HETEROCYCLES, Vol. 53, No. 5, 2000, pp. 1183 - 1191, Received, 17th January, 2000

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

Sagun Tandel and Edward R. Biehl*

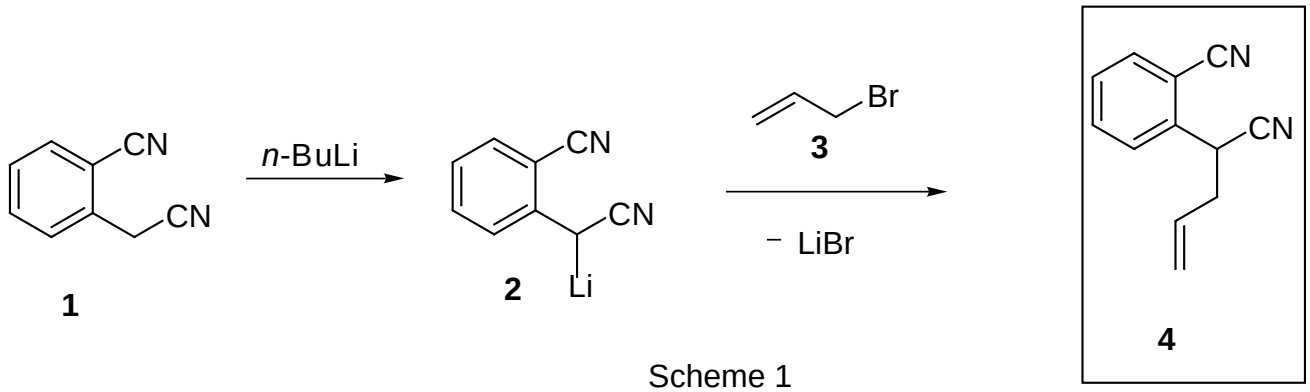
Chemistry Department, Southern Methodist University, Dallas, TX 75275, U. S. A.

Abstract – A one-step synthesis of titled compounds from the reaction of α-allyl-α-cyano-*o*–tolunitrile with lithium amides and alkylithiums is described. The reaction of lithiated primary alkyl amines, allkyl- and aryl-lithiums at -78^{O}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.

We[i] 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-aminoisooquinolines, an investigation of the use of α-sub-stituted 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 ^{1}H NMR spectrum of **4** were consistent with the proposed structure.



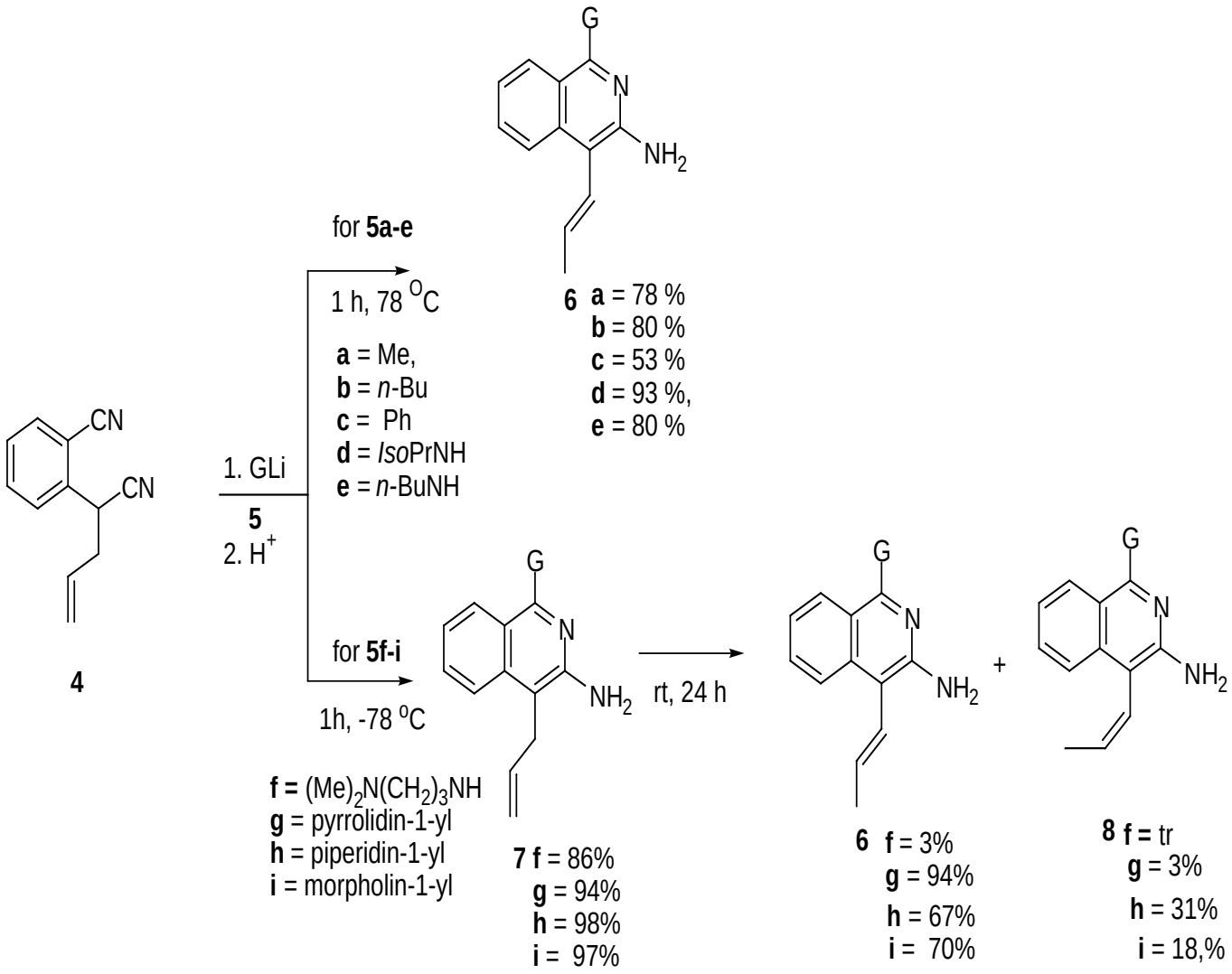
Scheme 1

The results of the reaction of **4** with various nucleophiles (**5a-l**) 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 ^{o}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 (**5l**) under similar conditions to give the corresponding 4-allyl derivatives (**7f-l**) 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 ^{o}C, only intractable tars were obtained.

The proposed structures were consistent with ^{1}H 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 ^{O}C is shown in Scheme 3. As shown, a molecule

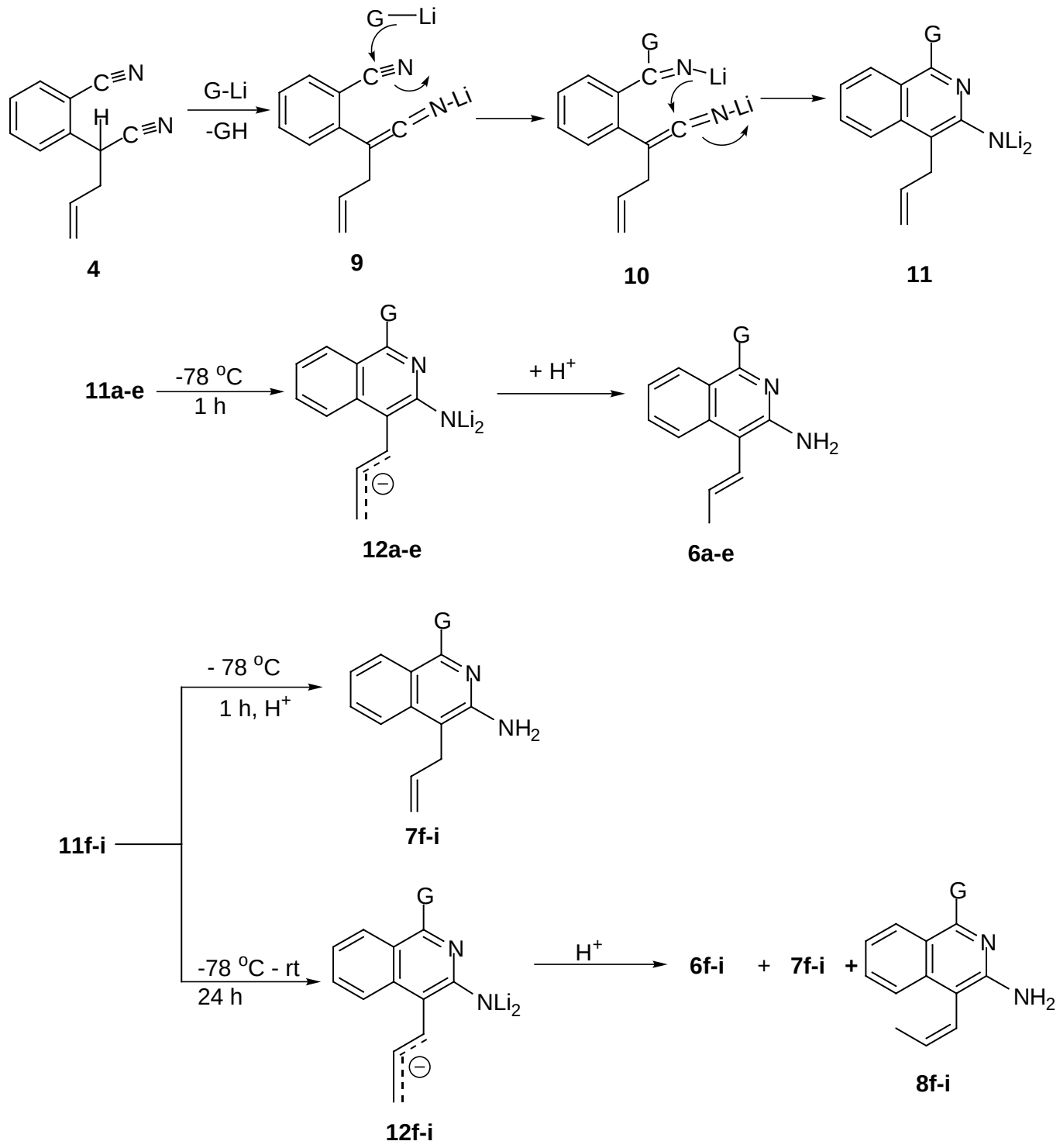
of GLi (**5**) first converts **4** to its lithium enamine derivative (**9**). This allows the remaining cyano group to undergo nucleophilic addition by another molecule of **5** giving the adduct (**10**) which



Scheme 2

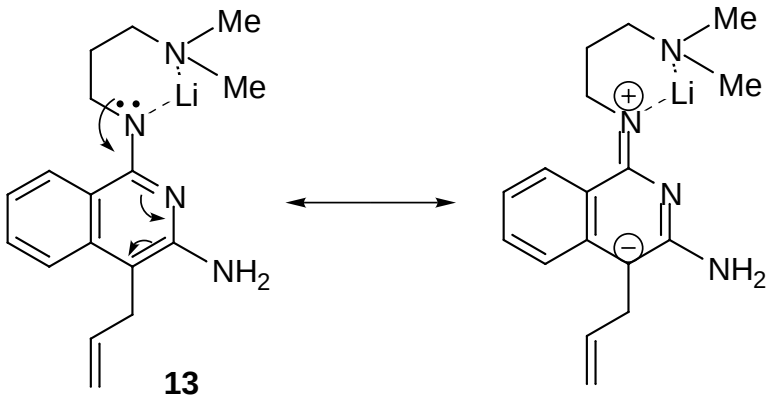
undergoes ring closure to dilithiated species (**11**). The intermediates (**11a-e**) are then converted to the allylic anions (**12a-e**) by the excess base (**5a-e**) which are converted to the thermo-dynamic products (**6a-e**). However under these conditions, the other nucleophilic bases (**5f-I**) 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-l**) may reflect the decreased acidity of the methylene hydrogens in **11g-l** 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 °C may be due to intramolecular stabilization depicted in Scheme 4, which, in effect, allows the 4-amino group to



13

Scheme 4

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-l**). 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 ^{o}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 allyl[3] 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^{TM} 550 FTIR spectrometer and the ^{1}H 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 ^{o}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 O_2-free N_2 *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 ($CDCl_3$) 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 $C_{12}H_{10}N_2$: 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 alkyllithiums 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. NH_4Cl (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 (Na_2SO_4), 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 ($CDCl_3$) 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%. ^{1}H 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, 23 H), 1.89-1.93 (m, 2H), 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}; ^{1}H 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 (CDCl3) 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}. ^{1}H 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}. ^{1}H NMR ($CDCl_3$) δ 0.99 (t, *J* = 7.2 Hz, 3 H), (d, *J* = 6.8 Hz, 6 H), 1.62 (d, *J* = 6.4 Hz, 3 H), 4.27. 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}; ^{1}H NMR ($CDCl_3$) δ1.63 (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}H NMR ($CDCl_3$) δ1.60 (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 $C_{17}H_{21}N_3$: 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}H NMR ($CDCl_3$) δ1.61 (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 $C_{16}H_{19}N_3O$: C, 71.35: H, 7.11; N, 15.60. Found: C, 71.41; H. 7.19: N, 15.70.

4-Alllyl- *N*^{1}-(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}H NMR ($CDCl_3$) δ1.86-1.93 (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 $C_{17}H_{24}N_4$: 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}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 $C_{16}H_{19}N_3$: C, 75.85; H, 7.56; N, 16.59. Found: C, 75.97; H, 7.80; N, 16.45.

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}H NMR ($CDCl_3$) δ1.69-1.70 (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 $C_{17}H_{21}N_3$: 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}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 $C_{16}H_{19}N_3O$: 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.

REFERENCES

1. A. Wang, H. Zhang, and E. Biehl, *Heterocycles*, 2000, **53**, 291.
2. K. Bowden, *Chem. Rev.,*1966, **66**, 119.
3. R. G. Kinsman, S. F. Dyke, and J. Mead, *Tetrahedron*, 1973, **29**, 4303
4. S. Kano, T. Yokomatsu, Y. Yuasa, and S. Shibuya, *Chem. Pharm. Bull*.,1985, **33**, 340.
5. M. Ishikura, I. Oda, and M. Terashima, *Heterocycles*, 1987, **26**, 1603.