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Synthesis and reactivity of 3-(2-chloroalkyl)-2,2-dihaloaziridines

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ABSTRACT

3-(2-Chloroalkyl)-2,2-dihaloaziridines were synthesized via cycloaddition of dihalocarbenes to the C=N double bond of β-chloroimines. Under the action of Lewis acids or HCl, N–C^3 bond cleavage occurred, giving rise to *N*-substituted 2,4-dichloro-3,3-dimethylbutanamides, which were further converted to 3-chloropyrrolidin-2-ones under alkaline conditions. When 2,2-dichloro-3-(2-chloro-1,1-dimethylethyl)-1-phenylaziridine was reacted with sodium methoxide, aziridine ring opening with N–C^2 bond cleavage took place, leading to methyl 4-chloro-3,3-dimethyl-2-(phenylamino)butanoate.

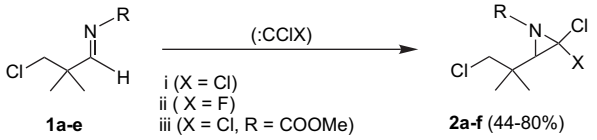
1. Introduction

The development of new efficient syntheses of halogenated nitrogen heterocycles and their precursors from reactive iminium ylides is a rather persisting problem in organic chemistry.[1–5] There are many methods available for the synthesis of halo substituted aziridines.[6] *C*-Alkyl substituted 2,2-dihaloaziridines have been very poorly investigated. So far, 1,3-di(*tert*-butyl)-2,2-dichloroaziridine[7] and 3-(*tert*-butyl)-2,2-dichloro-1-isopropylaziridine[8] are the only known alkyl substituted *gem*-dichloroaziridines. The most common method for the synthesis of 2,2-dihaloaziridines is the dihalocarbene–imine addition. Azomethine ylides generated from *C*-alkyl aldimines and halogenated carbenes, however, have been only rarely reported.[1] On the other hand, β-chloroimines have been used with success in the synthesis of various classes of organic compounds.[9–15] Therefore, it was supposed that a synthetic sequence involving cycloaddition of dihalocarbenes to β-chloroimines to give functionalized *gem*-dihaloaziridines followed by aziridine isomerization and subsequent transformations would be a potentially simple route to various acyclic and heterocyclic nitrogen-containing compounds.

The present report describes our examination of reactions of β-chloroimines with dichloro- and chlorofluorocarbenes and a preliminary reactivity study of the obtained aziridines.

2. Results and discussion

It was found that the reactions of β-chloroimines **1**[16] and dihalocarbenes generated by alkaline hydrolysis of chloroform (or dichlorofluoromethane) or thermocatalytic decomposition of sodium trichloroacetate in the presence of benzyltriethylammonium chloride (TEBA), leads to *gem*-dihaloaziridines **2a–f** in moderate to good yields (Scheme 1, Table 1).



1a-e **2a-f** (44-80%)

Scheme 1. Reactions of dihalocarbenes with β-chloroimines. Reagents and conditions: (i) method A_1: $CHCl_3$, 10 equiv KOH, 0.2 equiv TEBA, 5–13 h, 18–23 °C; (ii) method A_2: $CHCl_2F$, CH_2Cl_2, 10 equiv KOH, 0.2 equiv TEBA, 1.5 h, 8–11 °C; (iii) method B: 10 equiv CCl_3CO_2Na, $CHCl_3$, 0.2 equiv TEBA, 3 h, reflux.

Dihaloaziridines **2a–f** decompose very easily on silica. The use of silica gel for their isolation was possible only for *N*-phenyl substituted aziridines **2a** and **2f**. For preparative purification of these compounds it was better to use Al_2O_3 (**2a** and **2f**), while the purification of compounds **2b–e** was best performed by chromatography on Florisil. Aziridines **2b** and **2c** were isolated as a mixture with the corresponding amides **5b** and **5c**.

Attempts to prepare aziridine **2e** under the conditions of method A_1 all failed. Probably the imine **1e** and aziridine **2e** are too strong CH acids and therefore they may be deprotonated by the

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Table 1
Synthesis of 3-(2-chloroalkyl)-2,2-dihaloaziridines **2a–f**

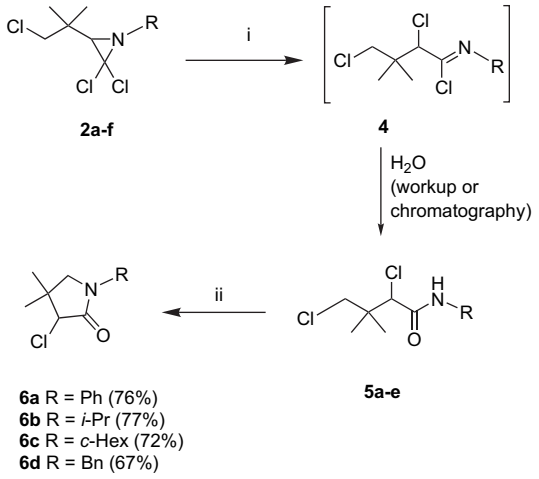
2	R	X	Method	Yield[a] (%)
2a	Ph	Cl	A_1	60
2b	*i*-Pr	Cl	A_1	49[b]
2c	*c*-Hex	Cl	A_1	44[b]
2d	Bn	Cl	A_1	47
2e	CH_2CO_2Me	Cl	B	58
2f	Ph	F	A_2	80[c]

[a] After column chromatography.
[b] Mixture with corresponding compound **5** (5%).
[c] Mixture of diastereoisomers.

excess potassium hydroxide applied for the generation of dichlorocarbene. On the other hand, dichlorocarbene generated by neutral method B reacts with imine **1e** to afford the target aziridine **2e**.

Chlorofluoroaziridine **2f** was obtained as a 15:1 (*trans*- and *cis*-HF) mixture of diastereoisomers (calculated from ^{1}H NMR spectra of the crude reaction mixture). The stereochemical identification of the two isomers was based on the H,F-coupling constants in ^{1}H NMR spectra. For the *trans*-isomer a vicinal H,F-coupling of 4 Hz was found, the *cis*-isomer showed a coupling constant of 8 Hz. The values of $J_{vic\text{-}HF}$ are in accordance with literature data of *trans*-chlorofluoroaziridines (3.5 Hz,[17] 4.5 Hz[18]), *cis*- and *trans*-monofluoroaziridines (2.5 and 5.5 Hz,[19] 2.5 and 6.1 Hz[20]). Similar stereoselectivity was observed for synthesis of 1,3-diphenyl-2,2-chlorofluoroaziridine,[17,18] chlorofluoroazirino[2,1-*e*][1,6]benzoxazocines (thiazocines),[3] 2-fluoro-2-phenylaziridines,[21] and 1,3-diaryl-2-fluoroaziridines[19] by carbene approaches. Opposite stereoselectivity was only observed for synthesis of 1-alkyl-3-phenyl-2-fluoroaziridines.[20]

Attempts to synthesize the *N*-*tert*-butyl-substituted dichloroaziridine **2g**, using both methods of dichlorocarbene generation, were unsuccessful. Instead, a small amount of **3** was isolated when using method B (Scheme 2). The formation of 3,3-dichloroazetidin-2-ones as side products from the reaction of imines with sodium trichloroacetate is known.[1,22–26] It is proposed, that the azetidin-2-one is formed without participation of dichlorocarbene, via reaction of the imine with trichloroacetyl chloride arising from thermolysis of sodium trichloroacetate.[27] Imines are known to react with trichloroacetyl chloride in the presence of triphenylphosphine[28] and with dichloroacetylchloride[29] to give dichloroazetidinones.



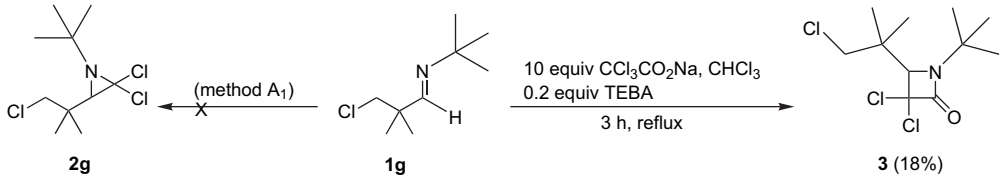
Scheme 3. Ring opening of 2,2-dichloroaziridines under acidic conditions and synthesis of 3-chloro-4,4-dimethylpyrrolidin-2-ones. Reagents and conditions: (i) 0.2–2.5 equiv $ZnCl_2 \cdot 1.5H_2O$, 1–4 h, 0 °C to rt; (ii) 0.1 equiv TEBA, 10 equiv NaOH, H_2O, CH_2Cl_2, o.n., rt.

Table 2
Synthesis of 2,4-dichloro-3,3-dimethylbutanamides **5a–e**

4	R	Reagent	Conditions	Yield[a] (%)
4a	Ph	$ZnCl_2$	rt, 1 h	73
4b	*i*-Pr	HCl_{aq}	rt, o.n.	24
4b	*i*-Pr	$ZnCl_2$	rt, o.n.	48
4c	*c*-Hex	HCl_{aq}	rt, o.n.	18
4c	*c*-Hex	$ZnCl_2$	0–5 °C, 2.5 h	38
4c	*c*-Hex	HCl_g	rt, 1 h	18
4d	Bn	$ZnCl_2$	0–5 °C, 2.5 h	59
4e	CH_2CO_2Me	$ZnCl_2$	rt, o.n.	33

[a] After column chromatography.

The stability of aziridines **2** and yields of compounds **5** strongly depend on the nitrogen substituent. In order to optimize the reaction conditions the type and amount of Lewis and protic acid (SbF_3, $ZnCl_2$, $BF_3 \cdot Et_2O$, $TiCl_4$, HCl_{aq}, HCl_g), the temperature and solvent were varied. The best results were obtained when a catalytic amount of $ZnCl_2$ in CH_2Cl_2 was used.



Scheme 2. Formation of 3,3-dichloroazetidin-2-one.

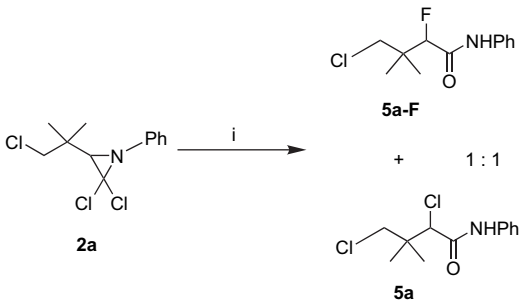
To extend the synthetic potential of the obtained functionalized *gem*-dihaloaziridines, we investigated their reaction with nucleophiles. It is known that for aziridines derived from acyclic imines rupture of the C–N bond opposite to the dichloromethylene group most often occurs.[6,25] In azirino-fused heterocycles, however, ring opening can occur through cleavage of any C–N bond.[2,3,30]

At first, we studied the reaction of compounds **2** in the presence of Lewis acids and HCl (Scheme 3, Table 2). It is proposed that complexation of the Lewis acid with the nitrogen atom (or protonation by HCl), followed by the N–C^3 bond cleavage, led to the corresponding imidoyl halides **4**, which are easily hydrolyzed to dichlorosubstituted amides **5**.[25] The formation of imidoyl halides by aziridine ring opening has been previously shown for thermal isomerization of 3,3-dihalo-1,2-diphenylaziridines[6,31,32] and Lewis acid-catalyzed ring expansion of dichloroazirinobenzoxazine (benzothiazine).[2]

The reaction of compound **2a** with an excess of $BF_3 \cdot Et_2O$ in CH_2Cl_2 at room temperature gave a complex mixture in which the fluorinated analogue of compound **5a** (2-fluoro-4-chloro-3,3-dimethyl-*N*-phenylbutanamide) can be detected in addition to compound **5a** (Scheme 4). This reaction is one more example of ring opening of aziridines using $BF_3 \cdot Et_2O$ as a fluorine source.[33]

Treatment of aziridine **2c** with aqueous HCl in Et_2O in a biphase system or hydrogen chloride gas in CH_3CN gave compound **5c** in 18% yield. Chlorofluoroaziridine **2f** was stable in the presence of $ZnCl_2$ in CH_2Cl_2. When 2,2-dichloroaziridine **2a** was reacted in the presence of $TiCl_4$, the product of ring opening and subsequent hydrolysis (compound **5a**) was detected on TLC as the only product.

The compounds **5** can be cyclized to 3-chloropyrrolidine-2-ones **6** under mild reaction conditions in the presence of sodium hydroxide and TEBA in CH_2Cl_2 in good yields (Scheme 3).



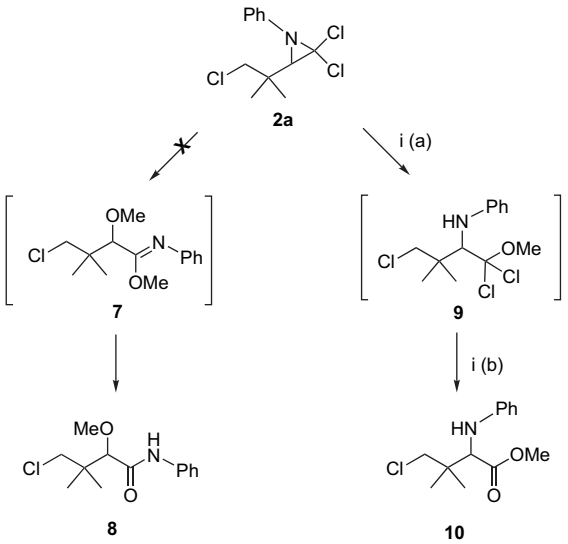
Scheme 4. Ring opening of 2,2-dichloroaziridine. Reagents and conditions: (i) 4 equiv $BF_3{\cdot}Et_2O$, CH_2Cl_2, o.n., rt.

3-Chloropyrrolidinones and their derivatives have been reported as medicinal fungicides[34] and herbicides.[35–39] However, only a few preparative routes are known from the literature. The most common method is the radical cyclization of α-halogenated *N*-allylacetamides.[40–44]

The reaction of aziridine **2a** with sodium methoxide in methanol was also investigated. Unexpectedly, it was found that the ring opening in that case occurs by the rupture of the N–C^2 bond (Scheme 5). The selection between the structures **8** and **10** in favor of the latter was based on NMR and IR spectroscopies. In the ^{1}H NMR spectrum of compounds **5a**–**e** the characteristic NH signal is observed at 6.15–8.00 ppm, in contrast to 4.11 ppm for compound **10**. In the ^{13}C NMR spectrum of compounds **5a**–**e** the peak C=O is located at 165–167 ppm, in contrast to 173.5 ppm for compound **10**. The bands of carbonyl stretching vibrations in IR spectra of these compounds are also different. For compounds **5a**–**e** it is 1650–1660 cm^{-1}, but for compound **10** it is 1730 cm^{-1}. Moreover, the spectra of the proposed structure **10** is in good agreement with data published for *N*-isopropyl and *N*-benzyl analogues prepared from 4-chloro-3,3-dimethylbutan-2-one in 6 steps.[45]

It should be mentioned that the N–C^2 bond cleavage in dihaloaziridines derived from acyclic imines takes place rather rarely. Mixture of products of ring opening in both directions have been observed in the reaction of bromination of 1,3-diaryl-2,2-dichloroaziridines.[46]

So, this reaction may present a short and simple route to functionalized α-amino esters, which can be converted to potentially physiological active small ring α-amino acids[45,47] and azaheterocycles.[47]



Scheme 5. Reaction of 2,2-dichloroaziridine **2a** with sodium methoxide in methanol. Reagents and conditions: (i) (a) 2.2 equiv NaOMe, MeOH (0.2 M), 3 h, rt; (b) CH_3CN, aq HCl (2 M), 15 min, rt, 82%.

3. Conclusion

In conclusion, the reaction of dihalocarbenes with β-chloroimines has proven to be an efficient and short method for the synthesis of a new elusive class of 3-(2-chloroalkyl)-2,2-dihaloaziridines. The latter compounds can easily be transformed to 2,4-dichlorobutanamides, 4-chloro-2-aminobutanoate, and 3-chloropyrrolidin-2-ones by selective C–N bond cleavage, and subsequent cyclization reactions.

4. Experimental

4.1. General

Melting points were determined on a Büchi melting point apparatus B-540; uncorrected values are given. GC–MS analyses were performed using an Interscience, GC 8000 series gas chromatograph with an EC™-5 column (length: 30 m, internal diameter: 0.32 mm, film thickness: 0.25 μm). Products are injected in a split injector (250 °C); the inert carrier gas is helium. The mass spectrometer is a Fisons Instruments MD 800 using electron impact (70 eV) as ionization method. HRMS was measured with a VGQuattro II mass spectrometer (positive ion mode). ^{1}H NMR spectra were recorded on a Bruker Avance DRX 250 spectrometer at 250 MHz, Bruker Avance II 500 spectrometer at 500 MHz, Bruker DPX 300 spectrometer at 300 MHz with internal standard TMS. ^{13}C NMR spectra were recorded on a Bruker Avance DRX 250 spectrometer at 63 MHz, Bruker Avance II 500 spectrometer at 125 MHz, Bruker DPX 300 spectrometer at 75 MHz with internal standard $CDCl_3$ (δ=77). ^{19}F NMR spectra were recorded on a Bruker Avance DRX 250 spectrometer at 235 MHz. ^{13}C NMR assignments were made using DEPT spectra. Infrared spectra were recorded with an Avatar 370 FT-IR apparatus (Thermo Nicolet) using the attenuated total reflection technology. Column chromatography was performed using Merck silica (diameter 40–63 μm), basic aluminum oxide and Florisil. TLC-analysis was performed on glass backed plates (Merck) coated with 0.2 mm silica $60F_{254}$. All solvents were purified according to standard procedures. Chloroform was washed with water to remove ethanol and dried by distillation over P_2O_5. Imines **1** were prepared according published procedures.[16] Microanalyses were performed on a EuroEA3000 (Eurovector).

4.2. Synthesis of aziridines 2a–d; typical procedure (method A_1)

Pellets of KOH (10 equiv) were added to a solution of imine **1** and TEBA (0.2 equiv) in $CHCl_3$ under vigorous stirring, keeping the temperature of the mixture at 21–23 °C (water bath). The mixture was stirred at this temperature for several hours until an aliquot from the reaction mixture showed no IR absorption due to C=N (1663–1668 cm^{-1}). Then the reaction mixture was filtered through the layer of anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was worked up in different ways, depending on the structure to give compounds **2** as pale-yellow oils. The purity of these compounds was satisfactory to be used in the following step. Correct elemental analyses of the dihaloaziridines **2** could not be obtained because of the presence of the corresponding amides **5**.

*4.2.1. 2,2-Dichloro-3-(2-chloro-1,1-dimethylethyl)-1-phenylaziridine (**2a**)*

This compound was obtained from imine **1a** (1.50 g, 7.7 mmol) in $CHCl_3$ (60 mL) during 6 h. The residue was chromatographed on basic Al_2O_3 (petroleum ether/Et_2O) to give compound **2a** (1.27 g, 60%). IR (ATR): 1491, 1599, 2969 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$):

δ 1.28 and 1.30 (2×3H, 2×s, 2×CH_3), 2.70 (1H, s, CH), 3.59 and 3.71 (2×1H, 2×d, J=11.1 Hz, CH_2Cl), 6.99–7.03 (2H, m, Ph), 7.11–7.17 (1H, m, Ph), 7.31–7.38 (2H, m, Ph). ^{13}C NMR (63 MHz, $CDCl_3$): δ 22.2 (CH_3), 23.4 (CH_3), 37.0 ($C(CH_3)_2$), 53.6 (CH_2), 57.5 (CH), 73.8 (CCl_2), 119.8 (CH_{Ph}), 124.4 (CH_{Ph}), 129.0 (CH_{Ph}), 145.2 (C_{Ph}). MS (EI, 70 eV): m/z (%)=281 (8) [M+4], 279 (23) [M+2], 277 (24) [M], 246 (22), 245 (16), 244 (28), 243 (53), 242 (39) [M−Cl], 230 (12), 228 (21) [M−CH_2Cl], 208 (23), 207 (12), 206 (40), 194 (14), 192 (32), 189 (29), 187 (35), 170 (34), 158 (38), 152 (42), 138 (45), 104 (100), 77 (97). MS (ESI): m/z (%)=287 (11) [M−Cl+CH_3CN+4], 286 (11) [M−Cl+CH_3CN+3], 285 (64) [M−Cl+CH_3CN+2], 284 (19) [M−Cl+CH_3CN+1], 283 (100) [M−Cl+CH_3CN], 196 (30).

4.2.2. 2,2-Dichloro-3-(2-chloro-1,1-dimethylethyl)-1-isopropylaziridine (**2b**)

This compound was obtained from imine **1b** (2.00 g, 12.4 mmol) in $CHCl_3$ (100 mL) during 7 h. The residue was unstable on silica gel and on basic Al_2O_3. Two ways of purification were used. Extraction by hexane (3×50 mL) led to a crude mixture (2.77 g) containing compounds **2b** (yield 87%) and **4b** (yield 5%) in ratio of 18:1 (calculated from ^1H NMR). Chromatography on Florisil (hexane/Et_2O) furnished a mixture (1.63 g) containing compounds **2b** (yield 49%) and **4b** (yield 5%) in ratio of 9:1. IR (ATR): 1468, 2875, 2972 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.13 and 1.14 (2×3H, 2×s, 2×CH_3), 1.15 and 1.31 (2×3H, 2×d, J=6.5 Hz, CH(CH_3)$_2$), 1.99 (1H, s, CH), 2.51 (1H, septet, J=6.2 Hz, $CH(CH_3)_2$), 3.44 and 3.60 (2×1H, 2×d, J=10.9 Hz, CH_2Cl). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8 (CH_3), 21.9 (CH_3), 22.3 (CH_3), 23.6 (CH_3), 36.2 ($C(CH_3)_2$), 53.5 (CH_2Cl), 55.2 ($CH(CH_3)_2$), 57.2 (CH), 76.9 (CCl_2). MS (EI, 70 eV), MS (ESI): no molecular ion was observed.

4.2.3. 2,2-Dichloro-3-(2-chloro-1,1-dimethylethyl)-1-cyclohexylaziridine (**2c**)

This compound was obtained from imine **1c** (1.30 g, 6.45 mmol) in $CHCl_3$ (70 mL) during 13 h (after 7 h the additional 3 equiv of KOH were added). The residue was unstable on silica and on basic Al_2O_3. Two ways of purification were used. Extraction by hexane (3×50 mL) led to a crude mixture (1.6 g) containing compounds **2c** (yield 78%) and **4c** (yield 9%) in ratio of 8:1 (calculated from ^1H NMR). Chromatography on Florisil (hexane/Et_2O) furnished a mixture (0.89 g) containing compounds **2c** (yield 44%) and **4c** (yield 5%) in ratio of 8:1. IR (ATR): 1450, 2856, 2932 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.14 and 1.16 (2×3H, 2×s, 2×CH_3), 1.25–1.48 (5H, m, CH_{2cHex}), 1.57–1.70 (3H, m, CH_{2cHex}), 1.75–1.85 (2H, m, CH_{2cHex}), 2.01 (1H, s, CH), 2.24–2.29 (1H, m, CH_{cHex}), 3.46 and 3.62 (2×1H, 2×d, J=10.9 Hz, CH_2Cl). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.3 (2×CH_3), 23.6, 24.1, 25.7, 31.5, 32.0 (CH_{2cHex}), 36.2 ($C(CH_3)_2$), 53.6 (CH_2Cl), 56.8 (CH), 61.9 (CH), 76.8 (CCl_2). MS (ESI): m/z (%)=291 (5) [M−Cl+CH_3CN+2], 289 (9) [M−Cl+CH_3CN], 288 (8) [M+H^++4], 286 (23) [M+H^++2], 284 (22) [M+H^+], 204 (54) [M+H^++2−CCl_2], 202 (100) [M+H^+−CCl_2].

4.2.4. 2,2-Dichloro-3-(2-chloro-1,1-dimethylethyl)-1-benzylaziridine (**2d**)

This compound was obtained from imine **1d** (1.30 g, 6.2 mmol) in $CHCl_3$ (90 mL) during 5 h. The residue was extracted by hexane (3×50 mL) to give crude product (1.23 g, 68%). Analytically pure product was obtained by chromatography on Florisil (hexane/Et_2O) (0.84 g, 47%). IR (ATR): 1454, 1497, 2932 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.94 and 1.09 (2×3H, 2×s, 2×CH_3), 2.06 (1H, s, CH), 3.15 and 3.39 (2×1H, 2×d, J=10.9 Hz, CH_2Cl), 3.68 and 4.18 (2×1H, 2×d, J=13.3 Hz, CH_2Ph), 7.30–7.40 (5H, m, Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.1 (CH_3), 22.6 (CH_3), 36.6 ($C(CH_3)_2$), 54.0 (CH_2Cl), 57.8 (CH), 57.9 (CH_2Ph), 77.5 (CCl_2), 127.7 (CH_{Ph}), 2×128.6 (CH_{Ph}), 137.0 (C_{Ph}). MS (ESI): m/z (%)=296 (22) [M+H^++4], 294 (97) [M+H^++2], 292 (100) [M+H^+].

4.3. Synthesis of compounds 2e and 3; typical procedure (method B)

Powdered sodium trichloroacetate (10 equiv) was added in small portions with stirring to a mixture of the imine **1** and TEBA (0.2 equiv) in refluxing $CHCl_3$. Then the mixture was filtered and the solvent was evaporated under reduced pressure and the residue was worked up in different ways.

4.3.1. Methyl 2-(2,2-dichloro-3-(2-chloro-1,1-dimethylethyl)aziridin-1-yl)acetate (**2e**)

This compound was obtained from imine **1e** (1.44 g, 7.5 mmol) in $CHCl_3$ (80 mL) over 3 h. The residue was extracted by ether (3×50 mL) to give crude product (1.78 g, 86%). Pure product was obtained by chromatography on Florisil (1.2 g, 58%). IR (ATR): 1585, 1754 (C=O), 2953 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.16 and 1.23 (2×3H, 2×s, 2×CH_3), 2.10 (1H, s, CH), 3.49 and 3.71 (2×1H, 2×d, J=16.7 Hz, CH_2Cl), 3.57 (2H, s, CH_2), 3.81 (3H, s, OCH_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ 22.2 (CH_3), 22.3 (CH_3), 36.8 ($C(CH_3)_2$), 52.2 (CH), 54.3 (CH_2), 54.9 (CH_2), 58.7 (OCH_3), 76.1 (CCl_2), 169.2 (C=O). MS (ESI): m/z (%)=281 (7) [M−Cl+CH_3CN+2], 279 (10) [M−Cl+CH_3CN], 278 (6) [M+H^++4], 276 (19) [M+H^++2], 274 (18) [M+H^+], 194 (32) [M+H^++2−CCl_2], 192 (100) [M+H^+−CCl_2].

4.3.2. 1-tert-Butyl-3,3-dichloro-4-(2-chloro-1,1-dimethylethyl)azetidin-2-one (**3**)

This compound was obtained from imine **1g** (0.50 g, 2.85 mmol) in $CHCl_3$ (40 mL) over 1.5 h. The residue was chromatographed on silica gel (hexane/Et_2O) to give compound **3**, as a pale-yellow oil (0.145 g, 18%). IR (ATR): 1776 (C=O) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.29 and 1.34 (2×3H, 2×s, 2×CH_3), 1.46 (9H, s, $C(CH_3)_3$), 3.56 and 3.84 (2×1H, 2×d, J=11.4 Hz, CH_2Cl), 4.30 (1H, s, CH). ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.4 (CH_3), 23.3 (CH_3), 29.0 ($C(CH_3)_3$), 38.3 ($C(CH_3)_2$), 53.5 (CH_2), 56.4 ($C(CH_3)_3$), 81.2 (CCl_2), 162.5 (C=O). MS (ESI): m/z (%)=331 (4) [M+CH_3CN+4], 329 (12) [M+CH_3CN+2], 327 (13) [M+CH_3CN], 290 (34) [M+H^++4], 288 (100) [M+H^++2], 286 (97) [M+H^+], 234 (4) [M+H^++4−$(CH_3)_2C{=}CH_2$], 232 (16) [M+H^++2−$(CH_3)_2C{=}CH_2$], 234 (18) [M+H^+−$(CH_3)_2C{=}CH_2$]. HRMS (ESI): m/z calcd for $C_{11}H_{18}Cl_3NO$+H: 286.0527; found: 286.0532.

4.4. Synthesis of 2-chloro-3-(2-chloro-1,1-dimethylethyl)-2-fluoro-1-phenylaziridine (2f) (method A_2)

Dichlorofluoromethane was bubbled through a vigorously stirred mixture of imine **1a** (1.5 g, 7.7 mmol), powdered KOH (4.30 g, 76.8 mmol), and TEBA (0.35 g, 1.5 mmol) in CH_2Cl_2 (60 mL) at 8–11 °C for 1.5 h. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. The residue was chromatographed on basic Al_2O_3 (petroleum ether/EtOAc) to give compound **2f**, as a mixture of diastereoisomers *trans*-HF (J_{HF}=4 Hz)/*cis*-HF (J_{HF}=8 Hz) ca. 15:1 (1.60 g, 80%) [ratio calculated from ^1H NMR spectra of the crude reaction mixture]. IR (ATR): 1491, 1595, 2977 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.21 and 1.24 (2×3H, 2×s, 2×CH_3) [major isomer], 1.26 and 1.30 (2×s, 2×CH_3) [minor isomer], 2.68 (1H, d, J_{HF}=4 Hz, CH) [major isomer], 2.84 (d, J_{HF}=8 Hz, CH) [minor isomer], 3.51–3.68 (m, CH_2Cl) [minor isomer], 3.59 (2H, d, J_{HF}=3 Hz, CH_2Cl) [major isomer], 6.98–7.01 (2H, m, Ph), 7.11–7.17 (1H, m, Ph), 7.31–7.38 (2H, m, Ph). ^{13}C NMR (63 MHz, $CDCl_3$) [major isomer]: δ 22.6 (d, J=2 Hz, CH_3), 23.4 (d, J=3 Hz, CH_3), 36.9 (d, J=6 Hz, $C(CH_3)_2$), 53.8 (d, J=2 Hz, CH_2Cl), 56.9 (d, J=14 Hz, CH), 96.7 (d, J=296 Hz, CFCl), 119.8 (d, J=3 Hz, CH_{Ph}), 124.4 (CH_{Ph}), 129.0 (CH_{Ph}), 145.1 (C_{Ph}). ^{19}F NMR (235 MHz, $CDCl_3$): δ −101.0 [major isomer], −102.7 [minor isomer]. MS (EI, 70 eV), MS (ESI): no molecular ion was observed.

4.5. Synthesis of amides 5a–e

*4.5.1. 2,4-Dichloro-3,3-dimethyl-N-phenylbutanamide (**5a**)*

A mixture of $ZnCl_2 \cdot 1.5H_2O$ (0.30 g, 1.8 mmol), aziridine **2a** (0.205 g, 0.74 mmol), and CH_2Cl_2 (7 mL) was stirred at room temperature for 1 h. Then $ZnCl_2$ was filtered off, the solvent was evaporated and the residue was chromatographed on silica gel (hexane/Et_2O). Yield 0.14 g (73%), colorless crystals, mp 111–112 °C (Et_2O–pentane). IR (ATR): 1664 (C=O), 3300 (NH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.25 and 1.28 (2×3H, 2×s, 2×CH_3), 3.59 and 3.70 (2×1H, 2×d, J=11.1 Hz, CH_2Cl), 4.58 (1H, s, CHCl), 7.15–7.19 (1H, m, Ph), 7.34–7.38 (2H, m, Ph), 7.52–7.54 (2H, m, Ph), 8.00 (1H, br s, NH). ^{13}C NMR (63 MHz, $CDCl_3$): δ 22.2 (CH_3), 22.5 (CH_3), 40.5 ($C(CH_3)_2$), 53.2 (CH_2), 66.1 (CHCl), 120.2 (CH_{Ph}), 125.2 (CH_{Ph}), 129.1 (CH_{Ph}), 136.7 (C_{Ph}), 165.2 (C=O). MS (ESI): m/z (%)=264 (10) [M+H^++4], 262 (72) [M+H^++2], 260 (100) [M+H^+], 226 (4) [M−Cl+2], 224 (12) [M−Cl]. Anal. Calcd for $C_{12}H_{15}Cl_2NO$: C, 55.40; H, 5.81; N, 5.38. Found: C, 55.27; H, 5.81; N, 5.54.

*4.5.2. 2,4-Dichloro-3,3-dimethyl-N-isopropylbutanamide (**5b**)*

Method A. A mixture of concentrated HCl (2 mL), crude aziridine **2b** (0.5 g), and Et_2O (5 mL) was stirred overnight at room temperature. Then, the mixture was poured into a saturated Na_2CO_3 solution, extracted with Et_2O (3×30 mL) and the combined extracts were dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on Al_2O_3 (hexane/Et_2O). Yield: 0.13 g (24%, calculated taking into account the amide already present in the starting aziridine).

Method B. A mixture of $ZnCl_2 \cdot 1.5H_2O$ (0.06 g, 0.37 mmol), aziridine **2b** (0.51 g, filtered through Florisil), and CH_2Cl_2 (30 mL) was stirred at room temperature overnight. Then $ZnCl_2$ was filtered, the solvent was evaporated and the residue was chromatographed on Al_2O_3 (hexane/Et_2O). Yield: 0.25 g (48%, calculated taking into account the amide already present in the starting aziridine), colorless crystals, mp 76–77 °C (hexane). IR (ATR): 1650 (C=O), 3284 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.17–1.22 (12H, m, 4×CH_3), 3.54 and 3.66 (2×1H, 2×d, J=11.3 Hz, CH_2Cl), 4.05 (1H, octet, J=6.9 Hz, C*H*$(CH_3)_2$), 4.40 (1H, s, CHCl), 6.15 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2 (CH_3), 22.3 (CH_3), 22.4 (CH_3), 22.5 (CH_3), 40.1 ($C(CH_3)_2$), 42.0 (*C*H$(CH_3)_2$), 53.4 (CH_2Cl), 65.8 (CHCl), 166.0 (C=O). MS (ESI): m/z (%)=230 (35) [M+H^++4], 228 (63) [M+H^++2], 226 (100) [M+H^+]. Anal. Calcd for $C_9H_{17}Cl_2NO$: C, 47.80; H, 7.58; N, 6.19. Found: C, 47.69; H, 7.54; N, 6.28.

*4.5.3. 2,4-Dichloro-3,3-dimethyl-N-cyclohexylbutanamide (**5c**)*

Method A. Compound **5c** (0.125 g, 18%, calculated taking into account the amide already present in the starting aziridine) was obtained from crude aziridine **2c** (0.5 g) at room temperature overnight.

Method B. Compound **5c** (0.21 g, 38%, calculated taking into account the amide already present in the starting aziridine) was obtained from aziridine **2c** (0.5 g, filtered through Florisil) at 0 °C (ice bath) during 2.5 h.

Method C. Hydrogen chloride gas was bubbled through a solution of aziridine **2c** (0.285 g, filtered through Florisil) in Et_2O (20 mL) during 1 h. Then the mixture was poured into water, extracted with Et_2O and the combined extracts were dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on Al_2O_3 (hexane/Et_2O). Yield: 0.07 g (18%, calculated taking into account the amide already present in the starting aziridine), colorless crystals, mp 118–119 °C (hexane). IR (ATR): 1647 (C=O), 3273 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.12–1.20 (4H, m, CH_{2cHex}), 1.17 and 1.19 (2×3H, 2×s, 2×CH_3), 1.32–1.40 (2H, m, CH_{2cHex}), 1.60–1.70 and 1.89–1.93 (2×2H, 2×m, CH_{2cHex}), 3.52 and 3.65 (2×1H, 2×d, J=10.9 Hz, CH_2Cl), 3.70–3.85 (1H, m, CH_{cHex}), 4.40 (1H, s, CHCl), 6.24 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2 (CH_3), 22.4 (CH_3), 24.6 (2×CH_{2cHex}), 25.4, 32.6, 32.8 (CH_{2cHex}), 40.1 ($C(CH_3)_2$), 48.7 (CH_{cHex}), 53.4 (CH_2Cl), 65.9 (CHCl), 165.9 (C=O). MS (ESI): m/z (%)=270 (10) [M+H^++4], 268 (71) [M+H^++2], 266 (100) [M+H^+]; Anal. Calcd for $C_{12}H_{21}Cl_2NO$: C, 54.14; H, 7.95; N, 5.26. Found: C, 54.23; H, 7.92; N, 5.27.

*4.5.4. 2,4-Dichloro-3,3-dimethyl-N-benzylbutanamide (**5d**)*

A mixture of $ZnCl_2 \cdot 1.5H_2O$ (0.075 g, 0.46 mmol), aziridine **2d** (0.68 g, 2.3 mmol), and CH_2Cl_2 (30 mL) was stirred at 0 °C (ice bath) during 4 h. Then the mixture was poured into water, extracted with CH_2Cl_2 (3×30 mL) and the combined extracts were dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica (petroleum ether/EtOAc). Yield 0.375 g (59%), mp 110.7–111.3 °C (Et_2O). IR (ATR): 1648 (C=O), 3279 (NH) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.19 and 1.21 (2×3H, 2×s, 2×CH_3), 3.55 and 3.67 (2×1H, 2×d, J=11.0 Hz, CH_2Cl), 4.48 (1H, s, CHCl), 4.51 (2H, d, J=1.5 Hz, C*H*$_2$Ph), 6.66 (1H, br s, NH), 7.29–7.40 (5H, m, Ph). ^{13}C NMR (63 MHz, $CDCl_3$): δ 22.2 (CH_3), 22.6 (CH_3), 40.3 ($C(CH_3)_2$), 44.0 (CH_2Ph), 53.4 (CH_2Cl), 65.8 (CHCl), 127.77 (CH_{Ph}), 127.79 (CH_{Ph}), 128.8 (CH_{Ph}), 137.5 (C_{Ph}), 167.1 (C=O). MS (ESI): m/z (%)=278 (10) [M+H^++4], 276 (70) [M+H^++2], 274 (100) [M+H^+]. Anal. Calcd for $C_{13}H_{17}Cl_2NO$: C, 56.95; H, 6.25; N, 5.11. Found: C, 56.72; H, 6.29; N, 5.11.

*4.5.5. Methyl 2-(2,4-dichloro-3,3-dimethylbutanamido)-acetate (**5e**)*

Method B. Compound **5e** was prepared from aziridine **2e** (0.56 g, 2.0 mmol, filtered through Florisil) at room temperature overnight. After workup, the residue was chromatographed on silica gel (petroleum ether/EtOAc) to give colorless crystals (0.17 g, 33%), mp 69–70 °C (Et_2O–petroleum ether). IR (ATR): 1660 (C=O), 1755 (C=O), 3366 (NH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.23 (6H, s, 2×CH_3), 3.57 and 3.68 (2×1H, 2×d, J=11 Hz, CH_2Cl), 3.80 (3H, s, OCH_3), 4.04 and 4.15 (2×1H, 2×dd, J=18.2 Hz, J=5.3 Hz, C*H*$_2CO_2CH_3$), 4.52 (1H, s, CHCl), 6.82 (1H, br s, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.1 (CH_3), 22.4 (CH_3), 40.3 ($C(CH_3)_2$), 41.4 (*C*H$_2CO_2CH_3$), 52.4 (OCH_3), 53.2 (CH_2Cl), 65.4 (CHCl), 167.1 (C=O), 169.7 (C=O). MS (ESI): m/z (%)=260 (10) [M+H^++4], 258 (77) [M+H^++2], 256 (100) [M+H^+]. HRMS (ESI): m/z calcd for $C_9H_{15}Cl_2NO_3$+H: 256.0502; found: 256.0507.

4.6. Reaction of aziridine 2a with $BF_3 \cdot Et_2O$

$BF_3 \cdot Et_2O$ (0.42 g, 2.960 mmol) was added dropwise to a stirred solution of compound **2a** (0.21 g, 0.8 mmol) in CH_2Cl_2 (7 mL) and the mixture was kept overnight at room temperature. The solvent was removed in vacuo and a complex mixture in which compounds **5a** and **5a–F** (1:1) could be detected in ^1H NMR was obtained. The residue was purified by column chromatography on silica (hexane–Et_2O). A mixture (30 mg) containing compounds **5a** and **5a–F** in a ratio of 1:2 was only isolated in addition to the mixture of two unknown compounds (140 mg). In the NMR spectra of the mixture following signals could be attributed to 4-chloro-2-fluoro-3,3-dimethyl-*N*-phenylbutanamide (**5a–F**). ^1H NMR (250 MHz, $CDCl_3$): δ 1.18 and 1.22 (2×3H, 2×d, J=1.4 Hz, 2×CH_3), 3.62 (2H, d, J=1.8 Hz, CH_2Cl), 4.98 (1H, d, J=47.9 Hz, CHF), 7.13–7.19 (1H, m, Ph), 7.32–7.38 (2H, m, Ph), 7.51–7.57 (2H, m, Ph), 7.98 (1H, br s, NH). ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.05 (d, J^3=7 Hz, CH_3), 21.06 (d, J^3=7 Hz, CH_3), 39.9 (d, J^2=18 Hz, $C(CH_3)_2$), 51.8 (d, J^3=7 Hz, CH_2), 93.9 (d, J^1=193 Hz, CHF), 120.2 (CH_{Ph}), 125.2 (CH_{Ph}), 129.1 (CH_{Ph}), 136.7 (C_{Ph}), 166.2 (d, J^2=19 Hz, C=O).

4.7. Synthesis of compounds 6a–d; typical procedure

A mixture of compound **5** (0.1 g), TEBA (0.01 g, 0.04 mmol), NaOH (0.17 g, 4.3 mmol), H_2O (0.3 mL), and CH_2Cl_2 (7 mL) was

vigorously stirred overnight at room temperature. Then water (5 mL) was added, the organic phase was separated and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel to give compound **6**.

*4.7.1. 3-Chloro-4,4-dimethyl-1-phenylpyrrolidin-2-one (**6a**)*

Yield: 65 mg (76%), colorless crystals, mp 65.8–66.4 °C (Et_2O–hexane). Spectroscopic data (^1H NMR) were in accordance with literature data.[40] IR (ATR): 1707 (C=O) cm^{-1}. ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2 (CH_3), 25.2 (CH_3), 38.2 ($C(CH_3)_2$), 58.6 (CHCl), 67.0 (CH_2N), 119.9 (CH_{Ph}), 125.1 (CH_{Ph}), 129.0 (CH_{Ph}), 139.0 (C_{Ph}), 168.7 (C=O). MS (ESI): *m*/*z* (%)=226 (31) [M+H$^+$+2], 225 (12) [M+H$^+$+1], 224 (100) [M+H$^+$].

*4.7.2. 3-Chloro-4,4-dimethyl-1-isopropylpyrrolidin-2-one (**6b**)*

Yield: 65 mg (77%), colorless crystals, mp 40–41 °C (pentane). IR (ATR): 1691 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 and 1.10 (2×3H, 2×d, *J*=3.1 Hz, 2×CH_3), 1.12 and 1.16 (2×3H, 2×s, 2×CH_3), 2.96 and 3.11 (2×1H, 2×d, *J*=9.8 Hz, CH_2N), 4.00 (1H, s, CHCl), 4.33 (1H, septet, *J*=6.5 Hz, C*H*(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1 (CH_3), 19.4 (CH_3), 21.9 (CH_3), 25.2 (CH_3), 38.3 ($C(CH_3)_2$), 42.7 ($CH(CH_3)_2$), 52.0 (CH_2N), 66.5 (CHCl), 168.8 (C=O). MS (ESI): *m*/*z* (%)=192 (34) [M+H$^+$+2], 190 (100) [M+H$^+$]. HRMS (ESI): *m*/*z* calcd for $C_9H_{16}ClNO$+H: 190.0993; found: 190.0999. Anal. Calcd for $C_9H_{16}ClNO$: C, 56.99; H, 8.50; N, 7.38. Found: C, 57.01; H, 8.36; N, 7.25.

*4.7.3. 3-Chloro-4,4-dimethyl-1-cyclohexylpyrrolidin-2-one (**6c**)*

Yield: 62 mg (72%), colorless crystals, mp 47.5–48.5 °C (hexane). IR (ATR): 1683 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.13 and 1.17 (2×3H, 2×s, 2×CH_3), 1.22–1.40 and 1.60–1.80 (2×5H, 2×m, CH_{2cHex}), 2.99 and 3.14 (2×1H, 2×d, *J*=9.4 Hz, CH_2N), 3.85–3.98 (1H, m, CH_{cHex}), 4.02 (1H, s, CHCl). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0 (CH_3), 25.10, 25.13, 25.22 (CH_{2cHex}), 25.25 (CH_3), 29.6, 29.9 (CH_{2cHex}), 38.4 ($C(CH_3)_2$), 50.7 (CH_{cHex}), 53.2 (CH_2N), 66.5 (CHCl), 168.9 (C=O). MS (ESI): *m*/*z* (%)=232 (37) [M+H$^+$+2], 230 (100) [M+H$^+$]. Anal. Calcd for $C_{12}H_{20}ClNO$: C, 62.73; H, 8.77; N, 6.10. Found: C, 62.94; H, 8.70; N, 6.17.

*4.7.4. 3-Chloro-4,4-dimethyl-1-benzylpyrrolidin-2-one (**6d**)*

The reaction mixture was vigorously stirred at reflux for 5 h. Yield: 60 mg (67%), pale-yellow oil. IR (ATR): 1697 (C=O) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.11 and 1.15 (2×3H, 2×s, 2×CH_3), 2.92 and 3.08 (2×1H, 2×d, *J*=9.7 Hz, CH_2N), 4.10 (1H, s, CHCl), 4.42 and 4.54 (2×1H, 2×d, *J*=14.6 Hz, CH_2Ph), 7.20–7.40 (5H, m, Ph). ^{13}C NMR (63 MHz, $CDCl_3$): δ 22.1 (CH_3), 25.4 (CH_3), 38.3 ($C(CH_3)_2$), 47.0 (CH_2Ph), 56.7 (CH_2N), 66.0 (CHCl), 127.8 (CH_{Ph}), 128.2 (CH_{Ph}), 128.7 (CH_{Ph}), 135.6 (C_{Ph}), 169.8 (C=O). MS (ESI): *m*/*z* (%)=240 (33) [M+H$^+$+2], 238 (100) [M+H$^+$]. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{16}ClNO$+H: 238.0993; found: 238.0999.

4.8. Synthesis of methyl 4-chloro-3,3-dimethyl-2-(phenylamino)butanoate (10)

To a solution of sodium methoxide in methanol (0.4 M, 10 mL) was added dropwise at stirring a solution of aziridine **2a** (0.5 g, 1.8 mmol) in methanol (10 mL). The mixture was stirred at room temperature during 3 h. Then, methanol was evaporated and acetonitrile (5 mL) and aqueous 2 M HCl (1 mL) were added to the residue. The mixture was stirred at room temperature during 15 min. Then, the mixture was poured into water, extracted with Et_2O and the combined extracts were dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel (hexane/Et_2O) to give a pale-yellow oil. Yield: 0.38 g (82%). IR (ATR): 1601, 1730 (C=O), 3386 (NH) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.11 (6H, s, 2×CH_3), 3.41 and 3.73 (2×1H, 2×d, *J*=10.9 Hz, CH_2Cl), 3.70 (3H, s, OCH_3), 4.11 (1H, br s, NH), 4.21 (1H, s, $CHCO_2CH_3$), 6.72–6.81 (3H, m, Ph), 7.15–7.22 (2H, m, Ph). ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.2 (CH_3), 22.9 (CH_3), 39.2 ($C(CH_3)_2$), 51.9 (OCH_3), 53.2 (CH_2Cl), 61.6 (CHCl), 114.7 (CH_{Ph}), 119.2 (CH_{Ph}), 129.4 (CH_{Ph}), 147.3 (C_{Ph}), 173.5 (C=O). MS (ESI): *m*/*z* (%)=258 (31) [M+H$^+$+2], 256 (100) [M+H$^+$], 220 (49) [M−HCl], 198 (20) [M−CO_2CH_3+2], 196 (58) [M−CO_2CH_3]. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{18}ClNO_2$+H: 256.1093; found: 256.1104.

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Supplementary data

Copies of ^1H NMR and ^{13}C NMR spectra for compounds **2**, **3**, **5**, **6** and **10** are included in Supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.05.121.

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