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Complex base-induced generation of 3,4-dehydroquinoline: a new access to quinoline derivatives

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Abstract—3,4-Dehydroquinoline was easily generated from 3-bromoquinoline and a complex base $NaNH_2$–*t*BuONa. Nucleophilic condensation of amines and thiolates were performed in good yields.

As part of a program of medicinal chemistry undertaken a few years ago,[1] we are pursuing investigations on the synthesis and reactivity of heterocycles containing nitrogen. Recently we were confronted with the preparation of quinoline derivatives. Our experience in arynic chemistry[1a,b,2] led us to consider the use of didehydroquinolines as intermediates. Taking account of the results previously obtained in the pyridine series,[2] we anticipated that these transient reactive species ought to be easily generated from appropriate halogenoquinolines and a complex base.[2] The major interest of this procedure, compared to the existing ones,[3,4] is that it can be conducted on a large scale and can use inexpensive reagents. Moreover, under our conditions anionic as well as neutral nucleophiles may react with the intermediates with low competition from the base used to generate them.

In the present paper, we report our first successful results obtained in this area. Firstly we tried to react primary and secondary amines with the commercially available 3-bromoquinoline **1** in the presence of the complex base $NaNH_2$–*t*BuONa in tetrahydrofuran. The reactions observed are summarized in Table 1.

These results deserve some comment. Overall yields vary from acceptable to very good. In fact the apparent lower yields obtained from primary amines are due to the formation of disubstituted products.[5]

Interestingly, the ratios **3**/**4** were always close to 1. This result is explained by a balance between electronic and steric effects. Indeed the electron-withdrawing effect of the nitrogen favors attack on C4, while steric hindrance of the hydrogen on C5 favors attack on the C3 position.

With these results in hand, we studied the condensation of thiolates as representative charged nucleophiles (Table 2).

The formation of isomers **6** and **7** in equivalent amounts supports the hetarynic intermediate and shows that no SN_{Ar} takes place. It is noteworthy that two equivalents of $NaNH_2$ were sufficient to perform the reaction. In fact an increase in the amount of this reagent (4 equivalents) allowed shorter reaction times, but led to the formation of appreciable amounts of 4-aminoquinoline.

The derivatives **4a** and **7a** were synthesized directly from 4-chloroquinoline by an SN_{Ar} reaction with very good yields.[6,7] This method could be used for the synthesis of compounds **4** and **7**.

In conclusion, quinoline derivatives **3**, **4**, **6** and **7** may be easily obtained by elimination–addition under our conditions.[8,9] The application to the synthesis of new heterocycles is actively pursued.

Keywords: dehydroquinoline; complex base $NaNH_2$–*t*BuONa; arynic chemistry.

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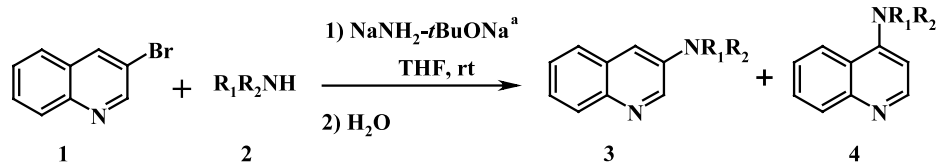
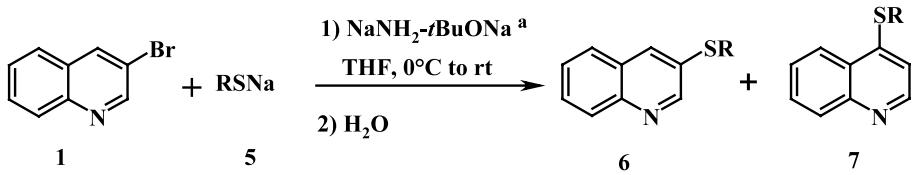
Table 1.



Amines **2**	Time (h)	**3**[b] (%)	**4**[b] (%)	**3**+**4**[b,d] (%)
Piperidine **2a**	1	**3a** 42	**4a** 40	82
Morpholine **2b**	1	**3b** 40	**4b** 40	80
Dipropylamine **2c**	1	**3c** 37	**4c** 37	74
1-Methylpiperazine **2d**	1	**3d** 36[c]	**4d** 36[c]	72
1-Benzylpiperazine **2e**	1	**3e** 38	**4e** 37	75
Isopropylamine **2f**	3	**3f** 25	**4f** 20	45
tert-Butylamine **2g**	3	**3g** 24	**4g** 23	47
4-Phenylbutylamine **2h**	3	**3h** 25	**4h** 25	50

[a] **1**:**2**:$NaNH_2$:*t*BuONa = 1:2:4:2.
[b] Isolated yields calculated from 3-bromoquinoline.
[c] Measured by NMR.
[d] Compounds **3** and **4** are easily separated by flash chromatography on silica gel.

Table 2.



Thiolates **5**	Time (h)	**6**[b] (%)	**7**[b] (%)	**6**+**7**[b,d] (%)
C_6H_5SNa **5a**	2	**6a** 40	**7a** 39	79
3-$MeOC_6H_4SNa$ **5b**	3	**6b** 39	**7b** 38	77
C_2H_5SNa[c] **5c**	4	**6c** 28	**7c** 25	53

[a] **1**:**5**:$NaNH_2$:*t*BuONa = 1:2:2:2.
[b] Isolated yields calculated from 3-bromoquinoline.
[c] HMPT (2.5×10^{-3} mol 2%) was added to solubilize the formed salt.
[d] Compounds **6** and **7** are easily separated by flash chromatography on silica gel.

Acknowledgements

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8. All new compounds were fully characterized by ^1H NMR, ^{13}C NMR, MS and IR spectra and gave correct elemental analysis.

9. **General procedure**: To the complex base prepared according to Ref. 1b was added, at 40°C, the amine (2 equiv.) or the thiolate (2 equiv.) (generated in situ with 2 equiv. of $NaNH_2$). The mixture was stirred for 2 h at 40°C. After cooling at 0°C, a solution of 3-bromoquinoline in THF was added. The mixture was stirred at rt. The reaction was monitored by TLC and stopped when the 3-bromoquinoline had disappeared. The mixture was then hydrolyzed at 0°C and extracted with CH_2Cl_2. The combined extracts were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified by flash chromatography on silica gel using as eluent ethyl acetate–hexane (5–30%).

Data for selected compounds **3e**–**4e** and **6b**–**7b**; **3e**: mp: 104–105°C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ ppm 8.79 (1H, d, $J=2.7$ Hz), 7.98 (1H, dd, $J=7.3$ Hz, $J=1.8$ Hz), 7.63–7.67 (1H, m), 7.40–7.49 (2H, m), 7.33–7.36 (4H, m), 3.30–3.31 (2H, m), 3.59 (2H, s, 2H), 3.30 (4H, t, $J=5.0$ Hz), 2.66 (4H, t, $J=5.0$ Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ ppm 145.6 (CH), 141.8, 139.9 (C), 129.0 (C), 128.8, 126.7, 126.0, 124.9 (CH), 113.8 (CH), 51.5 (CH_2), 29.3 ($4\times CH_2$); MS (IS) = 304.5 $(M+H)^+$. Anal. calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 78.87; H, 7.13; N, 13.55. **4e**: oil; ^{1}H NMR ($CDCl_3$, 250 MHz): δ ppm 8.70 (1H, d, $J=4.8$ Hz), 8.00–8.06 (2H, m), 7.60–7.66 (1H, m), 7.41–7.48 (1H, m), 7.35–7.37 (3H, m), 7.35 (1H, d, $J=4.8$ Hz), 7.25–7.31 (1H, m), 3.63 (2H, s), 3.24 (4H, t, $J=4.8$ Hz), 2.73 (4H, t, $J=4.8$ Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ ppm 156.5 (C), 150.3 (CH), 149.0 (C), 137.4, 129.4, 128.8 (CH), 128.6 (C), 127.9, 126.8, 124.7, 123.3 (CH), 123.0 (C), 108.2 (CH), 62.6 (CH_2), 52.6 ($2\times CH_2$), 51.7 ($2\times CH_2$); MS (IS) = 304.5 $(M+H)^+$. Anal. calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 78.94; H, 7.04; N, 13.61. **6b**: mp: 171–172°C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ ppm 8.51 (1H, d, $J=2.1$ Hz), 8.36 (1H, d, $J=8.5$ Hz), 7.84 (1H, $J=8.2$ Hz), 7.69–7.76 (1H, m), 7.51–7.57 (2H, m), 7.40–7.52 (2H, m), 6.99 (1H, d, $J=7.9$ Hz), 4.19 (3H, s) ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ ppm 158.5, 146.5, 143.1, 130.9 (C), 130.6, 130.1 (CH), 128.4 ($3\times$CH), 126.7, 126.1 ($3\times$CH), 125.4 (C), 115.4, 106.9 (CH), 56.2 (CH_3); MS (IS) = 268 $(M+H)^+$. Anal. calcd for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 71.63; H, 4.62; N, 5.15 **7b**: mp: 78–79°C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ ppm 8.58 (1H, d, $J=4.8$ Hz), 8.20 (1H, d, $J=8.2$ Hz), 8.09 (1H, $J=8.2$ Hz), 7.69–7.76 (1H, m), 7.53–7.60 (1H, m), 7.37 (1H, t, $J=7.9$ Hz), 7.10–7.18 (2H, m), 6.97–7.02 (1H, m), 6.83 (1H, d, $J=4.8$ Hz), 3.22 (3H, s), ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ ppm 160.5, 149.4 (CH), 148.3, 147.5 (C), 130.7 (CH), 130.6 (C), 129.9, 129.8, 127.2, 126.5 (CH), 125.9 (C), 123.4, 119.9, 118.0, 115.6 (CH), 55.4 (CH_3); MS (IS) = 268 $(M+H)^+$. Anal. calcd for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 71.97; H, 4.75; N, 5.37.