An Insight of the Reactions of Amines with Trichloroisocyanuric Acid

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Abstract: The reaction between amines or α-aminoacids with trichloroisocyanuric acid is studied under various conditions: *N*,*N*-dichloroamines, nitriles and ketones can be obtained from primary amines, while free aminoacids undergo oxidative decarboxylation to the corresponding nitrile of one less carbon atom.

Key words: dichloroamines, trichloroisocyanuric acid, nitriles, aminoacids

Trichloroisocyanuric acid, TCCA, belongs to the large group of *N*-chloroimides and amides that are used as bleaching agents, disinfectants, and bactericides owing to their function as chlorinating agents and oxidants.[1] Their properties are similar to those of *N*-chloroamines, which, however, are less stable. A few of them are also commonly used as chlorinating reagents and oxidants in organic synthesis: since chloroamines are easier to handle than chlorine gas or metal hypochlorites, they are widely used in organic synthesis in addition to their use in the purification of water or as sanitizing agents, for example, in swimming pools.

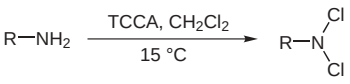
The most commonly used *N*-chloroamide is *N*-chlorosuccinimide (NCS) that contrary to TCCA and as other chloroamides are thermally unstable and can explode at elevated temperature. The theoretical available chlorine content is a value for the atom efficiency of these reagents: TCCA has the lowest bulk price in relationship to the amount of active chlorine. Last, but not least important, TCCA has the highest solubility of the three reagents in organic solvents and the lowest toxicity.[2]

However, although TCCA has been produced on large scale for use in domestic and industry since the 1950s, it has never had a valid breakthrough in organic applications, probably because earlier experiments have indicated a rather uncontrolled chlorination with TCCA in comparison to those using NCS. Ziegler and coworkers reported the use of TCCA as a reagent in organic synthesis for chlorination of alkenes in 1942.[3] Successively, TCCA has been used as aromatic chlorinating agent[4] and in other chlorination procedures.[1,5]

During our program on the use of [1,3,5] triazine derivatives in organic synthesis[6] we have reported a very mild and chemoselective oxidation of alcohols to both carbonyl[7] and carboxylic[8] compounds that uses trichloroisocyanuric acid in the presence of catalytic 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). We were interested to study the possibility to use TCCA in chlorination reaction of amines instead of NCS, owing to its lower cost and higher stability. During our studies, a report on selective mild oxidation of primary amines to nitriles with TCCA appeared in the literature[9] and in this context it appeared interesting to perform a more accurate investigation on the reactions between amines and TCCA.

Thus, benzylamine, as a model substrate, was dissolved in dichloromethane and treated with an equimolar amount of TCCA at low temperature (<20 °C). After one hour, TLC analysis showed the complete absence of the amine and the aqueous work-up of the reaction mixture afforded *N*,*N*-dichlorobenzylamine in quantitative yields. No presence of benzonitrile was noted.

In order to further control the literature report and to check if the formation of the nitrile should depend on the presence of TEMPO, the reaction was then repeated according to the procedure described in the article,[9] adding therefore the corresponding catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). Although TLC analysis confirmed the disappearance of the starting substrate after one hour, the reaction was however left at 10 °C for four hours as described[9] and then hydrolyzed. As above, *N*,*N*-dichlorobenzylamine was recovered quantitatively, again without any trace of benzonitrile.[10]



Scheme 1

The reaction reported in Scheme 1 was then applied to other primary amines. For avoiding any possible decomposition due to distillative procedures,[11] the chloroamines were recovered by elimination of the extraction solvent at room temperature and reduced pressure. In any case they were obtained as pure compounds from the reaction mixtures. Aromatic amine, such as aniline or naphthyl amine, reacts very slowly, the conversion being negligible even after twelve hours. Aliphatic amines even those containing aromatic groups, react more quickly, the conversion being practically quantitative after one hour at 15–20 °C.

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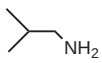
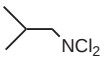
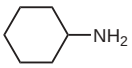
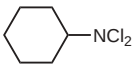
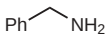
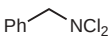
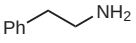
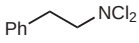
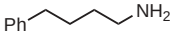
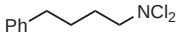
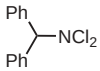
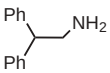
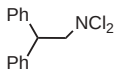
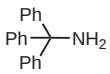
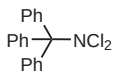
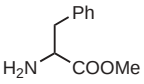
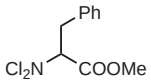
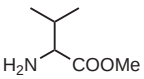
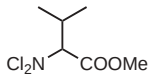
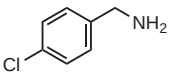
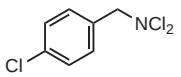
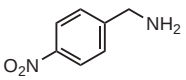
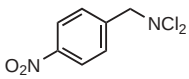
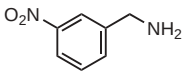
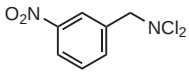
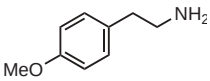
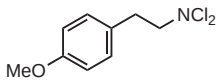
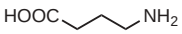
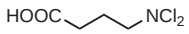
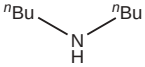
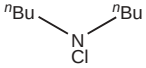
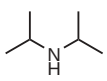
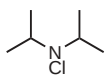
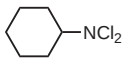
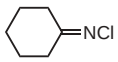
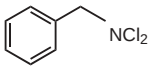
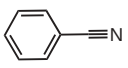
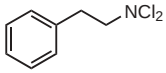
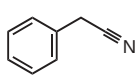
As shown from Table 1, in any case only the corresponding *N*,*N*-dichloroamines (**1**–**15**) were recovered. On examination of Table 1 some other observations can be made. Substituents on the aryl group do not seem to influence the trend of the reaction. Secondary amines react also to give the chloroamines (**16**, **17**),[12] but in this case a relevant amount of the elimination product is recovered.[13] In any case no traces of the corresponding nitrile were noted in the final organic product recovered. The results obtained with the primary amines are noteworthy and indicate a simple and mild approach to *N*,*N*-dichloroamines that may be synthetic intermediates for the preparation of nitriles and carbonyl compounds[14] from amines. Moreover, this method can be successfully applied on a large scale.

Table 1 Formation of Chloramines from Amines

Amine		Product	Time (h)	Yield (%)[a]
	**1**		0.5	100
	**2**		1	91
	**3**		1	98
	**4**		1	95
	**5**		1	93
	**6**		0.5	83
	**7**		1	70
	**8**		1	100
	**9**		1	85
	**10**		1	98
	**11**		1	77
	**12**		1	98
	**13**		1	95
	**14**		1	95
	**15**		0.75	94
	**16**		0.5	75[b]
	**17**		0.5	50[c]

[a] Determined on the recovered and purified product, conversion being complete.
[b] 25% Of *N*-butylidenebutan-1-amine was recovered too.
[c] 50% Of *N*-(propan-2-ylidene)propan-2-amine was recovered.

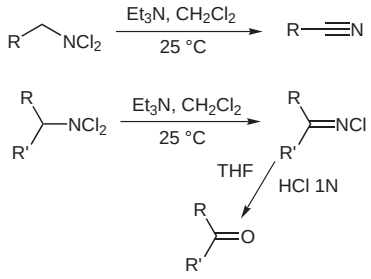
Table 2 Reaction of Dichloroamines with TEA

Run	Dichloroamine	Product	Time (h)	Yield (%)[a]
1	 **2**	 **18**	2	77
2	 **3**	 **19**	1.5	95
3	 **4**	 **20**	2	90
4	**5**	**21**	2	93
5	**14**	**22**	2	95
6	**7**	**23**	1.5	88
7	**9**	**24**	1.5	95

[a] Determined on the recovered and purified product, conversion being complete.

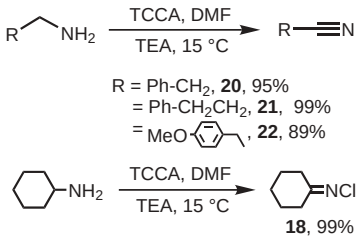
Therefore, we have treated the recovered *N*,*N*-dichloroamines with 3 equivalents of TEA in CH_2Cl_2 (Scheme 2). The results obtained and reported in Table 2 show that nitriles (**19**–**22**) or *N*-chloroimines (**18**, **23**, **24**) are obtained in relation to the structure of the amine employed.

The reactions were practically ended after two hours at room temperature, the conversion of the *N*,*N*-dichloroamines being complete in any case examined. By simple aqueous acidic work-up, nitriles were recovered from unbranched dichloroamines, whereas *N*-chloroimines were obtained from α-branched amines. It is notwithstanding that *N*,*N*-dichlorophenylalanine methyl ester yielded methyl 2-chloroimino-3-phenylpropanoate in excellent yield. The successive hydrolysis with HCl (1 N) in THF of the corresponding chloroimines afforded quantitatively the corresponding ketones (Scheme 2).



Scheme 2

Guided by the above experiments, we have checked the possibility to carry out the reaction under a one-pot procedure, introducing TEA directly in the reaction mixture. Curiously, no productive results were obtained using CH_2Cl_2 as solvent.[15] Different results were noted when DMF was used as solvent. In this case, the reaction can be carried out in a single step: under these conditions, 2-phenylethylamine afforded quantitatively phenylacetonitrile within four hours (Scheme 3).



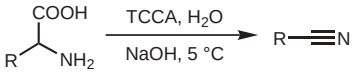
Scheme 3

Similar results were obtained even with other substrates: obviously, α-branched amines afforded only the corresponding *N*-chloroimines, as the subsequent hydrolysis to carbonyl compounds has to be conducted under acidic conditions.

The behavior of pyridyl amines is peculiar and different from that one of the other amines. In particular, the reaction of 2-(aminomethyl)pyridine with TCCA, under the conditions of Scheme 1, does not furnish the corresponding *N*,*N*-dichloroamine, as picolinonitrile is directly formed within one hour, without any presence of TEA. On the contrary, 2-(2-aminoethyl)pyridine, on reacting with TCCA in the absence of TEA) after one hour gives a complex mixture of 2-(pyridin-2-yl)acetonitrile, *N*-chloro-2-(pyridin-2-yl)ethanimine, and *N*,*N*-dichloro-2-(pyridin-2-yl)ethanamine.[16] 2-(Pyridin-2-yl)acetonitrile is the only product obtained by prolonging the reaction time or by adding TEA to the reaction mixture.

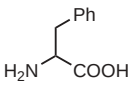
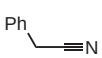
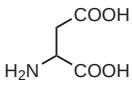
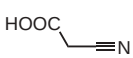
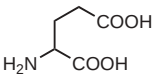
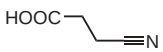
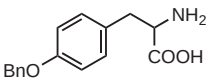
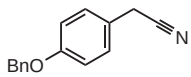
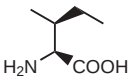
On the basis of the above results, we have investigated the chance to perform the oxidation of unprotected α-aminoacids by TCCA. Oxidation of α-aminoacids is an important process in the field of both synthetic organic and biological chemistry and two modes of oxidation have been developed: the oxidative transformation of an amino group into carbonyl[17] or nitro group[18] and oxidative decarboxylation.[19] The first transformation can be performed as described above, using TCCA in CH_2Cl_2 on α-amino esters, followed by acidic hydrolysis. For what concerns the oxidative decarboxylation, this leads to the formation of various carbonyl compounds or nitriles of one less carbon atom depending on the reagent and reaction conditions employed: *N*-bromosuccinimide and alkaline bromine have been employed with only moderate yields.

In our cases, the reaction can be performed with 2/3 equivalents of TCCA directly on an aqueous solution of the α-aminoacid under basic conditions (Scheme 4): after 30 minutes to one hour, the nitriles (**20**, **25**–**28**) can be recovered quantitatively (Table 3) without any trace of by-products.



Scheme 4

Table 3 Reaction of α-Aminoacids with TCCA

Run	Aminoacid	Nitrile	Time (h)	Yield (%)[a]
1		 **20**	0.5	98
2		 **25**	1	99
3		 **26**	0.5	90
4		 **27**	1	93
5		 **28**	0.5	98

[a] Determined on the recovered and purified product, conversion being complete.

It is worth of mentioning to note that in the case of α-aminoacids having multiple chiral centers such as isoleucine the reaction occurs without any racemization of the adjacent chiral center. Thus, from L-isoleucine, (*S*)-2-methylbutanenitrile (**28**), $[\alpha]_D^{25}$ +39.0 (*c* 1.5, $CHCl_3$)[20] was recovered. As advantages of these oxidations, the reagent is not toxic, is stable under the reaction conditions and the reaction proceeds in water under mild conditions. In addition, we should note that using the free α-aminoacid or the corresponding carboxylic ester (Table 1 and Table 2) different products could be obtained.

In conclusion, this work has shown an easy transformation of amines and α-aminoacids through reaction with TCCA: in all cases the yields are practically quantitative and the products recovered in pure form from the reaction mixture.[21] This method is characterized by mild reaction conditions, non-toxic by-products and easy reaction work-up, making it ideal for both laboratory and large scale.

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(21) All solvents and reagents were used as obtained from commercial source. Standard ^{1}H NMR and ^{13}C NMR were recorded from $CDCl_3$ solutions at 300 MHz and 75.4 MHz. Mass spectra were recorded at 70 eV with a direct probe for sample introduction. When possible, compounds were identified by comparison with authentic samples. All runs were conducted at least in duplicate.
General Preparation of *N*,*N*-Dichloroamines. The procedure for the chlorination of benzylamine (Table 1, run 3) is representative for all cases. Benzylamine (2.00 g, 19 mmol) was dissolved in CH_2Cl_2 (80 mL) and treated with TCCA (4.64 g, 19 mmol) at 0 °C. After the addition, the mixture was warmed to r.t. and stirred for the required time until completion. After 1 h, TLC analysis showed the complete absence of the amine, the reaction mixture was filtered on Celite and the solvent evaporated to yield *N*,*N*-dichlorobenzylamine(**3**) that was isolated without further purification (oil, 3.2 g, 98%). ^{1}H NMR: δ = 7.39 (s, 5 H), 4.68 (s, 2 H). ^{13}C NMR: δ = 135.1, 130.3, 129.5, 128.8, 79.1. MS: *m/e* (relative intensity): 179 (1), 177 (3), 176 (1), 175 (4), 112 (2), 106 (3), 105 (14), 104 (23), 103 (4), 92 (91), 91 (100), 79 (1), 78 (4), 77 (15), 76 (3), 65 (9), 63 (2), 51 (9).
General Procedure for the Preparation of Nitriles and *N*-Chloroimines from *N*,*N*-Dichloroamine. The reported procedure is representative: *N*,*N*-dichlorocyclohexanamine (**2**, 1.00 g, 6 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with TEA (2.56 mL, 18 mmol) at 25 °C. After 2 h, TLC analysis showed the complete absence of the *N*,*N*-dichloroamine. Then the reaction mixture was washed with H_2O (15 mL), with HCl 0.5 N (10 mL), dried on Na_2SO_4, filtered on Celite and concentrated in vacuo to yield *N*-chlorocyclohexanimine (**18**, oil, 0.61 g, 77%). ^{1}H NMR: δ = 2.60–0.95 (br m, 10 H). ^{13}C NMR: δ = 182.8, 36.9, 32.7, 26.9, 25.9, 25.1.
General One-Pot Procedure. The reported procedure is representative: Benzylamine (1.00 g, 9.5 mmol) was dissolved in DMF (10 mL) and treated with TEA (4 mL, 28.5 mmol), and with TCCA (2.32 g, 9.5 mmol) at 25 °C. After 4 h, the reaction mixture was quenched with H_2O (20 mL), and then it was extracted twice with Et_2O (15 mL). The organic layers were washed with H_2O (10 mL), then with HCl 0.5 N (10 mL), were dried (Na_2SO_4), and the solvent was evaporated to yield benzonitrile (**19**, 1.1 g, 95%).
General One-Pot Procedure for the Preparation of Nitriles from α-Aminoacids. The reported procedure is

representative: L-Phenylalanine (1.20 g, 7.6 mmol) was dissolved in an aq solution of 2 N NaOH (3.8 mL) and treated with TCCA (1.17 g, 5.1 mmol) at 25 °C. After 10 min, when TLC analysis showed the complete absence of the L-phenylalanine, the reaction mixture was treated with HCl (15 mL), followed by an aq solution of 3 N HCl (2.5 mL). After 10 min the mixture was extracted twice with Et_2O (15 mL). The organic layers were washed with H_2O (10 mL), dried on Na_2SO_4, filtered and concentrated in vacuo to yield 2-phenylacetonitrile (**20**, 0.87 g, 98%). ^{1}H NMR: δ = 7.38 (m, 5 H), 3.75 (s, 2 H). ^{13}C NMR: δ = 142.1, 129.1, 127.9, 127.8, 117.8, 23.5.

Some other examples: ***N*-Chlorodiphenylmethanimine (23):** ^{1}H NMR: δ = 7.76 (m, 4 H), 7.39 (m, 6 H). ^{13}C NMR: δ = 165.6, 132.9, 131.5, 129.2, 127.8. Anal. Calcd for $C_{13}H_{10}ClN$ (215.68): C, 72.39; H, 4.67; Cl, 16.44; N, 6.49. Found: C, 72.40; H, 4.66; Cl, 16.44; N, 6.50. The compound was dissolved in THF (10 mL) and treated with 10 mL of aq HCl (1 N) to yield 1.0 g of benzophenone, identified by comparison with an authentic sample.

Methyl-2-chloroimino-3-phenylpropanoate (24): ^{1}H NMR: δ = 7.30 (m, 5 H), 4.26 (s, 2 H), 3.83 (s, 2 H). ^{13}C NMR: δ = 172.3, 172.1, 137.5, 130.3, 129.1, 128.9, 128.7, 53.5, 38.5. Anal. Calcd for $C_{10}H_{10}ClNO_2$ (211.64): C, 56.75; H, 4.76; Cl, 16.75; N, 6.62. Found: C, 56.74; H, 4.76; Cl, 16.75; N, 6.60. The compound was then dissolved in THF (10 mL) and treated with 10 mL of aq HCl (1 N) to yield 1.0 g of methyl phenylpyruvate. ^{1}H NMR: δ = 8.15 (br s, 1 H), 7.30–7.14 (m, 5 H), 6.53 (s, 1 H), 3.93 (s, 3 H). ^{13}C NMR: δ = 162.4, 152.3, 137.5, 129.1, 128.9, 128.7, 104.5, 53.5.

(*S*)-2-Methylbutanenitrile (28): $[\alpha]_D^{25}$ +39 (*c* 1.5, $CHCl_3$). ^{1}H NMR: δ = 2.56 (d, *J* = 7 Hz, 1 H), 1.62 (m, 2 H), 1.31 (d, *J* = 7 Hz, 3 H), 1.08 (t, *J* = 7 Hz, 3 H). ^{13}C NMR: δ = 124.8, 27.1, 26.9, 17.4, 11.1.