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Concomitant morpholine ring contraction and pyridine lithiation in 4-morpholinopyridine: straightforward access to *N*-pyridyl oxazolidines

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ABSTRACT

The reaction of 4-morpholinopyridine with $TMSCH_2Li$ induced an unprecedented anionic ring contraction of the morpholine ring in an *exo*-trig mode while lithiating the pyridine ring regioselectively at C-3. The one-pot process offers a straightforward route to functional oxazolidinyl pyridines.

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4-Dialkylaminopyridines display unique electronic properties. Indeed the external nitrogen's lone pair is delocalized through the π-deficient pyridine ring deeply increasing the electron density at the pyridine nitrogen. The consequence is an enhanced nucleophilicity of this site, which has been extensively exploited for organocatalyzed acylation reactions especially with 4-dimethylaminopyridine (4-DMAP).[1] During the past decade, efforts have been made to elaborate more sophisticated analogues especially directed toward asymmetric organocatalysis.[2]

The incorporation of chiral moieties at the C-3 or C-2 position of the pyridine ring has been the focus of much attention. The strong polarization of the molecule has been turned into advantage to direct lithiations at both positions of the pyridine ring (Fig. 1).

The nucleophilicity of pyridine nitrogen was exploited to lithiate the C-2 position using two routes. Vedejs and co-workers applied the Kessar's strategy (BF_3 complexation and LiTMP lithiation) to introduce carbonyl compounds at C-2.[3] This reaction was recently performed by us in a more applicable and selective way using the BuLi–LiDMAE (LiDMAE = $Me_2N(CH_2)_2OLi$) aggregates[4] in non coordinating solvents. A strong coordination of lithium by pyridine nitrogen and subsequent aggregates formation placed *n*-BuLi in adequate position for H-2 proton abstraction. The metallation was successfully applied to 4-DMAP, 4-pyrrolo, 4-pyrrolidino, and 4-piperazinyl pyridines.[5] Of particular interest is also the acidifying effect of the pseudo-iminium form on the H-3 proton. Possibly due to a lack of appropriate basic reagent in the past, such a feature has been exploited only recently. Our group has reported the first lithiation of the C-3 position of 4-dimethylamino-, and 4-pyrrolidinopyridine using $TMSCH_2Li$-based reagents in THF.[6]

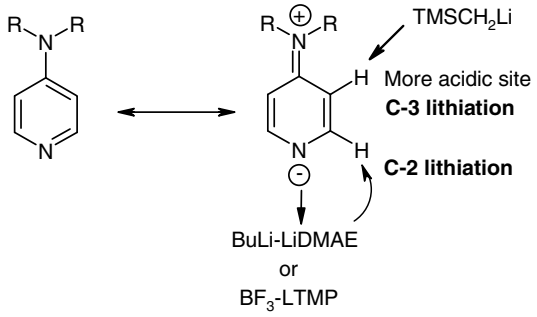

Figure 1. Electronic effects in 4-dialkylaminopyridines, potential lithiation sites.

As part of a program aiming at the lithiation of pyridine bearing polyheteroatomic substituents, we decided to investigate the C-3 lithiation in the presence of a coordinating atom on the amino substituent. In this context, 4-morpholinopyridine **1** was the substrate of choice since the presence of the oxygen could deeply modify the metallation pathway and give access to new selectivities. Indeed combined coordination of lithium and acidification by pyridine electron-withdrawing effect could lead to a competitive deprotonation of the morpholine ring α to nitrogen[7] (Fig. 2).

Thus, we examined the lithiation under various conditions. Our first attempts to react **1** with *n*-BuLi (−78 °C), *t*-BuLi (−78 °C), or

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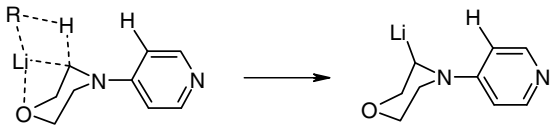


Figure 2. Potential deprotonation of the morpholine ring induced by directing effects of oxygen and pyridine acidity.

LTMP (−20 °C) in THF gave no reaction product or nucleophilic addition to the pyridine ring when the alkyllithiums were used at higher temperatures. Thus from our previous results on C-3 lithiation, we focused on the reaction of **1** with $TMSCH_2Li$ in THF. Since the potentially formed lithio morpholine could be expected to exhibit instability,[8] we chose to first check the integrity of the morpholine ring along the metallation by quenching the mixtures with methanol at low temperature. The reaction content was analyzed by GC (Table 1).

As shown, except at −78 °C or using a stoichiometric amount of base (entries 1 and 4), **1** was always turned into the oxazolidinylpyridine **2a**, indicating a deprotonation of the morpholine ring. To our knowledge, such isomerization of the morpholine ring under anionic conditions has not been reported yet.

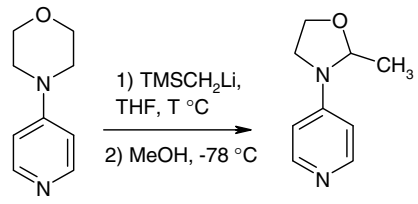
At least 2 equiv of $TMSCH_2Li$ were necessary for the reaction to proceed. At 0 °C, the **2a**:**1** ratio was found critically time dependent (see entries 3 and 5). The highest **2a:1** ratios were obtained at 20 °C (entries 6–8). The use of potential stabilizing agents expected to slow down the isomerization did not change significantly the reaction outcome.

To get a further insight into the reaction pathway, the lithiation was repeated under conditions of entries 1, 2, 3, and 6. The potentially formed lithio intermediates were intercepted with MeSSMe as electrophile, and the mixtures were analyzed by GC (Table 2).

The results are synthetically and mechanistically important. At first, no lithiated intermediate was trapped when the metallation was conducted at −78 °C, indicating that neither the morpholine nor the pyridine ring was metallated at such temperature. Of particular interest were the results of entries 2 and 3. Under these conditions, we were surprised to observe not only the formation of the expected oxazolidine but also the functionalization of the pyridine ring exclusively at C-3. Product **2b** was obtained in 69% yield when the reaction was performed at 0 °C, the remaining part being starting **1** and pyridyloxazolidine **2a**. Finally, the reaction performed at 20 °C gave only **2a** in 95% yield. A protonation of the lithio intermediates by the solvent could be suspected here.

This ring contraction–metallation sequence was unprecedented[9] and its origin was puzzling especially concerning the starting intermediates. The mechanism depicted on Scheme 1 could be proposed. At first it could be assumed that, whatever the pathway, the morpholine ring had to be lithiated to promote the ring contraction. Since 2 equiv of $TMSCH_2Li$ were needed to achieve the reaction, the formation of a dilithio intermediate could be postulated. The instable lithiated morpholine ring then probably underwent a fast ring opening leading to an enaminoalkoxide-type intermediate.[8a,b] Quenching by electrophile followed by hydrolysis then resulted in functionalization at C-3 of pyridine and ring closing in the *exo*-trig mode in agreement with the Baldwin rules leading to product **2b**.

Table 1
Reaction of **1** with $TMSCH_2Li$[a]

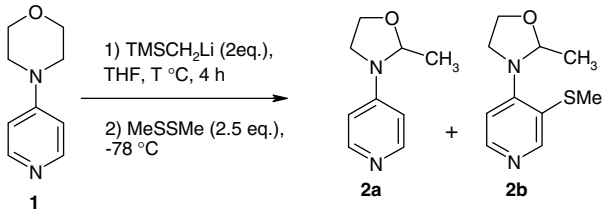


1 **2a**

Entry	$TMSCH_2Li$ additive (equiv)	*T* (°C)	Time (h)	**2a**:**1**[b]
1	2	−78	1–4	0:100
2	2	−25	4	88:12
3	2	0	4	90:10
4	1	0	4–5	0:100
5	2	0	2	65:35
6	2	20	2	97:3
7	3	20	1	95:5
8	3	20	2	98:2
9	2 + TMEDA (2)	0	4	92:8
10	2 + LiDMAE (1)	0	4	90:10

[a] Reaction performed on 0.92 mmol of **1**.
[b] Ratio determined by GC.

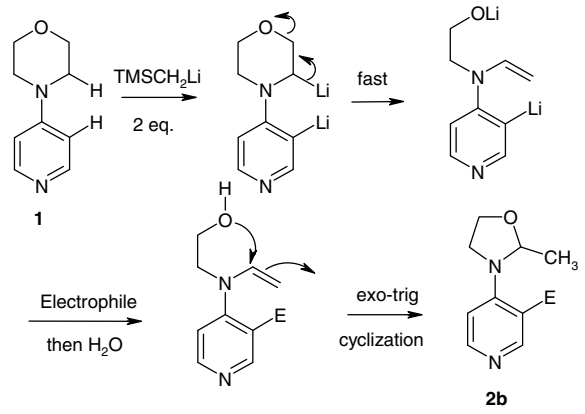
Table 2
Reaction of **1** with $TMSCH_2Li$ and electrophilic quenching[a]



1 **2a** **2b**

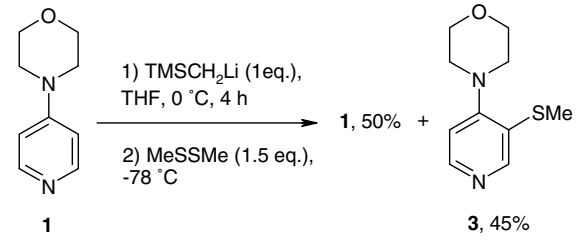
Entry	*T* (°C)	**1**[b] (%)	**2a**[b] (%)	**2b**[b] (%)
1	−78	95	–	–
2	−25	12	15	67
3	0	10	16	69
4	20	5	95	–

[a] Reaction performed on 0.92 mmol of **1**.
[b] Determined by GC.



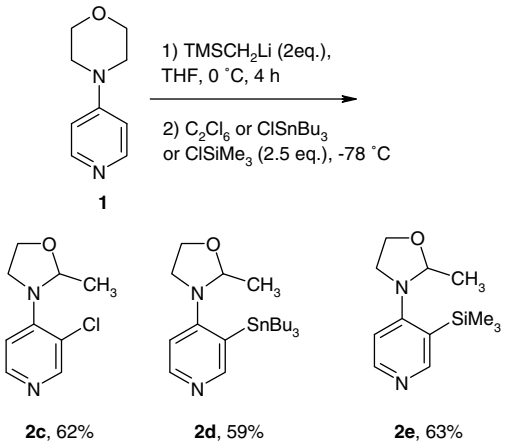
1 **2b**

Scheme 1. Proposed mechanism for concomitant ring contraction of morpholine ring and C-3 lithiation of pyridine ring.



1

Scheme 2. Reaction of **1** with 1 equiv of $TMSCH_2Li$ and trapping with electrophile.



Scheme 3. Synthesis of C-3 functional pyridyloxazolidines.

To get an additional insight on the nature of the initial lithiation site, we decided to trap the potentially formed intermediate under conditions of entry 4 (Table 1), that is, with 1 equiv of $TMSCH_2Li$. Under these conditions, compound **3** resulting from exclusive lithiation of the pyridine ring without ring contraction was obtained in 45% yield, the remaining part being unreacted **1** (Scheme 2). This result was in agreement with the those obtained after protonation in Table 1, revealing the retention of the morpholine ring. This indicated that the dilithio intermediate was probably formed after initial C-3 lithiation of the pyridine ring.

Finally, we examined the reaction with some electrophilic reagents (Scheme 3).[10] As shown, the expected chloro, tributylstannyl, and trimethylsilyl oxazolidinyl pyridines were obtained in good yields.

In summary, we have disclosed a new lithiation reaction of 4-morpholinopyridine. The reaction with $TMSCH_2Li$ induced an unprecedented ring contraction of the morpholine ring in an *exo*-trig mode while lithiating the pyridine ring regioselectively at C-3. This one-pot process offers a straightforward route to functional oxazolidinyl pyridines not easily accessible by other methods. Work is now progressing to extend the scope of the reaction which could be exploited nicely, especially in cascade processes.

Acknowledgement

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10. Lithiation of 4-morpholine and formation of functional pyridyloxazolidines. To a cold (0 °C) solution of 4-morpholinopyridine (302 mg, 0.92 mmol) in anhydrous THF (4 mL) was added dropwise $TMSCH_2Li$ (2 mL of a 0.92 M solution in hexanes, 1.84 mmol). The reaction medium was then stirred at 0 °C for 4 h. The orange solution was then cooled at −78 °C and treated dropwise with a solution of the appropriate electrophile (2 mmol) in anhydrous THF (2 mL). After a 1 h stirring period, the hydrolysis was performed at 0 °C with water (4 mL). The organic phase was then separated and the aqueous phase extracted twice with CH_2Cl_2 (10 mL). After drying of organic phases over $MgSO_4$ and evaporation of solvents, the crude product was purified by column chromatography using a 40:50:10 hexane/ethyl acetate/triethylamine mixture as eluent. *Spectroscopic data*: Compound **2c** (113 mg, 62%), NMR ^1H ($CDCl_3$): δ 8.32 (s, 1H), 8.16 (d, J = 6.2 Hz, 1H), 6.56 (d, J = 6.3 Hz, 1H), 5.55 (q, J = 5.2 Hz, 1H), 4.25 (m, 1H), 3.93 (m, 2H), 3.45 (m, 1H), 1.37 (d, J = 5.3 Hz, 3H). NMR ^{13}C ($CDCl_3$): δ 151.2, 149.1, 148.0, 114.3, 111.6, 87.4, 65.9, 49.4, 19.6. Anal. Calcd for $C_9H_{11}ClN_2O$: C, 54.42; H, 5.58; N, 14.10. Found: C, 54.12; H, 5.32; N, 13.87. Compound **2d**: (245 mg, 59%), NMR ^1H ($CDCl_3$): δ 8.33 (s, 1H), 8.25 (d, J = 5.8 Hz, 1H), 6.59 (d, J = 5.8 Hz, 1H), 5.26 (q, J = 5.3 Hz, 1H), 4.16 (m, 1H), 3.89 (m, 2H), 3.63 (m, 1H), 1.52 (m, 6H), 1.37–1.28 (m, 9H), 1.15 (m, 6H), 0.88 (t, J = 7.2 Hz, 9H). NMR ^{13}C ($CDCl_3$): δ 156.5, 153.2, 148.0 127.2, 110.6, 86.8, 63.5, 48.4, 29.1, 26.9, 19.9, 12.9, 11.2. Anal. Calcd for $C_{21}H_{38}N_2OSn$: C, 55.65; H, 8.45; N, 6.18. Found: C, 55.08; H, 8.62; N, 5.86. Compound **2e**: (136 mg, 63%) NMR ^1H ($CDCl_3$): δ 8.33 (s, 1H), 8.10 (d, J = 5.8 Hz, 1H), 6.45 (d, J = 5.8 Hz, 1H), 5.23 (q, J = 5.2 Hz, 1H), 4.09 (m, 1H), 3.68 (m, 2H), 3.33 (m, 1H), 1.35 (d, J = 5.2 Hz, 3H), 0.21 (s, 9H). NMR ^{13}C ($CDCl_3$): δ 153.0, 151.5, 146.7, 122.9, 108.7, 88.5, 64.2, 48.9, 19.7, −1.42. Anal. Calcd for $C_{12}H_{20}N_2OSi$: C, 60.97; H, 8.53; N, 11.85. Found: C, 61.15; H, 8.31; N, 12.09.