Novel parallel synthesis routes to nitrogen heterocycles via N-acyliminium ions.

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SUMMARY

NOVEL PARALLEL SYNTHESIS ROUTES TO NITROGEN HETEROCYCLES
VIA N-ACYLIMINIUM ION CHEMISTRY

Synthetic polymers from styrene are known since 1839, but it was not before 1963 that such a polymer was used as a synthetic tool. In that year in a landmark contribution, Merrifield described the first synthesis of a tetrapeptide on a solid support. There are several advantages to the synthesis of molecules on a solid phase: (i) since the product is attached to an insoluble polymer the workup can be reduced to a simple filtration step, thereby avoiding time consuming and tedious purification steps, (ii) due to this easy purification use of excess reagents to drive the reaction to completion is possible, and (iii) because the synthesis consists of repetitive cycles of deprotection, coupling and washing it is amenable to automated synthesis carried out on robotic systems. As a result, in the last decade much effort has been put in the ‘translation’ of reactions to the solid phase, the development of new linker systems for the attach/detachmen of molecules to the solid phase and the development of resin bound catalysts and reagents.

Given the importance of both iminium and N-acyliminium ion chemistry in classic organic synthesis, application of this type of chemistry to solid phase seems extremely valuable. In contrast with the examples of iminium ion reactions, only very few examples of N-acyliminium ion chemistry on the solid phase are known. Considering the expertise with the latter types of intermediates in our group, we set out explore their application on the solid phase. Thus, this thesis deals with the development of synthetic tools for the parallel synthesis of N-heterocycles via N-acyliminium ion chemistry. Two subjects are covered throughout the chapters: (i) the development and application of N-acyliminium ion chemistry on solid phase, and (ii) the N-acyliminium ion mediated synthesis of molecules that can be used as starting materials for further diversification via parallel chemistry.

In Chapter 1, general information on solid phase chemistry is presented as well as a short overview of the hitherto described examples of supported N-acyliminium ion chemistry.

In Chapter 2, the solid phase synthesis of a number of 2-substituted and 2,4-disubstituted pyrrolidines via N-acyliminium ion chemistry is described. The general strategy is depicted in eq 1.

\[ R_1 \quad H\quad N-y \quad R \]

A number of \( \gamma \)-aminoacetals were immobilised on resin via a carbamate function (viz. 1), thus incorporating the acyl moiety required for the N-acyliminium ion reaction in the linker system. Lewis acid mediated generation of the N-acyliminium ion 2 and trapping with
suitable C-nucleophiles provided the immobilised products 3, that were released from the resin by cleavage of the carbamate functionality to provide the pyrrolidines 4.

An important issue in this approach was the choice of the linker system. Although many linkers are known in literature, most of them are acid labile and therefore not compatible with the acidic conditions required to generate the N-acyliminium ion. Therefore, two tailor-made linker systems for N-acyliminium ion chemistry on solid support were designed and synthesised (Scheme 1).

Scheme 1

The synthesis of the linker systems started with the cesium carbonate mediated coupling of mercaptoethanol to Merrifield chloride resin 5 furnishing alcohol resin 6. Oxidation of the sulfide 6 using an excess of mCPBA to sulfone 7, followed by reaction with p-nitrophenyl chloroformate led to the 2-(alkylsulfonyl)ethoxycarbonyl (SEC) mixed carbonate resin 9. Alternatively, direct activation of resin 6 with p-nitrophenyl chloroformate led to the 2-(alkylthio)ethoxycarbonyl (TEC) mixed carbonate resin 8. Both resins were obtained in excellent yield as determined by elemental analysis.

Both linkers were - after conversion into the corresponding carbamates - tested for their stability towards a number of acids and bases. It was found that the TEC linker was completely stable under strongly basic and Lewis acidic conditions, but could be cleaved using strong protic acids such as TFA or triflic acid. The stability of the SEC linker was found to be complementary; it appeared stable towards protic and Lewis acids and weak tertiary amine bases such as DIPEA and NMM, but could be cleaved using strong bases such as DBU and NaOMe, operating via a β-elimination mechanism. An additional feature was that sulfide linker 8 could be converted into sulfone linker 9 allowing an even wider scope of reactions.

Resin 9 was functionalised with three γ-aminoacetalts (a-c) to give the N-acyliminium ion precursors 10a-c (Scheme 2). Treatment of these precursors with BF₃·OEt₂ generated the transient N-acyliminium ions, which were trapped by the nucleophiles to provide the product resins 11. Subsequent NaOMe mediated cleavage gave the pyrrolidine products 12.
It was found that allylsilanes were the best nucleophiles for these types of reactions. In case of the 2,4-disubstituted pyrrolidines, only the trans-diastereoisomer was obtained.

Scheme 2

![Scheme 2 diagram]

Chapter 3 deals with the solid phase synthesis of 2-substituted and 2,4-disubstituted piperidines via N-acyliminium ions. Initially, the same approach as for the pyrrolidines was applied. Six 8-aminoacetalts (a-f) were coupled with resin 9 to provide the precursors 13a-f (Scheme 3).

Scheme 3

![Scheme 3 diagram]

Surprisingly, treatment of these precursors with allyltrimethylsilane and BF₃·OEt₂, and subsequent cleavage not only provided the desired piperidine products, but also linear side products. To overcome this problem, the acetalts 13a-f were first cyclised in the presence of 1H-benzotriazole and a protic acid to the stable 2-Bt substituted precursors 14a-f. Subsequent N-acyliminium ion reaction and cleavage now provided solely the cyclic products 15. Again, in case of the 2,4-disubstituted piperidines, only the trans-diastereoisomer was obtained.

Chapter 4 features the synthesis of an 80-membered library of compounds starting from some of the 2-allylated products described in Chapters 2 and 3 (Scheme 4). Ozonolysis of the 2-allyl and 2-methallyl substituted heterocycles 16 led to the corresponding aldehydes and ketones 17, respectively. Subsequent reductive amination with five primary amines gave the secondary amines 18, that were reacted with four electrophiles to introduce the R²-substituent. The products 19 were then cleaved from the resin to provide the desired secondary amine products 20. It was found that the reductive amination worked best when
large excesses of the amine (50 equiv) and the reducing agent (NaHB(OAc)$_3$, 15 equiv) were used in the presence of acetic acid (75 equiv) on a resin with a low loading. In 72 out of 80 cases the desired product was obtained in reasonable yield and high purity. Additionally, the reductive amination with secondary amines and subsequent attempted dealkylation of the tertiary amine products is described.

**Scheme 4**

![Scheme 4](image)

Chapter 5 deals with the synthesis of 2,6-bridged 3-ketopiperazines using an N-acyliminium ion cyclisation as the key step. These products can be used as versatile scaffolds in combinatorial chemistry. The strategy is described in Scheme 5.

**Scheme 5**

![Scheme 5](image)
Suitably protected commercially available amino acids 21 and 22 were reacted using standard peptide coupling protocols to provide the dipeptides 23. Subsequent amine deprotection induced cyclisation to the corresponding diketopiperazines, which were methoxycarbonylated to provide the precursors 24. Chemoselective reduction of the activated C6 carbonyl of the diketopiperazine provided the N,O-hemiacetal 25. Acid-induced cleavage then generated the N-acyliminium intermediate 26, which was trapped by intramolecular nucleophilic attack of the side chain at the C2 position to provide the desired 2,6-bridged products 27.

In this chapter, the scope of the nucleophile in the cyclisation reaction was studied. It was found that aromatic, heteroaromatic and non-aromatic π-nucleophiles could be used. The successful cyclisation of a precursor containing an additional trans-C5 methyl group was also described. Finally, the cyclisation of a cis-C5 methyl group containing precursor was feasible using a highly nucleophilic indole substituted C2 side chain. The latter types of products are very interesting since this substitution pattern is also found in several natural products such as ecteinascidins, saframycins, safracins and quinocarcins, which all show antitumor or antibiotic activity.