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Gold(III)-Catalyzed Three-Component Coupling Reaction (TCC) Selective toward Furans

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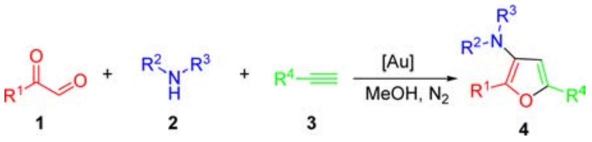
ABSTRACT



An efficient three-component coupling reaction toward a variety of furan derivatives has been developed. This cascade transformation proceeds via the gold-catalyzed coupling reaction of phenylglyoxal derivatives, secondary amines, and terminal alkynes, under the reaction conditions, that undergoes cyclization into the furan core.

The furan unit is one of the most important pharmacophores and is widely found in many biologically active compounds.[1] The synthesis of substituted furans has been the object of research for over a century, and a variety of well-established classical methods are now available.[2] The classical Paal–Knorr synthesis, discovered in 1884, remains one of the most powerful and versatile routes to the furan heterocycles. During the past 10 years, Lewis acid catalyzed synthesis of heterocycles especially furans[3] *via* intramolecular cycloisomerization reactions that involve an acetylenic functionality has attracted considerable attention due to its atom economy, although the substrates in this method require multistep synthesis. In particular, much attention has been focused toward the development of new and efficient methodologies for the synthesis of furans with the aid of gold, mainly as $AuCl_3$, as the most effective catalyst for cycloisomerizations leading to furans.[4] Selected successful examples are shown in Figure 1, including (a) alk-3-yn-1-ones; (b) alka-2,3-dien-1-ones; (c) alkynyloxiranes, and (d) (*Z*)-alk-2-en-4-yn-1-ols, which afford substituted furans in one step. Skrydstrup recently reported the addition of the ylides to the terminal alkynes to form 2,4-disubstituted furans with gold catalysis which undergo a carbene transfer/gold carbene formation process.[5]

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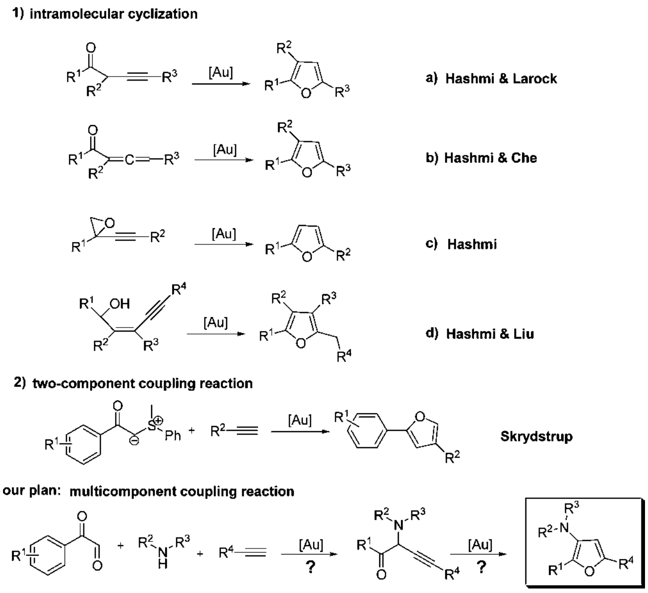
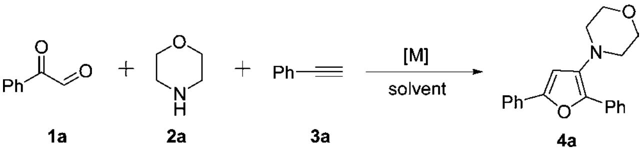


Figure 1. Au-catalyzed one-step formation of furans.

Table 1. Optimization of Reaction Conditions for the Preparation of **4a**[a]



entry	catalyst	*T* (°C)	solvent	yield (%)[b] **4a**
1	–	25	MeOH	–
2	CuI	25	MeOH	–
3	AuCl	25	MeOH	16
4	$AuCl_3$	25	MeOH	11
5	$AuBr_3$	25	MeOH	21
6	$NaAuCl_4\cdot 2H_2O$	25	MeOH	trace
7	$AuBr_3$	60	MeOH	75
8[c]	**$AuBr_3$**	**60**	**MeOH**	**91**
9[c]	$AuBr_3$	60	H_2O	14
10[c]	$AuBr_3$	60	DMF	15
11[c]	$AuBr_3$	60	toluene	54
12[c]	$AuBr_3$	110	toluene	23

[a] Standard reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), **3a** (2.0 mmol), catalyst (5 mol %), and solvent (2.0 mL) were heated in a tube for 12 h. [b] Isolated yield. [c] Proceed under a N_2 atmosphere.

One-pot multicomponent coupling reactions have emerged as an attractive and powerful strategy for the generation of C–C and C–heteratom in a step- and atom-economical fashion.[6] Among these, a number of novel heterocycle syntheses using aldehydes, alkynes, and amines as starting materials have been reported. In 2007, Liu and Yan developed a gold(III)-catalyzed multicomponent coupling/cycloisomerization reaction of heteroaryl aldehydes, amines, and alkynes to form aminoindolizines under solvent-free conditions or in water.[7] In 2009, a copper-catalyzed three-component coupling reaction of aldehydes, 2-aminopyridines, and terminal alkynes toward imidazoheterocycles has been explored in Gevorgyan's group.[8] Ji and co-workers demonstrated an approach to the complex butenolides from alkynes, amines, and glyoxylic acid in the presence of a gold catalyst.[9] However, an efficient synthesis with high chemo- and regioselectivity, which would enable access to multisubstituted furans, still remains a challenge.

With this background in mind, we were interested in realizing the formation of polysubstituted furans during a one-pot multicomponent coupling reaction. Then phenylglyoxals,[10] secondary amines, and terminal alkynes were chosen as substrates. We hypothesized that these three compounds would be coupled together under gold catalysis to represent the required propargylamine intermediate,[11] which, upon activation of the triple bond with gold, would undergo an intramolecular cyclization[4a−c] into target furans. We envisaged the process of this gold-catalyzed coupling reaction/cyclization would occur in one pot. This strategy possess more potential in the synthesis of complex furans, as the substrates are simple and available.

We commenced this project by investigating the reaction of phenylglyoxal monohydrate (**1a**), morpholine (**2a**), and phenylacetylene (**3a**) in the absence of catalyst in methanol at room temperature, but no desired compound was detected (Table 1, entry 1). The reaction also did not proceed when CuI was employed (Table 1, entry 2). Interestingly, the reaction produced the furan product **4a** in 16% yield in the presence of AuCl as the catalyst (Table 1, entry 3). A screening of gold sources indicated that $AuBr_3$ was the most effective catalyst for this transformation, affording the product in 21% yield (Table 1, entries 3−6). To our delight, the reaction could proceed smoothly at 60 °C with 5 mol % of $AuBr_3$, resulting in a

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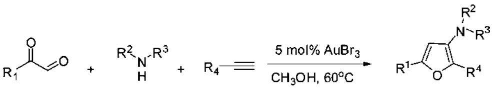
Table 2. $AuBr_3$-Catalyzed Three-Component Formation of Furans[a]



1 2 3 4

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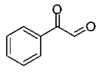
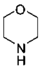
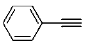
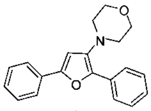
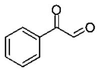
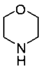
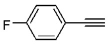
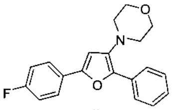
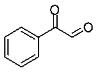
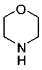
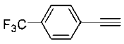
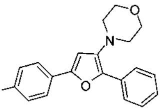
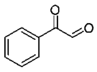
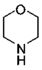
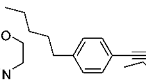
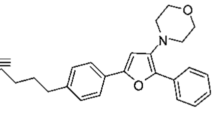
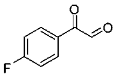
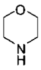
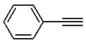
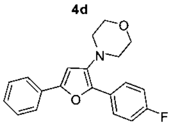
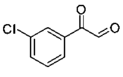
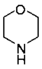
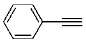
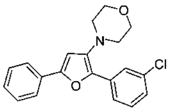
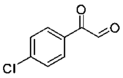
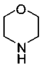
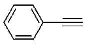
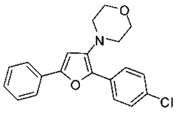
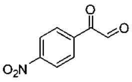
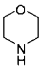
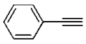
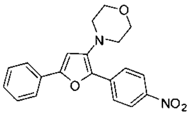
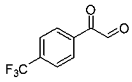
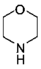
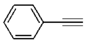
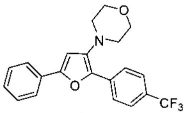
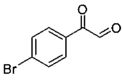
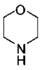
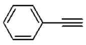
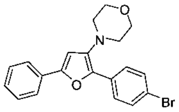
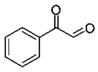
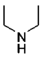
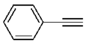
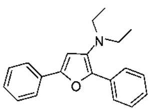
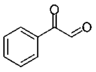
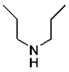
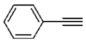
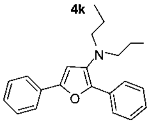
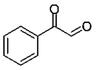
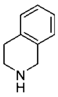
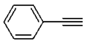
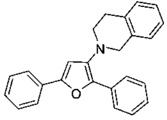
1	 1a	 2a	 3a	 4a	91
2	 1a	 2a	 3b	 4b	93
3	 1a	 2a	 3c	 4c	65
4	 1a	 2a	 3d	 4d	71
5	 1b	 2a	 3a	 4e	77
6	 1c	 2a	 3a	 4f	78
7	 1d	 2a	 3a	 4g	83
8	 1e	 2a	 3a	 4h	85
9	 1f	 2a	 3a	 4i	68
10	 1g	 2a	 3a	 4j	73
11	 1a	 2b	 3a	 4k	90
12	 1a	 2c	 3a	 4l	93
13	 1a	 2d	 3a	 4m	51

[a] Standard reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), **3a** (2.0 mmol), catalyst (5 mol %), and solvent (2.0 mL) were heated in a tube under a N_2 atmosphere for 12 h. [b] Isolated yield.

91% yield under a N_2 atmosphere (Table 1, entry 8). To further improve the efficiency of the reaction, several frequently used solvents were also examined. However, none of them could produce a higher yield, even at higher temperature (Table 1, entries 9−12).

With the optimized reaction conditions in hand, we probed the scope of different alkynes, phenylglyoxal derivatives, and secondary amines (Table 2). A variety of different groups at the aromatic moiety of alkynes, such as halogen, methyl, and pentyl, were well tolerated in these mild transformations. The alkyne substrates bearing an electron-withdrawing group compared to an electron-donating group were found to be more suitable to afford furan products (**4b**, **4c**, and **4d**, Table 2). Further exploration of the substrate scope involved various phenylglyoxal derivatives. Phenylglyoxal derivatives having a substituent at either the meta- (**1c**) or para-position (**1b**, **1d**, **1e**, **1f**, **1g**) could be employed; their corresponding products were obtained in moderate to good yields. However, **4i** (4-CF_3) was obtained in only 68% yield, due to its strong electron-withdrawing effect. Finally, to broaden the substrate scope, amines were also explored (**2b**, **2c**, and **2d**). It was found that the reaction successfully provided the trisubstituted furans in 51%−93% yields (**4k**, **4l**, **4m**, Table 2).

A plausible mechanism for the reaction of a phenylglyoxal monohydrate, secondary amine, and terminal alkyne is illustrated in Scheme 1, which is analogous to the Au-catalyzed cycloisomerization of complex butenolides from alkynes, amines, and glyoxylic acid.[12] First, a gold-catalyzed three-component coupling of a phenylglyoxal, an amine, and an alkyne occurred to afford NR^1R^2-substituted propargylic intermediate **5** *via* a Mannich−Grignard reaction.[13]

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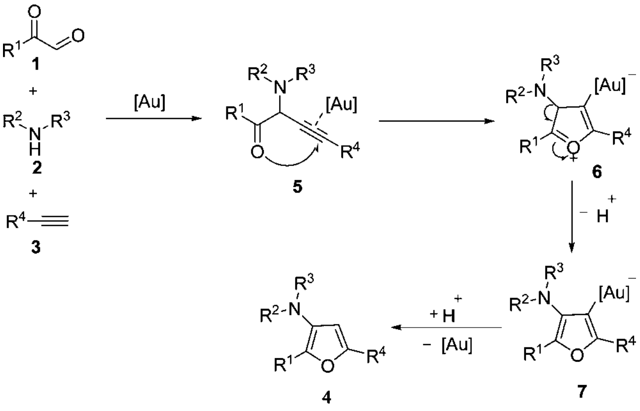
(12) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232.
(13) Wei, C. M.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584.

Scheme 1. Plausible Mechanism for the Reaction



Coordination of the triple bond in alkyne **5** to the gold catalyst enhances the electrophilicity of the alkyne, and the subsequent nucleophilic attack of the oxygen lone pair would produce the cation **6**, which undergoes deprotonation followed by demetalation to afford indolizines (Scheme 1).

In conclusion, we have demonstrated an efficient multicomponent coupling reaction of phenylglyoxal derivatives, secondary amines, and terminal alkynes. This cascade transformation of the coupling/cycloisomerization reaction proceeds using $AuBr_3$ as the catalyst under a N_2 atmosphere in methanol. The reaction outcomes provide a new strategy for the synthesis of three-substituted furans with high atom economy and high catalytic efficiency, which offers an efficient approach for the preparation of synthetic and medicinal furan derivatives. Further studies to extend the scope and synthetic utility of this Au-catalyzed cascade reaction are in progress in our laboratory.

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Supporting Information Available. Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.