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ARTICLE TYPE

Fe-promoted radical cyanomethylation/arylation of arylacrylamides to access oxindoles via cleavage of the sp^3 C–H of acetonitrile and the sp^2 C–H of phenyl group

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Radical cyanomethylation/arylation of arylacrylamides to access oxindoles by acetonitrile as the radical precursor is discribed. This reaction involved dual C–H bonds functionalization, including the sp^3 C–H of acetonitrile and the sp^2 C–H of phenyl group. A variety of functional groups, such as methoxy, ethyloxy carbonyl, chloro, bromo, iodo, nitro, trifluoromethoxy and trifluoromethyl groups are tolerated well.

The difunctionalization of activated alkenes has emerged as a powerful strategy in organic synthesis.[1] Recently, this strategy was applied for the synthesis of functionalized oxindoles by oxidative C–H functionalization/carbocyclization of N-arylacrylamides. Generally, there are two pathways for this transformation. The first is palladium-catalyzed cyclizations of N-arylacrylamides with different nucleophiles.[2] Another pathway is radical-initiated cyclizations with different radical precursors.[3] Very recently, radical oxidative 1,2-alkylarylation of N-arylacrylamides with an alkyl radical that formed from the cleavage of sp^3 C–H in the presence of radical initiator was developed but still less. For example, Li explored an iron-catalyzed oxidative alkylarylation of N-arylacrylamides with a sp^3 C–H bond adjacent to a heteroatom and an aryl sp^2 C–H.[4] Duan and Li reported the Cu-catalyzed and $IrCl_3$ facilitated 1,2-benzylarylation of N-arylacrylamides with benzylic sp^3 C–H bond and aryl sp^2 C–H bond, respectively.[5] Liu described a Cu-catalyzed oxidative alkylarylation of acrylamides with simple alkanes.[6]

The formations of L_nM-CH_2CN complexes by stoichiometric amounts of a transition metal (M = Rh, Ni, Ru etc.) to activate the sp^3 C–H bond of acetonitrile have been documented.[7] Recently, Pd-catalyzed the sp^3 C-H bond cleavage of acetonitrile was also developed.[2a,8] However, to the best of our knowledge, the sp^3 C–H bond cleavage of acetonitrile through the radical pathway is less reported.[9] Herein, we report a novel Fe-promoted cyanomethylation/arylation of arylacrylamides with acetonitrile to access oxindoles through a radical-type pathway (Scheme 1).

Recently, we reported the alkylarylation[10] and trifluoromethylation/arylation[11] of *N*-arylacrylamides by visible-light photoredox catalysis. Based on our interest in difunctionalization of *N*-arylacrylamide, initially, we examined the reaction of *N*-methyl-*N*-phenylmethacrylamide (**1a**) with CH_3CN in the presence of radical initiator such as DTBP, TBHP and BPO at 120 °C. To our delight, the desired product 3-(1,3-dimethyl-2-oxoindolin-3-yl)propanenitrile **3aa** was obtained in 21% yield in the presence of DTBP (Table 1, entry 1), along with byproduct **5aa** by carbomethylation of phenylacrylamide. Then, we attempted to promote the yield by adding some metal such as $FeCl_3$, $FeCl_2$, $Fe(acac)_2$, and CuI. To our delight, the yield was increased to 78% when 5 mol % of $Fe(acac)_2$ was subjected to the procedure (Table 1, entry 6).

Scheme 1. Radical cyanomethylation/arylation of arylacrylamide

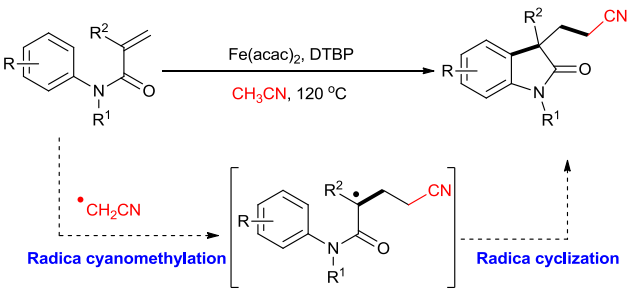
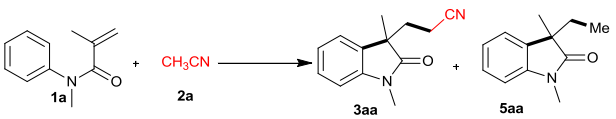


Table 1. Screening the optimal conditions.



Entry	[M]	radical initiator	Yield (%)[a]
1	---	DTBP	**3aa/5aa** = 21/18
2	---	TBHP	0
3	---	BPO	trace
4	$FeCl_2$	DTBP	**3aa/5aa** = 60/12
5	$FeCl_3$	DTBP	**3aa/5aa** = 52/15
6	**$Fe(acac)_2$**	**DTBP**	**3aa/5aa = 78/10**
7	$Cu(OAc)_2$	DTBP	trace
8	CuI	DTBP	trace
9	$Fe(acac)_2$	DTBP	0[b]

[a] Reaction conditions: **1a** (0.2 mmol), [M] (5 mol %), radical initiator (0.6 mmol) and **2a** (2 mL) under air for 12 h at 120 °C. TBHP = 70% solution in water. DTBP = di-*tert*-butyl peroxide. BPO = benzoyl peroxide. [b] 80 °C.

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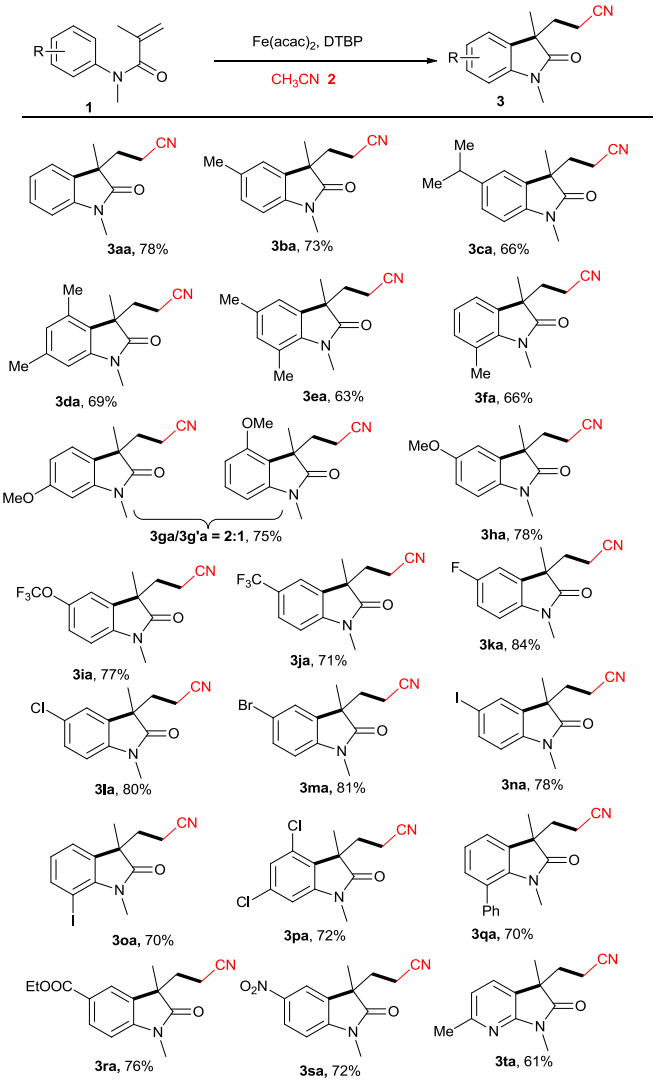
With the optimized reaction conditions in hand, we attempted to investigate the scope of *N*-arylacrylamides. As shown in Table 2, electron-donating groups such as methoxy and methyl as well as electron-withdrawing groups such as chloro, bromo, iodo, ethyloxy carbonyl, nitro, trifluoromethoxy and trifluoromethyl were tolerated well on the aryl rings, affording the products in good yields. Notably, halogen group (F, Cl, Br, I) in the oxindoles offers the potential further transformation by cross-coupling reactions. Steric hindrance on the aryl rings had some effect on the reaction. For example, arylacrylamides with *ortho* substituents such as **1e**-**1f** performed less reactive. To investigate the regioselectivity of the cyclization, a mixture of two expected regioisomers (**3ga**/**3g'a** = 2:1) was obtained for *meta*-substituted arylacrylamide **1g**. Importantly, the pyridine group was also suitable for this transformation, providing the product **3ta** in moderate yield.

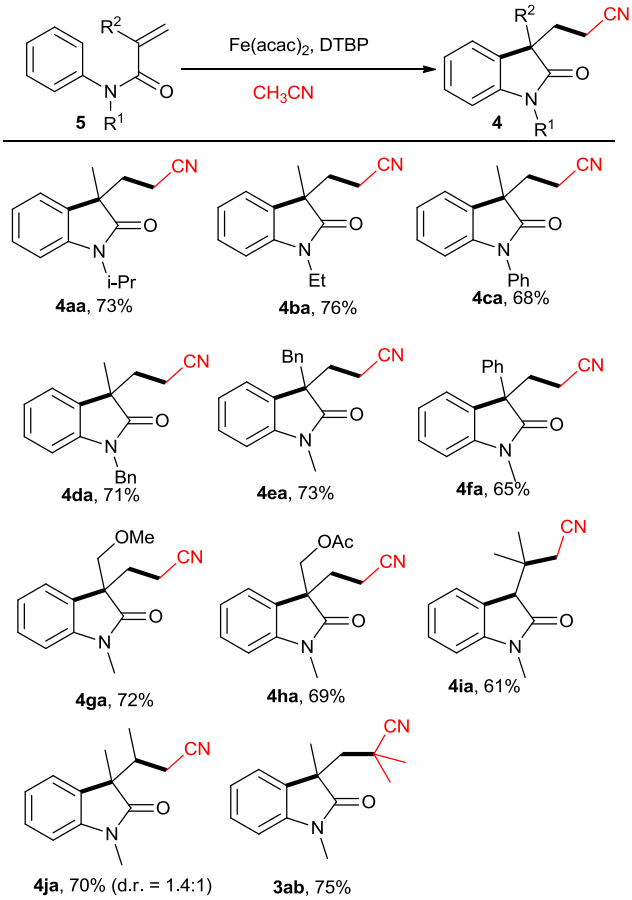
Table 2. Scope of arylacrylamides



Reaction conditions: **1a** (0.2 mmol), $Fe(acac)_2$ (5 mol %), DTBP (0.6 mmol) and **2a** (2 mL) under air for 12 h at 120 °C.

The effect of the protecting group on the nitrogen atom was investiged. The substrates bearing an alkyl on N atom (**4aa**-**4ba,** Table 3) proceeded higher yields than the substrate with aryl group on N atom (**4ca**). Substrates with various olefins were also examined. For substrates without a substituent at the α position (R_2=H) of the olefin, the desired product was not obtained. Substrates with benzyl, methoxymethyl, acetoxymethyl and phenyl groups at the α position afforded the products **4ea**–**4ha** in moderate yields. Substrates with trisubstituted olefins also provided the corresponding products in moderate yields (**4ia**-**4ja**). Notably, isobutyronitrile (**2b**) was also good partner.

Table 3. Scope of other arylacrylamides



[a] Reaction conditions: **1a** (0.2 mmol), $Fe(acac)_2$ (5 mol %), DTBP (0.6 mmol) and **2** (2 mL) under air for 12 h at 120 °C.

To gain insight into the mechanism for this difunctionalization of arylacrylamides, some control experiments were conducted. Intramolecular and intermolecular experiments were carried out. The results demonstrated that there is no kinetic isotope effect in either intramolecular (k_H/k_D = 1.1) (Scheme 2, eq. 1) or intermolecular experiments (k_H/k_D= 1.0) (Scheme 2, eq. 2). When 2.0 equivalents of 2,2,6,6-tetramethylpiperidine oxide (TEMPO) was added as a radical inhibitor, no desired product was observed. The KIE result of the experiment between CH_3CN and CD_3CN (k_H/k_D = 3.5) and KIE (k_H/k_D = 2.9) of individual reaction in CH_3CN and CD_3CN indicated that the sp^3 C–H bond

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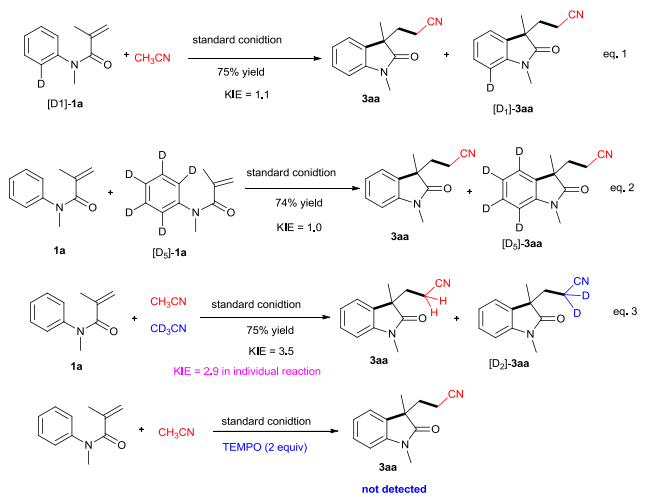
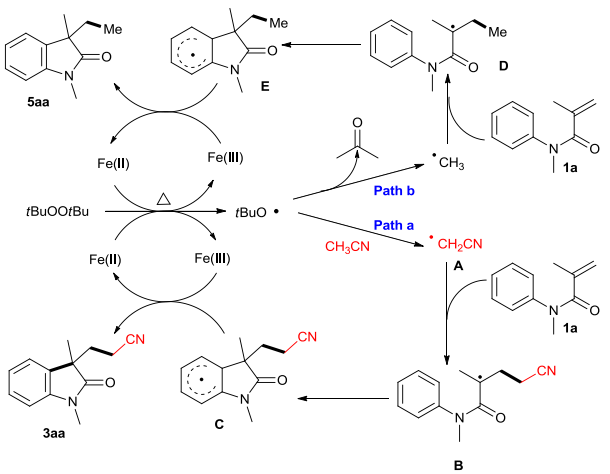
cleavage of acetonitrile is the rate-determining step (Scheme 2, eq. 3).[12]

Scheme 2. Preliminary mechanism studies



Based on the above experimental results, a possible mechanism (Scheme 3, Path a) is proposed. Initially, homolysis of DTBP is assisted by Fe(II) into a *tert*-butoxy radical and Fe(III).[13] CH_3CN is readily transformed into cyanomethyl radical **A** in the presence of a *tert*-butoxy radical. The addition of cyanomethyl radical **A** to arylacrylamide **1a** form the radical **B**, which occurs intramolecular cyclization to produce radical intermediate **C**. Finally, hydrogen abstraction of radical intermediate **C** by Fe(III) takes place to provide the product **3aa**. Path b provided the byproduct 3-ethyl-1,3-dimethylindolin-2-one **5aa** through radical carbomethylation of arylacrylamide.[14] The addition of the methyl radical which is generated from *tert*-butoxy radical by the loss of one equivalent of acetone to the arylacrylamide forms a radical species **D**, which occurs intramolecular cyclization to produce radical intermediate **E**. Finally, hydrogen abstraction of radical intermediate **E** by Fe(III) takes place to access the product **5aa**.

Scheme 3. Proposed mechanism



In conclusion, we have developed a radical cyanomethylation/arylation of arylacrylamides to access oxindoles by acetonitrile as the radical precursor. This reaction involved dual C–H bonds functionalization, including the sp^3 C–H of acetonitrile and the sp^2 C–H of phenyl group. The procedure was simple and tolerated a variety of functional groups, such as methoxy, ethyloxy carbonyl, chloro, bromo, iodo, nitro, trifluoromethoxy and trifluoromethyl groups.

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Notes and references

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