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Synthesis of aliphatic nitriles from cyclobutanone oxime mediated by sulfuryl fluoride (SO_2F_2)

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Abstract

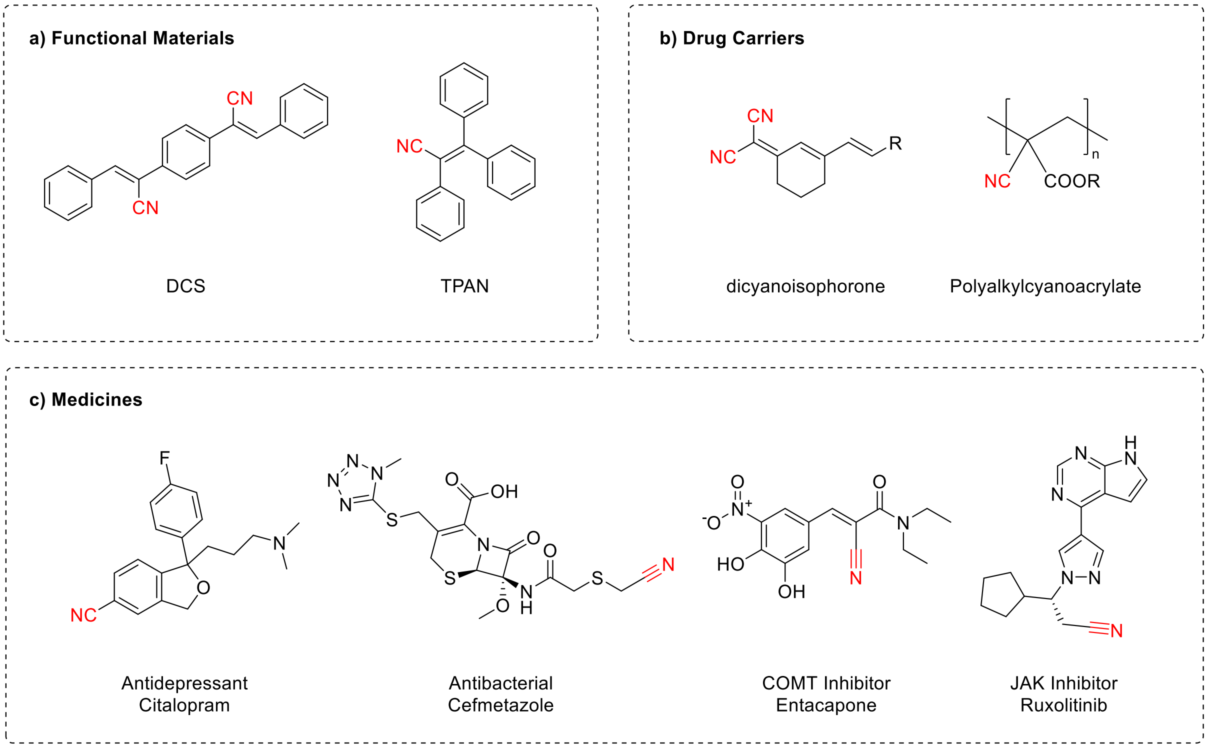
A SO_2F_2-mediated ring-opening cross-coupling of cyclobutanone oxime derivatives with alkenes was developed for the construction of a range of *δ*-olefin-containing aliphatic nitriles with (*E*)-configuration-selectivity. This new method feathers wide substrate scope, mild condition and direct N−O activation.

Keywords

Direct N−O activation; (*E*)-configuration-selectivity; Nitriles synthesis; Ring-opening cross-coupling; Sulfuryl fluoride (SO_2F_2)

Introduction

As an important functional group in organic molecules, the nitrile group is commonly existed in functional materials,[1,2] nanoscale drug carriers,[3-5] biologically valuable molecules and drugs (Scheme 1).[6,7] There are over 70 nitrile-containing drugs approved by the FDA for various indications and more than 140 additional nitrile-containing leads in clinical investigation.[8] Looking into changing the physicochemical properties, in the field of drug discovery, it is important to explore solutions to introduce necessary nitrile group on to a molecule for enhancing the interaction between the drug candidate and the target protein, to further improve the efficacy of the potential drug.[9] The nitrile group can also functionalize as a metabolic blocking site to inhibit the oxidative metabolism of molecules to improve metabolic stability *in vivo*.[10] Consequently, the development of novel synthetic methods and strategies toward nitrile group construction continues to be a focus for synthetic chemists.



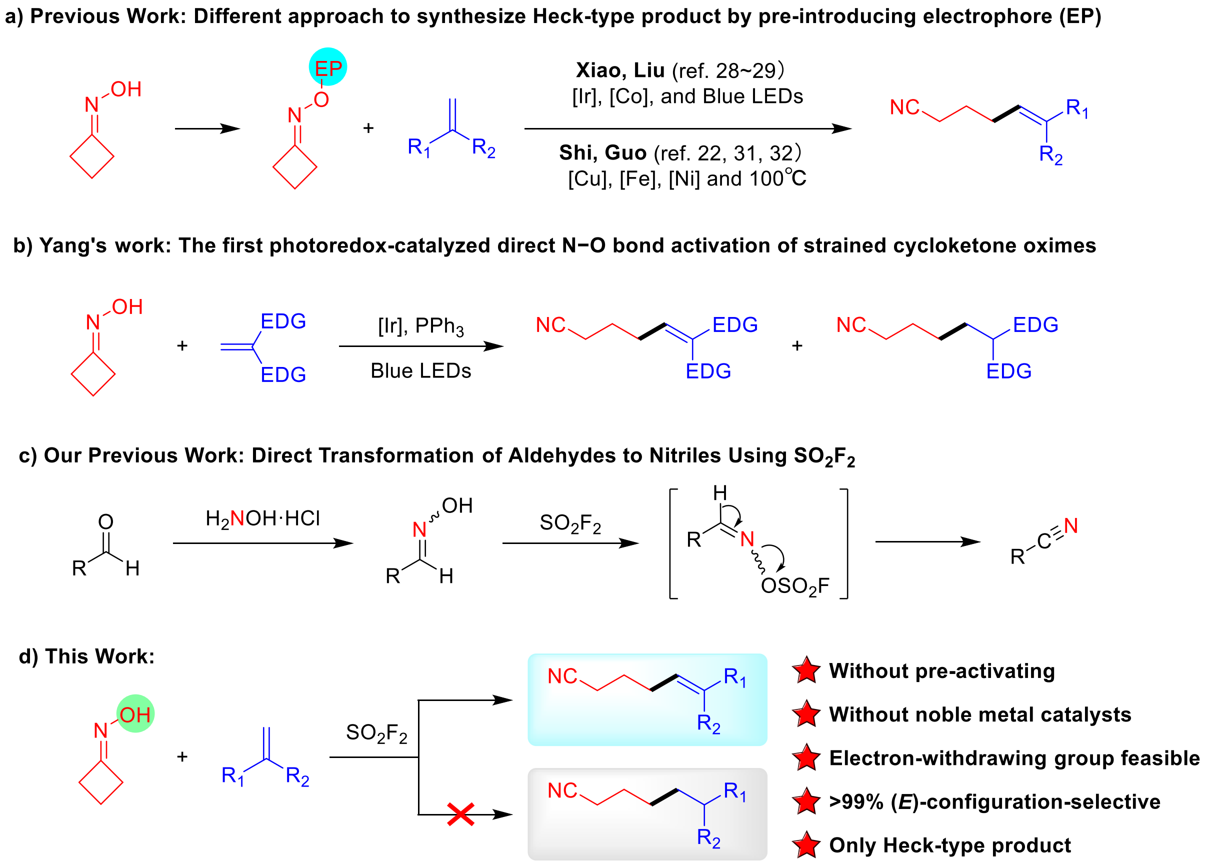
Scheme 1 Representative nitrile-containing functional materials, drug carriers, and medicines.

The cross-coupling reactions of C-C bonds catalyzed by transition-metal complexes play a crucial role in modern organic synthesis, as they make it feasible to synthesize complex structures from available components.[11-13] Indeed, the formation of C(sp^2)-C(sp^3) bonds by cross-coupling has developed rapidly in recent years,[14-16] but it still remains less advanced than the synthesis of C(sp^2)-C(sp^2) bonds.[17,18] This is attributed to the electron-rich of C(sp^3), which leading to the side reactions of alkyl intermediates.[19-21] Besides, most of the C(sp^2)-C(sp^3) reactions employ organic halides or organometallic reagents, which are not environmentally friendly.

Recently, based on the activation effect of *O*-acyloximes on N-O bond,[22-24] a synthesis method for *δ*-olefin-containing aliphatic nitriles by the radical C−C bond cleavage of cycloketone oxime esters derivatives was developed by Shi group (Scheme 2, a),[25] which emerged as an efficient strategy to construct C(sp^2)-C(sp^3)

bonds.[26-28] Later, Xiao[29], Liu[30] and Yang[31] achieved similar transformations through visible-light photocatalysis. In addition, Guo[32,33] improved the protocol by using low-cost nickel and iron catalysis. However, most of these advancements mainly relied on the excellent redox potential manipulation of cyclic oximes esters and adopted the pre-acylation activation strategies. Up to now, only one paper has employed an oxime for the generation of iminyl radical to obtain the similar product, in which, substrates were limited to the electron-rich alkenes (Scheme 2, b).[34,35]

On the other hand, sulfuryl fluoride (SO_2F_2),[36] a kind of inexpensive (about 1 $/kg), abundant and relatively inert electrophile and one of the major sulfur fluoride exchange (SuFEx) click chemistry reagents,[37,38] has been successfully applied as an electrophile to react with hydroxy groups to generate fluorosulfonate esters intermediates for activating in a variety of different transformations.[39-47] Lately, we discovered the SO_2F_2-mediated transformation of primary alcohols to nitriles, which underwent a aldoxime sulfonyl ester intermediate (Scheme 2, c).[48] Drawing inspiration from these excellent works, we contemplated that the N-O bond of cyclobutanone oxime derivatives could be activated by SO_2F_2 *in situ* to enable cleavage of the C−C bond, which could achieve this transformation without going through inefficient pre-introduction of electrophores. Herein, we describe how this concept was translated into experimental reality, leading to a new SO_2F_2-mediated C-C single bond cleavage method for constructing δ-olefin-containing aliphatic nitriles.

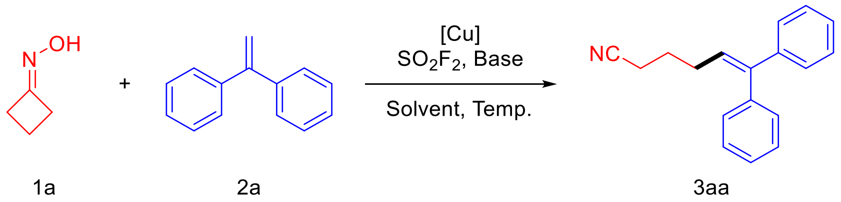


Scheme 2. Activating protocol of cyclobutanone oximes

Results and Discussion

Initially, cyclobutanone oxime (**1a**) and 1,1-Diphenylethylene (**2a**) were selected as starting materials to test the feasibility of the formation of 6,6-diphenylhex-5-enenitrile (**3aa**) in the presence of N, N-Diisopropylethylamine (DIPEA) and Cu(OTf)$_2$ in Dioxane/$PhCF_3$(1:1) under a SO_2F_2 atmosphere at 100℃. The desired product **3aa** was obtained in 24% yield (Table 1, entry 1). And according to the control experiment, SO_2F_2 is essential (Table 1, entry 2). Encouraged by the preliminary result, we then screened other bases, copper catalysts, solvents in order to improve the transformation efficiency (Table 1). The investigation of solvent effect revealed that in 1,4-dioxane the transformations performed the best (Table 1, entry 3-5). A variety of copper catalysts such as CuI, CuCN, Cu_2O were screened, in which some showed good catalytic activity catalysts (Table 1, entry 6-9), and Cu_2O was identified as most effective catalyst for the desired transformation. Accordingly, the loading of CuO_2 was studied, in which, increasing the loading of Cu_2O to 1.0 equivalent, the product **3aa** was obtained in good yield of 72% (Table 1, entry 10). Furthermore, the examination of the effect of base revealed CH_3COOK is the most suitable choice (Table 1, entry 11). Either increasing the temperature to 120℃ or decreasing to 80℃ resulted in an obviously decreased yield (Table 1, entry 13-14), which could probably be attributed to the decomposition of the highly active sulfonyl ester intermediate. The reaction time was also screened, as the yield did not change within the accuracy errors when the time was extended (Table 1, entry 15), among which, 12 hours was the optimal condition. (See the ESI† for more details)

Table 1 Screening the optimized reaction conditions.[a]

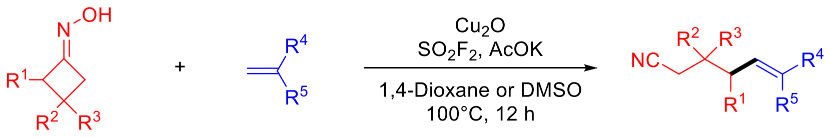


Entry	[Cu] Cat.	Base	Solvent	T(□)	Yield(%)[b]
1[c]	$Cu(OTf)_2$(10 mol%)	DIPEA	Dioxane/$PhCF_3$	100	24
2[c,d]	$Cu(OTf)_2$(10 mol%)	DIPEA	Dioxane/$PhCF_3$	100	N.D.
3[c]	$Cu(OTf)_2$(10 mol%)	DIPEA	$PhCF_3$	100	N.D.
4[c]	$Cu(OTf)_2$(10 mol%)	DIPEA	1,4-Dioxane	100	47
5[c]	$Cu(OTf)_2$(10 mol%)	DIPEA	CH_2Cl_2	100	39
6[c]	CuI(10 mol%)	DIPEA	1,4-Dioxane	100	41
7[c]	CuCN(10 mol%)	DIPEA	1,4-Dioxane	100	40
8[c]	Cu_2O(10 mol%)	DIPEA	1,4-Dioxane	100	55
9[c]	/	DIPEA	1,4-Dioxane	100	N.D.
10[c]	Cu_2O(100 mol%)	DIPEA	1,4-Dioxane	100	72
11[c]	Cu_2O(100 mol%)	CH_3COOK	1,4-Dioxane	100	75
12	Cu_2O(100 mol%)	CH_3COOK	1,4-Dioxane	100	83
13	Cu_2O(100 mol%)	CH_3COOK	1,4-Dioxane	80	54
14	Cu_2O(100 mol%)	CH_3COOK	1,4-Dioxane	120	64
15[e]	Cu_2O(100 mol%)	CH_3COOK	1,4-Dioxane	100	79

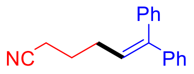
[a] Reaction conditions: A mixture of cyclobutanone oxime (**1a**, 1.5 mmol, 3.0 equiv.), 1,1-Diphenylethylene (**2a**, 0.5 mmol, 1.0 equiv.), copper catalyst and base (5.0 mmol, 10.0 equiv.) in extra dry solvent (0.1 M) was stirred at corresponding temperature under a SO_2F_2 atmosphere (balloon) for 12 h. [b] The yield was determined by HPLC using pure **3aa** as the external standard (t_R = 5.017 min, λ_{max} = 250.0 nm, water / methanol = 20 : 80 (v / v)). [c] 6.0 equiv. of base was used. [d] Under Ar atmosphere (balloon) instead of SO_2F_2. [e] The reaction lasted 16h.

With the optimized reaction conditions in hand, a further extension of other substrates possessing representative functional groups was conducted subsequently to investigate the reaction scope. (Table 2) Alkenes **2b-2e** with different steric effect reacted under the optimized conditions smoothly to deliver corresponding products **3ab** and **3ae** in moderate to good yields (56%-68%). It is important to note that the efficiency of this transformation is significantly influenced by the electronic effect on the aromatic rings of the olefins. The alkenes with electron-donating groups on their aromatic rings usually afforded higher yields of their corresponding products compared to those with electron-withdrawing groups (**3af-3aq**). Furthermore, the desired products were not even obtained when the starting materials were connected extra strong electron-withdrawing groups (such as nitro group) on their aromatic rings. In addition, a series of cyclobutanone oxime derivatives were also smoothly transformed into their corresponding nitriles in excellent yield (**3ba-3da**).

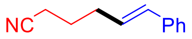
Table 2 Substrate scope of δ-olefin-containing aliphatic nitriles [a, b]



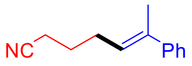
1 **2** **3**



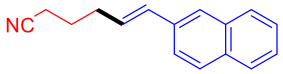
3aa, 83%



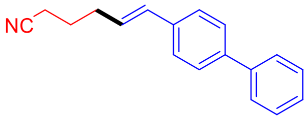
3ab, 68%



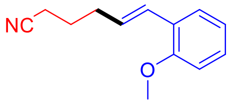
3ac, 66%



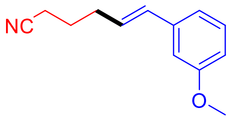
3ad, 56%



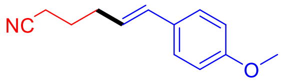
3ae, 62%



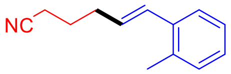
3af, 62%



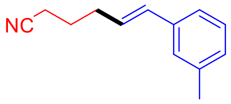
3ag, 52%



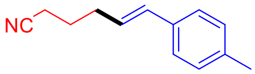
3ah, 63%



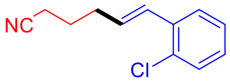
3ai, 64%



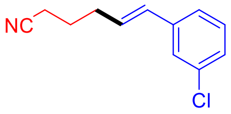
3aj, 55%



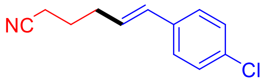
3ak, 36%



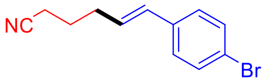
3al, 20%



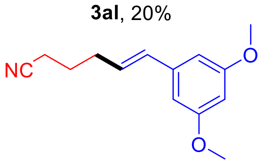
3am, 32%



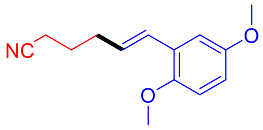
3an, 48%



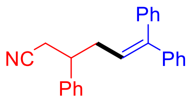
3ao, 42%



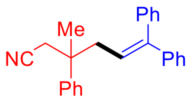
3ap, 62%



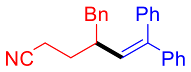
3aq, 51%



3ba, 75%



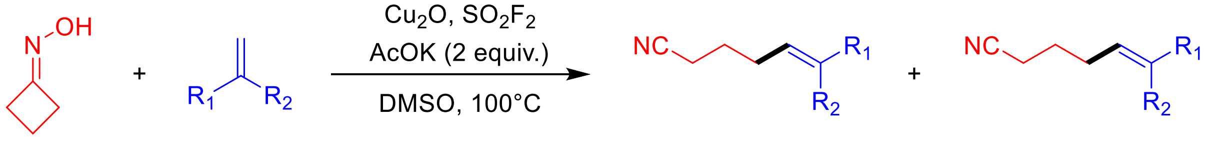
3ca, 70%



3da, 81%

[a] Reaction conditions: A mixture of cyclobutanone oxime derivatives (**1**, 3.0 mmol, 3.0 equiv.), alkene (**2**, 1.0 mmol, 1.0 equiv.), Cu_2O (1.0mmol, 1.0 equiv.) and potassium acetate (10.0 mmol, 10.0 equiv.) in extra dry Dioxane or DMSO (0.1 M) was stirred at 100℃ under a SO_2F_2 atmosphere (balloon) for 12 h. [b] Isolated yield.

Interestingly, when the loading of CH_3COOK was reduced to 2 equivalents, we obtained a mixture of unsaturated nitrile **3aa** and saturated nitrile **4** by column chromatography. (Scheme 3) We speculate that the reduction of the base equivalent may induce the ionization of **1a** and facilitate the ultimate addition process. The selectivity of bases for different process may attract significant attention for further applications.



1a **2a** **3aa** **4**

43% (r/r ≈ 1:1)

Scheme 3. Competition between two reactions caused by the reduction of base equivalent

Conclusion

In conclusion, we have developed a SO_2F_2-mediated ring-opening cross-coupling reaction of cyclobutanone oxime derivatives with alkenes for the synthesis of a class of novel elongated nitriles. The newly constructed *δ*-olefin-containing aliphatic nitriles possess an (*E*)-configuration of olefins. This transformation could be easily activated by SO_2F_2 *in situ* without undergoing the pre-introduction of electrophores.

Supporting Information

Supporting information text

Supporting Information File 1:

File Name: Supporting information

File Format: Docx

Title: Experimental information

Acknowledgements

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