A Convenient and Highly Regioselective One-Pot Synthesis of Quinolines by Addition of a Vilsmeier-Type Reagent to *N*-Arylimines

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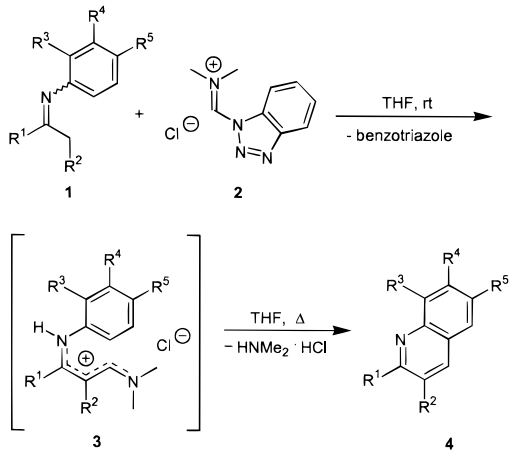
Quinolines and their derivatives occur in numerous natural products.[1] Many quinolines display interesting physiological activities and have found attractive applications as pharmaceuticals (e.g., antimalarial drugs such as quinine or chloroquine) and agrochemicals as well as being general synthetic building blocks.[1b] Many syntheses have been developed for quinolines,[2] but due to their great importance, the development of novel synthetic methods remains an active research area.[3]

The known syntheses of quinolines from enamines and Vilsmeier reagents either require a large excess of $POCl_3$ (or $POCl_3$ as a solvent) or are of limited scope (e.g., reactions of tertiary enamines and *N*-aryl Vilsmeier reagents are restricted to the synthesis of *N*-alkyl quinolinium salts).[4] However, Risch et al. recently showed that imines can be aminoalkylated (via the corresponding tautomeric secondary enamines) with high regioselectivity and in good yield with iminium salts such as $[RCH{=}NMe_2]^+Cl^-$ (R = H, Ph).[5] This prompted us to examine the analogous reactions of imines **1** with Vilsmeier-type reagents[6] in an attempt to overcome the limitations of the corresponding reactions of enamines. We chose to investigate the benzotriazole iminium salt **2**, which is readily available by refluxing a THF solution of equimolar amounts of *N*-trimethylsilylbenzotriazole, DMF, and $SOCl_2$.[7] Salt **2** acts as a stable synthetic chloroiminium salt $[ClCH{=}NMe_2]^+X^-$ equivalent (i.e., the benzotriazole moiety is easily substituted by nucleophiles), and **2** can be handled without special precautions. In addition, the use of **2** allows mild reaction conditions and a clean workup.

Scheme 1



Experiments monitored by NMR spectroscopy indicated that *N*-arylimines **1** react with iminium salt **2** in the expected manner providing the corresponding enaminoimine hydrochlorides (vinamidium salts) **3** at room temperature in virtually quantitative yields. Although preliminary attempts to isolate **3** as hydroperchlorates (by addition of aqueous $NaClO_4$ solution) or as enaminoimines (by addition of dilute NaOH) failed,[8] the enaminoimine hydrochlorides **3** can be transformed in high yields in situ into the corresponding quinolines **4** via a tandem cyclization−elimination process on refluxing in THF (Scheme 1).

The advantages of this approach include high yields, ready availability of the starting imines **1** and iminium salt **2**, and a procedure that is straightforward and of broad scope (Table 1), although attempts to transform *N*-phenylimines derived from methyl ketones into the corresponding quinolines have failed so far. Our method provides a highly efficient pathway for the synthesis of quinolines from ketones under mild conditions. It should also be suitable for sensitive substrates and be an advantageous alternative to the frequently used traditional quinoline syntheses, which require initial Vilsmeier transformation of the ketone into the corresponding β-chlorovinylaldehyde and high reaction temperatures (for recent examples, see lit.[3i,l]). In addition, our methodology allows the highly regioselective transformation of unsymmetrical imines into the corresponding quinolines. As in the analogous reactions of imines with preformed Mannich reagents,[5] the iminium salt **2** is attacked by the sterically less hindered α-position of the imine with high regioselectivity. Good regioselectivities are achieved even when the two α-C atoms of the imine are only marginally different (Table 1, entries 5, 10, and 11). This regioselectivity is only reversed when electron-

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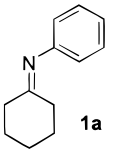
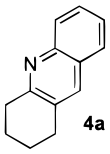
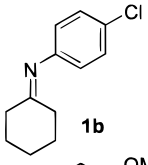
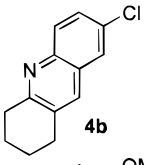
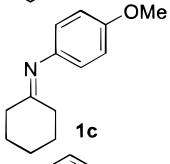
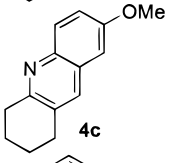
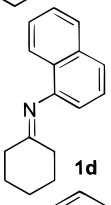
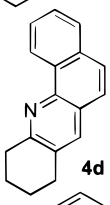
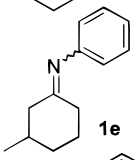
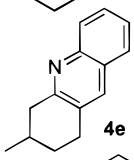
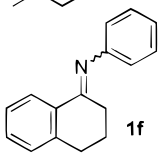
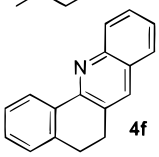
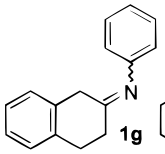
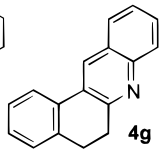
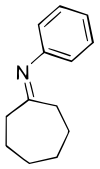
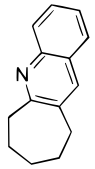
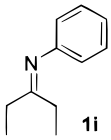
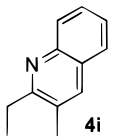
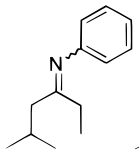
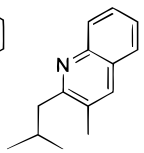
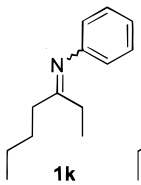
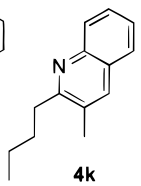
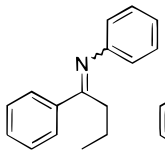
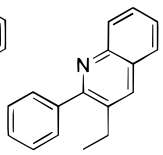
Table 1. Synthesis of Quinolines 4 by Addition of Benzotriazole Iminium Salt 2 to Imines 1

entry	imine **1**	quinoline **4**	yield (%)[a]
1	 **1a**	 **4a**	89
2	 **1b**	 **4b**	78
3	 **1c**	 **4c**	71
4	 **1d**	 **4d**	72
5	 **1e**	 **4e**	87
6	 **1f**	 **4f**	81
7	 **1g**	 **4g**	76
8	 **1h**	 **4h**	82
9	 **1i**	 **4i**	76
10	 **1j**	 **4j**	82
11	 **1k**	 **4k**	78[b]
12	 **1l**	 **4l**	65

[a] Isolated yields after column chromatography. The ratios of the regioisomers were determined by ^{1}H and ^{13}C NMR spectroscopy. Unless specified otherwise, the regioselectivity is ≥95%. [b] Only the major regioisomer, 2-butyl-3-methylquinoline (**4k**), is depicted. According to the ^{1}H NMR spectrum, the regioselectivity of the reaction (determined by comparing the integrals of the $ArCH_3$ singlet at 2.42 ppm and the $ArCH_2$ triplet at 2.71 ppm) is 85% (2-butyl-3-methylquinoline (**4k**)/2-ethyl-3-propylquinoline (**4k′**) = 85:15).

ics dictate that the sterically more hindered tautomeric enamine is virtually the exclusive intermediate (Table 1, entry 7).

In conclusion, we have developed a mild, straightforward and highly regioselective synthesis of quinolines. Its broad scope as well as the easy access to the starting materials should make this methodology widely applicable in organic synthesis.

Experimental Section

General Methods. Melting points were determined on a Koefler hot-stage apparatus and are not corrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ referenced to TMS, for the proton spectra, and to the solvent for the carbon spectra. THF was distilled under nitrogen from Na benzophenone prior to use. The *N*-arylimines **1**[9] and the benzotriazole iminium salt **2**[7] were prepared according to literature procedures.

General Procedure for the Synthesis of Quinolines 4. The reactions were conducted in a water-free apparatus under argon. To a solution of the imine **1** (4 mmol) in THF (20 mL) was added the iminium salt **2**[7] (5 mmol) in one portion. The mixture was stirred for 2−4 h at ambient temperature and subsequently refluxed overnight. Dilute NaOH (2 N, 40 mL) was added, and the resulting mixture was stirred vigorously for ca. 5 min. The organic phase was decanted off, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was removed in vacuo. Flash column chromatography of the crude product on silica gel (200−425 mesh; hexane/EtOAc = 3:1) provided the quinolines **4**.

a. 1,2,3,4-Tetrahydroacridine (4a): mp 52−53 °C (lit.[10] mp 53−54 °C); ^{1}H NMR δ 7.97 (d, J = 8.5 Hz, 1H), 7.71 (s, 1H),

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7.65−7.55 (m, 2H), 7.42−7.37 (m, 1H), 3.13−3.08 (m, 2H), 2.93−2.89 (m, 2H), 1.98−1.83 (m, 4H); ^{13}C NMR δ 159.1, 146.5, 134.7, 130.8, 128.3, 128.2, 127.1, 126.7, 125.3, 33.5, 29.1, 23.1, 22.8.

b. 7-Chloro-1,2,3,4-tetrahydoacridine (4b): mp 94−95 °C (lit.[11] mp 95−96 °C); ^{1}H NMR δ 7.88 (d, J = 9.1 Hz, 1H), 7.66 (s, 1H), 7.63 (s, 1H), 7.52 (d, J = 8.9 Hz, 1H), 3.09 (t, J = 6.1 Hz, 2H), 2.94 (t, J = 5.8 Hz, 2H), 1.98−1.96 (m, 2H), 1.89−1.87 (m, 2H); ^{13}C NMR δ 159.7, 144.9, 133.8, 132.0, 131.0, 129.9, 129.3, 127.7, 125.4, 33.5, 29.2, 23.0, 22.7.

c. 7-Methoxy-1,2,3,4-tetrahydroacridine (4c): mp 90−91 °C (lit.[11] mp 90−91 °C); ^{1}H NMR δ 7.86 (d, J = 9.1 Hz, 1H), 7.67 (s, 1H), 7.26−7.24 (m, 1H), 6.94 (d, J = 2.1 Hz, 1H), 3.89 (s, 3H), 3.08 (t, J = 6.3 Hz, 2H), 2.93 (t, J = 6.3 Hz, 2H), 1.97−1.85 (m, 4H); ^{13}C NMR δ 157.0, 156.5, 142.7, 133.8, 131.1, 129.7, 127.9, 121.1, 104.4, 55.4, 33.2, 29.2, 23.3, 22.9.

d. 8,9,10,11-Tetrahydrobenzo[*c*]acridine (4d): mp 94−95 °C (lit.[12] mp 95−96.5 °C); ^{1}H NMR δ 9.26 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.72−7.51 (m, 5H), 3.20 (t, J = 6.3 Hz, 2H), 2.94 (t, J = 6.3 Hz, 2H), 2.01−1.95 (m, 2H), 1.90−1.86 (m, 2H,); ^{13}C NMR δ 157.6, 144.4, 135.1, 133.3, 131.3, 131.2, 127.6, 127.5, 126.6, 126.5, 125.0, 124.8, 124.2, 33.6, 29.1, 23.4, 23.0.

e. 3-Methyl-1,2,3,4-tetrahydroacridine (4e): mp 71−72 °C (lit.[13] mp 72−73 °C); ^{1}H NMR δ 7.97 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.62−7.57 (m, 1H,), 7.44−7.39 (m, 1H), 3.26−3.19 (m, 1H), 3.05−2.88 (m, 2H), 2.74−2.64 (m, 1H), 2.07−1.94 (m, 2H), 1.54−1.41 (m, 1H), 1.14 (d, J = 6.5 Hz, 3H); ^{13}C NMR δ 159.1, 146.6, 134.6, 130.2, 128.4, 128.3, 127.1, 126.8, 125.4, 42.1, 31.0, 29.5, 28.5, 21.8.

f. 5,6-Dihydrobenzo[*c*]acridine (4f): mp 62−63 °C (lit.[14] mp 64 °C); ^{1}H NMR δ 8.57 (d, J = 7.4 Hz, 1H), 8.12 (d, J = 8.5, 1H), 7.88 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.66−7.61 (m, 1H), 7.47−7.33 (m, 3H), 7.27−7.23 (m, 1H), 3.12−3.07 (m, 2H), 3.00−2.96 (m, 2H); ^{13}C NMR δ 153.4, 147.6, 139.4, 134.7, 133.6, 130.5, 129.6, 129.4, 128.6, 127.9, 127.8, 127.3, 126.9, 126.1, 126.0, 28.8, 28.4.

g. 5,6-Dihydrobenzo[*a*]acridine (4g): mp 84−85 °C (lit.[15] mp 85 °C); ^{1}H NMR δ 8.27 (s, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.79−7.73 (m, 2H), 7.61 (t, J = 7.1 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H), 7.31−7.23 (m, 3H), 3.23 (t, J = 7.2 Hz, 2H), 3.00 (t, J = 7.4 Hz, 2H); ^{13}C NMR δ 159.1, 146.8, 137.3, 132.7, 129.3, 129.0, 128.3, 128.2, 127.9, 127.8, 127.7, 127.1, 125.9, 124.1, 32.7, 28.5.

h. 7,8,9,10-Tetrahydro-6*H*-cyclohepta[*b*]quinoline (4h): mp 91−92.5 °C (lit.[10] mp 93 °C); ^{1}H NMR δ 8.00 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.60 (t, J = 7.1 Hz, 1H), 7.43 (t, J = 7.1 Hz, 1H), 3.22−3.18 (m, 2H), 2.93−2.90 (m, 2H), 1.89−1.73 (m, 6H); ^{13}C NMR δ 164.6, 146.2, 136.4, 134.5, 128.4, 128.3, 127.3, 126.7, 125.6, 40.0, 35.4, 32.2, 28.8, 27.0.

i. 2-Ethyl-3-methylquinoline (4i): mp 56−57.5 °C; ^{1}H NMR δ 8.02 (d, J = 8.3 Hz, 1H), 7.76 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.59 (t, J = 8.2 Hz, 1H), 7.41 (t, J = 7.1 Hz, 1H), 2.97 (q, J = 7.6 Hz, 2H), 2.43 (s, 3H), 1.36 (t, J = 7.6 Hz, 3H);^{13}C NMR δ 163.1, 146.6, 135.5, 129.3, 128.5, 128.1, 127.2, 126.6, 125.5, 29.4, 19.0, 12.7. The ^{1}H and ^{13}C NMR spectra are in accordance with literature spectra.[16]

j. 2-Isobutyl-3-methylquinoline (4j): ^{1}H NMR δ 8.03 (d, J = 8.3 Hz, 1H), 7.77 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 8.3 Hz, 1H), 7.42−7.37 (m, 1H), 2.84 (d, J = 7.1 Hz, 2H), 2.42 (s, 3H), 2.32−2.23 (m, 1H), 0.99 (d, J = 6.6 Hz, 6H); ^{13}C NMR δ 161.6, 146.5, 135.5, 129.8, 128.5, 128.1, 127.1, 126.5, 125.4, 44.7, 28.5, 22.5, 19.5. Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.62; N, 7.03. Found: C, 84.62; H, 8.94; N, 7.36.

k. 2-Butyl-3-methylquinoline (4k) and 2-Ethyl-3-propylquinoline (4k′): ^{1}H NMR of **4k** (major regioisomer) δ 8.02 (d, J = 8.5 Hz, 1H), 7.74 (s, 1H), 7.65−7.55 (m, 2H), 7.42−7.37 (m, 1H), 2.93 (t, J = 8.0 Hz, 2H), 2.42 (s, 3H), 1.80−1.67 (m, 2H), 1.54−1.42 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H); ^{1}H NMR of **4k′** (minor regioisomer) δ 7.77 (s, 1H), 2.99 (q, J = 7.5 Hz, 2H), 2.71 (t, J = 7.7 Hz, 2H); ^{13}C NMR of **4k** (major regioisomer) δ 162.3, 146.5, 135.5, 129.3, 128.4, 128.1, 127.1, 126.5, 125.4, 36.1, 30.9, 22.9, 19.1, 13.9; ^{13}C NMR of **4k′** (minor regioisomer) δ 134.6, 128.1, 126.7, 34.2, 28.7, 23.3, 13.4. Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.62; N, 7.03. Found: C, 84.20; H, 8.74; N, 7.34.

l. 3-Ethyl-2-phenylquinoline (4l): mp 62 °C (lit.[17] mp 63 °C); ^{1}H NMR δ 8.14 (d, J = 8.3 Hz, 1H), 8.02 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 8.2 Hz, 1H), 7.55−7.39 (m, 6H), 2.78 (q, J = 7.5 Hz, 2H), 1.17 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 160.5, 140.9, 135.2, 134.8, 129.2, 128.7, 128.7, 128.6, 128.2, 128.0, 127.6, 126.8, 126.3, 25.9, 14.6.

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