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Iron-Catalyzed Domino Process for the Synthesis of α-Carbonyl Furan Derivatives via One-Pot Cyclization Reaction

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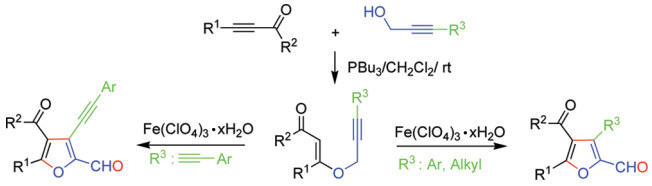

The $Fe(ClO_4)_3$-catalyzed intramolecular rearrangement/cyclization/oxidation reaction sequence for the synthesis of α-carbonyl furan derivatives from electron-deficient alkynes and 2-yn-1-ols is reported.

Transition-metal catalysis is a powerful tool that has been extensively investigated and well applied in modern organic synthesis.[1] Unfortunately, many of the highly efficient catalysts are derived from toxic heavy metals. Therefore, development of nontoxic transition-metal catalysts is a new trend in synthetic chemistry.

Compared with other transition metals, iron, one of the most abundant metals in the universe, is inexpensive, environmentally benign, readily available, and relatively nontoxic.[2,3] Since the pioneering research work of Tamura and Kochi,[4] iron catalysts have received much attention because of their effective properties. Over the past decades, iron catalysts have been extensively applied to various reactions, such as oxidation,[5] epoxidation,[6] addition,[7] cyclization,[8] etc. However, the iron-catalyzed C−C and C−O bond-forming reactions are underdeveloped and have become a long-term goal for synthetic chemists in modern organic synthesis.

Herein, we report a $Fe(ClO_4)_3$-catalyzed domino reaction for the synthesis of α-carbonyl furan derivatives from electron-deficient alkynes and 2-yn-1-ols. Furans exhibit particularly valuable and rich chemistry and extensive biological activity,[9] are useful as synthetic building blocks,[10] and are contained in many natural products.[11] Over the past decades, several methodologies for the construction of furan skeletons have been developed with Cu, Pd, Rh, Au, and Ag catalytic systems.[12,13] Those methodologies are convenient

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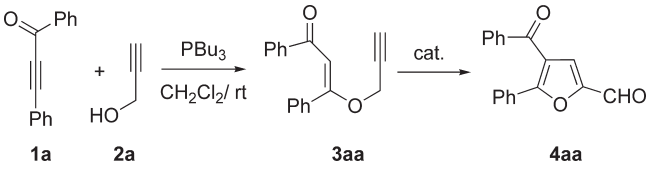
TABLE 1. Optimization of Reaction Conditions



entry	catalyst	solvent	T (°C)	yield (%)[a]
1	$Fe(acac)_3$ (>98%)	DMF	80	23
2	$FeCl_3$ (>98%)	DMF	80	35
3	$Fe(ClO_4)_3 \cdot xH_2O$[b] (>98%)	DMF	80	72
4	$Fe(NO_3)_3 \cdot 9H_2O$ (>99%)	DMF	80	18
5	$Fe_2(SO_4)_3 \cdot xH_2O$ (>97%)	DMF	80	20
6	$FeCl_2$ (>99%)	DMF	80	
7	$Fe(C_5H_5)_2$ (>99%)	DMF	80	
8	Fe powder (>99%)	DMF	80	
9		DMF	80	
10	$Fe(ClO_4)_3 \cdot xH_2O$	toluene	80	<5
11	$Fe(ClO_4)_3 \cdot xH_2O$	benzene	80	<5
12	$Fe(ClO_4)_3 \cdot xH_2O$	1,2-dichloroethane	80	47
13	$Fe(ClO_4)_3 \cdot xH_2O$	1,4-dioxane	80	54
14	$Fe(ClO_4)_3 \cdot xH_2O$	CH_3CN	80	58
15	$Fe(ClO_4)_3 \cdot xH_2O$	DMSO	80	80
16	$Fe(ClO_4)_3 \cdot xH_2O$	DMSO	100	76
17	$Fe(ClO_4)_3 \cdot xH_2O$	DMSO	50	71
18	$Fe(ClO_4)_3 \cdot xH_2O$	DMSO	rt	
19[c]	$Fe(ClO_4)_3 \cdot xH_2O$/CuI	DMSO	80	27
20[d]	$Fe(ClO_4)_3 \cdot xH_2O/CuBr_2$	DMSO	80	38

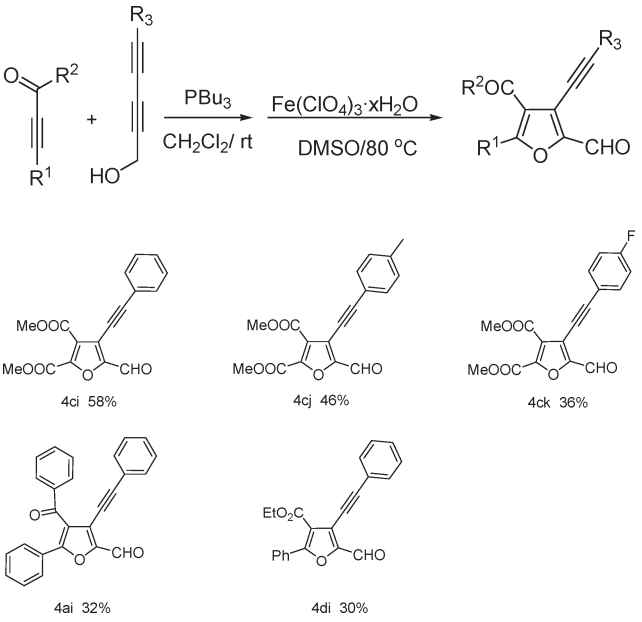
[a]Yield determined by GC. [b]*Caution!* Metal perchlorate salts can be explosive. [c]20 mol % $Fe(ClO_4)_3 \cdot xH_2O$, 100 ppm CuI. [d]20 mol % $Fe(ClO_4)_3 \cdot xH_2O$, 100 ppm $CuBr_2$.

with good yields. However, reports on the synthesis of α-carbonyl furans are relatively rare.[14] During our ongoing research to explore expedient routes to these types of compounds, we were delighted to find that iron could be a good catalyst for the construction of furans.

We recently developed a one-pot CuI-catalyzed domino process to synthesize functionalized furans.[15] Unfortunately, this domino reaction did not take place when 1,3-diphenylprop-2-yn-1-one was employed as the substrate instead of diethyl but-2-ynedioate. Inspired by our recent advances on oxygen-mediated transformations,[16] we developed a method for furan formation with iron salts as catalysts. The method is a facile alternative to the synthesis of highly functionalized α-carbonyl furans from electron-deficient alkynes and 2-yn-1-ol in a one-pot manner.

On the basis of our previous work and assumption,[15,17] we tried to find the best iron catalysts and optimize our reaction conditions by using **1a** and **2a** as the starting materials. In a typical procedure, a solution of **1a** (0.5 mmol), **2a** (0.5 mmol), and PBu_3 in CH_2Cl_2 was stirred at room temperature.[18] The solvent was evaporated under reduced pressure. Then a

SCHEME 1. Iron-Catalyzed Synthesis of α-Carbonyl-β-yne Furans



variety of iron catalysts (20 mol %) in DMF were added to the residue at 80 °C. The mixture was stirred until completion of the reaction (monitored by TLC). As shown in Table 1, the reaction could be catalyzed by Fe^{III} salts, such as $Fe(acac)_3$, $FeCl_3$, $Fe(ClO_4)_3 \cdot xH_2O$, $Fe(NO_3)_3 \cdot 9H_2O$, and $Fe_2(SO_4)_3 \cdot xH_2O$ (Table 1, entries 1−5). $Fe(ClO_4)_3 \cdot xH_2O$ was the most effective catalyst (Table 1, entry 3). The product **4aa** was not detected in the presence of Fe^{II} salts, Fe^0, or catalyst-free conditions (Table 1, entries 6−9), and **3aa** was obtained as the sole product. In addition, we tried to improve the yields by using various solvents. Among the solvents surveyed, low yields (<5%) of product **4aa** were found in toluene and benzene (Table 1, entries 10 and 11). However, higher yields of **3aa** were obtained in 1,2-dichloroethane, 1,4-dioxane, CH_3CN, and DMSO (Table 1, entries 12−15). DMSO was the most effective media for this domino reaction. The optimization of reaction temperature showed that 80 °C was optimal (Table 1, entries 16−18).

In order to exclude the possibility that trace copper in iron salts might affect the reaction,[19] $Fe(ClO_4)_3 \cdot xH_2O$ was analyzed by ICP. The analysis showed that the amount of Cu was below 5 ppm in the sample. Further experiments indicated the detrimental influence of copper salts. When a mixture of $Fe(ClO_4)_3 \cdot xH_2O$ with CuI or $CuBr_2$ was used as catalysts, the yields of **4aa** were only 27% and 38%, respectively (Table 1, entries 19 and 20). The results conformed that Fe played a crucial role in this intramolecular rearrangement/cyclization/oxidation reaction.

In order to explore the scope of this reaction, various electron-deficient alkynes and 2-yn-1-ols were evaluated at 80 °C with 20 mol % of $Fe(ClO_4)_3 \cdot xH_2O$ as the catalyst, and DMSO as solvent. The results are summarized in Table 2. The electron-deficient alkynes such as **1a**−**d** reacted well with alkynyl alcohols **2a**−**c** (Table 2, entries 1−9, 13−15). Different substituted 2-yn-1-ols, such as 2-thienyl, 3-nitrophenyl,

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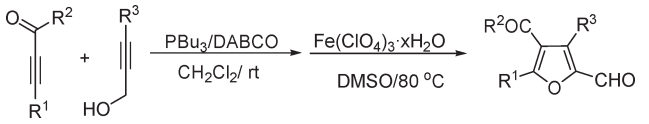
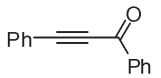
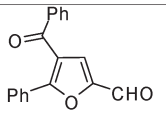
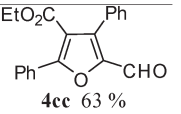
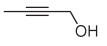
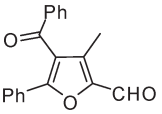
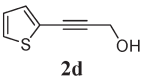
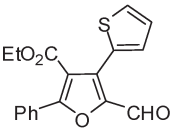
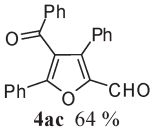
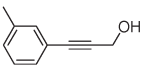
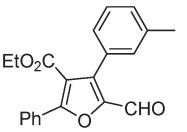
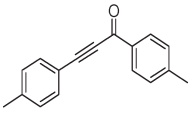
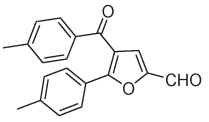
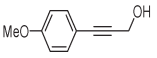
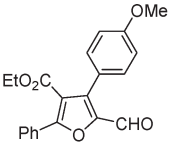
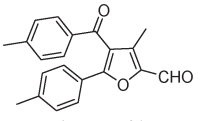
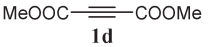
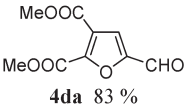
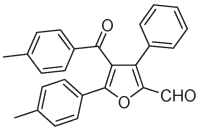
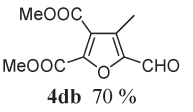
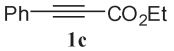
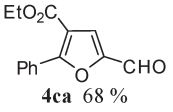
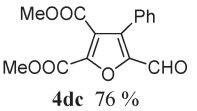
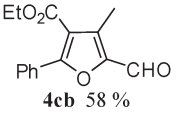
TABLE 2. Iron-Catalyzed Synthesis of α-Carbonyl Furans



entry	electronic-deficient alkynes	2-Yn-1-ol	product (yield %)	entry	electronic-deficient alkynes	2-Yn-1-ol	product (yield %)
1	 **1a**	 **2a**	 **4aa** 73 %	9	**1c**	**2c**	 **4cc** 63 %
2	**1a**	 **2b**	 **4ab** 62 %	10	**1c**	 **2d**	 **4cd** 58 %
3	**1a**	 **2c**	 **4ac** 64 %	11	**1c**	 **2e**	 **4ce** 57 %
4	 **1b**	**2a**	 **4ba** 63 %	12	**1c**	 **2f**	 **4cf** 53 %
5	**1b**	**2b**	 **4bb** 57 %	13[a]	 **1d**	**2a**	 **4da** 83 %
6	**1b**	**2c**	 **4bc** 59 %	14[a]	**1d**	**2b**	 **4db** 70 %
7	 **1c**	**2a**	 **4ca** 68 %	15[a]	**1d**	**2c**	 **4dc** 76 %
8	**1c**	**2b**	 **4cb** 58 %				

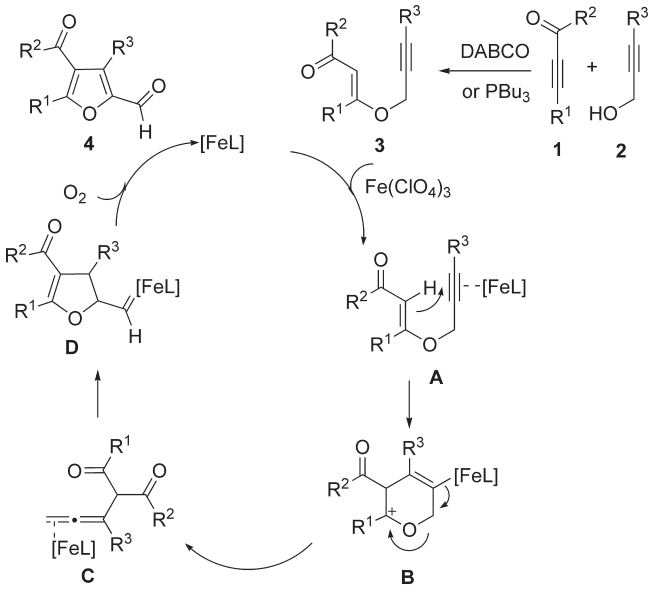
[a] **1d** (0.5 mmol), **2** (0.5 mmol) and DABCO in CH_2Cl_2 were stirred at room temperature to afford the product propargyl vinyl ether.

m-tolyl, 3-methoxyphenyl, and 2-pyridyl led to a beneficial effect on the reaction outcome, and in most cases the corresponding products (**4ca**−**cf**) were obtained in good yields (49−83%) (Table 2, entries 7−13). These results demonstrate that the domino process could occur with functional groups at different positions of the aromatic ring. It is worthy to note that the corresponding furans and all of the desired products were formed with high regioselectivity. In addition, α-carbonyl-*β*-yne furans were isolated in moderate yields when 2,4-diyn-1-ols were used (Scheme 1).

A plausible reaction mechanism for iron-catalyzed synthesis of furans is described in Scheme 2. First, DABCO- or PBu_3-promoted nucleophilic addition of propargyl alcohol (**2**) to electron-deficient alkyne (**1**) afforded enyne adduct **3**. Subsequenly, a 6-*endo-dig* addition of the enol ether onto the iron(III)−alkyne complex resulted in the formation of six-membered intermediate **B**, which collapsed into the *β*-allenic ketone **C**.[13h,15] Finally, *β*-allenic ketone underwent sequential cyclization, carbene-oxidation, and dehydration-oxidation to form furan **4**.

In summary, we have described an iron-catalyzed domino reaction for the synthesis of α-carbonyl furans from easily available starting materials in DMSO at 80 °C under atmospheric pressure. It could be expected that this new synthetic method will be applied widely in organic synthesis because α-carbonyl furans are extremely useful organic molecules as synthetic building blocks for the synthesis of elaborate heterocyclic compounds.

SCHEME 2. Plausible Mechanism



Experimental Section

General Procedure for the Synthesis of 4-Benzoyl-5-phenylfuran-2-carbaldehyde (4aa). A solution of 1,3-diphenylprop-2-yn-1-one **1a** (103 mg, 0.5 mmol), prop-2-yn-1-ol **2a** (28 mg, 0.5 mmol), and PBu_3 (0.1 mmol) in CH_2Cl_2 was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure. $Fe(ClO_4)_3$ and DMSO were added at 80 °C under atmospheric pressure. After completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure. Water (8 mL) was added, and the aqueous solution was extracted with diethyl ether (3 × 8 mL). The combined extracts were dried with anhydrous $MgSO_4$. The solvent was removed, and the crude product was separated by column chromatography to give pure **4aa** (101 mg, 73%). IR (KBr): 3028, 2834, 1650, 1602, 763. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.70 (s, 1H), 7.78−7.83 (m, 4H), 7.53−7.57 (m, 1H), 7.32−7.44 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.4, 177.5, 159.8, 150.3, 137.0, 133.6, 130.7, 129.7, 128.7,128.6, 128.2, 128.1, 123.7, 122.7. HRMS (EI): calcd for $C_{18}H_{12}O_3$ 276.0786, found 276.0780.

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Supporting Information Available: Compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.