under a H_2 atmosphere for 24 h. Workup followed by purification of the residue by flash chromatography (0.9:1:0.1 hexane–AcOEt–MeOH) gave 15.2 mg (72%) of **15** as a colorless liquid: $[\alpha]_D$ -49.7° (*c* 0.49, $CHCl_3$).

(1*S*,2*R*,8a*S*)-1,2-Dihydroxyindolizidine (4). By use of a procedure identical with that described for the preparation of *ent*-**4**, acetonide **15** (20 mg, 0.101 mmol) was hydrolyzed to give 12.1 mg (77%) of **4** as a colorless liquid: $[\alpha]_D$ -39.4°, $[\alpha]_{578}$ -43.0°, $[\alpha]_{546}$ -52.2°, $[\alpha]_{436}$ -85.1° (*c* 0.58, $CHCl_3$).

The diacetate, prepared as described by Colegate et al.,[13] showed the following optical rotation: $[\alpha]_D$ -71.9°, $[\alpha]_{578}$ -75.0°, $[\alpha]_{546}$ -84.3°, $[\alpha]_{436}$ -145° (*c* 0.54, $CHCl_3$).

Acknowledgment. This research was supported by P.H.S. Grant GM 30859. NMR and mass spectra were determined at Irvine with spectrometers purchased with the assistance of NSF Shared Instrumentation Grants. We wish to particularly thank Dr. Russell J. Molyneux (USDA Laboratory, Albany, CA) for GC comparisons of synthetic **4** and natural **4** and for allowing us to quote rotation data for natural **4** prior to publication. We also wish to thank Professors Gary E. Keck, Scott E. Denmark, and A. Richard Chamberlin for their insightful discussion.

Registry No. **4**, 108866-42-8; *ent*-**4**, 119904-08-4; **7**, 25581-41-3; **8**, 109720-67-4; **9**, 119795-67-4; (5*R*)-**10**, 119795-68-5; (5*S*)-**10**, 119904-05-1; (5*R*)-**11**, 119795-69-6; (5*S*)-**11**, 119904-06-2; **13**, 119795-70-9; **14**, 119795-71-0; **15**, 108796-01-6; *ent*-**15**, 119904-07-3; **16**, 108866-43-9; *ent*-**16**, 119904-09-5; **17**, 119795-72-1; **24**, 119795-73-2; **26**, 119795-74-3; **27**, 119795-75-4.

Reaction of 3-Amino-2-alkenimines with Alkali Metals: Unexpected Synthesis of Substituted 4-(Arylamino)quinolines

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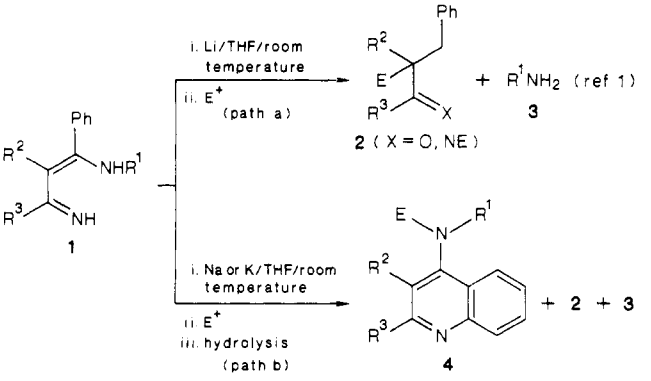
A study of the reduction of 3-amino-2-alkenimines **1** with alkali metals is reported. The nature of the alkali metal plays an important role in the course of the process. In this context, a new and simple method for the regioselective synthesis of 4-(arylamino)quinolines **4** from **1** and sodium or potassium is described.

We have recently described[1] a new synthetic procedure for the regiospecific reduction of 3-amino-2-alkenimine systems **1**[2] to saturated monocarbonyl compounds **2**. The method consists of the reaction of **1** with lithium in THF at room temperature and later addition of an electrophile (see Scheme I, path a).

In order to explore the generality of the method, we thought to extend this study to other alkali metals such as sodium and potassium, because the initial results[3] indicate that the course of the process was highly influenced by the nature of alkali metal. In this context, we describe here a new, simple, and unexpected method for the regioselective synthesis of substituted 4-(arylamino)-quinolines **4** from **1**.

The quinoline nucleus is found in many natural products, especially alkaloids.[4] Because of the importance of this ring system, numerous methods have been developed for the synthesis of its derivatives.[4] However, a bibliographical review shows that 4-amino-, and, particularly, 4-(arylamino)quinolines, some of which (e.g., camoquin[5] and its derivatives) show important antimalarial properties, are not easily obtainable.[6-12]

Scheme I



Results and Discussion

The treatment of 3-amino-2-alkenimines **1** with an excess of sodium or potassium at room temperature in an inert solvent such as THF produces intense color changes. After stirring of the mixture during several hours (4–10 h), and addition of an electrophile (H_2O, MeOH, IMe, or BrEt) (ratio electrophile:**1** ≥ 3), the reaction mixture was hydrolyzed leading to a mixture of compounds, in which besides **2** and **3**[13] (40–45% yield refered to **1**) variable amounts (42–48% of the overall chemical yield) of other

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(13) Carbonyl compounds **2** and amines **3** are the same as those obtained by treatment of **1** with lithium under the same reaction conditions. See ref 1.

0022-3263/89/1954-2596$01.50/0

Table I. 4-(Arylamino)quinolines 4 Obtained from 1 with Sodium in THF

compd	R^1	R^2	R^3	E	yield,[a] %	mp, °C
4a	Ph	Me	*p*-MeC_6H_4	H	40 (38)[b]	173–5
4b	Ph	Me	Ph	H	42	154–6
4c	*p*-MeC_6H_4	Me	*p*-MeC_6H_4	H	47	172–4
4d	*p*-MeC_6H_4	Me	Ph	H	42	170–2
4e	Ph	Me	c-C_6H_{11}	H	41	158–60
4f	*p*-MeC_6H_4	Et	Ph	H	42	oil[c]
4g	*p*-MeC_6H_4	Me	Ph	Me	43 (43)[b]	oil
4h	Ph	Me	*p*-MeC_6H_4	Me	43	118–20
4i	*p*-MeC_6H_4	Me	*p*-MeC_6H_4	Me	41	oil
4j	Ph	Me	Ph	Me	48 (43)[b]	121–3
4k	Ph	Me	*p*-MeC_6H_4	Et	44	oil

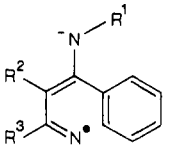
[a] In all cases is also obtained a mixture of 2 and 3 in 40–50% chemical yield (see Scheme I, path b). [b] By using potassium as alkali metal. [c] Not purified.

compounds identified as substituted 4-(arylamino)-quinolines 4 were obtained (see Scheme I, path b, and Table I).

The separation of the compounds 4 from the crude mixture was achieved by simple acid–base extraction when E = H. When E = alkyl the three compounds **2**, **3**, and **4** were separated by distillation under reduced pressure (see Experimental Section).

The structure of quinolines 4 was elucidated on the basis of their spectroscopic data and mass spectrometry. For instance, **4a** displays in ^1H NMR (80 MHz) characteristic signals at δ 2.30 (s, 3 H), 2.45 (s, 3 H), and 6.10 (br s, NH exchangeable with D_2O). The corresponding carbon atoms appear in ^{13}C NMR (20 MHz) at δ 16.5 (q) and 21.2 (q), and another characteristic signal appears at 161.3 (s) due to the C=N group in the quinoline ring. The MS spectra shows a molecular peak at *m/e* 324 (M^+).

The formation of 4 can be explained through a process of intramolecular cyclization in 1, probably via iminyl radicals **5**[14] (see below and Scheme III, via a). Very few



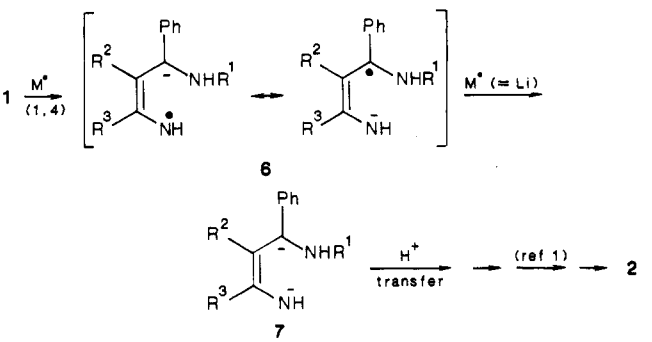
5

examples are known in the literature of such reactions. Thus, Forrester[15] has described a synthesis of quinolines through these intermediates generated from oximinoacetic acids.

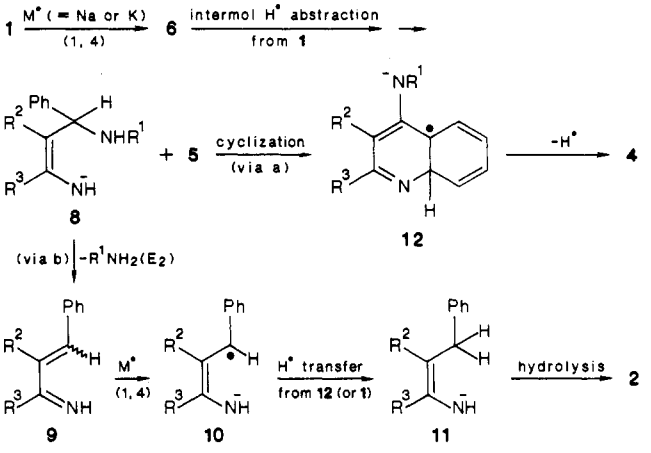
The formation of iminyl radicals **5**, as well as the different results obtained in the process of reduction according to the metal used, can be conveniently explained as follows: in the case of lithium[1] the anion-radical **6**, initially formed by addition of one electron to 1, participates in a second one-electron transfer reaction to form the corresponding dianion **7**, which leads to 2 following the mechanism indicated in ref 1 (Scheme II).

In the case of sodium or potassium, on the other hand, the anion-radical **6** tends to stabilize by intermolecular hydrogen abstraction from 1[16] giving rise to the monoanion **8** and the iminyl radical **5**, which by cyclization and aromatization leads to 4 (Scheme III, via a). On the other hand, **8** following the mechanism shown in Scheme III, via b, affords to the corresponding carbonyl or iminic compounds 2.[1]

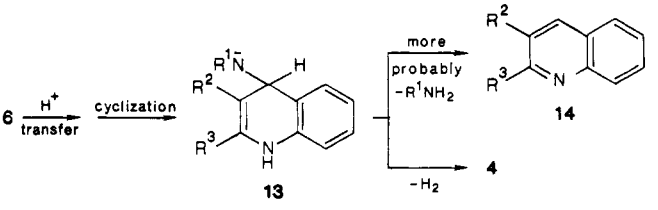
Scheme II



Scheme III



Scheme IV



The distinct ability of the anion-radical **6** to accept a second electron (the formation of dianions is favored by using lithium, which forms more covalent bonds to carbon than sodium and potassium) offers an explanation[17] for the different results obtained in the reduction process.[1,18]

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(16) Products resulting from the dimerization of the anion-radical **6** were not observed in any case.
(17) As has been suggested by a reviewer, another possible explanation is that the Li^+ cation produced from Li^0 is a more effective Lewis acid than Na^+ or K^+ and might be expected to facilitate 8 → 9 (Scheme III, via b) via complexing with the amine ion, which is eliminated.
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In this context, we should indicate that, the intramolecular cyclization of the anion-radical **6** would lead to the formation of dihydroquinoline derivative **13**, which in the aromatization would preferably lose amine (R^1NH_2) instead of hydrogen, giving rise, therefore, to another type of quinoline derivative **14** (Scheme IV).

Conclusions

The paper describes a new, simple, and regioselective synthesis of 4-(arylamino)quinolines **4** (compounds that are not easily available through other procedures) from 3-amino-2-alkenimines **1** and alkali metals such as sodium and potassium.

At the same time, it is demonstrated that the course of the process is highly affected by the nature of the alkali metal.[1]

Experimental Section

General Methods. Melting points are uncorrected. Infrared spectra were recorded in Nujol on a Pye-Unicam SP-1000 spectrophotometer. ^1H NMR spectra were determined on a Varian FT-80A or a Bruker AC-300 spectrometer with tetramethylsilane as internal reference. ^{13}C NMR spectra were determined on a Varian FT-80A or a Bruker AC-300 instrument. Mass spectra were taken on a Hewlett-Packard 5930A spectrometer. Elemental analyses were performed with a Perkin-Elmer 240 instrument.

Materials. 3-Amino-2-alkenimines **1** were prepared according to literature methods.[2a,19] The spectral data for compounds **2** that have not been described previously are included in the supplementary material. All reactions were run under argon. All organic extracts were dried over anhydrous sodium sulfate. Tetrahydrofuran (THF) was distilled from sodium benzophenone under argon prior to use. All other reagents were commercially available and were used as received.

General Preparative Procedure for 4-(Arylamino)-quinolines 4 (E = H) (4a–f). A solution of **1** (10 mmol) in anhydrous THF (20 mL) was added dropwise to a mixture of sodium or potassium (50 mmol) and anhydrous THF (20 mL) at room temperature. When the addition was complete, the yellow solution was stirred at room temperature for several hours (4–10 h). The yellow color slowly changed to deep purple. The excess of Na or K was removed from the resulting dark suspension and then treated with methanol and/or water (50 mmol). The mixture was stirred for 1–2 h, 100 mL of 2 N H_2SO_4 was added, and then the mixture was extracted with ether; the organic layer was dried over sodium sulfate, filtered, and evaporated. Compounds **2** (X = O, E = H) were thus separated. The aqueous layer was then treated with KOH until basic, extracted with ether, and evaporated. The residue was stirred with hexane and filtered. In this way, 4-(arylamino)quinolines **4** (E = H) were isolated as white solids and purified by recrystallization from *n*-hexane/chloroform (5:1). Reaction yields and melting points are listed in Table I.

From the filtrate, compounds **2** and amines **3** were distilled under reduced pressure and identified.[1]

3-Methyl-4-(phenylamino)-2-*p*-tolylquinoline (4a): IR (Nujol) 3200, 3160, and 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 2.45 (s, 3 H), 6.10 (br s, NH, exchangeable with D_2O), 6.70–8.30 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 161.32, 146.80, 144.52, 143.00, 139.00, 129.90–128.75, 125.71, 122.75, 120.40, 116.10, 21.25, 16.5; MS *m/e* 324 (M^+), 323. Anal. Calcd for $C_{23}H_{20}N_2$: C, 85.19; H, 6.17; N, 8.64. Found: C, 85.23; H, 6.08; N, 8.60.

3-Methyl-2-phenyl-4-(phenylamino)quinoline (4b): IR (Nujol) 3220, 3160, and 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 6.10 (br s, NH, exchangeable with D_2O), 6.70–8.30 (m, 14 H); ^{13}C NMR (C_6D_6) δ 161.20, 147.05, 144.52, 143.62, 141.20, 129.80–125.25, 122.51, 119.70, 115.41, 15.80; MS *m/e* 310 (M^+), 309. Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.16; H, 5.81; N, 9.03. Found: C, 85.27; H, 5.72; N, 9.01.

2-Cyclohexyl-3-methyl-4-(phenylamino)quinoline (4e): IR (Nujol) 3300, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–2.10 (m, 10 H), 2.30 (s, 3 H), 3.05 (m, 1 H), 5.80 (br s, NH, exchangeable with D_2O), 6.50–8.20 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 166.50, 147.51, 145.20, 142.51, 129.52, 129.20, 128.10, 125.23, 123.82, 123.20, 122.51, 119.70, 115.10, 43.21, 31.92, 26.83, 26.10, 13.75; MS *m/e* 316 (M^+). Anal. Calcd for $C_{22}H_{24}N_2$: C, 83.54; H, 7.59; N, 8.86. Found: C, 83.60; H, 7.53; N, 8.88.

Spectral data for compounds **4c**, **4d**, **4f**, and **2f** are included as supplemenary material.

General Preparative Procedure for 4-(Arylamino)-quinolines 4 (E = Alkyl) (4g–k). A solution of **1** (10 mmol) in anhydrous THF (20 mL) was added dropwise to a mixture of Na or K and anhydrous THF (20 mL) at room temperature. The subsequent operations were the same as those for compounds **4a–f**. The corresponding alkyl halide (40 mmol) was then added to the resulting solution, and the mixture was stirred for 2–4 h, treated with ice-cooled, concentrated KOH until basic, and extracted with ether. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was distilled under reduced pressure (0.001 Torr) to afford the amines **3** and the compounds **2**.[1] The corresponding 4-(arylamino)quinolines **4** were obtained from the not distillable residue and purified by recrystallization in *n*-hexane–chloroform (5:1) or flash chromatography (*n*-hexane/ether, 7:3).

Reaction yields and melting points are given in Table I.

3-Methyl-4-(methylphenylamino)-2-*p*-tolylquinoline (4h): IR (Nujol) 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H), 2.40 (s, 3 H), 3.40 (s, 3 H), 6.40–8.20 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 162.35, 149.80, 148.32, 147.71, 138.02, 137.80, 129.90–123.40, 117.22, 111.90, 37.80, 21.05, 15.80; MS *m/e* 338 (M^+), 323, 77. Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.21; H, 6.51; N, 8.28. Found: C, 85.18; H, 6.57; N, 8.17.

3-Methyl-4-(methylphenylamino)-2-phenylquinoline (4j): IR (Nujol) 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H), 3.40 (s, 3 H), 6.40–8.20 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 161.60, 150.08, 148.31, 147.85, 140.91, 129.91–123.52, 117.32, 112.02, 38.05, 15.82; MS, *m/e* 324 (M^+), 309, 77. Anal. Calcd for $C_{23}H_{20}N_2$: C, 85.19; H, 6.17; N, 8.64. Found: C, 85.08; H, 6.15; N, 8.70.

4-(Ethylphenylamino)-3-methyl-2-*p*-tolylquinoline (4k): IR (Nujol) 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3 H), 2.25 (s, 3 H), 2.43 (s, 3 H), 3.85 (m, 2 H), 6.50–8.15 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 161.63, 148.19, 147.76, 146.36, 137.54, 137.08, 129.34–123.16, 116.54, 111.36, 45.29, 20.46, 15.67, 12.53; MS *m/e* 352 (M^+), 337, 323, 77. Anal. Calcd for $C_{25}H_{24}N_2$: C, 85.22; H, 6.81; N, 7.95. Found: C, 85.05; H, 6.70; N, 7.83.

Spectral data for compounds **4g**, **4i**, and **2k** are included as supplementary material.

Registry No. **1** (R^1 = Ph, R^2 = Me, R^3 = *p*-MeC_6H_4), 71115-24-7; **1** (R^1, R^3 = Ph, R^2 = Me), 71115-28-1; **1** (R^1, R^3 = *p*-MeC_6H_4, R^2 = Me), 73305-96-1; **1** (R^1 = *p*-MeC_6H_4, R^2 = Me, R^3 = Ph), 71115-30-5; **1** (R^1 = Ph, R^2 = Me, R^3 = c-C_6H_{11}), 72923-07-0; **1** (R^1 = *p*-MeC_6H_4, R^2 = Et, R^3 = Ph), 119595-59-4; **2** (R^2 = Me, R^3 = *p*-MeC_6H_4, E = H, X = O), 4842-46-0; **2** (R^2 = Me, R^3 = *p*-MeC_6H_4, E = Et, X = O), 119595-60-7; **2** (R^2 = Me, R^3 = Ph, E = H, X = O), 4842-43-7; **2** (R^2 = Me, R^3 = c-C_6H_{11}, E = H, X = O), 113598-54-2; **2** (R^2 = Et, R^3 = Ph, E = H, X = O), 4842-44-8; **2** (R^2 = Me, R^3 = Ph, E = Me, X = O), 13031-08-8; **2** (R^2 = Me, R^3 = *p*-MeC_6H_4, E = Me, X = O), 113598-55-3; **3** (R^1 = Ph), 62-53-3; **3** (R^2 = *p*-MeC_6H_4), 106-49-0; **4a**, 119595-61-8; **4b**, 119595-62-9; **4c**, 119595-63-0; **4d**, 119595-64-1; **4e**, 119595-65-2; **4f**, 119595-66-3; **4g**, 119595-67-4; **4h**, 119595-68-5; **4i**, 119595-69-6; **4j**, 119595-70-9; **4k**, 119595-71-0.

Supplementary Material Available: Spectral data for compounds **2f,k** and **4c,d,f,g,i** (2 pages). Ordering information is given on any current masthead page.

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