Sequential 1,4- and 1,2-addition reactions to α,β-unsaturated N-acyliminium ions: a new strategy for the synthesis of spiro and bridged heterocycles

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Sequential 1,4- and 1,2-Addition Reactions to α,β-Unsaturated N-acyliminium Ions: A New Strategy for the Synthesis of Spiro and Bridged Heterocycles

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ABSTRACT

Novel bicyclic and tetracyclic spirocycles and tricyclic bridged heterocyclic systems can be readily prepared from sequential 1,4- and 1,2-addition reactions of latent bis-nucleophiles to α,β-unsatuated N-acyliminium ions.

N-acyliminium ions are well established important reactive intermediates in C-C and C-heteroatom bond forming reactions. Both intermolecular\textsuperscript{1,ab,c,d} and intramolecular\textsuperscript{e,f,g} versions have been extensively developed, the latter variants providing access to novel polycyclic, spirocyclic and bridged heterocyclic ring structures. In stark contrast, the chemistry of α,β-unsatuated N-acyliminium ions (e.g. 1 in Scheme 1) is largely undeveloped.\textsuperscript{2−4} In principle, these are attractive reactive intermediates for the one-pot synthesis of novel di-functionalized heterocycles e.g. 2 (Scheme 1) because of their potential for sequential 1,4- and 1,2-addition reactions with two nucleophiles (Nu\textsubscript{1} and Nu\textsubscript{2}) under acidic conditions. Significantly, when these two nucleophiles are tethered or latent bis-nucleophiles then


novel spirocyclic and bridged heterocycles 2 should be realized. These types of molecular architectures are common in bioactive natural products and therefore such a synthetic strategy would be expected to provide valuable scaffolds for new drug discovery and natural product synthesis programs. We report here the realization of this approach and the synthesis of new bi-, tri-, and tetra heterocyclic systems.

Scheme 1. Proposed reactivity of α,β-unsaturated N-acyliminium ions 1

To examine the feasibility of this approach the α,β-unsaturated N-acyliminium ion precursor 3a was treated with allyltrimethylsilane (1.2 equiv) in the presence of BF3•Et2O (2.0 equiv) in CH2Cl2 solution at 0 °C to rt for 1 h. This reaction rapidly furnished the (E)-enamide 4a (Scheme 2, see Supporting Information for this stereochemical assignment). However, extended reaction times (rt, 18 h) provided the novel spiro-tricyclic compound 5a in 66% yield, after purification by column chromatography, and in high diastereomeric excess (dr >98.2). 5 A NOESY correlation between the two methine protons in 5a allowed the assignment of its configuration. The observed stereochemical outcome is consistent with the mechanism shown in Scheme 2 in which the key spirocyclic-carbon bond forming step involves attack by the alkene to the iminium ion carbon from its less hindered face. Neighboring group participation by the OBn would lead to formation of the furan ring and loss of the Bn group. These reaction conditions were extended to the α,β-unsaturated N-acyliminium ion precursors 3b–d to give the corresponding spiro-tricyclic compounds 5b–d.

Scheme 2. Synthesis of spirotricycles 5a–d

5a (R = -CH2CH=CH2) (66%; dr > 98:2)
5b (R = -(CH2)2CH=CH2) (74%; dr > 98:2)
5c (R = -(CH2)3CH=CH2) (75%; dr > 98:2)
5d (R = -CH2Ph) (78%; dr > 98:2)

in good yields and high diastereomeric excess (dr >98:2) (Scheme 2).7 The piperidinone analogue 6 also gave the corresponding spiro-tricyclic 7 in 64% yield but under more forcing reaction conditions (80 °C, Scheme 3).

The analogous BF3•Et2O (2 equiv) promoted reactions of 3a–3d with 2-methallytrimethylsilane (1.2 equiv) produced the spiro-bicyclic products 8a–d in good yields.

Scheme 3. Synthesis of spirotricycle 7

(5) The same results were obtained from employing either 3a–d as a mixture of diastereomers or as the pure major or minor diastereomer.
Scheme 4. Synthesis of the spirobicycles 8

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
<th>DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a-3d BF₃•Et₂O, CH₂Cl₂, 0 °C to rt, 4 h</td>
<td>8a</td>
<td>77%</td>
<td>80:20</td>
</tr>
<tr>
<td>3a-3d BF₃•Et₂O, CH₂Cl₂, 0 °C to rt, 4 h</td>
<td>8b</td>
<td>76%</td>
<td>85:15</td>
</tr>
<tr>
<td>3a-3d BF₃•Et₂O, CH₂Cl₂, 0 °C to rt, 4 h</td>
<td>8c</td>
<td>83%</td>
<td>75:25</td>
</tr>
<tr>
<td>3a-3d BF₃•Et₂O, CH₂Cl₂, 0 °C to rt, 4 h</td>
<td>8d</td>
<td>82%</td>
<td>85:15</td>
</tr>
</tbody>
</table>

Scheme 5. Synthesis of bridged tricyclic compounds 13a,b and 14a,b and proposed mechanism

The bicyclic α,β-unsaturated N-acyliminium ion precursor 9 was treated separately with allyl- and 2-methallytrimethylsilane in the presence of BF₃•Et₂O. Under short reaction times (rt, 1 h) the adduct 10 (R = H, Me) could be isolated as a 1:1 mixture of separable diastereomers. The lack of diastereoselectivity is most likely due to the remotness of the stereogenic center in precursor 9 to the site of the first addition. Retreatment of the individual diastereomers of 10 to the above reaction conditions for 18 h gave pure diastereomers of the tricyclic bridged enamides 13a,b and 14a,b, respectively. Alternatively, treatment of 9 separately with allyl- and 2-methallytrimethylsilane for 18 h gave enamides 13a,b and 14a,b, respectively, as 1:1 mixtures of separable diastereomers. The identity of these compounds was established by 1D and 2D NMR spectroscopic analysis (see Supporting Information). The relative configuration of the methyl bearing methine group in 14a,b was established as exo with respect to the methylene bridge from 1D NOE difference experiments (see Supporting Information). A mechanism to explain the formation of these products is provided in Scheme 5. The initially formed tricyclic carbocation intermediate 11 undergoes a transannular 1,5-hydride shift to give the N-stabilized carbocation intermediate 12 which then gives enamine 13 or 14 upon loss of a proton. Such transannular 1,5-hydride

![Diagram](image-url)
shifts have precedent. Cases involving N-stabilization however, are rare. Further evidence for the enamide structure 13a was its reduction to 15 with NaCNBH₃ (Scheme 6). This result indicated that indeed the N-acyliminium ion intermediate 12 can be formed.

**Scheme 6. Reduction of tricyclic compound 13a**

![Chemical structure]

To further demonstrate the scope of these addition-cyclization reactions, compound 3a was treated separately with indole, 1,2-dimethoxybenzene and 1,2,3-trimethoxybenzene (1.2 equiv) and BF₃•Et₂O (2.0 equiv). In each case these reactions produced the corresponding spirocyclic compounds, 16a-c, respectively (Scheme 7, see Supporting Information for stereochemical assignments). In these reactions the electron rich aromatic component reacted via sequential intermolecular 1,4- and intramolecular 1,2-addition reactions, analogous to the reactions of 3a with allyltrimethysilane. The reasons for the high diastereoselectivity observed for only 16b are not clear. In the case of \(N,N\)-diethylyaminilane, the initial product was the 1,4-addition product (not shown) however when the reaction was heated at 80 °C in toluene the conjugated pyrrolidinone 16d was formed in 74% yield as a result of double bond migration from the exocyclic position to conjugation with the lactam carbonyl. In contrast, the reaction of 3a with benzofuran/BF₃•Et₂O at 80 °C gave the novel tetracyclic compound 16e from further Michael addition then formal 1,2-elimination of OMe from a benzofuran intermediate analogous to 16d.

The reaction of 17 (debenzyloxy 3d) with \(N,N\)-diethylyaminilane/BF₃•Et₂O at rt (2 h) gave the initial 1,4-addition product 18. Further treatment of 18 with indole/BF₃•Et₂O gave the pyrrolidinone 19, demonstrating the potential of this method for preparing 5,5-disubstituted pyrrolidinones (Scheme 8).

In conclusion, we have demonstrated that the sequential 1,4- and 1,2-addition reactions of latent bisnucleophiles to \(\alpha,\beta\)-unsaturated N-acyliminium ions allows for rapid access to novel spirocyclic, bridged and other multicyclic


**Scheme 7. Synthesis of heterocycles 16**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a + ArH</td>
<td>16</td>
</tr>
<tr>
<td>BF₃•Et₂O</td>
<td>solvent, temp</td>
</tr>
<tr>
<td>16a</td>
<td>(45%; dr = 75:25)²</td>
</tr>
<tr>
<td>16b(X = H)</td>
<td>(68%; dr &gt; 98:2)²</td>
</tr>
<tr>
<td>16c(X = OMe)</td>
<td>(70%, dr &gt; 70:30)²</td>
</tr>
<tr>
<td>16d</td>
<td>(74%)³</td>
</tr>
<tr>
<td>16e</td>
<td>(61%)³</td>
</tr>
</tbody>
</table>

**Scheme 8. Synthesis of substituted pyrrolidinones 18 and 19**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF₃•Et₂O</td>
<td>Et₂NCH₂H</td>
</tr>
<tr>
<td>Et₂NC₆H₅, CH₂Cl₂</td>
<td>0°C, 2 h (79%)</td>
</tr>
<tr>
<td>indole, CH₂Cl₂</td>
<td>0°C to rt, 3 h (45%)</td>
</tr>
</tbody>
</table>

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Supporting Information Available. Synthetic methods and characterization data for all compounds.
Copies of the $^1\text{H}$ and $^{13}\text{C}$ NMR spectra of all new compounds.

The authors declare no competing financial interest.