Pergamon

Bioorganic & Medicinal Chemistry 10 (2002) 3955–3964

BIOORGANIC & MEDICINAL CHEMISTRY

1-Alkoxycarbonyl-3-halogenoazetidin-2-ones as Elastase (PPE) Inhibitors

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Received 25 February 2002; accepted 10 July 2002

Abstract—A series of 1-alkoxycarbonyl-3-halogenoazetidin-2-ones, designed as potential suicide inhibitors of serine proteases, has been synthesized and evaluated against porcine pancreatic elastase (PPE). All the compounds were transient inhibitors, their activity depending mainly on the nature of the halogen substituent: bromo- and iodo- derivatives are more active (K_i ~2–22 μM) than 3-chloroazetidinones (K_i ~20–150 μM). The lipophilicity of the N-1 substituent appeared to exert a slightly positive effect.

Introduction

Inhibition of serine proteases by bicyclic azetidinones has been widely documented, since the discovery of the naturally-occurring penam and cephem antibiotics till the development of synthetic penem, carbapenem and cephemsulfone derivatives as inactivators of bacterial D,D-peptidases and β-lactamases[1,2] on the one hand, and mammalian elastases[3] on the other hand. Adequately substituted monocyclic azetidinones have been further considered as lead-structures for the inhibition of the previous enzymes[4,5] and other serine enzymes such as prostate specific antigen (PSA),[6] thrombin,[7] human cytomegalovirus protease (HCMV),[8] and human chymase.[9] The design of potentially active structures relies upon the combination of chemical reactivity (activation towards nucleophilic attack by a serine residue) and enzymic recognition (selective fit into the target-enzyme active site).[10]

A few years ago, we disclosed the activity of three representatives of 1-alkoxycarbonyl-3-bromoazetidin-2-ones towards porcine pancreatic elastase (PPE).[11] Our molecules were constructed in order to behave as suicide inhibitors by unmasking an isocyanate function under processing by the enzyme (Fig. 1). For that, the R^1 residue of the *N*-alkoxycarbonyl substituent was chosen as a small electron-withdrawing group ($R^1 = CH_2CX_3$) susceptible to improve the nucleofugal ability of OR^1. Experimentally, enzyme-catalyzed cleavage of the N1–C2 azetidinone bond could be observed, but not the departure of the potential leaving group; molecules **A** ($R^2 = Br$; $R^1 = CH_2Ph$, CH_2CCl_3, CH_2CF_3) are transient inhibitors of PPE (slowly deacylating substrates).[11]

In the continuation of this preliminary study, we have now examined a series of azetidinones **A** (Fig. 1) equipped with a lipophilic R^1 substituent in order to improve the interaction of the potential leaving group with the enzyme subsite S2′.[12–15] We have also considered the role of the R^2 substituent, fitting in the subsite S1, by the replacement of bromine with chlorine and iodine. Surprisingly, C3 monohalogenated and C4 unsubstituted azetidinones have been scarcely described in the field of organic synthesis,[16–19] as well as in the particular domain of serine proteases inhibition.[20,21]

Results

Synthesis

(3*S*)-(*tert*-Butyloxycarbonyl)aminoazetidin-2-one **1**, obtained in five steps from (*L*)-serine,[22] was chosen as the starting material for introducing the alkoxycarbonyl group at position N1. Treatment of **1** with lithium

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PII: S0968-0896(02)00304-8

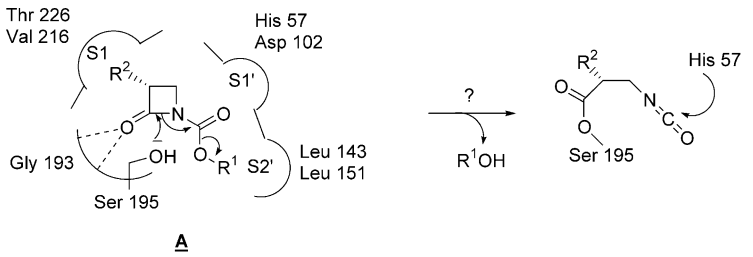


Figure 1. Expected mechanism of suicide-inhibition of elastase.

hexamethyldisilazide (LiHMDS) at low temperature followed by the addition of chloroformates **2** gave the N-1 substituted azetidinones **3**, contaminated with the bis-acylated compounds **4** (Scheme 1). Reagents **2**, offering the various lipophilic chains R^1, were prepared by reaction of the corresponding alcohols with triphosgene and pyridine.[23,24] Substitution products **3** and **4** have been isolated by column-chromatography on silica gel and characterized as usual (see Experimental, and Table 1, entries 1–7 and 8–14).

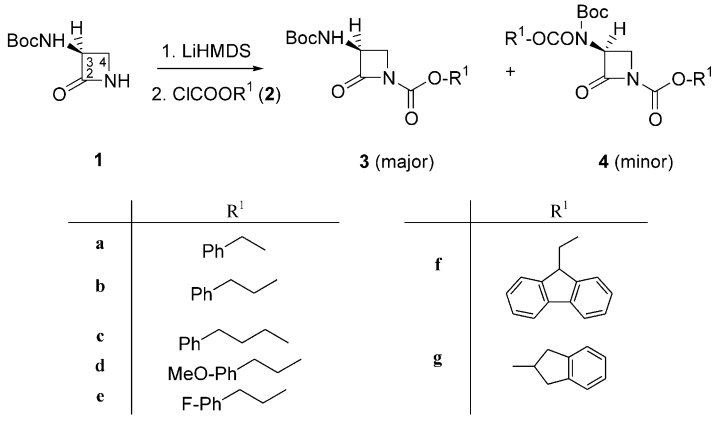
Since azetidinones **3** were not stable in neat trifluoroacetic acid (TFA), we examined other methods of Boc deprotection under neutral conditions. By using ammonium cerium(IV) nitrate (CAN) in refluxing acetonitrile,[25] we could easily cleave the Boc group on bis-acylated derivatives **4** (Scheme 2; Table 1, entries 15–17); however, the same method failed with precursors **3**, giving degradation products only. In this case, the best way to remove Boc group remained the acidic treatment, but under smooth conditions such as TFA in dichloromethane (1:10, v/v) or 3 N HCl in ethyl acetate (1:10, v/v).[26] The free amines **6** were not isolated, and directly transformed into the corresponding diazonium salts which were substituted in situ by a nucleophile (potassium bromide, chloride or iodide), according to a procedure[27] initially developed in the cephem series (Scheme 3). Applied to C4-unsubstituted monocyclic azetidinones, this reaction led to racemization.[11]

We first synthesized 3-bromoazetidinones **7a–g** (Table 1, entries 18–24). Purification of these compounds was a difficult task due to their instability on normal silica gel. Thus, preparative thin layer chromatographies were performed on silica gel plates previously neutralized with *N*-ethyl morpholine. 3-Chloroazetidinones **8a–c** and **8f** were similarly prepared (Scheme 3) and purified (Table 1, entries 25–28). However, in the crude mixtures, the presence of the corresponding 3-hydroxyl derivatives **10** was visible in the ^{1}H NMR spectra (H3 at 4.92 δ), resulting from a competition between chloride and water as nucleophiles. Such side-products **10** could not be detected during the synthesis of 3-bromoazetidinones **7a–g**, nor in the case of 3-iodoazetidinones **9a–b** (Table 1, entries 29–30), due to the good nucleophilicity of bromide and iodide.

All the 3-substituted azetidinones were characterized by a typical ABX pattern in ^{1}H NMR for protons H3, H4 and H4′: they appeared, respectively, at δ 4.8–4.9 ($J_{cis}\sim$5.8 Hz and $J_{trans}\sim$2.9 Hz), δ 3.6–3.8 and 3.9–4.2 ($J_{AB}\sim$7.8 Hz). In ^{13}C NMR, the β-lactam and urethane carbonyls gave signals at δ 160–165 and 148–150, respectively. Carbon C3 was found at δ 55–58 for the NHBoc series, at δ 40 for the bromo series, at δ 49 for the chloro derivatives and at δ 10 for the iodo derivatives. In IR, the β-lactam and urethane carbonyls showed bands at 1820–1825 and 1725–1735 cm^{-1}, respectively.

Biochemical Evaluation

Suicide inhibition of serine enzymes by synthetic inhibitors possessing a masked isocyanate function is scarcely described in the literature; such an electrophilic function usually results from Lossen and related rearrangements.[28–30] The mechanism we are interested in relies upon a simple elimination reaction initiated by the β-lactam ring opening. Some precedents exist about the

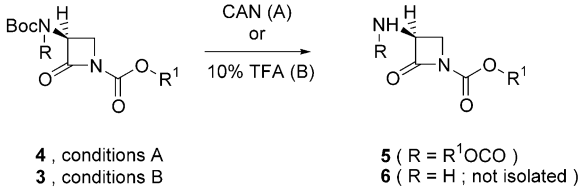


Scheme 1. Synthesis of compounds **3–4**.

Table 1. Yield of compounds **3–9**

Entry	R^1	C3 substituent	Compd	R_f (solvent)[a]	Yield (%)[b]
1	$PhCH_2$	*t*-BuOCONH	**3a**	0.4 (A)	77
2	$PhCH_2CH_2$	*t*-BuOCONH	**3b**	0.3 (A)	53
3	$PhCH_2CH_2CH_2$	*t*-BuOCONH	**3c**	0.3 (A)	34
4	*p*MeO-Ph-CH_2CH_2	*t*-BuOCONH	**3d**	0.4 (A)	70
5	*p*F-Ph-CH_2CH_2	*t*-BuOCONH	**3e**	0.4 (A)	37
6	Fluorenyl-CH_2	*t*-BuOCONH	**3f**	0.3 (A)	55
7	2-Indanyl	*t*-BuOCONH	**3g**	0.4 (A)	33
8	$PhCH_2$	$PhCH_2OCON(Boc)$	**4a**	0.9 (A)	12
9	$PhCH_2CH_2$	$PhCH_2CH_2OCON(Boc)$	**4b**	0.9 (A)	15
10	$PhCH_2CH_2CH_2$	$PhCH_2CH_2CH_2OCON(Boc)$	**4c**	0.9 (A)	20
11	*p*MeO-Ph-CH_2CH_2	*p*MeO-$PhCH_2CH_2OCON(Boc)$	**4d**	0.8 (A)	11
12	*p*F-Ph-CH_2CH_2	*p*F-$PhCH_2CH_2OCON(Boc)$	**4e**	0.9 (A)	3
13	Fluorenyl-CH_2	Fluorenyl-$CH_2OCON(Boc)$	**4f**	0.8 (A)	12
14	2-Indanyl	2-Indanyl-OCON(Boc)	**4g**	0.9 (A)	21
15	$PhCH_2$	$PhCH_2OCONH$	**5a**	0.4 (A)	57
16	$PhCH_2CH_2$	$PhCH_2CH_2OCONH$	**5b**	0.4 (A)	48
17	Fluorenyl-CH_2	Fluorenyl-CH_2OCONH	**5f**	0.6 (A)	63
18	$PhCH_2$	Br	**7a**	0.4 (B)	71
19	$PhCH_2CH_2$	Br	**7b**	0.4 (B)	69
20	$PhCH_2CH_2CH_2$	Br	**7c**	0.5 (B)	40
21	*p*MeO-Ph-CH_2CH_2	Br	**7d**	0.3 (B)	47
22	*p*F-Ph-CH_2CH_2	Br	**7e**	0.4 (B)	39
23	Fluorenyl-CH_2	Br	**7f**	0.3 (B)	39
24	2-Indanyl	Br	**7g**	0.4 (B)	50
25	$PhCH_2$	Cl	**8a**	0.4 (B)	31
26	$PhCH_2CH_2$	Cl	**8b**	0.4 (B)	34
27	$PhCH_2CH_2CH_2$	Cl	**8c**	0.4 (B)	63
28	Fluorenyl-CH_2	Cl	**8f**	0.3 (B)	47
29	$PhCH_2$	I	**9a**	0.4 (B)	67
30	$PhCH_2CH_2$	I	**9b**	0.4 (B)	65

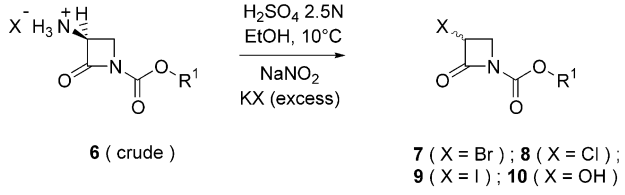
[a]A = CH_2Cl_2–AcOEt, 95:5 B = CH_2Cl_2.
[b]Isolated by column chromatography (entries 1–17) or preparative TLC (entries 18–30).



4, conditions A
3, conditions B

5 (R = R^1OCO)
6 (R = H ; not isolated)

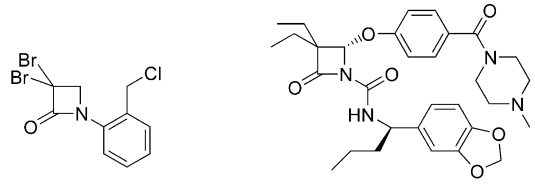
Scheme 2. Deprotection of compounds **3–4**.



6 (crude)

7 (X = Br) ; **8** (X = Cl) ;
9 (X = I) ; **10** (X = OH)

Scheme 3. Synthesis of compounds **7–10**.



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Wakselman *et al* [31]

Cvetovich *et al* [32]

Scheme 4. Reference compounds.

possible formation of isocyanate intermediates by chemical hydrolysis of activated (*N*-acyl or *N*-sulfonyl) carbamates; this has been discussed previously.[24]

We designed compounds **7–9** (see Table 1) as β-lactamic inhibitors of elastases based on our preliminary results[11] and the following considerations: (a) the C3 substituents, fitting the S1 pocket, are halogens[21] and *gem*-dihalogens[31] in the *N*-aryl-azetidin-2-ones developed by Wakselman et al.; the order of activity (Cl ~ F > Br) does not strictly reflect the electron-withdrawing effects of these substituents; (b) the C4 substituents of the Merck's inhibitors, such as L-694.458, act as leaving groups and do not strictly interact with the enzyme;[32] (c) The N1 substituents of the previous Merck's azetidinones, fitting the S′ pockets of elastase, are bulky and lipophilic urethane groups derived from substituted benzylamines[33] (Scheme 4). Accordingly, we selected as C3 and N1 substituents of the general structure **A** (Fig. 1) a series of halogen and arylalkyloxycarbonyl groups, respectively; the C4 substituent was suppressed, since the potential leaving group is now part of the N1 substituent.

Azetidinones **7–9** were evaluated for their inhibitory effect on porcine pancreatic elastase (PPE). The rates of enzyme-catalyzed hydrolysis of *N*-succinyl-Ala-Ala-Ala-*p*-nitroanilide (substrate) were measured in the presence of different concentrations of inhibitors. The variation

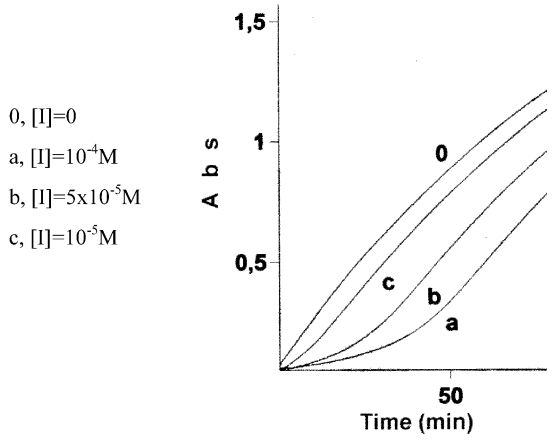


Figure 2. Inhibition of PPE.

of the absorbance at 410 nm was recorded as a function of time:[24] Figure 2 shows typical curves with the 'S' shape observed at the begining of the reaction (illustration with compound **7a**). Plots of V/V_i, corresponding to the ratios of initial rates of hydrolysis in the absence and the presence of inhibitors, versus the concentration of inhibitor gave a straight line which slope corresponds to $1/K_i$. The measured inhibition constants (K_i) are collected in Table 2.

All 3-bromoazetidinones **7** (Table 2, first column) exhibited quite similar activities with K_i values comprised between 2 and 22 μM; the best inhibitors corresponding to R^1 residues as benzyl (**7a**) or less flexible fluorenylmethyl (**7f**) and 2-indanyl (**7g**) groups. 3-Chloroazetidinones **8** (second column) appeared systematically about 5- to 10-fold less potent than the corresponding bromo derivatives. This result in opposite to the halogen effect reported by Wakselman et al.[31] stimulated our interest in the preparation and evaluation of some iodo compounds. Unfortunately, we found that 3-iodoazetidinones **9** (third column) are not better, but equally potent as the corresponding 3-bromoazetidinones **7**. The lipophilicity of the R^1 substituent appeared to exert a slightly positive effect since chloroazetidinone **8f** (R^1 = fluorenyl) was also equally potent as compounds **7b** and **7c**. All tested azetidinones behaved as transient inhibitors of PPE: complete enzyme activity was restored after about 3 h (see Experimental). Thus, the expected suicide mechanism of Figure 1 did not occur.

We have previously demonstrated, by ^{1}H NMR analysis, that the product of enzymic hydrolysis of **7a** is the *N*-(benzyloxycarbonyl)-β-aminoacid resulting from azetidinone ring opening.[11] Moreover, the enantioselectivity of this PPE-catalyzed reaction in favour of the (*R*)-enantiomer has been established by GC monitoring on a chiral phase.[11] Presently, compounds **7–9** were evaluated as racemic mixtures, and their selectivity of recognition was no more tested.

We have controlled that C3-halogen substituent is necessary for biological activity: related C3-unsubstituted **a–g**

Table 2. Inhibitory activity

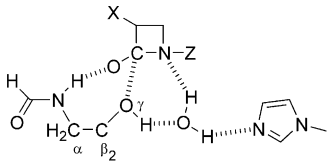
Entry	Compd	K_i (μM)	Compd	K_i (μM)	Compd	K_i (μM)
1	**7a**	2–5	**8a**	45–47	**9a**	6–8
2	**7b**	18–20	**8b**	159–161	**9b**	9–11
3	**7c**	20–22	**8c**	65–70		
4	**7d**	7–11				
5	**7e**	13–15				
6	**7f**	5–7	**8f**	19–21		
7	**7g**	5–10				

compounds are inactive or slightly active ($K_i > 10^3$ μM).[24] Synthetic intermediates **3** and **5** bearing (3*S*)-(alkoxycarbonyl)amino substituents were also tested against PPE and found to be inactive.[34]

Discussion

1-Alkoxycarbonyl-3-halogenoazetidin-2-ones constitute a class of serine protease inhibitors illustrated by their activity against porcine pancreatic elastase. This enzyme could be considered as a good model of human leukocyte elastase (HLE) in view of the great similarity of the respective active sites.[35] Compounds **7–9** transitorily block PPE with apparent inhibition constants in the micromolar range. Their mechanism most probably occurs via an acyl-enzyme intermediate which slowly deacylates.[11]

The C3 halogen substituent certainly increases the azetidinone chemical reactivity towards nucleophilic attack by Ser-195. This effect has been evaluated by theoretical methods.[36,37] The cleavage of the N1–C2 azetidinone bond is mimicked by a catalytic environment made of an imidazole as model of His-57, a water molecule as a transient vehicle of the proton, and the side chain of Ser-195 including the amide bond of the backbone which is involved in the stabilization of the oxyanion hole (Fig. 3). Such a model of concerted mechanism has been previously validated on class-A β-lactamases and enzymes of the trypsin family.[38] The ΔG values have been computed, at the ab initio level with a minimal basis set, by reference to the isolated partners.[24] The bromine electronic effect is expressed by the decrease of the energy barrier of about 3.2 kcal/mol. Inductive effects of bromine (Taft σ_I parameter = 0.44) and chlorine (Taft σ_I parameter = 0.46) are slightly different; however the biological activities of **7a** (X = Br) and **8a** (X = Cl) are significantly different (one order of magnitude), and in favour of the azetidinone bearing the less electronegative bromine substituent. This



X	Z	$\Delta G^{(a)}$
H	CO_2CH_2Ph	40.1
Br	CO_2CH_2Ph	36.9

(a) calculated energies (kcal/mol) at the transition states

Figure 3. Theoretical evaluation of nucleophilic attack in a model of elastase active site.

effect is not still further enhanced with the iodo compound **9a** (Taft σ_I parameter = 0.39). The experimental order of activity (Br ~ I > Cl ≫ H) could indeed reflect the best fit of the C3 substituent into the enzyme pocket S1, rather than the activating electronic effect only. Molecular volumes given by molar refractivity (MR) parameters are 13.9, 8.9 and 6.0 for I, Br and Cl, respectively.[39] In the seminal work of the Merck's group[40] concerning cephem derivatives as elastase inhibitors, the selected β-lactam substituent was OCH_3 (MR parameter = 7.9 and Taft σ_I parameter = 0.27).

By varying the nature of the R^1 group making part of the N1 alkyloxycarbonyl substituent, we could not improve the activity of the azetidinones **7**–**9**. The factors considered were: the length of the spacer connecting the aromatic residue to the carbamate function, the steric nature and substitution of the aromatic residue, and the flexibility of the N1 side chain. Our preliminary results[11] were confirmed: the suicide mechanism (irreversible inhibition) does not operate, compounds **7**–**9** behave as transient inhibitors (or slow substrates). We are currently examining the possibility to replace the alkyloxy residue (OR^1) with an alkylthioxy residue (SR^1) acting as a better potential leaving group.

Experimental

General

Reagents and solvents were purchased from Acros chimica, Aldrich or Fluka. Porcine pancreatic elastase (type 1) and *N*-succinyl-L-alanyl-L-alanyl-L-alanyl-*p*-nitroanilide were obtained from Sigma Chemical Co. Tetrahydrofuran was dried with sodium/benzophenone, then distilled. Column chromatographies were carried out with silica gel 60 (70–230 mesh ASTM) supplied by Merck. Preparative chromatographies were performed on silica gel plates $60F_{254}$ (Merck) of 2 mm thichness previously neutralised with *N*-ethyl morpholine. The IR spectra were recorded with a Perkin-Elmer 1710 instrument, only the most significant absorption bands being reported. The mass spectra were obtained with a Finnigan MAT TSQ-70 instrument. The microanalyses were performed at the Christopher Ingold Laboratories of the University College, London (Dr. A. Stones). The melting points were determined with an Electrothermal microscope and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 300 (at 300 MHz for proton and 75 MHz for carbon) or Brucker AM-500 spectrometers (at 500 MHz for proton and 125 MHz for carbon); the chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (internal standard). The high resolution mass spectra were obtained at the University of Mons, Belgium (Prof. R. Flammang). The optical rotations (±0.1°) were determined with a Perkin-Elmer 241 MC polarimeter.

Assay of PPE (porcine pancreatic elastase)

To 2 mL of the solution of substrate (solution of *N*-succinyl-L-alanyl-L-alanyl-L-alanyl-*p*-nitroanilide [2.7 mg in 200 μL of *N*-methyl pyrrolidone (NMP) diluted with Tris buffer (20 mL at 100 mM, pH 7.5 solution)] were added 20 μL of the solution of the tested compound (10^{-2}–10^{-4} M in NMP) and 67 μL of the solution of elastase [6×10^{-6} M in acetate buffer (50 mM, pH 5)]. The appearance of the substrate hydrolysis product (*p*-nitroaniline) was measured (with a Cary 210) at 410 nm as a function of time. Plots of V/V_i versus [I] (ratios of initial rates of hydrolysis in the absence and in the presence of inhibitors) gave the inhibition constants indicated in the Table 2. All experiments were performed two or three times.

The reversibility of the inhibition was controlled by the incubation/dilution method. The incubation solution consisted of 5 μL of inhibitor solution (10^{-3} M in DMSO), 34 μL of elastase solution (2.5×10^{-4} M in acetate buffer, 50 mM, pH 5) and 161 μL of Tris buffer (100 mM, pH 7.5). At various times (0, 5, 10, 15, 20, 30 min), 10 μL of the incubation solution were dissolved in 2 mL of the substrate solution (10^{-4} M in Tris buffer), and the enzyme activity was measured as before. No decrease of activity was recorded as a function of incubation time.

General procedure for the preparation of chloroformates (2)

Pyridine (1.01 mL, 12.5 mmol) was added dropwise (over 2 h) to an ice-cold solution of triphosgene (1.19 g, 4 mmol) in dry toluene (10 mL). After 1 h stirring at 0 °C, alcohol (10 mmol) was added dropwise (over 30 min). The mixture was allowed to reach room temperature and stirred overnight, then filtered. The precipitate was rinsed twice with toluene (2×20 mL). Concentration of the filtrates under vacuum gave crude **2** (75–85% yield) which was directly used in the acylation reaction of azetidinone **1**.

Chloroformates **2a** and **2f** are commercially available. Chloroformates **2b**, **2c**, and **2g** have been described elsewhere.[24]

***p*-Methoxyphenethyl chloroformate (2d).** ^1H NMR ($CDCl_3$, 300 MHz) δ 3.06 (t, J = 6.9 Hz, 2H, CH_2Ar), 3.89 (s, 3H, OCH_3), 4.55 (t, J = 6.9 Hz, 2H, OCH_2), 6.95 (d, J = 8.8 Hz, 2H, Ar), 7.22 (d, J = 8.8 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.3 (CH_2), 54.8 (OCH_3), 72.2 (OCH_2), 113.7 (CH_{Ar}), 129.5 (CH_{Ar}), 140.6 (C_{Ar}), 145.8 (C_{Ar}), 150.0 (CO).

***p*-Fluorophenethyl chloroformate (2e).** ^1H NMR ($CDCl_3$, 300 MHz) δ 3.01 (t, J = 6.7 Hz, 2H, CH_2Ar), 4.48 (t, J = 6.7 Hz, 2H, OCH_2), 6.99–7.05 (m, 2H, Ar), 7.16–7.21 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.1 (CH_2), 72.2 (OCH_2), 115.8 (CH_{Ar}), 130.5 (CH_{Ar}), 132.1 (C_{Ar}), 150.9 (CO), 163.8 (CF).

General procedure for the preparation of 1-alkoxycarbonyl-(3*S*)-(*t*-butoxycarbonyl) aminoazetidin-2-ones (3) and 1-alkoxycarbonyl-(3*S*)-(*t*-butoxycarbonyl) (alkoxycarbonyl) aminoazetidin-2-ones (4)

To a solution of azetidinone **1** (1 equiv) in dry THF (1 mmol/10 mL), was added, at −78 °C under argon

atmosphere, a solution of LiHMDS (1 equiv) in THF (1 mmol/5 mL), dropwise over 15 min. After a further 15 min of stirring at −78 °C, a solution of crude chloroformate **2** (1 equiv) in THF (1 mmol/mL) was added. The mixture was stirred for 1 h at −78 °C and 1 h at room temperature, then poured into water. Extraction with CH_2Cl_2 (three times), washing with brine, drying over $MgSO_4$ and concentration under vacuum gave crude **3** and **4**. Column chromatography on silica gel (elution with CH_2Cl_2–EtOAc, 95:5; then 90:10) furnished **4** (minor product, eluting first) and **3** (major product).

1-Benzyloxycarbonyl-3*S*-(*t*-butoxycarbonyl) aminoazetidin-2-one (3a). Yield from 1 mmol of **1**: 247 mg (77%) as a white solid; mp 147.5–148.5 °C; $[\alpha]_D^{20}$ −1.9 (*c* 0.1, CH_2Cl_2); IR (KBr) 3366, 2977, 1816, 1713 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 1.41 (s, 9H, *t*Bu), 3.71 (dd, $J=6.4$ Hz and 3.7 Hz, 1H, H-4), 3.91 (dd, $J=6.4$ Hz and 5.8 Hz, 1H, H-4′), 4.85 (ddd, $J=7.9$ Hz, 5.8 Hz and 3.7 Hz, 1H, H-3), 5.25 (s, 2H, OCH_2), 6.88 (d, $J=7.9$ Hz, 1H, NH), 7.25–7.50 (m, 5H, Ph); ^{13}C NMR (acetone-d_6, 75 MHz) δ 28.4 (CH_3), 46.8 (C-4), 58.1 (C-3), 68.1 (OCH_2), 80.2 (C–O), 128.9, 129.1 and 129.3 (CH_{Ar}), 136.7 (C_{Ar}), 149.9 (C=O carbamate), 155.8 (C=O Boc), 165.8 (C-2); MS (FAB$^+$) *m*/*z* 321 (MH^+). Anal. calcd for $C_{16}H_{20}N_2O_5$. H_2O: C, 56.80; H, 5.92; N, 8.28. Found: C, 56.94; H, 5.96; N, 7.96%.

1-Phenethyloxycarbonyl-3*S*-(*t*-butoxycarbonyl) aminoazetidin-2-one (3b). Yield from 1 mmol of **1**: 176 mg (53%) as a colorless oil; $[\alpha]_D^{20}$ −5.6 (*c* 5.35, CH_3OH); IR (film) 3369, 2977, 1819, 1712 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 1.41 (s, 9H, *t*Bu), 2.90 (t, $J=7.0$ Hz, 2H, CH_2Ph), 3.67 (dd, $J=6.3$ and 3.8 Hz, 1H, H-4), 3.86 (dd, $J=6.6$ and 6.3, 1H, H-4′), 4.23 (t, $J=7.0$ Hz, OCH_2), 4.84 (ddd, $J=8.0$, 6.6 and 3.8 Hz, H-3), 6.85 (d, $J=8.0$ Hz, 1H, NH), 7.20–7.36 (m, 5H, Ph); ^{13}C NMR (acetone-d_6, 75 MHz) δ 28.4 (CH_3), 35.9 (CH_2Ph), 47.0 (C-4), 58.4 (C-3), 67.5 (OCH_2), 80.5 (C–O), 127.5, 129.4 and 129.9 (CH_{Ar}), 130.1 (C_{Ar}), 150.0 (C=O carbamate), 155.8 (C=O Boc), 165.8 (C-2); MS (CI) *m*/*z* 333 (M−1). Anal. calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.37. Found: C, 61.31; H, 6.75; N, 8.19%.

1-(3′-Phenylpropyloxycarbonyl)-3*S*-(*t*-butoxycarbonyl) aminoazetidin-2-one (3c). Yield from 1 mmol of **1**: 118 mg (34%) as a colourless oil; $[\alpha]_D^{20}$ +6.0 (*c* 5.4, $CHCl_3$); IR (film) 3055, 2984, 1820, 1720 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 1.40 (s, 9H, *t*Bu), 2.07 (quint, $J=6.7$ Hz, 2H, $CH_2CH_2CH_2$), 2.71 (t, $J=6.7$ Hz, 2H, CH_2Ph), 3.69 (dd, $J=6.9$ and 3.9 Hz, 1H, H-4), 4.00 (dd, $J=6.9$ and 4.0 Hz, 1H, H-4′), 4.18 (t, $J=6.7$ Hz, 2H, OCH_2), 4.83 (ddd, $J=8.2$, 4.0 and 3.9 Hz, 1H, H-3), 6.84 (d, $J=8.2$ Hz, 1H, NH), 7.15–7.36 (m, 5H, Ph); ^{13}C NMR (acetone-d_6, 75 MHz) δ 28.4 (CH_3), 31.8 (CH_2), 32.6 (CH_2Ph), 46.9 (C-4), 55.0 (C-3), 66.1 (OCH_2), 80.7 (C–O), 126.7, 126.9 and 129.4 (CH_{Ar}), 142.3 (C_{Ar}), 150.2 (C=O carbamate), 156.2 (C=O Boc), 165.9 (C-2); MS (CI) *m*/*z* 347 (M−1). Anal. calcd for $C_{18}H_{24}N_2O_5$: C, 62.07; H, 6.90; N, 8.04. Found: C, 62.60; H, 7.21; N, 7.69%.

1-(4′-Methoxy-phenethyloxycarbonyl)-3*S*-(*t*-butoxycarbonyl) aminoazetidin-2-one (3d). Yield from 1 mmol of **1**: 254 mg (70%) as a colorless oil; IR (film) 3436, 2985, 1820, 1720 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 1.40 (s, 9H, *t*Bu), 2.87 (t, $J=6.8$ Hz, 2H, CH_2Ar), 3.66 (dd, $J=6.2$ and 3.8 Hz, 1H, H-4), 3.76 (s, 3H, OCH_3), 3.83 (dd, $J=6.8$ and 6.2 Hz, 1H, H-4′), 4.30 (t, $J=6.8$ Hz, 2H, OCH_2), 4.83 (ddd, $J=8.1$ Hz, 6.8 Hz and 3.8 Hz, 1H, H-3), 6.87 (d, $J=8.1$ Hz, 1H, NH), 6.95 (d, $J=8.8$ Hz, 2H, Ar), 7.22 (d, $J=8.8$ Hz, 2H, Ar); ^{13}C NMR (acetone-d_6, 75 MHz) δ 28.7 (CH_3), 35.3 (CH_2Ar), 46.8 (C-4), 55.6 (OCH_3), 58.3 (C-3), 67.8 (OCH_2), 80.1 (C–O), 114.8 (CH_{Ar}), 130.9 (CH_{Ar}), 131.2 (C_{Ar}), 150.0 (C=O carbamate), 155.6 (C=O Boc), 159.6 (C_{Ar}), 165.7 (C-2); MS (CI) *m*/*z* 363 (M-1). Anal. calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64. Found:C, 59.18; H, 6.76%.

1-(4′-Fluoro-phenethyloxycarbonyl)-3*S*-(*t*-butoxycarbonyl) aminoazetidin-2-one (3e). Yield from 1 mmol of **1**: 131 mg (37%) as a white solid; mp 121.5–122.5 °C; $[\alpha]_D^{20}$ +8.1 (*c* 1.2, $CHCl_3$); IR (KBr) 3443, 2984, 1821, 1721 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 1.41 (s, 9H, *t*Bu), 2.98 (t, $J=6.6$ Hz, 2H, CH_2Ar), 3.66 (dd, $J=6.3$ and 3.8 Hz, 1H, H-4), 3.85 (t, $J=6.3$ and 6.3 Hz, 1H, H-4′), 4.34 (t, $J=6.6$ Hz, 2H, OCH_2), 4.83 (ddd, $J=8.4$ Hz, 6.3 and 3.8 Hz, 1H, H-3), 6.85 (d, $J=8.4$ Hz, 1H, NH), 7.05 (t, $J=8.5$ Hz, 2H, Ar), 7.35 (dd, $J=8.5$ and 5.1 Hz, 2H, Ar); ^{13}C NMR (acetone-d_6, 75 MHz) δ 28.8 (CH_3), 34.9 (CH_2Ar), 46.9 (C-4), 58.3 (C-3), 67.5 (OCH_2), 80.2 (C–O), 116.0 (CH_{Ar}), 131.8 (CH_{Ar}), 135.0 (C_{Ar}), 150.0 (C=O carbamate), 155.8 (C=O Boc), 160.3 (C–F), 165.8 (C-2); MS (CI) *m*/*z* 351 ($C_{17}H_{21}N_2O_5F$, M−1), 123, 109, 96.

1-(9′-Fluorenylmethoxycarbonyl)-3*S*-(*t*-butoxycarbonyl) aminoazetidin-2-one (3f). Yield from 1 mmol of **1**: 226 mg (55%) as a white solid; mp 129.5–130.5 °C; $[\alpha]_D^{20}$ +12.3 (*c* 2.8, $CHCl_3$); IR (KBr) 3374, 2977, 1817, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.41 (s, 9H, *t*Bu), 3.76 (dd, $J=6.6$ Hz and 3.7 Hz, 1H, H-4), 3.88 (dd, $J=6.6$ and 6.6 Hz, 1H, H-4′), 4.30 (dd, $J=13.1$ and 7.4 Hz, 1H, OCH_A), 4.32 (dd, $J=13.1$ and 7.4 Hz, 1H, OCH_B), 4.43 (t, $J=7.4$ Hz, CH fluorenyl), 4.78 (ddd, $J=8.0$, 6.6 and 3.7 Hz, 1H, H-3), 5.32 (d, $J=8.0$ Hz, 1H, NH), 7.26–7.44 (m, 4H, Ar), 7.68–7.80 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.2 (CH_3), 46.5 (C-4), 46.7 (CH fluorenyl), 57.5 (C-3), 68.7 (OCH_2), 80.5 (C–O), 120.0, 125.4, 127.2 and 127.9 (CH_{Ar}), 141.3 (C_{Ar}), 143.2 (C_{Ar}), 149.2 (C=O carbamate), 154.6 (C=O Boc), 164.6 (C-2). Anal. calcd for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.85. Found: C, 67.95; H, 6.16; N, 6.53%.

1-(2′-Indanyloxycarbonyl)-3*S*-(*t*-butoxycarbonyl) aminoazetidin-2-one (3g). Yield from 1 mmol of **1**: 115 mg (33%) as a white solid; mp 114.5–115.5 °C; IR (KBr) 3055, 2986, 1819, 1718 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 1.45 (s, 9H, *t*Bu), 3.15 (dd, $J=17.2$ and 2.3 Hz, 2H, $ArCH_A$), 3.46 (dd, $J=17.2$ and 6.4 Hz, 2H, $ArCH_B$), 3.74 (dd, $J=6.7$ and 3.0 Hz, 1H, H-4), 4.15 (dd, $J=13.8$ and 6.7 Hz, 1H, H-4′), 4.89 (ddd, $J=13.8$, 8.2 and 3.0 Hz, 1H, H-3), 5.62 (m, 1H, CH indanyl), 6.88 (d, $J=8.2$ Hz, NH), 7.20–7.40 (m, 4H, Ar); ^{13}C

NMR (acetone-d_6, 75 MHz) δ 28.5 (CH_3), 40.1 and 40.2 (CH_2Ar), 40.3 (C-4), 46.9 (C-3), 75.8 (CH indanyl), 78.4 (C–O), 125.4 and 127.7 (CH_{Ar}), 141.1 (C_{Ar}), 141.8 (C=O Boc), 149.9 (C=O carbamate), 165.7 (C-2); MS (CI) m/z 347 ($C_{18}H_{22}N_2O_5$, M + 1), 117, 75.

1-Benzyloxycarbonyl-3*S*-(*t*-butoxycarbonyl) (benzyloxycarbonyl) aminoazetidin-2-one (4a). Yield from 1 mmol of **1**: 53 mg (12%) as a white solid; mp 100–101 °C; IR (KBr) 3040, 2980, 1817, 1749 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9H, *t*Bu), 3.72 (dd, $J = 6.6$ Hz and 4.1 Hz, 1H, H-4), 3.91 (dd, $J = 6.6$ Hz and 6.6 Hz, 1H, H-4′), 5.23 (s, 2H, CH_2O), 5.24 (s, 2H, CH_2O), 5.59 (dd, $J = 6.6$ and 4.1 Hz, 1H, H-3), 7.30–7.45 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.6 (CH_3), 45.1 (C-4), 59.4 (C-3), 68.1 (OCH_2), 69.5 (OCH_2), 85.2 (O–C), 128.3, 128.4, 128.5, 128.6, 128.7 and 128.9 (CH_{Ar}), 134.4 and 134.8 (C_{Ar}), 149.1 and 150.0 (C=O carbamate), 152.6 (C=O Boc), 162.9 (C-2); MS (FAB^-) m/z 453 (M−1).

1-Phenethyloxycarbonyl-3*S*-(*t*-butoxycarbonyl) (phenethyloxycarbonyl) aminoazetidin-2-one (4b). Yield from 1 mmol of **1**: 70 mg (15%) as a colorless oil; IR (film) 3062, 2977, 1824, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9H, *t*Bu), 3.02 (t, $J = 7.3$ Hz, 2H, CH_2Ph), 3.03 (t, $J = 7.2$ Hz, 2H, CH_2Ph), 3.68 (dd, $J = 6.5$ and 4.1 Hz, 1H, H-4), 3.81 (dd, $J = 6.6$ and 6.5 Hz, 1H, H-4′), 4.43 (t, $J = 7.3$ Hz, 2H, OCH_2), 4.45 (t, $J = 7.2$ Hz, 2H, OCH_2), 5.55 (dd, $J = 6.6$ Hz and 4.1 Hz, 1H, H-3), 7.17–7.35 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.7 (CH_3), 34.8 and 35.1 (CH_2Ph), 45.1 (C-4), 59.4 (C-3), 67.3 and 68.2 (OCH_2), 85.3 (O–C), 126.7, 126.8, 128.5, 128.6, 128.9 and 129.1 (CH_{Ar}), 136.9 and 137.1 (C_{Ar}), 149.3 and 150.0 (C=O carbamate), 152.8 (C=O Boc), 163.1 (C-2).

1-(3′-Phenylpropyloxycarbonyl)-3*S*-(*t*-butoxycarbonyl) (3′-phenylpropyloxycarbonyl) aminoazetidin-2-one (4c). Yield from 1 mmol of **1**: 102 mg (20%) as a white solid; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.51 (s, 9H, *t*Bu), 2.02 and 2.03 (quint, $J = 7.0$ Hz, 2H, $CH_2CH_2CH_2$), 2.72 (t, $J = 7.0$ Hz, 4H, 2×CH_2Ph), 3.73 (dd, $J_= 6.5$ Hz and 4.1°Hz, 1H, H-4), 3.84 (dd, $J = 6.5$ Hz and 6.5 Hz, 1H, H-4′), 4.25 and 4.26 (t, $J = 7.0$ Hz, 2H, OCH_2), 5.55 (dd, $J = 6.5$ and 4.1 Hz, 1H, H-3), 7.15–7.37 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.0 (CH_3), 30.1 and 30.2 ($CH_2CH_2CH_2$), 32.1 and 32.2 (CH_2Ar), 45.3 (C-4), 59.7 (C-3), 66.3 and 67.6 (OCH_2), 85.3 (O–C), 126.3, 128.2, 128.3, 128.6, 128.8 and 128.9 (CH_{Ar}), 140.9 and 141.0 (C_{Ar}), 149.7 and 150.3 (C=O carbamate), 153.1 (C=O Boc), 163.2 (C-2).

1-(4′-Methoxy-phenethyloxycarbonyl)-3*S*-(*t*-butoxycarbonyl) (4′-methoxy-phenethyloxycarbonyl) amino azetidin-2-one (4d). Yield from 1 mmol of **1**: 59 mg (11%) as a white solid; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 9H, *t*Bu), 2.84 (t, $J = 7.1$ Hz, 2H, CH_2Ar), 2.92 (t, $J_= 7.4$ Hz, 2H, CH_2Ar), 3.69 (dd, $J_= 6.2$ and 4.0 Hz, 1H, H-4), 3.76 (s, 6H, 2×OCH_3), 3.87 (dd, $J = 6.8$ and 6.2 Hz, 1H, H-4′), 4.24 (t, $J_= 7.1$ Hz, 2H, OCH_2), 4.35 (t, $J = 7.4$ Hz, 2H, OCH_2), 5.66 (dd, $J = 6.8$ and 4.0 Hz, 1H, H-3), 6.82–6.92 (m, 4H, Ar), 7.17–7.30 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.8 (CH_3), 34.2 and 34.5 (CH_2Ar), 45.3 (C-4), 55.3 and 55.4 (OCH_3), 59.7 (C-3), 67.6 and 68.6 (OCH_2), 85.3 (O–C), 114.2, 114.3, 129.3 and 130.0 (CH_{Ar}), 149.5 and 150.2 (C_{Ar}), 152.9 and 155.2 (C=O carbamate), 158.6 (C=O Boc), 158.7 and 158.8 (C_{Ar}), 163.1 (C-2).

1-(4′-Fluoro-phenethyloxycarbonyl)-3*S*-(*t*-butoxycarbonyl) (4′-fluoro-phenethyloxycarbonyl) aminoazeti din-2-one (4e). Yield from 1 mmol of **1**: 16 mg (3%) as a white solid; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 9H, *t*Bu), 2.98 and 3.00 (t, $J = 7.0$ Hz, 2H, CH_2Ar), 3.68 (dd, $J = 6.6$ and 4.1 Hz, 1H, H-4), 3.82 (dd, $J = 6.6$ and 6.6 Hz, 1H, H-4′), 4.36 and 4.41 (t, $J = 7.0$ Hz, 2H, OCH_2), 5.55 (dd, $J = 6.6$ Hz and 4.1 Hz, 1H, H-3), 6.93–7.07 (m, 4H, Ar), 7.17–7.31 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.9 (CH_3), 34.3 and 34.5 (CH_2Ar), 45.1 (C-4), 59.8 (C-3), 68.4 and 68.5 (OCH_2), 85.5 (O–C), 115.4, 115.8, 130.5 and 130.6 (CH_{Ar}), 147.1 (C_{Ar}), 153.2 (C=O carbamate), 158.4 (C=O Boc, C_{Ar}), 163.1 (C-2).

1-(9′-Fluorenylmethoxycarbonyl)-3*S*-(*t*-butoxycarbonyl) (9′-fluorenylmethoxycarbonyl) aminoazetidin-2-one (4f). Yield from 1 mmol of **1**: 75 mg (12%) as a white solid; IR (KBr) 3073, 2977, 1817, 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9H, *t*Bu), 3.72 (dd, $J = 6.6$ and 4.2 Hz, 1H, H-4), 3.88 (dd, $J = 6.6$ and 6.6 Hz, 1H, H-4′), 4.30 (t, $J = 6.6$ Hz, 2H, 2×CH fluorenyl), 4.52 (m, 4H, 2×OCH_2), 5.56 (dd, $J = 6.6$ and 4.2 Hz, 1H, H-3), 7.29–7.45 (m, 8H, Ar), 7.60–7.78 (m, 8H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.7 (CH_3), 45.1 (C-4), 46.5 (CH fluorenyl), 59.6 (C-3), 68.7 and 69.7 (OCH_2), 85.5 (O–C), 120.0, 120.1, 125.1, 125.4, 127.2, 127.3 and 128.0 (CH_{Ar}), 141.3 and 143.2 (C_{Ar}), 149.2 and 150.0 (C=O carbamate), 153.1 (C=O Boc), 162.9 (C-2).

1-(2′-Indanyloxycarbonyl)-3*S*-(*t*-butoxycarbonyl) (2′-indanyloxycarbonyl) aminoazetidin-2-one (4g). Yield from 1 mmol of **1**: 109 mg (21%) as a white solid; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 9H, *t*Bu), 3.05 and 3.15 (dd, $J = 6.8$ and 2.6 Hz, 2H, $ArCH_A$), 3.31 and 3.39 (dd, $J = 6.8$ and 6.8 Hz, 2H, $ArCH_B$), 3.65 (dd, $J = 6.6$ and 4.0 Hz, 1H, H-4), 3.78 (dd, $J = 6.6$ and 6.6 Hz, 1H, H-4′), 5.50 (dd, $J = 6.6$ and 4.0 Hz, 1H, H-3), 5.56 (m, 2H, 2×CH indanyl), 7.12–7.27 (m, 8H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.6 (CH_3), 39.3 (CH_2Ar), 45.2 (C-4), 59.4 (C-3), 79.3 (CH indanyl), 84.9 (O–C), 124.6 and 126.8 (CH_{Ar}), 139.8 (C_{Ar}), 149.0 and 150.5 (C=O carbamate), 152.4 (C=O Boc), 163.0 (C-2).

General procedure of Boc deprotection with CAN (5)

A solution of **4** (0.2 mmol) and CAN (0.04 mmol) in CH_3CN (5 mL) was refluxed for 10 min, then poured into water and extracted twice with CH_2Cl_2. The organic layers were washed with aqueous NH_4Cl, dried over $MgSO_4$, concentrated and purified by column-chromatography on silica gel (CH_2Cl_2–EtOAC, 95:5).

1-Benzyloxycarbonyl-3*S*-(benzyloxycarbonyl) aminoazetidin-2-one (5a). Yield 57% (white solid); mp

108–109 °C; IR (KBr) 3380, 3031, 2971, 1808, 1711 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 3.72 (dd, $J=6.6$ and 6.6 Hz, 1H, H-4), 3.85 (dd, $J=6.6$ and 4.0 Hz, 1H, H-4′), 4.95 (ddd, $J=8.3$, 6.6 and 4.0 Hz, 1H, H-3), 5.10 (s, 2H, OCH_2), 5.23 (s, 2H, OCH_2), 7.20 (d, $J=8.3$ Hz, 1H, NH), 7.30–7.50 (m, 10H, Ph); ^{13}C NMR (acetone–d_6, 75 MHz) δ 46.9 (C-4), 58.5 (C-3), 67.4 and 68.2 (OCH_2), 129.0, 129.1, 129.2, 129.3, 129.4 and 129.5 (CH_{Ar}), 136.8 and 137.8 (C_{Ar}), 149.0 and 149.9 (C=O carbamate), 165.4 (C-2); MS (CI) m/z 353 (M−1).

1-Phenethyloxycarbonyl-3*S*-(phenethyloxycarbonyl) aminoazetidin-2-one (5b). Yield 48% (pale yellow oil); IR (film) 3363, 3062, 2965, 1822, 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.94 (t, $J=7.0$ Hz, 2H, CH_2Ph), 3.03 (t, $J=7.2$ Hz, 2H, CH_2Ph), 3.70 (dd, $J=6.6$ and 3.7 Hz, 1H, H-4), 3.87 (dd, $J=6.6$ and 6.6 Hz, 1H, H-4′), 4.33 (t, $J=7.0$ Hz, 2H, OCH_2), 4.43 (t, $J=7.2$ Hz, 2H, OCH_2), 4.73 (ddd, $J=8.0$, 6.6 and 3.7 Hz, 1H, H-3), 5.32 (d, $J=8.0$ Hz, 1H, NH), 7.15–7.40 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.0 and 35.2 (CH_2Ph), 46.5 (C-4), 57.2 (C-3), 66.2 and 67.3 (OCH_2), 126.6, 126.8, 128.5, 128.6, 128.9 and 129.1 (CH_{Ar}), 137.0 and 137.5 (C_{Ar}), 149.1 and 155.4 (C=O carbamate), 164.0 (C-2); MS (CI) m/z 381 (M−1).

1-(9′-Fluorenylmethoxycarbonyl)-3*S*-(9′-fluorenylmethoxycarbonyl) aminoazetidin-2-one (5f). Yield: 63% (white solid); mp 189–190 °C; IR (KBr) 3342, 3056, 2929, 1817, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.73 (dd, $J=6.6$ and 3.9 Hz, 1H, H-4), 3.94 (dd, $J=6.6$ Hz and 6.6 Hz, 1H, H-4′), 4.23 (t, $J=6.6$ Hz, 2H, 2×CH fluorenyl), 4.38 (m, 4H, 2×OCH_2), 4.79 (ddd, $J=7.6$, 6.6 and 3.9 Hz, 1H, H-3), 7.25–7.48 (m, 8H, Ar), 7.68–7.80 (m, 8H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.7 (C-4), 47.4 (CH fluorenyl), 57.5 (C-3), 67.8 and 69.1 (OCH_2), 120.0, 120.3, 125.1, 125.5, 127.3, 127.4, 128.1 and 128.2 (CH_{Ar}), 141.4 and 143.3 (C_{Ar}), 149.4 and 155.5 (C=O carbamate), 163.7 (C-2).

General procedure for the preparation of 1-alkoxycarbonyl-3-bromoazetidin-2-ones (7)

Precursor **3** (1 equiv) was dissolved in an ice-cold solution of TFA (10%) in CH_2Cl_2 (1 mL/0.1 mmol). The solution was stirred for 3–4 h at 20 °C, then concentrated under vacuum. The residue was washed twice with cold ether and dried under vacuum to furnish quantitatively crude amine **6** as the trifluoroacetate salt. To this amine was added 2.5 N H_2SO_4 (1 mL/0.1 mmol) at 10 °C, KBr (5 equiv), ethanol (0.15 mL/0.1 mmol), and at least, an ice-cold solution of $NaNO_2$ (1.5 equiv) in water (0.25 mL/0.1 mmol) (dropwise addition). The mixture was stirred for 3 h 30 min at 6 °C, then extracted three times with $CHCl_3$. The organic phases were washed with cold brine, dried over $MgSO_4$, and concentrated under vacuum. Crude **7** was purified by preparative TLC on silica gel plates neutralised with 1% *N*-ethylmorpholine in CH_2Cl_2.

1-Benzyloxycarbonyl-3-bromoazetidin-2-one (7a). Yield from 0.71 mmol of **3a**: 142 mg (71%) as a pale yellow solid; HRMS (EI) calcd for $C_{11}H_{10}{}^{79}BrNO_3$: 282.9844. Found: 282.9841; other characterizations: see ref 11.

1-Phenethyloxycarbonyl-3-bromoazetidin-2-one (7b). Yield from 0.15 mmol of **3b**: 31 mg (69%) as a colorless oil; IR (film) 3055, 2986, 1824, 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.03 (t, $J=7.3$ Hz, 2H, CH_2Ph), 3.73 (dd, $J=7.8$ and 2.9 Hz, 1H, H-4), 4.14 (dd, $J=7.8$ and 5.8 Hz, 1H, H-4′), 4.44 (t, $J=7.3$ Hz, 2H, OCH_2), 4.82 (dd, $J=5.8$ and 2.9 Hz, 1H, H-3), 7.25–7.31 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.9 (CH_2Ph), 40.3 (C-3), 48.8 (C-4), 67.6 (OCH_2), 126.8, 128.5 and 129.0 (CH_{Ar}), 136.7 (C_{Ar}), 148.6 (C=O carbamate), 160.2 (C-2); HRMS (CI) calcd for $C_{12}H_{11}{}^{79}BrNO_3$ (M−1): 295.9922. Found: 295.9911.

1-(3′-Phenylpropyloxycarbonyl)-3-bromoazetidin-2-one (7c). Yield from 0.17 mmol of **3c**: 21 mg (40%) as a yellow oil; IR (film) 3055, 2986, 1826, 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.07 (quint, $J=7.6$ Hz, 2H, $CH_2CH_2CH_2$), 2.74 (t, $J=7.6$ Hz, 2H, CH_2Ph), 3.73 (dd, $J=7.8$ and 2.6 Hz, 1H, H-4), 4.14 (dd, $J=7.8$ and 5.8 Hz, 1H, H-4′), 4.28 (t, $J=7.6$ Hz, 2H, OCH_2), 4.82 (dd, $J=5.8$ and 2.6 Hz, 1H, H-3), 7.20–7.30 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.6 (CH_2), 31.8 (CH_2Ph), 40.3 (C-3), 48.7 (C-4), 66.5 (OCH_2), 126.0, 128.3 and 128.4 (CH_{Ar}), 140.6 (C_{Ar}), 148.7 (C=O carbamate), 160.2 (C-2); HRMS (CI) calcd for $C_{13}H_{15}{}^{81}BrNO_3$ (M+1): 314.0214. Found: 314.0207.

1-(4′-Methoxy-phenethyloxycarbonyl)-3-bromoazetidin-2-one (7d). Yield from 0.16 mmol of **3d**: 26 mg (47%) as a yellow oil; IR (film) 3055, 2987, 1823, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.96 (t, $J=7.3$ Hz, 2H, CH_2Ar), 3.73 (dd, $J=7.8$ and 2.9 Hz, 1H, H-4), 3.80 (s, 3H, OCH_3), 4.15 (dd, $J=7.8$ and 5.8 Hz, 1H, H-4′), 4.40 (t, $J=7.3$ Hz, 2H, OCH_2), 4.83 (dd, $J=5.8$ and 2.9 Hz, 1H, H-3), 6.86 (d, $J=8.7$ Hz, 2H, Ar), 7.29 (d, $J=8.7$ Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.0 (CH_2Ar), 40.3 (C-3), 48.8 (C-4), 55.1 (OCH_3), 67.8 (OCH_2), 113.9 (CH_{Ar}), 128.7 (C_{Ar}), 130.0 (CH_{Ar}), 148.7 (C=O carbamate), 158.4 (C_{Ar}), 160.2 (C-2); MS (CI) m/z 329 and 327 ($C_{13}H_{14}BrNO_4$, M), 135, 119, 91.

1-(4′-Fluoro-phenethyloxycarbonyl)-3-bromoazetidin-2-one (7e). Yield from 0.08 mmol of **3e**: 12 mg (39%) as a colorless oil; IR (film) 3055, 2987, 1822, 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.00 (t, $J=7.1$ Hz, 2H, CH_2Ar), 3.73 (dd, $J=7.7$ and 2.9 Hz, 1H, H-4), 4.15 (dd, $J=7.7$ and 5.8 Hz, 1H, H-4′), 4.41 (t, $J=7.1$ Hz, 2H, OCH_2), 4.83 (dd, $J=5.8$ and 2.9 Hz, 1H, H-3), 7.00 (t, $J=8.7$, 2H, Ar), 7.22 (dd, $J=8.7$ Hz and 5.3 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.1 (CH_2Ar), 40.3 (C-3), 48.7 (C-4), 67.5 (OCH_2), 115.3 (CH_{Ar}), 128.7 (C_{Ar}), 130.6 (CH_{Ar}), C=O carbamate and C–F not visible, 162.7 (C-2); MS (CI) m/z 316 and 318 ($C_{12}H_{11}BrFNO_3$, M+1), 123, 81.

1-(9′-Fluorenylmethoxycarbonyl)-3-bromoazetidin-2-one (7f). Yield from 0.3 mmol of **3f**: 41 mg (39%) as a yellow oil; IR (film) 3056, 2919, 1817, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.79 (dd, $J=7.8$ and 2.9 Hz, 1H, H-4), 4.21 (dd, $J=7.8$ and 5.8 Hz, 1H, H-4′), 4.30 (t, $J=7.3$ Hz, 1H, CH fluorenyl), 4.46 (dd, $J=10.8$ and 7.3 Hz, 1H, OCH_A), 4.50 (dd, $J=10.8$ and 7.3 Hz, 1H, OCH_B), 4.89 (dd, $J=5.8$ and 2.9 Hz, 1H, H-3), 7.33–7.43

(m, 4H, Ar), 7.71–7.78 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 40.3 (C-3), 46.4 (CH fluorenyl), 48.7 (C-4), 69.1 (OCH_2), 120.0, 125.2, 127.2 and 127.9 (CH_{Ar}), 141.2 and 142.9 (C_{Ar}), 148.7 (C=O carbamate), 160.2 (C-2); HRMS (EI) calcd for $C_{18}H_{14}{}^{79}BrNO_3$: 371.0157. Found: 371.0147.

1-(2′-Indanyloxycarbonyl)-3-bromoazetidin-2-one (7g). Yield from 0.33 mmol of **3g**: 51 mg (50%) as a yellow oil; IR (film) 3055, 2987, 1824, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.15 (dd, $J_=$17.0 Hz and 3.6 Hz, 1H, $ArCH_A$), 3.16 (dd, $J=17.0$ and 3.6 Hz, 1H, $ArCH_{A'}$), 3.39 (dd, $J=17.0$ and 6.6 Hz, 2H, $ArCH_B$ and $ArCH_{B'}$), 3.73 (dd, $J=7.7$ and 2.6 Hz, 1H, H-4), 4.14 (dd, $J=7.7$ and 5.8 Hz, 1H, H-4′), 4.80 (dd, $J=5.8$ Hz and 2.6 Hz, 1H, H-3), 5.58 (m, 1H, CH indanyl), 7.16–7.28 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 39.2 and 39.3 (CH_2Ar), 40.4 (C-3), 48.9 (C-4), 78.5 (CH indanyl), 124.5, 126.7 and 126.9 (CH_{Ar}), 139.5 (C_{Ar}), 148.4 (C=O carbamate), 160.3 (C-2); MS (CI) *m*/*z* 310 and 312 ($C_{13}H_{12}BrNO_3$, M + 1), 117, 91.

General procedure for the preparation of 1-alkoxycarbonyl-3-chloroazetidin-2-ones (8)

The procedure described for **7** was applied by replacing KBr with KCl.

1-Benzyloxycarbonyl-3-chloroazetidin-2-one (8a). Yield from 0.45 mmol of **3a**: 33 mg (31%) as a colorless oil; IR (film) 3058, 2977, 1824, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.69 (dd, $J=7.7$ and 3.2 Hz, 1H, H-4), 4.11 (dd, $J=7.7$ and 5.9 Hz, 1H, H-4′), 4.84 (dd, $J=5.9$ and 3.2 Hz, 1H, H-3), 5.29 (s, 2H, OCH_2), 7.30–7.48 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 49.1 (C-3), 54.2 (C-4), 68.4 (OCH_2), 128.5, 128.6 and 128.7 (CH_{Ar}), 136.1 (C_{Ar}), 148.2 (C=O carbamate), 160.1 (C-2); HRMS (EI) calcd for $C_{11}H_{10}{}^{35}ClNO_3$: 239.0358. Found: 239.0349.

1-Phenethyloxycarbonyl-3-chloroazetidin-2-one (8b). Yield from 0.53 mmol of **3b**: 45 mg (34%) as a yellow oil; IR (film) 3054, 2987, 1824, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.03 (t, $J=7.1$ Hz, 2H, CH_2Ph), 3.65 (dd, $J=7.7$ Hz and 3.0 Hz, 1H, H-4), 4.07 (dd, $J=7.7$ and 5.9 Hz, 1H, H-4′), 4.45 (t, $J=7.1$ Hz, 2H, OCH_2), 4.83 (dd, $J=5.9$ and 3.0 Hz, 1H, H-3), 7.25–7.32 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.9 (CH_2Ph), 49.0 (C-3), 54.3 (C-4), 67.6 (OCH_2), 126.7, 128.5 and 129.0 (CH_{Ar}), 136.7 (C_{Ar}), 148.6 (C=O carbamate), 160.2 (C-2); MS (EI) *m*/*z* 253 and 255 ($C_{12}H_{12}ClNO_3$, M), 105, 77.

1-(3′-Phenylpropyloxycarbonyl)-3-chloroazetidin-2-one (8c). Yield from 0.11 mmol of **3c**: 22 mg (63%) as a yellow oil; IR (film) 3055, 2987, 1825, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.07 (quint, $J=7.6$ Hz, 2H, CH_2–*CH*$_2$–CH_2), 2.74 (t, $J=7.6$, 2H, CH_2Ph), 3.64 (dd, $J=7.6$ and 2.8 Hz, 1H, H-4), 4.06 (dd, $J=7.6$ Hz and 5.8 Hz, 1H, H-4′), 4.28 (t, $J=7.6$ Hz, 2H, OCH_2), 4.83 (dd, $J=5.8$ and 2.8 Hz, 1H, H-3), 7.20–7.30 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.6 (CH_2), 31.8 (CH_2Ph), 48.9 (C-3), 54.3 (C-4), 66.5 (OCH_2), 126.0, 128.3 and 128.4 (CH_{Ar}), 140.6 (C_{Ar}), 148.8 (C=O carbamate), 160.2 (C-2); MS (CI) *m*/*z* 267 and 269 ($C_{13}H_{14}ClNO_3$, M), 119, 105, 91.

1-(9′-Fluorenylmethoxycarbonyl)-3-chloroazetidin-2-one (8f). Yield from 0.33 mmol of **3f**: 51 mg (47%) as a yellow oil; IR (film) 3052, 2987, 1819, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.71 (dd, $J=7.8$ Hz and 2.9 Hz, 1H, H-4), 4.14 (dd, $J=7.8$ and 5.8 Hz, 1H, H-4′), 4.30 (t, $J=7.3$ Hz, 1H, CH fluorenyl), 4.46 (dd, $J=10.8$ and 7.3 Hz, 1H, OCH_A), 4.50 (dd, $J=10.8$ and 7.3 Hz, 1H, OCH_B), 4.90 (dd, $J=5.8$ Hz and 2.9 Hz, 1H, H-3), 7.33–7.43 (m, 4H, Ar), 7.71–7.78 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 46.4 (CH fluorenyl), 49.0 (C-3), 54.4 (C-4), 69.2 (OCH_2), 120.0, 125.2, 127.2 and 127.9 (CH_{Ar}), 141.2 and 142.9 (C_{Ar}), 148.8 (C=O carbamate), 160.2 (C-2); HRMS (EI) calcd for $C_{18}H_{14}{}^{35}ClNO_3$: 327.0662. Found: 327.0664.

General procedure for the preparation of 1-alkoxycarbonyl-3-iodoazetidin-2-ones (9)

The procedure described for **7** was applied by replacing KBr with KI.

1-Benzyloxycarbonyl-3-iodoazetidin-2-one (9a). Yield from 0.3 mmol of **3a**: 66 mg (67%) as a yellow oil; IR (film) 3054, 2987, 1819, 1733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.81 (dd, $J=7.7$ and 3.0 Hz, 1H, H-4), 4.27 (dd, $J=7.7$ and 5.9 Hz, 1H, H-4′), 4.95 (dd, $J=5.9$ and 3.0 Hz, 1H, H-3), 5.28 (s, 2H, OCH_2), 7.34–7.48 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.8 (C-3), 50.2 (C-4), 68.9 (OCH_2), 128.7, 128.9 and 129.1 (CH_{Ar}), 134.9 (C_{Ar}), 148.6 (C=O carbamate), 161.5 (C-2); MS (EI) *m*/*z* 331 ($C_{11}H_{10}INO_3$, M), 204, 107, 91.

1-Phenethyloxycarbonyl-3-iodoazetidin-2-one (9b). Yield from 0.26 mmol of **3b**: 58 mg (65%) as a yellow oil; IR (film) 3055, 2987, 1818, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.03 (t, $J=7.2$ Hz, 2H, CH_2Ph), 3.78 (dd, $J=7.8$ and 3.2 Hz, 1H, H-4), 4.23 (dd, $J=7.8$ Hz and 5.9 Hz, 1H, H-4′), 4.44 (t, $J=7.2$ Hz, 2H, OCH_2), 4.94 (dd, $J=5.9$ Hz and 3.2 Hz, 1H, H-3), 7.22–7.35 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.5 (C-3), 34.9 (CH_2Ph), 49.3 (C-4), 67.5 (OCH_2), 126.8, 128.5 and 129.0 (CH_{Ar}), 136.8 (C_{Ar}), 148.6 (C=O carbamate), 161.8 (C-2); HRMS (CI) calcd for $C_{12}H_{12}INO_3$: 345.9940. Found: 345.9935.

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