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DIETHYL PHOSPHOROCYANIDATE(DEPC). A NOVEL REAGENT FOR THE CLASSICAL STRECKER'S α-AMINO NITRILE SYNTHESIS[1]

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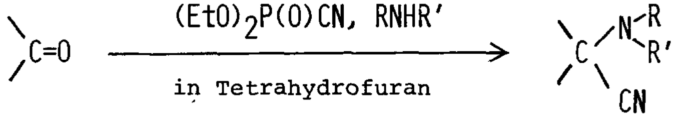
Diethyl phosphorocyanidate(DEPC) can be efficiently used for the synthesis of α-amino nitriles from carbonyl compounds and amines. The reaction may be called a modified Strecker synthesis.

The Strecker synthesis is a well-known classical procedure for the preparation of α-amino nitriles from aldehydes or ketones by their treatment with alkaline cyanides and salts of amines. Since the nitrile function of α-amino nitriles can be easily converted to the acid, this constitutes a convenient method for the preparation of α-amino acids.[2]

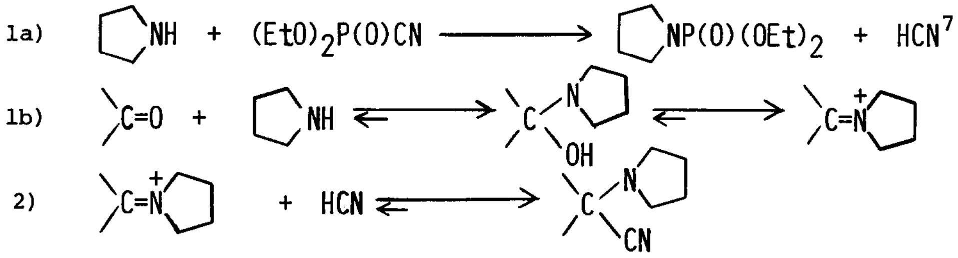
Recently we have reported[1] a new synthesis of α-amino nitriles by the reaction of enamines with diethyl phosphorocyanidate(DEPC, $(EtO)_2P(O)CN$),[3] which has been utilized as a reagent for the introduction of a C_1-unit. Further investigations on the α-amino nitrile synthesis using DEPC have revealed that α-amino nitriles can be efficiently prepared from carbonyl compounds with DEPC and amines under mild reaction conditions:



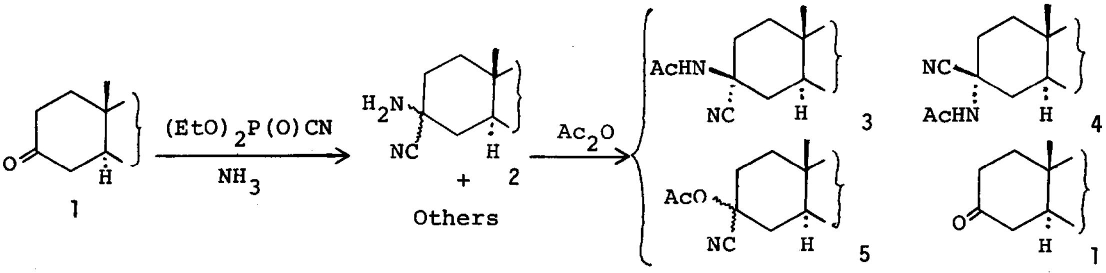
A representative procedure is as follows: To a mixture of 5α-cholestan-3-one(387 mg, 1 mM) and DEPC(196 mg, 1.2 mM) in tetrahydrofuran(5 ml) was added pyrrolidine(156 mg, 2.2 mM) in tetrahydrofuran(5 ml). The mixture was stirred at room temperature for 3 hr, and evaporated *in vacuo*. The crystalline residue was washed with methanol(20 ml) to give 3α-cyano-3β-(N-pyrrolidino)-5α-cholestane (445 mg, 95 %) as colorless small needles.[1]

The scope of this modified Strecker synthesis using DEPC is shown in Table In contrast to the aqueous conditions of the classical Strecker synthesis, the modified one is carried out under non-aqueous conditions. Heating under reflux in tetrahydrofuran may be necessary if the reaction sluggishly proceeds at room temperature. In case α-amino nitriles have been difficult to crystallize, they have been characterized by their conversion to either crystalline hydrochlorides with hydrogen chloride in ethyl acetate or iminium perchlorates[5] with 70 % aqueous perchloric acid.

5α-Cholestan-3-one(1) easily reacted with various amines, e.g., pyrrolidine, morpholine, piperidine, and benzyl amine, to give the corresponding α-amino nitriles[6] in excellent yields. Various cyclic ketones also underwent the modified Strecker synthesis to furnish the α-amino nitriles in good yields. 4-Phenyl-2-butanone as well as benzaldehyde caused no trouble to provide the α-amino nitriles. Although two equivalents of the amine have been generally used, one equivalent of the amine may be sufficient when used together with one equivalent of imidazole. The proposed mechanism using two equivalents of pyrrolidine is outlined below:



Reaction of 5α-cholestan-3-one(1) with DEPC and ammonia in chloroform gave the labile crude α-amino nitrile 2 as well as the other products. The crude mixture was treated with acetic anhydride in pyridine[8] to afford a mixture of the acetamido nitriles 3[9](64 %) and 4(12 %), the acetoxy nitrile 5(11 %), and the starting ketone 1(11 %).



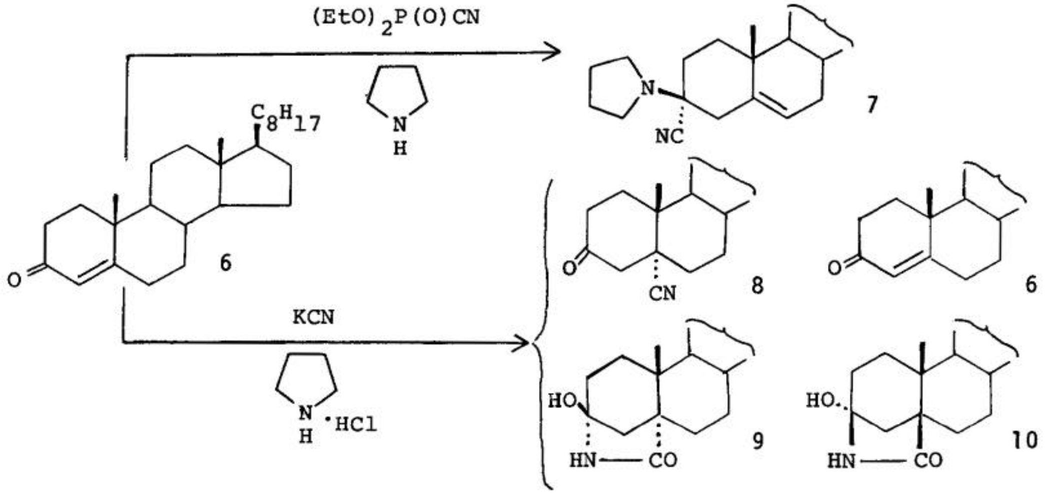
Another intriguing example of the modified Strecker synthesis is the reaction of 4-cholesten-3-one(6) with DEPC and pyrrolidine, which afforded the α-amino nitrile 7 in 62 % yield. On the contrary, the classical Strecker conditions using a mixture of potassium cyanide and pyrrolidine hydrochloride in aqueous tetrahydrofuran did not give any trace of α-amino nitriles. Instead, hydrocyanation[10] mainly occurred to give the cyano ketone 8(23 %), the lactams 9 and 10(1:1, 23 %) with recovery of the enone 6(20 %). These results strongly suggest the superiority of our novel procedure to the classical one.

In conclusion, the modified Strecker synthesis using DEPC offers a convenient, high-yield, and mild method for the preparation of α-amino nitriles and may be applicable to a wide scope of structural types.

TABLE. A MODIFIED STRECKER SYNTHESIS USING DEPC(*a*)

Carbonyl Compound	Amine	React. Condition Temp(*b*)/Time(hr)	α-Amino Nitrile[4]	Yield (%)
5α-Cholestan-3-one	Pyrrolidine	R.T./3	3α-Cyano-3β-(N-pyrrolidino)-5α-cholestane	95
5α-Cholestan-3-one	Pyrrolidine(*c*)	R.T./3	3α-Cyano-3β-(N-pyrrolidino)-5α-cholestane	84
5α-Cholestan-3-one	Morpholine	R.T./3	3α-Cyano-3β-(N-morpholino)-5α-cholestane	85
5α-Cholestan-3-one	Piperidine	Reflux/3	3α-Cyano-3β-(N-piperidino)-5α-cholestane	84
5α-Cholestan-3-one	Benzylamine	Reflux/3	3β-(N-Benzylamino)-3α-cyano-5α-cholestane	100
5α-Cholestan-3-one	Ammonia(*d*)	50-55°/19	3-Amino-3-cyano-5α-cholestane(*e*)	82
5β-Cholestan-3-one	Pyrrolidine	R.T./3	3-Cyano-3-(N-pyrrolidino)-5β-cholestane(*f*)	87
Cyclohexanone	Pyrrolidine	R.T./3	1-Cyano-1-(N-pyrrolidino)-cyclohexane(*f*)	80
Cyclooctanone	Pyrrolidine	Reflux/22	1-Cyano-1-(N-pyrrolidino)-cyclooctane(*g*)	88
Cyclododecanone	Pyrrolidine	Reflux/6	1-Cyano-1-(N-pyrrolidino)-cyclododecane(*f*)	82
5-Cyclohexadecenone	Pyrrolidine	Reflux/3	5-Cyano-5-(N-pyrrolidino)-1-cyclohexadecene(*g*)	75
2-Adamantanone	Pyrrolidine	Reflux/3	2-Cyano-2-(N-pyrrolidino)-adamantane(*g*)	93
4-Phenyl-2-butanone	Pyrrolidine	Reflux/13	2-Cyano-4-phenyl-2-(N-pyrrolidino)butyronitrile(*f*)	93
Benzaldehyde	Morpholine	R.T./3	2-(N-Morpholino)-2-phenyl-acetonitrile	73
Benzaldehyde	Aniline	55-60°/22	2-(N-Anilino)-2-phenyl-acetonitrile	74
4-Cholesten-3-one	Pyrrolidine(*h*)	Reflux/3	3α-Cyano-3β-(N-pyrrolidino)-5-cholestene	62

(*a*) Unless otherwise stated, the reactions were carried out as described in the representative procedure. (*b*) R.T. refers to room temperature. (*c*) Imidazole (1 eq) was used with pyrrolidine(1 eq). (*d*) Chloroform was used as a solvent. (*e*) See the text. (*f*) Characterized as a hydrochloride. (*g*) Characterized as an iminium perchlorate. (*h*) Two eq. of DEPC was used.



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References and Notes

1 New Methods and Reagents in Organic Synthesis 5. Part 4, see S. Harusawa, Y. Hamada, and T. Shioiri, Synthesis, in press.

2 J. March, "Advanced Organic Chemistry", 2nd ed., McGraw-Hill Kogakusha, Ltd., Tokyo, 1977, p. 874.

3 For a review, see T. Shioiri, Ann. Rep. Pharm. Nagoya City Univ.(Nagoya Shiritsu Daigaku Yakugakubu Kenkyu Nempo), 25, 1(1977).

4 All new compounds were fully characterized by NMR and IR spectral means and elemental composition.

5 The perchlorates of α-amino nitriles have been easily transformed to the iminium salts by recrystallization from ethanol.

6 The configurations at C-3 shown in Table have been tentatively assigned from the comparison of thermodynamic stabilities between 3α- and 3β-cyano derivatives, the former of which will be much more stable.[1]

7 Actually DEPC reacted with pyrrolidine in tetrahydrofuran to give O,O'-diethyl N-pyrrolidino phosphoramidate in 88 % yield.

8 Y. Maki, M. Sato, and K. Obata, Chem. Pharm. Bull.(Tokyo), 13, 1377(1965).

9 The IR spectrum of **3** was identical with that of 3β-acetamido-3α-cyano-5α-cholestane,[8] whose spectral chart was kindly sent by Prof. Y. Maki at Gifu College of Pharmacy.

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