Pergamon

Tetrahedron, Vol. 53, No. 41, pp. 14031-14042, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00908-3

Halogen Atom Transfer Radical Cyclization of N-Allyl-N-Benzyl-2,2-Dihaloamides to 2-Pyrrolidinones, promoted by Fe^0-$FeCl_3$ or CuCl-TMEDA

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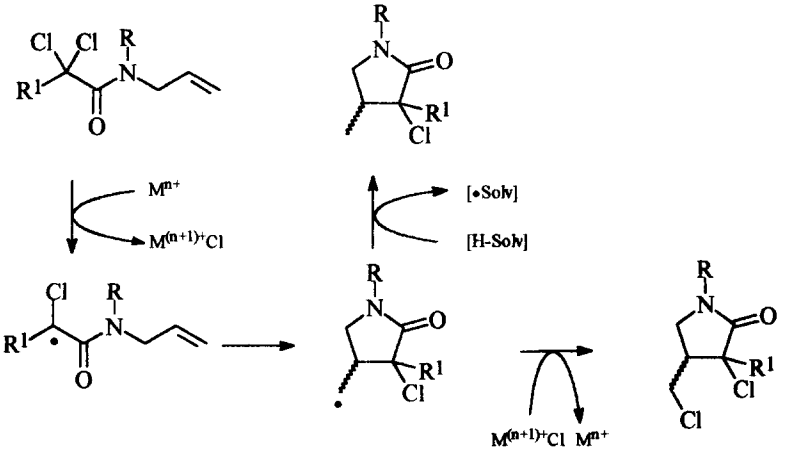
Abstract: The halogen atom transfer radical cyclization of a N-allyl-N-benzyl-2,2-dihaloamides to 2-pyrrolidinones has been carried out in high yields under mild conditions, in a reaction promoted by CuCl-TMEDA or Fe^0-$FeCl_3$ in acetonitrile or N,N-dimethylformamide, respectively.

Functionalized 2-pyrrolidinones (γ-lactams) are excellent starting materials for the synthesis of compounds having potential uses in medicine or agriculture.[1] γ-Lactams have been generally prepared by cyclization via acyl-nitrogen bond formation, or by substitution of butyrolactones with ammonia or amines.[2] In recent years intramolecular radical addition to C=C bonds has received great attention, as a powerful and versatile method for cyclization.[3] Among the radical routes to γ-lactams,[4-7] the cyclization of α-functionalized (usually halogenated) N-allyl amides is particularly interesting.[8]



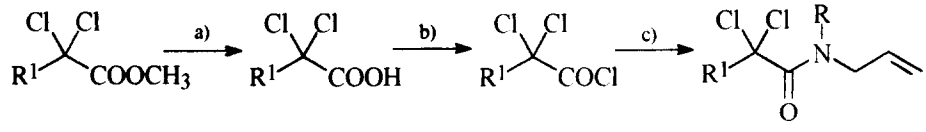
Scheme 1

Of the two main cyclization procedures, the tin method[9] or the atom transfer method,[10] the latter is not only safer and environmentally friendly, since toxic and difficult to remove tin compounds are not used, but it is synthetically more useful, as the products retain a versatile halogen atom at the expected site.[11] From Kharasch's early studies with peroxides as promoters,[12] the halogen atom transfer radical addition has achieved more selective and clean transformations with the use of redox catalysts (Scheme 1).[13]

$RuCl_2(PPh_3)_3$[10f-i,n,o] and CuCl-bipyridine (bipy)[10a,c,l,m,o] are the preferred promoters for *N*-allyl-α-polyhaloacetamides cyclization, with generally good results; the following disadvantages, however, must be considered: *i*) productivity is low owing to the high reaction dilution; *ii*) high amounts of these expensive catalysts are necessary for complete conversions; *iii*) aromatic solvents and relatively high temperatures (120-150°C) are used with $RuCl_2(PPh_3)_3$; and *iv*) stereoselectivity is poor.[10f] The substrates of these works were *N*-allyl-amides from commercially available dichloro- or trichloroacetyl chlorides; the $RuCl_2(PPh_3)_3$ reaction mechanism has been investigated by G. A. Slough.[10f,g]

In a continuation of our studies on halogen-atom-transfer radical addition,[14] and as a part of a project towards the synthesis of kainic acid derivatives,[9b] we report here that radical cyclization of N-allyl-N-benzyl-2,2-dihaloamides to 2-pyrrolidinones (γ-lactams) can be carried out in excellent yields under mild conditions, by the catalyst system CuCl-N,N,N',N'-tetramethylethylendiamine (TMEDA) or Fe^0-$FeCl_3$, in acetonitrile (AN) or N,N-dimethylformamide (DMF) respectively.

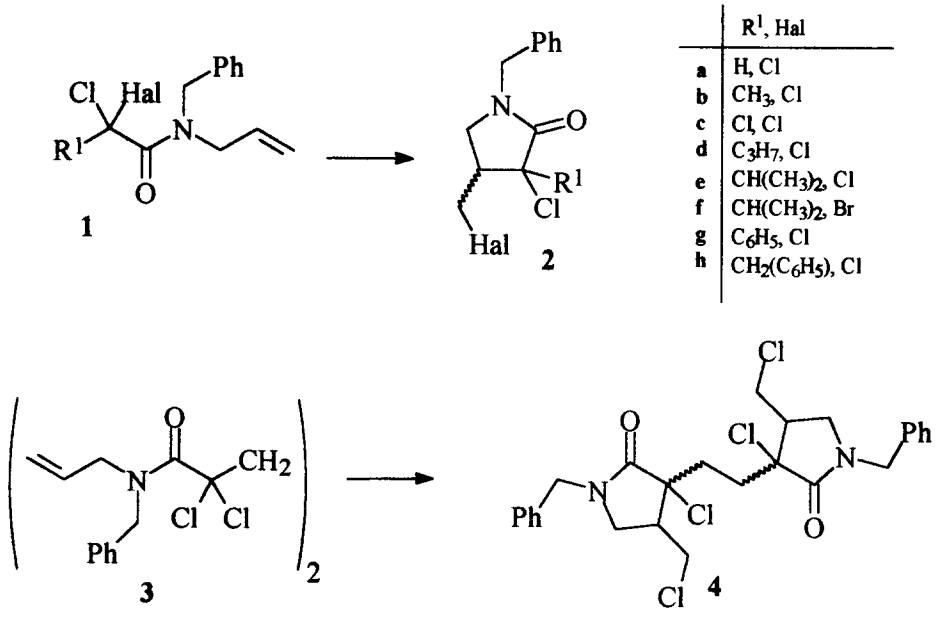
At first we attempted the preparation of γ-lactams from *N*-allyl-2,2-dihaloamides, on considering their easy preparation[15] and the good results obtained with Fe^0 as radical promoter in Kharasch additions of polyhalocompounds to alkenes.[14] Unsatisfactory results, however, were obtained owing to the poor chemoselectivity of the rearrangement and the moderate yields;[16] starting from N-allyl-2-Br-2-Cl-amides, γ-lactams showed halogen scrambling, whereas from the corresponding 2,2-diCl-analogues high amounts of mono chloro 2-pyrrolidinones were obtained. A literature survey[10] showed that the best yields in these reactions were always associated with the protection of the amidic hydrogen. Protection forces N-allyl-2,2-dihaloamides to a conformation more suitable for cyclization, favouring the rearrangement even at relatively low temperatures.[9i,m] Since both N-alkylation of N-allyl 2,2-dihaloamides, and amino-de-alkoxylation of methyl 2,2-dihaloesters by secondary amines were unsuccessful, we developed a very efficient two step procedure for the conversion of methyl 2,2-dihalo-carboxylates to N-protected N-allyl-2,2-dihaloamides, through a saponification followed by a chloro-de-hydroxylation (Scheme 2).[17]



a) LiOH, $(CH_3)_2CHOH/H_2O$ (1:1), -10°C. b) $C_2O_2Cl_2$, CH_2Cl_2, 20-40°C. c) secondary allylamine (3 eq.), CH_2Cl_2, 20-30°C, overall yield 85-98%.

Scheme 2

The ready prepared **1a** (Scheme 3) was selected as a model substrate. Benzylic protection of amidic hydrogen was choosed owing to its easy removal[18] and to the availability of efficient procedures for the preparation of optical active benzylic amines.[19] Moreover, these compounds can be synthones for chiral N-allyl-N-benzil-2,2-dihaloamides, in studies of diastereoselective halogen atom transfer radical routes to γ-lactams.[9c,e,g] Our approach to radical cyclization started from an iron-promoter; then we tried CuCl-amine catalysts.



Scheme 3

Cyclizations promoted by Fe^0-$FeCl_3$

As far as we know, the use of iron-promoters for N-allyl-α-polyhaloamides cyclization was neglected.[10q] After benzyl substitution of the amidic hydrogen of N-allyl-2,2-dichloropropanamide, Fe^0 promotes the transformation at 100°C of **1a** into **2a** in good yields, whereas unprotected amide does not react[16] even at 125°C. The formation of some monochloro cyclic adduct can be eliminated by using a mixture of Fe^0 and $FeCl_3$, a good radical trap.[20] The conproportionation between $FeCl_3$ and Fe^0 affords $FeCl_2$, another efficient reducing reagent, which can promote the halogen atom transfer radical addition;[20] furthermore the intermediate cyclic radical can now be effectively trapped through a ligand-transfer from $FeCl_3$, and not by H removal from solvent (Scheme 1).[21]

Besides benzyl, other protective groups (phenyl, alkyl, tosyl) have been tested with **1a**, but in no case we observed significatively better results. Sulfonyl protection, described as beneficial in these reactions,[10f] afforded relatively high amounts of N-allyl-N-benzyl-2-chloroacetamide and N-allyl-N-benzyl-acetamide as by-products

(ratio **2a**:by-products, 3.5:1). According to our previous observations about the solvent effect on iron reactivity,[14] DMF is the suitable solvent also with the combinate Fe^0-$FeCl_3$.

The *N*-allyl-*N*-benzyl-2,2-dichloroamides **1** and **3**, (Scheme 3) have been submitted to Fe^0-$FeCl_3$ promoted cyclization, obtaining 2-pyrrolidinones **2** and **4**, in fair to excellent yields (Table 1).

Table 1. The Fe^0-$FeCl_3$ promoted cyclization of N-allyl-N-benzyl-2,2-dichloroamides.[a]

substrate [$\cdot 10^{-3}$ mol]	product	T [°C]	t [h]	conv.[b] [%]	yield[c] [%]	*trans*:*cis*[d]	*trans*:*cis*[e]
1a [2]	**2a**	100	20	100	91	72:28	78:22
1a [6]	**2a**	100	28	99	94	84:16	-
1b [2]	**2b**	80	20	100	95	20:80	74:26
1b [6]	**2b**	80	28	99	96	23:77	-
1b [10]	**2b**	80	28	99	92	31:69	-
1c [2]	**2c**	80	20	98	94	-	-
1c [10]	**2c**	80	28	99	97	-	-
1d [2]	**2d**	80	20	100	94	22:78	-
1e [2]	**2e**	80	20	100	94	0:100	23:77
1f [2]	**2f**	80	20	100	65	0:100	-
1g [2]	**2g**	80	20	100	56	8:92	-
1h [2]	**2h**	80	20	100	70[f]	0:100	5:95
3 [2]	**4**	80	20	100	87	[g]	-

a) $3 \cdot 10^{-4}$ mol of Fe^0, $6 \cdot 10^{-4}$ mol of $FeCl_3$ and 4 ml of DMF were used. b) GC values. c) Yield of isolated product. d) Ratio determined by GC. e) trans/cis ratio observed[10f] with $RuCl_2(PPh_3)_3$. f) 17% of a tricyclic product from an intermolecular Friedel-Craft reaction of **2h** was observed. g) The ratio was not determined: mixture of diastereomers.

As results from 1a-1c show, yields are not significatively modified by increasing the substrate/promoter ratio from 6.7 to 33.3 in relatively concentrated mixtures. Dilution is therefore not necessary to obtain high yields; in fact oligomerization of protected N-allyl-2,2-dihaloamides is a quite difficult process, as observed by C. O-Yang.[22]

It is observed in Table 1 that replacement of C(3) hydrogen in **1a** with any substituent increases the reactivity, so that transformation can be carried out at 80°C. Notwithstanding the relative stability of benzylic radicals towards C=C additions,[14a,c] **1g** cyclizes in fair yields; in the transition state a conformation with the benzylic radical facing the olefin bond is likely achieved. A strong steric effect on the addition stereochemistry is shown by substrates **1e** and **1g-h**, all having bulky substituents adjacent to the radical centre; unlike results from **1e,h** with $RuCl_2(PPh_3)_3$,[10f,g] *cis* adducts are stereospecifically obtained.[23] When the substituent is the hydrogen atom (**1a**), the *trans* isomer is favoured.

Cyclizations promoted by CuCl-TMEDA

A 30% mol of CuCl-bipy (1:3) with respect to substrate in CH_2Cl_2 showed the highest activity as a promoter for selective conversion of N-protected N-allyl-trichloroacetamides into γ-lactams.[10e,l] The high

amounts of CuCl-bipy used by K. Itoh[10e,l] can be decreased to 10% mol by replacing CH_2Cl_2 with acetonitrile (AN) as solvent. Being bipy a quite expensive ligand, we tried other N-ligands for **1a** cyclization and found TMEDA as a better alternative. As it has been noted noted with Fe^0-$FeCl_3$, benzyl N-substitution gives very good transformation yield. It must be pointed out that whereas with more complex α-haloamides, e.g. **1h**, and at higher substrate concentrations, CuCl-bipy fails, CuCl-TMEDA gives very good results.

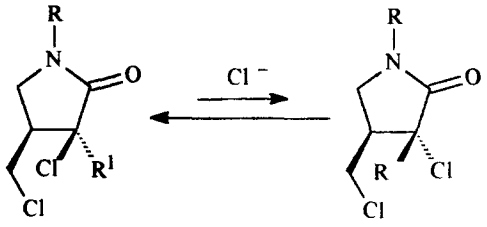
We therefore treated a number of N-allyl-N-benzyl-2,2-dichloroamides (Table 2) with CuCl-TMEDA obtaining good to excellent yields. Even a 2-Br-2-Cl substrate (**1f**) is quantitatively converted, provided that CuBr replaces CuCl to eliminate halogen scrambling.

As already found with Fe^0-$FeCl_3$, CuCl-TMEDA initiation favours *cis* diastereomers. An increase of substrate concentration reduces stereoselectivity, as is shown by the formation of *trans*-**2h** on triplicating **1h** concentration. Since *trans*-**2h** disappears when reaction time has been delayed 24 h further, it is clear that *cis* and *trans* interconvert, likely by a chloride nucleophilic substitution at C(3) (Scheme 4). The cyclization therefore does not work under cinetic control and the higher amounts of cis observed at higher substrate concentration agree with a slow equilibrium achievement.

Table 2. The CuCl-TMEDA promoted cyclization of N-allyl-N-benzyl-2,2-dichloroamides.[a]

substrate [· 10^{-3} mol]	product	T [°C]	t [h]	conv.[b] [%]	Yield[c] [%]	*trans*:*cis*[d]
1a [2]	**2a**	80	20	100	96	72:28
1a [4]	**2a**	60	28	100	97	80:20
1b [2]	**2b**	60	20	100	96	18:82
1b [10]	**2b**	60	28	100	99	37:63
1b [20]	**2b**	60	28	97	95	38:62
1c [2]	**2c**	60	20	99	96	-
1c [10]	**2c**	60	28	100	99	-
1d [2]	**2c**	60	20	100	98	14:86
1d [10]	**2d**	60	20	100	98	27:73
1d [20]	**2e**	60	20	100	97	43:57
1e [2]	**2e**	60	20	100	98	0:100
1e [10]	**2e**	60	20	100	98	0:100
1f [2][e]	**2f**	60	20	100	93	0:100
1f [10][e]	**2f**	60	20	100	92	0:100
1g [2]	**2g**	60	20	100	80	8:92
1g [10]	**2g**	60	20	76	73	19:81
1h [2]	**2h**	60	20	100	88[f]	0:100
1h [6]	**2h**	60	20	100	85[g]	11:89
3 [2]	**4**	60	20	100	90	[h]

a) $2 \cdot 10^{-4}$ mol of CuCl, $4 \cdot 10^{-4}$ mol of TMEDA and 4 ml of AN were used. b) GC values. c) Yield of isolated product. d) Ratio determined by GC. e) CuCl replaced by CuBr. f) 6% of a tricyclic product from an intermolecular Friedel-Craft reaction of **2h** was observed. g) 8% of the tricyclic adduct was observed. h) The ratio was not determined: mixture of diastereomers.



Scheme 4

Conclusions

Both Fe^0-$FeCl_3$ and CuX-TMEDA are effective promoters for halogen atom transfer radical cyclization of N-allyl-N-benzyl-2,2-dihaloamides to γ-lactams. Owing to the generally better yields, also at higher substrate concentrations, the lower operating temperature, and the easier work-up with AN, we consider CuCl-TMEDA a more advantageous promoter than Fe^0-$FeCl_3$.

On replacing the allyl group with a propargyl one in substrates **1a-b** the rearrangement quite fails; this can be explained by allylic group playing a role in the cleavage of the C-X bond, confirmed by the unsuccessful halogen removal from isosteric *N*-benzyl-*N*-propyl-2,2-dichloroamides in their halo-alkyl-addition to terminal alkenes.[24] The effectiveness of both promoters turns out also in the first HATRA rearrangement of N-benzyl-N-allyl-2-bromoamides into γ-lactams, with high conversions (>60%) and quantitative yields.

EXPERIMENTAL PART

^1H NMR and IR spectra were recorded on a Bruker DPX200 and a Philips PU 9716 spectrometers, respectively. Mass spectra were acquired on a combined HP 5890 GC - HP 5989A MS Engine. Reagents were standard grade commercial products and used without further purification. Fe^0 (filings) were purchased from BDH and CuCl and CuBr from Fluka. AN and DMF were dried over three batches of 3Å sieves (5% w/v, 12 h). *N*-allyl-*N*-benzyl-2,2-dihaloamides were prepared according to literature procedures.[17]

General procedure for methyl 2,2-dihalo-carboxylates hydrolysis. In a glass tube (10 ml) methyl 2,2-dihalocarboxylate (2 mmol), isopropyl alcohol (2 ml) and 1.5 M aq. LiOH (2 ml) were added. The stirred mixture was thermostatted at -7°C, acidified with 1.0 M aq. HCl (8 ml), after 15 minutes, and then extracted with CH_2Cl_2 (2 x 2 ml). The organic phases were collected and dried over $MgSO_4$. The 2,2-dihalocarboxylic acids, recovered after distillation of the solvent, required no further purification. Excellent results were also obtained in larger scale preparations.

Special case. Methyl 2,2-diCl-2-phenyl-acetate, methyl 2-Br-2-Cl-hexanoate and methyl 2-Br-2-Cl-3-phenyl-propanoate required thermostatation at -13°C.

General procedure for N-allyl-N-benzyl-2,2-dihaloamides preparation from 2,2-dihalocarboxylic acids.[25] The 2,2-dihalo-carboxylic acid (4.3 mmol) was weighed in a Schlenk tube fitted with a rubber seal, then dry CH_2Cl_2 (2.2 ml) and a drop of DMF were added under argon. The stirred mixture was thermostatted at 20-40°C, and oxalyl chloride (8 mmol) injected with a syringe. The side arm was then fitted with a $CaCl_2$ tube, and the stopcock opened to vent out the gases (CO, CO_2 and HCl) produced during the reaction. After 1-3 h,

solvent and exceeding oxalyl chloride were removed under reduced pressure. The crude acyl chloride was then diluted with CH_2Cl_2 (8 ml), thermostatted at 20-30°C and quenched with N-allyl-N-benzylamine (12 mmol). The reaction mixture was stirred for 1-5 h and then washed with 2.5% aq. HCl (2 x 5 ml). The organic phase was dried over $MgSO_4$, and evaporated. The crude N-allyl-N-benzyl-2,2-dihaloamides were purified by silica gel chromatography, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient; yields 85-98%. The procedure afforded excellent results also in larger scale preparations.

N-Benzyl-3-chloro-4-chloromethyl-pyrrolidin-2-one (2a): *Procedure A*: 0.017 g ($0.3 \cdot 10^{-3}$ mol) of iron filings and 0.516 g ($2 \cdot 10^{-3}$ mol) of **1a** were weighted in a Schlenk tube; then, a solution of 0.097 g ($0.6 \cdot 10^{-3}$ mol) of $FeCl_3$ in 4 ml of DMF was added under argon. The mixture was stirred at 100°C and after 20 h diluted with 20 ml of 2.5% HCl and extracted with 2 x 6 ml of CH_2Cl_2. The organic layer was dried over Na_2CO_3 and evaporated. Chromatographic separation by silica gel chromatography, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0.470 g of **2a** (91%), as a mixture of diastereomers, solid. IR (nujol): ν = 1715 (C=O). ^{1}H NMR ($CDCl_3$): δ = 2.75-3.0 [m, 1H, C(4)H], 3.10-3.27 [m, 1H, C(5)H], 3.32-3.95 [m, 3H, C(4)H and C(4)CH_2Cl], 4.42 [d, J = 7.4 Hz, 0.7 H, C(3)H, *trans*], 4.45 (d, J = 13.6 Hz, 1 H, benzyl H), 4.53 [d, J = 6.3 Hz, 0.3 H, C(3)H, *cis*], 4.60 (d, J = 13.6 Hz, 1 H, benzyl H), 7.2-7.45 (m, 5 H, aromatic H). MS (70 eV); *m/z* (%): 257 (5) [M^+], 222 (95) [M^+ - Cl], 91 (100). $C_{12}H_{13}Cl_2NO$ (258.2): calcd. C 55.83, H 5.08, N 5.43; found C 55.71, H 5.19, N 5.35.

Procedure B: 0.020 g ($0.2 \cdot 10^{-3}$ mol) of CuCl and 0.516 g ($2 \cdot 10^{-3}$ mol) of **1a** were weighted in a Schlenk tube; then 4 ml of AN and 0.047 g ($0.4 \cdot 10^{-3}$ mol) of TMEDA were added, under argon. The mixture was stirred at 80°C and after 20 h diluted with 20 ml of 2.5% HCl and extracted with 2 x 6 ml of CH_2Cl_2. The organic layer was dried over Na_2CO_3 and evaporated. Chromatographic separation by silica gel chromatography, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0.496 g of **2a** (96%), as a mixture of diastereomers.

N-Benzyl-3-chloro-4-chloromethyl-3-methyl-pyrrolidin-2-one (2b): *Procedure A*: 0.544 g ($2 \cdot 10^{-3}$ mol) of **1b** were used. Reaction mixture was thermostatted at 80°C. The crude product was cromatographed by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, and obtaining 0.517 g of **2b** (95%), as a mixture of diastereomers, oil. IR (film): ν = 1710 (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.70 [s, 0.36·3 H, CH_3C(3), *trans*], 1.86 [s, 0.64·3 H, CH_3C(3), *cis*], 2.58 [m, 0.64 H, C(4)H, *cis*], 2.97 [m, 0.36 H, C(4)H, *trans*], 3.0-3.15 [m, 1 H, C(5)H], 3.3-3.9 [m, 3 H, C(5)H and C(4)CH_2Cl], 4.35-4.75 (m, 2 H, benzyl H), 7.2-7.45 (m, 5 H, aromatic H). MS (70 eV); *m/z* (%): 271 (2) [M^+], 236 (78) [M^+ - Cl], 91 (100). $C_{13}H_{15}Cl_2NO$ (272.2): calcd. C 57.37, H 5.55, N 5.15; found C 57.42, H 5.67, N 5.26. *Procedure B*: 0.544 g ($2 \cdot 10^{-3}$ mol) of **1b** were used. Reaction mixture was thermostatted at 60°C. Crude product cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0,533 g of **2b** (98%), as a mixture of diastereomers.

N-Benzyl-3,3-dichloro-4-chloromethyl-pyrrolidin-2-one (2c): *Procedure A*: 0.585 g ($2 \cdot 10^{-3}$ mol) of **1c** were used; reaction mixture was thermostatted at 80°C. Crude product cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0.550 g of **2c** (94%), white solid, m.p. 89-90°C. IR (nujol): ν = 1710 (C=O). ^{1}H NMR ($CDCl_3$): δ = 3.0-3.2 [m, 2 H, C(5)H and C(4)H], 3.5 [m, 1 H, C(5)H], 3.7 [m, 1 H, C(4)CH_2Cl], 4.0 [dd, J = 4.0, 11.4 Hz, 1 H, C(4)CH_2Cl], 4.49 (d, J = 14.4 Hz, 1 H, benzyl H), 4.68 (d, J =

14.4 Hz, 1 H, benzyl H), 7.3-7.5 (m, 5 H, aromatic H). MS (70 eV); *m/z* (%): 291 (0.5) [M^+], 256 (43) [M^+ - Cl], 91 (100). $C_{12}H_{12}Cl_3NO$ (292,6): calcd. C 49.26, H 4.13, N 4.79; found C 49.40, H 4.27, N 4.91. *Procedure B*: 0.585 g ($2 \cdot 10^{-3}$ mol) of **1c** were used; reaction mixture was thermostatted at 60°C. Crude product cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0.562 g of **2c** (96%).

N-Benzyl-3-chloro-4-chloromethyl-3-propyl-pyrrolidin-2-one (2d): *Procedure A*: 0.600 g ($2 \cdot 10^{-3}$ mol) of **1d** were used; reaction mixture was thermostatted at 80°C. Crude product cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0.565 g of **2d** (94%), as a mixture of diastereomers, oil. IR (film): ν = 1735 (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.03 [t, 3H, $CH_3CH_2CH_2C(3)$], 1.49 [m, 2H, $CH_3CH_2CH_2C(3)$], 2.16 [m, 2H, $CH_3CH_2CH_2C(3)$], 2.74 [m, 0.87 H, C(4)H, *cis*], 2.92 [m, 0.13 H, C(4)H, *trans*], 3.0-3.25 [m, 1 H, C(5)H], 3.3-3.95 [m, 3 H, C(5)H and $C(4)CH_2Cl$], 4.45 (d, J = 14.7 Hz, 1 H, benzyl H), 4.63 (d, J = 14.7 Hz, 1 H, benzyl H), 7.2-7.5 (m, 5 H, aromatic H). MS (70 eV); *m/z* (%): 299 (0.7) [M^+], 264 (33) [M^+ - Cl], 257 (20) [M^+ - C_3H_6], 208 (43), 91 (100). $C_{15}H_{19}Cl_2NO$ (300.2): calcd. C 60.01, H 6.38, N 4.67; found C 60.16, H 6.53, N 4.52. *Procedure B*: 0.600 g ($2 \cdot 10^{-3}$ mol) of **1d** were used; reaction mixture was thermostatted at 60°C. Crude product cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0,589 g of **2d** (98%), as a mixture of diastereomers.

N-Benzyl-3-chloro-4-chloromethyl-3-isopropyl-pyrrolidin-2-one (2e): *Procedure A*: 0.600 g ($2 \cdot 10^{-3}$ mol) of **1e** were used; reaction mixture was thermostatted at 80°C. Crude cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0.566 g of *cis*-**2e** (94%), white solid, m.p. 72-73°C. IR (nujol): ν = 1710 (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.09 [d, J = 6.9 Hz, 3 H, $CH(CH_3)_2$], 1.22 [d, J = 6.9 Hz, 3 H, $CH(CH_3)_2$], 2.59 [sept, J = 6.9 Hz, 1 H, $CH(CH_3)_2$], 2.81 [m, 1 H, C(4)H], 3.10 [dd, J = 8.2, 10.1 Hz, 1 H, C(5)H], 3.49 [dd, J = 7.5, 10.1 Hz, 1 H, C(5)H], 3.67 [t, J = 11.1 Hz, 1 H, $C(4)CH_2Cl$], 3.84 [dd, J = 4.0, 11.1 Hz, 1 H, $C(4)CH_2Cl$], 4.51 (d, J = 14.7 Hz, 1 H, benzyl H), 4.60 (d, J = 14.7 Hz, 1 H, benzyl H), 7.2-7.5 (m, 5 H, aromatic H). MS (70 eV); *m/z* (%): 299 (2) [M^+], 264 (35) [M^+ - Cl], 214 (18), 208 (28), 91 (100). $C_{15}H_{19}Cl_2NO$ (300.2): calcd. C 60.01, H 6.38, N 4.67; found C 59.92, H 6.25, N 4.57. *Procedure B*: 0.600 g ($2 \cdot 10^{-3}$ mol) of **1e** were used. Reaction mixture was thermostatted at 60°C. Crude product cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0,590 g of *cis*-**2e** (98%).

N-Benzyl-4-bromomethyl-3-chloro-3-isopropyl-pyrrolidin-2-one (2f): *Procedure A*: 0.689 g ($2 \cdot 10^{-3}$ mol) of **1f** were used; reaction mixture was thermostatted at 80°C. Crude product cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0,625 g of **2f** (65%) and the two analogues (overall 28%) with scrambled halogen as inseparable mixture, oil. *Procedure B*: 0.689 g ($2 \cdot 10^{-3}$ mol) of **1f** were used; reaction mixture was thermostatted at 60°C. Crude product cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0.672 g of *cis*-**2f** (93%) and the two analogues (overall 4%) with scrambled halogen as inseparable mixture, oil. IR (film): ν = 1720 (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.09 [d, J = 7.0 Hz, 3 H, $CH(CH_3)_2$], 1.22 [d, J = 7.0 Hz, 3 H, $CH(CH_3)_2$], 2.59 [sept, J = 6.9 Hz, 1 H, $CH(CH_3)_2$], 2.85 [m, 1 H, C(4)H], 3.05 [dd, J = 8.3, 10.0 Hz, 1 H, C(5)H], 3.4-3.6 [m, 2H C(5)H and $C(4)CH_2Cl$], 3.67 [dd, J = 3.9, 10.0 Hz, 1 H, $C(4)CH_2Cl$], 4.49 (d, J = 14.7 Hz, benzyl H), 4.60 (d, J = 14.7 Hz, 1 H, benzyl H), 7.2-

7.5 (m, 5 H, aromatic H). MS (70 eV); *m/z* (%): 343 (1) [M^+], 308 (20) [M^+ - Cl], 264 (2) [M^+ - Br], 208 (26), 91 (100). $C_{15}H_{19}BrClNO$ (344.7): calcd. C 52.27, H 5.56, N 4.06; found C 52.20, H 5.66, N 4.19.

N-Benzyl-3-chloro-4-chloromethyl-3-phenyl-pyrrolidin-2-one (2g): *Procedure A*: 0.668 g ($2 \cdot 10^{-3}$ mol) of **1g** were used; reaction mixture was thermostatted at 80°C. Crude product cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0.375 g of *cis*-**2g** (56%), oil. IR (film): ν = 1720 (C=O). ^{1}H NMR ($CDCl_3$): δ = 3.01 [m, 1 H, C(4)H], 3.28 [dd, *J* = 8.8, 10.0 Hz, 1 H, C(5)H], 3.58 [dd, *J* = 6.9, 10.0 Hz, 1 H, C(5)H], 3.7-3.85 [m, 2 H, C(4)CH_2Cl], 4.54 (d, *J* = 14.7 Hz, benzyl H), 4.75 (d, *J* = 14.7 Hz, 1 H, benzyl H), 7.2-7.7 (m, 10 H, aromatic H). MS (70 eV); *m/z* (%): 299 (17) [M^+ + 1 - Cl], 264 (5), 117 (18), 118 (18), 91 (100). $C_{18}H_{17}Cl_2NO$ (334.2): calcd. C 64.68, H 5.13, N 4.19; found C 64.64, H 5.00, N 4.22. *Procedure B*: 0.668 g ($2 \cdot 10^{-3}$ mol) of **1g** were used; reaction mixture was thermostatted at 60°C. Crude product cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0.536 g of *cis*-**2g** (80%).

N-Benzyl-3-benzyl-3-chloro-4-chloromethyl-pyrrolidin-2-one (2h): *Procedure A*: 0.697 g ($2 \cdot 10^{-3}$ mol) of **1h** were used; reaction mixture was thermostatted at 80°C. Crude product cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0.488 g of *cis*-**2h** (70%), transparent solid, m. p. 70-73°C. IR (nujol): ν = 1715 (C=O). ^{1}H NMR ($CDCl_3$): δ = 2.68 [m, 1 H, C(4)H], 3.01 [t, *J* = 9.9 Hz, 1 H, C(5)H], 3.24 [dd, *J* = 7.4, 9.9 Hz, 1 H, C(5)H], 3.35 (d, *J* = 13.9 Hz, 1 H, benzyl H), 3.5-3.65 [m, 2 H, C(4)CH_2Cl], 3.71 (d, *J* = 13.9 Hz, 1 H, benzyl H), 4.46 (d, *J* = 14.8 Hz, benzyl H), 4.56 (d, *J* = 14.8 Hz, 1 H, benzyl H), 7.1-7.5 (m, 10 H, aromatic H). MS (70 eV); *m/z* (%): 347 (2) [M^+], 312 (30) [M^+ - Cl], 262 (7), 91 (100). $C_{19}H_{19}Cl_2NO$ (348.3): calcd. C 65.53, H 5.50, N 4.02; found C 65.62, H 5.65, N 3.96. *Procedure B*: 0.697 g ($2 \cdot 10^{-3}$ mol) of **1h** were used; reaction mixture was thermostatted at 60°C. Crude product cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0.614 g of *cis*-**2h** (88%).

N-Benzyl-3-[2-(N-Benzyl-3-chloro-4-chloromethyl-pyrrolidin-2-on-3-yl)-ethyl]-3-chloro-4-chloromethyl-pyrrolidin-2-one (4): *Procedure A*: 1.085 g ($2 \cdot 10^{-3}$ mol) of **3** were used; reaction mixture was thermostatted at 80°C. Crude cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0.944 g of **4** (87%), as a mixture of diastereomers, white solid. IR (nujol): ν = 1705 and 1720 (C=O). ^{1}H NMR ($CDCl_3$): δ = 2.2-2.7 [m, 4 H, C(3)CH_2CH_2C(3')], 2.7-3.0 [m, 2 H, C(4)H and C(4')H], 3.0-4.0 [m, 8H, C(5)H_2, C(5')H_2, C(4)CH_2Cl and C(4')CH_2Cl], 7.2-7.5 (m, 10H, aromatic H). MS (70 eV); *m/z* (%): 505 (6) [M^+ - Cl], 468 (3), 432 (6), 186 (31), 91 (100). $C_{26}H_{28}Cl_4N_2O_2$ (542.3): calcd. C 57.58, H 5.20, N 5.17; found C 57.45, H 5.06, N 5.30. *Procedure B*: 1.085 g ($2 \cdot 10^{-3}$ mol) of **3** were used; reaction mixture was thermostatted at 60°C. Crude cromatography by silica gel, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave 0.977 g of **4** (90%), as a mixture of diastereomers.

We thank the *C.N.R.* (Rome) and the *Ministero della Università e della Ricerca Scientifica e Tecnologica* (MURST) for financial assistance, and Dr. *L. De Buyck*, Department of Organic Chemistry, University of Gent (Belgium), for a sample of 2,2,5,5-tetrachloroadipic acid.

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(*Received in UK* 12 *June* 1997; *revised* 1 *August* 1997; *accepted* 7 *August* 1997)