Unsaturated Nitriles: A Domino Ozonolysis−Aldol Synthesis of Highly Reactive Oxonitriles

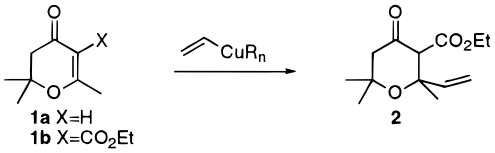
Fraser F. Fleming,* Adrian Huang, Vaqar A. Sharief, and Yifang Pu

Department of Chemistry and Biochemistry, Duquesne University, Pittsburgh, Pennsylvania 15282

Received February 28, 1997

Cycloalkenones have been valued as synthetic precursors almost since the birth of natural product synthesis.[1] The importance of cyclohexenones and cyclopentenones[2] as Michael acceptors is illustrated in a recent review[3] of organocopper reagents employed in natural product syntheses. Over half of the conjugate additions surveyed involve the reaction of an organocopper reagent with a cyclohexenone or a cyclopentenone.[3]

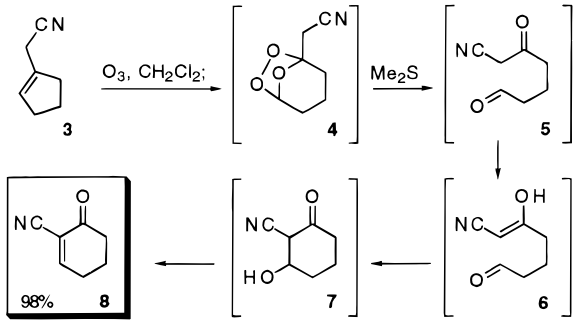
The demand for highly reactive cycloalkenones has led several groups[4] to prepare cycloalkenones that contain an additional electron-withdrawing group on the α-carbon. These doubly activated alkenes[5] are extremely reactive and have been employed in Diels−Alder[6] and Michael[7] reactions that are otherwise unsuccessful. For example,[8] in the synthesis of a forskolin analog, **1a** gave no conjugate addition products when treated with a variety of organocopper reagents, whereas **1b** smoothly reacted to afford the conjugate addition product **2** (eq 1).



(1)

The importance of highly activated Michael acceptors stimulated us to synthesize cyclic 1-oxo-2-cycloalkenyl-2-carbonitriles as potent electrophiles for nitrile-based conjugate addition reactions.[9] We envisaged a domino ozonolysis−aldol sequence[10] to unmask a β-ketonitrile and allow for a subsequent intramolecular aldol condensation followed by dehydration of the resultant aldol (Scheme 1). Execution of this sequence by ozonolysis of **3** in dichloromethane provides an intermediate ozonide **4**[11] that directly affords the desired 1-oxo-2-cyclohexenyl-2-carbonitrile[12] (**8**, 98% yield) upon exposure to dimethyl sulfide.[13] *The reaction proceeds under remarkably mild conditions, simply upon stirring the intermediate ozonide at room temperature in dichloromethane with no added acid or base.* The high efficiency and mild conditions of this domino ozonolysis−aldol sequence reflects the facile enolization[14] of ketonitriles and the rapid dehydration of cyano-aldols.[15]

Scheme 1



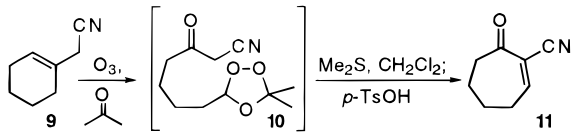
Direct extension of this domino ozonolysis−aldol sequence to the analogous seven-membered ring is operationally simple but inefficient. Ozonolysis of **9** (CH_2Cl_2, −78 °C) and reduction of the intermediate ozonide cleanly affords the desired nitrile **11** (13% yield), but the main product from this reaction is an insoluble polymeric material that is presumably an oligomeric peroxide. Bunnelle has performed several clever experiments[16] to show that oligomers form during cyclohexene ozonolyses when the intermediate carbonyl oxide is geometrically constrained from an intramolecular [3 + 2] cycloaddition with the ketone group. We minimized the polymerization by performing the ozonolysis of **9** in acetone that effectively intercepts the carbonyl oxide in an *intermolecular* cycloaddition (Scheme 2). Reduction of the resultant ozonide **10** and exposure to *p*-toluenesulfonic acid provides 1-oxo-2-cycloheptenyl-2-carbonitrile (**11**) in 58% yield.

We have generalized this domino ozonolysis−aldol sequence to synthesize substituted 5- and 6-membered oxonitriles. The precursors to these substituted oxonitriles are the ω-alkenyl β-ketonitriles **13** that are readily

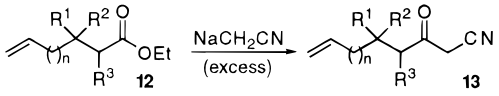
(1) Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1285.
(2) Ramaiah, M. *Synthesis* **1984**, 529.
(3) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.
(4) (a) Crimmins, M. T.; Huang, S.; Guise, L. E.; Lacy, D. B. *Tetrahedron Lett.* **1995**, *36*, 7061. (b) Funk, R. L.; Fitzgerald, J. F.; Olmstead, T. A.; Para, K. S.; Wos, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 8849. (c) Schultz, A. G.; Harrington, R. E. *J. Am. Chem. Soc.* **1991**, *113*, 4926. (d) Posner, G. H.; Mallamo, J. P.; Hulce, M.; Frye, L. L. *J. Am. Chem. Soc.* **1982**, *104*, 4180.
(5) For doubly activated alkenes prepared by selenoxide elimination see: (a) Reich, H. J.; Wollowitz, S. *Org. React.* **1993**, *44*, 1 and Table XI 254−272 in particular. (b) Liu, H.-J.; Yeh, W.-L.; Browne, E. N. C. *Can. J. Chem.* **1995**, *73*, 1135.
(6) (a) Liu, H.-J.; Browne, E. N. C. *Can. J. Chem.* **1987**, *65*, 1262. (b) Caine, D.; Harrison, C. R.; VanDerveer, D. G. *Tetrahedron Lett.* **1983**, *24*, 1353.
(7) (a) Lane, S.; Taylor, R. J. K. *Tetrahedron Lett.* **1985**, *26*, 2821. (b) Levison, B. S.; Miller, D. B.; Salomon, R. G. *Tetrahedron Lett.* **1984**, *25*, 4633.
(8) Boring, D. L.; Sindelar, R. D. *J. Org. Chem.* **1988**, *53*, 3617.
(9) (a) Fleming, F. F.; Pak, J. J. *J. Org. Chem.* **1995**, *60*, 4299. (b) Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305.
(10) Kretchmer, R. A.; Thompson, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 3379.
(11) Direct cyclization of the intermediate carbonyl oxide with the ketonitrile is precluded since the intermediate ozonide **4** has been isolated and characterized: Tzou, J.-R.; Huang, A.; Fleming, F. F.; Norman, R. E.; Chang, S.-C. *Acta Crystallogr.* **1996**, *C52*, 1012. Dimethyl sulfide reduction of **4** affords **8** in comparable yield.
(12) We prefer to name these compounds as nitriles in accordance with IUPAC nomenclature since the trivial name "α-cyanocyclohexenone" de-emphasizes the profound effect of the nitrile group on the reactivity of this compound: Fleming, F. F.; Pu, Y.; Tercek, F. *J. Org. Chem.*, submitted.
(13) **General Procedure.** A stream of ozone is passed through a cold (−78 °C), dichloromethane solution of the unsaturated nitrile until the distinctive blue color of ozone is observed. Ozonolysis is then terminated, and the excess ozone is displaced by passing a stream of nitrogen through the solution for 5−10 min. The solution is allowed to warm to room temperature, neat dimethyl sulfide is added, and the solution is then allowed to stir at room temperature for 5−30 h. Concentration of the crude product, followed by radial chromatography, provides the nitriles **14a**−**d**. The syntheses of **14a** and **14b** require terminating the ozonolysis immediately upon observation of excess ozone, purging with nitrogen, and then the dropwise addition of dimethyl sulfide at −78 °C. *Caution*: Care must be taken to prevent contact with these oxonitriles since minute quantities of these compounds, particularly **14a** and **14b**, cause headaches.
(14) Elnagdi, M. H.; Elmoghayar, M. R. H.; Elgemeie, G. E. H. *Synthesis* **1984**, 1.
(15) DiBiase, S. A.; Lipisko, B. A., Haag, A.; Wolak, R. A.; Gokel, G. W. *J. Org. Chem.* **1979**, *44*, 4640.
(16) Bunnelle, W. H. *Adv. Cycloaddit.* **1993**, *3*, 67.

S0022-3263(97)00381-2 CCC: $14.00

Scheme 2



prepared[17] from the corresponding ω-alkenyl esters[18] **12** by treatment with excess sodioacetonitrile (eq 2).

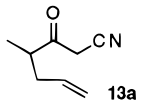
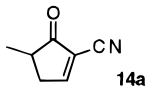
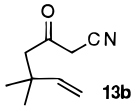
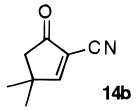
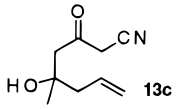
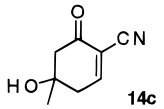
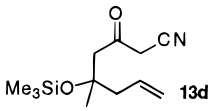
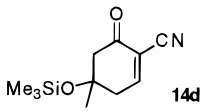


(2)

Ozonolysis of the β-ketonitriles **13a**−**d** proceeds cleanly and efficiently to provide the corresponding oxonitriles **14a**−**d** (Table 1). The cyclization of the intermediate aldehydes varies significantly with **13c** and **13d** cyclizing upon reduction with dimethyl sulfide. In contrast, the aldehydes from **13a** and **13b** cyclize much more slowly, and complete cyclization only occurs during silica gel chromatography. Silica gel is known to catalyze a related intermolecular Knoevenagel condensation.[19]

The domino ozonolysis−aldol sequence is effective with substituted ketonitriles and is even effective when the aldehyde intermediate is flanked by a *gem*-dimethyl group (entry 2, Table 1). The domino ozonolysis−aldol reaction of **13c** demonstrates that this domino reaction sequence tolerates labile functionality, since no dehydration occurs with any intermediates or the product. The high yield obtained with **13c** establishes that dehydration to aromatic phenols does not complicate these reactions.

Table 1. Tandem Ozonolysis−Aldol Cyclization of Unsaturated Ketonitriles

Entry	Substrate	Product	Yield (%)
1	 **13a**	 **14a**	83
2	 **13b**	 **14b**	91
3	 **13c**	 **14c**	98
4	 **13d**	 **14d**	57

The domino ozonolysis−aldol cyclization is a rapid and efficient method for preparing cyclic five-, six-, and seven-membered oxonitriles with various substitution patterns. Having developed a one-pot synthesis of cyclic oxonitriles, we are currently exploiting the unique reactivity of these highly activated alkenes.

Acknowledgment. Financial support from the Jacob and Frieda Hunkele Charitable Foundation and the Kresge Foundation is gratefully acknowledged.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of all new compounds and experimental procedures (24 pages).

JO9703818

(17) Eby, C. J.; Hauser, C. R. *J. Am. Chem. Soc.* **1957**, *79*, 723.

(18) Ethyl 2-methyl-4-pentenoate and ethyl 3,3-dimethyl-4-pentenoate are commercially available. Ethyl 3-hydroxy-3-methyl-5-hexenoate was prepared by a modification of the literature method: Wilson, W. K.; Baca, S. B.; Barber, Y. J.; Scallen, T. J.; Morrow, C. J. *J. Org. Chem.* **1983**, *48*, 3960. 5-Methyl-5-[(trimethylsilyl)oxy]-3-oxo-7-octenenitrile (**13d**) was prepared by silylation of **13c**.

(19) Brillon, D.; Sauvé, G. *J. Org. Chem.* **1992**, *57*, 1838.