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A highly efficient method for the α,β-dehydrogenation of α-amino esters and α-amino-β-diesters

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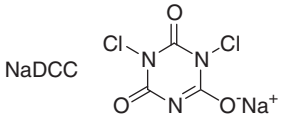
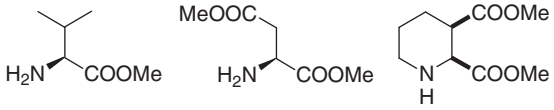
ABSTRACT

N-monochlorination of N-unprotected α-amino esters and α-amino-β-diesters was efficiently and very simply effected by using inexpensive effervescent sodium dichloroisocyanurate tablets for water disinfection in a biphasic organic solvent-water system. Subsequent dehydrochlorination provided α,β-didehydroaminoacid esters, whose hydrogenation would allow the starting compounds to be easily racemized.

Great interest in α,β-didehydroamino acids (DDAAs) derives from both their importance as synthetic intermediates and their presence in biologically active compounds.[1–3] Asymmetric hydrogenation of DDAA gives access to unnatural amino acids, whereas their symmetric hydrogenation yields racemic amino acids thus allowing an amino acid with undesired configuration, for instance the 'wrong' antipode resulting from a resolution process, to be racemized through α,β-unsaturation–saturation sequence.[4–7] However, such a racemization method needs short, clean and manageable reactions to be advantageously practiced. N-chlorination, followed by dehydrochlorination, satisfies these requirements if an efficient, stable and safe chlorinating agent is available and monochlorination can be quantitatively effected without previous N-protection. Many reagents for the synthesis of N-chloro derivatives of amino esters have been described, but few of them can be said to be non toxic, safe, rapid, mild and efficient at the same time, certainly not chlorine,[8] commercial bleach,[9] t-butyl hypochlorite,[10,11] Oxone® in the presence of NaCl[12] or calcium hypochlorite on alumina.[13] More recently, protocols for N-chlorination of amides with trichloroisocyanuric acid[14] and of *N*-Boc-protected amino esters with *N*,*N*′-dichlorobis(2,4,6-trichlorophenyl)urea[15] have been reported. During the course of our studies aimed at racemization of undesired enantiomers of amino esters and amino diesters, we focused on N-chlorination and dehydrochlorination as the simplest 'ad hoc' method and considered the possibility of directly monochlorinating the unprotected amino group with commercially available effervescent sodium dichloroisocyanurate (NaDCC) tablets in a biphasic organic solvent-water system.



After N-chlorination of hindered secondary amines with NaDCC was described by Zakrzewski in 1988,[16] few examples of NaDCC as a reagent in organic synthesis have been reported: halogenation–oxidation of ketoximes to gem-halonitro compounds,[17] of arylaldoximes to α-chloroarylaldoximes,[18] of 4-quinolone to 3-chloro-4-quinolone.[19]



1 **2** **3**

Herein, we describe a simple way to N-monochlorinate α-amino esters and α-amino-β-diesters, which are successively submitted to dehydrochlorination in order to create α,β-unsaturation. We selected the methyl esters of three representative amino acids, namely aliphatic monocarboxylic L-valine (**1**),[20] aliphatic α,β-dicarboxylic L-aspartic acid (**2**)[20] and alicyclic α,β-dicarboxylic

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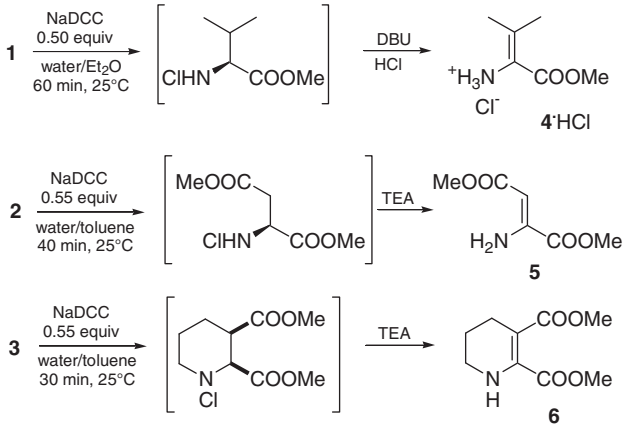

Scheme 1. Conversion of α-amino esters **1**, **2** and **3** into the corresponding α,β-unsaturated analogues **4**, **5** and **6**.

cis-hexahydroquinolinic acid (**3**),[21] with the aim of obtaining the corresponding α,β-dehydro derivatives, that are α,β-dehydrovalinate (**4**), dimethyl 2-aminofumarate (**5**) and dimethyl 1,4,5,6-tetrahydroquinolinate (**6**), by subsequent hydrogen chloride elimination (Scheme 1).

NaDCC was used in stoichiometric or slightly exceeding amount (0.5–0.55 mol per mol of amino ester) and in form of self-dissolving tablets containing 60% w/w NaDCC bihydrate together with adipic acid and sodium carbonate. The substrate was dissolved in toluene (**2** and **3**) or in diethyl ether (**1**). The solution was vigorously stirred at room temperature and in the presence of NaDCC tablets and of the minimum amount of water, necessary to produce tablet disaggregation. As shown by TLC and NMR analyses, N-chlorination was complete in 30′–60′ and no N,N-dichloro derivatives were detected. In the case of the N-chloroaminodiesters, the doubly conjugated C–C double bond was then formed through almost instantaneous hydrogen chloride elimination resulting from addition of a slight excess of triethylamine to the undried organic layer previously separated from the bottom water slurry. Pure **6**, which, to our knowledge, has never been described, and **5** were quantitatively isolated after removing the precipitated triethylamine hydrochloride and evaporating toluene.[22,23] For methyl N-chlorovalinate, dehydrochlorination required the use of DBU, a stronger base than TEA, and, differently from the two β-diesters, yielded the iminoester, which had to be converted into the hydrochloride of enaminoester **4**[24] by treatment with hydrogen chloride in diethyl ether, as described in the literature.[10]

The present α,β-dehydrogenation procedure, here applied to three exemplary aminoesters, can be extended to other congeners optionally changing the organic solvent (dichloromethane can replace diethyl ether and toluene) or modifying the dehydrochlorination conditions, if necessary. For instance, L-isoleucine methyl ester was quantitatively transformed into the *N*-chloro derivative[25] under the same conditions adopted for **1** and, like **1** and unlike **2** and **3**, required DBU to be dehydrochlorinated.

In conclusion, we have exploited the chlorinating property of inexpensive, stable and safe NaDCC to prepare α,β-unsaturated α-amino esters and α-amino-β-diesters from the corresponding saturated N-unprotected forms according to a very simple protocol, which assures quantitative yields in a short time avoiding any laborious reaction work-up. Due to the very mild conditions, the method, coupled with hydrogenation, could be advantageously applied both to racemize a number of unichiral aminocarboxylic and aminodicarboxylic acids derivatives, such as esters, amides, imides, anhydrides, and to invert their configuration.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.006.

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20. Methyl L-valinate and dimethyl L-aspartate were quantitatively liberated from the respective hydrochlorides, purchased from Aldrich, by treatment with equimolar sodium carbonate in diethyl ether.
21. Dimethyl *cis*-hexahydroquinolinate was prepared by hydrogenation of dimethyl pyridine-2,3-dicarboxylate (purchased from Aldrich) as described in Ref. 26.
22. Dimethyl L-aspartate (**2**) (520 mg, 3.22 mmol), liberated from its hydrochloride by Na_2CO_3 aq/diethyl ether extraction, was dissolved in toluene (10 ml) and added with fragments of 60% w/w sodium dichloroisocyanurate bihydrate tablets (790 mg, 1.85 mmol) and water (2 ml). After vigorous stirring for 40 min, the water phase was removed and TEA (0.5 ml) was added to the toluenic solution. Triethylamine hydrochloride immediately precipitated. After 1 h, the reaction mixture was filtered and the filtrate concentrated to give an oily residue, which was distilled about 60 °C at 0.2 torr yielding **5** (480 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.49 (s, 2H), 3.84 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 51.12, 53.34, 88.80, 146.32, 164.35, 170.48 (cf. spectra reported in Ref. 27); IR (neat) 3469, 3346, 2954, 1732, 1675, 1616, 1557, 1436 cm^{-1}; LC–ESI-MS/MS: calcd for $C_6H_{12}NO_5$ $[MH+H_2O]^+$ 178.16, found 178.09.
23. Dimethyl hexahydroquinolinate (**3**) (494 mg, 2.46 mmol) was dissolved in toluene (10 ml) and added with fragments of 60% w/w sodium dichloroisocyanurate bihydrate tablets (600 mg, 1.40 mmol) and water (1.5 ml). The mixture was vigorously stirred for 30 min. TLC analysis (eluent: 100:5:2.5 ethyl acetate/methanol/TEA) demonstrated complete conversion into the N-chlorinated intermediate. The water slurry was removed and the organic phase added with TEA (0.45 ml). TLC analysis (eluent: 90:10:3 toluene/methanol/TEA), performed after a few minutes, showed complete conversion into α,β-unsaturated amino diester. After stirring for 1 h, the reaction mixture was washed with water (2 × 2 ml), dried with sodium sulphate, filtered at 40 °C and concentrated to give **6** (460 mg), as a colourless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (br s, 1H), 3.80 (s, 3H), 3.62 (s, 3H), 3.20 (m, 2H), 2.33 (m, 2H), 1.79 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.64, 21.45, 41.15, 51.32, 53.04, 95.03, 146.22, 167.71, 168.11; IR (neat) 3336, 2951, 1732, 1683, 1588, 1525, 1434 cm^{-1}; LC–ESI-MS/MS: calcd for $C_9H_{14}NO_4$ $[MH]^+$ 200.21, found 200.10; calcd for $C_9H_{14}NO_4Na$ $[M+Na]^+$ 222.20, found 222.10.
24. Methyl L-valinate hydrochloride (1016 mg, 6.05 mmol) and sodium carbonate (641 mg, 6.05 mmol) were suspended in diethyl ether (30 ml). Water (1.5 ml) was added and the mixture was vigorously stirred for 30 min. The organic phase was transferred into another flask, added with fragments of 60% w/w sodium dichloroisocyanurate bihydrate tablets (1.4 g, 3.28 mmol) and water (2 ml) and again vigorously stirred for 60 min. ^{1}H NMR analysis (300 MHz, $CDCl_3$: δ 4.58 (d, 1H, J = 6.4 Hz), 3.80 (s, 3H), 3.39 (dd, 1H, J = 10.6 Hz, 6.4 Hz), 1.93 (pseudo octet, 1H, J = 6.4 Hz), 0.96 (t, 6H, J = 6.4 Hz); cf. spectrum reported

in Ref. 28) of a concentrated small sample of the ethereal phase indicated complete and neat conversion into *N*-monochloro derivative. TLC analysis (eluent: 100:5:2.5 ethyl acetate/methanol/TEA) confirmed the finding, showing the fast-running spot of the N-chlorinated amino ester and only traces of the slow-running methyl valinate. The bottom water slurry was removed and DBU (900 mg) was added. The reaction mixture was cooled at 0 °C and, after 30 min, precipitated DBU·HCl was filtered off. ^{1}H NMR analysis, in $CDCl_3$, of a concentrated small sample of the filtrate indicated that dehydrochlorination had quantitatively produced the iminoester (NH singlet at 11 δ, CH multiplet at 3.06 δ, geminal CH_3 signals about 1 δ instead of about 2 δ). The imminoester was tautomerized to the desired enamino ester hydrochloride by addition of 2.4 M HCl in diethyl ether (2.75 ml) to the ethereal filtrate at -70 °C, as reported in Ref. 10. After stirring at 0 °C for 5 h, the reaction mixture was concentrated obtaining pure **4**·HCl (950 mg) as a white solid: ^{1}H NMR (300 MHz, D_2O) δ 3.70 (s, 3H), 2.10 (s, 3H), 1.87 (s, 3H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.76 (br s, 3H), 3.74 (s, 3H), 2.14 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 22.40, 23.10, 53.11, 116.63, 149.16, 163.48; IR (neat) 1731, 1646, 1592, 1571, 1523, 1435 cm^{-1}; LC–ESI-MS/MS: calcd for $C_6H_{12}NO_2Na$ $[MH+Na]^+$ 153.16, found 153.16.

25. *N*-Chloro-L-isoleucine methyl ester: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (d, 1H, J = 10.9 Hz), 3.77 (s, 3H), 3.64 (dt, 1H, J = 10.9, 7.2 Hz), 1.73 (m, 1H, J = 7.2 Hz), 1.47 (t, 2H, J = 7.2 Hz), 0.93 and 0.91 (2 d, 6H, J = 7.2 Hz).
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