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A Convenient Synthesis of Di- and Trisubstituted γ-Pyrones

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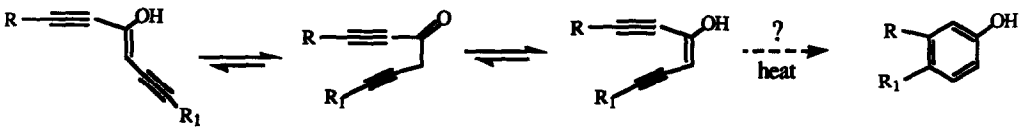
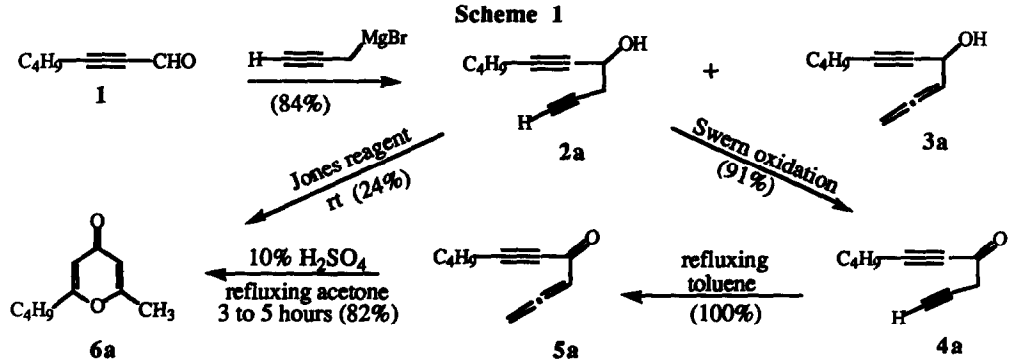
Abstract: Treatment of ketodiynes or allenynones with hot aqueous acid results in the facile formation of di- or tri-substituted γ-pyrones. The mechanism of this new process was established.

The enediyne class of antitumor antibiotics has generated intense interest within the synthetic community.[1] We were curious whether a 3-keto-1,5-diyne would undergo a Bergman cyclization[2] as shown below. If so, a ketone can be carried through a synthesis in numerous forms, offering flexibility in the synthetic design.



To test this concept, we treated ynal **1** with propargyl magnesium bromide to afford alcohol **2a** and allenic alcohol **3a** in a 4:1 ratio, respectively (Scheme 1).[3,4] Although Swern oxidation of **2a** afforded ketodiyne **4a**, this material failed to cycloaromatize under a variety of Bergman conditions and instead afforded allenynone **5a**, an isomerization product.[5] Surprisingly, the use of Jones reagent[6] to oxidize alcohol **2a** gave γ-pyrone **6a** in 24% yield; the balance of the material was allenynone **5a**. Further work

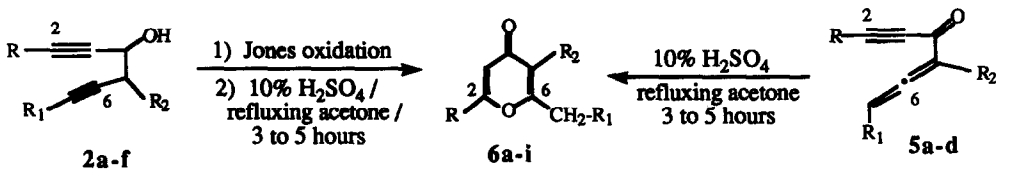
Scheme 1



showed that treatment of **5** with aqueous acid in refluxing acetone produced γ-pyrone **6** in 82% yield. Because the methods commonly used to prepare γ-pyrones are limited to the formation of 2,6-symmetrically substituted analogues,[7-9] we determined the scope of this cyclization and established its mechanism.

Table 1 presents five additional acid-promoted ketodiyne cyclizations which produce γ-pyrones substituted at C(2) and C(6) with different alkyl groups. In these cases, higher yields of pyrones were obtained if the crude oxidation product was cyclized without purification. We have also found that functionalized allenynones produce trisubstituted γ-pyrones using identical cyclization conditions. The requisite allenynone substrates were prepared from allenic alcohols using known procedures.[10,11]

Table 1

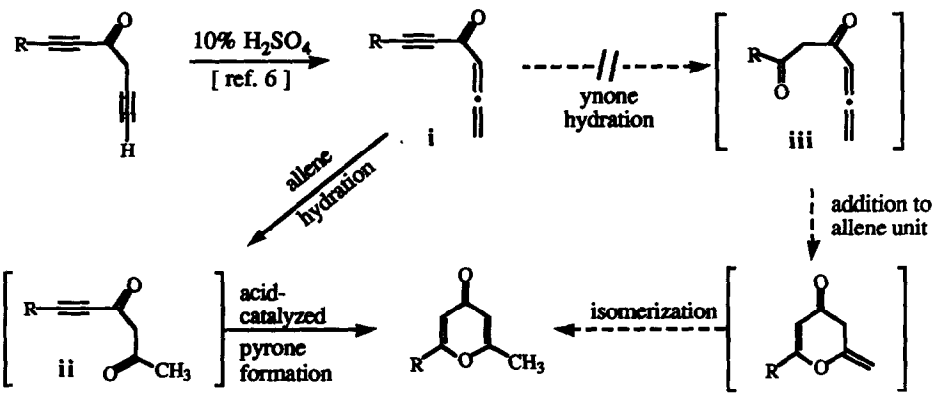


2a-f **6a-i** **5a-d**

Entry	Substrate	R	R^1	R^2	Product	Yield
1	2a	nC_4H_9	H	H	6a	82%
2	2b	CH_3	H	H	6b	75%
3	2c	nC_4H_9	C_6H_5	H	6c	66%
4	2d	nC_4H_9	nC_4H_9	H	6d	70%
5	2e	C_6H_5	nC_4H_9	H	6e	54%
6	2f	C_6H_5	H	H	6f	42%
7	5a	CH_3	H	H	6b	82%
8	5b	C_6H_5	H	CH_3	6g	79%
9	5c	nC_4H_9	H	nC_4H_9	6h	75%
10	5d	C_6H_5	H	nC_4H_9	6i	54%

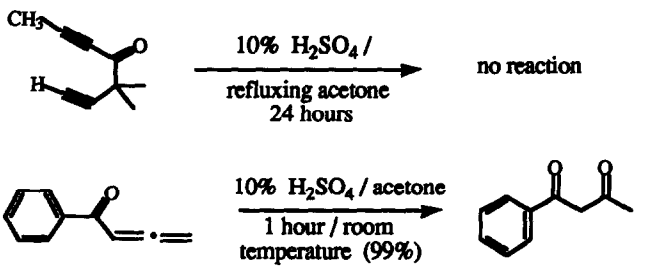
Scheme 2 presents our mechanistic rationalization of these results. The initial step is the irreversible isomerization of the ketodiyne to a conjugated allenynone intermediate as observed in Scheme 1. Hydration of the allenynone unit forms β-diketone ii, which undergoes acid-catalyzed pyrone formation. In theory, addition of water to the ynone moiety would produce β-diketone iii, which can form

Scheme 2



a pyrone upon further reaction with the allene moiety. However, we have established that the ynone moiety is inert under the acidic conditions employed, while the α-allenone functionality hydrolyzes easily (Equation 1).

Equation 1



In summary, we have found that 3-keto-1,5-diynes do not produce phenols via Bergman cyclization but can be hydrated to produce γ-pyrones. Moreover, functionalized di- or trisubstituted γ-pyrones can be easily prepared by cyclizing the appropriately substituted ketodiyne or allenynone precursor.

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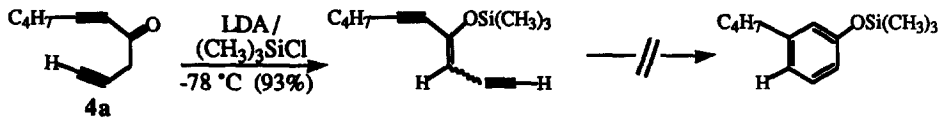
1. a) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Doyle, T. W. J. Am. Chem. Soc. **1987**, *109*, 3461. b) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. J. Am. Chem. Soc. **1987**, *109*, 3464. c) Danishefsky, S. J. ; Mantlo, N. B.; Yamashita, D. S. Schulte, G. J. Am. Chem. Soc. **1988**, *110*, 6890. d) Magnus, P.; Lewis, R. T.; Huffman, J. C. Ibid. **1988**, *110*, 6921. e) Nicolaou, K. C.; Oagawa, Y.; Zuccarello, G.; Kataoka, H. Ibid. **1988**, *110*, 7247. f) Wender, P. A.; Tebbe, M. J. Tetrahedron Lett. **1991**, *32*, 4863. g) Semmelhack, M. F.; Gallagher, J.; Cohen, D. Ibid. **1990**, *31*, 1521.

2. Bergman, R. G. Acct. Chem. Res. **1973**, *6*, 25.

3. a) The spectroscopic data obtained for all new compounds [^{1}H NMR, ^{13}C NMR, IR, and MS] were fully consistent with the assigned structures. b) Reaction conditions have not been optimized. c) All yields are isolated yields.

4. The selectivity of propargylic Grignard reagents can be influenced by reaction conditions. See: Place, P.; Verniere, C.; Gore, J. Tetrahedron **1981**, *37*, 1359.

5. Treatment of ketodiyne **4a** with LDA or other nonnucleophilic bases gave only allenynone **5a**. In addition, while we were able to trap the enolate intermediate as the corresponding silyl enol ether, this intermediate did not cycloaromatize, presumably due to the trapping of a Z enolate.



4a

6. Homopropargylic alcohols form simple allenic ketones upon oxidation with Jones reagent. See: Bol'schedvorskaya, R. L.; Pavlova, G. A.; Garrilov, L. D.; Alekseeva, N. V.; Vereshchagin, L. I. J. Org. Chem. USSR **1972**, *8*, 1927. b) Bertrand, M. C. R. Acad. Sci., Ser. C. **1957**, *244*, 1790.

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8. For other syntheses of γ-pyrones, see: a) McCombie, S. W.; Metz, W. A.; Nazareno, D.; Shankar, B. B.; Tagat, J. J. Org. Chem. **1991**, *56*, 4963. b) Wenkert, E.; Ananthanarayan, T. P.; Ferreira, V. F.; Hofmann, M. G.; Kim, H-S. Ibid. **1990**, *55*, 4975. c) Coleman, R. S.; Grant, E. B. Tetrahedron Lett. **1990**, *31*, 3677.

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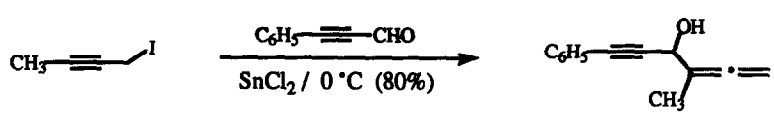
10. For a review of α-oxo-allene preparations, see: Schuster, H. F.; Coppola, G. M. "Allenes in Organic Synthesis," John Wiley and Sons, **1984**, New York, pp. 153-163 and references cited therein.

11. For example, allenynone **5b** was prepared by treating 1-iodo-2-butyne with 3-phenylpropynal, followed by Swern oxidation. See: Mukaiyama, T.; Harada, T. Chem. Lett. **1981**, 621.



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