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3-Bromo-propenyl acetate in organic synthesis: an expeditious route to 3-alkyl-4-acetoxy-5-iodomethyl isoxazolidines

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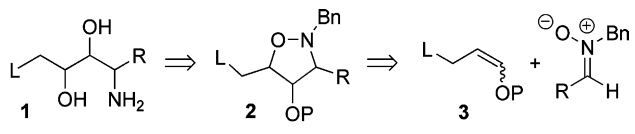
Abstract—*N*-Trimethylsilyloxy-*N*-benzyl-1-alkyl-2-acetoxy-3-buten-1-amines **13**, obtained in good yields and moderate diastereoselectivities by TMSOTf promoted α-acetoxyallylation of nitrones using metallic zinc and 3-bromo-propenyl acetate **11**, are exploited in a stereospecific 5-*exo*-trig iodocyclization reaction to afford 4,5-*cis*-3-alkyl-4-acetoxy-5-iodomethyl isoxazolidines **14**, promising starting materials for the synthesis of pyrrolidine azasugars.

1. Introduction

The 1,3-dipolar cycloaddition of nitrones is a classic tool to assemble 1,3-aminoalcohols, masked in the form of an isoxazolidine.[1] Searching for new routes to **1**, straightforward precursors of 3,4-dihydroxy-pyrrolidines, we focused our attention on isoxazolidine **2**, in principle accessible from a nitrone and dipolarophile **3** (Scheme 1).

The key reagent **3** should contain both an enolether or enolester functionality and a leaving group (L = sulfonate, halide, etc.). However, a careful search in the literature did not show any example of 1,3-dipolar cycloadditions using analogues of **3**. What is known is that inverse electron-demand 1,3-dipolar cycloadditions of nitrones with electron-rich alkenes generally favour formation of the undesired regioisomer, namely of 5-alkoxyisoxazolidines.[2]



Scheme 1.

In any case, we checked the reactivity of *C*-phenyl *N*-benzyl and of *C*-isopropyl *N*-benzyl nitrone with potential dipolarophiles **4**,[3] **5**[4] and **6** (Fig. 1), which fulfil the requirements of synthon **3**. Indeed, they contain the allylic chloride framework and an oxygen or boron substituent, the latter acting as a precursor of the hydroxyl group. Unfortunately, under thermal conditions (refluxing toluene), under microwave irradiation and in the presence of a catalytic amount of Lewis acid (trimethylsilyl triflate) no cycloaddition did occur with simple *C*-alkyl, *N*-benzyl nitrones.

Disappointed by these observations, we turned into an alternative multistep sequence, which is known to lead to 5-iodomethyl isoxazolidines **10**: this strategy is based on the nucleophilic addition of an allylic organometallic reagent **7** to a nitrone,[5] followed by cyclofunctionalization of the silylated adduct **9** to **10** by means of an

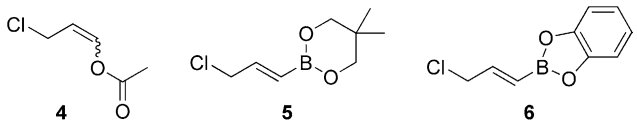


Figure 1.

Keywords: Nitrones; α-Hydroxyallylation; Trimethylsilyl triflate; Iodocyclization; 4-Acetoxy-5-iodomethyl isoxazolidines.
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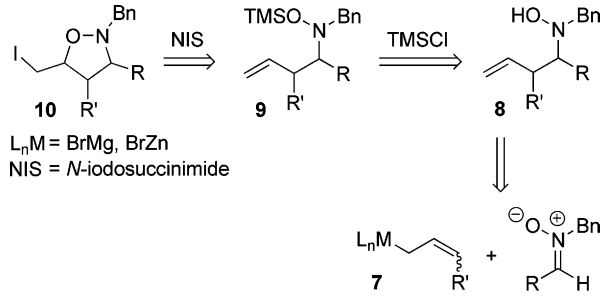
iodinating agent such as *N*-iodosuccinimide (NIS), as shown in Scheme 2.[6]



Scheme 2.

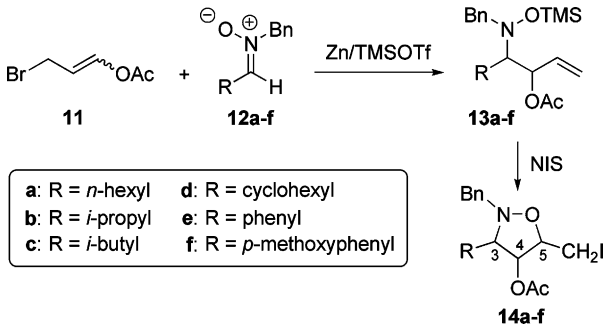
In a previous study, we coped with the difficulty to identify an organometallic species **7** carrying an oxygenated substituent (R′ = OR, OTMS, etc.), capable to react with nitrones and the only solution found at that time was the 3-*tert*-butyldimethylsilyloxy allyl lithium complex, developed by Still in the 1970s.[7]

In this letter, we wish to report (i) the α-acetoxyallylation of nitrones by means of 3-bromo-propenyl acetate (**11**)[8] and zinc, and (ii) a new regio- and diastereoselective synthesis of isoxazolidines **10** (R′ = AcO), not accessible via 1,3-dipolar cycloaddition.

2. Discussion

A first set of attempts to couple 3-bromo-propenyl acetate (**11**) with nitrones using zinc or indium metal, either under Barbier or Grignard conditions,[8] invariably failed. Since it is known that Lewis acid, and in particular trimethylsilyl triflate (TMSOTf), are able to force the addition of weak nucleophiles to nitrones,[9] eventually we succeeded by adopting the experimental conditions reported in Scheme 3.

This trimethylsilyl triflate-promoted procedure not only solved the problem of nitrone reactivity, but also allowed us to prepare the silylated hydroxylamine **13** in a one-pot reaction, thus formally integrating in a single process two distinct reactions, the acetoxyallylation step and the *O*-silylation step envisaged by the original



Scheme 3.

protocol reported in Ref. 6 (Scheme 2). In detail, TMSOTf (1 equiv) is added to the mixture of **11**, nitrone **12** and zinc powder in *N*,*N*-dimethylformamide (DMF), in a classical Barbier protocol. A reaction sequence takes place, consisting of a preliminary formation of a *N*-trimethylsilyloxy iminium ion, which successively undergoes nucleophilic addition by **11**. The latter reaction likely involves the adoption of open-chain *anti*-periplanar transition states (Fig. 2), which also account for the fair *syn*-diastereoselectivity displayed by nitrones **12a–f** (Table 1).[10]

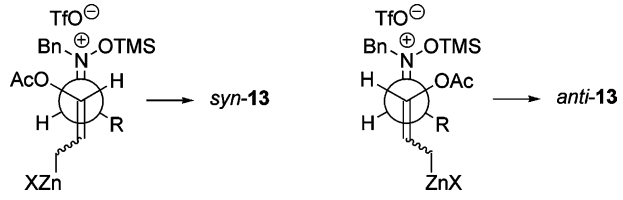


Figure 2.

The lower reactivity exhibited by *C*-*p*-methoxyphenyl-*N*-benzyl nitrone (**12f**) can be the result of the poor electrophilicity of the azomethine carbon due to electronic effects. After alkaline quenching, the mixture of *syn*- and *anti*-**13** was extracted with CH_2Cl_2 and analyzed by GC–MS. A standard protocol was adopted in entries 1–6 of Table 1.[11]

Table 1. One-pot synthesis of *O*-TMS hydroxylamines **13a–f**

Run	Nitrone **12**	**13** Yield[a] (%)	*syn*-**13**/*anti*-**13**[b]
1	**12a**	80	65/35
2	**12b**	72	75/25
3	**12c**	70	57/43
4	**12d**	87	80/20
5	**12e**	75	60/40
6	**12f**	27	70/30

[a] Yields refer to the mixture of inseparable isomeric adducts **13** isolated by flash-chromatography on silica gel. These yields are to be considered underestimated by a factor of 5–10% owing to partial protodesilylation on the column.

[b] Determined from GC–MS peak area ratios. Retention times of *syn*-**13** are regularly shorter than those of *anti*-**13**.

Table 2. Iodocyclization of *syn*- and *anti*-**14a–d**

Run	Starting **13**	Product **14**	Yield[a] (%)
1	*syn*-**13a**	3,4-*cis*-4,5-*cis*-**14a**	74
	anti-**13a**	3,4-*trans*-4,5-*cis*-**14a**	86
2	*syn*-**13b**	3,4-*cis*-4,5-*cis*-**14b**	65
	anti-**13b**	3,4-*trans*-4,5-*cis*-**14b**	84
3	*syn*-**13c**	3,4-*cis*-4,5-*cis*-**14c**	75
	anti-**13c**	3,4-*trans*-4,5-*cis*-**14c**	65
4	*syn*-**13d**	3,4-*cis*-4,5-*cis*-**14d**	74
	anti-**13d**	3,4-*trans*-4,5-*cis*-**14d**	95

[a] Isolated yields after column chromatography. Yields higher by a factor of 5–10% are obtained if NIS is directly added to the crude extraction mixture of *syn*/*anti*-**13**, omitting their chromatographic purification. This means that DMF present as co-solvent does not affect the reaction with NIS.

Table 3. ^{1}H NMR (600 MHz) chemical shifts (multiplicity, J in hertz) of representative hydrogens of isoxazolidines **14a–d**

14	H3	CH_2I	CH_2Ph	H5	H4
3,4-*cis*-4,5-*cis*-**14a**	3.09–3.14 (m)	3.18 (t, J = 9.7) 3.21 (dd, J = 6.4/9.7)	3.98 (d, J = 13.9) 4.11 (d, J = 13.9)	4.49 (ddd, J = 4.5/6.4/9.7)	5.81 (t, J = 4.5)
3,4-*trans*-4,5-*cis*-**14a**	2.98 (dt, J = 2.4/6.4)	3.24 (d, J = 7.3)	4.02 (d, J = 13.5) 4.08 (d, J = 13.5)	4.33 (dt, J = 4.8/7.3)	5.39 (dd, J = 2.4/4.8)
3,4-*cis*-4,5-*cis*-**14b**	3.00–3.12 (m)	3.09 (t, J = 9.7) 3.13 (dd, J = 7.0/9.7)	3.94 (d, J = 14.1) 4.01 (d, J = 14.1)	4.46 (dt, J = 3.2/7.0)	5.85 (br t, J = 3.4)
3,4-*trans*-4,5-*cis*-**14b**	2.81 (dd, J = 2.0/6.4)	3.21 (d, J = 7.4)	3.94 (d, J = 13.8) 4.08 (d, J = 13.8)	4.25 (dt, J = 4.7/7.4)	5.57 (dd, J = 2.0/4.7)
3,4-*cis*-4,5-*cis*-**14c**	3.15–3.18 (m)	3.18 (t, J = 9.7) 3.20 (dd, J = 6.5/9.7)	3.95 (d, J = 14.0) 4.08 (d, J = 14.0)	4.51 (ddd, J = 4.8/6.5/9.7)	5.80 (t, J = 4.8)
3,4-*trans*-4,5-*cis*-**14c**	3.12 (br t, J = 6.5)	3.25 (d, J = 7.1)	4.05 (d, J = 13.8) 4.13 (d, J = 13.8)	4.38 (br dt, J = 5.6/7.1)	5.39 (dd, J = 2.1/4.9)
3,4-*cis*-4,5-*cis*-**14d**	3.00–3.06 (m)	3.10 (t, J = 9.7) 3.13 (dd, J = 7.0/9.7)	3.94 (d, J = 14.2) 4.00 (d, J = 14.2)	4.45 (dt, J = 3.0/7.0)	5.85 (br t, J = 3.0)
3,4-*trans*-4,5-*cis*-**14d**	2.81 (dd, J = 1.8/6.6)	3.25 (d, J = 7.4)	4.02 (d, J = 13.4) 4.07 (d, J = 13.7)	4.24 (dt, J = 4.7/7.4)	5.58 (dd, J = 1.8/4.7)

The six adducts *syn*/*anti*-**13a–f** were then exposed to the action of NIS in $CHCl_3$ at 0–25 °C. To our surprise, the alkyl substituted adducts **13a–d**underwent efficient iodocyclization (Table 2),[12] while no more than traces of isoxazolidines were observed in the case of aryl substituted **12e** and **f**.[13]

Two features of the iodocyclization reaction are worth of note. From a kinetic point of view, following the reaction course (GC–MS), cyclization rates of *anti*-**13** were higher than those of *syn*-**13**, which led to more congested all-*cis* isoxazolidines. From a stereochemical point of view, a single isoxazolidine **14** was obtained from each adduct **13**; in particular, *syn*-**13** afforded 3,4-*cis*-4,5-*cis*-**14**, while 3,4-*trans*-4,5-*cis*-**14** was obtained from *anti*-**13**. Astonishing is the former cyclization, leading to the sterically crowded and thermodynamically less stable all-*cis* isoxazolidine. From each reaction mixture 3,4-*cis*-4,5-*cis*-**14** and 3,4-*trans*-4,5-*cis*-**14** were efficiently separated by flash-chromatography on silica gel and their stereochemical structures were determined by NOE techniques;[14] representative ^{1}H NMR data are reported in Table 3. Interesting trends, useful for diagnostic correlations, are apparent in Table 3: (i) H4 and H5 in 3,4-*cis*-4,5-*cis*-**14** always resonate downfield with respect to the 3,4-*trans*-4,5-*cis* isomer; (ii) H4 signal in 3,4-*cis*-4,5-*cis*-**14** is always a triplet, while in 3,4-*trans*-4,5-*cis*-**14** is a doublet of doublets, thus confirming the assigned stereochemistry; (iii) the two protons of the CH_2I group are chemically equivalent in 3,4-*trans*-4,5-*cis*-**14**, but not in 3,4-*cis*-4,5-*cis*-**14**, probably owing to hindered rotation around the C5–CH_2 bond.

To account for the exclusive 4,5-*cis* ring closure, it is useful to examine the early stage of the cyclization step, represented by conformations **A**, **B** and **C**, **D**, relative to *syn*- and *anti*-**13**, respectively (Fig. 3). In our opinion, conformers **B** and **D** enjoy an attractive through space electrostatic interaction between the acetoxy group and the iodonium unit, in relative gauche positions. Such

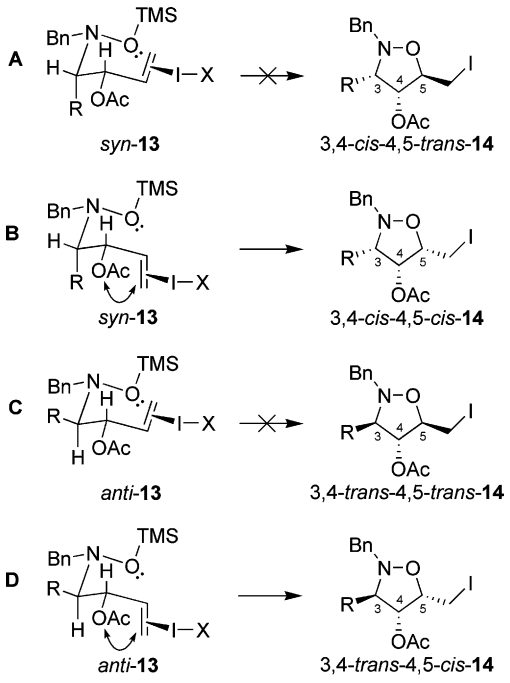


Figure 3.

an attractive interaction vanishes in conformers **A** and **C**, where the acetoxy and the iodonium groups are in *anti*-periplanar orientation.

3. Conclusions

In conclusion, new trisubstituted isoxazolidines **14**, not accessible via 1,3-dipolar cycloaddition reactions, are now available through a simple synthetic sequence, which involves the in situ *O*-silylation/acetoxyallylation of a *C*-alkyl nitrone, followed by a diastereoselective iodocyclization. In contrast to 1,3-dipolar cycloadditions, this two-step protocol ensures a perfect

control of regiochemistry and displays an unexpected diastereopreference leading to 4,5-*cis* isoxazolidines, independently of the *syn*- or *anti*-stereochemistry of the starting homoallylic hydroxylamine **13**. The resulting 3,4-*cis*-4,5-*cis*- and 3,4-*trans*-4,5-*cis*-3-alkyl-4-acetoxy-5-iodomethyl isoxazolidines **14** look as attractive potential precursors of diastereodefined dihydroxylated cyclic or open-chain amines.

Acknowledgments

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References and notes

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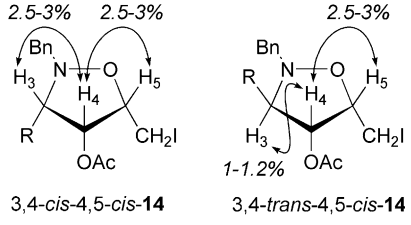
9. A common practice to force nitrone to react with poor nucleophiles, such silyl enol ethers, involves the use of Lewis acid to enhance azomethinic carbon electrophilicity upon oxygen complexation: see Ref. 5a–c.
10. Recently, Petrini et al. studied the reaction of **11** with imines produced in situ from α-amidoalkyl phenylsulfones, and reported an appreciable *anti*-diastereoselectivity: see Petrini, M.; Profeta, R.; Righi, P. *J. Org. Chem.* **2002**, *67*, 4530, Conversely, the addition of **11** to aldehydes, both in aqueous and in polar aprotic solvents, is characterized by a unique dependence of diastereoselectivity upon the nature of the aldehyde. While saturated aldehydes afford *anti* adducts, conjugated and aromatic aldehydes give *syn* adducts (Ref. 8).
11. *Typical experimental procedure for preparation of* **13**. Nitrone **12** (1 mmol) is added to a suspension of flame-dried zinc powder (1 mmol, 0.098 g) in anhydrous DMF (1 mL) and the heterogeneous mixture is cooled at 0 °C with an ice-bath. 3-Bromo-propenyl acetate **11** (1.5 mmol, 0.17 mL) and TMSOTf (1 mmol, 0.18 mL) are subsequently added at 0 °C and the reaction mixture is vigorously stirred for 5 h, allowing to reach room temperature. The reaction is quenched with saturated aqueous $NaHCO_3$ solution (2 mL), salts are removed by filtration on a short pad of Celite® and the aqueous phase is extracted with CH_2Cl_2 (3×5 mL). *O*-TMS hydroxylamines **13** are obtained almost pure by flash-chromatography purification on silica gel (cyclohexane/ethyl acetate 7:3); to avoid desilylation the elution should be as fast as possible.
12. *Typical experimental procedure for the iodocyclization reaction*. The mixture of silylated hydroxylamines **13** (0.7–0.8 mmol) was dissolved in $CHCl_3$ (5 mL), the solution was cooled at 0 °C and NIS (1 mmol, 0.23 g) was added. After being stirred in the dark for 24 h, allowing to reach room temperature, the reaction was quenched with aqueous $Na_2S_2O_3$ (2 mL) and the aqueous layer was extracted with $CHCl_3$ (3×5 mL). Isoxazolidines **14** were separated by flash-chromatography eluting with cyclohexane/ethyl acetate 98:2.
13. *O*-TMS hydroxylamines **13e** and **f** were recovered almost unchanged from the iodocyclization reaction mixture.
14. Typical NOE enhancements:



3,4-*cis*-4,5-*cis*-**14** 3,4-*trans*-4,5-*cis*-**14**