DIRECTED 2-METALATION OF *N,N*-DIETHYL *O*-3-(4-TRIMETHYLSILYL)PYRIDYL CARBAMATE. A SILICON PROTECTION ROUTE FOR HIGHLY SUBSTITUTED PYRIDINES†

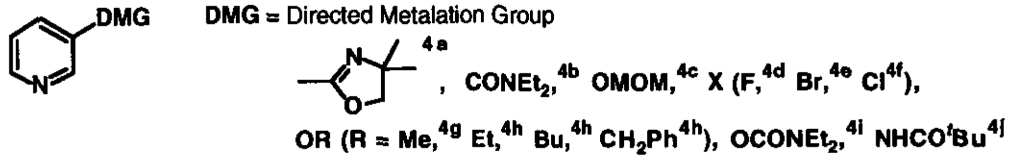
Masao Tsukazaki and Victor Snieckus*

Guelph-Waterloo Centre for Graduate Work in Chemistry, University of Waterloo,
Waterloo, Ontario, Canada N2L 3G1

Abstract– LiTMP metalation of *N,N*-diethyl *O*-3-(4-trimethylsilyl)pyridyl carbamate (**4**) followed by quenching with a number of carbon and heteroatom electrophiles affords a variety of 2-substituted derivatives (**5**) (**Table 2**) thus providing a versatile new methodology for the synthesis of polysubstituted pyridines.

The Directed *ortho* Metalation (DoM) reaction is currently a fertile playground for the regiospecific construction of polysubstituted aromatics.[1] In the context of heteroaromatics, the DoM reaction for π-excessive (furan, thiophene) rings is also a long recognized and widely explored process;[2] however, its application to π-deficient (pyridine, diazine) systems[3] was detained by the prior evidence that such low-LUMO MO substrates undergo facile nucleophilic attack by RLi and RMgX reagents. Despite this precognition, the past decade has witnessed the development of a number of DMGs, already of demonstrated utility in aromatic DoM chemistry, which promote pyridine *ortho* deprotonation thus allowing the emergence of new pyridine synthetic methodologies.[3] The body of knowledge for 3-DMG-substituted pyridines (**Scheme 1**) indicates primarily a 4-metalation regiochemistry for a variety of carbon- and heteroatom-based DMGs, 2-deprotonation has been achieved only for DMG = X and OR under carefully chosen conditions.[4] In continuation of our DoM studies on isomeric *O*-pyridyl carbamates,[4i] we have found that 2-deprotonation of *O*-3-pyridyl carbamate can be achieved by adapting the silicon protection tactic[5] for the more reactive C-4 metalation site (**4**). These results, disclosed herein, provide new synthetic regimens for the regiospecific construction of substituted pyridines which are inaccessible by available routes.

Scheme 1



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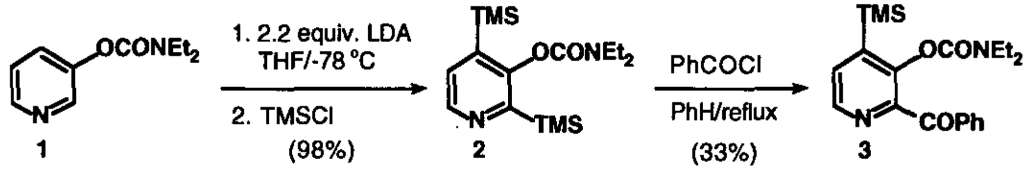
† Dedicated to Professor Ted Taylor in celebration of his 70th birthday and in recognition of his inspiring adventures in heterocyclic chemistry.

Powerful DMGs (e.g. $CONEt_2$, oxazoline , OMOM) promote kinetic 4-deprotonation presumably due to a strong base-DMG complexation effect while weak DMGs (e.g. X, OR) may favor 2-metalation owing to a preferred base-*N*-lone pair coordination. For the *O*-3-pyridyl carbamate, we found that the earlier observations of 4-deprotonation using *s*-BuLi/TMEDA[4i] or LDA[6] were duplicated also by metalation with *t*-BuLi or mesityl-Li in THF or Et_2O solution as evidenced by CD_3OD quench. However, when **1** (**Scheme 2**) was subjected to 2.2 equiv. of LDA followed by treatment with excess TMSCl, the 2,4-disilylated derivative (**2**) was obtained in 98% yields.[7] Following original observations by Pinkerton and Thames[8] of *ipso* carbo-desilylation of 2-TMS-pyridine, **2** was treated with excess benzoyl chloride to give **3**, an indication of a potential mild alternative to the metalation protocol for the introduction of carbon substituents into the 2-position (**Table 2**).

Scheme 2



The observed formation of **2** suggested that 2-deprotonation could be achieved on the 4-TMS-carbamate (**4**).[7] In the first set of experiments using several RLi reagents and $(PhS)_2$ as the electrophile (**Table 1**), low to modest yields of products(**5f**)(E = SPh) were obtained. Thus both *s*-BuLi/TMEDA and *t*-BuLi gave unsatisfactory results in THF (Entries 1 and 2). Somewhat higher yields were observed using *t*-BuLi in Et_2O at -78 °C (Entry

Scheme 3

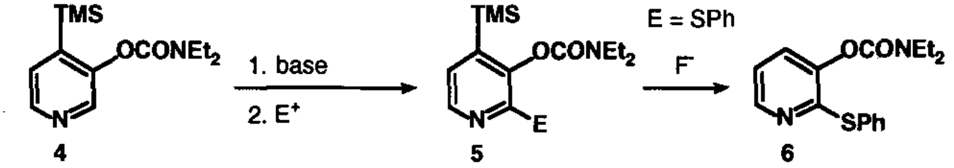


Table 1. Reactions of 4 with RLi Bases Using $(PhS)_2$ as the Electrophile

Entry	Base	Solvent	Temp, °C	Time, min	Yield of **5f**, %
1	*s*-BuLi/TMEDA	THF	-78	10	31
2	*t*-BuLi	THF	-78	15	29
3	*t*-BuLi	Et_2O	-78	15	43
4	*t*-BuLi	Et_2O	-110	10	49
5	*t*-BuLi/HMPA	Et_2O	-110	10	58
6	*n*-BuLi	THF	-78	10	0[a]
7	Mesityl-Li	THF	-78→ -15	60	0[b]

[a] Addition of *n*-BuLi to the pyridine ring of **4** was observed. [b] Starting material was recovered.

3) and -110 °C (Entry 4) while the best result was realized using *t*-BuLi/HMPA (Entry 5) at the latter temperature. *n*-BuLi and mesityl-Li proved completely unsatisfactory (Entries 6 and 7).

Table 2. Synthesis of Pyridine Derivatives Using LiTMP as Base

Entry	Method[a]	E+	Product	E	Yield, %
1	A	CD_3OD	**5a**	D	87[b]
2	A	^iPrCHO	**5b**	$CH(OH)Pr^i$	48
3	A	PhCHO	**5c**	CH(OH)Ph	82
4	A	Ph_2CO	**5d**	$C(OH)Ph_2$	56
5	A	PhCOCl	**3**	COPh	41
6	B	CCl_3CCl_3	**5e**	Cl	64
7	B	$(PhS)_2$	**5f**	SPh	79
8	B	Et_3SiCl	**5g**	$SiEt_3$	89
9	B	PhSeCl	**5h**	SePh	72

[a] Method A: 1.5 equiv. LiTMP. Method B: 1.2 equiv. of LiTMP. [b] 58% d_1-incorporation by ms.

Conditions for satisfactory and convenient 2-deprotonation of **4** were achieved using the hindered strong base, LiTMP (**Table 2**). Thus, in appreciation of the previous experience of Iwao on pyridine amides,[9] a short metalation time (5 min) at -78 °C followed by rapid electrophile quench led to 2-substituted products.[10] Preliminary results show that a variety of carbon and heteroatom electrophiles can be introduced in modest to good yields.[11] Furthermore, desilylation in a selected case using TBAF[12] led to the formation of **6** thus opening the door for further DoM chemistry.

In summary, using optimized conditions (LiTMP/THF/-78 °C/5 min), 2-deprotonation of *O*-3-pyridyl carbamates has been achieved, **4**→**5** by taking advantage of the silicon protection protocol[5] at C-4. In view of the facile unmasking of the reactive C-4 metalation site in **5** and the regioselective *ipso* carbo-desilylation reactivity of **2**, broader use of the developed methodology for the construction of substituted pyridines may be anticipated.[13]

ACKNOWLEDGEMENT

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7. Use of 1.1 equiv. of LDA led to a separable mixture of **4** (88%) and **2** (9%). See also ref 6.
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10. Metalation for 45 min followed by benzaldehyde quench gave **5c** (51%) together with 2-(*N,N*-diethylcarbamoyl)-4-TMS-3-hydroxypyridine (20%), the result of an anionic Fries rearrangement. See also ref 6.
11. The following procedure (Method A) is representative. To a solution of LiTMP (1.50 mmol, prepared *in situ* from *n*-BuLi and tetramethylpiperidine at 0 °C) in THF at -78 °C was added a solution of **4** (0.226 g, 1.00 mmol) in THF (0.5 ml). After 5 min, PhCHO (0.209 ml, 2.00 mmol) was added and the mixture was stirred for 15 min at -78 °C. The solution was then warmed to -20 °C and quenched with sat. NH_4Cl solution. Extraction with Et_2O followed by drying ($MgSO_4$) and column chromatography afforded pure **5c** (0.306 g, 82%) as colorless crystals, mp 71-72 °C (Et_2O-hexane).
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13. All new compounds show spectroscopic (ir, ^1H and ^{13}C nmr, ms) and combustion analysis data fully consistent with their proposed structures.

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