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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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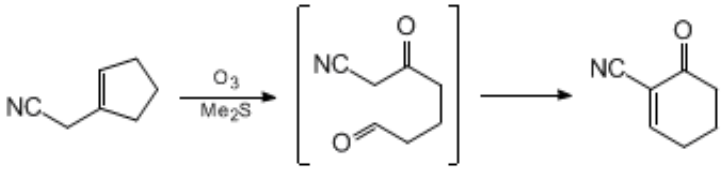
1-OXO-2-CYCLOHEXENYL-2-CARBONITRILE

[1-Cyclohexene-1-acetonitrile, 6-oxo-]



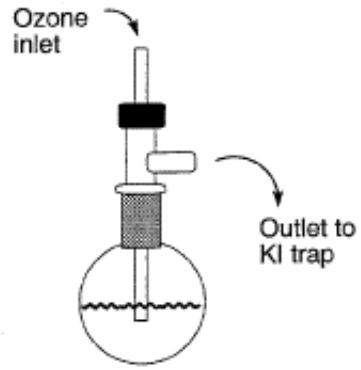
Submitted by Fraser F. Fleming[1] and Brian C. Shook[1] .
Checked by Anne F. Vergne and Marvin J. Miller.

1. Procedure

Caution! Ozone is extremely toxic and can react explosively with certain oxidizable substances. Ozone also reacts with some compounds to form explosive and shock-sensitive products. Ozone should only be handled by individuals trained in its proper and safe use and all operations should be carried out in a well-ventilated fume hood behind a protective safety shield. [Note added September 2009].

1-Oxo-2-cyclohexenyl-2-carbonitrile . A dry, 100-mL, round-bottomed flask containing a magnetic stirring bar is fitted with an inlet adapter for ozonolysis (Note 1, Figure 1) and charged with 1-cyclopenteneacetonitrile (5.0 g, 46.7 mmol, Note 2) and 60 mL of dry dichloromethane (Note 3). A gentle stream of dry ozone is passed through the solution and the flask is immediately cooled to –78°C (Note 4). Ozonolysis is continued until the distinctive blue color of excess ozone is first observed, ozonolysis is then terminated, and the excess ozone is removed by purging with a stream of nitrogen for 5-10 min. The solution is allowed to warm to room temperature, the ozonolysis adapter is replaced with a rubber septum, and neat dimethyl sulfide (3.9 g, 62.1 mmol, Note 5) is added via syringe. The solution is allowed to stir at room temperature for 36 hr during which time the solution changes in color from a pale yellow to dark red. The resulting solution is concentrated under reduced pressure using a rotary evaporator, and the resulting thick, red syrup is diluted with 40 mL of ethyl acetate and washed with water (3 × 25 mL, Note 6). The aqueous phase is extracted with ethyl acetate (3 × 25 mL), the organic phases are combined, rinsed with brine in order to remove all DMSO, dried ($MgSO_4$), filtered, and concentrated. The residual red oil (5.55 g, 98%) contains only trace impurities and can be used without purification in most cases (Note 7). If required, further purification is achieved by rapid radial chromatography (Note 8) on a 2-mm plate using the solvent delivery tip designed for a 4-mm plate and eluting with 50% ethyl acetate-hexane (Note 9). The desired fractions are combined and concentrated to provide 1-oxo-2-cyclohexenyl-2-carbonitrile (4.8 g, 85% yield) as a pink oil (Note 10).

Figure 1



2. Notes

1. A short length of glass tubing (I. D. = 3 mm) is submerged (1 cm) beneath the surface of the solvent and the outlet tubing is immersed in a saturated solution of potassium iodide .[2]
2. 1-Cyclopenteneacetonitrile was purchased from Oakwood Products and purified by Kugelrhor distillation (50-60°C at 5 mm) prior to ozonolysis. 1-Cyclopenteneacetonitrile from other suppliers (Aldrich and Acros) was treated similarly.
3. Dichloromethane was distilled from calcium hydride .
4. The ozone is dried by passing the gas through a trap containing concentrated sulfuric acid . The ozonolysis is initiated prior to cooling to –78°C to prevent a vacuum from forming that would otherwise cause the potassium iodide solution to be drawn into the reaction flask.
5. The dimethyl sulfide was purchased from Aldrich Chemical Company, Inc. , and used without purification.
6. This extraction procedure ensures removal of the dimethyl sulfoxide that is produced in the reaction.
7. The crude material reacts conjugately with phenylmagnesium bromide affording the addition product in 49% yield compared to 55% obtained using chromatographically pure 1-oxo-2-cyclohexenyl-2-carbonitrile .[3]
8. Rapid radial chromatography is essential since column chromatography results in significant irreversible adsorption of 1-oxo-2-cyclohexenyl-2-carbonitrile . For example, column chromatography of a relatively pure 3.0-g sample afforded only 0.5 g of pure 1-oxo-2-cyclohexenyl-2-carbonitrile . However, the checkers observed that a sample, purified as described by radial chromatography, survived flushing through a plug of silica gel.
9. The crude oxonitrile is dissolved in 10 mL of 50% ethyl acetate-hexane solution to afford a homogeneous solution. Incomplete removal of DMSO (Note 6) results in a two-phase mixture that, if loaded directly onto the silica plate, results in a diminished yield through partial absorption of the oxonitrile on the silica gel.
10. The product solidifies on standing at –4°C and can be stored neat at this temperature for several weeks or as a solution in benzene for at least two months. The spectral data are as follows: IR (film) cm^{-1}: 2233, 1698, 1615 ; ^{1}H NMR δ: 2.10 (br quintet, 2 H, J = 6), 2.53-2.61 (m, 4 H), 7.75 (t, 1 H, J = 4.2) ; ^{13}C NMR δ: 21.2 (t), 26.3 (t), 36.9 (t), 114.0 (s), 117.3 (s), 163.4 (d), 192.0 (s) . MS m/e 122 ($M + H^{+}$).

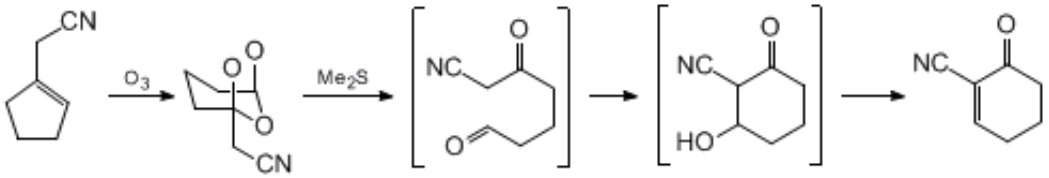
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

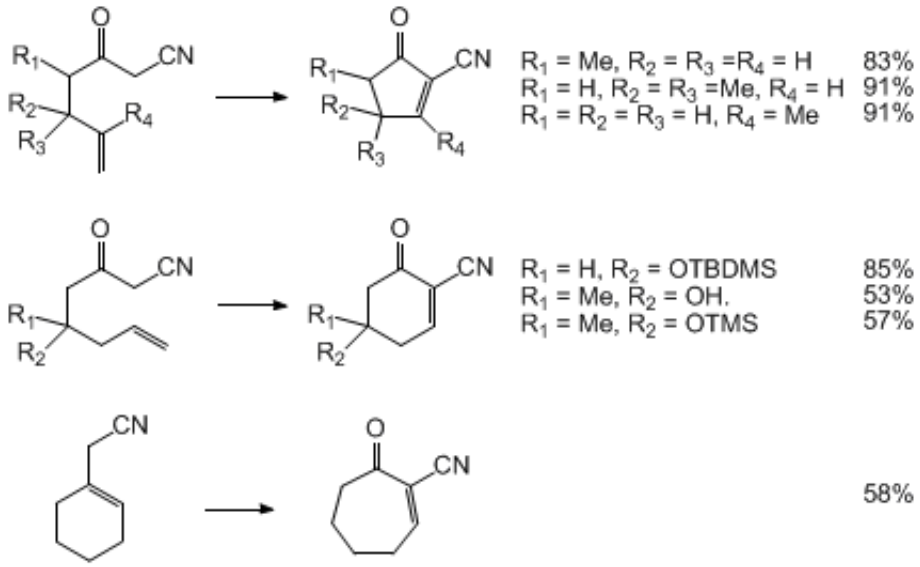
3. Discussion

Highly electron-deficient alkenes are valuable reactants for both cycloaddition and conjugate addition reactions. The demand for highly reactive cycloalkenones has resulted in several syntheses of cycloalkenones containing an additional electron-withdrawing group on the α-carbon.[4] Oxonitriles represent an ideal compromise between high reactivity and stability toward storage and chromatography.[5]

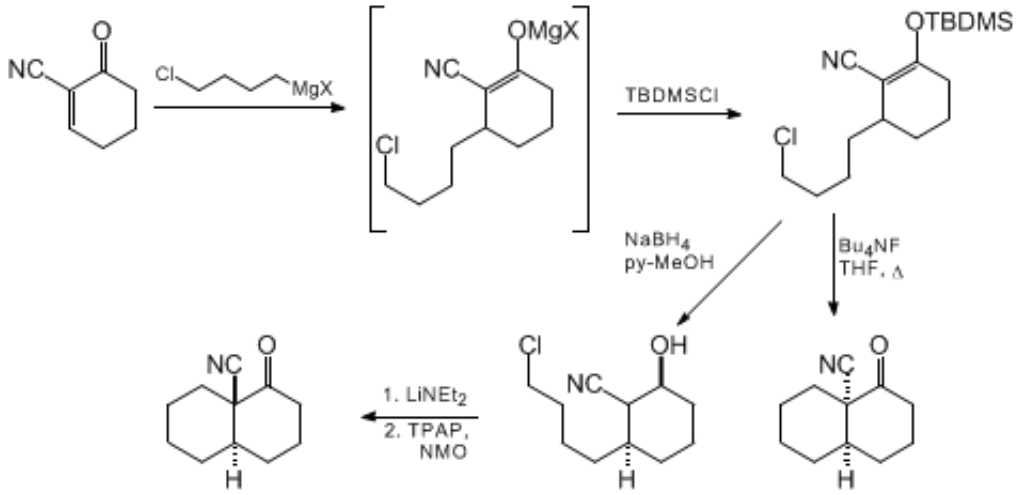
The conversion of cyclopentenacetonitrile to 1-oxo-2-cyclohexenyl-2-carbonitrile proceeds by a domino ozonolysis-aldol sequence (Scheme 1).[6] Isolation and characterization of the ozonide[7] preclude the direct cyclization of the intermediate carbonyl oxide and establish that the cyclization occurs after the addition of dimethyl sulfide . Subsequent formation of the bis-oxonitrile (^{1}H NMR analysis) occurs rapidly and is followed by a slower cyclization-dehydration to afford 1-oxo-2-cyclohexenyl-2-carbonitrile .



The domino ozonolysis-aldol sequence represents a general method for preparing 5-, 6-, and 7-membered cyclic oxonitriles (Scheme 2).[6] Cyclization to 6-membered ring oxonitriles proceeds as for the parent system, 1-oxo-2-cyclohexenyl-2-carbonitrile , whereas the corresponding 5- and 7-membered oxonitriles are less prone to cyclization. Cyclization of the 5- and 7-membered oxonitriles requires exposure of the aldehyde intermediates to acid or base in order to promote the geometrically more challenging cyclization.[6]



1-Oxo-2-cyclohexenyl-2-carbonitrile is an exceptional Michael acceptor that reacts conjugately with Grignard reagents without catalysis.[3] In most cases the intermediate enolates are silylated to afford substituted β-siloxy unsaturated nitriles, several of which are excellent precursors to cis- and trans-decalins (Scheme 3).[8] For example, unmasking the latent ketone enolate of siloxy unsaturated nitriles provides the cis-decalin in excellent yield while the trans-decalin is obtained from the same precursor by cyclizing the corresponding nitrile anion.



References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Oxo-2-cyclohexenyl-2-carbonitrile:
1-Cyclohexene-1-carbonitrile, 6-oxo- (11); (91624-93-0)

1-Cyclopenteneacetonitrile:
1-Cyclopentene-1-acetonitrile (9); (22734-04-9)

Ozone (8,9); (10028-15-6)

Dimethyl sulfide:
Methyl sulfide (8);
Methane, thiobis- (9); (75-18-3)