N,*N*′-Dichlorobis(2,4,6-trichlorophenyl)urea (CC-2): An Efficient Reagent for N-Chlorination of Amino Esters, Amide, and Peptides

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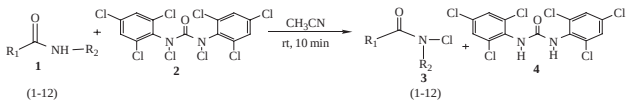
A simple, efficient, and rapid protocol for N-chlorination of various protected amino esters, amides, and peptides has been described. *N*,*N*′-dichlorobis(2,4,6-trichlorophenyl)urea has been used as a chlorinating agent and transformation takes place rapidly in mild conditions with quantitative yields.

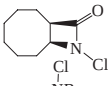
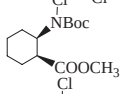
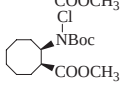
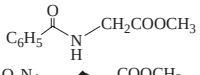
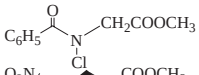
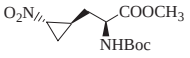
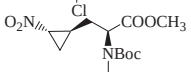
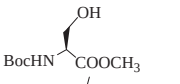
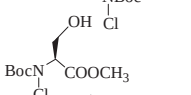
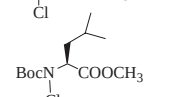
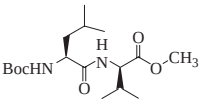
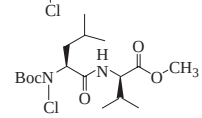
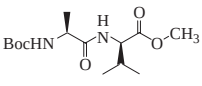
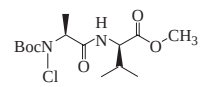
Halogenation in general and chlorination in particular, is one of the important biochemical mechanism used by mammalians as protection from pathogens.[1] N-chlorinated amino esters, are also of fundamental chemical interest as they show distinct physical, chemical, and biological properties.[2] These compounds exhibit pharmacological activity, because of their oxidizing action in aqueous, partial aqueous and non-aqueous media, which has further stimulated recent interest in their chemistry. Therefore, an understanding of the synthesis, properties and reactions of *N*-chloro derivatives of amino esters are of importance in medicinal chemistry. Although, myriad reagent[3] employed for the synthesis of *N*-chloro derivatives of amino esters have been reported, there is still scope for improvement, as the existing chlorinating methods suffers from one or more drawbacks, like use of toxic and hazardous reagent, long reaction time, harsh reaction conditions, short shelf life, difficulties in isolation of products, and formation of by-products leading to low yields. Moreover, N-chlorinated products so formed are unstable in the aqueous basic media. Advantages such as cleaner reactions, short reaction times and easy work up have kindled a special interest in the synthesis of *N*-chloro compounds of amino esters. During the course of our study on chlorination, we encountered a reagent namely *N*,*N*′-dichlorobis(2,4,6-trichlorophenyl)urea,[4] which is, mild, non-toxic, stable, safe, and efficient chlorine releasing reagent. It also has high concentration of active chlorine and previously has been used for the synthesis of α-chloronitoso compounds[5] and selective oxidation of sulfides to sulfoxides.[6] To the best of our knowledge, the reagent has also not been reported in the literature as chlorinating agent. Herein, we describe a convenient, rapid, environmental friendly and scaleable, method for the synthesis of *N*-chloro compounds of amino esters, amides, and peptides using *N*,*N*′-dichlorobis(2,4,6-trichlorophenyl)urea (**2**) in non-aqueous media. This method has allowed us to obtain excellent yields of N-chlorinated compounds **3** (1–12) in the reduced reaction time. The general synthetic method is given in Scheme 1.



Scheme 1.

Treatment of various amino esters, amides and dipeptides **1** (1–12) in the presence of **2** at room temperature afforded the corresponding *N*-chloro compounds **3** (1–12) in 10 min with quantitative yields Table 1. It is also evident from Table 1, that **2** does bring about a smooth N-chlorination of various α as well as β amino esters, carbamate, protected amino esters, tolerating sensitive functionalities such as, unprotected primary hydroxy group in N-Boc-protected serine methyl ester (Table 1, Entry 9). Similarly, this method can also be extended for the chlorination of highly strained bicyclic β-lactam (Table 1, Entry 4) and peptide[7] (Table 1, Entries 11 and 12). A number of previously unknown N-protected N-chlorinated amino acid

Table 1. N-chlorination of amino esters, amides, and peptides using CC-2

Entry	Substrate (**1**) (1–12)	Product[a] (**3**) (1–12)	Yield/%[b]
1.	$C_6H_5CONHCH_2C_6H_5$	$C_6H_5CONClCH_2C_6H_5$	92
2.			95
3.			90
4.			89
5.			90
6.			86
7.			94
8.			88
9.			85
10.			90
11.			92
12.			90

[a]All compounds have been characterized by IR, NMR, and MS. [b]Isolated yield.

esters containing a cyclopropane moiety (Table 1, Entry 8) could be prepared by this method.[8] Effect of solvents was studied on the chlorination of substrates and acetonitrile was found to be the most suitable solvent in terms of reaction time, yield, and work-up. Substituents present on the nitrogen atom of the substrate also did not have any effect on the chlorination. Most of the compounds have been found to be stable for 3 months at 25 °C except peptides (Table 1, Entries 11 and 12). Most probably, the chlorination takes place via the transfer of chlorine from **2** to the nitrogen of the various substrates used **1** (1–12).

The important advantage of this reaction is its occurrence at room temperature.[9] The noteworthy feature of this reagent is that the monitoring of the reaction is very easy; completion of reaction was confirmed by the precipitation of 1,3-bis(2,4,6-trichlorophenyl)urea (**4**), within 10 min, from the homogenous reaction medium. Furthermore, the reaction does not require any additional work up except filteration. The important application of these *N*-chloro compounds lies in their mild oxidizing properties; hence it can be used for the oxidative decontamination of hazardous chemicals.[10] Moreover, large number of pharmacologically active compounds can also be synthesized by following this method/reagent. In conclusion, we have exploited the chlorinating property of *N*,*N*′-dichlorobis(2,4,6-trichlorophenyl)urea (**2**) for the preparation of various *N*-chloro compounds. The striking features of the reagent are: short reaction time, wide applicability, easy work up procedures, recyclability (**4** was recovered, re-chlorinated and used for further reactions) and quantitative yields.

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7 *N*-Chloro-dipeptides are not stable for long, and undergo base-promoted decomposition.

8 N-Chlorination of the cyclopropyl-containing amino acid derivatives (Entry 8) with any of the other known reagents was hampered to a greater extent by some side processes furnishing the corresponding N-chlorinated products in low yield and purity.

9 (a) *Typical experimental procedure*: To a stirred solution of cyclic amide (Entry 2) (0.8 g, 0.01 mol) in acetonitrile (15 mL) *N*,*N*′-dichlorobis(2,4,6-trichlorophenyl)urea was added (2.4 g, 0.005 mol) at room temperature. The resulting mixture was stirred at room temperature for 10 min. The progress of reaction has been monitored by TLC (EtOAc: hexane 2:8). After the completion of reaction 1,3-bis(2,4,6-trichlorophenyl)urea precipitated indicating the completion of reaction. It was then filtered to remove the precipitate followed by the removal of solvent under vacuum to afford the pure products. Typical spectral data: **3**(5): Viscous oil, IR (film), ν_{max} 1737, 1236, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9H), 1.44 (m, 4H), 1.66 (m, 2H), 1.79 (m, 2H), 2.87 (dd, 1H, $J = 4.66$, 6.0 Hz), 3.67 (s, 3H), 4.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 21.5, 24.2, 25.2, 28.7, 37.6, 49.3, 56.7, 70.1, 157, 176; ESI-MS 292 (M + H). Anal. Calcd for $C_{13}H_{22}ClNO_4$: C, 53.51; H, 7.60; N, 4.80%. Found: C, 53.47; H, 7.55; N, 4.76%. **3**(6): Viscous oil, IR (film) ν_{max}: 1735, 1239, 1266 cm^{-1}: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26–1.29 (m, 8H), 1.40 (s, 9H), 1.50–1.64 (m, 4H), 2.87 (dd, 1H, $J = 4.1$, 6.6 Hz), 3.25 (m, 1H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.7, 24.9, 26.2, 27.2, 28.7, 30, 33.2, 45, 47, 50.7, 70.6, 157, 176. ESI-MS 320 (M + H). Anal. Calcd for $C_{15}H_{26}ClNO_4$: C, 56.33; H, 8.19; N, 4.38%. Found: C, 56.28; H, 8.10; N, 4.33%.

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