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Perfluorobutyliodide-assisted direct cyanomethylation of azoles and phenols with acetonitrile

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A perfluorobutyliodide-assisted transition-metal-free cyanomethylation of azoles and phenols with acetonitrile in the presence of NaH has been developed. The reaction proceeded smoothly under mild reaction conditions to give the cyanomethylated products in moderate to high yields. A mechanism involving the cyanomethyl radical through the C–H bond cleavage in acetonitrile was proposed.

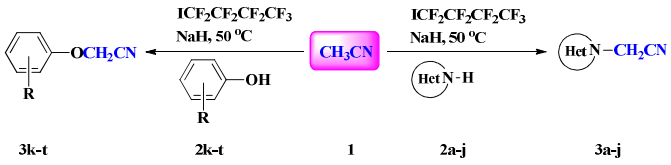
The cyanomethylation of organic compounds is an important chemical transformation due to the wide utility of the nitrile group as potent synthetic block for the construction of diverse complex molecules.[1] Recently, extensive efforts have been made toward the development of methods for introducing cyanomethyl group to different substrates.[2] As a consequence, various novel cyanomethylation reactions have increasingly emerged such as the photoassisted direct cyanomethylation of benzene with acetonitrile in the presence of Pd/TiO_2,[3] the cyanomethylation of aromatic alcohols with acetonitrile using $CuCl_2$ as the catalyst and O_2 as the oxidant[4] and the nickel cyanomethyl complex-catalyzed the coupling of aldehydes and acetonitrile.[5]

The methods for the preparation of cyanomethylated compounds typically require the use of prefunctionalized acetonitrile, including haloacetonitrile,[6] Me_3SiCH_2CN (TMSAN)[7] and isoxazole-4-boronic acid pinacol ester (acetonitrile anion equivalent).[8] The direct use of acetonitrile as starting material to undergo cyanomethylation reaction has attracted much interest in organic chemistry since it avoids substrate prefunctionalization.[9] Traditionally, the deprotonation of acetonitrile could proceed smoothly in the presence of strong bases (such as sodium amide) at very low temperature,[10] but the harsh reaction conditions limit this method.

Nowadays, transition-metal-catalyzed C–H bond activation of acetonitrile has become a straightforward and viable alternative approach to cyanomethylated compounds.[11] To date, most of the research in this area focuses on the cyanomethylation of carbonyl compounds,[12] activated alkenes (*N*-phenylacrylamides) [13] and imines.[14] However, direct *N*- and *O*-cyanomethylation of azole and phenol with acetonitrile still remains challenging.

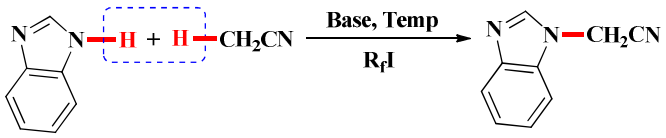
In addition, perfluoroalkyl iodides are usually utilized as perfluoroalkyl radical precursors.[15] However, the formation of radicals from these perfluoroalkyl radical sources is often initiated by precious metal photocatalysts,[16] radical initiators,[17] peroxides,[18] heat and light irradiation.[19] In 2014, Zhang and Studer reported the R_f–I bond in perfluoroalkyl iodide could be homolytically cleaved to generate a perfluoroalkyl radical with the assistance of Cs_2CO_3 in the absence of metal salt initiator.[20] Herein, we report the first example of NaH-mediated direct *N*- and *O*-cyanomethylation of azole and phenol *via* perfluorobutyl iodide-assisted cleavage of C−H bond of acetonitrile without transition metal catalyst (Scheme 1).

Scheme 1 Cyanomethylation of azoles and phenols with acetonitrile



At the start of our investigations, we chose the reaction between benzimidazole **2a** and acetonitrile in the presence of perfluorobutyl iodide as a model reaction to survey the reaction conditions (Table 1). Among the bases tested, NaH proved to be the most effective base for this reaction, affording product **3a** in 90% yield (entry 7). The use of other bases led to decreased yields (entries 1–6). No detectable amount of *N*-cyanomethylated benzimidazole **3a** was formed in the absence of base (entry 8). It was found that three equivalents of NaH were necessary to achieve this transformation (entries 7 and 9–11), but if the amount of NaH was increased to 3.5 equiv, the yield of **3a** decreased obviously (entry 12).

Table 1 Optimization of the reaction conditions[a]



2a **1** **3a**

Entry	CH_3CN (mL)	R_fI (equiv)	Temp (^oC)	Base (equiv)	Yield of **3a** (%)[b]
1	2.5	C_4F_9I (1.2)	50	NaOH (3.0)	10
2	2.5	C_4F_9I (1.2)	50	KOH (3.0)	25
3	2.5	C_4F_9I (1.2)	50	K_2CO_3 (3.0)	45
4	2.5	C_4F_9I (1.2)	50	K_3PO_4 (3.0)	50
5	2.5	C_4F_9I (1.2)	50	*t*BuOK (3.0)	66
6	2.5	C_4F_9I (1.2)	50	Cs_2CO_3 (3.0)	70
7	2.5	C_4F_9I (1.2)	50	NaH (3.0)	90
8	2.5	C_4F_9I (1.2)	50	None	0
9	2.5	C_4F_9I (1.2)	50	NaH (1.5)	70
10	2.5	C_4F_9I (1.2)	50	NaH (2.0)	83
11	2.5	C_4F_9I (1.2)	50	NaH (2.5)	85
12	2.5	C_4F_9I (1.2)	50	NaH (3.5)	74
13	2.5	C_4F_9I (0.5)	50	NaH (3.0)	50
14	2.5	C_4F_9I (1.0)	50	NaH (3.0)	76
15	2.5	C_4F_9I (1.5)	50	NaH (3.0)	88
16	2.5	None	50	NaH (3.0)	0
17	1.5	C_4F_9I (1.2)	50	NaH (3.0)	73
18	3.5	C_4F_9I (1.2)	50	NaH (3.0)	85
19	4.0	C_4F_9I (1.2)	50	NaH (3.0)	83
20	2.5	C_4F_9I (1.2)	25	NaH (3.0)	70
21	2.5	C_4F_9I (1.2)	65	NaH (3.0)	45
22	2.5	$CF_3(CF_2)_7I$ (1.2)	50	NaH (3.0)	85

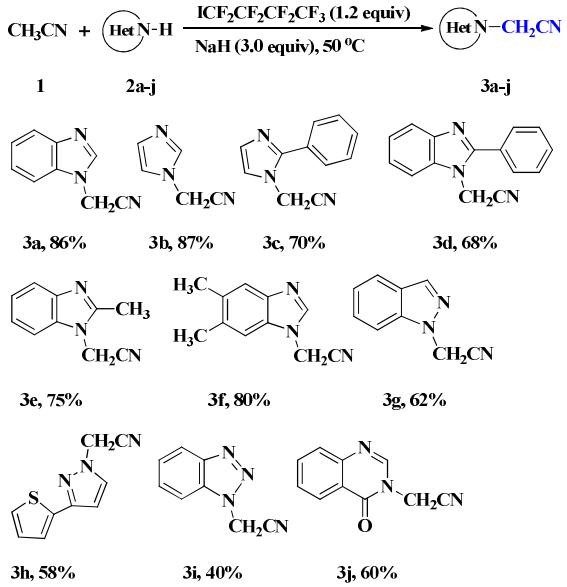
[a]Reaction conditions: **2a** (0.25 mmol), 24 h. [b]Yields determined by GC analysis and based on **2a**.

The addition of 1.2 equiv of perfluorobutyl iodide was required to obtain satisfactory yield (entry 7 and entries 13–15). The reaction did not proceed in the absence of perfluorobutyl iodide (entry 16). The acetonitrile was used as both substrate and solvent. Increasing or decreasing the amount of CH_3CN slightly diminished the yield of **3a** (entries 17–19). The use of 2.5 mL of CH_3CN could provide a good yield. The effect of the temperature on the reaction was also examined (entries 20–21). The results indicated that 50 °C was the optimal temperature for this reaction. Finally, no obvious difference was observed by replacing perfluorobutyl iodide with perfluorooctyl iodide (entry 22).

To survey the generality of this transformation, a variety of azoles were allowed to react with acetonitrile under the optimized conditions as in entry 7 in Table 1. The results are summarized in

Table 2. Most azoles could afford the *N*-cyanomethylated products in moderate to high yields. Both benzoimidazole derivatives (**2a**, **2d**, **2e** and **2f**) and imidazole derivatives (**2b** and **2c**) underwent the cyanomethylation reaction smoothly irrespective of whether benzene ring is present or not. The optimized conditions were also suitable for the *N*-cyanomethylation of benzo-fused pyrazole (1*H*-indazole, **2g**) and pyrazole derivative **2h**, however, the yields decreased appreciably. 1*H*-Benzo[d][1,2,3]triazole **2i** could react with acetonitrile, but the desired product **3i** was obtained in low yield. It is noteworthy that quinazolin-4(3*H*)-one **2j** is also compatible with this reaction and the cyanomethylated product was obtained in moderate yield. Unfortunately, when 1*H*-indole was used as substrate, less than 20% of the expected product was detected (GC-MS). It appears that the basicity of the azoles played a crucial role in the reaction. With a decrease in the basicity, benzoimidazole or imidazole derivatives, 1*H*-indazole or 1*H*-pyrazole, 1*H*-Benzo[d][1,2,3]triazole and 1*H*-indole led to sharply descending reaction efficiency. The order of reactivity, imidazole>pyrazole>1*H*-Benzo[d][1,2,3]triazole>1*H*-indole, is in accordance with the order of their basicities.

Table 2 Cyanomethylation of various azoles with acetonitrile[a b]

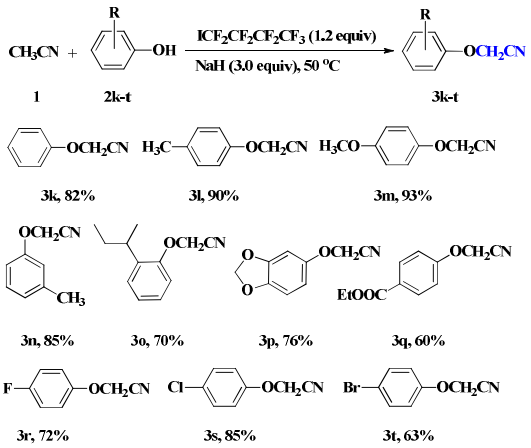


[a] Reaction conditions: **1** (10 mL), azoles (1.0 mmol), *n*-C_4F_9I (1.2 equiv), NaH (3.0 equiv), 50 °C, 24 h. [b] Isolated yields.

To expand the scope of this novel transformation, the reactions of acetonitrile **1** with various substituted phenols **2k–t** were carried out under identical reaction conditions as outlined above and representative results were summarized in Table 3. Phenol derivatives with electron donating group such as CH_3 and OCH_3 (**2l** and **2m**) at *para* position afforded excellent yields of aryloxyacetonitriles, whereas those with electron donating group at *meta* or *ortho* position provided the corresponding cyanomethylated products in moderate to good yields (**3n–p**). Phenols bearing relatively weak electron-withdrawing substituents such as ester and halogen were also tolerated, providing the products in moderate yields (**3q–t**). The reactions of 4-nitrophenol and 4-hydroxybenzonitrile with acetonitrile hardly proceeded and no desired products were observed due to the presence of strong electron-withdrawing group on the benzene ring.

In addition, when aniline, amino pyridine or benzyl alcohol was used as substrate, only trace amount of cyanomethylation product was detected. Furthermore, the replacement of acetonitrile with propionitrile or phenylacetonitrile led to the failure of this novel reaction. It might be due to steric effect of ethyl and phenyl group.

Table 3 Cyanomethylation of various substituted phenols with acetonitrile[a b]

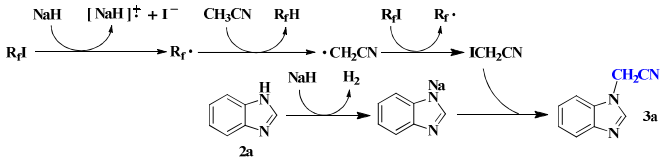


[a] Reaction conditions: **1** (10 mL), substituted phenols (1.0 mmol), *n*-C_4F_9I (1.2 equiv), NaH (3.0 equiv), 50 °C, 12 h. [b] Isolated yields.

To gain possible insights into the reaction mechanism, several control experiments were conducted. Under the optimized reaction conditions, a radical scavenger such as hydroquinone (0.5 equiv), TEMPO (2.0 equiv) and galvinoxyl (2.0 equiv) was added separately, the yields of the reactions between benzimidazole **2a** and acetonitrile **1** decreased significantly (7%, 56% and 35%, respectively). These studies indicated that the reaction may proceed *via* a radical pathway. In addition, when the reaction was performed in the absence of benzimidazole **2a** in the model reaction, 2-iodoacetonitrile was detected (19%, GC-MS). This result clearly revealed that the reaction involved the formation of the key intermediate ICH_2CN in the earlier stage of the reaction.

Based on the above observations, a plausible reaction mechanism is depicted in Scheme 2 (with **2a** as the example). It has been reported that Cs_2CO_3[20,21a], Na_2CO_3[21b], enamines[21c,d] could be used as a radical initiator for the cleavage of C–I bond in perfluoroalkyl iodide to produce perfluoroalkyl radical (R_f•). In the course of optimization of the reaction conditions, we found that other base such as Cs_2CO_3, *t*BuOK, K_3PO_4 and K_2CO_3 could also provide moderate yield of desired product. Therefore, we assume that NaH worked as radical initiator.[22] In initiation step, the cleavage of C–I bond in perfluoroalkyl iodide with the assistance of NaH resulted in the formation of perfluoroalkyl radical (R_f•). The R_f radical can undergo hydrogen abstraction from the CH_3CN to generate the cyanomethyl radical (•CH_2CN) and R_fH. Subsequently, the cyanomethyl radical attacks perfluoroalkyl iodide to produce the key intermediate, ICH_2CN along with perfluoroalkyl radical. Finally, the reaction of ICH_2CN with sodium salt of benzimidazole afforded the cyanomethylated product **3a**.

Scheme 2 Possible mechanism for the reaction of benzimidazole **2a** with acetonitrile



In summary, we have developed the first perfluoroalkyl iodide-promoted cyanomethylation of azoles and phenols with acetonitrile in the presence of NaH through a cyanomethyl radical pathway. The transformation proceeded efficiently in the absence of transition metal catalyst or other additional radical initiator. The main advantage of this method is that the acetonitrile could be used directly without prefunctionalization of it with halogen. Further studies to expand the scope of the C–H bond cleavage of CH_3CN with the assistance of perfluorobutyl iodide are underway in our laboratory.

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