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A Decarboxylative C(sp^3)-N Bond Forming Reaction to Construct 4-Imidazolidinones *via* Post-Ugi Cascade Sequence in One Pot

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Abstract. A post-Ugi one-pot cascade was developed to access 4-imidazolidinones through an intramolecular decarboxylative C(sp^3)-N bond forming reaction. The reaction has a broad tolerance for a variety of substituted aldehydes, anilines, isocyanides and glyoxylic acids. The cascade reaction scope was expanded to synthesize spiroimidazolidinone by the replacement of aldehyde with aliphatic ketone in the Ugi reaction. Subsequently, the methodology was applied to synthesize the core structures of pharmaceuticals GSK2137305 and SCH 900822 under the mild and facile conditions with one purification. This cascade reaction generates opportunities for the tailored synthesis of a range of biologically active 4-imidazolidinones through tuneable Ugi inputs.

Keywords: 4-Imidazolidinones; Spiroimidazolidinone; Decarboxylation; One-pot; Multicomponent reactions (MCRs)

Imidazolidin-4-one is an important structural moiety existed in many natural products [(-)-Dysibetaine PP],[1] pharmaceuticals [Hetacillin],[2] and privileged scaffolds of anticonvulsant compounds[3] and antimalarial agents[4] (Fig. 1). Similar imidazolones were also found in both natural products and pharmaceuticals such as Kottamide,[5] SCH900822, GSK2137305,[6] and Glucagon Receptor Antagonists.[7]

Owing to the importance of imidazolidin-4-one and imidazolone, synthetic strategies were developed to produce these types of structures. Traditional methods for the preparation of substituted-4-imidazolidinones depend on the condensation of α-aminoacetamides with ketone or aldehyde substrates

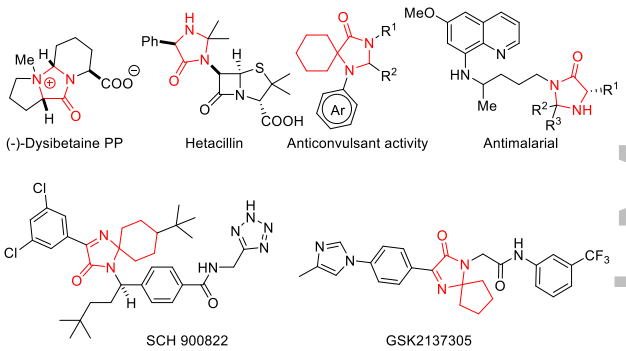
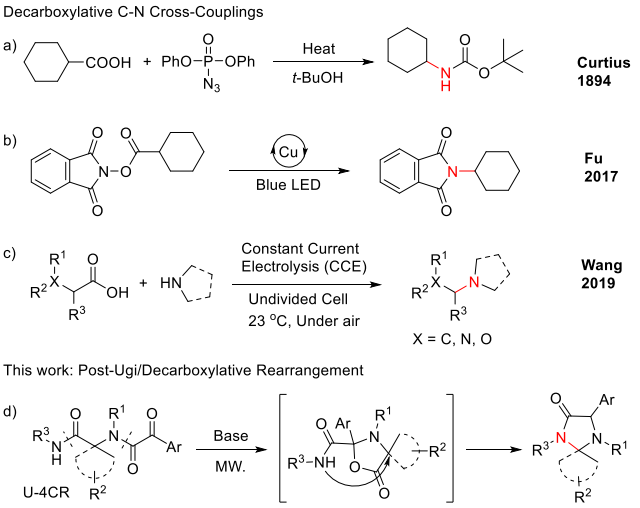


Figure 1. Bioactive compounds containing the 4-imidazolidinone cores.

to form the C-N bond directly.[8] Curtius rearrangement[9a-c] (Scheme 1a), Buchwald-Hartwig reaction[9d], reductive amination with carbonyls[9e] and Mitsunobu reaction[9f] are very commonly used for the preparation of C(sp^3)−N bond. Very recently, the decarboxylative C(sp^3)−N cross-coupling was reported by Fu *via* photoredox and copper catalysis (Scheme 1b).[10] Another decarboxylative C(sp^3)−N formation has been developed through electro-chemical oxidation of amino acids, which expanded from the intramolecular to the intermolecular reaction (Scheme 1c).[11] However, the pre-activation of carboxylic acids is still required for the decarboxylation via a metal catalysis and/or photochemistry condition. The poor availability of starting materials is another drawback.[12] Therefore, cost-effective and environmentally-friend conditions with simple work-ups would be still desirable. As a part of our continued efforts to develop cascade reactions for therapeutic development,[13] herein, we

report a novel post-Ugi 4-component (U-4CR) cascade reaction for the synthesis of 4-imidazolones as depicted in Scheme 1d.

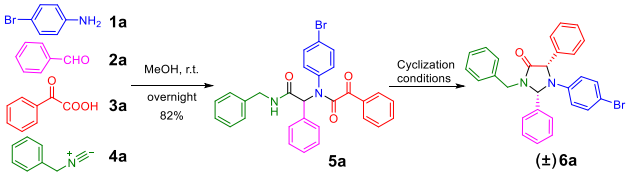


Scheme 1. Decarboxylative nitrogen-nucleophile fragment coupling.

4-Bromoaniline (**1a**), benzaldehyde (**2a**), phenylglyoxylic acid (**3a**), and benzyl isocyanide (**4a**) were stirred in methanol overnight at room temperature to afford the Ugi adduct **5a** in an excellent yield (Table 1). The subsequent cyclization in DMF at 150 °C in the presence of triethanolamine (TEOA) gave the decarboxylased 4-imidazolidinone analogue **(±)6a**. The loss of exchangeable proton in ^{1}H NMR spectrum and two carbonyl carbons in ^{13}C NMR spectrum strongly suggests a novel chemical structure. However, the post Ugi cyclization reaction did not initially furnish product **(±)6a** in an acceptable yield (only 27%, entry 1), and required further optimization with variations in temperature, time, solvent, and base.

Optimization studies for the cyclization of this cascade were then conducted (Table 1). Gratifyingly, elevating temperature from 130 °C to 170 °C for 10 min in DMF with TEOA improved the reaction yield from 27% to 62% for **(±)6a** (entry 5). No desired product was isolated in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), which led to the decomposition of **5a** (entries 6-8). Different temperatures and reaction times were next evaluated with diisopropylamine (DIPA, entries 9-13), and the yield was further improved to 88% (entry 12). Et_3N were less effective under the similar conditions to synthesize compound **(±)6a** (entries 15-17) and inorganic bases gave no desired compound **(±)6a** (entries 18-21). The reaction didn't yield compound **(±)6a** in a higher yield in different solvents (DMSO, MeCN, EtOH, and dioxane) with DIPA than in DMF (entries 22-25). The best result was obtained with 5.0 equiv. of DIPA in 88% yield under microwave irradiation at 170 °C for 10 min.

Table 1. Optimization of the cyclization step.[a]



entry	solvent	base	eq.	MW. temp.(°C)	time (min)	yield **(±)6a**(%)[b]
1	DMF	TEOA	5.0	150	10	27
2	DMF	TEOA	5.0	140	10	<10
3	DMF	TEOA	5.0	130	10	<5
4	DMF	TEOA	5.0	120	10	trace
5	DMF	TEOA	5.0	170	10	62
6	DMF	DBU	2.0	100	10	0
7	DMF	DBU	2.0	120	10	0
8	DMF	DBU	2.0	140	10	0
9	DMF	DIPA	5.0	150	10	44
10	DMF	DIPA	5.0	160	10	67
11	DMF	DIPA	5.0	160	20	79
12	**DMF**	**DIPA**	**5.0**	**170**	**10**	**88**
13	DMF	DIPA	5.0	180	10	76
14	DMF	DIPE	5.0	170	10	68
15	DMF	Et_3N	5.0	140	10	21
16	DMF	Et_3N	5.0	150	10	47
17	DMF	Et_3N	5.0	170	10	63
18	DMF	K_2CO_3	2.0	100	10	0
19	DMF	KOH	2.0	100	10	0
20	DMF	EtONa	2.0	100	10	0
21	DMF	KOAc	2.0	100	10	0
22	DMSO	DIPA	2.0	170	10	74
23	Dioxane	DIPA	2.0	140	10	<5
24	MeCN	DIPA	2.0	140	10	28
25	EtOH	DIPA	2.0	140	10	<10

[a] The reactions were carried out with **5a** (0.3 mmol), base, and solvent (1.5 mL) under microwave irradiation.
[b] Yield (%) for compound **(±)6a** based on peak area of the product by HPLC analysis at 254 nm.

With the optimized conditions in hand, we proceeded to investigate the scope of the reaction to prepare a small library of 4-imidazolidinone **(±)6** (Table 2). In all cases, initial Ugi products **5** were obtained in good yields following the removal of the reaction solvent without further purification. A variety of different starting materials were successfully employed under the optimized conditions for the construction of structurally diverse 4-imidazolidinones **(±)6a-s** in a diastereoselective manner with yields in the range of 50-74%, indicating a good functional group tolerance. In addition, the relative stereochemistry of compound **(±)6n** (CCDC 1910097)[14] was unambiguously determined to be *syn*-relationship between two aryl substituents by X-

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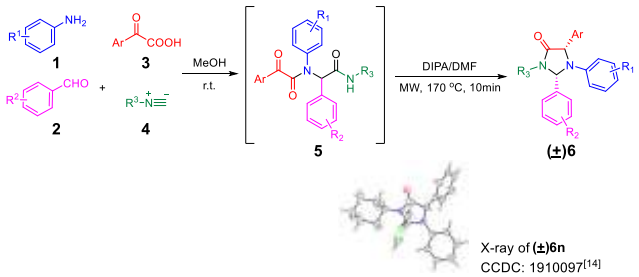
ray crystallography (See SI for details). It is noteworthy that the product of Ugi adducts **5a-s** did not require purification by column chromatography, with the crude product having no discernible impact on the overall yield of final products.

Table 2. Scope of the Ugi/decarboxylation leading to 4-imidazolidinones **(±)6a-s**.[a]

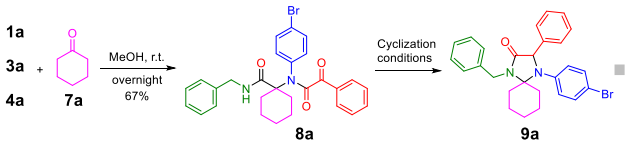


compd	R^1	R^2	R^3	Ar	yield (±)6(%)
(±)6a	4-Br	H	Bn	Ph	73
(±)6b	3-Br	3,4-di-Cl	Bn	Ph	55
(±)6c	4-Cl	4-OMe	Bn	Ph	51
(±)6d	3-Cl-4-F	H	Bn	Ph	74
(±)6e	4-OCH_3	H	Bn	Ph	56
(±)6f	4-F	4-Me	Bn	Ph	63
(±)6g	H	4-Cl	Bn	Ph	68
(±)6h	3,4-di-OMe	H	Bn	Ph	52
(±)6i	H	H	Bn	4-Br-C_6H_4	57
(±)6j	H	3-Br	Bn	Furyl	54
(±)6k	4-Br	H	Cy	Furyl	50
(±)6l	4-Cl	H	Bn	Ph	66
(±)6	3-Br	H	PhC_2H_4	Ph	61
(±)6n	H	4-Br	Cy	Ph	58
(±)6o	4-F	H	Bn	Ph	64
(±)6p	4-F	4-Cl	Cy	4-OMe-C_6H_4	52
(±)6q	4-F	4-Cl	Bn	Ph	60
(±)6r	4-Cl	H	Cy	4-Br-C_6H_4	56
(±)6s	3-Cl-4-F	H	PhC_2H_4	4-OMe-C_6H_4	51

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), **3** (0.5 mmol) and **4** (0.5 mmol) in MeOH (1.0 mL) under air; After workup, added DIPA (5.0 eq.) in DMF (3.0 mL), at 170 °C for 10 min under MW; isolated yields for two steps. MW = microwave irradiation.

During the past few years, α-keto acids have been widely used for the decarboxylative cross-coupling reaction in the presence of metal catalysts.[15] In addition, it has been reported for the synthesis of nitrogen-containing heterocycles via the U-4CR with α-keto acids in many literatures.[16] Faggi *et al.* disclosed the treatment of the Ugi-4CR adducts assembled from aliphatic ketones, anilines, α-keto acids, and isocyanides with methanolic potassium hydroxide to afford 2,5-dioxo-1,3-diphenyl-3-hydroxy-1,4-diazaspiro[5.5]undecane.[17] In order to expand the scope of this novel cascade reaction, aldehyde was replaced with aliphatic ketone in the Ugi reaction as shown in Table 3. Fully substituted compound **8a** was synthesized upon the replacement of aldehyde **2a** with cyclohexanone **7a** (Table 3).

Table 3. Optimization of the reaction conditions for compound **9a**.[a]



entry	solvent	base	eq.	MW. temp.(°C)	time (min)	yield **9a** (%)[b]
1	DMF	DIPA	5.0	170	10	NR
2	DMF	DIPA	5.0	180	20	NR
3	DMF	DIPEA	5.0	180	20	NR
4	DMF	Et_3N	2.0	180	20	NR
5	DMF	DABCO	2.0	180	20	NR
6	DMF	DBU	2.0	120	10	NR
7	DMF	DBU	2.0	140	10	NR
8	DMF	DBU	2.0	160	10	trace
9	DMF	DBU	2.0	180	10	36%
10	DMF	DBU	2.0	180	20	49%
11	DMF	DBU	2.0	200	10	68%
12	**DMF**	**DBU**	**2.0**	**200**	**20**	**89%**
13	DMF	DBU	2.0	200	30	71%
14	DMF	K_2CO_3	2.0	180	10	0
15	DMF	KOH	2.0	180	10	0
16	DMF	EtONa	2.0	180	10	0
17	DMF	KOAc	2.0	180	10	NR
18	DMSO	DBU	2.0	200	20	<10
19	Diox	DBU	2.0	140	20	NR
20	DCE	DBU	2.0	120	20	NR
21	MeCN	DBU	2.0	120	20	NR

[a] The reactions were carried out with **8a** (0.3 mmol), base, and solvent (1.5 mL) under MW.
[b] Yield (%) for compound **9a** based on peak area of the product by HPLC analysis at 254 nm.

With compound **8a** in hand, we have initially used the previously optimized conditions (5.0 equiv. of DIPA under microwave irradiation at 170 °C for 10 min in DMF) established in Table 3 to synthesize compound **9a**. The targeted compound **9a** was not detected unexpectedly. Further reaction condition optimization was then investigated. Several weak organic bases were tested firstly and the reaction didn't give the desired product with starting material

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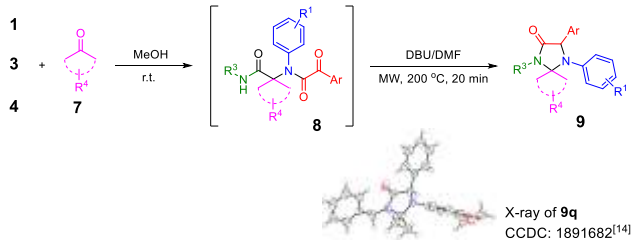
8a intact (Table 4, entries 1-6). When DBU was used, a trace amount of the decarboxylative product **9a** was found under the microwave irradiation at 160 °C for 10 min (Table 4, entry 8). Elevating temperature to 200 °C for 20 min, compound **9a** was isolated with 89% yield. Inorganic bases didn't give the desired product 4-imidazolidinone **9a** (entries 14-17). The 1D and 2D NMR analysis of the decarboxylative product **9a** confirmed the chemical structure of 4-imidazolidinone (see supplementary data). Different solvents were evaluated in the presence of DBU, and the results were dissatisfied (entries 18-21). The optimal conditions are therefore established as 2.0 equiv. DBU in DMF at 200 °C for 20 min (Table 3, entry 12).

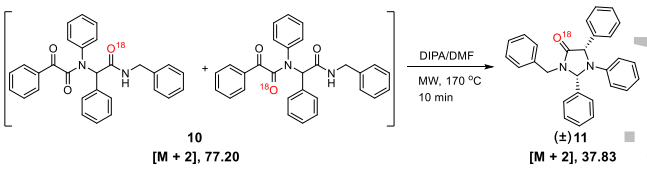
Table 4. Scope of the Ugi/decarboxylation leading to spiroimidazolones **9a-s**.[a]



compd	R^1	R^3	R^4	Ar	yield **9** (%)
9a	4-Br	Bn	Cyclohexyl	Ph	60
9b	4-OMe	Bn	Cyclohexyl	Ph	51
9c	4-F	Bn	Cyclohexyl	Ph	62
9d	3-Cl	Bn	Cyclohexyl	Ph	60
9e	H	Bn	Cyclohexyl	Ph	52
9f	4-Br	Bn	Cyclopentyl	Ph	64
9g	3,4-di-OMe	Bn	Cyclopentyl	Furyl	54
9h	H	Bn	Cyclopentyl	4-Br-C_6H_4	56
9i	4-Cl	3-F-Bn	Cyclopentyl	4-OMe-C_6H_4	72
9j	3-Br	Bn	Cyclopentyl	4-OMe-C_6H_4	55
9k	4-Br	Bn	Cyclobutyl	Ph	59
9l	4-Br	Bn	dimethyl	Ph	68
9m	4-Br	PhC_2H_4	dimethyl	Ph	61
9n	3-Cl-4-F	Bn	dimethyl	Ph	65
9o	4-Br	Cy	dimethyl	Ph	53
9p	4-F	Bn	dimethyl	Piperonylic	51
9q	3,4-di-OMe	Bn	dimethyl	Ph	59
9r	4-Br	Bn	dimethyl	Furyl	56
9s	4-OMe	Cy	dimethyl	4-Br-C_6H_4	54

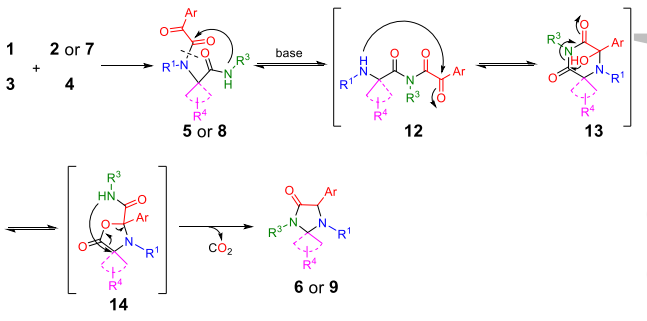
[a] Reaction conditions: **1** (0.5 mmol), **7** (0.5 mmol), **3** (0.5 mmol) and **4** (0.5 mmol) in MeOH (1.0 mL) under air; After workup, added DBU (2.0 eq.) in DMF (3.0 mL), at 200 °C for 20 min under MW.

Encouraged by the remarkable yield at the optimized conditions, we investigated the scope of this cascade reaction by varying starting materials. In all cases, initial Ugi products **8** were obtained in good yields following the removal of reaction solvent. The crude Ugi products were then used directly without further purification to give 4-imidazolidinone **9** in 51-72% yields with four different aliphatic ketones involved (Table 4). The chemical structure of **9q** (CCDC 1891682)[14] was confirmed through X-ray crystallography (in the Supporting Information).



Scheme 2. A control experiment of the oxygen-isotope distribution ratio (%) for the synthesis of compound **(±)11.**

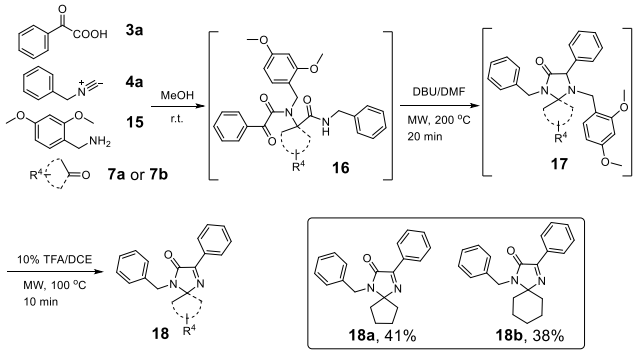
To evaluate the reaction mechanism, a control experiment was conducted to gain mechanistic insight in Scheme 2. In order to prove the C=O bond of an amide involved in decarboxylation, phenylglyoxylic acid labeled with O^{18} was used for the preparation of the Ugi product **10** (see Scheme 2 and SI for details). About half amount of O^{18} atom was missing from the major product **(±)11** isolated from the sequential cyclization reaction, which confirmed the hypothesis.



Scheme 3. Plausible mechanism for compounds **6** and **9**.

A plausible mechanism for the formation of compounds **6** or **9** from the Ugi products **5** or **8** is therefore proposed in Scheme 3. Free NH from the amide attacks the α-carbonyl to generate the intermediate **12**. The intermediate **12** could afford the 6-member ring piperazinedione **13** after the attack of β-carbonyl from free NH. Under the basic conditions assisted with microwave irradiation, the OH group would break another

amide bond to provide compound **14** with a 5-member-ring system. Upon the liberation of CO_2, a new C(sp^3)-N bond would be formed after the attack of NH to the spiro-carbon to afford imidazolidinone **6** in a diastereoselective manner with *syn*-configuration or spiroimidazolidinone **9**. Interestingly, this post-Ugi decarboxylation occurred with the cleavage of two amide bonds under microwave irradiation with an organic base.



Scheme 4. The synthesis of spiroimidazolidinone **18**. Yield of isolated product for one-pot procedure with three steps.

The core structure of spiroimidazolidinones is the main structural unit of GSK2137305 and SCH 900822, a glycine transporter type 1 inhibitor and a potent and selective glucagon receptor antagonist, respectively.[18-19] For the synthetic applications of this new cascade reaction, retro-synthetically, spiroimidazolidinone **18** could be obtained by removing 2,4-dimethoxybenzyl group from compound **17**. The synthesis of the spiroimidazolidinone core is shown in Scheme 4. 2,4-Dimethoxybenzylamine **15**, cyclohexanone **7a** or cyclopentanone **7b** were used to afford the Ugi adduct **16**. With the optimal conditions for the decarboxylative cross-coupling reaction with DBU, compound **17** could be obtained. Under the acidic conditions with TFA, 2,4-dimethoxybenzyl group was removed to give spiroimidazolidinone **18**. This procedure provided a facile and efficient way for the construction of functionalized spiroimidazolidinones in one-pot and could provide analogues to GSK2137305 and SCH 900822 for further SAR studies.

In conclusion, we have developed a post-Ugi/decarboxylative C(sp^3)-N bond formation cascade reaction that proceeds under microwave irradiation to construct 4-imidazolidinones and drug-like spiroimidazolones. A small library collection of targeted products has been prepared under mild reaction conditions with good yields and a simple operation procedure. This novel cascade reaction could generate immense opportunity for the tailored synthesis of a range of scaffolds to easily access novel molecular space. Further screening of 4-imidazolidinones and spiroimidazolones in the cancer cell lines is in progress.

Experimental Section

General procedures for compound 6: A solution of amine **1** (0.50 mmol) and aldehyde **2** (0.50 mmol) in MeOH (1 mL) was stirred at room temperature for 10 min in a 5 mL microwave vial. Acid **3** (0.50 mmol) and isonitrile **4** (0.50 mmol) were added to the vial sequentially, and the resulting mixture was stirred at room temperature overnight. Ater the reaction was completed monitoring by TLC, the resulting reaction mixture was concentrated under a gentle stream of nitrogen. The resulting residue was dissolved in DMF (3 mL) with the same microwave vial. DIPA (2.5 mmol) was then added to the vial, which was sealed and heated under microwave irradiation at 170 °C for 10 min. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give a residue, which was diluted with EtOAc (15 mL), before being washed sequentially with 1N HCl, saturated $NaHCO_3$ solution and brine. The organic solution was then dried over $MgSO_4$ and concentrated to the residue, which was purified by column chromatography over silica gel eluting with a gradient of ethyl acetate/hexane (0 to 30%) to afford the relative compound **6**.

General procedures for compound 9: A solution of amine **1** (0.50 mmol) and ketone **7** (0.50 mmol) in MeOH (1 mL) was stirred at room temperature for 30 min in a 5 mL microwave vial. Acid **3** (0.50 mmol) and isonitrile **4** (0.50 mmol) were added to the vial sequentially, and the resulting mixture was stirred at room temperature overnight. Ater the reaction was completed monitoring by TLC, the resulting reaction mixture was concentrated under a gentle stream of nitrogen. The resulting residue was dissolved in DMF (3 mL) with the same microwave vial. DBU (1.0 mmol) was then added to the vial, which was sealed and heated under microwave irradiation at 200 °C for 20 min. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give a residue, which was diluted with EtOAc (15 mL), before being washed sequentially with 1N HCl, saturated $NaHCO_3$ solution and brine. The organic solution was then dried over $MgSO_4$ and concentrated to the residue, which was purified by column chromatography over silica gel eluting with a gradient of ethyl acetate/hexane (0 to 60%) to afford the relative compound **9**.

General procedures for compound 18: A solution of aniline **15** (1 mmol) and ketone **7a** or **7b** (1 mmol) in MeOH (2 mL) was stirred at room temperature for 10 min in a 5 mL microwave vial. Benzoylformic acid **3a** (1 mmol) and benzylisocyanide **4a** (1 mmol) were added to the vial sequentially, and the resulting mixture was stirred at room temperature overnight. Ater the reaction was completed monitoring by TLC, the resulting reaction mixture was concentrated under a gentle stream of nitrogen. The resulting residue was dissolved in DMF (3 mL) with the same microwave vial. DBU (2.0 mmol) was then added to the vial, which was sealed and heated under microwave

irradiation at 200 °C for 20 min. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give a residue, which was diluted with EtOAc (15 mL), before being washed sequentially with 1N HCl, saturated $NaHCO_3$ solution and brine. The organic solution was then dried over $MgSO_4$ and concentrated to the residue, which was dissolved in 10% TFA/DCE (2 mL) heating at 100 ℃ for 10 min. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give a residue, which was diluted with EtOAc (15 mL), before being washed saturated $NaHCO_3$ solution and brine. The organic solution was then dried over $MgSO_4$ and concentrated to the residue, which was purified by column chromatography over silica gel eluting with a gradient of ethyl acetate/hexane (0 to 30%) to afford the relative compound **18**.

Acknowledgements

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References

[1] D. R. Ijzendoorn, P. N. M. Botman, R. H. Blaauw, *Org. Lett.* **2006**, *8*, 239.

[2] W. J. Gottstein, C. U. Kim, K. M. Shih, and D. N. McGregor, *J. Med. Chem.* **1978**, *21*, 240.

[3] M. N. Aboul-Enein, A. A. S. El-Azzouny, O. A. Saleh, K. M. Amin, Y. A. Maklad, R. M. Hassan, *Arch. Pharm. Chem. Life Sci.* **2015**, *348*, 575.

[4] M. J. Araújo, J. Bom, R. Capela, C. Casimiro, P. Chambel, P. Gomes, J. Iley, F. Lopes, J. Morais, R. Moreira, E. de Oliveira, V. do Rosário, N. Vale, *J. Med. Chem.* **2005**, *48*, 888.

[5] D. R. Appleton, M. J. Page, G. Lambert, M. V. Berridge, B. R. Copp, *J. Org. Chem.* **2002**, *67*, 5402.

[6] a) J. P. Graham, N. Langlade, J. M. Northall, A. J. Roberts, A. J. Whitehead, *Org. Process Res. Dev.* **2011**, *15*, 44; b) S. Ueda, M. Su, S. L. Buchwald, *J. Am. Chem. Soc.* **2012**, *134*, 700.

[7] D. DeMong, X. Dai, J. Hwa, M. Miller, S. I. Lin, L. Kang, A. Stamford, W. Greenlee, W. Yu, M. Wong, B. Lavey, J. Kozlowski, G. Zhou, D. Y. Yang, B. Patel, A. Soriano, Y. Zhai, C. Sondey, H. Zhang, J. Lachowicz, D. Grotz, K. Cox, R. Morrison, T. Andreani, Y. Cao, M. Liang, T. Meng, P. McNamara, J. Wong, P. Bradley, K. I. Feng, J. Belani, P. Chen, P Dai, J. Gauuan, P. Lin, H. Zhao, *J. Med. Chem.* **2014**, *57*, 2601.

[8] a) T. R. Blackmore, P. E. Thompson, *Heterocycles*, **2011**, *83*, 1953; b) P. Bedos, M. Amblard, G. Subra, P. Dodey, J. M. Luccarini, J. L. Paquet, D. Pruneau, A. Aumelas, J. Martinez, *J. Med. Chem.* **2000**, *43*, 2387; c) N. Vale, F. Nogueira, V. E. Do Rosário, P. Gomes, R. Moreira, *Eur. J. Med. Chem.* **2009**, *44*, 2506.

[9] a) T. Curtius, Hydrazide und Azide organischer Säuren I. Abhandlung, *J. Prakt. Chem.* **1894**, *50*, 275; b) A. K. Mailyan, J. A. Eickhoff, A. S. Minakova, Z. Gu, P. Lu, A. Zakarian, *Chem. Rev.* **2016**, *116*, 4441; c) A. K. Ghosh, M. Brindisi, A. Sarkar, *ChemMedChem* **2018**, *13*, 2351; d) J. Bariwal, E. Van der Eycken, *Chem. Soc. Rev.* **2013**, *42*, 9283; e) S. Gomez, J. A. Peters, T. Maschmeyer, *Adv. Synth. Catal.* **2002**, *344*, 1037; f) K. C. Kumara Swamy, N. N. Bhuvan Kumar, E. Balaraman, K. V. P. Pavan Kumar, *Chem. Rev.* **2009**, *109*, 2551.

[10] W. Zhao, R. P. Wurz, J. C. Peters, G. C. Fu, *J. Am. Chem. Soc.* **2017**, *139*, 12153.

[11] X. Shao, Y. Zheng, L. Tian, I. Martín-Torres, A. M. Echavarren, Y. Wang, *Org. Lett.* **2019**, *21*, 9262.

[12] a) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; b) H. Wang, X. Gao, Z. Lv, T. Abdelilah, A. Lei, *Chem. Rev.* **2019**, *119*, 6769; c) H.-Q. Do, S. Bachman, A. C. Bissember, J. C. Peters, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 2162; d) Q. M. Kainz, C. D. Matier, A. Bartoszewicz, S. L. Zultanski, J. C. Peters, G. C. Fu, *Science* **2016**, *351*, 681; e) C. D. Matier, J. Schwaben, J. C. Peters, G. C. Fu, *J. Am. Chem. Soc.* **2017**, *139*, 17707; f) Y. Liang, X. Zhang, D. W. C. MacMillan, *Nature* **2018**, *559*, 83.

[13] a) J. Lei, G.-T. Song, Y.-F. Luo, D.-Y. Tang, W. Yan, H. Li, Z.-Z. Chen, Z.-G. Xu, *Org. Chem. Front.* **2020**, *7*, 737; b) Z.-Z. Chen, S.-Q. Li, Y.-J. Zhang, D.-Y. Tang, J.-P. Meng, J. Lei, H. Li, Z.-G. Xu, *Org. Lett.* **2018**, *20*, 7811; c) Z.-G. Xu, S.-Q. Li, J.-P. Meng, D. Y. Tang, L.-J. He, J. Lei, H.-K. Lin, H. Li, Z.-Z. Chen, *Chem. Eur. J.* **2018**, *24*, 6732.

[14] CCDC 1910097 (**6n**) and CCDC 1891682 (**9q**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac,uk/data_request/cif.

[15] a) C. Wang, S. Wang, H. Li, J. Yan, H. Chi, X. Chen, Z. Zhang, *Org. Biomol. Chem.* **2014**, *12*, 1721; b) T. Zhang, N. Wang, Y. Xing, *J. Org. Chem.* **2018**, *83*, 7559; c) X. Zhang, W. Weng, H. Liang, H. Yang, B. Zhang, *Org. Lett.* **2018**, *20*, 4686.

[16] a) Z. Xu, G. Martinez-Ariza, A. P. Cappelli, S. A. Roberts, C. Hulme, *J. Org. Chem.* **2015**, *80*, 9007; b) A. M. Socha, N. Y. Tan, K. L. Laplante, J. K. Sello, *Bioorg. Med. Chem.* **2010**, *18*, 7193; c) G. P. Liao, E. M. M. Abdelraheem, C. G. Neochoritis, K. Kurpiewska, J. Kalinowska-Tłuścik, D. C. McGowan, A. Dömling, *Org. Lett.* **2015**, *17*, 4980; d) D. P. Zarezin, O. I. Shmatova, V. G. Nenajdenko, *Org. Biomol. Chem.* **2018**, *16*, 5987; d) V. Krieger, A. Hamacher, C. G. W. Gertzen, J. Senger, M. R. H. Zwinderman, M. Marek, C. Romier, F. J. Dekker, T. Kurz, M. Jung, H. Gohlke, M. U. Kassack, F. K. Hansen, *J. Med. Chem.* **2017**, *60*, 5493; e) H. Mofakham, A. Shaabani, S. Mousavifaraz, F. Hajishaabanha, S. Shaabani, S. W. Ng, *Mol. Divers.* **2012**, *16*, 351.

[17] C. Faggi, A. Neo, S. Marcaccini, G. Menchi, J. Revuelta, *Tetrahedron Lett.* **2008**, *49*, 2099.

10.1002/adsc.202000736

[18] a) H. Zhao, R. Wang, P. Chen, B. T. Gregg, M. M. Hsia, W. Zhang, *Org. Lett.* **2012**, *14*, 1872; b) D. E. DeMong, I. Ng, M. W. Miller, A. W. Stamford, *Org. Lett.* **2013**, *15*, 2830; c) N. Xing, J. Huang, P. Wang, L. Luo, S. Zheng, L. He, *Org. Biomol. Chem*. **2020**, *18*, 2175.

[19] a) J. Lau, C. Behrens, U. G. Sidelmann, L. B. Knudsen, B. Lundt, C. Sams, L. Ynddal, C. L. Brand, L. Pridal, A. Ling, D. Kiel, M. Plewe, S. Shi, P. Madsen, *J. Med. Chem.* **2007**, *50*, 113; b) J. T Kodra , A. S. Jørgensen, B. Andersen, C. Behrens, C. L. Brand, I. T. Christensen, M. Guldbrandt, C. B. Jeppesen, L. B. Knudsen, P. Madsen, E. Nishimura, C. Sams, U. G. Sidelmann, R. A. Pedersen, F. C. Lynn, J. Lau, *J. Med. Chem.* **2008**, *51*, 5387.

10.1002/adsc.202000736

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A Decarboxylative C(sp^3)-N Bond Forming Reaction to Construct 4-Imidazolidinones *via* Post-Ugi Cascade Sequence in One Pot

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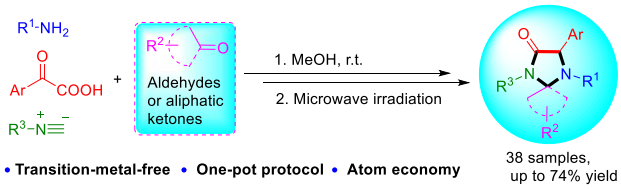

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