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A Novel Acid Stable/Base Labile Carbamate Linker for *N*-Acyliminium Ion Reactions on Solid Support

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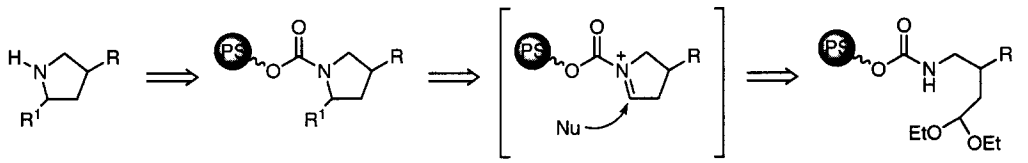
Abstract

The development of a novel carbamate linker optimized for solid phase *N*-acyliminium ion chemistry is reported. Some 2- and 2,4-substituted pyrrolidines were synthesized *via* addition of several carbon nucleophiles to immobilized *N*-acyliminium ions. A β-sulfonylethyl carbamate linker appeared especially useful; readily synthesized, stable towards Lewis acids and easily cleavable.

Keywords: solid-phase synthesis; pyrrolidines; *N*-acyliminium ion; base-labile linker

Pyrrolidines constitute an important structural moiety which occurs frequently in natural products and biologically active compounds.[1] Therefore, they may serve as versatile scaffolds for combinatorial synthesis. In this letter we describe the functionalization of pyrrolidines at the 2-position *via* the addition of carbon nucleophiles to the immobilized *N*-acyliminium ions **3**.



1 2 3 4 (1)

The general strategy is outlined in equation 1. We envisioned that the desired pyrrolidines **1** might be obtained *via* cleavage of the carbamate functionality of the immobilized systems **2**. These compounds, in turn, should be available from the solid phase-bound amino acetals **4** *via* $BF_3{\cdot}OEt_2$-mediated *N*-acyliminium ion generation and trapping with suitable nucleophiles. In this research, the linker system was an important item of

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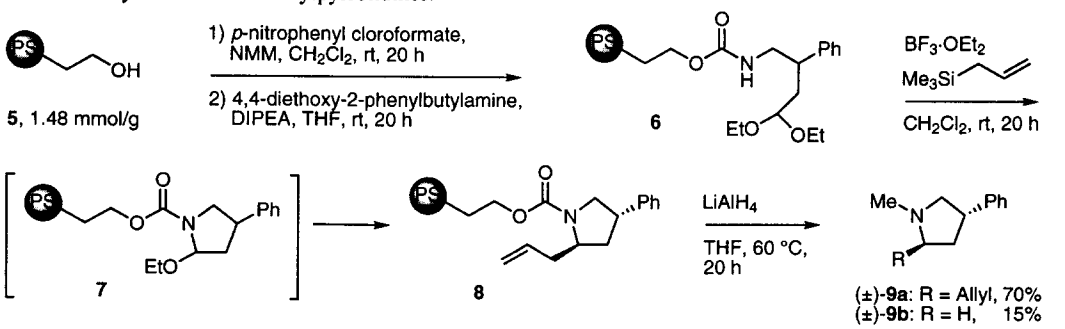
concern. In a previous article,[2] we reported the solid phase synthesis of homoallylic amines *via* *N*-acyliminium ion chemistry. Unfortunately, the yields in this approach were rather moderate, probably due to premature cleavage of the Wang resin-derived carbamate linkage by the acidic conditions required to generate the *N*-acyliminium ion.[3] Therefore, we decided to design a new linker system that is orthogonal to Lewis acidic reaction conditions.

Initially, an ethyl carbamate linker was considered, starting from hydroxyethylated polystyrene **5**. This resin was activated using *p*-nitrophenyl chloroformate[4] and subsequently coupled to 4,4-diethoxy-2-phenylbutylamine[5] to give precursor **6**. Addition of $BF_3{\cdot}OEt_2$ induced cyclization to the corresponding *N,O*-acetal **7**, which *in situ* formed the *N*-acyliminium ion that was trapped with allyltrimethylsilane to give the product resin **8**. Unfortunately, several reagents effective in solution (*i.e.* Me_3SiI, BnOLi) failed to cleave the carbamate functionality. In our hands, only LAH-reduction of the carbamate to the *N*-methyl group gave a satisfactory result.[6] Thus, product **9a** was obtained as a single *trans*-diastereomer (proven by NOE-studies) in 70% yield starting from resin **5**, together with 15% of side product **9b**, which probably resulted from reduction of unreacted *N,O*-acetal **7**.

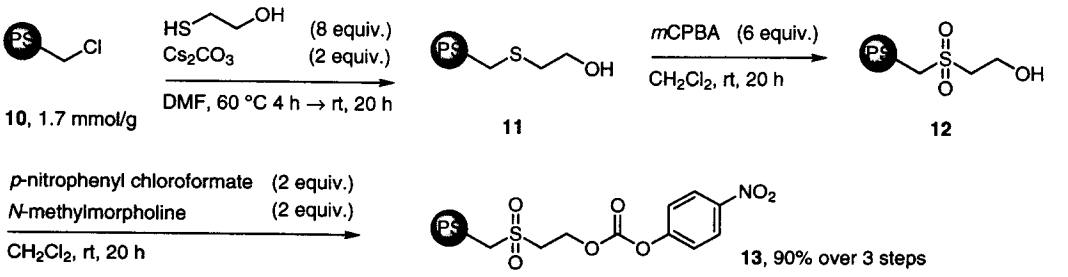
Scheme 1. Synthesis of *N*-methylpyrrolidines.



A drawback of this method is that it only provides *N*-methylamines. To overcome this limitation we decided to synthesize a taylor-made linker that would be stable to Lewis acids and allow cleavage under basic conditions. The 2-methylsulfonylethoxycarbonyl (Msc) protecting group, developed by Tesser and coworkers in the seventies as a cheap and readily available Fmoc-equivalent, seemed ideal for our purposes.[7] The Msc-group can be cleaved *via* β-elimination using a strong base, but is stable to tertiary amine bases such as DIPEA, TEA and NMM.[8]

The synthesis of the linker system started with cesium carbonate-mediated coupling of mercaptoethanol to Merrifield resin **10** to furnish alcohol resin **11**. The sulfide was then oxidized to the sulfone using an excess of *m*CPBA in CH_2Cl_2.[9] Subsequent reaction with *p*-nitrophenyl chloroformate led to the mixed carbonate resin **13** in an overall yield of 90%.

Scheme 2. Synthesis of the linker system.



The yield was determined *via* elemental analysis of the nitrogen content of the resin.[10] In the IR-spectrum of resin **13**, the sulfone (1110, 1320 cm^{-1}), carbonyl (1765 cm^{-1}) and the nitro group (1346, 1524 cm^{-1}) absorptions could be readily identified. Resin **13** was then functionalized with the amino acetals **14a–c**[5] to give the *N*-acyliminium ion precursors **15a–c**. Treatment with $BF_3{\cdot}OEt_2$ and a nucleophile then provided resins **16a–c**, which were subjected to a 1.0 M solution of NaOMe in THF/MeOH to give the pyrrolidines **1** with concomitant loss of CO_2 (Scheme 3).

Scheme 3. Synthesis and cleavage of the pyrrolidines

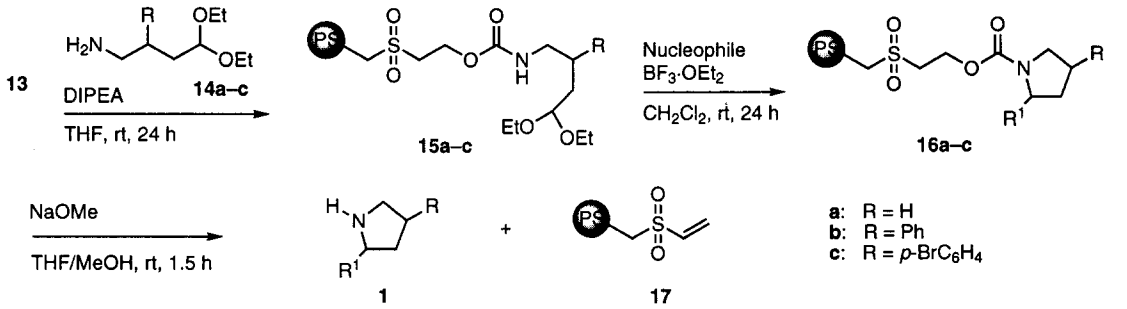
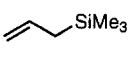
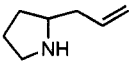
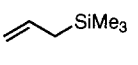
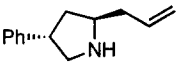
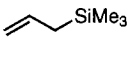
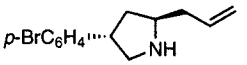
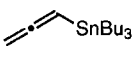
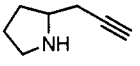
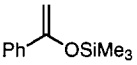
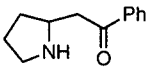
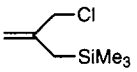
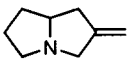


Table 1

entry	substrate	nucleophile	product		yield (%)[a]
1	**15a**			**18**[b]	98
2	**15b**			**19**	81
3	**15c**			**20**	84
4	**15a**			**21**[b]	59[c]
5	**15a**			**22**[b]	36
6	**15a**			**23**[b]	75

[a]Isolated yield over three steps from resin **13**. [b]Isolated as the HCl-salt. [c]Contaminated with *ca.* 15% of the corresponding allene.

Reaction of the aminoacetal resin **15a** with allyltrimethylsilane proceeded in nearly quantitative yield (Table 1, entry 1). The reaction of the more sterically hindered substrates **15b** and **15c** with allyltrimethylsilane also proceeded in high yields (entries 2 and 3). The *trans*-stereochemistry was unambiguously proven *via* tosylation of **19** and subsequent NOE-studies. Especially the aryl bromide group of substrate **15c** offers the possibility for further functionalization *via* Pd-chemistry. Initially, an excess of pyrrolidine was added during the cleavage reaction, to prevent addition of the product to vinylsulfone resin **17** in a Michael type reaction.[11] However, an equally good yield (using substrate **15b**, entry 2) was obtained without pyrrolidine, showing that addition of the product **19** to **17** does not take place. IR data of the resin after the cleavage reaction showed complete disappearance of the carbamate carbonyl absorption. A number of different nucleophiles were then investigated. For example, a propargyl functionality was introduced using allenyltributyltin as the nucleophile (entry 4). Surprisingly, reaction of the silyl enol ether of acetophenone with **15a** resulted in a moderate yield of

22 (36%) after cleavage.[12] Finally, using 2-(chloromethyl)allyltrimethylsilane as the nucleophile, the initial product largely cyclized under the cleavage conditions to give the pyrrolizidine derivative **23** together with substitution of the chloride by methoxide (1:0.3 ratio). As expected, cleavage using a 1.0 M solution of KO^{t}Bu in THF, followed by prolonged stirring at rt to complete the cyclization, led to pyrrolizidine **23** in 75% yield (entry 6).

In summary, we have developed a new acid stable/base labile linker system, which is efficiently synthesized and can be used to immobilize amines *via* a carbamate functionality. The linker is stable under Lewis acidic ($BF_3{\cdot}OEt_2$) and weakly basic (NMM, DIPEA) conditions and is highly suitable for *N*-acyliminium ion chemistry on solid phase. Cleavage is readily effected in quantitative yield *via* β-elimination by using NaOMe or KO^{t}Bu. Currently, we are investigating the scope and limitations of this linker system with respect to its compatibility with acids and bases.

Acknowledgment

Dr. P. H. H. Hermkens (N.V. Organon, Oss, NL) is kindly acknowledged for providing an optimized procedure for the synthesis of **12**. These investigations are supported (in part) by the Netherlands Research Council for Chemical Sciences (CW) with financial aid from the Netherlands Technology Foundation (STW).

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12. In solution, the corresponding phenyl carbamate gave the cyclized product in 85% yield.
13. Typical experimental procedure: 500 mg of the resin (**15a–c**) was suspended in dry CH_2Cl_2 (5 mL). At 0 °C, the nucleophile (10 equiv.) and $BF_3{\cdot}OEt_2$ (3 equiv.) were added. After stirring for 17 h at rt, the resin was filtered off and washed with CH_2Cl_2, MeOH (repeat twice), CH_2Cl_2, Et_2O (repeat twice), CH_2Cl_2, and dried *in vacuo* (50 °C). To a suspension of this resin (**16a–c**) in THF (3 mL) was added a 3 M solution of NaOMe in MeOH (1.5 mL). After stirring the reaction mixture for 1 h at rt, the resin was filtered off and washed with CH_2Cl_2, MeOH (repeat twice) and CH_2Cl_2. The filtrate was partially concentrated and 1 M NaOH was added. The water layer was extracted twice with Et_2O. For entries 2 and 3: The solvent was evaporated and the residue was further purified by a SPE-column (Isolute, silica), solvent system: CH_2Cl_2/MeOH 100:0 → 95:5 → 90:10 → 0:100. For entries 1 and 4–6: The combined ether layers were extracted twice with 1 M HCl and the water layer was evaporated to give the products as their HCl salts. All products exhibited satisfactory ^{1}H-NMR, ^{13}C-NMR, IR and FABMS spectral data. Selected spectral data for compound **20**: IR (film): 3275 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 5.77–5.87 (m, 1H), 5.15 (dd, J = 7.1, 1.5 Hz, 1H), 5.1 (dd, J = 10.2, 0.7 Hz, 1H), 4.14 (br. s, 1H), 3.48–3.54 (m, 2H), 3.3–3.38 (m, 1H), 2.92 (t, J = 9.8 Hz, 1H), 2.31–2.45 (m, 2H), 1.98–2.02 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 141.82, 134.56, 131.39, 128.70, 119.96, 117.36, 58.22, 53.76, 43.29, 39.63, 38.59; HRMS (FAB) calcd. for $C_{13}H_{17}N^{79}Br$: 266.0544 (MH^+), found: 266.0552.