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The Direct Electrophilic Cyanation of β-Keto Esters and Amides with Cyano Benziodoxole

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Yao-Feng Wang, Jiasheng Qiu, Dejie Kong, Yongtao Gao, Feipeng Lu, Pran Gopal Karmaker, Fu-Xue Chen*

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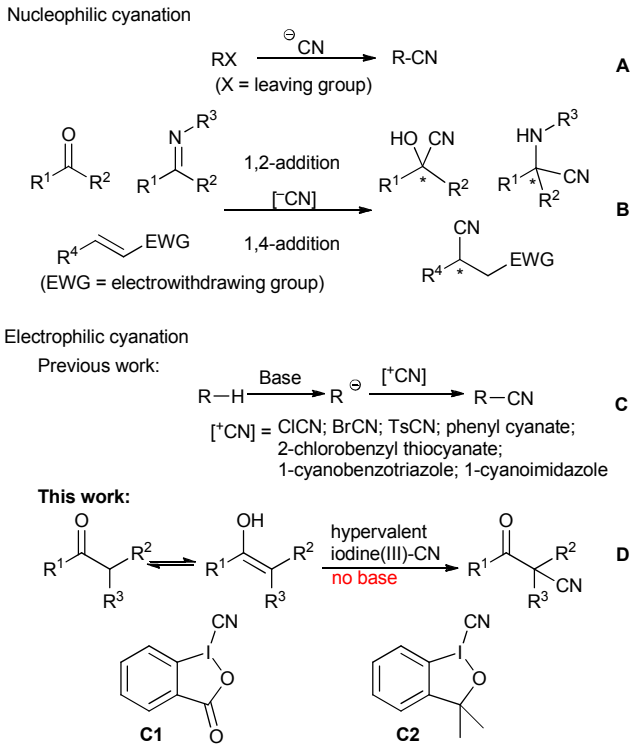
The direct electrophilic α-cyanation of β-keto esters and amides has been developed using hypervalent iodine benziodoxole-derived cyano reagent. It accomplishes within 10 min without any catalyst in DMF at room temperature. Thus, the highly functionalized quaternary carbon-centered nitriles were produced in high to excellent yields.

Introduction of cyano group into varying substrates has received considerable research attention because it has been found an important functional group among natural products, pharmaceuticals, materials, agrochemicals as well as versatile intermediate with diverse transformations.[1] Generally, the strategies for cyanation mainly include nucleophilic and electrophilic reactions. Typically, nucleophilic substitution of RX (X = leaving group) with inorganic cyanides is widely employed in both lab and industry (Scheme 1, A). In the last decades, considerable progress has been achieved in nucleophilic additions of cyanide to electrophiles (Scheme 1, B). Among them, racemic and asymmetric synthesis of cyanohydrins through 1,2-addition of cyanide to aldehydes and ketones,[2] synthesis of α-amino-nitriles with imines (Strecker reaction),[2g,3] and preparation of *β*-cyano-carbonyl compounds via 1,4-addition of cyanide with *α,β*-unsaturated carbonyl substrates,[4] have been well established and/or comprehensively reviewed (Scheme 1, B). By contrast, the electrophilic cyanation has been less explored in literature.[5] However, it was mostly accomplished under strong basic conditions (Scheme 1, C).

On the other hand, *α*-functionalization of carbonyl compounds could directly produce large numbers of interesting synthetic building blocks and molecules.[6] Various transformations, especially through the electrophilic reaction pathway, have been developed such as *α*-fluorination[7] and halogenation,[8] hydroxylation,[9] arylation,[10] trifluoromethylation,[7b,11] triluoromethylthiolation,[12] and azidation.[13] Therefore, it was hypothesized direct cyanation could be achieved through electrophilic substitution of carbonyl compounds with hypervalent iodine(III)-CN reagent (Scheme 1, D). Herein we report the first *α*-cyanation of *β*-keto esters and amides within **10** min using cyanobenziodoxole **C1** as the electrophilic cyanating agent.



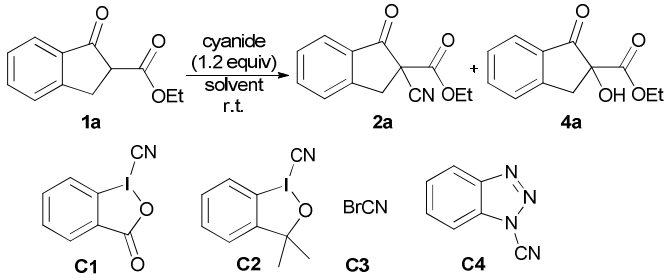
Scheme 1 Strategies for direct cyanation.

Considering the high reactivity of hypervalent iodine reagent,[6c,6d,14] hypervalent iodine(III)-CN reagents (**C1, C2**) were prepared following modified procedures.[15] Addition of 1.5 mol% of CsF made the synthesis of cyanobenziodoxole **C1** from acetoxyiodinane precursor and Me_3SiCN finished in a short time and improved yield on gram scale, which was reported by Zhdankin[16a] in the direct cyanation of methyl of *N,N*-dimethylaryl amines and by

Kita[16b]. The treatment of the chloroiodinane precursor with KF was followed by a substitution reaction with Me_3SiCN to produce the desired cyanoiodinane **C2** in 45% yield (not optimized).[15]

With these electrophilic cyanating agents in hand, acidic *β*-keto ester **1a** was chosen as the model substrate to establish the direct cyanation reaction with results listed in Table 1. To our delight, a complete conversion of **1a** to the desired nitrile **2a** in 83% yield was initially observed with **C1** in DMF without any catalyst (Entry 1). Surprisingly, only hydroxyl product **4a** was isolated in 68% yield with **C2** (Entry 2). Then, other known cyanating agents cyanogen bromide (**C3**)[5g] and 1-cyanobenzotriazole (**C4**)[5h,5i] were examined giving no desired **2a** but **4a** instead to some extent (Entries 3-4). Subsequently, screening of different solvents was carried out. Poor yields were obtained in CH_2Cl_2 and CH_3CN, while toluene and THF gave **4a** as main product (Entries 5-8). Other non-polar solvents hardly yielded any conversion as the poor solubility of **C1** in them. Interestingly, in CH_2Cl_2, Lewis acid $Cu(OTf)_2$ catalyzed the title reaction to some extent (Entry 9 vs 5), which could be a clue to the asymmetric version. DMF was found the best solvent partially because of the good solubility of **C1** in it. Excellent yield (95%) was achieved in concentrated reaction medium (Entry 10).

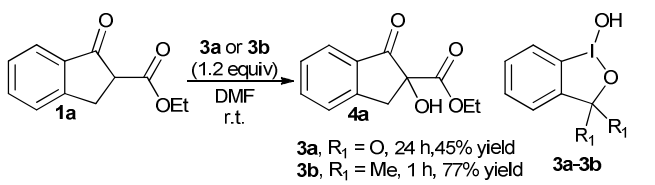
Table 1 Optimization of the Cyanation of **1a**[a]



Entry	Cyanide	Solvent	Time (h)	Yield (%)[b]	
				2a	**4a**
1	**C1**	DMF	0.15	83	–
2	**C2**	DMF	3	–	68
3	**C3**	DMF	3	trace	23
4	**C4**	DMF	3	–	trace
5	**C1**	CH_2Cl_2	12	trace	–
6	**C1**	toluene	12	–	27
7	**C1**	THF	12	9	36
8	**C1**	CH_3CN	12	trace	–
9[c]	**C1**	CH_2Cl_2	12	17	–
10[d]	**C1**	DMF	0.15	95	–

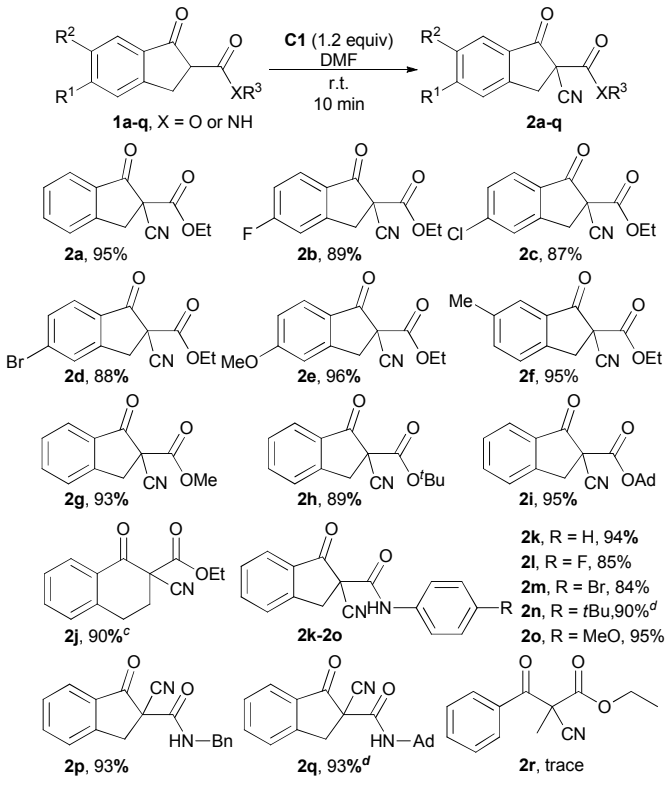
[a] Unless otherwise noted, the reaction conditions are as follow: **1a** (0.1 mmol), cyanide (0.12 mmol, 1.2 equiv), solvent (0.5 mL), room temperature. [b] Isolated yield. [c] 20 mol% $Cu(OTf)_2$ was used. [d] Solvent (0.2 mL).

As shown in Table 1, **C2** and **C3** gave more byproduct **4a** than **C1** which was attributed to their low stabilities. Moreover, the yield of **4a** increased with prolonged reaction time in each solvent which could be understood as the possible slow hydrolysis of these cyano hypervalent iodine reagents in the presence of moisture in solvent.[17] Such hydroxylation reaction was known in literature using *N*-sulfonyloxaziridines, and others.[9] To further verify it, hydroxy hypervalent iodine reagents **3a** and **3b** were prepared and applied to the reaction affording **4a** in 45% and 77% yield, respectively (Scheme 2). And the prepared **3b** produced **4a** more quickly than **C2** (Scheme 2, **3b** vs Entry 2, Table 1).



Scheme 2 Control experiments.

With the optimized conditions, the substrate scope of the direct electrophilic cyanation of keto esters and amides was investigated and the results were showed in Scheme 3. Various *β*-keto esters derived from indanone gave the corresponding products with excellent yields (**2a**-**2i**). The nitrile product derived from tetralone (**2j**) was obtained in good yield though the reaction is a little slower. Cyanation of keto amides **1k-1o** were also accomplished in good to excellent yields. However, this protocol has its limitation: no conversion was observed in the case of acyclic keto ester (**1r**).



Scheme 3 Substrate scope of the electrophilic cyanation.[a]

[a] Unless otherwise noted, the reaction conditions are as follow: **1** (0.1 mmol), **C1** (0.12 mmol, 1.2 equiv), DMF (0.2 mL) at room temperature for 10 min. [b] Isolated yield. [c] **C1** (0.2 mmol, 2 equiv); reaction time: 1 h. [d] reaction time: 0.5 h. Ad = adamantyl.

In summary, we have developed an efficient direct electrophilic cyanation of β-keto esters and amides with cyano benziodoxole reagent without any catalyst. The cyano hypervalent iodine(III)-CN (**C1**) was used as electrophilic cyanating agent for the first time. The highly functionalized quaternary carbon-centered nitriles were obtained in excellent yields within 10 minutes. Further studies are

underway to expand the reaction scope and develop the asymmetric version.

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Notes and references

School of Chemical Engineering & the Environment, Beijing Institute of Technology, 5 South Zhongguancun street, Haidian district, Beijing 100081, China. Fax: (+86)10-68918296. E-mail: fuxue.chen@bit.edu.cn

† Electronic Supplementary Information (ESI) available: Experiment procedure, characterization data, ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c000000x/

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17 **C1** is more stable than **C2**. So, **C2** may hydrolysis faster than **C1** and thus gives more oxidized side product **4a**. Consequently, in the case of sluggish substrate and/or low solubility of the cyanating agent moisture must be strictly avoided.