Bromine–lithium exchange under non-cryogenic conditions: $TMSCH_2Li$–LiDMAE promoted C-2 lithiation of 2,3-dibromopyridine†

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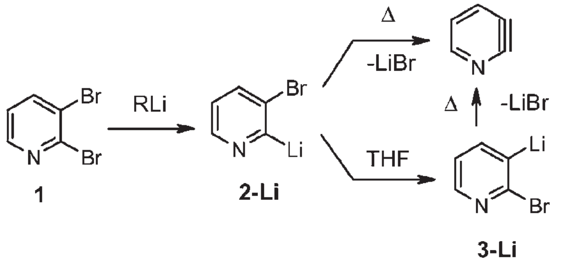
The first C-2 selective bromine–lithium exchange in 2,3-dibromopyridine was performed at 0 °C in toluene using the $TMSCH_2Li$–LiDMAE reagent.

Dibromopyridines are versatile heterocyclic compounds. Their unique reactivity has been nicely exploited in syntheses of ligands[1,2] and bioactive molecules.[3] Depending on the position of bromines on the pyridine ring selective functionalizations can be realized. In this context, halogen–lithium exchange has received much attention and efficient methodologies have been developed to control the exchange regioselectivity. The nature of the solvent, the lithiating agent and the temperature were found to have dramatic effects on the reaction outcome. For example, with *n*-BuLi, bromine at C-5 of 2,5-dibromopyridine was exclusively exchanged in THF (−100 °C)[4] while bromine at C-2 was mainly replaced in toluene (−50 or −78 °C).[5] The main issue was here to prevent the isomerization of 2-lithiopyridine into the thermodynamically favoured 5-lithiopyridine. This was essentially achieved using toluene as non-coordinating solvent and diluted medium. As a relevant improvement, we have recently reported that exclusive C-2 lithiation could be realized cleanly under non-cryogenic conditions (0 °C)[6] using the new $TMSCH_2Li$–LiDMAE (LiDMAE = $Me_2N(CH_2)_2OLi$) reagent.[7,8]

To further examine the scope of the process, we investigated the lithiation of 2,3-dibromopyridine **1**, a valuable starting material for the synthesis of fused polyheterocyclic compounds taking advantage of the vicinal bromines[9–11] and polyaromatics.[12] However, this vicinity could also be turned into a drawback for the selectivity of lithiation reactions. Indeed, in addition to the potential isomerization of lithiated species, the formation of pyridyne upon elimination of lithium bromide could also occur when the reaction is performed under non-cryogenic conditions.[13,14] The reaction of **1** with lithium reagents has been studied in detail by Quéguiner and coworkers.[15,16] They have clearly demonstrated, by treating **1** with *n*-BuLi in THF at −60 °C, that a fast isomerization of **2-Li** into **3-Li** occurred giving exclusively the latter intermediate (Scheme 1). This selectivity has been exploited further by several groups to introduce functionalities at C-3.[17,18] Thus the selective formation and stabilization of 2-lithio-3-bromopyridine from **1** remains challenging and urges the development of applicable methodologies.



Scheme 1 Possible isomerization and degradation during lithiation of 2,3-dibromopyridine.

Taking into account our previous works, it was clear that the lithiations had to be performed in a non-coordinating solvent to prevent the exchange at C-3. First experiments in pure hexane were sluggish due to the weak solubility of **1** in this solvent. Thus **1** was reacted with *n*-BuLi and $TMSCH_2Li$-based lithiating agents in toluene and lithiated species were subsequently quenched with methanol (Table 1).‡

The experiments showed that 3-bromopyridine **2** could be obtained as the main product in toluene showing the strong influence of this solvent on the stabilization of the 2-lithio intermediate compared to THF. The reaction outcome was found to be highly dependent upon the temperature and the basic system used. Indeed *n*-BuLi, although completing the reaction, always led to mixtures of **2** and **3** whatever the stoichiometry and temperature (entries 1 and 2). The use of the BuLi–LiDMAE reagent did not change the course of the reaction (entry 3). The **2** : **3** ratio was dramatically modified by increasing the temperature from −78 °C to 0 °C where **3** was formed almost exclusively (entry 4). An attempt to perform the exchange directly at 0 °C only led to complete degradation of the starting material (entry 5).

The results with $TMSCH_2Li$ were in strong contrast. While not reactive at −78 °C due its poor solubility in hexane at that temperature (entry 6), this reagent performed a clean metallation at −20 or 0 °C affording **2** as the main product producing a lower amount of **3** than did *n*-BuLi (entries 7–9). The effect of LiDMAE was remarkable since the reaction with $TMSCH_2Li$–LiDMAE (2/1)[19] afforded **2** exclusively in up to 98% yield in 0.5 h (entry 10). Note that no degradation of the substrate into 2,3-pyridyne was observed at 0 °C as might be expected. Interestingly, the selectivity was maintained even after 3 h of metallation time (entry 11). Degradation occurred when the reaction medium was warmed from 0 °C to rt

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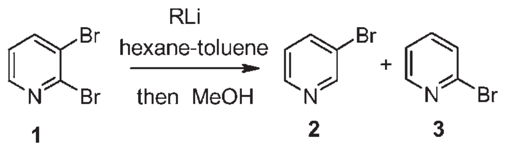
Table 1 Lithiation of **1** with *n*-BuLi and $TMSCH_2Li$-based reagents in toluene[a]



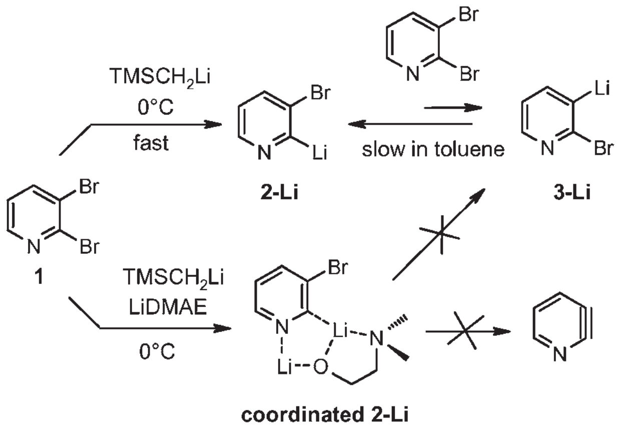
Entry	RLi (eq)	T/°C	t/h[b]	**1** (%)[c]	**2** (%)[c]	**3** (%)[c]
1	BuLi (1.2)	−78	1	1	68	30
2	BuLi (2)	−78	1	—	70	30
3	BuLi (2)–LiDMAE (2)	−78	1	6	63	29
4	BuLi (2)	−78 (1 h) then 0 (1 h)		—	4	96
5	BuLi (2)	0	1	—[e]	—[e]	—[e]
6	$TMSCH_2Li$ (1.2)	−78	1	>95[d]	—	—
7	$TMSCH_2Li$ (1.2)	−20	1	2	83	14
8	$TMSCH_2Li$ (2)	−20	1	—	77	23
9	$TMSCH_2Li$ (2)	0	0.5	—	80	19
10	$TMSCH_2Li$ (2)–LiDMAE (1)	0	0.5	—	>98	—
11	$TMSCH_2Li$ (2)–LiDMAE (1)	0	3	—	97	—
12	$TMSCH_2Li$ (2)–LiDMAE (1)	0 (0.5 h) then rt (0.5 h)		—[e]	—[e]	—[e]

[a] Reactions performed on 0.92 mmol of **1**. [b] Time necessary for complete conversion of **1** (TLC). [c] Ratios determined by ^1H NMR. [d] $TMSCH_2Li$ was poorly soluble at this temperature. [e] Intractable mixtures were obtained.

(entry 12). All attempts to trap a potentially formed 2,3-pyridyne with furan failed.[20]

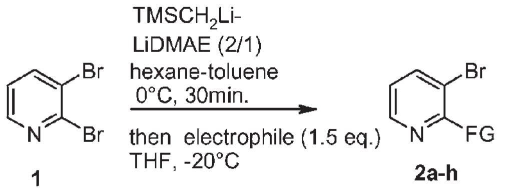
To our knowledge, this is the first example of formation and stabilization of the 2-lithio-3-bromopyridine under non-cryogenic conditions.[21]

A mechanism could be proposed to explain the observed selectivities (Scheme 2). From previous works, the **2-Li** to **3-Li** isomerization was known to proceed by reaction of **2-Li** with unreacted **1**;[16] the use of non-coordinating toluene considerably slowed this reaction in contrast with THF explaining the formation of **2** as the main product besides **3**. However, this isomerization was favoured by increasing the temperature from −78 °C to 0 °C with *n*-BuLi indicating that **3-Li** was thermodynamically formed and that **2-Li** was the kinetically formed intermediate. In contrast with *n*-BuLi, $TMSCH_2Li$ could be used directly at 0 °C thus consuming **1** faster leaving a lower amount available for isomerization explaining the higher **2** : **3** ratio. The exclusive formation of **2-Li** in the presence of LiDMAE at 0 °C could result from the fast consumption of **1** by $TMSCH_2Li$ and subsequent robust coordination by the aminoalkoxide allowing the stabilization of **2-Li** and preventing subsequent isomerization and pyridyne formation. This stabilization effect was supported by the retention of selectivity even after 3 h of metallation (Table 1 entry 11).



Scheme 2 Proposed lithiation pathways for reaction with $TMSCH_2Li$ and $TMSCH_2Li$–LiDMAE.

Table 2 Preparation of C-2 functional 3-bromopyridines[a]



Electrophile	Product		
	FG		Yield (%)[b]
$ClSiMe_3$	$SiMe_3$	**2a**	76
C_2Cl_6	Cl	**2b**	65
I_2	I	**2c**	58
$ClSnBu_3$	$SnBu_3$	**2d**	65
$PhCONMe_2$	COPh	**2e**	60
t-BuCN	CO*t*-Bu	**2f**	73
PhCHO	CH(OH)Ph	**2g**	59
o-AnisylCHO	CH(OH)*o*-anisyl	**2h**	79

[a] Reactions performed on 1.84 mmol of **1**. [b] Isolated yields after column chromatography.

Finally the synthetic usefulness of this new lithiation was investigated. The best metallation conditions (Table 1 entry 10) were reproduced and the lithiopyridines quenched with a set of electrophiles (Table 2). All the expected products were obtained in good yield including silane, halides, stannane, ketones and alcohols. It was remarkable that a minimal amount of electrophile had to be used. This was an additional beneficial effect of the low nucleophilicity of $TMSCH_2Li$.

In summary, we have realized the first selective C-2 lithiation of 2,3-dibromopyridine using $TMSCH_2Li$–LiDMAE in toluene. The reaction was achieved under non-cryogenic conditions without formation of pyridyne and isomerization. This clean and applicable process opened access to a range of 2-functional 3-bromopyridine synthons.

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Notes and references

‡ **General procedure for selective C-2 lithiation of 2,3-dibromopyridine.** To a solution of 2-dimethylaminoethanol (164 m g, 1.84 mmol) in hexane (6 mL) cooled at 0 °C was added dropwise $TMSCH_2Li$ (6 mL, 5.52 mmol) under a nitrogen atmosphere. After stirring for 30 min at the same temperature, a solution of 2,3-dibromopyridine (436 mg, 1.84 mmol) 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 mmol) in THF (2 mL) at −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), 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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19 Other $TMSCH_2Li$–LiDMAE formulations have been tested. The 3 : 1 ratio gave identical results, the 1 : 1 or 2 : 2 ratios gave lower conversions with similar selectivity and the 1 : 2 ratio did not convert the substrate. These stoichiometric effects were in good agreement with our previous works using $TMSCH_2Li$–LiDMAE (see refs. 6 and 7).

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