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REDUCTION OF Δ^2-ISOXAZOLINES-2. A FACILE SYNTHESIS OF 3(2H)-FURANONES.

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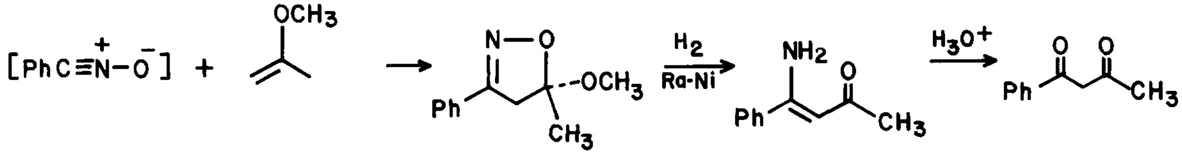
Abstract. A simple synthesis of the 3(2H)-furanone ring system is described.

The 3(2H)-furanone moeity is a central structural unit in a growing number of natural products including simple compounds such as bullatenone and geiparvarin and more complex compounds such as jatrophone, the eremantholides, and lychnophorolide.[2] Many of these 3(2H)-furanone natural products possess significant tumor-inhibiting properties. Previous approaches to the 3(2H)-furanone unit have generally relied upon carbonyl condensation or acetylene hydration.[3] In the context of synthesis of furanone anti-tumor agents, we have developed a new and general approach to the 3(2H)-furanone ring system from simple and readily available building blocks.

Central to our strategy is the well known fact that acid catalyzed cyclodehydration of an α'-hydroxy-1,3-diketone produces an appropriately substituted furanone.[3] Thus, the problem reduces to synthesis of an appropriately substituted diketone or its equivalent. Recently, we have developed a novel approach to the formation of aldol adducts involving cycloaddition, rather than carbonyl addition, in the key carbon-carbon bond forming reaction.[4] The sequence involves nitrile oxide-olefin cycloaddition followed by hydrogenolysis-hydrolysis of the resultant Δ^2-isoxazoline.[5] It is readily apparent that employment of a heteroatom substituted olefin in the cycloaddition reaction would give the functional equivalent of a 1,3-dicarbonyl compound. As illustrated in equation 1, cycloaddition of *in situ* generated phenyl nitrile oxide with 2-methoxypropene produced 3-phenyl-5-methoxy-5-methyl-Δ^2-isoxazoline (1).[6] Raney-nickel catalyzed reduction[7] (15/1 MeOH/H_2O, RT, H_2 1 atm.) gave the expected vinylogous amide 2, which upon exposure to aqueous acid yielded 1-phenyl-1,3-butanedione (3). The overall transformation accomplishes indirect acylation of a carbonyl compound without employment of a carbonyl condensation reaction.

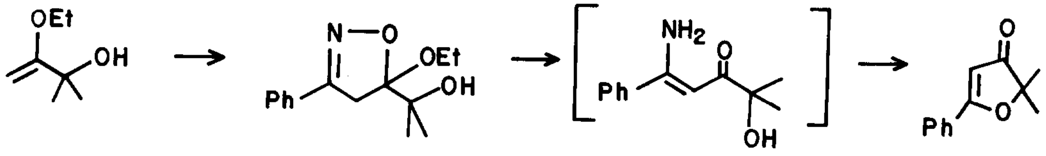
Eq. 1



1 2 3

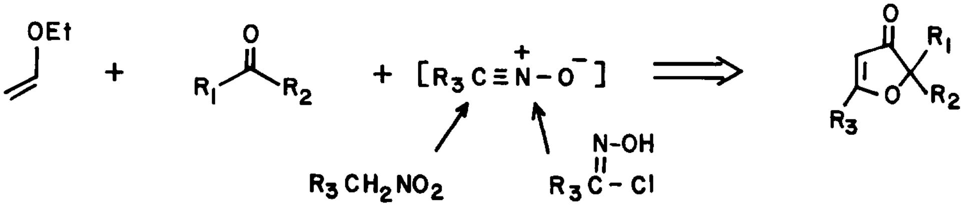
The above strategy has been applied to develop a simple three-component route to substituted 3(2H)-furanones (Eq. 3). This is illustrated by the total synthesis of bullatenone, a simple natural product isolated from a New Zealand shrub[1] (Eq. 2.). Cycloaddition of alcohol 4 (readily available from addition of α-lithioethyl vinyl ether to acetone[8]) and phenyl nitrile oxide gave isoxazoline 5 in 76% yield after recrystallization from Et_2O/hexane (mp 73-75°C). Standard Raney-nickel mediated reduction produced 6, which was not isolated, but directly acidified after removal of the catalyst. In such a manner, bullatenone (7) was produced in 77% yield, mp 66.5-67.5°C(lit. 67.5-68.5), identical in all respects with published data.[3] It is pointed out that 6 is effectively an equivalent to an α'-hydroxy-β-diketone precursor.

Eq. 2



4 5 6 7

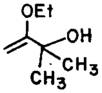
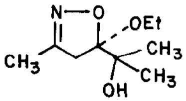
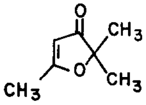
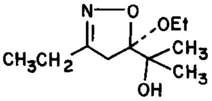
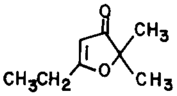
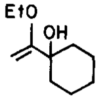
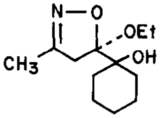
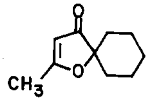
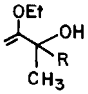
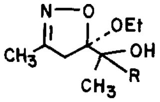
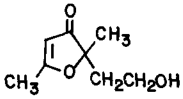
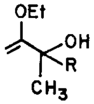
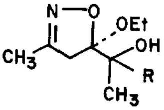
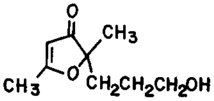
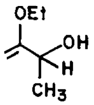
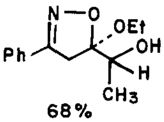
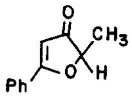
The Table lists other furanones prepared in this manner. 3-Ethyl-5,5-dimethyl-3(2H)-furanone (Entry 2) has been previously converted to geiparvarin in a single step.[3b] Crude yields of the reduction product were generally near quantitative. No effort was made to optimize the conditions employed for cyclodehydration(THF, H_2O, HCL, RT).[3] Aliphatic nitrile oxides were generated in situ from the corresponding nitro compound by treatment with phenyl isocyanate (Et_3N; PhH) according to Mukaiyama.[9b] Under these conditions, tertiary alcohols are not affected. In each case, the furanone is produced in short order with reasonable overall yield from three simple precursors, ethyl vinyl ether, an aldehyde or ketone, and an in situ generated nitrile oxide, as represented below.[10] We hope this method will find general applicability for the synthesis of both simple and complex 3(2H)-furanones.



Eq. 3

Acknowledgement. We are grateful to the American Cancer Society (IN-58S) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. The Health, Research, and Services Foundation is also thanked for partial support.

TABLE

Entry	Nitrile oxide[a] ($RC\equiv N^{+}-O^{-}$)	Enol ether[b]	Cycloadduct	3(2H)-Furanone
1	R = CH_3	 4	 76%	 77%
2	CH_3CH_2	4	 98% (mp 73.5-75)	 65%
3	CH_3		 94% (mp 68-68.5)	 66%
4	CH_3	 [c] R = CH_2CH_2OTHP	 [c,d] 80%	 50%
5	CH_3	 R = $CH_2CH_2CH_2OSi$ ±	 [c,d] 78%	 51%
6	Ph[e]		 [c] 68%	 62% (mp 60-62°)

Footnotes to the Table

a) generated *in situ* from the corresponding primary nitro compound[9]
b) prepared by addition of α-lithioethyl vinyl ether to the appropriate aldehyde or ketone[8].
c) mixture of diastereomers
d) the blocking group is cleaved during cyclodehydration
e) generated from the oxime chloride, see ref. 6.

References

1) a. Recipient of a Dreyfus Foundation Grant for Newly Appointed Young Faculty in Chemistry (1981-86). b. Univ. of Pittsburgh undergraduate research participant.

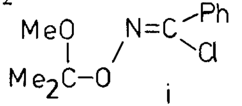
2) Bullatenone: Parker, W.; Raphael, R. A.; Wilkinson, D. I. *J. Chem. Soc.* (1958), 3871. Geiparvarin: Dreyer, D. L.; Lee, A. *Phytochemistry*, (1972), *11*, 763. Eremantholides: LeQuesne, P. W.; Levery, S. B.; Menachery, M.D.; Brennan, T. F.; Raffauf, R. F., *J. Chem. Soc. Perkin Trans. I* (1978), 1572. Lychnophorolide: LeQuesne, P. W.; Menachery, M.D.; Pastore, M. P.; Kelley, C. J.; Brennan, T. F.; Onan, K. D.; Raffauf, R. F., *J. Org. Chem.* (1982), *47*, 1519.

3) a. For references dealing with the synthesis and chemistry of 3(2H)-furanones see: Smith, A. B., III; Levenberg, P. A.; Jerris, P. F.; Scarborough, R. M., Jr.; Wovkulich, P. M., *J. Am. Chem. Soc.* (1981), *103*, 1501. b. Jerris, P. J.; Smith, A. B., III, *Tetrahedron Lett.* (1980), *21*, 711.

4) Curran, D. P. *J. Am. Chem. Soc.* (1982), *104*, 4024. Curran, D. P. manuscript submitted.

5) For an approach based on isoxazoles see: Casnati, G.; Quilico, A.; Ricca, A.; Vita Finzi, P. *Gazz. Chem. Ital.* (1966), *96*, 1073. Casnati, G.; Ricca, A. *Tetrahedron Lett.* (1967), 327.

6) Interestingly, cycloaddition under the normal conditions,[9a] (addition of Et_3N to an ether solution of olefin and oxime chloride) gave only traces of the expected cycloadduct. The major product was identified as i based on the following data: ^1H-NMR (300 MHz, $CDCl_3$) δ 7.92(2H,dd); 7.41(3H,m), 3.32(3H,s); 1.63(6H,s); ^{13}C-NMR(75MHz, $CDCl_3$) δ 137.8(s), 133.2(s), 130.4(d), 128.3(d), 127.4(d), 105.6(s), 49.4(q), 23.9(q); MS 229, 227(M+); 198, 196 ($M-OCH_3$), calc: 196.0529, found: 196.0529. Anal. C,H. This problem was avoided by brief pre-generation of the nitrile oxide at 0°C (Et_3N, Et_2O) followed by olefin addition.



i

7. Boric acid was not required for these reductions and was generally omitted (see ref. 4).

8) Baldwin, J. E.; Hofle, G.; Lever, O. W., Jr. *J. Am. Chem. Soc.* (1974), *96*, 7125. Soderquist, J. A.; Hsu, G. J.-H. *Organomet.* (1982), *1*, 830.

9) a. Grundmann, C.; Grunanger, P. "The Nitrile Oxides", Springer-Verlag, New York (1971). b. Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* (1960), *82*, 5339.

10) All new compounds exhibited satisfactory spectral data. New furanones gave satisfactory elemental analysis and/or high resolution mass spectra.

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