Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 9589–9592
Tetrahedron Letters

Diastereoselective preparation of novel tetrahydrooxazinones via heterocycloaddition of *N*-Boc, *O*-Me-acetals

Patricia Gizecki, Ramzi Ait Youcef, Céline Poulard, Robert Dhal and Gilles Dujardin*

Unité de Chimie Organique Moléculaire et Macromoléculaire, UMR 6011 CNRS Université du Maine, 72085 Le Mans Cedex 9, France

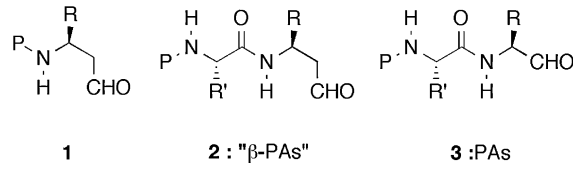
Received 10 September 2004; revised 27 October 2004; accepted 27 October 2004
Available online 11 November 2004

Abstract—Under Lewis acid conditions, reaction of *N*-Boc, *O*-Me acetals with the (*R*)-(+)-*O*-vinyl-pantolactone does not lead to the expected dihydrooxazine, but to the corresponding tetrahydrooxazinone, as a result of the loss of the *t*-Bu group. A diastereoselective and asymmetrical way to these new heterocyclic compounds is described, together with the first evidence of their ability to undergo *N*-acylation.

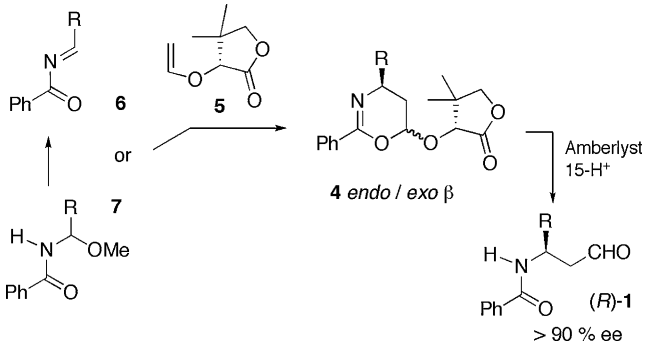
The enantioselective synthesis of protected β-aminoaldehydes is of specific interest in the chemistry of β-peptides derivatives. More particularly, *N*-protected β-aminoaldehydes **1** (Scheme 1) are key intermediates in order to prepare reduced peptides[1] and 'carba' peptides.[2] As a new development of β-aminoaldehyde chemistry, it would then be interesting to consider getting access to *C*-terminal β-peptide aldehydes **2** (β-PAs). *C*-Terminal peptides aldehydes **3** (PAs) display important biological activities as inhibitors of proteolytic enzymes[3] (Aspartic: HIV protease, renin; cysteinic: cathepsins). For this purpose, we considered if PAs homologues **2** could be obtained via *C*-protected derivatives of β-aminoaldehydes **1**.

We have recently disclosed an enantioselective route to β-benzamidoaldehydes **1** (P = Bz) via the hydrolysis of a dihydrooxazine **4** that is asymmetrically obtained by heterocycloaddition of (*R*)-*O*-vinyl pantolactone **5** with a *N*-benzoyl benzaldimine **6** or its synthetic equivalent, the *N*, *O*-acetal **7**,[4] in the presence of a Lewis acid catalyst ($Yb(fod)_3$) or promoter ($SnCl_4$) (Scheme 2).

Considering that *N*-protected β-aminoaldehydes **1** with a *N*-Boc protecting group would be even more interesting for the present project, we next experimented this pathway with new *N*-Boc-protected cycloreactants. We report here that under similar reaction conditions, both *N*-Boc benzaldimine **8a**[5] and *N*-Boc, *O*-Me acetal **9a** do not lead to the expected dihydrooxazine, but to the tetrahydrooxazinone **10a**, as a result of the loss of the *t*-Bu group (Scheme 3). The tetrahydrooxazinone **10a** thus obtained is representative of a novel class of



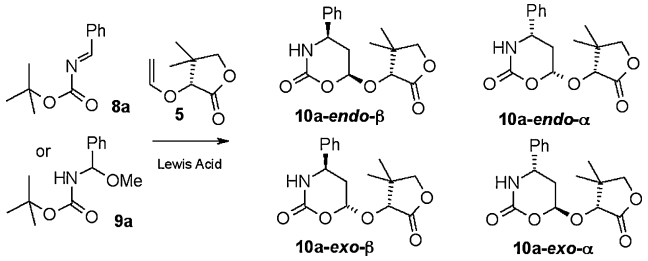
Scheme 1.



Scheme 2.

Keywords: Oxazinones; *N*,*O*-Acetals; Asymmetric synthesis; Pantolactone; Chiral vinyl ether.
* Corresponding author. Tel.: +33 243833344; fax: +33 243833902; e-mail: dujardin@univ-lemans.fr

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.154



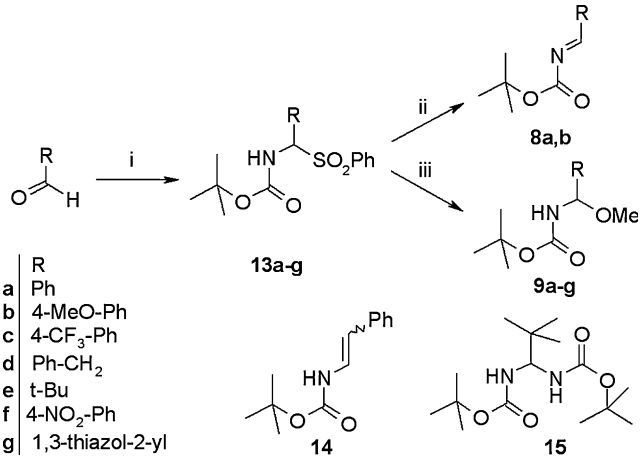
Scheme 3.

heterocyclic compounds[6] that are very promising as precursors enabling the peptide-like coupling of the amine function of a *C*-protected β-aminoaldehyde **1**. In this report, we describe convenient conditions to obtain various tetrahydrooxazinones **10** in a diastereoselective and asymmetrical way, and we show that it is possible to convert such heterocycles into *N*-acylated derivatives (e.g., **11**, **12**).

A preliminary study, conducted on **8a** and **9a** allowed us to know how to determine the influence of the Lewis acid on the reactivity and the stereochemical outcome of the reaction (Scheme 3, Table 1). Contrariwise to its *N*-benzoyl equivalent **6**, the *N*-Boc imine **8a** displays no reactivity towards vinyl ether **5** in the presence of a catalytic amount of $Yb(fod)_3$ (entry 1). Clean formation of the tetrahydrooxazinone **10a** was observed when using one equivalent of $SnCl_4$ at low temperature (entry 3). The conversion into **10a** proved to be incomplete, but highly stereoselective: the exclusive formation of *exo*-β and *endo*-β diastereoisomers was thus observed.[7] Better conversions into **10a** were obtained when using stoichiometric amounts of $BF_3{\cdot}Et_2O$ at higher temperatures (entries 4 and 5), but in these cases the facial selectivity decreased and a significant degradation of the imine **8a** was observed. When starting from the more stable *N*-Boc, *O*-Me acetal **9a** at −40 °C, the conversion was complete with one equivalent of TMSOTf (entry 6), but the facial selectivity proved to be higher when using $BF_3{\cdot}Et_2O$ or $SnCl_4$ (entries 7 and 8). Optimal conditions were finally reached using 1.1 equiv of $SnCl_4$ at −40 °C (entry 9).

The extension of the cycloaddition method in order to get variably substituted 4-aryl and 4-alkyl tetrahydrooxazinones **10** required the preparation of *N*-Boc imines **8** or of various *N*-Boc, *O*-Me acetals **9** obtained through the corresponding sulfones **13** (Scheme 4, Table 2). The sulfones **13a–g** were prepared in satisfactory yields using the Engberts' method,[8] with the exception of the sulfone **13e** which was prepared by the Petrini's method.[9] The elimination reaction of the sulfones **13** with the Kanazawa's method[5] gave heterogeneous results.

The conditions used (K_2CO_3, THF, reflux) to get the *N*-Boc imines **8** were satisfactory only when applied to the aryl substrates **13a** (R = Ph) and **13b** (R = *p*-MeO–Ph). Under these conditions, **13d** (R = Bn) underwent isomerization and gave **14**, **13e** (R = *t*-Bu) was converted into the bis-carbamate **15**, **13f** (R = *p*-NO_2–Ph) remained unchanged and the **13g** (R = thiazolyl) was degraded. Because of the difficulties we had to get an access to the imines **8**, we favoured the preparation of *N*-Boc, *O*-Me acetals **9** that can be easily obtained via basic methanolysis of the corresponding sulfones **13** (Scheme 4, Table 2).



Scheme 4. Reagents and conditions: (i) *t*-Bu carbamate, sodium benzenesulfinate, formic acid, methanol (THF for **13e**), water, rt; (ii) K_2CO_3, THF, reflux; (iii) MeONa, MeOH.

Table 1. Formation of the tetrahydrooxazinone **10a** under various Lewis acid conditions

	8–9[a]	Catalyst (equiv/**5**)	T °C (time)	% Conv. **10a/5**[d]	Diastereomeric distribution of **10a**[c]				% Yield[d] **10a**-*exo*-β
					exo-β	*endo*-β	*exo*-α	*endo*-α	
1	**8a**	$Yb(fod)_3$ (0.05)	[b]	0					
2	**8a**	$Yb(OTf)_3$ (0.05)	0–reflux (2 d)	0					
3	**8a**	$SnCl_4$ (1)	−78 (15 min)	66	87	13	0	0	
4	**8a**	$BF_3{\cdot}OEt_2$ (1)	−40 (1 h 30 min)	81	95	3	2	0	64
5	**8a**	$BF_3{\cdot}OEt_2$ (1)	−18 (15 min)	100	84	10	5	0	
6	**9a**	TMSOTf (1)	−40 (1 h 30 min)	100	86	2.5	6	5.5	
7	**9a**	$BF_3{\cdot}OEt_2$ (1)	−40 (1 h 30 min)	93	93	5	2	ε	67
8	**9a**	$SnCl_4$ (1)	−40 (1 h 30 min)	91	95	4	1	ε	
9	**9a**	$SnCl_4$ (1.1)	−40 (1 h)	100	93	6	1	0	70

[a] **5** (1 equiv), **8a** or **9a** (1.1 equiv) in CH_2Cl_2, otherwise noted.
[b] Cyclohexane, reflux, 3 d; toluene, reflux, 1 d.
[c] By ^1H NMR.
[d] After chromatography on SiO_2.

Table 2. Preparation of *N*-Boc, *O*-Me acetals **9** and imines **8**

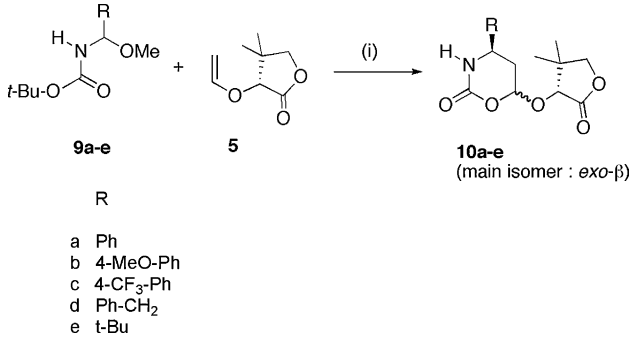
R	13	% Yield	9	% Yield	8	% Yield
Ph	**a**[a]	79	**a**	98	**a**[a]	98
p-MeO–Ph	**b**	66	**b**	78	**b**	87
p-CF_3–Ph	**c**	85	**c**	79	**c**	—
Ph–CH_2	**d**	89	**d**	89	**d**	0[b]
t-Bu	**e**	65	**e**	75	**e**	0[c]
p-NO_2–Ph	**f**	75	**f**	94	**f**	0[d]
1,3-Thiazol-2-yl	**g**	58	**g**	84	**g**	0[e]

[a] See Ref. 5.
[b] Isomerization of **8d** into the enecarbamate **14** (88%).
[c] Exclusive formation of bis-carbamate **15**.
[d] No reaction.
[e] Degradation.

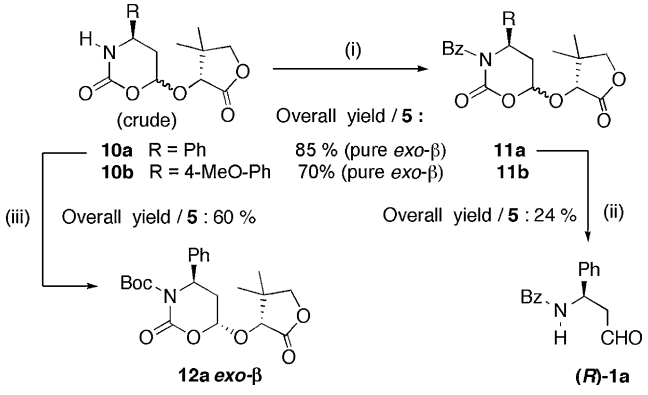
Thanks to the optimized conditions for the preparation of the tetrahydrooxazinone **10a** (Table 1, entry 9), the analogous compounds **10b–e** were conveniently obtained from the corresponding *N*-Boc, *O*-Me acetals **9** (Scheme 5, Table 3). The cycloaddition reaction was conducted in the presence of $SnCl_4$ at −40 °C for the adducts **10b–c**, and at −78 °C for the more sensitive substrates **10d** (R = Bn) and **10e** (R = *t*-Bu), leading homogeneously to satisfactory conversions (74–100%). However, given the relative instability of adducts **10** on silica gel, the yields of isolated products were in most cases notably lower than those expected on the basis of the conversion rates. In all cases, the preferential formation of the *exo*-diastereoisomers and a high β-facial selectivity (⩾98/2) were observed. Application of this reaction to the thiazolyl *N*, *O*-acetal **9g** (R = 1,3-thiazolyl) seemed promising since the corresponding adduct, bearing two orthogonally-protected aldehyde groups[10] could lead to useful derivatives of aspartic aldehyde. Unfortunately, no reaction occurred in this case.

Moreover, in order to evaluate the ability to *N*-acylate these new compounds, standard *N*-benzoylation conditions were tested on the crude intermediate tetrahydrooxazinones **10a** and **b** (Scheme 6).After chromatographic purification, the *N*-benzoylated products **11a** (R = Ph) and **11b** (R = *p*-MeO–Ph) were isolated as pure single *exo*-β isomers in good overall yields (85 and 70%, respectively). Alternatively, the *N*-Boc derivative **12a** was conveniently obtained in 60% yield starting from the *exo*-β adduct **10a**.

The absolute configuration of the tetrahydrooxazinone **10a** thus obtained from the (*R*)-*O*-vinyl pantolactone **5**[11] (Table 3, entry 1) was determined after chemical correlation with aldehyde (*R*)-**1a** (Scheme 6).[4] The crude *N*-benzoyl tetrahydrooxazinone **11a** was directly submitted to hydrolysis in acidic medium, and the aldehyde **1a** was isolated after chromatography (24% overall yield from **5** and **9a**). On the basis of the ^{1}H NMR analysis in the presence of a chiral shift reagent ((+)-Eu(tfc)$_3$ 30 mol%), the β-benzamidoaldehyde (*R*)-**1a** thus identified[4]



Scheme 5. Reagents and conditions: (i) $SnCl_4$, CH_2Cl_2, low temperature.



Scheme 6. Reagents and conditions: (i) benzoyl chloride, Et_3N, 4-DMAP, CH_2Cl_2, rt; (ii) 6M HCl, THF, rt; (iii) Boc_2O, Et_3N, 4-DMAP, dichloromethane, 0 °C.

Table 3. Diastereoselective access to tetrahydrooxazinones **10a–e**

R	10	T °C	Conversion[a] 10/5	Diastereomeric distribution of **10**[b]				% Yield[c] **10**-*exo*-β
				exo-β	*endo*-β	*exo*-α	*endo*-α	
Ph	**a**	−40	100	93	6	1	0	70
p-MeO–Ph	**b**	−40	88	91	7	2	0	60
p-CF_3–Ph	**c**	−40	74	94	6	ε	0	34
Ph–CH_2	**d**	−78	100	93	6	1	0	18
t-Bu	**e**	−78	80	90	10	ε	0	30
1,3-Thiazol-2-yl	—	−40	0	—	—	—	—	0

[a] **5** (1 equiv), **9** (1.1 equiv), $SnCl_4$ (1.1 equiv), dichloromethane, 1 h.
[b] Determined by ^{1}H NMR (%) of the crude product.
[c] Isolated yields of pure *exo*-β isomer after chromatography on SiO_2.

with a 97% ee allowed us to confirm the β facial feature of the starting tetrahydrooxazinone **10a**.

In conclusion, the present study has demonstrated the synthetic usefulness of $SnCl_4$ as a promoting Lewis acid for the asymmetrical synthesis of a novel class of tetrahydrooxazinones of type **10**. As the preparation of *N*-Boc imines **8** does not show any general feature, the use of new *N*-Boc, *O*-Me acetals **9** precursors, easily obtained from the corresponding sulfones **13**, was exemplified. The heterocyclic reaction of these *N*, *O*-acetals **9** with the (*R*)-*O*-vinyl pantolactone **5** led to the formation of the tetrahydrooxazinones **10a**–**e** with a high β facial selectivity (⩾98/2). The ability of these heterocyclic compounds to undergo *N*-acylation was demonstrated by the easy conversion of **10a** into its corresponding *N*-benzoyl and *N*-Boc derivatives. Extension of this methodology to the synthesis of other *N*-acylated compounds is in progress in our laboratory, one main project being the access by this pathway[12] to *C*-terminal β-peptide aldehydes **2**.

Acknowledgements

We would like to thank Simon Bazolo and Nicolas de Veaublanc for the preparation of the sulfones **13** and of the *N*-Boc, *O*-Me acetals **9**.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.10.154. Experimental procedures, characterization and spectroscopic assignment for representative compounds **8**–**13**.

References and notes

1. Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 9457.
2. (a) Rodriguez, M.; Aumelas, A.; Martinez, J. *Tetrahedron Lett.* **1990**, *31*, 5153; (b) Rodriguez, M.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* **1990**, *31*, 7319; (c) Llinares, M.; Devin, C.; Azay, J.; Bergé, G.; Fehrentz, J. A.; Martinez, J. *Eur. J. Med. Chem.* **1997**, *32*, 767.
3. Fehrentz, J. A.; Paris, M.; Heitz, A.; Velek, J.; Winternitz, F.; Martinez, J. *J. Org. Chem.* **1997**, *62*, 6792, and references cited therein.
4. (a) Gizecki, P.; Dhal, R.; Toupet, L.; Dujardin, G. *Org. Lett.* **2000**, *2*, 585; (b) Gizecki, P.; Dhal, R.; Poulard, C.; Gosselin, P.; Dujardin, G. *J. Org. Chem.* **2003**, *68*, 4338.
5. Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238.
6. The relevant literature seems restricted to a recent synthesis of a *N*-butyl 6-acyloxy tetrahydrooxazinone via [4+2] cycloaddition of a *N*-acyliminium ion generated by electrochemical oxidation: Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J. *Org. Lett.* **2003**, *2*, 945.
7. Diastereoisomeric distribution was determined in ^{1}H NMR by comparison with previously observed data of dihydrooxazine **4a** (R = Ph).[4] As a typical example of the correlations that can be established between ^{1}H diastereotopic signals of compounds **4a** and **10a**, the chemical shifts of the *N*, *O*-acetalic protons H-6 are in the following range: δ *endo*-β > δ *exo*-α > δ *exo*-β.
8. Engberts, J. B. F. N.; Strating, J. *Recl. Trav. Chim.* **1965**, *84*, 842.
9. Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970.
10. (a) Altman, L. J.; Richheimer, S. L. *Tetrahedron Lett.* **1971**, *12*, 4709; (b) Dondoni, A.; Marra, A.; Perrone, D. *J. Org. Chem.* **1993**, *58*, 275.
11. The (*R*)-(+)-*O*-vinyl-pantolactone **5** used in this study was found to have 98.5% ee (determined by chiral GC).[4b]
12. Conversion of **10a** into **1a** via **11a** can be considered as a model of *N*-*trans*-acylation that could be extended to α/β-aminoacid-type *N*-coupling reagents.