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ARTICLE TYPE

A Radical-Promoted Site-Specific Cross Dehydrogenative Coupling of Heterocycles with Nitriles

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A first free-radical triggered site-specific cross dehydrogenative coupling reaction of heterocycles with simple nitriles is developed. It allows efficient and facile access to various C-2 cyanoalkylated furans, thiophenes, indoles, and pyrroles. The extremely high selectivities in this case indicate that functionalization of inert C-H bond could be well-controlled by radical initiation.

One C-C bond formation via cleavage of dual C-H bonds, also named cross-dehydrogenative coupling (CDC),[1] represents the most atom-economic, clean, and efficient strategies in synthetic organic chemistry. In the past decades, considerable developments in transition-metal-catalyzed (sp^2)C-H functionalization has been achieved.[2-3] However, it remains challenging to functionalize an inert (sp^3)C-H bond.[4] Hence, exploration of highly efficient methods for dehydrogenative C-C bond construction via direct (sp^3)C-H functionalization is highly desirable.[5]

Cyano is a versatile functional group in organic synthesis, which can be facilely converted into the corresponding carboxylic acid, amide, and amine. Especially, heterocycles bearing those functional groups are widely found in pharmaceuticals and natural products (Figure 1). Introduction of cyano group by selective functionalization of the *α*-cyano C-H of simple aliphatic nitrile is one of the most environmentally benign, safe, and low-toxic methods.[6] Two main strategies for this transformation have been studied in the past decades. One is polar reaction of electrophile with the enolate form of nitrile under strong base conditions.[7] The other is hydrogen-atom-transfer (HAT) pathway, which can be applied in cyanoalkylation of molecules other than that limited to electrophiles. As demonstrated in Scheme 1, although the bond dissociation energy (BDE) gap of the C-H bonds is less than 5 kcal/mol,[8] the α-cyano C-centered radical would be generated prior to others. The delocalization of electrons in single occupied molecular orbital (SOMO) and π orbital could stabilize the (*α*-CN) C-centered radical.

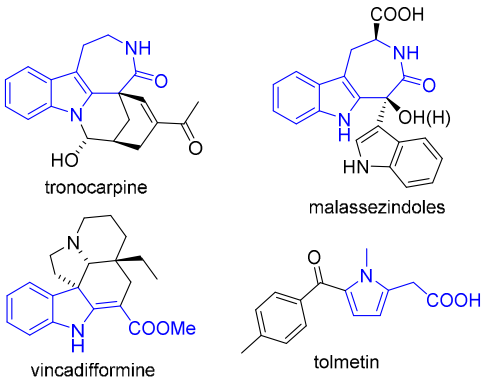
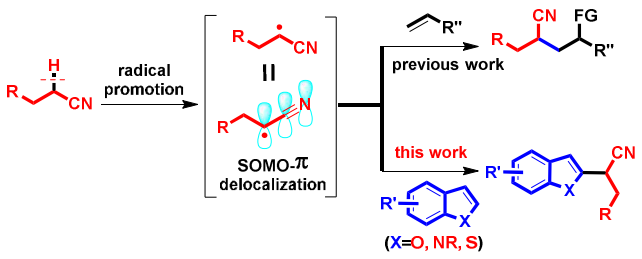


Figure 1 C2-cyanoalkylated heterocycles derivative pharmaceuticals and natural products.

Previous studies focus on atom-transfer radical addition (ATRA) reactions of simple nitriles with olefins.[9] For example, radical reactions of nitriles with a series of activated alkenes such as *N*-aryl methacrylamides,[10] styrenes,[11] and allylic alcohols[12] etc. In 2013, Yoshida et al reported a Pd/TiO_2-promoted dehydrogenative radical coupling of acetonitrile with benzene under photo-irradiation.[13] Very recently, we reported an ATRA reaction of nitrile with unactivated alkene, which allowed convenient access to alkyl nitriles.[14] Of particular interest are free-radical initiated C-C bond formation by selective functionalization of inert C-H bonds.[15] We began to wonder whether other types of radical reactions of simple nitriles could be realized. Fortunately, we successfully accomplished a radical CDC reaction of aliphatic nitrile with heterocycle. It represents the first example, to the best of our knowledge, of dehydrogenative C-C formation by using heterocycle with alkyl nitrile (Scheme 1).



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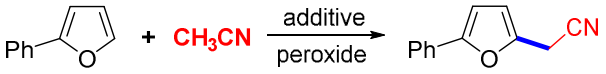
Scheme 1. Radical-Triggered Functionalization of Aliphatic Nitrile.

Considering that the α-cyano C-centered radical should be electrophilic, electron-rich heterocycles were chosen as substrates to modify the reaction conditions (Table 1). Over 60 reactions of 2-phenylfuran with acetonitrile were carried out (see SI). We found that additive and peroxide are important to this system. No desired product was obtained by using *tert*-butyl-hydroperoxide (TBHP), di-*tert*-butyl peroxide (DTBP), and benzoyl peroxide (BPO) etc (entries 1-2). But promoted by CuI, bis(4-*t*-butyl cyclohexyl)peroxy dicarbonate (TBCP) and *tert*-butyl-peroxybenzoate (TBPB) gave the products in 29% and 39% yields, respectively (entries 3-4). Dicumyl peroxide (DCP) raised the yield up to 52% (entries 5-7). Then a series of additives were screened (entries 8-11). CuCl was found to be also effective to this transformation. Finally, although moderate yield of the desired product can be isolated, the regio-selectivity is surprisingly high. No isomer is detected by NMR.

Table 1. Modification of the typical reaction conditions. [a]

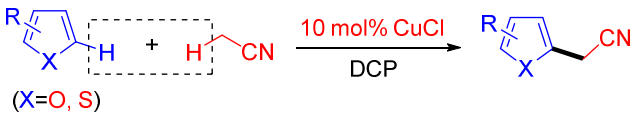


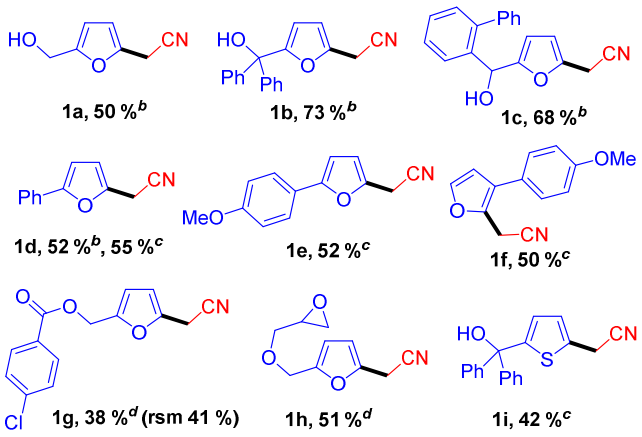
entry	additive	peroxide	CH_3CN (mL)	yield (%)[b]
1	CuI	TBHP	5	-
2	CuI	DTBP	5	-
3	CuI	TBCP	5	29
4	CuI	TBPB	5	39
5	CuI	DCP	5	40
6	CuI	DCP	3	26
7	**CuI**	**DCP**	**7**	**52**
8	CuBr	DCP	7	42
9	**CuCl**	**DCP**	**7**	**53**
10	$FeCl_2$	DCP	7	35
11[c]	**CuCl**	**DCP**	**7**	**55**

[a] Reaction conditions: 2-phenylfuran (1 equiv, 0.20 mmol), additive (10 mol%), peroxide (3 equiv), acetonitrile as solvent, N_2, sealed tube, 110 °C, 12 h, unless otherwise noted. [b] Isolated yields. [c] 115 °C.

As shown in **Table 2**, C-2 cyanoalkylation of various furans and thiophenes was achieved. A wide range of functional groups such as hydroxyl, electron-rich aryl, ester, as well as epoxyl can be well-survived. Surprisingly, **1f** was isolated as the only product and no C-5 cyanoalkylated compound was detected. The stability of the radical intermediate might critically contribute to the selectivity prior to the steric effect.

Table 2. Radical CDC reaction of acetonitrile with furans and thiophenes.[a]





[a] Reaction conditions: heterocycle (1 equiv, 0.20 mmol), additive (10 mol%), DCP (3 equiv), acetonitrile (7 mL) as solvent, N_2, sealed tube, 12 h, isolated yields, unless otherwise noted. [b] additive: CuI, 110 °C; [c] additive: CuCl, 115 °C; [d] additive: CuCl (20 mol%), DCP (6 equiv), 115 °C.

It can be seen from **Table 3** that a wide range of *N*-heterocycles such as indoles and pyrroles are amenable to this system. 1-Methyl-1*H*-indole gave 36% yield of the desired product (**2a**) under condition b (10 mol% CuI, 110 °C). Under conditions c (10 mol% CuCl, 115 °C) and d (10 mol% CuCl, 130 °C), **2a** was isolated in 40% and 65% yields, respectively. Moderate to good yields of the cyanomethylated products were isolated with 1,n-dimethyl-1*H*-indoles (**2b-2e**). 1,3-Dimethyl-1*H*-indole led to product in a relatively high yield, which might be due to formation of a tertiary radical intermediate. In addition, moderate yield of products were obtained with halogenated 1-methyl-1*H*-indoles (F, Cl, Br) (**2f-2h**). 1-Methyl-1*H*-indoles bearing electron-withdrawing groups such as $-CO_2Me$ also gave moderate yield of the corresponding product (**2i**). And 1-methyl tryptophols with hydroxyl protection produced the desired products in moderate yields (**2j** and **2k**). 1-Methyl indoles with both e-withdrawing and e-donating substituents in C-3 position gave good isolated yield of cyanoalkylated products (**2l** and **2m**). It suggests that the stability of the radical intermediate might affect the efficiency of the reaction more critical over the electronic effect. Gratifyingly, 1-ethyl-1*H*-indoles and 1-(1*H*-indol-1-yl)ethanone are also amenable to this reaction despite of relatively low efficiency (**2n** and **2o**). Furthermore, other *N*-heterocycles were screened. A mixture of C-2 and C-3 cyanoalkylation isomers were obtained with a ratio of 7/1 with 1-methyl-1*H*-pyrrolo[2,3-b]pyridine (**2p**). Several substituted pyrroles were proved to be effective substrates in this system (**2q-2t**). Interestingly, a *t*-butyloxy carbonyl (Boc-) cleavage product (**2s'**) was isolated with *tert*-butyl 2-(4-methoxyphenyl)-1*H*-pyrrole-1-carboxylate (**2s**). Finally, butyronitrile also gave the desired α-cyano C-C bond forming product without detection of any other isomer (**2t**).

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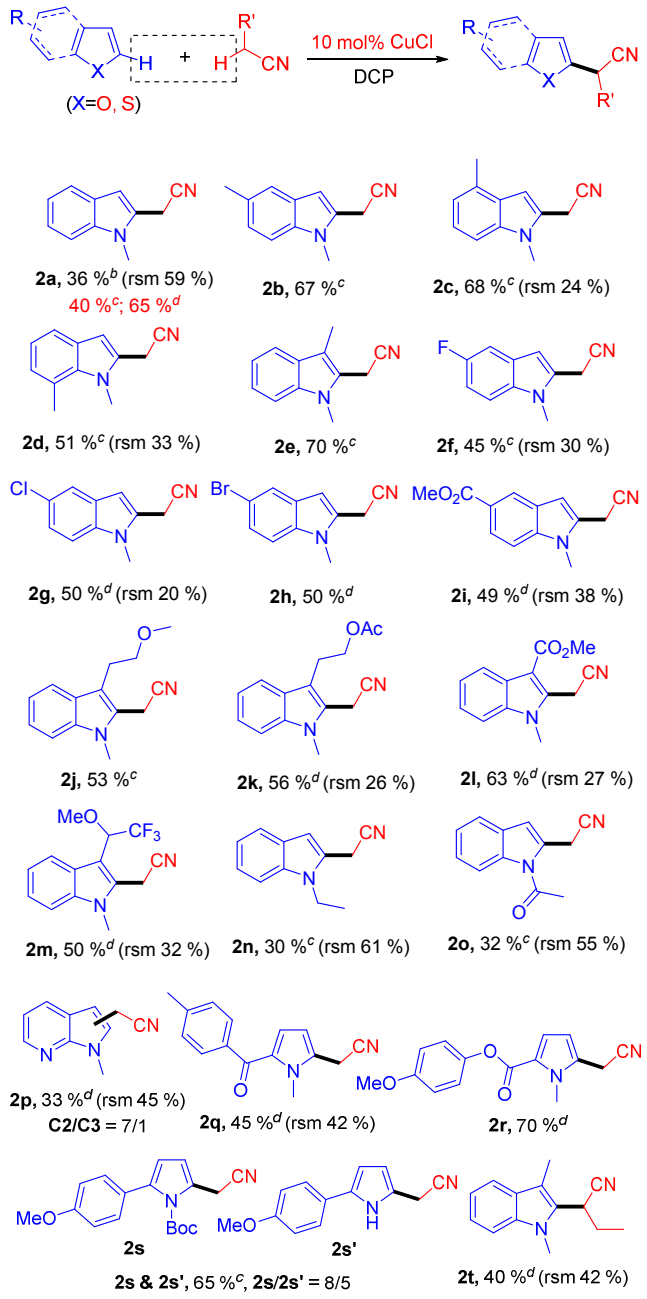
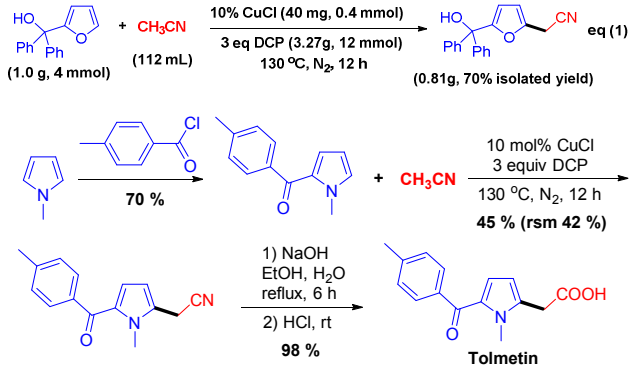
Table 3. Radical CDC reaction of nitrile with *N*-heterocycles.[a]



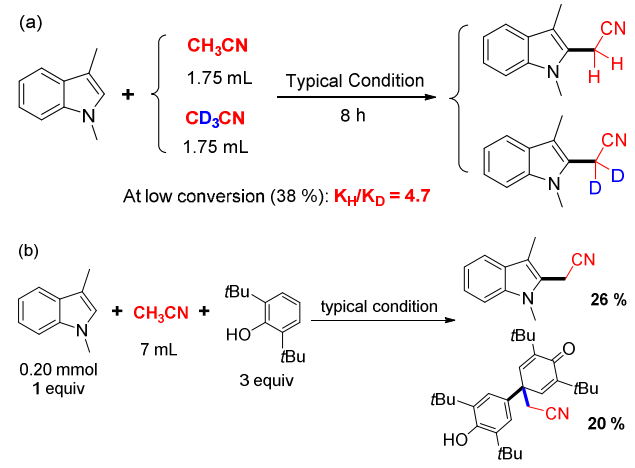
[a] Reaction conditions: heterocycle (1 equiv, 0.20 mmol), additive (10 mol%), DCP (3 equiv), acetonitrile (7 mL) as solvent, N_2, sealed tube, 12 h, isolated yields, unless otherwise noted. [b] additive: CuI, 110 °C; [c] additive: CuCl, 115 °C; [d] additive: CuCl, 130 °C.

Large scale experiment shows that this reaction could be conveniently scaled-up to gram level (eq 1). Moreover, this strategy could be applied in preparation of some pharmaceuticals. For example, as depicted in Scheme 2, Tolmetin, a non-steroidal anti-inflammatory drug, can be efficiently formed by this approach. It is more step-economic and safer than previous protocols.[16]



Scheme 2. Synthesis of Tolmetin by using this strategy.

To get insight into the mechanism, a set of experiments were carried out (Scheme 3). An intermolecular competing kinetic isotope effect (KIE) via NMR integration measurement was investigated, and it was found that the initial KIE is significant (K_H/K_D = 4.7). It indicates that cleavage of the α-cyano C_{sp3}-H bond might be involved in the rate-determining step (Scheme 3a). Additionally, a radical trapping experiment using 2,6-di-*tert*-butylphenol was also carried out (Scheme 3b). As a result, only 26% yield of **2e** was generated, which is much lower than before. In addition, a radical adduct 2-(3,3',5,5'-tetra-*tert*-butyl-4'-hydroxy-4-oxo-1,4-dihydro-[1,1'-biphenyl]-1-yl)acetonitrile was isolated in 20% yield, which suggests that the α-cyano methylenyl radical intermediate should be formed in this system.



Scheme 3. Mechanistic studies.

Based on the experimental results and the literature precedent,[17] a plausible radical addition/elimination pathway is proposed in Scheme 4. Initially, one electron oxidation of Cu(I) by DCP produces Cu(II), *t*-BuO$^-$ anion, acetophenone, and methyl radical. Subsequently, HAT from nitrile to methyl radical generates CH_4 and α-cyano methylenyl radical intermediate **A** (not **A'**), which adds to heterocycle leading to radical **B** (not **B'**). Next there are two main possible pathways leading to the final product. One might be a radical anion **C** and *t*-BuOH formed via deprotonation of **B** by *t*-BuO$^-$ anion.[17a] And then single electron oxidation of the radical anion again by DCP affords the product and regenerates the methyl radical. The other might be direct HAT from radical **B** by methyl radical giving the final product.

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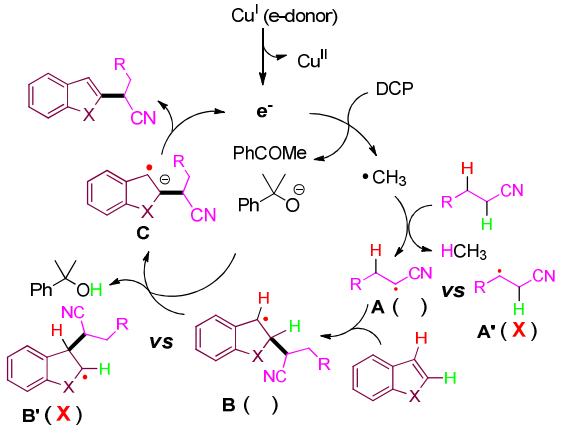

Scheme 4. Suggested mechanism.

In summary, a free-radical-triggered CDC reaction of heterocycles with simple nitriles is developed. Through this novel strategy, a wide range of C-2 cyanoalkylated heterocycles such as furan, thiophene, indole, and pyrrole can be synthesized site-specifically. This example further shows that highly selective functionalization of inert C-H bond can be achieved and well-controlled by radical promotion in some cases.

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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