A Simple Protocol for Efficient N-Chlorination of Amides and Carbamates

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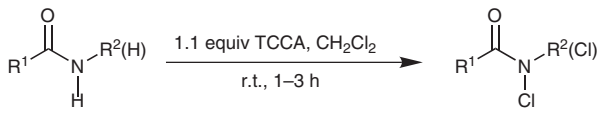
Abstract: N-Chlorination of various amides, lactams, and carbamates with very cheap trichloroisocyanuric acid proceeds efficiently under very mild conditions. Excellent results were also observed for the *N*-chlorination of carbamates of free amino acids.

Key words: amides, amino acids, N-chlorination, trichloroisocyanuric acid

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] Its properties are similar to those of *N*-chlorosuccinimide (NCS), which, however, is less stable. During our program on the use of [1,3,5] triazine derivatives in organic synthesis[2] we were interested to study the possibility to use TCCA in oxidation[3] and chlorination[4] reactions. It is in fact known that *N*-halo compounds are versatile reagents in organic synthesis.[5] In particular *N*-chloroamides and *N*-chlorocarbamates are sources of amidyl and carbamoyl radicals[6] and precursors of α,β-dehydro amino acids.[7]

These compounds are generally prepared by N-chlorination with chlorine,[8] commercial bleach,[9] *t*-butyl hypochlorite,[6,7,10] and, more recently, with Oxone® in the presence of NaCl[11] or calcium hypochlorite on moist alumina.[12] Unfortunately, these methods have certain drawbacks. The concentration of 'active' chlorine in commercial bleach is time depending, *t*-butyl hypochlorite is a hazardous reagent owing to its instability and spontaneous combustibility. Oxone® and calcium hypochlorite are more efficient. However, they require heat and in the last case long reaction times.

Therefore, in continuing our studies for developing new methods of transformation of functional groups under mild conditions, we decided to investigate the use of TCCA in the conversion of amides and carbamates into their *N*-chloro derivatives.



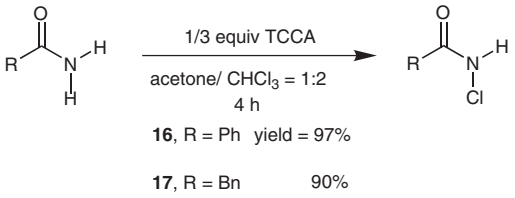
Scheme 1

When the starting compound is treated with 1.1 equivalent of TCCA in dichloromethane at room temperature (Scheme 1), *N*-chloroamides and carbamates are obtained in very good yields (≥90%). To avoid any possible decomposition due to distilling procedures, the chloroamides were recovered by elimination of the solvent at room temperature and reduced pressure. In all cases, they were obtained as pure compounds from the reaction mixtures.

The reactions were generally fast and were terminated within 1–3 hours (Table 1), when the starting material was an amide or a *N*-Boc protected amino acid derivative. The rate of the reaction seemed to depend on steric factors. In fact, carbamates reacted slower than simple amides and in the presence of sterically bulky groups, such as Cbz or Fmoc groups, the reaction proceeded slowly (entries 12–15) and could be accelerated raising the reaction temperature at the reflux of the solvent.

It is important to note that, contrary to what observed in using other methodologies,[10–12] the N-chlorination can be carried out on the carbamates of 'free' amino acids, without protecting the carboxylic moiety and with comparable yields.[13]

Primary amides yielded *N*,*N*-dichloroamides under the above conditions (entries 1 and 2). However, the reaction can be carried out to form the mono *N*-chloroamides, simply using 0.33 equivalent of TCCA and operating in acetone:chloroform 1:2 (Scheme 2).[14]



Scheme 2

The chlorination reaction is slightly slower in these cases: the target compounds, **16**[15] and **17**,[16] were, however, recovered chemically pure and in excellent yields (> 90%).

In conclusion, this work has shown an easy transformation of amides, lactams, and carbamates of α-amino acids into the corresponding N-chlorinated compounds through reaction with TCCA: in all cases the yields are practically quantitative and the products recovered in pure form from the reaction mixtures. 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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Table 1 N-Chlorination of Amides, Lactams, and Carbamates with TCCA

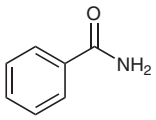
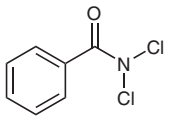
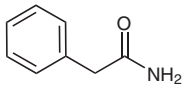
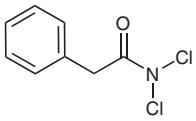
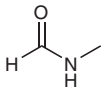
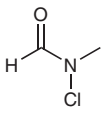
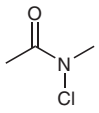
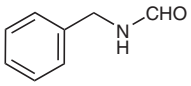
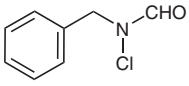
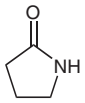
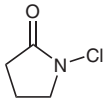
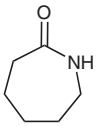
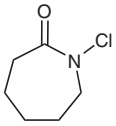
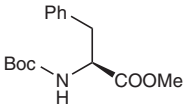
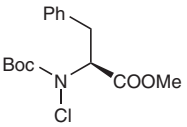
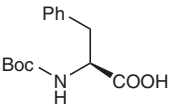
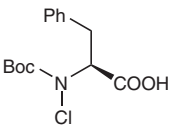
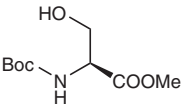
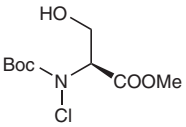
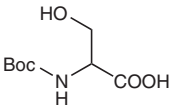
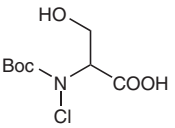
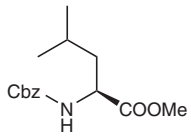
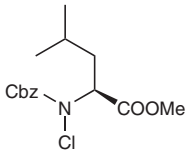
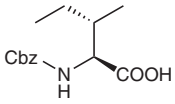
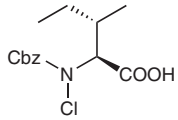
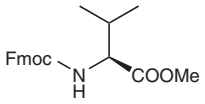
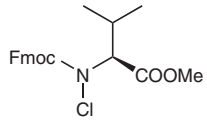
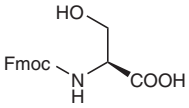
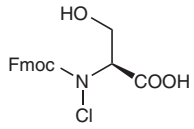
Entry	Starting compound	Product	Reaction time (h)	Yield (%)
1		 **1**	2	93[17]
2		 **2**	1	90
3		 **3**	2	97
4		 **4**	1	96[18]
5		 **5**	1	95[19]
6		 **6**	2	99[12]
7		 **7**	1	99[12]
8		 **8**	3	99[12]
9		 **9**	3	90
10		 **10**	3	99[12]
11		 **11**	3	90

Table 1 N-Chlorination of Amides, Lactams, and Carbamates with TCCA (continued)

Entry	Starting compound	Product	Reaction time (h)	Yield (%)
12		 **12**	10	90
13		 **13**	12	91
14		 **14**	21	97
15		 **15**	7	91

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(12) Larionov, O. V.; Kozhushkov, S. I.; de Meijere, A. *Synthesis* **2003**, 1916.
(13) All solvents and reagents were used as obtained from commercial source. Standard ^{1}H NMR and ^{13}C NMR were recorded at 300 MHz and 75.4 MHz, from $CDCl_3$ solutions. Mass spectra were recorded at 70 eV with a direct probe for sample introduction. All known compounds have analytical data corresponding to literature data. All runs were conducted at least in duplicate.

Typical Procedure for the Preparation of *N*-Chloroamides.

Trichloroisocyanuric acid (5.25 mmol) was added at 0 °C to a well stirred solution of the amide (5 mmol) in CH_2Cl_2 (30 mL) and the mixture was kept at r.t. for the required time, monitoring (TLC) till completion. Then the mixture was filtered on Celite and the solution evaporated under reduced pressure affording the *N*-chloro derivative.

Spectroscopic Data of Selected Compounds:

(*S*)-2-(*N*-Chloroamino-*N*-*tert*-butoxycarbonyl)-3-phenylpropanoic Acid (9): $[\alpha]_D^{25}$ –54.98 (*c* 1, CH_2Cl_2). ^{1}H NMR: δ = 10.51 (s, 1 H), 7.35–7.05 (m, 5 H), 4.60 (m, 1 H), 3.35–2.92 (m, 2 H), 1.40 (s, 9 H) ppm. ^{13}C NMR: δ = 174.9, 156.0, 139.4, 128.9, 128.5, 127.1, 79.5, 54.4, 37.7, 28.2 ppm. MS (ES+): *m/e* (relative intensity) = 301 (32), 300(1), 299 (100). IR (film): 1255 cm^{-1}.

(*S*)-Methyl 2-(*N*-Chloramino-*N*-benzyloxycarbonyl)-4-methylpentanoate (12): $[\alpha]_D^{20}$ –19.81 (*c* 0.5, CH_2Cl_2). ^{1}H NMR: δ = 7.40–7.30 (m, 5 H), 5.27 (s, 2 H), 4.99 (dd, *J* = 3.90, 11.70 Hz, 1 H), 3.70 (s, 3 H), 2.06–1.85 (m, 1 H), 1.77–1.59 (m, 2 H), 0.94 (d, 6 H) ppm. ^{13}C NMR: δ = 170.3,

156.2, 135.3, 128.9, 128.5, 127.8, 66.9, 53.4, 52.4, 41.6, 24.2, 23.0, 20.7 ppm. MS (ES+): *m/e* (relative intensity) = 315 (34), 314 (15), 313 (100). IR (film): 1243 cm^{-1}.

(2*S*,3*S*)-2-*N*-Chloramino-*N*-benzyloxycarbonyl)-3-methylpentanoic Acid (13): $[\alpha]_D^{20}$ –4.52 (*c* 0.5, CH_2Cl_2). ^1H NMR δ = 7.37–7.29 (m, 5 H), 5.08 (s, 2 H), 4.43–4.33 (m, 1 H), 2.02–1.80 (m, 1 H), 1.62–1.39 (m, 1 H), 1.28–1.13 (m, 1 H), 0.92 (m, 6 H) ppm. ^{13}C NMR: δ = 173.8, 156.3, 135.1, 128.8, 128.4, 128.2, 69.4, 58.2, 37.5, 24.6, 15.4, 10.3 ppm. MS (ES+): *m/e* (relative intensity) = 301 (32), 300(6), 299 (100). IR (film): 1267 cm^{-1}.

(*S*)-Methyl 2-[*N*-Chloramino-*N*-(9*H*-fluoren-9-yl)methoxycarbonyl]-3-methylbutanoate (14): $[\alpha]_D^{20}$ –4.13 (*c* 0.1, CH_2Cl_2). ^1H NMR: δ = 7.62 (d, 2 H), 7.56 (d, 2 H), 7.26–7.13 (m, 4 H), 4.47–4.35 (m, 2 H), 4.30 (m, 1 H), 4.19 (t, 1 H), 3.76 (s, 3 H), 2.25–2.10 (m, 1 H), 0.97 (d, 3 H), 0.92 (d, 3 H) ppm. ^{13}C NMR: δ = 172.6, 156.0, 145.4, 138.7, 128.9, 128.1, 125.4, 120.9, 67.8, 59.0, 53.4, 52.2, 31.1, 18.8, 17.5 ppm. MS (ES+): *m/e* (relative intensity) = 389 (35), 387 (100), 388 (19), 390 (5). IR (film): 1216 cm^{-1}. Anal. Calcd for $C_{21}H_{22}ClNO_4$ (387.86): C, 65.03; H, 5.72; Cl, 9.14; N, 3.61. Found: C, 65.05; H, 5.78; Cl, 9.18; N, 3.64.

(*S*)-2-[*N*-Chloramino-*N*-(9*H*-fluoren-9-yl)methoxycarbonyl]-3-hydroxypropanoic Acid (15): $[\alpha]_D^{20}$ –11.96 (*c* 0.2, CH_2Cl_2). ^1H NMR: δ = 10.41 (s, 1 H), 7.43 (d, 2 H), 7.27–7.12 (m, 6 H), 6.47 (br s, 1 H), 4.46 (s, 2 H), 4.18–3.70 (m, 4 H) ppm. ^{13}C NMR: δ = 173.8, 156.6, 145.2, 144.8, 129.0, 128.2, 125.2, 120.8, 67.9, 55.9, 46.8 ppm. MS (ES+): *m/e* (relative intensity) = 363 (28), 361 (100), 336 (19), 364 (5). IR (film): 1230 cm^{-1}. Anal. Calcd for $C_{18}H_{16}ClNO_5$ (361.07): C, 59.76; H, 4.46; Cl, 9.80; N, 3.87. Found: C, 59.72; H, 4.48; Cl, 9.80; N, 3.84.

(14) **Typical Procedure for the Preparation of *N*-Chloroamides from Primary Amides.**
Trichloroisocyanuric acid (1.60 mmol) was added slowly, in small portions, and at 0 °C to a well stirred solution of the amide (5 mmol) in dry acetone:$CHCl_3$ (1:2 solution, 30 mL) and the mixture was kept at r.t. for the required time, monitoring (TLC) till completion. Then the mixture was filtered on Celite and the solution evaporated under reduced pressure affording the *N*-chloro derivatives **16** and **17**.[13,16]

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