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Stereoselective Access to Trans-2,5-Disubstituted Pyrrolidine Derivatives by Nucleophilic Addition to Bicyclic N-Acyliminium Ion

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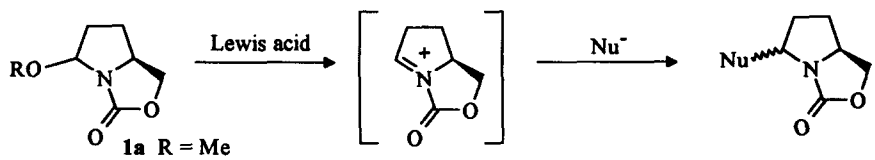
Abstract **: 5-Alkoxy-pyrroloxazolidin-3-ones 1 were stereoselectively prepared from (S)-pyroglutamic acid. Treatment of 1 with a Lewis acid generated *in situ* the N-acyliminium 2, which was trapped by various π-nucleophiles leading selectively to *trans* pyrrolidine derivatives 3.**

In the course of our continuing efforts towards the synthesis of alkaloids containing pyrrolizidine or indolizidine skeletons, we focused our attention on a stereoselective access to *trans* 2,5-disubstituted pyrrolidines. Among the various available methods to introduce a substituent at the α-position of a cyclic amine, the nucleophilic addition to N-acyliminium ions constitutes a powerful tool. Previous works have shown that the degree of stereoselectivity depends on the nature of both the nucleophile and the various substituents[1] of the iminium ring. Thus, π-nucleophiles generally add to N-acyliminium ions derived from proline with a high degree of *cis* selectivity.[2] However, T.Shono and coworkers[2] have briefly mentionned the only known example of a highly selective *trans* addition of a π-nucleophile (allyltrimethylsilane) on the bicyclic N-acyliminium 2 generated *in situ* from aminoether **1a** (Scheme 1). We thus assumed that the nucleophilic addition would occur on the convex (less hindered) face of this iminium, regardless the nature of the nucleophile, leading with a high degree of selectivity to the *trans* oxazolidinones **3**.



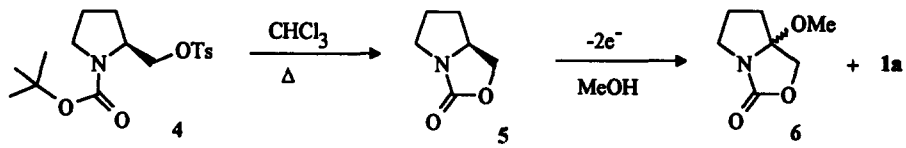
1a R = Me
1b R = Et
1c R = iPr
1d R = CH_2CF_3

2 **3**

Scheme 1

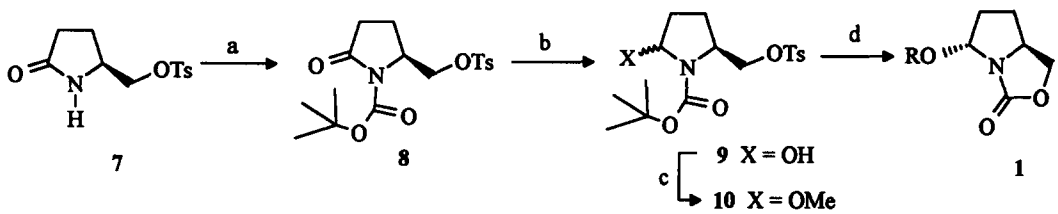
We report herein the preparation of aminoethers **1**, and the preliminary results on their reactivity with some nucleophiles in the presence of Lewis acids.

Initially, we tried to access to the required mixed acetal **1** by electrochemical oxidation of oxazolidinone **5**. The latter was obtained from compound **4**, easily available from proline in three steps,[4] by intramolecular displacement of a tosylate.[3] Unfortunately, anodic methoxylation of oxazolidinone **5** predominantly afforded the undesired 2-methoxylated regioisomer **6** (ratio **1a/6** : 1/3).



Scheme 2

Various experimental conditions were examined (temperature, current density, electrolyte...) without improvement of the observed regioselectivity.[5] These disappointing results prompted us to consider the preparation of the target compound **1** by a reductive way as illustrated in scheme 3.



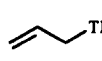
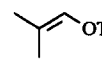
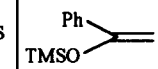
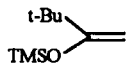
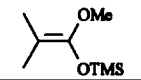
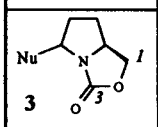
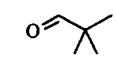
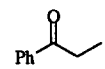
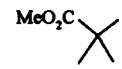
Reagents : a) Boc_2O, DMAP, NEt_3, CH_3CN (87%); b) $LiBHEt_3$, CH_2Cl_2 then H_2O_2. (99%); c) $HC(OMe)_3$, PPTS, MeOH (68%); d) $CHCl_3$, ROH, reflux (36-42%).

Scheme 3

The tosylated intermediate **7**, obtained in large scale in three steps from (S)-pyroglutamic acid according to a known procedure,[6] was protected as the *t*-butylcarbamate **8**. Chemoselective partial reduction with lithium triethylborohydride at -78°C[7] cleanly provided hemiaminal **9** as a diastereomeric mixture. Subsequent refluxing of aminoether **10** in methanol gave the desired bicyclic compound **1a** in modest yield (37%). Likewise, when refluxed in various binary systems $CHCl_3$-ROH (MeOH, EtOH, iPrOH, CF_3CH_2OH), the hemiaminal **9** directly and exclusively led through a one-pot two-step procedure to the corresponding *trans* α-alkoxyoxazolidinones **1a-d** in comparable yields (36-42%). The stereoselectivity observed at this stage augured well for the subsequent nucleophilic displacements of the alkoxy groups.

The key aminoether **1b** in hand, we investigated its reactivity with various nucleophiles (Table 1). Upon treatment of this compound with a variety of Lewis acids (BF_3-OEt_2, $TiCl_4$, TMSOTf) at -78°C in dichloromethane, the *in situ* generated N-acyliminium **2** was trapped by allyltrimethylsilane giving rise to compounds **3a** (entry a). In all cases, yields (60-65%) and diastereoselectivity (96:4) were comparable with those reported by T.Shono[2] from aminoether **1a**. The *trans* configuration of the major isomer of **3a** was ascertained by chemical correlation after comparison of its spectroscopic data with those of a *cis*-enriched sample.[8] Next, we examined the reactivity of N-acyl iminium **2** with other nucleophiles (Table 1) such as TMSCN, silyl enol ethers and organocopper reagents. Whereas the latter gave incomplete conversion rate following the L.G. Wistrand's procedure[1] (<30%), use of *t*-butylisocyanide and 1-trimethylsiloxy-1,3-butadiene only resulted in polymerisation of the nucleophiles. Though reacting efficiently, TMSCN induced a modest facial preference[1b] (entry b). Reaction with various silyl enol ethers afforded compounds **3** in moderate to good yields (entries c-f), with high diastereomeric excesses ranging from 88 to 100%. In the cases where both isomers were detectable, we observed that the C-1 and the C-3 chemical shifts of the major one appeared respectively upfield and downfield compared to those of the minor one (Table 1). Moreover, X-ray analysis

Table 1 : Reactions of aminoether **1b** with various nucleophiles

Entry[a]	a	b	c	d	e	f
Nucleophiles		TMSCN				
	Nu = 					
Yields[b] (%)	65	95	43[d]	86	83	73
Ratios[c] *trans*:*cis*	96:4	70:30	100:0	94:6	100:0	97:3
^{13}C-1 δ (ppm) *trans* (*cis*)	67.5 (69.4)	67.7 (69.4)	67.0 (-)[e]	67.8 (69.1)	67.8 (-)[e]	66.9 (68.2)
^{13}C-3 δ (ppm) *trans* (*cis*)	161.5 (156.3)	160.1 (156.8)	162.2 (-)[e]	161.3 (157.0)	161.3 (-)[e]	161.9 (154.7)

[a] All additions were performed on 1 mmol scale in CH_2Cl_2 using TMSOTf (3 eq.) as the Lewis acid from -78°C to RT. The products were isolated by silica gel chromatography and all spectroscopic data were in accordance with the assigned structures. [b] Isolated yields. [c] The diastereomeric ratios were determined by capillary GC. [d] This yield doesn't take into account an other batch of aldehyde **3c** which remained contaminated by an unidentified compound after chromatography. [e] Not observed

perfomed on two crystalline compounds secured on the one hand the *cis* stereochemistry of the minor isomer of **3b** (the major one being an oil) and on the other hand, the *trans* stereochemistry of the major isomer of **3d**. We therefore assigned a *trans* configuration to all the major isomers obtained.

Thus, with the exception of the small (linear) reagent TMSCN, the addition of various nucleophiles occured preferentially on the convex face of the N-acyliminium **2**, leading to a high degree of *trans* selectivity of the adducts **3**. This iminium seems to be a promising chiral synthon to gain access to *trans* 2,5-disubstituted pyrrolidines. Further synthetic applications to indolizidine and pyrrolizidine alkaloids are under current investigation in our laboratory.

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References and Notes

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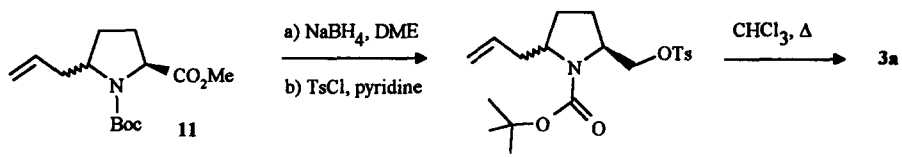
4. Compound **4** was obtained after reduction of proline with $LiAlH_4$ in THF, followed by successive treatment with Boc_2O ($CHCl_3$, NaCl, $NaHCO_3$, H_2O at reflux) then TsCl in pyridine.
5. A similar regioselectivity was observed in the case of bicyclic oxazinones : Driessens, F.; Hootele, C. *Can. J. Chem.* **1990**, 211.
6. Rosset, S.; Célérier, J.P.; Lhommet, G. *Tetrahedron Lett.* **1991**, *32*, 7521-7525.
7. Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreno, M.C.; Garcia Ruano, J.L. *Tetrahedron Lett.*, **1994**, *35*, 2053-2056.
8. A mixture of *trans* and *cis* intermediates **11** (30:70) derived from proline[2] was converted into oxazolidinones in three steps according to the following scheme :



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