An Inexpensive Procedure for Reductive Aminations Using Dimethylamineborane on Millimolar and Molar Scale

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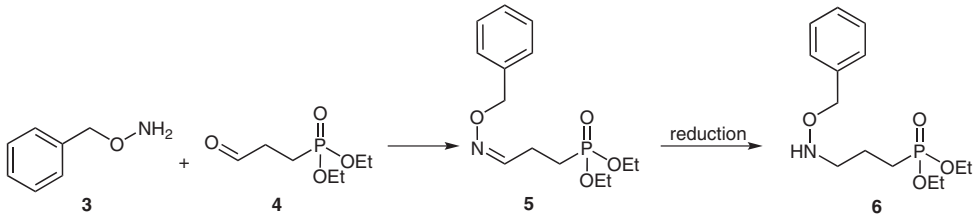
Received 23 January 2009; revised 26 January 2009

PSP No 159

Abstract: We have developed an inexpensive and easy procedure for reductive aminations using dimethylamineborane instead of cyanoborohydride. Dimethylamineborane is easily prepared from readily available inexpensive starting materials and can be used without isolation even on molar scale.

Key words: amines, aminations, hydrides, imines, medicinal chemistry



Scheme 1

Between 1.5 and 3 million people die from malaria every year, most of them children. Because of the increasing resistance of *Plasmodium falciparum*, the causative agent of malaria tropica, to many of the presently available drugs there is an urgent need for new efficient antimalarial agents.[1]

Fosmidomycin (**1**, Figure 1) is such a novel drug. It inhibits the mevalonate-independent isoprenoid synthesis, a target hitherto unexploited in antimalarial drug development. The combination of fosmidomycin with clindamycin has been safe and effective in various clinical trials.[2]

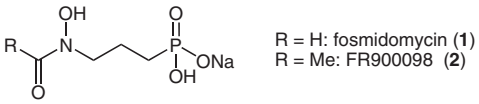


Figure 1 Fosmidomycin and FR900098

FR 900098 (**2**) is structurally closely related to fosmidomycin. It is about twice as active as fosmidomycin in vitro and in a mouse model. FR900098 is therefore a candidate for further development.[3] For preclinical development an effective and inexpensive synthesis is mandatory.

In the course of our studies towards a novel synthesis of FR900098 we encountered the necessity to perform an inexpensive and easy reductive amination of 3-oxopropylphosphonic acid diethyl ester (**4**) or the appropriate dibenzyl ester with *O*-benzylhydroxylamine (**3**) (Scheme 1). This reaction was hitherto done with sodium cyanoborohydride as the reducing agent.[4] This reagent is very toxic, expensive, and the resulting product has to be purified by column chromatography, which is a special disadvantage when the reaction has to be carried out on larger scale. Therefore, we searched for another reducing agent which primarily should be less expensive than sodium cyanoborohydride and appropriate for use in mole-scale synthesis.

Amineboranes are known as selective reducing agents for imines, oximes, and other functional groups[5] and they are less toxic than cyanoborohydride. So we evaluated different amineboranes as well as sodium borohydride in the reduction of oxime **5** using 2 mmol in each case for the initial test. The results in comparison with sodium cyanoborohydride are summarized in Table 1. There was no reduction with sodium borohydride. Reaction with triethylamineborane gave a product of good purity in yields comparable to the yield obtained with sodium cyanoborohydride. The use of trimethylamineborane resulted in lower yields and the bad purity made column chromatography necessary. Reduction with 1.1 equivalents dimethylamineborane (borane-dimethylamine complex) yielded more than 90% product in good purity. Only very few impurities were detected by NMR spectroscopy.

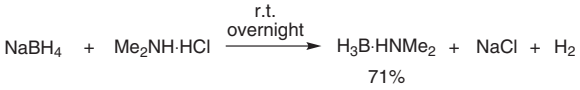
Although dimethylamineborane is less expensive than sodium cyanoborohydride we wanted to reduce the costs further by preparing the reagent ourselves. The synthesis was carried out according to a patent from Shirol Yakuhin

SYNTHESIS 2009, No. 10, pp 1757–1759
Advanced online publication: 14.04.2009
DOI: 10.1055/s-0028-1088046; Art ID: Z01409SS

Table 1 Reduction of Benzyloxyiminopropylphophonic Acid Diethyl Ester with Different Reducing Agents

Reducing agent	Equiv used	Acid	Yield (%)	Comment
$NaCNBH_3$	3	HCl	70–85% (overall yield based on aldehyde)	after chromatography
$NaBH_4$	different amounts	HCl, AcOH, CF_3CO_2H	no reduction	
$Et_3N{\cdot}BH_3$	2	HCl	80	without chromatography
	1.1	HCl	87	without chromatography
$Me_3N{\cdot}BH_3$	2	HCl	53	after chromatography
	1.1	HCl	26	after chromatography
$Me_2NH{\cdot}BH_3$	2	HCl	67	after chromatography
	1.1	HCl	91	without chromatography

Co. by the reaction of dimethylamine hydrochloride with sodium borohydride in 1,2-dimethoxyethane (Scheme 2).[6] We carried out this procedure at the first time as described in this patent, isolated the product, and characterized.



Scheme 2 Synthesis of dimethylamineborane

To further simplify the procedure, we developed a modification without the need to isolate the reducing agent. The aldehyde **4** and *O*-benzylhydroxylamine (**3**) are reacted in one flask to form the oxime; the synthesis of the reducing agent is carried out in a second flask. After evaporation of the 1,2-dimethoxyethane from the dimethylamineborane, the methanolic solution of the oxime is added dropwise to the residue, followed by addition of hydrochloric acid. The product is isolated by extraction. No further purification is necessary. There are only minor impurities detectable by ^{1}H NMR spectroscopy. This procedure was successful on both millimolar and molar scales. The smallest batch was prepared using 5 mmol of aldehyde **4** (yield: 1.43 g, 95%); the largest batch was synthesized from 1.59 mol of aldehyde **4** (yield: 443 g, 92%).[7]

In summary, we have developed a procedure for the reductive amination by freshly preparing the reducing agent dimethylamineborane from common available inexpensive starting materials. This procedure led to products in yields of more than 90% in good purity and without chromatographic purification.

^{1}H NMR spectra were recorded on Jeol Lambda 500 delta and Jeol JNM-GX-400 spectrometers. IR spectra were recorded on a Nicolet 510P FT-IR spectrometer. Column chromatography was carried out using silica gel 60 (0.062–0.200 mm) from Macherey-Nagel and silica gel 60 (0.040–0.063 mm) from Merck.

Benzyloxyiminopropylphosphonic Acid Diethyl Ester (5)
Aldehyde **4** (36.89 g, 0.19 mol) was placed in a flask and a solution of *O*-benzylhydroxylamine (**3**; 30.33 g, 0.19 mol) in MeOH (50 mL) was added dropwise. The reaction mixture was heated to 40 °C for 4 h. H_2O (50 mL) was added and the resulting solution was extracted with EtOAc (3 × 100 mL). The organic extracts were combined, dried (Na_2SO_4), and evaporated to give 52.37 g of **5** (0.175 mol, 92%). The product was used for the reactions with different reducing agents without further purification.

IR (film): 3064, 3032, 2983, 2931 (CH), 1720 cm^{-1} (C=N).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27–1.34 (m, 6 H, 2 × CH_3), 1.85–1.96 (m, 2 H, PCH_2), 2.44–2.51 and 2.58–2.65 (2 m, 2 H, PCH_2CH_2), 3.98–4.13 (m, 4 H, 2 × $POCH_2$), 5.03 + 5.09 (2 s, 2 H, OCH_2), 6.74 + 7.43 (2 t, ^3J = 5.3 Hz, 1 H, N=CH), 7.25–7.36 (m, 5 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.38 (d, $^3J_{C-P}$ = 5.8 Hz, 2 × CH_3), 19.33 (d, $^2J_{C-P}$ = 4.8 Hz, PCH_2CH_2), 22.26 + 22.53 (2 d, $^1J_{C-P}$ = 142 Hz, PCH_2), 61.65, 61.70, 61.74 (2 × $POCH_2$), 75.70 + 75.90 ($NOCH_2$), 127.78, 127.82, 127.94, 128.14, 128.21, 128.33, 128.45, 128.48 (5 CH_{Ar}), 137.47 + 137.73 (C_{Ar}), 149.27 + 150.00 (2 d, $^3J_{C-P}$ = 15.4 Hz, C=N).

^{31}P NMR (161 MHz, $CDCl_3$): δ = 30.83 + 30.95.

Dimethylamineborane
In a three-necked round bottomed flask equipped with a condenser and a thermometer was suspended $Me_2NH{\cdot}HCl$ (8.16 g, 0.10 mol) in 1,2-dimethoxyethane (15 mL). The reaction mixture was cooled in an ice bath. Solid $NaBH_4$ (3.98 g, 0.105 mol) was added in a manner so that the temperature was kept below 20 °C. The mixture was stirred overnight at r.t. The solvent was evaporated and the residue was treated with 5% aq NaOH (20 mL) and extracted with EtOAc (3 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated; yield: 4.19 g (0.711 mol, 71%); viscous oil.

IR (film): 3229 (NH), 2999, 2952 (CH), 2367, 2265 cm^{-1} (BH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.52 (q, J = 95.6 Hz, 3 H, BH_3), 2.58 + 2.59 (2 s, 6 H, 2 × CH_3), 3.77 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 44.62 (CH_3).

^{11}B NMR (160 MHz, $CDCl_3$): δ = –15.12 (q, J = 95.6 Hz, BH_3).

Benzyloxyaminopropylphosphonic Acid Diethyl Ester (6)
Aldehyde **4** (16.19 g, 83.4 mmol) was placed in a flask and a solution of *O*-benzylhydroxylamine (**3**; 10.30 g, 83.4 mmol) dissolved in MeOH (20 mL) was added dropwise. The reaction mixture was heated to 40 °C for 4 h. The oxime was not isolated. The methanolic solution was used the next day for the reduction. In another three-necked round bottomed flask equipped with a condenser and a thermometer were suspended $Me_2NH{\cdot}HCl$ (10.90 g, 0.133 mol) in 1,2-dimethoxyethane (30 mL). The mixture was cooled in an ice bath. Solid $NaBH_4$ (5.50 g, 0.145 mol) was added in a manner so that the

temperature was kept below 20 °C. The mixture was stirred overnight at r.t. The borane complex was not isolated. The solvent was evaporated at the rotary evaporator and the residue was used as reducing agent in the next step. The methanolic solution of benzyloxyiminopropylphosphonic acid diethyl ester (**5**), prepared as above, was added dropwise to the reducing agent. Aq 32% HCl (34 mL) was added dropwise with ice cooling and the mixture was stirred overnight. The pH was adjusted to 10 with aq KOH and the solution was extracted with EtOAc (3 × 250 mL). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated to afford 23.08 g of **6** (76.6 mmol, 92%). Spectroscopic data matched with the literature data.[4]

IR (film): 3247 (NH), 3032, 2982, 2908 cm^{-1} (CH).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, ^3J = 7.1 Hz, 6 H, 2 × CH_3), 1.78–1.90 (m, 4 H, PCH_2CH_2), 2.97 (t, ^3J = 6.5 Hz, 2 H, NCH_2), 4.03–4.14 (m, 4 H, 2 × $POCH_2$), 4.68 (s, 2 H, OCH_2), 7.27–7.36 (m, 5 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.42 (d, $^3J_{C-P}$ = 6.0 Hz, 2 × CH_3), 20.58 (d, $^2J_{C-P}$ = 4.8 Hz, PCH_2CH_2), 23.19 (d, $^1J_{C-P}$ = 142 Hz, PCH_2), 52.09 (d, $^3J_{C-P}$ = 17.2 Hz, NCH_2), 61.43 (d, $^2J_{C-P}$ = 6.7 Hz, 2 × $POCH_2$), 76.33 (OCH_2), 127.78, 128.34, 128.42 (CH_{Ar}), 137.82 (C_{Ar}).

^{31}P NMR (161 MHz, $CDCl_3$): δ = 32.76.

Acknowledgment

This publication was generated in the context of the AntiMal project, funded under the 6th Framework of the European Community (Contract No. IP-018834). The authors are solely responsible for its content; it does not represent the opinion of the European Community and the Community is not responsible for any use that might be made of the information contained therein.

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