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Aminomethylation of lithiated nicotinamide: access to new pyridolactams

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Abstract

New 2,3-dihydropyrrolopyridinones were conveniently prepared by trapping lithiated pyridine carboxamides with highly reactive formimines. In this Letter, we report that a wide range of N-functionalised compounds can be synthesised in one step by this process, allowing the presence of ethers, acetals or ester moieties.

Keywords: Pyridine; Metalation; Formimine; Lactam; Aminomethylation

1. Introduction

The synthesis of isoindolinones is widely reported in the literature,[1] whereas their aza-analogue derivatives such as 2,3-dihydropyrrolopyridinones are much less described. As depicted in Scheme 1, formation of the C–C bond of the lactam can be achieved via five different methodologies. Couture and co-workers[2] were the first to describe a process based on aromatic nucleophilic substitution with phosphonic enolates, as an efficient way to obtain azaisoindolinones especially in benzenic series. Then, his group developed a further strategy accomplished by a two steps sequence involving the quenching with DMF of a dilithiated isonicotinamide derivative.[3] This relevant approach involved the C–C bond formation before the C–N intramolecular bond. Substituted 3-(arylmethylene)-pyrrolopyridinones were efficiently synthesised by Cossy and co-workers using Pd(0)-catalysed Heck–Suzuki–Miyaura domino reactions.[4] Clayden's group[5] obtained pyridine-derived synthons, taking advantage of the π-deficient character of the heterocycle, which allows intramolecular nucleophilic addition of a benzylic carbanion followed by oxidative rearomatisation. We recently disclosed that the condensation of a Mannich equivalent with a tertiary amide derived from nicotinic acid or its isomers could also efficiently lead to this structure.[6] The aminomethylated intermediate, bearing both electrophilic and nucleophilic centres, is a versatile intermediate for the synthesis of pyrrolopyiridinones. These five methods open the way to different structures covering a wide range of potential targets.

In the course of using nicotinic acid derivatives as building blocks, we worked out a straightforward synthesis of N-functionalised 2,3-dihydropyrrolopyridinones as precursors for new heterocyclic compounds by modulating the alkyl group of substituted formimines. *N*-Alkyl formimines constitute a family of imines, which are extremely reactive[7] despite the absence of electron-withdrawing groups on the nitrogen atom. Our conceptual strategy for the synthesis of N-functionalised 2,3-dihydropyrrolopyridinones is detailed in Scheme 2 and consists in the reaction of a lithiated pyridine carboxamide with in situ generated formimines.

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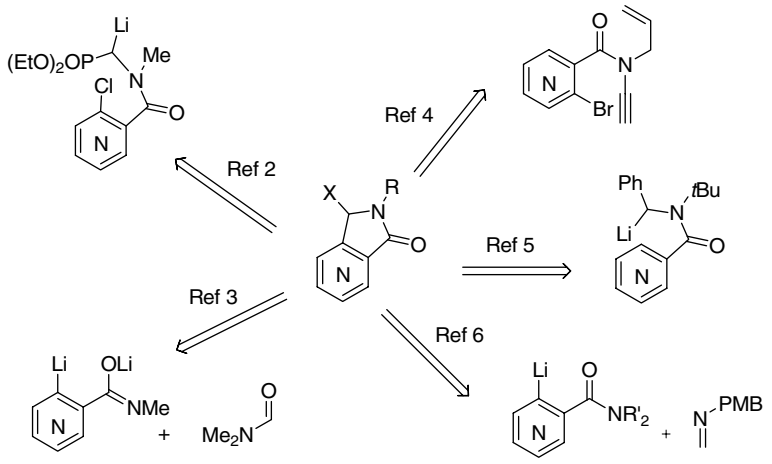
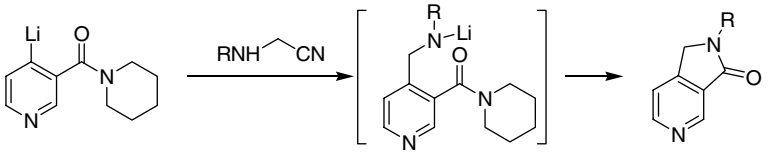


Scheme 1. C–C bond formation in pyridolactam syntheses.



Scheme 2. Synthesis of pyrrolopyiridinones using the tandem aminomethylation–cyclization reaction.

Precedence for this approach was provided in 1984 by Overman who showed that unstable formimines were formed in situ by reacting organolithiums or Grignard reagents with secondary *N*-cyanomethylamines. These formimines allowed further lactamisation of esters and synthesis of azetidinones.[8]

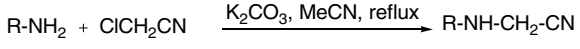
2. Results and discussion

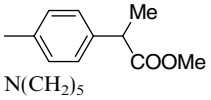
Due to their high propensity for trimerisation, *N*-alkyl formimines require in situ generation through elimination of cyanide ion starting from cyanomethylamines. Despite the toxicity of the released cyanide ions, cyanomethylamines are useful compounds for this reaction. In particular, their preparation is very easy and does not give rise to polyalkylated compounds. As listed in Table 1, we first prepared some cyanomethylamines by N-alkylation with chloroacetonitrile.

This reaction was conducted in refluxing acetonitrile for 3 h in the presence of potassium carbonate and gave good yields of pure products after distillation,[9] except in the case of piperidine hydrazine (entry 10). In the case of aromatic amines, the reaction was slow but accelerated by the addition of sodium iodide providing *N*-arylcyanomethylamines in very good yields (entries 8 and 9).

Given the easy access to these N-substituted cyanomethylamines, aminomethylation of lithiated *N*-piperidylnicotinamide and further cyclization were explored. The results of performing this tandem reaction are displayed in Table 2. The *ortho*-lithiated nicotinamide was generated at −78 °C in THF with lithium 2,2,6,6-tetramethylpiperidine (LiTMP, 3 equiv) and immediately treated with 1 equiv of cyanomethylamine derivative. After 7 h at −78°C, the reaction was quenched with aqueous NH_4Cl. This reaction took place with moderate to good yields. We were pleased to notice that the presence of functional groups such as masked aldehydes (entries 3 and 4) or protected alcohols (entries 5 and 6) did not interfere with the reaction conditions. To our surprise, subjecting the methyl ester derivative to this reaction conditions results in cyclisation (entry 7). The modest yield is presumably due to a possible

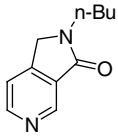
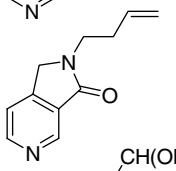
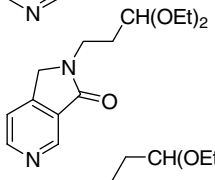
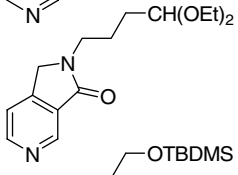
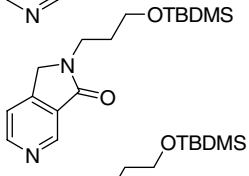
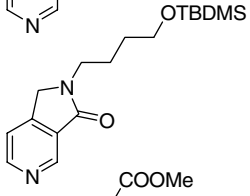
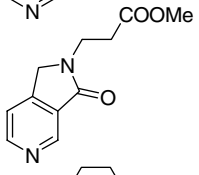
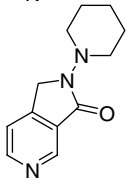
Table 1
Preparation of cyanomethylamines



Entry	R	Yield (%)
1	$(CH_2)_3CH_3$	81
2	$(CH_2)_2CH{=}CH_2$	90
3	$(CH_2)_2CH(OEt)_2$	65
4	$(CH_2)_3CH(OEt)_2$	63
5	$(CH_2)_2COOMe$	92[a]
6	$(CH_2)_3OTBDMS$	88[b]
7	$(CH_2)_4OTBDMS$	95[b]
8	*p*-Me(C_6H_4)	95[c]
9		98[c]
10	$N(CH_2)_5$	35

[a] Prepared from the hydrochloride salt, with an additional equivalent of K_2CO_3.
[b] Yields obtained over two steps: alkylation of 3-aminopropanol then protection with TBDMSCl/imidazole.
[c] Reaction was conducted in the presence of 1 equiv NaI.

Table 2
New N-functionalised 2,3-dihydropyrrolopyridinones

Entry	Product	Yield (%)
1		42
2		53
3		53
4		69
5		52
6		67
7		28
8		25

N-deprotection via β-elimination of methyl acrylate. In addition, the reactivity of a hydrazine-derived compound (entry 8) was examined, the tandem reaction leading in this case to an original *N*-amino structure. However, when *N*-aryl formimines were used, the aminomethylation took place but further lactamisation was sluggish, due to lowered reactivity of the conjugated lithium amide.

3. Conclusion

In summary, the new 2,3-dihydropyrrolopyridines synthesis we have developed shows the compatibility of the aminomethylation–lactamisation process with different functional groups. This opens the way to various heterocyclic compounds, since further C–C bond formations can be envisaged between the lactamic methylene and electrophilic moieties branched on the starting cyanomethylamines. The synthesis of new heterocyclic compounds is currently under investigation.

4. Experimental

The following procedure for the synthesis of 2-(3,3-diethoxypropyl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (Table 2, entry 3), is illustrative:

To a stirred solution of *n*-butyllithium (1.6 M, 2.96 mL, 4.74 mmol) in anhydrous THF (50 mL) was added dropwise 2,2,6,6-tetramethylpiperidine (0.81 mL, 4.74 mmol) at −10 °C. The solution was allowed to stir at 0 °C for 30 min then cooled to −78 °C. Piperidine nicotinamide (302 mg, 1.59 mmol) in anhydrous THF (5 mL) was added in 5 min immediately followed by dropwise addition of 3,3-diethoxypropylaminoacetonitrile (297 mg, 1.59 mmol) in anhydrous THF (5 mL). The reaction was kept at this temperature for 7 h and was quenched with aqueous ammonium chloride (10%) and extracted with diethyl ether (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The product was purified by flash chromatography through SiO_2 (dichloromethane/isopropanol/triethylamine: 20:1:0.2, $R_f = 0.63$) to give the pyridolactam (219 mg, 53%) as a yellow liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): 1.15 (t, $J = 7.0$ Hz, 6H), 2.00 (dt, $J = 5.4$ Hz, 5.7 Hz, 2H), 3.49 (m, 2H), 3.67 (m, 4H), 4.45 (s, 2H), 4.57 (t, $J = 5.7$ Hz, 1H), 7.42 (dd, $J = 0.8$ Hz, 5.1 Hz, 1H), 8.74 (d, $J = 5.1$ Hz, 1H), 9.08 (d, $J = 0.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 15.4, 32.6, 38.7, 50.1, 62.1, 101.5, 118.2, 129.1, 146.0, 149.8, 151.3, 166.9; IC(+)-MS (MH+) $m/z = 265$, 219, 191; Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.09; H, 8.47; N, 10.12.

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References and notes

1. (a) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org. Biomol. Chem.* **2007**, *5*, 1466; (b) Couture, A.; Deniau, E.; Lamblin, M.; Lorion, M.; Grandclaudon, P. *Synthesis* **2007**, *9*, 1434; (c) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **2007**, *63*, 2664; (d) Lee, S.; Shinji, C.; Ogura, K.; Shimizu, M.; Maeda, S.; Sato, M.; Yoshida, M.; Hashimoto, Y.; Miyachi, H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4895; (e) Moreau, A.; Lorion, M.; Couture, A.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2006**, *71*, 3303; (f) Inoue, S.; Kim, R.; Hoshino, R.; Honda, K. *Chem. Commun.* **2006**, 1974; (g) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **2006**, *62*, 5787; (h) Tsuritani, T.; Kii, S.; Akao, A.; Sato, K.; Nonoyama, N.; Mase, T.; Yasuda, N. *Synlett* **2006**, 801; (i) Kobayashi, K.; Hase, M.; Hashimoto, K.; Fujita, S.; Tanmatsu, M.; Morikawa, O.; Konishi, H. *Synthesis* **2006**, *15*, 2493; (j) Deniau, E.; Enders, D.;

Couture, A.; Grandclaudon, P. *Tetrahedron: Asymmetry* **2005**, *16*, 875; (k) Comins, D. L.; Schilling, S.; Zhang, Y. *Org. Lett.* **2005**, *7*, 95; (l) Comins, D. L.; Hiebel, A.-C. *Tetrahedron Lett.* **2005**, *46*, 5634; (m) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Org. Biomol. Chem.* **2005**, *3*, 2305; (n) Khan, M. W.; Reza, A. F. G. M. *Tetrahedron* **2005**, *61*, 11204; (o) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2004**, *69*, 4527; (p) Grigg, R.; Sridharan, V.; Thayaparan, A. *Tetrahedron Lett.* **2003**, *44*, 9017.

2. Hoarau, C.; Couture, A.; Cornet, H.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2001**, *66*, 8064.
3. Rys, V.; Couture, A.; Deniau, E.; Lebrun, S.; Grandclaudon, P. *Synlett* **2004**, 2233.
4. Couty, S.; Liégault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511.
5. Clayden, J.; Hamilton, S. D.; Mohammed, R. T. *Org. Lett.* **2005**, *17*, 3673.
6. Deguest, G.; Devineau, A.; Bischoff, L.; Fruit, C.; Marsais, F. *Org. Lett.* **2006**, *8*, 5889.
7. (a) Guillemin, J. C.; Denis, J. M. *J. Chem. Soc., Chem. Commun.* **1985**, 951; (b) Guillemin, J. C.; Denis, J. M. *Tetrahedron* **1988**, *44*, 4431.
8. (a) Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 1635; (b) Overman, L. E.; Osawa, T. *J. Am. Chem. Soc.* **1985**, *107*, 1698.
9. *Caution*! A high vacuum pump should be used to avoid thermal decomposition of the aminonitrile and release of gaseous HCN.