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FACILE CONVERSION OF CARBOXAMIDES TO NITRILES

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Summary: Alkyl, aralkyl, aryl, heteroaryl carboxamides bearing various functionalities are readily converted to the corresponding nitriles in good yields using the liquid "diphosgene", trichloromethyl chloroformate, as dehydrating agent. In many cases, the procedure does not require extraction, and hence offers a very simple work-up.

The preparation of nitriles by the dehydration of carboxamides is very well documented.[1-24] Certain amides have been converted to nitriles with the basic reagents, where relative drastic conditions have been employed.[1-4] Some examples have involved mesitamide with sodium hydroxide in refluxing ethylene glycol,[1] benzamide with "deficient" amount of lithium aluminum hydride,[2] phenylacetamide with 3.3 equivalents of n-butyl lithium,[3] and benzamide with silazanes at 220° for several hours.[4] On the other hand acidic reagents appear to offer milder conditions and better yields: Trichloroacetyl chloride,[5] ethyl polyphosphate,[6] trimethylsilyl polyphosphate,[7] cyanuric chloride/dimethylformamide,[8] Vilsmeier reagent,[9] triethoxydiiodophosphorane,[10] trifluoroacetic anhydride,[11] triphenylphosphine ditriflate,[12] titanium tetrachloride,[13] triphenylphosphine,[14] boron trifluoride,[15] chlorosilane,[16] chlorosulfonyl isocyanate,[17] thionyl chloride /dimethylformamide,[18] phosphoryl chloride/pyridine,[19] aluminum chloride,[20] tosyl chloride/pyridine,[20] phosphorous pentoxide,[21] and thionyl chloride.[22] However, there still exists a need for the development of new, mild methods for this conversion.

In this paper, we wish to report a simple dehydration of carboxamides to nitriles using the liquid "diphosgene", trichloromethyl chloroformate. Alkyl, aralkyl, aryl, and heteroaryl carboxamides bearing various functionalities were converted to the corresponding nitriles in good yields as shown in TABLE 1.

A typical procedure is as follows: Preparation of 3,5-dinitrobenzonitrile (CAUTION).[25] In a well-ventilated hood, trichloromethyl chloroformate[26] (2 ml) was added dropwise to a cold (0-5°), stirred solution of 3,5-dinitrobenzamide (2.1 g; 10 mmol) in trimethyl phosphate (6.3 ml). The reaction mixture was then slowly heated to 60° for 5 minutes to ensure the completion of the reaction and also to drive away any generated phosgene.[27] After cooling down in an ice-water bath, the reaction mixture was vigorously stirred and ice-water (10 g) was added to destroy any trace of phosgene and chloroformate. The precipitated solid product was filtered, washed with water to eliminate trace of HCl and trimethyl phosphate, and air-dried; yield: 1.88 g (96%), m.p. 127-129°, IR and NMR are consistent with the assigned structure. Recrystallization from isopropyl ether gave an analytically pure product, m.p. 130-131°.

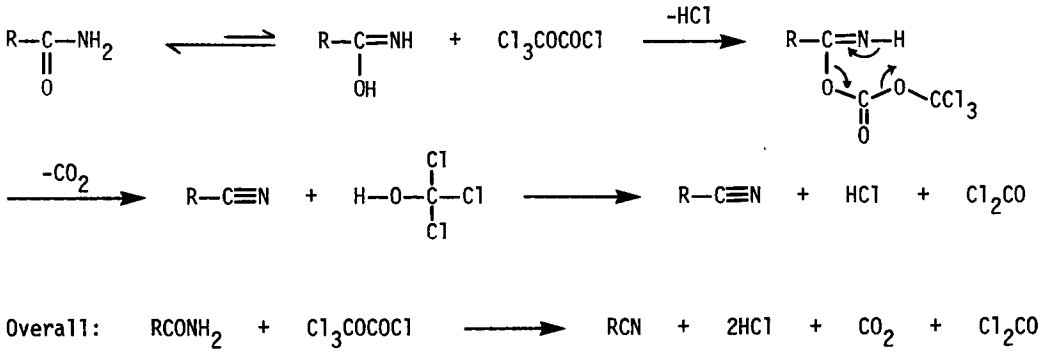
TABLE 1: Conversion of Carboxamides to Nitriles

#	CARBOXAMIDE	PRODUCT[a]	YIELD (%)	MP. or BP.(^{o}C)/Torr
1	$(CH_3)_3CONH_2$	$(CH_3)_3CN$	76[b]	105^{o}/755
2	$H_2NCO(CH_2)_6CONH_2$	$NC(CH_2)_6CN$[c]	87	120^{o}/0.1
3	dl-Thioctic Acid Amide	dl-Thioctonitrile	92	--[d]
4	c-$C_3H_5CONH_2$	c-C_3H_5CN	86	135^{o}/755
5	c-$C_6H_{11}CONH_2$	c-$C_6H_{11}CN$	93	47^{o}/1.2
6	1-Naphthylacetamide	1-Naphthylacetonitrile	96	107^{o}/0.3
7	2-$MeOC_6H_4CH_2CONH_2$	2-$MeOC_6H_4CH_2CN$	91	67-69^{o}
8	trans-Cinnamamide	trans-Cinnamonitrile	79	84^{o}/0.3
9	$C_6H_5C\equiv C-CONH_2$	$C_6H_5C\equiv C-CN$	90	37-39^{o}
10	2-$HOC_6H_4CONH_2$	2-HOC_6H_4CN	89	96-97^{o}
11	4-$HOC_6H_4CONH_2$	4-HOC_6H_4CN	94	114-115^{o}
12	4-$MeOC_6H_4CONH_2$	4-$MeOC_6H_4CN$	97	58-60^{o}
13	2-$O_2NC_6H_4CONH_2$	2-$O_2NC_6H_4CN$	93	108-110^{o}
14	3,5-$(O_2N)_2C_6H_3CONH_2$	3,5-$(O_2N)_2C_6H_3CN$	96	130-131^{o}
15	2-$ClC_6H_4CONH_2$	2-ClC_6H_4CN	91	45-46^{o}
16	2,6-$Cl_2C_6H_3CONH_2$	2,6-$Cl_2C_6H_3CN$	95	143-144^{o}
17	4-$BrC_6H_4CONH_2$	4-BrC_6H_4CN	95	113-114^{o}
18	2-$IC_6H_4CONH_2$	2-IC_6H_4CN	88	54-55^{o}
19	1-Naphthalenecarboxamide	1-Cyanonaphthalene	79	106^{o}/0.2
20	2-Naphthalenecarboxamide	2-Cyanonaphthalene	97	65-66^{o}
21	9-Anthracenecarboxamide	9-Cyanoanthracene	86	177-179^{o}
22	2-Thiophenecarboxamide	2-Thiophenecarbonitrile	77	46^{o}/1.0
23	2-Furancarboxamide	2-Furancarbonitrile	81	150^{o}/755
24	Nicotinamide	3-Cyanopyridine	0	--

a) All known nitriles show physical and spectral properties identical to those reported in the literature.
b) The low yield is probably due to the volatility of the product.
c) Double amounts of trichloromethyl chloroformate were employed.
d) Isolated as an oil, NMR and IR data are consistent with the assigned structure.

In cases where the product separated as an oil, ether was added and the organic layer was washed with water, 5% sodium bicarbonate, brine, dried over magnesium sulfate, and evaporated to an oil. In all cases, the IR spectra showed the disappearance of the carbonyl absorption and the appearance of the nitrile group.

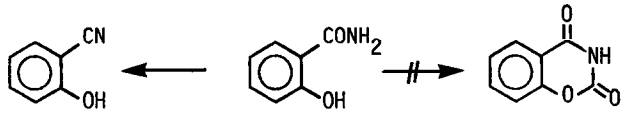
By analogy to the general mechanism proposed for this type of dehydration by a derivatized acidic reagent, the reaction probably undergoes according to the pathway and the stoichiometry shown in the following scheme:



Overall: $RCONH_2 + Cl_3COCOCl \longrightarrow RCN + 2HCl + CO_2 + Cl_2CO$

We believe that the liberated phosgene (Cl_2CO) does not further react with another molecule of carboxamide since in a separate experiment under similar conditions, carboxamide remained intact in the presence of excess amount of phosgene. In fact, it has been reported that carboxamides react with phosgene only in the presence of pyridine,[23] or at higher temperature.[24]

Interestingly enough, 2-hydroxybenzamide (entry # 10) dehydrated easily to 2-cyanophenol in good yield without any contamination of the expected cyclic adduct.



Athough the reaction appears to be fairly general, it should be mentioned that pentafluorobenzamide reacted very slowly with $Cl_3COCOCl$ (only 10% completion after 2 hours); also nicotinamide remained intact after heating for 2 hours; this is probably due to the insolubility of nicotinamide.HCl in trimethyl phosphate (HCl salt is formed in situ).

When dioxane, acetonitrile, and tetrahydrofuran were used as solvents, the reaction seems to slow down dramatically as shown in TABLE 2:

TABLE 2: Solvent Effect for the Dehydration of Carboxamides

Substrate	Solvent	Time to Completion[a]	Condition
trans-Cinnamamide	$(MeO)_3PO$	15 minutes	60^o
	Dioxane	120 "	70^o
	CH_3CN	150 "	Reflux
	THF	300 "	Reflux
2-Chlorobenzamide	$(MeO)_3PO$	5 "	R.T.
	Dioxane	120 "	70^o
	CH_3CN	120 "	Reflux
	THF	240 "	Reflux
Trimethylacetamide	$(MeO)_3PO$	2 "	R.T.
	THF	2 "	R.T.

a) The progress of the reaction was followed by TLC.

In conclusion, the good yield, the short reaction period, the simple work-up, and the fairly mild condition demonstrate the usefulness and the versatility of this synthetic method. This report therefore offers an alternative to the well documented dehydration of carboxamides.

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25. CAUTION: Paper soaked with a solution of 10% p-dimethylaminobenzaldehyde and colorless diphenylamine in ethanol, then dried, will turn from yellow to deep orange in the presence of the maximum allowable concentration of phosgene. See the Merk Index for further details and precautions.
26. Purchased from Fluka Chemical Corp., Hauppauge, New York 11787.
27. To ensure the dehydration, the reaction mixture was cooled to $+10^o$; another 1 ml of trichloromethyl chloroformate was added, and heating was resumed for another 5 minutes.

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