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Synthesis of Tetrahydronaphthoazetidinones, 2,5-Dioxo-1,4-methanobenzoazepines and 3-Hydroxypyrrolidinones Through Copper-Assisted Post-Ugi Reactions

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Abstract: Copper-assisted post-Ugi reactions enable access to different heterocyclic systems, tetrahydronaphthoazetidinone, 2,5-dioxo-1,4-methanobenzoazepine and 3-hydroxypyrrolidinone derivatives. The described process affords complex scaffolds from readily available acyclic precursors using simple protocols.

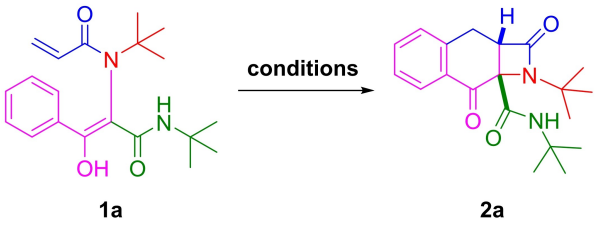
Keywords: Multicomponent reactions; radical reactions; copper; lactams; post-Ugi reactions

Introduction

Multicomponent reactions (MCRs) represent powerful synthetic approaches for the preparation of complex molecules.[1] Efficiency, atom economy, diversity and accessibility are hallmarks of MCRs. The Ugi four-component reaction is an isocyanide-based multicomponent reaction of prominent relevance.[2] Coupled to post-Ugi modifications, this type of reactions have proved as a valuable synthetic strategy to access a large number of complex functionalized heterocyles.[3] In particular, different methodologies for the synthesis of heterocyclic systems employing the Ugi reaction followed by radical cyclizations have been described in the last few years. Among them, (1) the incorporation of additional functional groups on the Ugi adduct, e. g. xanthates,[4] alkyl iodides,[5] aryl halides,[6] alkynes[7] or activated methylene groups,[8] which favors the formation of the required radicals, and (2) the use of functionalization achieved in the Ugi reaction, both the secondary[9] or tertiary[10] amides and the peptidyl position,[11] to get these first radicals.

Results and Discussion

As part of our ongoing interest in developing new strategies for the synthesis of lactams based on Ugi/post-condensation sequences,[12] we envisaged the possibility of synthesizing these compounds using the Ugi reaction followed by radical cyclizations. In this way, we planned to carry out the Ugi reaction with two doubly functionalized reactants, arylglyoxals to obtain β-ketoamides[13] in which the acidic position would favor the generation of radicals through a carbanion-radical relay,[14] and acrylic acid derivatives to trigger the intramolecular radical addition.[15] Initial screening for this cyclization was performed using acrylamide **1a** (Scheme 1), obtained through a four-component Ugi reaction involving phenylglyoxal, acrylic acid, *tert*-butylamine and *tert*-butyl isocyanide in 68% yield (see Electronic Supporting Information, ESI). Firstly, we tried the copper(II) oxidative conditions described by El Kaïm for the synthesis of spiroindolines.[11a] In this way, Ugi adduct **1a** was treated with one equivalent of copper(II) acetate and DBU in boiling THF, but most of the Ugi adduct was recovered, even when the reaction time was increased to 18 h. However, an unexpected fused system, tetrahydronaph-



Scheme 1. Synthesis of tetrahydronaphthoazetidinone **2 a** from Ugi adduct **1 a** in different conditions.

thoazetidinone **2 a** (Scheme 1), was isolated in 6% yield (Entry 1, Table 1). Encouraged by the interest of this complex fused azetidinone, we tried different reaction conditions to obtain this new compound in an efficient way. Different conditions were assayed using various copper(II) salts, turning out that in these cases the presence of a base was necessary (Entry 2, Table 1) and that acetonitrile was a better choice than THF (Entries 3 *vs* 1 and 5 *vs* 4, Table 1), although yields were too low in all the explored conditions.

To improve these results, we tried copper(I) chloride as initiator of the radical reaction,[16] trying different solvents (Entries 6–9, Table 1). The reaction worked in acetonitrile with a comparable yield to that obtained when $Cu(OAc)_2$ and DBU were employed (Entries 3 and 7, Table 1). Gratefully, the yield increased significantly when non-degasified dry acetonitrile was used (Entry 10 *vs* 7, Table 1), observing a drastic improvement when the reaction was carried out under a nitrogen atmosphere (Entry 11, Table 1). This result can be explained by the decrease of the oxidative cleavage of Ugi adducts to α-ketoamides.[17] Moreover, tetrahydronaphthoazetidinone **2 a** was also obtained by reducing the amount of CuCl (Entries 12 and 13, Table 1).

Table 1. Chemical results in the synthesis of tetrahydronaphthoazetidinone **2 a** from Ugi adduct **1 a** in different conditions (atm = atmosphere).

Entry	Conditions[a]			**2 a** (%)
	Copper salt (equiv.)	Solvent	Atm.	
1	$Cu(OAc)_2$ (1)[b]	THF	Air	6[d,e]
2	$Cu(OAc)_2$ (1)	THF	Air	–[d,f]
3	$Cu(OAc)_2$ (1)[b]	CH_3CN	Air	15[e]
4	$CuCl_2$ (1)[b]	THF	Air	5[e]
5	$CuCl_2$ (1)[b]	CH_3CN	Air	8[e]
6	CuCl (1)	THF	Air	–[d][f]
7	CuCl (1)	CH_3CN	Air	17[e]
8	CuCl (1)	MeOH	Air	–[d,f]
9	CuCl (1)	Toluene	Air	7[e]
10	CuCl (1)	dry CH_3CN[c]	Air	42[e]
11	CuCl (1)	dry CH_3CN[c]	N_2	82
12	CuCl (0.3)	dry CH_3CN[c]	N_2	81
13	CuCl (0.1)	dry CH_3CN[c]	N_2	75

[a] The reactions were carried out in boiling solvents for 18 h.
[b] DBU (1 equiv.) was added.
[c] Dried over 4 Å-molecular sieves.
[d] The Ugi adduct was recovered.
[e] α-Ketoamide resulting from the cleavage of the Ugi adduct was identified as a by-product.
[f] Not detected.

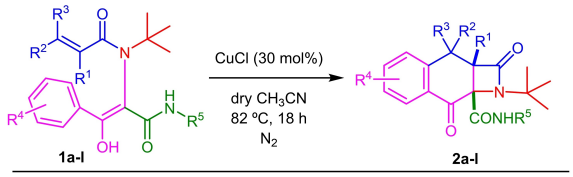
Bearing these results in mind, we decided to examine the scope of this reaction. In this way, different Ugi adducts **1** were prepared from glyoxals, α,β-unsaturated carboxylic acids, isocyanides and *tert*-butylamine (see ESI). Interestingly, simple refluxing of solutions of Ugi adducts **1** with CuCl (30 mol%) in dry acetonitrile under a nitrogen atmosphere for 18 h afforded radical cyclization products, except for piruvaldehyde derivatives which afforded complex mixtures and further experiments were not conducted. However, the chemical results were strongly dependent on the substitution pattern of the acrylamide fragment.

On one hand, acrylic, 2-fluoroacrylic or 3,3-dimethylacrylic acid derivatives **1 a-i**,**k**,**l** afforded exclusively tetrahydronaphthoazetidinone derivatives **2** (Entries 1–9 and 11–12, Table 2), while 2-bromoacrylic acid derivative **1 j** afforded exclusively 3-methylidenazetidinone **2 j'** (Entry 10, Table 2). The addition of TEMPO in the synthesis of **2 a** allowed to trap the azetidinone intermediate radical **B** *via* a cross-coupling reaction (see Scheme 2 and ESI).

On the other hand, when methacrylic, atropic, crotonic, cinnamic, tiglic, 1-cyclopentenecarboxylic or 1-cyclohexenecarboxylic acid derivatives **1 m–t** were used, the 5-*endo*-trig cyclization was preferred. However, the results were highly dependent on the reaction atmosphere. Thus, when the reactions were carried out under a nitrogen atmosphere, 2,5-dioxo-1,4-methanobenzoazepines **3** were obtained along with an unexpected major compound, 3-hydroxypyrrolidinones **4**, instead of the predicted non-hydroxylated pyrrolidinone.[11c] However, when the reaction was performed in an air atmosphere, 3-hydroxypyrrolidinones **4** were the only detected product in most cases. Nevertheless, the observed diastereoselectivity was quite low, except for the cyclopentenyl and cyclohexenyl derivatives (Table 3).

Finally, we tried to optimize the synthesis of 2,5-dioxo-1,4-methanobenzoazepines **3**, since as far as we know only a single method has been described for the synthesis of these fused systems.[18] In order to achieve the proposed goal, we planned to carry out the reaction in the total absence of oxygen, using degasified dry acetonitrile under a nitrogen atmosphere. Moreover, taking into account that we argued that oxygen was necessary to achieve the reaction with copper(I) salts and to complete the catalytic cycle (see the proposed mechanism in Scheme 2), we used a combination of copper(II) acetate with DBU in equimolar amounts.

Table 2. Synthesis of tetrahydronaphthoazetidinones **2 a–l** from Ugi adducts **1 a–l**.[a]



Entry	1	2, Yield
1	**1a** $R^5 = tC_4H_9$	**2a**, 82%[b]
2	**1b** $R^5 = cC_6H_{11}$	**2b**, 50%
3	**1c** $R^5 = CH_2C_6H_5$	**2c**, 65%
4	**1d** $R^5 = CH_2CO_2C_2H_5$	**2d**, 64%
5	**1e** $R^5 = 4\text{-}CH_3OC_6H_4$	**2e**, 58%
6	**1f** $R^5 = 4\text{-}FC_6H_4$	**2f**, 62%
7	**1g** $R^4 = CF_3$	**2g**, 63%
8	**1h** $R^4 = CH_3$	**2h**, 53%
9	**1i**	**2i**, 56%
10	**1j**	**2j'**, 89%[c]
11	**1k**	**2k**, 70%
12	**1l**	**2l**, 87%

[a] Reaction conditions: **1** (1 mmol), CuCl (30 mol%), dry CH_3CN (25 mL), nitrogen atmosphere, 82 °C, 18 h.
[b] The addition of TEMPO (2 mmol) led to **1 a-TEMPO** in 88% yield (see ESI).
[c] 3-Methylidenazetidin-2-one **2 j'** instead of the corresponding tetrahydronaphthoazetidinone.

Therefore, the reactions were performed under these conditions, and thankfully the corresponding benzoazepines **3** were obtained as the major product (Table 4), but only from Ugi adducts where these compounds were observed in the previously tested conditions (see Table 3).

The structures of these heterocycles were determined by the usual spectroscopic techniques, and the relative configuration of stereogenic centers was determined by NOESY experiments. Moreover, structural analyses of compounds **2 b**, **3 q**, **4m**$_{diast2}$, **4n**$_{diast1}$ and **4 q** by single-crystal X-ray diffraction confirmed the determined structures (Figure 1; see also ESI).[19]

A plausible mechanism accounting for the formation of the different compounds is depicted in Scheme 2. Thus, in the presence of copper(I) chloride, the process would begin via a redox reaction, with oxygen acting as the oxidant and the acidic medium required to initiate the reaction[20] being provided by the Ugi adduct (A–H) in its enol form. In this way, a $Cu(acac)_2$-type complex (CuA_2) would be generated. This proposal is supported by the experimental results obtained when copper(II) acetate was used in the presence of DBU. Once this complex is formed, the presence of the enol tautomer of the Ugi adduct would

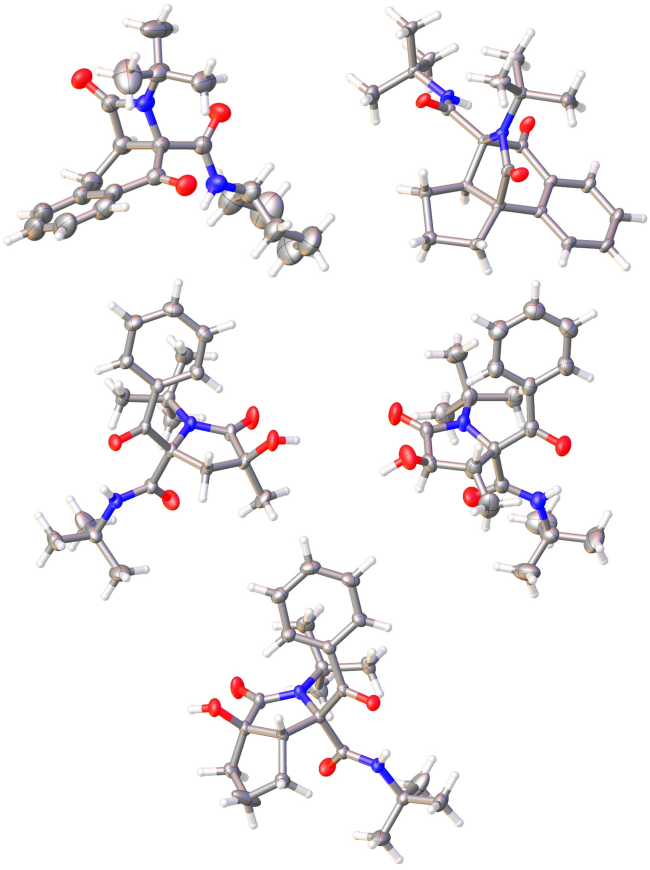
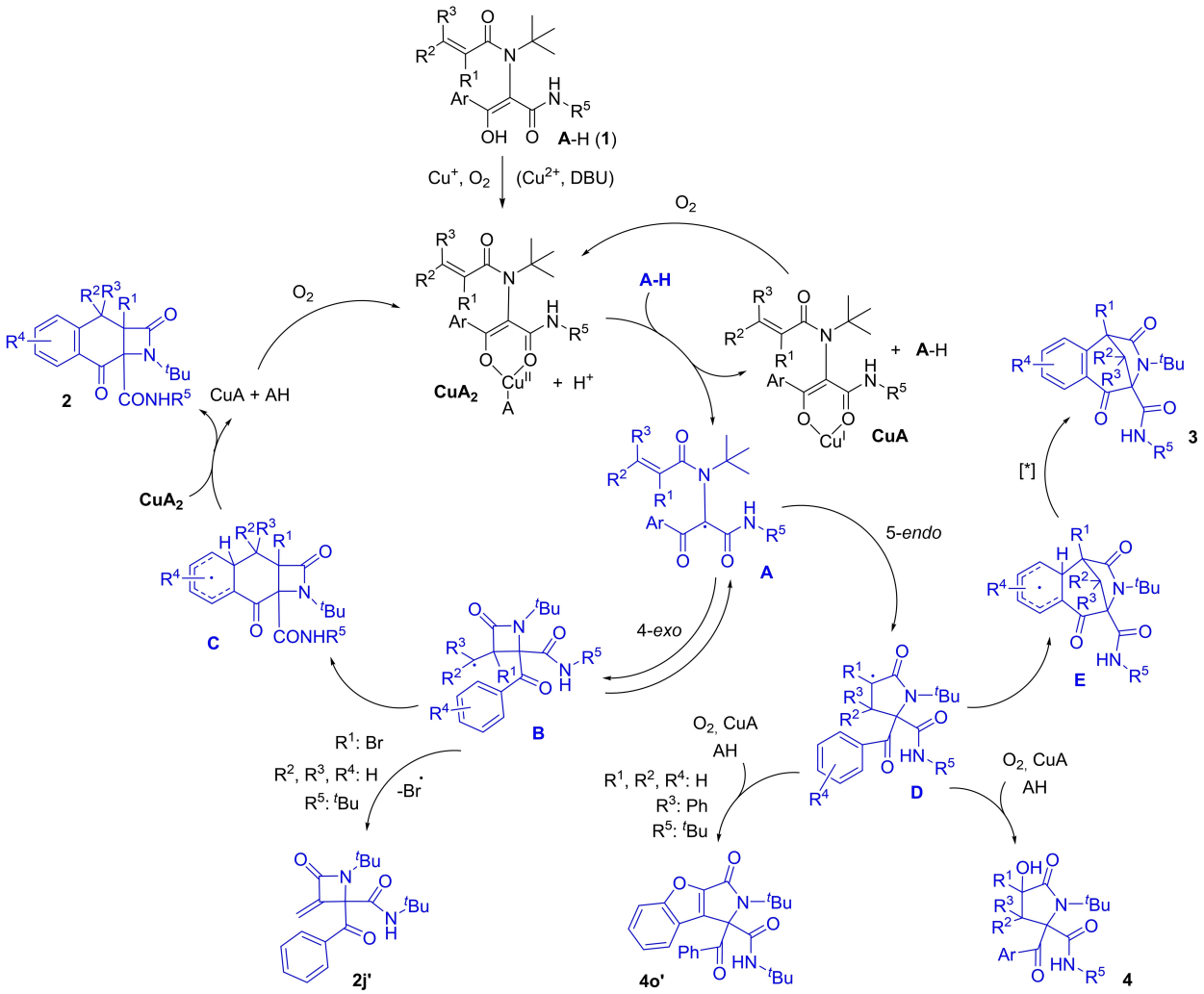


Figure 1. X-ray molecular structures of, from top to bottom and from left to right, **2 b**, **3 q**, **4m**$_{diast2}$, **4n**$_{diast1}$ and **4 q**. The thermal ellipsoid plot (Olex2) is at the 40% probability level.

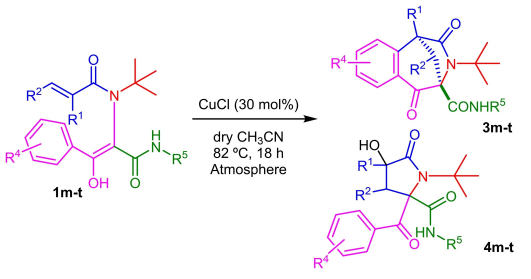


Scheme 2. Plausible mechanism that would account for the formation of compounds **2**, **2 j'**, **3**, **4** and **4 o'**. [*] The proposed catalytic cycle for the synthesis of **3** from radical **E** would be similar to that proposed for the synthesis of **2** from radical **C**.

favor again a redox reaction with the generation of the acetylacetonate-type radical **A** and a copper(I) complex, CuA.[21] An intramolecular cyclization on the double bond of the acrylamide subunit on radical **A** could take place in two different positions, which would explain the different chemical results obtained. Thus, a 4-*exo*-trig cyclization would lead to the intermediate azetidinone radical **B** (detected by the addition of TEMPO) where a 5-*endo*-trig cyclization would drive to pyrrolidinone radical **D**. The azetidinone radical **B** can undergo an intramolecular radical addition on the aromatic ring of the acyl group in C4, yielding tetrahydronaphthoazetidinone radical **C**. In the case of 2-bromoacrylamide derivative **1 j**, elimination of a bromine radical in the azetidinone radical **B** yields 3-methylidenazetidinone **2 j'**. A similar intramolecular addition on pyrrolidinone radical **D** would account for the formation of 2,5-dioxo-1,4-methanobenzoazepine radical **E**. The termination step for the synthesis of fused lactams **2** and **3** or 3-hydroxypyrrolidinones **4** would be explained again by redox reactions involving copper salts: through an oxidation of cyclohexadienyl radical **C** or **E** followed by deprotonation in the synthesis of **2** or **3**, respectively, or through a Fenton-type fragmentation of superoxo radicals generated by reaction of radical **D** with molecular oxygen in the synthesis of **4**,[22] which concurs with the formation of benzofuropyrrolone **4 o'**.

The selectivity observed in the cyclization step seems to be driven by the substitution on the acrylamide subunit of the Ugi adduct, what can be explained by the different stability of *s-cis* and *s-trans* conformers. In this way, a conformational analysis of Ugi adducts **1 a** and **1 t**, derived from acrylic acid and 1-cyclohexene-1-carboxylic acid respectively, was carried out by DFT calculations using Gaussian 16.[23] Thus, the most stable *s-cis* conformation of the acrylamide fragment on the Ugi adduct **1 a** would favor

Table 3. Synthesis of 2,5-dioxo-1,4-methanobenzoazepines **3 m–t** and 3-hydroxypyrrolidinones **4 m–t** from Ugi adducts **1 m–t**.[a]



Entry	1	Atm	3, Yield[b][c]	4, Yield[b] (d.r.)[g]
1	**1m**	N_2	**3m**, 21%	**4m**, 47% (d.r. 64:36)[h]
2	**1m**	Air	--[d]	**4m**, 53% (d.r. 60:40)[h]
3	**1n**	N_2	--[d][e]	**4n**, 63% (d.r. 29:25:23:23)[i]
4	**1n**	Air	--[d][e]	**4n**, 62% (d.r. 30:24:23:23)[i]
5	**1o**	N_2	--[d][f]	**4o**, 51% (d.r. 9:21:57:13)[i]
6	**1o**	Air	--[d][f]	**4o**, 47% (d.r. 22:-[d]:47:31)[i]
7	**1p**	N_2	--[d]	**4p**, 71% (d.r. 62:38:-[d]:-[d])[i]
8	**1p**	Air	--[d]	**4p**, 73% (d.r. 28:42:30:-[d])[i]
9	**1q** R^4 = H, R^5 = tC_4H_9	N_2	**3q**, 35%	**4q**, 57%[j]
10	**1q** R^4 = H, R^5 = tC_4H_9	Air	--[d]	**4q**, 62%[j]
11	**1r** R^4 = H, R^5 = nC_4H_9	N_2	**3r**, 35%	**4r**, 45%[j]
12	**1r** R^4 = H, R^5 = nC_4H_9	Air	**3r**, 6%	**4r**, 62%[j]
13	**1s** R^4 = F, R^5 = tC_4H_9	N_2	**3s**, 30%	**4s**, 60%[j]
14	**1s** R^4 = F, R^5 = tC_4H_9	Air	--[d]	**4s**, 70%[j]
15	**1t**	N_2	**3t**, 37%	**4t**, 43%[k]
16	**1t**	Air	--[d]	**4t**, 60%[k]

[a] Reaction conditions: **1** (1 mmol), CuCl (30 mol%), dry CH_3CN (25 mL), air or nitrogen atmosphere (as specified), 82 °C, 18 h.

[b] Overall yield of isolated product, as stereoisomer mixture.

[c] A single diastereomer was observed in all cases. Relative configurations are given in ESI.

[d] Not detected.

[e] Equimolar diastereomer mixture of tetrahydronaphthoazetidinone **2 n** (see ESI) was isolated in 19 and 28% overall yields in an air and under a nitrogen atmosphere, respectively.

[f] Benzofuropyrrolone **4 o'** (see ESI) was isolated in 17 and 36% yield in an air and under a nitrogen atmosphere, respectively.

[g] Determined by ^{1}H NMR analysis.

[h] Relative configuration (3*R**,5*S**):(3*R**,5*R**).

[i] Relative configuration (3*R**,4*S**,5*R**):(3*R**,4*R**,5*S**):(3*R**,4*R**,5*R**):(3*R**,4*S**,5*S**).

[j] A single diastereomer (1*R**,3a*R**, 6a*S**) was observed.

[k] A single diastereomer (1*R**,3a*R**,7a*S**) was observed.

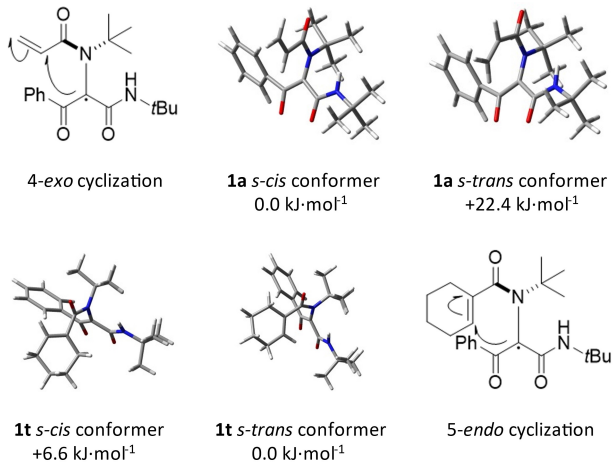


Figure 2. Calculated energies (in the gas phase) for conformations of Ugi adducts **1 a** and **1 t**.

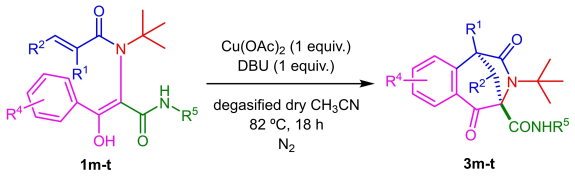
the 4-*exo*-trig attack leading to the azetidinone radical **B**, while the preferred *s-trans* conformation on the cyclohexenyl derivative **1 t** would favor the 5-*endo*-trig attack, resulting in the pyrrolidinone intermediate radical **D** (Figure 2; see also ESI).

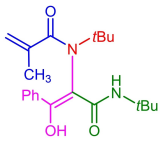
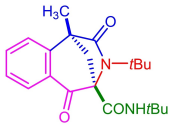
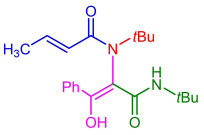
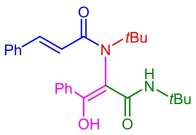
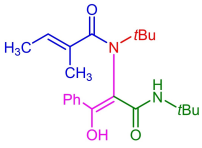
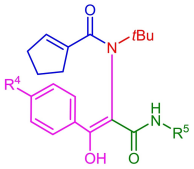
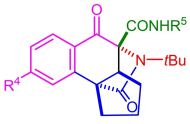
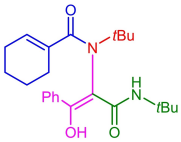
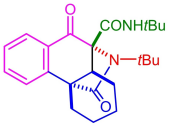
Other amines have been used in these experiments. Interestingly, hydrogen atom transfer was observed when non-quaternary C(sp^3) amines were used. These reactions are currently being studied by our research group.

Conclusion

In this work we have described the synthesis and characterization, both in solution and in the solid state, of highly functionalized tetrahydronaphthoazetidinone, 2,5-dioxo-1,4-methanobenzoazepine and 3-hydroxypyrrolidinone derivatives through copper-assisted post-Ugi reactions, using affordable starting materials and simple protocols. We have demonstrated the impor-

Table 4. Synthesis of 2,5-dioxo-1,4-methanobenzoazepines **3 m–t** from Ugi adducts **1 m–t**.[a]



Entry	1	3, Yield[b]
1	 **1m**	 **3m**, 86%
2	 **1n**	–[c][d]
3	 **1o**	–[c][e]
4	 **1p**	–[c][f]
5	 **1q** R^4 = H, R^5 = tC_4H_9	 **3q**, 62%
6	**1r** R^4 = H, R^5 = nC_4H_9	**3r**, 62%
7	**1s** R^4 = F, R^5 = tC_4H_9	**3s**, 59%
8	 **1t**	 **3t**, 65%

[a] Reaction conditions: **1** (1 mmol), $Cu(OAc)_2$ (1 mmol), DBU (1 mmol), degasified dry CH_3CN (25 mL), nitrogen atmosphere, 82 °C, 18 h.
[b] Isolated product overall yield.
[c] Not detected.
[d] Equimolar diastereomer mixture of tetrahydronaphthoazetidinone **2 n** was isolated in 35% overall yield.
[e] Complex mixture of compounds.
[f] The major products were the diastereomers of saturated pyrrolidinone **3 p'** (d.r. 51:49) and unsaturated pyrrolidinone **3 p"** resulting from disproportionation of the corresponding **D** radical (see Scheme 2 and ESI).

tance of both the substitution pattern of the Ugi adduct's acrylamide fragment and the type of atmosphere, oxidizing or inert, under which radical cyclization reactions are performed in the obtention of fused lactams and 3-hydroxypyrrolidinones. Moreover, we have proposed a mechanism accounting for the formation of the observed products.

Experimental Section

General procedure for the synthesis of tetrahydronaphthoazetidinones **2**: Copper(I) chloride (0.3 mmol, 0.3 equiv.) and the corresponding Ugi adduct (1 mmol, 1 equiv.) were placed in a two-neck round-bottom flask under a nitrogen atmosphere. The reagents were dissolved in dry acetonitrile (25 mL) and the reaction mixture was heated to reflux with a heating block for 18 h, after which the solvent was removed in a rotary evaporator. The residue was dissolved in ethyl acetate (30 mL) and the corresponding solution was washed with a 1 M hydrochloric acid aqueous solution (2×40 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The product was purified by flash column chromatography (SiO_2, hexane/ethyl acetate).

General procedure for the synthesis of 2,5-dioxo-1,4-methanobenzoazepines **3**: Copper(II) acetate (1 mmol, 1 equiv.) and the corresponding Ugi adduct (1 mmol, 1 equiv.) were placed in a two-neck round-bottom flask, connected to a condenser, dried under vacuum and filled with nitrogen. Degasified dry acetonitrile (25 mL) and DBU (1 mmol, 1 equiv.) were then added. The reaction mixture was heated to reflux with a heating block for 18 h, after which the solvent was removed in a rotary evaporator. The residue was dissolved in ethyl acetate (30 mL) and the corresponding solution was washed with a 1 M hydrochloric acid aqueous solution (2×40 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The product was purified by flash column chromatography (SiO_2, hexane/ethyl acetate).

General procedure for the synthesis of 3-hydroxypyrrolidinones **4**: Copper(I) chloride (0.3 mmol, 0.3 equiv.) was added to a suspension of the corresponding Ugi adduct (1 mmol, 1 equiv.) in dry acetonitrile (25 mL). The reaction mixture was heated to reflux with a heating block for 18 h, after which the solvent was removed in a rotary evaporator. The residue was dissolved in ethyl acetate (30 mL) and the corresponding solution was washed with a 1 M hydrochloric acid aqueous solution (2×40 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The product was purified by flash column chromatography (SiO_2, hexane/dichloromethane to either pure dichloromethane or dichloromethane/ethyl acetate).

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