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Multi-Component Reactions 13: Synthesis of γ-Lactams as Part of a Multi-Ring System via Ugi-4-Centre-3-Component Reaction

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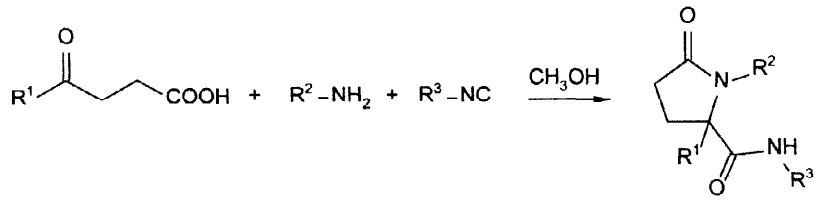
Abstract: Preparation of γ-lactams **2a-h** and **4a-h** as part of a bi-or tri-cycle system in a one-pot Ugi-4-centre-3-component reaction (U-4C-3CR). A 3-keto or aldo acid was used as bifunctional educt. The application of C-protected amino acids as amine components enables an intramolecular condensation forming 2,6-piperazinediones **5a-h**, connected to the γ-lactam system (1,4-diazabicyclo[4.3.0]nonane-3,5,9-triones).

The article of Gross and Gloede [1], published in 1968, and the knowledge of Ugi reaction [2,3] led us to further investigation of the U-4C-3CR. Now it is possible to synthesise variable substituted γ-lactams in a one-pot reaction in very high yields without by-products. Due to the publications of Harriman [4] and Short and Mjalli[5], we now publish our own results in this area.

At first we tried, if the intramolecular Ugi-Reaction is more general than the system decribed in ref. 1 and generated γ-lactams in a one-pot Ugi reaction. To find out the optimal conditions for this intramolecular U-4C-3CR we started our experiments with levulinic acid **1a-e** as keto-acid component. The results are listed in **Table 1**.



1a-h **2a-h**

Scheme 1: Intramolecular U-4C-3CR with levulinic acid **1a-e** or 3-benzoylpropionic acid **1f-h**.

Because of these promissing results we considered, that a more bulky keto-acid, e.g. 3-benzoylpropionic-acid **1f-h**, must give similar products. It turned out, that the reaction stopped on the stage of the imine, when performed at room temperature. However, when done under reflux **2f-h** was obtained almost completely.

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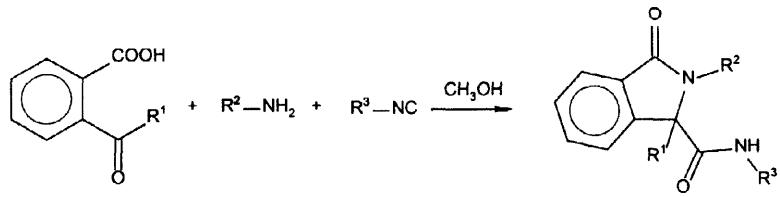
Table 1: γ-Lactams **2a-h** as U-4C-3CR-products from levulinic acid **1a-e** resp. 3-benzoylpropionic acid **1f-h**.[6,7]

No.	R^1	R^2	R^3	4 yield (%)
2a	$-CH_3$	$-(CH_2)_2CH_3$	$-C(CH_3)_3$	100
2b	$-CH_3$	$-(CH_2)_2CH_3$	$-CH_3$	100
2c	$-CH_3$	$-(CH_2)_2CH_3$	$-CH_2CO_2Et$	85
2d	$-CH_3$	$-CH_2(C_6H_5)$	$-C(CH_3)_3$	87
2e	$-CH_3$	$-CH_2(C_6H_5)$	$-CH_3$	100
2f	$-C_6H_5$	$-(CH_2)_2CH_3$	$-C(CH_3)_3$	73
2g	$-C_6H_5$	$-(CH_2)_2CH_3$	$-CH_3$	64
2h	$-C_6H_5$	$-CH_2(C_6H_5)$	$-C(CH_3)_3$	75

After this preliminary studies with aliphatic keto-acids, we were looking for further systems, as well bearing 1,4-functionality, as being different to the investigated molecules. We found, that phthalaldehydic acid **3a-d**, containing in 4-position to the acid functionality a aldo function, bound over a phenylic ring system, matched these criterias. An entry with aliphatic amines led to the target product with a yield of often more than 80 % **4a-d**. Now it was possible to form a bicyclus in a one-step-Ugi reaction.



3a-h **4a-h**

Scheme 2: Intramolecular U-4C-3CR with phthalaldehydic acid **3a-d** resp. 2-acetyl benzoic acid **3e-h**.

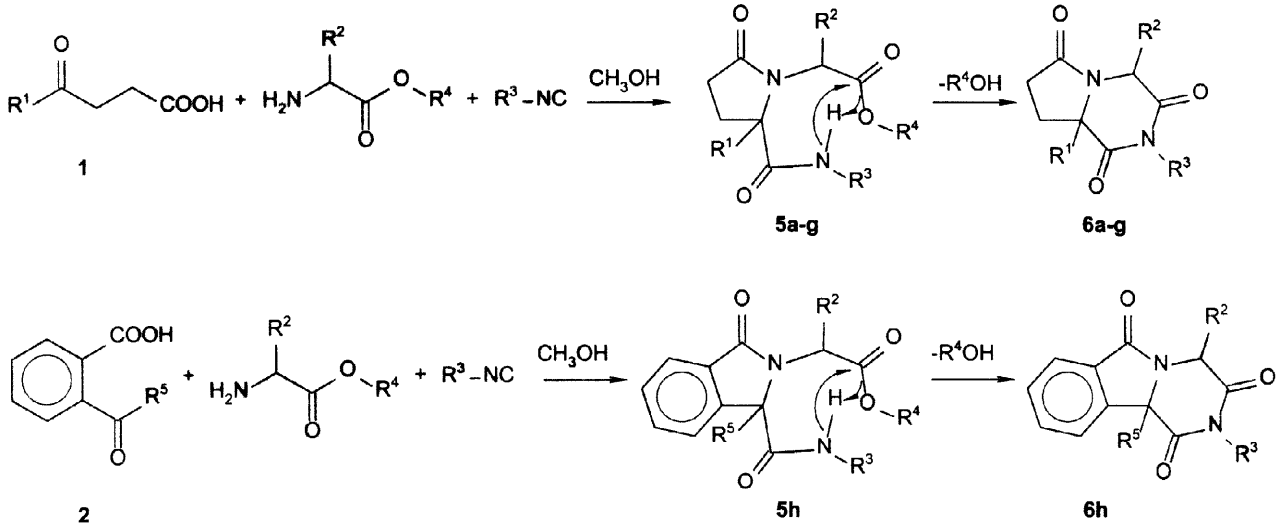
Table 2: γ-Lactams as U-4C-3CR products with phthalaldehydic acid **3a-d** resp. 2-acetylbenzoic acid **3e-h**.[6,8]

No.	R^1	R^2	R^3	yield (%)
4a	-H	$-(CH_2)_2CH_3$	$-C(CH_3)_3$	85
4b	-H	$-(CH_2)_2CH_3$	$-c-C_6H_5$	100
4c	-H	$-(CH_2)_2CH_3$	$-CH_2CO_2CH_3$	67
4d	-H	$-CH_2(C_6H_5)$	$-C(CH_3)_3$	83
4e	$-CH_3$	$-(CH_2)_2CH_3$	$-C(CH_3)_3$	79
4f	$-CH_3$	$-(CH_2)_2CH_3$	$-CH_3$	77
4g	$-CH_3$	$-CH_2(C_6H_5)$	$-C(CH_3)_3$	84
4h	$-CH_3$	$-CH_2(C_6H_5)$	$-CH_3$	79

Next we tried, if 2-acetylbenzoic acid **3e-h** reacts in the same way. This reaction as well stopped at the imine stage at room temperature,. If the reaction was stirred under reflux for 48 h, the U-4C-3CR-product was isolated in high yield. **4e-h**.

The knowledge of the 5-center-4-component-Ugi-reaction (U-5C-4CR)[9] led us to the idea using C-protected amino acids as amine components. (**Scheme 3**). The substructure of these products is the same as the structure

of a U-5C-4CR-product. So the following cyclisation to 2,6-piperazinediones between the ester function and the amid function of the formerly isocyanide should also be possible.[9] This would be a short way to form a bi- or tricyclus with a U-4C-3CR.



Scheme 3: Formation of 1,4-diazabicyclo[4.3.0]nonane-3,5,9-triones **6a-h** through combination of U-4C-3CR with U-4C-5CR.

Table 3: U-4C-3CR with C-protected amino acids as amine components:[10,11]

No.	R^1	R^2	R^3	R^4	R^5	**5** yield (%)	**6** yield (%)
6a	$-CH_3$	-H	$-CH_2CO_2CH_3$	$-CH_3$	/	67	7
6b	$-CH_3$	$-CH(CH_3)_2$	$-C(CH_3)_3$	$-CH_3$	/	100	33
6c	$-CH_3$	-H	$-CH_3$	$-CH_2CH_3$	/	100	5
6d	$-CH_3$	$-CH_2CH(CH_3)_2$	$-CH_2CO_2CH_3$	$-CH_3$	/	99	30
6e	$-CH_3$	$-CH_2CH(CH_3)_2$	$-CH_2CO_2CH_2CH_3$	$-CH_3$	/	81	20
6f	$-(C_6H_5)$	$-CH(CH_3)_2$	$-CH_3$	$-CH_3$	/	84	25
6g	$-(C_6H_5)$	$-CH(CH_3)_2$	$-CH_3$	$-CH_2CH_3$	/	58	19
6h	/	-H	$-C(CH_3)_3$	$-CH_2CH_3$	-H	72	5

The 1,4-diazabicyclo[4.3.0]nonane-3,5,9-triones **6a-h** are separated from the U-4C-3CR-products by flash chromatography. It seems as if only one diastereomeric molecule **5** is able to form the 2,6-piperazinediones **6**. That is not surprising due to the three dimensional arrangement of the γ-lactam rests of the two formed diastereomeric molecules. That means that there is also a diastereomeric division during the cyclisation.
Our results in this area are not yet optimised, but we are optimistic, that we will increase the yield of the cyclisation in the near future.

REFERENCES AND NOTES

1 Gross, U.; Gloede, J.; Keitel, I, ; Kunath, D. *J. prakt. Chem.***1968**, *37*, 192-199.

2 Ugi. I. *Isonitrile Chemistry*, Academic Press, New York, 1971.
3 Ugi, I.; **Dömling, A.; Hörl, W.** *Endeavour* **1994,** *18*, 115-122.
4 Harriman, G. *Tetrahedron Lett.*, **1997,** *38*, 5591-5594.
5 Short, K. M.; Mjalli, A. M. M.*Tetrahedron Lett.* **1997,** *38*, 359-362.
6 Reaction procedure: 5 mmol of amine (resp. of C-protected amino acid ·HCl and 5 mmol of triethylamine), soluted in 5 mL of methanol, were added under stirring to a solution of 5 mmol of the 3 oxo acid **1a-h resp. 3a-h** in 40 mL of methanol. After the solution was stirred for an additional hour to form the imine, 5 mmol of the isocyanide, dissolved in 5 ml of methanol, were added. The reaction mixture was stirred for 24 hours at room temperature (in the case of levulinic acid **1a-e** and phthalaldehydic acid **2a-e**) or for 48 hours under reflux (in the case of 3-benzoylpropionic acid **1f-h** and 2-acetylbenzoic acid **2f-h**). The solvent was removed under reduced pressure. The reaction residue was solved in 50 ml $CHCl_3$, washed twice with H_2O and dried over Na_2SO_4 (for propionic- or benzyl amine) resp. solved in EE and filtrated from NEt_3 ·HCl (in the case of C-protected amino acids). The solvent was removed under reduced pressure and the product was recrystallised from EE/hexane.
7 All produced compounds are identified by ^1H and ^{13}C NMR spectra and GC/MS spectra. For example: **2e**: ^1H NMR($CDCl_3$) δ 1.42 (s, 3H), 2.33 (m, 2H), 2.47 (m, 2H), 2.56 (d, 3H, J=4.6Hz), 4.32 (d, 1H, J=15.0Hz), 4.60 (d, 1H, J=15.0Hz), 6.05 (sb, 1H), 7.30 (m, 5H). ^{13}C NMR($CDCl_3$) δ 176.2, 173.7, 137.8, 128.7, 128.0, 127.6, 67.6, 44.6, 33.4, 29.5, 26.4, 23.0. **2f**: ^1H NMR ($CDCl_3$) δ 0.75 (t, 3H, J=7.5Hz), 1.34 (s, 9H), 1.41 (m, 2H), 2.20-2.38 (m, 2H), 2.88-2.32 (m, 2H), 3.25-3.38 (m, 2H), 5.54 (sb, 1H), 7.40 (m, 5H). ^{13}C NMR($CDCl_3$) δ 179.0, 175.7, 137.0, 128.8, 128.4, 127.9, 74.8, 51.9, 41.0, 34.7, 31.1, 28.4, 21.3, 10.9.
8 All produced compounds are identified by ^1H and ^{13}C NMR spectra and GC/MS spectra. For example: **4d**: ^1H NMR($CDCl_3$) δ 1.17 (s, 9H), 4.45 (d, 1H, J=14.6Hz), 5.08 (d, 1H, J=14.6Hz), 4.75 (s, 1H), 5.59 (sb, 1H), 7.32 (m, 5H), 7.48-7.58 (m, 3H), 7.83 (d, 1H, J=7.0Hz). ^{13}C NMR($CDCl_3$) δ 168.2, 166.2, 145.4, 141.3, 136.1, 132.5, 129.0, 128.5, 128.1, 123.8, 122.9, 64.2, 45.9, 26.3. **4g**: ^1H NMR ($CDCl_3$) δ 1.00 (t, 3H, J=7.3Hz), 1.19 (s, 9H), 1.72 (s, 3H), 1.65 (m, 1H), 1.84 (m, 1H), 3.34 (ddd, 1H), 3.51 (ddd, 1H), 5.29 (sb, 1H), 7.43-7.62 (m, 3H), 7.83 (d, 1H, J=7.0Hz). ^{13}C NMR($CDCl_3$) δ 169.1, 161.2, 147.5, 132.3, 130.1, 128.8, 123.7, 121.3, 69.9, 51.4, 43.0, 28.3, 22.0, 21.1, 11.7.
9 Ugi, I.; Hörl, W.; Hanusch-Kompa, C.; Schmid, T.; Herdtweck, E. *Heterocycles*, **1997** in press.
10 Reaction procedure: To a solution of 8 mmol of potassium *tert.*-butoxide in THF 4 mmol of the **5a-h**, dissolved in 5 mL of THF were added. The reaction mixture is stirred under reflux for 48 h. The solvent is removed *in vacuo* and the residue is solved in 50 mL of $CHCl_3$ and washed twice with water. The 1,4-diazabicyclo[4.3.0]nonane-3,5,9-triones **6a-h** are separated by flash chromatography.
11 All produced compounds are identified by ^1H and ^{13}C NMR spectra and GC/MS spectra. For example: **3d**: ^1H NMR($CDCl_3$) δ 0.99 (d, 3H, J=6.2Hz, -CH($C\underline{H}_3$)CH_3), 1.07 (d, 3H, J=6.2Hz, -CH(CH_3)$C\underline{H}_3$), 1.67 (s, 3H, -C_q-$C\underline{H}_3$), 1.70-1.91 (m, 3H, (CH_3)$_2$-C$\underline{H}$-C$\underline{H}_2$-CH-), 2.10-2.21 (m, 1H, -$COCH_2$-C($\underline{H}$)H-C_q-), 2.32-2.45 (m, 1H, -$COCH_2$-C(H)$\underline{H}$-C_q-), 2.52-2.63 (m, 2H, -CO-C$\underline{H}_2$-CH_2-C_q-), 3.76 (s, 3H, -CO_2-C$\underline{H}_3$), 4.48 (d, 1H, J=17.0Hz, -N-C($\underline{H}$)H-CO_2CH_3), 4.56 (d, 1H, J=17.0Hz, -N-C(H)$\underline{H}$-CO_2CH_3), 5.06 (dd, J=10.2Hz, J=5.3Hz, (CH_3)$_2$CHCH_2-C$\underline{H}$-). ^{13}C NMR($CDCl_3$) δ 174.4, 173.4, 170.5, 167.8, 62.2, 52.5, 52.2, 42.2, 40.7, 31.0, 28.7, 24.7, 22.9, 22.6, 21.4.