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1,4-Addition Ugi Reaction Using Cyclic α,β-Unsaturated Ketone as Substrate

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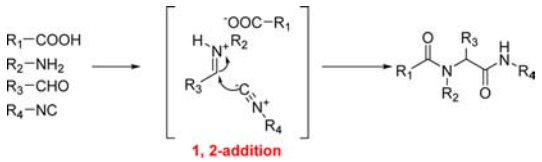
Supporting Information

ABSTRACT: A four-component, 1,4-addition Ugi reaction using cyclic α,β-unsaturated ketones, carboxylic acids, amines, and isocyanides was developed for the first time. By combining this reaction with Michael addition, nucleophilic substitution, and C−N bond formation reactions, bicyclic and tricyclic scaffolds with pyridinone and quinolinone moieties, two basic units among a variety of natural products and pharmaceuticals, were constructed.

Multicomponent reactions (MCRs), in which the product is composed of parts of several substrates that react in a programmed sequence, have been widely used in diversity- and target-oriented syntheses to synthesize biologically active natural products and pharmaceuticals.[1,2] The Ugi reaction is a classic and atom-economical multicomponent reaction that produces α-acylaminoamides from aldehydes or ketones, carboxylic acids, amines, and isocyanides.[3] To broaden the application of this powerful reaction, numerous variations have been developed including the Ugi−Smiles reaction,[4] Ugi−Joullié reaction,[5] and interrupted Ugi reaction.[6] The normal Ugi reaction involves the 1,2-addition of isocyanides to iminium ions (Scheme 1).

Scheme 1. Mechanism of Normal Ugi Reaction



However, Ugi reactions involving the 1,4-addition of isocyanides to α,β-unsaturated iminium ions have rarely been reported. The main reason may be that the Michael addition of amine to α,β-unsaturated ketones or aldehyde prevents the formation of the key iminium ion in the Ugi reaction. The only example was reported by Ugi in 1963, where a three-component reaction based on *N*-alkylquinolinium, carboxylic acids, and isocyanides gave *N*-alkyl-3-acyl-1,4-dihydroquinoline-4-carboxamides in poor to moderate yields (Scheme 2).[7] Hence, to broaden the substrate scope of the 1,4-addition Ugi, the development of four-component 1,4-addition Ugi reactions and their application to diversity-oriented synthesis is very significant. Herein, we report an Ugi reaction involving cyclic α,β-unsaturated ketones, carboxylic acids, amines, and isocyanides as substrates in which a 1,4-addition occurs in place of the conventional 1,2-addition (Scheme 3). In contrast to a normal Ugi reaction, 1,4-addition Ugi reaction produces β-keto amide with a β,γ-enamine. The more reactive functional groups (ketones, amines and alkenes

Scheme 2. Three-Component 1,4-Addition Ugi Reaction

Scheme 3. Four-Component 1,4-Addition Ugi Reaction

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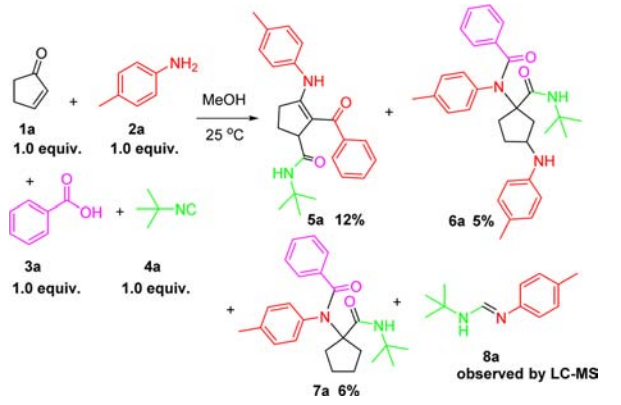
versus amides) could facilitate the use of the 1,4-addition Ugi product in post-Ugi reactions.

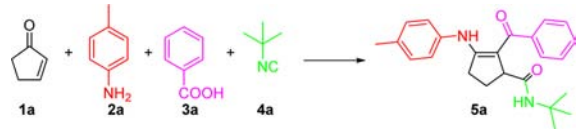
Our previous research indicated that when acyclic α,β-unsaturated aldehydes like cinnamaldehyde were used as substrates only the normal Ugi reaction took place.[8] However, when acrolein was used as the aldehyde component, the reaction was very messy. These results suggested that for acyclic α,β-unsaturated aldehydes if the substitution in the β-position was a small group then a Michael addition could take place between the amine and α,β-unsaturated aldehyde. Moreover, acrolein is very easy to polymerize. It is known that to realize a four-component 1,4-addition Ugi reaction the key is to generate α,β-unsaturated imines. In 2014, Carbó, Whiting, and co-workers investigated the formation of α,β-unsaturated imines by the addition of amines to α,β-unsaturated aldehydes and ketones using computational techniques and IR spectroscopy and found that cyclic enonoes preferred to form α,β-unsaturated imines instead of β-amino ketones.[9] Hence, we used cyclopent-2-en-1-one (**1a**), *p*-toluidine (**2a**), benzoic acid (**3a**), and 2-isocyano-2-methylpropane (**4a**) as substrates in the 1,4-addition Ugi reaction in methanol at 25 °C. To our delight, the desired product **5a** was obtained in 12% yield, in addition to two major byproducts **6a** and **7a**, which were isolated via column chromatography. After careful analysis of the mass spectrum of the reaction mixture, we tentatively identified another byproduct, **8a**, using the mass data (m/z = 191, M + H^+)[10] (Scheme 4).

Scheme 4. 1,4-Addition Ugi Reaction Using Cyclopent-2-en-1-one (1a)



In order to optimize the reaction conditions, other solvents such as *N*,*N*-dimethylformamide (DMF) and $CHCl_3$ were examined; we found that these solvents were less effective than methanol (Table 1, entries 2 and 3). Notably, when anhydrous methanol was used as the solvent, the yield decreased slightly (Table 1, entry 4). Therefore, mixtures of methanol and water were employed, and we found that a 1:1 mixture of methanol and water gave the best yield of 26% (Table 1, entries 5−10). The reason may be that the polar solvent could stabilize the iminium ion and carboxylate anion of the Ugi reaction.[11] Next, several reaction temperatures were screened. When the temperature of the reaction was increased from 25 to 60 °C, the yield of the reaction increased from 26% to 30% (Table 1, entries 9 and 11−13). However, a further increase of the reaction temperature to 70 °C led to a decreased yield (Table 1, entry 14). Finally, we examined the effect of reaction concentration and found that decreasing the reaction concentration to 0.25 M or increasing the

Table 1. Optimization of the Four-Component, 1,4-Addition Ugi Reaction



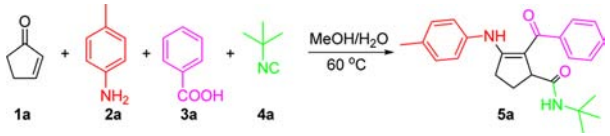
entry	temp (°C)	solvent A (volume, mL)	solvent B (volume)	yield[b] (%)
1	25	MeOH (2.0)		14
2	25	DMF (2.0)		5
3	25	$CHCl_3$ (2.0)		3
4	25	MeOH (2.0)		12[c]
5	25	MeOH (1.8)	H_2O (0.2)	15
6	25	MeOH (1.6)	H_2O (0.4)	19
7	25	MeOH (1.4)	H_2O (0.6)	23
8	25	MeOH (1.2)	H_2O (0.8)	24
9	25	MeOH (1.0)	H_2O (1.0)	26
10	25	MeOH (0.8)	H_2O (1.2)	21
11	40	MeOH (1.0)	H_2O (1.0)	27
12	50	MeOH (1.0)	H_2O (1.0)	28
13	60	MeOH (1.0)	H_2O (1.0)	30
14	70	MeOH (1.0)	H_2O (1.0)	27
15	60	MeOH (2.0)	H_2O (2.0)	23
16	60	MeOH (0.5)	H_2O (0.5)	28

[a]**1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), and **4a** (1.0 mmol) in solvent (1−4 mL) was reacted at 25−70 °C for 12 h. [b]Isolated yields. [c]Anhydrous MeOH was used.

reaction concentration to 1.0 M diminished the yield (Table 1, entries 15 and 16).

Next, the amounts of the four reaction components were optimized (Table 2). According to the structure of the

Table 2. Optimization of the Ratio of 1a, 2a, 3a, and 4a in the 1,4-Addition Ugi Reaction



entry	**1a** (mmol)	**2a** (mmol)	**3a** (mmol)	**4a** (mmol)	yield[b] (%)
1	1	1	1	1	30
2	1	2	2	2	43
3	1	3	3	3	49
4	1	4	4	4	45
5	1	1	3	3	12
6	1	3	1	3	22
7	1	3	3	1	26
8	1	2	3	3	31
9	1	3	2	3	39
10	1	3	3	2	38

[a]**1a** (1.0−3.0 mmol), **2a** (1.0−3.0 mmol), **3a** (1.0−3.0 mmol), and **4a** (1.0−3.0 mmol) in $MeOH/H_2O$ = 1 mL/1 mL at 60 °C for 12 h. [b]Isolated yields.

byproducts, more equivalents of **2a** and **4a** were consumed in the formation of **6a** and **8a**. Therefore, in order to improve the reaction yield, the amounts of **2a** and **4a** were increased from 1 to 2 equiv based on **1a**, and the amount of **3a** was increased accordingly to adjust the pH of the reaction. To our delight, the yield increased from 30% to 43% (Table 2, entries 1 and 2). When

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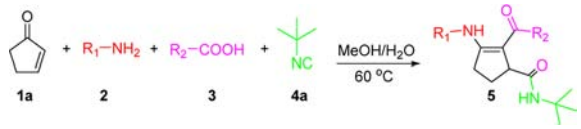
the amounts of **2a**, **3a**, and **4a** were increased to 3 equiv, the yield increased to 49% (Table 2, entry 3). However, further increasing the equivalents of **2a**, **3a**, and **4a** to 4 equiv led to a decrease in the yield (Table 2, entry 4). Other amounts of **1a**, **2a**, **3a**, and **4a** were screened, but none of them gave better results than **1a**/**2a**/**3a**/**4a** = 1:3:3:3 (Table 2, entries 5−10). Thus, the optimized reaction conditions were as follows: **1a** (1.0 mmol), **2a** (3.0 mmol), **3a** (3.0 mmol), **4a** (3.0 mmol), MeOH/H_2O (1:1, 2.0 mL) at 60 °C.

With the optimized reaction conditions in hand, the generality and substrate scope of **1a** and **4a** were examined with a series of amines (**2a**−**j**) and acids (**3a**−**h**); the results are summarized in Table 3 and Scheme 5. In regard to the amine component, high

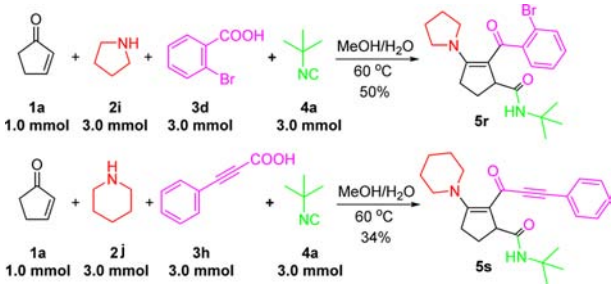
Table 3. 1,4-Addition Ugi Reaction Using 1a, 4a, and a Series of Amines and Acids As Substrates



entry	2, R_1 =	3, R_2 =	yield[b] (%)
1	**2b**, *p*-FC_6H_4	**3a**, Ph	**5b**, 45
2	**2c**, *p*-$MeOC_6H_4$	**3a**, Ph	**5c**, 51
3	**2d**, 2,4-$F_2C_6H_3$	**3a**, Ph	**5d**, 23
4	**2e**, 2,4-$Me_2C_6H_3$	**3a**, Ph	**5e**, 33
5	**2f**, Bn	**3a**, Ph	**5f**, 56
6	**2g**, *n*-Bu	**3a**, Ph	**5g**, 36
7	**2h**, $N_3CH_2CH_2$−	**3a**, Ph	**5h**, 43
8	**2f**, Bn	**3b**, *p*-$MeOC_6H_4$	**5i**, 59
9	**2f**, Bn	**3c**, *p*-NCC_6H_4	**5j**, 58
10	**2f**, Bn	**3d**, *o*-BrC_6H_4	**5k**, 77
11	**2f**, Bn	**3e**, *o*-FC_6H_4	**5l**, 81
12	**2f**, Bn	**3f**, 2-furyl	**5m**, 78
13	**2f**, Bn	**3g**, Me	**5n**, 48
14	**2f**, Bn	**3h**, PhCC−	**5o**, 88
15	**2h**, *n*-Bu	**3h**, PhCC−	**5p**, 78
16	**2a**, *p*-MeC_6H_4	**3h**, PhCC−	**5q**, 56

[a]Reaction conditions: **1a** (1.0 mmol), **2b**−**h** (3.0 mmol), **3a**−**3h** (3.0 mmol), and **4a** (3.0 mmol) in MeOH/H_2O = 1 mL/1 mL at 60 °C for 12 h. [b]Isolated yields.

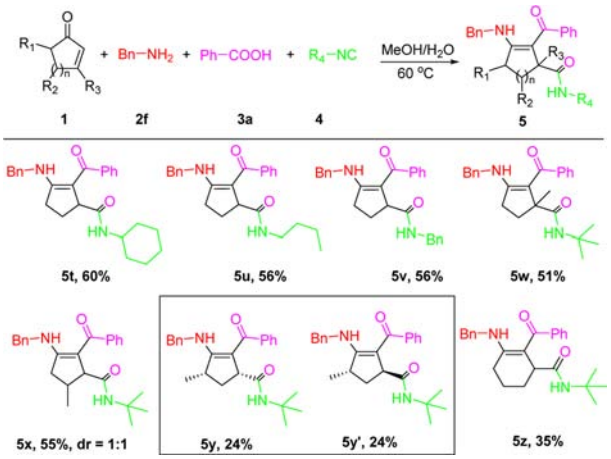
Scheme 5. 1,4-Addition Ugi Reaction Using Secondary Amines



functional group tolerance was observed when **3a** was employed as the acid component. Anilines with electron-donating (**2c** and **2e**) and electron-withdrawing groups (**2b** and **2d**) as well as aliphatic amines (**2f**−**h**) were tolerated under the optimized conditions (Table 3, entries 1−7). In regard to the acid component, the reaction proceeded smoothly when benzylamine **2f** was employed as the amine (Table 3, entries 8−14). Aromatic acids including benzoic acid with electron-donating (**3b**) and electron-withdrawing substituents (**3c**−**e**), heterocyclic acids (**3f**), as well as aliphatic acids including acetic acid (**3g**) and 3-phenylpropiolic acid (**3h**) afforded the desired products in moderate to excellent yields. Notably, when secondary amines including pyrrolidine (**2i**) and piperidine (**2j**) were used, the desired products **5r** and **5s** were obtained in 50% and 34% yields, respectively (Scheme 5). To confirm the structure of the 1,4-addition Ugi product, a single crystal of **5k** was analyzed by X-ray diffraction analysis.[10]

To further expand the substrate scope of the reaction, other isocyanides and cyclic *α*,*β*-unsaturated ketones were tested. Compared with *tert*-butyl isocyanide (**4a**), less bulky isocyanides including cyclohexyl isocyanide (**4b**), *n*-butyl isocyanide (**4c**), and benzyl isocyanide (**4d**) gave the desired products in better yields (**5t**, **5u**, and **5v** vss **5a**). When substituted cyclopent-2-en-1-ones including 3-methylcyclopent-2-en-1-one (**1b**), 4-methylcyclopent-2-en-1-one (**1c**), and 5-methylcyclopent-2-en-1-one (**1d**) were employed as the ketone, the desired products **5w**, **5x**, **5y**, and **5y′** were obtained in 51%, 55%, 24%, and 24% yields, respectively. Notably, **5s** was obtained as a 1:1 mixture of diastereoisomers that could not be separated by column chromatography, while **5y** and **5y′** could be separated and were both obtained in 24% yield (Scheme 6).

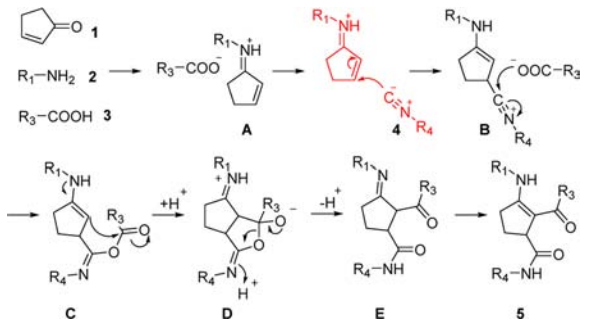
Scheme 6. 1,4-Addition Ugi Reaction Using 2f, 3a, and a Series of Cyclic *α*,*β*-Unsaturated Ketones and Isocyanides



[a]Reaction conditions: **1a**−**1e** (1.0 mmol), **2f** (3.0 mmol), **3a** (3.0 mmol), and **4a**−**d** (3.0 mmol) in MeOH/H_2O = 1 mL/1 mL at 60 °C for 12 h. Isolated yields.

On the basis of our results, a plausible reaction mechanism for the 1,4-addition Ugi reaction was proposed (Scheme 7).

Scheme 7. Proposed Mechanism of 1,4-Addition Ugi Reaction



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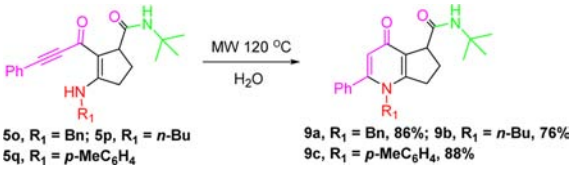
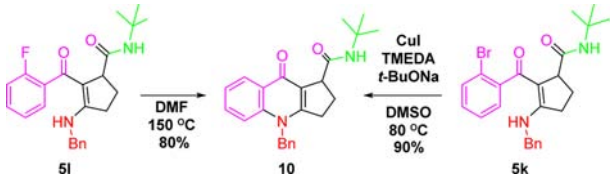
Compound **1a** reacted with amine **2** in the presence of acid **3** to form α,β-unsaturated imine ion **A**. The 1,4-addition of **A** by isocyanide **4** generated enamine **B**, which was attacked by a carboxylate ion to give intermediate **C**. Rearrangement of **C** via translocation of the acyl group afforded imine **E**, which was transformed into product **5** via imine−enamine tautomerization.

To generate more complex molecular skeletons, the developed reaction was combined with Michael addition, nucleophilic substitution, and C−N bond formation reactions as post-Ugi reactions. Using this strategy, bicyclic scaffolds with pyridinone moieties **9a**, **9b**, and **9c** (Scheme 8) as well as a tricyclic scaffold with a quinolinone moiety **10** (Scheme 9) were obtained in good yields.

Scheme 8. 1,4-Addition Ugi Reaction Followed by Michael Addition



Scheme 9. 1,4-Addition Ugi Reaction Followed by Nucleophilic Substitution and C−N Bond Formation Reactions



In summary, we developed a 1,4-addition Ugi reaction using cyclic α,β-unsaturated ketones, carboxylic acids, amines, and isocyanides. To the best of our knowledge, this reaction is the first example of a four-component 1,4-addition Ugi reaction. Moreover, this reaction was combined with Michael addition, nucleophilic substitution, and C−N bond formation reactions to construct bicyclic and tricyclic scaffolds with pyridinone and quinolinone moieties, respectively. Further applications of this reaction in diversity-oriented synthesis are being invested in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02493.

Experimental procedures and characterization data for all compounds (PDF)

X-ray data for compound **5k** (CIF)

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Notes

The authors declare no competing financial interest.

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