J. Braz. Chem. Soc., Vol. 7, No. 5, 371-377 , 1996.
Printed in Brazil.

0103 – 5053 $6.00 + 0.00

Article

Study of the Cine-Rearrangement and the Cinesubstitution of 2,2-Dihalocyclobutanones

José Renato Cagnon, Jacqueline Marchand-Brynaert and Léon Ghosez

Laboratoire de Chimie Organique de Syntèse, Universisté catholique de Louvain, place Louis Pasteur 1, B - 1348 Louvain-La-Neuve, Belgium,

E-mail: ghosez@chor.ucl.ac.be

Received: August 1, 1996

Este trabalho relata o estudo do cine-rearranjo e cine-substituição de uma série de 3-alquil-2,2-dihalociclobutanonas como estratégia sintética para a preparação de ciclobutanonas altamente funcionalizadas. Nossos estudos mostram que a aplicação desta metodologia é limitada aos substratos substituidos por um grupo volumoso em C-3. Para os demais casos, foram obtidas misturas de isômeros de ciclobutanonas. A reação da 3-butyl-2,2-diclorociclobutanona com metanol em presença de base conduz à formação de um produto de dupla cine-substituição.

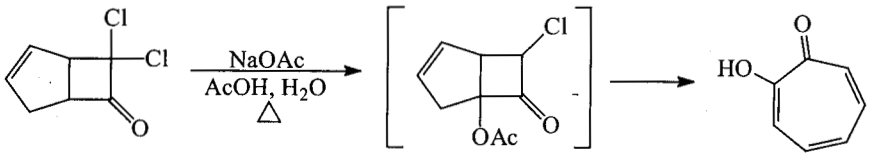
The cine-rearrangement and cine-substitution of a series of 3-alkyl-2,2-dichlorocyclobutanones have been studied in the context of a synthesis of polyfunctitonalized cyclobutanones which were required as synthetic intermediates. Our studies showed that the scope of the rearrangement is limited to substrates bearing bulky substituents at C-3. In other cases, mixtures of isomeric cyclobutanones are obtained. Reaction of 3-butyl-2,2-dichlorocyclobutanone with methanol in the presence of a base yielded a product of double cine-substitution.

Keywords: *cine-substitution, cine-rearrangement, 3-alkyl-2,2-dichlorocyclobutanones*

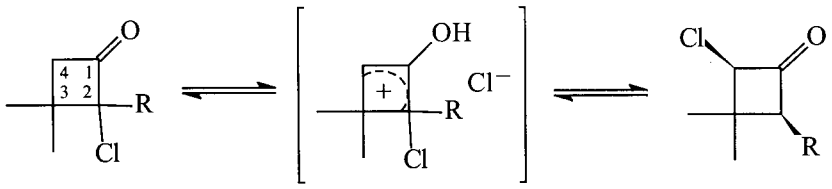
Introduction

The first example of a cine-substitution on a dichlorocyclobutanone was reported in 1965 by Stevens *et al.* as a key step in a short synthesis of tropolone (Scheme 1)[1]. The mechanism of this unusual transformation was later analysed by Bartlett and Ando[2-3]. α-Halogenocyclobutanones undergo an efficient and stereoselective cine-rearrangement to α'-halogenocyclobutanones in the presence of a catalyst (tertiary amine, HX, or quaternary ammonium salts)[4].The reaction is an equilibrium which probably involves the formation of an ion-pair intermediate (Scheme 2). The cine-rearrangement is also a key step in a short and versatile synthesis of dichlorovinylcyclopropanecarboxylic acids which are precursors of synthetic pyrethroids 5. Further applications of the cine-rearrangement and cine-substitution have been reported[6-7].

In recent years we have become interested in the design and synthesis of novel inhibitors of bacterial transpeptidases[8]. Substituted cyclobutanones and cyclobutenones were envisaged as potential alkylating agents of these serine proteases[9]. Herein we report a study of a sequence involving a haloketene-olefin cycloaddition followed by a cine-rearrangement or cine-substitution as a potential route towards the target molecules.



Scheme 1.



R = CH_2CCl_3, Cl, CH_3, CH_2CH_3

Scheme 2.

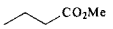
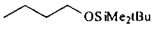
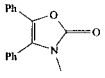
Results and discussion

Synthesis of 2,2-dihalocyclobutanones

Cyclobutanones **1** were prepared by cycloaddition of dichloro- or dibromoketene to the corresponding olefins **2**. Ketenes were generated *in situ* from the reaction of activated zinc with trichloro- or tribromoacetyl chloride (Scheme 3)[1,10-11]. Non-commercial olefins were prepared according to literature procedures. The results of the cycloaddition step are shown in the Table 1.

The reaction of dibromoketene with N-vinyl phtalimide gave a crude mixture containing the expected dibromocyclobutanone **1h** and some unreacted **2h**. In contrast with adduct **1g**, compound **1h** could not be purified by recrystallisation. Chromatography on silica gel gave the isomeric cyclobutanone **3h** resulting from a cine-rearrangement catalysed by silica gel (Scheme 4). The three signals (dd) observed for three non-equivalent protons of **2h** were replaced by a doublet at 5,87 δ corresponding to the equivalent α-protons of **3h** and a triplet at 5,05 δ as excepted for the highly structure **3h**.

Table 1. Cycloadditions of dichloroketene to ofefins **2a-g**.

2	R	Method	yields of 1 (%)
a	*n*-Bu	B	72[a]
b	*t*-Bu	B	68[a]
c		B	76[a]
d		B	68[c]
e	PhS	B	66[b]
f		A	85[b]
g		A	79[d]

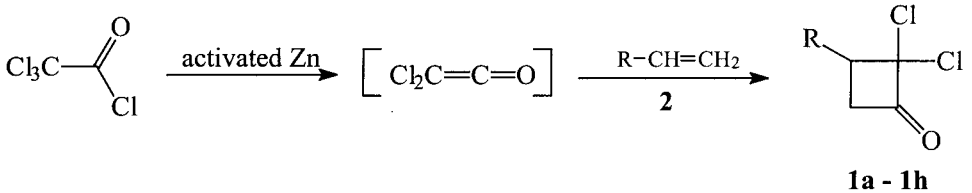
(a) Purification by bulb-to-bulb distillation; (b) purification by recrystallisation; (c) purification by flash chromatography; (d) prepared according to the procedure described by Dumas, S., dissertation, Université de Louvain, 1995, purification by recrystallisation.

Cine-rearrangement of 1 a-g

Cyclobutanones **1 a-g** were submitted to the experimental conditions used in earlier work on cine-rearrangements (Scheme 5) (Table 2)[4].

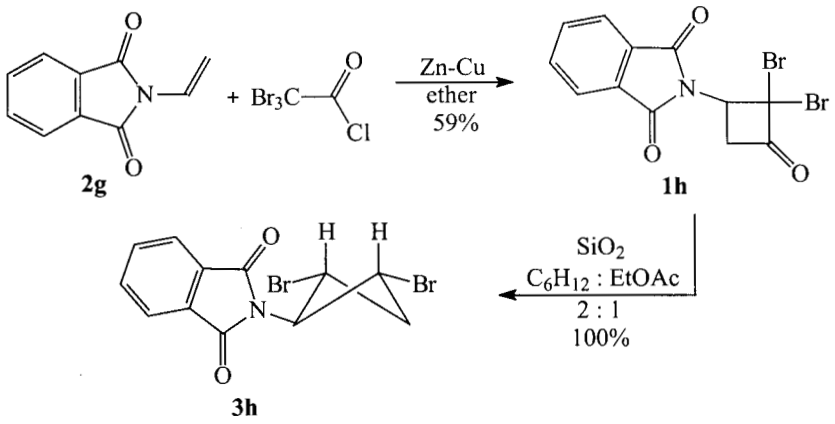
Reactions were followed by tlc or glc. When a reaction was over, the crude mixture was analysed by ^{1}H-NMR. In all but one case (entry b), the crude mixtures were rather complex. Reactions of **1a** and **1c** lead to a mixture of starting material and rearranged product **3a** and **3c**. Compound **1d** gave a complex mixture containing ~24% of rearranged product **3d**. The reactions of **1e**, **f**, **g** with a catalytic amount of Et_3N in refluxing toluene yielded only degradation products. The use of quaternary ammonium salts as catalysts was also unsuccessful. As described above for **1h**, compound **1g** underwent the cine-rearrangement when chromatographed on silica gel. However, in this case, the product contained a mixture of rearranged and unrearranged cyclobutanones **3g** and **1g**.

All rearranged products **3** are characterized by a doublet at 4,5-5,5 ppm (equivalent protons at C_2 and C_4). Compound **3b** which was formed in high yields could be purified by chromatography. Its structures and stereochemistry were established by ^{1}H-NMR (Scheme 6). Protons H-2 and H-4 are equivalent and give rise to a doublet at 4,6 ppm. The high value (9,2 Hz) of the coupling constant with H-3 indicates a trans diaxial relationship between H-3 and both H-2 and H-4. These observations correspond to the most stable configuration and conformation of **3b**[4].



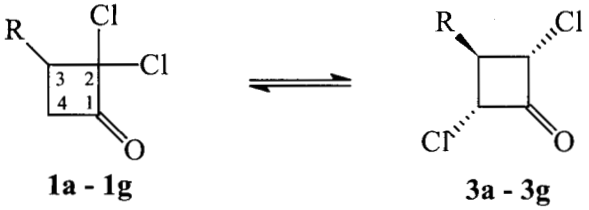
1a - 1h

Scheme 3.



2g **1h** **3h**

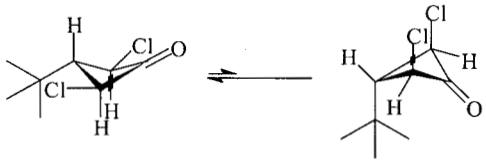
Scheme 4.



1a - 1g **3a - 3g**

Scheme 5.

It is rather dangerous to draw conclusions from the results of Table 2 because the cine-rearrangement was always accompanied by the formation of many by-products. It seems however quite clear that the rearrangement is driven by steric factors. When **R** is a very bulky group such as *t*-butyl or when the carbon C-3 bears two methyl groups[4], the equilibrium is totally shifted towards the rearranged cyclobutanone. With less bulky groups (**1a, c, g**), mixtures of rearranged and unrearranged products are obtained (Scheme 7).



Scheme 6.

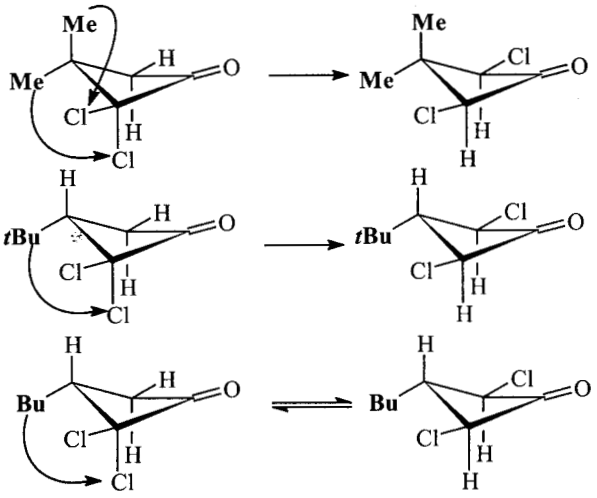
At this point is did not appear that the cine-rearrangement could fulfil our requirement for a method of wide scope to reach our target molecules. Only one compound **3h**, which is functionalised on the four carbon atoms of the ring represents an useful intermediate for our needs.

We therefore checked whether it was possible to drive the equilibrium towards the rearranged product by trapping an intermediate by a external nucleophile which would react irreversibly[4]. Thus compound **1a** was reacted with 2 equiv. of sodium hydroxide in a large excess of methanol (Scheme 8). The main product **4** resulted from a retroaldol reaction. A product **5** resulting from a double substitution reaction was also formed albeit in lower yields. The forma-

Table 2. Cine-rearrangements of **1 a-g**.

Entry	Conditions	**3** (%)	Products **1** (%)	Others
a	Et_3N (0.05 eq.), toluene, Δ	28	30	unidentified
	Hex_4NCl/120 °C	-	-	complex mixture
b	Et_3N (0.05 eq.), toluene, Δ	84[a]	-	-
c	Et_3N (0.05 eq.), toluene, Δ	29	40	unidentified
	$BnBu_3NCl$ (3 eq.), 110 °C	-	-	complex mixture
d	Et_3N (0.05 eq.), toluene, Δ	24	-	complex mixture
e,f	Et_3N (0.05 eq.), toluene, Δ	-	-	complex mixture
g	Et_3N (0.05 eq.), toluene, Δ	-	-	complex mixture
	Silica gel, AcOEt, 20 °C	24	52	unidentified

(a) yields of isolated product.



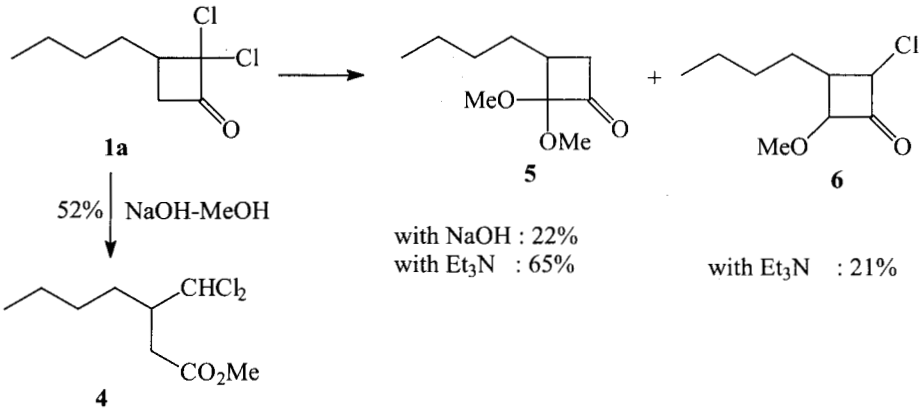
Scheme 7.

tion of **4** could be suppressed by the use of a weaker base: when triethylamine was used, compound **5** was obtained in 65% yield. We could also isolate an unstable product **6** (21% yield) resulting from a mono cine-substitution reaction. The formation of **4**, **5** and **6** can be readily explained by the mechanism described in Scheme 9.

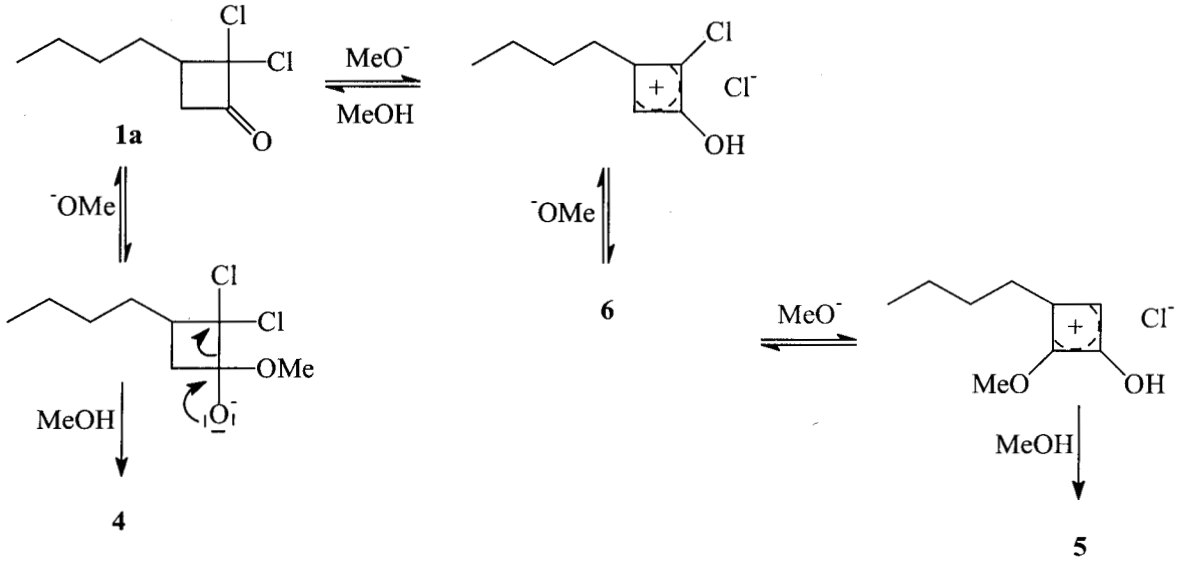
Thus, our expectation had been fulfilled. Addition of an external nucleophile drove the rearrangement to completion. However the reaction cannot be stopped at the stage of a mono-substituted product. This substantially reduces the synthetic potential of these rearrangements in the context of our synthetic target.

Experimental

Melting points were determined with a Leitz apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer Models 681 and FT-1740 and on a Nicolet



Scheme 8.



Scheme 9.

FT-205 instrument. ^{1}H-NMR spectra were recorded at 200 MHz on Varian Gemini-200 and VXR-200, at 300 MHz on Varian Gemini-300, and at 500 MHz on Bruker AM-500. Mass spectra were recorded on a Finnigan MAT-TSQ 700 spectrometer under electronic impact (I.E. 70 eV) or chemical ionisation conditions (100 eV, ionising gas CH_4/NO_2). Elemental analyses were performed at University College Microanalytic Laboratory, London, UK. The HRMS analyses were performed at the University of Mons (Belgium) by Prof. Flammang. All solvents were predried by standard methods. Distillations were effected with short (4 cm) vigreux column. Bulb-to-bulb distillations were performed with a Büchi Kugelrohr apparatus. Flash chromatographies were carried out on silica gel Merk 60 (230-400 mesh). Other chromatographic separations used Merk 60 silica gel (70-230 mesh).

Synthesis of Olefins

Methyl hex-5-enoate **(2c)**

Hex-5-enoic acid was prepared according to Cardinale *et al.*[12] and esterified with diazomethane as usual.

6-(tert-butyldimethylsilyloxy)hex-1-ene **(2d)**

To a solution of *tert*-butyl dimethylsilylimidazole [prepared from the reaction of 8.1 g (119 mmol) of imidazole and 9.0 g (59.8 mmol) of *tert*-butyldimethylsilylchloride for 5 min in 40 mL of DMF] was added slowly a solution of 5-hexen-1-ol in 10 mL of DMF. The mixture was refluxed for 12 h, then poured into cold water (100 mL). The aqueous phase was extracted with ether (3 x 50 mL). The combined organic phases was dried over $MgSO_4$ and evaporated to leave a yellow oil which purified by flash chromatography (cylohexane 10: ethyl acetate 1) to give 10.3 g of **2d** (93% yield): ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.81-5.56 (m, 2 H), 4.90 (m, 1 H), 3.61 (t, 2 H, J = 6 Hz), 2.06 (m, 2 H), 1.60-1.20 (m, 4 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 138.9, 114.3, 63.0, 33.5, 32.2, 26.0, 25.1, 18.3, -5.3; Anal. calc. for $C_{12}H_{26}OSi$ (%): C, 67.21; H, 12.22 - Found (%): C, 67.23; H, 12.49.

4,5-diphenyl-3-vinyloxazolidin-2-one **(2f)**

2f was prepared according to Busacca *et al.*[13]

N-vinyl phthalimide **(2g)**

A solution of 20 g (79 mmol) of N-bromoethyl phthalimide and 13 mL (87 mmol) of DBU in 150 mL of dry CH_2Cl_2 was refluxed for 12 h. Excess of DBU (13 mL) was added, and the solution was refluxed for an additional period of 12 h, then cooled and treated with 150 mL of 5% aqueous HCl. The organic phase was separated, washed with brine and dried over anhydrous $MgSO_4$. Evaporation gave a yellow solid which was recrystallised from *n*-hexane to give 13 g (97% yield) of **2g** : m.p. 79-81 °C; IR (neat, cm^{-1}) ν 1785, 1730, 1647; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.78-7.72 (m, 4 H), 6.83 (dd, 1 H, J = 16 Hz and J = 10 Hz), 6,05 (d, 1 H, J = 16 Hz), 5.03 (d, 1 H, J = 10 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 165.8, 134.0, 131.0, 123.4, 123.1, 103.8; MS m/z: 173 (M^+), 146 (100%), 104, 76.

[2+2] Cycloaddition Procedures

The reactions were carried out under argon atmosphere.

Method A: A solution of trihalogenoacetyl chloride (1.2-1.5 equiv.) in dry ether (1 mL/mmol) was added over a period of 2 h, at -10 °C, to a suspension of Zn-Cu[14] (1.5-2 equiv.) in ether (1 mL/mmol) containing the olefin (1 equiv.). The mixture was stirred overnight at room temperature, then filtered. The solution was washed with water, 10% aqueous $NaHCO_3$ and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave the crude adduct.

Method B: A solution of trichloroacetyl chloride (1.2-1.5 equiv.) in dry ether (1 mL/mmol) was added dropwise (1-2 h), at room temperature, to a suspension of zinc powder (2-4 equiv.) in ether (2-1 mL/mmol) containing the olefin (1 equiv.), and placed into a sonication bath. After four additional hours of sonication, the mixture was filtered and worked-up as described in method A.

3-Butyl-2,2-dichlorocyclobutanone **(1a)**

1a was prepared according to method B, from 5g (69.4 mmol) of 1-hexene **2a**, 7.8 g (120 mmol) of Zn powder and 9.9 mL (89 mmol) of trichloroacetyl chloride. Bulb to bulb distillation (98-100 °C/12 mmHg) gave 8.3 g (72% yield) of a colorless oil: IR (neat, cm^{-1}) ν 1811; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.35 (m, 1 H), 2.92 (m, 2 H), 1.90-1.35 (m, 6 H), 0.95 (t, 3 H, J = 6.8 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 192.7, 88.8, 47.6, 45.8, 30.9. 39.4, 22.3, 13.7; MS m/z: 152 (M^+- CH_2=C=O), 117, 56(100%).

3-tert-Butyl-2,2-dichlorocyclobutanone **(1b)**

1b was prepared according to method B, from 3g (35.6 mmol) of 3,3-dimethyl-1-butene **2b**, 4.7 g (71.3 mmol) of Zn powder and 6.0 mL (53.5 mmol) of trichloroacetyl chloride. Bulb to bulb distillation (114-115 °C/14 mmHg) gave 4.7 g (68% yield) of a colorless oil: IR (neat, cm^{-1}) ν 1810; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.22-3.18 (m, 2 H), 2.84 (dd, 1 H, J = 11.6 Hz and J = 9.8 Hz), 1.49 (s, 9 H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 192.5, 87.2, 55.9, 43.3, 33.2, 27.4; HRMS: 194.027 (calc. for $C_8H_{12}Cl_2O$: 194.026).

Methyl 4-(2,2-dichloro-3-oxocyclobutyl)butyrate **(1c)**

1c was prepared according to method B, from 7.1g (55.4 mmol) of methyl hex-5-enoate **2c**, 7.3 g (116.3 mmol) of Zn powder and 7.8 mL (69.4 mmol) of trichloroacetyl chloride. Bulb to bulb distillation (143-146 °C/14 mmHg) gave 9.7 g (73% yield) of a colorless oil: IR (CH_2Cl_2, cm^{-1}) ν 1808, 1734, 1422, 1270; ^{1}H-NMR (500 MHz, $CDCl_3$) δ

3.62 (s, 3 H), 3.31 (dd, 1 H, J = 17.6 Hz and J = 9.5 Hz), 2.93 (dd, 1 H, J = 17.6 Hz and J = 9.5 Hz), 2.84 (m, 1 H), 2.34 (m, 2 H), 1.88 (m, 1 H), 1.74-1.66 (m, 2 H), 1.60 (m, 1 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 192.4, 173.3, 88.5, 51.5, 47.6, 45.6, 33.3, 30.6, 22.6; MS m/z: 240 (M^+), 206, 207, 197 (100%); Anal. calc. for $C_9H_{12}Cl_2O_3$ (%): C, 45.22; H, 5.05; Cl, 29.45 - Found (%): C, 45.19; H, 5.00; Cl, 29.10.

3-[4-(tert-Butyldimethylsilyloxy)butyl]-2,2-dichlorocyclobutanone (**1d**)

1d was prepared according to method B, from 5.0 g (23.3 mmol) of 6-(tert-butyldimethylsilyloxy)hex-1-ene **2d**, 6,0 g (91.8 mmol) of Zn powder and 3.9 mL (35 mmol) of trichloroacetyl chloride. Flash chromatography (cyclohexane 20: ethyl acetate 1) gave 5.2 g (68% yield) of a colorless oil: IR (neat, cm^{-1}) ν 1812, 1103, 838; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.59 (t, 2 H, J = 6 Hz), 3.30 (dd, 1 H, J = 17.0 Hz and J = 9.2 Hz), 2.82 (m, 2 H), 1.94-1.48 (m, 6 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.8, 88.8, 62.6, 47.7, 46.0, 32.4, 31.1, 25.9, 23.8, 18.3, -5.3; HRMS: 325.351 (calc. For $C_{14}H_{26}Cl_2O_2Si$: 325.352).

3-Phenylthio-2,2-dichlorocyclobutanone (**1e**)

1e was prepared according to method B, from 1.9 mL (14.7 mmol) of phenylthioethylene **2e**, 3.8 g (58.8 mmol) of Zn powder and 2.5 mL (22 mmol) of trichloroacetyl chloride. Crystallisation from petroleum ether-CH_2Cl_2 gave 2.4 g (66% yield) of a white solid: m.p. 50-52 °C; IR (KBr, cm^{-1}) ν 1814, 1583, 1438, 1382; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.50-732 (m, 5 H), 4.32 (dd, 1 H, J = 10.0 Hz and J = 8.6 Hz), 3.75 (dd, 1 H, J = 18.4 Hz and J = 9.9 Hz), 3.24 (dd, 1 H, J = 18.4 Hz and J = 8.6 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 191.0, 133.5, 130.8, 129.3, 127.7, 90.4, 51.6, 49.3; MS m/z: 246 (M^+), 137, 109 (100%); Anal. calc. for $C_{10}H_8Cl_2SO$ (%): C, 48.60; H, 3.26; S, 12.37 - Found (%): C, 48.24; H, 3.19; S, 12.41.

3-(2-Oxo-4,5-diphenyloxazolin-1-yl)-2,2-dichlorocyclobutanone (**1f**)

1f was prepared according method A, from 1 g (3.8 mmol) of 4,5-diphenyl-3-vinyloxazolidin-2-one **2f**, 0.5 g (7.6 mmol) of Zn-Cu and 0.65 mL (11.4 mmol) of trichloroacetyl chloride. Crystallisation from ether gave 1.14 g (85% yield) of a colorless solid: m.p. 173-177 °C; IR (CH_2Cl_2, cm^{-1}) ν 1821, 1759, 1456, 1422, 1370, 1264; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.61-7.23 (m, 10 H), 4.65 (dd, 1 H, J = 10.7 Hz and J = 6.5 Hz), 4.41 (dd, 1 H, J = 18.5 Hz and J = 10.4 Hz), 3.66 (dd, 1 H, J = 18.5 Hz and J = 6.5 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 189.5, 153.2, 135.4-123.2, 89.3, 56.0, 44.6; HRMS: 373.026 (calc. for $C_{19}H_{13}Cl_2NO_3$: 373.027).

3-Phthalimido-2,2-dichlorocyclobutanone (**1g**)

1g was prepared according method A, from 8.0 g (46 mmol) of N-vinyl phthalimide **2g**, 4.8 g (73.5 mmol) of Zn-Cu and 7.7 mL (77.5 mmol) of trichloroacetyl chloride. Crystallisation from ether (0 °C, overnight) gave 10.3 g (79% yield) of a white solid: m.p. 134-136 °C; IR (CH_2Cl_2, cm^{-1}) ν 1820, 1785, 1730, 1380; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.00-7.85 (m, 4 H), 5.29 (dd, 1 H, J = 10.2 Hz and J = 6.1 Hz), 4.37 (dd, 1 H, J = 18.3 Hz and J = 6.1 Hz), 3.88 (dd, 1 H, J = 18.3 Hz and J = 10.2 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 189.8, 167.4, 134.6, 131.2, 123.9, 88.0, 53.3, 45.5; MS m/z: 283 (M^+), 241, 206 (100%), 173.

3-Phthalimido-2,2-dibromocyclobutanone (**1h**)

1h was prepared according method A, from 4.0 g (23 mmol) of N-vinyl phthalimide **2g**, 2.4 g (36.5 mmol) of Zn-Cu and 10.8 g (36.5 mmol) of tribromoacetyl chloride. Precipitation from ether (0 °C, overnight) gave 5.1 g (59% yield) of a white solid: IR (CH_2Cl_2, cm^{-1}) ν 1820, 1784, 1730, 1387; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.90-7.78 (m, 4 H), 5.37 (dd, 1 H, J = 10.3 Hz and J = 5.9 Hz), 4.37 (dd, 1 H, J = 18.2 Hz and J = 5.9 Hz), 3.93 (dd, 1 H, J = 18.2 Hz and J = 10.3 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 189.0, 167.0,133.9, 131.0, 124.0, 88.9, 54.1, 44.6; MS m/z: 377, 375, 373, 173 (100%), 144.

Cine-rearrangements

3-tert-Butyl-2,4--dichlorocyclobutanone (**3b**)

A solution of 1 g (5.1 mmol) of 3-tert-butyl-2,2-dichlorocyclobutanone **1b** and 0.035 mL (0.24 mmol) of triethylamine in 20 mL of toluene was refluxed for 15 h. After solvent evaporation, the residue was flash-chromatographed (cyclohexane 10: ethyl acetate 1) to give 0.84 g (84% yield) of colorless crystals: m.p. 28-30 °C; IR (neat, cm^{-1}) ν 1806, 1475; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.63 (d, 2 H, J = 9.2 Hz), 2.37 (t, 1 H, J = 9.2), 1.13 (s, 9 H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 192.8, 58.1, 57.8, 57.8, 32.1, 27.0; MS m/z: 196, 194, 118, 83 (100%); R_F (cyclohexane 5: ethyl acetate 1) = 0.46; Anal. calc. for $C_8H_{12}Cl_2O$ (%): C, 49.25; H, 6.19; Cl, 36.34 - Found (%): C, 49.45; H, 6.33; Cl, 34.32.

3-Phthalimido-2,4-dibromocyclobutanone (**3h**)

A solution of 1 g (2.7 mmol) of 3-phthalimido-2,2-dibromocyclobutanone **1h** in 20 mL of cyclohexane-ethyl acetate (1:1) was stirred for 24 h at 20 °C in the presence of 1 g of silica gel. Filtration and solvent evaporation gave 1.0 g (100% yield) of a white solid: m.p. 172-174 °C; IR (CH_2Cl_2, cm^{-1}) ν 1822, 1785, 1730, 1380; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.96-7.82 (m, 4 H), 5.87 (d, 2 H, J = 7.7 Hz), 5.05 (t, 1 H, J = 7.7 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 189.8, 167.2, 134.9, 131.2, 124.0, 54.0, 45.5; Anal. calcd.

for $C_{12}H_7Br_2NO_3$ (%): C, 38.64; H, 1.89; N, 3.75 - Found (%): C, 38.61; H, 2.12; N, 3.70.

Cine-substitutions

Methyl 3-(dichloromethyl)heptanoate **(4)**

A solution of 0.41 g (10.2 mmol) of NaOH in 15 mL of methanol was added over 3 min to a solution of 1 g (5.1 mmol) of 3-butyl-2,2-dichlorocyclobutanone **1a** in 8 mL of THF. After 20 min. of stirring, water was added (30 mL) and the solution was extracted with ether (5 x 20 mL). The organic phase was dried over $MgSO_4$, then evaporated and flash-chromatographed (cyclohexane 15: ether 1) to give 0.60 g (52% yield) of **4** and 0.21 g (22% yield) of **5**. Compound **4** is a colorless oil: R_F (cyclohexane 10: ethyl acetate 1) = 0.56; IR (neat, cm^{-1}) ν 1736, 1438, 1219; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.00 (d, 1 H, J = 2.9 Hz), 3.70 (s, 3 H), 2.72 (dd, 1 H, J = 16.0 Hz and J = 5.4 Hz), 2.55 (m, 1 H), 2.44 (dd, 1 H, J = 16.0 Hz and J = 6.8 Hz), 1.65-1.31(m, 6 H), 0.91 (t, 3 H, J = 6.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.5, 76.6, 51.7, 45.6, 34.7, 30.2, 28.8, 22.5, 13.8; MS m/z: 226, 195, 143 (100%), 74; Anal. calc. for $C_9H_{16}Cl_2O_2$ (%): C, 47.59; H, 7.10; Cl, 31.21 - Found (%): C, 47.64; H, 7.17; Cl, 31.38.

3-Butyl-2,2-dimethoxycyclobutanone **(5)** *and 3-butyl-2-chloro-4-methoxycyclobutanone* **(6)**

A solution of 0.8 mL (5.6 mmol) of Et_3N in 2 mL of methanol was added dropwise toa solution of 1 g (5.1 mmol) of 3-butyl-2,2-dichlorocyclobutanone **1a** in 20 mL of methanol. The mixture was stirred overnight at room temperature, then concentrated. The residue was dissolved in ether (25 mL), washed with 10% aqueous HCl, and dried over $MgSO_4$. Solvent evaporation and flash-chromatography (cyclohexane 7: ethyl acetate 1) gave 0.62 g (65% yield) of **5** and 0.21 g (21% yield) of **6**. Compound **5** is a colorless oil: R_F (cyclohexane 7: ethyl acetate 1) 0.46; IR (neat, cm^{-1}) ν 1796, 1466, 1221; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.39 (s, 3 H), 3.30 (s, 3 H), 2.93 (m, 1 H), 2.53-2.45 (m, 2 H), 1.82-1.32 (m, 6 H), 0.93(t, 3 H, J = 6.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 204.1, 111.7, 51.8, 50.0, 46.3, 38.4, 30.0, 29.0, 22.6, 13.9; HRMS: 158.131 (calc. for $C_{10}H_{18}Cl_2O_3$-: 158.131). Compound **6** is a colorless oil: R_F (cyclohexane 7: ethyl acetate 1) 0.16; IR (neat, cm^{-1}) ν 1800, 1466; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.22 (m, 2 H), 3.53 (s, 3 H), 2.30 (m, 1 H), 1.84-1.35 (m, 6 H), 0.95 (t, 3 H, J = 7.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 198.8, 90.2, 60.0, 58,2, 44.4, 29.9, 28.5, 22.3, 13.7; MS m/z: 190, 159, 118 (100%), 75.

Acknowledgments

This work was supported by CNPq, CAPES, le Ministère de l'Education, de la Recherche et de la Formation (Action concertée 91/96-145), les Services fédéraux des Affaires scientifiques, techniques et culturelles (PAI n 19) et l'Université catholique de Louvain.

References

1. Stevens, J.C.; Reich, D.A.; Brandt, D.R.; Fautain, K.R.; Gheughan, E.J. *J. Am. Chem. Soc.* **1965**, *87*, 5257.
2. Bartlett, P.D. *Pure Appl. Chem.* **1971**, *27*, 597.
3. Bartlett, P.D.; Ando, T. *J. Am. Chem. Soc.* **1970**, *92*, 7518.
4. Bellus, D.; Martin, P.; Greuter, H.; Rihs, G.; Winkler, T. *Helv. Chim. Acta* **1981**, *64*, 2571.
5. Bellus, D.; Martin, P.; Greuter, H. *J. Am. Chem. Soc.* **1979**, *101*, 5853.
6. Butenschön, H. *Chem. Ber.* **1994**, *127*, 137.
7. Paryzek, Z.; Blaszczyk, K. *Liebigs Ann. Chem.* **1995**, 341.
8. Marchand-Brynaert, J.; Ghosez, L. *Non B-lactams Analogs of Penicillins and Cephalosporins in Recent Progress in Chemical Synthesis of Antibiotics*; Springer Verlag ed.; Ohno, M.; Lukacs, G. **1990**, pp 727.
9. Ghosez, L.; Dive, G.; Dumas, S.; Génicot, C.; KumLi, F.; Love, C.; Marchand-Brynaert, J. *in Proceedings 3rd Internat. Symp. on Chem. Synth. Antibiot. and Related Microbial Products*; Krohn, K.; Kirst, H.; Maas, H., Eds; VCH Oublishers:, **1993** pp 177.
10. Ghosez, L.; Montaigne, R.; Mollet, P. *Tetrahedron Lett.* **1966**, 135.
11. Brady, W.T. *J. Org. Chem.* **1966**, *31*, 2676.
12. Cardinale, G.; Laan, J.A.M.; Ward, J.P. *Tetrahedron* **1985**, *41*, 2899.
13. Busacca, C.A.; Johnson, R.E.; Swestock, J. *J. Org. Chem.* **1993**, *58*, 3299.
14. Hassner, A.; Larry, R.K. *J. Org. Chem.* **1978**, *23*, 3173.