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Radical addition of nitrones to acrylates mediated by SmI_2: asymmetric synthesis of γ-amino acids employing carbohydrate-based chiral auxiliaries†

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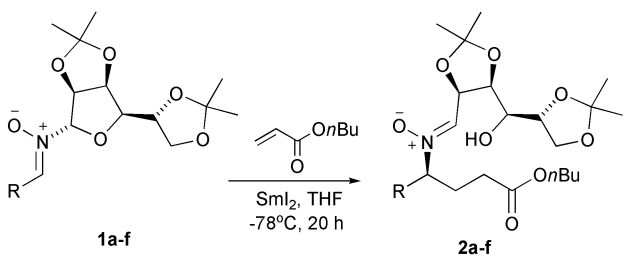
Received (in Cambridge, UK) 7th April 2004, Accepted 3rd June 2004
First published as an Advance Article on the web 19th July 2004

Alkyl nitrones possessing *N*-substituted sugars as chiral auxiliaries were found to effectively undergo an SmI_2-mediated radical addition to *n*-butyl acrylate affording γ-amino acid derivatives with high diastereomeric control.

In recent publications, we and others have demonstrated the ability of alkyl nitrones to undergo a SmI_2-mediated radical addition to either acrylates or acrylamides *via* an intermediate involving a nitrogen analogue of a ketyl radical anion.[1–3] The methodology provides a new route to γ-amino acids directly or to γ-amino acids as constituents of small peptides. Extension of this C–C bond forming reaction to the use of acrylates possessing chiral auxiliaries such as *N*-methylephedrine afforded γ-amino acids with diastereoselectivities up to 9 : 1.[1] Vallée, Py and coworkers have revealed the possibility of employing a chiral auxiliary on the nitrone, although it is not evident how this group can be removed.[2] Recently, Carreira and coworkers published highly diastereoselective additions of terminal alkynes to nitrones bearing *N*-substituted sugars.[4,5] In our quest to identify an efficient asymmetric version of this nitrone-based radical addition reaction, we now demonstrate that D-mannose and D-ribose bearing alkyl nitrones can readily be exploited in these radical addition reactions leading to γ-amino acids with good and opposite diastereomeric control.

Initial experiments were performed with the *N*-D-mannose substituted nitrone **1a** (Scheme 1, R = cyclohexyl) easily prepared by the treatment of the mannose glycosidic *N*-hydroxylamine with cyclohexanecarboxaldehyde in the presence of $MgSO_4$. Addition of an ethereal solution of SmI_2 (0.1 M in THF, 2.5 equiv.) containing 2 equiv. of *t*-BuOH to a cold solution of **1a** and *n*-butyl acrylate (1 equiv.) in THF provided after 20 h the coupling product **2a** in high yield after column chromatography (Table 1, entry 1). Equally pleasing was the presence of just a sole diastereomer as determined by the ^{1}H NMR spectrum of the crude product. Other nitrones were also effective providing the γ-amino acid derivatives **2b–d** with high diastereoselectivities (entries 2–4). The newly created stereogenic center was assigned the (*R*)-configuration on the basis of a single crystal X-ray structure of **2b** (Fig. 1).‡ Surprisingly, the solid state structure also revealed that the sugar residue had ring-opened affording a new nitrone as depicted in Scheme 1.[6]§ This is quite unexpected considering that similar observations were not made for the products in the alkyne addition studies, where the corresponding hydroxylamines were isolated.[4]



Scheme 1

Alkyl nitrones lacking an α-substituent, as with **1e** and **1f**, were less rewarding in their coupling attempts as the products were obtained in low yields. In addition, the products proved to be an inseparable mixture of the nitrones **2e** and **2f** and their corresponding hydroxylamines (ring-closed products). Only in the case of **2e** was a fraction of the nitrone product obtained in near pure form after column chromatography. Although, upon standing for 10 min in $CDCl_3$, this product reconverted to the same mixture of the two isomers. It has earlier been demonstrated that the addition of water to SmI_2 has a rate accelerating effect on the radical addition of nitrones to α,β-unsaturated esters.[2] When **1e** and **1f** were subjected to similar coupling conditions, though with the exception that the *t*-BuOH was replaced by 8 equivalents of water, a similar rate increase was observed and with greatly improved coupling yields (Table 1, entries 5 and 6). Unfortunately, the mixture of the two isomers prevented assignment of the diastereomeric excesses of these reactions.

In order to prepare the addition products with the opposite absolute configuration at the new stereogenic center, we have tested alkyl nitrones bearing a C5-deoxy-D-ribose auxiliary (Scheme 2).[7]¶ Here too, the addition products **4a–c** were obtained in good yields and with high diastereoselectivities (Table 2, entries 1–3), indicating that the C5-substituent in both sugars plays no role in chirality transfer in the addition step. In one attempt in the coupling with **3a**, the reaction was performed in the presence of water. Whereas a rate acceleration was observed, the diastereoselectivity remained as before. The relative configuration of the γ-amino acid derivative **4a** was also confirmed by a single crystal X-ray structure (see ESI†) and the new stereogenic center possessed the opposite absolute

Table 1 Radical addition of alkyl nitrones **1** to *n*-butyl acrylate[a]

Entry	R	Product	Yield (%)	Ds[b]
1	Cyclohexyl	**2a**	80	> 95 : 5
2	Isopropyl	**2b**	76	> 95 : 5
3	Cyclopentyl	**2c**	74	> 95 : 5
4	2-Ethylbutyl	**2d**	73	> 95 : 5
5[c]	Isobutyl	**2e**	54	N.d.[d]
6[c]	$Ph(CH_2)_2$	**2f**	68	N.d.[d]

[a] Isolated yields after column chromatography. [b] Diastereomeric selectivity. [c] *t*-BuOH was replaced by 8 equiv. of H_2O. [d] Not determined.

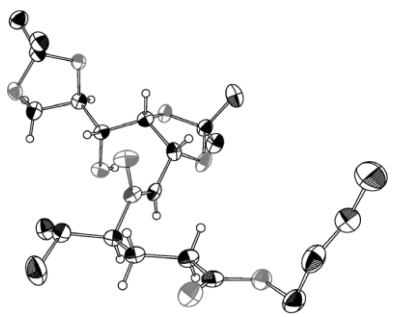


Fig. 1 Crystal structure representation of the addition product **2b**.

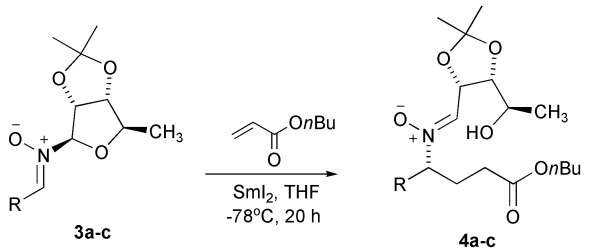
† Electronic Supplementary Information (ESI) available: crystallographic data of **2b** and **4a**, experimental procedure and spectral data. See http://www.rsc.org/suppdata/cc/b4/b405141f/

DOI: 10.1039/b405141f

configuration compared to **2b**.‖ As with **2b**, the sugar preferred an acyclic structure.

As earlier mentioned, the diastereomeric control was measured directly from the ^{1}H and ^{13}C NMR spectra of the crude reaction mixtures. For example, in the case of **2a**, this required for comparison the presence of the other diastereomer **6**, which was easily prepared in two steps from **4a** (Scheme 3). First, removal of the sugar auxiliary by acidic hydrolysis furnished directly the *N*-hydroxyl γ-amino acid **5**, thereby revealing the ability to liberate the amino acid from the carbohydrate component. Subsequent nitrone formation with 2,3:5,6-diisopropylidene-D-mannofuranose then provided the diastereomer **6**.**

With respect to the stereochemical outcome of these reactions, we propose a model in which reduction of the sugar bearing nitrone results in the formation of a ketyl radical-like intermediate (see Fig. 2). Complexation of the oxygen bound Sm^{III} ion to the C2-alkoxy group of the sugar thereby prevents rotation around the C1–N bond.

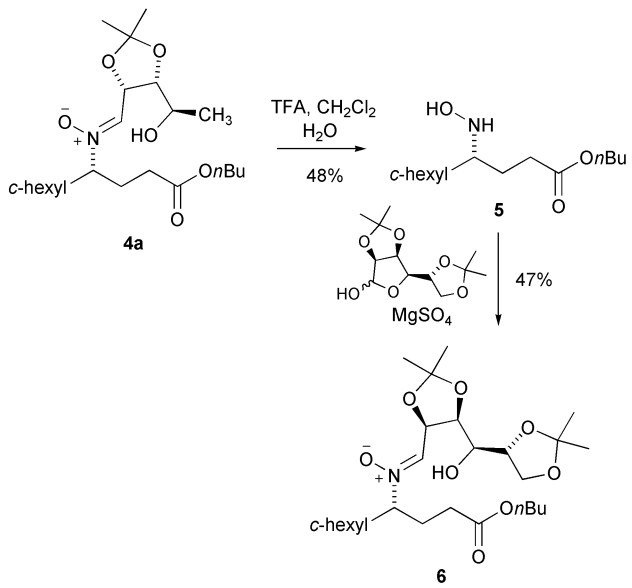


Scheme 2

Table 2 Radical addition of alkyl nitrones **3** to *n*-butyl acrylate[a]

Entry	R	Product	Yield (%)	Ds[b]
1	Cyclohexyl	**4a**	71	> 95 : 5
2	Isopropyl	**4b**	57	> 95 : 5
3	Cyclopentyl	**4c**	58	> 95 : 5

[a] Isolated yields after column chromatography. [b] Diastereomeric selectivity.



Scheme 3

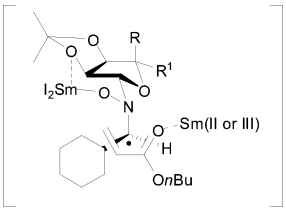


Fig. 2 Schematic model explaining the stereochemical outcome radical addition reactions.

Addition of the carbon centered radical to the electrophilic alkene then occurs from its least hindered face.

In summary, we have developed an asymmetric version of the radical addition of alkyl nitrones to acrylates promoted by samarium diiodide. Efforts to adapt this methodology to more elaborate substrates is currently in process.

Financial support for this work is gratefully acknowledged from the Danish Natural Science Research Council, The Holm Foundation and the University of Aarhus. This paper is dedicated to the memory of Professor Christian Pedersen.

Notes and references

‡ Crystal data for **2b**: $C_{23}H_{41}NO_8$, M = 459.57, orthorhombic, a = 6.540(7), b = 19.97(2), c = 20.00(2) Å, U = 2612(5) Å^3, T = 120 K, space group $P2_12_12_1$ (no. 19), Z = 4, μ(Mo–Kα) = 0.087 mm^{-1}, 45712 reflections measured, 3145 unique, 1922 significant ($> 3\sigma(I)$) used in all calculations. The final $R(F)$ was 0.049. CCDC 236553. See http://www.rsc.org/suppdata/cc/b4/b405141f/ for crystallographic data in .cif format.

§ The ^{1}H NMR spectrum of **2b** in $CDCl_3$ also revealed the structure of the compound to best be represented by the nitrone as seen by the doublet at 6.96 ppm.

¶ Carreira and coworkers have studied the use of an erythronolactone-derived auxiliary in order to provide propargylic *N*-hydroxylamines of opposite absolute configuration.[4] However, the high price of this four carbon sugar, allowed us to examine other sugars such as the C5-deoxyribose derivative. This sugar *N*-hydroxylamine was easily prepared in five steps starting from D-ribose according to a literature procedure.[7,8]

‖ Crystal data for **4a**: $C_{22}H_{39}NO_6$, M = 413.54, orthorhombic, a = 5.379(1), b = 15.901(3), c = 27.782(6) Å, U = 2376.2(8) Å^3, T = 120 K, space group $P2_12_12_1$ (no. 19), Z = 4, μ(Mo–Kα) = 0.083 mm^{-1}, 53147 reflections measured, 5347 unique, 3481 significant ($> 3\sigma(I)$) used in all calculations. The final $R(F)$ was 0.048. CCDC 236554. See http://www.rsc.org/suppdata/cc/b4/b405141f/ for crystallographic data in .cif format.

** Hydrolysis of **2b** provided the corresponding *N*-hydroxyl γ-amino acid in a 56% yield.

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