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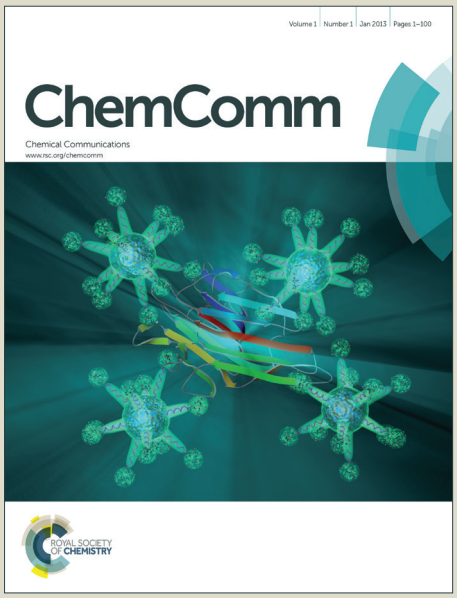

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ARTICLE TYPE

Radical Cascade Cyanomethylation of Activated Alkenes to Construct Cyano Substituted Oxindoles

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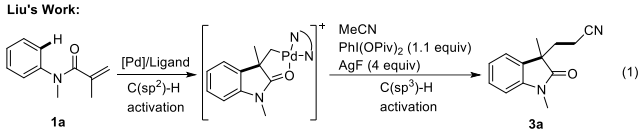
Cyanomethyl radical was easily generated from acetonitrile by using DTBP, which was applied to a cascade alkene addition and cyclization reaction to construct useful oxindole derivatives. This protocol features simple manipulation, cheap reagent and a broad substrate scope. In addition, nitro substituted oxindoles were also synthesized for the first time.

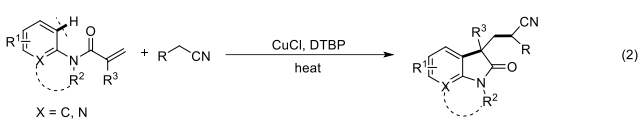
Cyanomethylation is a synthetically useful reaction because cyano group can easily convert to amino, carboxyl, alkyl, aldehyde and ester groups.[1] An attractive approach is to use acetonitrile directly through C–H activation due to the highly efficient atom economy and the avoidance of prefunctionalization. Early efforts on the C–H activation of acetonitrile by using stoichiometric amounts of transition metals such as Fe, Rh, Ru, Ir, Ni, and Au have been well documented.[2] A recent advance is the catalytic C–H activation, which is still rare.[3] An elegant example is the oxidative dicarbonation of *N*-aryl acrylamides **1** to construct cyano substituted oxindole derivatives **3** through a cascade Pd-catalyzed C(sp^2)–H and C(sp^3)–H activation reported by Liu group (Eq. 1).[4] However, the drawbacks are also apparent: the use of precious Pd catalyst with nitrogen-containing ligand as well as the requirement of an oxidant $PhI(OPiv)_2$ (1.1 equiv) and a key additive AgF (4 equiv). A more concise synthesis is highly desirable.

Liu's Work:



(1)

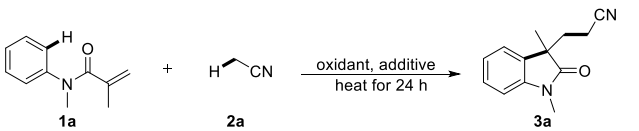
This work:



(2)

Oxindoles are ubiquitous heterocyclic scaffolds existing in a wide variety of natural products, pharmaceuticals, and bioactive molecules.[5] Over the past few years, substantial substituted oxindoles have been synthesized via radical cascade reactions of alkenes with simple reagents such as azide, ether, aldehyde, cycloalkane, dichloromethane and alcohol, etc.[6] Herein, we would like to present a practical and efficient radical cyanomethylation of alkenes to construct cyano substituted oxindoles by simply using DTBP as the radical initiator.

Table 1 Optimization of the reaction conditions.[a]



Entry	Oxidant	Additive	Yield (%)[b]
1[c]	DTBP	CuCl	32
2[c]	TBHP	CuCl	N. R.
3[c]	PIDA	CuCl	Trace
4[c]	H_2O_2	CuCl	N. R.
5[c]	$K_2S_2O_8$	CuCl	N. R.
6[c]	DDQ	CuCl	N. R.
7[d]	DTBP	CuCl	50
8[e]	DTBP	CuCl	80
9	DTBP	CuCl	82
10[f]	DTBP	CuCl	80
11	DTBP	-	34
12[g]	DTBP	CuCl	45
13[h]	DTBP	CuCl	76
14	DTBP	$Cu(OAc)_2$	78
15	DTBP	$ZnCl_2$	30
16	DTBP	$IrCl_3$	80
17	DTBP	$FeCl_3$	77
18[i]	DTBP	CuCl	76

[a] Reaction conditions: **1a** (0.25 mmol), oxidant (3.0 equiv), additive (10 mol%) and MeCN (2.0 mL) at 120 °C under nitrogen atmosphere for 24 h. [b] Isolated yield. [c] Oxidant (2.0 equiv), MeCN (1.0 mL). [d] MeCN (1.0 mL). [e] MeCN (1.5 mL). [f] MeCN (2.5 mL). [g] At 100 °C. [h] At 130 °C. [i] CuCl (5 mol%). N. R. = no reaction.

Due to our continuous interests in C(sp^3)–H activation for coupling reactions,[7] we initialize a reaction involving *N*-methyl-*N*-phenylmethacrylamide **1a** (0.25 mmol) as the starting material in the presence of 2 equiv. of DTBP (Table 1). The blank reaction in 1 mL MeCN at 120 ˚C for 24 hours afforded compound **3a** in 32% yield (entry 1), which was fully characterized by HRMS, ^1H and ^{13}C NMRs. Other oxidant such as TBHP, H_2O_2, $K_2S_2O_8$, DDQ and $PhI(OAc)_2$ resulted in either no reaction or only trace amount of **3a** (entries 2-6). Increasing the amount of DTBP promoted the yield to 50% (entry 7). Varying the amount of MeCN showed that the best yield of 82% was obtained in 2 mL MeCN (entries 8-10). Without CuCl, **3a** was also obtained in 32% yield (entries 11). These results indicated a possible radical process and a Lewis acid role of CuCl.[6f,8] The dramatic

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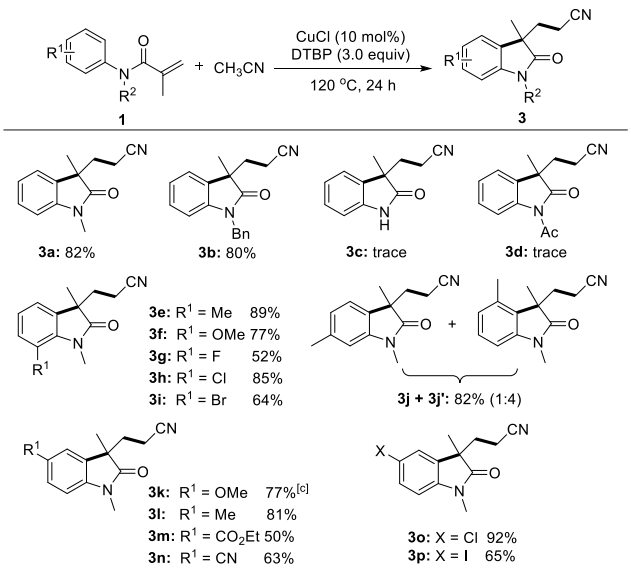
suppression of this reaction by the addition of a stoichiometric amount of radical inhibitors, such as TEMPO and BHT (2,6-di-*tert*-butylphenol), confirmed the radical pathway (See SI).

The preliminary results were rather surprising and particular interesting because MeCN is commonly considered as a stable solvent and widely used in a range of radical reactions.[9] Actually, the C–H bond homolysis of MeCN to generate cyanomethyl radical is not so easy and seldom presented in the literature.[10] For example, Marks and Lewis et al reported a photocatalyzed cyanomethylation reaction in 1981. A unique light-absorbing ground state complex of Ag(I)-norborene cleaved into norborene cation radical, which then abstracted a hydrogen atom from MeCN to generate cyanomethyl radical.[10a] In 2013, The Yoshida group found that a Pd/TiO_2 hybridised catalyst could generate cyanomethyl radical from MeCN under light (405 nm) irradiation, but the quantum yield was as low as only 0.22%.[10c] These processes are far less practical in regard to very limited substrate scope, expensive transition metal catalysts involved or low yields. Therefore, we decided to further optimize our reaction conditions.

Lowering the reaction temperature significantly decreased the yield while elevating the temperature slightly decreased the yield (entries 12-13). Other metal salts such as $Cu(OAc)_2$, $ZnCl_2$ and $FeCl_3$ were less effective except that $IrCl_3$ gave a similar yield (entries 14-17). Cutting the amount of CuCl in half slightly lowered the yield (entry 18). Finally, the optimal conditions were set to be in the presence of CuCl (10 mol%) and DTBP (3.0 equiv) in CH_3CN (2.0 mL) at 120 °C for 24 h, and the desired product **3a** was obtained in 82% yield (entry 9).

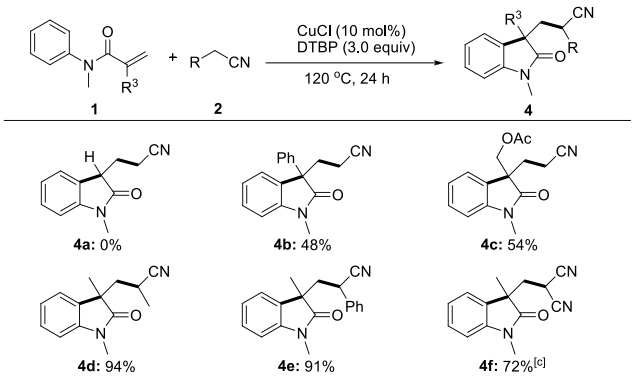
Table 2 Radical cyanomethylation of activated alkenes with acetonitrile.[a,b]



[a] Reaction conditions: **1a** (0.25 mmol), CuCl (10 mol%), DTBP (3.0 equiv) in CH_3CN (2.0 mL) at 120 °C under nitrogen atmosphere for 24 h. [b] Isolated yield. [c] CH_3CN (3.0 mL).

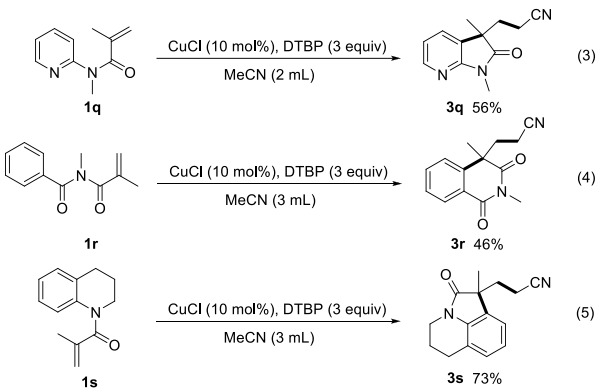
With the optimal conditions in hand, the scope of *N*-arylacrylamides was investigated (Table 2). While the *N*-methyl and *N*-benzyl *N*-phenylacrylamides gave the corresponding oxindoles in good yields (**3a**-**b**), the *N*-H and *N*-acetyl *N*-phenylacrylamides gave only trace amount of the targeted products (**3c**-**d**). The substrates with both electron-withdrawing and electron-donating groups on the phenyl ring afforded the desired products in moderate to excellent yields (**3e**-**3p**). A range of functional groups, such as methyl, methoxyl, ester, cyano and halide groups were all tolerated, which provided opportunities for further modification. No steric effect on the phenyl ring was observed in this reaction because the *ortho*-substituted substrates gave comparable yields (**3e-i**). When *m*-methyl substituted *N*-arylacrylamide was employed, two regioisomers **3j** and **3j'** were obtained in a 1:4 ratio.

Table 3 Radical cyanomethylation of activated alkenes with nitriles.[a,b]



[a] Reaction conditions: **1** (0.25 mmol), CuCl (10 mol%), DTBP (3.0 equiv) and nitriles (2.0 mL) at 120 °C under nitrogen atmosphere for 24 h. [b] Isolated yield. [c] Malononitrile (20 equiv).

Next, various substituted alkenes and nitriles were tested and the results are included in Table 3. For alkenes **1**, the *mono*-substituted alkene (R^3 = H) was ineffective in this reaction and gave no product **4a**. The gem-disubstituted substrates (R^3 = phenyl and acetoxymethyl) furnished the corresponding products in 48% and 54% yields, respectively (**4b** and **4c**). For nitriles, propionitrile and phenylacetonitrile performed better than acetonitrile and afforded oxindoles **4d** and **4e** in excellent yields. Finally, malononitrile could also undergo this reaction to provide dicyanomethyl oxindole **4f** in 72% yield.



To further evaluate the utility of this chemistry and expand substrate scope, a few representative enamides were tested. To our delight, Aza-2-oxindole derivative **3q** was obtained in 56% yield when *N*-pyridinylacrylamides was used (Eq. 3). With regard to substrate **1r**, an interesting six-membered-ring product **3r** was generated (Eq. 4). Notably, this approach was also suitable for tetrahydroisoquinoline derivative and provided the corresponding tricyclic product **3s** in 73% yield (Eq. 5).

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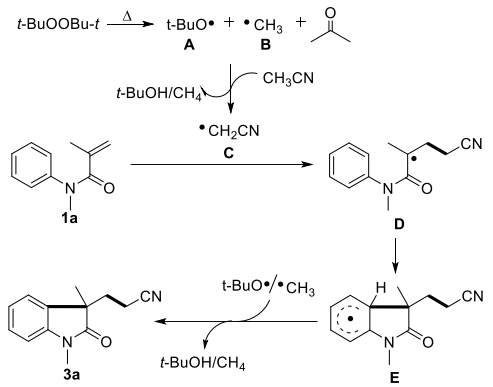
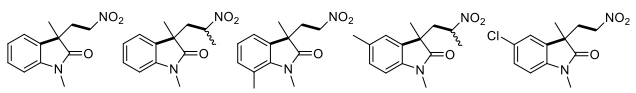
Based on the above observations and previous mechanistic studies,[6] A plausible mechanism was proposed in Scheme 1. The homolysis of DTBP by heating initiate the *t*-butoxyl radical **A**, methyl radical **B** and acetone.[11] **A** or **B** then abstracted an *α*-hydrogen of MeCN to generate the cyanomethyl radical **C**. The selective addition of **C** to C=C double bond of *N*-arylacrylamide **1a** delivered intermediate **D**, which intramolecularly cyclized to form **E**. The hydrogen abstraction on the aryl ring by **A** or **B** gave oxindole **3a** as the desired product. CuCl might act as a Lewis acid to stabilize the radical intermediates.[6f,8]



Scheme 1 Proposed mechanism.

It needs to mention that, following the same radical mechanism, the nitromethylation could also occur under the same reaction conditions to furnish nitromethyl oxindoles, which have previously not been reported yet. The selective examples are listed in Scheme 2.



Scheme 2 Nitro substituted oxindoles obtained via radical cascade reaction.

In summary, we have shown a concise and practical cyanomethylation as well as nitromethylation of *N*-phenylacrylamides through a radical pathway to construct substituted oxindoles. The simplicity and the broad substrate scope made this method much more practical than the transition metal catalyzed reaction. To the best of our knowledge, the C–H bond activation of MeCN demonstrated in this manuscript is the most simple and efficient process so far. Exploitation of other reactions is currently underway in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental procedures, characterization data, and copies of NMR spectra]. See DOI: 10.1039/b000000x/

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