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Selective *N*-Dealkylation of Tertiary Amines Derived from Phenylglycinol or Ephedrine Family

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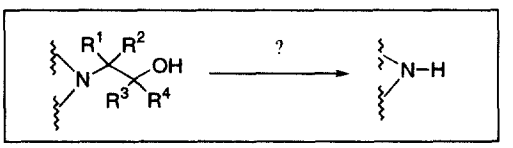
Abstract: Tertiary amines bearing an hydroxyethyl group derived from phenylglycinol, norephedrine or norpseudoephedrine can be selectively dealkylated using a two-step sequence involving treatment with thionyl chloride in THF, followed by reaction with an excess of potassium cyanide in THF:DMSO. These conditions are compatible with the presence of an insaturation or a benzyl ether in the substrate.

Keywords: Dealkylation, amino alcohols, asymmetric synthesis.

In the chiral pool, 1,2-amino alcohols are probably amongst the most important components.[1] First, these molecules serve as a chiral source for the elaboration of widely used chiral auxiliaries, Evans' oxazolidinones[2] being an exemple. Additionally, and this is a special feature for this class of compounds, their amino moiety can be incorporated into the target molecule. Though this represents an immolative process with respect to the chiral source, this methodology is frequently used for the asymmetric synthesis of nitrogen containing compounds, owing to the availability of the starting chiral inductors.[3] Nevertheless, the efficiency of this strategy stems from the ease of cleavage of the amino alcohol residue, as schematized below (Scheme 1) and this explains why phenyl glycinol (R^1=Ph, R^2=R^3=R^4=H) is often used in these transformations. Indeed, *N*-debenzylation by hydrogenolysis is a mild and efficient procedure to achieve this goal.[4]

Scheme 1



Many compounds, however, cannot tolerate these conditions of debenzylation, since they are not compatible with the presence of an unsaturation in the substrate. In order to solve this problem, other methods have been devised, such as deprotection of *N*-benzylamides using alkali metals reduction[5] or the two-step procedure described by Meyers[6] involving thiophenylation of the amino alcohol appendage followed by reductive fragmentation with LiDBB. Marazano[7] also proposed a solution which involves the oxidation of the primary alcohol, followed by the condensation with 2,4-dinitrophenylhydrazine and fragmentation of the resulting hydrazone. However, a mild and selective solution to this problem still remains to be found.

In the course of the synthesis of (-)-desoxoprosopinine,[8] we were recently faced with the problem of the selective removal of the (*R*)-phenylglycinol residue in the piperidine derivative **1**. Preliminary experiments showed that treatment of this compound with lithium in ammonia effected cleanly an *O*-debenzylation, without

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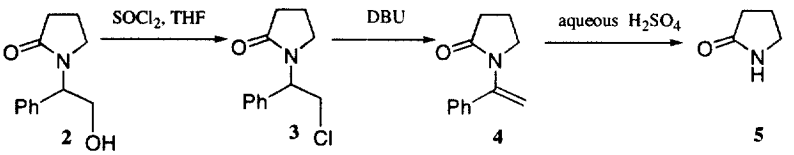
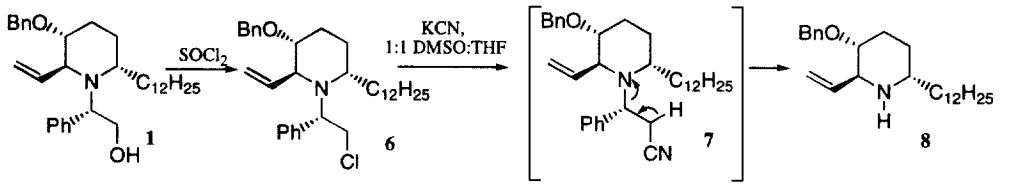
any trace of the product resulting from *N*-debenzylation. Furthermore, reaction with α-chloroethyl chloroformiate,[9] known as a selective *N*-debenzylation reagent, gave only the undesired carbonate of the primary alcohol. These disappointing results led us to test on **1** the three-step sequence described by Villieras *et al* [10] for the deprotection of lactams related to **2**. This sequence is summarized in Scheme 2 and involves (*i*) treatment with $SOCl_2$, giving the corresponding chloride **3**, (*ii*) DBU-mediated dehydrohalogenation affording the corresponding enamide **4** and (*iii*) hydrolysis of this enamide.

Scheme 2



Thus, treatment of **1** with $SOCl_2$ in THF gave quantitatively the corresponding chloride **6**, but we were unable to find conditions to effect the second step of the sequence i. e. the deshydrohalogenation. We eventually found that reaction of **6** with an excess of KCN (10 equiv.) in a 1:1 mixture of THF:DMSO gave directly the desired amine (89% overall yield) through an *in situ* β-elimination of the transient β-amino nitrile **7** (Scheme 3):

Scheme 3



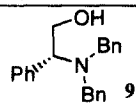
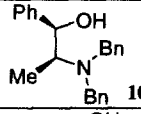
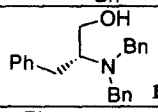
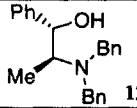
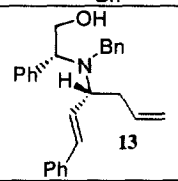
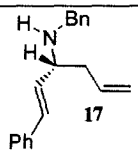
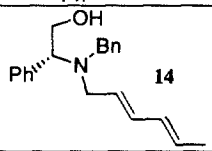
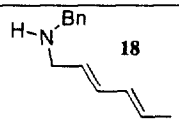
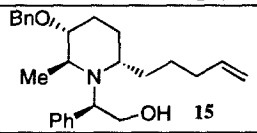
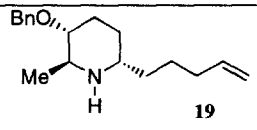
The object of this Letter is to analyse the scope of this new two-step sequence for selective *N*-dealkylations. To this end, the behaviour of β-amino alcohols **8-14** was studied under standardized conditions.[11] Results are collected in the following table.

These results clearly demonstrate that this methodology has a wide scope, since even ephedrine family-derived tertiary amines can be dealkylated under these conditions (entries 2, 4). From a practical point of view it should be noted (i) that the use mixture of solvents used in the last step[11] is essential, since extensive polymerisation occured when treatment with KCN was effected in pure DMSO, (ii) that heating does not significantly shorten the reaction time but lowers the yield. An interesting result, that clearly delineates the scope of this method is the behaviour of β-aminoalcohol **11** (entry 3): no elimination occured in this case. Analysis of the crude reaction mixture showed the presence of the chloride and nitrile derived from **11** in a respective 20:80 ratio, but no formation of dibenzylamine. Therefore, the presence of a phenyl ring on the β-amino alcohol residue seems to be crucial for the success of the operation. In these cases, the produced acrylonitrile derivative is of course much stable, due to conjugation with the aromatic moiety.

Finally, our methodology was applied to substrate **20**,[12] containing a carbamate moiety instead of a tertiary amine. However, reaction of the corresponding chloride **21** with KCN did not give the expected result but furnished the enamide **23**. In this case, elimination by the cyanide anion was competitive with respect to substitution, probably through nucleophilic assistance of the carbamate moiety, to give an oxoiminium

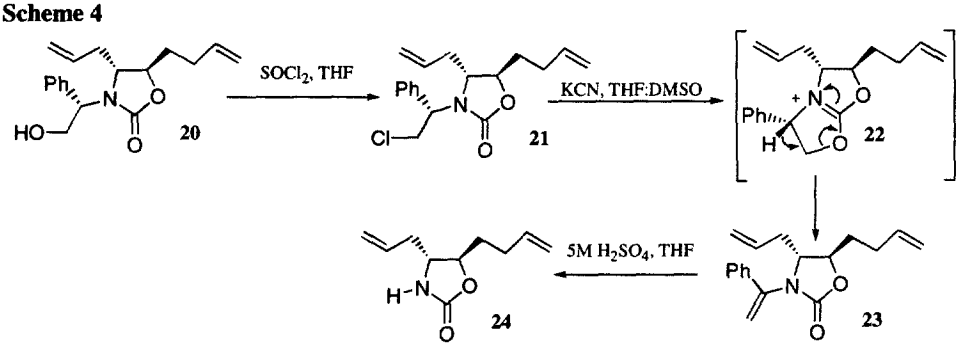
intermediate **22**. Nonetheless, hydrolysis of the produced enamide **23** gave the desired oxazolidinone **24** with a 60% overall yield (Scheme 4):

Table: Two step dealkylation of tertiary amines

Entry	Substrate[13]	Released amine	Yield (%)[a]
1	 **9**	 **16**	65
2	 **10**	**16**	50
3	 **11**	**16**	0
4	 **12**	**16**	67
5	 **13**	 **17**	61
6	 **14**	 **18**	77[b]
7	 **15**	 **19**	72

a: Yield of isolated products. b: Compounds **14** and **18** were obtained with a 75% purity as determined by GC and NMR, together with overreduced inseparable related alkenes.

Scheme 4



In summary, this procedure of *N*-dealkylation by a two-step sequence should provide a new tool in the area of asymmetric synthesis of nitrogen containing targets that make use of phenylglycinol or ephedrine family-derived β-amino alcohols as the chiral source.

References and notes

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11. **Typical procedure**: To a solution of the amino alcohol (1 mmol) in THF (10 ml) was added dropwise thionyl chloride (2 mmol). The solution was stirred at rt for 1h and evaporated to dryness. The residue was taken up in DMSO (5 ml) and THF (5 ml) and KCN (10 mmol) was added. After the suspension had been stirred at rt for 48-72h, water (20 ml) was added. The mixture was extracted with ether, the organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude amine was then purified by flash chromatography.
12. Agami, C.; Amiot, F.; Couty, F.; Dechoux, L.; Kaminsky, C.; Venier, O. *Tetrahedron: Asymmetry*, **1998**, *9*, 3955-58.
13. Amino alcohols **8-11** were prepared by dibenzylation of the corresponding amino alcohol (BnBr, K_2CO_3, CH_3CN). Amino alcohol **12** was synthetised by benzylation of the corresponding amino alcohol, prepared according to Allin, S. M.; Button, M. A. C.; Baird, R. D. *Synlett*, **1998**, 1117-19. Amino alcohol **13** was prepared by reduction ($NaBH_3CN$) of the imine resulting from the condensation between (*R*)-phenyl glycinol and 2, 4-hexadienal, followed by benzylation.