Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201500096

DDQ-mediated Direct C(sp^3)–H Cyanation of Benzyl Ethers and 1,3-Diarylpropenes under Solvent- and Metal-free Conditions

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Received: January 31, 2015; Revised: April 15, 2015; Published online: June 18, 2015

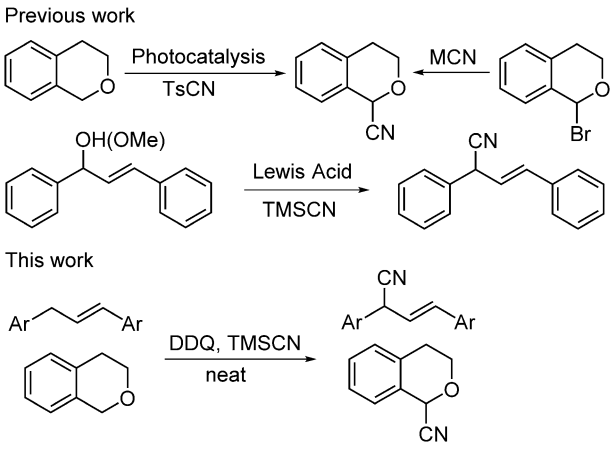
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500096.

Abstract: A direct cyanation of benzyl ethers and 1,3-diarylpropenes with TMSCN was performed under solvent- and metal-free conditions. This oxidative cross dehydrative coupling (CDC) reaction was promoted by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and provided rapid access to a broad range of nitriles in good to excellent yields.

Keywords: 1,3-diarylpropene; benzyl ether; C(sp^3)–H functionalization; cyanation; DDQ

Direct functionalization of C(sp^3)–H bonds is a rapid and effective method for constructing structurally complex molecules, especially those with interesting biological activities. For this reason, significant research efforts have been directed towards the development of new synthetic methods for C(sp^3)–H bond functionalization, in particular C(sp^3)–H bonds that are adjacent to heteroatoms.[1] Several recent studies have reported the development of powerful methods for the functionalization of C(sp^3)–H bonds using metals or other oxidative reagents to afford C–C and C–X bonds, which can be useful for the synthesis of tetrahydroquinoline derivatives.[2] However, reports studying the functionalization of O–C(sp^3)–H bonds using cross dehydrative coupling (CDC) methods have been relatively scarce until recently. This may be due to the fact that O–C(sp^3)–H bonds are less reactive and generally possess less biological relevance compared to C(sp^3)–H bonds adjacent to nitrogen.

Among these reports concerning the functionalization of O–C(sp^3)–H bonds, direct sp^3–sp^3 and sp^3–sp^2 C–C bond formations are well studied.[3] In addition, sp^3–sp C–C bond formation *via* coupling with terminal alkynes has been reported by Li and Jiao using DDQ as an oxidant with catalytic amounts of either AgOTf or $Fe(OTf)_2$. A trityl ion was also used recently by Liu as an oxidative reagent for the coupling of ether with potassium alkynyltrifluoroborate to form sp^3–sp C–C bond.[6] Inoue also demonstrated that photoexcited benzophenone can act as a C–H activator and generate carbon radicals that are subsequently trapped by tosyl cyanide to afford the corresponding nitriles using excess amounts of several different substrates including ethers, alcohols, amines, alkanes and alkylbenzenes (Scheme 1).[7] It is well established that the cyano group serves as a versatile functional group in organic synthesis since it can be easily converted into a variety of different functionalities and branched carbon skeletons. Furthermore, cyano groups are



Scheme 1. Synthesis of cyanide derivatives of 1,3-diarylpropenes and benzylic ethers.

found in numerous natural products and synthetic materials with interesting biological activities.[8] While 1-cyano isochroman compounds are traditionally synthesized by reacting cyclic acetals with a metal cyanide, this strategy requires an additional step when isochroman is used as a starting material.[9] As part of our ongoing work towards the development of new methods for the functionalization of C(sp^3)–H bonds adjacent to heteroatoms,[10] we herein report the cyanation reaction of benzyl ethers and 1,3-diarylpropenes with TMSCN using a CDC approach under solvent- and metal-free conditions.[11,12]

DDQ was initially evaluated as an oxidative dehydrogenating reagent for the coupling of isochroman (**1a**) with TMSCN under metal-free conditions and proved to be a very efficient reagent for the C(sp^3)–H functionalization of tetrahydroisoquinolines and isochromans.[13] The desired product (**2a**) was obtained when the reaction was refluxed in dichloromethane and 1,2-dichloroethane in 51% and 20% yields, respectively (Table 1, entries 1–2). Several other solvents were evaluated and found to give higher yields, including benzene, toluene, THF and CH_3CN (Table 1, entries 3–6). Interestingly, the reaction did not proceed at all when water or DMF were used as the solvent (Table 1, entries 7–8). Notably, highest yield of the desired product (**2a**) was achieved when the reaction was conducted neat at 80 °C (Table 1, entry 9). These conditions appeared to be optimal, with further decreases or increases in the reaction temperature and time leading to reduced yields (Table 1, entries 10–13). In addition, decreasing the amount of TMSCN added to the reaction resulted in a slight decrease in yield. Several co-oxidative systems were also investigated, including O_2/DDQ (0.1 equiv), MnO_2/DDQ (0.1 equiv) and *t*-BuOOH/DDQ (0.1 equiv). However, all of these systems gave lower yields of the desired product. Other cyanide sources, including $K_3Fe(CN)_6$, NH_4HCO_3/DMSO and $CH_2(CN)_2$, failed to provide any of the desired product.

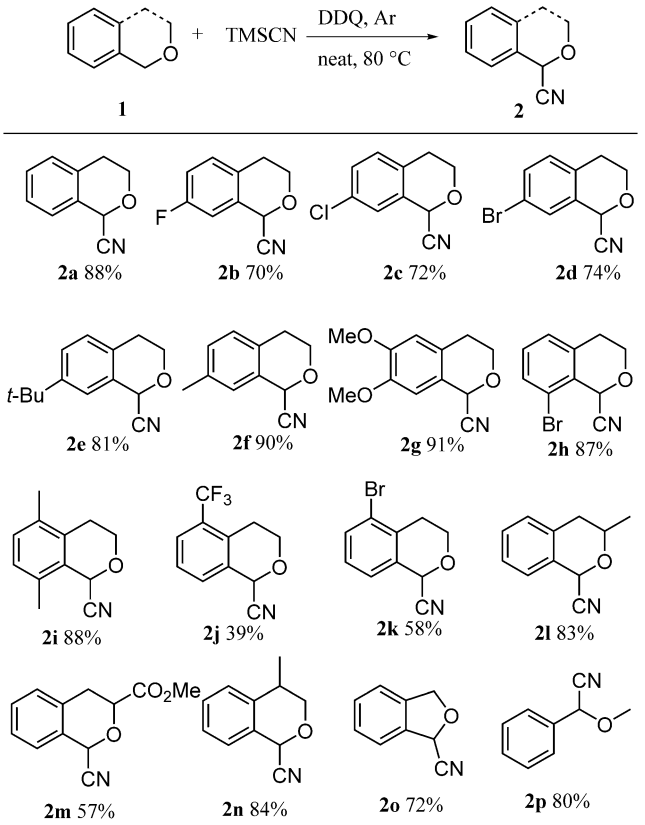
Using our optimized conditions, we proceeded to investigate the substrate scope of this cyanation reaction using various benzyl ethers (Table 2). First, the effect of different substituents on the phenyl ring was investigated. Our results showed that the substituent at the C-7 position of the isochroman ring has a significant effect on the cyanation reaction (**2b–f**). For example, the presence of a halogenated substituent at this position resulted in reduced yields (70–74%) of the corresponding nitriles, compared to that of electron-donating and sterically bulky groups such as methyl and *tert*-butyl groups. Furthermore, the 6,7-dimethoxy substrate bearing, two electron-donating groups, generated the highest yield, with the corresponding nitrile **2g** being isolated in 91% yield. Isochromans with substituents at the C-8 or C-6,8 posi-

Table 1. Optimization of reaction conditions for the synthesis of nitrile **2a** from isochroman (**1a**).[a]

Entry	Solvent	Temp [°C]	Time	Yield[%][b]
1	DCM	reflux	2.5 h	51
2	DCE	reflux	5 h	20
3	PhH	reflux	2.5 h	84
4	$PhCH_3$	reflux	2 h	75
5	THF	reflux	4 h	76
6	CH_3CN	reflux	5 h	72
7	H_2O	reflux	2 h	0
8	DMF	80	2.5 h	0
9	neat	80	1.5 h	88
10	neat	r.t.	8 h	33
11	neat	60	4.5 h	79
12	neat	100	85 min	53
13	neat	80	1 h	78
14	neat	80	1.5 h	66[c]

[a] 0.5 mmol of **1a**, 0.6 mmol of DDQ and 1.5 mmol of TMSCN in 2 mL of solvent under an atmosphere of Ar.
[b] Isolated yield.
[c] 1.5 equivalent of TMSCN (0.75 mmol) was used.

Table 2. DDQ mediated direct cyanation of benzylic ethers.[a,b]



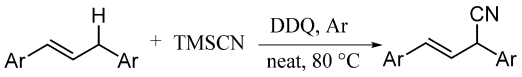
[a] 0.5 mmol of **1**, 0.6 mmol of DDQ and 1.5 mmol of TMSCN under Ar.
[b] Isolated yield.

tions afforded similar results to **2a**. However, substituting a bromo or trifluoromethyl group at the C-5 position resulted in significantly reduced yields of 58% and 39%, respectively. The presence of a methyl substituent at the C-3 position of the pyrane ring (**2l**) led to the yield of 83%, whereas the introduction of an ester substituent at the same position (**2m**) led to an even more drop in the yield to 57%. However, 4-methylisochroman yielded the nitrile **2n** in 84% yield. We were pleased to find that applying the optimized conditions to the symmetrical benzylic ether, phthalane, afforded the corresponding mono-cyano product **2o** in 72% yield. Furthermore, the acyclic benzylic ether also reacted smoothly under the optimized conditions to give the desired nitrile **2p** in 80% yield. Unfortunately, the use of benzyl phenyl ether as a substrate failed to provide any of the desired coupling products.

Encouraged by these results, we further explored the scope of this transformation using several other substrates bearing a benzylic C(sp^3)–H bond. Based on previous literature concerning the CDC reaction of compounds containing C(sp^3)–H bonds, we selected 1,3-diarylpropenes as suitable substrates for our new cyanation conditions.[14] To the best of our knowledge, our work is the first report of an oxidative coupling using **3** to give the corresponding 1-cyano-1,3-diarylpropene **4** through direct C(sp^3)–H functionalization.[15] As shown in Table 3, treatment of **3a** under our standard conditions provided **4a** in 74% yield. This result indicates that this new cyanation reaction can be applied to the direct functionalization of C(sp^3)–H bonds adjacent to 1-phenylallylic carbon atoms as well as heteroatoms. Halogenated groups were also well tolerated at the C-4 position of the phenylpropenyl ring of the substrates investigated, giving the corresponding nitriles **4b–d** in moderate yields (57–62%). However, the substrate bearing a methyl group at this position gave a reduced yield of 50% for the desired product **4e**. In addition, when 1,3-(4′-*tert*-butyl)diphenylpropene was subjected to the same optimized cyanation conditions, the reaction proceeded smoothly to give the nitrile product **4f** in 68% yield. No product was observed when 1-phenylpropene was submitted to these reaction conditions.

In conclusion, we have developed an efficient reaction for the coupling of benzylic ethers and 1,3-diarylpropenes with TMSCN in the presence of DDQ under metal- and solvent-free conditions. This method provides rapid access to benzylic nitriles in good to excellent yields. Further research efforts aimed towards exploring the application of CDC and tandem reactions to C(sp^3)–H bonds of benzylic ethers and other substrates are currently underway.

Table 3. DDQ mediated direct cyanation of 1,3-diarylpropenes.[a]



3 4

Entry	3, Ar	4, Yield[%][b]
1	**3a**, Ph	**4a**, 74
2	**3b**, 4-F-C_6H_4	**4b**, 57
3	**3c**, 4-Cl-C_6H_4	**4c**, 62
4	**3d**, 4-Br-C_6H_4	**4d**, 58
5	**3e**, 4-Me-C_6H_4	**4e**, 50
6	**3f**, 4-*t*Bu-C_6H_4	**4f**, 68

[a] 0.5 mmol of **3**, 0.6 mmol of DDQ and 1.5 mmol of TMSCN under Ar.
[b] Isolated yield.

Experimental Section

General Procedure

To a mixture of trimethylsilyl cyanide (1.5 mmol) and DDQ (0.6 mmol) was added isochroman (0.5 mmol). The resulting mixture was stirred at 80 °C under argon for about 1.5 h and then cooled to room temperature. The resulting suspension was diluted with diethyl ether. The combined organics was washed with $NaHCO_3$ and brine, dried over Na_2SO_4 and then, filtered and concentrated. The crude product was then purified by silica gel chromatography (petroleum ether/ethyl acetate = 10:1) to give the desired nitrile **2a** as a white solid in 89% yield.

Acknowledgements

We gratefully acknowledge the Nature National Science Foundation of China (21372056, 21202027, 21102057, 91127010), Changjiang Scholars and Innovative Research Team in Chinese University (IRT 1231) and the Scientific Research Foundation of Hangzhou Normal University for Young Teachers (2012QD L001) for their financial support.

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