Modified nucleosides from nitrones: a new and efficient stereoselective approach to isoxazolidinyl thymidine derivatives

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The addition of the sodium enolate of methyl acetate to the *N*-benzyl nitrone 4 derived from D-glyceraldehyde affords the 3-substituted isoxazolidin-5-one 6a with a high degree of *syn* selectivity and in quantitative chemical yield; its further elaboration leads to the preparation of the important isoxazolidine nucleoside analogue 2a in enantiomerically pure form.

Nucleoside analogues have aroused a considerable amount of attention because of their biological activity.^{1,2} In particular, modified nucleosides, such as lamivudine **1a** and its 5-fluoro derivative **1b** show potent specific, competitive anti-HIV activities.³ Also, nucleosides **2** and **3** containing an isoxazolidine moiety have been described to have promising



therapeutic utility in the development of anti-AIDS agents.⁴ As a consequence, syntheses of isoxazolidinyl nucleosides of type 2 and 3 have been recently reported.^{5,6}

Recent investigations in this laboratory have revealed that chiral α -alkoxy and α -amino nitrones serve as versatile chiral building blocks in the preparation of several naturally occurring nitrogen-containing compounds.⁷ Here we present a successful implementation of this strategy directed to the stereoselective synthesis of isoxazolidinyl nucleosides **2**.

The key step of our approach consists of the stepwise addition of an ester enolate to a chiral nitrone in order to construct the isoxazolidine ring. It had been described by Trombini and coworkers that both ketone silyl enol ethers and vinylketene acetals add to nitrones in the presence of trimethylsilyl triflate.8 Kita and co-workers reported that α -alkoxy nitrones undergo nucleophilic additions with ketene silvl acetals to give the corresponding β -(siloxyamino) esters in good yields and stereoselectivity.9 With this background in mind we felt that the ready availability of the enantiomerically pure nitrone derived from 1,2-di-O-isopropylidene-D-glyceraldehyde10 and the wellprecedented stereodirecting effect of the dioxolane group7 made $\hat{4}$ an ideal starting material. The addition of nitrone $\hat{4}$ to 1.5 equiv. of the lithium enolate of methyl acetate (LDA and methyl acetate) afforded a 75:25 mixture of diastereomeric isoxazolidinones 6 in 60% isolated yield (Scheme 1).‡

The β -(hydroxyamino) ester was not observed in the crude product and only compounds **6**, coming from an intramolecular cyclization, were obtained. The stereochemistry of the obtained isoxazolidines **6** was ascertained by an X-ray crystallographic analysis of a single crystal of the major diastereomer *syn*-**6a**.§



Scheme 1

The stereochemical outcome of the reaction is in accord with Kita's results⁹ and our own previous data concerning the nucleophilic additions to α -alkoxy nitrones.¹¹ Efforts to improve both the diastereoselectivity and the chemical yield by variation of the counterion and the solvent, plus attempts of stereocontrol of the reaction by addition of a Lewis acid, are summarised in Table 1.

In all cases, sodium enolates afforded the syn adduct **6a** as the only product of the reaction (ds \ge 95%) in excellent chemical yield (Table 1, compare entries 1–4 with 5, 6 and 9), the solvent only having a slight influence on the chemical yield of the process. Guided by our previous results¹¹ on nucleophilic additions to **4** we next carried out the reaction in the presence of 1.0 equiv. of diethylaluminium chloride (Table 1, entries 7, 8 and 10). Unfortunately, the chemical yield was rather low (20–25%) in all cases, substantial amounts of starting nitrone being recovered. This behaviour suggests that the Lewis acid used as a pre-complexing agent of the nitrone eliminates the sodium enolate from the reaction mixture by forming the corresponding aluminium enolate, which is unable to react with **4**.

Thus, metal exchange should proceed rapidly at the expense of nucleophilic addition, which proceeds in only 20–25%

Table 1 Stereoselective addition of enolates to nitrone 4

Entry	R	Base (solvent)	6a : 6b	Yield ^b (%)
1	Me	LDA (THF)	75:25	60
2	Me	$LDA(Et_2O)$	70:30	54
3	Me	LiHMDS (THF)	86:14	68
4	Me	LiHMDS (Et ₂ O)	60:40	70
5	Me	NaHMDS (THF)	≥95:5	100
6	Me	NaHMDS (Et ₂ O)	≥95:5	95
7	Me	NaHMDS (THF) ^a	34:66	25
8	Me	NaHMDS (Et ₂ O) ^a	30:70	22
9	Et	NaHMDS (THF)	≥95:5	93
10	Et	NaHMDS (Et ₂ O) ^a	32:68	20

^{*a*} 1.0 equiv. of Et₂AlCl was used. ^{*b*} Isolated yield of the crude mixture of diastereomers.



Scheme 2 Reagents and conditions: i, DIBAL-H, -80 °C, CH₂Cl₂, 2 h, 80%; ii, Ac₂O, Py, 0 °C, 1 h, 82%; iii, 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine, TMSOTf, CH₂Cl₂, room temp., 2 h, 63%; iv, NaIO₄ (aq.), SiO₂, CH₂Cl₂, room temp., 20 min, then NaBH₄, MeOH, 0 °C, 90 min, 89%

yield.¶ The lower reactivity of aluminium enolates has been described in nucleophilic additions to imines.¹² A further confirmation of that hypothesis emerged from the fact that an identical result was obtained when nitrone **4** was made to react with the aluminium enolate of methyl acetate prepared *in situ* from methyl acetate and diethylaluminium chloride as described.¹³ Nevertheless, despite these adverse results concerning the chemical yield, a reversal of the diastereofacial selectivity was observed (Table 1, entries 7, 8 and 10) and the *anti* isomer **6b** could be fully characterized‡ and used in further transformations.

Treatment of syn-6a with DIBAL-H in CH₂Cl₂ at -80 °C afforded lactols 7 as a 60:40 mixture of anomers. The first order 300 MHz ¹H NMR spectrum of the mixture provided unequivocal information on their structures. Acetylation of 7 as described⁶ afforded only unreacted starting material when stoichiometric amounts of reagents were used; on the other hand, an excess reagents led to deprotection of the acetonide moiety. If, however, compounds 7 were treated at 0 °C with Ac₂O and pyridine a 76: 24 mixture of anomeric acetates 8 was formed in 82% combined yield, with the α anomer predominating. Coupling of 8 with 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine¹⁴ using the glycosylation methodology developed by Vörbruggen¹⁵ afforded the N¹-nucleoside 9 as a 22:78 mixture of α/β anomers in which the acetonide moiety had been hydrolysed (Scheme 2). The major β isomer (depicted in Scheme 2) was easily separated by column chromatography (100% EtOAc, $R_f \alpha$ -isomer = 0.13, $R_f \beta$ -isomer = 0.23, visualized with UV at 254 nm). Finally, oxidative cleavage (NaIO₄) of the diol unit followed by in situ reduction with NaBH₄ generated the desired isoxazolidine nucleoside 2b in good overall yield as summarised in Scheme 2.

As expected from these results, nitrone **4** behaved as an excellent precursor to other related isoxazolidinyl nucleosides, and thus further studies on its reactivity are underway.

This research was supported by MEC (Madrid, Spain). We are grateful to Professor S. Castillon for helpful discussions. One of us (S. F.) thanks the MEC (Madrid, Spain) for a contract.

Notes and References

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‡ All new compounds exhibited consistent spectral (¹H and ¹³C NMR, IR) and analytical data. Optical rotations: 20 ± 2 °C (*c* 1, CHCl₃). Selected data

for **6a**: mp 60–62 °C, $[\alpha]_D$ + 122.6. For **6b**: mp 75–77 °C, $[\alpha]_D$ –9.7. For **9**: mp 182–183 °C, $[\alpha]_D$ –12.2 (*c* 0.34, MeOH). For **2b**: sticky foam, $[\alpha]_D$ +6.1 (*c* 0.80, MeOH); δ_H (CDCl₃) 1.70 (br s, 1 H, OH), 1.77 (d, 3 H, J 1.2, CH₃), 2.29 (ddd, 1 H, J 3.6, 8.5, 13.7, H_{2a}), 2.99 (dd, 1 H, J 7.4, 13.7, H_{2b}), 3.15 (ddt, 1 H, J 3.6, 5.2, 8.6, H₃), 3.68 (dd, 1 H, J 5.0, 11.7, H_{4a}), 3.79 (dd, 1 H, J 3.3, 11.7, H_{4b}), 3.92 (d, 1 H, J 13.9, CH₂Ph), 4.32 (d, 1 H, J 13.9, CH₂Ph), 5.986 (dd, 1 H, J 3.6, 7.4, H₁), 7.23–7.50 (m, 6 H, ArH + CH), 8.47 (br s, 1 H, NH).

§ *Crystal data* for **6a**: C₁₅H₁₉NO₄, monoclinic, space group *P*₂₁, *a* = 6.011(1), *b* = 8.039(1), *c* = 15.598 (2) Å, β = 92.680 (10)°, *V* = 752.9(2) Å³, *Z* = 2, *D_c* = 1.223 g cm⁻³, μ = 0.089 mm⁻¹. Of the 1452 unique measured reflections, 1182 with $I \ge 2\sigma(I)$ were used in the refinement. *R*(on F²) = 3.83, *R_w* = 9.07. The data were collected on a Siemens P4 diffractometer with graphite monochromated Mo-K α radiation ω -2 θ scan technique (2.61 $\le \theta \le 23.99$). The structure was solved by direct methods using the SHELXS-86 package.¹⁶ All other calculations were accomplished by SHELXL-93.¹⁷ CCDC 182/729.

¶ Similar results were observed with other Lewis acids such as ZnCl₂, ZnBr₂ or MgBr₂. In all cases the yield dropped considerably.

 $\|$ The anomeric configurations were confirmed by $^1\mathrm{H}\,\mathrm{NMR}$ (300 MHz) and NOE experiments.

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Received in Glasgow, UK, 4th August 1997; 7/05673G