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Microwave-assisted synthesis of 4*H*-benzo[*f*]imidazo[1,4]diazepin-6-ones via a post-Ugi copper-catalyzed intramolecular Ullmann coupling

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ABSTRACT

An efficient post-Ugi copper-catalyzed intramolecular Ullmann coupling strategy has been elaborated for the diversity-oriented synthesis of 4*H*-benzo[*f*]imidazo[1,4]diazepin-6-ones and the scope and limitations of this protocol are investigated.

Introduction

The 4*H*-benzo[*f*]imidazo[1,4]diazepin-6-one scaffold is widely present in various natural products and pharmaceuticals[1] (Fig. 1) exhibiting potent biological activities on the γ-aminobutyric acid type A ($GABA_A$) receptors.[2] The commercially available flumazenil, a high-affinity $GABA_A$-B_Z site antagonist, has been used to treat benzodiazepine intoxication,[3] as well as to improve cognitive function in Alzheimer's patients.[4] On the other hand, sarmazenil and bretazenil have been served as the partial agonist for $GABA_A$ receptors to rapidly re-awaken anaethetized animals[5] and treat organophosphate poisoning,[6] respectively.

The classically used strategy[7] for the synthesis of 4*H*-benzo[*f*]imidazo[1,4]diazepin-6-one derivatives starts from the reaction of isatoic anhydride with a suitable amino acid, generating benzo[*e*][1,4]diazepine-2,5-diones, which upon treatment with ethyl isocyanoacetate, under strongly basic conditions, produces the corresponding 4*H*-benzo[*f*]imidazo[1,4]diazepin-6-ones. Some improvements of this approach have been reported.[8] However, these methods suffer from harsh reaction conditions and are restricted in the scope of the substitution pattern.

In recent years, the combination of multicomponent reactions[9] with transition metal-catalysis[10] has become one of the most important tools for diversity-oriented synthesis of complex molecules in few steps.[11] Interested in improving the synthetic methodology for 4*H*-benzo[*f*]imidazo[1,4]diazepin-6-ones, we recently developed a novel efficient diversity-oriented post-Ugi/gold(I)-catalyzed heteroannulation process for the synthesis of imidazo[1,4]diazepin-7-ones[12] (Scheme 1). However, the absence of a fused aryl ring system in the imidazo[1,4]diazepin-7-one scaffold decreases the structural resemblance with commercially available imidazobenzodiazepinone drugs (Fig. 1), and the employment of an expensive gold catalyst restricts its industrial scope.

Therefore, the development of a powerful and efficient strategy to prepare 4*H*-benzo[*f*]imidazo[1,4]diazepin-6-ones is still desirable. Due to unique advantages like dramatical acceleration of transformations, increased yields, and cleaner reactions,

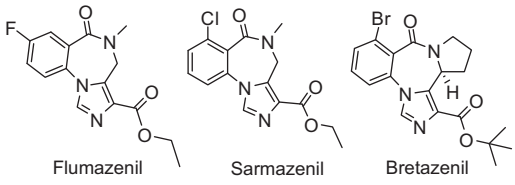

Figure 1. Drugs possessing the 4*H*-benzo[*f*]imidazo[1,4]diazepin-6-one scaffold.

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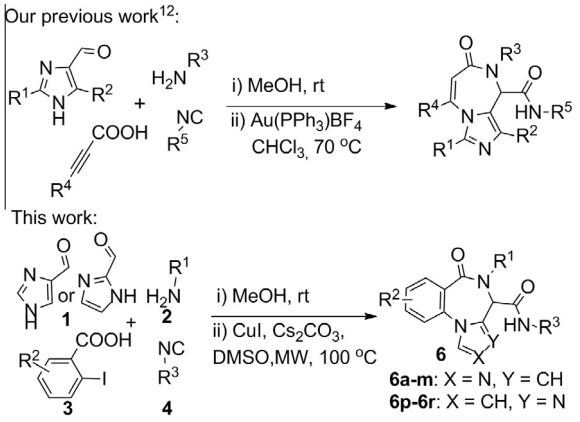
0040-4039/



Scheme 1. Comparison of this work with our previous work.

microwave-assisted organic synthesis has served as a powerful tool for the generation of medium-sized heterocycles.[13] In continuation of our efforts to synthesize bioactive important heterocyclic compounds, we developed a microwave-assisted post-Ugi copper-catalyzed intramolecular Ullmann coupling approach for the synthesis of 4*H*-benzo[*f*]imidazo[1,4]diazepin-6-ones (Scheme 1).

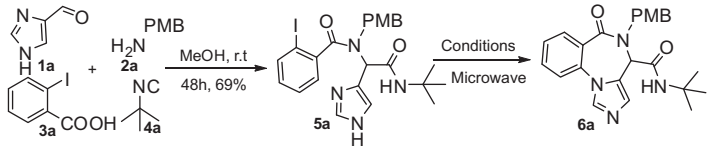
Results and discussion

The Ugi-adduct **5a** was synthesized via the Ugi-4CR (Ugi four-component reaction)[9] of imidazole-4-carbaldehyde (**1a**), *p*-methoxybenzylamine (**2a**), 2-iodobenzoic acid (**3a**), and *tert*-butyl isonitrile (**4a**) in 69% yield. This was chosen as a model substrate to optimize the reaction for the intramolecular Ullmann coupling under microwave irradiation. The reaction produced 4*H*-benzo[*f*]imidazo[1,4]diazepin-6-one **6a** in 26% and 34% yields employing 10 mol % of CuI at 100 °C for 30 min in DMF or DMA, respectively (Table 1, entries 1 and 2). When changing the solvent to DMSO, the yield was increased to 78% (Table 1, entry 3). Reduction of the reaction temperature to 80 °C led to a lower yield of 40% (Table 1, entry 4). Employing various copper salts such as CuBr, CuCl, $Cu(OAc)_2$, and $Cu(OTf)_2$, no improvement of the yield was observed (Table 1, entries 5–8). Moreover, using another base such as potassium carbonate or sodium carbonate did not increase the yield (Table 1, entries 9 and 10). The application of L-proline and (*R*,*R*)-(−)-*N*,*N*′-dimethyl-1,2-cyclohexanediamine as ligand delivered the desired product in lower yields of 65% and 60%, respectively (Table 1, entries 11 and 12). Diminishing the catalyst loading to 5 mol % resulted in a decreased yield of 45% (Table 1, entry 13). Using 20 mol % of CuI, a slightly lower yield of **6a** was observed (Table 1, entry 14).

To investigate the scope and limitations of our optimized protocol (Table 1, entry 3), diversely substituted Ugi-adducts **5b**–**r** were prepared and subjected to these conditions. Mostly the intramolecular Ullmann coupling proceeded smoothly giving 4*H*-benzo[*f*]imidazo[1,4]diazepin-6-ones **6** in moderate to good yields. Various substituents on the aromatic ring of the acid and the amine are well tolerated. Surprisingly, in the case of C-2 or C-5 substituted imidazole-4-carbaldehyde, decomposition of the starting material was observed (Table 2, entries 14 and 15). Moreover, the imidazole-2-carbaldehyde was employed for the formation of Ugi-adducts **5p**, **5q**, and **5r**, which were subjected to intramolecular Ullmann coupling delivering the corresponding products **6p**, **6q**, and **6r** in 85%, 76%, and 69% yields, respectively (Table 2, entries 16–18).

Based on previous investigations of Ullmann coupling,[14] a plausible mechanism for this copper(I)-catalyzed intramolecular reaction is depicted in Scheme 2. The coordination of copper(I) iodine with the amine of the Ugi-adduct **5a** produces the intermediate A. The Cu(I) inserts into the aryl iodine bond delivering intermediate B. Finally, reductive elimination leads to the regeneration of the copper(I) catalyst and the formation of the 4*H*-benzo[*f*]imidazo[1,4]diazepin-6-one **6a**.

Table 1
Optimization of the intramolecular Ullmann coupling reaction[a]



Entry	Catalyst (mol %)	Base	Solvent	Temp (°C)	Yield[b] (%)
1	CuI (10)	Cs_2CO_3	DMF	100	26
2	CuI (10)	Cs_2CO_3	DMA	100	34
3	CuI (10)	Cs_2CO_3	DMSO	100	78
4	CuI (10)	Cs_2CO_3	DMSO	80	40
5	CuBr (10)	Cs_2CO_3	DMSO	100	50
6	CuCl (10)	Cs_2CO_3	DMSO	100	42
7	$Cu(OAc)_2$ (10)	Cs_2CO_3	DMSO	100	60
8	$Cu(OTf)_2$ (10)	Cs_2CO_3	DMSO	100	52
9	CuI (10)	K_2CO_3	DMSO	100	61
10	CuI (10)	Na_2CO_3	DMSO	100	55
11	CuI (10)	Cs_2CO_3	DMSO	100	65[c]
12	CuI (10)	Cs_2CO_3	DMSO	100	60[d]
13	CuI (5)	Cs_2CO_3	DMSO	100	45
14	CuI (20)	Cs_2CO_3	DMSO	100	73

[a] All the reactions were run on 0.10 mmol scale of Ugi adduct **5a** with base (2 equiv), solvent (1 mL) under microwave irradiation at 100 or 80 °C and 100 W maximum power for 30 min.
[b] Yields are isolated yields.
[c] 20 mol % of L-proline was used.
[d] 20 mol % of (*R*,*R*)-(−)-*N*,*N*′-dimethyl-1,2-cyclohexanediamine was used; Tf = trifluoromethanesulfonyl, PMB = *p*-methoxybenzyl.

Table 2
Scope and limitations of the intramolecular Ullmann coupling[a]

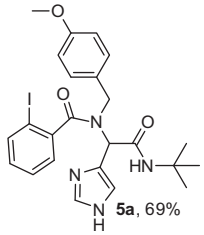
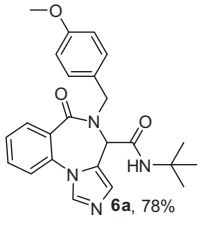
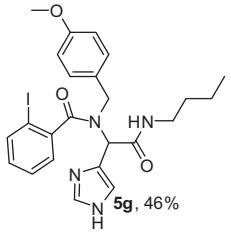
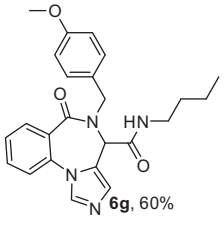
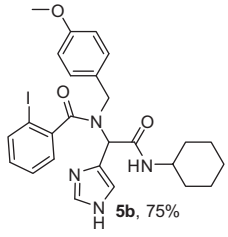
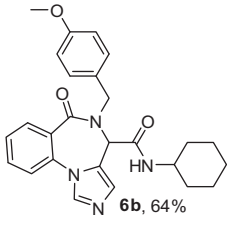
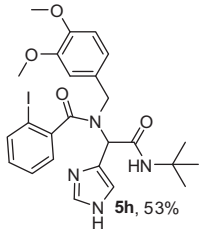
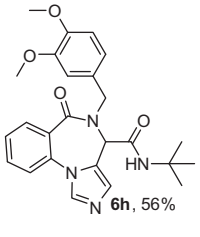
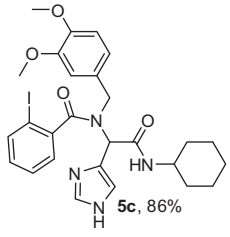
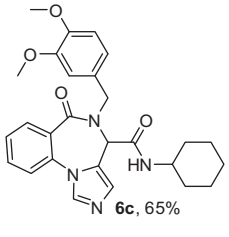
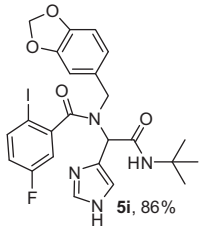
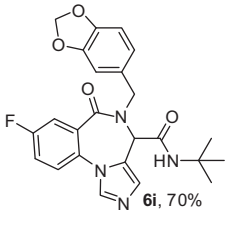
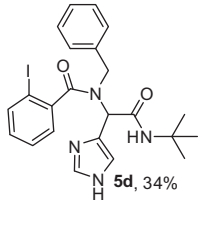
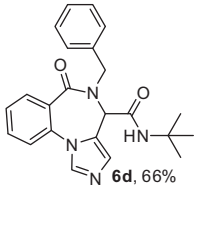
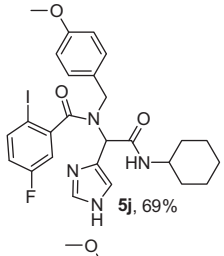
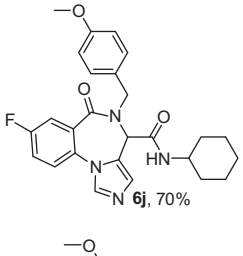
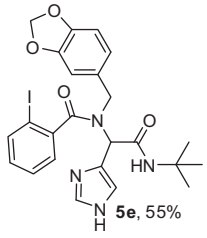
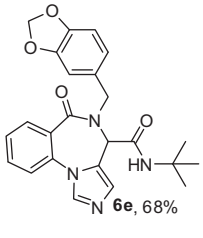
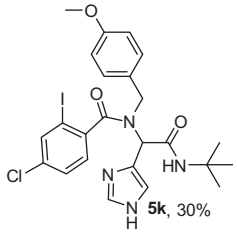
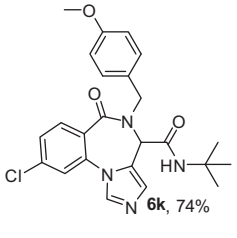
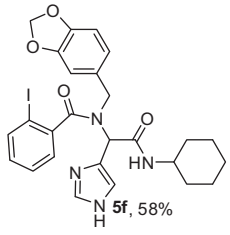
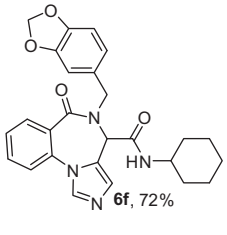
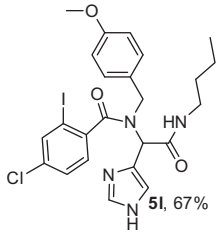
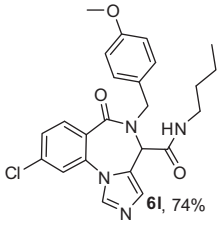
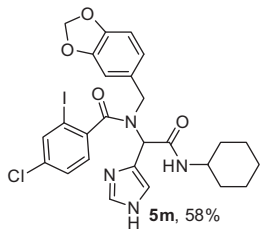
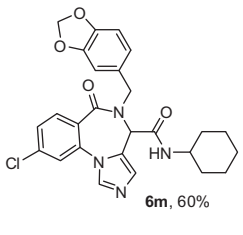
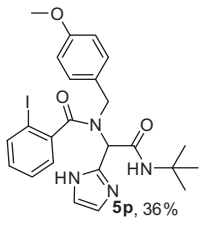
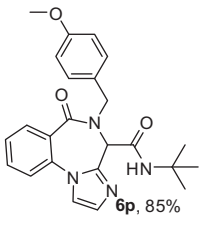
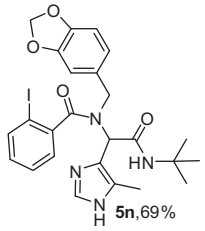
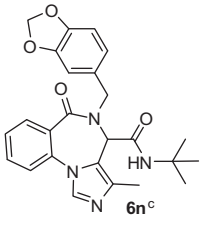
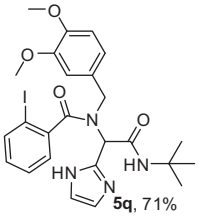
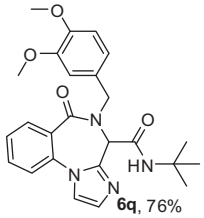
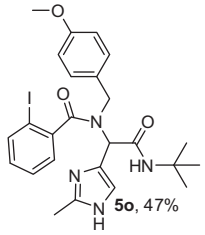
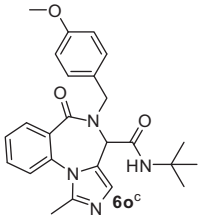
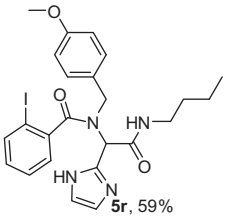
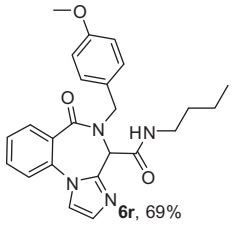
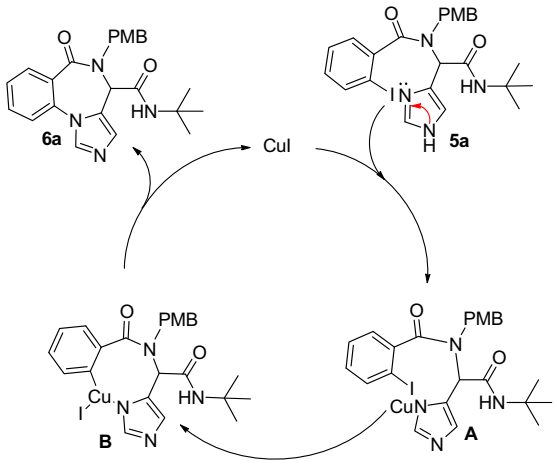
Entry	Ugi adduct **5** (% yield[b])	4*H*-Benzo[*f*]imidazo[1,4]diazepin-6-ones **6** (% yield[b])	Entry	Ugi adduct **5** (% yield[b])	4*H*-Benzo[*f*]imidazo[1,4]diazepin-6-ones **6** (% yield[b])
1	 **5a**, 69%	 **6a**, 78%	7	 **5g**, 46%	 **6g**, 60%
2	 **5b**, 75%	 **6b**, 64%	8	 **5h**, 53%	 **6h**, 56%
3	 **5c**, 86%	 **6c**, 65%	9	 **5i**, 86%	 **6i**, 70%
4	 **5d**, 34%	 **6d**, 66%	10	 **5j**, 69%	 **6j**, 70%
5	 **5e**, 55%	 **6e**, 68%	11	 **5k**, 30%	 **6k**, 74%
6	 **5f**, 58%	 **6f**, 72%	12	 **5l**, 67%	 **6l**, 74%
13	 **5m**, 58%	 **6m**, 60%	16	 **5p**, 36%	 **6p**, 85%

Table 2 (*continued*)

Entry	Ugi adduct **5** (% yield[b])	4*H*-Benzo[*f*]imidazo[1,4]diazepin-6-ones **6** (% yield[b])	Entry	Ugi adduct **5** (% yield[b])	4*H*-Benzo[*f*]imidazo[1,4]diazepin-6-ones **6** (% yield[b])
14	 **5n**, 69%	 **6n**[c]	17	 **5q**, 71%	 **6q**, 76%
15	 **5o**, 47%	 **6o**[c]	18	 **5r**, 59%	 **6r**, 69%

[a] Reactions were run on a 0.30 mmol scale under the optimized conditions (Table 1, entry 3).
[b] Isolated yields.
[c] The starting material was decomposed.



Scheme 2. Plausible mechanism for the intramolecular Ullmann coupling.

Conclusion

In conclusion, we have developed an expedient copper-catalyzed, diversity-oriented intramolecular Ullmann coupling strategy to prepare 4*H*-benzo[*f*]imidazo[1,4]diazepin-6-ones from commercially available building blocks. The diversity of the desired products is guaranteed by the first step, the Ugi-4CR.

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Supplementary data

Supplementary data (general experiment details, the copies of ^{1}H and ^{13}C NMR spectra of the compounds and their HRMS data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.023.

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