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Gold-Catalyzed Three-Component Tandem Process: An Efficient and Facile Assembly of Complex Butenolides from Alkynes, Amines, and Glyoxylic Acid

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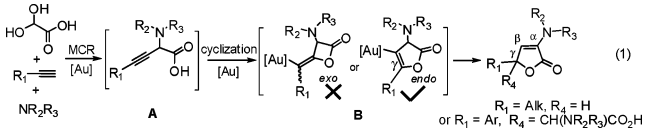
Butenolides are prevalent structural motifs in more than 13 000 natural products,[1] some acting as antibiotic, antifungal, antifouling, or anticancer agents[2] as well as pharmaceuticals such as Merck's Rofecoxib. General and convenient methods for construction of butenolide skeletons bearing multiple reactive sites for further functionalizations are of great interest.[3] Herein, we report an expeditious and practical gold-catalyzed multicomponent reaction (MCR) for the formation of polysubstituted butenolides in a tandem manner. This MCR consists of a novel *direct* alkyne−amine−glyoxylic acid coupling, intramolecular cyclization of α-N-substituted *β*-alkynoic acid **A**, and subsequent reaction (eq 1). Copper salts, which have been utilized extensively in aldehyde−amine−alkyne coupling,[4] cannot trigger the first step in our tandem course, indicating the exceptional catalytic ability of gold to generate **A** from alkyne, amine, and glyoxylic acid. The transformation of **A** to **B**, to the best of our knowledge, is the first example of gold-catalyzed cyclization of alkynoic acids in exclusive endo-dig fashion.[5] The unique reactivity of the cyclization intermediate is revealed by intermolecular electrophilic trapping, which introduces an α-amino acid moiety and thus builds a highly congested quaternary carbon center at the *γ* position in the butenolide architecture.

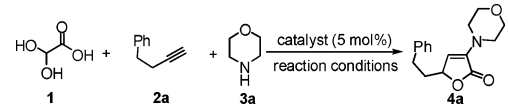


(1)

Demands for facile and efficient generation of complex and diverse druglike small molecules continue to stimulate the design and development of conceptually innovative strategies in the synthetic community. In this context, tandem processes enabling multiple bond-forming events to occur in a one-pot manner using gold catalysts have been elegantly demonstrated, affording structurally appealing carbo- or heterocyclic ring systems through the remarkably reactive versatility of gold with *π* bonds.[6] However, most gold catalysis, in either intramolecular or two-component style, requires preformed and relatively complex precursors. In this communication, we illustrate a new gold-initiated tandem pattern with prominent synthetic efficacy from molecular simplicity to complexity, including an MCR that combines simple and commercially available raw materials, a subsequent intramolecular functional-group-pairing reaction, and a secondary MCR. Furthermore, the ability to apply a single catalyst for the above processes could significantly enhance the operational convenience.

In the initial attempt, gold catalysts were attempted for reactions of glyoxylic acid (**1**), 4-phenyl-1-butyne (**2a**), and morpholine (**3a**). $AuBr_3$ and $AuCl_3$ were able to catalyze the formation of butenolide **4a** (Table 1, entries 1−7), while copper salts and Brønsted acids were found to be inactive (entries 8 and 9). Apparently, the yields were improved in methanol along with smooth heating (entry 5). Other solvents, such as CH_2Cl_2, CH_3CN, and H_2O (entries 2, 3, and 6) and use of ligands (entry 7) failed to increase the yields.

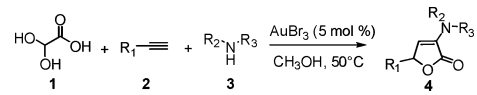
Table 1. Optimization Study:[a] Tandem Access to Butenolides

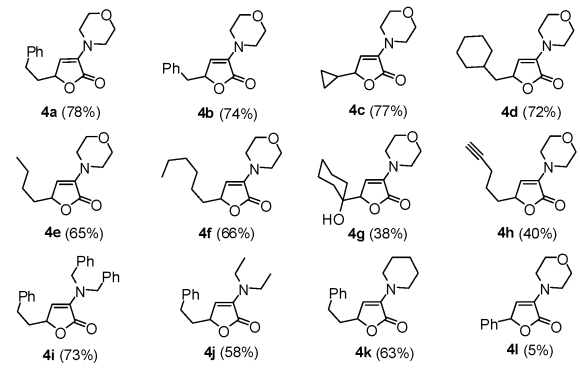


entry	catalyst	reaction conditions	yield (%)[b]
1	$AuCl_3$	CH_2Cl_2, r.t., 24 h	10
2	$AuBr_3$	CH_2Cl_2, r.t., 24 h	24
3	$AuBr_3$	CH_3CN, r.t., 24 h	39
4	$AuBr_3$	CH_3OH, r.t., 24 h	56
5	**$AuBr_3$**	**CH_3OH, 50 °C, 8 h**	**78**
6	$AuBr_3$	H_2O, 50 °C, 8 h	trace
7	$AuBr_3$/dppf[c] or PPh_3	CH_3OH, 50 °C, 8 h	<40
8	CuBr, $CuBr_2$, CuI	CH_2Cl_2, r.t., 24 h	0[d]
9	HBr, H_3PO_4, TfOH	CH_3OH, 50 °C, 72 h	0[d]

[a] Reaction conditions: **1** (1 mmol), **2a** (2 mmol), **3a** (1.2 mmol). [b] Isolated yields. [c] dppf =1,1′-bis(diphenylphosphino)ferrocene. [d] No **A**, **4a**, or other product was detected.

Table 2. Gold-Catalyzed Three-Component Formation of Butenolides **4**[a,b]





[a] Conditions: **1** (1 mmol), **2** (2.0 mmol), **3** (1.2 mmol). [b] Isolated yields.

With the optimal reaction conditions in hand, the scope and limitation of this reaction were tested with various combinations of alkynes and amines (Table 2). For example, the terminal alkynol was tolerated, providing a handle for subsequent orthogonal reactivity (**4g**). Similarly, the aliphatic chain bearing two terminal alkyne moieties also afforded the expected butenolides with one remaining alkyne for further manipulation (**4h**). However, the aromatic alkyne phenylacety-

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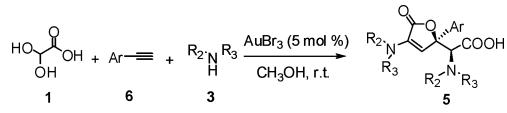
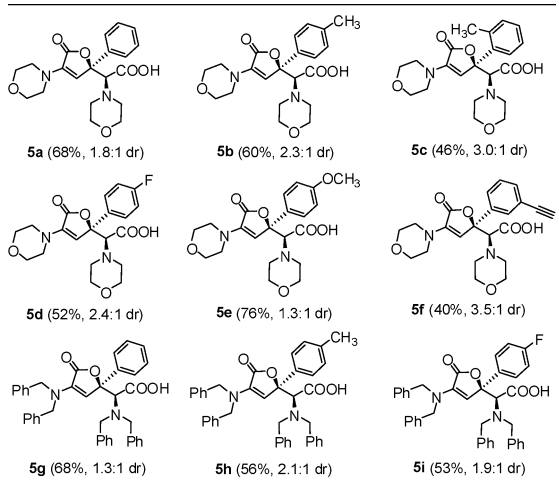
lene gave product **4l** in only 5% yield. The major isolated product was butenolide **5a** having a tethered an α-amino acid moiety at the γ position. It was envisaged that the γ-carbon was trapped by iminium ion to achieve a higher level of atom economy and molecular complexity. After optimization of the reaction, we found that butenolide **5a** could be produced with a yield of 68% in methanol under very mild condition (25 °C). Aliphatic alkynes failed to afford butenolides similar to **5a**.

To further investigate the unique reactivity of the in situ-generated cyclization intermediate, other aromatic alkynes and amines were used as substrates. As expected, phenylacetylene bearing representative substituents along with either a cyclic secondary amine (morpholine) or an acyclic amine (dibenzylamine) could deliver the desired butenolides (Table 3). It is noteworthy that these products represent a novel kind of unnatural α-amino acid that could serve as a versatile building block for polypeptide analogue research in drug discovery. The α-amino acid moieties could also work as efficient attachment handles on the butenolide skeleton, leading to greater diversity through further manipulation.

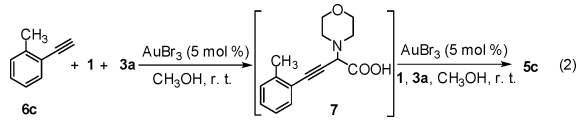
Table 3. Tandem Process Using Aromatic Alkynes[a,b]





[a] Conditions: **1** (2 mmol), **6** (1 mmol), **3** (2 mmol). The relative configuration of *anti*-**5g** was established by X-ray analysis and nuclear Overhauser effect spectroscopy together with conformational analysis.[7] The remaining products' relative configurations were assigned by analogy. Isolated yields are listed. [b] The diastereomeric ratios (syn:anti) were determined by ^{1}H NMR analysis (**5a**−**f**) or HPLC (**5g**−**i**).

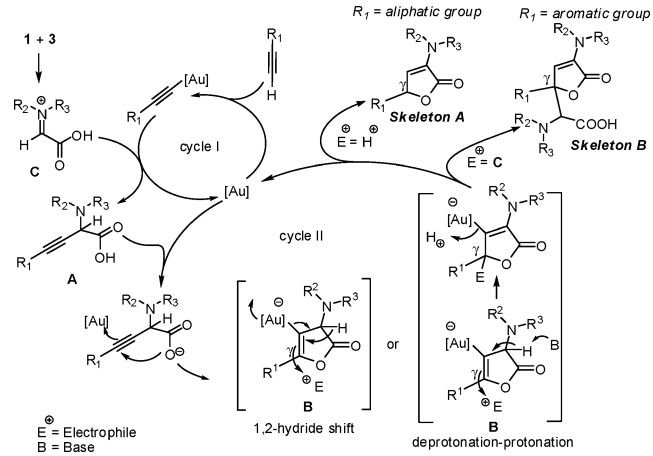
To shed light on the reaction mechanism, attempts to isolate the intermediate **A** were made. In almost all cases, the cyclization was too rapid, and **A** could not be detected directly. Fortunately, compound **7** could be isolated in low yield through a fast preparative TLC method in the initial catalytic stage, when **6c** was used as the starting material. Treatment of **7** with gold catalyst under the standard procedure allowed the cyclization of **7** and formation of **5c** (eq 2).



(2)

On the basis of the above results and previous studies,[5] we have proposed the following mechanism shown in Scheme 1. First, gold-catalyzed three-component coupling of alkyne, amine, and glyoxylic acid occurs, affording α-N-substituted β-alkynoic acid **A** through an addition reaction involving a gold acetylide intermediate as the nucleophile (cycle I). Next, gold-promoted endo-dig cyclization of **A** leads to the active intermediate **B**, which is finally transformed to butenolides via electrophilic trapping along with a deprotonation−protonation sequence or 1,2-hydride shift pathway.[8]

Scheme 1. Tentative Mechanism



In summary, we have developed a gold-catalyzed three-component tandem process for the synthesis of two new types of butenolides. This tandem reaction consists of two catalytic processes in which more than four chemical bonds are formed in the presence of a single gold catalyst. In addition, two sequential carbon−carbon bond-forming reactions are involved in the construction of butenolide skeleton **B**. The present tandem protocol, which utilizes three commercially available starting materials to assemble highly functionalized butenolides, provides a useful synthetic method and expands the area of gold catalysis. Studies of the detailed mechanism and its application are ongoing.

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Supporting Information Available: Experimental procedures, characterization data for new compounds, and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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