Preparation of 3-Haloquinolines from 3-Amino-2-halo-2-alkenimines

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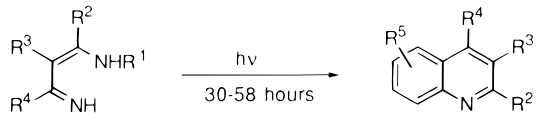
The quinoline ring system occurs in natural products, especially alkaloids.[1] The quinoline skeleton is often used for the design of many synthetic compounds with pharmacological properties such as nitroxaline, chloroquine, which is one example of an antimalarial compound, the tetrahydroquinoline derivative oxamniquine, which is used to eradicate blood flukes, a major cause of disease in tropical regions, and quinolone derivatives, which show a high antibacterial activity.[2] In particular, halogen-containing quinolines are of significant interest because halogen atoms sometimes play a pivotal role in bioactive compounds and they provide a further avenue for structural elaboration.[3]

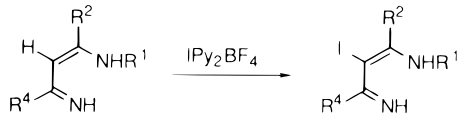
We have previously reported the synthesis of substituted quinolines by irradiation of 3-amino-2-alkenimines (Scheme 1).[4] Considering the significance of the haloquinoline substrates, we undertook a study of the photochemical behavior of halo-functionalized alkenimines. Taking into account our experience in iodination reactions with bis(pyridine)iodonium(I) tetrafluoroborate[5] and the simplicity of functionalization of 3-amino-2-alkenimines at the 2-position,[6,7] we carried out the preparation of 3-amino-2-iodo-2-alkenimines (Scheme 2).[8] We report here the results obtained for the irradiation of 3-amino-2-halo-2-alkenimines.

Irradiation of 3-Amino-2-iodo-2-alkenimines. The ultraviolet absorption spectrum of 3-(*p*-tolylamino)-2-iodo-1,3-diphenyl-2-alkenimine **1a** in methanol shows bands at 212, 222, and 366 nm ($\epsilon \approx$ 17 500, 14 800, and 3100, respectively). These data are related to that described for the photocyclization of alkenimines.[4] Therefore, we carried out the irradiation of a 10^{-2} M solution

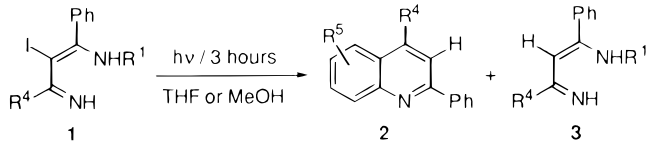
Scheme 1



Scheme 2



Scheme 3



a $R^1 = p\text{-MeC}_6H_4$, R^4 = Ph, R^5 = 6-Me

of the iodofunctionalized alkenimine **1a** in methanol using a medium-pressure mercury lamp through quartz. The complete consumption of starting product (3 h) was monitored by ^{1}H NMR spectroscopy. This reaction gives the quinoline **2a** together with the alkenimine resulting from the iodine atom photocleavage **3a** (Scheme 3), instead of the expected iodoquinoline, as it is elucidated from the spectroscopic data (^{1}H and ^{13}C NMR) and mass spectrometry. We have verified that direct irradiation of alkenimine **3** (prepared according to ref 9) did not suffer any appreciable change for 3 h. Therefore, the quinoline **2a** should be produced by iodine loss after cyclization. In fact, the irradiation of aryl halides is a well-documented process that usually results in an initial homolysis of the C−halogen bond,[10] and the photodebromination of quinolines and isoquinolines has already been described.[11]

The photodebromination of quinolines should occur through a mechanism involving an electron transfer from a nucleophile followed by hydrogen transfer from the solvent.[11] The electron transfer process is favored upon increasing the solvent polarity.[12] Thus, the irradiation was assayed in a less polar solvent, benzene. In this case, the formation of iodoquinoline **4a** as well as the quinoline **2a** and traces of **3a** was observed. The most advantageous rate, in relation to **4a**, was found at 8 h of reaction time (Scheme 4 and Table 1). The increase in the reaction time can be explained by the energy loss because of benzene absorption. Similar results were obtained with several iodoalkenimines. The larger photodeiodination after 24 h of irradiation should be noted. Quinolines **2** and **4** were isolated and purified by column chromatography (silica gel, hexane−ether, 3:1) and analyzed by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. All reported quinolines show spectral data

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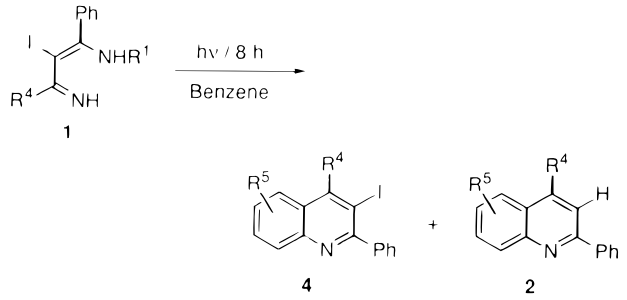
Scheme 4



a R^1 = *p*-MeC_6H_4, R^4 = Ph, R^5 = 6-Me
b R^1 = *p*-MeC_6H_4, R^4 = *p*-MeC_6H_4, R^5 = 6-Me
c R^1 = Ph, R^4 = Ph, R^5 = H
d R^1 = *o*-MeC_6H_4, R^4 = *p*-MeC_6H_4, R^5 = 8-Me
e R^1 = Ph, R^4 = *p*-MeC_6H_4, R^5 = H

Table 1. Irradiation of 3-Amino-2-iodo-2-alkenimines 1[a]

1[b]	R^1	R^4	R^5	**4**[c] (%)	**2**[c] (%)	**4/2** ratio[d]
a	*p*-MeC_6H_4	Ph	6-Me	32	23	1/0.8
b	*p*-MeC_6H_4	*p*-MeC_6H_4	6-Me	28	23	1/0.9
c	Ph	Ph	H	31	18	1/0.7
d	*o*-MeC_6H_4	*p*-MeC_6H_4	8-Me	26	19	1/0.8
e	Ph	*p*-MeC_6H_4	H	36	22	1/0.7
e	Ph	*p*-MeC_6H_4	H	5	79	1/14[e]

[a] Irradiation in benzene, through quartz, during 8 h for 1 mmol of alkenimine **1** with a 125 W mercury lamp (starting **1** was completely consumed). [b] Prepared according to ref 8. [c] Yields of isolated quinolines, relative to starting **1**, purified by column chromatography (silica, hexane−ether 3:1). [d] Quinoline **4**/**2** ratios, determined by ^{1}H NMR spectra of the crude reaction. [e] After 24 h of irradiation.

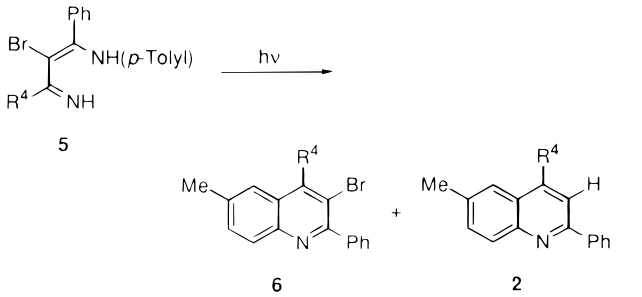
and elemental analyses in accordance with the given structures.

Irradiation of 3-Amino-2-bromo-2-alkenimines. To compare the photochemical behavior of the iodinated compounds with their analogous bromine and chlorine, we have synthesized the compounds from halogenation of 3-amino-2-alkenimines with both *N*-bromosuccinimide and *N*-chlorosuccinimide, respectively.[6]

The ultraviolet absorption spectrum of 3-(*p*-tolylamino)-2-bromo-1,3-diphenyl-2-alkenimine **5a** in methanol shows bands at 210, 258, and 348 nm ($\epsilon \approx$ 28 200, 16 700, and 4400, respectively). The previous approach was extended to the irradiation of bromoalkenimines **5**. Under these conditions, compounds **5** led to the formation of bromoquinolines **6** and debrominated quinolines **2** (Scheme 5). The obtained rates depend on the solvent polarity and reaction time. Bromoquinolines are obtained when tetrahydrofuran is used as solvent. This can be easily explained considering the larger C−Br bond photochemical stability.[13] After 1.5 h of irradiation in tetrahydrofuran, the bromoquinoline is the major product while at 4 h it has been converted into the debrominated quinoline. As expected, the debromination process is slowed in benzene. Toluene exhibits similar absorption to benzene but a higher polarity, and consistently, after 12 h of irradiation the bromoquinoline **6a**/quinoline **2a** rate (1/0.61) is smaller than in benzene (1/0.54) at the same reaction time.

Irradiation of 3-Amino-2-chloro-2-alkenimines. The ultraviolet absorption spectrum of 3-(*p*-tolylamino)-

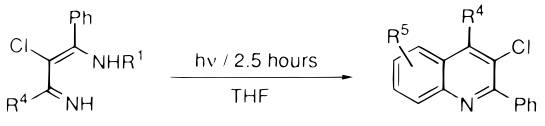
Scheme 5



5[a]	R^4	Solvent	Time (h)[b]	**6** (%)[c]	**2** (%)[c]	**6/2** ratio[d]
a	Ph	THF	1.5	51	4	1/0.1
a	Ph	THF	4	5	59	1/11
a	Ph	Benzene	4	51	18	1/0.40
a	Ph	Benzene	8	60	26	1/0.48
a	Ph	Benzene	12	53	25	1/0.54
a	Ph	Toluene	12	44	23	1/0.61
b	*p*-MeC_6H_4	Benzene	8	58	25	1/0.46

[a] Prepared according to ref 6. [b] Irradiation time through quartz for 1 mmol of alkenimine **5** with a 125 W mercury lamp. [c] Yields of isolated quinolines, relative to starting **5**, purified by column chromatography (silica, hexane−ether 3:1). [d] Quinoline **6**/**2** ratios, determined by ^{1}H NMR spectra of the crude reaction.

Scheme 6



7[a]	R^1	R^4	R^5	**8** (%)[b]
a	*p*-MeC_6H_4	Ph	6-Me	> 95
b	*p*-MeC_6H_4	*p*-MeC_6H_4	6-Me	> 95
c	Ph	Ph	H	> 95
d	*o*-MeC_6H_4	*p*-MeC_6H_4	8-Me	> 95

[a] Prepared according to ref 6. [b] Yields of isolated chloroquinolines **8**, relative to starting alkenimine **7** with a 125 W mercury lamp.

2-chloro-1,3-diphenyl-2-alkenimine **7a** in methanol shows bands at 208, 254, and 354 nm ($\epsilon \approx$ 31 400, 19 300, and 7100, respectively). In this case, the irradiation of choloroalkenimines **7** leads to the formation of 3-chloroquinolines **8** in quantitative yields after 2.5 h of irradiation in tetrahydrofuran (Scheme 6). Dechlorination was not observed.

In conclusion, the irradiation of haloalkenimines leads to the formation of 3-haloquinolines. Moreover, the reaction with chloro derivatives is quantitative, and bromo- and iodoquinolines can be easily isolated in good yields from the reaction crudes. Due to its mildness, simplicity, cleanness, and quickness, we anticipate this procedure should prove widely applicable. In addition, its interest is enhanced since 3-haloquinolines often exhibit pharmacological properties and can be further functionalized. The experimental and theoretical study of the reaction mechanisms for the cyclization and photodehalogenation processes are in progress.

Experimental Section

General Aspects. ^{1}H and ^{13}C spectra were recorded on a Bruker ARX-300 spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were run on a HP 5987 A apparatus.

(13) See, for example: Kropp, P. J.; McNeely, S. A.; Davis, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 6907. Davidson, R. S.; Goodin, J. W.; Kemp, G. *Adv. Phys. Org. Chem.* **1984**, *20*, 191.

Elemental analyses were performed on a Perkin-Elmer 240 elemental analyzer. All solvents were purified by standard procedures and freshly destilled prior to use. Reagents were of commercial grade (Aldrich). 3-Amino-2-iodo-2-alkenimines were prepared in accordance with the described method in ref 4 and bromo- and chloroalkenimines according to ref 6.

General Procedure: Irradiation of 3-Amino-2-halo-2-alkenimines. A solution of 3-amino-2-halo-2-alkenimine (1 mmol) in the corresponding anhydrous solvent (50 mL) was irradiated, at room temperature under argon atmosphere, using a medium-pressure mercury lamp (125 W) until the consumption of starting product was complete (monitored by ^{1}H NMR, see Table 1 and Schemes 5 and 6). The solution was evaporated under reduced pressure, and the resulting quinoline was purified by column chromatography (silica, hexane−ether 3:1).

3-Iodo-6-methyl-2,4-diphenylquinoline (4a): ^{1}H NMR δ 2.41 (s, 3 H), 7.14 (s, 1 H), 7.24−7.34 (m, 3 H), 7.41−7.68 (m, 8 H), 8.05 (d, J = 8.6 Hz, 1 H); ^{13}C NMR δ 160.8, 153.8, 145.4, 143.7, 142.2, 137.3, 132.3, 129.2, 129.0, 129.0, 128.5, 128.4, 128.3, 127.9, 127.2, 125.4, 98.6, 21.7. Anal. Calcd for $C_{22}H_{16}NI$: C, 62.72; H, 3.83; N, 3.32. Found: C, 62.70; H, 3.75; N, 3.41.

3-Iodo-6-methyl-2-phenyl-4-*p*-tolylquinoline (4b): ^{1}H NMR δ 2.41 (s, 3 H), 2.49 (s, 3 H), 7.16−7.18 (m, 3 H), 7.36−7.65 (m, 8 H), 8.05 (d, J = 8.6 Hz, 1 H); ^{13}C NMR δ 160.8, 153.9, 145.4, 143.8, 139.3, 138.1, 137.2, 133.3, 129.2, 129.0, 129.0, 128.9, 128.4, 127.9, 127.4, 125.5, 98.9, 21.7, 21.5. Anal. Calcd for $C_{23}H_{18}NI$: C, 63.46; H, 4.17; N, 3.22. Found: C, 63.47; H, 4.22; N, 3.19.

3-Iodo-2,4-diphenylquinoline (4c): ^{1}H NMR δ 7.21−7.76 (m, 13 H), 8.17 (d, J = 8.6 Hz, 1 H); ^{13}C NMR δ 154.6, 147.2, 146.8, 143.6, 142.0, 130.0, 129.3, 129.2, 129.2, 129.0, 128.5, 128.5, 128.4, 127.9, 127.2, 126.8, 98.4. Anal. Calcd for $C_{21}H_{14}NI$: C, 61.93; H, 3.46; N, 3.44. Found: C, 61.93; H, 3.55; N, 3.37.

3-Iodo-8-methyl-2-phenyl-4-*p*-tolylquinoline (4d): ^{1}H NMR δ 2.49 (s, 3 H), 2.81 (s, 3 H), 7.17 (d, J = 8.2 Hz, 2 H), 7.26−7.31 (m, 2 H), 7.37 (d, J = 8.2 Hz, 2 H), 7.45−7.57 (m, 4 H), 7.71−7.75 (m, 2 H); ^{13}C NMR δ 160.0, 154.7, 145.9, 143.9, 139.8, 138.1, 137.5, 129.9, 129.7, 129.1, 129.1, 129.0, 128.3, 127.6, 126.8, 124.9, 98.4, 21.4, 18.0. Anal. Calcd for $C_{23}H_{18}NI$: C, 63.46; H, 4.17; N, 3.22. Found: C, 63.43; H, 4.05; N, 3.29.

3-Iodo-2-phenyl-4-*p*-tolylquinoline (4e): ^{1}H NMR δ 2.49 (s, 3 H), 7.19 (d, J = 8.1 Hz, 2 H), 7.37 (d, J = 8.1 Hz, 2 H), 7.43−7.77 (m, 8 H), 8.15 (d, J = 8.2 Hz, 1 H); ^{13}C NMR δ 161.8, 154.8, 146.8, 143.7, 139.1, 138.3, 130.0, 129.2, 129.2, 129.1, 128.9, 128.5, 127.9, 127.9, 127.1, 126.9, 98.8, 21.4. Anal. Calcd for $C_{22}H_{16}NI$: C, 62.72; H, 3.83; N, 3.32. Found: C, 62.70; H, 3.79; N, 3.39.

3-Bromo-6-methyl-2,4-diphenylquinoline (6a): ^{1}H NMR δ 2.42 (s, 3 H), 7.15 (s, 1 H), 7.33−7.36 (m, 2 H), 7.45−7.58 (m, 7 H), 7.71−7.74 (m, 2 H), 8.06 (d, J = 8.6 Hz, 1 H); ^{13}C NMR δ 158.2, 148.8, 144.9, 141.0, 138.2, 137.3, 132.0, 129.3, 129.2, 128.8, 128.6, 128.4, 128.2, 127.8, 127.6, 125.0, 118.5, 21.7. Anal. Calcd for $C_{22}H_{16}NBr$: C, 70.60; H, 4.31; N, 3.74. Found: C, 70.57; H, 4.18; N, 3.85.

3-Bromo-6-methyl-2-phenyl-4-*p*-tolylquinoline (6b): ^{1}H NMR δ 2.42 (s, 3 H), 2.49 (s, 3 H), 7.16−7.18 (m, 3 H), 7.36−7.65 (m, 8 H), 8.05 (d, J = 8.6 Hz, 1 H); ^{13}C NMR δ 157.9, 149.0, 144.9, 141.0, 137.2, 135.2, 132.0, 131.0, 129.3, 129.2, 129.1, 128.4, 128.3, 128.1, 127.8, 125.1, 118.6, 21.7, 21.4. Anal. Calcd for $C_{23}H_{18}NBr$: C, 71.14; H, 4.67; N, 3.61. Found: C, 71.16; H, 4.70; N, 3.57.

3-Chloro-6-methyl-2,4-diphenylquinoline (8a): ^{1}H NMR δ 2.39 (s, 3 H), 7.17 (s, 1 H), 7.34−7.37 (m, 2 H), 7.44−7.56 (m, 7 H), 7.76−7.79 (m, 2 H), 8.07 (d, J = 8.6 Hz, 1 H); ^{13}C NMR δ 156.5, 146.2, 144.9, 139.4, 137.3, 135.9, 131.8, 129.5, 129.4, 129.3, 128.6, 128.5, 128.3, 127.9, 127.6, 126.3, 124.7, 21.7. Anal. Calcd for $C_{22}H_{16}NCl$: C, 80.11; H, 4.89; N, 4.25. Found: C, 80.09; H, 4.79; N, 4.33.

3-Chloro-6-methyl-2-phenyl-4-*p*-tolylquinoline (8b): ^{1}H NMR δ 2.41 (s, 3 H), 2.49 (s, 3 H), 7.19−7.27 (m, 3 H), 7.33 (d, J = 8.1 Hz, 2 H), 7.42−7.51 (m, 4 H), 7.74 (d, J = 8.1 Hz, 2 H), 8.07 (d, J = 8.2 Hz, 1 H); ^{13}C NMR δ 156.4, 146.2, 144.6, 139.4, 138.0, 137.1, 132.8, 131.6, 129.4, 129.2, 129.1, 129.1, 128.5, 127.9, 127.7, 126.3, 124.7, 21.6, 21.3. Anal. Calcd for $C_{23}H_{18}NCl$: C, 80.34; H, 5.28; N, 4.07. Found: C, 80.40; H, 5.39; N, 4.01.

3-Chloro-2,4-diphenylquinoline (8c): ^{1}H NMR δ 7.33−7.82 (m, 13 H), 8.2 (d, J = 8.6 Hz, 1 H); ^{13}C NMR δ 157.4, 146.8, 145.9, 139.2, 135.6, 129.4, 129.4, 129.3, 129.3, 128.7, 128.4, 128.3, 127.9, 127.5, 127.1, 126.2, 125.9. Anal. Calcd for $C_{21}H_{14}NCl$: C, 79.87; H, 4.47; N, 4.44. Found: C, 79.86; H, 4.40; N, 4.49.

3-Chloro-8-methyl-2-phenyl-4-*p*-tolylquinoline (8d): ^{1}H NMR δ 2.47 (s, 3 H), 2.83 (s, 3 H), 7.22−7.50 (m, 10 H), 7.86−7.92 (m, 2 H); ^{13}C NMR δ 155.5, 147.0, 145.1, 139.7, 138.0, 137.6, 133.3, 129.9, 129.4, 129.3, 129.1, 128.6, 127.7, 127.3, 126.8, 126.1, 124.1, 21.4, 18.1. Anal. Calcd for $C_{23}H_{18}NCl$: C, 80.34; H, 5.28; N, 4.07. Found: C, 80.33; H, 5.25; N, 4.11.

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