Sequential 1,2-Addition−Electrocyclic Ring Closures Involving Acyclic α,β-Unsaturated Iminiums: A Formal [3 + 3] Cycloaddition Strategy to Unique Pyranyl Spirocycles

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A formal [3 + 3] cycloaddition reaction of α,β-unsaturated aldehydes or ketones with monoketone or 1,3-diketone equivalents could serve as a viable strategy leading to complex six-membered heterocycles (**A** + **B** → **C** in Figure 1).[5] However, the synthetic scope of this strategy has been limited to only a few examples.[6,7] In general, reactions of α,β-unsaturated aldehydes or ketones with 1,3-dicarbonyl systems suffer from the regiochemical issues caused by the competing 1,2- versus 1,4-addition and the C- versus O-addition.[6] These problems usually result in diverse reaction pathways that lead to complex mixtures of reaction products where the desired six-membered heterocycles are either not found or isolated in low yields. Although the use of certain cyclic enals that possess diminished conjugation has led to improved regiochemical control,[7] a general solution remains elusive. Our continued synthetic efforts toward arisugacin[7a,8−10] (Figure 1) have led us to explore such a strategy. Specifically,

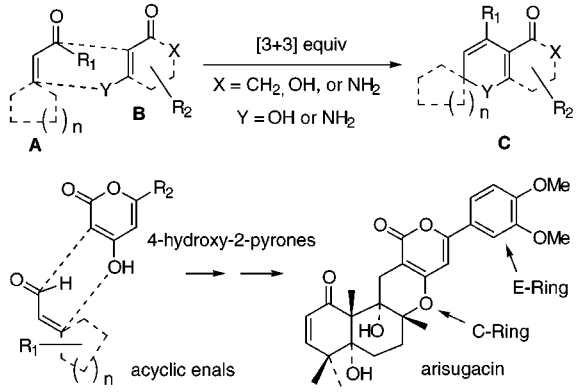
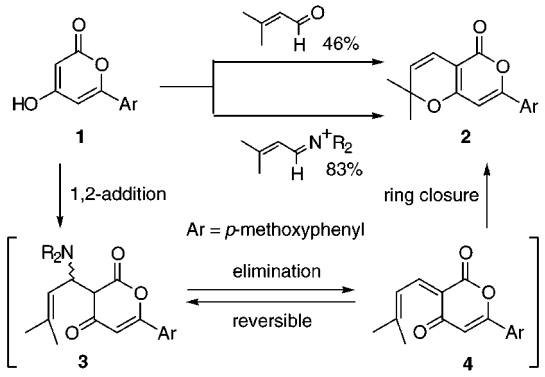


Figure 1.

we have studied cycloaddition reactions of acyclic α,β-unsaturated iminiums with 1,3-dicarbonyl systems and have chosen 4-hydroxy-2-pyrones as the 1,3-diketone equivalent since the DE-ring of arisugacin has been deemed structurally

Scheme 1



significant in the inhibition of acetylcholinesterase (AChE).[8] We report here results of our initial investigation of this formal cycloaddition strategy and its utility in synthesis of unique spiro pyranyl systems.

Our initial solution for solving the regiochemical issue was to block the β-position of the enal. As shown in Scheme 1, the pyrone **1**[11] was treated with 3-methyl-2-butenal in the presence of 0.5 equiv of L-proline (not very soluble in EtOAc) in anhydrous EtOAc[6,7a] at 85 °C under nitrogen (sealed flask) and after 48 h afforded the pyran **2**[12] in moderate 46% yield. No other products were observed to arise from other potential reaction pathways. Although this protocol offered improvement, further mechanistic evaluation revealed a much better solution to this problem. A postulated mechanistic pathway could involve C-1,2-addition to the aldehyde[13] assisted by an amine to provide an intermediate such as **3** (Scheme 1). After elimination (proposed to be reversible here) of the amino group, a 6π-electron electrocyclic ring closure of **4**[14] could then follow, providing the cyclized product **2**. This tandem 1,2-addition−electrocyclic ring-closure process could formally constitute a [3 + 3] cycloaddition reaction.

Given this mechanistic model, it was perceived that the 1,2-addition may be greatly facilitated if the α,β-unsaturated iminium intermediate could be generated prior to the addition of nucleophiles (4-hydroxy-2-pyrones in this case). The 3-methyl-2-butenal was stirred in the presence of 1.0 equiv of piperidine (with better solubility in anhydrous EtOAc) and 1.0 equiv of Ac_2O in EtOAc at 85 °C in a sealed flask for 45 min. The presumed iminium solution was then transferred without cooling to the solution of pyrone **1** in EtOAc. After the solution was stirred at 85 °C in a sealed flask for 36 h, the pyran **2** was obtained in 83% yield.

As summarized in Table 1, using this protocol, reactions of 3-methyl-2-butenal with 4-hydroxy-2-pyrones (**5**, **7**, **9**, **11**, and **13**) afforded various cyclized products (**6**, **8**, **10**, **12**, and **14**) in excellent yields (entries 1−5). More significantly, a variety of acyclic α,β-unsaturated enals containing only one β-substituent could be used. Both acyclic α,β-unsaturated

(1) UMN Undergraduate Research Participants, 1997−1998.
(2) Recipient of 1998 Pharmacia-Upjohn Summer Fellowship.
(3) Recipient of 1998 Pfizer Summer Fellowship.
(4) Chemistry Department Research Scientist for NMR.
(5) Examples of [3 + 3] cycloaddition reactions in the truest sense are extremely scarce. There are limited examples of metal-mediated [3 + 3] cycloaddition reactions. For recent reviews, see: (a) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. Examples of formal [3 + 3] cycloaddition reactions in a stepwise manner are too vast to document.
(6) For a leading reference with acyclic α,β-unsaturated aldehydes, see: de March, P.; Moreno-Mañas, M.; Casado, J.; Pleixats, R.; Roca, J. L.; Trius, A. *J. Heterocycl. Chem.* **1984**, *21*, 1369.
(7) For examples of using cyclic enals: (a) Hua, D. H.; Chen, Y.; Sin, H.-S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J.-P.; Chiang, P. K. *J. Org. Chem.* **1997**, *62*, 6888. (b) Jonassohn, M.; Sterner, O.; Anke, H. *Tetrahedron* **1996**, *52*, 1473.
(8) For a leading reference, see: Otoguro, K.; Kuno, F.; Õmura, S. *Pharmacol. Ther.* **1997**, *76*, 45.
(9) Obata, R.; Sunazuka, T.; Tian, Z.; Tomoda, H.; Harigaya, Y.; Õmura, S.; Smith, A. B., III. *Chem. Lett.* **1997**, 935.
(10) (a) Hsung, R. P. *Heterocycles* **1998**, *48*, 421. (b) Hsung, R. P. *J. Org. Chem.* **1997**, *62*, 7904. (c) Granum, K. G.; Merkel, G.; Mulder, J. A.; Debbins, S. A.; Hsung, R. P. *Tetrahedron Lett.* **1998**, 9597.
(11) For preparations of pyrones, see: Hsung, R. P.; Douglas, C. J.; Skelenica, H. Manuscript in preparation.
(12) All new compounds are characterized by ^{1}H NMR, ^{13}C NMR, FTIR, and mass spectroscopy.
(13) The regioisomeric product resulting from an O-1,2-addition was ruled out on the basis of ^{1}H NMR assignment.[6,7a]
(14) For an example of this electrocyclic ring closure, see: Shishido, K.; Hiroya, K.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1986**, 971.

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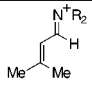
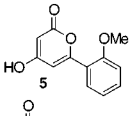
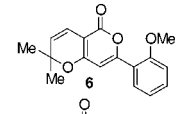
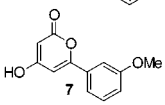
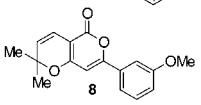
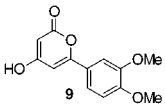
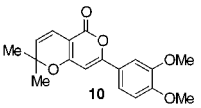
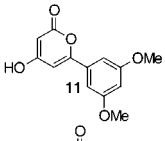
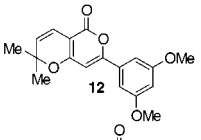
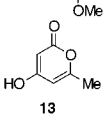
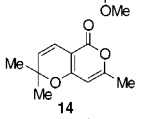
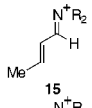
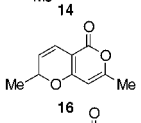
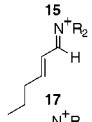
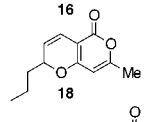
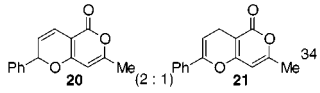
Table 1. Reactions of α,β-Unsaturared Iminiums

Entry	Iminium[a]	Pyrones	Products	Yield[b]
1				73%
2				82
3				84
4				65
5				72
6				66
7				52
8				34

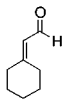
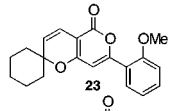
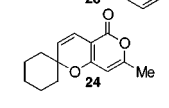
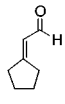
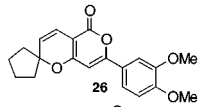
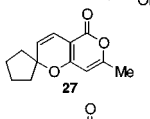
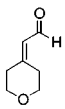
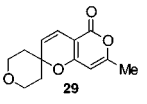
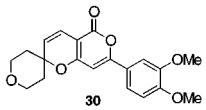
[a] All reactions were carried out in anhydrous EtOAc. Commercial enals were filtered through silica gel prior to use. The ratio of enals to acetic anhydride to piperidine is 1:1:1, and the ratio of enals to 4-hydroxy-2-pyrones is 2:1 except for entries 3 and 4 where it is 2.5:1. Ac_2O was added at −10 °C. Reactions were carried out at 85 °C in a sealed flask under nitrogen for 24−48 h after transferring the iminium solution to pyrone. [b] All yields were isolated yields.

iminiums **15** and **17** generated from the corresponding enals afforded cyclized products **16** and **18** in good yields (entries 6−8). Although the iminium **19** derived from cinnamaldehyde provided only a moderate yield of cyclized product **20** and **21** as a mixture (2:1), these products have not been isolated in any previous literature attempts.[6] All of these pyranyl heterocycles are CDE-ring analogues of arisugacin, and we are currently evaluating their inhibitory potential against AChE.

Given the synthetic potential of this reaction, we explored reactions of α,β-unsaturated cycloalkylidene acetaldehydes in an attempt to generate interesting pyranyl spirocycles. As summarized in Table 2, cycloalkylidene acetaldehydes **22** and **25** could be subjected to the same reaction conditions to give the corresponding spirocycles **23**, **24** and **26**, **27** in excellent yields (entries 1−4). In addition, 4-tetrahydropyranylidene acetaldehyde **28** provided synthetically interesting pyranyl spirocycles **29** and **30** in 55% and 73% yields, respectively (entries 5 and 6).

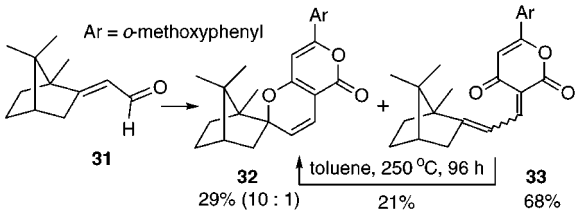
We then attempted to control the stereochemistry of the spiro carbon by using chiral alkylidene acetaldehydes. When the α,β-unsaturated iminium ion derived from camphylidene acetaldehyde **31** (only one olefinic isomer) was reacted with the pyrone **5** at 110 °C for 96 h, the spirocycle **32** was obtained in 29% yield with a diastereomeric ratio of 10:1. Stereochemistry of the major isomer was assigned according to NOE experiments. A major product isolated in 68% yield

Table 2. Preparations of Pyranyl Spirocycles

Entry	Enals[a]	Pyrones[b]	Products	Yield[c]
1		5		68%
2		13		86
3		9		63
4		13		43
5		13		55
6		9		73

[a] Reactions were carried out as described in Table 1. [b] The ratio of enal to pyrone is 2.5:1. [c] Isolated yields.

Scheme 2



was spectroscopically assigned as the uncyclized product **33**. Although only one isomer of **33** was observed, stereochemistry of the olefin exocyclic to the pyrone moiety could not be easily distinguished. However, when **33** was heated in toluene at 250 °C in a sealed tube for 96 h, the cyclized product **32** was obtained in 21% yield with a ratio of 10:1 in favor of the same major isomer, in addition to unreacted **33** (Scheme 2). The high temperature and long reaction time suggest that the cyclization step was quite slow due to the steric encumbrance of camphor group. This model reaction not only indicates that a high degree of stereochemical control at the quaternary center can be achieved by using chiral enals, but further study of this model could provide insight into the mechanism of this cyclization process.

We have explored a formal [3 + 3] cycloaddition strategy that is synthetically useful for constructing pyranyl heterocycles and novel spirocycles. We are currently studying the synthetic scope of this reaction as well as the stereochemical control of the spirocenter.

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Supporting Information Available: Experimental procedures as well as ^1H NMR spectral and characterization data are given for all new compounds.

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