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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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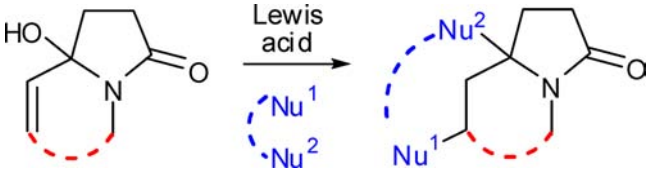
ABSTRACT



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-unsaturated *N*-acyliminium ions.

N-Acyliminium ions are well established important reactive intermediates in C−C and C−heteroatom bond forming reactions.[1] Both intermolecular[1a,b,e,f] and intramolecular[1a−d,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-unsaturated *N*-acyliminium ions (e.g., **1** in Scheme 1) is largely undeveloped.[2−4] In principle, these are attractive reactive intermediates for the one-pot synthesis of novel difunctionalized heterocycles, e.g. **2** (Scheme 1), because of their potential for sequential 1,4- and 1,2-addition reactions with two nucleophiles (Nu^1 and Nu^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,[4] 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 tetraheterocyclic systems.

To examine the feasibily of this approach the α,β-unsaturated *N*-acyliminium ion precursor **3a** was treated with allyltrimethylsilane (1.2 equiv) in the presence of $BF_3 \cdot Et_2O$ (2.0 equiv) in CH_2Cl_2 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

(1) For reviews on *N*-acyliminium ions, see: (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856. (c) Maryanoff, B. E.; Zhang, H.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628. (d) Gaskell, S. N.; Duffy, L. J.; Allin, S. M. *Nat. Prod. Commun.* **2008**, *3*, 1825–1835. (e) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339–368. (f) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513–541. (g) Martinez-Estibalez, U.; Gomez-SanJuan, A.; Garcia-Calvo, O.; Aranzamendi, E.; Lete, E.; Sotomayor, N. *Eur. J. Org. Chem.* **2011**, 3610–3633.

(2) For Diels−Alder reactions of α,β-unsaturated *N*-acyliminium ions with dienes, see: (a) Zou, Y.; Che, Q.; Snider, B. B. *Org. Lett.* **2006**, *8*, 5605–5608. (b) O'Connor, P. D.; Körber, K.; Brimble, M. A. *Synlett* **2008**, 1036–1038.

(3) For addition reactions of nucleophiles to cyclic α,β-unsaturated *N*-acyliminium ions derived from *N*-acyl-1,2-dihydropyridines, see: (a) Kozikowski, A. P.; Park, P.-u. *J. Org. Chem.* **1984**, *49*, 1676–1678. (b) Torii, S.; Inokuchi, T.; Takagishi, S.; Akahoshi, F.; Uneyama, K. *Chem. Lett.* **1987**, 639–642. (c) Hanson, G. J.; Russell, M. A. *Tetrahedron Lett.* **1989**, *30*, 5751–5754. (d) Alegret, C.; Riera, A. *J. Org. Chem.* **2008**, *73*, 8661–8664. (e) For an exocyclic version, see: O'Conner, P. D.; Marino, M. G.; Guéret, S. M.; Brimble, M. A. *J. Org. Chem.* **2009**, *74*, 8893–8896.

(4) See for example: (a) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165–193. (b) Takao, K.-i.; Tadano, K.-i. *Heterocycles* **2010**, *81*, 1603–1629.

(5) The same results were obtained from employing **3a**−**d** either as a mixture of diastereomers or as the pure major or minor diastereomer.

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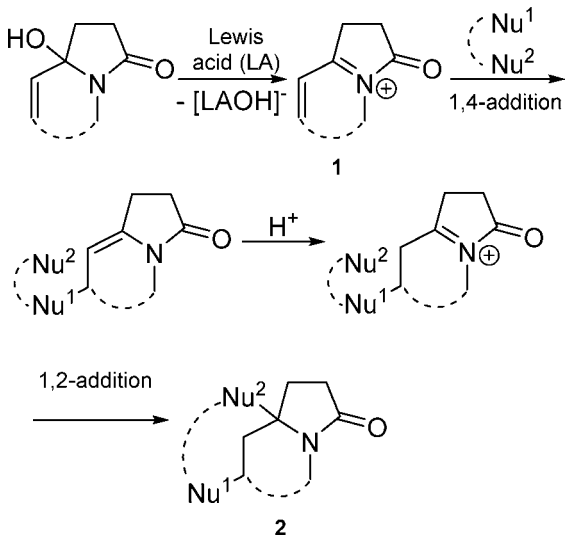
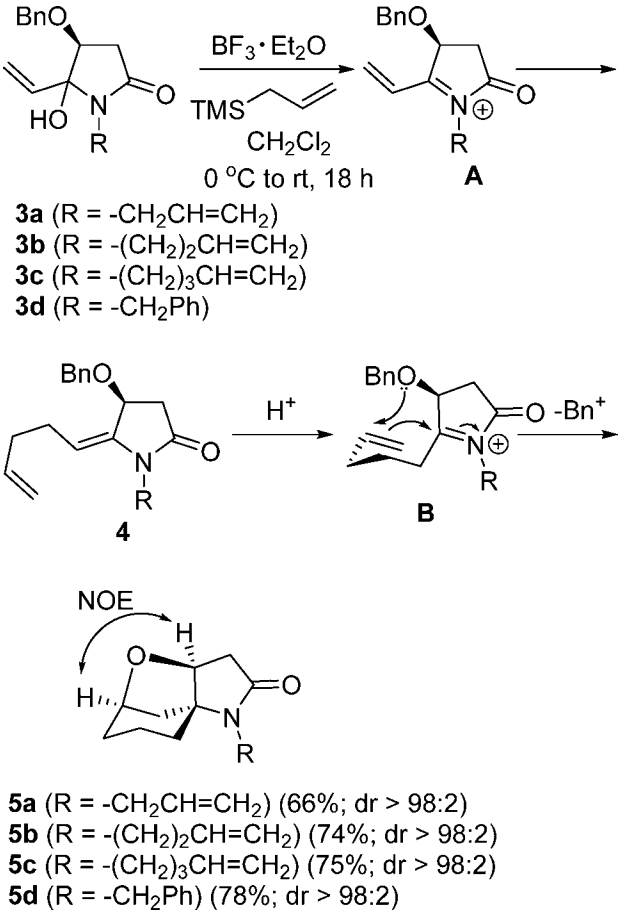
Scheme 1. Proposed Reactivity of α,β-Unsaturated *N*-Acyliminium Ions **1**



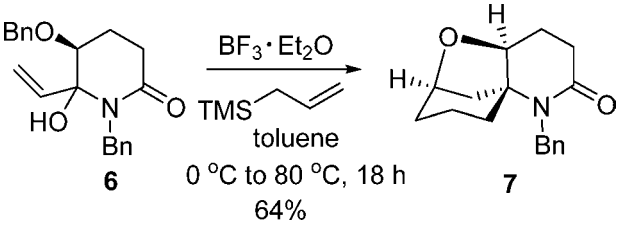
Scheme 2. Synthesis of Spirotricycles **5a**–**d**



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** in good yields and high diastereomeric excess (dr >98:2) (Scheme 2).[5] The piperidinone analogue **6** also gave the corresponding spirotricyclic **7** in 64% yield but under more forcing reaction conditions (80 °C, Scheme 3).[6,7]

The analogous $BF_3 \cdot Et_2O$ (2 equiv) promoted reactions of **3a**–**3d** with 2-methallyltrimethylsilane (1.2 equiv) produced the spiro-bicyclic products **8a**–**d** in good yields and as mixtures of diastereomers (dr = 75–85:25–15). The position of the double bond in compounds **8a**–**d** was evident from the singlet multiplicity of the alkene methine proton in their ^1H NMR spectra and the correlation of this proton with the methine proton, C*H*(OBn), in the 1D NOE difference spectrum of **8a**. In these examples, the OBn group remained intact most likely due to the more

Scheme 3. Synthesis of Spirotricycle **7**



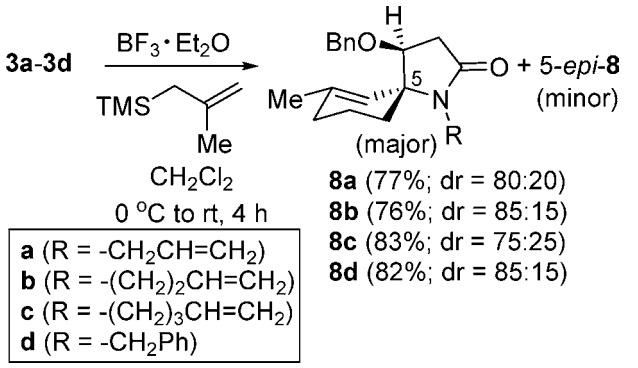
hindered nature of the incipient spirocyclic tertiary carbocation intermediate, analogous to **B** which prefers to undergo β-elimination rather than a substitution reaction. Indeed OBn participation in these cases would be thermodynamically less likely due to the smaller difference in stability between the aforementioned tertiary carbocation intermediate and the benzyl cation that could result from OBn participation.

The 4-deoxybenzyl analogue of **3d** gave the diene **4e** and the spirocycle **8e** upon treatment with allyltrimethylsilane/$BF_3 \cdot Et_2O$ and 2-methallyltrimethylsilane/$BF_3 \cdot Et_2O$, respectively (Figure 1). The result of the former reaction clearly indicated the importance of the OBn group in

(6) For pioneering work on the synthesis of spirocyclic heterocycles from solvolysis reactions of alkene tethered saturated *N*-acyliminium ion precursors, see: (a) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, 1515–1518. (b) Evans, D. A.; Thomas, E. W. *Tetrahedron Lett.* **1979**, 411–414.

(7) For some recent examples of the synthesis of spirocyclic heterocycles from alkene tethered saturated *N*-acyliminium ion precursors, see: (a) Abe, H.; Takaya, K.-i.; Watanabe, K.; Aoyagi, S.; Kibayashi, C.; Katoh, T. *Heterocycles* **2010**, *82*, 257–261. (b) Liu, J.; Swidorski, J. J.; Peters, S. D.; Hsung, R. P. *J. Org. Chem.* **2005**, *70*, 3898–3902. (c) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2005**, *127*, 1473–1480. (d) Liu, J.; Hsung, R. P.; Peters, S. D. *Org. Lett.* **2004**, *6*, 3989–3992.

Scheme 4. Synthesis of the Spirobicycles **8**



promoting the spirocyclization-ether bond forming process. The result of the latter was consistent with the results shown in Scheme 4.

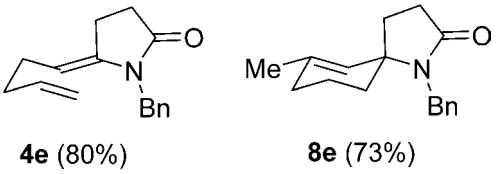
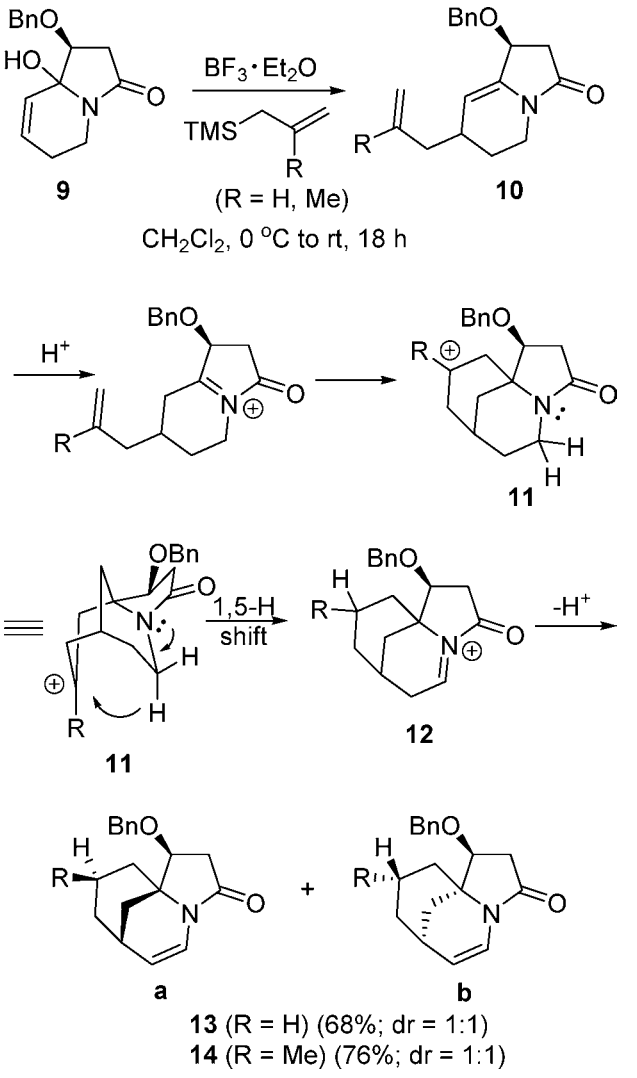


Figure 1. Synthesis of compounds **4e** and **8e**.

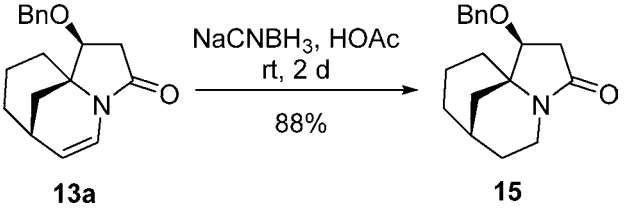
The bicyclic α,β-unsaturated *N*-acyliminium ion precursor **9** was treated separately with allyl- and 2-methallyltrimethylsilane in the presence of $BF_3 \cdot Et_2O$. Under short reaction times (rt, 1 h) the adduct **10** (R = H, Me) could be isolated as a 1:1 mixture of separable diastereomers. The lack of diastereoselectivity is most likely due to the remoteness of the stereogenic center in precursor **9** in relation 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** and **13b**, respectively. Alternatively, treatment of **9** separately with allyl- and 2-methallyltrimethylsilane 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

Scheme 5. Synthesis of Bridged Tricyclic Compounds **13a**,**b** and **14a**,**b** and Proposed Mechanism



transannular 1,5-hydride shift to give the *N*-stabilized carbocation intermediate **12** which then gives enamide **13** or **14** upon loss of a proton. Such transannular 1,5-hydride shifts have precedent.[8] Cases involving *N*-stabilization, however, are rare. Further evidence for the enamide structure **13a** was its reduction to **15** with $NaCNBH_3$ (Scheme 6). This result indicated that indeed the *N*-acyliminium ion intermediate **12** can be formed.

Scheme 6. Reduction of Tricyclic Compound **13a**



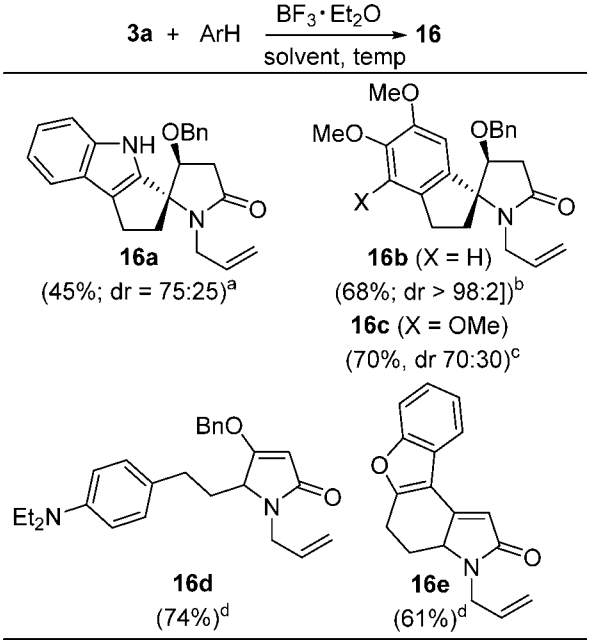
(8) (a) Rademacher, P.; Mohr, P. C. *Org. Biomol. Chem.* **2007**, *5*, 2698–2703. (b) Guo, X.; Paquette, L. A. *J. Org. Chem.* **2005**, *70*, 315–320. (c) Magnus, P.; Ujjainwalla, F.; Westwood, N.; Lynch, V. *Tetrahedron* **1998**, *54*, 3069–3092. (d) Ourisson, G.; Stehelin, L.; Lhomme, J. *J. Am. Chem. Soc.* **1971**, *93*, 1650–1657. (e) Traynham, J. G.; Foster, A. W. *J. Am. Chem. Soc.* **1971**, *93*, 6216–6220. (f) Doyle, M. P.; Parker, W. *J. Chem. Soc., Chem. Commun.* **1970**, 755–756.

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 $BF_3 \cdot Et_2O$ (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*-diethylaniline, 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 *exo*-cyclic position to conjugation with the lactam carbonyl. In contrast, the reaction of **3a** with benzofuran/$BF_3 \cdot Et_2O$ at 80 °C gave the novel tetracyclic compound **16e** from further Michael addition and then formal 1,2-elimination of $^-$OBn from a benzofuran intermediate analogous to **16d**.

The reaction of **17** (debenzyloxy **3d**) with *N*,*N*-diethylaniline/$BF_3 \cdot Et_2O$ at rt (2 h) gave the initial 1,4-addition product **18**. Further treatment of **18** with indole/$BF_3 \cdot Et_2O$ gave the pyrrolidinone **19**, demonstrating the potential of this method for preparing 5,5-disubstituted pyrrolidinones (Scheme 8).

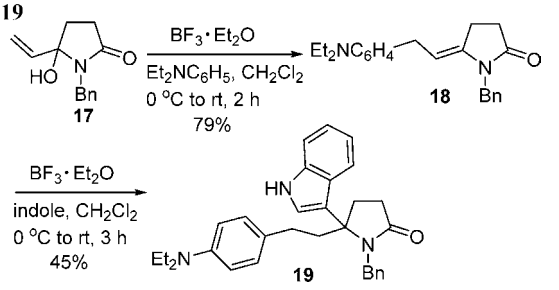
In conclusion, we have demonstrated that the sequential 1,4- and 1,2-addition reactions of latent bisnucleophiles to α,β-unsaturated *N*-acyliminium ions allows for rapid access to novel spirocyclic, bridged, and other multicyclic heterocycles. While spirocyclic systems related to **8** and **16b**,**c** can be accessed in a stepwise fashion, using more traditional saturated *N*-acyliminium chemistry,[1,6,7] the current method is compatible with the inclusion of relatively reactive heterocycles (e.g., indole and benzofuran) that could not be so easily introduced into the *N*-acyliminium precursors using the Grignard reagent protocols of these earlier methods.[1,6,7,9]

Scheme 7. Synthesis of Heterocycles **16**[a]



[a] CH_2Cl_2, 0 °C, 1 h. [b] CH_2Cl_2, rt, 16 h. [c] CH_2Cl_2, −20 °C, 2 h. [d] Toluene, 80 °C, 18 h.

Scheme 8. Synthesis of Substituted Pyrrolidinones **18** and **19**



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Supporting Information Available. Synthetic methods and characterization data for all compounds. Copies of the ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(9) (a) Bahajaj, A. A.; Moore, M. H.; Vernon, J. M. *Tetrahedron* **2004**, *60*, 1235–1246. (b) Bailey, P. D.; Morgan, K. M.; Smith, D. I.; Vernon, J. M. *Tetrahedron* **2003**, *59*, 3369–3378. (c) Chihab-Eddine, A.; Daiech, A.; Jilale, A.; Decroix, B. *Heterocycles* **2002**, *58*, 449–456.

The authors declare no competing financial interest.