New Protocol for Efficient *N*-Chlorinations of Amides and Carbamates[1]

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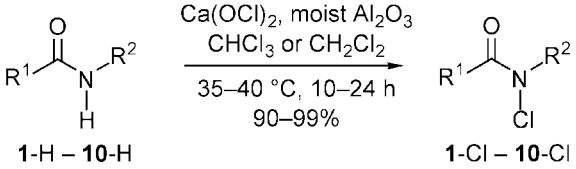
Abstract: *N*-Chlorination of various amides, carbamates and lactams with inexpensive and stable calcium hypochlorite on moist alumina proceeds smoothly and efficiently, e.g. the technically important 1-chlorohexahydroazepin-2-one (**3**-Cl) and 1-chloropyrrolidin-2-one (**7**-Cl) were obtained in 95% and 98% yield, respectively. Excellent results were also observed for the *N*-chlorination of protected amino acid esters with a cyclopropane moiety to give derivatives such as methyl (*tert*-butoxycarbonylchloroamino)cyclopropylacetate (**1**-Cl), methyl (benzyloxycarbonylchloroamino)cyclopropylacetate (**2**-Cl), methyl 1-(*tert*-butoxycarbonylchloroamino)cyclopropanecarboxylate (**5**-Cl) and methyl *trans*-2-(*tert*-butoxycarbonylchloroamino)cyclopropanecarboxylate (**6**-Cl) in 99%, 96%, 90% and 97% yield, respectively.

Key words: amides, amino acids, *N*-chlorination, calcium hypochlorite, alumina



Scheme 1 For details see Table 1.

N-Chloro derivatives have found use as valuable intermediates in a host of oxidation[2] as well as rearrangement[3] reactions, and as precursors to α,β-dehydro-α-aminocarboxylic acids,[4] to amidyl and carbamoyl radicals,[5] and to substituted protected amino acids.[6] A number of procedures for the synthesis of such compounds have been described, including *N*-chlorinations with chlorine,[7] sodium hypochlorite,[8] *tert*-butyl hypochlorite,[4,5,9] and Oxone® in the presence of sodium chloride.[10] However, the methods known-to-date all have certain drawbacks. For instance, sodium hypochlorite has a short shelf lifetime, and *tert*-butyl hypochlorite is a hazardous reagent due to its spontaneous combustibility. In the most recent and most efficient method,[10] fivefold excesses of Oxone®, having a relatively low percentage of active oxygen, as well as sodium chloride have to be employed, thus hampering its use for large scale preparations.

On the other hand, commercial calcium hypochlorite is a stable, inexpensive and safe reagent. It has a high concentration of active chlorine and relatively low molecular weight. It has previously been used for selective oxidations of thiols to disulfides,[11] and sulfides to sulfoxides.[12] In the course of studies directed towards the synthesis of new α,β-dehydro-α-aminocarboxylic acids containing a three-membered ring,[13] we encountered only meagre yields and selectivities employing the previously developed *N*-chlorination protocols. Thus, we decided to investigate the applicability of commercial calcium hypochlorite for the synthesis of *N*-chloro-substituted amides, carbamates, and lactams.

Indeed, calcium hypochlorite does bring about a smooth *N*-chlorination of various lactams and a diverse set of carbamate-protected amino acids (Scheme 1 and Table 1), tolerating such sensitive functionalities as an unprotected primary hydroxy group in *N*-Boc-protected serine methyl ester (Table 1, entry 4).

A number of previously unknown *N*-protected *N*-chlorinated amino acid esters containing a cyclopropane moiety could be prepared by this new method.[14] This protocol allows for easy scale-up to multigram quantities of the *N*-chloro derivatives, due to lower loading of moist alumina[15] which mediates the process and can be reused at least 7 times without any loss in yields or chemoselectivity, and higher efficiency of calcium hypochlorite as *N*-chlorinating agent.

^{1}H and ^{13}C NMR spectra were recorded at 250 (^{1}H), and 62.9 [^{13}C, additional DEPT (Distortionless Enhancement by Polarization Transfer)] MHz on a Bruker AM 250 instrument in $CDCl_3$ solution, $CHCl_3$/$CDCl_3$ as internal reference; δ in ppm, *J* in Hz. IR spectra were measured as oils between KBr plates on a Bruker IFS 66 (FT-IR) spectrophotometer. MS (EI): Finnigan MAT 95 instrument. $CHCl_3$ was washed with 98% H_2SO_4, dried over $MgSO_4$, and distilled from 4 Å molecular sieves, CH_2Cl_2 was distilled from P_2O_5. Commercial GR *for analysis* $CHCl_3$ (Merck) was also used as purchased. Moist alumina was prepared according to the published pro-

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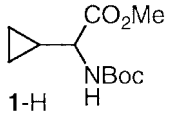
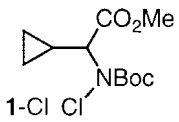
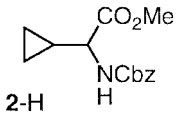
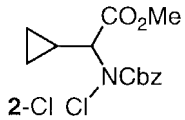
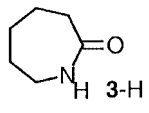
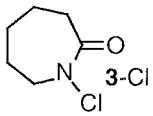
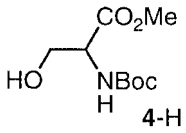
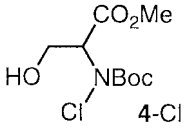
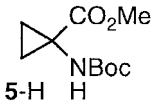
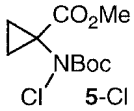
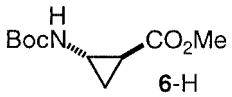
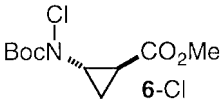
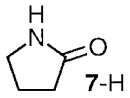
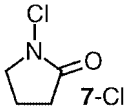
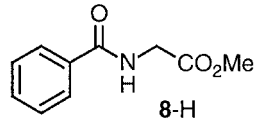
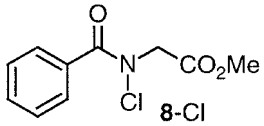
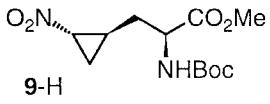
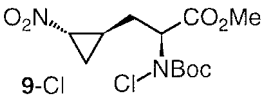
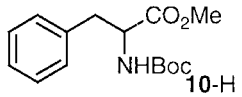
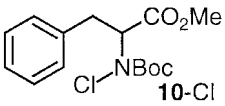
Table 1 *N*-Chlorination of Amides, Carbamates, and Lactams with Calcium Hypochlorite on Moist Alumina

Entry	Starting Material	Product	Reaction Time (h)	Yield (%)
1	 **1**-H	 **1**-Cl	14	99
2	 **2**-H	 **2**-Cl	12	96
3	 **3**-H	 **3**-Cl	10	95
4	 **4**-H	 **4**-Cl	20	93
5	 **5**-H	 **5**-Cl	24	90
6	 **6**-H	 **6**-Cl	10	97
7	 **7**-H	 **7**-Cl	12	98
8	 **8**-H	 **8**-Cl	18	98
9	 **9**-H	 **9**-Cl	18	97
10[a]	 **10**-H	 **10**-Cl	22	99

[a] The reaction was carried out in dichloromethane at 35 °C.

tocol.[15a] Methyl *tert*-butoxycarbonylaminocyclopropylacetate (**1**-H),[13,16] methyl benzyl-oxycarbonylaminocyclopropylacetate (**2**-H),[13,16] methyl 2-(*tert*-butoxycarbonylamino)-3-hydroxypropionate (**4**-H),[17] methyl 1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylate (**5**-H),[18] methyl *trans*-2-(*tert*-butoxycarbonylamino)cyclopropanecarboxylate (**6**-H),[19] methyl 2-*N*-*tert*-butoxycarbonylamino-3-(2-*trans*-nitrocyclopropyl)propionate (**9**-H),[20] and (*N*-*tert*-butoxycarbonyl)phenylalanine (**10**-H)[21] were prepared according to published procedures. All other chemicals were used as commercially available (Merck, Acros, BASF, Bayer, Hoechst, Degussa AG, and Hüls AG). Organic extracts were dried over $MgSO_4$. All reactions were performed in a two-necked round-bottomed flask equipped with a magnetic stirring bar, a thermometer and a reflux condenser protected from atmospheric moisture with a calcium chloride tube. Teflon joint sleeves were used as a substitute for the silicon grease soluble in $CHCl_3$ or CH_2Cl_2. Elemental analyses of several *N*-chloro derivatives were attempted, but gave incorrect results in spite of sufficient purity as determined by NMR spectroscopy. Indeed, to the best of our knowledge, no elemental analysis for the *N*-chlorinated protected amino acid esters has ever been reported in the literature.

General Procedure GP1

$Ca(OCl)_2$ (Aldrich, technical grade, ground in a mortar, 20 mmol, 2.86 g), moist alumina (10 g), and $CHCl_3$ (50 mL) were efficiently stirred at 40 °C for 10 min. A solution of the starting material (10 mmol) in $CHCl_3$ (10 mL) was then added, and the mixture was stirred at 40 °C until the starting material had disappeared [monitored by TLC (hexane–Et_2O, 1:1), 10–24 h]. The solids were re-

moved by filtration, and the filtrate was concentrated under reduced pressure to give the desired *N*-chloro derivative. Compound **10**-Cl was prepared in CH_2Cl_2 at 35 °C.

Methyl *N*-(*tert*-Butoxycarbonyl)-*N*-chloroaminocyclopropylacetate (1-Cl)
From **1**-H (57.4 g, 250.6 mmol), $Ca(OCl)_2$ (108.5 g, 759 mmol), and Al_2O_3 (398 g) in $CHCl_3$ (700 mL), compound **1**-Cl (62.5 g, 99%) was obtained according to GP1 as a colorless oil.

IR (film): 1262 cm^{-1}.

^1H NMR: δ = 0.40–0.46 (m, 1 H), 0.51–0.59 (m, 1 H), 0.61–0.68 (m, 1 H), 0.78–0.85 (m, 1 H), 1.37–1.45 (m, 1 H), 1.49 (s, 9 H), 3.78 (s, 3 H), 3.95 (d, *J* = 9.5 Hz, 1 H).

^{13}C NMR: δ = 3.38 (CH_2), 5.72 (CH_2), 11.55 (CH), 27.81 (CH_3), 52.29 (CH_3), 68.42 (CH), 83.39 (C), 154.88 (C), 169.94 (C).

MS (EI): *m*/*z* = 263.3 (1) [M^+], 160.2 (5), 104.1 (23), 57.1 (100), 41.0 (17).

Methyl *N*-Benzyloxycarbonyl-*N*-chloroaminocyclopropylacetate (2-Cl)
From **2**-H (3.10 g, 11.77 mmol), $Ca(OCl)_2$ (3.37 g, 23.58 mmol), and Al_2O_3 (11 g), compound **2**-Cl (3.37 g, 96%) was obtained according to GP1 as a colorless oil.

IR (film): 1266 cm^{-1}.

^1H NMR: δ = 0.40–0.46 (m, 1 H), 0.55–0.64 (m, 2 H), 0.80–0.87 (m, 1 H), 1.38–1.45 (m, 1 H), 3.75 (s, 3 H), 4.05 (d, *J* = 9.5 Hz, 1 H), 5.22 (s, 2 H), 7.30–7.39 (m, 5 H.

^{13}C NMR: δ = 3.48 (CH_2), 5.86 (CH_2), 11.47 (CH), 52.50 (CH_3), 68.42 (CH), 68.26 (CH_2), 127.94 (CH), 128.36 (CH), 128.52 (CH), 135.28 (C), 155.94 (C), 169.57 (C).

MS (DCI): m/z = 315.2 (7) [M+NH_4^+], 281.2 (100), 264.2 (32), 204.1 (7), 108.0 (6).

1-Chlorohexahydroazepin-2-one (3-Cl)[4a,7,10,22,23]
From **3**-H (1.70 g, 15.0 mmol), $Ca(OCl)_2$ (4.29 g, 30.0 mmol), and Al_2O_3 (14 g), compound **3**-Cl (2.10 g, 95%) was obtained according to GP1 as a colorless oil.

IR (film): 1247 cm^{-1}.

^1H NMR: δ = 1.61–1.85 (m, 6 H), 2.56–2.71 (m, 2 H), 3.75–3.87 (m, 2 H).

^{13}C NMR: δ = 22.82 (CH_2), 27.02 (CH_2), 29.19 (CH_2), 35.95 (CH_2), 58.14 (CH_2), 173.20 (C).

Methyl 2-(*N*-*tert*-Butoxycarbonyl-*N*-chloroamino)-3-hydroxypropionate (4-Cl)[10]
From **4**-H (0.21 g, 0.96 mmol), $Ca(OCl)_2$ (0.275 g, 1.92 mmol), and Al_2O_3 (1.0 g), compound **4**-Cl (0.226 g, 93%) was obtained according to GP1 as a colorless oil.

IR (film): 1236 cm^{-1}.

^1H NMR: δ = 1.45 (s, 9 H), 3.72 (s, 3 H), 3.82–4.10 (m, 2 H), 4.40 (br s, 1 H), 4.87 (dd, *J* = 5.4, 7.9 Hz, 1 H).

^{13}C NMR: δ = 27.73 (3 CH_3), 52.41 (CH_3), 60.02 (CH_2), 65.38 (CH), 83.95 (C), 154.76 (C), 168.58 (C).

Methyl 1-(*N*-*tert*-Butoxycarbonyl-*N*-chloroamino)cyclopropanecarboxylate (5-Cl)
From **5**-H (4.10 g, 19.05 mmol), $Ca(OCl)_2$ (5.60 g, 39.2 mmol), and Al_2O_3 (18 g), compound **5**-Cl (4.28 g, 90%) was obtained according to GP1 as a colorless oil.

IR (film): 1252 cm^{-1}.

^1H NMR: δ = 1.39–1.48 (m, 2 H), 1.45 (s, 9 H), 1.75–1.80 (m, 2 H), 3.73 (s, 3 H).

^{13}C NMR: δ = 27.70 (CH_2+3 CH_3), 46.85 (C), 52.36 (CH_3), 83.15 (C), 154.65 (C), 171.34 (C).

MS (DCI): *m*/*z* = 267.2 (40) [M + NH_4^+], 233.2 (100), 177.2 (87), 133.1 (16), 116.0 (11).

Methyl *trans*-2-(*N*-*tert*-Butoxycarbonyl-*N*-chloroamino)cyclopropanecarboxylate (6-Cl)
From **6**-H (1.20 g, 5.57 mmol), $Ca(OCl)_2$ (1.59 g, 11.14 mmol), and Al_2O_3 (6 g), compound **6**-Cl (1.35 g, 97%) was obtained according to GP1 as a colorless oil.

IR (film): 1234 cm^{-1}.

^1H NMR: δ = 1.40–1.58 (m, 2 H), 1.55 (s, 9 H), 2.09 (ddd, *J* = 2.5, 2.5, 6.5 Hz, 1 H), 3.32 (ddd, *J* = 2.7, 2.7, 3.0 Hz, 1 H), 3.70 (s, 3 H).

^{13}C NMR: δ = 18.82 (CH_2), 25.91 (CH), 27.78 (3 CH_3), 43.78 (CH), 51.88 (CH_3), 83.59 (C), 154.79 (C), 171.71(C).

MS (DCI): *m*/*z* = 267.2 (45) [M + NH_4^+], 233.2 (55), 177.2 (100), 150.1 (42), 116.0 (94).

1-Chloropyrrolidin-2-one (7-Cl)[24]
From **7**-H (3.00 g, 35.25 mmol), $Ca(OCl)_2$ (10.08 g, 70.50 mmol), and Al_2O_3 (30 g), compound **7**-Cl (4.13 g, 98%) was obtained according to GP1 as a colorless oil.

IR (film): 1243 cm^{-1}.

^1H NMR: δ = 2.13–2.25 (m, 2 H), 2.42 (dd, *J* = 7.0, 12.7 Hz, 2 H), 3.60 (dd, *J* = 7.0, 8.0 Hz, 2 H).

^{13}C NMR: δ = 17.73 (CH_2), 27.29 (CH_2), 51.77 (CH_2), 172.57 (C).

Methyl *N*-Benzoyl-*N*-chloroaminoacetate (8-Cl)
From **8**-H (0.52 g, 2.69 mmol), $Ca(OCl)_2$ (0.787 g, 5.50 mmol), and Al_2O_3 (2.30 g), compound **8**-Cl (0.60 g, 98%) was obtained according to GP1 as a colorless oil.

IR (film): 1215 cm^{-1}.

^1H NMR: δ = 3.81 (s, 3 H), 4.47 (s, 2 H), 7.40–7.51 (m, 3 H), 7.58–7.62 (m, 2 H).

^{13}C NMR: δ = 52.53 (CH_3), 55.39 (CH_2), 127.82 (CH), 128.46 (CH), 131.19 (CH), 132.43 (C), 167.53 (C), 171.86 (C).

MS (EI): *m*/*z* = 227.1 (5) [M^+], 105.1 (100), 77.0 (89), 51.1 (59).

Methyl 2-(*N*-*tert*-Butoxycarbonyl-*N*-chloroamino)-3-(2-*trans*-nitrocyclopropyl)propanoate (9-Cl)
From **9**-H (0.35 g, 1.21 mmol), $Ca(OCl)_2$ (0.358 g, 2.50 mmol), and Al_2O_3 (1.20 g), compound **9**-Cl (0.38 g, 97%) was obtained according to GP1 as a colorless oil.

IR (film): 1251 cm^{-1}.

^1H NMR: δ = 1.13–1.27 (m, 1 H), 1.50 (s, 9 H), 1.84–1.89 (m, 1 H), 1.91–2.01 (m, 3 H), 3.77 (s, 3 H), 4.12–4.15 (m, 1 H), 4.92–5.00 (m, 1 H).

^{13}C NMR: δ = 17.20 (CH), 18.24 (CH_2), 22.50 (CH), 27.85 (3 CH_3), 30.06 (CH_2), 52.79 (CH_3), 58.84 (CH), 84.25 (C), 153.9 (C), 169.10 (C).

MS (DCI): *m*/*z* = 340.2 (43) [M + NH_4^+], 306.3 (100), 250.2 (88), 189.1 (4).

Methyl 2-(*N*-*tert*-Butoxycarbonyl-*N*-chloroamino)-3-phenylpropanoate (10-Cl)[10]
From **10**-H (1.70 g, 6.1 mmol), $Ca(OCl)_2$ (2.64 g, 18.9 mmol), and Al_2O_3 (9.70 g), compound **10**-Cl (1.90 g, 99%) was obtained according to GP1 as a colorless oil.

IR (film): 1235 cm^{-1}.

^1H NMR: δ = 1.32 (s, 9 H), 3.16 (dd, *J* = 10.8, 14.5 Hz, 1 H), 3.34 (dd, *J* = 4.5, 14.5 Hz, 1 H), 3.80 (s, 3 H), 5.14 (dd, *J* = 4.5, 10.8 Hz, 1 H), 7.24–7.28 (m, 5 H).

^{13}C NMR: δ = 27.7 (3 CH_3), 34.6 (CH_2), 52.6 (CH_3), 64.2 (CH), 83.4 (C), 126.8 (2 CH), 128.5 (2 CH), 129.1 (CH), 136.6 (C), 154.2 (C), 169.7 (C).

MS (DCI): *m*/*z* = 331.2 (100) [M + NH_4^+], 275.1 (10), 231.1 (24), 180.1 (4).

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