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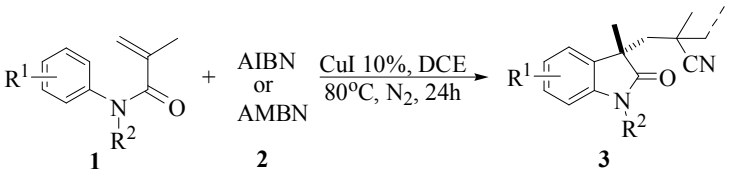
Graphical Abstract：



1 **2** **3**

R^1 = H, Me, Et, OMe, OCF_3, Br, F

R^2 = Me, Et, Phenyl, 4-Methylphenyl, 4-Methoxyphenyl

18 examples

50-99% yields

A CuI promoted radical addition/cyclization of azobisisobutyronitrile with alkenes for the preparation of 3-(2′-cyano alkyl) oxindoles was developed.

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ARTICLE TYPE

Copper Promoted radical addition/cyclization of Azobisisobutyronitrile with Arylacrylamides: a Convenient Process to Synthesize 3-(2´-cyano Alkyl) Oxindoles

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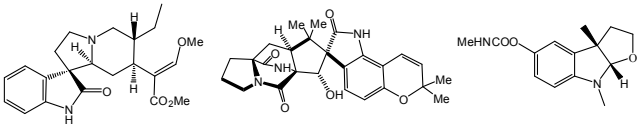
A CuI promoted radical addition/cyclization of azobisisobutyronitrile with alkenes was developed. The reaction provided a facile pathway for synthesis of 3-(2´-cyano alkyl) oxindoles. The cyano group is versatile for facile conversion into a diverse class of functionalities.

Oxindoles are important heterocycles found in a wide range of bioactive natural products and pharmaceutical molecules (Scheme1).[1] Recently, metal-catalyzed functionalization of arylacrylamides with various nucleophiles has drawn considerable attention, which promises a novel pathway for the synthesis of various functional oxindoles.[2] However, usually strong bases or ligands were needed in these reactions. Very recently, direct oxidative cyclization of phosphate,[3a] $TMSN_3$,[3b] $TMSCF_3$,[3c] $NaNO_2$,[3d] 1,3-dicarbonyl,[3e] aldehyde,[3f] $C(sp^3)$-H bond adjacent to a heteroatom,[3g] alkanes[3h] with arylacrylamides were investigated. Most of the protocols were suggested to undergo a cascade radical addition/cyclization pathway.



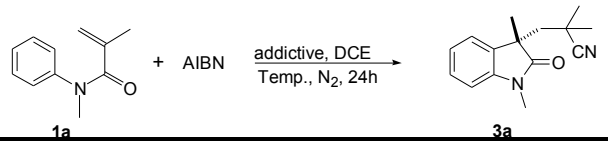
Scheme 1. Some natural products and biologically active reagents containing 3,3-disubstituted oxindole motif.

Free radical reactions have been extensively investigated as powerful and versatile methods for alkene functionalization and preparation of cyclic compounds.[4] 2,2-Azobisisobutyronitrile (AIBN), a well known radical initiator, usually accompany with Bu_3SnH, was widely utilized in free-radical-cycloaddition reactions.[5] For instance, five-membered α,β-unsaturated[6a] lactams, 4-aminopyrolidines[6b] were synthesized in this way. Despite the high activity, the application of AIBN as a substrate is really rare.

In 1981, the coupling of AIBN and aromatic N-oxides was reported.[7a] In 2001, the reaction between quinones and AIBN was studied.[7b] In 2013, Han group discovered a copper-mediated direct aryl C-H cyanation with AIBN.[7c] Recently, the copper catalized cascade radical reaction of AIBN with cinnamic acids was reported by Huang,[7d] which provided a new strategy for tuning the electron transfer between radicals and enolates. Owing to the great importance of alkyl nitriles either as a key building block in natural products and designed molecules or as a versatile latent group for facile conversion into a diverse class of functionalities (for example, RCOOH, $RCONH_2$, RCHO, RCH_2NH_2, RCN_4), the development of efficient methods for the synthesis of alkyl nitriles constitutes a continuing focus in synthetic organic chemistry.[8] Generally, as in S_N2 reaction and Michael addition reaction, electron-withdrawing group (such as -CN, -COOR, -COR) is needed in the α-position of nitrile group for the formation of alkyl nitriles. In 2011, Liu group tried oxidative difunctionalization of arylacrylamides with acetonitrile in the presence of AgF and $PhI(OPiv)_2$, giving the desired alkylization product.[9] Nevertheless, when iPrCN was tested, the corresponding product was not obtained. We envisaged that the highly active free radical generated by AIBN may react with arylacrylamides effectively and economically, resulting in 3-(2´-cyano alkyl) oxindole with two quaternary carbon center.

Herein, we report our study on the addition and cyclization of the *a*-cyanoalkyl radical with arylacrylamides. To explore the feasibility of our planned domino process, we first targeted the synthesis of **3a** from *N*-methyl-*N*-phenylmethacrylamide (**1a**) and AIBN. To our delight, the radical addition/cyclization cascade process can occur at 70 °C (Table 1, entry 1). The product **3a** was formed in 20% yield at 80 °C (Table 1, entry 2). Increasing the dosage of AIBN to 2 e.q. or 3 e.q., the desired product was isolated in 30% and 50% yields, respectively (Table 1, entries 3 and 4). The yield was further increased to 54% in the presence of 10 mol% $Pd(OAc)_2$, indicating that metal salt $Pd(OAc)_2$ can promote the reaction (Table 1, entry 5). So several metal salts, such as CuI, $Fe(acac)_3$, $AgNO_3$ were screened to enhance the yield of **3a** on this template reaction (Table 1, entry 6-8). Excitingly, the employment of CuI (10 mol%) had a strong effect on the reaction (Table 1, entry 6), providing 88% yield of product **3a** . The $Fe(acac)_3$ was also a very helpful catalyst (Table 1, entry 7). Yet the $AgNO_3$ was not helpful (Table 1, entry 8). In further exploration, when 0.5 e.q. CuI was added, the reaction did not perform better (Table 1, entry 9).

Table 1. Optimization of the Reaction Conditions.[a]

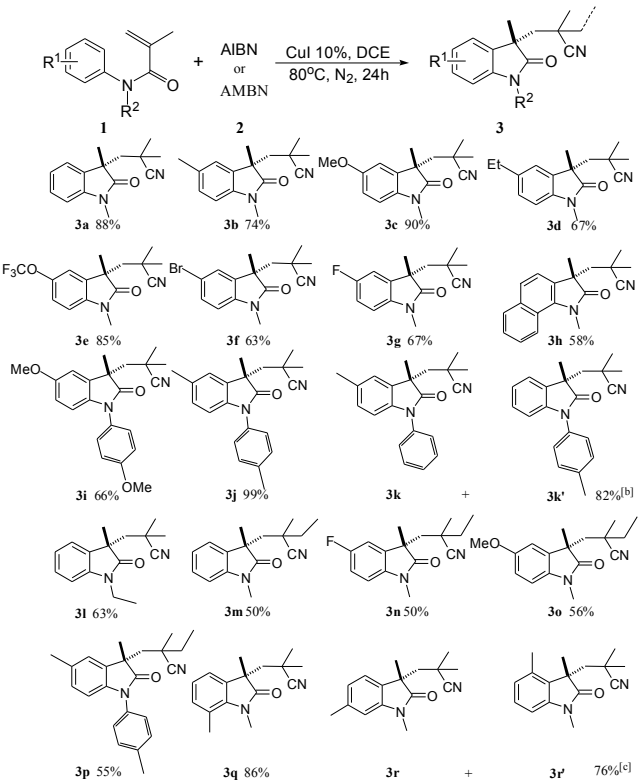


Entry	AIBN[e.q.]	Additives	Temp[°C]	Yield[%][b]
1	1.2	-	70	7
2	1.2	-	80	20
3	2	-	80	30
4	3	-	80	50
5	3	$Pd(OAc)_2$10%	80	54
6	**3**	**CuI 10%**	**80**	**88**
7	3	$Fe(acac)_3$10%	80	84
8	3	$AgNO_3$ 10%	80	45
9	2	CuI 50%	80	86

[a] Reaction conditions: substrate **1a** (0.5 mmol), additives and AIBN (dissolved in 1 mL DCE was added through micro injection pump) in DCE (1.0 mL) under N_2 atmosphere for 24 h. [b] Isolated Yield.

With the optimized reaction conditions in hand, the scope of substrates was investigated as shown in Scheme 2. Firstly, the effect of substituted groups on the aryl ring was probed. Both electron withdrawing and donating substituted substrates worked well to deliver the desired product in good to excellent yields. Comparatively the electron-deficient derivatives were somewhat less reactive (**3a**-**3g**). However, the yield of **3d** was relatively low (about 67%). Maybe the *p*-ethyl on the aryl ring participated competing reaction with the terminal alkene. In addition, the *ortho*- or *meta*-substituted substrates also reacted well (**3q**, **3r**). The reaction tolerated a series of functional groups, such as bromo-, fluoro- and trifluoromethyl groups. It was noteworthy that the bromo- and fluro- groups survived well under the reaction conditions, which were suitable for further potential functionalization (**3f**, **3g**). Following, an investigation of different *N*-protected substrates showed that *N*-methyl, *N*-ethyl and *N*-phenyl substrates also worked well, leading to the corresponding products in good yields (**3i**-**3l**). The desired **3j** was generated even up to 99% yield. Importantly, the applicable scope was not limited to AIBN, azobisisovaleronitrile (AMBN), though less reactive, can also react with these substrates and moderate yields were obtained (**3m**-**3p**).

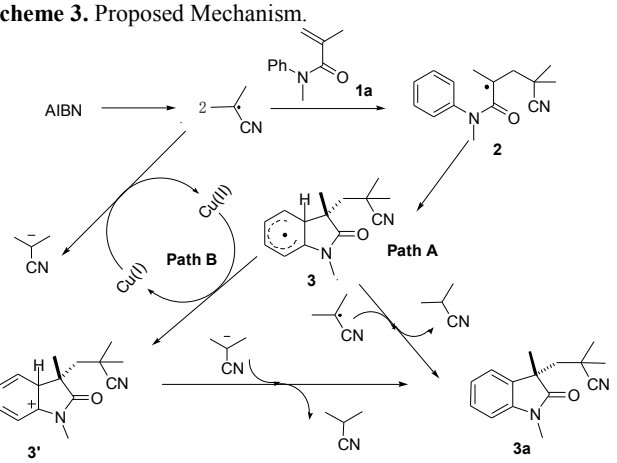
Scheme 2. Tandem radical addition/cyclization of *N*-arylacrylamides with **2** .[a]



[a] Reaction conditions: substrate **1** (0.5 mmol), CuI (0.05 mmol) and **2** (1.5 mmol dissolved in 1 mL DCE was added through micro injection pump in DCE (1.0 mL) under N_2 atmosphere for 24 h. [b] The ratio of **3k**:**3k'** is 73:27. [c] The ratio of **3r**:**3r'** is 62:38 , according to NMR.

According to all the above results and the previous reports, a plausible mechanism was proposed as shown in Scheme 3. The first step is AIBN extruding a molecule of N_2 to form the 2-cyanoprop-2-yl radical. Then 2-cyanoprop-2-yl radical subseque-tly adds to the double bond of *N*-methyl-*N*-phenylmethacrylamide **1a** to give radical intermediate **2**.

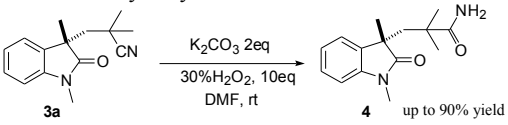
Scheme 3. Proposed Mechanism.



Cyclization of radical **2** would generate radical intermediate **3**. Subsequently, the reaction may proceed by two different pathways: in path A, intermediate **3** would be converted to oxindole **3a** by the loss of one hydrogen radical to 2-cyanopropyl radical. Another possibility is that the 2-cyanoprop-2-yl radical

may be converted to 2-cyanoprop-2-yl anion by single electron transfer (SET) with Cu(I) while the intermediate **3** may be converted to the corresponding cation **3'** by single electron transfer (SET) with Cu(II). Finally, **3'** could be easily deprotonated by the 2-cyanoprop-2-yl anion generating the desired product **3a**.

Scheme 4. Hydrolysis of **3a**.



Reaction conditions: substrate **3a** (0.5 mmol), K_2CO_3 1mmol, 30% H_2O_2 0.56 mL, DMF 4mL, stired at room temperature for 24h.

It was worth mentionning that the 3-(2´-cyano Alkyl) Oxindole derivatives have the potential for converting into a diverse class of functionalities. Here we carried out an hydrolysis experiment to give an example (Scheme 4).

Conclusions

In conclusion, we developed a CuI promoted radical addition/cyclization of arylacrylamides and provided a facile pathway leading to 3-(2´-cyano alkyl) oxindoles. The coupling of AIBN with alkenes provided a new method for the synthesis of cyano products, which may be versatile for facile conversion into a diverse class of functionalities. Some products may even be effective precursor for physostigmine analogue.[10]

Acknowledgment

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Notes and references

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‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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