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

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CHAPTER 1

INTRODUCTION

1.1 Brief History of Solid Phase 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 (Scheme 1.1).

Scheme 1.1

![Image of chemical reaction scheme]

1. styrene/ divinylbenzene copolymer

2. Cbz-AA1-OH, NEt3, dioxane

3. 30% HBr/AcOH, then NEt3

4. Cbz-AA2-OH, DCC, DMF

5. Cbz-AA3-OH, DCC, DMF

6. Cbz-AA4-OH, DCC, DMF

7. 10% 2 M NaOH/EtOH (2x)

Key:

a) Cbz-AA1-OH, NEt3, dioxane; b) 30% HBr/AcOH, then NEt3; c) Cbz-AA2-OH, DCC, DMF; d) Cbz-AA3-OH, DCC, DMF; e) Cbz-AA4-OH, DCC, DMF; f) 10% 2 M NaOH/EtOH (2x).

A Cbz protected amino acid was coupled to the chloromethylated styrene/divinylbenzene copolymer 1 to obtain the immobilised amino acid 2. Subsequent deprotection of the amine, neutralisation and coupling of the second amino acid provided the dipeptide 3. These steps were repeated twice to give the resin bound tetrapeptide 4. Another Cbz-deprotection, followed by basic hydrolysis of the ester function eventually provided the desired tetrapeptide 5. It appeared that there were several advantages to application of this solid phase protocol: (i) since the product was attached to an insoluble polymer the workup could be reduced to a simple filtration step, thereby avoiding time consuming and tedious purification steps, (ii) due to the easy purification use of excess reagents to drive the reaction to completion was possible, and (iii) because the synthesis consisted of repetitive cycles of deprotection, coupling and washing, it was amenable to automated synthesis carried out on robotic systems. Some early contributions to its use for general organic synthetic purposes were made by Leznoff, Fréchet and Rapoport. However, until the early nineties, the potential of solid phase organic synthesis was not widely recognized and its use was essentially limited to polypeptide and oligonucleotide chemistry. The renaissance of solid phase synthesis was initiated by the advent of novel high throughput methods for biological screening in the pharmaceutical and agrochemical
industry. Considering the history of solid phase reactions, it is not surprising that the first ideas for the combinatorial synthesis of compound libraries were reported by chemists such as Geysen and Houghten who were working in the polypeptide area. In the beginning, there was a strong focus on libraries *via* solid phase methodology available from peptide and oligonucleotide chemistry, leading to the synthesis of mixtures of thousands of compounds using the so-called ‘split synthesis’ method. With a progressing sophistication of the solid supported synthetic strategies and an increasing desire for more complex products, the combinatorial approaches gradually shifted towards the parallel synthesis of small libraries of compounds; nowadays most libraries are actually synthesised as arrays of single compounds. As a result, in the last decade, a lot of effort has been put in the ‘translation’ of reactions to a solid support, the development of new linker systems for the attach/detachment of molecules to the solid phase, and the development of resin bound catalysts and reagents. Considering the progress made in the development of automated synthesis and the still increasing demand for new compounds by the pharmaceutical industry it is clear that solid phase chemistry will be an active field of research for years to come.

1.2 Iminium Ion Chemistry

1.2.1 Iminium Ion Chemistry on Solid Support

Solution phase iminium ion reactions are very well known, and have been frequently applied in the synthesis of biologically active substances and natural products. Despite the wide scope, examples of such reactions on a solid support do exist, but are certainly not as abundant.

\[
\begin{align*}
R^1 & \rightarrow R^2 \\
R^3 & \rightarrow \text{N} \rightarrow R^4
\end{align*}
\]

The iminium ion (6, eq 1.1) is most often generated *in situ*, but can be a stable species (e.g. Eschenmoser salt). The iminium ion is the reactive intermediate in the well-known Mannich reaction and has been used in inter- and intramolecular reactions. Only relatively few examples of iminium ion reactions on solid support are known, the majority of which are Pictet-Spengler reactions and Ugi multicomponent reactions. A representative example of Li and coworkers is shown in Scheme 1.2 (*vide infra*). Removal of the Fmoc-group from the Wang resin bound amino acid 7, followed by attachment of the second amino acid using standard coupling conditions and subsequent coupling of Fmoc-tryptophane using the same protocol and deprotection afforded precursor 8. The immobilised tryptophane was then reacted with Fmoc-glycinal using 1% of TFA in dichloromethane to generate the tetrahydro-β-carbole derivative 9 as an approximate 1:1 mixture of diastereoisomers. Subsequent coupling of two additional amino acids using the
The aforementioned protocol delivered the desired intermediate 10, which was deprotected and cleaved from the resin using TFA to provide peptidomimetic 11.

**Scheme 1.2**

An intermolecular iminium ion reaction on solid support was reported by Kobayashi and coworkers. A 48-membered library was constructed using a Mannich-type three component reaction. (eq 1.2).

An aldehyde and an aniline were condensed to generate the corresponding imine. Activation of this imine with scandium triflate generated an iminium ion that was trapped by the resin bound enol ether 12. Subsequent cleavage of products 13 was effected using lithium borohydride to provide γ-amino alcohols 14 in high yields (55–88%).
1.2.2 N-Acyliminium Ion Chemistry on Solid Support

The electrophilicity of the iminium ion can be greatly enhanced by attaching an electron-withdrawing carbonyl group onto the nitrogen atom (viz. 16, eq 1.3).21

\[
\begin{align*}
&\text{R}^1\text{LG}\text{R}^2 \\
\rightarrow \\
&\text{R}^3\text{N}^+\text{R}^4
\end{align*}
\]

15

\[
\begin{align*}
&\text{R}^1\text{+R}^2 \\
\rightarrow \\
&\text{R}^3\text{N}^+\text{R}^4
\end{align*}
\]

16

(1.3)

The most usual way to generate this so-called N-acyliminium ion is by Lewis or protic acid induced cleavage of an acetal such as 15. In most cases, the leaving group is a hydroxyl or alkoxy group. Because of the high instability of these types of intermediates, N-acyliminium ions are always generated in situ. Due to its enhanced reactivity as compared to iminium ions, the scope of the nucleophiles that can be used in intermolecular reactions is different. An array of nucleophiles has been used including allylsilanes, enol ethers, cuprates, trimethylsilyl cyanide and various electron rich aromatic rings. At the start of this project, application of N-acyliminium ion chemistry for the production of libraries via solid phase methods was rare.

The first example of N-acyliminium ion chemistry on resin was reported by Wipf and Cunningham,22 who developed a solid phase protocol for the Biginelli23 dihydropyrimidine synthesis (Scheme 1.3).

Scheme 1.3

17 \rightarrow a \rightarrow 18 \rightarrow b

19 \rightarrow \rightarrow 20

21 \rightarrow 22

key: a) 4-Ureidobutyric acid, EDCI, DMAP, DMF; b) R'CHO, R'OOC(O)CH=CHC(O)R^3, HCl, THF; c) TFA/CH_2Cl_2.
Commercially available Wang resin 17 was esterified with 4-ureidobutyric acid to provide immobilised urea 18, to which an aromatic aldehyde, a β-ketoester and catalytic HCl were added. The initially formed N-acyliminium ion 19 was intercepted by the β-ketoester to provide intermediate 20, which spontaneously lost water to generate the products 21, which were cleaved from the resin using TFA. In this way a small library of ten dihydropyrimidines 22 was synthesised in high yields of 80-98%. Considering the commercial availability of a large number of aldehydes and the straightforward synthesis of β-ketoesters, very large numbers of dihydropyrimidines are potentially available. More recently, two adaptations of this protocol, using an immobilised β-ketoester and a polymer bound thiouronium salt, respectively, were reported by Kappe and coworkers.\textsuperscript{24}

Patek et al. reported the synthesis of a supported precursor for solution phase N-acyliminium ion reactions (Scheme 1.4).\textsuperscript{25}

\begin{center}
\textbf{Scheme 1.4}
\end{center}

\begin{center}
\begin{tikzpicture}
\node (T) at (0,0) {$\text{T}$};
\node (23) at (-1.5,-1) {$\text{HO}$};
\node (24) at (-1.5,-2) {$\text{Br}\text{OEt}$};
\node (25) at (1.5,-1) {$\text{R}^1\text{Et}$};
\node (26) at (1.5,-2) {$\text{H}_2\text{N}$};
\node (27) at (1.5,-3) {$\text{HNu}$};
\node (28) at (1.5,-4) {$\text{HNu}$};
\node (29) at (1.5,-5) {$\text{HNu}$};
\node (30) at (1.5,-6) {$\text{HNu}$};

\draw[->] (T) -- (23);
\draw[->] (23) -- (24);
\draw[->] (24) -- (25);
\draw[->] (25) -- (26);
\draw[->] (26) -- (27);
\draw[->] (27) -- (28);
\draw[->] (28) -- (29);
\draw[->] (29) -- (30);

\node at (1.5,-7) {$\text{R}^1 = \text{Bn}, \text{MeO(}CH_2\text{)}_2$};
\node at (1.5,-8) {$\text{R}^2 = \text{Me}, \text{Bn}, ^{1}\text{Pr}$};
\node at (1.5,-9) {$n = 1, 2$};

\end{tikzpicture}
\end{center}

\textit{key:} a) 2-Bromo-1,1-diethoxyethane, quinolinium p-toluenesulfonate, 1,2-dichloroethane; b) 2M R'NH$_2$, DMSO; c) Fmoc-AA2-OH, TFFH, DIPEA, 1,2-dichloroethane, then 20% piperidine/DMF; d) HNu(CH$_2$)$_2$COOH, TFFH, DIPEA, 1,2-dichloroethane; e) HCOOH.

Functionalisation of polyethylene grafted polystyrene resin 23 (tentagel-OH) with α-bromoacetaldehyde diethylacetal, followed by displacement of the bromide with an amine generated glycinal diethyl acetal equivalent 25. Coupling of a second amino acid and Fmoc-deprotection provided dipeptide 26, which was acylated with a nucleophile to give the N-acyliminium ion precursor 27. Formic acid induced cleavage of this precursor generated the oxycarbenium ion 28, that was trapped intramolecularly by the amide nitrogen. Subsequent abstraction of the second alkoxy group generated the N-acyliminium ion 29, which
immediately reacted with the nucleophile to give product 30 in reasonable yield and high purity. The nucleophile was either the side chain or the nitrogen atom of an amino acid.

An example where the reactive intermediate remained on the solid support was reported by Munoz and coworkers.²⁶ They adapted the work of Comins²⁷ to the solid phase to synthesise a number of 2-substituted N-acyl-dihydro-4-pyridones (Scheme 1.5).

**Scheme 1.5**

![Scheme 1.5](image)

key: a) 4-Hydroxypyridine, PPh₃, DEAD, THF/DMF; b) R⁴C(O)Cl, THF; c) R⁵MgX, THF; d) 1M TFA/THF.

Commercially available Wang resin 17 was loaded with 4-hydroxypyridine under Mitsunobu conditions to afford ether 31. Treatment of this pyridine derivative with several acid chlorides afforded the intermediate N-acylpyridinium ions 32 that were reacted with different Grignard reagents to afford the 1,2-dihydropyridines 33. Cleavage of the products was effected with 1M TFA in THF to provide the 2-substituted N-acyl-dihydro-4-pyridones 34 in low to reasonable yields and in good purity.

The first example of a carbamate tethered N-acyliminium ion on solid support was reported by Meester et al.,²⁸ who translated a solution phase protocol developed by Veenstra et al.²⁹ for the synthesis of protected homoallylic amines to the solid support (Scheme 1.6).

**Scheme 1.6**

![Scheme 1.6](image)

key: a) 4-NO₂C₆H₄OC(O)Cl, NMM, CH₂Cl₂; b) NH₃/MeOH, DMF; c) BF₃·OEt₂, MeCN; d) 50 % TFA/CH₂Cl₂.
Commercially available Wang resin 17 was activated using 4-nitrophenyl chloroformate and reacted with ammonia to provide the immobilised carbamate 35. This carbamate was reacted with an aromatic aldehyde and an allylsilane under Lewis acidic conditions in a one-pot three component N-acyliminium ion reaction. Lewis acid mediated removal of the hydroxy group from the intermediate aminal 36 provided the transient N-acyliminium ion 37, which was trapped by the allylsilane to provide the immobilised products 38. Subsequent TFA mediated cleavage afforded the homoallylic amines 39. Using three allylsilanes and 28 aromatic aldehydes, a 44-membered library was synthesised. It was found that the reaction proceeded best using a large excess of aldehyde (20 equiv) and allylsilane (10 equiv) and only a slight excess of BF₃·OEt₂ (1.1 equiv) in order to avoid premature cleavage of the product. The best yields were obtained with electron rich aldehydes, whereas electron poor or aliphatic aldehydes did not react at all. Use of different nucleophiles, such as enol ethers or malonates, did not give any product either.

A related example was reported by Mioskowski and coworkers.³⁰ Merrifield resin 1 was coupled with 4-hydroxybenzamide to give the immobilised amide 40 (Scheme 1.7).

**Scheme 1.7**

![Scheme 1.7](image)

key: a) 4-Hydroxybenzamide, NaH, DMF; b) RCHO, TFA, HC(OMe)₃, THF; c) allyltrimethylsilane, BF₃·OEt₂, CH₂Cl₂; d) 60% TFA/CH₂Cl₂.

Treatment of this amide with an aldehyde in the presence of TFA and triethyl orthoformate provided the stable aminal 41. In this case, not only electron rich aromatic aldehydes, but also electron poor aromatic aldehydes, heteroaromatic aldehydes and aliphatic aldehydes could be used to provide the aminals in fair to good yields (45–85%). Two of these precursors were treated with BF₃·OEt₂ to generate the intermediate N-acyliminium ion, which was trapped by allyltrimethylsilane. Subsequent cleavage using TFA provided the homoallylic amides 43a and 43b in good yields.

An N-acyl variant of the Pictet-Spengler condensation was published by Wang and Ganesan in the synthesis of demethoxyfumitremorgine C analogues (Scheme 1.8).³¹
The commercially available Fmoc-(S)-tryptophan immobilised on Wang-resin (44) was deprotected using 20% of piperidine in DMF and the free amine was reacted with several aromatic, aliphatic and unsaturated aldehydes. Treatment of the resulting imines 45 with Fmoc-protected amino acid chlorides induced the N-acyliminium ion Pictet-Spengler cyclisation, together with simultaneous introduction of the \( R^2 \) group to provide the tetrahydro-\( \beta \)-carboline 46. Subsequent Fmoc-deprotection by piperidine, with concomitant cyclorelease via diketopiperazine formation, afforded the desired demethoxyfumitremorgine C analogues 47 as approximately 1:1 cis/trans-mixtures in reasonable to good yields (36-88%) over four steps. An identical approach was reported by van Loevezijn et al., who used Fmoc-chloride instead of amino acid chlorides, to induce the N-acyl Pictet Spengler reaction. Subsequent deprotection of the resulting Fmoc-protected tetrahydro-\( \beta \)-carbolines and coupling with an amino acid provided the same products (46, vide supra) as Ganesan. Although the latter route is two steps longer, it has the advantage that it only uses commercially available starting materials.

1.3 Purpose and Outline of the Investigation

This thesis deals with the development of novel synthetic tools for the solid phase synthesis of CNS active compounds. Two subjects are covered: (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 combinatorial chemistry.

In Chapter 2, the development of a tailor-made carbamate linker system for N-acyliminium ion chemistry on solid support is described. The stability of the linker system was determined and it was then used in the synthesis of a number of 2-substituted and 2,4-
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disubstituted pyrrolidines starting from immobilised linear γ-amino acetal. The scope with respect to the nucleophiles that can be used in the intermolecular N-acyliminium ion coupling was determined.

A modification of this protocol is described in Chapter 3, where immobilised δ-amino acetals were first cyclised to 2-benzotriazolyl-substituted piperidines. These precursors were then further derivatised via an N-acyliminium ion reaction with several nucleophiles to afford a number of 2-substituted and 2,4-disubstituted piperidines.

In Chapter 4, the synthesis of an 80-membered library is described. The library was synthesised by derivatisation of some of the products described in Chapters 2 and 3. The key steps were the ozonolysis of immobilised 2-allylated pyrrolidines and piperidines to generate the corresponding aldehydes and ketones. Reductive amination with various primary amines and subsequent reaction of the resulting secondary amines with suitable electrophiles generated a diamine library.

The solution phase synthesis of 2,6-bridged 3-ketopiperazines is described in Chapter 5. The key step in the synthesis is the cyclisation of a monoketopiperazine side chain onto an N-acyliminium ion. A systematic study of the scope of the nucleophilic side chain is described. Furthermore, the stereoselective introduction of additional groups at the C5 position was investigated. The final products may be attractive starting materials for library synthesis.

Parts of this thesis have been published or will be published in the near future. 33

1.4 References and Notes

Chapter 1


16 Mannich, C.; Arch. Pharm. 1912, 250, 647.


Introduction
