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A Green Synthetic Route to Imides from Terminal Alkynes and Amides by Simple Solid Catalysts

Xiongjie Jin, Kazuya Yamaguchi, and Noritaka Mizuno*
Department of Applied Chemistry, School of Engineering, The University of Tokyo,
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656

(Received April 23, 2012; CL-120352; E-mail: tmizuno@mail.ecc.u-tokyo.ac.jp)

An atom-efficient and green synthetic route to highly valuable imides (54–92% yields) from terminal alkynes and amides has been developed. This new route is composed of two consecutive reactions, that is, (i) the reported $Cu(OH)_2$-catalyzed cross-coupling of terminal alkynes and amides to ynamides and (ii) the Sn–W mixed oxide-catalyzed regioselective hydration of ynamides.

Imides are very important synthetic intermediates in a wide range of organic synthesis[1,2] and essentially useful as pharmacophores in many biologically active compounds such as immunosuppressants,[2a] antibiotics,[2b] antifeedants,[2c] and cytotoxic anticancer agents.[2d] To date, great progress has been made for the development of synthetic routes to imides;[1,2f] for example, (i) acylation of amides with carboxylic acid derivatives such as chlorides, anhydrides, and esters, (ii) aminocarbonylation of aryl bromides, (iii) the reaction of isonitriles and carboxylic acids, (iv) oxidative decarboxylation of amino acids, and (v) oxygenation of amides. However, at present, imides have still generally been prepared by the "nongreen" step-by-step procedure of deprotonation of amides with strong bases such as *n*-butyllithium followed by acylation with acyl halides (Figure 1). In this antiquated procedure, several side reactions[2f] such as elimination to nitriles, formation of triacylamides, and acyl group scrambling proceed in some cases, and generation of at least stoichiometric amounts of wastes such as butane and lithium halides are inevitable. Hence, from the environmental point of view, the development of atom-efficient and green routes to these important compounds is highly desirable.

Very recently, we have reported that simple $Cu(OH)_2$ can efficiently catalyze cross-coupling of terminal alkynes and amides to ynamides; for example, the cross-coupling of phenylacetylene (**1a**) and 1,3-oxazolidin-2-one (**2a**) gave 3-(phenylethynyl)oxazolidin-2-one (**3aa**) in 91% yield (Scheme 1).[3] The substrate scope for the cross-coupling is very broad with respect to both terminal alkynes and amides (Figures S1 and S2[7]). The reaction employs air as a terminal oxidant and produces only water as a sole by-product.

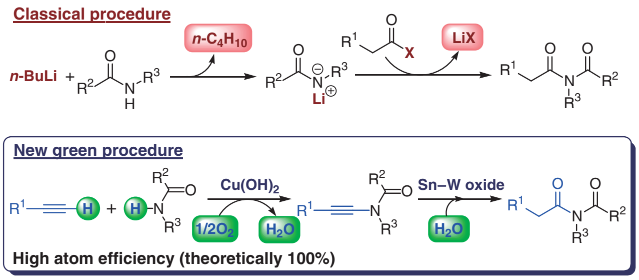
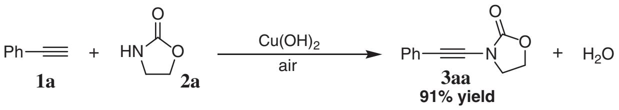


Figure 1. Synthetic procedure for imides.

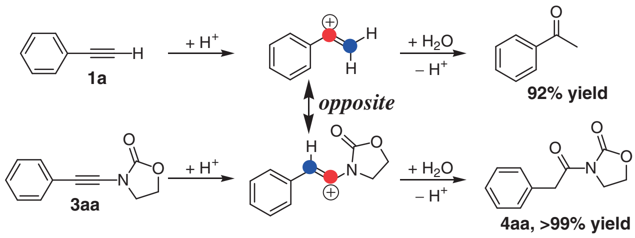
The cross-coupling products of ynamides are very attractive compounds. Thus, the substitution of amide functionalities to terminal alkynes to form ynamides can strongly polarize the triple bonds, and the carbon atom adjacent to the amide functionality becomes more susceptible to nucleophilic attack than another sp-hybridized carbon atom. By employing the reactivities, highly regio- and stereoselective transformations have been realized to date.[4]

From the above-mentioned unique reactivity of ynamides, we expected that hydration of ynamides possibly regioselectively proceeds to give the corresponding imides. Thus, the Brønsted acid-catalyzed hydration of an ynamide **3aa** was initially carried out. We used the Sn–W mixed oxide catalyst for the hydration, which is reported to be active for the Markovnikov hydration of various terminal alkynes.[5a] In this study, we found that the regioselectivity for **3aa** was completely opposite to that for a terminal alkyne **1a**, and that the hydration of **3aa** regioselectively proceeded to give the corresponding imide of 3-(2-phenylacetyl)oxazolidin-2-one (**4aa**) in >99% yield (Scheme 2).

From the result of the above regioselective hydration and our previous finding of the $Cu(OH)_2$-catalyzed cross-coupling,[3] we came up with an idea to construct a new green synthetic route to imides, that is, the combination of the reported $Cu(OH)_2$-catalyzed cross-coupling of terminal alkynes and amides and the newly found Sn–W mixed oxide-catalyzed regioselective hydration of ynamides (Figure 1).



Scheme 1. Oxidative cross-coupling of phenylacetylene and 2-oxazolidinone (Figure S2).[3,7]



Scheme 2. The Sn–W mixed oxide-catalyzed hydration of **1a** and **3aa**. Yields were determined by gas chromatography using biphenyl as an internal standard. Reaction conditions for **3aa**: **3aa** (0.1 mmol), Sn–W mixed oxide (50 mg), H_2O (0.3 mmol), mesitylene (1 mL), 100 °C, under air (1 atm), 1 h. Reaction conditions for **1a**: **1a** (0.5 mmol), Sn–W mixed oxide (50 mg), H_2O (1 mmol), cyclooctane (2 mL), 100 °C, under air (1 atm), 1 h.

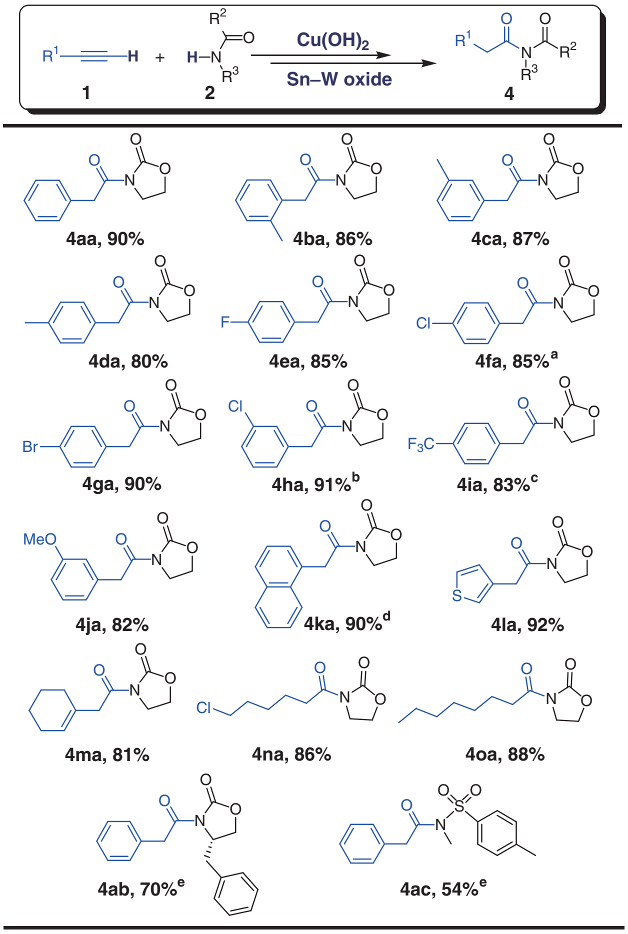


Figure 2. Sequential synthesis of imides. The isolated yields (based on **1**) are reported. See Figure S2 for the reaction conditions for cross-coupling steps. For the hydration steps, Sn–W mixed oxide (50 mg), H_2O (0.3 mmol), 100 °C, 1 h. Other reaction time: [a]3, [b]5, [c]24, and [d]2 h. [e]Yields were determined by GC using biphenyl as an internal standard.

This unprecedented route intrinsically produces no wastes, and the atom efficiency is theoretically 100%. The procedure is also very simple;[6] after completion of the cross-coupling (Figure S2[7]), $Cu(OH)_2$, a base, and the remaining amides are filtered off followed by addition of the filtrate to the reactor containing the Sn–W mixed catalyst and water. The regioselectivities for the hydration steps were higher than 99% in all cases. Through this novel synthetic route, various kinds of structurally diverse imides could successfully be synthesized in high to excellent yields (Figure 2). The isolated yields of the imide products are summarized in Figure 2 (unless otherwise noted). In the $Cu(OH)_2$-catalyzed cross-coupling of terminal alkynes and amides as well as the Sn–W mixed oxide-catalyzed regioselective hydration, no further conversion of substrate was observed upon separation of the catalysts by simple filtration during the reaction. Thus, this can rule out any contribution to the observed catalysis from metal species that leached into the reaction solution, and the observed catalysis is intrinsically heterogeneous.

Aromatic alkynes with electron-donating as well as electron-withdrawing substituents all smoothly reacted to give the corresponding *N*-acyloxazolidinones in high yields. In the case of halo-substituted aromatic alkynes, the desired imides were obtained in high yields without dehalogenation. Therefore, it would be possible to utilize these halo-functionalities for further modification of the imide molecules. A heteroatom-containing alkyne, 3-ethynylthiophene, was efficiently reacted with an amide to afford the corresponding imide in a high yield. In addition, not only aromatic alkynes but also aliphatic ones could act as good substrates. Oxazolidinone and sulfonamide derivatives could be utilized as nitrogen nucleophiles in the present catalyst system.

In summary, we have successfully developed an efficient synthetic route to imides by the $Cu(OH)_2$-catalyzed aerobic oxidative cross-coupling of terminal alkynes and amides followed by the Sn–W mixed oxide-catalyzed regioselective hydration. From this new procedure, various kinds of imides could be obtained in moderate to high yields (54–92% yields).

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5 Very recently, we have reported that the Sn–W mixed oxide can act as an efficient heterogeneous Brønsted acid catalyst for alkyne hydration,[5a] C–C bond-forming reactions,[5b] and conversion of saccharides to furan derivatives:[5c] a) X. Jin, T. Oishi, K. Yamaguchi, N. Mizuno, *Chem.—Eur. J.* **2011**, *17*, 1261. b) Y. Ogasawara, S. Uchida, K. Yamaguchi, N. Mizuno, *Chem.—Eur. J.* **2009**, *15*, 4343. c) K. Yamaguchi, T. Sakurada, Y. Ogasawara, N. Mizuno, *Chem. Lett.* **2011**, *40*, 542.
6 A typical procedure for synthesis of imides: Into a Pyrex-glass screw cap vial (volume: ca. 20 mL) were successively placed $Cu(OH)_2$ (5 mol % with respect to an alkyne), a base (5–20 mol %), an alkyne (0.1 mmol), an amide (2–3 equivalents with respect to an alkyne), and mesitylene (1 mL). A Teflon-coated magnetic stir bar was added, and the reaction mixture was vigorously stirred at 100–120 °C under 1 atm of air. After completion of the cross-coupling of a terminal alkyne and an amide, $Cu(OH)_2$, a base, and the remaining amide are filtered off. Then, the filtrate was added to a Pyrex-glass screw cap vial (volume: ca. 20 mL) containing the Sn–W oxide catalyst (50 mg), water (0.3 mmol), and a Teflon-coated magnetic stir bar, and the reaction mixture was vigorously stirred at 100 °C. After the reaction was completed, the crude reaction mixture was directly subjected to column chromatography on silica gel (*n*-hexane/ethyl acetate = 9/1–2/3 (v/v)), giving the analytically pure imide (see the Supporting Information in more detail[7]).
7 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.