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One-pot regioselective synthesis of β-lactams by a tandem Ugi 4CC/S_N cyclization

Xiao-Hua Zeng [a,b,†], Hong-Mei Wang [a,b,†], Yan-Mei Yan [a], Lei Wu [a], Ming-Wu Ding [a,*]

[a] Key Laboratory of Pesticide & Chemical Biology of Ministry of Education, Central China Normal University, Wuhan 430079, PR China
[b] Institute of Medicinal Chemistry, Hubei University of Medicine, Shiyan 442000, PR China

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ABSTRACT

β-Lactam scaffold was fabricated regioselectively by a facile one-pot base-mediated synthesis. The reactions of bromoacetic acid **1**, primary amines **2**, isocyanides **3**, and arylglyoxals **4** produced 2-aroyl-4-oxoazetidine-2-carboxamides **6** in good yields via a one-pot tandem Ugi condensation and intramolecular C-alkylation at room temperature in the presence of Cs_2CO_3.

1. Introduction

Multicomponent reactions (MCRs) are useful tool for diversity-oriented and complexity-generating synthesis of various heterocycles with novel properties.[1] The Ugi reaction is an effective and atom-economical multicomponent reaction, which assembled aldehyde (or ketone), amine, isonitrile, and carboxylic acid to afford a significantly more complex α-acylamino-carboxamide adduct that has received increased attention in view of its utility in the synthesis of nitrogen heterocyclic compounds.[2]

The β-lactam, as a four-membered heterocyclic ring, is the core structure of several antibiotic families. After the discovery of β-lactam antibiotics, the past few decades have witnessed notable growth in the field of β-lactam chemistry, especially the β-lactams with π electron-withdrawing substituents on their 3- and/or 4-position(s).[3] Apart from their clinical use as antibacterial agents, some β-lactams have also been utilized as therapeutic agents for cholesterol absorption inhibitor,[4] and as a potent mechanism based inhibitor of several enzymes like chymase,[5] leukocyte elastase,[6] and human cytomegalovirus protease.[7] These compounds have also been used as intermediate in the preparation of various heterocyclic compounds with biological significance.[8]

There are many known methods for synthesis of β-lactams.[9] The Ugi four-component condensation is also used to prepare β-lactams by reactions between β-amino acids, aldehydes, and isocyanides.[10] Some β-lactams have been even obtained by the Passerini or Ugi reaction and subsequent post-condensations.[11] Ugi-type reaction of β-keto acids, amines with isonitriles have been reported to give β-lactam derivatives as well.[12]

In our previous work, we described a direct synthesis of 5-oxopyrrolidine-2-carboxamides by a Ugi reaction of Baylis–Hillman acids, primary amines, arylglyoxals, and isocyanides.[13] We envisioned that if α-bromocarboxylic acid **1** was used instead of Baylis–Hillman acid, the above approach might produce β-lactams **6**, piperazine-2,5-diones **7** or 2*H*-1,4-oxazin-3(4*H*)-ones **8** by intramolecular C-, N-, or O-alkylation (Scheme 1). It was reported that piperazine-2,5-diones or β-lactams were obtained by Ugi reaction and subsequent intramolecular N- or C-alkylation in the presence of potassium hydroxide, starting from α-chloroacetic acid, aldehyde, amine, and isocyanides.[10b,14] The regioselectivity of the above approach was related to the aldehyde used.[15] Continuing our interest in I-MCR mediated synthesis of heterocycles,[16] we wish to disclose herein a one-pot regioselective synthesis of previously seldom reported 2-acyl-β-lactam-2-carboxamides by a tandem Ugi 4CC/S_N cyclization of bromoacetic acid, primary amine, arylglyoxal, and isocyanide.

2. Results and discussion

Initially, we selected the bromoacetic acid **1**, *tert*-butylamine **2a**, 4-chlorophenylglyoxal **3a**, and cyclohexylisocyanide **4a** as the reactants (Scheme 2). When the bromoacetic acid **1a**, 4-chlorophenylglyoxal **2a**, *tert*-butylamine **3a**, and cyclohexylisocyanide **4a** was stirred in methanol at room temperature for 24 h, the 2-acyl-4-oxoazetidine-2-carboxamide derivative **6a** was directly obtained albeit in low yield (31%, Table 1, entry 1). The expected Ugi product **5a** was also isolated from the reaction mixture (18%) and ^{1}H NMR analysis of **5a** revealed that it existed exclusively as the enol form. Similar to our previous report, the detection of reaction mixture revealed that the pH of the solution

* Corresponding author. Tel.: +86 15327200455; fax: +86 27 67862041; e-mail addresses: mwding@mail.ccnu.edu.cn, dmw10@126.com (M.-W. Ding).
† X.H. Zeng and H.M. Wang are first coauthors and contributed equally to this work.

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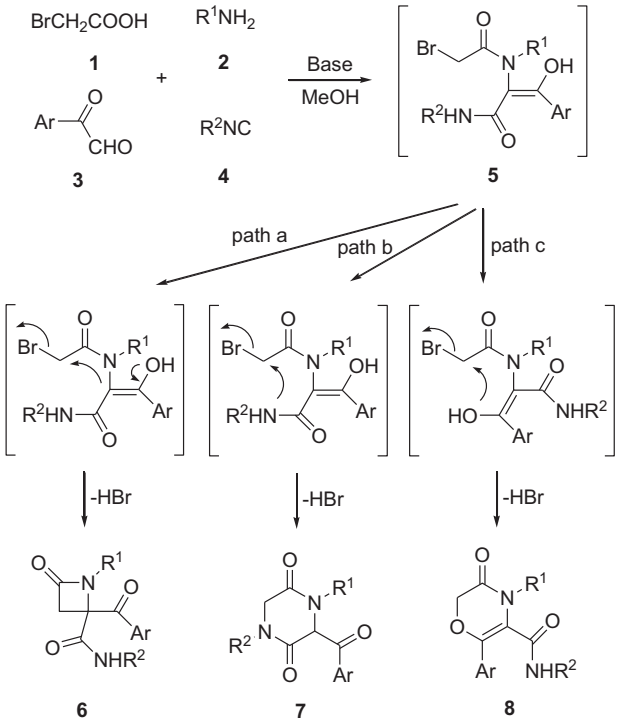
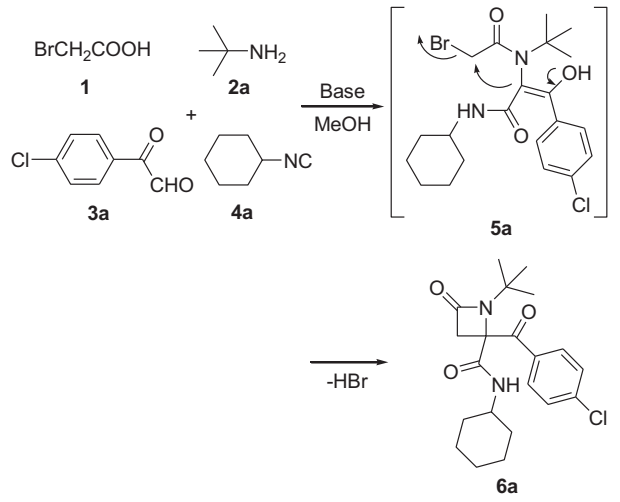


Scheme 1. Proposed tandem Ugi 4CC/S_N cyclization.

decreased from 7 to 4 during the reaction process and reached the minimum in 4 h, after which the reaction took place slowly accompanying side reactions. This evidence implies that the intramolecular substitution reaction of intermediate **5a** occurs even under acidic condition with release of HBr, which resulted in the change of pH value of the reaction mixture. Finally when a base was added to adjust the pH of the solution to 6 during the reaction process, good yields of **6a** were reached (Table 1, entry 2–5). The best result was obtained as Cs_2CO_3 was used as a base (Table 1, entry 5). This is probably due to its stronger basicity and good solubility in the solvent. Although intramolecular ring-closure competition between four-membered and six-membered ring is generally accepted to lead to six-membered ring, the above reaction produced four-membered β-lactams **6** with high regioselectivity and no other possible six-membered product (piperazine-2,5-dione **7** or 2*H*-1,4-oxazin-3(4*H*)-one **8** shown in Scheme 1) was isolated from the reaction mixture.



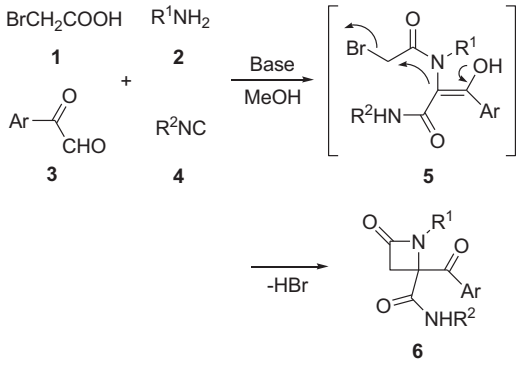
Scheme 2. Preparation of compound **6a**.

Table 1
Optimization of the reaction conditions about **6a**

Entry	Base	Condition	Product	Yield[a] (%)
1	—	rt/24 h	**6a** (**5a**)	31 (18)
2	K_2CO_3	rt/12 h	**6a**	69
3	$NaHCO_3$	rt/12 h	**6a**	71
4	NEt_3	rt/12 h	**6a**	65
5	Cs_2CO_3	rt/12 h	**6a**	84

[a] Isolated yields.

With the optimized condition, various bromoacetic acid **1**, amine **2**, arylglyoxal **3**, and isocyanide **4** were employed for the reaction, utilizing Cs_2CO_3 as a base to adjust the pH of the solution to 6 during the reaction process (Scheme 3). In preparation of compounds **6a**–**6h** (Table 2, when R^1 is *t*-Bu), the reactions proceeded similarly to give the corresponding β-lactams **6a**–**6h** in 77–93% yield. As the above approach was applied to prepare compounds **6i**–**6s** (Table 2), the initially formed Ugi products **5i**–**5s** cyclized more slowly but also gave the corresponding β-lactams **6i**–**6s** in 58–83% yield.



Scheme 3. Preparation of compounds **6a**–**6s**.

Table 2
Preparation of compounds **6a**–**6s**

	Ar	R^1	R^2	Yield[a] (%)
6a	4-ClC_6H_4	*t*-Bu	*c*-C_6H_{11}	84
6b	4-ClC_6H_4	*t*-Bu	*t*-Bu	93
6c	4-BrC_6H_4	*t*-Bu	*t*-Bu	90
6d	4-$NO_2C_6H_4$	*t*-Bu	*t*-Bu	85
6e	4-$NO_2C_6H_4$	*t*-Bu	*c*-C_6H_{11}	82
6f	4-ClC_6H_4	*t*-Bu	*n*-Bu	77
6g	4-$NO_2C_6H_4$	*t*-Bu	*n*-Bu	79
6h	4-BrC_6H_4	*t*-Bu	*n*-Bu	80
6i	4-ClC_6H_4	*i*-Pr	*t*-Bu	83
6j	4-BrC_6H_4	*n*-Pr	*t*-Bu	73
6k	4-$NO_2C_6H_4$	*i*-Pr	*t*-Bu	78
6l	4-ClC_6H_4	*n*-Pr	*t*-Bu	77
6m	4-BrC_6H_4	*i*-Pr	*c*-C_6H_{11}	74
6n	4-$NO_2C_6H_4$	*i*-Pr	*c*-C_6H_{11}	72
6o	4-ClC_6H_4	4-ClC_6H_4	*t*-Bu	74
6p	4-ClC_6H_4	C_6H_5	*c*-C_6H_{11}	71
6q	4-ClC_6H_4	4-$CH_3C_6H_4$	*t*-Bu	63
6r	4-ClC_6H_4	C_6H_5	*t*-Bu	68
6s	4-BrC_6H_4	4-$CH_3C_6H_4$	*c*-C_6H_{11}	58

[a] Isolated yields.

As shown in Table 2, the yields of the products were related to the R^1 group of amine **2**. When various aliphatic amines were used, the reaction produced β-lactams **6** in good to high yields (71–93%, Table 2, compounds **6a**–**6n**). However, as the aromatic amine was

utilized, moderate yields of the products **6o**–**6s** were obtained (58–74%, Table 2). The formation of the β-lactams **6** can be rationalized in terms of an initial Ugi reaction to give the adduct **5**, which directly undergoes intramolecular nucleophilic substitution to give the four-membered β-lactams **6** over the six-membered piperazine-2,5-dione or 2*H*-1,4-oxazin-3(4*H*)-one through the enol form of intermediate **5**. The high regioselectivity of the reaction is probably owing to that the intramolecular C-alkylation of intermediate **5** occurs under acidic condition, in which N- or O-alkylation of intermediate **5** is avoided.

Compounds **6a**–**s** were confirmed by their spectral data. For example, the ^{1}H NMR spectrum of **6a** shows two doublets at 3.57 and 3.00 ppm due to the CH_2 of the β-lactam ring. The signals of CONHCH are found at 6.94 ppm and 3.82 ppm as doublets and multiplets, respectively. The signals of other CH_2 and CH_3 appear at 1.95–1.13 ppm as multiplets. The signals attributable to the Ar–Hs are found at 7.73 and 7.43 ppm as two doublets. The ^{13}C NMR spectrum data in **6a** showed the signals of C=O and CON carbon at 194.6, 168.1, and 164.7 ppm. The quaternary carbon of the β-lactam ring absorbs at 69.3 ppm. The MS spectrum of **6a** shows molecular ion peak and $M^+-CONHC_6H_{11}$ at *m*/*z* 390 and 264 with 4% and 33% abundance. Furthermore a single crystal for **6i** was obtained from the CH_2Cl_2/ethanol solution of **6i**, and X-ray structure analysis verified the proposed structure (Fig. 1).

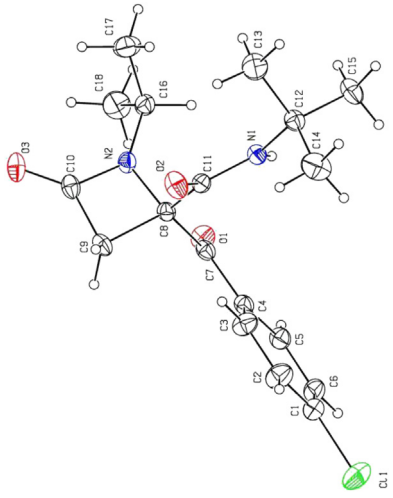


Fig. 1. ORTEP drawing of **6i** with 50% probability thermal ellipsoids (with only one enantiomer shown).

3. Conclusion

we have developed a simple synthesis of β-lactams with two π electron-withdrawing substituents on their 4-position via a regioselective one-pot Ugi 4CC/S_N cyclization. Due to the mild reaction condition, good yields, and easily accessible starting material, we think that this new synthetic approach discussed here has the potential in synthesis of various 2-acyl-β-lactam-2-carboxamides, which are of considerable interest as potential biological active compounds or pharmaceuticals.

4. Experimental

4.1. General

Melting points were determined using a X-4 model apparatus and were uncorrected. MS were measured on a Finnigan Trace MS spectrometer. NMR were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury 600 or 400 spectrometer and resonances relative to TMS. Elementary analyses were taken on a Vario EL III elementary analysis instrument. The X-ray diffraction data were collected on a *Bruker SMART AXS CCD* diffractometer, Mo Kα, 2θ=1.86–27.50°.

4.2. One-pot synthesis of 4-oxoazetidine-2-carboxamide 6

*4.2.1. 1-(tert-Butyl)-2-(4-chlorobenzoyl)-N-cyclohexyl-4-oxoazetidine-2-carboxamide (**6a**).* A mixture of the bromoacetic acid **1** (0.14 g, 1 mmol), *tert*-butylamine **2a** (R^1=*t*-Bu, 0.07 g, 1 mmol), and 4-chlorophenylglyoxal **3a** (Ar=4-ClC_6H_4, 0.17 g, 1 mmol) was stirred in methanol (5 mL) at room temperature for 10 min, then cyclohexylisocyanide **4a** (R^2=*c*-C_6H_{11}, 0.11 g, 1 mmol) was added to the solution. The mixture was stirred at room temperature and the pH value of the solution was adjusted to 6 using Cs_2CO_3 during the reaction process. After stirring for 12 h, the mixture was chilled and the resulted solid was then filtered, recrystallized from ether to give product **6a** as white solid (0.33 g, 84%), mp 189–190 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.73 (d, *J*=8.4 Hz, 2H, Ar–H), 7.43 (d, *J*=8.4 Hz, 2H, Ar–H), 6.94 (d, *J*=7.2 Hz, 1H, NH), 3.82–3.81 (m, 1H, NCH), 3.57 (d, *J*=14.4 Hz, 1H, CH_2^a), 3.00 (d, *J*=14.4 Hz, 1H, CH_2^b), 1.95–1.13 (m, 19H, $5CH_2$ and $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 194.6, 168.1, 164.7, 139.9, 132.8, 130.2, 128.8, 69.3, 56.9, 49.1, 46.9, 32.6, 27.9, 25.3, 24.9. MS (*m*/*z*, %) 390 (M^+, 4), 264 (33), 209 (46), 139 (61), 113 (69), 57 (100). Anal. Calcd for $C_{21}H_{27}ClN_2O_3$: C, 64.52; H, 6.96; N, 7.17. Found: C, 64.68; H, 7.18; N, 7.11.

*4.2.2. N,1-Di-tert-butyl-2-(4-chlorobenzoyl)-4-oxoazetidine-2-carboxamide (**6b**).* Operation as above with *tert*-butylisocyanide **4b** (0.08 g, 1 mmol), compound **6b** (0.34 g, 93%) was also isolated as white solid. Mp: 224–226 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.74 (d, *J*=8.4 Hz, 2H, Ar–H), 7.43 (d, *J*=8.4 Hz, 2H, Ar–H), 6.35 (s, 1H, NH), 3.52 (d, *J*=14.8 Hz, 1H, CH_2^a), 3.01 (d, *J*=14.4 Hz, 1H, CH_2^b), 1.50 (s, 9H, $3CH_3$), 1.38 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 194.8, 168.1, 164.6, 139.9, 132.9, 130.3, 128.8, 69.9, 56.8, 52.4, 47.2, 28.3, 27.9; MS (*m*/*z*, %) 364 (M^+, 2), 264 (32), 209 (63), 139 (50), 113 (63), 57 (100). Anal.Calcd for $C_{19}H_{25}ClN_2O_3$: C, 62.54; H, 6.91; N, 7.68. Found: C, 62.51; H, 7.11; N, 7.49.

*4.2.3. 2-(4-Bromobenzoyl)-N,1-di-tert-butyl-4-oxoazetidine-2-carboxamide (**6c**).* Operation as above with 4-bromophenylglyoxal **3b** (Ar=4-BrC_6H_4, 0.21 g, 1 mmol), compound **6c** (0.37 g, 90%) was also isolated as white solid. Mp: 219–220 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.66 (d, *J*=8.4 Hz, 2H, Ar–H), 7.60 (d, *J*=8.4 Hz, 2H, Ar–H), 6.38 (s, 1H, NH), 3.52 (d, *J*=14.4 Hz, 1H, CH_2^a), 3.01 (d, *J*=15.0 Hz, 1H, CH_2^b), 1.49 (s, 9H, $3CH_3$), 1.38 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 195.0, 168.1, 164.5, 133.2, 131.8, 130.4, 128.8, 69.8, 56.8, 52.4, 47.4, 28.3, 27.8. MS (*m*/*z*, %) 408 (M^+, 3), 308 (30), 253 (63), 169 (42), 155 (12), 113 (68), 57 (100); Anal. Calcd for $C_{19}H_{25}BrN_2O_3$: C, 55.75; H, 6.16; N, 6.84. Found: C, 55.63; H, 6.32; N, 6.58.

*4.2.4. N,1-Di-tert-butyl-2-(4-nitrobenzoyl)-4-oxoazetidine-2-carboxamide (**6d**).* Operation as above with 4-nitrophenylglyoxal **3c** (Ar=4-$NO_2C_6H_4$, 0.18 g, 1 mmol), compound **6d** (0.32 g, 85%) was also isolated as white solid. Mp: 208–209 °C, lit.[17] 209–211 °C; ^{1}H NMR (DMSO-d_6, 600 MHz) δ (ppm) 8.35 (s, 1H, NH), 8.32 (d, *J*=8.4 Hz, 2H, Ar–H), 7.94 (d, *J*=8.4 Hz, 2H, Ar–H), 3.80 (d, *J*=15.0 Hz, 1H, CH_2^a), 3.04 (d, *J*=15.0 Hz, 1H, CH_2^b), 1.41 (s, 9H, $3CH_3$), 1.30 (s, 9H, $3CH_3$); ^{13}C NMR (DMSO-d_6, 150 MHz) δ (ppm) 195.2, 168.6, 164.2, 149.6, 139.2, 129.6, 123.7, 70.4, 55.5, 51.6, 46.1, 28.0, 27.6. MS (*m*/*z*, %) 375 (M^+, 2), 275 (46), 220 (100), 113 (41), 57 (88). Anal. Calcd for $C_{19}H_{25}N_3O_5$: C, 60.79; H, 6.71; N, 11.19. Found: C, 60.63; H, 6.59; N, 11.45.

*4.2.5. 1-(tert-Butyl)-N-cyclohexyl-2-(4-nitrobenzoyl)-4-oxoazetidine-2-carboxamide (**6e**).* Operation as above with

cyclohexylisocyanide (0.11 g, 1 mmol), compound **6e** (0.33 g, 82%) was also isolated as white solid. Mp: 229–230 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.30 (d, J=8.4 Hz, 2H, Ar–H), 7.95 (d, J=8.4 Hz, 2H, Ar–H), 6.91 (br, 1H, NH), 3.81–3.79 (m, 1H, NCH), 3.57 (d, J=14.4 Hz, 1H, CH_2^a), 3.06 (d, J=15.0 Hz, 1H, CH_2^b), 1.95–1.16 (m, 19H, $5CH_2$ and $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 194.3, 168.1, 164.4, 149.9, 139.3, 129.7, 123.5, 69.3, 57.0, 49.7, 48.7, 46.4, 28.4, 27.4, 24.7. MS (m/z, %) 401 (M^+, 4), 275 (31), 251 (24), 220 (63), 113 (54), 57 (100). Anal. Calcd for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6.78; N, 10.47. Found: C, 62.92; H, 6.93; N, 10.24.

*4.2.6. 1-(tert-Butyl)-N-butyl-2-(4-chlorobenzoyl)-4-oxoazetidine-2-carboxamide (**6f**).* Operation as above with 4-chlorophenylglyoxal **3a** (Ar=4-ClC_6H_4, 0.17 g, 1 mmol) and *n*-butylisocyanide (0.08 g, 1 mmol), compound **6f** (0.28 g, 77%) was also isolated as white solid. Mp: 159–160 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.73 (d, J=8.4 Hz, 2H, Ar–H), 7.43 (d, J=8.4 Hz, 2H, Ar–H), 7.35 (s, 1H, NH), 3.59 (d, J=14.4 Hz, 1H, CH_2^a), 3.39–3.25 (m, 2H, NCH_2), 3.00 (d, J=15.0 Hz, 1H, CH_2^b), 1.55–1.53 (m, 2H, CH_2), 1.48 (s, 9H, $3CH_3$), 1.37–1.33 (m, 2H, CH_2), 0.92 (t, J=7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 194.5, 169.0, 165.0, 139.9, 132.7, 130.2, 128.8, 69.1, 56.9, 46.7, 39.9, 31.0, 27.9, 20.1, 13.6. MS (m/z, %) 364 (M^+, 4), 250 (8), 225 (37), 209 (21), 139 (47), 113 (38), 57 (100). Anal. Calcd for $C_{19}H_{25}ClN_2O_3$: C, 62.54; H, 6.91; N, 7.68. Found: C, 62.29; H, 6.93; N, 7.75.

*4.2.7. 1-(tert-Butyl)-N-butyl-2-(4-nitrobenzoyl)-4-oxoazetidine-2-carboxamide (**6g**).* Operation as above with 4-nitrophenylglyoxal **3c** (Ar=4-$NO_2C_6H_4$, 0.18 g, 1 mmol), compound **6g** (0.30 g, 79%) was also isolated as white solid. Mp: 166–167 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 183–185 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.29 (d, J=6.4 Hz, 2H, Ar–H), 7.94 (d, J=7.2 Hz, 2H, Ar–H), 7.57 (s, 1H, NH), 3.62 (d, J=14.0 Hz, 1H, CH_2^a), 3.39–3.29 (m, 2H, NCH_2), 3.04 (d, J=14.0 Hz, 1H, CH_2^b), 1.82–1.39 (m, 13H, $2CH_2$ and $3CH_3$), 0.94 (t, J=4.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 194.1, 168.9, 164.7, 149.9, 139.2, 129.7, 123.4, 69.2, 57.0, 30.9, 28.3, 27.3, 20.1, 14.0, 13.1; MS (m/z, %) 375 (M^+, 11), 261 (17), 225 (55), 169 (78), 113 (28), 57 (100). Anal. Calcd for $C_{19}H_{25}N_3O_5$: C, 60.79; H, 6.71; N, 11.19. Found: C, 60.78; H, 6.85; N, 11.14.

*4.2.8. 2-(4-Bromobenzoyl)-1-(tert-butyl)-N-butyl-4-oxoazetidine-2-carboxamide (**6h**).* Operation as above with 4-bromophenylglyoxal **3b** (Ar=4-BrC_6H_4, 0.21 g, 1 mmol), compound **6h** (0.33 g, 80%) was also isolated as white solid. Mp: 149–150 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.66 (d, J=7.6 Hz, 2H, Ar–H), 7.60 (d, J=7.6 Hz, 2H, Ar–H), 6.95 (s, 1H, NH), 3.56 (d, J=14.4 Hz, 1H, CH_2^a), 3.38–3.27 (m, 2H, NCH_2), 3.02 (d, J=14.4 Hz, 1H, CH_2^b), 1.53–1.33 (m, 13H, $2CH_2$ and $3CH_3$), 0.92 (t, J=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 194.4, 168.9, 165.0, 133.0, 131.8, 130.0, 128.4, 69.1, 56.8, 30.9, 28.3, 27.3, 20.0, 13.9, 13.1; MS (m/z, %) 408 (M^+, 4), 250 (95), 139 (100), 113 (46), 43 (35). Anal. Calcd for $C_{19}H_{25}BrN_2O_3$: C, 55.75; H, 6.16; N, 6.84. Found: C, 55.63; H, 6.24; N, 6.67.

*4.2.9. N-(tert-Butyl)-2-(4-chlorobenzoyl)-1-isopropyl-4-oxoazetidine-2-carboxamide (**6i**).* Operation as above with *iso*-propylamine (0.06 g, 1 mmol), 4-chlorophenylglyoxal **3a** (Ar=4-ClC_6H_4, 0.17 g, 1 mmol), and *tert*-butylisocyanide **4b** (0.08 g, 1 mmol), and stirring for 24 h, compound **6i** (0.29 g, 83%) was also isolated as white solid. Mp: 209–210 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.80 (d, J=7.2 Hz, 2H, Ar–H), 7.46 (d, J=7.2 Hz, 2H, Ar–H), 6.93 (s, 1H, NH), 3.75 (d, J=13.8 Hz, 1H, CH_2^a), 3.71–3.67 (m, 1H, NCH), 3.30 (d, J=14.4 Hz, 1H, CH_2^b), 1.55 (d, J=6.6 Hz, 3H, CH_3), 1.40 (d, J=6.6 Hz, 3H, CH_3), 1.32 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 194.9, 165.7, 164.7, 140.6, 131.9, 130.0, 129.9, 129.2, 129.1, 68.8, 52.6, 49.0, 48.2, 28.4, 27.8, 21.5, 21.1, 20.4; MS (m/z, %) 350 (M^+, 4), 250 (95), 139 (100), 113 (46), 43 (35). Anal. Calcd for $C_{18}H_{23}ClN_2O_3$: C, 61.62; H, 6.61; N, 7.98. Found: C, 61.77; H, 6.71; N, 7.71.

*4.2.10. 2-(4-Bromobenzoyl)-N-(tert-butyl)-4-oxo-1-propylazetidine-2-carboxamide (**6j**).* Operation as above with *n*-propylamine (0.06 g, 1 mmol) and 4-bromophenylglyoxal **3b** (Ar=4-BrC_6H_4, 0.21 g, 1 mmol), compound **6j** (0.29 g, 73%) was also isolated as white solid. Mp: 150–152 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.73 (d, J=8.4 Hz, 2H, Ar–H), 7.63 (d, J=7.8 Hz, 2H, Ar–H), 5.68 (s, 1H, NH), 3.74 (d, J=14.4 Hz, 1H, CH_2^a), 3.50–3.36 (m, 2H, NCH_2), 3.16 (d, J=14.4 Hz, 1H, CH_2^b), 1.77–1.69 (m, 2H, CH_2), 1.31 (s, 9H, $3CH_3$), 0.95 (t, J=7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 195.3, 165.8, 165.6, 132.6, 132.2, 130.1, 129.6, 68.8, 52.7, 46.0, 45.0, 28.4, 21.9, 11.5; MS (m/z, %) 394 (M^+, 2), 294 (62), 209 (61), 183 (50), 155 (100), 57 (36). Anal. Calcd for $C_{18}H_{23}BrN_2O_3$: C, 54.69; H, 5.86; N, 7.09. Found: C, 54.63; H, 6.00; N, 6.91.

*4.2.11. N-(tert-Butyl)-1-isopropyl-2-(4-nitrobenzoyl)-4-oxoazetidine-2-carboxamide (**6k**).* Operation as above with *iso*-propylamine (0.06 g, 1 mmol) and 4-nitrophenylglyoxal **3c** (Ar=4-$NO_2C_6H_4$, 0.18 g, 1 mmol), compound **6k** (0.28 g, 78%) was also isolated as white solid. Mp: 207–208 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.33 (d, J=8.4 Hz, 2H, Ar–H), 8.03 (d, J=7.6 Hz, 2H, Ar–H), 6.60 (s, 1H, NH), 3.78–3.74 (m, 1H, NCH), 3.71 (d, J=14.4 Hz, 1H, CH_2^a), 3.09 (d, J=14.4 Hz, 1H, CH_2^b), 1.55 (d, J=6.6 Hz, 3H, CH_3), 1.43 (d, J=6.6 Hz, 3H, CH_3), 1.37 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 194.5, 166.4, 164.3, 150.3, 138.5, 129.7, 123.7, 68.7, 52.6, 49.0, 48.0, 28.4, 28.0, 21.6; MS (m/z, %) 361 (M^+, 2), 261 (100), 219 (18), 177 (93), 113 (32), 57 (32). Anal. Calcd for $C_{18}H_{23}N_3O_5$: C, 59.82; H, 6.41; N, 11.63. Found: C, 59.74; H, 6.53; N, 11.81.

*4.2.12. N-(tert-Butyl)-2-(4-chlorobenzoyl)-4-oxo-1-propylazetidine-2-carboxamide (**6l**).* Operation as above with *n*-propylamine (0.06 g, 1 mmol) and 4-chlorophenylglyoxal **3a** (Ar=4-ClC_6H_4, 0.17 g, 1 mmol), compound **6l** (0.27 g, 77%) was also isolated as white solid. Mp: 162–163 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.81 (d, J=8.4 Hz, 2H, Ar–H), 7.46 (d, J=8.4 Hz, 2H, Ar–H), 5.53 (s, 1H, NH), 3.75 (d, J=14.8 Hz, 1H, CH_2^a), 3.48–3.37 (m, 2H, NCH_2), 3.17 (d, J=14.4 Hz, 1H, CH_2^b), 1.78–1.59 (m, 2H, CH_2), 1.31 (s, 9H, $3CH_3$), 0.95 (t, J=7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 194.9, 165.8, 165.7, 140.7, 132.0, 130.1, 129.1, 68.7, 52.6, 45.9, 27.8, 21.8, 12.0, 11.2; MS (m/z, %) 350 (M^+, 2), 250 (100), 166 (90), 139 (79), 111 (21), 57 (28). Anal. Calcd for $C_{18}H_{23}ClN_2O_3$: C, 61.62; H, 6.61; N, 7.98. Found: C, 61.67; H, 6.75; N, 7.86.

*4.2.13. 2-(4-Bromobenzoyl)-N-cyclohexyl-1-isopropyl-4-oxoazetidine-2-carboxamide (**6m**).* Operation as above with *iso*-propylamine (0.06 g, 1 mmol), cyclohexylisocyanide (0.11 g, 1 mmol), and 4-bromophenylglyoxal **3b** (Ar=4-BrC_6H_4, 0.21 g, 1 mmol), compound **6m** (0.31 g, 74%) was also isolated as white solid. Mp: 199–200 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.69 (d, J=8.4 Hz, 2H, Ar–H), 7.61 (d, J=8.4 Hz, 2H, Ar–H), 6.52 (d, J=7.6 Hz, 1H, NH), 3.80–3.70 (m, 3H, 2NCH and CH_2^a), 3.03 (d, J=14.4 Hz, 1H, CH_2^b), 1.96–1.07 (m, 16H, $5CH_2$ and $2CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 194.8, 165.8, 164.7, 132.3, 132.2, 129.9, 129.3, 68.1, 49.8, 49.0, 48.0, 25.1, 24.5, 21.5, 21.1; MS (m/z, %) 420 (M^+, 2), 294 (50), 209 (49), 155 (100), 111 (26), 43 (28). Anal.Calcd for $C_{20}H_{25}BrN_2O_3$: C, 57.01; H, 5.98; N, 6.65. Found: C, 57.05; H, 6.17; N, 6.88.

*4.2.14. N-Cyclohexyl-1-isopropyl-2-(4-nitrobenzoyl)-4-oxoazetidine-2-carboxamide (**6n**).* Operation as above with 4-nitrophenylglyoxal **3c** (Ar=4-$NO_2C_6H_4$, 0.18 g, 1 mmol), compound **6n** (0.28 g, 72%) was also isolated as white solid. Mp: 190–192 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.32 (d, J=8.4 Hz, 2H, Ar–H), 8.01 (d, J=8.4 Hz, 2H, Ar–H), 6.91 (s, 1H, NH), 3.80–3.77 (m, 2H, 2NCH), 3.71 (d,

J=14.4 Hz, 1H, CH_2^a), 3.11 (d, J=14.4 Hz, 1H, CH_2^b), 1.94–1.13 (m, 16H, $5CH_2$ and $2CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 194.4, 166.3, 164.4, 150.4, 138.6, 129.6, 123.8, 68.1, 49.2, 48.6, 45.7, 32.5, 24.9, 21.4, 20.8; MS (m/z, %) 387 (M^+, 3), 262 (100), 177 (81), 155 (62), 111 (26), 43 (30). Anal. Calcd for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50; N, 10.85. Found: C, 61.85; H, 6.74; N, 10.72.

*4.2.15. N-tert-Butyl-2-(4-chlorobenzoyl)-1-(4-chlorophenyl)-4-oxoazetidine-2-carboxamide (**6o**).* Operation as above with 4-chlorophenylamine (0.13 g, 1 mmol), *tert*-butylisocyanide (0.08 g, 1 mmol), and 4-chlorophenylglyoxal **3a** (Ar=4-ClC_6H_4, 0.17 g, 1 mmol), compound **6o** (0.31 g, 74%) was also isolated as white solid. Mp: 164–165 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.80–7.24 (m, 8H, Ar–H), 6.50 (s, 1H, NH), 3.84 (d, J=15.0 Hz, 1H, CH_2^a), 3.35 (d, J=15.0 Hz, 1H, CH_2^b), 1.27 (s, 9H, $3CH_3$); ^{13}C NMR (CDCl3, 150 MHz) δ (ppm) 193.1, 165.5, 162.7, 140.6, 135.4, 131.9, 130.5, 130.4, 129.1, 128.9, 120.3, 69.8, 52.8, 47.5, 28.2; MS (m/z, %) 418 (M^+, 4), 318 (25), 279 (100), 262 (25), 139 (95), 111 (29), 57 (37). Anal. Calcd for $C_{21}H_{20}Cl_2N_2O_3$: C, 60.15; H, 4.81; N, 6.68. Found: C, 60.08; H, 4.72; N, 6.54.

*4.2.16. 2-(4-Chlorobenzoyl)-N-cyclohexyl-1-phenyl-4-oxoazetidine-2-carboxamide (**6p**).* Operation as above with phenylamine (0.09 g, 1 mmol) and cyclohexylisocyanide (0.11 g, 1 mmol), compound **6p** (0.29 g, 71%) was also isolated as white solid. Mp: 171–172 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.84 (d, J=8.4 Hz, 2H, Ar–H), 7.52–7.16 (m, 6H, Ar–H), 6.18 (br, 1H, NH), 3.90–3.69 (m, 2H, NCH and CH_2^a), 3.40 (d, J=15.2 Hz, 1H, CH_2^b), 1.77–0.87 (m, 10H, $5CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 193.1, 165.8, 162.8, 140.3, 136.9, 132.3, 130.5, 128.9, 128.8, 125.3, 118.9, 69.0, 49.3, 47.5, 32.3, 25.1, 24.7; MS (m/z, %) 410 (M^+, 2), 271 (94), 262 (25), 189 (100), 139 (53), 104 (44). Anal. Calcd for $C_{23}H_{23}ClN_2O_3$: C, 67.23; H, 5.64; N, 6.82. Found: C, 67.07; H, 5.71; N, 6.58.

*4.2.17. N-tert-Butyl-2-(4-chlorobenzoyl)-1-p-tolyl-4-oxoazetidine-2-carboxamide (**6q**).* Operation as above with 4-methylphenylamine (0.11 g, 1 mmol) and *tert*-butylisocyanide (0.08 g, 1 mmol), compound **6q** (0.25 g, 63%) was also isolated as white solid. Mp: 131–132 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.82 (d, J=8.8 Hz, 2H, Ar–H), 7.45–7.38 (m, 4H, Ar–H), 7.10 (d, J=8.4 Hz, 2H, Ar–H), 6.28 (s, 1H, NH), 3.84 (d, J=15.2 Hz, 1H, CH_2^a), 3.32 (d, J=14.8 Hz, 1H, CH_2^b), 2.32 (s, 3H, CH_3), 1.23 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 193.6, 165.6, 162.9, 140.4, 135.4, 134.2, 132.2, 130.5, 129.5, 129.0, 120.0, 70.0, 52.6, 47.3, 28.2, 20.9; MS (m/z, %) 398 (M^+, 4), 298 (24), 259 (100), 203 (89), 139 (67), 91 (32), 57 (28). Anal. Calcd for $C_{22}H_{23}ClN_2O_3$: C, 66.24; H, 5.81; N, 7.02. Found: C, 66.17; H, 5.93; N, 7.23.

*4.2.18. N-tert-Butyl-2-(4-chlorobenzoyl)-1-phenyl-4-oxoazetidine-2-carboxamide (**6r**).* Operation as above with phenylamine (0.09 g, 1 mmol), compound **6r** (0.26 g, 68%) was also isolated as white solid. Mp: 159–160 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.83 (d, J=6.8 Hz, 2H, Ar–H), 7.53–7.17 (m, 7H, Ar–H), 6.10 (br, 1H, NH), 3.85 (d, J=14.8 Hz, 1H, CH_2^a), 3.35 (d, J=14.8 Hz, 1H, CH_2^b), 1.21 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 193.3, 165.7, 162.9, 140.2, 136.8, 132.1, 130.4, 128.9, 128.8, 125.3, 119.2, 69.8, 52.6, 47.3, 28.1; MS (m/z, %) 384 (M^+, 2), 284 (58), 245 (100), 189 (82), 139 (94), 77 (32), 57 (44). Anal. Calcd for $C_{21}H_{21}ClN_2O_3$: C, 65.54; H, 5.50; N, 7.28. Found: C, 65.78; H, 5.41; N, 7.11.

*4.2.19. 2-(4-Bromobenzoyl)-N-cyclohexyl-1-p-tolyl-4-oxoazetidine-2-carboxamide (**6s**).* Operation as above with 4-methyl phenylamine (0.11 g, 1 mmol), cyclohexylisocyanide (0.11 g, 1 mmol), and 4-bromophenylglyoxal **3b** (Ar=4-BrC_6H_4, 0.21 g, 1 mmol), compound **6s** (0.27 g, 58%) was also isolated as white solid. Mp: 163–164 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.74 (d, J=7.6 Hz, 2H, Ar–H), 7.60 (d, J=8.4 Hz, 2H, Ar–H), 7.36 (d, J=6.8 Hz, 2H, Ar–H), 7.09 (d, J=7.2 Hz, 2H, Ar–H), 6.45 (br, 1H, NH), 3.82–3.78 (m, 2H, NCH and CH_2^a), 3.35 (d, J=14.8 Hz, 1H, CH_2^b), 2.32 (s, 3H, CH_3), 1.81–0.90 (m, 10H, $5CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 193.2, 165.9, 162.5, 134.7, 134.4, 132.6, 131.7, 130.3, 129.1, 128.8, 118.6, 68.6, 49.2, 47.2, 32.1, 25.0, 24.6, 20.8; MS (m/z, %) 468 (M^+, 1), 343 (7), 284 (89), 203 (100), 118 (32), 91 (21). Anal. Calcd for $C_{24}H_{25}BrN_2O_3$: C, 61.41; H, 5.37; N, 5.97. Found: C, 61.16; H, 5.49; N, 5.81.

4.3. Isolation of 2-(2-bromo-*N*-*tert*-butylacetamido)-3-(4-chlorophenyl)-*N*-cyclohexyl-3-oxopropanamide 5a

A mixture of the bromoacetic acid **1a** (0.14 g, 1 mmol), *tert*-butylamine **2a** (R^1=*t*-Bu, 0.07 g, 1 mmol), and 4-chlorophenyl glyoxal **3a** (Ar=4-ClC_6H_4, 0.17 g, 1 mmol) was stirred in methanol (5 mL) at room temperature for 10 min, then cyclohexylisocyanide **4a** (R^2=*c*-C_6H_{11}, 0.11 g, 1 mmol) was added to the solution. The mixture was stirred at room temperature for 24 h and was chilled. The solution was condensed and the residue was chromatagraphed to give product **5a** as white solid (0.085 g, 18%). Mp: 161–162 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 15.48 (s, 1H, OH), 7.41 (s, 4H, Ar–H), 5.78 (d, J=7.8 Hz, 1H, NH), 4.24–4.18 (m, 2H, CH_2), 3.91–3.86 (m, 1H, NCH), 2.02–1.23 (m, 10H, CH_2), 1.16 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 170.2, 169.7, 168.3, 136.9, 132.4, 129.3, 128.8, 107.4, 61.8, 49.2, 32.8, 30.2, 28.7, 27.8, 24.4.; MS (m/z, %) 470 (M^+, 2), 346 (33), 139 (61), 111 (69), 57 (100). Anal. Calcd for $C_{21}H_{28}BrClN_2O_3$: C, 53.46; H, 5.98; N, 5.94. Found: C, 53.72; H, 6.06; N, 5.78.

5. Crystallographic material

Compound **6i**: formula $C_{18}H_{23}ClN_2O_3$, colorless crystal. The crystal is of triclinic, space group P-1 with a=6.8083(17) Å, b=11.074(3) Å, c=12.607(3) Å, β=83.901(4)°, V=929.3(4) $Å^3$, Z=2, D_c=1.254 g/cm^3, F(000)=372, μ=0.223 mm^{-1}, R=0.0636 and wR=0.2016 for 3228 observed reflections with $I>2\sigma(I_0)$. Crystallographic data for **6i** have been deposited in the Cambridge Crystallographic Data Center as supplementary publication number CCDC975513. Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.04.033. These data include MOL files and InChiKeys of the most important compounds described in this article.

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