



Cite this: *Green Chem.*, 2022, **24**, 7988

Base-selective access to highly functionalized heterocycles from multicomponent Ugi adducts†

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Received 3rd August 2022,
Accepted 23rd September 2022

DOI: 10.1039/d2gc02896d

rsc.li/greenchem

Selection of the appropriate base in Ugi/post-condensation sequences allows the selective syntheses of different ring-size functionalized lactams. The developed methodology uses inexpensive bases under mild and non-sensitive conditions leading to the facile generation of molecular diversity from simple synthons.

1. Introduction

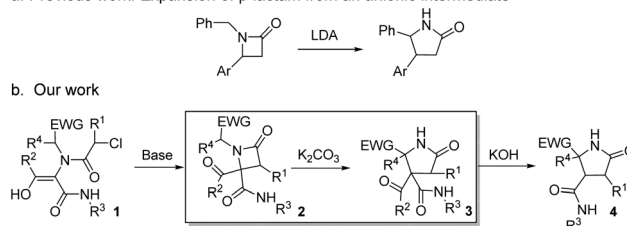
The increasing demand for the development of new and efficient syntheses of N-heterocycles is explained mainly by their importance in the pharmaceutical and fine chemicals industries.¹ The synthesis of highly functionalized heterocycles remains a major challenge and continues to drive an intense research effort.² 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.³ 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.⁴

The ring expansion of β -lactams is one of the various approaches to the synthesis of γ -lactam skeletons,⁵ favored due to the β -lactam ring strain.⁶ 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)⁷ or 3-(2-aminoalkyl)-2-azetidinone derivatives,⁸ 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,⁹ 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.¹⁰ The examples within this latter methodology are very scarce,¹¹ 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.¹² 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 func-

a. Previous work. Expansion of β -lactam from an anionic intermediate



Scheme 1 (a) Previous work on ring expansion of β -lactams through an anionic rearrangement and (b) summary of N-heterocycles synthesized from common Ugi adducts.

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†Electronic supplementary information (ESI) available. CCDC 2193426, 2193428–2193430 and 2193435. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d2gc02896d>



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 sequence¹³ 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.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*-alkylation¹⁵ (entry 2 vs. 4, Table 2). However, when cyclization with lithium carbonate was attempted, the Ugi adduct was recovered (entry 5, Table 2),

Table 1 Synthesis of Ugi adducts **5**

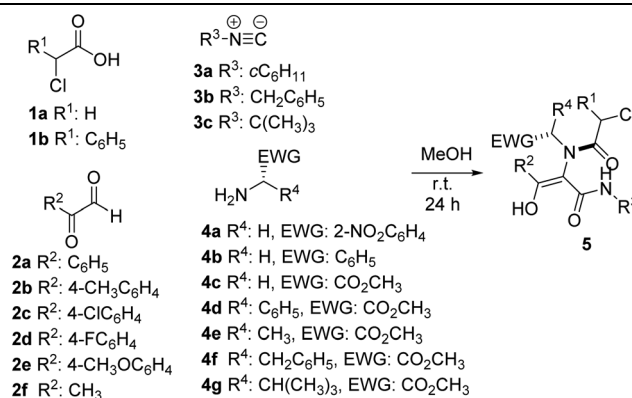
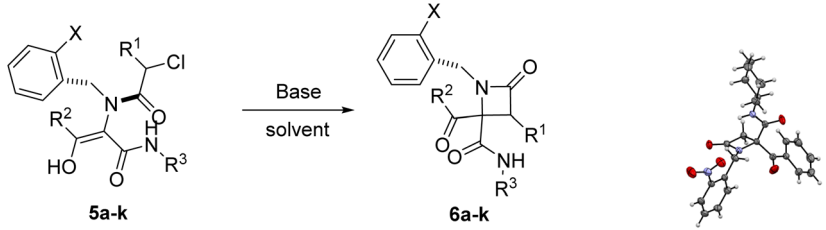


Table 2 Synthesis of β -lactams **6a–k** from Ugi adducts **5a–k**, all of them derived from benzyl amines, and X-Ray molecular structure of azetidinone **6a**. The ORTEP plot is at the 30% probability level

					
Entry	5 (R^1 , R^2 , R^3 , X)	Base	Equiv.	6 ^a (%)	d.r. ^b
1	5a (H, C ₆ H ₅ , cC ₆ H ₁₁ , NO ₂)	NEt ₃ ^c	3	6a (58)	—
2	5a (H, C ₆ H ₅ , cC ₆ H ₁₁ , NO ₂)	K ₂ CO ₃ ^d	1.1	6a (14) ^f	—
3	5a (H, C ₆ H ₅ , cC ₆ H ₁₁ , NO ₂)	K ₂ CO ₃ ^d	2	6a (—) ^g	—
4	5a (H, C ₆ H ₅ , cC ₆ H ₁₁ , NO ₂)	Na ₂ CO ₃ ^d	1.1	6a (40) ^f	—
5	5a (H, C ₆ H ₅ , cC ₆ H ₁₁ , NO ₂)	Li ₂ CO ₃ ^d	1.1	6a (—) ^h	—
6	5a (H, C ₆ H ₅ , cC ₆ H ₁₁ , NO ₂)	CS ₂ CO ₃ /LiCl ^e	1 : 10	6a (65) ^f	—
7	5a (H, C ₆ H ₅ , cC ₆ H ₁₁ , NO ₂)	CS ₂ CO ₃ /LiI ^e	1 : 10	6a (92)	—
8	5a (H, C ₆ H ₅ , cC ₆ H ₁₁ , NO ₂)	CS ₂ CO ₃ /LiI ^e	1 : 2	6a (88) ^f	—
9	5b (H, C ₆ H ₅ , CH ₂ C ₆ H ₅ , NO ₂)	CS ₂ CO ₃ /LiI ^e	1 : 2	6b (79)	—
10	5c (H, C ₆ H ₅ , C(CH ₃) ₃ , NO ₂)	CS ₂ CO ₃ /LiI ^e	1 : 2	6c (67)	—
11	5d (H, 4-CH ₃ C ₆ H ₄ , cC ₆ H ₁₁ , NO ₂)	CS ₂ CO ₃ /LiI ^e	1 : 2	6d (73)	—
12	5e (H, 4-ClC ₆ H ₄ , cC ₆ H ₁₁ , NO ₂)	CS ₂ CO ₃ /LiI ^e	1 : 2	6e (72)	—
13	5f (H, 4-FC ₆ H ₄ , cC ₆ H ₁₁ , NO ₂)	CS ₂ CO ₃ /LiI ^e	1 : 2	6f (68)	—
14	5g (H, 4-CH ₃ OC ₆ H ₄ , cC ₆ H ₁₁ , NO ₂)	CS ₂ CO ₃ /LiI ^e	1 : 2	6g (76)	—
15	5h (H, CH ₃ , cC ₆ H ₁₁ , NO ₂) ^b	CS ₂ CO ₃ /LiI ^e	1 : 2	6h (90)	—
16	5i (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , NO ₂)	CS ₂ CO ₃ /LiI ^e	1 : 2	6i (84)	24 : 76 ^{i,j}
17	5i (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , NO ₂)	NEt ₃ ^c	3	6i (93)	87 : 13 ^{i,j}
18	5j (C ₆ H ₅ , 4-FC ₆ H ₄ , cC ₆ H ₁₁ , NO ₂)	NEt ₃ ^c	3	6j (86)	86 : 14 ^{i,j}
19	5k (H, C ₆ H ₅ , cC ₆ H ₁₁ , H)	CS ₂ CO ₃ /LiI ^e	1 : 2	6k (87)	—

^a Yield after purification. ^b Diastereomeric ratio determined by ¹H NMR. ^c In ethanol at room temperature and ultrasonication, 2 h. ^d In acetone 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**. ^h The Ugi adduct was recovered. ⁱ Relative configuration (3*R**,4*R**)/(3*R**,4*S**). ^j 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 halides 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.¹⁶ 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 chemoselective *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 potass-



Chemical reaction scheme showing the conversion of compound **51-t** to compound **61-t** using a base in a solvent.

Compound **51-t** (starting material) is a 4-chloro-2-hydroxy-1-methoxycarbonyl-3,4-dihydro-2H-pyridine derivative. It features substituents R^1 , R^2 , R^3 , and R^4 .

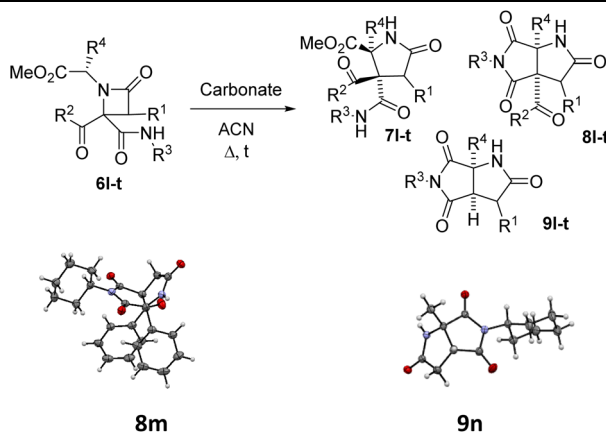
Reaction conditions: Base, solvent.

Compound **61-t** (product) is a 4-oxo-2-methoxycarbonyl-3,4-dihydro-2H-pyridine derivative, where the chlorine atom has been replaced by a carbonyl group.

^a Yield after purification. ^b Diastereomeric ratio determined by ¹H NMR. ^c In acetonitrile at reflux, 12 h. ^d In ethanol at room temperature and ultrasonication, 2 h. ^e In acetone at reflux, 12 h. ^f Complex reaction mixture. ^g Mixture of *O*-alkylation and a new compound identified as a fused pyrrolidinone-imide **8** obtained as the major product. ^h Mixture of *O*-alkylation and a new compound identified as γ -lactam **7a**. ⁱ The Ugi adduct was recovered. ^j Relative configuration (3*R**,4*R**)/(3*R**,4*S**). ^k Both diastereoisomers were separated and fully characterized. ^l Only the major diastereoisomer was isolated and fully characterized (n.d.: not detected).

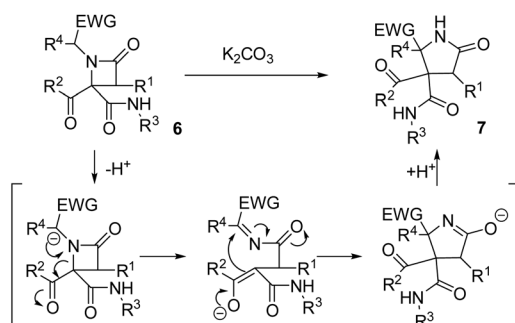
2.2.2. Expansion reactions on azetidines derived from α -aminoesters. Expansion reactions for aminoester derivatives also took place, but the results were highly dependent on the nature of the aminoester and chloroacetic acid derivatives, as well as on the base used (Table 5). In this way, lactams derived from 2-chloro-2-phenylacetic acid **1b** and aminoesters afforded a major expansion product, although the chemical result depended on the relative configuration on *C4/C5*, which in turn was controlled by the size of the substituent on the aminoester (R^4). Thus, the expansion of azetidinones derived from glycine **6q** (R^4 : H), alanine **6s** (R^4 : CH_3) and phenylalanine **6t** (R^4 : CH_2Ph) afforded the corresponding γ -lactam (**7q**, **7s** and **7t**), with a relative *trans* disposition of methoxycarbonyl substituents on *C5* and cyclohexylaminocarbonyl groups on *C4*, which prevented the intramolecular *N*-acylation (entries 14 and 18–20, Table 5). However, phenylglycine derivative **6r** (R^4 : Ph) yielded γ -lactam **8r** fused with an imide ring resulting

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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 (R^1, R^2, R^3, R^4)	Carbonate	Equiv.	t (h)	7 (%) ^a	8 (%) ^a	9 (%) ^a
1	6l (H, C ₆ H ₅ , cC ₆ H ₁₁ , H)	CS ₂ CO ₃	1.2	1	—	—	9l (73)
2	6l (H, C ₆ H ₅ , cC ₆ H ₁₁ , H)	K ₂ CO ₃	1.2	12	7l (18)	—	9l (58)
3	6m (H, C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅)	CS ₂ CO ₃ ^{b,c}	2.2	1	—	—	9m (65)
4	6m (H, C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅)	K ₂ CO ₃ ^{b,c}	1.1	12	—	8m (83)	—
5	6m (H, C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅)	CS ₂ CO ₃	1.2	1	—	8m (30)	9m (52)
6	6m (H, C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅)	K ₂ CO ₃	1.2	12	—	8m (68)	9m (12)
7	6n (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH ₃)	CS ₂ CO ₃	1.2	1	—	—	9n (75)
8	6n (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH ₃)	K ₂ CO ₃	1.2	12	7n (58)	8n (9)	9n (10)
9	6o (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH ₂ C ₆ H ₅)	CS ₂ CO ₃	1.2	1	—	—	9o (57)
10	6o (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH ₂ C ₆ H ₅)	K ₂ CO ₃	1.2	12	7o (38)	8o (36)	9o (10)
11	6p (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH(CH ₃) ₂)	CS ₂ CO ₃	1.2	1	—	—	9p (65)
12	6p (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH(CH ₃) ₂)	K ₂ CO ₃	1.2	12 ^d	—	8p (5)	—
13	6p (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH(CH ₃) ₂)	K ₂ CO ₃	1.2	72	—	8p (78)	9p (8)
14	6q (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , H)	CS ₂ CO ₃	1.2	72 ^e	7q ^f (32) ^g	—	—
15	6q (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , H)	CS ₂ CO ₃	2.0	12	— ^h	—	—
16	6r (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅)	K ₂ CO ₃ ^{b,c}	1.2	5	—	8r (70)	—
17	6r (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅)	CS ₂ CO ₃	1.2	1	—	8r (72)	—
18	6s (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , CH ₃)	K ₂ CO ₃	1.2	12	7s ⁱ (75)	—	—
19	6s (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , CH ₃)	CS ₂ CO ₃	1.2	1	7s ⁱ (80)	—	—
20	6t (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , CH ₂ C ₆ H ₅)	CS ₂ CO ₃	1.2	1	7t ⁱ (67)	—	—

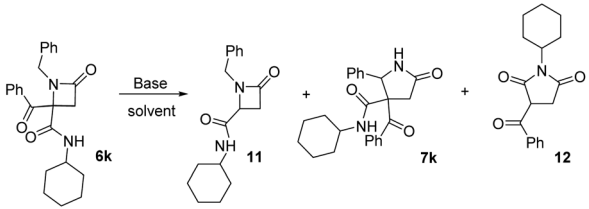
^a Yield after purification. ^b Synthesis carried out from the Ugi adduct. ^c Mixture of *O*-alkylation and expansion products. ^d After 12 h most of the azetidine was recovered. ^e After 72 h some azetidine was recovered. ^f Two diastereomers were observed (d.r. 68:32). ^g Yield referred to the major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

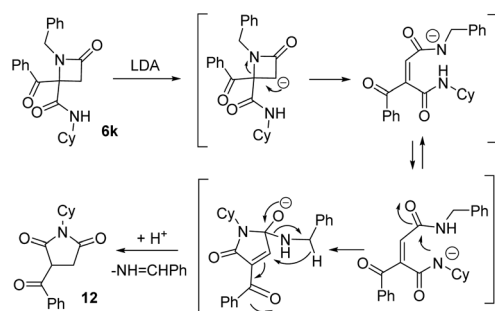
Entry	4 (R^1, R^3, EWG)	10 (%) ^a	d.r. ^{b,c}
1	7a (H, cC ₆ H ₁₁ , 2-NO ₂ C ₆ H ₄)	10a (76)	>98:2
2	7b (H, CH ₂ C ₆ H ₅ , 2-NO ₂ C ₆ H ₄)	10b (58)	>98:2
3	7c (H, C(CH ₃) ₃ , 2-NO ₂ C ₆ H ₄)	10c (72)	>98:2
4	7i (C ₆ H ₅ , cC ₆ H ₁₁ , 2-NO ₂ C ₆ H ₄)	10i (—) ^d	—
5	7l (H, cC ₆ H ₁₁ , CO ₂ CH ₃)	10l (—) ^e	—

^a Yield after purification. ^b Diastereomeric ratio determined by ¹H NMR. ^c Relative configuration (4*R**,5*S**) in the major diastereomer, determined by NOESY experiments. ^d The γ -lactam was recovered. ^e Complex reaction mixture.



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


Entry	Base	Solvent	Equiv.	11 (%)	7k (%)	12 (%)
1	K ₂ CO ₃ ^a	Acetone	1.1	—	—	—
2	KOH ^b	EtOH	Cat.	94	—	—
3	LDA ^c	THF	1.2	21	23 ^{d,e}	—
4	LDA ^c	THF	3.0	—	27 ^{d,e}	14

^a Reflux, 12 h. Azetidinone **6k** was recovered. ^b Ultrasonication, 30 min.^c Room temperature, 5 h. ^d Diastereomeric ratio determined by ¹H NMR as 1 : 1. ^e Diastereoisomers were not separated.**Scheme 3** Results for the treatment of azetidinone **6l** with base and proposed mechanism for the synthesis of succinimide **12** (Cy = cyclohexyl).

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 azetidinone **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 azetidinone **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 *N*-substituent on the azetidine system.

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 Cannizzaro-type reaction, would afford imide **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

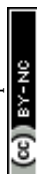
There are no conflicts to declare.

Acknowledgements

Funding from Consejería de Educación de la Junta de Castilla y León and European Regional Development Fund (ERDF) (project BU075G19 and project BU067P20) and MCIN/AEI/10.13039/501100011033 [grant PID2020-117610RB-I00] is gratefully acknowledged. B. G.-S. and I. C.-B. thank Consejería de Educación de la Junta de Castilla y León, European Social Fund (ESF) and ERDF for their predoctoral (B. G.-S) and post-doctoral (I. C.-B.) contracts.

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