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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2123–2125

Process for preparing Ezetimibe intermediate by enantioselective CBS catalyzed ketone reduction with BH_3–DEA prepared in situ☆

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Received 28 November 2006; revised 22 January 2007; accepted 23 January 2007
Available online 27 January 2007

Abstract—The (*S*) alcohol in the benzylic position of compound **2**, a key intermediate in the synthesis of the cholesterol lowering agent Ezetimibe, was introduced by the (*R*)-MeCBS catalyzed asymmetric carbonyl reduction of ketone **1** using borane diethylaniline complex (BDEA) as the reducing agent. The latter was prepared in situ from sodium borohydride ($NaBH_4$), diethylaniline (DEA) and dimethylsulfate ($DMSO_4$). BDEA prepared in situ offers considerable advantages from the industrialization standpoint (cost and stability on storage of the reagents) over commercial solutions of BH_3–THF (BTHF) or BH_3–DMS (BMS). The effect of critical reaction parameters such as addition mode of reagent, temperature, solvent, reaction quenching as well as LiCl addition on the selectivity has been examined. This reaction has been successfully applied in the process for the preparation of key intermediate **2** for Ezetimibe.

A process to prepare the (*S*) alcohol in the benzylic position of compound **2** by reduction of ketone **1** with BTHF enhanced by *para*-toluenesulfonic acid has been described in the literature.[1] BTHF is known to be unstable on storage (THF ring opening) and explosions on storage have been reported.[2] Therefore, the use of BTHF at industrial scale can be cumbersome from the logistic and supply chain standpoint.

The reactivity of BTHF presents in this case a major drawback from the industrialization standpoint. Indeed to overcome the reduction of the amide bond of compound **2** (compound **4**), BTHF must be added to a solution of compound **1** in the presence of MeCBS and THF (reverse addition process). This requires a particular set-up of the industrial equipment which does not fit easily in multi products workshop. Moreover, BTHF is only available at 1 M concentration which makes the process productivity low from a production standpoint. The only positive outcome of using BTHF is that two hydrides over three theoretically available can be used in the reduction process to obtain a good stereoselectivity as compared with BDMS or BDEA where only one hydride can be used Scheme 1.

BDMS presents an advantage in this process from the industrialization standpoint over BTHF. Indeed, BDMS is more stable than BTHF, thus the amide bond of compound **2** is not easily reduced. A classic reagent addition can be used for this reaction with this reagent. However, as pointed out by the authors,[1] the use of BMS leads to environmental concerns due to release of methylsulfide.

BDEA is even more stable than BDMS. The dissociation of BDEA to give B_2H_6 and DEA only occurs at 100 °C.[3] One can imagine that using BDEA, a classic addition process can be used for this process. Moreover, DEA is easily recovered from the reaction and recyclable. Unfortunately, commercial solutions of BDEA are far more expensive than BTHF of BMS solutions.

In situ generation of BH_3 has been investigated in depth over the years to overcome the issues of cost and stability of BTHF. Unfortunately, combinations like $NaBH_4$/H_2SO_4,[4a] $NaBH_4/BX_3$ (X=Cl, F),[4a] $NaBH_4$/TMSCl,[4b] $NaBH_4$/MeI,[4a] do not give pure enough BTHF to be used in the MeCBS catalyzed asymmetric carbonyl reduction of ketone or worse the process is too hazardous ($NaBH_4/H_2SO_4$) from the industrialization standpoint.

☆ This chemistry was disclosed in our patent WO 2005/035540.

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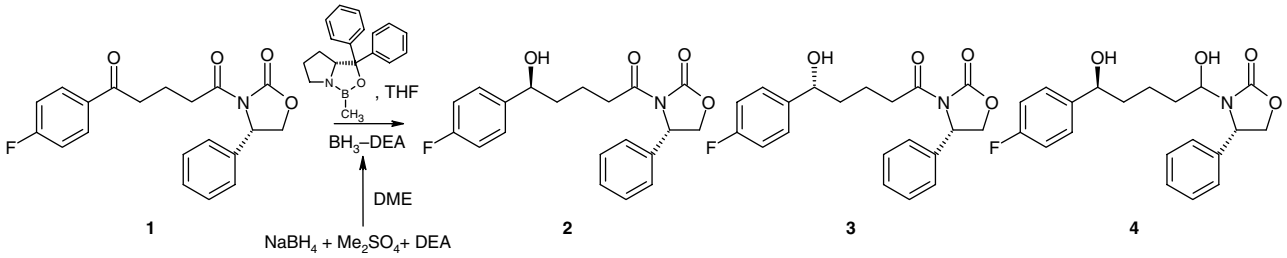
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.01.118



Scheme 1. (*R*)-MeCBS catalyzed reduction of **1**.

A process to generate BTHF in situ from $NaBH_4$ and $DMSO_4$ is described in the literature.[5] $DMSO_4$ is an industrial reagent at PPG-SIPSY already used in several large scale processes. So, we decided to investigate the generation in situ of BDEA from $NaBH_4$, DEA and $DMSO_4$, Eq. 1.

$$Me_2SO_4 + NaBH_4 + DEA \rightarrow BH_3\text{–}DEA + MeOSO_3Na \quad (1)$$

Because BH_3 forms a stable complex with DEA, the choice of the solvent for the generation reaction was not limited to THF. We found that monoglyme (DME) gave the best results from the yield standpoint and from the stirring point of view, presumably because of the higher solubility of $NaBH_4$ in DME than in THF. The reaction proceeds smoothly at 40 °C and a small excess of $DMSO_4$ is enough to drive the reaction to completion. The volume of methane released during the course of the reaction indicates that the yield is nearly quantitative. Because of the stability of BH_3–DEA complex, B_2H_6 does not escape from the reaction mixture even under the methane stream.

In parallel, we studied the reduction of compound **1** with commercially BDEA with MeCBS in DME. As expected we found trace amounts (<1%) of compound **4** using the normal reagent addition. However, the de (vs compound **3**) was slightly less than the de's reported with BTHF or BDMS (Table 1, entries 1 and 2). We found that when using THF as co-solvent during the asymmetric carbonyl reduction of compound **1**, the de was comparable to the de reported with BTHF or BDMS (Table 1, entry 4). We also showed that the optimum temperature for the reduction from the de standpoint is 20 °C (Table 1 entries 3–5).

Encouraged by the above results, we decided to telescope the two processes to assess the quality of our BDEA generated in situ.

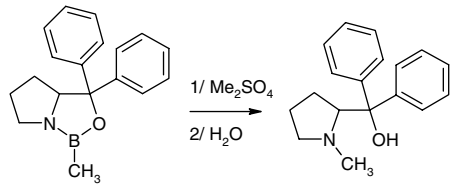
Using 5% of MeCBS, the de obtained was slightly less than the de obtained with commercial BDEA (Table 1, entries 4 and 6). A carefully examination of the reaction mixture showed that *N*-methyl-diphenylprolinol was present in the crude product. *N*-Methyl diphenylprolinol was attributed to the reaction of MeCBS with the residual $DMSO_4$ (Scheme 2).

Our hypothesis was that this side reaction of MeCBS with $DMSO_4$ reduces the amount of catalyst available for the asymmetric reaction and thus reduces the de of

Table 1.

Entry	Borane source Solvent	Reaction conditions	de[b] (%)	Compound **4** (%)	Chemical purity (area %) Toluene area not integrated
1	BDMS[1]	Normal addition	>98	<1	
2	BDEA Commercial solution DME	Normal addition 20 °C	93.5	0.9	>95
3	BDEA Commercial solution THF/DME	Normal addition 0 °C	94.1	0.2	>95
4	BDEA Commercial solution THF/DME	Normal addition 20 °C	98.9	0.7	>95
5	BDEA Commercial solution THF/DME	Normal addition 40 °C	94.9	6.6	89
6	BDEA in situ THF/DME	Normal addition 20 °C	97.6	2.8	>95
7	BDEA in situ THF/DME	Normal addition 20 °C LiCl	98.2	4.9	>90
8[c]	BDEA in situ 1 equiv THF/DME	Normal addition 20 °C	98.3	2.3	95
9[a]	BDEA in situ THF/DME	Normal addition 20 °C	94	2.9	>94

All the reactions were carried out with 5% MeCBS catalysis.
[a] Reaction was carried out with 5% HCBS catalysis.
[b] de were determined by HPLC on a Chiralcel ODH column.
[c] See Ref. 7 for the experimental procedure.



Scheme 2. N-Methylation of MeCBS.

compound **2**. Indeed, the relationship between ee and catalyst ratio is well established, due to the competition with non-stereoselective reduction with the borane source.

In order to suppress this side reaction, we needed to find a way to remove the excess of $DMSO_4$. The excess of $DMSO_4$ is mandatory to avoid having residual $NaBH_4$ which has a negative impact on the de as mentioned in the literature.[1]

$DMSO_4$ reacts with a variety of nucleophiles. The choice was guided by the compatibility of the nucleophile with BH_3, that is, which does not give a stable complex with BH_3. A chloride, Eq. 2, rapidly appeared to be the best choice even if the literature mentions a negative impact on the ee.[6] We anticipated that methylchloride is not a strong enough electrophile to react with MeCBS and would anyway escape from the reaction mixture at 40 °C.

$$Me_2SO_4 + Cl^- \rightarrow MeCl + MeOSO_3^- \qquad (2)$$

Adding LiCl to the reaction mixture before the addition of MeCBS did produce methylchloride gas and gave compound **2** with a de in line with the de obtained with commercial BDEA (Table 1, entries 4 and 7).

In order to ensure a good scaleup of the process, we looked at the reaction mixture stability. We found that on aging, the amount of compound **4** increases significantly. This increase was a concern because the reaction mixture is quenched by adding the reaction to an aqueous solution in order to control the release of hydrogen. We expected the quenching time to increase with the scale. We got around this problem by reducing the theoretical amount of BDEA to one strict equivalent against compound **1** (i.e., using one strict equivalent of $NaBH_4$) and by quenching the reaction with acetone to destroy any residual active hydrides (Table 1, entry 8) before the hydrolysis.

In summary, a process to produce in situ BDEA compatible with MeCBS asymmetric carbonyl reduction of ketone has developed and successfully applied to a key intermediate in the synthesis of the cholesterol lowering agent Ezetimibe. This process uses cheap, raw, storable and recyclable (DEA) reagents. The process has been extended to HCBS (Table 1, entry 9).

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7. Procedure (Table 1, entry 8): Under nitrogen, 1.28 g (33.8 mmol) of $NaBH_4$ was suspended in 24 ml of DME; 5.4 g (35.5 mmol) of DEA was then added. The mixture was heated up to 40 °C then 4.47 g (35.5 mmol) of $DMSO_4$ was added slowly to the previous suspension. The reaction was maintained at 40 °C until a clear solution was obtained. 286 mg (6.8 mmol) of LiCl was then added. The reaction mixture was then cooled to room temperature (20 °C) then 1.7 ml of a 1 M (*R*)-MeCBS in toluene (1.7 mmol) was added. Ketone **1** [12 g (33.8 mmol)] was dissolved in 24 ml of THF and added over a 1 h period to the previous reaction mixture. The reaction was then maintained at 20 °C for 10 min then 6 g (100 mmol) of acetone was rapidly added. 6.07 g (43.9 mmol) of potassium carbonate was dissolved in 72 ml of water. The reaction mixture was then added to the carbonate solution. The aqueous phase was discarded. The organic phase was partially concentrated and taken up in 72 ml of toluene. The organic phase was washed with 36 ml of water, twice with 30 ml of 10% sulfuric acid (50 mmol) then with 36 ml of water. The organic phase was concentrated under vacuum to dryness to give 13 g of a viscous oil, compound **2**.