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Studies on the α-lithiation-*in situ* intramolecular nucleophilic addition reactions of 2-acyl-*N*-sulfonylpyrroles

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ABSTRACT

Treatment of 2-acyl-*N*-sulfonylpyrroles with LDA resulted in the formation of benzo[*e*]pyrrolo[1,2-*b*][1,2]thiazine 5,5-dioxides in moderate to good isolated yields.

The α-lithiation of *N*-sulfonylpyrroles followed by trapping with electrophiles is a reliable way to obtain 2-substituted pyrroles [1]. As part of our continued interest toward the synthesis of polycyclic ring systems embedding pyrroles [2], we need to get access to substituted pyrrole-2-carboxylate. To this end, we treated *N*-tosylpyrrole **1** with LDA, followed by reaction with dimethyl carbonate (Scheme 1). The reaction yielded pyrrole-2-carboxylate **2** and pyrrole-2,5-dicarboxylate **3** in 27% and 31% isolated yields, respectively. Besides, a small amount of compound **4** was also obtained. Literature search indicated that such structural motifs possess appreciable antitumor activity [3], which are also potential 5-HT_6 receptor ligands [4]. Evidently, **4** was formed *via* α-lithiation of the benzene ring of **2** and subsequent intramolecular nucleophilic addition to the ester functionality [5–7]. Indeed, treatment of **2** with LDA resulted in the formation of **4** in 44% isolated yield (Scheme 2). Inspired by the results, we then decided to explore the details of the α-lithiation-*in situ* intramolecular nucleophilic addition reactions of 2-acyl-*N*-arylsulfonylpyrrole derivatives.

We commenced our study using 2-benzoyl-1-tosylpyrrole **5a** as substrate, and the results for the optimization of reaction conditions were listed in Table 1. The desired product **6a** was obtained in 73% isolated yield by treatment of **5a** with 2 equiv. of LDA at −78 °C in THF (Entry 1). No reaction occurred in the presence of NaH or LiH (Entries 2, 3), and only trace amount of **5a** was obtained when LiHMDS was applied (Entry 4). ^{i}PrMgCl as base gave a mixture of products, and no trace of **6a** was evident on TLC plate (Entry 5). With LDA as base, neither variation of its equivalents (Entries 6, 7) nor raising the reaction temperature (Entries 8, 9) could give a better result. The reaction could not be driven to completion in the presence of 1.5 equiv. of LDA, while de-tosylation of **5a** began to take place in the presence of 2.5 equiv. of LDA.

With the optimal conditions in hand, the α-lithiation-*in situ* intramolecular nucleophilic addition reaction of a variety of 2-acyl-*N*-arylsulfonylpyrroles and analogues was investigated. The results were summarized in Table 2 and Scheme 3. Reaction of 2-acyl-*N*-tosylpyrroles **5b-e** proceeded smoothly to give the corresponding products **6b-e** in moderate to good isolated yields. It is noteworthy that no products resulting from aldol condensation were obtained for substrates **5c-e** with an enolizable ketone moiety. Next, 2-benzoylpyrroles bearing different *N*-arylsulfonyl moiety were investigated. While 2-benzoyl-*N*-phenylsulfonylpyrrole **5f** reacted smoothly to provide **6f** in moderate isolated yield, reaction of substrate **5g** with an electron-withdrawing nitro group substituted benzene ring was less satisfactory and gave a mixture of products from which **6g** was isolated in 20% yield only. Reaction of 2-benzoyl-*N*-(3-fluorophenylsulfonyl)pyrrole **5h** was governed by regioselective lithiation under the joint effect of the sulfonyl and the fluoro group [8] to provide **6h** in 46% isolated yield. The alternative product resulting from 6-lithiation of **5h** and subsequent intramolecular nucleophilic addition was not observed. When 2-benzoyl-*N*-(*o*-tosyl)pyrrole **5i** was used as substrate, **6i** with a seven-membered ring was obtained solely in good isolated yield. Under the conditions, imidazole and pyridine derivatives **6j** and **6k** (Scheme 3) could also be obtained, albeit in low yield.

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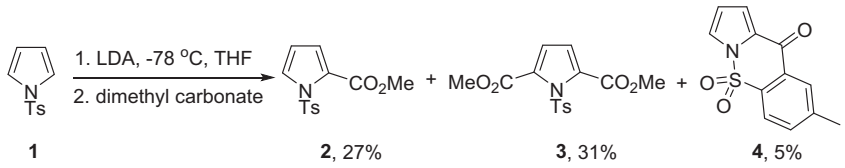
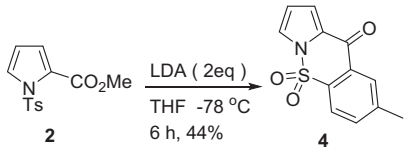


Scheme 1. Results for the α-lithiation of *N*-tosylpyrrole **1** and subsequent reaction with dimethyl carbonate.

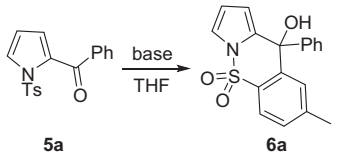


Scheme 2. Synthesis of **4** *via* α-lithiation-*in situ* intramolecular nucleophilic addition reaction of **2**.

Having established the methodology, further transformations of the products were then explored. Thus, treatment of **6i** with conc. HCl in acetone resulted in the formation of pyrrolo[1,2-*b*]benzothiazepine derivative **7** in 97% isolated yield (Scheme 4). Similarly, **6c** could be converted into the elimination product **8**, subsequent Diels – Alder reaction of which with benzyne afforded benzoindole derivative **9** in excellent isolated yield.

In summary, we have described an efficient α-lithiation-*in situ* intramolecular nucleophilic addition reaction sequence toward the synthesis of annulated sultam derivatives. The reaction can tolerate a range of functional groups including enolizable ketones.

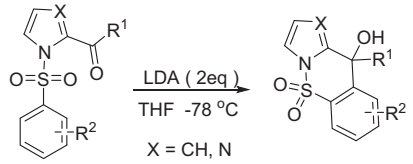
Table 1
Optimization of reaction conditions.

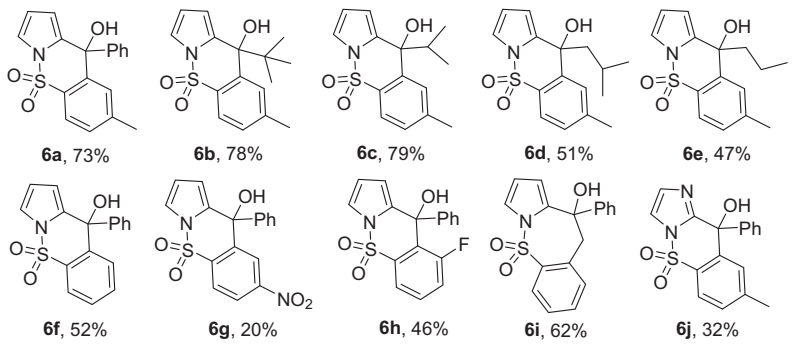


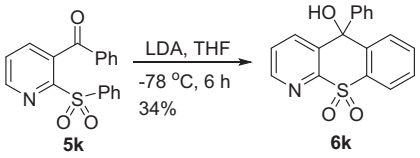
Entry	Base	Equiv.	Temp. (°C)	Yield[a] (%)
1	**LDA**	**2.0**	**−78**	**73**
2	NaH	2.0	−78	0[b]
3	LiH	2.0	−78	0[b]
4	LiHMDS	2.0	−78	trace
5	^{i}PrMgCl	2.0	−78	0[c]
6	LDA	1.5	−78	32
7	LDA	2.5	−78	41
8	LDA	2.0	−60	51
9	LDA	2.0	−40	17

[a] Isolated yield. [b] No reaction occurred. Starting material recovered. [c] Mixture of products. No desired product **6a** was obtained.

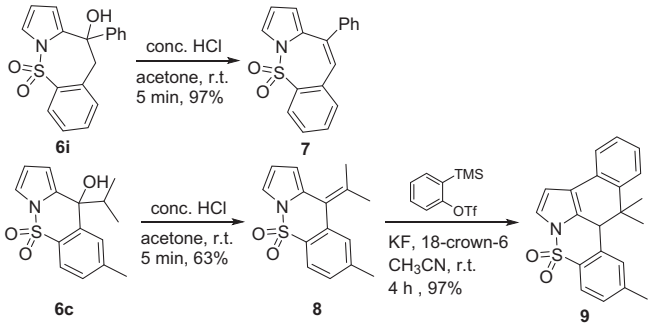
Table 2
Substrate scope.







Scheme 3. Synthesis of **6k**.



Scheme 4. Synthesis of **7** and **9**.

Moreover, this method may open a new window toward the synthesis of polyheterocyclic ring systems.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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