Synthetic Methods

DOI: 10.1002/ange.201006590

Stereodivergent Synthesis of Substituted N,O-Containing Bicyclic Compounds by Sequential Addition of Nucleophiles to *N*-Alkoxybicyclolactams**

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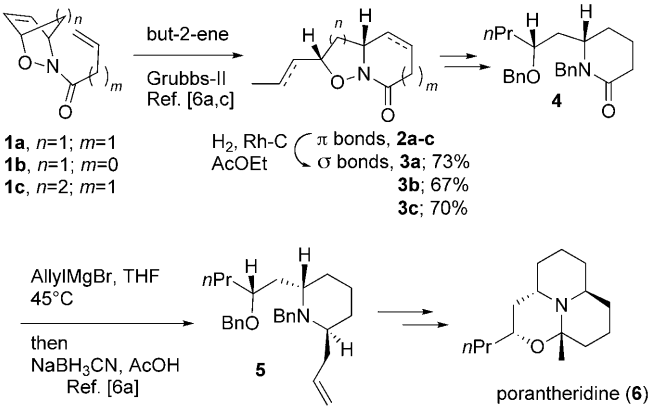
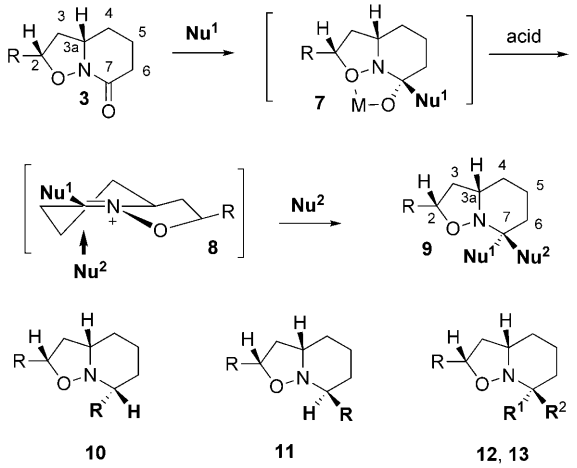
The functionalization of amides by the direct addition of two successive nucleophiles to the carbonyl group for the synthesis of cyclic or acyclic amines is a topic of growing interest. Usually the amide is activated as a chloro or triflyloxyiminium intermediate,[1] a thioamide,[2] or an imide[3] before the successive addition of organometallic reagents, hydride, or other nucleophiles. However, the direct addition of Grignard reagents with heating, or organolithium compounds at room temperature, to bicyclic lactams followed by hydride reduction has been reported.[4] The same sequence with amides or N-alkyl monocyclic lactams is less common but has precedent.[5]

In fact, we successfully employed this latter strategy to construct stereoselectively the 2,6-*trans*-disubstituted piperidine framework **5** of porantheridine (**6**) from isoxazolidino-[2,3-*a*]piperidin-7-one **4**, which we had obtained from our efficient and straightforward ring-rearrangement metathesis of the strained bicyclic nitroso Diels–Alder adduct **1a** (Scheme 1).[6] Nevertheless, our synthetic scheme required the cleavage of the N–O bond and the benzylation of the resulting lactam prior to the key step; the benzyl group had to be removed afterward. Therefore, it would be of great interest to realize the successive addition of two nucleophiles directly onto isoxazololactam **3**; a high level of stereoselectivity should be induced by the shape of the bicyclic framework. The realization of this "one-pot" sequence would improve the efficiency of the overall process by eliminating extra protection/deprotection steps.[7] The N–O bond would, in fact, act as a protecting group and, more importantly, as an activating and stabilizing group. The addition of the first nucleophile would be possible under milder conditions than with the corresponding alkyl amide[8] and would form the relatively stable chelated intermediate **7**, which is related to the N-methoxy Weinreb amides that are known not to undergo twofold addition of the first nucleophile[9] (Scheme 2). Addition of acid would then generate the transient alkoxyimmium species **8**.[10] The presence of the cyclic isoxazolidine would force the side chain at position C3a of the alkoxypiperidinium unit in a pseudoequatorial position, and the stereoelectronically preferred axial attack of a nucleophile should lead diastereoselectively to **9**.[11]



Scheme 1. Ring-rearrangement metathesis of nitroso Diels–Alder cycloadducts and our previous synthesis of porantheridine (**6**).



Scheme 2. Strategy of sequential nucleophilic addition.

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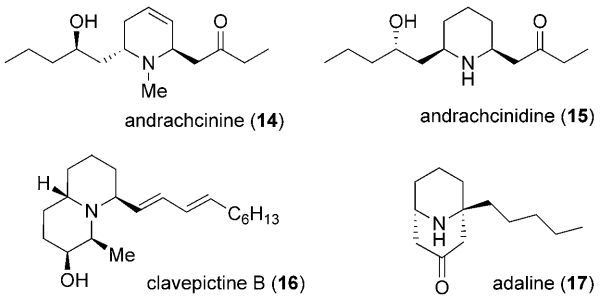
[**] We thank the CNRS and Université Paris-Sud 11 for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201006590.

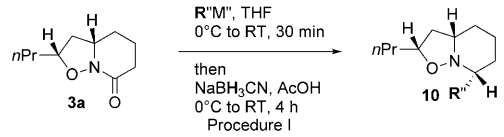
Such a strategy is inspired by the pioneering work of Kibayashi et al., who realized the successive addition of a Grignard reagent and sodium borohydride to related tetrahydroxazino[2,3-*a*]piperidin-8-ones to obtain 4a,8-*cis*-tetrahydroxazino[2,3-*a*]piperidines.[12] The application of the Kibayashi procedure to our isoxazolidino[2,3-*a*]piperidin-7-ones **3a** would indeed deliver 3a,7-*cis*-isoxazolidino[2,3-*a*]piperidines **10**. Furthermore, access to the *trans* diastereoisomer from the same intermediate would be useful. To do so, we intend to reverse the order of addition of the hydride and the organometallic reagents to lead to 3a,7-*trans*-isoxazolidino[2,3-*a*]piperidines **11** in a diastereodivergent manner. Moreover, we wish to synthesize 7,7-disubstituted isoxazolidinopiperidines **12** and **13** by the successive addition of an organometallic reagent followed by a second carbon nucleophile, thus creating important tetrasubstituted stereocenters (Scheme 2). This overall strategy would be particularly suited for the synthesis of various alkaloids that contains a *cis*- or *trans*-2-[*syn*-(hydroxyalkyl)]-6-alkyl-piperidine framework[13] as depicted in Scheme 3.

We first investigated the formation of the 3a,7-*cis* isomers **10** from **3a** as our test substrate to validate our methodology (Table 1). The addition of *n*-butylmagnesium chloride or *n*-butyllithium at room temperature followed by sodium cyanoborohydride and acetic acid delivered as expected the 3a,7-*cis*-isoxazolidino[2,3-*a*]piperidine **10** as a single diastereoisomer in 50% yield (Table 1, entries 1 and 2). This procedure was extended to allyl, phenyl, methyl, and ethyl



Scheme 3. 2,6-Disubstituted piperidine alkaloid targets.

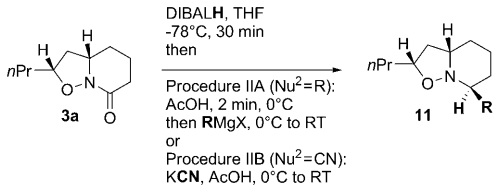
Table 1: Diastereoselective synthesis of 3a,7-*cis*-isoxazolidino[2,3-*a*]-piperidines **10**.



Entry	R″M″	Product	Yield [%][a]
1	*n*BuLi	**10a** (R = *n*Bu)	50
2	*n*BuMgCl	**10a** (R = *n*Bu)	50
3	EtMgBr	**10b** (R = Et)	51
4	MeMgBr	**10c** (R = Me)	57
5	allylMgBr	**10d** (R = allyl)	65
6	PhMgBr	**10e** (R = Ph)	55

[a] Yield of isolated product after flash column chromatography; only one diastereomer detected.

Table 2: Diastereoselective synthesis of 3a,7-*trans*-isoxazolidino[2,3-*a*]-piperidines **11**.



Entry	Nu^2 reagent	Product	Yield [%] (d.r.)[c]
1[a]	*n*BuMgCl	**11a** (R = *n*Bu)	40 (5:1)
2[a]	allylMgBr	**11d** (R = allyl)	50 (10:1)
3[a]	PhMgBr	**11e** (R = Ph)	54 (10:1)
4[b]	KCN	**11f** (R = CN)	66 (1:0)

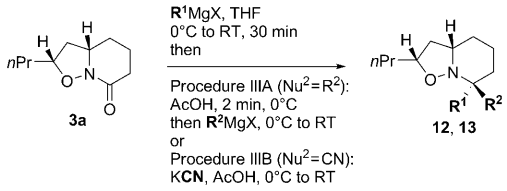
[a] Procedure IIA. [b] Procedure IIB. [c] Yield of isolated product after flash column chromatography (diastereomeric ratio).

magnesium bromide, and in each case only the desired *cis* diastereoisomer was detected (50–65% yield; Table 1, entries 3–6).[14,15]

Our next task was to examine the formation of the *trans* isomer by reversing the order of addition of the organometallic and the hydride reagents (Table 2). We had to switch from sodium cyanoborohydride to a more reactive hydride like diisobutylaluminum hydride (DIBALH), which is known to reduce Weinreb amides into aldehydes. After we subjected our bicyclic N-alkoxylactams to DIBALH at −78 °C, acetic acid was added for a short time to form the required N-alkoxyiminium species. Addition of allyl- and phenylmagnesium bromide at 0 °C resulted in the desired 3a,7-*trans*-isoxazolidino[2,3-*a*]piperidines **11d** (50% yield) and **11e** (54%) with good diastereoselectivity (Table 2, entries 2 and 3).[15] The addition of an alkyl Grignard reagent like *n*-butylmagnesium chloride also produced the *trans* compound **11a** but with a moderate yield of 40% and a diastereoselectivity of 5:1 d.r. (Table 2, entry 1). Addition of a cyanide as the second nucleophile yielded **11f** as one diastereoisomer (Table 2, entry 4).[16,17]

Having met our goal of preparing both *cis* and *trans* diastereoisomers in a diastereodivergent manner, we targeted the addition of two carbon nucleophiles on the same substrate (Table 3). We first examined the sequential addition of two Grignard reagents with formation of the iminium intermediate by treatment with acetic acid. When allylmagnesium bromide was used as the second nucleophile, dialkyl isoxazolidinopiperidines **12** were obtained with complete diastereoselectivity (Table 3, entries 1 and 2). Although the yields are modest, this is still a useful transformation since a tetrasubstituted stereocenter has been created in a straightforward manner. But more rewarding was the successive addition of a Grignard reagent and potassium cyanide with acetic acid. Single diastereoisomers of the N-alkoxyaminonitriles (**13a–e**; Table 3, entries 3–7) were obtained with satisfactory yields.[18] α-Aminonitriles are known to be useful building blocks in synthesis.[19] Moreover, several antitumor agents like the tetrahydroisoquinoline alkaloids contain an α-aminonitrile moiety, which is a masked iminium intermediate, that act as a DNA alkylating agent.[20] Interest-

Table 3: Diastereoselective synthesis of 7,7-disubstituted isoxazolidino-[2,3-*a*]piperidines.



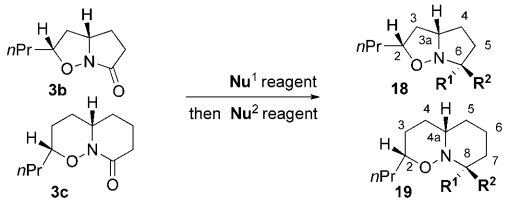
Entry	Nu[1] reagent, R^1MgX	Nu[2] reagent	Product	R^1	R^2	Yield [%][c]
1[a]	*n*BuMgCl	allylMgBr	**12a**	*n*Bu	allyl	34
2[a]	MeMgBr	allylMgBr	**12b**	Me	allyl	28
3[b]	*n*BuMgCl	KCN	**13a**	*n*Bu	CN	63
4[b]	EtMgBr	KCN	**13b**	Et	CN	56
5[b]	MeMgBr	KCN	**13c**	Me	CN	70
6[b]	allylMgBr	KCN	**13d**	allyl	CN	73
7[b]	PhMgBr	KCN	**13e**	Ph	CN	70

[a] Procedure IIIA. [b] Procedure IIIB. [c] Yield of product isolated after flash column chromatography; only one diastereomer detected.

ingly, the corresponding N-alkoxyaminonitriles are not as well established,[21] and the synthesis of the compounds that we present here represents an opportunity to develop their chemistry and biology.

In addition to substrate **3a**, we decided to extend the general strategy described here to isoxazolo[2,3-*a*]pyrrolidin-6-one **3b** and morpholino[2,3-*a*]piperidin-8-one **3c** (Table 4). In preliminary investigations 3a,6-*cis*-isoxazolo[2,3-*a*]pyrrolidines[14] **18a,d** were obtained by addition of a Grignard reagent followed by sodium cyanoborohydride and acetic acid (Table 4, entries 1 and 2).[22] N-alkoxyaminonitriles **19a**,**c**,**e**,**f** were obtained by addition of an organometallic reagent or DIBALH to **3c** followed by potassium cyanide and acetic acid (Table 4, entries 3–6).

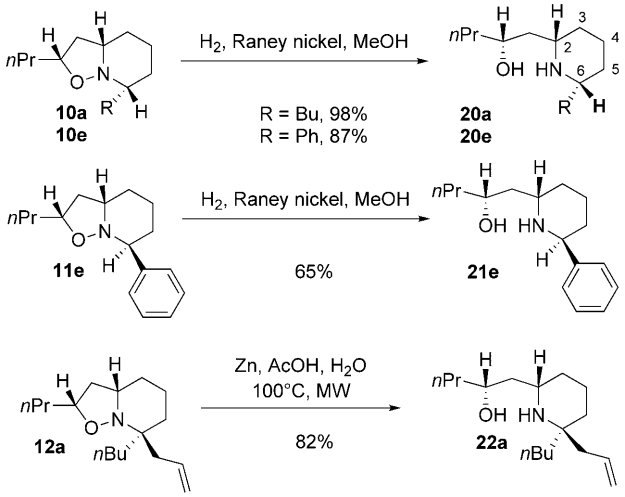
Table 4: Diastereoselective synthesis of 6-substituted isoxazolo[2,3-*a*]pyrrolidine and 8-substituted morpholino[2,3-*a*]piperidines.



Entry	Substr.	Nu[1] reagent	Nu[2] reagent	Prod.	R^1	R^2	Yield [%] (d.r.)[d]
1[a]	**3b**	*n*BuMgCl	$NaBH_3CN$	**18a**	*n*Bu	H	45 (10:1)
2[a]	**3b**	allylMgBr	$NaBH_3CN$	**18d**	allyl	H	57 (7:1)
3[c]	**3c**	BuLi	KCN	**19a**	Bu	CN	69 (1:0)
4[c]	**3c**	MeMgBr	KCN	**19c**	Me	CN	69 (1:0)
5[c]	**3c**	PhMgBr	KCN	**19e**	Ph	CN	66 (1:0)
6[b]	**3c**	DIBALH	KCN	**19f**	H	CN	88 (20:1)

[a] Procedure I: RMgX, 0°C to RT, 30 min then $NaBH_3CN$, AcOH, 0°C to RT. [b] Procedure IIB: DIBALH, −78°C, 30 min then KCN, AcOH, 0°C to RT. [c] Procedure IIIB: R″M″, 0°C to RT, 30 min then KCN, AcOH, 0°C to RT. [d] Yield of product isolated after flash column chromatography (diastereomeric ratio).

The substituted N,O-containing bicycles thus obtained could represent new scaffolds for drug discovery. Indeed, we are currently screening the biological activity of these compounds. Furthermore, these substrates are obvious precursors of piperidine alkaloids and their analogues, for which the cleavage of the N–O bond is required.[23] This was accomplished efficiently by hydrogenation of compounds **10a**,**e** and **11e** with Raney nickel (Scheme 4). We were also



Scheme 4. Cleavage of the N–O bond in selected compounds **10**–**12**. MW = microwave treatment.

able to cleave the N–O bond without reducing the double bond of **12a** with zinc in acetic acid.

In conclusion, we have devised a highly diastereoselective and diastereodivergent "one-pot" synthesis of 3a,7-*cis*- and –*trans*-isoxazolidino[2,3-*a*]piperidines from a bicyclic N-alkoxylactam through the sequential addition of nucleophiles. Tetrasubstituted stereocenters could be generated with complete diastereoselectivity. This efficient procedure relies on the ability of the N–O bond to act as a protecting group, as an activating group towards nucleophilic addition, and as a stabilizing group to prevent the double addition of the first nucleophile. Research towards the enantioselective[24] total synthesis of alkaloids is underway and will be published in due course.[24]

Received: October 20, 2010
Published online: December 29, 2010

Keywords: alkylation · N,O heterocycles · nucleophilic addition · stereoselectivity

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[14] NOE relationships were observed between H3a and H7 for **10**, H3a and H6 for **18**, and between H2 and H6 for **20**; see the Supporting Information.

[15] As in 2,6-disubstituted piperidine models, we observed that the NMR chemical shift of C5 of **10a–e** and **11a–f** (C4 of **20a,e** and **21e**) is $\delta = 19$–21 ppm for a *trans* relationship and $\delta = 24$–25 ppm for a *cis* relationship. See Ref. [11a] and: E. L. Eliel, D. Kandasamy, C.-y. Yen, K. D. Hargrave, *J. Am. Chem. Soc.* **1980**, *102*, 3698 – 3707.

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[17] With our procedure a greater array of nucleophiles can be added after DIBALH in contrast to the Sato–Chida procedure (Ref. [16]), which is limited to CN and allyl. Moreover, the Sato–Chida procedure was not applicable to our substrate **3a** since we were not able to isolate **11d** by this method.

[18] An X-ray crystal structure of compound **13e** was obtained. CCDC 796656(**13e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[21] Selected examples: a) X. Ding, K. Taniguchi, Y. Hamamoto, Sada, S. Fujinami, Y. Ukaji, K. Inomata, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1069 – 1083; b) I. Zadrozna, J. Kurkowska, H. Kruszewska, *Farmaco* **2005**, *60*, 948 – 954; c) A. Zanobini, M. Gensini, J. Magull, D. Vidovic, S. I. Kozhushkov, A. Brandi, A. de Meijere, *Eur. J. Org. Chem.* **2004**, 4158 – 4166.

[22] The addition of DIBALH to **3b** followed by acetic acid and a Grignard reagent (Procedure IIa) was unsatisfactory.

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