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Direct Synthesis of Highly Substituted Furans from Acyloins and Active Methylene Compounds Catalyzed by Bismuth Triflate

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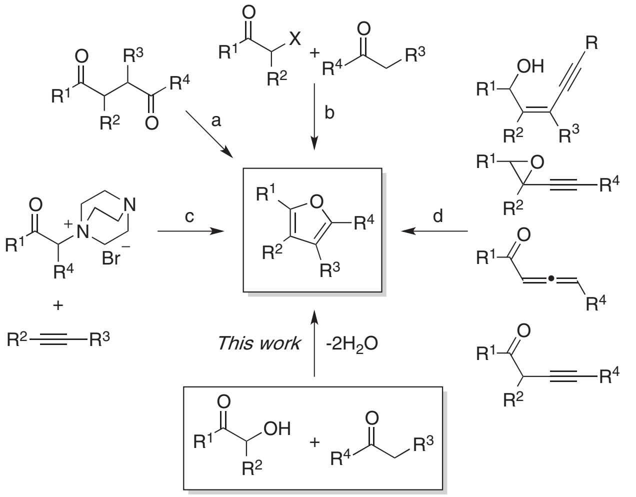
$Bi(OTf)_3$ was found to be an effective catalyst for a tandem condensation/cyclization of acyloins and β-diketones or β-keto esters to afford highly substituted furans in good yields.

Furan skeletons are prevalent in many natural and important pharmaceutical substances,[1] and also widely recognized as useful intermediates in synthetic organic chemistry.[2] To synthesize the molecules, numerous methods have been explored; representative examples are depicted in Scheme 1. Among them, the oldest and most powerful methods would be (a) Paal–Knorr and (b) Feist–Bénary synthesis,[3] in which 1,4-dione compounds act as starting substrates or intermediates. (c) The reaction of activated alkynes using an ammonium ylide is also an effective route to access the furan skeletons.[4] Recently, alternative procedures, (d) transition-metal-catalyzed cycloisomerization of alcohols, epoxides, and ketones containing alkyne and allene moieties, have been demonstrated.[5] Unfortunately, in most cases, the limitation lies in the fact that the requisite starting materials, especially those having suitable substituents are somewhat difficult to prepare. Therefore, the development of a more practical method that can be used for furan synthesis with fewer limitations is desired.

On the other hand, acyloins are readily available substrates by means of the well-studied condensation reaction of aldehydes or esters.[6] We speculated that the acyloins would be good electrophiles in a condensation of active methylene compounds like β-diketones and β-keto esters to produce the corresponding 1,4-diones.[7] The obtained intermediates could sequentially cyclize to produce highly substituted furans under the same media (This work). The consecutive reaction eliminates only H_2O as a side product, thus, the protocol would be an ideal process for the furan synthesis.[8]

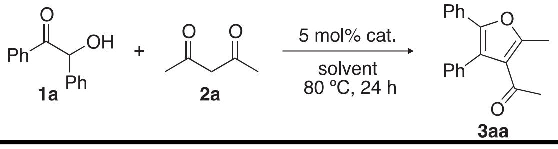


Scheme 1.

To test the feasibility of such hypothesis, benzoin (**1a**) was chosen as a model substrate to react with acetylacetone (**2a**). To our delight, the expected condensation/cyclization smoothly proceeded with 5 mol % of $Bi(OTf)_3$ in toluene in 80 °C for 24 h, leading to the tetrasubstituted furan **3aa** in 99% yield (Entry 1, Table 1). Other Lewis and Brønsted acids like $Cu(OTf)_2$, $Fe(OTf)_3$, $Sc(OTf)_3$, $Zn(OTf)_2$, and TfOH were ineffective in the reaction, resulting in lower or negligible yields of **1a** (Entries 2–7). In particular, using $Cu(OTf)_2$, $Fe(OTf)_3$, and TfOH caused the oxidation of **1a** to supply benzil (Entries 2, 3, and 7).[9] The bismuth counter ion was very important for efficient reaction, that is, $BiCl_3$ and $Bi(NO_2)_3$ did not work well (Entries 8 and 9). Additionally, we confirmed that the present reaction did not occur without $Bi(OTf)_3$. Solvent effects where also significant; DCE and MeCN were effective similar to toluene (Entries 10 and 11), but THF resulted in much lower yield of **3aa** (Entry 12), wherein the oxidation mainly proceeded.

Optimized conditions in hand, we next examined the scope of active methylene compounds **2** in this furan synthesis.[10] These results are summarized in Table 2. β-Keto ester **2b** and amide **2c** could also successfully react with **1a** to afford the corresponding furans **3ab** and **3ac** in good yields (Entries 2

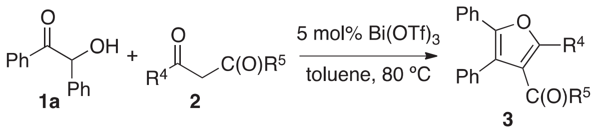
Table 1. Screening of catalysts in the reaction of **1a** with **2a**[a]

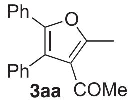
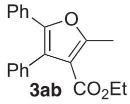
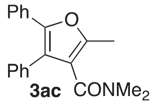
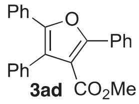
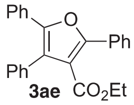
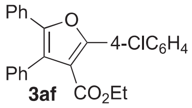
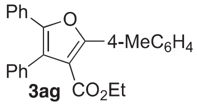
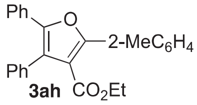


Entry	Catalyst	Solvent	Yield of **3aa**/%[b]	Conv. of **1a**/%[b]
1	$\mathbf{Bi(OTf)_3}$	**toluene**	**99**	**99**
2	$Cu(OTf)_2$	toluene	24	60
3	$Fe(OTf)_3$	toluene	9	42
4	$Sc(OTf)_3$	toluene	trace	17
5	$Zn(OTf)_2$	toluene	trace	5
6	$BF_3 \cdot OEt_2$	toluene	trace	4
7	TfOH	toluene	trace	71
8	$BiCl_3$	toluene	trace	5
9	$Bi(NO_2)_3$	toluene	trace	4
10	$Bi(OTf)_3$	DCE	99	99
11	$Bi(OTf)_3$	MeCN	76	99
12	$Bi(OTf)_3$	THF	5	77

[a]All reactions were carried out using **1a** (0.24 mmol), **2a** (0.48 mmol), catalyst (5 mol %), and toluene (2.4 mL). [b]Determined by GC with tridecane as an internal standard.

Table 2. Reaction of **1a** and active methylene compounds **2**



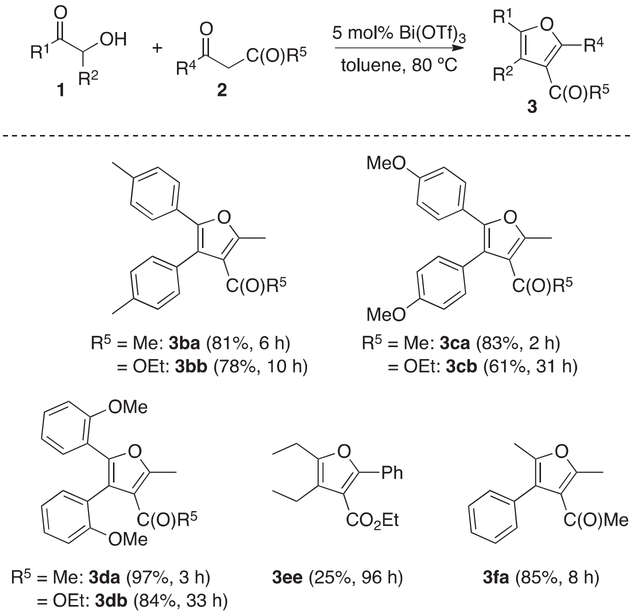
Entry	R^4, R^5 (**2**)	Time/h	Products	Yield/%[a]
1	Me, Me (**2a**)	24	 **3aa**	94
2	Me, OEt (**2b**)	24	 **3ab**	89
3[b]	Me, NMe_2 (**2c**)	23	 **3ac**	74
4	Ph, OMe (**2d**)	12	 **3ad**	90
5	Ph, OEt (**2e**)	11	 **3ae**	84
6	4-ClC_6H_4, OEt (**2f**)	10	 **3af**	90
7	4-MeC_6H_4, OEt (**2g**)	15	 **3ag**	88
8[c]	2-MeC_6H_4, OEt (**2h**)	12	 **3ah**	91

[a]Isolated yield. [b]20 mol % $Bi(OTf)_3$, reaction temperature: 100 °C. [c]Reaction temperature: 50 °C.

and 3). Aryl β-keto esters **2d–2h** were more reactive. These reactions completed in reduced time (Entries 4–8). The size of the β-keto ketones and esters **2** has a significant influence on the reaction. Thus, β-keto ester possessing bulkier substituents like *tert*-butyl and *tert*-butoxy groups at the R^4 and R^5 positions, respectively, did not give the corresponding furans even at higher temperature (120 °C) and longer reaction time (96 h), where all substrates remained quantitatively unchanged.

Next, this methodology was extended to the reaction with other diaryl acyloins (Scheme 2). *para*- or *ortho*-Substituted aryl acyloins smoothly reacted with active methylene compounds **2a** and **2b**, giving rise to the corresponding furans in good yields. Interestingly, dialkyl acyloin like **1e** also participated in the reaction to afford a furan **3ee**. Additionally, this method could apply to furan synthesis from an unsymmetrical acyloin to supply **3fa** in good yield.

In summary, we have demonstrated a mild and direct process for synthesis of highly substituted furans from simple and readily available starting materials using $Bi(OTf)_3$ catalyst. This reaction releases H_2O only as a side product. Therefore, this method is useful a procedure to synthesize furan derivatives in term of environmental protection. Further synthetic applications of this protocol are currently on going.



Scheme 2.

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