcd for $C_{21}H_{16}BrN$: C, 69.62; H, 4.45; N, 3.87. Found: C, 69.42; H, 4.61; N, 3.79.

1-Bromo-4-chloro-2-(2-isocyano-2-phenylpropyl)benzene (3f): a colorless oil; R_f 0.40 (hexane); IR (neat) 2130 cm^{-1}; ^1H NMR (500 MHz) δ 1.83 (s, 3H), 3.23 (d, *J* = 13.7 Hz, 1H), 3.49 (d, *J* = 13.7 Hz, 1H), 7.01–7.13 (m, 2H), 7.34–7.46 (m, 5H), 7.49 (d, *J* = 8.6 Hz, 1H). HR MS. Calcd for $C_{16}H_{14}BrClN$ (M+H): 333.9999. Found: *m/z* 333.9994.

1-Bromo-4-chloro-2-[2-isocyano-2-(3-methoxyphenyl)propyl]benzene (3g): a colorless oil; R_f 0.41 (Et_2O–hexane 1:10); IR (neat) 2131, 1606 cm^{-1}; ^1H NMR (400 MHz) δ 1.81 (s, 3H), 3.22 (d, *J* = 13.7 Hz, 1H), 3.48 (d, *J* = 13.7 Hz, 1H), 3.83 (s, 3H), 6.90 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.98 (dd, *J* = 2.9, 2.0 Hz, 1H), 7.02 (d, *J* = 9.8 Hz, 1H), 7.11–7.14 (m, 2H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 9.8 Hz, 1H). HR MS. Calcd for $C_{17}H_{16}BrClNO$ (M+H): 364.0105. Found: *m/z* 364.0092.

1-Bromo-4-chloro-2-(2-isocyano-2-phenylbutyl)benzene (3h): a pale-yellow oil; R_f 0.33 (Et_2O–hexane 1:50); IR (neat) 2131 cm^{-1}; ^1H NMR (400 MHz) δ 0.86 (t, *J* = 7.3 Hz, 3H), 1.98–2.07 (m, 1H), 2.20–2.27 (m, 1H), 3.19 (d, *J* = 13.7 Hz, 1H), 3.58 (d, *J* = 13.7 Hz, 1H), 7.00 (d, *J* = 2.9 Hz, 1H), 7.09 (dd, *J* = 8.8, 2.9 Hz, 1H), 7.33–7.43 (m, 5H), 7.47 (d, *J* = 8.8 Hz, 1H). HR MS. Calcd for $C_{17}H_{16}BrClN$ (M+H): 348.0155. Found: *m/z* 348.0147.

1-Bromo-2-(2-isocyano-2-phenylpropyl)-4-methoxybenzene (3i): a colorless oil; R_f 0.41 (Et_2O–hexane 1:10); IR (neat) 2131 cm^{-1}; ^1H NMR (400 MHz) δ 2.04 (s, 3H), 3.22 (d, *J* = 13.7 Hz, 1H), 3.50 (d, *J* = 13.7 Hz, 1H), 3.69 (s, 3H), 6.70–6.73 (m, 2H), 7.33–7.44 (m, 4H), 7.47 (d, *J* = 7.8 Hz, 2H). HR MS.

Calcd for $C_{17}H_{17}BrNO$ (M+H): 330.0494. Found: *m/z* 330.0479.

1-Bromo-2-(2-isocyano-2-phenylbutyl)-4-methoxybenzene (3j): a pale-yellow oil; R_f 0.25 (Et_2O–hexane 1:20); IR (neat) 2131 cm^{-1}; ^1H NMR (400 MHz) δ 0.83 (t, *J* = 7.4 Hz, 3H), 1.97–2.02 (m, 1H), 2.20–2.26 (m, 1H), 3.18 (d, *J* = 14.3 Hz, 1H), 3.60 (d, *J* = 14.3 Hz, 1H), 3.66 (s, 3H), 6.66 (d, *J* = 2.9 Hz, 1H), 6.68 (dd, *J* = 8.6, 2.8 Hz, 1H), 7.32–7.35 (m, 1H), 7.38–7.42 (m, 5H). HR MS. Calcd for $C_{18}H_{19}BrNO$ (M+H): 344.0651. Found: *m/z* 344.0638.

Typical Procedure for the Preparation of Dihydroisoquinolines (6). 3-Methyl-3-phenyl-3,4-dihydroisoquinoline (6a). To a stirred solution of **3a** (0.12 g, 0.41 mmol) in Et_2O (5 mL) at –78 °C was added *n*-BuLi (1.6M in hexane; 0.41 mmol) dropwise. After 5 min, saturated aqueous NH_4Cl (10 mL) was added, and the mixture was warmed to room temperature and extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (anhydrous Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel to give **6a** (53 mg, 58%); a white solid; mp 62–63 °C (hexane–CH_2Cl_2); IR (neat) 1628 cm^{-1}; ^1H NMR (500 MHz) δ 1.50 (s, 3H), 3.04 (d, *J* = 16.0 Hz, 1H), 3.15 (d, *J* = 16.0 Hz, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.28–7.37 (m, 5H), 7.55 (dd, *J* = 8.0, 1.1 Hz, 2H), 8.46 (s, 1H); ^{13}C NMR (125 MHz) δ 27.51, 38.70, 60.17, 125.66, 126.35, 127.15, 127.26, 127.69, 127.97, 128.16, 131.36, 135.10, 147.94, 158.42; MS *m/z* 221 (100, M^+). Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.76; H, 6.96; N, 6.24.

3-(3-Methoxyphenyl)-3-methyl-3,4-dihydroisoquinoline (6b): a pale-yellow oil; R_f 0.42 (AcOEt–hexane 1:3); IR (neat) 1626, 1601 cm^{-1}; ^1H NMR (500 MHz) δ 1.49 (s, 3H), 3.03 (d, *J* = 16.0 Hz, 1H), 3.13 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H), 6.76 (ddd, *J* = 8.0, 1.7, 1.1 Hz, 1H), 7.11–7.16 (m, 3H), 7.25 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.27–7.32 (m, 2H), 7.35 (td, *J* = 7.4, 1.7 Hz, 1H), 8.46 (s, 1H); ^{13}C NMR (125 MHz) δ 27.52, 38.66, 55.15, 60.19, 111.56, 111.97, 127.14, 127.23, 127.70, 127.95, 129.06, 131.33, 135.09, 142.84, 149.76, 158.33, 159.48; MS *m/z* 251 (100, M^+). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.07; H, 6.92; N, 5.37.

3-(4-Chlorophenyl)-3-methyl-3,4-dihydroisoquinoline (6c): a colorless needles; mp 98–99 °C (hexane–CH_2Cl_2); IR (KBr) 1625 cm^{-1}; ^1H NMR (500 MHz) δ 1.47 (s, 3H), 3.00 (d, *J* = 16.6 Hz, 1H), 3.09 (d, *J* = 16.6 Hz, 1H), 7.15 (d, *J* = 6.9 Hz, 1H), 7.28–7.38 (m, 5H), 7.49 (d, *J* = 8.6 Hz, 2H), 8.44 (s, 1H); ^{13}C NMR (125 MHz) δ 27.52, 38.60, 59.89, 127.19 (2C), 127.31, 127.60, 127.97, 128.24, 131.49, 132.12, 134.79, 146.55, 158.63; MS *m/z* 255 (100, M^+). Anal. Calcd for $C_{16}H_{14}ClN$: C, 75.14; H, 5.52; N, 5.48. Found: C, 75.09; H, 5.58; N, 5.21.

3-Ethyl-3-phenyl-3,4-dihydroisoquinoline (6d): a pale-yellow oil; R_f 0.31 (AcOEt–hexane 1:5); IR (neat) 1629 cm^{-1}; ^1H NMR (400 MHz) δ 0.77 (t, *J* = 7.3 Hz, 3H), 1.84–2.04 (m, 2H), 3.08 (d, *J* = 16.1 Hz, 1H), 3.15 (d, *J* = 16.1 Hz, 1H), 7.13–7.33 (m, 7H), 7.48 (d, *J* = 7.8 Hz, 2H), 8.51 (s, 1H); ^{13}C NMR (125 MHz_3) δ 8.70, 34.63, 36.19, 63.04, 126.17, 126.34, 126.99, 127.10, 127.86, 127.95, 128.19, 131.24,

135.26, 145.52, 158.67; MS *m/z* 235 (100, M^+). Anal. Calcd For $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.59; H, 7.30; N, 5.91.

3,3-Diphenyl-3,4-dihydroisoquinoline (6e): a white solid; mp 116–118 °C (hexane–CH_2Cl_2); IR (KBr) 1629 cm^{-1}; ^1H NMR (400 MHz) δ 3.48 (s, 2H), 7.15 (t, *J* = 7.4 Hz, 2H), 7.21–7.25 (m, 7H), 7.35–7.38 (m, 5H), 8.54 (s, 1H); ^{13}C NMR (125 MHz) δ 37.89, 65.73, 126.39, 127.09, 127.19, 127.36, 127.52, 127.91, 128.13, 131.66, 135.37, 147.09, 159.18; MS *m/z* 283 (100, M^+). Anal. Calcd for $C_{21}H_{17}N$: C, 89.01; H, 6.05; N, 4.94. Found: C, 88.73; H, 6.02; N, 4.94.

6-Chloro-3-methyl-3-phenyl-3,4-dihydroisoquinoline (6f): a pale-yellow oil; R_f 0.39 (THF–hexane 1:6); IR (neat) 1627 cm^{-1}; ^1H NMR (500 MHz) δ 1.50 (s, 3H), 3.01 (d, *J* = 16.0 Hz, 1H), 3.12 (d, *J* = 16.0 Hz, 1H), 7.15 (d, *J* = 1.1 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.26–7.29 (m, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.52 (d, *J* = 7.4 Hz, 2H), 8.43 (s, 1H); ^{13}C NMR (125 MHz) δ 27.66, 38.48, 60.02, 125.60, 126.09, 126.53, 127.40, 128.18, 128.21, 128.25, 128.42, 137.03, 147.35, 157.27; MS *m/z* 255 (100, M^+). Anal. Calcd for $C_{16}H_{14}ClN$: C, 75.14; H, 5.52; N, 5.48. Found: C, 75.08; H, 5.79; N, 5.21.

6-Chloro-3-(3-methoxyphenyl)-3-methyl-3,4-dihydroisoquinoline (6g): a pale-yellow oil; R_f 0.46 (AcOEt–hexane 1:3); IR (neat) 1623 cm^{-1}; ^1H NMR (500 MHz) δ 1.49 (s, 3H), 3.00 (d, *J* = 16.0 Hz, 1H), 3.11 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H), 6.77 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.08–7.11 (m, 2H), 7.15 (s, 1H), 7.24–7.28 (m, 3H), 8.42 (s, 1H); ^{13}C NMR (125 MHz) δ 27.67, 38.47, 55.22, 60.31, 111.63, 112.01, 117.98, 126.07, 127.40, 128.21, 128.42, 129.19, 129.21, 137.03, 149.17, 157.25, 159.54; MS *m/z* 285 (100, M^+). Anal. Calcd for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; N, 4.90. Found: C, 71.45; H, 5.65; N, 4.60.

6-Chloro-3-ethyl-3-phenyl-3,4-dihydroisoquinoline (6h): a pale-yellow oil; R_f 0.38 (AcOEt–hexane 1:3); IR (neat) 1628 cm^{-1}; ^1H NMR (500 MHz) δ 0.77 (t, *J* = 7.4 Hz, 3H), 1.85–2.04 (m, 2H), 3.05 (d, *J* = 16.0 Hz, 1H), 3.12 (d, *J* = 16.0 Hz, 1H), 7.13 (br s, 1H), 7.17–7.23 (m, 3H), 7.29 (dd, *J* = 8.0, 7.4 Hz, 2H), 7.44 (dd, *J* = 8.0, 1.1 Hz, 2H), 8.48 (s, 1H); ^{13}C NMR (125 MHz) δ 8.66, 34.77, 36.00, 62.87, 126.25, 126.35, 126.54, 127.23, 128.05, 128.26, 136.85, 137.21, 144.95, 157.52, 157.54; MS *m/z* 269 (100, M^+). Anal. Calcd for $C_{17}H_{16}ClN$: C, 75.69; H, 5.98; N, 5.19. Found: C, 75.59; H, 6.03; N, 5.04.

6-Methoxy-3-methyl-3-phenyl-3,4-dihydroisoquinoline (6i): a white solid; mp 72–74 °C (hexane–CH_2Cl_2); IR (KBr) 1626, 1606 cm^{-1}; ^1H NMR (400 MHz) δ 1.62 (s, 3H), 2.98 (d, *J* = 15.6 Hz, 1H), 3.12 (d, *J* = 15.6 Hz, 1H), 3.83 (s, 3H), 6.68 (d, *J* = 2.0 Hz, 1H), 6.77 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 2H), 7.53 (dd, *J* = 7.4, 2.0 Hz, 2H), 8.37 (s, 1H); ^{13}C NMR (125 MHz) δ 27.61, 39.21, 55.27, 59.79, 111.79, 113.74, 121.52, 125.65, 126.27, 128.10, 138.98, 137.28, 147.99, 157.71, 161.89; MS *m/z* 251 (100, M^+). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 80.96; H, 6.89; N, 5.62.

3-Ethyl-6-methoxy-3-phenyl-3,4-dihydroisoquinoline (6j): a pale-yellow oil; R_f 0.30 (AcOEt–hexane 1:3); IR (neat) 1626, 1606 cm^{-1}; ^1H NMR (400 MHz) δ 0.77 (t, *J* = 7.4 Hz, 3H), 1.85–2.04 (m, 2H), 3.04

(d, *J* = 16.6 Hz, 1H), 3.11 (d, *J* = 16.6 Hz, 1H), 3.80 (s, 3H), 6.67 (d, *J* = 1.7 Hz, 1H), 6.73 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 8.0, 7.4 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 8.42 (s, 1H); ^{13}C NMR (125 MHz) δ 8.70, 34.69, 36.71, 55.28, 62.67, 111.60, 113.71, 122.06, 126.12, 126.34, 127.93, 128.85, 137,47, 145.65, 158.02, 161.80; MS *m/z* 265 (100, M^+). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.49; H, 7.17; N, 5.09.

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