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Formal Cycloaddition Reactions of Vinylogous Amides with α,β-Unsaturated Iminiums. A Strategy for Constructing Piperidinyl Heterocycles

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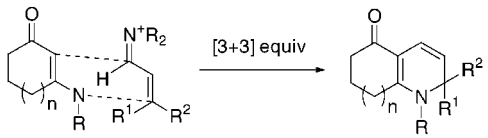
ABSTRACT



A formal [3 + 3] cycloaddition strategy for constructing piperidinyl heterocycles from vinylogous amides and α,β-unsaturated iminiums is described here. These reactions proceed well, leading to various heterocycles that could serve as useful synthetic building blocks. Comparative studies between the reactivities of vinylogous amides and other 1,3-diketo systems have also been examined. Preferences for the nitrogen atom during the electrocyclic ring closure step are noted in these reactions, and preliminary calculations suggest that these preferences could result from electronic factors.

We recently reported a formal [3 + 3] cycloaddition reaction[3] in which α,β-unsaturated iminium intermediates were condensed with 4-hydroxy-2-pyrones through a sequence involving C-1,2-addition, possible reversible β-elimination, and six-π-electron electrocyclic ring closure.[4] This formal cycloaddition reaction proved to be a useful entry to a diverse array of pyranyl heterocycles specifically fused to 2-pyrones.[4] This initial study provided a significant solution to the regiochemical problems caused by the competing 1,2- versus 1,4-additions and the C- versus O-addition in these reactions.[5,6] However, the synthetic scope remained largely limited because only 4-hydroxy-2-pyrones have been employed. The synthetic utility of this formal cycloaddition reaction would be greatly expanded if other 1,3-dicarbonyl systems could also be employed as nucleophilic equivalents of 4-hydroxy-2-pyrones. As illustrated in Figure 1, if 1,3-dicarbonyl systems (**A**) such as vinylogous amides are used, by proceeding through the proposed intermediates, this reaction could lead to useful nitrogen-containing heterocyclic structures (**C**). Given this novel strategy for constructing complex heterocycles and its potential in the synthesis of relevant natural products,[6a,7,8] we investigated reactions of various of 1,3-dicarbonyl equivalents with α,β-unsaturated iminiums. We report here our first realization of this formal

(1) UMN Undergraduate Research Participant, 1998−1999, and a Recipient of 1998 Pharmacia-Upjohn Summer Research and LANDO-NSF REU Fellowships.

(2) UMN Chemistry Department Research Scientist for NMR Spectroscopy.

(3) Examples of [3 + 3] cycloaddition reactions in the truest sense are extremely scarce, and there are only 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.

(4) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690.

(5) de March, P.; Moreno-Mañas, M.; Casado, J.; Pleixats, R.; Roca, J. L.; Trius, A. *J. Heterocycl. Chem.* **1984**, *21*, 1369.

(6) (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.

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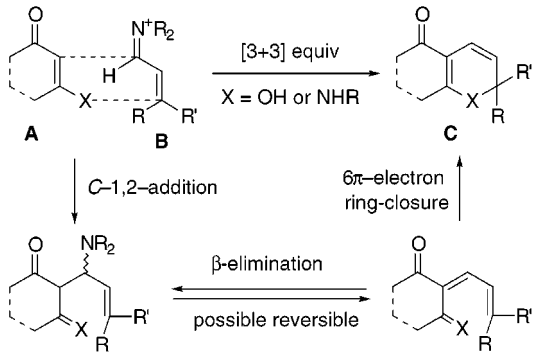
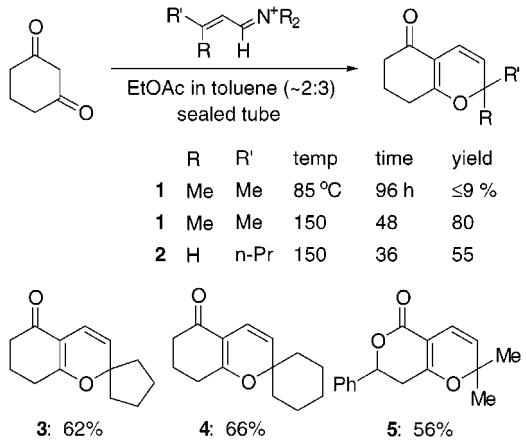


Figure 1.

cycloaddition reaction involving vinylogous amides as a unique approach for synthesis of piperidinyl heterocycles.

Our preliminary studies of the cycloaddition reactions of 1,3-diketones with α,β-unsaturated iminium revealed the relatively low reactivity of diketones in comparison with that of 4-hydroxy-2-pyrones.[4] A series of attempts to effect the reaction of 1,3-cyclohexadione were unsuccessful. When 1,3-cyclohexadione was heated to 85 °C in EtOAc with the α,β-unsaturated iminium intermediate pregenerated from 3-methyl-2-butenal using equimolar piperidine and acetic anhydride, the desired pyranyl product **1**[9] was isolated in only ≤9% yield after prolonged reaction time (Scheme 1). However,

Scheme 1



	R	R'	temp	time	yield
1	Me	Me	85 °C	96 h	≤9 %
1	Me	Me	150	48	80
2	H	n-Pr	150	36	55

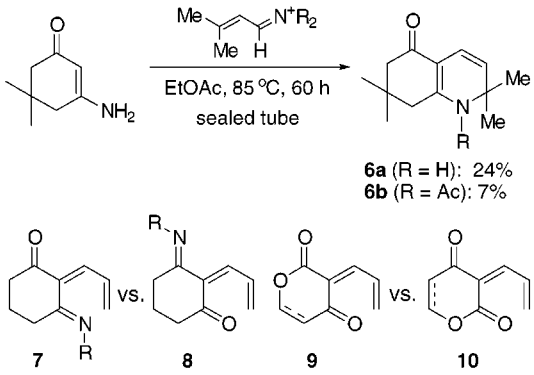
3: 62% **4**: 66% **5**: 56%

when the temperature was raised and the solvent system was switched to a toluene/EtOAc mixture, the reaction proceeded in a synthetically useful manner to give the pyranyl cycloadducts **1** and **2** in 80% and 55% yields, respectively.[10]

Further studies revealed that interesting spirocycles such as **3** and **4** could also be obtained in 62% and 66% yield, respectively, under the same reaction conditions in 20−36 h using cycloalkylidene acetaldehydes. When 4-keto-6-phenyl-δ-lactone was used as a 1,3-dicarbonyl equivalent and condensed with 3-methyl-2-butenal, the desired cycloadduct **5** was obtained in 56% yield. However, this reaction had to be carried out at 85 °C, and the reaction time was much longer (120 h). At higher temperatures, decomposition of the starting lactone occurred. Compounds **1**−**5** should be synthetically useful because these pyranyl heterocycles are functionally rich, and the pyranyl heterocycle **5** in particular contains the lactone moiety that can provide further synthetic utility.

Having established the reactivity of 1,3-diketo systems, we quickly turned our focus to vinylogous amides with the intention of constructing piperidinyl heterocycles. The reaction of 3-amino-5,5-dimethyl-2-cyclohexen-1-one with the α,β-unsaturated iminium derived from 3-methyl-2-butenal was carried out at 85 °C in EtOAc to give the piperidine derivatives **6a** and **6b** in 24% and 7% yields, respectively (Scheme 2).[11] The compound **6b** was likely a result of

Scheme 2



acetylation of **6a** under the reaction conditions. Although the combined yield was rather low, formation of the cycloadduct indicated the feasibility of constructing piperidinyl heterocycles via this methodology. Given the proposed mechanism, this reaction suggests a preference for the imine nitrogen[12] over the keto oxygen during the six-π-

(7) For our studies related to arisugacin see: (a) Hsung, R. P. *J. Org. Chem.* **1997**, *62*, 7904. (b) Hsung, R. P. *Heterocycles* **1998**, *48*, 421. (c) Granum, K. G.; Merkel, G.; Mulder, J. A.; Debbins, S. A.; Hsung, R. P. *Tetrahedron Lett.* **1998**, 9597. (d) Degen, S. J.; Mueller, K. L.; Shen, H. C.; Mulder, J. A.; Golding, G. M.; Wei, L.-L.; Zificsak, C. A.; Hsung, R. P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 973. (e) Douglas, C. J.; Skelenica, H. M.; Shen, H. C.; Mathias, D. S.; Golding, G. M.; Hsung, R. P.; Degen, S. J.; Morgan, C. D.; Mueller, K. L.; Seurer, L. M.; Shih, R. A. *Tetrahedron*, submitted for publication.

(8) For isolation of arisugacin see: (a) Otoguro, K.; Kuno, F.; Õmura, S. *Pharmacol. Ther.* **1997**, *76*, 45. For another study related to arisugacin see: (b) Obata, R.; Sunazuka, T.; Tian, Z.; Tomoda, H.; Harigaya, Y.; Õmura, S.; Smith, A. B., III. *Chem. Lett.* **1997**, 935.

(9) All new compounds have been characterized by ^{1}H NMR, ^{13}C NMR, FTIR, and mass spectroscopy.

(10) For earlier examples of reactions of 1,3-diketones with α,β-unsaturated aldehydes see: (a) Tietze, L. F.; van Kiedrowski, G.; Berger, B. *Synthesis* **1982**, 683. (b) de Groot, A.; Jansen, B. J. M. *Tetrahedron Lett.* **1975**, 3407. There were some disagreements in these citations regarding reaction yields and conditions.

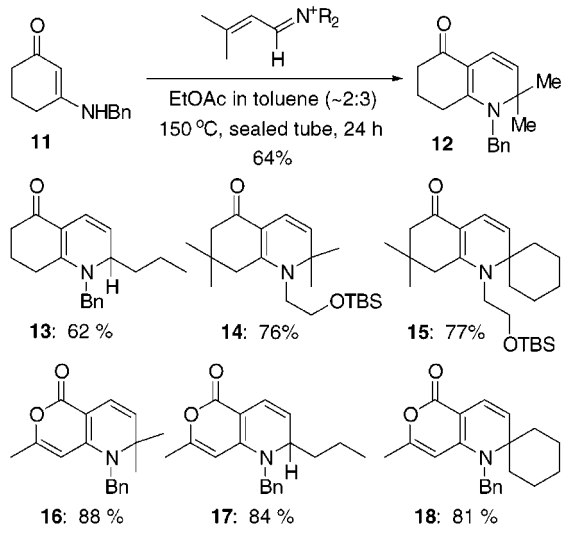
(11) The regiochemical issues were assigned by nOe experiments later on compound **14**.

(12) We are assuming that the imine nitrogen rather than an iminium species is involved in the ring closure because of the presence of excess piperidine. For a related reference see: Kametani, T.; Kajiwara, M.; Fukumoto, K. *Tetrahedron* **1974**, *30*, 1053.

electron electrocyclic ring closure (**7** vs **8**). Along with our earlier studies[4] and the isolation of compound **5**, it appears that the keto oxygen is preferred over ester oxygen in the ring closure step (**9** vs **10**).

Further experiments showed that protection of the vinylogous amides as well as higher reaction temperatures were key to the success of the cycloaddition reaction. When the vinylogous amide **11** containing a benzyl group was subjected to the optimized reaction conditions, the piperidine **12** was isolated in 64% yield (Scheme 3). The synthetic scope

Scheme 3



of this reaction was quickly established by the preparations of various piperidinyl heterocycles **13**−**15** in good yields (62%−77%) with comparable reaction duration (15−36 h). These piperidinyl heterocycles were specifically selected because they represent potentially useful synthetic building blocks. For example, we are currently exploring the possibility of using compound **13** as an intermediate for synthesis of pumilotoxins.[13] Compounds **14** and **15** demonstrated that the nitrogen can contain a tethered functionality and that piperidinyl spirocycles can also be prepared under these conditions.

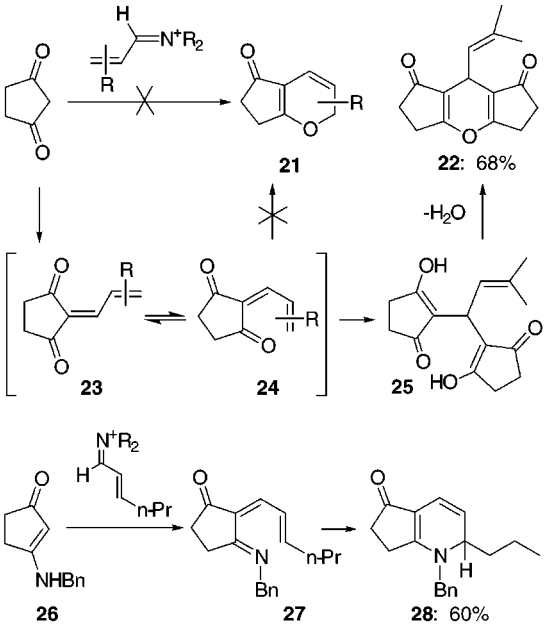
Finally, reactions of 6-methyl-4-(benzylamino)-2-pyrone were also examined, leading to piperidinyl compounds **16**−**18** in high yields (81%−88%). Since acyclic vinylogous amides have not been successful in this formal cycloaddition reaction, 4-amino-2-pyrones could serve as an equivalent of acyclic vinylogous amides, given ample precedents of efficient ring opening of the adjacent 2-pyrones.[8b] Hence, compounds **16**−**18** are essentially functionalized 2*H*-pyridine derivatives, and the spirocycle **18** may serve as a model entry to natural products such as histrionicotoxin.[14]

(13) For a review see: Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1993; Vol. 43, p 185.

(14) For recent syntheses of histrionicotoxin see: (a) Carey, S. C.; Aratani, M.; Kishi, Y. *Tetrahedron Lett.* **1985**, 5887. (b) Stork, G.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 5875.

In further comparative studies between 1,3-diketones and vinylogous amides in [3 + 3] cycloadditions, we observed an intriguing contrast between the reactivities of 1,3-cyclopentadione and vinylogous amide **26**. When 1,3-cyclopentadione was reacted with a variety of α,*β*-unsaturated iminiums under these conditions, no desired product (shown as **21** in Scheme 4) was isolated. Although only the

Scheme 4



diketone **22** was rigorously isolated (68% yield) and characterized, in all other cases, the only identifiable product was the structural analogue of **22**. Formation of compound **22** can be envisioned to occur through dehydration of the intermediate **25**, which could be derived from a second 1,4-addition of 1,3-cyclopentadione to the dienone intermediates **23** and **24** (two possible conformers). Hence, the isolation of **22** suggests that, for reactions of 1,3-cyclopentadione, the electrocyclic ring closure step is either slow or is arrested at the dienone intermediate **24** and that a second 1,4-addition either occurs faster or is more favored.

In contrast, the vinylogous amide **26** reacted well under the same reaction conditions. For example, the reaction of **26** with 2-hexenal provided the desired piperidine **28** in 60% yield. This suggests that the electrocyclic ring closure was more favored for the diene imine intermediate **27**[12] than for the intermediate **24**. Our preliminary empirical calculations indicate that these reactivity differences as well as those mentioned earlier (see Scheme 2) are likely due to the electronic preference for the nitrogen atom during the electrocyclic ring closure.[15,16] We are currently investigating details of these preferences. Nevertheless, this experimental observation not only provides important mechanistic details but, more significantly, also suggests a much broader synthetic scope of vinylogous amides in this formal cycloaddition reaction.

We have described here a formal [3 + 3] cycloaddition strategy that is synthetically useful for constructing piperidinyl heterocycles from vinylogous amides and α,β-unsaturated iminiums. We are currently exploring the synthesis of various relevant natural products involving this strategy as well as addressing other stereochemical issues.

(15) Our semiempirical molecular orbital calculations (Spartan Program: PM3) suggest that the HOMO of the imine nitrogen in the intermediate **7** or **27** appears to overlap the best with the LUMO of the carbon at which the bond formation occurs, and the HOMO of the keto oxygen atom in the intermediate **24** appears to have the worst overlap with the LUMO of the carbon at which the bond formation occurs. The assumption here is that the direction of the ring closure starts with the heteroatom.[16]

(16) Shishido, K.; Ito, M.; Shimada, S.-I.; Fukumoto, K.; Kametani, T. *Chem. Lett.* **1984**, 1943.

Acknowledgment. R.P.H. wishes to thank Professors Steve Ley and Gilbert Stork for invaluable discussions. We also thank the University of Minnesota for financial support in the forms of Start-up Fund and Grant-in-Aid of Research, Artistry and Scholarship (CUFS No. 1003-519-5984). H.M.S. thanks the UMN Chemistry Department for a Kolthoff Graduate Fellowship.

Supporting Information Available: Text giving experimental procedures as well as figures giving ^{1}H NMR spectral and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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