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Bis-imine primary amine protection of the dialkyltriamine, norspermidine

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ABSTRACT

This Letter details the particular use of salicylaldehyde (2-hydroxybenzaldehyde) for the regiospecific protection of primary amines in a representative polyamine, norspermidine (*N*-(3-aminopropyl)propane-1,3-diamine) under mild reaction conditions in high yield. The lack of intramolecular hexahydropyrimidine formation allowed for subsequent N^2-acylation and N^2-alkylation reactions, typical of polyamine synthetic strategies.

The chemoselective manipulation of dialkyltriamines is useful for the preparation of metal multidentate ligands,[1] molecular probes[2–5] and bio-conjugates across a wide spectrum of potential applications.[6] Examples include cancer diagnostics and therapy;[7–9] low molecular mass organic gelators;[10,11] dynamic combinatorial libraries;[12] self-assembled organic nano-structures[13,14] and photochromic Schiff base macrocycles.[15] Such chemical manipulations are also useful for total synthesis involving polyalkylamines, for example, using spermidine, norspermidine and *sym*-homospermidine.[6,16]

From the available amine protection strategies (e.g., carbamate, amide and imine/Schiff base; Fig. 1) a novel strategy is presented for the less often utilized bis-imine selective functionalization of primary amines.[6,17] In this Letter, the bis-imine strategy for the protection of *N*-(3-aminopropyl)propane-1,3-diamine, also known as norspermidine, is shown. The attraction of the Schiff base approach stems from the ease of selective imine formation from primary alkylamines in the presence of intramolecular secondary and higher substituted alkylamines under mild reaction conditions. Unaffected amine functional groups are then available for further regiospecific procedures pertaining to a particular synthetic target goal.

Our investigation began with the optimization of reaction conditions for imine formation utilizing a range of preparative methods chosen from the literature for their capacity to provide high

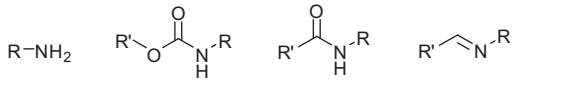
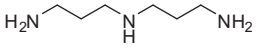


Figure 1. Some protecting group options for primary amine function.



Norspermidine /
N^1-(3-aminopropyl)propane-1,3-diamine

Figure 2. Representative dialkyltriamine used in this study.

yields and mild reaction conditions. 1-Propylamine and benzaldehyde (yielding *N*-benzylidenepropan-1-amine) were chosen as a structurally representative monomeric model reaction under: solvent-free, microwave assisted;[18] room temperature;[15] acid-catalyzed; trimethyl orthoformate reagent addition;[19] Montmorillonite K10 catalyzed[18] and in water,[15] methanol[15,20] and ethanol[14] solvents. These methodologies were selected as they had been presented in the literature as being facile and high yielding. Product was only recovered by simple stoichiometric mixture of reactants in alcohol solution. It was found that the most favourable conditions were 0.5 M solution (of 1-propylamine) at room temperature overnight in methanol using one equivalent of benzaldehyde, as previously demonstrated by other groups.[15,20] The ^{1}H NMR spectrum of the non-purified imine product, *N*-benzylidenepropan-1-amine, is provided as part of Supplementary data.

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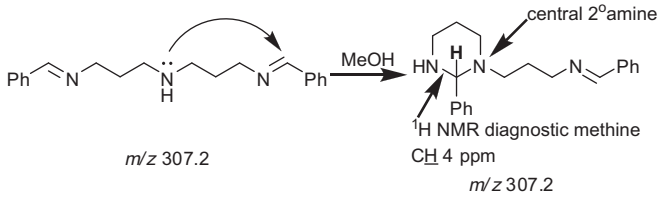


Figure 3a. Intramolecular cyclization observed with α,ω-bis(benzylideneimino) dipropylenetriamine.

Having optimized the reaction conditions for imine formation, norspermidine was selected as a representative polyamine backbone with widespread interest for a range of synthetic targets[6] (Fig. 2). Interestingly, this dialkyltriamine has shown innate anti-tumour activity.[21,22]

An aromatic aldehyde, benzaldehyde, was chosen as the protecting reagent due to its additional usefulness as a chromophoric moiety, being a practical aid in monitoring reaction progress by TLC and simplifying chromatographic purification by UV detection.

A complication that soon became apparent was the intramolecular 6-*endo-trig* ring closure to form an isomeric and cyclic 1-substituted hexahydropyrimidine[20] (Fig. 3a). This side reaction robs the central secondary amine of its capacity to be further substituted in subsequent chemical transformations (such as alkylation and acylation, as it is transformed to a tertiary amine) and renders the initially-added imine protecting group immutable to subsequent removal. The presence of this cyclized side product gave rise to a diagnostic signal from its unique methine C*H* signal at ca. δ 4 ppm in the ^{1}H NMR spectrum, even though the mass spectrum reports the expected molecular mass due to the isobaric nature of the linear and cyclic structural isomers (Fig. 3b).

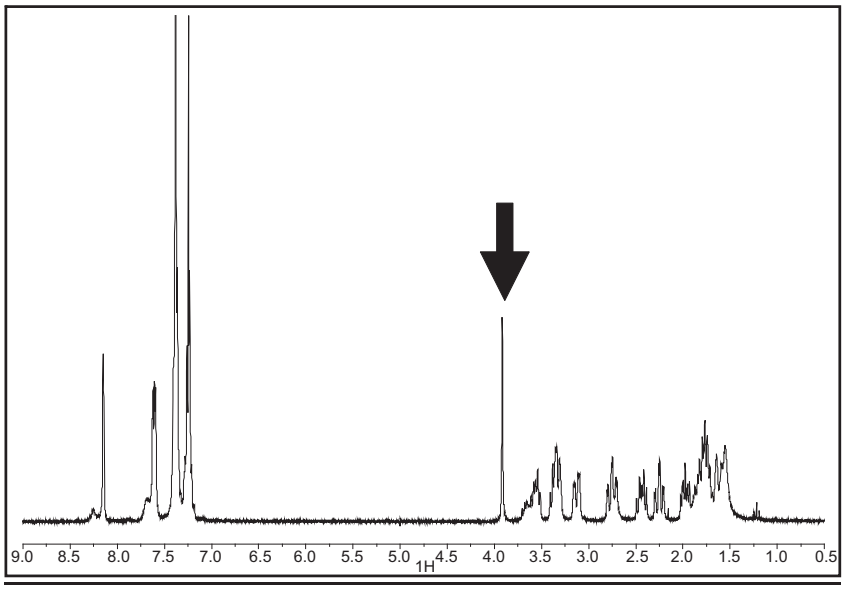
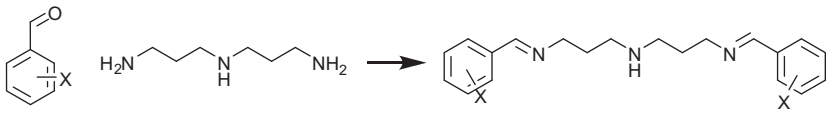


Figure 3b. ^{1}H NMR of undesired cyclic 1-substituted hexahydropyrimidine showing characteristic resonance at ca. δ = 4 ppm of methine C*H*. Reaction of norspermidine with benzaldehyde.

Table 1
Selection of benzaldehyde for linear bis-imine formation



Benzaldehyde substituent	% Linear bis-imine[a]	% Tetrahydropyrimidine[a]
H	41	59
2-OH	**95**	**5**
3-OH	45	55
4-OH	Quinoid structure[b]	
2-OMe	43	57
3-OMe	26	74
4-OMe	45	55

The significance of the emboldened letters are to signify the unique ability of the 2-hydroxybenzaldehyde to yield a linear bis-imine protected triamine unencumbered by the cyclic hexahydropyrimidine contaminant.

[a] Amount of linear bis-imine and cyclic tetrahydropyrimidine determined by integration of ^{1}H NMR signals of C*H*=N of imine and methine C*H* of tetrahydropyrimidine as $CDCl_3$ solutions of crude reaction product mixtures.

[b] 4-Hydroxybenzaldehyde yielded only the keto tautomer.

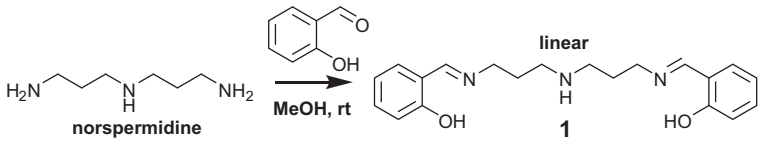
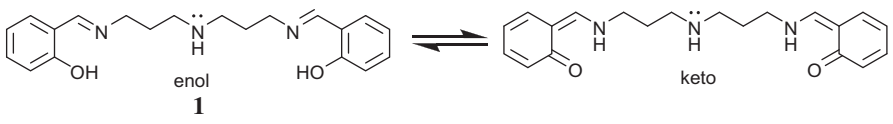


Figure 4. Synthesis of linear α,ω-bisimine protected norspermidine, without hexahydropyrimidine contamination.



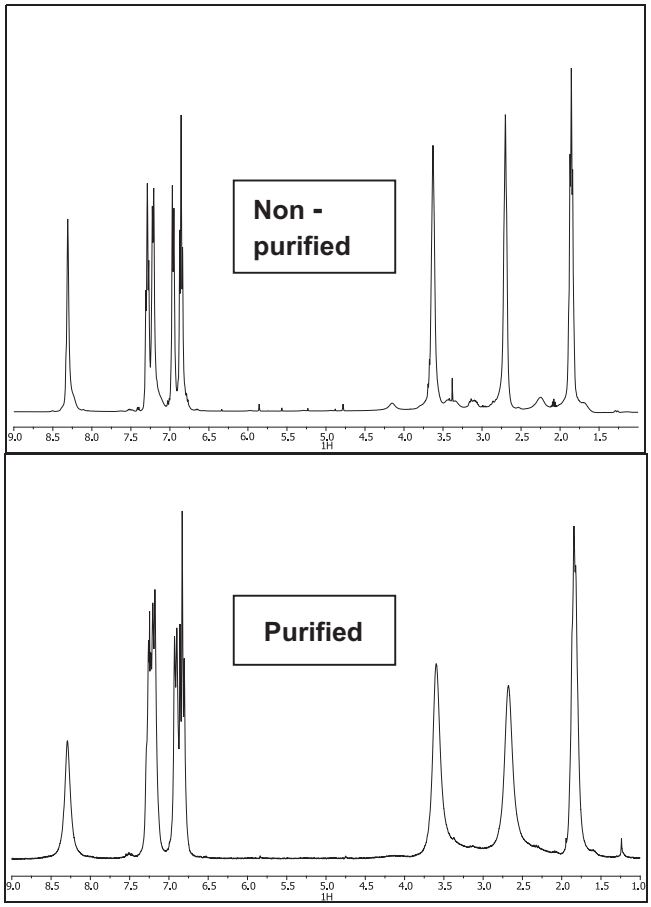


Figure 5. Structure and ^{1}H NMR spectra ($CDCl_3$)—top, non-purified crude reaction mixture and bottom, purified by flash chromatography—of the desired α,ω-bisimine protected norspermidine.

A series of six substituted benzaldehydes (Table 1) were selected to investigate electronic and steric effects on linear bis-imine formation in norpsermidine. ^{1}H NMR spectra of each of the crude reaction mixtures were recorded, as $CDCl_3$ solutions, to determine the distribution between the desired linear and byproduct cyclic isomer formation. It was immediately evident that a combination of steric bulk at the *ortho*-position coupled with an ability to form an intramolecular hydrogen bond was the essential pre-requisite for linear bis-imine **1** formation.[11,14] (Fig. 4). Salicylaldehyde (2-hydroxybenzaldehyde) was unique in its ability to form the bis-imine in almost quantitative yield. Notably, the NMR spectra of crude and purified **1** were essentially identical pointing to the high yield and cleanliness of this reaction[23] (Fig. 5). Keto-enol tautomerism considerations revealed that 4-hydroxybenzaldehyde formed the *para*-quinoid keto structure exclusively. Being more symmetrical, the NMR spectra of **1** were simpler and had fewer peaks. Compare Figures 3b and 5.

In order to demonstrate the synthetic utility of imine protecting group strategy, molecule **1** was subjected to alkylation and acylation reactions at the N2-position representative of widely applied chemical modifications of polyamine backbones.

Molecule **1** was N^2-acylated with benzoic anhydride (yielding **2**); di-*tert*-butyl dicarbonate (Boc) **3** and benzyl chloroformate (Z) **4** in anhydrous ethanol with TEA base, stirring at room temperature overnight. Following chromatographic purification, yields of 68–91% were obtained. Molecule **1** was also successfully

N^2-alkylated with benzyl bromide **5**, propargyl bromide **6** and allyl bromide **7** in anhydrous chloroform with TEA base and potassium iodide catalyst stirring at room temperature overnight. Following chromatographic purification, yields of 62–75% were realised. Deprotection of imine protecting groups from representative N^2-benzoyl and N^2-benzyl compounds **2** and **5**, respectively, was effected with 50% (*v*/*v*) TFA in dichloromethane by stirring for 2 h at room temperature. To the best of our knowledge, this is the first report of TFA deprotection of an imine/Schiff base protecting group. Purification by reverse phase column chromatography gave N^2-benzyl- and N^2-benzoylnorpsermidine, **8** and **9** respectively, in moderate yield (ca. 60%) thereby validating the bis-imine protection strategy. All compounds were characterized by 1D and 2D NMR, IR and HR-MS. These spectra are available as Supplementary data.

NMR spectra revealed some interesting aspects of the structures of these molecules. The ^{1}H NMR signals of the bis-imine protected triamine, **1**, were very broad. Unexpectedly, the alkyl methylene ^{13}C NMR signals were also broadened (see Supplementary data). Spectra recorded in d_1-chloroform were compared to those recorded in less viscous d_3-acetonitrile to no avail. The phenolic O*H* and amine N*H* signals were not evident in the NMR spectrum of **1**, although the O*H* hydrogens were observed for all N^2-substituted molecules (**2–7**) prepared from it. The observed line broadening was attributed to extensive hydrogen bonding and rapid proton exchange in solution. The N^2-acylated molecules, **2**, **3** and **4**, also displayed broadened NMR signals (both ^{1}H and ^{13}C) with distinct signals for seemingly equivalent atoms. This was attributed to stable intramolecular hydrogen bond formation. In contrast, the corresponding N^2-alkylated molecules, **5**, **6** and **7** reported highly resolved signals revealing distinctive spin–spin coupling patterns. Hydrogen bonding between the phenolic OH functions and the N^2-substituent was not possible in these molecules.

In conclusion, it has been demonstrated that the use of salicylaldehyde (2-hydroxybenzaldehyde) as an imine protection reagent for primary amine functions in a polyamine. This reaction may have potential utility for imine protection of primary amine groups and will spur further development of organic polyamine synthesis and applications.

Acknowledgements

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Supplementary data

Supplementary data (chromatography trace, ESI+ MS, NMR and IR data for bis-imine protected norspermidine, **1** and its N^2-substituted derivatives **2**–**9**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.070.

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23. *Typical synthesis procedure*: Bis-imine protected norspermidine. To a solution of norspermidine (0.25 mmoles, 33 mg, 35 μL) in anhydrous methanol (0.4 mL) was added dropwise salicylaldehyde (0.50 mmoles, 61 mg, 53 μL) at room temperature under a stream of argon gas. The bright yellow solution was stirred at room temperature overnight, evaporated and purified by medium pressure chromatography (MPLC) on a 4 g silica column using a DCM/MeOH gradient. Reaction was also performed successfully up to 5 mmole scale. Yield: 82% (70 mg) of α,ω-bis(*o*-hydroxybenzylideneimino)norspermidine. ^{1}H NMR (400 MHz, CD_3CN, δ ppm): C*H*$_2$ 1.77 (m, 4H), 2.60 (M, 4H), 3.59 (m, 4H); C*H* 6.85 (m, 4H), 7.27 (m, 4H); C*H*═N 8.37 (m, 2H) Phenolic O*H* and N*H* not observed due to rapid proton exchange. ^{13}C{^{1}H} NMR (101 MHz, CD_3CN): *C*H$_2$ 32.3, 48.5, 58.2; *C*H 117.9, 119.9, 132.9, 133.4, 162.6; *C* 120.3, 167.0. Assignments by COSY, HSQC, HMBC. LR MS (ESI+): 339.5 *m*/*z*. Elemental analysis (calcd): C: 70.53 (70.77); H: 7.19 (7.42); N: 12.15 (12.38). IR (cm^{-1}): 3453, 3054, 1633, 1279, 757. Full spectra displayed in Supplementary data.