Organic LETTERS

Letter

pubs.acs.org/OrgLett

Method for Direct Synthesis of α-Cyanomethyl-β-dicarbonyl Compounds with Acetonitrile and 1,3-Dicarbonyls

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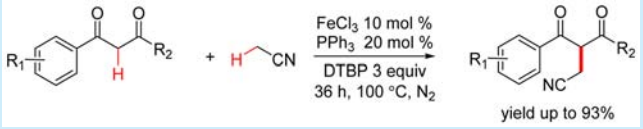
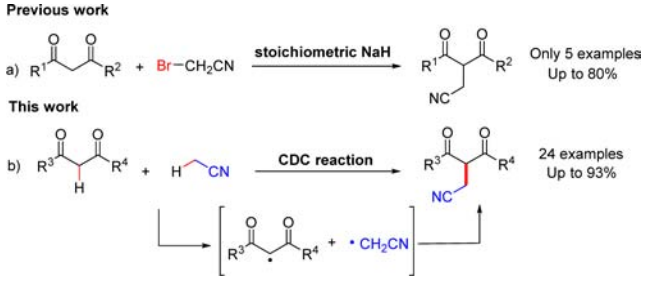
Supporting Information

ABSTRACT: A novel and efficient method for the synthesis of α-cyanomethyl-β-dicarbonyls in moderate to excellent yields is developed by using inactive CH_3CN and simple 1,3-dicarbonyls. A radical mechanism is proposed under the ESI-MS (electrospray ionization mass spectrometry) analysis results of control experiments.



Compounds, containing cyanoalkyl fragments, could be widely found in natural products and pharmaceuticals.[1] These derivatives are not only used as the target products but also for the synthesis of heterocycles, amines, carbonyl acids, etc.[2] Besides the potential applications in medicine and organic synthesis,[3] 1,3-diketones with a cyanoalkyl moiety (α-cyanomethyl-β-dicarbonyls) might be employed in metal complexation and "host−guest" chemistry. Despite these attractive properties of cyanomethyl dicarbonyls, its synthetic method is not well investigated. To the best of our knowledge, only one method exists so far, alkylation of β-dicarbonyl compounds with prefunctionalized cyanomethyl halogenides in the presence of stoichiometric strong base,[3a,4] which could be a major obstacle to studying such substances (Scheme 1, a).

Scheme 1. Synthetic Method of α-Cyanomethyl-β-dicarbonyl Compounds



Recently, the radical-mediated cross-dehydrogenative-coupling (CDC) reaction has been a useful tool for realizing the direct allylation,[5] carboxylation,[6] and heteroarylation[7] of β-dicarbonyl compounds to construct the C−C bond via atom-economic and environmentally friendly procedure. The studies of alkylation on the α-position were only limited to the coupling with cycloalkanes,[8] (cyclo)ethers,[9] and benzylic compounds.[10] On the other hand, some reports demonstrated that α-cyano carbon-centered radicals could be generated by peroxides, metal complexes, or visible light[11] using inactive alkyl nitriles. To date, a number of biologically active compounds have been synthesized via the addition of these active α-cyano carbon-centered radicals.[11n,k,p] Based on the inspiring results reported herein, we report a convenient and efficient direct cyanomethylation on the α-position of β-dicarbonyls using unsubstituted acetonitrile via Fe-catalyzed radical CDC reaction.

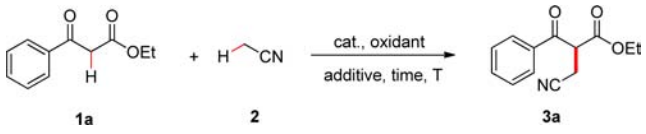
Initially, the model reaction of ethyl benzoylacetate (**1a**) with acetonitrile (**2**) could be carried out in the presence of $Fe_2(CO)_9$, PPh_3, and di-*tert*-butyl peroxide (DTBP) to give the desired product **3a** in 76% yield (Table 1, entry 1). Other tested iron salts such as $Fe(OAc)_2$, $Fe_2(acac)_3$, and $FeCl_2$ did not improve the reaction yield excluding $FeCl_3$ (Table 1, entries 2−5). No reaction occurred with TBHP, dicumyl peroxide, or $(NH_4)_2S_2O_8$ (Table 1, entries 6−8). The results showed that the PPh_3 ligand was necessary to optimize the reaction conditions (Table 1, entries 9−12). To our delight, the yield was increased to 88% when the catalyst loading was reduced to 10 mol % (Table 1, entry 13). A higher yield (93%) was obtained at 100 °C in 36 h (Table 1, entries 14 and 15).

Under the optimized reaction conditions, the scope and limitation of various β-dicarbonyls were investigated (Scheme 2). Generally, all tested ethyl benzoylacetates were able to tolerate this catalyzed system to afford the desired product **3a**−**p** in moderate to excellent yields. The product yields with *meta*-substituted ethyl benzoylacetates (**3a**−**i**) were higher than those with *para*-substituted ethyl benzoylacetates (**3k**−**n**), except **3j**. Because of the steric effect of ethyl *o*-methylbenzoylacetates, a trace amount of **3q** was formed. Although this catalytic system was incompatible with ethyl 3-(furan-2-yl)-3-oxopropanoate (**1s**), the ethyl 3-oxo-3-(thiophene-2-yl)propanoate could react with CH_3CN to give **3r** in 54% yield. When the substituent group of the ester fragment

Received: June 28, 2016
Published: August 11, 2016

DOI: 10.1021/acs.orglett.6b01871
Org. Lett. 2016, 18, 4151−4153

Table 1. Optimization of the Reaction Conditions[a]



1a 2 3a

entry	catalyst	oxidant	additive	yield[b] (%)
1	$Fe_2(CO)_9$	DTBP	PPh_3	76
2	$Fe(OAc)_2$	DTBP	PPh_3	71
3	$Fe_2(acac)_2$	DTBP	PPh_3	58
4	$FeCl_2$	DTBP	PPh_3	60
5	$FeCl_3$	DTBP	PPh_3	81
6	$FeCl_3$	TBHP	PPh_3	trace
7	$FeCl_3$	dicumyl peroxide	PPh_3	trace
8	$FeCl_3$	$(NH_4)_2S_2O_8$	PPh_3	trace
9	$FeCl_3$	DTBP		65
10	$FeCl_3$	DTBP	4,4′-bipyridine	34
11	$FeCl_3$	DTBP	bis(diphenyl-phosphno) methane	42
12	$FeCl_3$	DTBP	1,10-phenanthroline hydrate	34
13	$FeCl_3$	DTBP	PPh_3	88[c]
14	$FeCl_3$	DTBP	PPh_3	89[d]
15	**$FeCl_3$**	**DTBP**	**PPh_3**	**93**[e]

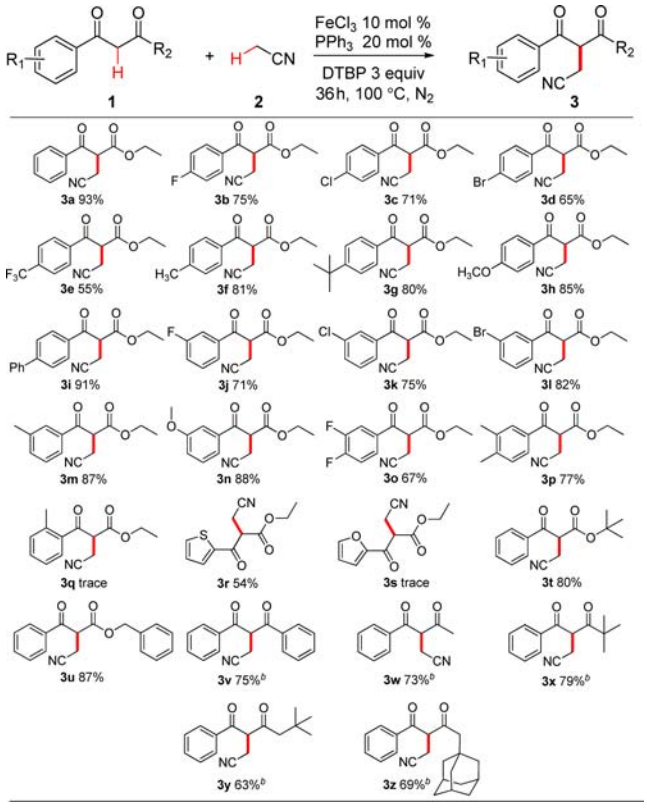
[a]Reaction conditions: **1a** (0.25 mmol), catalyst (20 mol %), additive (20 mol %), oxidant (3 equiv), CH_3CN (2 mL) in a sealed tube under N_2 at 100 °C (oil bath) for 24 h. [b]Isolated yield. [c]10 mol % of $FeCl_3$. [d]120 °C. [e]36 h.

was changed to *tert*-butyl or benzyl, the corresponding products **3t** and **3u** could be also prepared in good yields. In addition, the reaction with diketones **1v**–**z** were carried out only at 120 °C to afford products **3v**–**z** in moderate yields.

Subsequently, several controlled experiments were investigated to gain insights on this transformation (Scheme 3). The result of the intermolecular competing kinetic isotope effect (KIE) study (K_H/K_D = 8.9 for acetonitrile and K_H/K_D = 9.0 for dicarbonyl **1a**) suggested that the rate-determining step was the Csp^3–H bond cleavage of acetonitrile and dicarbonyls (Scheme 3, eq I). The reaction was completely quenched with the radical scavenger 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) or butylated hydroxytoluene (BHT). Under the standard conditions in the presence of BHT for 1 h, two strong molecular ion peaks (m/z = 260.2011 and 433.2351) were detected by ESI-MS (electrospray ionization mass spectrometry) and attributed to $[BHT\text{-}\mathbf{2} + H]^+$ (exact mass: 260.2009) and $[BHT\text{-}\mathbf{1a} + H]^+$ (exact mass 433.2349). In addition, we found another one (m/z = 131.9297) from the reaction with TEMPO, which could be attributed to $[ClFeCH_2CN + H]^+$ (exact mass 131.9298) (Scheme 3, eq II). Although no product **3a** was isolated in the absence of DTBP, a small amount of α-cyanomethyl dicarbonyl **3a** (37%) was obtained under standard condition without $FeCl_3$. These results indicated the following: (i) the free radicals might be involved in this process, and the premier (t-BuO$^\bullet$) radical could be obtained from the decomposition of DTBP; (ii) the complex $Cl–Fe^{II}–CH_2CN$ might be the active catalytic species for this conversion; (iii) only a small amount of **3a** generated via the coupling of radicals **A** and **B**, and this way was not the main synthesis path of product **3a**.

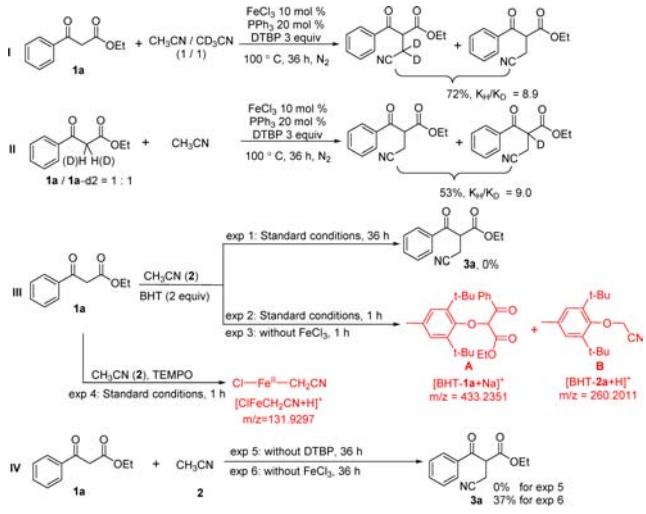
On the basis of the above results and literature precedent,[5−11] a tentative mechanism for the novel cyanomethylation of β-dicarbonyls is proposed in Scheme 4. Initially, the radical initiator DTBP produced the premier radical (t-BuO$^\bullet$). Subsequently, t-BuO$^\bullet$ could be used to generate the Fe(II) species **E** and radicals **A** and **B**. Then, the cyanomethylation proceeded as follows: (a) radicals **A** and **B** might direct react with each other to afford **3a**; (b) radical **B** attacked Fe(III) enolate **C** to afford the radical **D** which released Fe(II) species to give **3a**; (c) after homolytic cleavage of Fe(II)–C bond (**E**), the obtained cyanomethyl radical **B** might be involved in path

Scheme 2. Fe-Catalyzed Radical CDC Reaction of Acetonitrile with 1,3-Dicarbonyls



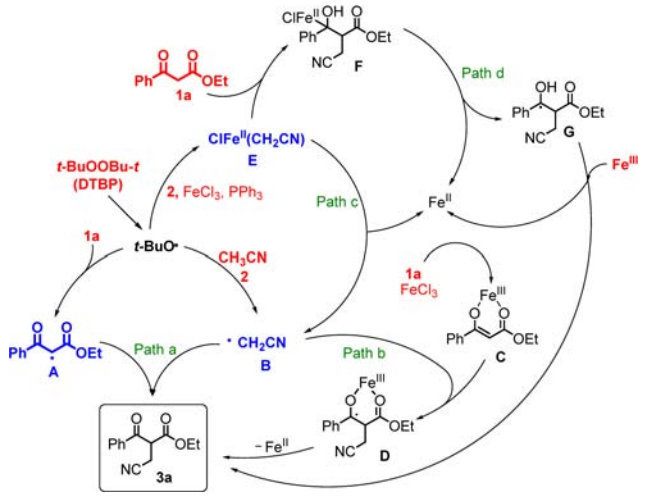
[a]Reaction conditions: **1a** (0.25 mmol), catalyst (10 mol %), additive (20 mol %), oxidant (3 equiv), CH_3CN (2 mL) in a sealed tube under N_2 at 100 °C (oil bath) for 36 h. [b]120 °C.

Scheme 3. Mechanistic Studies



DOI: 10.1021/acs.orglett.6b01871
Org. Lett. 2016, 18, 4151−4153

Scheme 4. Proposed Reaction Mechanism



b; (d) through a nucleophilic attack of **1a** on Fe(II) complex **E**, the intermediate **F** could also proceed homolytic cleavage to form radical **G**. After that, radical **G** was oxidized by Fe(III) to transform **3a** and Fe(II). Finally, all released Fe(II) species were oxidized by DTBP for further cycles.

In summary, we have reported a simple and efficient Fe-catalyzed CDC reaction of 1,3-dicarbonyls with inactivated acetonitrile for the preparation of α-cyanomethyl-β-dicarbonyls. Various 1,3-dicarbonyls were well tolerated in this methodology to give the corresponding desired products in moderate to excellent yields. Based on the control experiments, we propose that the transformation might proceed via a radical process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01871.

Detailed experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation (NSF) of China (21172200 and 21302172).

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DOI: 10.1021/acs.orglett.6b01871
Org. Lett. 2016, 18, 4151−4153