

A NEW SYNTHESIS OF NITRILES

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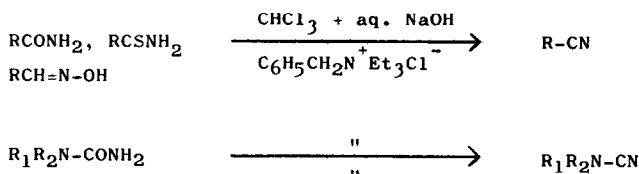
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The dehydration of amides or aldoximes to yield nitriles generally requires Lewis acids and vigorous reaction conditions, which prevent one from applying the method to thermally labile nitriles. Recently some efforts have been made to achieve the dehydration under milder conditions. For example, amides and aldoximes were dehydrated with triphenylphosphine and carbon tetrachloride at 60°C<sup>1)</sup> or with titanium tetrachloride and base at 0°C or at room temperature.<sup>2)</sup> Aldoximes were also dehydrated with cyanuric chloride at room temperature<sup>3)</sup> or with phenyl chloroformate at 100°C.<sup>4)</sup> We now wish to report a new synthesis of nitriles, which is carried out under mild conditions and in an alkaline medium.

The present method consists of the dehydration of amides, thioamides, aldoximes and ureas with dichloromethylene, a carbene, which can be generated in situ in an organic solvent. A phase-transfer catalyst<sup>5)</sup> was utilized with great success, because the reaction took place essentially in a heterogeneous medium.

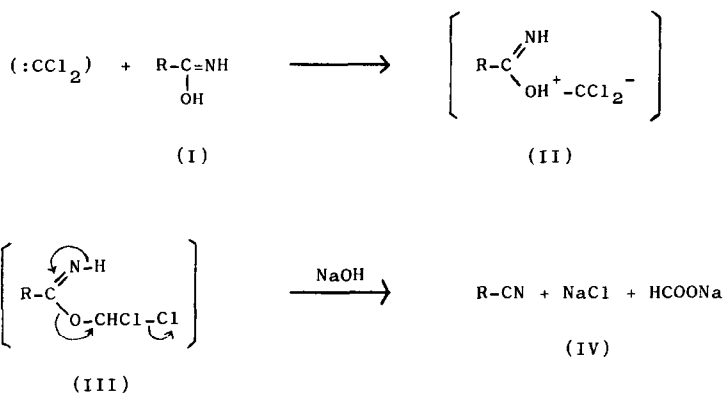


The following procedure represents a typical example for the dehydration.

A mixture of 6.05 g (50 mmole) of benzamide, 0.34 g (1.5 mmole) of triethylbenzylammonium chloride, 180 g (1.5 mole) of chloroform and 40 g (0.5 mole) of 50% aqueous sodium hydroxide solution was stirred vigorously at room temperature for 2 hours. The reaction was slightly exothermic and soon started to impart red colour to the mixture. The reaction mixture, including large amount of white precipitates, was extracted with chloroform and the organic layer was washed and dried over sodium sulfate and finally separated by distillation to afford 4.33 g of benzonitrile (84% yield).

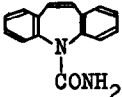
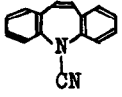
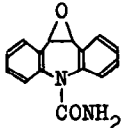
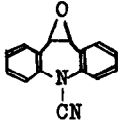
The reaction conditions and results are summarized in the Table. The process is simple and convenient. A wide variety of substrates can be dehydrated to yield nitriles as is seen in the Table. However, it is obvious that there are certain limitations to the application of the method. For instance, amides sensitive to alkali (e.g. cyanoacetamide) cannot be used as starting materials. Furthermore, when substrates contain such groups as an electron-rich carbon-carbon double bond like enamine, amino<sup>6)</sup> or hydroxy group,<sup>7)</sup> these groups may also react with dichloromethylene.

Although the mechanism of the reaction is not clear at present, a plausible mechanism might be depicted as follows:



Dichloromethylene produced in an organic layer would react with an imino-form (I) of amide to yield an intermediate (II), which upon proton migration followed by fragmentation would produce a nitrile (IV), together with sodium chloride and sodium formate.

Synthesis of Nitriles by Dehydration

No	Substrate	Temp.	Time	Product	Yield
1 a)	$C_6H_5CONH_2$	$22^\circ C$	2 hr	$C_6H_5CN$	84% b)
2	$C_6H_5CH_2CONH_2$	40	3	$C_6H_5CH_2CN$	75 b)
3	$C_6H_5CH=CHCONH_2$	22	2	$C_6H_5CH=CHCN$	52 b)
4	$CH_3CH_2CONH_2$	40	3	$CH_3CH_2CN$	45 c)
5	$NH_2CO-(CH_2)_4-CONH_2$	22	2	$NC-(CH_2)_4-CN$	12 c)
6	$C_6H_5CSNH_2$	22	6	$C_6H_5CN$	67 c)
7	$C_6H_5CH=N-OH$	22	2	$C_6H_5CN$	51 c)
8 e) i)		22	2	 g)	82 d)
9 f)		40	15	 h)	58 d)

All the reactions were carried out at the molar ratio 1:30:10:0.03 for the substrate,  $CHCl_3$ , 50% aq. NaOH, and  $C_6H_5CH_2N^+Et_3 Cl^-$  (from lot 1 to lot 7)

a) In the absence of triethylbenzylammonium chloride, the yield of benzonitrile was 4% with 52% recovery of the starting material. b) Distillation. c) V.P. C. analysis. d) Column chromatography. e) The molar ratio of the substrate,  $CHCl_3$ , 50% aq. NaOH, and  $C_6H_5CH_2N^+Et_3 Cl^-$  was 1:75:20:0.03. f) The molar ratio above was 1:60:40:0.03. g) m.p.  $109-110^\circ C$ , nmr (in  $CDCl_3$ )  $\delta$ . 6.75(s. 2H), 7.1-7.5(m. 8H). h) m.p.  $145-148^\circ C$ , nmr. (in  $CDCl_3$ )  $\delta$ . 4.16(s. 2H), 7.2-7.7(m. 8H). i) When forty eq. of sodium hydroxide was used, dichloromethylene reacted also with the carbon-carbon double bond to give 1,1-dichloro-1a,10b-dihydrodibenzo(b,f)cycloprop(d)azepine-6(1H)-carboxynitrile (yield, 41%).

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