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# 1,4-Dehydrochlorination of 1-(1-haloalkyl)-3,4-dihydroisoquinolines as a convenient route to functionalized isoquinolines

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ABSTRACT

1-Chloroalkyl-, 1-(2,2-dichloroalkyl)-, and 1-(trichloromethyl)-3,4-dihydroisoquinolines are synthesized by chlorination of 1-alkyl-3,4-dihydroisoquinolines with *N*-chlorosuccinimide. These novel chlorinated 3,4-dihydroisoquinolines are suitable precursors for functionalized isoquinolines by aromatization involving sequential 1,4-dehydrochlorination, tautomerization, and nucleophilic substitution.



The frequent occurrence of the isoquinoline skeleton in a large number of alkaloids and in several bioactive compounds has led to significant interest in the synthesis of a variety of functionalized isoquinolines, as well as their tetrahydro- and dihydro-derivatives.[1] The wide range of activities of the isoquinolines is remarkable and includes antibacterial, antimalarial, and antipyretic activities (berberine alkaloids),[2] anti-HIV activity (michellamines),[3] muscle relaxing activity (papaverine),[4] heart regulating activity (hygenamine),[5] and activity against Parkinson's disease (oliveroline).[6] In addition, a number of halogenated isoquinolines show interesting biological activities[7] and are versatile intermediates for the synthesis of isoquinoline natural products.[8] Therefore, the development of straightforward procedures to synthesize functionalized isoquinolines as basic frameworks for further elaboration continues to be an active research topic.

The Bischler–Napieralski reaction is one of the most effective methods for the synthesis of 3,4-dihydroisoquinoline derivatives.[9] It is also known that α-chloroimines are suitable building blocks for the synthesis of a wide range of heterocyclic compounds.[10] Herein, we report a method combining these two methodologies resulting in a new and convenient synthesis of halogenated 3,4-dihydroisoquinolines and their use for further elaboration of the isoquinoline skeleton.

3,4-Dihydroisoquinolines **2a–h**[11] were synthesized in 67–91% yield (Table 1) from amides **1a–h** by the Bischler–Napieralski reaction (Scheme 1)[12] via cyclocondensation with polyphosphoric acid (PPA) in toluene at reflux for 10–12 h. Under these conditions, the synthesis of 3,4-dihydroisoquinolines **2i,j** ($R^1$ = H, OMe, $R^2$ = H, OMe, $R^3$ = Cl) from the corresponding α-chloro carboxylic amides **1i,j** was unsuccessful. However, it was found that treatment of compounds **1i,j** with phosphorus pentoxide in *o*-xylene at reflux for 1–2 h gave rise to compounds **2i,j** in 91–97% yield (Table 1).

A well-known method for the α-chlorination of imines involves their treatment with *N*-chlorosuccinimide.[9,13] Thus 3,4-dihydroisoquinolines **2a–h** were treated with 2 equiv of *N*-chlorosuccinimide in carbon tetrachloride. The reaction was initiated by refluxing the mixture for 1 min after which the reaction was stirred at room temperature for the indicated time (Scheme 1, Table 1).

Under these conditions, 3,4-dihydroisoquinolines **2a–e,g,h** were smoothly chlorinated to yield 1,1-dichloromethyl-3,4-dihydroisoquinolines **3a–e,g,h** in 85–98% yield. As the reaction rates for successive introduction of the chlorine atoms are of the same magnitude, the reaction could not be applied to produce monochlorodihydroisoquinolines. Also, treatment of 3,4-dihydroisoquinolines **2a** and **2b** with 2 equiv of NCS led to the synthesis of the dichloro derivatives (**3a,b**) together with the trichloro derivatives (**4a,b**). However, the ratio of the two derivatives depended largely on the temperature of the reaction. The dichloro

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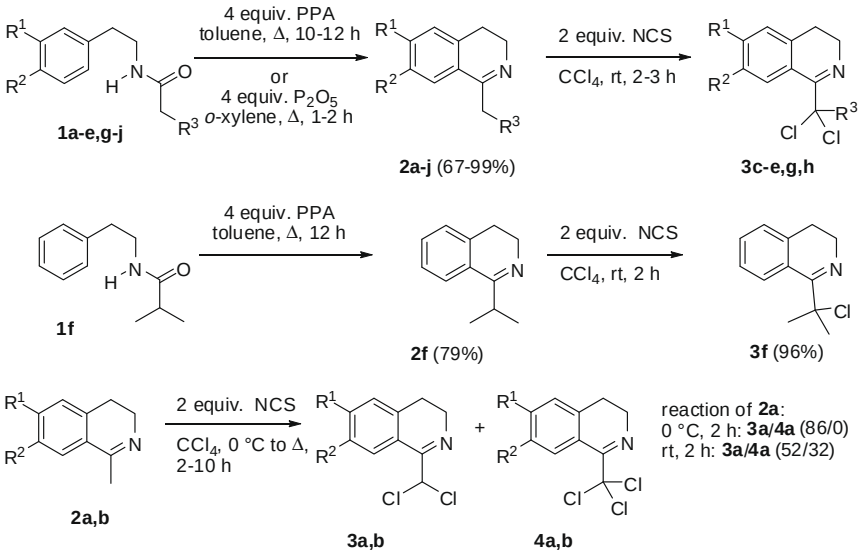
**Table 1**
Bischler–Napieralski reaction of carboxylic amides **1** and chlorination of dihydroisoquinolines **2** with *N*-chlorosuccinimide

| Product | $R^1$ | $R^2$ | $R^3$ | Reaction conditions | Yield (%) | Mp or bp (mmHg) |
|---|---|---|---|---|---|---|
| **2a** | H | H | H | 4 equiv PPA, toluene, Δ, 10 h | 67 | 110–116 °C (12)[11] |
| **2b** | OMe | OMe | H | 4 equiv PPA, toluene, Δ, 10 h | 74 | 103–105 °C[12b] |
| **2c** | H | H | Me | 4 equiv PPA, toluene, Δ, 12 h | 73 | 120–125 °C (13)[11] |
| **2d** | OMe | OMe | Me | 4 equiv PPA, toluene, Δ, 12 h | 95 | Colorless oil[12b] |
| **2e** | H | H | Et | 4 equiv PPA, toluene, Δ, 10 h | 84 | 75–80 °C (0.2)[11] |
| **2f** | / | / | / | 4 equiv PPA, toluene, Δ, 12 h | 79 | 65–70 °C (0.2)[11] |
| **2g** | H | H | SEt | 4 equiv PPA, toluene, Δ, 10 h | 91 | 88–90 °C (0.02) |
| **2h** | OMe | OMe | SEt | 4 equiv PPA, toluene, Δ, 10 h | 91 | 118–120 °C (0.03) |
| **2i** | H | H | Cl | 4 equiv $P_2O_5$, *o*-xylene, Δ, 1 h | 91 | 160–161 °C[a] |
| **2j** | OMe | OMe | Cl | 4 equiv $P_2O_5$, *o*-xylene, Δ, 2 h | 97 | 207 °C[a,8d] |
| **3a** | H | H | H | 2 equiv NCS, $CCl_4$, 0 °C, 2 h | 86 | Colorless oil |
| **4a** | H | H | H | 4 equiv NCS, $CCl_4$, Δ, 10 h | 96 | Colorless oil |
| **4b** | OMe | OMe | H | 4 equiv NCS, $CCl_4$, Δ, 10 h | 94 | Colorless oil |
| **3c** | H | H | Me | 2 equiv NCS, $CCl_4$, rt, 3 h | 98 | Colorless oil |
| **3d** | OMe | OMe | Me | 2 equiv NCS, $CCl_4$, rt, 3 h | 85 | Colorless oil |
| **3e** | H | H | Et | 2 equiv NCS, $CCl_4$, rt, 2 h | 98 | Colorless oil |
| **3f** | / | / | / | 2 equiv NCS, $CCl_4$, rt, 2 h | 96 | Colorless oil |
| **3g** | H | H | SEt | 2 equiv NCS, $CCl_4$, rt, 3 h | 85 | Colorless oil |
| **3h** | OMe | OMe | SEt | 2 equiv NCS, $CCl_4$, rt, 3 h | 98 | Colorless oil |

[a] Melting point of the HCl salt.



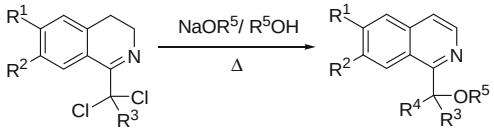

**Scheme 1.**

derivative **3a** and the trichloro derivative **4a** were obtained in a 52/32 ratio at room temperature and in an 86/0 ratio at 0 °C. The trichloro derivative **4a** could be obtained selectively in 96% yield upon treatment of compound **2a** with 4 equiv of NCS in $CCl_4$ at reflux. In the case of 3,4-dihydroisoquinoline **2b**, the trichloro-3,4-dihydroisoquinoline **4b** was obtained similarly in 94% yield.

The conversion of 1-(dichloromethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline **3b**, prepared in 64% yield by Bischler–Napieralski reaction of *N*-homoveratryl-1,1-dichloroacetamide, into the corresponding isoquinoline in 80–94% yield by treatment with base has been demonstrated.[14] Therefore, the dichloro-3,4-dihydroisoquinolines **3a**,**c**,**e** were treated with different alkoxides in order to obtain the isoquinolines **5**. Treatment of compounds **3a**,**c**,**e** with 4 equiv of sodium methoxide (2 N) in methanol or 4 equiv of sodium ethoxide (1 N) in ethanol under reflux for 4–16 h resulted in the synthesis of isoquinolines **5a**,**b**,**d**,**e** in 73–94% yield (Table 2). The mechanism of the aromatization of the dichloro-3,4-dihydroisoquinolines **3** is outlined in Scheme 2. In the presence of base, compounds **3** are deprotonated at the 3-position, followed by 1,4-dehydrochlorination to give 2-azadienes **6**. These intermediates are deprotonated again at the 4-position and are converted to compounds **7**, which undergo a subsequent substitution by methoxide to produce compounds **5**. In the case of the trichloroisoquinoline **4a**, the same mechanism applies and is followed by a second substitution of the residual chloride by methoxide leading to the formation of **5c** in 70% yield.

The substitution reaction of chloroisoquinolines **7** is, however, dependent on the nucleophilicity of the reagent. When compounds **3b** and **3c** were treated with three equivalents of potassium *tert*-butoxide (low nucleophilicity) in THF under reflux for 6 h, 1-vinyl-isoquinolines **8a**,**b** were formed by dehydrochlorination in 75–88% yield (Scheme 3). In the case of monochloromethyldihydroisoquinolines, treatment of **2i**,**j** with 3 equiv

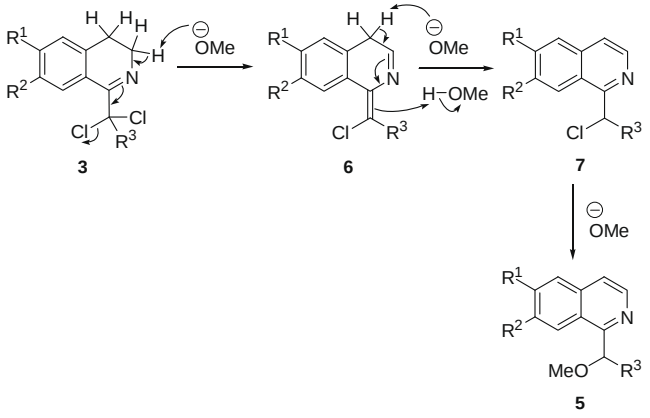
**Table 2**
Synthesis of isoquinolines **5** upon treatment of dichloro-3,4-dihydroisoquinolines **3a**,**c**,**e** and trichloro-3,4-dihydroisoquinoline **4a** with different alkoxides




**3a,c,e**
**4a**

**5a-e**

| Product | Substrate | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Reaction conditions | Yield of **5** (%) |
|---|---|---|---|---|---|---|---|---|
| **5a** | **3a** | H | H | H | | | 4 equiv NaOMe in MeOH (2 N), Δ, 4 h | 80 |
| | | H | H | H | H | Me | | |
| **5b** | **3a** | H | H | H | | | 4 equiv NaOEt in EtOH (1 N), Δ, 4 h | 94 |
| | | H | H | H | H | Et | | |
| **5c** | **4a** | H | H | Cl | | | 4 equiv NaOMe in MeOH (2 N), Δ, 4 h | 70 |
| | | H | H | H | OMe | Me | | |
| **5d** | **3c** | H | H | Me | | | 4 equiv NaOMe in MeOH (2 N), Δ, 16 h | 75 |
| | | H | H | Me | H | Me | | |
| **5e** | **3e** | H | H | Et | | | 4 equiv. NaOMe in MeOH (2 N), Δ, 4 h | 73 |
| | | H | H | Et | H | Me | | |




**Scheme 2.**

of potassium *tert*-butoxide in diethyl ether at room temperature for 30 h led to 1-methylisoquinolines **10a**,**b** in 84–88% yield (Scheme 4).

In conclusion, 3,4-dihydroisoquinolines **2** were chlorinated using NCS in $CCl_4$ leading to new dichlorinated-3,4-dihydroisoquinolines **3** in 67–97% yield, which were subsequently converted to the novel alkoxylated isoquinolines **5** on treatment with methoxide or ethoxide.[15] Depending on the substitution pattern at the 1-position, 1-vinylisoquinolines, and 1-methylisoquinolines could be obtained, selectively.

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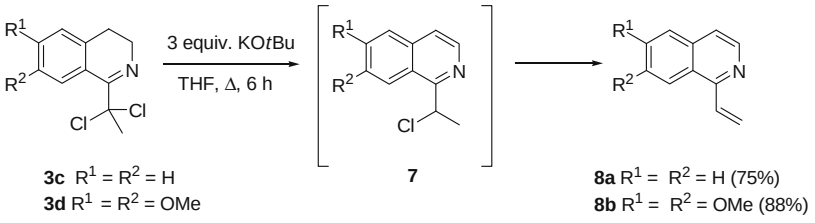
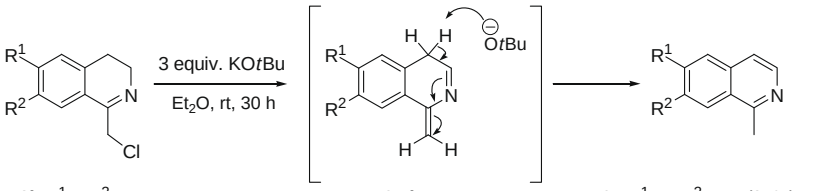



**3c** $R^1 = R^2 = H$
**3d** $R^1 = R^2 = OMe$

**7**

**8a** $R^1 = R^2 = H$ (75%)
**8b** $R^1 = R^2 = OMe$ (88%)

**Scheme 3.**




**2i** $R^1 = R^2 = H$
**2j** $R^1 = R^2 = OMe$

**9a,b**

**10a** $R^1 = R^2 = H$ (84%)
**10b** $R^1 = R^2 = OMe$ (88%)

**Scheme 4.**

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15. All new compounds were fully characterized on the basis of IR, MS, $^1$H NMR, and $^{13}$C NMR spectroscopy. Spectral data of selected compounds can be found below. *Compound* **3a**: Colorless oil (purity >95%), no purification due to decomposition of the compound on silica gel; $^1$H NMR (270 MHz, $CDCl_3$): $\delta$ 2.63 (2H, t, $J$ = 7.5 Hz, H-4), 3.74 (2H, t, $J$ = 7.5 Hz, H-3), 6.56 (1H, s, $CHCl_2$), 6.91–7.49 (3H, m, 3 × CH=), 7.69–7.81 (1H, m, CH=); $^{13}$C NMR (68 MHz, $CDCl_3$): $\delta$ 25.5 (C-4), 47.0 (C-3), 71.1 ($CHCl_2$), 124.1 (=$C_{quat}$), 126.2 (CH=), 126.6 (CH=), 127.9 (CH=), 131.6 (CH=), 138.3 (=$C_{quat}$), 162.0 (C-1); IR (NaCl): $\nu_{max}$ 1621 cm$^{-1}$; MS *m/z* (%): 213/215/217 ($M^+$, 33), 178/180 (100), 151 (10), 150 (6), 149 (10). *Compound* **5a**: Colorless oil, purification by flash chromatography on silica gel; $^1$H NMR (270 MHz, $CDCl_3$): $\delta$ 3.38 (3H, s, OMe), 4.96 (2H, s, $CH_2$OMe), 7.29–7.70 (4H, m, 3 × CH= and H-4), 8.01–8.39 (1H, m, CH=), 8.41 (1H , d, $J$ = 5.8 Hz, H-3); $^{13}$C NMR (68 MHz, $CDCl_3$): $\delta$ 58.3 (OMe), 75.0 ($CH_2O$), 120.9 (CH=), 125.5 (CH=), 127.0 (CH=), 127.1 (CH=), 127.2 (=$C_{quat}$), 129.9 (CH=), 136.3 (=$C_{quat}$), 141.6 (CH=), 157.0 (C-1); IR (NaCl): $\nu_{max}$ 1622, 1582, 1560, 1450, 1189, 1100 cm$^{-1}$; MS *m/z* (%): no $M^+$, 149 (6), 146 (6), 115 (13), 43 (100). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.46; H, 6.58; N, 7.88.