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# A New Entry of Copper-Catalyzed Four-Component Reaction: Facile Access to $\alpha$-Aryl $\beta$-Hydroxy Imidates

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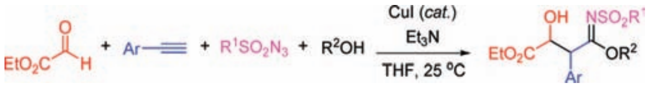
## ABSTRACT



**$\alpha$-Aryl $\beta$-hydroxy imidates are efficiently obtained by the four-component reaction of ethyl glyoxylates, aryl acetylenes, sulfonyl azides, and alcohols using a copper catalyst. The developed procedure is characterized by high selectivity, mild reaction conditions, a wide substrate scope, and an excellent functional group tolerance. Facile transformations of the obtained sulfonylimidate moiety to other carbonyl groups such as sulfonamides or esters were also demonstrated.**

Multicomponent reactions (MCRs)[1] constitute an ideal approach to transformations for generating complex molecular skeletons in one pot. The Ugi four-component reaction (4-CR),[2] in which primary amines, oxo species, carboxylic acids, and isocyanides react, is one of the most representative MCRs leading to $\alpha$-acylamino amides (peptoids) under ambient conditions. It can be regarded that the isocyanide-based Ugi 4-CR is an expansion of the Passerini three-component reaction (3-CR),[3] which affords depsipeptides and $\beta$-peptide analogs from the coupling of ketones, carboxylic acids, and isocyanides. This example offers an insightful demonstration that a modification of reacting components in previously established MCRs may lead to a new version of transformations with great additional significance.

We have recently developed the Cu-catalyzed 3-CR of 1-alkyne, sulfonyl- or phosphoryl azide, and various nucleophiles such as amine, alcohol, water, and pyrrole to afford amidines, imidates, amides, and 2-iminopyrrole derivatives, respectively.[4] The reactions are featured to show a wide substrate scope, a high tolerance to various functional groups, and very mild reaction conditions.

Although a wide range of biologically interesting compounds are readily obtained with good efficiency, selectivity, and synthetic applicability, a limitation in our catalytic 3-CR procedure has been pointed out: a substituent $\alpha$ to the imino or carbonyl position cannot be directly introduced.[5,6]

The mechanistic pathway of the Cu-catalyzed 3-CR was proposed to proceed via a reactive ketenimine intermediate (**A**), generated in situ by the catalytic cycloaddition of

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(1) For recent reviews, see: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.

(2) (a) Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267–268. (b) Ugi, I. *Angew. Chem.* **1962**, *74*, 9–22.

(3) (a) Passerini, M.; Simone, L. *Gazz. Chim. Ital.* **1921**, *51*, 126–129. (b) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 388–391.

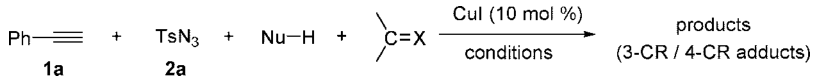
(4) (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038–2039. (b) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046–16047. (c) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347–1350. (d) Chang, S.; Lee, M.; Jung, D. Y.; Yoo, E. J.; Cho, S. H.; Han, S. K. *J. Am. Chem. Soc.* **2006**, *128*, 12366–12367. (e) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1897–1900. (f) Cho, S. H.; Hwang, S. J.; Chang, S. *Org. Synth.* **2008**, *85*, 131–137. (g) Kim, J. Y.; Kim, S. H.; Chang, S. *Tetrahedron Lett.* **2008**, *49*, 1745–1749. (h) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 2836–2839. (i) Yoo, E. J.; Chang, S. *Org. Lett.* **2008**, *10*, 1163–1166.

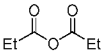
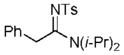
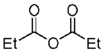
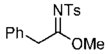
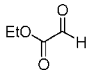
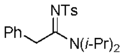
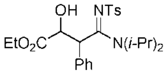
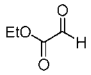
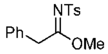
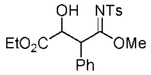
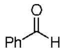
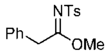
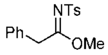
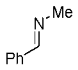
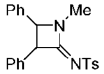
(5) For an example of $\alpha$-substitution of *N*-phosphryl amidines, see: Kim, S. H.; Jung, D. Y.; Chang, S. *J. Org. Chem.* **2007**, *72*, 9769–9771.

(6) For a recent example of $\alpha$-substitution of preisolated *N*-sulfonyl imidates, see: Matsubara, R.; Berthiol, F.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 1804–1805.

10.1021/ol900023t CCC: $40.75

**Table 1.** Examination of Various Combinations for the Development of Cu-Catalyzed 4-CR[a]

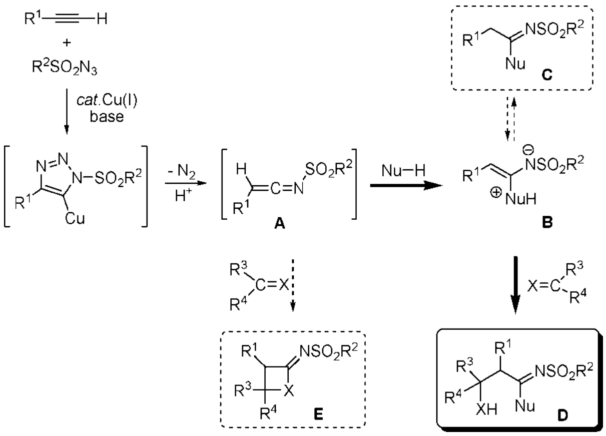


| entry | Nu-H | C=X | conditions (additive/solvent) | product (%)[b,c] | | | |
|---|---|---|---|---|---|---|---|
| | | | | 3-CR adduct | | 4-CR adduct | |
| 1 | $(i\text{-Pr})_2NH$ |  | none/$CHCl_3$ |  | 66 | – | |
| 2 | MeOH |  | $Et_3N/CHCl_3$ |  | 12 | – | |
| 3 | $(i\text{-Pr})_2NH$ |  | none/$CH_2Cl_2$ |  | 33 |  | 18<br>(51:49) |
| 4 | MeOH |  | $Et_3N/CH_2Cl_2$ |  | 9 |  | 59[d]<br>(52:48) |
| 5 | MeOH |  | $Et_3N/CH_2Cl_2$ |  | 53 | – | |
| 6 | MeOH | PhN=O | $Et_3N/CHCl_3$ |  | 4 | – | |
| 7 | MeOH |  | $Et_3N/CHCl_3$ |  | 59 | – | |

[a] **1a** (0.5 mmol), **2a** (0.6 mmol), nucleophile (0.75 mmol), electrophile (1.0 mmol), and CuI (10 mol %) were stirred under the mentioned reaction conditions at 25 °C for 12 h. [b] $^1H$ NMR yield (internal standard was 1,1,2,2-tetrachloroethane). [c] Number in the parenthesis is the ratio of two diastereomers determined by $^1H$ NMR. [d] When the reaction was carried out in $CHCl_3$, the same yield of the 4-CR adduct was obtained.

1-alkyne and sulfonyl azide followed by ring opening of the corresponding triazole species (Scheme 1).[7] On the basis of this mechanistic consideration, it was envisioned that a new type of 4-CR protocol could be plausible by the simultaneous employment of pronucleophiles (Nu-H) and electrophiles in one pot. It was predicted that a suitable combination of the two components would be highly important for the successful realization of 4-CRs.

**Scheme 1**



In fact, an adduct **B** derived from the reaction of ketenimine **A** with a nucleophile will end up with a 3-CR product **C** if a proton transfer process from **B** to **C** becomes irreversible. In addition, selective reactivity of employed electrophiles would be another key issue of consideration because a direct cycloaddition of those species with the ketenimine intermediate **A** is also possible as an undesired reaction, thereby leading to a 3-CR product **E** and inhibiting the formation of the 4-CR product **D**. Indeed, elegant examples of this direct cyclization were already demonstrated.[8] It should be mentioned that the products obtainable from the prospective 4-CR would be highly valuable from the aspect of organic synthesis and combinatorial approach because they bear elaborate neighboring functional groups.[9]

At the outset of our studies, we first screened plausible combinations of potential nucleophiles and electrophiles in test reactions with phenylacetylene (**1a**) and *p*-toluenesulfonyl azide (**2a**) under various conditions (Table 1). When an anhydride was employed, the desired 4-CR product was not observed and only 3-CR products were obtained in varied

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(7) (a) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154–3157. (b) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1730–1733. (c) Yoo, E. J.; Ahlquist, M.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *J. Org. Chem.* **2008**, *73*, 5520–5528.

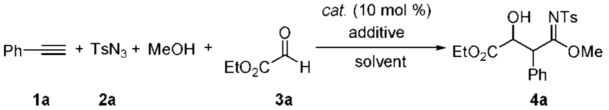
(8) (a) Whiting, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3157–3161. (b) Xu, X.; Cheng, D.; Li, J.; Guo, H.; Yan, J. *Org. Lett.* **2007**, *9*, 1585–1587.

(9) For recent examples of α-aryl carbonyl compounds, see: (a) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155. (b) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137–2139. (c) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074–13075.

efficiencies depending on the nature of nucleophiles (entries 1 and 2). Interestingly, when ethyl glyoxylate and amine were used, only a slight amount of 4-CR adduct was produced along with a major 3-CR adduct, amidine (entry 3). However, the yield of 4-CR product was significantly increased with the use of alcohol nucleophile (entry 4). The obtained α-phenyl *β*-hydroxy imidate displayed no diastereoselectivity, giving almost the same ratio of *syn*/*anti* isomers. On the other hand, a simple aldehyde such as benzaldehyde did not participate in the 4-CR reaction (entry 5). The use of other electrophiles such as nitrosobenzene or imine derivatives did not provide significant outcomes (entries 6 and 7).

On the basis of the promising results obtained above, we further attempted to optimize the 4-CR conditions using phenylacetylene (**1a**), *p*-toluenesulfonyl azide (**2a**), methanol, and ethyl glyoxylate (**3a**) (Table 2). Choice of solvents and base additives was important for achieving high efficiency, and THF and triethylamine were selected, respectively (entries 4−6).[10] However, the effect of copper species and external ligands was less visible. In addition, the combined use of copper catalyst and Lewis acid additive did not affect the reaction efficiency (entry 9).

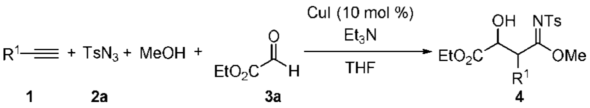
**Table 2.** Reaction Optimization of 4-CR[a]

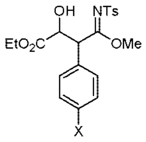
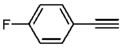
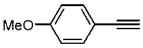
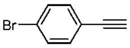
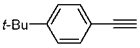
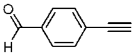
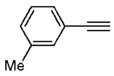
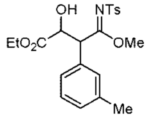
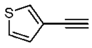
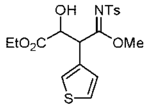
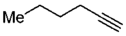
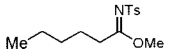


| entry | catalyst | solvent | additive | yield (%)[b,c] |
|---|---|---|---|---|
| 1 | CuI | $CHCl_3$ | | <1 |
| 2 | CuI | $CHCl_3$ | DBU[d] | <1 |
| 3 | CuI | $CHCl_3$ | 2,6-lutidine | 11 (52:48) |
| 4 | CuI | $CHCl_3$ | $Et_3N$ | 59 (53:47) |
| 5 | CuI | $CH_3CN$ | $Et_3N$ | 47 (55:45) |
| 6 | CuI | THF | $Et_3N$ | 71 (51:49) |
| 7 | $Cu(OTf)_2$ | THF | $Et_3N$ | 66 (53:47) |
| 8 | CuI | THF | TBTA[e,f] | 71 (52:48) |
| 9 | CuI | THF | $Sc(OTf)_3$[f] | 67 (52:48) |

[a] A solution of **1a** (0.6 mmol), **2a** (0.6 mmol), **3a** (0.5 mmol), methanol (2.5 mmol), additive (1.5 mmol), and catalyst (10 mol %) in solvent (1.0 mL) was stirred for 12 h at 25 °C. [b] $^1$H NMR yield (internal standard was 1,1,2,2-tetrachloroethane). [c] Diastereomeric ratio determined by $^1$H NMR. [d] When a stoichiometric amount of DBU was used, no 3-CR or 4-CR adduct was observed. [e] TBTA = tris(benzyl-triazolylmethyl)amine. [f] $Et_3N$ (1.5 mmol) was also added.

**Table 3.** Various α-Aryl Imidates by Cu-Catalyzed 4-CR[a]



| entry | alkyne (1) | product (4) | | yield (%)[b,c] |
|---|---|---|---|---|
| 1 | Ph—≡ |  | X = H | 80 (51:49) |
| 2 |  | | F | 82 (50:50) |
| 3 |  | | OMe | 64 (52:48) |
| 4 |  | | Br | 75 (52:48) |
| 5 |  | | *t*-Bu | 81 (58:42) |
| 6 |  | | C(O)H | 72 (68:32) |
| 7 |  |  | | 75 (52:48) |
| 8 |  |  | | 84 (50:50) |
| 9 |  |  | | 91[d] |

[a] A solution of **1** (1.2 equiv), **2a** (1.2 equiv), **3a** (0.5 mmol), methanol (5.0 equiv), $Et_3N$ (3.0 equiv), and CuI (10 mol %) in THF (1.0 mL) was stirred at 25 °C for 24 h. [b] Isolated yield. [c] Diastereomeric ratio determined by $^1$H NMR. [d] Corresponding 4-CR product was detected in less than 5% yield.

The optimized reaction conditions were subsequently applied to a range of alkyne substrates (Table 3). In general, the reaction with aryl acetylenes proceeded smoothly to afford the desired 4-CR products in moderate to high yields. Efficiency of this procedure was not much influenced by the electronic variation of substituents. The reaction conditions were completely tolerated to various functional groups examined. The products were obtained with almost the same ratio of two diastereomers in most cases. However, a moderate ratio of diastereoselectivity was observed with a substrate of 4-ethynylbenzaldehyde (entry 6). Whereas heteroaromatic acetylenes readily participated in the 4-CR (entry 8), aliphatic alkynes were less efficient, giving only poor yields of 4-CR products along with a major 3-CR product, imidate (entry 9).

The scope of other counterparts of sulfonyl azides and alcohols was then investigated (Table 4). All types of sulfonyl azides examined worked with high efficiency, affording the desired 4-CR products in satisfactory yields. Indeed, electronic or steric variation on the azide component exhibited small effects on the reaction efficiency, and the corresponding α-aryl *β*-hydroxy imidates were obtained in good yields. In addition, the new 4-CR reaction was highly facile with a wide range of primary alcohols to provide the corresponding products in good yields. However, when secondary alcohols were used, the reaction became sluggish, affording 4-CR products in only poor yields (entry 11).

The Cu-catalyzed 4-CR reaction could also be successfully expanded to include electrophiles other than ethyl glyoxylate. For example, under the identical reaction conditions, phenyl glyoxal (**5**) readily participated in the coupling reaction with phenylacetylene (**1a**), *p*-toluenesulfonyl azide (**2a**), and

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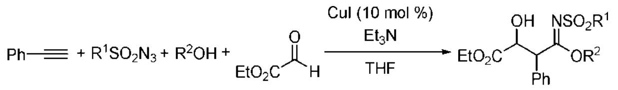
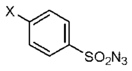
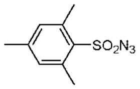
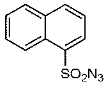
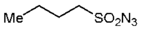
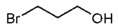
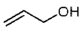
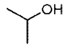
(10) See Supporting Informationfor details.

**Table 4.** Substrate Scope of Sulfonyl Azides and Alcohols[a]

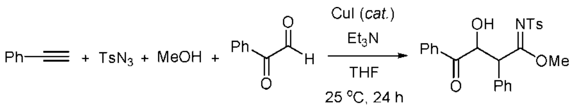


**1a** **2** **3a** **4**

| entry | $R^1SO_2N_3$ | | $R^2OH$ | yield (%)[b,c] |
|---|---|---|---|---|
| 1 |  | X = H | MeOH | 74 (53:47) |
| 2 | | Cl | MeOH | 74 (52:48) |
| 3 | | OMe | MeOH | 78 (57:43) |
| 4 | | *t*-Bu | MeOH | 80 (55:45) |
| 5 |  | | MeOH | 72 (57:43) |
| 6 |  | | MeOH | 81 (50:50) |
| 7 |  | | MeOH | 54 (58:42) |
| 8 | $TsN_3$ (**2a**) | | BnOH | 78 (62:38) |
| 9 | **2a** | |  | 64 (60:40) |
| 10 | **2a** | |  | 65 (57:43) |
| 11 | **2a** | |  | 25 (55:45)[d] |

[a] A solution of **3a** (0.5 mmol), **1a** (1.2 equiv), **2** (1.2 equiv), indicated alcohol (5.0 equiv), $Et_3N$ (3.0 equiv), and CuI (10 mol %) was stirred in THF (1.0 mL) at 25 °C for 24 h. [b] Isolated yield. [c] Diastereomeric ratio determined by $^1H$ NMR. [d] $^1H$ NMR yield (internal standard was 1,1,2,2,-tetrachloroethane).

methanol to provide the corresponding α-aryl *β*-hydroxy imidate (**6**) in synthetically acceptable yield (eq 1).[11]

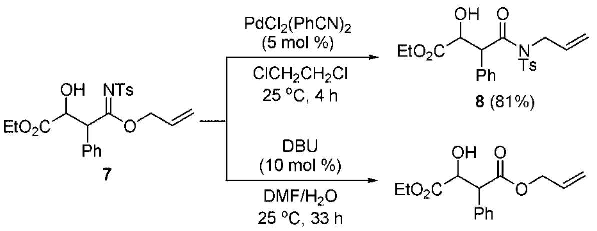


(1)

**1a** **2a** **5** **6**

55% (52:48)

**Scheme 2**



**7** **8** (81%) **9** (53%)

Synthetic applicability of the obtained α-aryl *β*-hydroxy imidates was next briefly invesigated (Scheme 2). In analogy with our earlier transformation protocol from simple allylimidates to amides,[4c] a Pd-catalyzed [3,3]-sigmatropic rearrangement of *β*-hydroxy allylimidate (**7**) was found highly efficient under mild conditions to give *N*-allyl *N*-sulfonamide in a good yield (**8**).[12] In addition, upon treatment of **7** with catalytic amounts of DBU under hydrolytic conditions, an aldol product of α-aryl *β*-hydroxy ester (**9**) was readily obtained, thus demonstrating that the present approach can be utilized as an aldol surrogate.[6]

In summary, we have developed a new Cu-catalyzed 4-CR of aryl acetylenes, sulfonyl azides, alcohols, and conjugated aldehydes leading to α-aryl *β*-hydroxy imidates in good yields.[13] The process appears to represent a high efficiency and selectivity, mild reaction conditions, and an excellent functional group tolerance. Since the developed procedure readily offers an α-aryl *β*-hydroxy imino moiety, which is a highly important synthetic building block ranging from simple and readily avaliable compounds, it might serve as a new preparative alternate to replace the conventional methods.

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**Supporting Information Available:** Experimental details and $^1H$ and $^{13}C$ NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Matsubara, R.; Doko, T.; Uetake, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3047–3050.

(12) (a) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901–2910. (b) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218–224.

(13) **Representative Experimental Procedure (Table 3).** To a stirred mixture of **3a** (0.5 mmol), **1a** (0.6 mmol), **2a** (0.6 mmol), methanol (2.5 mmol), and CuI (10 mol %) in THF (1 mL) was added $Et_3N$ (1.5 mmol) under $N_2$. After the mixture was stirred for 24 h at 25 °C, it was quenched by adding saturated $NH_4Cl$ solution and 1 N HCl. Then, the aqueous layer was extracted with $CH_2Cl_2$. The crude residue was purified by flash column chromatograph to give the desired product.