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O-Silyl triflate-promoted addition of diethyl phosphite to chiral aldonitrones. A rapid access to complex α-amino phosphonates and their *N*-hydroxy derivatives

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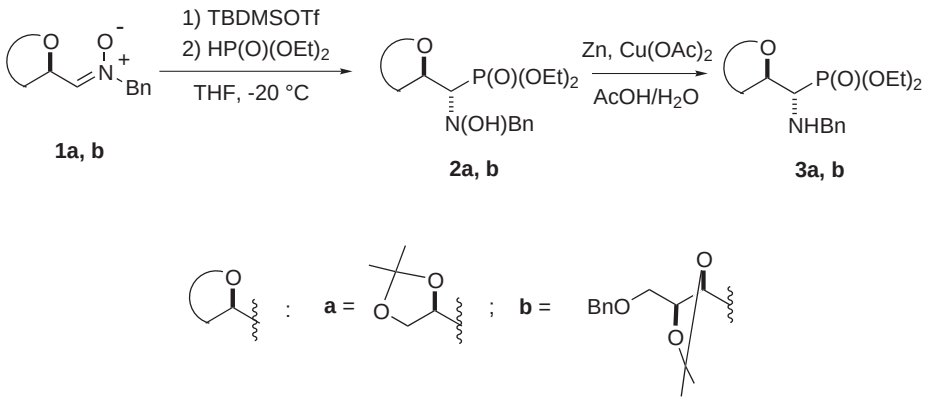
Abstract—The addition reaction of diethyl phosphite to *O*-silylated *N*-benzyl nitrones derived from chiral α-alkoxy and *N*-Boc α-amino aldehydes has been studied as a stereoselective carbon–phosphorus bond forming process for the synthesis of polyhydroxylated α-amino and α,β-diamino phosphonates. Key intermediates are the corresponding *N*-hydroxy α-amino phosphonates.

α-Amino phosphonates as phosphorus isosteres of α-amino carboxylates and isopolar analogues of α-amino phosphates, constitute a class of compounds of current interest owing to their use in biological studies and in medicinal and pharmaceutical chemistry.[1] Most notably among the various methods for preparing these compounds[1,2] is that reported by Vasella and co-workers employing the addition of metal phosphites or trimethylsilyl phosphite to *N*-glycosyl nitrones.[3] Moreover, this route represents one of the few examples of addition of heteronucleophiles to nitrones,[4] a class of C=N compounds whose valuable role in synthetic methodologies is steadily increasing.[5] Recent investigations in our laboratories have been dealing with both nitrone chemistry[6] and phosphonic acid synthesis.[7] These earlier studies led us to investigate the addition of diethyl phosphite to *N*-benzyl nitrones derived from chiral α-alkoxy and *N*-protected α-amino aldehydes. Our nitrone–phosphite approach is complementary to that of Vasella[3] as it provides an entry to hitherto unreported polyhydroxylated α-amino and α,β-diamino phosphonic acids. Also *N*-hydroxy α-amino phosphonate derivatives, the primary adducts in this approach, constitute a class of biologically important compounds[8]



Scheme 1.

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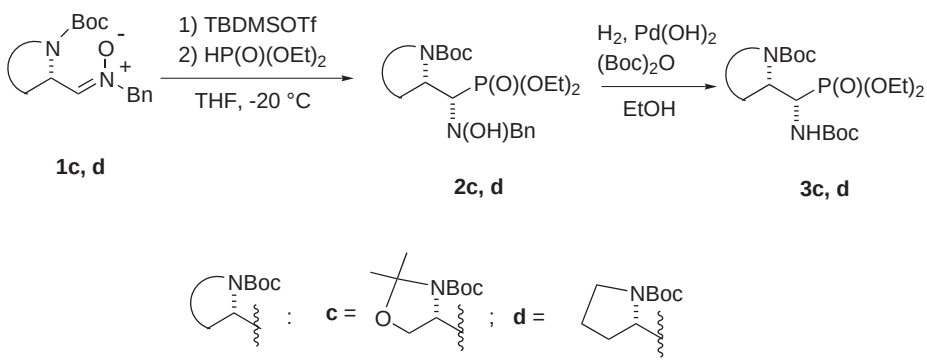
as phosphorus isosteres of the corresponding carboxylic acids.[9] The initial results of these studies are reported below.

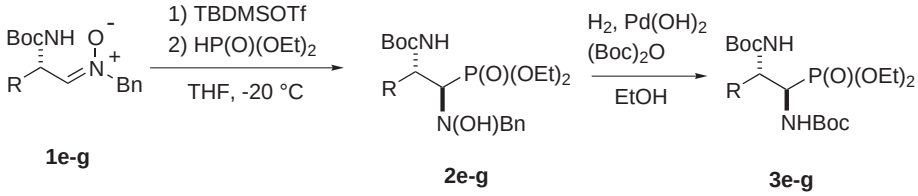
While a mixture of the D-glyceraldehyde-derived nitrone[6b] **1a** and diethylphosphite in anhydrous THF at room temperature did not result in the formation of any reaction product, treatment of **1a** with 1.1 equiv. of *tert*-butyldimethylsilyl triflate (TBDMSOTf)[10] at −20°C followed by the addition of the same phosphorus reagent afforded after 10 min, the *N*-hydroxy α-amino phosphonate **2a** (70% yield) as a single isolated product (Scheme 1).[11] The structure of **2a** as established by X-ray crystallography[12] showed the *anti* relationship between the resulting *N*-hydroxyamino group and the pre-existing alkoxy group. The formation of the *anti*-adduct is in agreement with the stereochemical outcome observed in earlier addition reactions of various nucleophiles to **1a** pre-complexed with Lewis acids.[6b,13] The removal of the hydroxy group from the nitrogen atom of **2a** was carried out by treatment with a mixture of $Zn/Cu(OAc)_2$ according to our earlier procedure.[6d] The resulting alkoxylated *N*-Bn α-amino phosphonate **3a** was isolated in 60% yield by flash chromatography. The same procedure was repeated starting from the L-threose-derived nitrone[6a] **1b** to give sequentially the *N*-hydroxy α-amino phosphonate **2b** (70% yield) and the reduced product **3b** (60% yield). Also in this case the structure of the expected[6] *anti*-adduct **2b** was assigned by X-ray crystallography.[12]

Successful reactions were registered also with α-amino nitrones derived from natural α-amino acids. Thus, treatment of the TBDMSOTf-precomplexed nitrone[14] **1c** derived from *N*-Boc serinal acetonide (Garner aldehyde) with diethylphosphite under the same conditions as above (THF, −20°C, 10 min) afforded exclusively the *syn*-adduct **2c** as a syrup, isolated in 80% yield by flash chromatography (Scheme 2).[11] The removal of both the benzyl and hydroxy groups from the nitrogen atom of **2c** with the concomitant protection of the amino group as a *tert*-butyl urethane was carried out in one step by hydrogenation over $Pd(OH)_2$ in the presence of $(Boc)_2O$. The resulting *N*-Boc protected α,β-diamino phosphonate **3c** was isolated in 61% yield. The same reaction sequence was applied to the prolinal-derived nitrone **1d** to give the corresponding *syn*-adduct **2d** and the α,β-diamino phosphonate **3d**. The NMR spectra of the *syn*-adducts **2c** and **2d** showed similar features to those of the *syn*-hydroxylamines derived from the reaction of the same nitrones **1c** and **1d** with various nucleophiles.[15] It has been suggested that the adducts exist in a rigidified conformation due to hydrogen-bonding between the *N*-OH and CO of *N*-Boc, which leads the hydrogen atoms of the two adjacent stereocenters to adopt an antiperiplanar disposition. Indeed the ^1H NMR spectra from −40 to −55°C showed $^3J_{H,H}$ coupling constant values between these atoms of 10.37 Hz for **2c** and 10.20 Hz for **2d**. Moreover, the spectra did not change in the range of temperature between 25 and −55°C and showed a low field chemical shift for the hydroxyamino proton at various concentrations in the range of 7.6 and 7.9 ppm. It has to be noted that high levels of *syn*-selectivity have been observed in earlier addition reactions of organometals to *N*,*N*-diprotected α-amino nitrones either in the absence or in the presence of pre-complexing agents.[14a,15]

The reactions of *N*-monoprotected α-amino nitrones **1e–g** whose progenitors were alanine, phenylalanine and leucine, respectively, afforded the corresponding *N*-hydroxy α-amino phosphonates **2e–g** in very good yields (70–80%). Each adduct appeared by NMR analysis to be constituted by a major diastereomer, more than 95%, which was easily isolated by flash chromatography (Scheme 3).[11] The structure of product **2g** as established by X-ray crystallography[12] showed the *anti* relationship between the NHBoc and N(OH)Bn group. We observed the same stereochemical outcome in the addition reaction of 2-lithiothiazole to the nitrone derived from *N*-monoprotected serinal.[14a] These results and those reported in Scheme 2 confirm the tunable *syn–anti* stereoselectivity of the addition reaction to α-amino nitrones by bis- and monoprotection of the amino group. Hence, it appeared reasonable to assign the same configuration of **2g** to the products **2e** and **2f**. Unfortunately, we have been unable to transform these products into cyclic ureas for structural assignment by NMR analysis because of their substantial epimerization and decomposition. Finally, each individual pure isomer was subjected to catalytic hydrogenation over $Pd(OH)_2$ in the presence of $(Boc)_2O$ and transformed into the corresponding *N*-Boc protected α,β-diamino phosphonates **3e–g** in satisfactory yields (ca. 60%).[11]



Scheme 2.



1e-g **2e-g** **3e-g**

e, R = Me; **f**, R = $PhCH_2$; **g**, R = Me_2CHCH_2

Scheme 3.

In conclusion, we have presented a method for the stereoselective synthesis of α-amino phosphonates and their *N*-hydroxy derivatives by aminophosphonation of carbohydrate and amino acid derivatives using nitrone-based chemistry. The method appears quite promising for the synthesis of other compounds with a wide range of molecular diversity in the chain and future efforts will be made in this direction.

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11. All new compounds shown in Schemes 1–3 gave satisfactory analytical data and NMR spectra consistent with their structures. Some physical characteristics are reported here: **2a**: mp = 113–114°C (Et_2O), $[\alpha]_D^{20} = +20.0$ (*c* 0.9, $CHCl_3$); **2b**: mp = 115–118°C (EtOAc), $[\alpha]_D^{20} = -6.1$ (*c* 1.1, $CHCl_3$); **2c**: syrup, $[\alpha]_D^{20} = +4.4$ (*c* 1.9, $CHCl_3$); **2d**: syrup, $[\alpha]_D^{20} = +7.2$ (*c* 0.9, $CHCl_3$); **2e**: syrup, $[\alpha]_D^{20} = -25.0$ (*c* 0.8, $CHCl_3$); **2f**: syrup, $[\alpha]_D^{20} = -23.3$ (*c* 0.2, $CHCl_3$); **2g**: syrup, $[\alpha]_D^{20} = -50.0$ (*c* 0.5, $CHCl_3$); **3a**: oil, $[\alpha]_D^{20} = +20.0$ (*c* 1.0, $CHCl_3$); **3b**: oil, $[\alpha]_D^{20} = -5.0$ (*c* 1.3, $CHCl_3$); **3c**: syrup, $[\alpha]_D^{20} = -45.8$ (*c* 0.9, $CHCl_3$); **3d**: syrup, $[\alpha]_D^{20} = -38.0$ (*c* 1.3, $CHCl_3$); **3e** (major product): syrup, $[\alpha]_D^{20} = -21.6$ (*c* 0.5, $CHCl_3$); **3f** (major product): syrup, $[\alpha]_D^{20} = -15.5$ (*c* 0.6, $CHCl_3$); **3g** (major product): syrup, $[\alpha]_D^{20} = -23.2$ (*c* 1.2, $CHCl_3$).
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