1. Introduction

The increasing demand for the development of new and efficient syntheses of N-heterocycles is explained mainly by their importance in the pharmaceutical and fine chemicals industries. The synthesis of highly functionalized heterocycles remains a major challenge and continues to drive an intense research effort. Different selective methodologies have been described, although many of them present drawbacks such as the need for expensive reagents, specific substrates, harsh or sensitive conditions or long synthetic sequences. Furthermore, some substitution patterns have not been described yet despite their promising applications as bioactive compounds or as intermediates in the synthesis of other compounds, mainly due to limitations of synthetic methodologies.

The ring expansion of β-lactams is one of the various approaches to the synthesis of γ-lactam skeletons, favored due to the β-lactam ring strain. Single-step synthetic methodologies illustrating this reaction can be classified into three main categories: (a) intramolecular transamidation from the proper amino-substituted azetidinone, as 4-(1-aminoalkyl) or 3-(2-aminoalkyl)-2-azetidinone derivatives, which takes place through the N1–C2 cleavage and is the most common one, (b) the rearrangement favored by an electron-deficient position through the C3–C4 cleavage, as the expansion of 4-(1-haloalkyl)-2-azetidinones to γ-lactams via N-acyliminium intermediates, and (c) the rearrangement resulting from an anionic position generated by strong bases, as the benzylic anions generated by LDA in N-benzyl-4-arylazetidinones which rearrange to a γ-lactam through a proposed imine anion intermediate originated in the C4–N1 cleavage. The examples within this latter methodology are very scarce, probably due to the specificity of the substrates needed as well as the reaction conditions (LDA or n-BuLi in anhydrous THF) employed to achieve the expansion (Scheme 1a).

We envisaged the possibility of expanding the scope of this reaction to other substrates, and we planned to use Ugi/post-condensation sequences, seizing their huge potential to yield structurally complex molecules in expedited syntheses from a reduced number of steps. Surprisingly, in addition to the applicability of this strategy to a broad spectrum of substrates, we have found that a rational design of β-lactams, selectively synthesized from Ugi adducts, enables the expansion to highly functionalized γ-lactams using weak bases, under mild and non-moisture-sensitive conditions (box in Scheme 1b). Thus, we have found that variation of the nature of the base employed leads to the selective synthesis of differently functio-

Scheme 1  (a) Previous work. Expansion of β-lactam from an anionic intermediate
(b) Our work
nalized N-heterocyclic systems, some of them with unprecedented functionalization patterns, from common multicomponent Ugi adducts (Scheme 1b).

2. Results and discussion

2.1. Synthesis of azetidinones through Ugi/cyclization sequences

2.1.1. Synthesis of Ugi adducts. Initially, we decided to employ the methodology described for the synthesis of azetidinones through an Ugi/cyclization sequence\textsuperscript{13} implementing a crucial change for our purposes, the use of α-CH activated amines to favor their ulterior deprotonation.

In this way, we prepared different Ugi adducts 5 using 2-nitrobenzylamine 4a, benzylamine 4b and α-amino acid methyl esters 4c–g as amines, along with chloroacetic acids 1a–b, glyoxals 2a–f and different isocyanides 3a–c (Table 1). As we expected, in all cases the enol tautomer was the only one observed, but the spontaneous cyclization never took place.\textsuperscript{14}

2.1.2. Synthesis of azetidinones from Ugi adducts. For the next stage, we observed that the cyclization to azetidinone strongly depended on several factors such as the substituents on the Ugi adduct coming from the halocarboxylic acid and the amine and the base employed. As this step was decisive for our purposes, we looked for the most general optimal conditions.

In this way, different bases were employed in order to achieve the selective cyclization of Ugi adduct 5a to the corresponding azetidinone 6a. Initially, we tried triethylamine under different conditions. It turned out that the use of three equivalents of this base in ethanol and ultrasonication for 1 hour afforded azetidinone 6a with a moderate yield (entry 1, Table 2). Then, we tried potassium and sodium carbonates but the obtained yield was low, because the O-alkylation product was obtained along with the desired C-alkylation compound. Despite this result we observed the influence of cation size, as the smaller sodium cation favors C-alkylation\textsuperscript{15} (entry 2 vs. 4, Table 2). However, when cyclization with lithium carbonate was attempted, the Ugi adduct was recovered (entry 5, Table 2).

![Diagram](Image)

**Table 1** Synthesis of Ugi adducts 5

| Entry | 1 (R\textsuperscript{1}) | 2 (R\textsuperscript{2}) | 3 (R\textsuperscript{3}) | 4 (R\textsuperscript{4}, EWG) | 5\textsuperscript{a} (%) |
|-------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1     | 1a (H)                   | 2a (C\textsubscript{6}H\textsubscript{5}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4a (H, 2-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}) | 5a (89)                 |
| 2     | 1a (H)                   | 2a (C\textsubscript{6}H\textsubscript{5}) | 3b (CH\textsubscript{3}C\textsubscript{6}H\textsubscript{4}) | 4a (H, 2-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}) | 5b (67)                 |
| 3     | 1a (H)                   | 2a (C\textsubscript{6}H\textsubscript{5}) | 3c (C\textsubscript{6}H\textsubscript{11}) | 4a (H, 2-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}) | 5c (59)                 |
| 4     | 1a (H)                   | 2b (4-CH\textsubscript{2}C\textsubscript{6}H\textsubscript{4}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4a (H, 2-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}) | 5d (86)                 |
| 5     | 1a (H)                   | 2c (4-ClC\textsubscript{6}H\textsubscript{4}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4a (H, 2-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}) | 5e (85)                 |
| 6     | 1a (H)                   | 2d (4-FC\textsubscript{6}H\textsubscript{4}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4a (H, 2-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}) | 5f (86)                 |
| 7     | 1a (H)                   | 2e (4-CH\textsubscript{2}OC\textsubscript{6}H\textsubscript{4}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4a (H, 2-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}) | 5g (54)                 |
| 8     | 1a (H)                   | 2f (CH\textsubscript{3}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4a (H, 2-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}) | 5h (39)                 |
| 9     | 1b (C\textsubscript{6}H\textsubscript{5}) | 2a (C\textsubscript{6}H\textsubscript{5}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4a (H, 2-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}) | 5i (93)                 |
| 10    | 1b (C\textsubscript{6}H\textsubscript{5}) | 2d (4-FC\textsubscript{6}H\textsubscript{4}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4a (H, 2-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}) | 5j (86)                 |
| 11    | 1a (H)                   | 2a (C\textsubscript{6}H\textsubscript{5}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4b (H, C\textsubscript{6}H\textsubscript{5}) | 5k (78)                 |
| 12    | 1a (H)                   | 2a (C\textsubscript{6}H\textsubscript{5}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4c (H, CO\textsubscript{2}CH\textsubscript{3}) | 5l (52)                 |
| 13    | 1a (H)                   | 2a (C\textsubscript{6}H\textsubscript{5}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4d (H, CO\textsubscript{2}CH\textsubscript{3}) | 5m (70)                 |
| 14    | 1a (H)                   | 2a (C\textsubscript{6}H\textsubscript{5}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4e (CH\textsubscript{3}CO\textsubscript{2}CH\textsubscript{3}) | 5n (65)                 |
| 15    | 1a (H)                   | 2a (C\textsubscript{6}H\textsubscript{5}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4f (CH\textsubscript{2}CH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{3}) | 5o (55)                 |
| 16    | 1a (H)                   | 2a (C\textsubscript{6}H\textsubscript{5}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4g (CH\textsubscript{2}CH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{3}) | 5p (78)                 |
| 17    | 1b (C\textsubscript{6}H\textsubscript{5}) | 2a (C\textsubscript{6}H\textsubscript{5}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4c (H, CO\textsubscript{2}CH\textsubscript{3}) | 5q (83)                 |
| 18    | 1b (C\textsubscript{6}H\textsubscript{5}) | 2a (C\textsubscript{6}H\textsubscript{5}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4d (C\textsubscript{6}H\textsubscript{5}CO\textsubscript{2}CH\textsubscript{3}) | 5r (76)                 |
| 19    | 1b (C\textsubscript{6}H\textsubscript{5}) | 2a (C\textsubscript{6}H\textsubscript{5}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4e (CH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{3}) | 5s (81)                 |
| 20    | 1b (C\textsubscript{6}H\textsubscript{5}) | 2a (C\textsubscript{6}H\textsubscript{5}) | 3a (C\textsubscript{6}H\textsubscript{11}) | 4f (CH\textsubscript{2}CH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{3}) | 5t (82)                 |

\textsuperscript{a} Yield after purification.
Table 2  Synthesis of β-lactams 6a–k from Ugi adducts 5a–k, all of them derived from benzyl amines, and X-Ray molecular structure of azetidinone 6a. The ORTEP plot is at the 30% probability level.

| Entry | 5 (R₁, R₂, R₃, X) | Base | Equiv. | 6a (%) | d.r. b |
|-------|-------------------|------|--------|--------|--------|
| 1     | 5a (H, C₆H₅, C₆H₅, NO₂) | NEt₃ | 3      | 6a (58) | —      |
| 2     | 5a (H, C₆H₅, C₆H₅, NO₂) | K₂CO₃ a | 1.1    | 6a (14) | —      |
| 3     | 5a (H, C₆H₅, C₆H₅, NO₂) | K₂CO₃ a | 2      | 6a (—)  | —      |
| 4     | 5a (H, C₆H₅, C₆H₅, NO₂) | Na₂CO₃ d | 1.1    | 6a (40) | —      |
| 5     | 5a (H, C₆H₅, C₆H₅, NO₂) | Li₂CO₃ b | 1.1    | 6a (—)  | —      |
| 6     | 5a (H, C₆H₅, C₆H₅, NO₂) | Cs₂CO₃/LiCl f | 1:10  | 6a (65) | —      |
| 7     | 5a (H, C₆H₅, C₆H₅, NO₂) | Cs₂CO₃/LiI f | 1:10  | 6a (92) | —      |
| 8     | 5a (H, C₆H₅, C₆H₅, NO₂) | Cs₂CO₃/LiI f | 1:2   | 6a (88 f) | —      |
| 9     | 5b (H, C₆H₅, CH₂C₆H₄, NO₂) | Cs₂CO₃/LiI f | 1:2   | 6b (79) | —      |
| 10    | 5c (H, C₆H₅, C(CH₃)₃, NO₂) | Cs₂CO₃/LiI f | 1:2   | 6c (67) | —      |
| 11    | 5d (H, 4-CH₃C₆H₄, C₆H₅, NO₂) | Cs₂CO₃/LiI f | 1:2   | 6d (73) | —      |
| 12    | 5e (H, 4-ClC₆H₄, C₆H₅, NO₂) | Cs₂CO₃/LiI f | 1:2   | 6e (72) | —      |
| 13    | 5f (H, 4-FC₆H₄, C₆H₅, NO₂) | Cs₂CO₃/LiI f | 1:2   | 6f (68) | —      |
| 14    | 5g (H, 4-CH₂CH₂C₆H₄, C₆H₅, NO₂) | Cs₂CO₃/LiI f | 1:2   | 6g (76) | —      |
| 15    | 5h (H, CH₂C₆H₄, C₆H₅, NO₂) | Cs₂CO₃/LiI f | 1:2   | 6h (90) | —      |
| 16    | 5i (C₆H₅, C₆H₅, C₆H₅, NO₂) | Cs₂CO₃/LiI f | 1:2   | 6i (84) | 24:76 j |
| 17    | 5j (C₆H₅, C₆H₅, C₆H₅, NO₂) | NEt₃ e | 3      | 6j (93) | 87:13 j |
| 18    | 5k (H, C₆H₅, 4-FC₆H₄, C₆H₅, NO₂) | NEt₃ e | 3      | 6k (87) | 86:14 j |

* Yield after purification. b Diastereomeric ratio determined by 'H NMR. c In ethanol at room temperature and ultrasonication, 2 h. d In acetonitrile at reflux, 12 h. e In acetonitrile at reflux, 12 h. f O-Alkylation by-product. g Mixture of O-alkylation and a new compound identified as γ-lactam 7a.

The Ugi adduct was recovered. h Relative configuration (3R*, 4R*)/(3R*, 4S*). i Diastereoisomers were not separated, characterized as a mixture.

probably due to the low solubility of this salt in organic solvents.

To overcome this limitation, we decided to work with the more soluble cesium carbonate in the presence of an excess of lithium halide to exchange the counter cation. The use of lithium chloride (10 equiv.) improved the C-alkylation yield although the O-alkylation product was still observed (entry 6, Table 2) but, fortunately, the use of lithium iodide yielded β-lactam 6a as a single compound (entry 7, Table 2); furthermore, the amount of this salt may be reduced to 2 equivalents without a significant decrease in chemical yield (entry 8, Table 2), except for the phenylglycine derivative 6m (entries 2 vs. 4, Table 3). These findings could be explained not only by the smaller counter cation, lithium, which binds tightly to oxygen, but also by the Finkelstein transhalogenation reaction. Gratefully, this cyclization strategy proved to be general. Thus, simple refluxing of solutions of Ugi adducts 5 with a combination of cesium carbonate and lithium iodide (1:1:2 equiv.) in acetonitrile for 12 hours afforded in almost all cases the corresponding 2-azetidinones 6. However, triethylamine (3 equiv.) in ethanol and ultrasonication for 2 hours proved to be most often the best choice for the cyclization of 2-chloro-2-phenylacetic derivatives (entries 16 vs. 17, Table 2) as a more efficient strategy. Therefore, this last methodology was chosen as the cyclization strategy for the synthesis of 6i-j and 6q-t. In this way, we achieved chemo- and stereoselective C-alkylation in the cyclization step from Ugi adducts 5, crucial for our purposes in the subsequent synthesis of γ-lactams.

The stereochemical outcome in these reactions was also quite remarkable as the diastereoselectivity observed was fairly good when only one reactant incorporated a stereogenic center, but not when 2-chloro-2-phenylacetic acid (used as a racemate) was combined with α-aminoesters (entries 11–17, Table 3). In addition, the stereochemical results for the 2-chloro-2-phenylacetic acid derivatives were strongly dependent on the cyclization methodology (entry 16 vs. 17, Table 2). Nevertheless, given that the relative configuration of these lactams was not important in the next step, as it will be shown below, the isolation of diastereomers of these β-lactams was not necessary.

2.2. Synthesis of γ-lactams through expansion reactions

During the optimization studies for the synthesis of β-lactams, we gathered some valuable data about the expansion reaction. On one hand, we observed that the treatment of Ugi adduct 5a with two equivalents of potassium carbonate (entry 3, Table 2) afforded γ-lactam 7a as a by-product. On the other hand, the treatment of phenylglycine derivatives 5m and 5r with potas-

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lum carbonate (1.1 equiv.) afforded fused pyrrolidino- 
imides 8 as the major product (entries 5 and 14, Table 3). We 
proposed that the syntheses of these γ-lactams probably pro-
cceeded through the expansion of the corresponding β-lactam 
acting as intermediate.

2.2.1. Expansion reactions on azetidines derived from acti-
vated benzyl amines. In order to demonstrate this fact, we 
tried the expansion to γ-lactam 7a from the isolated β-lactam 
6a. As we expected, the treatment of this azetidinone with po-
tassium carbonate in refluxing acetone for 12 hours afforded 
γ-lactam 7a almost quantitatively and, furthermore, with com-
plete diastereoselectivity (entry 1, Table 4).

The possibility of synthesizing new, complex, and highly 
functionalized γ-lactams through a new and simple method-
ology prompted us to explore the potential of this reaction.
Thankfully, all azetidin-2-ones 6 treated with carbonate 
afforded expansion products, although the results depended 
on the nature of the aminoester and chloroacetic acid derivatives, as 
well as on the base used (Table 5). In this way, lactams derived 
from 2-chloro-2-phenylacetic acid 1b and aminoesters afforded 
a major expansion product, although the chemical result 
depended on the relative configuration of C4/C5, which in 
turn was controlled by the size of the substituent on the amin-
oester (R3). Thus, the expansion of azetidinones derived from 
glycine 6q (R3: H), alanine 6s (R3: CH3) and phenylalanine 6t 
(R3: CH2Ph) afforded the corresponding γ-lactam (7q, 7s and 
7t), with a relative trans disposition of methoxycarbonyl sub-
stituents on C5 and cyclohexylaminocarbamoyl groups on C4, 
which prevented the intramolecular N-acylation (entries 14 
and 18–20, Table 5). However, phenylglycine derivative 6r 
(R3: Ph) yielded γ-lactam 8r fused with an imide ring resulting

| Entry | R1, R2, R3, R4 | Base | Equiv. | d.r. (%) | 
|-------|----------------|------|--------|----------| 
| 1     | 5H, C6H5, C6H11, H | Cs2CO3/LiF | 1:2 | 6l [78] | 
| 2     | 5m, C6H5, C6H11, C6H3 | Cs2CO3/LiF | 1:2 | 6m (—) | 
| 3     | 5m, C6H5, C6H11, C6H3 | NEt3 | 3 | 6m (—) | 
| 4     | 5m, C6H5, C6H11, C6H3 | Cs2CO3/LiF | 1:10 | 6m (81) | 
| 5     | 5m, C6H5, C6H11, C6H3 | K2CO3 | 1.1 | 6m (—) | 
| 6     | 5n, C6H5, C6H11, C6H3 | Cs2CO3/LiF | 1:2 | 6n (90) >98:2 | 
| 7     | 5n, C6H5, C6H11, C6H3 | NEt3 | 3 | 6n (—) | 
| 8     | 5o, C6H5, C6H11, C6H3 | Cs2CO3/LiF | 1:2 | 6o (81) >98:2 | 
| 9     | 5o, C6H5, C6H11, C6H3 | NEt3 | 3 | 6o (—) | 
| 10    | 5p, C6H5, C6H11, C6H3 | Cs2CO3/LiF | 1:2 | 6p (73) >98:2 | 
| 11    | 5q, C6H5, C6H11, C6H3 | Cs2CO3/LiF | 1:2 | 6q (71) 55:45 | 
| 12    | 5q, C6H5, C6H11, C6H3 | NEt3 | 3 | 6q (77) 54:46 | 
| 13    | 5r, C6H5, C6H11, C6H3 | NEt3 | 3 | 6r (45) 84:16 | 
| 14    | 5r, C6H5, C6H11, C6H3 | K2CO3 | 1.1 | 6r (—) | 
| 15    | 5s, C6H5, C6H11, C6H3 | Cs2CO3/LiF | 1:2 | 6s (90) 53:24:18:11 | 
| 16    | 5s, C6H5, C6H11, C6H3 | NEt3 | 3 | 6s (93) 30:26:26:18 | 
| 17    | 5t, C6H5, C6H11, C6H3 | NEt3 | 3 | 6t (75) 58:35:7: n.d. | 

* Yield after purification. ** Diastereomeric ratio determined by 1H NMR. % In acetonitrile at reflux, 12 h. In ethanol at room temperature and 
ultrasonication, 2 h. Complex reaction mixture. Mixture of O-alkylation and a new compound identified as a fused pyrrolidinone-imide 8 obtained as 
the major product. Mixture of O-alkylation and a new compound identified as γ-lactam 7a. The Ugi adduct was recovered. Relative configuration (3R*,4R*)/(3R*,4S*). Both diastereoisomers were separated and fully characterized. Only the major dia-
stereoisomer was isolated and fully characterized (n.d.; not detected).
Table 4 Expansion products resulting from the basic treatment of β-lactams 6a–k derived from benzyl amines and X-Ray molecular structures of pyrrolidinones 7d and 7jadiast2. The ORTEP plot is at the 30% probability level.

| Entry | R1, R2, R3, X | % yield | d.r.  
|-------|--------------|---------|---------
| 1     | H, C6H5, C6H4NO2 | 7a (90) | >98 : 2  
| 2     | H, C6H5, CH2CH3 | 7b (79) | 97 : 3  
| 3     | H, C6H5, C(CH3)3 | 7c (67) | >98 : 2  
| 4     | H, 4-C6H4CH3, C6H4NO2 | 7d (71) | 92 : 8  
| 5     | H, 4-ClC6H4, C6H4NO2 | 7e (44) | >98 : 2  
| 6     | H, 4-FC6H4, C6H4NO2 | 7f (42) | >98 : 2  
| 7     | H, 4-CH2OC6H4, C6H4NO2 | 7g (71) | >98 : 2  
| 8     | H, CH2CH3, C6H4NO2 | 7h (76) | >98 : 2  
| 9     | C6H5, C6H4CH3, C6H4NO2 | 7i (92) | 64 : 36 : n.d. : n.d.  
| 10    | C6H5, 4-FC6H4, C6H4NO2 | 7j (91) | 57 : 43 : n.d. : n.d.  
| 11    | H, C6H5, C6H4, H | 7k (71) | —  

*Yield after purification. Relative configuration determined by 1H NMR in the reaction mixture. Relative configuration determined by NOESY and X-ray diffraction experiments. Yield as mixture of diastereomers. Relative configuration determined by NOESY and X-ray diffraction experiments. Azetidine 6k was recovered. Treatment of azetidine 6k with different bases has been further investigated (see Scheme 3).

from the intramolecular N-acylation, which is explained by the relative cis disposition of the aforesaid substituents (entries 16 and 17, Table 5). These results were similar when cesium or potassium carbonate were employed as bases, although the use of cesium carbonate was more efficient as the reaction time was notably reduced (entry 18 vs. 19, Table 5). Moreover, the phenylglycine derivative was obtained directly from the Ugi adduct, as the higher acidity of the α-CH substituent on the nitrogen of the azetidinone favored its deprotonation (entry 16, Table 5). Furthermore, a single diastereomer was observed, except for glycine derivative 7q (R3: H). Nevertheless, expansion of azetidinones 6l–p, derived from aminoesters and 2-chloroacetic acid 1a, was highly dependent on the nature of the carbonate employed. Thus, the use of cesium carbonate gave cleaner results, yielding new bicyclic compounds 9 which resulted from expansion followed by spontaneous intramolecular N-acylation and debenzoylation reactions. Meanwhile, when potassium carbonate was employed, up to three different compounds were observed, γ-lactam 7, the fused imide-lactam 8 and the debenzoylated fused imide-
lactam 9 (entries 8 and 10, Table 5). Again, the phenylglycine derivative was the only one which gave the fused γ-lactam 8m selectively (entry 4, Table 5) starting from the corresponding Ugi adduct.

Thus, the chemical results for the aminoester series were controlled mainly by the substituents size, firstly by the C3 substitution on the γ-lactam (R1) (entries 1–13 vs. 14–20, Table 5) and secondly by the C5 substitution (R3) (entries 8, 10 and 13, Table 5), which is explained by the steric hindrance exerted by the different substituents, and additionally by the nature of the carbonate employed. This shows the importance of the counter cation on the stereoselectivity of enolate reactions, which is reflected on the chemical result (entries 7, 9 vs. 8, 10, Table 5). These results are remarkable taking into account that ring expansion is promoted by a weak base in a mild solvent under an air atmosphere, in contrast to the strong bases and dry atmosphere needed for the ring expansion previously reported; moreover, high diastereoselectivities are observed in these syntheses.

2.3. Mechanism proposal for the expansion reaction

In order to understand the mechanism of expansion reactions, it is important to emphasize two significant points in their stereochemical outcome: (1) the results were independent of the diastereomeric purity of the β-lactam employed, which simplifies the experimental work to a great extent, and (2) the use of enantiomerically pure α-aminoesters leads to γ-lactams as racemates. In this way, an anionic rearrangement can be proposed starting from the deprotonation of the acidic position in the N-substituent of the azetidinone favoring its opening, which would destroy the chiral centers on C4 and the N-substituent on azetidinone 6, affording an intermediate containing an imine and an enolate, which would react intramolecularly yielding the corresponding pyrrolidinone (Scheme 2).

2.4. Synthesis of debenzoylated γ-lactams

As γ-lactams fused with an imide ring 8 were debenzoylated under some of the conditions tried (entries 1–3, 5–11 and 13, 15, Table 5), we tried the debenzoylation for the different γ-lactams synthesized, in order to obtain a new family of pyrrolidine-2-ones. Thus, the treatment of pyrrolidin-2-ones 7a–c with a catalytic amount of potassium hydroxide in ethanol at room temperature afforded the corresponding deacylated pyrrolidin-2-one 10 as the result of a retro-Claisen reaction; moreover, the only cis diastereoisomer was observed by 1H NMR in the reaction mixture (entries 1–3, Table 6). However, when we tried debenzoylation on lactams derived from 2-chloro-2-phe-nylacetic acid and/or α-aminoester derivatives, it was unsuccessful, probably due to steric hindrance for the former and saponification of the ester group for the latter (entries 4 and 5, Table 6).

2.5. Study of the expansion reaction on azetidine 6k, derived from a non-activated benzyl amine

Finally, we studied the expansion on azetidine 6k, derived from a non-activated amine. As noted above, the azetidine
Table 5  Expansion products resulting from the basic treatment of β-lactams 6l–t derived from α-aminoesters and X-Ray molecular structures of fused pyrrolidinone-imides 8m and 9n. The ORTEP plot is at the 30% probability level

| Entry | 6 (R1, R2, R3, R4) | Carbonate | Equiv. | t (h) | 7 (%) | 8 (%) | 9 (%) |
|-------|---------------------|-----------|--------|-------|-------|-------|-------|
| 1     | 6l (H, C6H5, C6H12, H) | Cs2CO3    | 1.2    | 1     | —     | —     | 9l (73) |
| 2     | 6l (H, C6H5, C6H12, H) | K2CO3, b,c | 1.2    | 12    | 7l (18) | —     | 9l (58) |
| 3     | 6m (H, C6H5, C6H12, C6H3) | K2CO3, b,c | 2.2    | 1     | —     | —     | 9m (65) |
| 4     | 6m (H, C6H5, C6H12, C6H3) | K2CO3, b,c | 1.1    | 12    | 8m (83) | —     | —     |
| 5     | 6m (H, C6H5, C6H12, C6H3) | K2CO3      | 1.2    | 1     | —     | 8m (30) | 9m (52) |
| 6     | 6m (H, C6H5, C6H12, C6H3) | K2CO3      | 1.2    | 12    | —     | 8m (68) | 9m (12) |
| 7     | 6n (H, C6H5, C6H12, CH3) | K2CO3      | 1.2    | 1     | —     | —     | 9n (75) |
| 8     | 6n (H, C6H5, C6H12, CH3) | K2CO3      | 1.2    | 12    | 7n (58) | 8n (9) | 9n (10) |
| 9     | 6o (H, C6H5, C6H12, C6H3CH3) | Cs2CO3 | 1.2    | 1     | —     | —     | 9o (57) |
| 10    | 6o (H, C6H5, C6H12, C6H3CH3) | K2CO3 | 1.2    | 12    | 7o (38) | 8o (36) | 9o (10) |
| 11    | 6p (H, C6H5, C6H12, CH(CH3)3) | Cs2CO3 | 1.2    | 1     | —     | —     | 9p (65) |
| 12    | 6p (H, C6H5, C6H12, CH(CH3)3) | K2CO3 | 1.2    | 12    | —     | 8p (5)  | —     |
| 13    | 6p (H, C6H5, C6H12, CH(CH3)3) | K2CO3 | 1.2    | 12    | 7p (78) | —     | 9p (8)  |
| 14    | 6q (C6H5, C6H5, C6H12, H) | Cs2CO3 | 1.2    | 12    | 7q (32) | —     | —     |
| 15    | 6q (C6H5, C6H5, C6H12, H) | Cs2CO3 | 2.0    | 12    | —     | —     | —     |
| 16    | 6r (C6H5, C6H5, C6H12, C6H3CH3) | K2CO3 | 1.2    | 5     | —     | 8r (70) | —     |
| 17    | 6r (C6H5, C6H5, C6H12, C6H3CH3) | Cs2CO3 | 1.2    | 1     | —     | 8r (72) | —     |
| 18    | 6s (C6H5, C6H5, C6H12, CH3) | K2CO3 | 1.2    | 12    | 7s (75) | —     | —     |
| 19    | 6s (C6H5, C6H5, C6H12, CH3) | K2CO3 | 1.2    | 1     | 7s (80) | —     | —     |
| 20    | 6s (C6H5, C6H5, C6H12, CH3) | Cs2CO3 | 1.2    | 1     | 7s (67) | —     | —     |

a Yield after purification. b Synthesis carried out from the Ugi adduct. c Mixture of O-alkylation and expansion products. d After 12 h most of the azetidine was recovered. e After 72 h some azetidine was recovered. f Two diastereomers were observed (d.r. 68 : 32). g Yield referred to the major diastereomer after purification. h Complex reaction mixture. i A single diastereomer was observed.

Scheme 2  Proposed mechanism for the anionic rearrangement from azetidinones 6 to pyrrolidinones 7.

Table 6  Debenzoylation of pyrrolidine-2-ones 7

| Entry | 4 (R1, R2, EWG) | 10 (%) | d.r. h,i |
|-------|-----------------|--------|----------|
| 1     | 7a (H, C6H5, 2-NO2C6H4) | 10a (76) | >98:2 |
| 2     | 7b (H, CH2C6H5, 2-NO2C6H4) | 10b (58) | >98:2 |
| 3     | 7c (H, C(CH3)3, 2-NO2C6H4) | 10c (72) | >98:2 |
| 4     | 7i (C6H5, C6H12, 2-NO2C6H4) | 10i (—) | — |
| 5     | 7j (H, C6H11, CO2CH3) | 10j (—) | — |

a Yield after purification. b Diastereomeric ratio determined by 1H NMR. c Relative configuration (4R*,5S*) in the major diastereomer, determined by NOESY experiments. d The γ-lactam was recovered. e Complex reaction mixture.
was recovered when it was treated with potassium carbonate (entry 11, Table 4). This proves the key role of acidity of the α-CH substituent on the nitrogen, so we tested stronger bases. When we tried potassium hydroxide debenzoylated azetidine 11 was the only product observed (entry 2, Table 7). Therefore, we tried LDA in dry THF, which afforded γ-lactam 7k but in low yield, with the result depending on the amount of base employed. Thus, when 1.2 equivalents were used, γ-lactam 7k was obtained together with debenzoylated azetidine 11 (entry 3, Table 7) because of the presence of traces of water in the medium. In order to reduce the formation of this compound we increased the amount of LDA employed (3.0 equiv.). In this way, the formation of azetidinone 11 was not observed, but a new compound identified as succinimide 12 was generated (entry 4, Table 7). These results highlight the importance of the nature of the base employed. Thus, when 1.2 equivalents were used, γ-lactam 7k was recovered. Moreover, it was the only product observed (entry 2, Table 7). This succinimide was probably generated through the competing formation of a C-anion on the azetidine ring. Thus, the new C-anion would favor the ring opening to a diamide anion, which after an intramolecular cyclization to a five-member ring followed by an intramolecular Cannizaro-type reaction, would afford inside 12 (Scheme 3).

3. Conclusions

These results show the versatility of Ugi adducts in the synthesis of highly functionalized N-heterocycles through post-condensation reactions. Different ring-size lactams with different substituents have been synthesized using simple protocols, in many cases with a high diastereoselectivity. Moreover, the rational design of Ugi adducts allows the synthesis of β-lactams which rearrange to γ-lactams using simple, economical and low moisture-sensitive bases, in an air atmosphere and in a robust manner. Interestingly, the substitution patterns achieved in some structures have not been reported before.

Conflicts of interest

There are no conflicts to declare.

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References

1 (a) Heterocycles in Life and Society, ed. A. F. Pozharskii, A. T. Soldatenkov and A. R. Katrizky, John Wiley & Sons, Ltd, 2nd edn, 2011, pp. 209–244; (b) C. Lamberth, Pest Manage. Sci., 2013, 69, 1106–1114; (c) E. Vitaku, D. T. Smith and J. T. Njardarson, J. Med. Chem., 2014, 57, 10257–10274.
2 (a) A. Lei, J. P. Waldkirch, M. He and X. Zhang, Angew. Chem., Int. Ed., 2002, 41, 4526–4529; (b) P. Y. Ng, Y. Tang, W. M. Knop, H. S. Stadler and J. T. Shaw, Angew. Chem., Int. Ed., 2007, 46, 5352–5355; (c) J. Yu, F. Shi and L.-Z. Gong, Acc. Chem. Res., 2011, 44, 1156–1171; (d) R. Narayan, M. Potowski, Z. J. Jia, A. P. Antonchick and H. Waldmann, Acc. Chem. Res., 2014, 47, 1296–1310; (e) A. McNally, B. Haffemayer, B. S. L. Collins and M. J. Gaunt, Nature, 2014, 510, 129–133; (f) N. Fuentes, W. Kong, L. Fernández-Sánchez, E. Merino and C. Nevado, J. Am. Chem. Soc., 2015, 137, 964–973; (g) A. P. Taylor, R. P. Robinson, Y. M. Fobian, D. C. Blakemore, L. H. Jones and O. Fadeyi, Org. Biomol. Chem., 2016, 14, 6611–6637; (h) A. Geranurimi and W. D. Lubell, Org. Lett., 2018, 20,

Table 7 Products resulting from the basic treatment of γ-lactam 6k derived from benzylamine

| Entry | Base | Solvent | Equiv. | 11 (%) | 7k (%) | 12 (%) |
|-------|------|---------|--------|--------|--------|--------|
| 1     | KOH  | Acetone | 1.1    | —      | —      | —      |
| 2     | KOH  | EtOH    | Cat.   | 94     | 23d,e  | —      |
| 3     | LDA  | THF     | 1.2    | 21     | 27d,e  | —      |
| 4     | LDA  | THF     | 3.0    | —      | —      | 14     |

d Reflux, 12 h. Azetidine 6k was recovered. e Ultrasonication, 30 min. f Room temperature, 5 h. g Diastereomeric ratio determined by 1H NMR as 1 : 1. h Diastereoisomers were not separated.

Scheme 3 Results for the treatment of azetidine 6l with base and proposed mechanism for the synthesis of succinimide 12 (Cy = cyclohexyl).
For the synthesis of $\beta$-lactams see: (a) C. R. Pitts and T. Lectka, *Chem. Rev.*, 2014, 114, 7930–7953; (b) S. Hosseyni and A. Jarrahpour, *Org. Biomol. Chem.*, 2018, 16, 6840–6852; For the synthesis of $\gamma$-lactams see: (c) F. Rivas and T. Ling, *Org. Prep. Proced. Int.*, 2016, 48, 254–295; (d) J. Caruano, G. G. Muccioli and R. Robiette, *Org. Biomol. Chem.*, 2016, 14, 10134–10156.

4 (a) S. Dandapani and L. A. Marcaurelle, *Nat. Chem. Biol.*, 2010, 6, 861–863; (b) A. Barker, J. G. Kettle, T. Nowak and J. E. Pease, *Drug Discovery Today*, 2013, 18, 298–304.

5 S. Comesse, M. Sanselme and A. Daïch, *J. Org. Chem.*, 2008, 73, 5566–5569.

6 B. Alcaide, P. Almendros and C. Aragoncillo, *Chem. Rev.*, 2007, 107, 4437–4492.

7 (a) B. Alcaide, P. Almendros, C. Aragoncillo, R. Callejo and M. P. Ruiz, *J. Org. Chem.*, 2013, 78, 10154–10165; (b) B. Alcaide, P. Almendros, R. Martin-Montero and M. P. Ruiz, *Adv. Synth. Catal.*, 2016, 358, 1469–1477.

8 (a) S. Kano, T. Ebata and S. Shibuya, *Chem. Pharm. Bull.*, 1979, 27, 2450–2455; (b) T. J. Fleck, W. W. McWhorter Jr., R. N. DeKam and B. A. Pearlman, *J. Org. Chem.*, 2003, 68, 9612–9617.

9 (a) W. Van Brabandt and N. De Kimpe, *J. Org. Chem.*, 2005, 70, 3369–3374; (b) W. Van Brabandt, R. Van Landeghem and N. De Kimpe, *Org. Lett.*, 2006, 8, 1105–1108; (c) S. Dekeukeleire, M. D’Hooge and N. De Kimpe, *J. Org. Chem.*, 2009, 74, 1644–1649; (d) M. D’hooge, S. Dekeukeleire, E. Leemans and N. De Kimpe, *Pure Appl. Chem.*, 2010, 82, 1749–1759.

10 T. Durst, R. Van Den Elzen and M. J. LeBelle, *J. Am. Chem. Soc.*, 1972, 94, 9261–9263.

11 (a) J. Escalante and M. A. Gonzalez-Tototzin, *Tetrahedron: Asymmetry*, 2003, 14, 981–985; (b) T. Sakai, K. Yamada and K. Tomioka, *Chem. – Asian J.*, 2008, 3, 1486–1493; (c) M.-J. Lee and C. Ahn, *Bull. Korean Chem. Soc.*, 2016, 37, 580–583.

12 (a) Z. Xu, F. De Moliner, A. P. Cappelli and C. Hulme, *Angew. Chem., Int. Ed.*, 2012, 51, 8037–8040; (b) U. K. Sharma, N. Sharma, D. D. Vachhani and E. V. Van der Eycken, *Chem. Soc. Rev.*, 2015, 44, 1836–1860; (c) Y. He, Z. Li, K. Robeyns, L. Van Meervelt and E. V. Van der Eycken, *Angew. Chem., Int. Ed.*, 2018, 57, 272–276; (d) S. Wang, Y. Tao, J. Wang, Y. Tao and X. Wang, *Chem. Sci.*, 2019, 10, 1531–1538; (e) K. Singh, B. K. Malviya, P. K. Jaiswal, V. P. Verma, S. S. Chimni and S. Sharma, *Org. Lett.*, 2019, 21, 6726–6730.

13 X.-H. Zeng, H.-M. Wang, Y.-M. Yan, L. Wu and M.-W. Ding, *Tetrahedron*, 2014, 70, 3647–3652.

14 P. Pertejo, A. Sancho-Medina, T. Hermosilla, B. González-Saiz, J. Gómez-Ayuso, R. Quesada, D. Moreno, I. Carreira-Barral and M. García-Valverde, *Molecules*, 2021, 26, 919.

15 L. M. Jackman and B. C. Lange, *Tetrahedron*, 1977, 33, 2737–2769.

16 H. Finkelstein, *Ber. Dtsch. Chem. Ges.*, 1910, 43, 1528–1532.

17 Y. Hu, R. L. Bishop, A. Luxenburger, S. Dong and L. A. Paquette, *Org. Lett.*, 2006, 8, 2733–2737.