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Journal Name

COMMUNICATION

Fe-Catalyzed Tandem Cyclization for the Synthesis of 3-Nitrofurans from Homopropargylic Alcohols and $Al(NO_3)_3·9H_2O$

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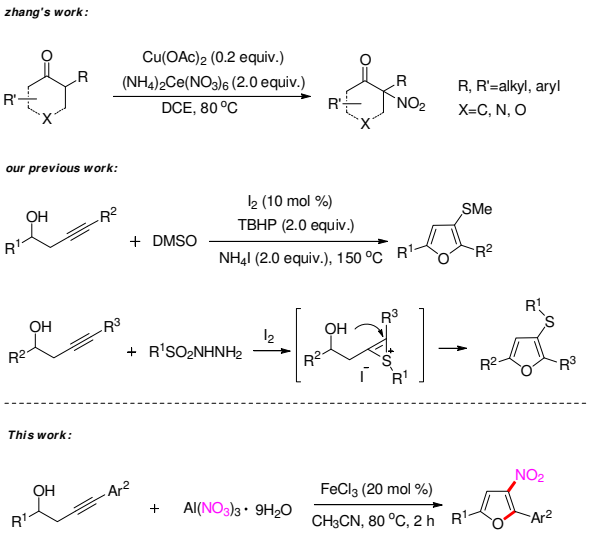
$Al(NO_3)_3·9H_2O$ as the nitro source for the synthesis of 3-nitrofurans from homopropargylic alcohols through Fe-catalyzed tandem cyclization is described. In this transforamtion, the substituted nitrofurans are obtained through nitration and cyclization. The substrate homopropargylic alcohols with different groups proceeded smoothly in this process and the desired substituted nitrofurans are obtained in moderate yields.

Nitro-containing compounds are widely used as high-energy materials, dyes, pharmaceuticals, perfumes and plastics.[1] Among them, the nitrofuran derivatives are widely used as building pharmaceutical and biologically active molecules.[2] For example, nitrofurazone and nitrofurantoin (NFZ and NFT) are widely used to against common infections.[3]

The methods of synthesize nitro compounds have received great attentions in organic chemical synthesis. Classical nitration of C-C bonds and C-hetero bonds have been significantly developed and the approaches are mainly including the strategies of electrophilic substitution using nitronium cation[4] (NO_2^+) and nucleophilic substitution with nitrite anion[5] (NO_2^-). In the recent years, *tert*-butyl nitrite (TBN) as model nitration reagent for introducing nitro group has been well exploited. The groups of Maiti[6] and Prabhu[7] have made great contributions on the synthesis of substituted nitroolefins with TBN. Despite the great applications of TBN in nitration, obvious drawbacks of TBN are highly exothermic decomposition at elevated temperatures and potential hazardous.[8] Recently, the efficient metal-catalyzed nitration with nitrates have been well developed. The outstanding features of nitrates as the nitro source are inexpensive and readily available. Zhang's group reported a challenging method about copper-assisted direct nitration of cyclic ketones with ceric ammonium nitrate (CAN) (scheme 1).[9] The group of Zhang also reported an elegant approach about meta-selective C–H nitration of arenes with $Cu(NO_3)_2·3H_2O$.[10] However, most of reports about nitration are focused on introducing nitro group to arene,[11] alkene or alkane and there is less research on the tandem cyclization to construct nitro-containing heterocyclic compounds.



Scheme 1. Previous works

The most common methods for the synthesis of the nitro furans are mainly concentrated on the direct nitration of furan with highly acidic reaction conditions (HNO_3).[12] So the synthesis of 3-nitrofuran is still highly desirable and also remains great challenge. Our group had developed several methods to synthesize methylthiofurans and sulfanylfurans from homopropargylic alcohols through tandem cyclization reaction (scheme 1).[13] Inspired by the works of utilization nitrates and our experiences in construction substituted furans

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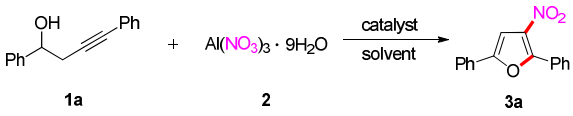
Table 1. Optimization of reaction conditions [a]



1a 2 3a

Entry	NO_2 source (X equiv.)	Solvent	Catalyst	Temp(℃)	Yield (%)[b]
1	$Fe(NO_3)_3{\cdot}9H_2O$	CH_3CN	$FeCl_3$	80	55
2	$Cu(NO_3)_3{\cdot}3H_2O$	CH_3CN	$FeCl_3$	80	43
3	$Bi(NO_3)_3{\cdot}5H_2O$	CH_3CN	$FeCl_3$	80	Trace
4	$NH_4Ce(NO_3)_6$	CH_3CN	$FeCl_3$	80	30
5	$Al(NO_3)_3{\cdot}9H_2O$	CH_3CN	$FeCl_3$	60	55
6[c]	$Al(NO_3)_3{\cdot}9H_2O$	CH_3CN	$FeCl_3$	80	60
7	$Al(NO_3)_3{\cdot}9H_2O$	CH_3CN	$FeCl_3$	120	53
8	**$Al(NO_3)_3{\cdot}9H_2O$**	**CH_3CN**	**$FeCl_3$**	**80**	**65**
9	$Al(NO_3)_3{\cdot}9H_2O$	CH_3CN	$BF_3{\cdot}Et_2O$	80	54
10	$Al(NO_3)_3{\cdot}9H_2O$	CH_3CN	Tf_2O	80	55
11	$Al(NO_3)_3{\cdot}9H_2O$	CH_3CN	CuCl	80	46
12	$Al(NO_3)_3{\cdot}9H_2O$	DMF	$FeCl_3$	80	17
13	$Al(NO_3)_3{\cdot}9H_2O$	CH_3NO_2	$FeCl_3$	80	26
14	$Al(NO_3)_3{\cdot}9H_2O$	C_6H_5Cl	$FeCl_3$	80	26
15	$Al(NO_3)_3{\cdot}9H_2O$	THF	$FeCl_3$	80	24

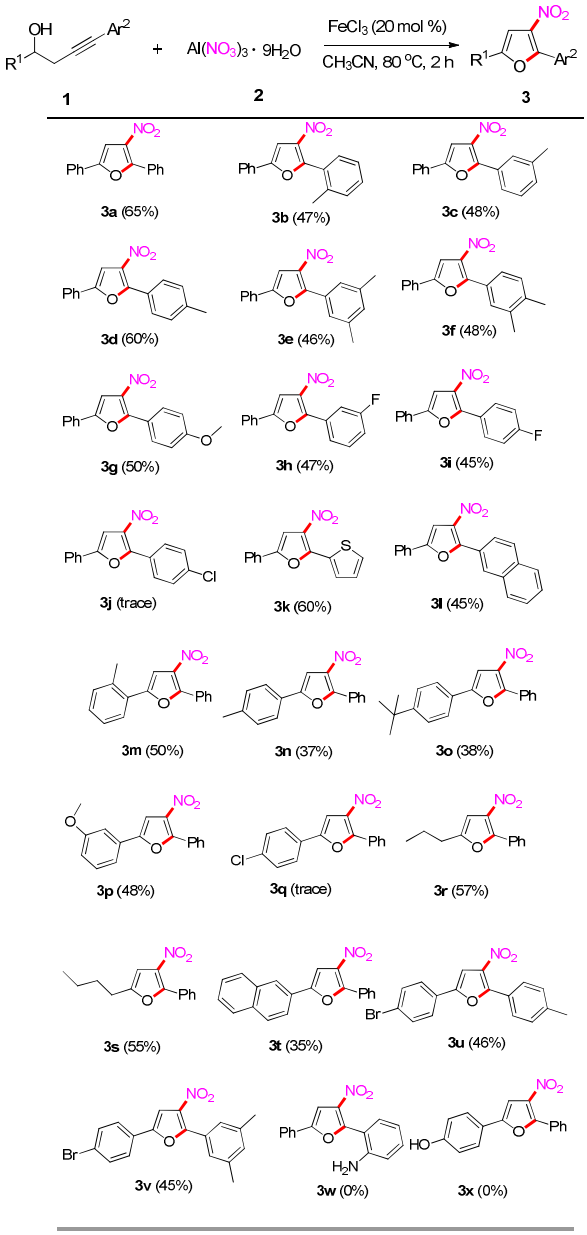
[a] Reaction conditions: **1a** (0.2 mmol), NO_2 sources (0.1 mmol), catalyst (20 mol %), solvent (2 mL), 80 ℃. [b] Yields of isolated products. [c] Under nitrogen. DMF = *N*,*N*-Dimethylformamide, Tf_2O = Trifluoromethane sulfonic anhydride.

through tandem cyclization, herein, we reported a straightforward method to synthesize 3-nitrofuran with homopropargylic alcohols and aluminum nitrate nonahydrate under mild condition. (Scheme 1).

Our investigation was commenced firstly with the 1,4 diphenylbut-3-yn-1-ol (**1a**) as substrate, $Fe(NO_3)_3{\cdot}9H_2O$ as nitration agent and 20 mol % of $FeCl_3$ as catalyst in acetonitrile (MeCN) at 80℃ under air. The desired product 3-nitro-2,5-diphenylfuran (**3a**) was isolated in 55% yield (table 1, entry 1). A series of metal nitro compounds, such as $Al(NO_3)_3{\cdot}9H_2O$, $Bi(NO_3)_3{\cdot}5H_2O$, $Fe(NO_3)_3{\cdot}9H_2O$, $Cu(NO_3)_3{\cdot}3H_2O$ and $NH_4Ce(NO_3)_6$ were also evaluated for this reaction and the $Al(NO_3)_3{\cdot}9H_2O$ was found as the most effective nitro source for this process and the yield was increased to 65% (Table1, entries 1-5). Further, various solvents were also screened and the acetonitrile was the most efficient solvent for this transformation and the isolated **3a** was obtained in 65% yield (Table 1, entry 8 and entries 12-15). The employment of $FeCl_3$ as catalysts gave a better yield than $BF_3{\cdot}Et_2O$, Tf_2O and CuCl (Table 1, entries 8-11). When the dose of AcOH was changed to 20 mol %, the yield was afforded in 88%. The result of changing temperature revealed that there was no effect on the yield (Table 1, entries 5 and 7). So the optimized conditions were established as shown in Table 1, entry 8.

We next examined the substrate scope of homopropargylic alcohols under the optimized conditions in hand. As illustrated in Scheme 2, a series of homopropargylic alcohols with electron-donating or withdrawing groups on benzene rings reacted with substrate **2** smoothly, generating the desired

Scheme 2. Scope of substituted homopropargylic alcohols



nitro furans in moderate yields. The optimized conditions were consistent with various homopropargylic alcohols with electron-donating substituents Me, *di*Me, and OMe groups on the aryl ring. Fluorine-containing derivatives of homopropargylic alcohols could also tolerated in this transformation, giving the corresponding products **3h** and **3i** with moderate yields. The substrates **1j** and **1q** with Cl group could not work under the optimized conditions and only trace amount of desired products was detected. In addition, the homopropargylic alcohols **1k**, **1l** and **1t** with thienyl or naphthyl group also can perform well in this transformation and the desired product **3k**, **3l** and **3t** were isolated in 60%, 45% and 35% yields. Further investigation disclosed that the alkyl groups on

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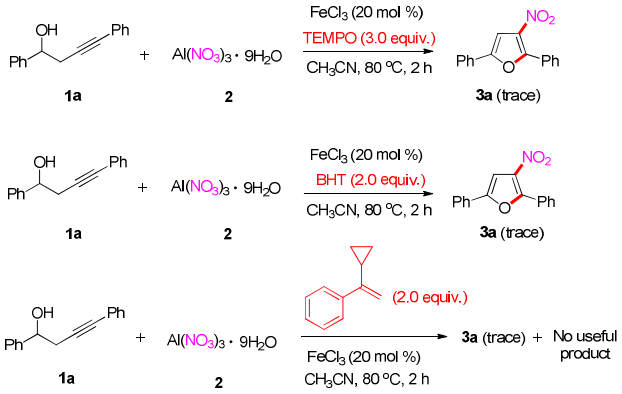
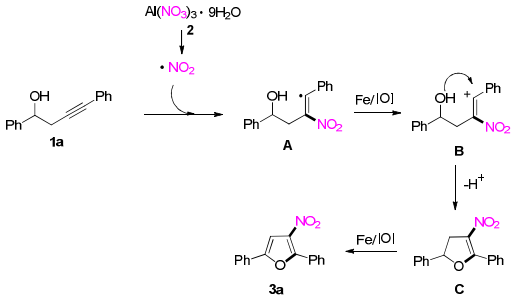
Scheme 3. Control experiments



homopropargylic alcohols also tolerated well in this reaction and the desired products were isolated in 55% and 57% yields (Scheme 2, **3r** and **3s**). The desired substituted nitrofurans with electron-donating and electron-withdrawing substituents on the benzene rings were also obtained in 46% and 45% yields from this process, respectively (Scheme 2, **3u** and **3v**). Unfortunately, the substrates with the -NH_2, and –OH group on the benzene ring did not fit this reaction system and no desired products was detected.

To gain insight into the possible mechanism of the nitro-cyclization reaction, several control experiments were performed (scheme 3). The radical inhibitor, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and butylated hydroxytoluene (BHT) were added to the reaction and only a trace amount of **3a** was detected, which indicated that a radical process should be included in this process. The nitro radical was also not be trapped by compound of the (1-cyclopropylvinyl)benzene under standard conditions.

Scheme 4. Proposed mechanism



On the basis of the above results, a plausible mechanism is proposed as shown in Scheme 4. The formation of the nitroradical from the substrate **2** under the standard conditions should be the initial step. Then the radical addition between the substrate **1a** and nitro radical is occurred to generate the radical intermediate **A**.[14] The cation intermediate **B** is afforded from the **A** through oxidation under Fe-catalyzed reaction system. Subsequently, the intermediate **C** is formed through intramolecular nucleophilic addition of the **B**. Finally, intermediate **C** produces the desired product **3a** through Fe catalyzed oxidative aromatization.

In summary, we have developed a straightforward method for the synthesis of 3-nitrofurans with homopropargylic alcohols and aluminum nitrate nonahydrate, affording the substituted nitro furans in moderate yields. This method constitutes a concise access to nitrofurans through radical nitration and tandem intermolecular cyclization. Using nontoxic and inexpensive $Al(NO_3)_3 \cdot 9H_2O$ as the nitro source is another notable feature. Therefore, this reaction will provide a practical method for the synthesis of nitro compounds.

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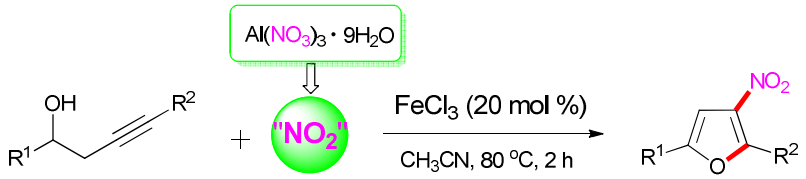

- **$Al(NO_3)_3 \cdot 9H_2O$ as the nitro source directly!**
- **Fe-catalyzed tandem cyclization for the synthesis of 3-nitrofurans**