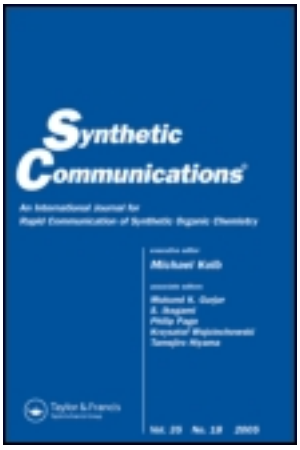


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# 2,3-PYRIDYNE FORMATION BY FLUORIDE-INDUCED DESILYLATION-ELIMINATION

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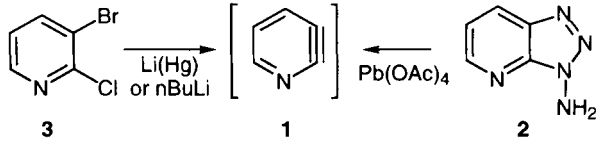
**Abstract:** The formation of 2,3-pyridyne by a desilylation-elimination sequence employing anhydrous CsF is reported.

The preparation of 2,3-pyridyne (**1**; 2,3-didehydropyridine) has been the target of many research endeavors over the past few decades.[1] For example, this transient species has been prepared using the oxidation of the aminotriazolopyridine[2] **2** and by a halogen-metal exchange-elimination sequence starting from 3-bromo-2-chloropyridine (**3**) and employing nBuLi[3] or Li(Hg) (Scheme 1).[4] In each of these cases the formation of 2,3-pyridyne was inferred by its successful trapping by a cyclic diene in a presumed [4+2] cycloaddition.




**3** **1** **2**

**Scheme 1**

As part of our research directed at developing mild methods for substituted 2,3-pyridyne formation, we recently reported the formation of 4-methoxy-2,3-pyridyne via two new methods, that of directed-deprotonation-elimination and

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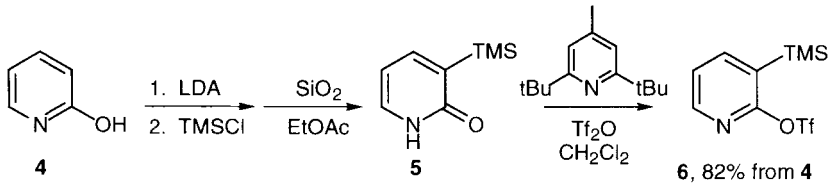
fluoride-induced desilylation-elimination.[5] We wondered whether the 4-methoxy substituent was required for efficient 2,3-pyridyne formation and whether the method of desilylation-elimination would be applicable to the formation of the parent hetaryne. Snieckus has shown that the desilylation-elimination methodology works very well for the formation of 3,4-pyridyne[6] and similar reaction conditions have been employed to prepare benzyne, even in the presence of protic cosolvents.[7] These successes notwithstanding, we were also aware of the failure of TBAF (tetra-N-butylammonium fluoride) to induce 2,3-pyridyne formation.[8]

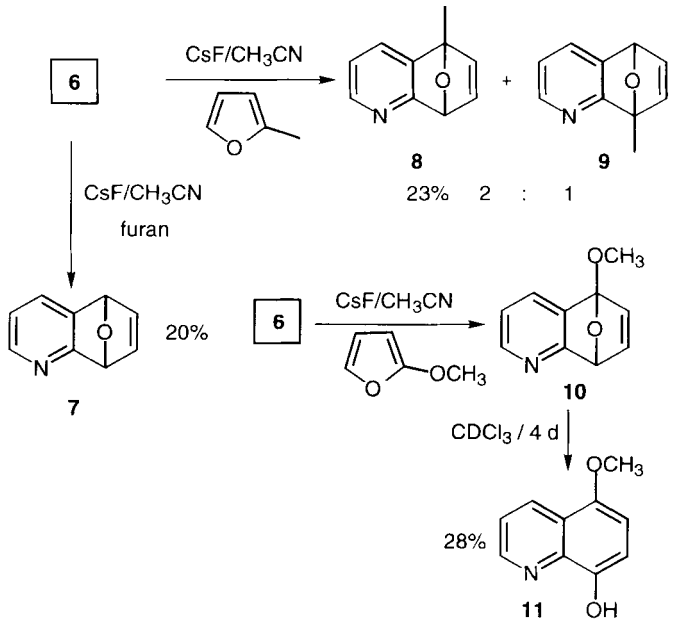
To answer our questions, 2-trifoyl-3-trimethylsilylpyridine was prepared by a two-step process based on the method of Effenberger.[8] 2-Hydroxypyridine[9] (**4**) was treated with 2.2 equivalents of LDA in ether and then 2.3 equivalents of TMSCl (Scheme 2). Treatment of the crude reaction mixture (after concentration in vacuo) with ethyl acetate/$SiO_2$ gave 3-trimethylsilyl-2-pyridone (**5**). Pyridone **5** was converted to the desired silylpyridyl triflate **6** (82% from **4**) by reaction of it with TMSOTf/2,6-di-t-Bu-4-methylpyridine/$CH_2Cl_2$[10] followed by workup and flash chromatography.




**Scheme 2**

We surmised that the failure of TBAF to produce 2,3-pyridyne might have been due to the presence of disadvantageous water. Therefore, we utilized CsF as the desilylating agent, taking the extra precaution of flame-drying this solid in vacuo prior to its use. 2,3-Pyridyne formation and trapping was conveniently effected by addition of a solution of 2-trifoyl-3-trimethylsilylpyridine in anhydrous $CH_3CN$ (distilled from $CaH_2$) to a suspension of CsF and a furan in $CH_3CN$ (Scheme 3). This heterogeneous reaction mixture was stirred for 15-18 h under Ar. Workup and flash chromatography gave the trapped adducts shown in Scheme 3. Reaction of 2,3-pyridyne formed in this fashion with furan gave 5,8-dihydro-5,8-epoxyquinoline **7** in 20% yield.[11] Trapping of 2,3-pyridyne with 2-methylfuran gave a 23% yield of a 2:1 ratio of 8-hydro-5-methyl-5,8-epoxyquinoline (**8**) and 5-hydro-8-methyl-5,8-epoxyquinoline (**9**), this ratio being in agreement with that reported previously for this cycloaddition reaction.[12] Finally, reaction of the

hetaryne with 2-methoxyfuran led to what was presumed to be the epoxyquinoline **10**. This epoxyquinoline underwent acid-catalyzed ring-opening in $CDCl_3$ over a period of four days to give after chromatography a 28% yield of 5-methoxy-8-quinolinol (**11**).[13,14]




**Scheme 3**

In conclusion, we have discovered that 2-trifoyl-3-trimethylsilylpyridine is, indeed, a good source of the reactive 2,3-pyridyne intermediate, and that 2,3-pyridyne formed by this desilylation-elimination route undergoes formal cycloaddition reactions with furan, 2-methyl and 2-methoxyfuran. Apparently, quenching of the anion formed upon initial desilylation must compete effectively with the formation of the highly strained 2,3-pyridyne system.[15] Anhydrous conditions, therefore, are more important for the formation of 2,3-pyridyne than for the related benzyne case. These findings may corroborate the concerted elimination process that has been suggested for the latter process.[7b]

This mild method of 2,3-pyridyne formation should allow us to develop a general approach to quinoline derivatives given that we have now shown that formation of the reactive intermediate can be effected at room temperature under essentially non-nucleophilic conditions and is not dependent on pyridine

substitution. We are currently exploring this avenue of research and will report our results in due course.

## Experimental

**3-Trimethylsilyl-2-pyridone (5).** A solution of LDA was prepared by adding 18.2 mL (23.7 mmol) of 1.3 M nBuLi in hexanes to a solution of 3.30 mL (23.5 mmol) of diisopropyl amine in 43 mL of $Et_2O$ which was cooled in an ice bath then allowed to warm to rt. The LDA solution was added dropwise to 1.0216 g (10.742 mmol) of 2-hydroxypyridine (**3**) and the heterogeneous mixture was stirred. After 30 min 3.15 ml (24.8 mmol) of TMSCl was added and the slurry was allowed to stir for 17 h during which time a white precipitate formed. The mixture was filtered and the solvent removed in vacuo to leave a yellow oil. Flash chromatography with EtOAc yielded 637 mg (35%) of the desired material and a mixture of the desired material and its disilylated precursor. Stirring this mixture in an EtOAc/$SiO_2$ slurry followed by flash chromatography afforded 943 mg (53%) of the desired material for a total yield of 88%. Mp 112.0-114.0 °C; IR (thin film) 3200-2500, 1635, 1538, 1469, 1243, 839, 766 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 12.88 (br s, 1H), 7.54 (dd, 1H, *J*=6.5 and *J*=2.2 Hz), 7.35 (dd, 1H, *J*=6.5 and 2.2 Hz), 6.23 (apparent t, 1H, *J*=6.5 Hz), 0.28 (s, 9H); $^{13}C$ NMR ($CDCl_3$) δ 168.0, 147.6, 135.8, 106.8, -1.6; MS m/z (rel intensity) 167 ($M^+$, 14), 153 (14), 152 (100), 134 (8); Anal calcd. for $C_8H_{13}N_1O_1Si_1$: C, 57.44; H, 7.83; N, 8.37. Found: C, 57.64; H, 7.84; N, 8.38.

**2-Trifluoromethanesulfonyl-3-trimethylsilylpyridine (6).**[8] To a solution of 606 mg (3.62 mmol) of 3-trimethylsilyl-2-hydroxypyridine (**5**) and 821.1 mg (3.999 mmol) of 2,6 di-t-butyl-4-methylpyridine in 14.5 mL (0.25 M) of $CH_2Cl_2$ was added dropwise 0.67 mL (4.0 mmol) of trifluoromethanesulfonic anhydride. A precipitate formed as the mixture was allowed to stir for 1 h. The solvent was removed in vacuo and the residue was washed with pentane. The combined organics were concentrated and, after flash chromatography with 5% E/H, afforded 1.013 g (93%) of **3** as a colorless oil. $^1H$ NMR ($CDCl_3$) δ 8.33 (dd, 1H, *J*=4.9 and 2.1 Hz), 7.93 (dd, 1H, *J*=7.3 and 2.1 Hz), 7.32 (dd, 1H, *J*=7.3 and 4.9 Hz), 0.38 (s, 9H); $^{13}C$ NMR d 161.0, 148.9, 147.1, 125.4, 123.4, 118.7 (q, $J_{CF}$=318 Hz), 1.4; TLC $R_f$ = 0.3 (5% E/H): The bulky base 2,6 di-t-butyl-4-methylpyridine was recovered in 87% yield by the treatment of the filtrate with 10% NaOH and extraction with pentane.

**5,8-Dihydro-5,8-epoxyquinoline (7).**[12] To a mixture of 154.2 mg (1.015 mmol) of CsF and 0.24 mL (3.3 mmol) of furan in 2.3 mL $CH_3CN$ was added dropwise a solution of 98.1 mg (0.328 mmol) of 2-trifluoromethanesulfonyl-3-trimethylsilylpyridine (**6**) in 1.0 mL $CH_3CN$ (total 0.1M). The mixture was allowed to stir at rt for 15 h. The solvent was removed in vacuo, 1N $NH_4Cl$ was added, and this aqueous solution was extracted with 3x6 ml $CH_2Cl_2$. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. Flash chromatography afforded 9.4 mg (20%) of **7** as a brown oil. $^1H$ NMR δ 8.03 (dd, 1H, *J*=5.4 and 1.5 Hz), 7.41 (dd, 1H, *J*=7.2 and 1.5), 7.13 (dd, 1H, *J*=5.4 and 1.8 Hz), 7.07 (dd, 1H, *J*=5.4 and 1.8 Hz), 6.84 (dd, 1H, *J*=7.2 and 5.4 Hz), 5.78 (d, 1H, *J*=1.8 Hz), 5.60 (d, 1H, *J*=1.8 Hz).

**8-Hydro-5-methyl-5,8-epoxyquinoline (8) and 5-hydro-8-methyl-5,8-epoxyquinoline (9).**[12] To a mixture of 601.5 mg (3.960 mmol) of CsF and 1.2 mL (13 mmol) of 2-methylfuran in 9.6 mL $CH_3CN$ was added dropwise a solution of 388.9 mg (1.299 mmol) of 2-trifluoromethanesulfonyl-3-trimethylsilylpyridine (**6**) in 3.2 mL $CH_3CN$ (total 0.1M). The mixture was allowed to stir for 18.5 h. The solvent was removed in vacuo, $H_2O$ was added, and the mixture was extracted 3x15 mL $CH_2Cl_2$. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated to give a 2:1 ratio of 5-methyl:8-methyl products. Flash chromatography with 50% E/H afforded a total of 47.3 mg (23%) of separable oils: **5-methyl (8)**, $^1H$ NMR ($CDCl_3$) δ 8.00 (dd, 1 H, *J*=5.4 and 1.2 Hz), 7.33 (dd, 1H, *J*=7.2 and 1.2 Hz), 7.11 (dd, 1H, *J*=5.5 and 2.0 Hz), 6.84 (dd, 1H, *J*=7.2 and 5.4 Hz), 6.80 (d, 1H, *J*=5.5), 5.52 (d, 1H, *J*=2.0 Hz), 1.93 (s, 3H); $^{13}C$ NMR ($CDCl_3$) δ 174.1, 146.3, 144.4, 143.6, 143.4, 124.9, 119.3, 89.2, 82.6, 15.5; $R_f$=0.33 (50% E/H). **8-methyl (9),** $^1H$ NMR ($CDCl_3$) δ 8.04 (dd, 1 H, *J*=5.4 and 1.5 Hz), 7.38 (dd, 1H, *J*=7.1 and 1.5 Hz), 7.07 (dd, 1H, *J*=5.4 and 1.8 Hz), 6.85 (d, 1H, *J*=5.4), 6.82 (dd, 1H, *J*=7.1 and 5.4 Hz), 5.68 (d, 1H, *J*=1.8 Hz), 1.93 (s, 3H); $^{13}C$ NMR ($CDCl_3$) δ 173.6, 145.11, 145.06, 143.6, 143.3, 126.1, 119.1, 89.5, 80.9, 14.0; $R_f$= 0.40 (50% E/H).

**5-Methoxy-8-quinolinol (11).**[13] To a mixture of 430.0 mg (2.831 mmol) of CsF and 0.86 mL (9.3 mmol) of 2-methoxyfuran in 7.0 mL of $CH_3CN$ was added dropwise a solution of 278.4 mg (0.9299 mmol) of 2-trifluoromethanesulfonyl-3-trimethylsilylpyridine (**6**) in 2.3 mL of $CH_3CN$ (total 0.1 M). The mixture was allowed to stir for 18 h. The solvent was removed in vacuo, $H_2O$ was added, and

this solution was extracted 3x15 mL $CH_2Cl_2$. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated to give initially a crude 64% yield of the epoxyquinoline (**10**): $^1H$ NMR ($CDCl_3$) δ 8.03 (dd, 1 H, *J*=5.4 and 1.5 Hz), 7.47 (dd, 1H, J=7.1 and 1.5 Hz), 7.18 (dd, 1H, J=5.6 and 2.1 Hz), 6.90 (dd, 1H, *J*=7.1 and 5.4 Hz), 6.86 (d, 1H, J=5.6 Hz), 5.53 (d, 1H, J=2.1 Hz), 3.71 (s, 3H); Over a period of four days in $CDCl_3$ this epoxyquinoline rearranged to the hydroxyquinoline (**11**) which was recrystallized from hexanes to afford 45.3 mg (28%) of a solid. Mp 80.8-82.2 °C (lit.[13] mp 83-85 °C) $^1H$ NMR ($CDCl_3$) δ 8.79 (dd, 1H, *J*=4.4 and 1.7 Hz), 8.53 (dd, 1H, J=8.6 and 1.7 Hz), 7.42 (dd, 1H, *J*=8.4 asnd 4.4 Hz), 7.07 (d, 1H, *J*=8.4), 6.77 (d, 1H, *J*=8.4), 3.94 (s, 3H); $^{13}C$ NMR ($CDCl_3$) δ 148.5, 147.8, 146.1, 138.7, 131.5, 121.1, 121.0, 109.0, 105.1, 56.0.

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