

A SYNTHETIC METHOD FOR DIRECT CONVERSION OF KETONES INTO CYANIDES.<sup>1</sup>

INTRODUCTION OF A ONE CARBON UNIT.

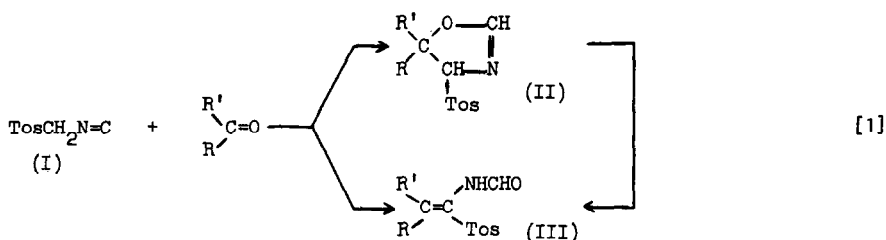
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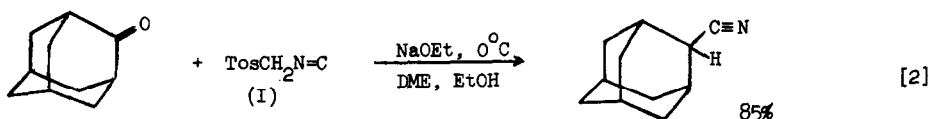
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The usefulness of tosylmethylisocyanide (TosMIC) in the synthesis of several azoles has been shown in a recent series of papers.<sup>2</sup> Two different types of product have been obtained thus far by reaction of TosMIC (I) with ketones<sup>3,4</sup>, see Scheme [1]. It also has been shown that tosyl-



substituted 2-oxazolines (II) are intermediates in the formation of III.<sup>4</sup>

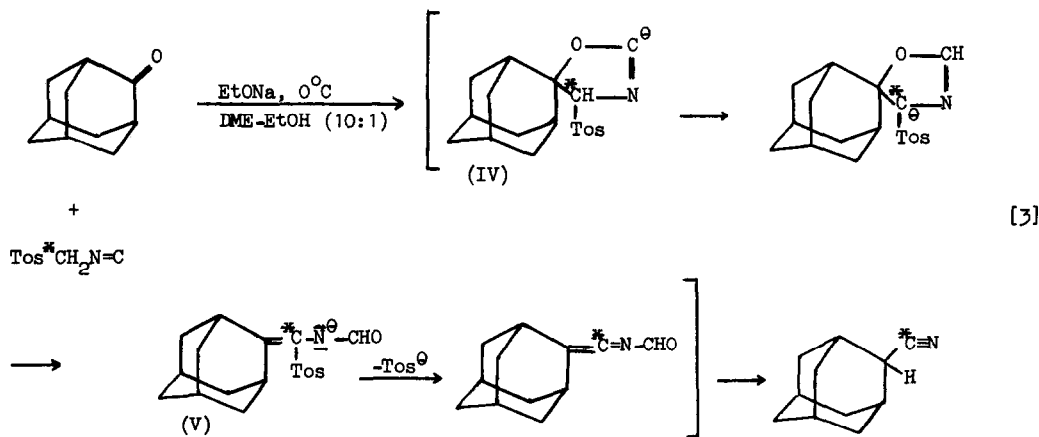
Recently, we reported a seeming exception to Scheme [1], in that adamantanone was converted to 2-cyanoadamantane.<sup>5</sup>



We now wish to report the extension of this reaction into a general synthetic method for the conversion of ketones to cyanides. Furthermore, as in Scheme [1], tosyl-substituted oxazolines (II) again appear to be intermediates in this conversion. As will be shown below, the product

actually formed depends strongly on the reaction conditions.

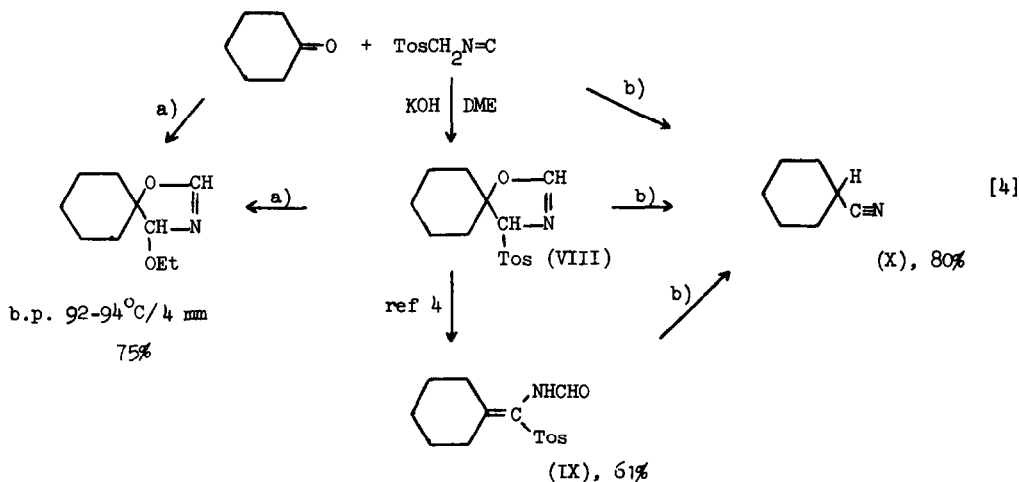
The first indications for a 2-oxazoline intermediate were obtained from  $^{14}\text{C}$ -labeling experiments. Reaction [2] gave  $^{14}\text{C}$ -labeled 2-cyanoadamantane when use was made of TosMIC, carrying the label in the methylene group. The reaction proceeded without loss of specific activity. Consequently, the isocyanato carbon, and not the methylene carbon, was removed in this reaction. This is consistent with the following mechanistic interpretation:



The 2-oxazoline formed by protonation of IV was too unstable to be isolated, although its presence in solution was indicated by IR. Additional evidence for this intermediate was obtained by the isolation of two derivatives, formed under somewhat different reaction conditions. With TlOEt in absolute EtOH, the sole product was the ethoxy-substituted 2-oxazoline (VI), m.p. 74-78°C, 92% yield. Using the same base (TlOEt) in dimethoxyethane (DME) resulted in a double addition product, to which structure VII has been assigned (m.p. 159-160°C, 47% yield, stereochemistry not elucidated)



Further support for the intermediacy of IV, as well as V, was obtained by a detailed study of the reaction of TosMIC with cyclohexanone, which gives analogous results as indicated in Scheme [4].



a) with  $\text{TiOEt}$  in absolute EtOH

b) with  $t\text{-BuOK}$  in DME —  $t\text{-BuOH}$  (5:1), see further ref. 6

The cyclohexyl derivatives VIII and IX, corresponding to the adamantane derivatives IV and V, are well defined stable crystalline compounds.<sup>3,4</sup> They could be used equally well as cyclohexanone and TosMIC themselves for the preparation of cyclohexylcyanide (X).

Next, the above results were developed into a general synthetic method for the conversion of ketones to cyanides ( $\text{R}_2\text{C}=\text{O} \rightarrow \text{R}_2\text{CH}-\text{C}\equiv\text{N}$ ). This transformation, which is carried out in a single operation<sup>6</sup>, is quite effective and gives yields of 75-85% of distilled products (see Table). The yield from the reaction of the sterically hindered  $t$ -butylmethylketone however, is considerably lower (36%).

Our new method is superior, both in yield and procedure, to a recently published method<sup>7</sup>, which proceeds through thermal decomposition (at 180° in decaline) of the HCN-adduct of tosyl hydrazones.

TABLE

<u>Ketone</u>	<u>Cyanide</u>	<u>Yield</u>	<u>B.p. (°C)</u>
Adamantanone	2-Cyanoadamantane <sup>5</sup>	85%	181-182°(m.p.)
Cycloheptanone	Cycloheptylcyanide <sup>8</sup>	80%	85- 86°/10 mm
Cyclohexanone	Cyclohexylcyanide	80%	64- 66°/12 mm
Heptanone-4	4-cyanoheptane	75%	64°/11 mm
$t$ -Butyl methyl ketone	2-cyano-3,3-dimethylbutane <sup>9</sup>	36%	40-42°/15 mm
Acetophenone	1-phenylpropionitrile	80%	74-78/1 mm
$p$ -Bromoacetophenone	1-( $p$ -bromophenyl)propionitrile	79%	112-116/1 mm

The present method for the synthesis of cyanides from ketones is clearly to be differentiated from the well-documented conversion of aldehydes into cyanides that contains the same number of carbon atoms.<sup>10</sup>

Acknowledgement These investigations were supported by the Netherlands Foundation for Chemical Research (SON).

#### Notes and References

1. a) This letter is considered Chemistry of Sulfonylmethylisocyanides, Part 7.  
b) For Part 6, see A.M. van Leusen, H. Siderius, B.E. Hoogenboom and Daan van Leusen, Tetrah. Letters, 1972, 5337.
2. See ref. 1b and previous papers in this series.
3. A.M. van Leusen, B.E. Hoogenboom and H. Siderius, Tetrah. Letters, 1972, 2369 and unpublished results.  $\alpha, \beta$ -Unsaturated ketones give pyrroles, see ref. 1b.
4. U. Schöllkopf and R. Schröder, Angew. Chem., 84, 289, Intern. Ed., 11, 311 (1972);  
U. Schöllkopf, R. Schröder and E. Blume, Liebigs Ann. Chem., 766, 130 (1972);  
Acid-catalyzed hydrolysis of III leads to the formation of carboxylic acids.
5. O.H. Oldenzien and A.M. van Leusen, Synth. Comm., 2, 281 (1972).
6. To a solution of the appropriate ketone and isocyanide in DME, cooled at 0°C, is added a solution of t-BuOK (2 eq.) in t-BuOH-DME (1:1). After stirring for 45 minutes at 0°C, the temperature is raised to 20°C and stirring is continued for another hour. The reaction mixture is poured into water and the water layer is extracted with pentane. Removal of pentane and distilling the residue gives the pure cyanide. Conversion of VIII or IX to X are carried out under the same conditions.
7. S. Cacchi, L. Caglioti and G. Paolucci, Chem. and Ind. (London) (1972) 213.
8. E. Müller and H. Huber, Chem. Ber., 96, 670 (1963).
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