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Arife Yazici
*University of Wollongong*, arife@uow.edu.au

Stephen G. Pyne
*University of Wollongong*, spyne@uow.edu.au

## Publication Details

Yazici, A. & Pyne, S. G. (2013). 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. Organic Letters, 15 (22), 5878-5881.

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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

**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.

**Keywords**
sequential, 4, 1, 2, addition, reactions, unsaturated, n, acyliminium, ions, strategy, synthesis, spiro, bridged, heterocycles, CMMB

**Disciplines**
Medicine and Health Sciences | Social and Behavioral Sciences

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# xSequential 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

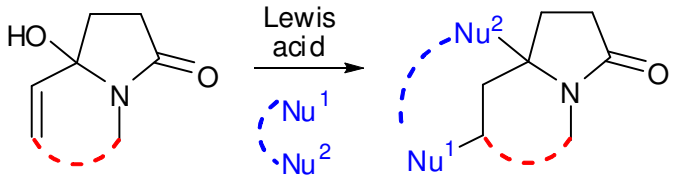
**Arife Yazici and Stephen G. Pyne***

*School of Chemistry, University of Wollongong, Wollongong, New South Wales, 2522, Australia*

*spyne@uow.edu.au*

**Received Date (will be automatically inserted after manuscript is accepted)**

## 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–c,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 di-functionalized heterocycles e.g. **2** (Scheme 1) because of their potential for sequential 1,4- and 1,2-addition reactions with two nucleophiles ($Nu^1$ and $Nu^2$) under acidic conditions. Significantly, when these two nucleophiles are tethered or latent bis-nucleophiles then

(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.; J. H. Cohen, I. J. Turchi, C. A. Maryanoff, *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.

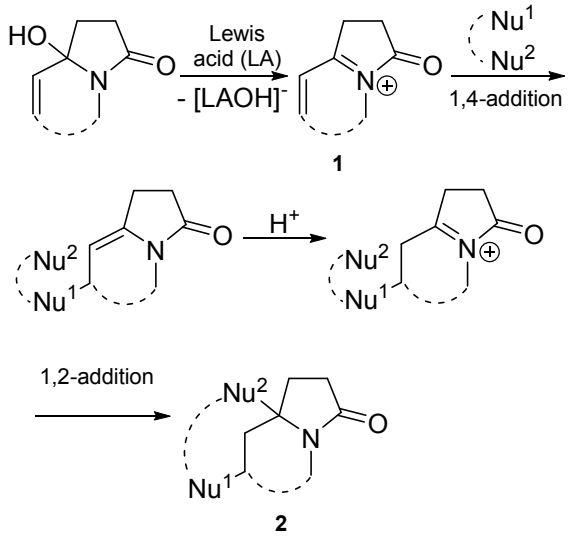
(2) For Diels–Alder reactions of α,β-unsaturated *N*-acyliminium ions with dienes, see: (a) Zou, Y.; Che, Q.; Snider, B. B. *Org. Lett.* **2006**, *8*, 5605–5608. (b) O'Connor, P. D.; Körber, K.; Brimble, M. A. *Synlett* **2008**, 1036–1038.

(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, Ashoke C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165–193. (b) Takao, K.-i.; Tadano, K.-i. *Heterocycles* **2010**, *81*, 1603–1629.

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 tetra heterocyclic systems.

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

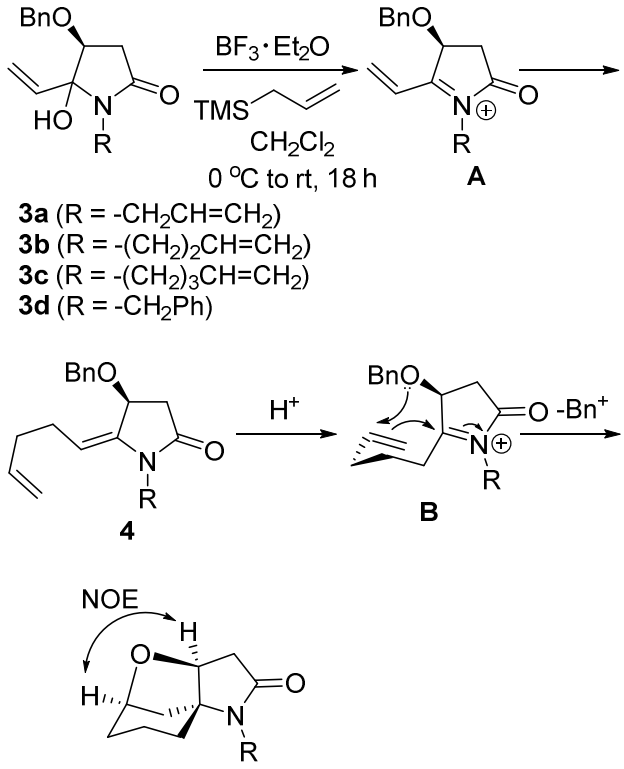



To examine the feasibily of this approach the α,β-unsaturated *N*-acyliminium ion precursor **3a** was treated with allyltrimethylsilane (1.2 equiv) in the presence of $BF_3$•$Et_2O$ (2.0 equiv) in $CH_2Cl_2$ solution at 0 °C to rt for 1 h. This reaction rapidly furnished the (*E*)-enamide **4a** (Scheme 2, see Supporting Information for this stereochemical assignment). However, extended reaction times (rt, 18 h) provided the novel spiro-tricyclic compound **5a** in 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**

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

(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.

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

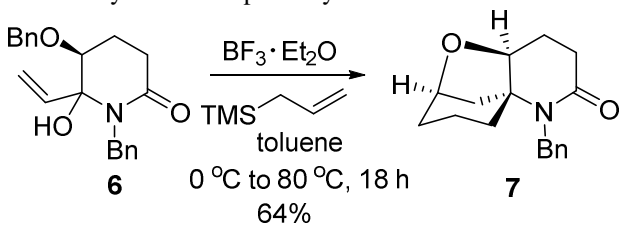



**5a** (R = -$CH_2CH=CH_2$) (66%; dr > 98:2)
**5b** (R = -$(CH_2)_2CH=CH_2$) (74%; dr > 98:2)
**5c** (R = -$(CH_2)_3CH=CH_2$) (75%; dr > 98:2)
**5d** (R = -$CH_2Ph$) (78%; dr > 98:2)

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

The analogous $BF_3$•$Et_2O$ (2 equiv) promoted reactions of **3a–3d** with 2-methallyltrimethylsilane (1.2 equiv) produced the spiro-bicyclic products **8a–d** in good yields

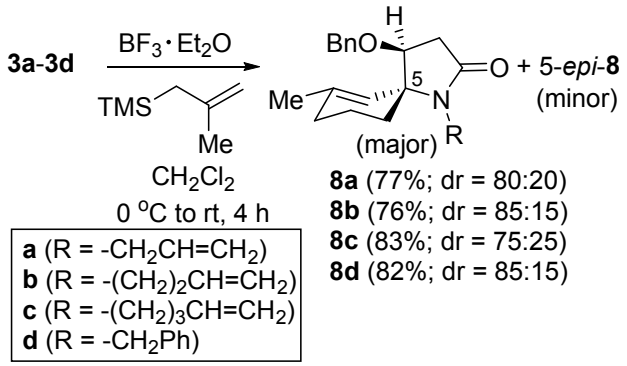
**Scheme 3.** Synthesis of spirotricycle **7**




(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**




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 $^1$H 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 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/$BF_3$•$Et_2O$ and 2-methallyltrimethylsilane/$BF_3$•$Et_2O$, respectively (Figure 1). The result of the former reaction clearly indicated the importance of the OBn group in promoting the spirocyclization-ether bond forming process. While that of the latter was consistent with the results shown in Scheme 4.

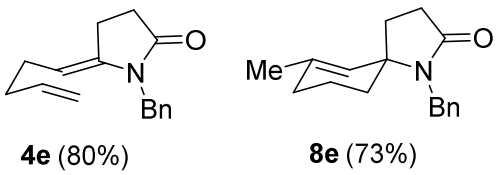
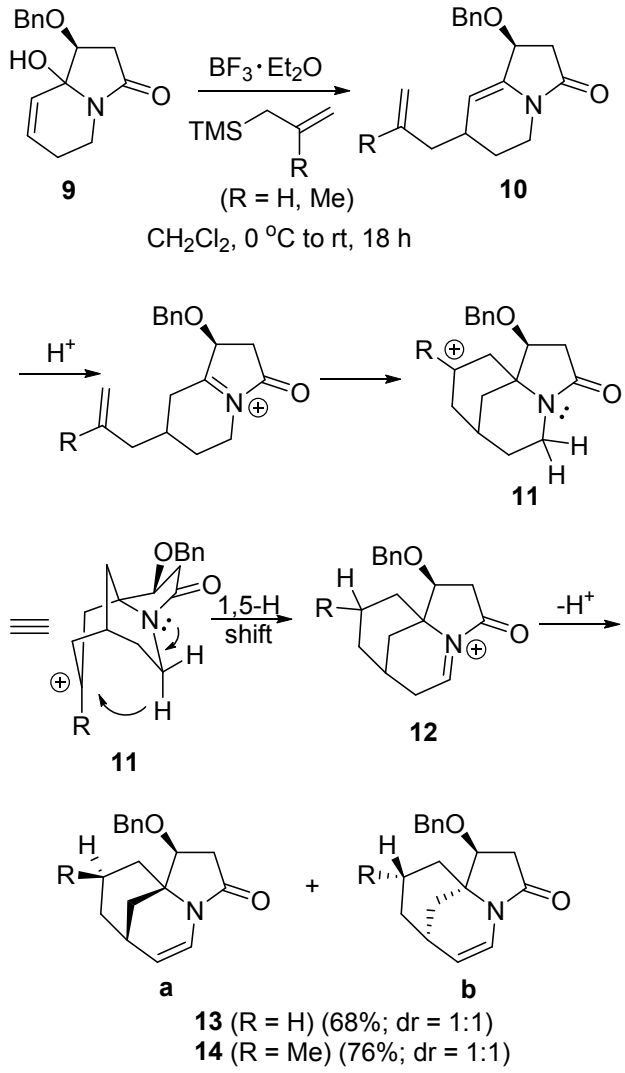



**Figure 1.** Synthesis of compounds **4e** and **8e**.

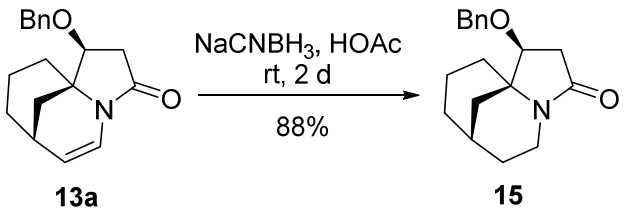
The bicyclic α,β-unsaturated *N*-acyliminium ion precursor **9** was treated separately with allyl- and 2-methallyltrimethylsilane in the presence of $BF_3$•$Et_2O$. Under short reaction times (rt, 1 h) the adduct **10** (R = H, Me) could be isolated as a 1:1 mixture of separable diastereomers. The lack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

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



shifts have precedent.[9] 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**



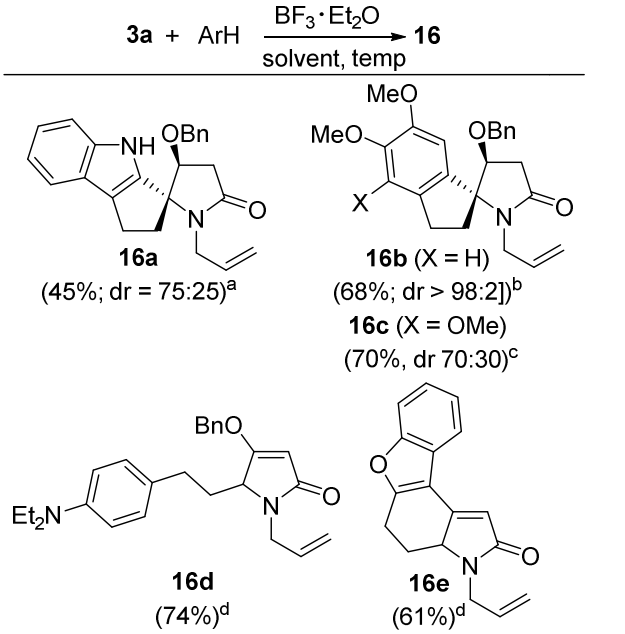

**13a** **15**

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 $BF_3$•$Et_2O$ (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/$BF_3$•$Et_2O$ at 80 °C gave the novel tetracyclic compound **16e** from further Michael addition then formal 1,2-elimination of OBn from a benzofuran intermediate analogous to **16d**.

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

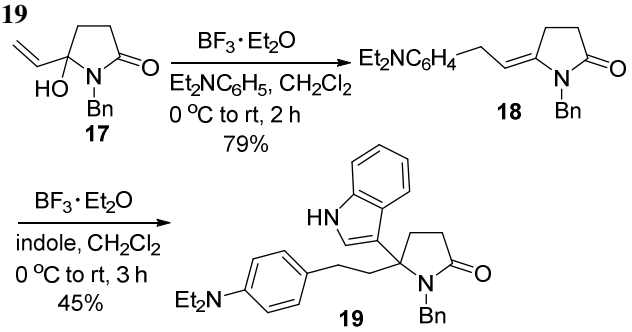
In conclusion, we have demonstrated that the sequential 1,4- and 1,2-addition reactions of latent bisnucleophiles to α,β-unsaturated *N*-acyliminium ions allows for rapid access to novel spirocyclic, bridged and other multicyclic heterocycles. While spirocyclic systems related to **8** and **16b**,**c** 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.[1,6,7,10]

**Scheme 7.** Synthesis of heterocycles **16**




[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**




**Acknowledgment.** We thank the Australian Research Council and the University of Wollongong for support.

**Supporting Information Available.** Synthetic methods and characterization data for all compounds.

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Copies of the $^{1}H$ and $^{13}C$ NMR spectra of all new compounds.

The authors declare no competing financial interest.