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TMSCH$_2$Li and TMSCH$_2$Li−LiDMAE: Efficient Reagents for Noncryogenic Halogen−Lithium Exchange in Bromopyridines

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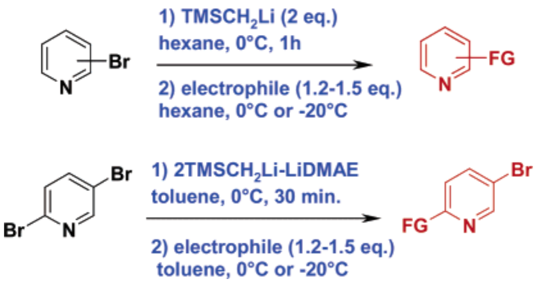
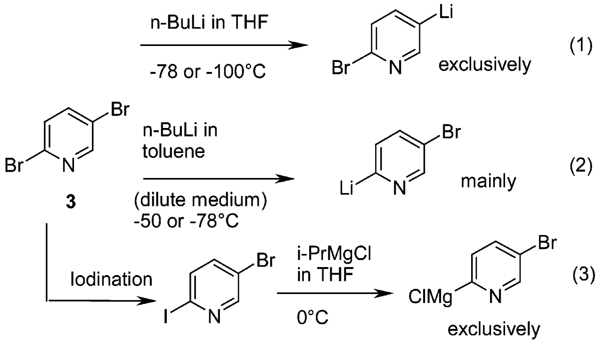


TMSCH$_2$Li and TMSCH$_2$Li−LiDMAE have been used efficiently for bromine−lithium exchange in 2-bromo-, 3-bromo-, and 2,5-dibromopyridines under noncryogenic conditions, while low temperatures (−78 to −100 °C) are always needed with *n*-BuLi. The aminoalkoxide LiDMAE induced a remarkable C-2 selectivity with 2,5-dibromopyridines in toluene at 0 °C, which was unprecedented at such a temperature. The lithiopyridines were successfully reacted with electrophiles also under noncryogenic conditions giving the expected adducts in good yields.

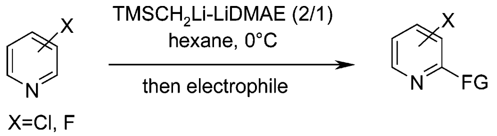
Metal−halogen exchange in 2,5-dibromopyridine **3** has been the subject of much attention motivated by the usefulness of this doubly reactive intermediate for the synthesis of ligands[1,2] and biologically active compounds.[3] First studies by Parham[4] and further developments by other groups[1,2] clearly established that the C-5 position could be lithiated selectively with *n*-BuLi in THF at −78 or −100 °C (Scheme 1, eq 1).

In contrast, Wang[5] reported the control of the C-2 lithiation to be more problematic. Due to the instability of 2-lithio-5-bromopyridine, careful attention to reaction temperature (−50 or −78 °C), solvent (toluene), as well as dilution was needed to avoid C-2 to C-5 isomerization and degradation (Scheme 1, eq 2).

SCHEME 1. Metal−Halogen Exchanges Reported in the Literature



SCHEME 2. Metalation of Electrophilic Halogenopyridines with TMSCH$_2$Li−LiDMAE



An alternative to this sensitive lithiation process has been reported recently by Song,[6] who realized the magnesium halogen exchange at C-2 under noncryogenic conditions (0 °C) using *i*-PrMgCl in THF. The reaction proceeded smoothly allowing the preparation of a range of C-2-substituted derivatives. However, since the magnesation of 2,5-dibromopyridine was known to occur mainly at C-5,[7] the authors had to exchange bromine at C-2 for iodine to direct the reaction toward the desired position, thus implying an additional step and added expense to the transformation (Scheme 1, eq 3).

Thus, the search for new reagents able to promote the clean bromine−lithium exchange in pyridines under easily applicable conditions remains challenging.

Recently, we have reported a new lithiating agent TMSCH$_2$Li−LiDMAE (with LiDMAE = Me$_2$N(CH$_2$)$_2$OLi)[8−10] which promoted the clean C-6 deprotonation of chloropyridines and even of the highly sensitive fluoropyridines at 0 °C when used in hexane (Scheme 2).[8] This unprecedented reactivity contrasted with those of our previous reagent BuLi−LiDMAE for which low temperatures (−78 to −100 °C) were needed to prevent concomitant nucleophilic addition.[11]

This high level of functional tolerance at 0 °C led us to consider TMSCH$_2$Li for the selective bromine−lithium exchange in 2,5-dibromopyridine under noncryogenic conditions.

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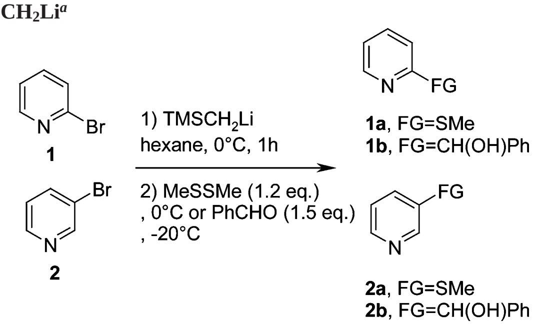
TABLE 1. Bromine−Lithium Exchange in 1 and 2 with $TMSCH_2Li$[a]



$TMSCH_2Li$ (equiv)	substrate	electrophile	yield[b] (%)
2	**1**	MeSSMe	**1a**, 94[c]
1.5	**1**	MeSSMe	**1a**, 70[d]
1	**1**	MeSSMe	**1a**, 47[d]
2	**2**	MeSSMe	**2a**, 88[c]
2	**1**	PhCHO	**1b**, 86[c]
2	**2**	PhCHO	**2b**, 88[c]

[a] Reaction performed on 1.84 mmol of **1** or **2**. [b] Isolated yield. [c] The GC analysis revealed conversions >98%. [d] The remainder was unreacted **1**.

SCHEME 3. Proposed Pathway for $TMSCH_2Li$ Consumption

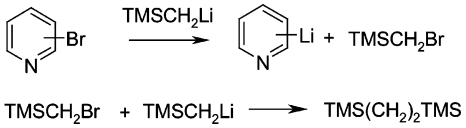
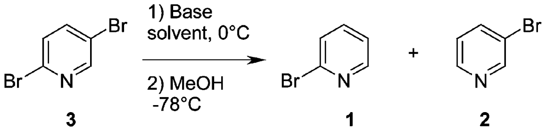


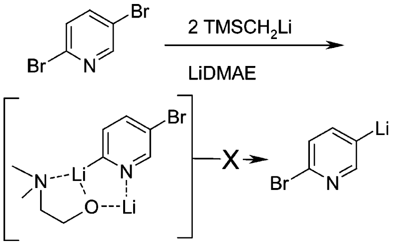
TABLE 2. Metalation of 3 with $TMSCH_2Li$-Based Reagents[a]



entry	$TMSCH_2Li$ (equiv)	LiDMAE (equiv)	solvent	time (h)	**1**[b] (%)	**2**[b] (%)	S.M.[b] (%)
1	2		toluene	1	29	38	23
2	2		toluene	2	22	24	
3	2		hexane	2	5	80	14
4	2	1	hexane	2	15	84	<1
5	2	1	toluene	0.5	4	**95**	<1
6	2	1	toluene	1	5	**94**	<1
7	2	1	toluene	2	7	**92**	<1
8	2		THF	0.5			
9	2		Et_2O	0.5	65	10	

[a] Reaction performed on 1.84 mmol of **3**. [b] GC yields. S.M.: starting material.

SCHEME 4. Proposed Intermediate for Stabilization of 5-Bromo-2-lithiopyridine



Since no data was available about the reactivity of $TMSCH_2Li$ in such halogen−metal exchange reaction, we first investigated its behavior at 0 °C toward 2- and 3-bromopyridine in hexane (Table 1). Bromine−lithium exchange in such substrates was known to need very low temperature (−78 to −100 °C) with *n*-BuLi in THF to avoid dimerization, side deprotonation and subsequent aryne formation with the latter.[12]

Interestingly, $TMSCH_2Li$ accomplished the bromine−lithium exchange at 0 °C very cleanly with the two substrates. The exchange product was obtained exclusively in high yield. In particular, no product resulting from side deprotonation of **2** was detected. The yields decreased proportionally to the amount of $TMSCH_2Li$, and 2 equiv of $TMSCH_2Li$ were necessary for completion of the exchange. An explanation is the formation of reactive $TMSCH_2Br$ which subsequently consumed $TMSCH_2Li$ along the exchange process. $TMS(CH_2)_2TMS$ was found present in NMR spectra and GC analysis of the crude mixtures (Scheme 3).

The metalation and the electrophilic condensation step were realized in the same solvent and at similar temperatures. Large excesses of electrophiles were not necessary despite the use of 2 equiv of $TMSCH_2Li$. The excess of the basic reagent was here probably consumed by $TMSCH_2Br$ before addition of the electrophile.

$TMSCH_2Li$ was found to be practical and selective for the bromine−lithium exchange in monobromopyridines at 0 °C. This result was strongly encouraging for trying it in the selective C-2 lithiation of 2,5-dibromopyridine **3**. The reaction was investigated under various conditions with focus on solvent effects. The metalation mixtures were quenched with MeOH and analyzed by GC (Table 2).

As shown, in toluene, which was the best solvent reported for selective C-2 lithiation with *n*-BuLi at −78 °C,[5] $TMSCH_2Li$ led to a mixture of **1** and **2** at 0 °C. Extended reaction time led to C-2 to C-5 isomerization and degradation of **3** (entries 1 and 2).

In contrast, in hexane, $TMSCH_2Li$ gave 80% of C-2 metalation with a small amount of C-5 metalation (entry 3). The effect of $TMSCH_2Li$−LiDMAE on the reaction outcome was also examined. In hexane, the aminoalkoxide induced a complete conversion but a loss in selectivity was noted. The effect of incorporating LiDMAE was remarkable in toluene leading to the C-2 metalation in 95% yield with only 4% of the other isomer after 30 min at 0 °C. Extended reaction time did not produce notable isomerization of the lithiated species (entries 5−7).

The effect of coordinating solvents was also examined (entries 8 and 9) to attempt the metalation of the C-5 position. In THF, only degradation was observed while diethyl ether led to the expected C-5 lithiation in 65% yield.

$TMSCH_2Li$−LiDMAE was, to our knowledge, the first reagent to regioselectively lithiate 2,5-dibromopyridine at 0 °C. The selectivity could be explained by chelation of 2-lithio intermediate by LiDMAE ensuring stabilization and preventing the C-2 to C-5 isomerization (Scheme 4). The reason for a lower selectivity in hexane remains unclear but could be due to a slower formation of the 2-lithiopyridine in this less polar solvent.

The synthetic usefulness of this new lithiation process was then finally illustrated by reaction with a set of electrophilic reagents (Table 3). All of the electrophiles reacted efficiently providing the expected products in good yields comparable with

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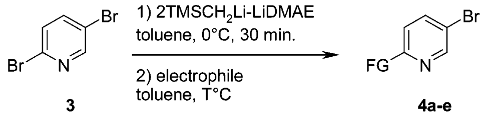
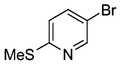
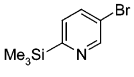
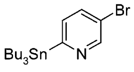
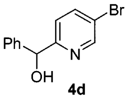
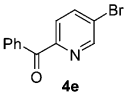
TABLE 3. Reaction with Electrophilic Reagents[a]



Entry	Electrophile (eq.)	T°C	Product	Yield (%)[b]
1	MeSSMe (1.2)	0	 **4a**	79
2	$ClSiMe_3$ (1.2)	0	 **4b**	77
3	$ClSnBu_3$ (1.2)	0	 **4c**	65
4	PhCHO (1.5)	-20	 **4d**	76
5	$PhCONMe_2$ (1.5)	-20	 **4e**	70

[a] Reaction performed on 1.84 mmol of **3**. [b] Isolated yield after column chromatography. The conversions were >97% in each case.

those obtained using BuLi at low temperatures (−78 °C)[5] or by the magnesation process.[6] The quenching step consumed reasonable amounts of electrophiles (20−50% excess compared to **3**) despite the use of 2 equiv of $TMSCH_2Li$, and the condensation step could be realized efficiently at 0 or −20 °C in toluene.

In summary, we have discovered a new reactivity of $TMSCH_2Li$ and $TMSCH_2Li-LiDMAE$ reagents. These reagents are suitable for selective bromine-lithium exchange and subsequent functionalization of several bromopyridines in apolar solvents. The effect of LiDMAE on the selectivity in bromine-lithium exchange of 2,5-dibromopyridine is remarkable. The transformation proceeds under noncryogenic conditions consuming only small excesses of electrophiles opening access to a potentially scalable process.

Experimental Section

Procedure for Bromine−Lithium Exchange in 2,5-Dibromopyridine. To a solution of 2-dimethylaminoethanol (164 mg, 1.84 mmoles) in toluene (6 mL) cooled at 0 °C was added dropwise (trimethylsilyl)methyllithium (5.52 mmol, 6 mL of a 0.92 M solution in hexane) under a nitrogen atmosphere. After being stirred for 30 min at the same temperature, a solution of 2,5-dibromopyridine (436 mg, 1.84 mmoles) in toluene (2 mL) was added dropwise. The obtained red solution was then stirred for 30 min at 0 °C and treated dropwise with a solution of the appropriate electrophile (2.2 or 2.76 mmol) in toluene (2 mL) at 0 or −20 °C. After 1 h of stirring, the mixture was hydrolyzed with water (10 mL). The organic layer was then extracted with diethyl ether (10 mL) and dried over $MgSO_4$, and the solvents were evaporated. The crude product was subjected to GC analysis and finally purified by column chromatography using hexane−AcOEt mixtures as eluent.

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Supporting Information Available: Experimental details and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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