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Synthesis of *p*-amino-*N*,*N*′-dihydroxybenzamidine using a TBDMS protecting group protocol

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ABSTRACT

A synthetic route to *p*-amino-*N*,*N*′-dihydroxybenzamidine is established using a TBDMS protecting group strategy starting with *p*-nitrobenzhydroxamic acid chloride, which is transformed to *O*,*O*′-bis(*tert*-butyldimethylsilyl)-*N*,*N*′-dihydroxybenzamidine. Reduction with sodium dithionite occurs without degradation of the dihydroxyamidine functional group. Deprotection with ammonium fluoride is fast and efficient. This is important because no other possibility to synthesize this derivative has been found up to now. Furthermore, TBDMS protecting group strategy is proved to be adaptable to other substituted *N*,*N*′-dihydroxybenzamidines.

Introduction

N,*N*′-Dihydroxybenzamidines are efficient prodrugs of benzamidines since they raise their bioavailability to a great extent.[1,2] They exceed characteristics of amidoximes. In turn, in vivo reduction to the active agent amidine proceeds fast and complete.[2,3] The synthesis of various *para*-substituted *N*,*N*′-dihydroxybenzamidines has been realized successfully. The general synthetic strategy starts from substituted benzaldoximes[4] which are chlorinated with *N*-chlorosuccinimide (NCS) to benzhydroxamic acid chlorides[5] using published procedures. By reacting benzhydroxamic acid chlorides with hydroxylamine a number of *N*,*N*′-dihydroxybenzamidines were synthesized.[6] Using this protocol for the synthesis of *para*-amino-*N*,*N*′-dihydroxybenzamidine turned out not to be appropriate for this special and hitherto unknown derivative because chlorination of the respective oxime with NCS or *tert*-butyl-*N*-chlorocyanamide (CBCA)[7] does not lead to the intermediate *p*-aminobenzhydroxamic acid chloride. The *para*-amino derivative **6** is of special interest because it represents the most simple phenylogous dihydroxyguanidine. Moreover, some anticoagulants contain a *p*-aminobenzamidine group being essential for the desired effect. *N*,*N*′-Dihydroxyamidines are known to be unstable against acids[8] and bases[9,10], reductive conditions as well as high temperature, preferably leading to the respective benzamidoximes. Thus, protecting group strategies are limited since protection and deprotection have to be compatible with these requirements. Therefore, there is a need for a synthetic strategy leading to *para*-amino-*N*,*N*′-dihydroxybenzamidine **6** as a model compound to be applicable also in more complex prodrugs.

Results and discussion

Previous results showed that already the approach of *p*-aminobenzhydroxamic acid chloride and its *N*-methyl, *N*-ethyl and *N*,*N*-dimethyl derivatives resulted in a mixture of undesired byproducts especially caused by ring chlorination, so a synthetic strategy using protecting groups was necessary. We considered the *tert*-butyldimethylsilyl group as a sterically demanding protecting group being a suitable choice.[11] There is continuing interest in evaluating the formation and also special reagents and conditions of cleavage for this group.[12] The reaction started with *para*-nitrobenzhydroxamic acid chloride **1** (Table 1). Addition of *O*-tetrahydro-2*H*-pyranylhydroxylamine (NH_2OTHP)[13] or *tert*-butyldimethylsilylhydroxylamine ($NH_2OTBDMS$)[14] which were synthesized according to literature procedures led to *O*,*O*-diprotected *p*-nitro-*N*,*N*′-dihydroxybenzamidines **2** and **4**. Both derivatives were purified by flash chromatography which was very comfortable in the case of **4** because of its high lipophilic character allowing an elution with pure cyclohexane. The obtained compounds in turn had to be reduced to the appropriate *p*-amino derivatives **3** and **5**. Hydrogenation with catalytic amounts of palladium on charcoal (Pd/C) under mild conditions with a pressure of 2 atm for 10 h led to *p*-aminobenzamidine. Also reducing the

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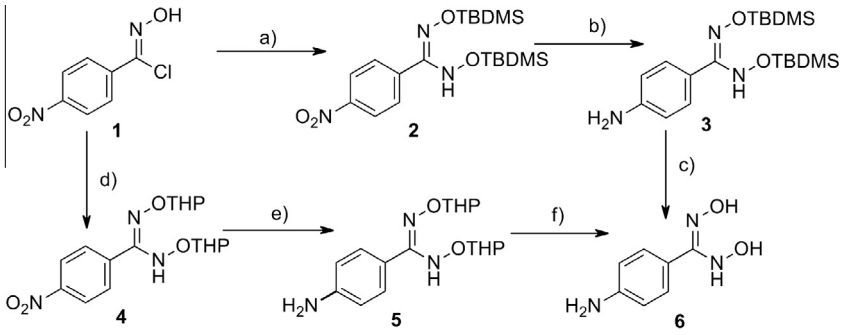
Table 1
Reaction conditions for the different steps of the synthesis of *p*-amino-*N*,*N*′-dihydroxybenzamidine **6**



Entry	Reaction step	Reactant	Reagent	Product	Temperature	Solvent	Reaction-time	Mobile phase (flash chromatography)	Yield (%)
1	a	**1**	2 equiv $NH_2OTBDMS$	**2**	rt	DCM	10 d	Cyclohexane	75
2	b	**2**	10 equiv $Na_2S_2O_4$	**3**	rt	Water/THF	3 h	Cyclohexane/ethyl acetate 8:2	23
3	c	**3**	11 equiv NH_4F	**6**	rt	MeOH	15 min	DCM/MeOH 9:1	41
4	d	**1**	4 equiv NH_2OTHP	**4**	rt	DCM	6 d	Cyclohexane/ethyl acetate 9:1	53
5	e	**4**	10 equiv $Na_2S_2O_4$	**5**	rt	Water/THF	3 h	Cyclohexane/ethyl acetate 5:5	17
6	f	**5**	2 equiv PTSA	**6**	0 °C	MeOH	1 h	DCM/MeOH 9:1	11

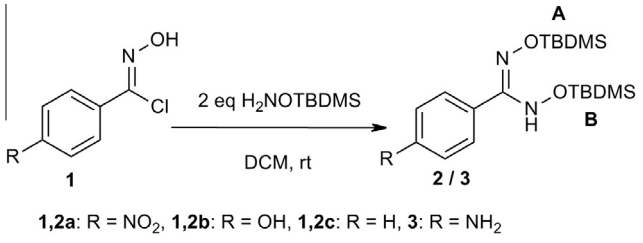


Figure 1. General synthesis of *para*-substituted *O*,*O*′-di-*tert*-butyldimethylsilyl-*N*,*N*′-dihydroxybenzamidines **2a–c**.

pressure and reaction time to 1 atm and 1 h resulted in an undesired reduction of the functional dihydroxyamidine group to *p*-aminobenzamidine and -amidoxime. Microwave irradiation for 15 min and 80 °C with cyclohexene and Pd/C as a smooth reduction method led to the same products. *p*-Nitro-*O*,*O*′-diprotected *N*,*N*′-dihydroxybenzamidines **2** and **4** were still detected when microwave irradiation time and temperature were decreased, but no *p*-amino-*O*,*O*′-diprotected derivative **3** or **5** (or even *p*-amino-*N*,*N*′-dihydroxybenzamidine **6**) was found. Successful reduction was eventually achieved by using an access of the smooth reagent sodium dithionite dissolved in water.[15] This solution was dropped slowly to **2** or **4** dissolved in THF with stirring at room temperature. After three hours the reaction was completed since no more reactant **2** or **4** could be detected by TLC analysis. $FeCl_3$ reacted with *O*,*O*′-di-TBDMS derivatives **2** and **3** to give a typical blue colour which was also observed for the *O*,*O*′-THP derivatives **4** and **5** upon heating, allowing simple colorimetric detection of the products on TLC.

Yields were moderate and suffered from amidine and amidoxime byproducts which further demonstrated the sensitivity of dihydroxyamidines towards reductive conditions even in a protected form. Flash chromatography (cyclohexane/ethyl acetate) of both product mixtures afforded the desired products **3** and **5**. Deprotection of *p*-amino-*O*,*O*′-ditetrahydro-2*H*-pyranyldihydroxybenzamidine **5** was performed with $MgBr_2$ in ethyl ether[16] and with acetyl chloride in methanol,[17] described as mild and efficient methods but did not succeed with **5**. With *p*-toluenesulfonic acid (PTSA) in methanol[18] *p*-amino-*N*,*N*′-dihydroxybenzamidine **6** could be detected but yields were very low. *p*-Amino-*O*,*O*′-di-*tert*-butyldimethylsilyl-*N*,*N*′-dihydroxy-benzamidine **3** was cleaved very fast with a great excess of ammonium fluoride in methanol[19] leading to better yields.[20] Less ammonium fluoride and longer reaction time led to partially uncleaved products. Flash chromatography with dichloromethane/methanol was applied. In contrast to all other dihydroxyamidines prepared previously[6] **6** is insoluble in ethyl acetate. Its properties as the simplest phenylogous dihydroxyguanidine have to be investigated. *p*-Amino-*N*,*N*′-dihydroxybenzamidine **6** is of special interest as a model compound for prodrugs of *p*-aminobenzamidines.

Table 2
^{15}N and ^{29}Si NMR values of the synthesized *para*-substituted *O*,*O*′-bis(*tert*-butyldimethylsilyl)-*N*,*N*′-dihydroxybenzamidines **2a–c** (Fig. 1) in comparison with the reagent $NH_2OTBDMS$

Entry	R	Hammett's σ	Reactant	Product	Reaction time	Yield (%)	$^{15}N^c$ A	$^{15}N^c$ B	$^1J_{NH}$ in Hz[d]	$^{29}Si^e$ A	$^{29}Si^e$ B
1[a]	—	—	--	$NH_2OTBDMS$		—	122.0		—	26.07	
2	NO_2	0.81	**1a**	**2a**	10 d	75	317.1	141.3	80	29.09	30.60
3	OH	−0.38	**1b**	**2b**	6 d	55	292.1	138.2	80	27.43	30.10
4	H	0	**1c**	**2c**	8 d	58	310.0	142.6	81	27.39	29.59
5[b]	NH_2	−0.57	—	**3**	—	—	306.6	142.7	80	26.71	29.31

[a] Reagent was synthesized according to literature procedure.[14]
[b] For additional information see Table 1.
[c] ^{15}N NMR spectra were recorded in $CDCl_3$. Values are given in ppm, relative to external CH_3NO_2 in $CDCl_3$ (δ = 381.6 ppm).
[d] Measured with two-dimensional NMR experiments (^1H, ^{15}N HMBC).
[e] ^{29}Si NMR spectra were recorded in $CDCl_3$. Values are given in ppm, relative to external TMS in $CDCl_3$ (δ = 0.00 ppm).

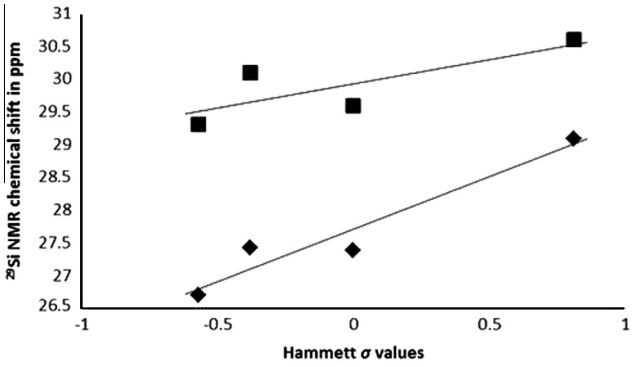


Figure 2. Correlation of ^{29}Si NMR chemical shifts of the functional group of *O,O′*-bis(*tert*-butyldimethylsilylated) *para*-substituted *N,N′*-dihydroxybenzamidines **2a–c** and **3** with Hammett σ values. ■ δ (^{29}Si (A)) = 1.59 σ + 27.71, r^2 = 0.93; ♦ δ (^{29}Si (B)) = 0.74 σ + 29.93, r^2 = 0.63, see Figure 1.

The sensitivity of *O,O′*-unsubstituted dihydroxyamidines especially towards bases and reductive conditions affords convenient protecting groups for the synthesis of more complex compounds. The option to synthesize di-*tert*-butyldimethylsilyl derivatives of different *para*-substituted benzhydroxamic acid chlorides **1** demonstrated the adaptability of the synthesis strategy to a wide range of hydroxamic acid chlorides (Fig. 1).

Reaction conditions and yields of every derivative **2a–c** were similar and deprotection with ammonium fluoride afforded all p-substituted *N,N′*-dihydroxybenzamidines as the desired products.[21] Thus, a variety of TBDMS-protected dihydroxyamidines can be synthesized (Table 2). The ^{29}Si NMR shifts show a correlation with the Hammett constant which is rather crude due to the small number of data points (Fig. 2). Comparable correlations have been reported by Schraml for silylated benzhydroxamic acids.[22] The correlations with Hammett's σ for all nuclei (^{1}H, ^{13}C, ^{15}N, ^{29}Si) are given in the Supplementary material section. Unequivocal assignment of the chemical shifts especially for the two different silyl residues was performed with two-dimensional NMR measurements, that is ^{1}H, ^{13}C HSQC, ^{1}H, ^{29}Si HMBC and ^{1}H, ^{1}H NOESY experiments.

Supplementary data

Supplementary data (full synthetic protocols and analytical and spectroscopic data of the compounds (^{1}H and ^{13}C NMR chemical shifts, mass spectra, IR spectra, melting points, elementary analyses)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.048.

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20. To a solution of 3.16 mmol (1.25 g) *p*-amino-*O,O′*-bis(*tert*-butyldimethylsilyl)-*N,N′*-dihydroxybenzamidine **3** in 10 mL methanol 11 equiv of ammoniuim fluoride (34.81 mmol, 1.313 g) in 10 mL methanol are added. Reaction mixture is stirred for further 5 min and disappearance of **3** is followed by TLC (cyclohexane/ethylacetate 1:1). The product **6** occurs near the baseline of the TLC plate indicated as blue spots with 2% aqueous $FeCl_3$ solution. Methanol is evaporated and the residue is dissolved in ethyl acetate. Insoluble byproduct is filtered off. The filtrate is applied on silica for flash chromatography with dichloromethane/methanol gradient as the mobile phase and silica as the solid phase. The isolated crude product is triturated with ethyl acetate/cyclohexane 2:1 to give 1.288 mmol (215 mg) **6** as a light yellow solid in 41% yield.
21. To a solution of 16 mmol (3.208 g) of *p*-nitrobenzhydroxamic acid chloride in 50 mL of DCM is added 4.704 g (32 mmol) of TBDMS-hydroxylamine and the solution is stirred for 10 d at room temperature. Precipitated byproduct is filtered off. The solvent is evaporated and the remainder is subjected to flash chromatography on silica gel (Merck, 60) with elution with cyclohexane. Evaporation of the solvent affords 12 mmol (5.101 g) of *p*-nitro-*O,O′*-di-*tert*-butyldimethylsilyl-*N,N′*-dihydroxybenzamidine **2a** in 75% yield.
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