Synthesis of Substituted 4-(Arylamino)quinolines from Irradiation of 3-Amino-3-aryl-2-alkene Imines in the Presence of Tetrafluoroboric Acid

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Irradiation of 3-amino-3-aryl-alkene imines **1** in the presence of one equivalent of tetrafluoroboric acid leads to the formation of substituted 4-(arylamino)quinolines **2**. The best yields (good to nearly quantitative) of compounds **2** are obtained when methanol is used as solvent.

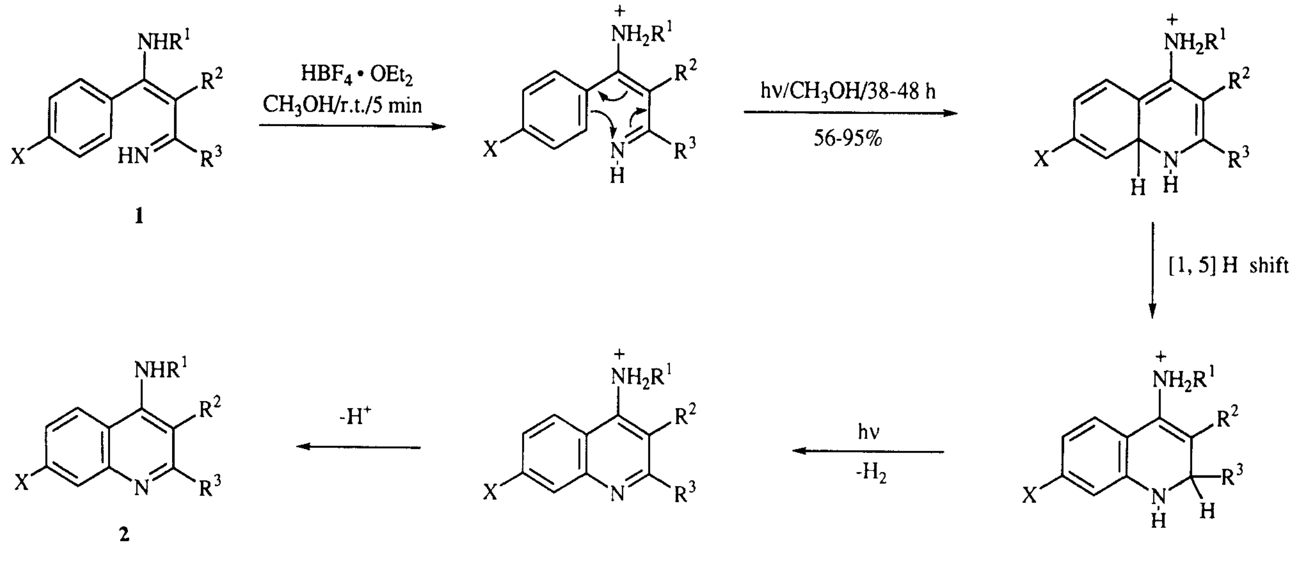
A great number of methods for the synthesis of quinoline derivatives have been developed[1-4] because of the abundant occurrence of the quinoline skeleton in many natural products, especially alkaloids.[4-6] In the last years, due to the discovery of antitumor antibiotics, the interest in polysubstituted quinoline rings has been reactivated.[7,8] However, 4-amino- and, particularly, 4-(arylamino)quinolines are not easily obtainable.[9-16] In the course of our research we have developed a new synthetic procedure to obtain 4-(arylamino)quinolines.

We have recently described the irradiation of 3-amino-2-alkene imines **1** with a medium-pressure mercury lamp through Pyrex glass ($\lambda > 300$ nm) to give substituted quinolines.[17] The photoreaction is considered to proceed via a six π electron electrocyclic process. This prompted us to study the photochemistry of the protonated 3-amino-2-alkene imines. To notice the effect of this protonation, first we recorded the ultraviolet spectra of compounds **1** in the presence of an excess of tetrafluoroboric acid observing the displacement of the band at 340–360 nm to the visible region accompanied by an absorption increase. This kind of displacement in acid media has been found for unsaturated imines but with shorter absolute values (ca. 20 nm for 2-alkene imines).[18] This fact can be associated with a larger conjugation in the molecule and, therefore, a different photochemical behavior can be expected.

The direct irradiation of a 10^{-2} M solution of **1** in the presence of one equivalent of tetrafluoroboric acid using a medium-pressure mercury lamp without filter (through quartz) gives substituted 4-(arylamino)quinolines **2** (Scheme) in good to nearly quantitative yields.

Cyclization occurs at the *ortho* position of the aryl group attached at 3, in contrast with that involving R^1 already reported.[17] A six π electron electrocyclic process followed by hydrogen migration to give the corresponding amine is presumed. As secondary amines lose molecular hydrogen to yield imines under irradiation,[19-22] particularly when the aromatization of nitrogen heterocycles is involved,[23] the quinoline precursor is easily aromatized under the reaction conditions to form **2**.

In this reaction, solvent plays an important role. Thus, the methanolic solution gives the highest yields while irradiation in tetrahydrofuran or diethyl ether leads to poor conversions of **1** in some cases, and in toluene the previously described quinolines[17] are obtained. These facts are in agreement with the different stabilization of protonated alkene imines based on the solvent used. Table 1 shows the synthesized substituted 4-(arylamino)quinolines **2** in methanol. When the irradiation is performed through Pyrex glass ($\lambda > 300$ nm) the same results are observed (at the expense of increase of reaction time). This kind of six π electron photoannulation in acid medium has been previously described to obtain quinolines



Scheme

Table 1. 4-(Arylamino)quinolines **2** Obtained from Azadienes **1** in MeOH

	Azadiene 1[a]				Time (h)[b]	Product[c]	Yield (%)[d]	mp(°C)
	R^1	X	R^2	R^3				
1a	4-MeC$_6$H$_4$	H	Me	Ph	40	**2a**	95	170–172[e]
1b	4-MeC$_6$H$_4$	H	Me	4-MeC$_6$H$_4$	40	**2b**	85	172–174[f]
1c	Ph	H	Me	4-ClC$_6$H$_4$	40	**2c**	80	183–185
1d	2,6-Me$_2$C$_6$H$_3$	H	Me	Ph	40	**2d**	63	224–225
1e	Ph	Cl	Me	Ph	40	**2e**	81	176–178
1f	2-MeC$_6$H$_4$	H	H	4-MeC$_6$H$_4$	38	**2f**	80	170–171
1g	4-MeC$_6$H$_4$	H	H	c-C$_6$H$_{11}$	48	**2g**	56	171–173
1h	4-MeC$_6$H$_4$	H	Et	c-C$_6$H$_{11}$	38	**2h**	75	127–129
1i	4-MeC$_6$H$_4$	H	CH$_2$=CHCH$_2$	Ph	38	**2i**	70	oil
1j	4-MeC$_6$H$_4$	H	HC≡CCH$_2$	Ph	45	**2j**	75	159–161
1k	4-MeC$_6$H$_4$	H	PhCH$_2$	Ph	40	**2k**	80	oil

[a] **1a–1g** were synthesized according to reference 28, and **1h–1k** according to reference 29.
[b] Irradiation time through quartz, for 1 mmol of azadiene **1** with a 125 W mercury lamp.
[c] Satisfactory microanalyses obtained: C ± 0.29, H ± 0.18, N ± 0.23.
[d] Yield of isolated products, relative to starting material **1**, not optimized. The products were purified by column chromatography (silica gel, hexane/Et$_2$O, 3 : 1) and recrystallized (hexane/THF, 5 : 1)
[e] Lit.[16] mp 170–172 °C
[f] Lit.[16] mp 172–174 °C

Table 2. MS and NMR Spectral Data of Compounds **2**

2	MS (70 eV) *m/z* (%)	^{1}H NMR (CDCl$_3$/TMS) δ, J (Hz)	^{13}C NMR (CDCl$_3$/TMS) δ
a	324 (M$^+$, 40), 307 (4), 154 (10), 105 (7), 91 (4), 77 (7), 40 (100)	2.2 (s, 3 H, CH$_3$), 2.3 (s, 3 H, CH$_3$), 6.2 (s, 1 H, NH), 6.7–7.8 (m, 12 H$_{\text{arom}}$), 8.1 (d, 1 H$_{\text{arom}}$, J = 8.0)	161.6, 147.3, 144.5, 141.8, 141.2, 130.1, 129.7, 129.7, 128.9, 128.7, 128.1, 128.0, 125.6, 123.1, 122.7, 121.0, 116.7, 20.5, 16.5
b	338 (M$^+$, 52), 324 (20), 307 (7), 154 (12), 105 (7), 91 (5), 77 (11), 40 (100)	2.2 (s, 3 H, CH$_3$), 2.3 (s, 3 H, CH$_3$), 2.4 (s, 3 H, CH$_3$), 6.2 (s, 1 H, NH), 6.7–7.8 (m, 11 H$_{\text{arom}}$), 8.1 (d, 1 H$_{\text{arom}}$, J = 8.4)	161.6, 147.3, 144.5, 141.9, 138.3, 137.8, 130.1, 129.7, 129.4, 128.9, 128.8, 128.6, 125.5, 123.0, 122.7, 121.1, 116.7, 21.2, 20.5, 16.6
c	346 [(M + 2)$^+$, 8], 344 (M$^+$, 26), 343 (100), 309 (40), 231 (5), 153 (15), 115 (4), 77 (10)	2.3 (s, 3 H, CH$_3$), 6.1 (s, 1 H, NH), 6.7–7.9, m, 12 H$_{\text{arom}}$), 8.1 (d, 1 H$_{\text{arom}}$, J = 8.6)	160.4, 147.3, 144.3, 144.2, 139.5, 134.2, 130.4, 129.7, 129.2, 129.0, 128.4, 126.0, 123.4, 122.7, 121.5, 120.6, 116.3, 16.6
d	338 (M$^+$, 75), 323 (100), 309 (20), 231 (13), 161 (25), 103 (25), 77 (77)	2.0 (s, 3 H, CH$_3$), 2.2 (s, 6 H, CH$_3$), 6.0 (s, 1 H, NH), 7.1–7.7 (m, 11 H$_{\text{arom}}$), 8.1 (d, 1 H$_{\text{arom}}$, J = 8.1)	161.3, 147.2, 146.8, 141.6, 139.9, 131.1, 129.9, 129.0, 128.7, 128.4, 128.1, 127.9, 125.1, 124.8, 121.1, 120.0, 113.3, 19.1, 16.5
e	346 [(M + 2)$^+$, 4], 344 (M$^+$, 13), 309 (2), 171 (5), 153 (6), 105 (6), 77 (10), 40 (100)	2.2 (s, 3 H, CH$_3$), 6.2 (s, 1 H, NH), 6.7–7.8 (m, 12 H$_{\text{arom}}$), 8.1 (s, 1 H$_{\text{arom}}$)	162.7, 147.8, 144.3, 144.0, 140.7, 134.5, 129.8, 129.3, 128.9, 128.6, 128.3, 128.2, 126.5, 124.5, 121.6, 120.9, 116.4, 16.4
f	324 (M$^+$, 93), 323 (100), 309 (23), 233 (16), 154 (8), 77 (5)	2.2 (s, 3 H, CH$_3$), 2.4 (s, 3 H, CH$_3$), 6.6 (s, 1 H, NH), 6.9–7.9 (m, 12 H$_{\text{arom}}$), 8.1 (d, 1 H$_{\text{arom}}$, J = 8.1)	158.1, 149.0, 148.4, 138.7, 137.8, 137.5, 133.2, 131.2, 130.0, 129.3, 129.1, 127.2, 127.0, 125.8, 125.1, 124.6, 119.4, 118.2, 99.5, 21.1, 17.7
g	316 (M$^+$, 76), 309 (17), 261 (100), 248 (20), 116 (3), 91 (3), 77 (3)	1.1–2.0 (m, 10 H, CH$_2$), 2.2 (s, 3 H, CH$_3$), 2.7 (m, 1 H, CH), 6.8 (s, 1 H, NH), 6.9–8.1 (m, 9 H$_{\text{arom}}$)	167.5, 148.6, 147.8, 137.4, 133.8, 130.1, 129.4, 129.1, 124.2, 122.4, 119.5, 118.6, 99.8, 47.8, 32.7, 26.4, 25.9, 20.9
h	344 (M$^+$, 76), 329 (17), 315 (12), 289 (100), 185 (6), 91 (80), 77 (7)	1.2 (t, 3 H, CH$_3$), 1.4–2.0 (m, 10 H, CH$_2$), 2.3 (s, 3 H, CH$_3$), 2.8 (q, 2 H, CH$_2$), 3.1 (m, 1 H, CH), 5.7 (s, 1 H, NH), 6.5–7.8 (m, 7 H$_{\text{arom}}$), 8.1 (d, 1 H$_{\text{arom}}$, J = 8.2)	166.2, 147.6, 143.5, 143.0, 129.7, 129.7, 129.2, 128.5, 128.2, 124.9, 123.8, 123.5, 115.8, 42.7, 32.6, 26.8, 26.8, 26.0, 20.5, 15.0
i	350 (M$^+$, 100), 321 (22), 301 (11), 259 (18) 159 (24), 91 (16), 77 (22)	2.3 (s, 3 H, CH$_3$), 3.5 (d, 2 H, CH$_2$), 5.0–5.3 (dd, 2 H, =CH$_2$), 6.1 (m, 1 H, =CH), 6.2 (s, 1 H, NH), 6.6–7.8 (m, 12 H$_{\text{arom}}$), 8.1 (d, 1 H$_{\text{arom}}$, J = 8.0)	166.5, 147.9, 146.1, 142.3, 141.0, 135.8, 130.4, 129.8, 129.7, 129.1, 128.6, 128.2, 128.2, 125.3, 124.6, 122.6, 121.4, 116.9, 116.6, 35.5, 20.6
j	348 (M$^+$, 100), 333 (13), 243 (10), 217 (8), 167 (23), 153 (7), 105 (6), 77 (9)	2.2, s, 1 H, ≡CH), 2.3 (s, 3 H, CH$_3$), 3.6 (d, 2 H, CH$_2$), 6.5 (s, 1 H, NH), 6.6–7.8 (m, 12 H$_{\text{arom}}$), 8.1 (d, 1 H$_{\text{arom}}$, J = 8.6)	160.2, 148.1, 146.0, 142.0, 140.5, 130.7, 130.6, 129.9, 129.7, 129.3, 128.9, 128.4, 125.4, 124.6, 122.7, 119.7, 117.0, 80.8, 71.1, 20.6, 19.6
k	400 (M$^+$, 100), 309 (19), 294 (4), 191 (6), 153 (35), 91 (11), 77 (12)	2.3 (s, 3 H, CH$_3$), 4.1 (s, 2 H, CH$_2$), 5.8 (s, 1 H, NH), 6.5–7.8 (m, 17 H$_{\text{arom}}$), 8.1 (d, 1 H$_{\text{arom}}$, J = 8.2)	161.7, 147.9, 146.1, 141.9, 140.8, 138.9, 130.6, 130.4, 129.6, 129.2, 128.9, 128.6, 128.2, 128.2, 127.7, 126.5, 125.4, 124.4, 122.9, 116.9, 114.9, 34.8, 20.5

from benzalcycloalkanone oximes[24] and isoquinolines.[25,26]

4-(Arylamino)quinolines **2** were analyzed by ^{1}H- and ^{13}C-NMR spectroscopy and mass spectrometry (Table 2). In each case, only the formation of one single regioisomer was observed. It is important to point out that our method provides completely different substituted quinolines by varying only the medium of acidity. Also, as distinguished from the photochemical behavior, compounds **1** suffer cyclocondensation under thermic conditions (100 °C) in the presence of Lewis acid between C_2 and the *ortho* position of R^1 to afford quinolines instead of aminoquinolines **2**.[27]

In summary, we have described a new, easy, versatile and regioselective synthesis of a large number of 4-(arylamino)quinolines **2** substituted by methyl, ethyl, allyl, propargyl, benzyl, aryl and cyclohexyl groups. This versatility is enhanced when one considers that these compounds are not easily obtainable, for example, only **2a** and **2b** have been recently reported.[16]

^{1}H and ^{13}C spectra were recorded on a Bruker AC-300 spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were run on a HP 5987 A apparatus. Elemental analyses were performed on a Perkin-Elmer 240 Elemental Analyzer. GC analyses were carried out on a Varian Vista 6000 gas chromatograph using a OV-101 column. Reagents and solvents were of commercial grades (Merck and Aldrich). Compounds **1** were prepared in accordance with the described methods in references 28 and 29.

Irradiation of 3-Amino-2-alkene Imines; General Procedure:

A solution of 3-amino-2-alkene imine **1** (1 mmol) and HBF_4 (1 mmol, 0.14 mL of a 54% ethereal solution) in anhydr. MeOH (50 mL) was irradiated, at r.t. under Ar atmosphere, using a medium-pressure mercury lamp (125 W) until the complete consumption of starting product (monitored by ^{1}H NMR, see Table 1). The solution was evaporated under reduced pressure and the residue was treated with $NaHCO_3$ (25 mL, 10% aq solution) and extracted with Et_2O (3 x 25 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The resulting aminoquinoline **2** was purified by column chromatography (silica gel, hexane/Et_2O, 3:1) and recrystallized (hexane/THF, 5:1).

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