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One-Pot Synthesis of 2,3-Dihydro-pyrrolopyridinones Using in Situ Generated Formimines

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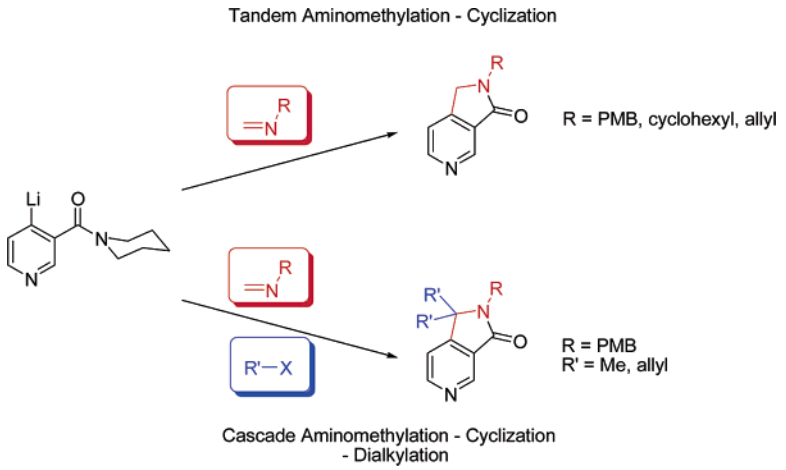
ABSTRACT



A novel one-pot methodology is described for the synthesis of functionalized pyrrolopyridinones using in situ generated formimines and an ortho-lithiated pyridinecarboxamide species. Depending on the reaction conditions, this procedure allows versatile access to aminomethylated pyridinecarboxamides, 2,3-dihydro-pyrrolopyridinones, or 1,1-dialkylated 2,3-dihydro-pyrrolopyridinone derivatives.

The synthesis of isoindolinones is widely reported in the literature.[1] These compounds have a common intermediate skeleton with numerous alkaloids and display various biological properties of pharmaceutical interest.[2]

Introducing a nitrogen atom in the aromatic ring could provide the opportunity to modulate the pharmacodynamic and kinetic properties of these dihydro-pyrrolopyridinones.[3]

Although isoindolinones are ubiquitous moieties used by the pharmaceutical industry, only two syntheses of these aza-analogue derivatives, also known as dihydro-pyrrolopyridinones, have been reported. At first, Couture et al. described a method based on aromatic nucleophilic substitution.[4] More

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recently, Clayden et al. used an *N*-*tert*-butyl *N*-benzylnicotinamide in the presence of a large excess of base to trigger the C−C bond formation.[5]

We propose here an alternative approach based on a nucleophilic addition of an ortho-lithiated pyridinecarboxamide on a formimine, followed by intramolecular cyclization. This route would not only broaden the choice of substituents on the nitrogen atom of the lactam but also enable the dialkylation of the exocyclic methylene.

The directed ortho metalation is a powerful methodology for the functionalization of aromatic and heteroaromatic compounds because lithiated derivatives display high reactivity toward a wide range of electrophiles.[6] Metalation of pyridines has been studied extensively by our group, and the synthetic value of this methodology has been determined.[7] Carboxamides are well-known as ortho-directing groups because of their complexing ability. Previous studies on the metalation of pyridine-3-carboxamides have highlighted a good regioselectivity at C4.[8] Moreover, the amide carbonyl can allow further nucleophilic ring closure. Therefore, dihydro-pyrrolopyridinones could be advantageously synthesized via a tandem "metalation−functionalization" sequence using N-substituted formimine as an electrophile. This approach is depicted in the retrosynthetic analysis shown in Figure 1.

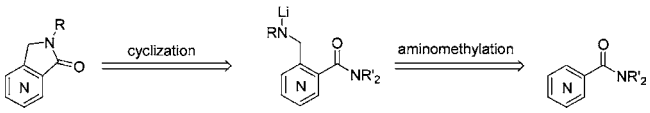


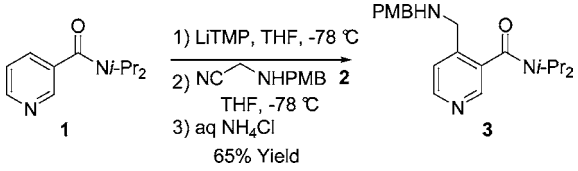
Figure 1. Retrosynthesis of 2,3-dihydro-pyrrolopyridinone using an aminomethylation−cyclization reaction.

Surprisingly and to the best of our knowledge, aminomethylation of lithiated pyridine derivatives is not described in the literature. The aminomethylation reaction is an important method for the synthesis of β-lactams using ester enolates as nucleophiles.[9] Examples of nucleophilic attacks are numerous, and they generally involve imines activated with electron-withdrawing groups and subsequent deprotection of the amine. Examples using unactivated imines are sparse. Less-hindered formimines readily react with organometallic compounds. Nevertheless, as their degradation occurs even at low temperatures due to their rapid polymerization,[10] they need to be formed in situ and trapped by the lithiated species.

In the present paper, we report the use of formimines as a versatile tool for the synthesis of different isomers of 2,3-dihydro-pyrrolopyridinones.

Our study started by the aminomethylation of a sterically hindered nicotinamide. *N*,*N*-Diisopropyl nicotinamide **1** was ortho-lithiated at C4 with complete regioselectivity by treating with an excess of lithiated 2,2,6,6-tetramethylpiperidine (LiTMP) in THF at −78 °C. When using lithium diisopropylamide (LDA) in anhydrous THF, only dimerized nicotinamide was obtained, resulting from addition of the lithiated nicotinamide on the starting material at C4.[8] The initial addition of *N*-(cyanomethyl)-*p*-methoxybenzylamine **2** to the preformed solution of ortho-lithiated *N*,*N*-diisopropylnicotinamide, followed by quenching with NH_4Cl, furnished the uncyclized intermediate **3** in good yield (Scheme 1).

Scheme 1. Aminomethylation of *N*,*N*-Diisopropylnicotinamide



Mechanistic considerations would suggest that the lithiated adduct resulting from the addition of the lithiated pyridinecarboxamide onto the formimine could react further via intramolecular addition onto the carboxamide (Figure 2). We

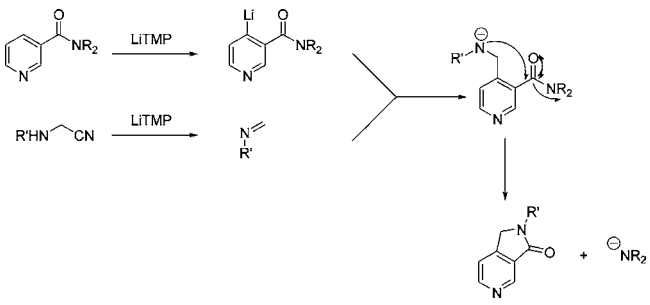


Figure 2. Mechanism of the tandem aminomethylation−cyclization reaction.

suspected that this cyclization could be favored through a judicious choice of the amino leaving group of the carboxamide.

We then turned our attention to a less-hindered nicotinamide to facilitate subsequent cyclization. Initial experiments were aimed at screening various nicotinamides and varying

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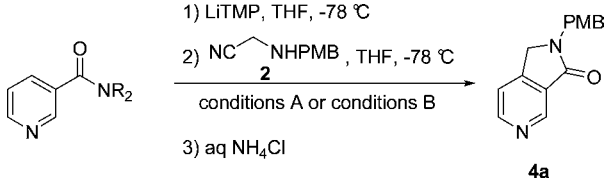
Table 1. Optimizing the Aminomethylation−Cyclization Tandem Reaction



	conversion[a] of carboxamides into 2,3-dihydro-pyrrolopyridinone	
substrate: NR_2	conditions A −78 °C, 7 h	conditions B −78 °C to −10 °C, 16 h
NEt_2 **5**	52	54
NBn_2 **6**	0	0
NPh_2 **7**	12	18
piperidine **8**	88	43
pyrrolidine **9**	54	34
N-(allyl)$_2$ **10**	34	0
morpholine **11**	36	15

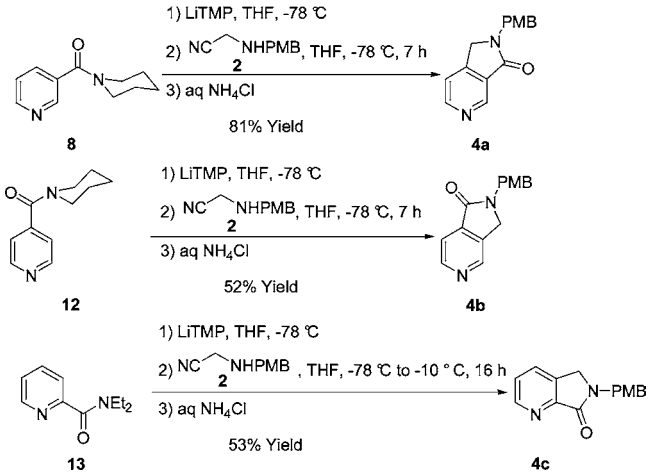
[a] Estimated conversion by ^{1}H NMR with 1,3,5-trimethylbenzene as an internal standard.

the temperature profile of the reaction. As listed in Table 1, *N*,*N*-diethylnicotinamide **5** afforded a better conversion in conditions B than in conditions A. On the contrary, piperidine nicotinamide **8** gave excellent conversion without any trace of noncyclized product at −78 °C but led to partial degradation when the temperature was allowed to increase. More hindered nicotinamides, such as compounds **6** and **7**, gave lower yields in both conditions.

The piperidine carboxamide **8** seemed to be more adapted to mild conditions (conditions A), both avoiding degradation and allowing good conversion. In this case, 2-(4-methoxybenzyl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one **4a** was isolated in 81% yield.

To broaden the scope of this methodology, we applied the same procedure to both available isomers of nicotinic acid (Scheme 2). Reaction of piperidine isonicotinamide **12** with *N*-(cyanomethyl)-*p*-methoxybenzylamine gave 2-(4-methoxybenzyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-1-one **4b** in 52% yield. Unfortunately, reaction of piperidine picolinamide under the same conditions afforded mainly the dimerized product observed previously.[8] 6-(4-Methoxybenzyl)-5*H*-pyrrolo[3,4-*b*]pyridin-7(6*H*)-one **4c** was successfully obtained in 53% yield starting from *N*,*N*-diethylpicolinamide **13** under conditions B.

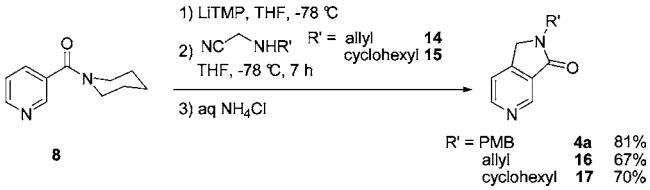
Scheme 2. Tandem Aminomethylation−Cyclization of Lithiated Pyridine Carboxamides



This tandem reaction gives easy access to 2,3-dihydropyrrolopyridinones in good yields and in a one-pot procedure, thus making it a valuable tool for future functionalization of such compounds.

We then envisaged the N-substitution of the lactam by changing the *N*-(cyanomethyl)amine (Scheme 3). 2-(Allylamino)acetonitrile **14** and 2-(cyclohexylamino)acetonitrile **15** were then prepared and engaged in the aminomethylation−cyclization reaction to give the cyclized compounds **16** and **17** in 67% and 70% yields, respectively.

Scheme 3. Modification of the Formimine: Varying the N-Substitution of the 1*H*-Pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

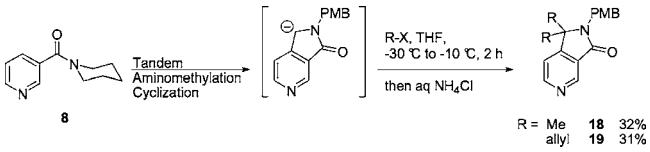


Because of the electron-withdrawing character of both the lactam moiety and the π-deficient heterocycle, we can suppose that the pyrrole methylene may undergo deprotonation. This hypothesis was previously verified in the isoindolinone series.[11] This implies that a possible functionalization of this position could be achieved owing to either the excess of LiTMP or the nitrogen base liberated from the secondary amide during the cyclization process. To confirm this hypothesis, we tried to perform an aminomethylation−cyclization−alkylation cascade on a lithiated nicotinamide.

Using our previous conditions, metalation of **8** followed by reaction with *N*-(cyanomethyl)-*p*-methoxybenzylamine and quenching with alkylating agents at −30 °C allowed the formation of dialkylated compounds **18** and **19** (Scheme 4). The use of one molar equivalent of the alkylating agent also resulted in dialkylated compounds.

In summary, we have developed a short and efficient methodology for the preparation of 2,3-dihydro-pyrrolo-

Scheme 4. Aminomethylation−Cyclization−Dialkylation Cascade Starting from a Lithiated Pyridine Carboxamide



pyridinones, by reacting ortho-lithiated pyridinecarboxamides with formimines. Subsequent in situ dialkylation of the exocyclic methylene gives access to functionalized 2,3-dihydro-pyrrolopyridinones.

These sequences could be used to produce key building blocks for the syntheses of valuable natural product analogues.

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

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