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Direct Synthesis of Nitriles from Aldehydes Using an *O*-Benzoyl Hydroxylamine (BHA) as the Nitrogen Source

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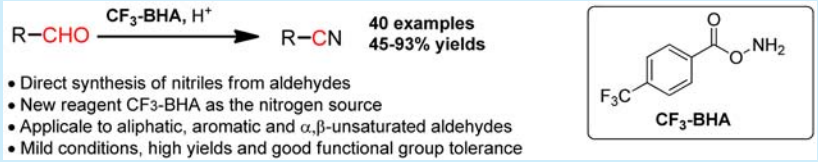
Supporting Information



ABSTRACT: The direct synthesis of nitriles from commercially available or easily prepared aldehydes has been achieved. *O*-(4-CF_3-benzoyl)-hydroxylamine (CF_3-BHA) was utilized as the nitrogen source to generate *O*-acyl oximes in situ with aldehydes, which can be converted to a nitrile with the assistance of a Brønsted acid. Several aliphatic, aromatic, and α,β-unsaturated nitriles that contain different functional groups were prepared in high yields (up to 94% yield). This method has notable advantages, such as simple and mild conditions, high yields, and good functional group tolerance.

The cyano group is one of the most important functional groups, and it exists in many natural products and biologically active molecules.[1] Furthermore, nitriles can be used as versatile building blocks in the synthesis of natural products, pharmaceuticals, agricultural chemicals, and dyes.[2] Therefore, the development of efficient methods for nitrile preparation has attracted intense interest from synthetic chemists.[3] Traditional methods for preparing nitriles, such as the Sandmeyer reaction,[4] the Rosenmund–von Braun reaction,[5] cyanide–halide exchange reactions,[1b,6] and the dehydration of amides or oximes,[7] generally involve complicated operations, heavy metal waste, toxic reagents (e.g., KCN or CuCN), or harsh reaction conditions (e.g., $POCl_3$ and high temperature). In recent decades, aldehydes have been used as ideal synthetic precursors for nitriles due to their ready availability and ease of use.[8−10] These methods suffer from limited substrate scope, complicated operations, and low functional group compatibility.[8] Some strong oxidants are typically essential for the conversion of aldehydes to nitriles, which also lowers functional group tolerance.[8,9] Therefore, the direct synthesis of nitriles from aldehydes under simple conditions with high functional group compatibility is still a synthetic challenge although it is highly useful.[10,7k] Additionally, the selection of the nitrogen source is crucial to this transformation.

Very recently, we synthesized a series of substituted *O*-benzoyl hydroxylamines (BHAs), such as *O*-(4-cyanobenzoyl)-hydroxylamine (CN-BHA, **1a**) and *O*-(4-CF_3-benzoyl)-hydroxylamine (CF_3-BHA, **1b**).[11] These BHAs can serve as the nitrogen source for the conversion of aryl or vinyl aldehydes to aza-arenes under photoredox catalysis (Figure 1a).[11b] When the vinyl aldehyde **2**, was subjected to the photocatalytic conditions via irradiation with white LEDs, the quinoline **3** was observed in a 34% NMR yield. Interestingly, the nitrile **4** was also produced in a 18% NMR yield (Figure 1b). Further

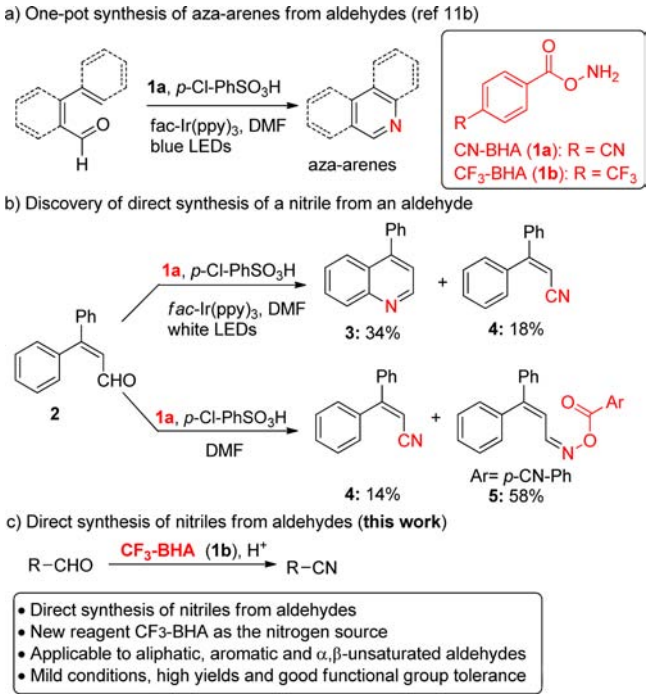


Figure 1. Serendipitous nitrile formation from an aldehyde and BHA.

experiments demonstrated that the photocatalyst and visible light irradiation were not necessary for conversion of the aldehyde **2** to the nitrile **4**. Treatment of the aldehyde **2** with CN-BHA (**1a**) and *p*-Cl-benzenesulfonic acid (CBSA) without

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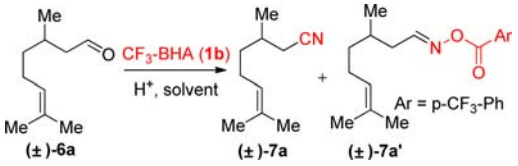
a photocatalyst and visible light irradiation produced the nitrile product **4** in a 14% NMR yield, together with the *O*-acyl oxime **5** in a 58% NMR yield. These results imply that the direct synthesis of nitriles from aldehydes is feasible when BHA is used as the nitrogen source (Figure 1c). Next, we produced a general methodology to directly synthesize nitriles from aldehydes with BHA as the nitrogen source, based on this serendipitous discovery.

The systematic condition screening began with the reaction of racemic citronellal ((±)-**6a**) with CF_3-BHA (**1b**) to form the corresponding nitrile (±)-**7a**. When the solution of (±)-**6a** with **1b** in DMF was stirred at room temperature without any additives, the desired nitrile (±)-**7a** was obtained in a 30% yield based on the ^{1}H NMR analysis. The major side product, *O*-acyl oxime (±)-**7a′**, was obtained in a 60% yield (Table 1, entry 1).

Table 1. Optimized Reaction Conditions[a]



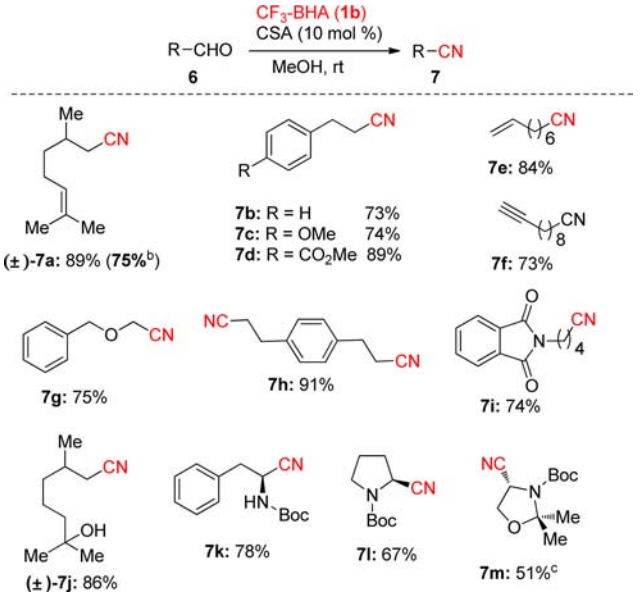
entry	additive	solvent	7a/%[b]	7a′/%[b]
1	–	DMF	30	60
2	CBSA	DMF	67	13
3	CBSA	DMA	40	44
4	CBSA	DMSO	24	40
5	CBSA	NMP	33	28
6	CBSA	MeOH	87	0
7	CBSA	EtOH	74	4
8	CBSA	DCM	26	59
9	CBSA	CH_3CN	30	56
10	CBSA	toluene	35	56
11	CBSA	THF	44	30
12	CH_3CO_2H	MeOH	27	63
13	Cl_3CCO_2H	MeOH	83	0
14	$PhSO_3H$	MeOH	70	0
15	$PhCO_2H$	MeOH	32	65
16	*p*-CF_3-$PhCO_2H$	MeOH	22	74
17	TFA	MeOH	92	0
18	**CSA**	**MeOH**	**92(89**[c]**)**	**0**
19[d]	CSA	MeOH	92	0

[a]Reaction conditions: A solution of (±)-**6a** (0.2 mmol), **1b** (0.24 mmol), and an additive (0.02 mmol) in the indicated solvent (2.0 mL) was stirred at rt for 24 h. [b]^{1}H NMR yield. [c]Isolated yield. [d]CN-BHA (**1a**) was used instead of **1b**. CBSA = *p*-Cl-benzenesulfonic acid. CSA = L-(−)-camphorsulfonic acid.

The *O*-acyl oxime (±)-**7a′** was converted to the nitrile, (±)-**7a**, with the help of a Brønsted acid (*vide infra*). A catalytic amount of CBSA (10 mol %) was added to the reaction mixture as an additive. A cleaner reaction was observed with a 67% yield of (±)-**7a** and a 13% yield of (±)-**7a′** (entry 2). The solvent screening showed that protic solvents, such as MeOH and EtOH, are better solvents and gave 87% and 74% yields of the desired nitrile, respectively (entries 6 and 7). Then, the Brønsted acid was examined (entries 12−18). CSA and TFA were more suitable for this transformation with the same NMR yield (92% yield and 89% isolated yield for CSA). CN-BHA (**1a**) also served as the nitrogen source with an identical efficiency (entry 19). Because CF_3-BHA can be prepared from more inexpensive starting materials compared with CN-BHA, CF_3-BHA was chosen for further investigation.

After determining the optimized reaction conditions, the synthetic potential of this reaction was investigated, and the results are summarized in Schemes 1 and 2. First, a series of

Scheme 1. Conversion of Aliphatic Aldehydes to Nitriles[a]



[a]Reaction conditions: A mixture of **6** (0.2 mmol), **1b** (0.24 mmol), and CSA (0.02 mmol, 10 mol %) in MeOH (2.0 mL) was stirred at rt. The yields are for the isolated products. [b]The reaction was performed on a 8.0 mmol scale. [c]The reaction temperature was 50 °C.

aliphatic aldehydes were tested (Scheme 1). Generally, acceptable to good isolated yields (51−91%) were obtained regardless of the functional groups on the aldehydes (**7a**−**m**). Different functional groups, such as a double bond (**7a** and **7e**), a triple bond (**7f**), an ester (**7d**), an ether (**7g**), a lactam (**7i**), a hydroxyl group (**7j**), an amide (**7k**−**7m**), and a ketal (**7m**), tolerated these conditions. The steric effect affected this formation significantly, and bulky aldehydes, such as the Garner aldehyde, were converted to the corresponding nitrile **7m**, but at an elevated temperature (50 °C). The dialdehyde also produced the dinitrile **7h** in a good yield (91%) with 2.4 equiv of **1b**. The reaction was scaled up to the gram scale (8 mmol) with a slightly lower yield (75%).

We next explored the applicability of this strategy to aromatic aldehydes. The above established conditions were not applicable to aromatic aldehydes (only 23% yield of the desired aromatic nitrile was obtained even at 50 °C). However, after a slight modification, aromatic aldehydes could be also transformed into the corresponding nitriles in DME at 80 °C with the help of 30 mol % of TFA and using the same nitrogen source (for the condition optimization, see the Supporting Information). Satisfactory yields were achieved for a broad range of aromatic aldehydes under these modified conditions (Scheme 2a). Several aromatic nitriles (**9a**−**9q**) were prepared in 45−94% yields depending on the position and electronic properties of the substitutions on the benzene rings. Some sensitive functional groups, such as free phenol (**9h**) and ketone (**9j**), were compatible with this reaction. Heteroarene-nitriles, such as indole (**9m**), pyrrole (**9n**), pyridine (**9o**),

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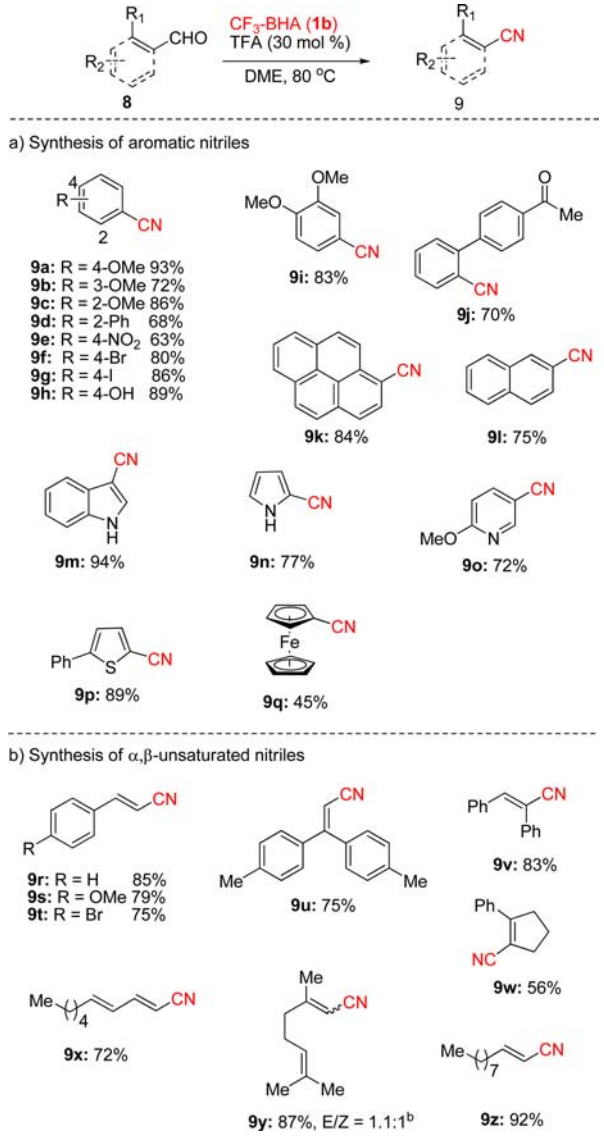
Scheme 2. Conversion of Aromatic and α,β-Unsaturated Aldehydes to Nitriles[a]



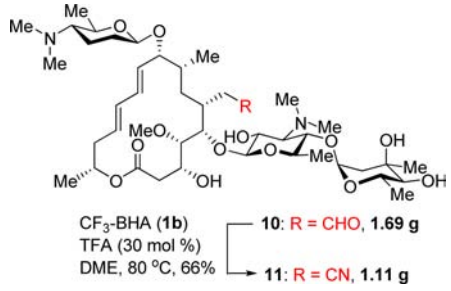
[a]Reaction conditions: A mixture of **8** (0.2 mmol), **1b** (0.3 mmol), and TFA (0.06 mmol, 30 mol %) in DME (2.0 mL) was stirred at 80 °C. The yields are for the isolated product. [b]The corresponding aldehyde **8y** was a 1:1 mixture of the *E*- and Z-isomers.

thiophene (**9p**), and ferrocene (**9q**), were also prepared using this method.

The success with aliphatic and aromatic nitriles inspired us to explore the possibility of preparing more synthetically challenging α,β-unsaturated nitriles from α,β-unsaturated aldehydes using a similar strategy. To our delight, the identical conditions for aromatic aldehydes were applicable to α,β-unsaturated aldehydes. Thus, a series of di- and trisubstituted α,β-unsaturated nitriles (**9r**–**9z**) were produced in 56–92% yields via this method (Scheme 2b). Notably, no Michael addition, which was often observed as a major side reaction in the synthesis of α,β-unsaturated nitriles from the corresponding aldehydes,[10a] was observed.

A functional-group-enriched macrolide antibiotic, named spiramycin,[12] which is widely used in clinics to treat toxoplasmosis and other soft tissue infections was employed to demonstrate the practicability of this new method (Scheme 3). Commercially available spiramycin (**10**, 1.69 g) was treated

Scheme 3. Gram Scale and Late-Stage Modification of Spiramycin



with **1b** (1.5 equiv) and TFA (30 mol %) in DME at 80 °C to furnish the corresponding nitrile **11** (1.11 g) in a 66% yield without flash column chromatography. This strategy afforded a macrolide-based nitrile, which may possess biological activity. Additionally, the sensitive functional groups, such as olefin, tertiary amine, glucoside, lactone, and free hydroxyl, which are in the same molecule, are compatible with our method.

Control experiments were conducted to determine the mechanism of this reaction (Figure 2a). Without the Brønsted

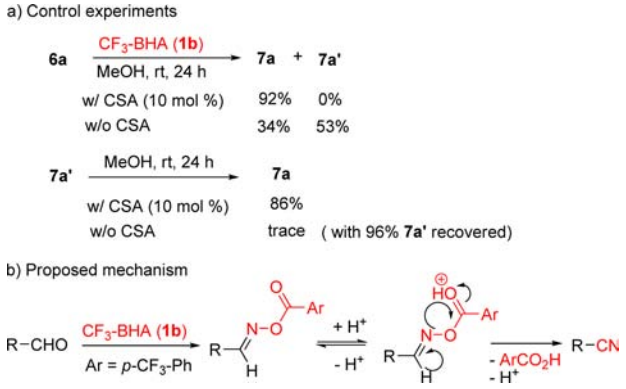


Figure 2. Mechanistic details.

acid, the aldehyde **6a** was fully converted into the *O*-acyl oxime **7a′** but only less than half of the *O*-acyl oxime **7a′** was converted into the nitrile **7a**. The preformed *O*-acyl oxime **7a′** produced the nitrile **7a** in an 86% NMR yield with the help of the Brønsted acid. We observed that almost no conversion of the preformed *O*-acyl oxime **7a′** to the nitrile **7a** occurred in the absence of the Brønsted acid. Thus, a possible mechanism was proposed, as depicted in Figure 2b. First, an *O*-acyl oxime was generated from the aldehyde and CF_3-BHA. The protonated *O*-acyl oxime produced a nitrile after losing a proton and a carboxylic acid.

In summary, we have described a direct synthesis of nitriles from commercially available or easily prepared aldehydes. *O*-(4-CF_3-benzoyl)-hydroxylamine (CF_3-BHA) was utilized as the nitrogen source to generate *O*-acyl oximes in situ with aldehydes, which can be converted to a nitrile with the assistance of a Brønsted acid. Several functionalized aliphatic, aromatic, and α,β-unsaturated nitriles were prepared in high yields. The late-stage modification of spiramycin to the corresponding nitrile on a gram scale was also achieved in a satisfactory yield. The advantages, such as simple and mild

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conditions, high yields, and good functional group tolerance, may lead to application of this method for the synthesis of nitriles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02547.

Full experimental and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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