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TETRAHEDRON: *ASYMMETRY*

First enantioselective synthesis of a 1-(trimethylsilyl)alkylamine[1]

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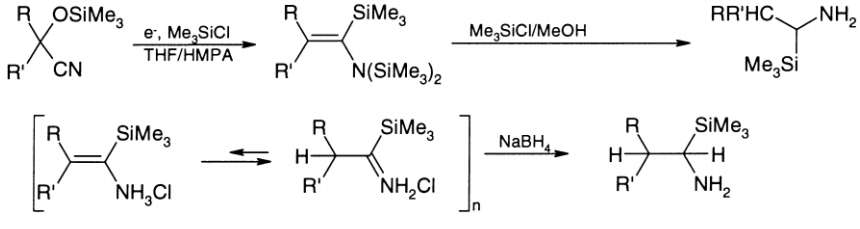
Abstract

Reduction of *n*-propanoyltrimethylsilane NH-imine with the complex hydride $LiBH_4$/diethyltartrate in THF yielding enantiomerically enriched 1-(trimethylsilyl)butylamine with a 60% enantiomeric excess is the first example of the enantioselective synthesis of such an amine. Other combinations of solvent (ether or THF), hydride ($NaBH_4$ or $LiAlH_4$) and chiral inductor (mono- or diol) failed.

1. Introduction

We reported recently two syntheses of racemic 1-(trimethylsilyl)alkyl-amines ('RSMA').[2,4] The first synthesis consisted of the direct electroreductive silylation of *N*-silylimines and alkylnitriles, followed by an appropriate treatment of the silazanes formed.[3] Borohydride reduction of acylsilane imines derived from acylsilane enamines was the second method (Scheme 1).[4]



Scheme 1. General preparations of racemic RSMA

In the last procedure (Scheme 1), methanol probably reacted in the first step with chlorosilane to form 'dry' hydrogen chloride which cleaved the N–Si bonds (with nucleophilic assistance of the chlorine atom onto the silicon atom) to lead to an enaminium chloride which isomerized into the corresponding iminium chloride by a proton shift. The methanol could also have reacted with $NaBH_4$ (acting as a $NaH:BH_3$ mixture) to form sodium dimethoxyborane $NaBH_2(OMe)_2$ (or $NaH/HB(OMe)_2$); then the

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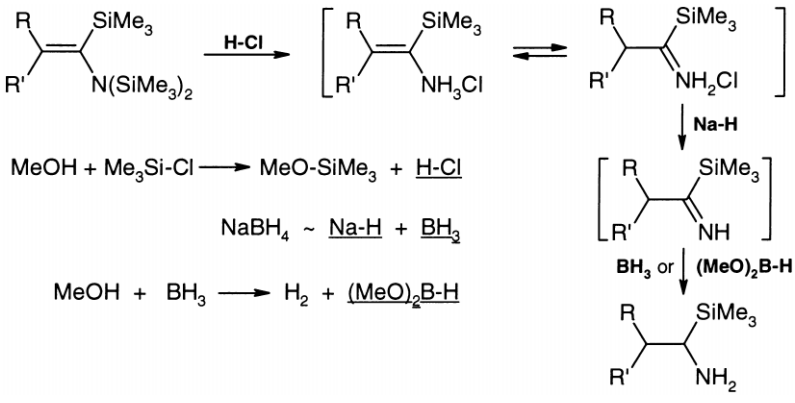
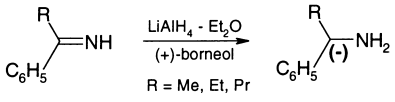
imine was released from its salt by NaH and the C=N bond was reduced to the desired amine by borane or dimethoxyborane (Scheme 2).



Scheme 2. Proposed pathway for the transformation of acylsilane enamines into racemic RSMA

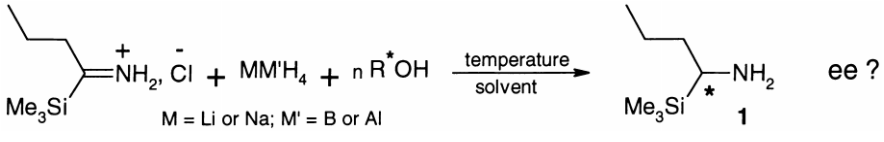
RSMA gained interest since it was demonstrated that the Si–C–N framework could be associated with various biological activities.[5] In this context, the need for stereoselective and/or stereospecific syntheses of theses amines became evident.

When we initiated this work, some chiral α-silylated amino derivatives had been described in the literature,[6] but none of these were a primary amine except that obtained by Tacke[6c] through enzymatic hydrolysis of its corresponding amide. Moreover, no general method for preparing chiral organic amines through asymmetric reduction of imines existed in the literature, though some success was attained with specific examples, sometimes with good enantiomeric excesses. Three main techniques were used for this purpose: (a) hydrogenation of imines in the presence of a chiral catalyst;[7,8] (b) reduction of imines where the nitrogen bears a chiral substituent;[9] (c) reduction of imines using chiral reagents, generally a modified mixed hydride such as alcalin aluminohydrides[10–12] and borohydrides;[13] and finally modified boranes such as Itsuno[14] or Corey's reagents,[15] oxaborolidines[16] or borane/chiral phosphine complexes.[17] Among these, Cervinka's reduction of imines employing a LAH/(+)-borneol mixture (Scheme 3) suggested [even if the enantiomeric excesses (*ee*s) were lower than 10%] that chiral RSMA could be obtained after slight modifications had been made to our preparation of racemic RSMA from acylsilane enamines (Scheme 1).



Scheme 3. Cervinka's preparation of chiral primary amines from NH imines

We report here the first result of our investigation, chiral 1-(trimethylsilyl)butylamine, **1**, being the target model molecule (Scheme 4).



Scheme 4. Envisioned synthesis of **1**

Table 1
Enantioselective synthesis of amine **1** using L-(+)-tartrates (–CHOHCOOR)$_2$

exp.	R	hydride	solvent	yield (%)	$[\alpha]_D^{20}$ (MeOH)	ee (%)	$[\alpha]_D^{20}$ calc*
1	ethyl	$NaBH_4$	THF	42	+ 3.6 (c = 1.17)	39	10.83
2	ethyl	$NaBH_4$	Et_2O	36	+ 2.8 (c = 0.98)	31	11.07
3	t-butyl	$NaBH_4$	THF	48	+ 3.7 (c = 1)	36	9.73
4	i-propyl	$NaBH_4$	THF	45	0 (c = 0.99)	0	
5	ethyl	$LiBH_4$	THF	43	+ 6.1 (c = 1)	60	9.83

* calculated absolute specific rotation of 1.

2. Results and discussion

In spite of its poor efficiency, Cervinka's procedure presented the advantage that the chiral alcohol used as an inductor will be easily separated from the amine during the work-up and thus could be re-used without any loss of material. Using this procedure, we discovered that no chiral RSMA was formed. Thus we decided to check the different factors which could have some influence on this reaction. Two other monoalcohols, (−)-menthol and the bisacetonide of α-D-glucofuranoside,[12,18–20] were tested, varying at each stage the solvent (diethyl ether or THF), the reducing agent ($NaBH_4$ or $LiBH_4$), and its ratio to alcohol. In each case, the alcohol and the hydride were mixed in the solvent at 5°C, then the iminium salt was reacted at 20°C.[21] After the work-up, the alcohol was recovered completely, and the RSMA formed was analyzed through its specific rotation and the enantiomeric excess measured by an original ^{29}Si NMR method.[22] None of these variations influenced the enantioselectivity of the reaction. This failure could be attributed to a lack of rigidity of the reducing agent, so we then considered 1,2-diols. However, *R*-(−)-1-phenyl-1,2-ethanediol did not lead to a better result.

By contrast, L-(+)-diethyl tartrate, a frequently encountered[23] inductor from the chiral pool, gave rise to an enantioselective synthesis of **1**, with a 40% enantiomeric excess when the reaction was performed in THF (Table 1, experiments 1–2). It should be noted that a bulkier inductor, *t*-butyl L-(+)-tartrate, gave almost the same result (Table 1, experiment 3) and, surprisingly, *i*-propyl L-(+)-tartrate, an inductor which has been recommended,[24] led to a racemic mixture (Table 1, experiment 4). Finally, an increase in the selectivity (60% *ee*) was obtained by using lithium borohydride instead of sodium borohydride (Table 1, experiment 5).

On the basis of the measurements of the specific rotation and the evaluations of the *ee* that we made, we estimated the absolute specific rotation of **1** to be about 10° (Table 1).

3. Conclusions

The influence of different parameters (the alcohol and its nature, the alcohol/hydride ratio, the temperature and the solvent) on the enantioselectivity of the asymmetric reduction of an acylsilane iminium chloride by a reducing agent formed from alkali alumino- or borohydride and a chiral mono- or diol, has been studied. The best result (60% *ee*) was obtained using lithium borohydride and

diethyl tartrate in THF at 20°C. This represents the first enantioselective synthesis of the RSMA, 1-(trimethylsilyl) alkylamine, **1**.

The scope and limitations of this methodology are currently under study and results will be published in due course.

4. Experimental

4.1. General data

Gas chromatographic (GC) analyses were performed on a Hewlett Packard 5890 (series II) temperature programmable chromatograph equipped with ionization flame detector and capillary column (CPSIL, 25 m×0.25 μm). Infrared spectra (neat compounds) were obtained from a Perkin–Elmer 457 infrared spectrometer. A Nicolet 20 SXC GC instrument connected to a Carlo–Erba GC 6000 Vega chromatograph (PTE, 25 m×0.25 mm capillary column) was used for FTIR studies. ^{1}H NMR spectra were obtained using a Bruker AC 250 (250.133 MHz, solvent $CDCl_3$, internal reference $CHCl_3$ at 7.27 ppm) spectrometer. A Bruker AC 200 (50.32 MHz, solvent $CDCl_3$ as internal reference at 77.39 ppm) was used for recording ^{13}C NMR spectra.

4.2. Starting materials

Reagent-grade HMPA (Aldrich)[25] was used without purification. THF was distilled over benzophenone/sodium and ether over LAH and kept under argon. Trimethylsilyl chloride, kindly supplied by Rhône-Poulenc Co. (France), was distilled over magnesium turnings prior to use and kept under an argon atmosphere.

4.3. 1-Trimethylsilyl-1-[bis(trimethylsilyl)amino]but-1-ene

This acylsilane enamine used as the starting material was prepared following a procedure described in the literature.

4.4. 1-Trimethylsilyl-1-butyliminium chloride

Into a 250 ml two necked round-bottomed flask equipped with a potash-filled drying tube, a pressure-equalizing dropping 100 ml funnel fitted with a rubber septum, and a magnetic stirring bar, acylsilane enamine (0.1M, 28.7 g) and methanol (100 ml) were introduced. The mixture was cooled with an external iced-water bath and trimethylsilyl chloride (0.1M, 11 g) was slowly dropped from the funnel. At the end of the addition, the temperature of the reaction mixture was allowed to return to ambient and stirring was continued for 2 h. The volatile compounds were then eliminated with a rotatory evaporator (20 mm Hg). After being washed three times with diethyl ether and dried under vacuum (0.1 mm Hg) for 2 h, the expected solid was collected (16.8 g, 94% yield): ^{1}H NMR (CD_3OD) δ 0.02 (s, 9H, $Si(CH_3)_3$), 0.63 (t (J_3=7), 3H, CH_2–CH_3), 1.38 (m, 2H, CH_2–CH_3), 2.45 (t (J_3=9), 2H, CH_2–CH_2); ^{13}C NMR (CD_3OD) δ −4.3 ($Si(CH_3)_3$), 12.4 (CH_3), 18.3 (CH_2–CH_3), 41.2 (CH_2–CH_2), 221.3 (–C=N); IR $\nu_{C=N}$ (cm^{-1}) 1669.

4.5. Reduction of the iminium chloride in the presence of chiral alcohols

4.5.1. General procedure

Into a 100 ml flame-dried round-bottomed flask equipped with a condenser (connected to a potash drying tube), a magnetic stirring bar, a nitrogen inlet and a rubber septum, were introduced 30 ml of freshly distilled solvent and 12 mmol of the hydride. The flask was kept in an ice bath so that the temperature of the reaction medium was 0–5°C, and the chiral alcohol (2 equivalents for mono-ols, 1 equivalent for diols) was added. During the addition, evolution of hydrogen occured. Stirring was continued for 4 h at 0°C. Then iminium chloride (1.8 g, 10 mmol) was introduced and stirring was continued for 15 h at ambient temperature. Evaporation of the solvent on a rotatory evaporator left a white solid which was taken up with 30 ml of diethyl ether. The suspension thus obtained was treated carefully with 15 ml of iced water. The aqueous layer was acidified with 10% HCl until pH 3 and the mixture kept stirring for 30 min. This layer was separated from the etheral solution and extracted again with ether (3×15 ml). The alcohol was recovered in 95–98% yield from the combined dried ether extracts. The aqueous solution was made basic with solid sodium hydroxide and **1** was recovered in a satisfactorily pure state after extraction with ether, drying the solution over sodium sulfate and evaporation of the solvent.

Reagents and solvents were as follows: Chiral mono-ols: (+)-borneol, (−)-menthol, 1,2;5,6-di-*O*-ispropylidene-α-D-glucofuranoside. Diols: *R*-(−)-1-phenyl-1,2-ethanediol, L-(+)-ethyl-, *i*-propyl- and *t*-butyl-tartrates. Hydrides: $LiAlH_4$, $NaBH_4$ and $LiBH_4$. Solvents: diethyl ether, THF.

In every case, amine **1** had physico-chemical data in good agreement with those reported previously.[4]

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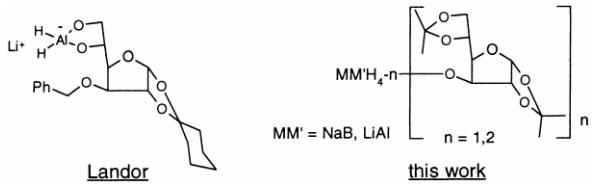

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