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Synthesis of tetrasubstituted furans via In-catalyzed propargylation of 1,3-dicarbonyl compounds-cyclization tandem process

Xunbo Feng, Ze Tan *, De Chen, Youming Shen, Can-Cheng Guo *, Jiannan Xiang *, Chengliang Zhu

College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, PR China

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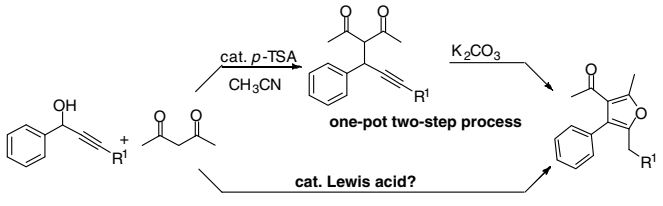
ABSTRACT

An efficient method to synthesize tetrasubstituted furans using simple starting materials such as propargylic alcohols and 1,3-dicarbonyl compounds has been developed. It was discovered that $InCl_3$ could catalyze this transformation efficiently while other simple iron, copper and silver salts were proven to be ineffective.

The synthesis of furans has always been an area of intensive research by synthetic chemists due to their wide presence in a variety of natural products and pharmaceuticals.[1] They can also serve as important intermediates for many organic transformations. Classical methods for their syntheses[2] involve the uses of Diels–Alder reactions, condensations, cross-couplings, etc. However, methods for the synthesis of highly substituted furans are still limited. During the last decade progress on this front[3] has been made via various isomerization and cyclization processes catalyzed by Pd,[3a,f] Cu,[3d] Ag,[3i] Au,[3e,g,h] Ru,[3b] etc. But most of them require the preparation of rather advanced starting materials such as alkynones and allenones. Synthesis of furans starting from simple compounds is still rare. Recently, Sanz et al. reported efficient propargylation[4a] and benzylation[4b] of 1,3-dicarbonyl compounds catalyzed by *p*-toluenesulfonic acid (PTSA hereafter). In several cases,[4a] they demonstrated that the substitution products could be transformed to tetrasubstituted furans by adding stoichiometric amount of K_2CO_3 to the reaction mixture (Scheme 1). Though the two-step one-pot synthesis of furan from simple starting material is attractive, the need to stop the reaction in the middle and add stoichiometric amount of K_2CO_3 to induce the desired cyclization makes the procedure much less desirable. Therefore, there is much room to be improved. Inspired by the recent huge influx of reports on In-,[5,6] Fe-catalysis,[7] and their extensive uses as Lewis acids, we envision that the same transformation can be catalyzed by Lewis acids such as Indium or Iron salts, eliminating the need for K_2CO_3, thus making the reaction truly catalytic. We report herein a highly efficient procedure for the synthesis of tetrasubstituted furans using propargylic alcohol, 1,3-diketones or 1,3-ketoesters, and catalytic amount of $InCl_3$.[8]



Scheme 1. Synthesis of tetrasubstituted furans from propargylic alcohol and 1,3-dicarbonyl compounds.

In- and Fe-catalysis has received much attention lately because of the relatively cheap prices of Indium and Iron salts compared to some of the noble metals and their environmental friendliness due to their low toxicity. They have been used frequently as Lewis acids and a plethora of transformations have been developed. In this context, recent reports of In- and Fe-catalyzed benzylation[9,10] of aromatics and 1,3-dicarbonyl compounds are particularly relevant. In order to make our procedure operationally simple, several common, commercially available indium and iron salts were screened as catalysts (Table 1). The reaction of 1-phenyl-2-nonyn-1-ol with acetylacetone was chosen as the model reaction as this type of starting material has worked very well for Sanz et al. It was found that the choices of catalyst and solvent were very important for effecting the furan formation. For example, the use of $FeCl_3$ in refluxing dichloroethane only led to the substitution product **B**. With stronger Lewis acid such as $InCl_3$, the major product is still the substitution product **B** accompanied by a small amount of desired furan **A** when the reaction was performed in refluxing dichloroethane. Finally, running the reaction in chlorobenzene at 110 °C afforded the desired furan **A** in excellent yield. Surprisingly, when the much more Lewis acidic $In(OTf)_3$ was used as catalyst, the reaction gave a complex mixture. We surmised that other byproducts such as indene derivatives arising from Friedel–Crafts type reaction of the phenyl ring with the carbonyl group could also be formed.[11] This clearly suggested that the success of the reaction critically hinged on the use of Lewis acid with appropriate acidity. Lewis acids that are either too strong or too weak are not effective

* Corresponding authors. Tel.: +86 0731 882 2400; fax: 86 0731 8822484 (Z.T.).
E-mail address: ztanze@gmail.com (Z. Tan).

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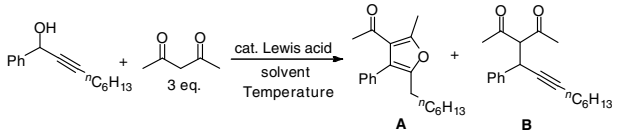
Table 1
Optimization of reaction conditions



Catalyst	Solvent	Temperature (°C)	Time (h)	Product (yield %)
$FeCl_3$	$ClCH_2CH_2Cl$	Reflux	12	**B** (⩾95)
$InCl_3$	$ClCH_2CH_2Cl$	Reflux	24	**A** (<10) **B** (83)
$InCl_3$	Chlorobenzene	110	20	**A** (68)[a]
$InCl_3$	Chlorobenzene	110	20	A (89)
$In(OTf)_3$	Chlorobenzene	110	24	Messy
$CuBr_2$	Chlorobenzene	110	24	**B** Only
CuBr	Chlorobenzene	110	20	**B** Only
CuCl	Chlorobenzene	110	20	**B** Only
CuI	Chlorobenzene	110	20	No reaction
AgCl	Chlorobenzene	110	20	No reaction
AgI	Chlorobenzene	110	20	No reaction
AgOTf	Chlorobenzene	110	20	Messy

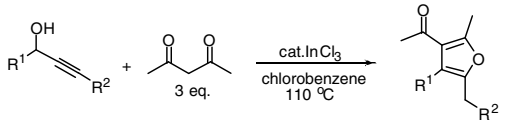
[a] Only 2 equiv of acetylacetone was used.

for the transformation to take place efficiently. For comparison, several copper and silver salts were tested too. Only product **B** was obtained with catalysts $CuBr_2$, CuCl, and CuBr, while the use of CuI, AgCl, or AgI resulted in no reaction. The use of AgOTf gave a complex mixture. We also found that the use of three equivalent of acetylacetone was necessary to achieve high yield. Otherwise the yield of furan is lower. Based on the above results, we decided to set reacting the propargyl alcohol with three equivalent of acetylacetone and 10 mol % of $InCl_3$ in chlorobenzene at 110 °C as the standard condition.[12]

After optimizing the reaction conditions, we set out to investigate the scope of the reaction. When the phenyl ring in 1-phenyl-2-nonyn-1-ol was replaced with a simple alkyl group such as the isopropyl group, its reaction with acetylacetone only produced the Meyer–Schuster rearrangement product.[13] This result is consistent with what was reported by Sanz et al.[4a] It also highlights the need to have a benzylic cation which is sufficiently long-lived to react with 1,3-dicarbonyl compounds. Next, the scope of the substrate was further explored as summarized in Table 2. The reactions of substrates bearing chloro and methyl substituents on the phenyl ring with acetylacetone proceeded smoothly, giving the desired furans in 87% and 81% yield, respectively (Table 2, entries 2 and 4). On the other hand, substrate bearing *p*-methoxyl group gave a complex mixture (Table 2, entry 3). It is thought that the electron rich aromatic ring can also participate in the second cyclization step. As for the substituent on the alkyne moiety, all substrates bearing alkyl, aryl, trimethylsilyl groups all gave satisfactory results. It is interesting to note that 1-phenyl-2-propyn-1-ol, a terminal alkyne containing propargyl alcohol could also participate in the reaction, even though the yield is lower and the reaction rate is somewhat slower (Table 2, entry 8). With the trimethylsilyl-substituted alkyne containing propargylic alcohols, we were surprised to find that the final products obtained did not contain the TMS group (Table 2, entries 5–7). Instead, the TMS group was replaced with a hydrogen atom. Since the reaction of trimethylsilyl-substituted alkyne containing propargyl alcohol with acetylacetone was faster than the one without the TMS group, we reasoned that the trimethylsilyl group was probably lost after the furan formation. It should be noted that our yields of furans are significantly higher than those of the PTSA-catalyzed version though we do not know whether this is due to the use of excess amount of nucleophile or not.

As shown in Table 3, a variety of tetrasubstituted furans bearing a carboxylate group can be readily synthesized by replacing acetylacetone with ethyl acetoacetate. The yields of furans are lower than those of acetylacetone. This may be due to the fact that 1,3-diketones are better nucleophiles than 1,3-ketoesters. It is also worthwhile to note that the reaction of propargylic alcohols with simple ketones such as acetone did not succeed either.

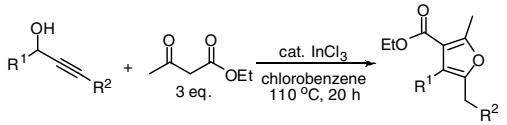
Table 2
Synthesis of furans via In-catalyzed propargylation of 1,3-diketones-cyclization tandem process



Entry	R^1	R^2	Time (h)	Yield[a] (%)	R^2
1	Phenyl	n-C_6H_{13}	20	89	n-C_6H_{13}
2	*p*-Chlorophenyl	n-C_6H_{13}	20	87	n-C_6H_{13}
3	*p*-Methoxyphenyl	n-C_6H_{13}	20	Messy	
4	*p*-Methylphenyl	n-C_6H_{13}	24	81	n-C_6H_{13}
5	Phenyl	TMS	22	83	[b]
6	*p*-Chlorophenyl	TMS	20	80	[b]
7	*p*-Methylphenyl	TMS	16	76	[b]
8	Phenyl	H	32	53	H
9	*p*-Methylphenyl	n-C_4H_9	24	81	n-C_4H_9
10	Phenyl	n-C_4H_9	24	91	n-C_4H_9
11	Phenyl	Phenyl	24	70	Phenyl
12	*p*-Chlorophenyl	Phenyl	24	80	Phenyl
13	*p*-Methylphenyl	Phenyl	24	65	Phenyl
14	Phenyl	*p*-Chlorophenyl	24	76	*p*-Chlorophenyl
15	*p*-Chlorophenyl	*p*-Chlorophenyl	24	89	*p*-Chlorophenyl

[a] All yields are isolated yields.
[b] TMS group was replaced with a hydrogen atom.

Table 3
Synthesis of furans via In–catalyzed propargylation of ethyl acetoacetate-cyclization tandem process

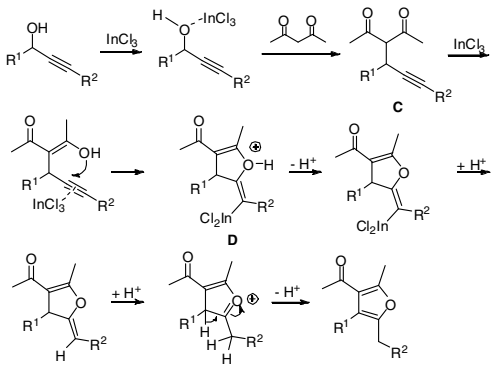


Entry	R^1	R^2	Yield[a] (%)	R^2
1	Phenyl	n-C_6H_{13}	56	n-C_6H_{13}
2	*p*-Chlorophenyl	TMS	65	[b]
3	*p*-Methylphenyl	TMS	61	[b]
4	Phenyl	*p*-Chlorophenyl	46	*p*-Chlorophenyl
5	Phenyl	TMS	63	[b]
6	Phenyl	n-C_4H_9	53	n-C_4H_9
7	*p*-Methylphenyl	n-C_4H_9	44	n-C_4H_9

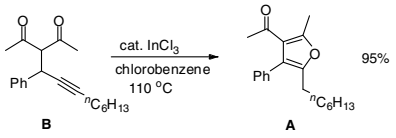
[a] All yields are isolated.
[b] TMS group was replaced with a hydrogen atom.

A tentative mechanism for the reaction is outlined in Scheme 2. First, the $InCl_3$ catalyst coordinates with the oxygen atom of the propargyl alcohol to generate a carbocation, which is subsequently trapped by the dicarbonyl compounds to form the substitution product **C**. Next, the $InCl_3$ catalyst coordinates with the triple bond in **C** and the triple bond was attacked by the lone-pair electrons of the carbonyl group to generate **D**. The carbon–indium bond was protonized[6f,i] and the desired furan product was obtained through a series of proton addition/elimination, double bond isomerization processes (Scheme 2).

In order to confirm that the cyclization step was truly catalyzed by $InCl_3$, we first isolated the substitution product **B**, and then treated it with catalytic amount of $InCl_3$ in chlorobenzene. After 12 h at



Scheme 2. Possible mechanism for the furan formation.



Scheme 3.

110 °C, the desired product **A** was isolated in 95% yield (Scheme 3). This result firmly established the fact that furans were indeed produced through intermediate **C** and $InCl_3$ did catalyze the cyclization process.

In summary, we have developed an efficient protocol for the synthesis of tetrasubstituted furans from propargylic alcohols and 1,3-dicarbonyl compounds. The success of the method depended on the use of $InCl_3$ as catalyst. Our reaction is relatively favorable compared with the reported method in terms of both the product yields and operational simplicity. Our method uses only a catalytic amount of $InCl_3$, requiring no stop in the middle of the reaction and it also does not require the addition of stoichiometric amount of base to effect the cyclization step. The procedure that we developed not only extended the scope of In-catalysis but also could be complementary to the existing methods for the synthesis of furans. It could be easily adapted for combinatory library synthesis. Detailed mechanistic investigation on this particular transformation is still ongoing.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.142.

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12. *General procedure for the synthesis of furans via In-catalyzed propargylation of 1,3-dicarbonyl compounds-cyclization tandem process: Synthesis of 3-acetyl-5-n-*heptyl-2-methyl-4-phenylfuran (A). In a 25-mL round-bottomed flask equipped with a reflux condenser were placed acetylacetone (300 mg, 3 mmol), 1-phenyl-2-nonyn-1-ol (216 mg, 1 mmol), 10 mol % $InCl_3$ (22 mg, 0.1 mmol) and 5 mL of chlorobenzene. The mixture was heated to 110 °C for 20 h under N_2 before it was cooled to room temperature. The mixture was diluted with ether and quenched with saturated NH_4Cl. The organic phase was separated and the aqueous phase was extracted twice with ether. The organic phases were combined, dried over $MgSO_4$, and concentrated via vacua. The crude product was purified through column chromatography (silica gel, petroleum ether/ethyl acetate, 30/1) to afford 266 mg of the desired furan A in 89% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 6.8 Hz, 3H), 1.2–1.3 (m, 8H), 1.5–1.6 (m, 2H), 1.90 (s, 3H), 2.45 (t, J = 7.2 Hz, 2H), 2.54 (s, 3H), 7.24 (d, J = 7.6 Hz, 2H), 7.3–7.45 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.99, 14.25, 22.53, 25.69, 28.41, 28.80, 28.89, 30.65, 31.63, 120.57, 122.85, 127.28, 128.31 (2C), 129.93 (2C), 133.78, 151.04, 156.20, 196.06; IR: 1562, 1674, 2856, 2927 cm^{-1}; LRMS (CI) for $C_{20}H_{26}O_2$ $[M+H]^+$ calcd 299, found 299.
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