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Stabilizing *N*-tosyl-2-lithioindoles with bis(*N*,*N*′-dimethylaminoethyl) ether—a non-cryogenic procedure for lithiation of *N*-tosylindoles and subsequent addition to ketones

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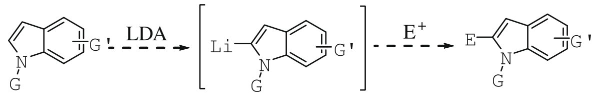
ABSTRACT

A practical procedure suitable for large scale lithiation of *N*-tosylindoles and subsequent addition to ketones is described. Bis(*N*,*N*′-dimethylaminoethyl) ether was found to stabilize 2-lithio-*N*-tosylindole **1A** at −25 °C [The temperatures cited are internal temperatures unless otherwise stated]. Addition of this reagent allows the lithiation of *N*-tosyl indoles and subsequent addition to ketones to operate at −25 °C, a temperature suitable for large scale reactions.

The nucleophilic addition of 2-lithiated indoles to electrophiles provides a straightforward method for the functionalization of indole analogs at the 2-positions (Fig. 1).[1] Typically, an indole derivative equipped with a suitable directing group, such as *N*-tosyl or *N*-Boc group, is treated with a lithiating reagent at −70 °C,[10a] and the resulting 2-lithioindole species is treated with an electrophile to produce a functionalized indole analog. The requirement of low temperatures, mostly due to the instability of the lithiated intermediates, often limits the application of this reaction on large scale. An 'in situ trapping' method specifically addressing this issue was recently reported.[2] In this approach, *N*-Boc-indoles are lithiated at 0 °C in the presence of silylchlorides or boronate esters, which react with the lithiated intermediates immediately after they are generated, thus preventing the decomposition of the latter. Another method involves the more stable 2-magnesioindoles, which can be generated at room temperature.[3]

Recently we required a procedure for the large scale preparations of an indole analog that contains a 2-dialkylhydroxymethyl moiety (structure **2**, Fig. 2). A procedure developed by our colleagues in the research division involves treatment of *N*-tosyl-5-bromoindole (**1**) with lithium diisopropylamide (LDA) at −70 °C followed by addition of an appropriate ketone. Though convenient on small scales, the low temperature required presented difficulty for scale up. In the absence of applicable literature solutions,[4] we set out to investigate if the lithiation-addition sequence can be modified to operate at −25 °C or higher to suit large scale operations.

We started our studies by treating compound **1** with LDA at −70 °C and −25 °C, respectively. The resulting mixtures were then treated separately with 2-butanone. The HPLC trace of the reaction mixture at −70 °C consisted of 76%[10b] of the desired product **2a**, 6% of the starting material **1** and other minor peaks (Table 1, entry 1). In contrast, the HPLC trace of the reaction mixture at −25 °C showed multiple peaks,[5] with 43% of compound **2a** and 11% of the starting material **1** (Table 1, entry 2). Apparently, a significant amount of the lithiated intermediate **1A** decomposed at −25 °C.

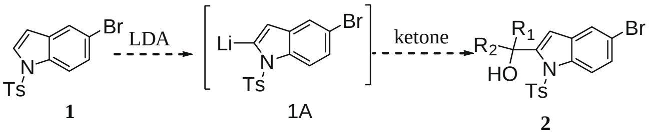


Directing group G = Ts, Boc, etc

Figure 1. Reaction of 2-lithioindoles with electrophiles.

To stabilize the lithiated intermediate, we considered using chelating diamines, such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), as additives.[6] Thus, the reaction at −25 °C was repeated in the presence of 1.5 equiv of TMEDA. To our disappointment, the reaction profile was similar to that without the additive, with 46% of **2a** (Table 1, entry 3).

The report that bis(*N*,*N*′-dimethylaminoethyl) ether effectively modulates the reactivity of Grignard reagents[7] prompted us to test this reagent as the additive. Thus, bis(*N*,*N*′-dimethylaminoethyl)



2a, R_1 = Me, R_2=Et

Figure 2. Lithiation of *N*-tosyl 5-bromoindole (**1**) and addition to ketones.

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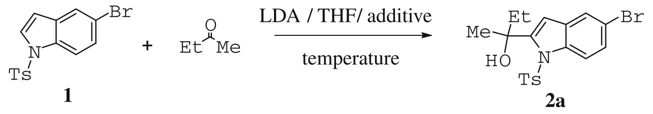
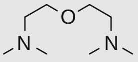
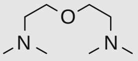
Table 1
Screening of reaction conditions



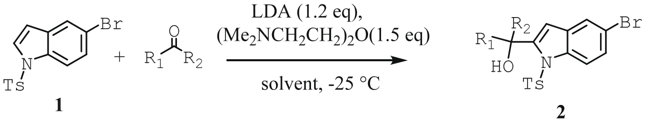
Entry	Additive	Temperature (°C)	HPLC purity[a] (%)	
			2a	**1**
1	none	−70	76	6
2	none	−25	43	11
3	TMEDA (1.5 equiv)	−25	46	9
4	 (1.5 equiv)	−25	79	11
5	 (1.5 equiv)	0	62	20

[a] HPLC area percentage at 254 nM.

ether (1.5 equiv) was added to a solution of compound **1** in THF. The solution was then treated with LDA at −25 °C for 30 minutes before 2-butanone was added. The reaction mixture was shown by HPLC to contain 79% of product **2a** and 11% of compound **1** (Table 1, entry 4), indicating that the decomposition of the lithiated intermediate was largely suppressed.

Encouraged by this result, we further increased the reaction temperature to 0 °C. However, the reaction mixture at this temperature contained more starting material **1** (20%), with 62% of the desired compound **2a** (Table 1, entry 5).

Table 2
Lithiation of **1** and subsequent reaction with ketones in the presence of bis(*N*,*N*′-dimethylaminoethyl) ether



2a. R_1 = Me, R_2 = Et
2b. R_1 = Me, R_2 = Me
2c. R_1,R_2 = -$(CH_2)_3$-
2d. R_1,R_2 = -(CH2)5-
2e. R_1,= Me, R_2 = Ph

Entry	R^1, R^2	Solvents	HPLC Purity (%) of **2**[e,f]	Yield (%), product
1	Me, Me	THF	74	60[a], **2b**
2	Me, Et		79	71[b], **2a**
3	−$(CH_2)_3$−		82	65[b], **2c**
4	−$(CH_2)_5$−		62	48[b], **2d**
5	Ph, Me		38[d]	35[a], **2e**
6	Me, Me	4:1 Tol–THF	69	68[a], **2b**
7	Me, Et		76	71[b], **2a**
8	−$(CH_2)_5$−		73	64[b], **2d**
9	Ph, Me		81	61[c], **2e**

[a] Purified by silica gel chromatography using hexane–EtOAc as the eluting solvents.
[b] Purified by crystallization from MeOH–H_2O.
[c] Purified by crystallization from acetone–hexane.
[d] Reaction mixture contains 60A% of the starting material **1**.
[e] HPLC area percentage at 254 nM.
[f] The major by-product in these reactions is the starting material **1**, typically 10–15% in the reaction mixtures.

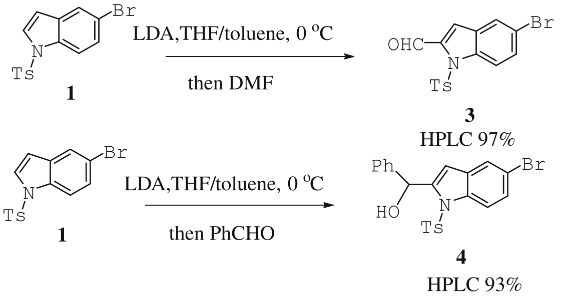


Figure 3. Control experiments using PhCHO and DMF as the electrophiles.

Further experiments focused on the reaction at −25 °C, using different ketone electrophiles and with 1.5 equiv of bis(*N*,*N*′-dimethylaminoethyl) ether. The initial set of experiments was conducted in THF. As shown in Table 2, reactions involving aliphatic ketones gave good yields (Table 2, entries 1–4). However, when acetophenone (**1**) was tested, the reaction gave 38% of the desired product **2** and 60% of the starting material **1**. Change of reaction solvent to 4:1 toluene–THF improved the result. In this system, the reaction produced 81% of product **2e** with 10% of the starting material **1** (Table 2, entries 5 and 9). Another set of experiments showed that the 4:1 toluene–THF solvent system was suitable with other ketones as well (Table 2, entries 6–8).

It was noticed that all the reactions involving ketone electrophiles contained residual starting material **1** that could not be further converted with excess amount of LDA. To determine the source of the residual starting material, two control experiments were carried out using the non-enolizable electrophiles phenyl aldehyde (PhCHO) and dimethylformamide (DMF). Compound **1** was lithiated with LDA in the presence of 1.5 equiv of bis(*N*,*N*′-dimethylaminoethyl) ether at 0 °C, and the lithiated intermediate was then reacted, separately, with PhCHO and DMF. The reactions produced 97% and 93% of products **3** and **4**, respectively, with <3% of the starting material **1** observed. These results showed that the unreacted starting material involving ketone electrophiles is due to ketone enolizations, and that the lithiated intermediate **1A** is stabilized by bis(*N*,*N*′-dimethylaminoethyl) ether even at 0 °C (Fig. 3).

A general experimental procedure follows.[8] To a solution of compound **1** (1.0 equiv) in 4:1 toluene–THF (10 mL of solvent mixture per gram of starting material **1**) under N_2 was added bis(*N*,*N*′-dimethylaminoethyl) ether (1.5 equiv). The solution was cooled to −25 °C. LDA (1.2 equiv, 1.8 M in heptane/ethylbenzene/THF, Aldrich) was added at such a rate that the reaction temperature does not exceed -20 °C. After 30 min, a ketone (2.0 equiv) was added. The mixture was stirred at −25 °C for 15 min and then warmed up to room temperature over 1 h. The reaction was quenched with 1 N HCl at 0 °C and the reaction mixture was extracted with EtOAc. The organic layer was washed with saturated NaCl, dried over Na_2SO_4, and concentrated. The crude product was further purified by either silica gel chromatography or crystallization to give product **2**.

To summarize, we found that bis(*N*,*N*′-dimethylaminoethyl) ether can stabilize 2-lithiated *N*-tosyl lithioindole species. Addition of this reagent allows the lithiation of *N*-tosyl indoles and subsequent addition to ketones to be carried out at −25 °C, a temperature suitable for large scale preparations. Though not fully explored, the procedure described may find applications when other electrophiles are involved and when non-cryogenic temperatures are desirable.[9]

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.120.

References and notes

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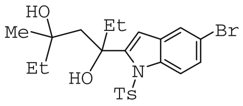
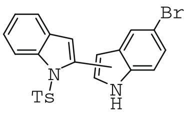
3. Kondo, Y.; Yoshida, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2331–2332.
4. (a) The 'in situ trapping' approach described in Reference **2** cannot be applied to our situation due to the reactivity of ketones toward LDA. (b) The procedure described in reference **3** was investigated using 2-butanone as the electrophile. No desired addition product was observed, likely due to ketone enolization under the reaction conditions.
5. In the absence of bis(*N*,*N*′-dimethylaminoethyl) ether, the HPLC trace of the reaction mixtures at −25 °C showed several pronounced peaks not fully identified. LC–MS analysis suggested that some peaks correspond to structures **I** and **II**. These side products were mostly suppressed by the addition of bis(*N*,*N*'-dimethylaminoethyl) ether.

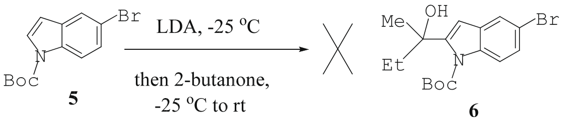


I



II

6. The 'stabilizing' effects of TMEDA toward organolithium species are well documented, though the mechanism of these effects has been the topics of much discussion, see: (a) Shapiro, R. H. *Org. React.* **1976**, *23*, 405; (b) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448–454; (c) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654.
7. Wang, X.-J.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 5593–5595.
8. (a) All reactions were run under nitrogen atmosphere in oven-dried flasks. (b) The examples in Tables 1 and 2 were run on scales of 2 g to 10 g. (c) Solvents used were commercial anhydrous solvents. (d) Bis(*N*,*N*′-dimethylaminoethyl) ether was purchased from Aldrich and dried over 4 Å molecular sieves to KF <300 ppm. Other reagents were used as purchased.
9. *N*-Boc indoles are not suitable substrates. When *N*-Boc 5-bromoindole was treated with LDA at −25 °C followed by addition of 2-butanone, multiple peaks were observed on HPLC, with <5A% of the desired addition product.



10. (a) The temperatures cited are internal temperatures unless otherwise stated. (b) All HPLC purities are area percentage measured at 254 nM.