RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2015, **5**, 64961

Received 16th June 2015
Accepted 13th July 2015

DOI: 10.1039/c5ra11530b

www.rsc.org/advances

DBU-promoted cyclization of vinyl isocyanides with ethers *via* the functionalization of a C(sp^3)–H bond for the synthesis of isoquinolines†

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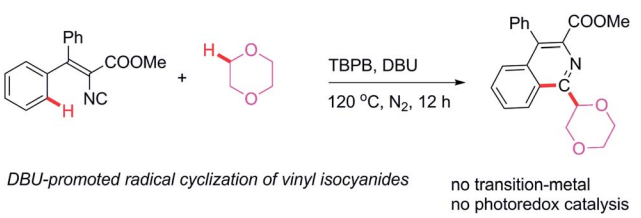
A DBU-promoted cascade functionalization of a C(sp^3)–H bond adjacent to oxygen and a radical cyclization reaction of vinyl isocyanides were developed. The reaction was carried out without the use of any metal catalysts or photoredox catalysis, which provides easy access to multi-functionalized isoquinolines.

Selective C–H bond functionalization has become an active research topic in organic chemistry and emerged as a powerful tool to construct complex molecules due to high atom-economy and alleviating the need for prefunctionalized substrates.[1] Direct functionalization of relatively unreactive C(sp^3)–H bonds,[2] especially the C(sp^3)–H bonds adjacent to a heteroatom, is of high value in organic synthesis as functionalized ethers and amines widely exist in natural products and bioactive compounds.[3] In recent years, a number of C(sp^3)–H bond functionalization and cross-dehydrogenative coupling (CDC) reactions of ethers and alcohols have been developed to construct ethers and alcohol derivatives.[4] Tu and other groups have developed a cascade C(sp^3)–H bond functionalization and addition reaction of several alkenes[5] and alkynes,[6] affording hydroalkylation products. Recently, Ji's group explored a metal-free functionalization of the C(sp^3)–H bond of ethers and a 1,2-aryl migration cascade process resulting in α-aryl-β-oxyalkylated carbonyl ketones with good yields.[7] However, the metal-free functionalization of the C(sp^3)–H bond of ethers followed by intermolecular or intramolecular cyclization reactions remains a great challenge and is less explored.[8]

Isonitriles belong to an important class of organic intermediates, which could directly construct heterocycles with high efficiency.[9,10] For example, the cyclization of 2-alkenylphenylisocyanide has been used as a key step for the total synthesis of aspidophytine.[11] Recently, the radical initiated cyclization of aryl isonitriles has been well developed and several radical precursors,[12] including ethers and alcohols,[13] have been developed to construct substituted phenanthridines. However, the cyclization of vinyl isonitriles to synthesize substituted isoquinolines has been less explored and only a few examples have been reported. Recently, Xu's group developed a manganese-catalyzed oxidative radical cascade reaction of vinyl isocyanides for the synthesis of aryl isoquinolines with boronic acids as aryl radical precursors.[14] Yu's group reported the light-promoted cyclization reactions of vinyl isocyanides with diaryliodonium salts or the Umemoto's trifluoromethylation reagent.[15] The Studer group developed a method for the synthesis of 1-trifluoromethylated isoquinolines *via* a radical trifluoromethylation of isonitriles.[16] However, pre-functionalized substrates, transition metals and light conditions are usually needed for these transformations. Furthermore, the functionalization of the C(sp^3)–H bond adjacent to an oxygen atom has never been explored to trigger the cyclization of vinyl isocyanides. So, the development of a simple metal-free radical cyclization of vinyl isocyanides with ethers and alcohols becomes highly desirable. Herein, we would like to report a facile metal-free functionalization of a C(sp^3)–H bond adjacent to oxygen and the subsequent cyclization reaction of vinyl isocyanides affording 1-ether group substituted isoquinolines (Scheme 1).



Scheme 1 The metal-free radical cyclization reaction.

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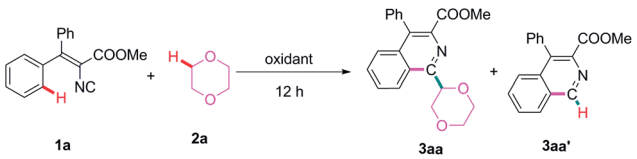
† Electronic supplementary information (ESI) available: Experimental procedures, full spectroscopic data for compound **3** and copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c5ra11530b

Table 1 Optimization of the reaction conditions for the reaction of methyl 2-isocyano-3,3-diphenylacrylate **1a** and 1,4-dioxane **2a**[a]

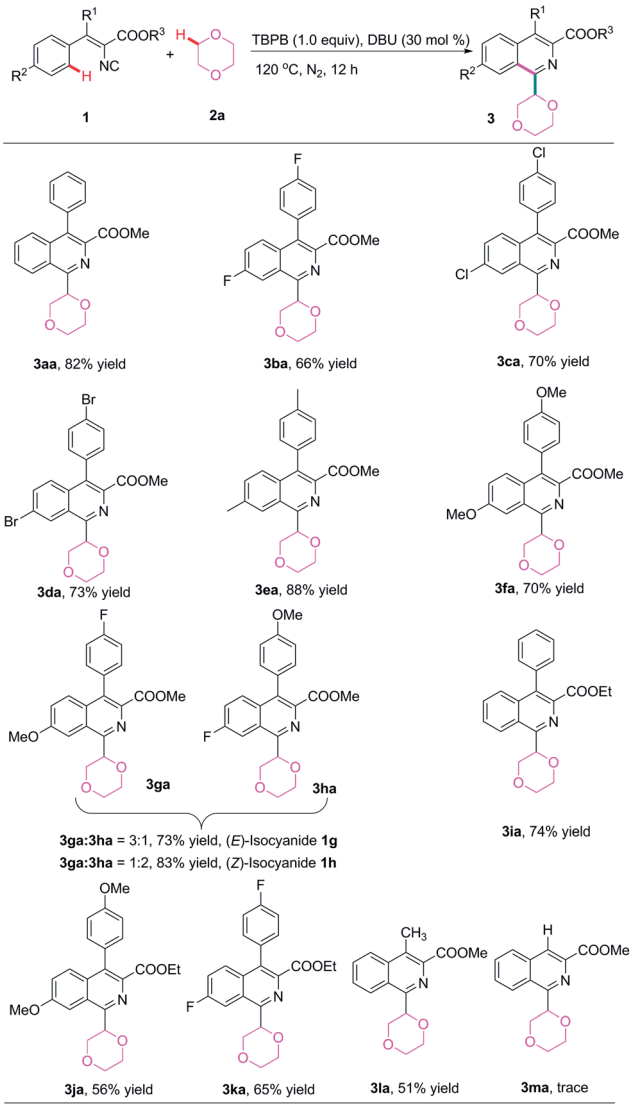


Entry	Oxidant (equiv.)	Catalyst (mol%)	Temp (°C)	Yield[d] (%) (**3aa**/**3aa**′)
1	DTBP (2.0)[e]	—	120	36/1[b]
2	H_2O_2 (2.0)[f]	—	120	31/24[b]
3	BPO (2.0)[g]	—	120	63/15[b]
4	TBPA (2.0)[h]	—	120	41/3[b]
5	TBPB (2.0)[i]	—	120	65/2[b]
6	TBPB (2.0)	—	120	48/2[j,b]
7	TBPB (2.0)	CuBr (20)	120	30/25[c]
8	TBPB (2.0)	Cu_2O (20)	120	55/5[c]
9	TBPB (2.0)	$Cu(OAc)_2$ (20)	120	32/11[c]
10	TBPB (2.0)	$Mn(OAc)_3 \cdot 2H_2O$ (20)	120	42/40[c]
11	TBPB (2.0)	$MnCl_2$ (20)	120	40/27[c]
12	TBPB (2.0)	*t*-BuOK (30)	120	68/1[c]
13	TBPB (2.0)	K_2CO_3 (30)	120	46/1[c]
14	TBPB (2.0)	DMAP (30)	120	54/0[c]
15	TBPB (2.0)	DBU (30)	120	72/0[c]
16	TBPB (2.0)	DBU (30)	90	70
17	TBPB (2.0)	DBU (30)	130	64
18	TBPB (1.0)	DBU (30)	120	82
19	TBPB (3.0)	DBU (30)	120	53
20	TBPB (1.0)	DBU (10)	120	75
21	TBPB (1.0)	DBU (50)	120	80

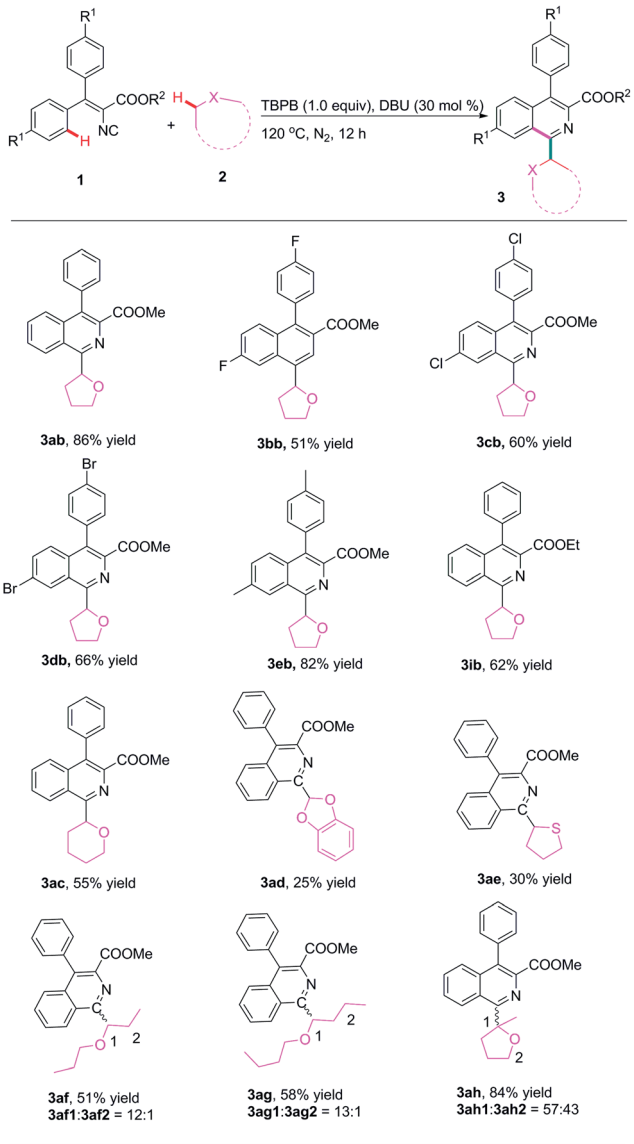
[a] Reaction conditions: **1a** (0.2 mmol), 1,4-dioxane **2a** (2.0 mL), oxidant, 12 h, N_2 atmosphere. [b] Yield determined using ^{1}H NMR with CH_2Br_2 as the internal label. [c] Yield determined using ^{1}H NMR after column chromatography isolation. [d] Isolated yield based on **1a**. [e] DTBP: di-*tert*-butyl peroxide. [f] 30% H_2O_2 in water. [g] BPO: benzoyl peroxide. [h] TBPA: *tert*-butyl peracetate. [i] TBPB: *tert*-butyl peroxybenzoate. [j] Under air.

The initial reaction of methyl 2-isocyano-3,3-diphenylacrylate (**1a**) was carried out using 2.0 equiv. of DTBP as the oxidant in 1,4-dioxane (**2a**) under a nitrogen atmosphere at 120 °C affording the expected product **3aa** in very poor yield after 12 h (36%, entry 1, Table 1). Then, 30% H_2O_2 in water was tried for this reaction, and no obvious improvement was found (entry 2). It was noticeable that the reactions with other oxidants, such as BPO, TBPA and TBPB, gave dramatically increased chemical yields (entries 3–5). TBPB was the best oxidant and 65% yield was found. Running the reaction in air gave a lower yield of **3aa**, which disclosed that the reaction has to be done under an inert atmosphere (48% yield, entry 6). The by-product methyl 4-phenylisoquinoline-3-carboxylate (**3aa**′) was also detected from these reactions. To improve the chemoselectivity, several metal catalysts were tried in the reaction. However, even worse chemoselectivity and lower chemical yields were found (entries 7–11). Interestingly, when some organic bases, including DMAP (entry 14) and DBU (entry 15), as well as the inorganic bases *t*-BuOK (entry 12) and K_2CO_3 (entry 13) were used as catalysts for this reaction, excellent chemoselectivities were obtained. In particular, the reaction in the presence of DBU only gave the desired product **3aa** with a higher yield (72%, entry 15). Increasing the temperature to 130 °C or decreasing the temperature to 90 °C resulted in slightly lower chemical yields (entries 16 and 17). Finally, the loading amount of the oxidant and DBU was investigated, which showed that 1.0 equiv. of TBPB and 30 mol% of DBU were the best reaction conditions (entries 18–21).

Then, the scope of this radical cyclization reaction with vinyl isocyanides was examined, and the results are summarized in Scheme 2. Several substituted groups on the aromatic ring, including fluoro (**3ba**), chloro (**3ca**), bromo (**3da**), methyl (**3ea**), and methoxyl (**3fa**) were tolerated in this reaction, and afforded the corresponding 1-ether group substituted isoquinolines in moderate to good yields. It was noticed that the reactions of the substrates with different substituted aromatic rings (**1g** and **1h**) also proceeded smoothly, resulting in the expected product in good chemical yields but with moderate regioselectivities (**3ga** and **3ha**). The substrates with the ethyl ester group at the terminal position of the vinyl group also worked well in the reaction (**3ia–3ka**), resulting in the product with slightly lower yields compared to those substrates with the methyl ester group (**3aa**, **3fa** and **3ba**). Finally, when the methyl group was used as the substituent on the vinyl moiety instead of a phenyl ring, it also worked well giving the expected product in 51% yield (**3la**). However, almost no product was observed if a hydrogen atom existed at this position on the vinyl group (**3ma**).



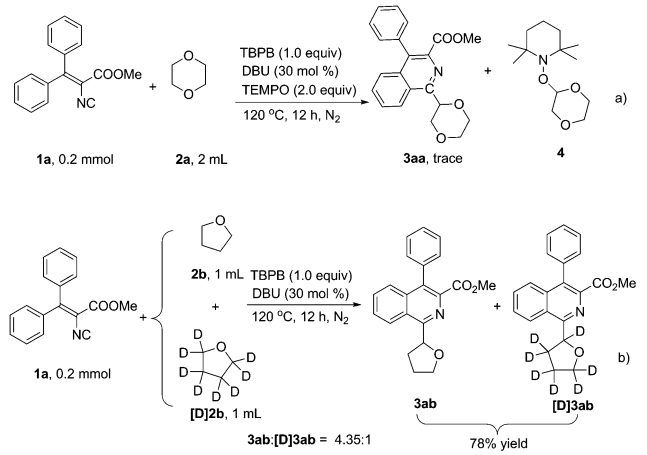
Scheme 2 Cyclization reaction of vinyl isocyanides with 1,4-dioxane **2a**.



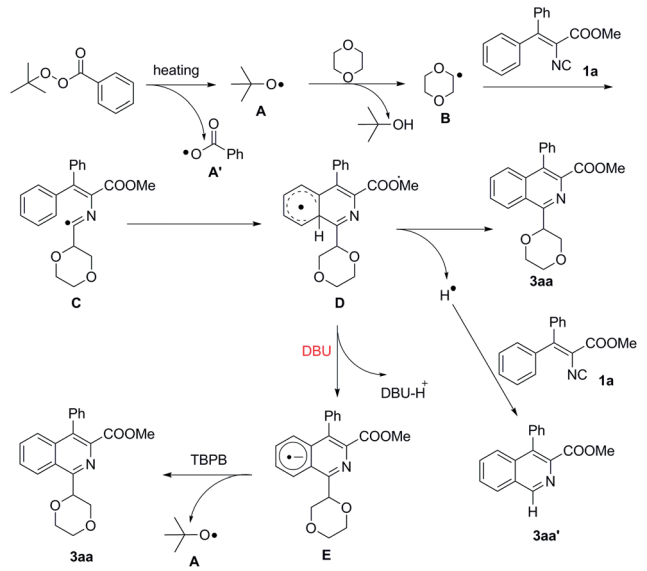
Scheme 3 Cyclization reaction of vinyl isocyanides with other cyclic esters **2**.

Then, various ethers were investigated in this radical cyclization reaction of 2-isocyano-3,3-diphenylacrylate (**1**) (Scheme 3). As shown in Scheme 3, tetrahydrofuran (**2b**) could react well with methyl and ethyl 2-isocyano-3,3-diphenylacrylate (**1a** and **1i**) resulting in the desired products **3ab** and **3ib** (86% and 62%, respectively). Fortunately, several substituted vinyl isocyanides could also react well with tetrahydrofuran giving the corresponding product (**3bb–3eb**). Tetrahydropyran and benzo[*d*][1,3]dioxole were also tolerated in this reaction affording the expected substituted isoquinolines with 55% and 25% yield, respectively (**3ac** and **3ad**). Tetrahydrothiophene was a suitable substrate for this reaction resulting in the expected 1-tetrahydrothiophene substituted product with 30% chemical yield (**3ae**). The reactions with these two linear ethers also proceeded well, affording the corresponding products with 51% and 58% yields respectively. The reactions also gave excellent regioselectivities, with ratios of 12 : 1 and 13 : 1 for products **3af** and **3ag**, respectively. 2-MeTHF also worked well in this reaction, affording the desired product with 84% chemical yield and 57 : 43 regioselectivity.

Finally, studies on the investigation of the reaction mechanism were carried out. When a radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction of 1,4-dioxane, the reaction was completely inhibited and no desired cyclic product was observed (Scheme 4a). Only the coupling product (**4**) with 1,4-dioxane was detected using MS. This result discloses that the reaction proceeds through a radical process. Also, an intermolecular competing kinetic isotope effect (KIE) experiment was conducted with tetrahydrofuran and [D]-tetrahydrofuran as starting materials (Scheme 4b). An obvious KIE was found with the ratio of 4.35 : 1 ($k_H : k_D$), which shows that the cleavage of the C(sp^3)–H bond to form the ether radical may be involved in the rate-determining steps of this procedure.



Scheme 4 Investigation of the reaction mechanism.



Scheme 5 The possible mechanism.

Based on the above results and previous reports,[13] a plausible reaction mechanism for this cyclization reaction was supposed (Scheme 5). Firstly, the decomposition of TBPB generates a *tert*-butoxy radical intermediate **A** and a benzoate radical **A′** under heating, the former reacts with 1,4-dioxane to give the radical **B** through C(sp^3)–H bond cleavage. The intermediate **B** adds to isonitrile **1a** and affords the intermediate **C**. Subsequently, the intramolecular radical cyclization of intermediate **C** generates the cyclohexadienyl radical **D**. In the presence of DBU, intermediate **D** undergoes deprotonation to give a radical anion **E**. Finally, the radical anion **E** gets oxidized by TBPB to afford the product **3aa** along with a *tert*-butoxy radical **A** and a benzoate anion.[13b,13c,17] If no DBU is added, intermediate **D** undergoes a radical process to give the final product **3aa** along with a hydrogen radical. The hydrogen radical reacts with **1a** to give the by-product, methyl 4-phenylisoquinoline-3-carboxylate (**3aa′**).

Conclusions

In summary, a DBU-promoted cascade C(sp^3)–H bond functionalization of ethers and a radical cyclization reaction of vinyl isocyanide were reported. The reaction tolerated a wide range of substrates and could be performed under simple conditions. This reaction involves new C(sp^3)–C(sp^2) and C(sp^2)–C(sp^2) bond formations, which provide straightforward and atom-economical access to multi-functionalized isoquinolines from readily available starting materials. The current reaction has the limitation of an ether solvent, and only THF and 1,4-dioxane afforded synthetically good yields. This will be further investigated in our future study on this reaction.

Acknowledgements

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (No. 21102071 and 21472082).

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