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2,3-Dihydro-4*H*-pyran-4-ones and 2,3-Dihydro-4-pyridinones by Cyclizations of α,β-Unsaturated 1,3-Diketones

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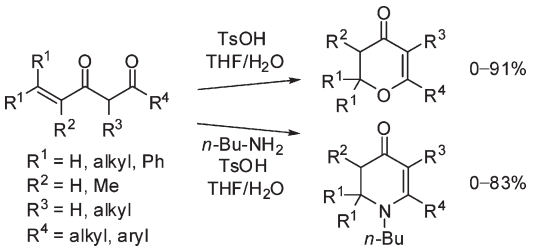

A variety of α,β-unsaturated 1,3-diketones cyclize to 2,3-dihydro-4*H*-pyran-4-ones in an acidic aqueous medium, with exceptions being α,β-unsaturated 1,3-diketones in which the β carbon is substituted by a phenyl group. Addition of 1-butanamine to the reaction medium results in the formation of 2,3-dihydro-4-pyridinones, which appear to arise via an initial 1,4-addition of the amine to the α,β-unsaturated 1,3-diketones.

Introduction

Hetero-Diels−Alder cyclizations and stepwise processes that are formal [4 + 2] reactions have emerged as important methods for the synthesis of molecules containing 2,3-dihydro-4*H*-pyran-4-one **1**,[1] but the older method of acid-mediated cyclization of 5-hydroxy-1,3-diketones, e.g., **2**, continues to have relevance.[2,3] In the latter method, the stereochemistry of the carbinol center is preserved in the cyclized product,[3] and so this cyclization involves the dehydration of an intermediate hemiketal rather than initial dehydration of the alcohol followed by cyclization of the α,β-unsaturated 1,3-diketone, e.g., **3**. However, there are surprisingly few examples of α,β-unsaturated 1,3-diketones cyclizing to 2,3-dihydro-4*H*-pyran-4-ones.[4−6] The papers by Gelin[5] dealt with the specific case of acylation of the magnesium enolate of β-ketoesters with unsaturated acid chlorides that lead to concomitant cyclization to afford 2,3-dihydro-4*H*-pyran-4-one-3-carboxylates. The mechanism of the cyclization of an α,β-unsaturated 1,3-diketone may

(1) For example: (a) Danishefsky, S.; Kerwin, J. F. Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358–360. (b) Danishefsky, S.; Harvey, D. F.; Quallich, G.; Uang, B. J. *J. Org. Chem.* **1984**, *49*, 393–395. (c) Johannsen, M.; Yao, S.; Jørgensen, K. A. *Chem. Commun.* **1997**, 2169–2170. (d) Zipp, G. G.; Hilfiker, M. A.; Nelson, S. G. *Org. Lett.* **2002**, *4*, 1823–1826. (e) Winkler, J. D.; Oh, K. *Org. Lett.* **2005**, *7*, 2421–2423. (f) Yang, W.; Shang, D.; Liu, Y.; Du, Y.; Feng, X. *J. Org. Chem.* **2005**, *70*, 8533–8537. (g) Mukaiyama, T.; Kitazawa, T.; Fujisawa, H. *Chem. Lett.* **2006**, *35*, 328–329. (h) Denmark, S. E.; Heemstra, J. R. Jr. *J. Org. Chem.* **2007**, *72*, 5668–5688.

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(3) For examples in synthesis, see: (a) Jin, M.; Taylor, R. E. *Org. Lett.* **2005**, *7*, 1303–1305. (b) Calad, S. A.; Ćiraković, J.; Woerpel, K. A. *J. Org. Chem.* **2006**, *72*, 1027–1030.

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(5) (a) Gelin, S.; Gelin, R. *Bull Soc. Chim. Fr.* **1968**, *1*, 288–298. (b) Gelin, R.; Gelin, S.; Dolmazon, R. *Tetrahedron Lett.* **1970**, *42*, 3657–3660. (c) Gelin, S. *Tetrahedron Lett.* **1975**, *48*, 4255–4258. (d) Dolmazon, R.; Gelin, S. *J. Org. Chem.* **1984**, *49*, 4003–4007. (e) Dolmazon, R.; Gelin, S. *J. Heterocycl. Chem.* **1985**, *22*, 793–795.

(6) Casey, M.; Donnelly, J. A.; Ryan, J. C.; Ushioda, S. *ARKIVOC* **2003**, 310–327.

(7) (a) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757–4778. (b) Alajarín, M.; Sánchez-Andrada, P.; Vidal, A.; Tovar, F. *J. Org. Chem.* **2005**, *70*, 1340–1349. (c) Kleinke, A. S.; Li, C.; Rabasso, N.; Porco, J. A. Jr. *Org. Lett.* **2006**, *8*, 2847–2850. (d) Tambar, U. K.; Kano, T.; Zepernick, J. F.; Stoltz, B. M. *Tetrahedron Lett.* **2007**, *48*, 345–350. (e) Shoji, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1672–1690. It has been reported that under basic conditions some α,β-unsaturated 1,3-diketones give carbocyclic products via 6π-electrocyclic reactions: Smith, A. B. III; Kilényi, S. N. *Tetrahedron Lett.* **1985**, *26*, 4419–4422.

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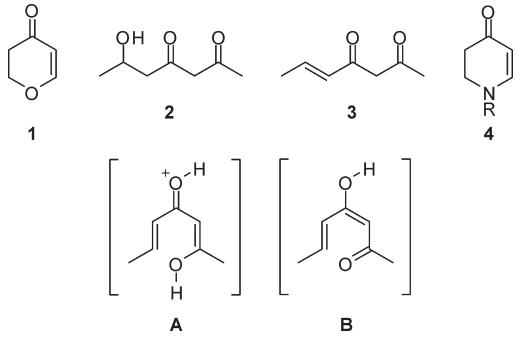
be via the protonated, enolic form **A** or by 6π-electrocyclization of the fully conjugated enol **B**.[7]



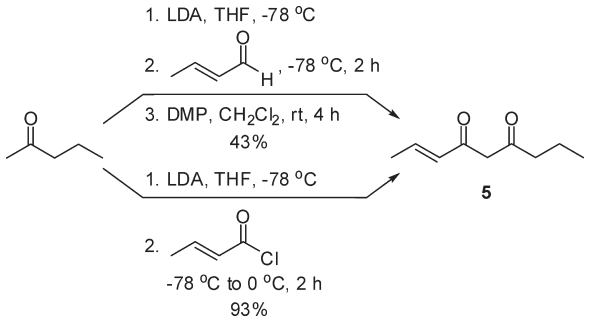
For the synthesis of a 2,3-dihydro-4-pyridinone ring **4**, hetero-Diels–Alder reactions or stepwise, formal [4 + 2] transformations involving imines have been employed usually.[8] Recently, the microwave-assisted formation of 2,3-dihydro-4-pyridinones from an α,β-unsaturated 1,3-diketone and simple primary amines in the presence of Montmorillonite K-10 was reported, and the mechanism was proposed to be via a transient imine.[9] Additions of Grignard reagents to 1-acyl-4-methoxypyridinium salts have been exploited many times by Comins.[10] Also, although never postulated in the formation of a 2,3-dihydro-4-pyridinone, aza-6π-electrocyclization might be a viable annulation mechanism.[11]

A study of the efficiencies of cyclization of variously carbon-substituted analogues of **3** to produce **1** has not appeared, and neither has a study of the analogous cyclization to give **4**. Herein, we present our findings with respect to these annulations.

Results and Discussion

Preparation of α,β-Unsaturated 1,3-Diketones. The synthesis of non-2-ene-4,6-dione (**5**) (Scheme 1) was our test reaction for the formation of the α,β-unsaturated 1,3-diketones. It was found, based on the procedure by Casey et al.,[6] that α,β-unsaturated acid chloride, *trans*-crotonoyl chloride, reacted with the kinetic enolate of the 2-pentanone to give **5** in significantly higher yield than the two-step approach of the reaction of *trans*-crotonaldehyde with the same enolate followed by oxidation of the intermediate β-hydroxy ketone

SCHEME 1



using Swern oxidation,[12] IBX,[13] or Dess–Martin periodinane (DMP).[14] Accordingly, most of the α,β-unsaturated 1,3-diketones (Table 1) used in this study were produced in adequate yield from α,β-unsaturated acid chlorides and ketones. No *O*-acylated product was detected. However, a yield of 24% for the preparation in this way of **6** prompted us to carry out its synthesis by reaction of the aldehyde with the enolate, followed by oxidation with DMP; this gave **6** in 54% yield. Poor reactivity of the enolate of 4-cyanoacetophenone with α,β-unsaturated acid chlorides necessitated reaction of the enolate of the α,β-unsaturated ketone with 4-cyanobenzoyl chloride to produce **16**. It was convenient, due to the availability of the α,β-unsaturated ketone, also to make **10** via the enolate of this ketone, although the yield of **10** was only 24%.

Cyclization of α,β-Unsaturated 1,3-Diketones to 2,3-Dihydro-4*H*-pyran-4-ones. The cyclization of **5** was assessed in different media (Scheme 2). Under every set of conditions that was tried (Table 2), the 2,3-dihydro-4*H*-pyran-4-one **18** was produced, and the yields ranged from 30 to 66%. The use of methanol as the solvent was problematic because **18** was contaminated by the product of conjugate addition of the alcohol **19** in approximately 10% yield and by another unidentified byproduct that was chromatographically very similar to **18**. NMR analysis of the crude reaction mixtures suggested that the reaction in DMSO might have produced **18** most quickly. Cyclization was slower in THF/acidic water, and 24% of **5** was recovered even after 29 h under reflux, but the ease of workup made this procedure more attractive to assess a range of α,β-unsaturated 1,3-diketones.

The 2,3-dihydro-4*H*-pyran-4-one products of heating solutions of the series of α,β-unsaturated 1,3-diketones **6**–**17** in acidic 1:1 THF/water are summarized in Table 1. Cyclizations of substrates with methyl substitution α to the central oxygen (**6** → **20** and **8** → **22**) were clearly less efficient than the cyclization of **5**. This was likely due to an added difficulty in attaining a reactive geometry because the cyclic substrate **7** cyclized to **21** more efficiently than **5**. Substitution of the β carbon of the starting alkene was required because **9** gave no detectable (NMR) amount of the corresponding 2,3-dihydro-4*H*-pyran-4-one, only intractable material was

(8) (a) Kerwin, J. F. Jr.; Danishefsky, S. *Tetrahedron Lett*. **1982**, *23*, 3739–3742. (b) Danishefsky, S.; Vogel, C. *J. Org. Chem*. **1986**, *51*, 3915–3916. (c) Kunz, H.; Pfrengle, W. *Angew. Chem., Int. Ed. Engl*. **1989**, *28*, 1067–1068. (d) Waldmann, H.; Braun, M. *J. Org. Chem*. **1992**, *57*, 4444–4451. (e) Huang, Y.; Rawal, V. H. *Org. Lett*. **2000**, *2*, 3321–3323. (f) Alaimo, P. J.; O'Brien, R. III; Johnson, A. W.; Slauson, S. R.; O'Brien, J. M.; Tyson, E. L.; Marshall, A. L.; Ottinger, C. E.; Chacon, J. G.; Wallace, L.; Paulino, C.; Connell, S. *Org. Lett*. **2008**, *10*, 5111–5114.

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(10) (a) Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem*. **1990**, *55*, 2574–2576. (b) Comins, D. L.; Hong, H. *J. Org. Chem*. **1993**, *58*, 5035–5036. (c) Comins, D. L.; Hong, H. *J. Am. Chem. Soc*. **1993**, *115*, 8851–8852. (d) Comins, D. L.; Kuethe, J. T. *Org. Lett*. **1999**, *1*, 1031–1033. (e) Comins, D. L.; Fulp, A. B. *Org. Lett*. **1999**, *1*, 1941–1943. (f) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc*. **1999**, *121*, 2651–2652. (g) Young, D. W.; Comins, D. L. *Org. Lett*. **2005**, *7*, 5661–5664. (h) McCall, W. S.; Grillo, T. A.; Comins, D. L. *J. Org. Chem*. **2008**, *73*, 9744–9751.

(11) (a) Maynard, D. F.; Okamura, W. H. *J. Org. Chem*. **1995**, *60*, 1763–1771. (b) Sydorenko, N.; Hsung, R. P.; Vera, E. L. *Org. Lett*. **2006**, *8*, 2611–2614. (c) Vincze, Z.; Mucsi, Z.; Scheiber, P.; Nemes, P. *Eur. J. Org. Chem*. **2008**, 1092–1100.

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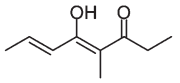
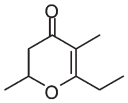
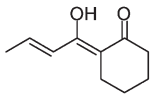
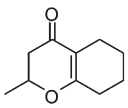
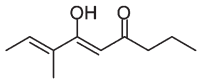
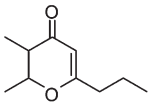
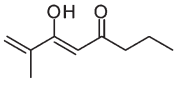
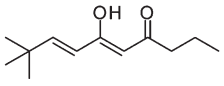
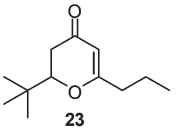
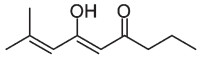
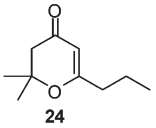
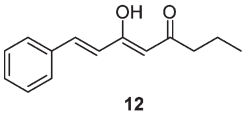
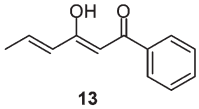
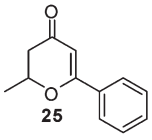
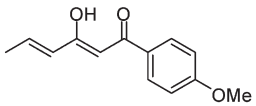
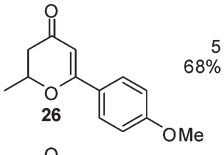
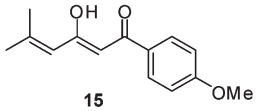
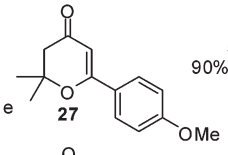
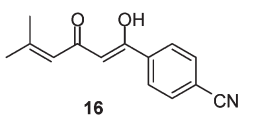
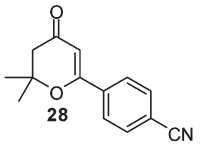
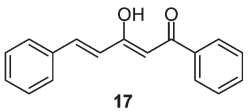
(13) Inoue, M.; Sato, T.; Hirama, M. *J. Am. Chem. Soc*. **2003**, *125*, 10772–10773.

(14) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4156–4158.

(15) The predominant enol forms were identified using ^{1}H and ^{13}C NMR spectra and 2D correlations (HSQC and HMBC). The ratios of enol to keto forms could be assessed by integration of clearly separated signals in the ^{1}H NMR spectra.

TABLE 1. α,β-Unsaturated 1,3-Diketones, Shown in Their Predominant Tautomeric Forms in $CDCl_3$,[15] and Their Cyclization Products in THF/Water (1:1) with TsOH

1,3-diketone	2,3-dihydro-4*H*-pyran-4-one	reaction time yield [BRSM]
 **6**	 **20**	51 h 55% [74%]
 **7**	 **21**	16 h 91%
 **8**	 **22**	72 h 33% [65%]
 **9**	–	51 h 0%
 **10**	 **23**	51 h 46% [90%]
 **11**	 **24**	50 h 68% [87%]
 **12**	–	30 h 0%
 **13**	 **25**	51 h 59% [95%]
 **14**	 **26**	51 h 68% [87%]
 **15**	 **27**	51h 90% [100%]
 **16**	 **28**	51 h 82%
 **17**	–	51 h 0%

SCHEME 2

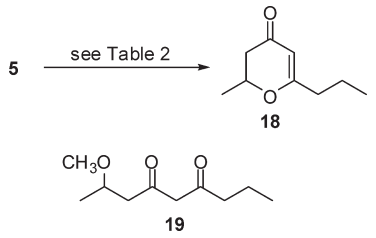
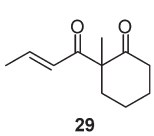
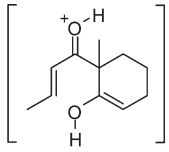


TABLE 2. Cyclization of 5

solvent, concn of **5**	*T* (°C), time (h)	additive (equiv)	yield of **18** (%)
anhydrous methanol, 0.02 M	reflux, 16		31
anhydrous methanol, 0.02 M	reflux, 22	TsOH, 0.1	44
anhydrous methanol, 0.02 M	reflux, 16	NEt_3, 1	44
acetic acid, 0.03 M	100, 15		30
DMSO, 0.06 M	95, 18		67
THF/water (1:1), 0.03 M	reflux, 20		59
THF/water (1:1), 0.05 M	reflux, 29	TsOH, 0.1	66
THF, 0.05 M	reflux, 29	TsOH, 0.1	46

obtained. While substitution of this carbon with *tert*-butyl (**10**) seemed to attenuate the rate of cyclization relative to a methyl substituent, destruction of the starting compound was not a competitive process. Relative to the compounds with a single methyl group on the β carbon of the starting alkene, e.g., **5**, **13**, and **14**, double methyl substitution of the β carbon, as in **11**, **15**, and **16**, had no obvious dilatory effect on reactivity, and **24**, **27**, and **28**, respectively, were obtained in good yield. On the other hand, substitution of the β carbon with a phenyl group, as in **12** and **17**, suppressed cyclization, and 2,3-dihydro-4*H*-pyran-4-ones were not detected. A phenyl substituent, or a substituted phenyl group, α to the first carbonyl, as in **13**−**16**, led to cyclized products **25**−**28** with yields equal to, or better than, the yield of **18** from **5**. It should be mentioned that the α,β-unsaturated 1,3-diketone **29**, for which enolization to attain the putatively reactive forms **A** and **B**, is blocked but which might cyclize through the unconjugated enol **C**, remained unchanged under the acidic THF/water conditions.

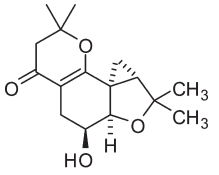

29


C

Model Reactions toward Pestaloficiol A. Pestaloficiol A **30** is a recently described natural product with anti-HIV activity.[16] The construction of the 2,3-dihydro-4*H*-pyran-4-one moiety onto a bicyclic ketone was explored as a model for the synthesis of **30**. Dulcère[17] had reported the formation of

(16) Liu, L.; Tian, R.; Liu, S.; Chen, X.; Guo, L.; Che, Y. *Bioorg. Med. Chem.* **2008**, *16*, 6021–6026.

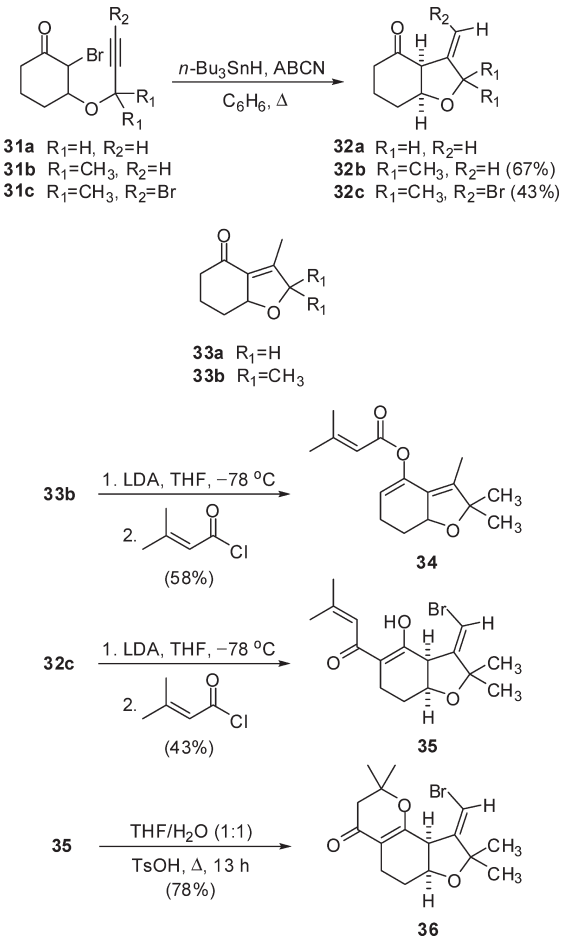
(17) (a) Dulcère, J.-P.; Rodriguez, J.; Santelli, M.; Zahra, J. P. *Tetrahedron Lett.* **1987**, *28*, 2009–2012. (b) Dulcère, J.-P.; Mihoubi, M. N.; Rodriguez, J. *J. Org. Chem.* **1993**, *58*, 5709–5716.



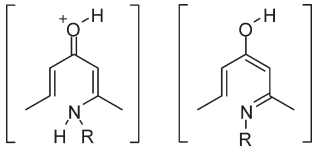
30

the bicyclic ketone **32a** in two steps first by reacting propargyl alcohol with cyclohexenone in the presence of NBS and H_2SO_4 to give the bromo ether **31a** (90−95% yield) and, second, by effecting radical cyclization of **31a** with tri-*n*-butyltin hydride to give **32a** in 88−92% yield. Acid-induced isomerization of **32a** to **33a** took place efficiently. We investigated this transformation starting with cyclohexenone and the dimethyl propargyl alcohol, and the bromo ether **31b** was obtained, albeit in a modest yield (Scheme 3). The bromo ether cyclized in the presence of tri-*n*-butyltin hydride to give the bicyclic ketone **32b** in 67% yield. The *cis* ring fusion was assumed by analogy with related reactions.[17,18] Alkene isomerization of **32b** to **33b** occurred upon treatment with acid,

SCHEME 3



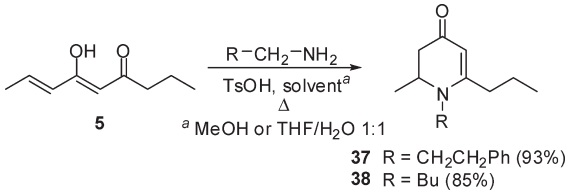
and even during chromatography or during storage at room temperature. An attempt was made to *C*-acylate **33b** with an α,β-unsaturated acid chloride in order to prepare a substrate that might cyclize to a 2,3-dihydro-4*H*-pyran-4-one. However, only the conjugated, *O*-acylated product **34** was obtained. A bromine-substituted propargyl alcohol also added to cyclohexenone, and the resulting dibromo-ether **31c** underwent radical cyclization to provide **32c**. In contrast with **32b**, this bicyclic compound did not isomerize during flash chromatography or upon storage at room temperature. Its kinetic enolate was *C*-acylated by an α,β-unsaturated acid chloride to give **35**. It was gratifying that when **35** was heated in 1:1 THF/water with 0.1 equiv of TsOH, cyclization occurred smoothly to afford the 2,3-dihydro-4*H*-pyran-4-one **36** in 78% yield.



D **E**

Cyclization of α,β-Unsaturated 1,3-Diketones to 2,3-Dihydro-4-pyridinones. Cyclization of either an enamine derived from an α,β-unsaturated 1,3-diketone, in the geometry **D**, or of the corresponding imine in the geometry **E**,[9] might provide 2,3-dihydro-4-pyridinones by ionic or pericyclic pathways. It was hypothesized that if an amine could form the enamine or imine rapidly relative to the rate of cyclization to the 2,3-dihydro-4*H*-pyran-4-one, then one might envisage admixture of an α,β-unsaturated 1,3-diketone with an amine in a suitable medium providing the 2,3-dihydro-4-pyridinone in a single operation. This idea was tested using the α,β-unsaturated 1,3-diketone **5** with 1.1 equiv of aniline, cyclohexanamine, 1-phenylethanamine, 2-phenylethanamine, 2-propanamine, 1-butanamine, and glycine; under reflux in methanol and in THF/water (1:1) in the presence of 0.1 equiv of TsOH. Only 2-phenylethanamine and 1-butanamine provided any 2,3-dihydro-4-pyridinones, and these were isolated in very good yield (Scheme 4). Thus, it seems that the amine must be an unencumbered primary amine. The remainder of the amines gave mixtures of products that seemed by NMR to include enamines and some 2,3-dihydro-4*H*-pyran-4-one **18**.

SCHEME 4

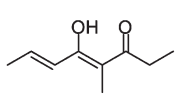
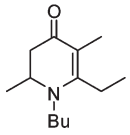
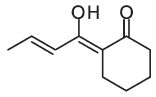
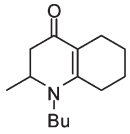
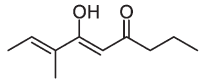
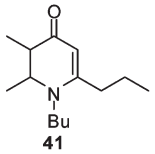
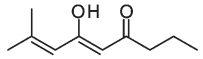
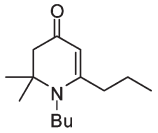
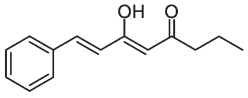
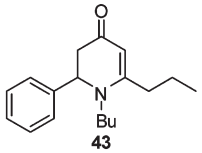
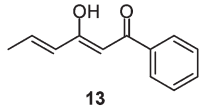
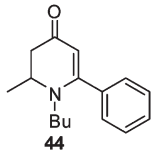
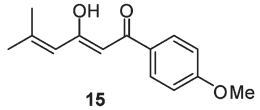
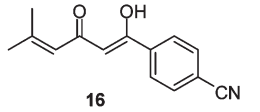


Some other α,β-unsaturated 1,3-diketones were heated with 1-butanamine (5 equiv) in acidic THF/water. The results are shown in Table 3.[19] There is no obvious correlation between the yields of the 2,3-dihydro-4*H*-pyran-4-ones versus the yields of the 2,3-dihydro-4-pyridinones. The most pronounced contrasts were the reactions of **12**, **15**, and **16**. Diketone **12** had failed to produce any 2,3-dihydro-4*H*-pyran-4-one, but 2,3-dihydro-4-pyridinone **43** was obtained,

(18) Schinzer, D.; Jones, P. G.; Obierey, K. *Tetrahedron Lett.* **1994**, *35*, 5853–5856.

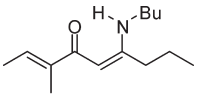
(19) In addition, neither **10** nor **17** gave any cyclized product. Some downfield signals in the ^{1}H NMR spectra of the reaction mixtures suggested that enamines had formed.

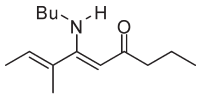
TABLE 3. Cyclization of α,β-Unsaturated 1,3-Diketones to 2,3-Dihydro-4-pyridinones in THF/Water (1:1) with TsOH and 1-Butanamine (5 equiv) with Reaction Times and Isolated Yields

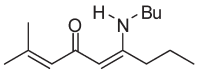
1,3-diketone	2,3-dihydro-4-pyridinone	reaction time yield
 **6**	 **39**	29 h 81%
 **7**	 **40**	3.5 h 83%
 **8**	 **41**	24 h 30%
 **11**	 **42**	23 h 54%
 **12**	 **43**	26 h 40%
 **13**	 **44**	19 h 47%
 **15**	–	23 h 0%
 **16**	–	23 h 0%

although the yield of **43** was modest. More dramatically, diketones **15** and **16** had provided some of the best yields of 2,3-dihydro-4*H*-pyran-4-ones but no 2,3-dihydro-4-pyridinones.

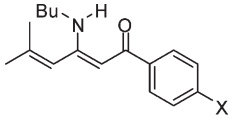
The crude reaction mixtures from **8**, **11**, **12**, and **13** contained material that appeared from the ^{1}H NMR spectra to include enamine moieties. The major enamines were isolated from the reaction of **8**, and these proved to be a 7:1 mixture of **45** and **46**, in a combined yield of 53%. Enamine **47** was obtained in 18% yield from the reaction of **11**. In order to gain some clues regarding the mechanism for the formation of the 2,3-dihydro-4-pyridinones, **47** was reheated in acidic THF/water. After 24 h, **47** was still the major species in solution. There was a minor amount of the 2,3-dihydro-4*H*-pyran-4-one **24** but only a trace of **42**. Also, when the 2,3-dihydro-4*H*-pyran-4-one **18** was heated for 24 h with 1-butanamine in acidic THF/water the major part of the product appeared to be a mixture of enamines, but 2,3-dihydro-4-pyridinone **38** was not detected. Thus, it appeared that a 2,3-dihydro-4-pyridinone was not derived either from the enamine or from the 2,3-dihydro-4*H*-pyran-4-one.

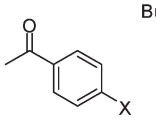

45

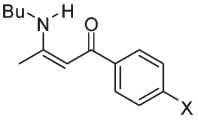

46

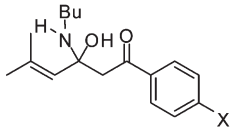

47

1,3-Diketone **15** failed to provide any 2,3-dihydro-4-pyridinone, but three compounds **48**−**50** were identified as the main components of the product mixture. From **16**, the analogous compounds **51**−**53** were the major components in the product mixture. Compounds **48** and **51** were enamines related to **45**−**47**, and, given the experiment with **47**, it can be presumed that they could not cyclize in acidic THF/water. The generation of compounds **49**, **50**, **52**, and **53**, with truncated carbon chains, indicated pathways for the diversion of the α,β-unsaturated 1,3-diketones from the pathway toward the 2,3-dihydro-4-pyridinones. The acetophenones **49** and **52** might have been derived from a protonated form of the common intermediate to enamines **48** and **51**, i.e., hemiaminal **54**, by a retro-aldol process. Enamines **50** and **53** could be rationalized by initial 1,4-attack of the amine, followed by a retro-Mannich reaction, and then by enamine formation from the resulting truncated 1,3-diketone (Scheme 5). That **15** and **16** provided no 2,3-dihydro-4-pyridinones was consistent with the stability of the iminium ion **55** relative to the less substituted iminium ions that would have been produced from most of the other α,β-unsaturated 1,3-diketones.


48 X = OMe
51 X = CN

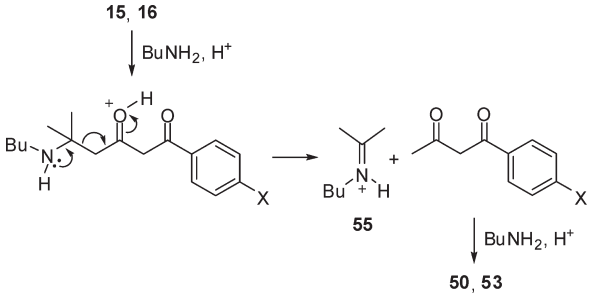

49 X = OMe
52 X = CN


50 X = OMe
53 X = CN

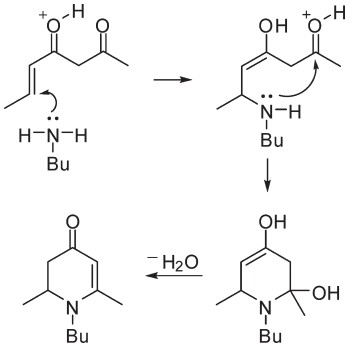

54

With the suggestion that 1,4-additions of the amine may be competitive with the formation of enamines, which did not react further to give 2,3-dihydro-4-pyridinones, the mechanism for the formation of the 2,3-dihydro-4-pyridinones is therefore postulated to be mainly by initial 1,4-addition of the amine followed by intramolecular enamine formation (Scheme 6). Furthermore, it may be suggested that even the formation of the 2,3-dihydro-4*H*-pyran-4-ones might be

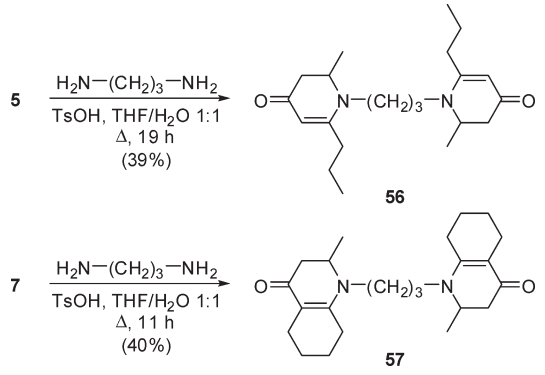
SCHEME 5



SCHEME 6



SCHEME 7



due, at least partly, to an initial 1,4-addition of water to the α,β-unsaturated 1,3-diketones.

Finally, two examples of double reactions of diamines were demonstrated (Scheme 7). When 2 equiv of **5** and 1 equiv of 1,3-propanediamine were heated in acidic THF/water, ^{1}H NMR analysis of the reaction mixture indicated almost complete conversion to **56** (a mixture of diastereomers by NMR). This product was difficult to purify by chromatography on silica gel, and so the isolated yield was a disappointing 39%. Repeating this process with **7** gave **57**, but this was, once again, not well recovered from silica gel (40%).

In conclusion, the efficiency of cyclization of α,β-unsaturated 1,3-diketones to provide 2,3-dihydro-4*H*-pyran-4-ones was viable, except in instances in which the β position of the alkene was either unsubstituted or substituted by a phenyl group. The one-pot cyclization of α,β-unsaturated 1,3-diketones and amines was restricted to primary amines with minimal substitution near the amino-carbon, but yields were adversely affected by reaction pathways leading to enamines and to intermediates that were prone to chain-shortening reactions.

Experimental Section

General Procedure for the Preparation of 2,3-Dihydro-4*H*-pyran-4-ones: 2,3-Dihydro-2-methyl-6-propyl-4*H*-pyran-4-one (18). A solution of α,β-unsaturated 1,3-diketone **5** (38 mg, 0.25 mmol) and TsOH (5 mg, 0.02 mmol) in THF/H_2O (1:1) (6.0 mL) was heated under reflux for 29 h. The solution was brought to rt, and H_2O and ether were added. The aqueous phase was extracted thoroughly with ether. The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash chromatography of the residue using pentane containing an increasing proportion of ether provided **18** (25 mg, 66%) as a liquid, and 9 mg of **5** was recovered. For **18**: IR (film) 1726 (m), 1666 (s), 1603 (s) cm^{-1}; ^{1}H NMR δ 5.32 (1H, s), 4.49 (1H, m), 2.40 (2H, m), 2.21 (2H, m), 1.60 (2H, sextet, J = 7.4 Hz), 1.45 (3H, d, J = 6.4 Hz), 0.95 (3H, t, J = 7.4 Hz); ^{13}C NMR δ 193.0 (0), 177.6 (0), 104.0 (1), 75.6 (1), 42.7 (2), 36.7 (2), 20.4 (3), 19.8 (2), 13.6 (3); HRMS (ESI) 177.0883, calcd for $C_9H_{14}O_2Na^+$ 177.0886.

9-(Bromomethylene)-5,6,6a,8,9,9a-hexahydro-2,2,8,8-tetramethyl-2*H*-furo[2,3-*h*]chromen-4(3*H*)-one (36). Following the procedure for **18**, **35** gave **36** (78%) after 13 h as a solid: mp 116−118 °C; IR (film) 3058 (w), 1674 (m), 1657 (s), 1609 (s) cm^{-1}; ^{1}H NMR δ 6.24 (1H, d, J = 1.2 Hz), 4.37 (1H, m), 3.64 (1H, m), 2.59 (1H, d, J = 16.4 Hz), 2.49 (1H, dd, J = 16.1, 5.0 Hz), 2.43 (1H, d, J = 16.4 Hz), 2.25 (1H, m), 2.09 (1H, m), 1.52 (1H, m), 1.46 (3H, s), 1.37 (3H, s), 1.32 (3H, s), 1.24 (3H, s); ^{13}C NMR δ 192.2 (0), 164.9 (0), 152.0 (0), 110.3 (0), 102.4 (1), 82.4 (0), 79.7 (0), 73.7 (1), 47.7 (1), 47.5 (2), 29.8 (3), 28.2 (3), 27.3 (3), 25.1 (3), 23.8 (2), 14.5 (2); HRMS (ESI) 363.0539, calcd for $C_{16}H_{21}BrO_3Na^+$ 363.0566.

General Procedure for the Preparation of 2,3-Dihydro-4-pyridinones. To a solution of the α,β-unsaturated 1,3-diketone (0.05 M) in THF/water (1:1) was added the amine (for **37** and **38**: 1.1 equiv of 2-phenylethanamine and 1-butanamine; for **39**−**44**: 5 equiv of 1-butanamine) followed by TsOH (10 mol %). The mixture was heated under reflux until TLC indicated the disappearance of the diketone. The mixture was cooled to rt, and H_2O (10 mL) and Et_2O (20 mL) were added. The aqueous phase was re-extracted with Et_2O. The combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash chromatography was carried out using pentane containing an increasing proportion of ether and then EtOAc containing and increasing proportion of MeOH. For reaction times and yields, see Table 3.

2,3-Dihydro-2-methyl-1-(2-phenylethyl)-6-propyl-4-pyridinone (37): viscous liquid; ^{1}H NMR δ 7.33 (2H, m), 7.26 (1H, m), 7.20 (2H, m), 4.92 (1H, s), 3.73 (1H, dt, J = 14.6, 7.2 Hz), 3.50 (1H, dp, J = 6.7, 2.2 Hz), 3.18 (1H, dt, J = 14.6, 7.2 Hz), 2.89 (2H, t, J = 7.2 Hz), 2.67 (1H, dd, J = 16.3, 6.8 Hz), 2.16−1.97 (3H, m), 1.49 (2H, m), 1.18 (3H, d, J = 6.7 Hz), 0.94 (3H, t, J = 7.3 Hz); ^{13}C NMR δ 190.1 (0), 163.0 (0), 138.0 (0), 128.8 (2C, 1), 128.7 (2C, 1), 126.9 (1), 98.3 (1), 54.0 (1), 50.2 (2), 41.6 (2), 36.8 (2), 34.9 (2), 21.2 (2), 14.9 (3), 13.8 (3); HRMS (ESI) 258.1853, calcd for $C_{17}H_{23}NOH^+$ 258.1852.

1-Butyl-2,3-dihydro-2-methyl-6-propyl-4-pyridinone (38): viscous liquid; IR (film) 1733 (m), 1613 (s), 1530 (s) cm^{-1}; ^{1}H NMR δ 4.92 (1H, s), 3.62 (1H, dp, J = 6.7, 2.2 Hz), 3.45 (1H, ddd, J = 14.8, 8.8, 6.6 Hz), 2.95 (1H, ddd, J = 14.6, 9.0, 6.5 Hz), 2.73 (1H, dd, J = 16.2, 6.6 Hz), 2.23 (1H, m), 2.17−2.08 (2H, m), 1.66−1.46 (4H, m) 1.37 (2H, sextet, J = 7.4 Hz), 1.20 (3H, d, J = 6.7 Hz), 0.97 (3H, t, J = 7.3 Hz), 0.96 (3H, t, J = 7.3 Hz); ^{13}C NMR δ 189.9 (0), 163.3 (0), 98.0 (1), 53.5 (1), 48.3 (2), 41.7 (2), 35.2 (2), 32.2 (2),

21.3 (2), 20.0 (2), 14.9 (3), 13.83 (3), 13.80 (3); HRMS (ESI) 210.1847, calcd for $C_{13}H_{23}NOH^+$ 210.1852.

Preparation of Three-Carbon-Tethered 2,3-Dihydro-4-pyridinones. To a solution of the α,β-unsaturated 1,3-diketone (0.05 M, 2 equiv) in THF/water (1:1) was added 1,3-propanediamine (1 equiv) followed by TsOH (10 mol %). The mixture was heated under reflux until TLC indicated the disappearance of the diketone (19 h for **5**, 11 h for **7**). The mixture was cooled to rt, and H_2O (10 mL) and CH_2Cl_2 (20 mL) were added. The aqueous phase was re-extracted thoroughly with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash chromatography was carried out using a stepwise mobile phase proceeding from 50% Et_2O/pentane to 20% to 40% MeOH/EtOAc.

1,1′-(Propane-1,3-diyl)bis(2,3-dihydro-2-methyl-6-propyl-4-pyridinone) (56): 1:1 mixture of diastereomers; viscous liquid; IR (film) 3063 (w), 1709 (w), 1614 (s), 1536 (s) cm^{-1}; ^1H NMR [signal for second diastereomer where discernible] δ 4.92 [4.91] (2H, br s), 3.60 (2H, br sextet, $J = 6.8$ Hz), 3.55−3.45 (2H, m), 3.05−2.96 (2H, m), 2.67 (2H, dd, $J = 16.3$, 6.6 Hz), 2.22−2.04 (6H, m), 1.90 (2H, m), 1.49 (4H, symmetrical m), 1.17 (6H, d, $J = 6.6$ Hz), 0.93 (6H, t, $J = 7.4$ Hz); ^{13}C NMR [signal for second diastereomer where discernible] δ 189.8 (2C, 0), 162.5 [162.4] (2C, 0), 98.9 [98.8] (2C, 1), 53.6 [53.5] (2C, 1), 45.4 [45.3] (2C, 2), 41.8 (2C, 2), 35.2 [35.1] (2C, 2), 30.4 [30.3] (2), 21.14 [21.11] (2C, 2), 14.6 (2C, 3), 13.6 (2C, 3); HRMS (ESI) 369.2500, calcd for $C_{21}H_{34}N_2O_2Na^+$ 369.2512.

1,1′-(Propane-1,3-diyl)bis(2,3,5,6,7,8-hexahydro-2-methylquinolin-4-one) (57): 1:1 mixture of diastereomers; viscous liquid; IR (Nujol) 1602 (s), 1537 (s) cm^{-1}; ^1H NMR [signal for second diastereomer where discernible] δ 3.56−3.46 (4H, m), 2.92 [2.89] (2H, t, $J = 7.3$ Hz), 2.69 [2.66] (2H, dd, $J = 6.6$, 2.7 Hz), 2.36 [2.32] (2H, t, $J = 5.2$ Hz), 2.29−2.08 (8H, m), 1.88−1.78 (2H, pentet, $J = 7.5$ Hz), 1.72 (2H, m), 1.65−1.46 (4H, m), 1.37 (2H, m), 1.13 (6H, d, $J = 6.6$ Hz); ^{13}C NMR [second diastereomer] δ 188.89 [188.87] (2C, 0), 156.4 [156.3] (2C, 0), 105.93 [105.87] (2C, 0), 52.9 [52.8] (2C, 1), 45.2 [45.0] (2C, 2), 41.94 [41.92] (2C, 2), 30.3 [30.2] (2), 27.5 (2C, 2), 22.4 (2C, 2), 21.7 (2C, 2), 21.6 (2C, 2), 14.73 [14.70] (2C, 3); HRMS (ESI) 393.2498, calcd for $C_{23}H_{34}N_2O_2Na^+$ 393.2512.

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