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One-Pot Synthesis of Protected Homoallyl Amines

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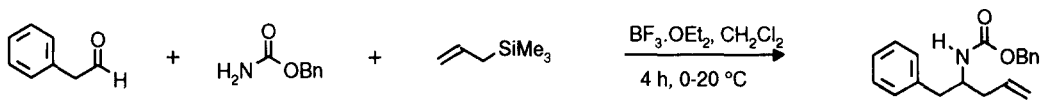
Abstract: An efficient one-pot procedure for the synthesis of protected homoallyl amines from aldehydes or aldehyde acetals, carbamates and allyltrimethylsilane under influence of borontrifluoride etherate was developed. Scope and limitations of the aldehyde and carbamate components are reported.

Acylated homoallyl amines are important synthons for many synthetic applications, notably for acyliminium chemistry[1]. Homoallyl amines are usually synthesized via reaction of allyl organometallics with imines[2,3], iminium ions[2,3], acylimines[2a,4] or acyliminium ions[2a,4]. In this paper we wish to present a one-pot, three component reaction of an aldehyde, a carbamate and allyltrimethylsilane in the presence of borontrifluoride etherate to give protected homoallyl amines in high yields.

In connection with an ongoing program towards the development of non-peptidic NK_1 antagonists[5] we required an efficient synthesis for the protected homoallylamine **3**, an important intermediate for the *trans* selective construction of 2-alkyl-4-aminopiperidines[5b,c]. When equimolar amounts of phenylacetaldehyde (**1**), benzyl carbamate (**2**) and allyltrimethylsilane in methylene chloride were treated with 1.2 eq. borontrifluoride etherate for 5 h at 0-20°C, the protected homoallyl amine **3** was isolated in 80% yield. Encouraged by this result we studied the scope and limitations of this reaction with respect to the aldehyde and amide employed in the process. The results are summarized in the Table[6].

Scheme 1



1 (1 eq.) **2** (1 eq.) (1 eq.) **3**, 80%

Allyltrimethylsilane was used as the allylation agent in all reactions. Generally excellent yields were obtained with 1-1.2 equivalent of borontrifluoride etherate at 0-20°C in methylene chloride or acetonitrile as a solvent. All aromatic and aliphatic aldehydes gave good to excellent results using benzyl carbamate (entries 1-9) or methyl carbamate (entry 18) as the amide component and borontrifluoride etherate as the Lewis acid. Acetal derivatives of aldehydes (entries 14-17) reacted equally well, thereby circumventing problems associated with the poor stability of the corresponding aldehydes. Steric hindrance in the aldehyde component does not seem to play a significant role (sequence of entries 2-5,18). The chiral glucose derived aldehyde **11**[7] containing two acetal functions gave the product **27**[8] with moderate selectivity (entry 9). Electron rich and electron poor aromatic aldehydes both participated efficiently (entries 7 and 8). Some electron deficient aldehydes gave minor amounts of homoallyl alcohols **36** resulting from direct addition of allyltrimethylsilane to the aldehyde (entries 7 and 9).

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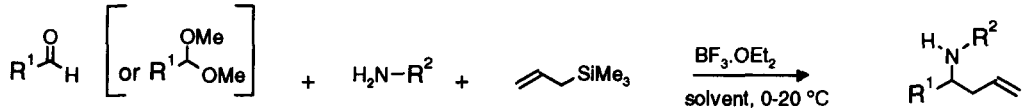
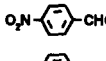
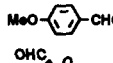
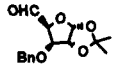
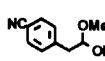
Scheme 2

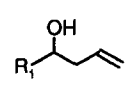


1,4-11 12-13 14-19 3,20-35

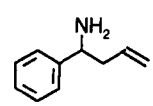
Table

Entry	Aldehyde		Amide	Solvent (Time)	$BF_3{\cdot}OEt_2$ (eq.)	Yield %	Product[a]
1		1	 2	CH_2Cl_2 (4 h)	(1.2)	80[c]	3
2	CH_3CHO	4	2	" (3 h)	(1.2)	72[b]	20
3		5	2	" (2 h)	(1.2)	96[c]	21
4		6	2	" (2 h)	(1.2)	70[b]	22
5		7	2	CH_3CN (2 h)	(1.2)	88[b]	23
6		8	2	" (2 h)	(1.2)	95[c]	24
7		9	2	" (2 h)	(1.0)	85[c,d]	25
8		10	2	CH_2Cl_2 (3 h)	(1.2)	84[c]	26
9		11	2	CH_3CN (1 h)	(1.2)	68[c,d] (5:1)	27
10		8	 14	" (20 h)	(1.2)	78[c]	28
11	8		 15	" (1 h)	(1.2)	45[c,e]	29
12	8		15	" (6 h)	(0.6)	74[c]	29
13	8		 16	" (20 h)	(1.2)	41[c]	30
14		12[9]	2	" (3 h)	(1.0)	71[c]	31
15		13	 17	" (20 h)	(1.0)	60[c]	32
16	13		 18	" (3 h)	(1.0)	83[c]	33
17	13		 19	" (1 h)	$SnCl_4$ (1.0)[f]	75[b,g]	34
18		6	19	" (3 h)	(1.0)	79[b]	35

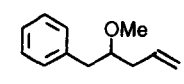
(a) All products gave satisfactory ^{1}H-NMR, MS and elementary analytical data. (b) Yields after distillation. (c) Yields after chromatography. (d) Traces of **36** were identified as side products. (e) The amine **37** was isolated in 22% yield. (f) Carried out at -10°C. (g) The side product **38** was isolated in 13% yield.



36



37



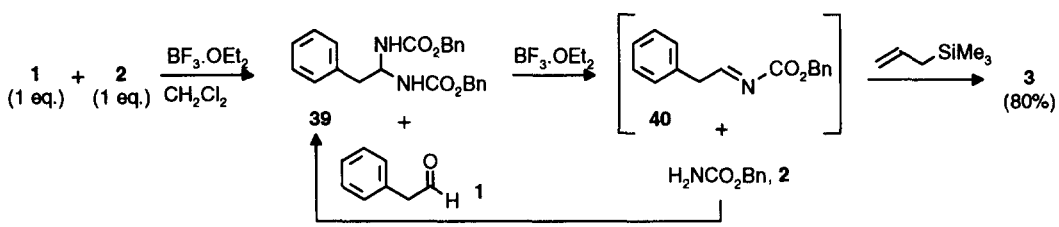
38

The mono substituted urea **14** reacted in high yield but slower (entry 10). The Boc-protected homoallyl amine **29** was unstable under the standard reaction conditions and, in addition, free amine **37** was isolated in 22% yield. However, by lowering the amount of borontrifluoride etherate to 0.6 equivalents a good yield of **29** was obtained (entries 11 and 12). The butyramide **16** reacted sluggishly and gave **30** in poor yield. Sulfonamides also participate in the reaction. Tosylamide **17** gave **32** in moderate yield because the reaction did not go to completion (entry 15). However, the sulfonylurea **18**[10] reacted cleanly and gave a high yield of **33** (entry 16). Alternatively, tin tetrachloride was used effectively at a somewhat lower temperature (-10°C, entry 17). The use of titanium tetrachloride or trifluoromethyl sulfonic acid led to decomposition of the reaction mixture.

Mechanistic considerations.

Typically, shortly after the introduction of the Lewis acid into the reaction mixture a thick white precipitate formed. When the reaction depicted in Scheme 1 was quenched at this point, a white crystalline solid was isolated. This material proved to be identical with the bisurethane **39**[11] (Scheme 3). Bisurethane derivatives of aldehydes have been used as precursors for the *in situ* generation of acylimines[12] for use in e.g. cycloaddition reactions[13] and amidoalkylations[14]. The intermediate acylimine **40** is presumably the species that undergoes nucleophilic attack by allyltrimethylsilane in the reactions described here (Scheme 3). When **39** was treated with allyltrimethylsilane in the presence of borontrifluoride etherate, **3** was produced in 66% yield together with benzyl carbamate **2**. It is remarkable that for most aldehydes no homoallyl alcohols were produced as a result of a direct attack of the allylsilane at the aldehyde (Sakurai reaction), despite the fact that free aldehyde is present until the reaction is completed. Presumably the intermediate acylimine **40** is a much better electrophile compared to the aldehyde **1** and/or the strength of the Lewis acid is moderated by complexation with the carbamate functionality. Furthermore, it is interesting to note that the best yields were obtained when exactly one equivalent of each reagent was employed in the reaction.

Scheme 3



In conclusion, we developed a mild, efficient and practical method for the preparation of protected homoallyl amines. The reaction has a wide scope with respect to the aldehyde and primary amide components.

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6. Typical procedure: Under an inert atmosphere of nitrogen a magnetically stirred mixture of 10 mmol aldehyde, 1.14 g (10 mmol) allyltrimethylsilane and 1.51 g (10 mmol) benzyl carbamate in 15 ml of methylene chloride in a 50 ml roundbottomed flask was cooled with an ice bath to 0-5°C. Borontrifluoride etherate (1.26 ml, 10 mmol) was added in one portion[15]. After a few minutes, a thick white precipitate formed, which slowly dissolved as the reaction progressed to completion. After 30 minutes the ice bath was removed and the reaction mixture was allowed to warm up to ambient temperature. The reaction was monitored by TLC analysis, and was usually complete after 3 hours. The mixture was poured into saturated aqueous $NaHCO_3$ and diluted with 30 ml toluene. The organic phase was washed with brine (10 ml x2) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure the crude product was purified by distillation or chromatography on silica gel (hexane/ethyl acetate as eluent).

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8. Stereochemistry not determined.

9. Compound **12** was prepared in analogy to a published procedure: Hey, D.H.; Williams, J.M. *J. Chem. Soc.* **1950**, 1682.

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11. To an ice cooled solution of 1.2 g (10 mmol) of **1** and 3.02 g (20 mmol) of **2** in diethyl ether was added 1.25 ml.(10 mMol) borontrifluoride etherate. After 1 h the reaction mixture was quenched with 10% aqueous Na_2CO_3. The mixture was filtered and the crystalline product was washed with water and diethyl ether. Recrystallization of the crude product from isopropanol gave **39** in 76% yield. Mp. 170-172°C.

12. Acylimines, being in general unstable species, are isolable when stabilizing substituents are present. See for instance: (a) Vidal, J.; Guy, L.; Stérin, S.; Collet, A. *J. Org. Chem.* **1993**, *58*, 4791. (b) Dobrev, A.; Benin, V.; Nechev, L. *Liebigs Ann. Chem.* **1992**, 863. (c) Malassa, I.; Matthies, D. *Chemiker Zeitung* **1987**, *111*, 181. (d) Kupfer, R.; Meier, S.; Wuerthwein, E.-U. *Synthesis* **1984**, 688.
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15. The reaction is slightly exothermic and a precipitate which often forms during the reaction can cause stirring problems. On large scale it is advisable to change the mode of addition by simultaneously adding a methylene chloride solution of aldehyde, carbamate and allyltrimethylsilane and a methylene chloride solution of borontrifluoride etherate to the well stirred and cooled reaction mixture.

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