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Synthesis of Homoallylic Amines *via N*-Acyliminium Ion Reactions on Solid Support[#]

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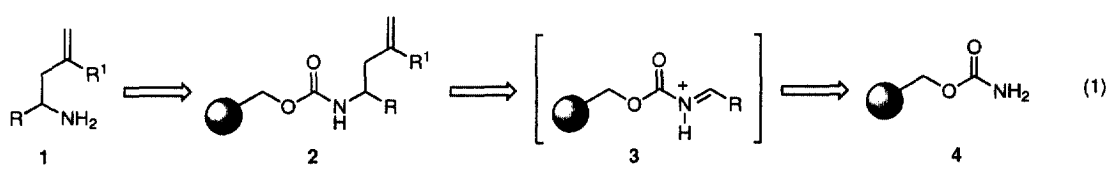
Abstract

The synthesis of a library of homoallylic amines is reported. The key step in the synthesis is a one-pot *N*-acyliminium ion coupling involving a solid phase-bound carbamate, an aldehyde and an allylsilane under Lewis acid conditions.

Keywords: solid phase synthesis; amines; combinatorial chemistry; allylation

Solid phase organic chemistry is an efficient tool in the synthesis of libraries of compounds for biological screening [1–3]. Although the synthetic diversity of solid phase organic chemistry is growing rapidly, the 'translation' of solution phase into solid phase chemistry is still needed in order to expand its value for the pharmaceutical industry [4,5]. Considering the abundance of examples of the versatility of *N*-acyliminium ions as intermediates for CC-bond formation in the synthesis of linear amines, *N*-heterocycles [6] and natural products [7,8], we envisioned that it would be useful to investigate the potential of this type of reaction on solid phase.



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[#] This paper is dedicated to Prof. W. N. Speckamp on the occasion of his 65th birthday.

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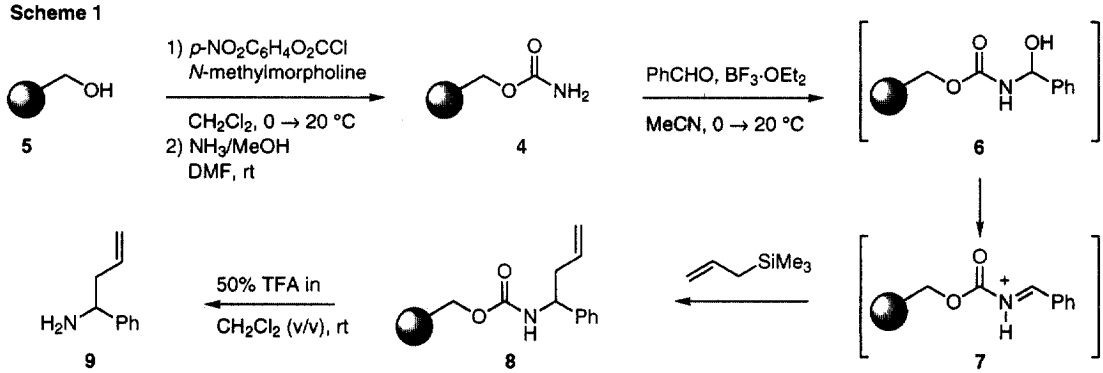
Thus, in this article we wish to report the synthesis of a library of homoallylic amines **1** *via* a solid-supported three-component condensation, starting from the carbamate **4** and proceeding *via* the immobilized *N*-acyliminium species **3** (eq 1).

In order to study the solid phase *N*-acyliminium ion reaction, we used a protocol that was recently developed at Novartis by Veenstra *et al.* for the solution phase synthesis of protected homoallylic amines [9]. The synthesis involved a one-pot three component reaction of an aldehyde, a carbamate or a tosylamide and an allylsilane under the influence of $BF_3{\cdot}OEt_2$. We studied the scope and limitations of this reaction on solid phase with respect to the linker system, the aldehyde and the nucleophile.

The first choice concerned the use of a readily cleavable linker. Although the Wang linker is labile under moderately acidic conditions, we anticipated that under the mildly acidic conditions reported for this reaction ($BF_3{\cdot}OEt_2$, 0→20 °C) hardly any cleavage would be observed. Therefore, a model system was set up starting from the Wang resin **5** (Scheme 1), which was activated using *p*-nitrophenyl chloroformate [10] and reacted with ammonia to provide the immobilized carbamate **4** in 90% yield (over 2 steps, determined by elemental analysis [11]).[1]

Scheme 1



Then, the optimal solid phase conditions were established using the condensation of **4** with benzaldehyde and allyltrimethylsilane as a model reaction. The amount of aldehyde, allylsilane and Lewis acid was varied, while the reaction time was determined using MAS-NMR. Eventually, it was found that the highest yield of **9** (43% after chromatography) was obtained by using a large excess of the aldehyde and allyltrimethylsilane (20 and 10 equiv, respectively) and only a small amount of the Lewis acid $BF_3{\cdot}OEt_2$ (1.1 equiv, in order to avoid release from the resin) after 2 h in MeCN at rt.[2] Under these conditions cleavage of the Wang linker was

[1] Experimental procedure: after conversion of resin **5** into the corresponding carbonate [10], the resin (5.34 g, approximately 0.64 mmol/g, 3.41 mmol) was suspended in DMF (150 mL) and a saturated NH_3/MeOH solution (10.3 mL, 20.5 mmol) was added. After stirring for 18 h at rt, the resin was filtered off, washed with DMF (100 mL), CH_2Cl_2 (100 mL) and EtOH (100 mL, the last two steps were repeated four times) and Et_2O (2 × 100 mL). After drying *in vacuo* (50 °C) the immobilized carbamate **6** (4.88 g, approximately 0.69 mmol/g) was obtained.

[2] Typical experimental procedure: the carbamate resin **6** (100 mg, 0.69 mmol/g, 0.07 mmol) was suspended in dry MeCN (1.5 mL) and cooled to −5 °C. Then, benzaldehyde (142 µL, 1.40 mmol), allyltrimethylsilane (110 µL, 0.69 mmol) and $BF_3{\cdot}OEt_2$ (9 µL, 0.07 mmol) were added and the reaction mixture was stirred for 2 h under a nitrogen atmosphere at room temperature. The suspension was filtered and the resin was washed with MeCN (3 mL), CH_2Cl_2 (3 mL) and EtOH (3 mL); the last two steps were repeated four times. After drying *in vacuo* (50 °C), the resin was suspended in 50% TFA in CH_2Cl_2 (v/v) and stirred at rt for 2 h. The suspension was filtered, the resin was washed with CH_2Cl_2 (3 × 2 mL) and the collected filtrates were evaporated. The product was purified using SPE chromatography (silica, 0 → 10% MeOH in CH_2Cl_2) to give 4.4 mg (0.03 mmol) of **9** as a light yellow oil.

slow, whereas at higher temperature and with stronger Lewis acids ($SnCl_4$, $TiCl_4$) significant decomposition of the linker system was encountered. In addition to $BF_3{\cdot}OEt_2$, the reaction was carried out using $Sc(OTf)_3$ as the Lewis acid, but in this case no significant difference in reactivity between the two Lewis acids was found.

Attempts to increase the yield – especially by adding reagents that would turn the hydroxy group of the intermediate aminal **6** into a good leaving group – were unsuccessful: additives such as benzotriazole, acetic anhydride, TMSOTf and TMSCl did not show any increase in the yield of the reaction.

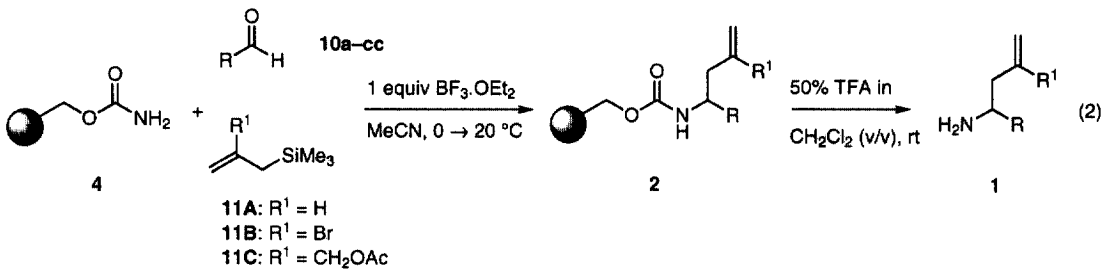
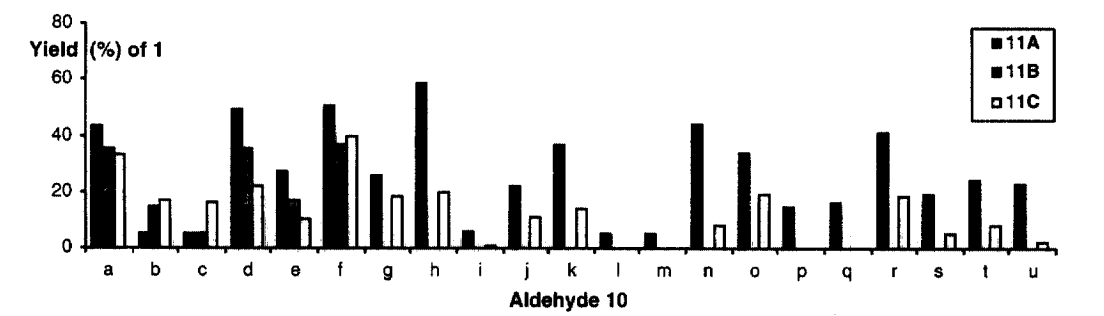
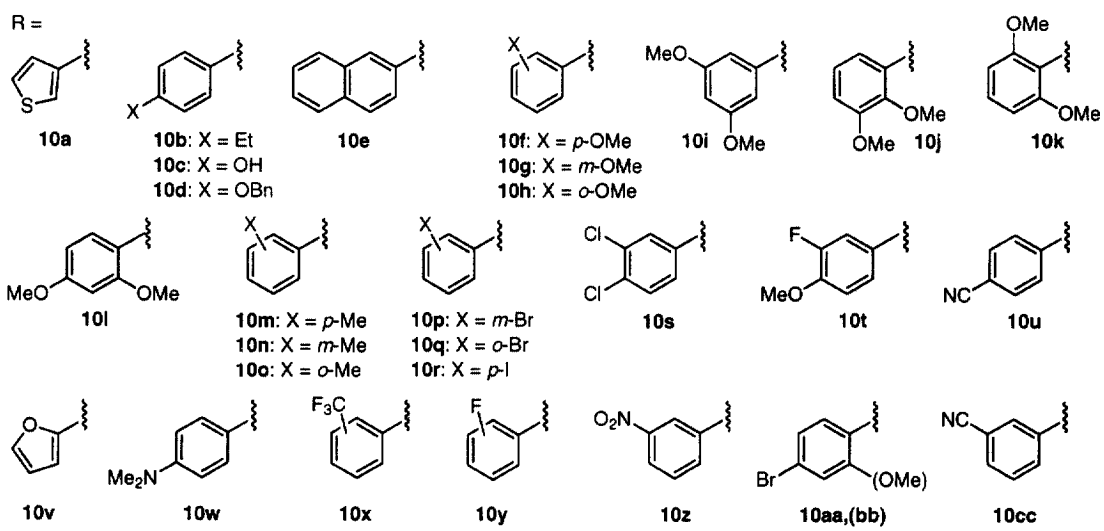


Table 1





Despite the somewhat modest yield, we decided to synthesize a library of the amines **1** on a synthesis robot (SYRO, Multisyntech) based on these conditions using the resin **4**, the aldehydes **10a–cc** and the allylsilanes **11A–C** (eq 2). This choice was based on initial experiments with different nucleophiles (allylsilanes, malonates, silyl enol ethers) and different aldehydes (aromatic and aliphatic) to determine the scope of the reaction. In general, neither reactions with malonates or silyl enol ethers, nor reactions with aliphatic aldehydes gave good results. The allylsilanes **11A–C** were used in combination with aldehydes **10a–f**, while only **11A** and **C** were used in combination with aldehydes **10g–cc**; the aldehydes **10v–cc**, however, did not give any product at all. The best results of these experiments are shown in Table 1. The yields of products **1** were determined starting from resin **4** and include automatic purification over a short SPE-column. The products were characterized by LRMS (electron spray) and partially by ^{1}H NMR; their purity was verified with HPLC. Clearly, electron rich aldehydes (*e.g.* **10d**, **10f–g**) gave the best results, whereas electron poor aldehydes did not react at all. Surprisingly, introduction of two electron donating substituents (**10i–o**) did not lead to an increase of the yield. In addition, allyltrimethylsilane was shown to be the best nucleophile, while the acetate and in particular the vinyl bromide gave lower yields.

In summary, with the synthesis of this library of around 40 homoallylic amines we have proven for the first time the viability of *N*-acyliminium ion reactions on solid support. A limiting factor for improving the yields was the use of the Wang linker, which was not compatible with strongly acidic reaction conditions. Therefore, we are currently investigating linker systems that are orthogonal with the acidic conditions in order to raise the yields, but also to widen the scope of this three-component reaction with respect to the aldehydes and the nucleophiles.

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