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Copper(I)-Catalyzed Heterocyclization of α-Acyl-α-alkynyl Ketene Dithioacetals: Synthesis of 3-Cyanofurans

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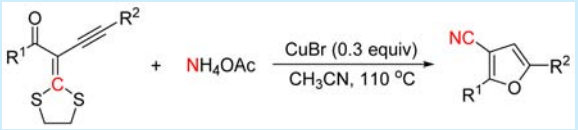
Supporting Information

ABSTRACT: A new method for the synthesis of 3-cyanofurans via Cu(I)-catalyzed heterocyclization of α-acyl-α-alkynyl ketene dithioacetals in the presence of ammonium acetate has been developed. The procedure generates the cyano moiety in situ with ammonium acetate as the nitrogen source. Based upon experimental observations, a plausible reaction mechanism is proposed.



Polysubstituted furans not only represent an important class of five-membered heterocycles prevalent in natural products, pharmaceuticals, and agrochemicals[1] but also represent versatile building blocks in organic synthesis.[2] Among them, the 3-substituted furyl moiety has immense importance on account of the roles it plays in various biologically active molecules. In particular, 3-cyanofurans constitute ideal building blocks for the elaboration of more complex scaffolds, owing to the versatile chemistry of the cyano group.[3] To date, a number of synthetic strategies toward 3-cyanofurans have been developed. Traditional methods for preparing 3-cyanofurans include functional group transformation (dehydration of amides/aldoximes),[4] cyanide-(pseudo)-halide exchange reactions,[5] and direct C−H cyanation reactions,[6] which generally involve complicated operations, poor functional group tolerance, toxic reagents such as MCN (M = Cu, K, Na, or Zn), or harsh reaction conditions (Scheme 1a). In recent decades, cyclization reactions of organic precursors bearing a "CN" moiety have been used for 3-cyanofurans synthesis.[7] These methods suffer from additional operations for preparing cyano-containing substrates in advance (Scheme 1b). Therefore, the development of new cyclization methods to access 3-cyanofurans by in situ formation of a "CN" unit is still an extremely attractive yet challenging goal. Herein, we report the first example of generating a "CN" unit in situ by using ammonium acetate as a nitrogen source in Cu(I)-catalyzed cyclization of α-acyl-α-alkynyl ketene dithioacetals for the synthesis of 3-cyanofurans (Scheme 1c).[8]

Using (*E*)-4-(1,3-dithiolan-2-ylidene)-1,6-diphenylhex-1-en-5-yn-3-one (**1a**) as a test substrate, optimal conditions were first sought for the cyclization process. When I_2 was employed as in Larock's electrophile-induced cyclization of 2-(1-alkynyl)-2-alken-1-ones,[9] no cyclized product was obtained and only decomposition of the starting material was observed (Table 1, entry 1). Several commonly used transition metal salts in the cyclization of acyclic precursors were tested as the catalyst to conduct the reaction.[10] Intriguingly, the use of Ag_2CO_3 offered (*E*)-5-phenyl-2-styrylfuran-3-carbonitrile (**2a**) in varied yield depending on the loading of Ag_2CO_3 (entries 2−4). However, this method required a stoichiometric amount of Ag_2CO_3 for an excellent yield. To our delight, similar efficiency was obtained by the use of catalytic amounts of CuBr (entries 5−6). Then, a series of other copper salts (CuI, CuCl, $CuCl_2$, and $Cu(OAc)_2$) were evaluated, wherein CuBr was most effective, while the Cu(II) salt gave no desirable product (entries 7−10). Upon examining the solvents, MeCN proved to be the most suitable for this transformation (entries 11−14). We then turned our attention to the effect of temperature. As illustrated in entries 15−17, we found that the reaction proceeded efficiently at 110 °C, while either high or low temperatures gave inferior results. A control experiment verified the requirement of CuBr (entry 18).

Scheme 1. Synthesis of 3-Cyanofurans

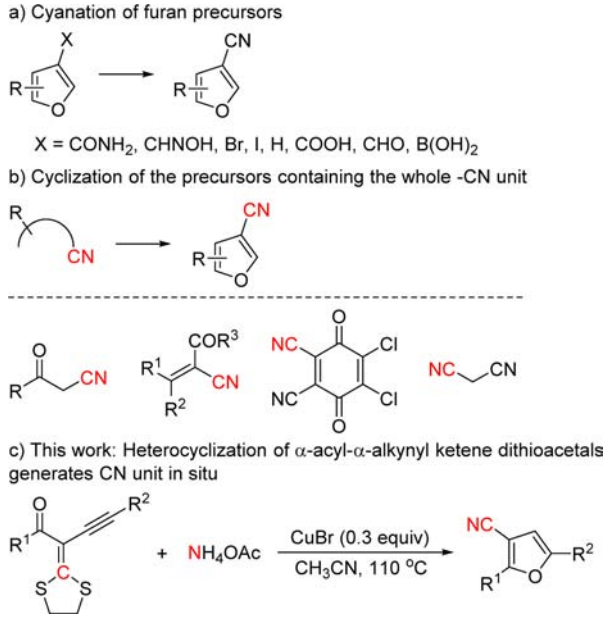


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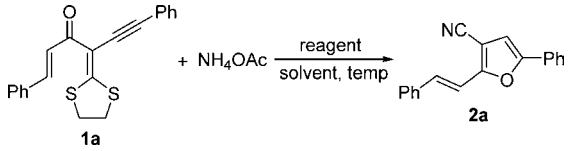
Table 1. Optimized Reaction Conditions[a]



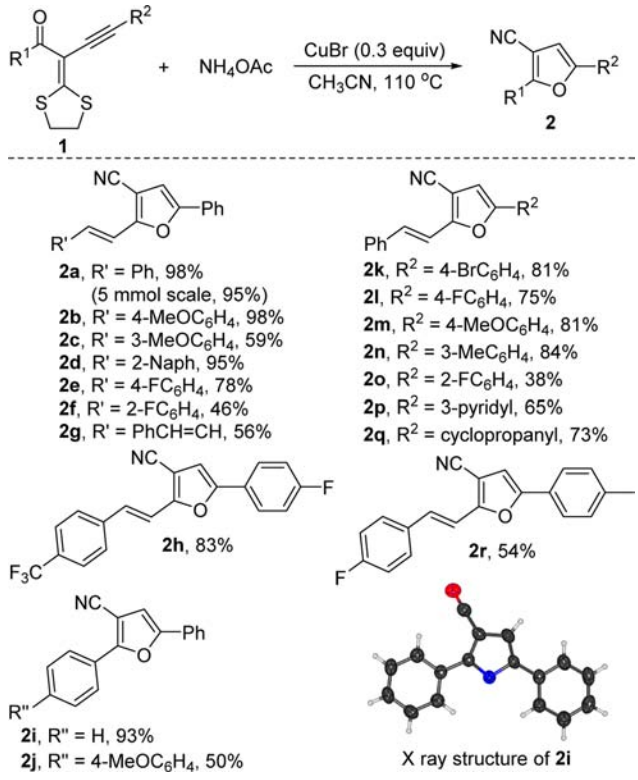
entry	reagent (equiv)	solvent	temp (°C)	2a/%[b]
1	I_2 (3.0)	CH_3CN	rt to 100	0
2	Ag_2CO_3 (0.2)	CH_3CN	100	30
3	Ag_2CO_3 (1.0)	CH_3CN	100	98
4	Ag_2CO_3 (2.0)	CH_3CN	100	95
5	CuBr (0.1)	CH_3CN	100	68
6	CuBr (0.3)	CH_3CN	100	93
7	CuI (0.3)	CH_3CN	100	17
8	CuCl (0.3)	CH_3CN	100	trace
9	$CuCl_2$ (0.3)	CH_3CN	100	0
10	$Cu(OAc)_2$ (0.3)	CH_3CN	100	0
11	CuBr (0.3)	DMF	100	40
12	CuBr (0.3)	THF	100	26
13	CuBr (0.3)	toluene	100	15
14	CuBr (0.3)	DMSO	100	42
15	**CuBr (0.3)**	**CH_3CN**	**110**	**98**
16	CuBr (0.3)	CH_3CN	120	96
17	CuBr (0.3)	CH_3CN	90	70
18	–	CH_3CN	110	0

[a]Reaction conditions: A solution of **1a** (0.2 mmol), NH_4OAc (0.4 mmol), and a reagent in the indicated solvent (2.0 mL) was stirred for 5 h. [b]Isolated yield.

With the optimized reaction conditions in hand, we proceeded to investigate the synthetic potential of this transformation, and the results are summarized in Scheme 2. We were pleased to find that a number of multisubstituted 3-cyanofurans were successfully prepared with fair to excellent yields. First, substituents on the acyl moiety were investigated (**2a–j**). Arylalkenoyl substrates, having either electron-donating or -withdrawing aryl groups, were viable in the reaction, although arylalkenoyl substrates with electron-donating substrates displayed higher reactivity than those with electron-withdrawing groups. Gram scale synthesis of **2a** was achieved in 95% yield demonstrating the practicability of the transformation. Naphthyl and alkenyl substrates were also productive (**2d** and **2g**). Aroyl substrates also reacted with ammonium acetate to afford the corresponding products (**2i–j**). Furthermore, a set of substituents at the terminal alkyne moiety were evaluated under the standard conditions (**2k–r**). Substrates with either electron-donating or -withdrawing groups on the phenyl ring could be used to generate the corresponding products in good yields. Efficiency was not much influenced by electronic variation on the aryl moiety at the terminal alkyne albeit the 2-F group leading to a dramatically decreased yield (**2o**). When the pyridine group was used as a substituent, the product could be obtained in 65% yield (**2p**). An alkyne bearing cyclopropyl substituent was compatible with the reaction system (**2q**). A substrate with a terminal alkyne was not a viable substrate for this cyclization reaction. The structure of **2i** was successfully confirmed by X-ray crystallography.[11]

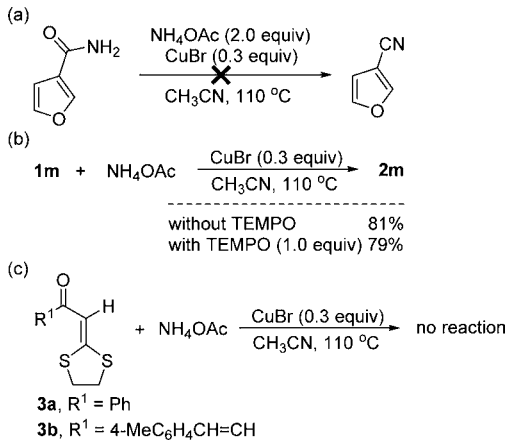
In order to gain some insight into this transformation, a series of control experiments were conducted. The amide could not transform into a nitrile under the standard reaction conditions (Scheme 3a). This result ruled out the possibility of

Scheme 2. Scope of α-Acyl-α-alkynyl Ketene Dithioacetals[a]



[a]Reaction conditions: A mixture of **1** (0.2 mmol), NH_4OAc (0.4 mmol), and CuBr (0.06 mmol, 0.3 equiv) in MeCN (2.0 mL) was stirred at 110 °C for 5–12 h. The yields are for the isolated products.

Scheme 3. Control Experiments



an amide as the intermediate in this procedure. Addition of 1 equiv of tetramethylpiperidine-1-oxyl (TEMPO) had almost no effect on the reaction, indicating that a radical process might not be involved (Scheme 3b). The reactions of **3a** and **3b**[12] with ammonium acetate failed to afford 1,4-addition products under the standard reaction conditions. This result suggested that the transformation might not be triggered by the 1,4-addition of ammonium acetate (Scheme 3c).

On the basis of the above-mentioned experimental results and previous reports,[10] a plausible mechanism is proposed in Scheme 4. The simultaneous coordination of the triple bond and sulfur atom of α-acyl-α-alkynyl ketene dithioacetals to a copper(I) catalyst enhances the electrophilicity of the triple

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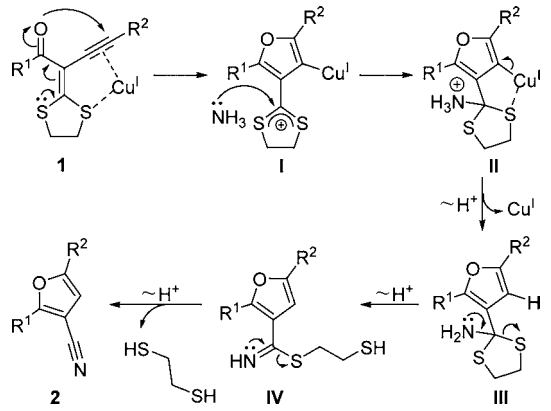
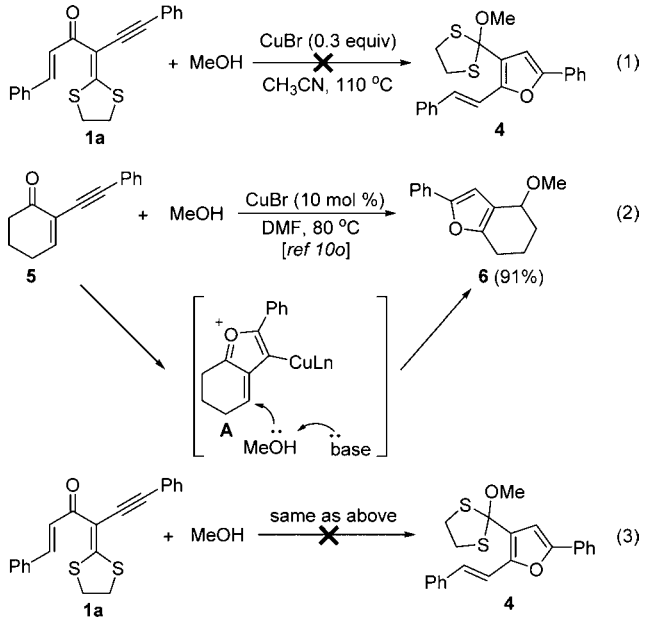
Scheme 4. Proposed Plausible Mechanism for the Copper-Catalyzed Cyclization of α-Acyl-α-alkynyl Ketene Dithioacetals



bond,[10o,13] and subsequent nucleophilic attack of the carbonyl oxygen on the electron-deficient triple bond generates the thionium ion intermediate **I** (or the sulfur-stabilized carbocation intermediate).[10] Afterward, the intermolecular nucleophilic attack of ammonia on the carbon atom of thionium **I** and subsequent protonation of the carbon−copper bond afford intermediate **III** and regenerate the copper(I) catalyst. Finally, tandem cleavage of the two carbon−sulfur bonds takes place to give the final product.[14]

While alcohol nucleophiles were being investigated, the reaction of **1a** with MeOH was carried out under the optimal reaction conditions (eq 1). A mixture of unidentified



compounds was produced, and no corresponding furan **4** was observed. It has been reported that copper(I) can catalyze the cyclization of **5** with MeOH in DMF to form furan **6** via the oxonium ion intermediate **A** (eq 2).[10o] The use of DMF, which acts as a Lewis base to deprotonate a proton of methanol, is essential for the reaction. However, under the same conditions as mentioned above, when the reaction of **1a** with MeOH was performed in DMF, no reaction occurred (eq 3). These comparative results can be explained simply by the theory of "hard and soft" nucleo- and electrophiles.[15] The thionium ion intermediate **I** is considered to be a "softer" electrophile than the oxonium ion intermediate **A** owing to the carbocation stabilization by two sulfur atoms. Therefore, the oxygen of the alcohol, being more electronegative than nitrogen, unfavorably attacks as a relatively "harder" nucleophile onto the soft electrophilic thionium ion intermediate **I**.

In summary, we have illustrated the first Cu-catalyzed cyclization of α-acyl-α-alkynyl ketene dithioacetals by in situ forming a "CN" unit in the product using ammonium acetate as the nitrogen source. This method proceeds through a sequential cyclization and triple C−N bond formation cascade and provides a valuable one-pot assembly of 3-cyanofurans from a broad range of α-acyl-α-alkynyl ketene dithioacetals with excellent yields and functional group tolerance.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00785.

Full experimental and characterization data for all compounds (PDF)

Crystallographic data for **2i** (CIF)

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Notes

The authors declare no competing financial interest.

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