

**CONVENIENT SYNTHESIS OF 1-SUBSTITUTED DERIVATIVES
OF 4-([E]-1-PROPENYL)- AND 4-ALLYL-3-AMINOISOQUINOLINES**

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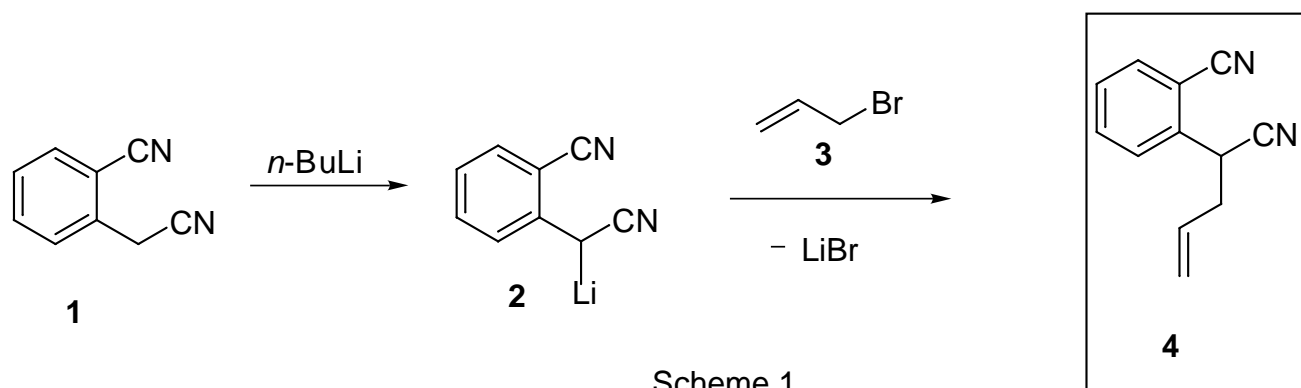
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Abstract – A one-step synthesis of titled compounds from the reaction of α -allyl- α -cyano-*o*-tolunitrile with lithium amides and alkyllithiums is described. The reaction of lithiated primary alkyl amines, alkyl- and aryl-lithiums at -78°C gave 1-substituted 4-([E]-1-propenyl)-3-aminoisoquinolines, whereas lithiated cyclic amides and 3-dimethylaminopropyl amide under similar conditions afforded 1-substituted 4-allyl-3-aminoisoquinolines. 1-Substituted 4-([E]-1-propenyl)-3-aminoisoquinolines were obtained as major product when reactions of the lithiated cyclic amides were performed at room temperature for 24 h. An explanation in terms of the effect of 4-substituents on the acidity of the α -methylene hydrogens is given.

Weⁱ showed recently that α -cyano-*o*-tolunitrile (**1**) reacts with a variety of lithium amides, alkyllithiums and phenyllithium to yield the corresponding 1-substituted amino-, 1-alkyl- and 1-phenyl derivative of 3-aminoisoquinoline.¹ To see if this methodology could be extended to the synthesis of 1,4-disubstituted 3-aminoisoquinolines, an investigation of the use of α -substituted derivatives of **1** was initiated.

We report herein the synthesis of 1-substituted derivatives of 4-allyl- and 4-([E]-1-propenyl)-3-amino-4-isoquinolines from the reaction of α -allyl- α -cyano-*o*-tolunitrile with a series of nucleophiles. The starting dinitrile, α -allyl- α -cyano-*o*-tolunitrile (**4**) was easily prepared by a two-step synthesis, shown in Scheme 1, by treating α -cyano-*o*-tolunitrile (**1**) with *n*-BuLi and allowing the α -lithiated derivative (**2**) to react with allyl bromide (**3**). The splitting patterns and

relative areas of the allylic hydrogens revealed in the ^1H NMR spectrum of **4** were consistent with the proposed structure.

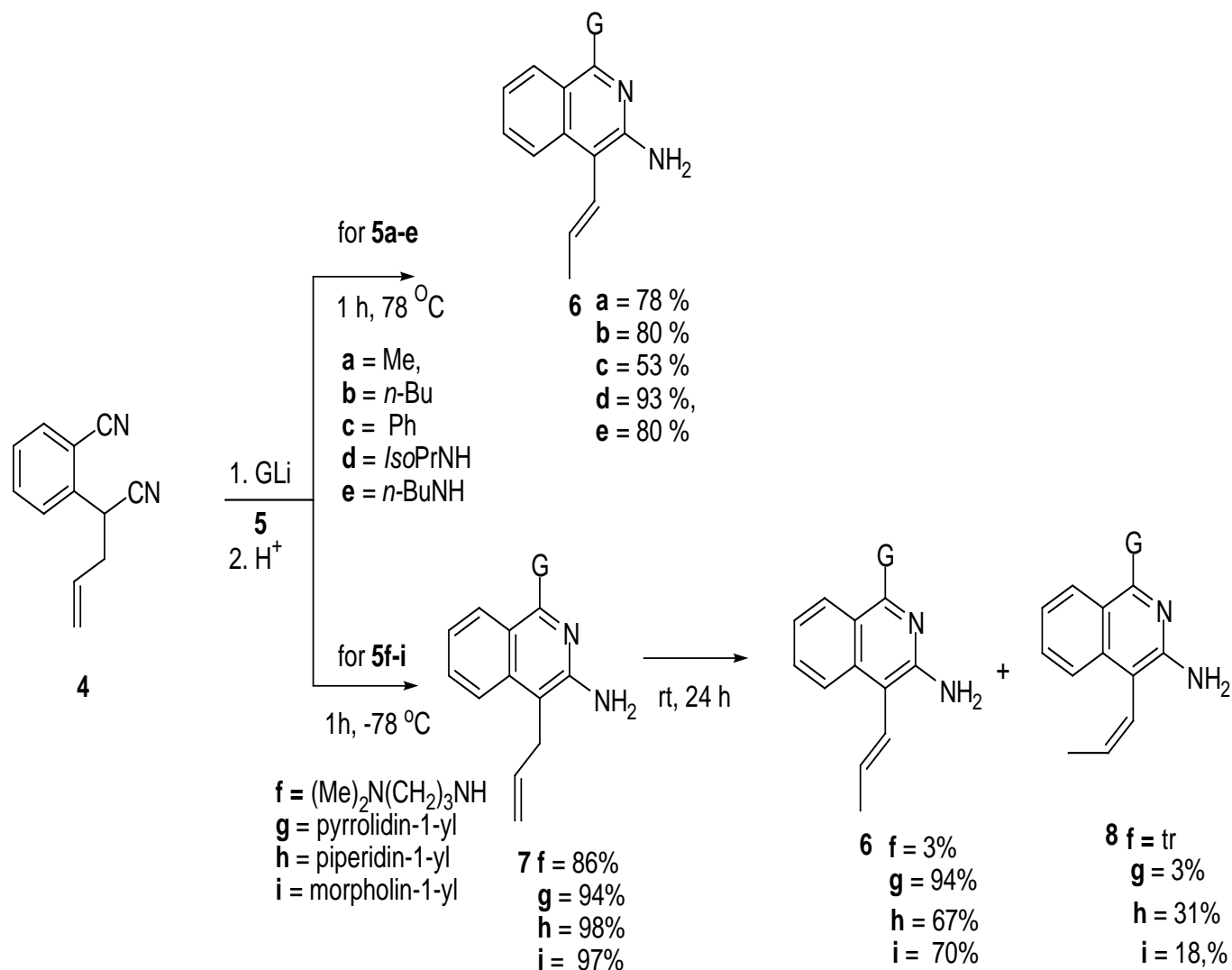


The results of the reaction of **4** with various nucleophiles (**5a-i**) are shown in Scheme 2. As shown, **4** reacted with methyllithium (**5a**) *n*-butyllithium (**5b**) and phenyllithium (**5c**) as well as lithium isopropyl- (**5d**) and lithium *n*-butylamide (**5e**) at $-78\text{ }^\circ\text{C}$ for 1 h to give the corresponding 1-substituted 3-amino-4- (*[E]*-1-propenyl]isoquinolines (**6a-e**) in moderate to excellent yields (50-93%). On the other hand, **4** reacted with lithium 3-dimethylaminopropyl amide (**5f**), lithium pyrrolidide (**5g**), lithium piperidide (**5h**) and lithium morpholide (**5i**) under similar conditions to give the corresponding 4-allyl derivatives (**7f-i**) in good to excellent yields (86-97%). When the reactions of **5g-i** were monitored by GC/MS analysis as the reaction temperature was raised to room temperature, it was found that **7g-i** slowly underwent isomerization predominantly to the 4-*E* product (**6g-i**). After stirring at room temperature for 24 hours, the isomerization was essentially complete giving the *E*-products (**6g-i**) in yields ranging from 67-94%. In addition, significant amounts of the *Z*-isomer (**8h**, 33% and **8i**, 18%) were obtained from the respective reactions of **5h** and **5i**. However, the reaction of **5f** gave the 4-allyl product (**7f**) in 85% yield with only a minor amount (3%) of the *E*-product (**6f**). To see if this reaction could be extended to secondary amines and aromatic amines, the reaction of lithiated aniline (**5j**), *N*-methylaniline (**5k**), and *N*-methylbenzylamine were carried out. However, these reactions failed to react even after stirring for 48 h. When the reaction mixtures were heated to $100\text{ }^\circ\text{C}$, only intractable tars were obtained.

The proposed structures were consistent with ^1H NMR and ^{13}C NMR spectral data. For example, the coupling constants for the olefinic hydrogens are around 10.5 Hz, which is indicative of *trans* coupling. In addition, long range coupling between the 1-olefinic hydrogen and the 5H-of the isoquinoline ring was observed for all isoquinolines, with the maximum coupling constant of 1.5 Hz being observed for **6a**.

A possible mechanism for the reaction at $-78\text{ }^\circ\text{C}$ is shown in Scheme 3. As shown, a molecule

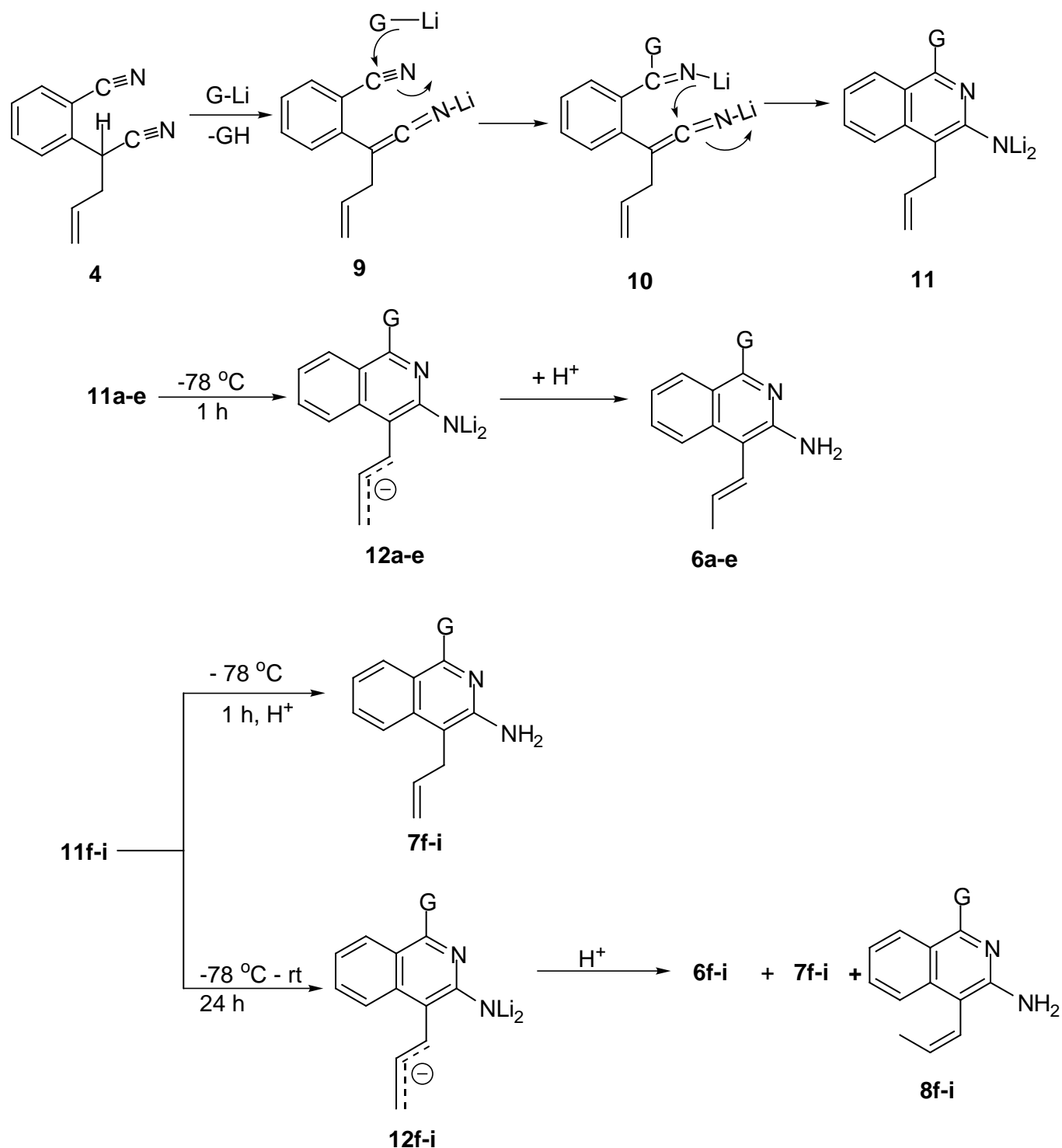
of GLi (**5**) first converts **4** to its lithium enamine derivative (**9**). This allows the remaining cyano group to undergo nucleophilic addition by another molecule of **5** giving the adduct (**10**) which



Scheme 2

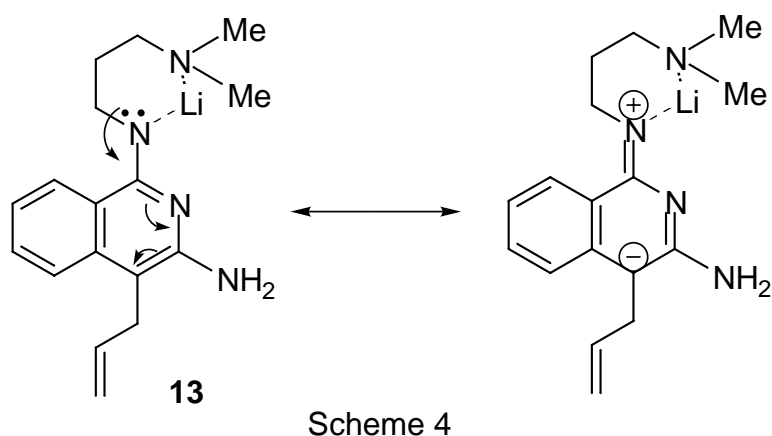
undergoes ring closure to dilithiated species (**11**). The intermediates (**11a-e**) are then converted to the allylic anions (**12a-e**) by the excess base (**5a-e**) which are converted to the thermodynamic products (**6a-e**). However under these conditions, the other nucleophilic bases (**5f-i**) are unable to deprotonate **11f-i** to **12f-i**, and thus **11f-i** simply awaits proton quenching to give the allyl products (**7g-i**). The need for greater reaction time and temperature for the reactions involving cyclic amides (**5g-i**) may reflect the decreased acidity of the methylene hydrogens in **11g-i** as compared to those in **11a-e**. The decrease in acidity may be due to strong resonance interactions between the cyclic ring and the nitrogen-containing isoquinoline ring. Such an interaction results from the ability of these two rings to adopt a coplanar configuration. The greater acidity of the methylene hydrogens in the 4-isopropylamino and 4-*n*-butyl derivatives

(**11d,e**) as compared to **11f-i** probably reflects the decreased delocalization of the strong



Scheme 3

resonance interactions between the cyclic ring and the nitrogen-containing isoquinoline ring. Such an interaction results from the ability of these two rings to adopt a coplanar configuration. That the 3-dimethylpropylamino compound (**7g**) fails to isomerize **6g** at $-78\text{ }^\circ\text{C}$ may be due to intramolecular stabilization depicted in Scheme 4, which, in effect, allows the 4-amino group to



adopt a pseudo 6-membered ring structure (**13**). Such a configuration should allow the lone pair electrons adopt a pseudo 6-membered ring structure (**13**). Such a configuration should allow the lone pair electrons on the 1-nitrogen atom to participate in resonance similar to that of the cyclic amino products (**7g-i**). To show that the isomerization of **7f** was not base dependent, we found that **7f** did not isomerize when treated with *n*-butyllithium at $-78\text{ }^{\circ}\text{C}$.

Finally, the failure of lithiated aromatic amides (**5j-i**) to react with **4** probably is due to their inability to convert the dinitrile (**4**) to intermediate (**9j-i**). This is consistent with the lower basicities of these amides as compared to the amides (**5a-i**).²

In conclusion, we have shown that 1,3,4-substituted isoquinolines can be prepared by a convenient, one-step synthesis using readily available starting materials. Furthermore, the introduction of the 1-propenyl and allyl group to the 4-position will greatly increase the synthetic flexibility at that position. There are only a few literature reports for introducing allyl³ and 1-propenyl groups^{4,5} onto the isoquinoline ring. These generally require multistep syntheses and/or are low-yield processes.

EXPERIMENTAL

General Data: Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. IR spectra were recorded on a Nicolet Magna-IR™ 550 FTIR spectrometer and the ^1H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker AVANCE DRX-400 Multi-nuclear NMR spectrometer; chemical shifts were referenced to TMS as internal standard. The MS were run on a HP G1800C, GCD SeriesII. Elemental analyses were obtained from SMU Microanalytical Laboratory Services. The amines and α -cyano-*o*-tolunitrile, which were distilled or recrystallized before use. The alkyllithiums and phenyllithium were purchased from Aldrich Chemical Company and used as received. The glassware was heated at $125\text{ }^{\circ}\text{C}$ in an oven overnight prior to use. The reactions carried out

in glassware, which had been heated at 125 °C overnight prior to use, under an atmosphere of dry O₂-free N₂ via balloon.

Preparation of α -Allyl- α -cyano-*o*-tolunitrile (4): To the solution of α -cyano-*o*-tolunitrile (2.84 g, 20 mmol) in THF (15 mL) was added BuLi (8 mL of 2.5 M solution, 20 mmol) at -70 °C. After stirring for 10 min, a solution of allyl bromide (12.1 g, 100 mmol) in THF (50 mL) was added slowly at -70 °C. A vigorous reaction ensued and the reaction mixture turned dark. The reaction mixture was allowed to warm to rt where it was stirred for 4-5 h then quenched with methanol. The reaction mixture was then diluted with dichloromethane, washed twice with water, followed by brine, and dried over sodium sulfate. Solvent evaporation afforded a crude oily product (which was found a mixture of mono- and di-allylated product by GC). The crude product was purified by silica gel chromatography using hexane eluent to yield 1.64 g, (45%) of α -allyl- α -cyano-*o*-tolunitrile as colorless liquid. IR (neat) ν_{\max} 2249, 2225, 1643, 733, 650 cm⁻¹. ¹H NMR (CDCl₃) δ 2.75-2.79 (m, 2 H), 4.38 (t, J = 7.4 Hz, 1 H), 5.27 (d, J = 17.8 Hz, 1 H), 5.28 (d, J = 11.4 Hz, 1 H), 5.89 (m, 1 H), 7.54-7.79 (m, 1H). MS m/e 182, 142, 141, 115, 114. Anal. Calcd for C₁₂H₁₀N₂: C, 79.10; H, 5.53; N, 15.39. Found: C, 79.15; H, 5.60; N, 15.47.

General Procedure for the Preparation of Titled Compounds (6a-i and 8f-i). In a flame-dried flask flushed with nitrogen, the lithium amide was prepared by adding 6.4 mL of *n*-BuLi (10 mmol, 1.6 M in hexane) to a solution of the appropriate amine (10 mmol) in THF (30 mL) at -78 °C. The alkylolithiums and phenyllithium (15 mmol) were added directly to THF (30 mL). After stirring for 10 min, α -allyl- α -cyano-*o*-tolunitrile (182 mg, 1 mmol) in THF (15 mL) was added over 5 min. The stirring was continued for 10 min at -78 °C, then the reaction mixture was allowed to warm to rt, where it was stirred for an additional 2 h. The reaction mixture then was quenched with sat. aq. NH₄Cl (30 mL), and the THF evaporated under reduced pressure to give a residue which was extracted with dichloromethane (2 X 20 mL). The combined extracts were washed with brine (2 X 20 mL), dried (Na₂SO₄), and concentrated (rotary evaporator). The remaining mixture was subjected to flash column chromatography (silica gel) using a mixture of hexane/acetone (9:1) as the eluent to give a liquid product. The elemental analyses and NMR spectral data of isolated compounds (6) are given below.

3-Amino-1-methyl-4-([*E*]-1-propenyl)isoquinoline (6a): colorless oil, 78%. ¹H NMR (CDCl₃) δ 1.59 (d, J = 8.4 Hz, 3 H), 2.86 (s, 3 H), 4.46 (br s, 2 H), 6.12-6.17 (m, 1 H), 6.45 (d, J = 11.0

Hz, 1 H), 7.26-7.28 (m, 1 H), 7.51-7.54 (m, 1 H), 7.51-7.54 (m, 1 H), 7.98 (d, $J = 8.4$ Hz, 1 H). Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.91; H, 7.22; N, 14.39.

3-Amino-1-*n*-butyl-4-([*E*]-1-propenyl)isoquinoline (6b): colorless oil, 87%. 1H NMR ($CDCl_3$) δ 1.08 (t, $J = 7.2$ Hz, 3 H), 1.56-1.58 (m, 2 H), 1.66-1.68 (d, $J = 7.5$ Hz, 2 H), 1.89-1.93 (m, 2 H), 4.55 (br s, 2 H), 6.19-6.23 (m, 1 H), 6.51 (d, $J = 10.8$ Hz, 1 H), 7.30-7.34 (m, 1 H), 7.56 (t, $J = 7.6$ Hz, 1 H), 7.70 (d, $J = 8.0$ Hz, 1 H), 8.08 (d, $J = 8.8$ Hz, 1 H). MS m/z 240 (P), 225, 198. Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 79.92; H, 8.45; N, 11.45.

3-Amino-1-phenyl-4-([*E*]-1-propenyl)isoquinoline (6c): colorless oil, 53%. IR (nujol) ν_{max} 3472, 3387, 3157, 1607, 935, 738, 699 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.65 (d, $J = 6.8$ Hz, 3 H), 4.61 (br s, 2 H), 6.21-6.23 (m, 2 H), 6.50 (d, $J = 11.4$ Hz, 1 H), 7.20-7.28 (m, 1 H), 7.52-7.55 (m, 4 H), 7.68-7.71 (m, 1 H), 7.95 (d, $J = 8.4$ Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 15.5, 106.3, 122.0, 122.8, 123.8, 123.5, 128.5, 128.7, 128.8, 130.2, 130.3, 132.5, 138.0, 140.1, 151.0, 159.6. MS $m/e/$ 260 (P), 245 (B). Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 82.92; H, 6.22; N, 10.49.

3-Amino-1-isopropylamino-4-([*E*]-1-propenyl)isoquinoline (6d): colorless oil, 93%. IR (nujol) ν_{max} 3357, 2259, 1686 cm^{-1} . 1H NMR ($CDCl_3$) δ 1.33 (d, $J = 6.8$ Hz, 6 H), 1.62 (d, $J = 6.4$ Hz, 3 H), 4.27 (br s, 2 H), 4.48 (sept, $J = 6.8$ Hz, 1 H), 4.96 (d, $J = 6.8$ Hz, 1 H), 6.00 (m, 1 H), 6.38 (dd, $J = 11.4$ Hz, $J = 1.5$ Hz, 1 H), 7.12 (m, 1 H), 7.44-7.50 (m, 2 H), 7.59 (d, $J = 8.4$ Hz, 1 H). MS m/z 241 (P and B), 226, 198. Anal. Calcd for $C_{15}H_{19}N_3$: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.87; H, 8.05; N, 17.40.

3-Amino-1-*n*-butylamino-4-([*E*]-1-propenyl)isoquinoline (6e): colorless oil, 80%. IR (neat) ν_{max} 3054, 2986 cm^{-1} . 1H NMR ($CDCl_3$) δ 0.99 (t, $J = 7.2$ Hz, 3 H), 1.62 (d, $J = 6.8$ Hz, 6 H), 1.62 (d, $J = 6.4$ Hz, 3 H), 4.27 (br s, 2 H). MS m/z 255 (P), 228, 212. Anal. Calcd for $C_{16}H_{21}N_3$: C, 72.56; H, 8.29; N, 16.46. Found: C, 72.71; H, 8.34; N, 16.60.

3-Amino-4-([*E*]-1-propenyl)-1-(pyrrolidin-1-yl)isoquinoline (6g): colorless oil, 86%. IR (neat) ν_{max} 3464, 3397, 3165, 1608, 967, 733, 691 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.63 (d, $J = 6.0$ Hz, 3 H), 1.97-2.00 (m, 4 H), 3.81-3.84 (m, 4 H), 4.25 (br s, 2 H), 6.03-6.04 (m, 1 H), 6.38 (d, $J = 10.9$ Hz, 1 H), 7.07-7.10 (m, 1 H), 7.41-7.43 (m, 1 H), 7.48-7.51 (m, 1 H), 8.09 (d, $J = 8.6$ Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 14.5, 15.4, 23.1, 32.6, 35.5, 105.0, 122.0, 122.5, 124.0, 124.1, 126.2, 130.0, 132.1, 137.5, 150.6, 161.5. MS, m/z 253 (P), 200, 105 (B). Anal. Calcd for $C_{16}H_{19}N_3$: C, 75.85; H, 7.56; N, 16.59. Found: C, 75.97; H, 7.80; N, 16.45.

3-Amino-4-([E]-1-propenyl)-1-(piperidin-1-yl)isoquinoline (6h): colorless oil, yield, 90%.

$^1\text{H NMR}$ (CDCl_3) δ 1.60 (m, 5 H), 1.77-1.83 (m, 4 H), 3.37 (m, 4 H), 4.71 (br s, 2 H), 6.05-6.09 (m, 1 H), 6.46 (d, $J = 10.8$ Hz, 1 H), 7.14 (m, 1 H), 7.27 (m, 1 H), 7.43-7.47 (m, 1 H), 7.96 (d, $J = 8.4$ Hz, 1 H). Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_3$: C, 76.37; H, 7.92; N, 15.72. Found: C, 76.52; H, 7.99; N, 15.86.

3-Amino-4-([E]-1-propenyl)-1-(morpholin-1-yl)isoquinoline (6i): colorless liquid, yield, 70%. $^1\text{H NMR}$ (CDCl_3) δ 1.61 (d, $J = 2$ Hz, 3 H), 3.52 (t, $J = 6$ Hz, 4 H), 4.1 (m, 1 H), 6.40 (d, $J = 9.6$ Hz, 1 H), 7.20 (q, $J = 7.2$ Hz, 1 H), 7.47 (t, $J = 6.8$ Hz, 1 H), 7.59 (d, $J = 8.4$ Hz, 1 H), 7.98 (d, $J = 8.4$ Hz, 1 H). Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}$: C, 71.35; H, 7.11; N, 15.60. Found: C, 71.41; H, 7.19; N, 15.70.

4-Allyl- *N*'-(3-dimethylaminopropyl)isoquinoline-1,3-diamine (7f): colorless oil, 85%. IR (neat) ν_{max} 3456, 3353, 3072, 1600, 986, 900, 772, 730 cm^{-1} . $^1\text{H NMR}$ (CDCl_3) δ 1.86-1.93 (m, 2H), 2.38 (s, 6 H), 2.58 (t, $J = 6.4$ Hz, 2 H), 3.47 (t, $J = 3.7$ Hz, 2 H), 3.66 (t, $J = 4.8$ Hz, 2 H), 4.25 (br s, 2 H), 5.03 (dd, $J = 17.2$ Hz, $J = 11.2$ Hz, 1 H), 5.04 (dd, $J = 11.2$, $J = 17.2$ Hz, 1 H), 5.95 (m, 1 H), 7.13 (m, 1 H), 7.28 (m, 1 H), 7.57 (d, $J = 8.4$ Hz, 1 H), 7.67 (d, $J = 8.4$ Hz, 1 H). Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{N}_4$: C, 71.29; H, 8.51; N, 19.70. Found: C, 71.35; H, 8.44; N, 19.73.

4-Allyl-3-amino-1-(pyrrolidin-1-yl)isoquinoline (7g): colorless oil: 98%. IR (neat) ν_{max} 3456, 3353, 3072, 1600, 986, 900, 772, 730 cm^{-1} . $^1\text{H NMR}$ (CDCl_3) δ 1.63 (d, $J = 6.0$ Hz, 3 H), 1.97-2.01 (m, 4 H), 3.81-3.84 (m, 2 H), 4.25 (br s, 2 H), 5.02-5.10 (m, 2 H), 5.96-6.02 (m, 1 H), 7.09-7.13 (m, 1 H), 7.45-7.49 (m, 1H), 7.61 (d, $J = 8.5$ Hz, 1 H), 8.10 (d, $J = 8.5$ Hz, 1 H). ^{13}C Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3$: C, 75.85; H, 7.56; N, 16.59. Found: C, 75.97; H, 7.80; N, 16.45.

4-Allyl-3-Amino-1-(piperidin-1-yl)isoquinoline (7h): colorless oil, 98%. IR (neat) ν_{max} 3467, 3381, 3069, 1613, 911, 735, 688 cm^{-1} . $^1\text{H NMR}$ (CDCl_3) δ 1.69-1.70 (m, 2 H), 1.82-1.85 (m, 4 H), 3.30-3.33 (m, 4 H), 3.54-3.57 (m, 2 H), 4.25 (br s, 2 H), 5.02-5.10 (m, 2 H), 5.96-6.02 (m, 1 H), 7.17-7.19 (m, 1 H), 7.48-7.51 (m, 1H), 7.67 (d, $J = 8.5$ Hz, 1 H), 8.00 (d, $J = 8.5$ Hz, 1 H). ^{13}C NMR (CDCl_3) δ 25.5, 26.9, 30.7, 53.3, 100.4, 115.8, 117.7, 121.5, 122.2, 126.9, 130.1, 135.6, 139.8, 151.2, 161.5. Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_3$: C, 76.37; H, 7.92; N, 15.72. Found: C, 76.58; H, 8.00; N, 15.78.

4-Allyl-3-amino-1-(morpholin-4-yl)isoquinoline (7i): colorless oil: 98%. IR (neat) ν_{max} 3456, 3353, 3072, 1600, 986, 900, 772, 730 cm^{-1} . $^1\text{H NMR}$ (CDCl_3) δ 3.78 (m, 4H), 3.56-3.57 (m, 2 H), 3.95-3.98 (m, 4 H), 4.30 (s, 2 H), 4.97 (t, $J = 7.4$ Hz, 1 H), 5.03 (d, $J = 17.8$ Hz, 1 H), 5.98 (m, 1 H), 7.19-7.23 (m, 1H), 7.52-7.54 (m, 1 H), 7.71 (d, $J = 8.5$ Hz, 1 H), 8.04 (d, $J = 8.4$ Hz,

1 H). ^{13}C NMR (CDCl_3) δ 30.54, 52.3, 67.5, 101.3, 116.0, 117.2, 121.8, 122.3, 126.3, 130.2, 135.3, 139.7, 150.9, 160.1. Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}$: C, 71.35; H, 7.11; N, 15.60. Found: C, 71.44; H, 7.16; N, 15.77.

ACKNOWLEDGEMENTS

This work was supported, in part, by grants from the Welch Foundation, Houston, TX, and the Petroleum Fund, administered by the American Chemical Society.

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