



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

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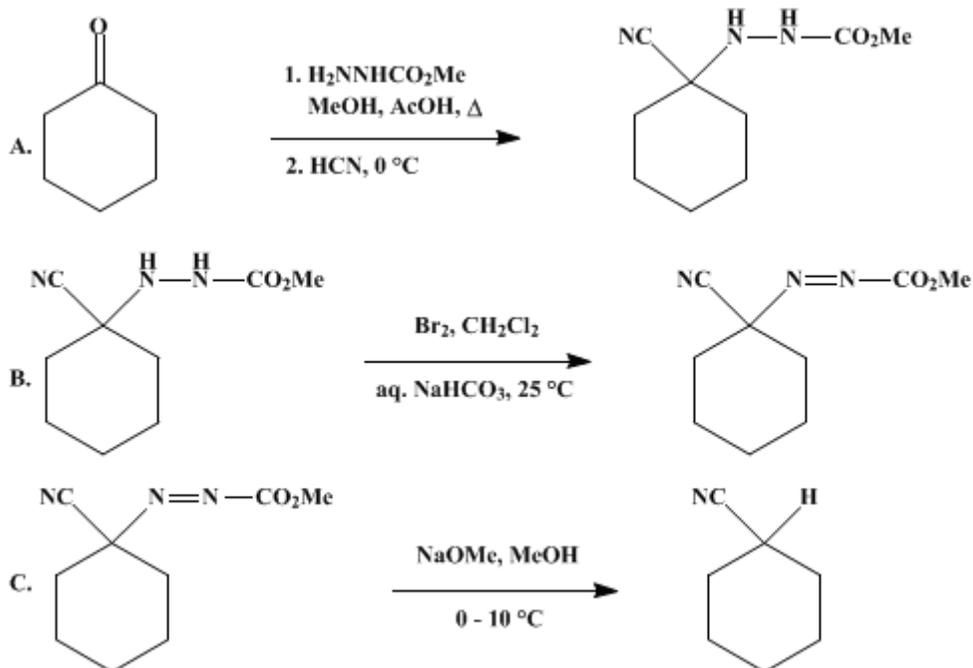
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 6, p.334 (1988); Vol. 58, p.101 (1978).*

## NITRILES FROM KETONES: CYCLOHEXANECARBONITRILE



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### 1. Procedure

*Caution! Because of the toxicity of hydrogen cyanide, this procedure should be conducted in a well-ventilated hood, and rubber gloves should be worn. (See also (Note 3).)*

A. *Methyl 2-(1-cyanocyclohexyl)hydrazine carboxylate (1)*. A 100-ml., three-necked flask equipped with a reflux condenser, thermometer, magnetic stirring bar, and gas-exhaust tube (Note 1) is charged with 9.0 g. (0.10 mole) of methyl carbazate (Note 2), 20 ml. of methanol, 2 drops of acetic acid, and 9.8 g. (0.10 mole) of cyclohexanone. The resulting mixture is refluxed for 30 minutes, then cooled to 0° and treated with 6 ml. (0.15 mole) of hydrogen cyanide (Note 3), added dropwise over a period of 3 minutes. After approximately 15 minutes the solution is allowed to warm to room temperature, during which time the hydrazine **1** crystallizes (Note 4) and (Note 5). After 2 hours the resulting mixture is vacuum filtered, and the crystalline residue is washed with 10 ml. of cold methanol (Note 6), yielding 17.7 g. of hydrazine **1**. Concentration of the filtrate provides an additional 1.4 g. of product. The total yield of crude hydrazine **1**, m.p. 130–133°, (Note 7) is 97%. Recrystallization (methanol–pentane) provides an analytically pure sample, m.p. 135–136°.

B. *Methyl 2-(1-cyanocyclohexyl)diazene carboxylate (2)*. A 5.5 M solution of bromine in dichloromethane is added dropwise to a vigorously stirred mixture of 19.1 g. (0.0970 mole) of hydrazine **1**, 75 ml. of dichloromethane, 75 ml. of water, and 22 g. (0.26 mole) of sodium hydrogen carbonate in a 250-ml. flask, until a persistent, positive potassium iodide–starch paper test is obtained (Note 8). Excess bromine is discharged with aqueous sodium sulfite, the phases are separated, and the aqueous phase is extracted with two 50-ml. portions of dichloromethane. The combined organic extracts are washed with 30 ml. of water, dried over magnesium sulfate, filtered, concentrated using a rotary evaporator, and distilled, yielding 17.3 g. (93%) of the diazene **2** as a clear, bright yellow oil, b.p. 95–97° (0.2 mm.) (Note 7).

C. *Cyclohexanecarbonitrile* (**3**). A 100-ml., three-necked, round-bottomed flask fitted with a thermometer, a magnetic stirring bar, and an addition funnel is charged with 2.7 g. (0.050 mole) of sodium methoxide and 25 ml. of methanol. The solution is cooled in ice and stirred while a solution of 17.3 g. (0.0887 mole) of diazene **2** in 10 ml. of methanol is added dropwise at a rate that maintains the solution temperature at 0–10° (Note 9). Stirring is continued for an additional 30 minutes at ambient temperature, and the mixture is poured into 70 ml. of water. The resulting solution is extracted with five 20-ml. portions of pentane, and the combined organic extracts are dried over magnesium sulfate, filtered, concentrated, and distilled to provide 8.6–9.4 g. (78–86%) of carbonitrile **3**, b.p. 117–119° (90 mm.) (Note 10).

## 2. Notes

1. The tube is connected to the top of the reflux condenser and attached to a length of tygon tubing. The end of the tubing is positioned in the exhaust vent of the hood to remove any hydrogen cyanide vapor.
2. Methyl carbazate was prepared by the method of Diels.<sup>4</sup> This reagent is available from Aldrich Chemical Company, Inc., under the name methyl hydrazinocarboxylate. All other chemicals used in this sequence were of the highest purity commercially available and were not further purified before use.
3. Hydrogen cyanide can be purchased from Fumico Inc., Amarillo, Texas. When large amounts of HCN are used, it is recommended that amyl nitrite pearls and an oxygen cylinder with mask be available. These in combination are effective antidotes for HCN poisoning. The checkers prepared HCN according to the method in *Org. Synth., Coll. Vol. 1*, 314 (1941). The use of smaller quantities of HCN results in slower reaction and reduced yield.
4. Spontaneous crystallization usually occurs within 30 minutes; if not, crystallization is induced by scratching the bottom of the reaction flask.
5. The solid formed at this point usually interferes with stirring. The yield of product, however, is not affected by the nature of mixing beyond this point.
6. The methanol is used to transfer any residual material from the reaction flask as well as to wash the residue.
7. Further purification of this intermediate is unnecessary for the preparation of nitriles.
8. The endpoint of this oxidation is indicated by the appearance in the reaction mixture of a red-orange color caused by excess bromine.
9. Nitrogen is vigorously and instantaneously evolved as each drop is added.
10. Physical and analytical characterizations of cyclohexanecarbonitrile (**3**) agree with literature reports:<sup>5</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>),  $\delta$  (multiplicity, number of protons, assignment): 1.30–2.00 (m, 10H, 5CH<sub>2</sub>), 2.40–2.90 (m, 1H, CHCN). The average overall yield of cyclohexanecarbonitrile (**3**) from cyclohexanone is 85% when the diazene **2** is distilled and 86–90% when crude diazene is used directly. The submitter reported 8.9 g. (92%) of carbonitrile **3**.

## 3. Discussion

The transformation of ketones to nitriles has been accomplished with varying success using several methods including cyanide displacement reactions of acetates<sup>6</sup> and halides<sup>7</sup> obtained from ketones; cyanohydrin formation, dehydration, and reduction of the unsaturated nitriles;<sup>8</sup> reaction of tosylhydrazones with potassium cyanide followed by pyrolysis of the cyanohydrazine;<sup>9</sup> and reaction of tosylmethylisocyanide with ketones.<sup>10</sup> Related transformations of ketones and ketone derivatives to nitrile derivatives have also been reported.<sup>11</sup>

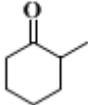
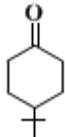
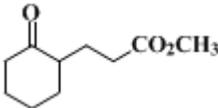
This procedure uses readily available reagents and provides a simple, efficient method for nitrile synthesis. The entire sequence of four steps can be performed in a single day. Although product formation in the second step is presumably thermodynamically controlled, the cyanohydrazine is favored in all cases studied except with aryl ketones. A water–methanol solution of ammonium chloride and potassium cyanide may also be employed for cyanohydrazine formation, but lower yields (*ca.* 60%) are obtained. The third step, a conveniently performed titration procedure with bromine as oxidant, can be effected with other oxidizing reagents such as 4-phenyl-4*H*-1,2,4-triazole-3,5-dione, *tert*-butyl hypochlorite, and Jones reagent.<sup>12</sup> The final diazene decomposition step is induced with bases and nucleophiles such as methoxide, ethoxide, hydroxide, and iodide. The diazene decomposition can be extended to the preparation of  $\alpha$ -methylnitriles and  $\alpha$ -carboalkoxynitriles.<sup>13</sup>

This procedure is general for the preparation of secondary nitriles (Table I), and can be used in the presence of other functional groups by the appropriate choice of oxidation and decomposition reagents.<sup>14</sup>

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 9, 281](#)

TABLE I  
KETONE TO NITRILE TRANSFORMATION

Ketone	Diazene Yield (%) <sup>a</sup>	Nitrile Yield (%) <sup>b</sup> (ratio of diastereomers)
	95	89 (50:50)
	94	97 (58:42)
	94	90 (50:50)

<sup>a</sup>Distilled yield based on starting ketone, obtained without purification of intermediate hydrazine.

<sup>b</sup>Yield based on purified [diazene](#) as determined by chromatographic analysis.

## References and Notes

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

HCN

Methyl 2-(1-cyancyclohexyl)diaxenecarboxylate

Jones reagent

acetic acid (64-19-7)

methanol (67-56-1)

ammonium chloride (12125-02-9)

sodium sulfite (7757-83-7)

sodium hydrogen carbonate (144-55-8)

Cyclohexanone (108-94-1)

hydrogen cyanide (74-90-8)

bromine (7726-95-6)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

sodium methoxide (124-41-4)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Cyclohexanecarbonitrile (766-05-2)

diazene (3618-05-1)

tosylmethylisocyanide (36635-61-7)

methyl carbazate,  
methyl hydrazinocarboxylate (6294-89-9)

tert-Butyl hypochlorite (507-40-4)

Methyl 2-(1-cyanocyclohexyl)hydrazine carboxylate (61827-29-0)

4-phenyl-4H-1,2,4-triazole-3,5-dione (4233-33-4)

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