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Alkoxyamine-cyanoborane adducts: efficient cyanoborane transfer agents†

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We report the synthesis of the hitherto unknown zwitterionic alkoxyamino cyanoboranes by reduction of *O*-alkyloximes with sodium cyanoborohydride; unprecedented cyanoboronated *N*-alkoxyformamidines were also isolated as by-products. Boronated alkoxyamines were found to be efficient cyanoborane transfer agents towards more basic amines, including aminosugars; they were also successfully transformed into neoglyco-conjugates by the neoglycorandomization reaction with reducing sugars.

Much effort has been devoted to the preparation of organoboron compounds; such derivatives exhibit unique structural and chemical profiles which make them valuable intermediates and catalysts in organic synthesis,[1] including asymmetric processes. Boron-containing compounds are widely used in hydroborations,[2] reductions,[3] cross-coupling reactions (*e.g.* Suzuki–Miyaura reaction),[4] or cycloadditions,[5] among others.

Organoboron derivatives are also of great interest from a biological and pharmacological point of view.[6] In this context, α-aminoboronic acids, considered as isoelectronic analogues of amino acids, have been reported as inhibitors of proteases;[7] aminocarboxyboranes, and their precursors amine-cyanoboranes[8] have shown antifungal, antibacterial, antiarthritic, and anti-inflammatory properties.[9] Some cyanoboronated nucleosides have been reported to act as potent antitumor agents in mammalian cell lines, and to possess antiinflammatory and hypolipidemic activities.[10]

Furthermore, numerous organoboron derivatives have been assayed in imaging studies[11] and radiotherapy, as boron carriers to tumor cells for the boron neutron capture therapy (BNCT),[12] which has been demonstrated to be a successful treatment against some tumoral malignancies, with efficiency comparable to conventional radiotherapy. Therefore, new effective methods to prepare boron-containing amino derivatives are of relevance in synthetic, bioinorganic, and pharmaceutical chemistry.

Herein we report the synthesis of the first examples of *N*-alkoxyamine-cyanoboranes by an experimentally-simple procedure and their use as cyanoborane transfer agents towards aliphatic amines.

O-Alkyloximes **1** and **2** were prepared by condensation of chloroacetaldehyde diethylacetal with *N*-alkyl(methyl, benzyl)-oxyamine hydrochlorides in water medium (Scheme 1). For the oxime **3**, the *N*-benzyloxyamine hydrochloride was previously transformed into the *N*-benzyloxyamine sulfate in order to avoid mixtures of **2** and **3**, *in situ* produced by nucleophilic displacement of Br by chloride when reacting bromo-acetaldehyde diethylacetal with *N*-benzyloxyamine hydrochloride. The liquid oximes **1–3** were obtained in high yields (81, 84, 74%, respectively) as mixtures of the *E/Z* isomers in roughly 2 : 1 ratios, as deduced from the NMR spectra.

We have accomplished the reduction of *O*-alkyl oximes **1–3** with sodium cyanoborohydride in glacial acetic acid,
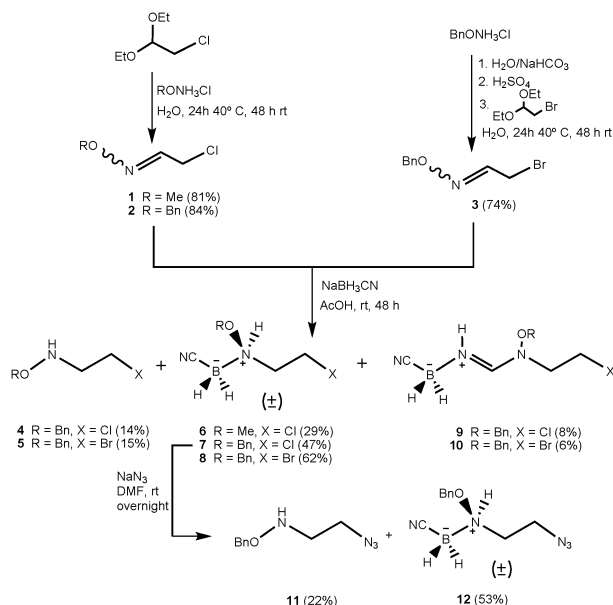
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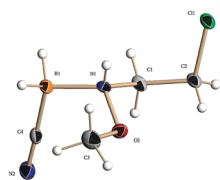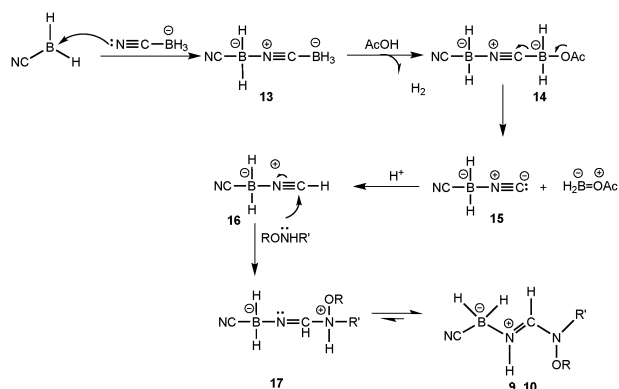

Scheme 1

Fig. 1 ORTEP drawing of **6**.

conditions commonly used for reducing oximes. Surprisingly, the expected *N*-alkyloxy-*N*-(2-haloethyl)amines **4** and **5** were obtained as minor compounds after chromatographic purification (the volatile methoxy derivative was not isolated). The hitherto unknown zwitterionic *N*-cyanoboronated-*N*-alkoxyamines **6–8** were isolated as the major compounds (29–62%), obtained as crystalline derivatives stable to air and silica purification. To our knowledge, no boronated derivatives have been previously reported in the reduction of *O*-alkyloximes with boron-containing reducing agents.

Boronated derivatives **6–8** were characterized by NMR spectroscopy, including ^{11}B-NMR, MS, and single crystal X-ray crystallography‡ (Fig. 1 depicts ORTEP drawing of **6** showing thermal ellipsoids at the 50% probability level). ^{1}H-NMR spectra of compounds **6–8** showed a broad signal located at roughly 2 ppm, and associated to the BH_2CN protons; furthermore, the benzylic protons of **7** and **8** appeared as diastereotopic signals, due to the chiral nitrogen. ^{11}B-NMR spectra of **7** exhibited a broad triplet at −21 ppm, with a coupling constant of 90 Hz, which agrees with the proposed structure. X-Ray diffraction structures of **6–8** confirmed that they crystallize as racemic compounds.

Remarkably, cyanoboronated *N*-benzyloxy-*N*-(2-haloethyl)-formamidines **9** and **10** were also isolated in modest yields (8% and 6%, respectively) upon reduction of **2** and **3** (Scheme 1). The high coupling constants between the protons of the amidino group (16.2 and 15.9 Hz, respectively) indicate a *trans* arrangement of such protons. No previous reports on cyanoboronated amidines can be found in the literature.

We postulate that the formation of formamidine derivatives can take place by reaction of the cyanoborohydride anion with cyanoborane (Scheme 2) to afford adduct **13**; further reaction with acetic acid can lead to the intermediate **16**, which can be trapped by *N*-alkoxyamines **4** and **5** to furnish formamidines **9** and **10**.
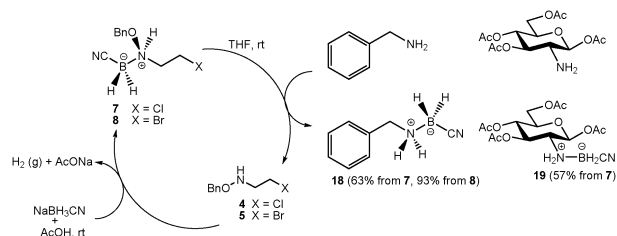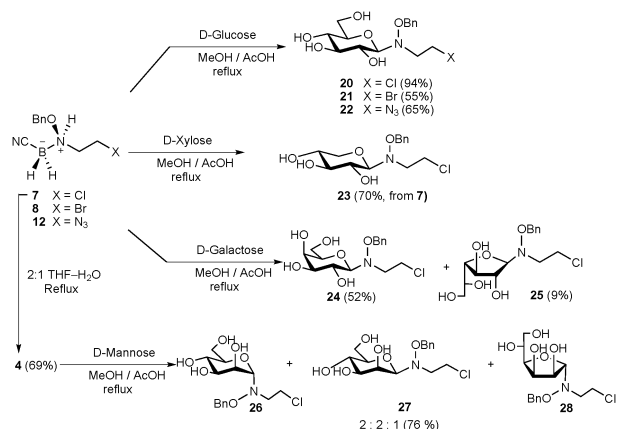

Scheme 3

The presence of a haloalkyl moiety in compounds **6–8** makes them suitable for being transformed into a variety of derivatives; compound **7** was subjected to nucleophilic displacement of the chlorine atom with sodium azide in DMF to give a separable mixture of cyanoboronated derivative **12** (53%) and benzyloxyamine **11** (22%), obtained by a partial deboronation reaction.

We have also explored the ability of cyanoboronated *N*-alkoxyamines to behave as new boron transfer agents towards amines; for that purpose we chose as model compounds cyanoboronated benzyloxyamines **7** and **8**, which were subjected to reaction with benzylamine and tetra-*O*-acetyl-β-D-glucosamine under mild conditions to give **18** and **19** in a 57–93% yield (Scheme 3). Alkoxyamine cyanoborane **7** was regenerated (63% yield) by treatment of **4** with sodium cyanoborohydride in acetic acid. The number of amino-boranes derived from carbohydrates is scarce, limited to oxazaborolidine[13] and cyanoborane-nucleoside adducts.[10]

These results suggest that cyanoboronated *N*-alkoxyamines act as effective cyanoborane transfer agents probably due to the lower basicity of alkoxyamines compared to amines. The reaction can be performed at rt, in contrast with reported procedures involving the use of other transfer agents in refluxing diethyl ether or dimethoxyethane.[14]

We have also accomplished the preparation of neoglyco-conjugates **20–25** from cyanoboronated *N*-benzyloxyamines **7**, **8** and **12** by an *N*-glycosylation reaction with D-glucose, D-xylose and D-galactose in methanolic acetic acid (Scheme 4). The distribution of isomeric *N*-glycosides was found to be dependent on the nature of the carbohydrate.

Such a chemoselective reaction, originally developed by Peri and co-workers[15] and currently known as neoglyco-randomization,[16] is a very robust glycosylation methodology

Scheme 2

Scheme 4

which involves treatment of an alkoxyamine with a non-activated reducing sugar. We have simplified the original conditions used by Peri, by replacing DMF and the acetic/acetate buffer by greener MeOH and catalytic amounts of glacial acetic acid to furnish the corresponding β-glycopyranosides **20–23** in a totally stereoselective fashion in short reaction times and from good to almost quantitative yields (55–94%), starting from D-glucose or D-xylose and cyanoboronated N-alkoxyamines **7**, **8** and **12** (Scheme 4).

Similarly, by coupling D-galactose with **7**, a separable mixture of β-D-galactopyranoside **24** (52%) and β-D-galacto-furanoside **25** (9%) was obtained (Scheme 4); remarkably, no equilibration was observed in solution.

The syntheses of N-glycosides **20–25** constitute the first examples of cyanoboronated N-alkoxyamines being transformed into N-glycosides *via* the neoglycorandomization reaction; the outcome of the reaction proved to be compatible with alkoxy-amines bearing a cyanoborane moiety and a variety of functional groups such as halides and azido.

The same kind of reaction was assayed on non-boronated alkoxyamine **4** (Scheme 4), obtained either by reduction of **2**, as indicated in Scheme 1, or by removal of the cyanoborane moiety of **7** by refluxing in aqueous THF. For D-mannose, a non-separable mixture of α- and β-D-mannopyranosides **26**, **27** and α-D-mannofuranoside **28** were obtained in a 2 : 2 : 1 ratio and in a 76% yield after chromatographic purification. The same ratio was obtained starting from alkoxyamine cyanoborane **7**.

We have also extended the previous reactions to carbo-hydrate-derived alkoxyamines. In this context, reaction of partially-protected *xylo*-configured aldehyde **29** with BnONH$_2$·HCl afforded the corresponding oxime **30** (Scheme 5) as a stereoisomeric 2 : 1 E/Z mixture (87% yield). NaBH$_3$CN-mediated reduction of **30** using the same conditions as indicated in Scheme 1 furnished a separable mixture of alkoxyamine **31** and alkoxyamine cyanoborane **32** (5 : 1 diastereoisomeric ratio) in almost quantitative overall yield (68% and 22%, respectively). No formamidine was detected.

Coupling of **31** with reducing sugars (D-glucose, D-xylose and D-galactose) under glycosylation conditions led to the corresponding β-D-glycopyranosyl pseudodisaccharides **33–35** (85–90%) in a totally stereoselective fashion. Remarkably for **35**, no furanosyl glycoside was detected, unlike the previous reaction of **7** with D-galactose, which indicates that stereoselectivity of the glycosylation reaction is strongly dependent on the aglycone nature.
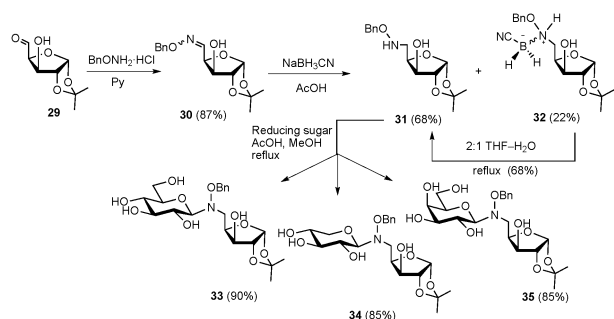
In conclusion, we have developed a novel procedure for the preparation of the hitherto unknown cyanoboronated N-alkoxyamines by reduction of O-alkyloximes with sodium cyanoborohydride in acetic acid. Title compounds were efficiently used as cyanoborane transfer agents towards aliphatic amines, including aminosugars under mild conditions. The novel and efficient preparation of N-glycosides from cyanoboronated N-alkoxyamines under glycorandomization conditions is also reported.

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Scheme 5