EurJOC
European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201200163

An Efficient and General Iron-Catalyzed One-Pot Synthesis of Furans via α-Hydroxy Ketones and Activated Alkynes

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Keywords: Alkynes / Furans / α-Hydroxy ketones / Iron / Oxygen heterocycles

A new practical and economical process for the synthesis of substituted furan derivatives has been developed by an $FeCl_3$-catalyzed reaction of α-hydroxy ketones with activated alkynes. This methodology represents a highly efficient synthetic route to electron-deficient furans for which catalytic approaches are scarce. Furthermore, this transformation is associated with readily available substrates, good yields, and mild conditions.

Introduction

Furans are a fundamental class of five-membered heterocycles, which have been found as key structural units in many natural products.[1]They are not only prevalent in an extensive variety of biologically and medicinally important molecules,[2] but also used as a building blocks in organic synthesis.[3] These advantages have prompted a search for better methods to synthesize furans. Generally, there are mainly two routes to construct furan derivatives:[4] (i) cyclization of allenyl ketones,[5] alkynyl ketones,[5d,6] enynols,[5d,7] alkynyl epoxides[8] or propargyl ethers;[9] (ii) cyclization of 1,4-dicarbonyl compounds (Paal–Knorr synthesis). Although a number of synthetic methods for the preparation of substituted furans have been reported, it is essential to develop new strategies for the synthesis of furans under much milder conditions and the use of simpler catalytic systems.

Iron is one of the cheapest and most abundant metals on earth.[10] Despite its advantages, it is surprising that iron plays a diminutive role in the field of catalysis[11] compared to other transition metals such as palladium and rhodium. Therefore, the development of a more practical Fe-catalyzed system that can be used to prepare complex and diverse heterocyclic compounds under mild conditions is desired.

Very recently, our group reported convenient one-pot domino processes for the synthesis of highly functionalized polysubstituted furan derivatives through different transition-metal-catalyzed cyclizations.[12] To extend the scope of furan derivatives, we have designed and developed a new efficient one-pot protocol for the construction of furans. In this paper, we described a facile iron-catalyzed strategy to prepare the furan derivatives from electron-deficient alkynes and α-hydroxy ketones.

Results and Discussion

The intermediate product of dimethyl 2-(1-methyl-2-oxopropoxy)maleate (**3**) was easily prepared through nucleophilic addition of dimethyl but-2-ynedioate (**1a**) with 3-hydroxybutan-2-one (**2a**) in the presence of DABCO. A typical procedure is: **1a** (0.5 mmol), **2a** (0.5 mmol) and DABCO in CH_2Cl_2 were stirred at room temperature. Then the solution was concentrated to dryness under reduced pressure. Subsequently, a variety of iron catalysts were examined at 90 °C, and the results are summarized in Table 1. Initially, we examined the reaction in the presence of 10 mol-% $FeCl_3{\cdot}6H_2O$ (entry 1). We were pleased to observe that the reaction proceeded smoothly in 8 h to afford exclusively **3aa** in 34% yield (Table 1, Entry 1). Other iron catalysts, such as $Fe(ClO_4)_3{\cdot}xH_2O$, $Fe(acac)_3$, $Fe(NO_3)_3{\cdot}9H_2O$, $Fe_2(SO_4)_3{\cdot}xH_2O$, $Fe(DBM)_3$, Fe_2O_3, $FeCl_2$ (Entries 2–8), were also examined in this reaction, but the yields of product **3aa** dropped sharply. Interestingly, it was found that the desired product **3aa** was obtained in 66% yield, when CH_3CO_2H was added to the reaction mixture. The results encouraged us to check other additives, such as $PhCO_2H$, F_3CO_2H, HCl, TsOH, L-proline (Entries 10–14), but they led to lower yields of product **3aa**. In most of these cases, only traces of the product were found by TLC, and most of the intermediate **3** had disappeared (Table 1, Entries 11–13). To our delight, there was a significant difference with the addition of $FeCl_3$, because the corresponding product **3aa** was not detected without the presence of $FeCl_3$ during the reaction

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200163.

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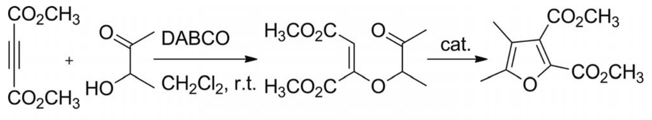
Table 1. Optimization of reaction conditions.[a]



1a **2a** **3** **3aa**

Entry	Catalyst	Additive	Solvent	T [°C]	t [h]	Yield [%][b]
1[c]	$FeCl_3{\cdot}6H_2O$ (>98%)	–	DMSO	90	8	34
2	$FeClO_4{\cdot}xH_2O$ (>98%)	–	DMSO	90	8	26
3[d]	$Fe(acac)_3$ (>98%)	–	DMSO	90	8	11
4	$Fe(NO_3)_3{\cdot}9H_2O$ (>99%)	–	DMSO	90	8	16
5	$Fe_2(SO_4)_3{\cdot}xH_2O$ (>97%)	–	DMSO	90	8	25
6[e]	$Fe(DBM)_3$ (>98%)	–	DMSO	90	8	10
7	Fe_2O_3 (>98%)	–	DMSO	90	8	22
8	$FeCl_2$ (>99%)	–	DMSO	90	8	–
9	$FeCl_3{\cdot}6H_2O$	CH_3CO_2H	DMSO	90	8	66
10	$FeCl_3{\cdot}6H_2O$	$PhCO_2H$	DMSO	90	8	46
11	$FeCl_3{\cdot}6H_2O$	F_3CO_2H	DMSO	90	8	trace
12	$FeCl_3{\cdot}6H_2O$	HCl	DMSO	90	8	–
13	$FeCl_3{\cdot}6H_2O$	TsOH	DMSO	90	8	–
14	$FeCl_3{\cdot}6H_2O$	L-proline	DMSO	90	8	40
15	–	CH_3CO_2H	DMSO	90	8	–
16	$AlCl_3$	CH_3CO_2H	DMSO	90	8	55
17	$ZnCl_2$	CH_3CO_2H	DMSO	90	8	63
18	$Yb(OTf)_3$	CH_3CO_2H	DMSO	90	8	50
19	$Sc(OTf)_3$	CH_3CO_2H	DMSO	90	8	11
20	$FeCl_3{\cdot}6H_2O$	CH_3CO_2H	CH_3CN	90	8	73
21	$FeCl_3{\cdot}6H_2O$	CH_3CO_2H	DCE	90	8	49
22	$FeCl_3{\cdot}6H_2O$	CH_3CO_2H	1,4-dioxane	90	8	38
23	$FeCl_3{\cdot}6H_2O$	CH_3CO_2H	toluene	90	8	53
24	$FeCl_3{\cdot}6H_2O$	CH_3CO_2H	DMF	90	8	65
25	$FeCl_3{\cdot}6H_2O$	CH_3CO_2H	CH_3CN	60	8	85
26	$FeCl_3{\cdot}6H_2O$	CH_3CO_2H	CH_3CN	40	8	77
27	$FeCl_3{\cdot}6H_2O$	CH_3CO_2H	CH_3CN	120	8	61
28	$FeCl_3{\cdot}6H_2O$	CH_3CO_2H	CH_3CN	r.t.	8	–
29[f]	$FeCl_3{\cdot}6H_2O/CuCl_2$	CH_3CO_2H	CH_3CN	60	8	82
30[g]	$FeCl_3{\cdot}6H_2O/CuCl$	CH_3CO_2H	CH_3CN	60	8	36

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), 10 mol-% of catalysts and 5 mol-% of DABCO, 10 mol-% of additives in 2 mL of solvent at room temp. to 120 °C for 8 h. [b] Yield determined by GC. [c] < 5 ppm Cu (Aldrich). [d] acac = pentane-2,4-dione. [e] DBM = dibenzoyl methane. [f] 100 ppm $CuCl_2$. [g] 100 ppm CuCl.

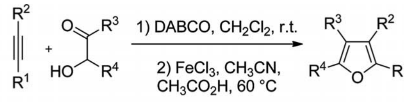
(Table 1, Entry 15). Other catalyst, such as $AlCl_3$, $ZnCl_2$ $Yb(OTf)_3$ and $Sc(OTf)_3$, were also tested, and it was found that $FeCl_3$ was the best one (Table 1, Entries 16–19). Solvent effects were also investigated. It was found that compound **3aa** could be obtained in 73% yield in CH_3CN (Table 1, Entry 20), but when 1,2-dichloroethane (DCE), 1,4-dioxane, toluene or DMF were employed, the reaction was severely retarded (Table 1, Entries 11–24). Finally, we examined the effect of temperature (Entries 25–28), and the results show that the optimal temperature is 60 °C.

To eliminate the influence of active copper traces from iron salts in this transformation, $FeCl_3$ was analyzed by ICP, yielding a content of only < 5 ppm Cu. Further investigations of the influences of copper salts on the reaction had been carried out. $FeCl_3$ with $CuCl_2$ or CuCl (100 ppm) were employed as cocatalysts, and the product was obtained in 82% and 36% yield, respectively (Table 1, Entries 29, 30). These results clearly indicate that the Fe catalyst plays a crucial role in this transformation.

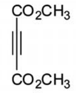
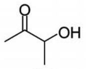
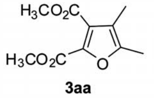
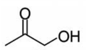
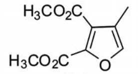
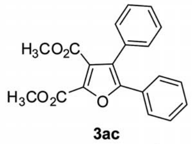
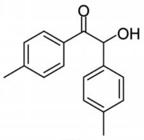
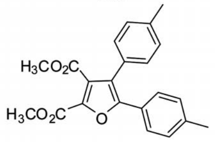
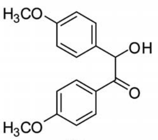
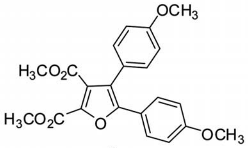
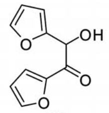
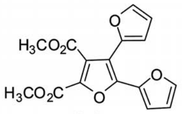
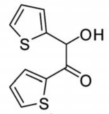
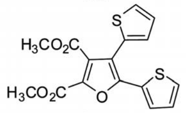
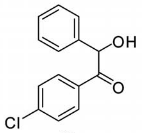
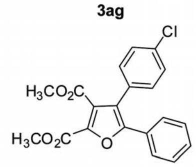
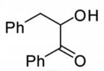
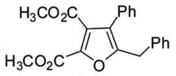
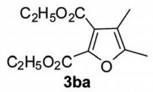
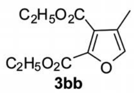
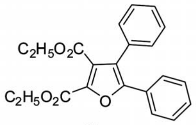
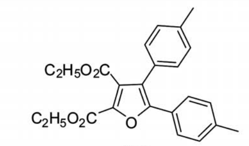
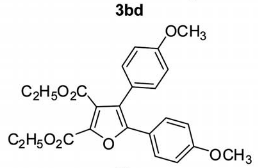
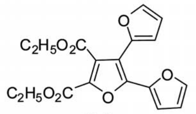
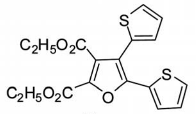
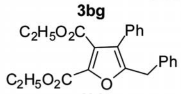
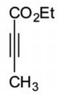
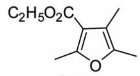
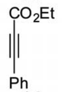
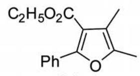
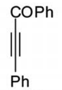
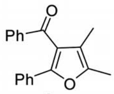
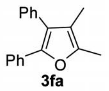
With optimal reaction conditions in hand, we explored the scope of this $FeCl_3$-catalyzed reaction, and the results are outlined in Table 2. By using **1a** as a fixed substrate, we carried out the reactions with various types of α-hydroxy ketones bearing aromatic and aliphatic substituted. In all these cases we found that the corresponding products could be obtained in good yields (Entries 1–8). These results indicated that the reaction conditions are compatible with a number of functional groups in the α-hydroxy ketones. When diethyl but-2-ynedioate (**1b**) was examined as a substrate, the desired furans were obtained in good yields (Table 2, Entries 10–17).

We next evaluated the scope of this transformation with respect to using **2a** as a fixed substrate. Other electron-deficient alkynes, such as ethyl but-2-ynoate (**1c**), ethyl 3-phenylpropiolate (**1d**) and 1,3-diphenylprop-2-yn-1-one (**1e**), were checked. To our delight the corresponding furan derivatives were obtained in moderate to good yields (Table 2, Entries 18–20). All these cases clearly indicate that

Table 2. Substrate scope for the synthesis of furan derivatives.[a]



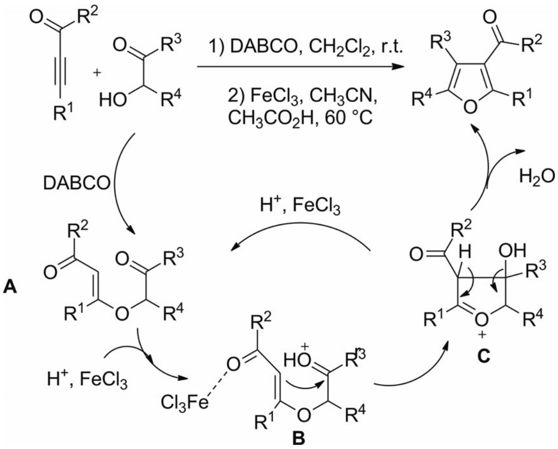
1a–1e **2a–2i** **3**

Entry	Alkynoate	α-Hydroxy ketone	Product	Yield [%][b]
1	 **1a**	 **2a**	 **3aa**	81
2	**1a**	 **2b**	 **3ab**	76
3	**1a**	**2c**	 **3ac**	79
4	**1a**	 **2d**	 **3ad**	77
5	**1a**	 **2e**	 **3ae**	79
6	**1a**	 **2f**	 **3af**	73
7	**1a**	 **2g**	 **3ag**	71
8	**1a**	 **2h**	 **3ah**	78
9	**1a**	 **2i**	 **3ai**	72
10	 **1b**	**2a**	 **3ba**	57
11	**1b**	**2b**	 **3bb**	76
12	**1b**	**2c**	 **3bc**	74
13	**1b**	**2d**	 **3bd**	73
14	**1b**	**2e**	 **3be**	71
15	**1b**	**2f**	 **3bf**	70
16	**1b**	**2g**	 **3bg**	71
17	**1b**	**2i**	 **3bi**	73
18[c]	 **1c**	**2a**	 **3ca**	66
19[c]	 **1d**	**2a**	 **3da**	69
20[c]	 **1e**	**2a**	 **3ea**	70
22	 **1f**	**2a**	 **3fa**	–

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), 10 mol-% of $FeCl_3$ and 5 mol-% of DABCO, 10 mol-% of CH_3OOH in 2 mL of CH_3CN at 60 °C for 8 h. [b] Isolated yields. [c] PBu_3 substituted DABCO as a catalyst.

the reaction condition both bear various types of electron-deficient alkynes and α-hydroxy ketones. Unfortunately, the desired product and intermediate were not detected during the reaction, when non-activated diphenylacetylene (**1f**) was tested as the substrate (Table 2, Entry 21).

A plausible mechanism accounting for the cycloaddition process is depicted in Scheme 1. DABCO-promoted nucleoaddition of an α-hydroxy ketones to an electron-deficient alkyne forms adduct **A**, which is activated by $FeCl_3$ and H^+ to generate **B**. The coordination of H^+ to the carbonyl group lowers the electron density of the carbon–oxygen double bond, which makes the nucleophilic attack of the α-carbon atom toward the carbonyl carbon atom possible to form intermediate **C**. Finally, intermediate **C** undergoes sequential dehydration and deprotonation to give **3** as the desired product.



Scheme 1. Working mechanism for the cycloaddition process.

Conclusions

This paper described the FeCl$_3$-catalyzed one pot cycloaddition of α-hydroxy ketones to activated alkynes. The reaction provides a convergent approach to generate a C–C and a C–O bond for the synthesis of furan derivatives in moderate to good yields. Further studies will be focused on utilizing this catalytic system in organic synthesis, and applications of these methodologies are underway and will be reported in future publications.

Supporting Information (see footnote on the first page of this article): Experimental procedures and NMR spectra.

Acknowledgments

This work was financially supported by the Foundation for Distinguished Young Talents in Higher Educationof Guangdong, China (LYM11083).

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Received: February 11, 2012