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Direct synthesis of nitriles from aldehydes with hydroxylamine-*O*-sulfonic acid in acidic water

Dylan J. Quinn, Graham J. Haun, Gustavo Moura-Letts *

Department of Chemistry and Biochemistry, Rowan University, 201 Mullica Hill Rd., Glassboro, NJ 08028, USA

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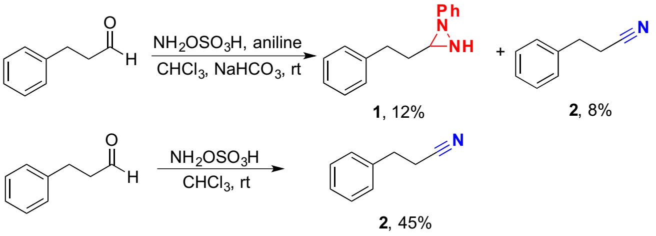
ABSTRACT

Herein is reported the selective transformation of aldehydes to nitriles in the presence of hydroxylamine-*O*-sulfonic acid (NH_2OSO_3H) as a source of the *N* atom and acidic water. The reaction works with high yields for a large array of aromatic and aliphatic aldehydes, as well as hindered aldehydes and conjugated aldehydes without purification. The reaction conditions are very mild and tolerate a wide array of functional groups. In principle, the reaction can be completed in vinegar.

Substituted nitriles are a key molecular scaffold in the field of organic chemistry;[1] they are used as building blocks for the preparation of other functional groups,[2] dyes,[3] materials,[4] and natural products.[5] Nitriles are also a recurrent pharmacophore among commercially available drugs.[6] Thus, the development of more efficient synthetic methods for the synthesis of nitriles remain a goal in the scientific community.[7] Most methods available require the displacement of a good leaving group by toxic cyanide sources (KCN, CuCN)[8] or dehydration of amides and oximes under harsh conditions (high temperatures and aggressive reagents).[9] These methods have historically suffered from poor substrate scope, toxicity of reagents, difficult purifications, low yields, use of expensive and sensitive catalysts, and generation of large amounts of organic waste.[10] Recently, it has been shown that Cu(II)/TEMPO with NH_4OAc and Ag nanoparticles with $K_4Fe(CN)_6$ efficiently promote the formation of nitriles from aldehydes.[11] Moreover, *O*-(4-CF_3-benzoyl)-hydroxylamine and CSA as an organic acid catalyst have been shown to promote the same reaction with a large scope.[12] These improved methods still require complicated purifications and separation methods to remove inorganic and organic impurities from reagents, catalyst, and unreacted substrates. Therefore a metal-free, general method for the synthesis of nitriles from aldehydes remains a challenge for the organic chemistry community.



Scheme 1. Nitrile synthesis discovery.

Recently, we discovered that amines and aldehydes in the presence of hydroxyl amine-*O*-sulfonic acid (NH_2OSO_3H) and $NaHCO_3$ selectively provide substituted diaziridines.[13] However, we found that for substrates with poor conversion (anilines), hydrocinnamaldehyde was transformed into diaziridine **1** in 12% and nitrile **2** in 8% yield (Scheme 1). This result indicated that aldehyde/NH_2OSO_3H condensation followed by elimination becomes a competitive pathway over aldehyde/aniline condensation followed by diaziridine formation.

Based on this observation, we reacted hydrocinnamaldehyde with NH_2OSO_3H in $CHCl_3$ at room temperature and we obtained nitrile **2** in 48% conversion and 35% yield. This result was highly encouraging and we decided to evaluate the reaction variable to optimize the synthesis of nitrile **2** (Table 1). We first focused on understanding the effect of the stoichiometry of NH_2OSO_3H, finding that large excess did not increase either conversion or yield (entries 1 and 2). We then tried the reaction in H_2O and the yield was slightly lower, similar results were found with ACN (entries 3 and 4). We then discovered that at slightly higher temperatures the conversion and yield for nitrile **2** significantly increased (entries 5 and 6). However, the reaction productivity plateaued

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* Corresponding author.
E-mail address: moura-letts@rowan.edu (G. Moura-Letts).

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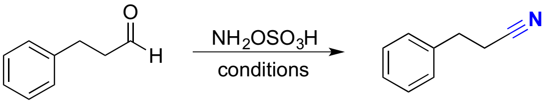
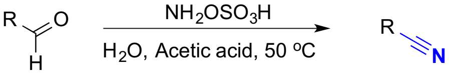
Table 1
Nitrile synthesis reaction optimization

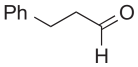
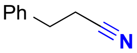
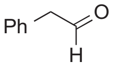
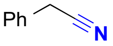
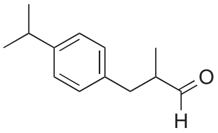
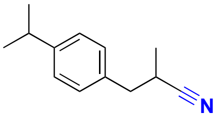
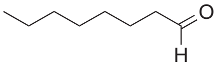
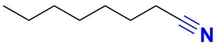
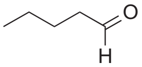
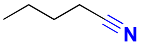
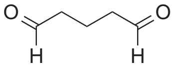
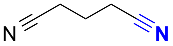
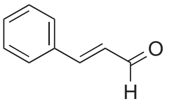
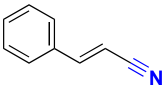
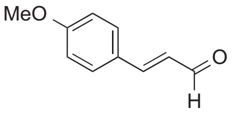
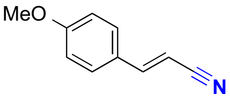
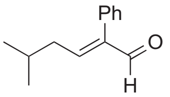
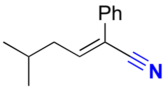
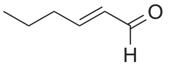
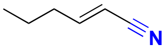


Entry	Stoichiometry[a]	Solvent	Additive[b]	Temperature (°C)	Yield[c] (%)
1	1:2	$CHCl_3$	None	rt	45
2	1:1.5	$CHCl_3$	None	rt	44
3	1:1.5	H_2O	None	rt	38
4	1:1.5	ACN	None	rt	25
5	1:1.5	$CHCl_3$	None	40	48
6	1:1.5	$CHCl_3$	None	50	64
7	1:1.5	$ClCH_2CH_2Cl$	None	60	58
8	1:1.5	$ClCH_2CH_2Cl$	None	80	60
9	1:1.5	H_2O	None	50	58
10	1:1.5	ACN	None	50	60
11	1:1.5	DMSO	None	50	40
12	1:1.5	$ClCH_2CH_2Cl$	PTSA	50	75
13	1:1.5	$ClCH_2CH_2Cl$	TFA	50	79
14	1:1.5	[TMG][LA]	None	50	53
15	1:1.5	[TMG][LA]	TFA	50	84
16	1:1.5	[TMGPS][TFA]	None	50	80
17	1:1.5	[TMGPS][TFA]	H_2O	50	82
18	1:1.5	H_2O	TFA	50	91
19	1:1.5	H_2O	Acetic acid	50	95
20	1:1.5	Vinegar	None	50	94
21	1:1.25	H_2O	Acetic acid	50	93
22	1:1.1	H_2O	Acetic acid	50	94

[a] Aldehyde:NH_2OSO_3H.
[b] 1 equiv of additive.
[c] Isolated yields.

Table 2
Nitrile synthesis reaction scope



Entry	Aldehyde	Nitrile	Yield[a,b] (%)
1			95
2			92
3			94
4			90[c]
5			88
6			86
7			89
8			87
9			86[c]
10			92

[a] Reaction conditions: Aldehyde (1 mmol), Acetic acid (1 mmol), 1 mL of H_2O and NH_2OSO_3H (1.1 mmol) were mixed and heated to 50 °C for 6 h.
[b] Isolated yields.
[c] Reaction crude was purified by standard silica gel chromatography.

around 60% yield at higher temperatures in dichloroethane (entries 7 and 8).

Due to the continued low conversion and based on previous results with protic solvent at high temperatures, we evaluated the reaction productivity with H_2O, ACN and DMSO at 50 °C, finding that the yields remained moderate (entries 9–11). Despite the acidic nature of NH_2OSO_3H, we hypothesized that an exogenous acid would improve the reaction conversion. We found that with an equivalent of PTSA in dichloroethane at 50 °C, nitrile **2** was obtained in a significantly higher yield (75%, entry 12). Trifluoroacetic acid as an exogenous acid also improved the reaction productivity (79% yield, entry 13). Despite the good conversion and yields, we hypothesized that acidic ionic liquids may provide a more suitable medium for this transformation. Our laboratory is also focused on introducing Brønsted acid ionic liquids (BAILs) as green and recyclable options for organic transformations.[14] We found that tetramethylguanidinium lactate [TMG][LA] efficiently promoted the formation of nitrile **2** in moderate yield (53% yield, entry 14) and in the presence of TFA nitrile **2** was isolated in 84% yield (entry 15).

Tetramethylguanidinium propanesulfonic acid trifluoromethylacetate [TMGHPS][TFA] successfully promoted the transformation of hydrocinnamaldehyde to nitrile **2** with NH_2OSO_3H in 80% yield at 50 °C and 84% with H_2O as an additive (entries 16 and 17). Other BAILs proved to be less productive for this transformation or required significantly higher temperatures. We then tried H_2O with TFA and were surprised to find that conversion and yield increased quite considerably (91% yield, entry 18). Acetic acid provided a slightly better yield. To further validate the robustness of the transformation we ran the reaction in vinegar which afforded similar high yields (entries 19 and 20). We still wanted to improve the stoichiometry of the reaction, and found that conversion and yield remained very high with very little excess of NH_2OSO_3H (entries 21 and 22). Under these conditions we were able to directly extract the pure organic product without further purification.

We then focused on enals as substrates for this reaction. We would expect the 1,4-addition with NH_2OSO_3H to be much less favored over the 1,2-addition pathway, and found that cinnamaldehyde and *p*-methoxycinnamaldehyde indeed provided the respective nitriles in very high yields (89% and 87%, entries 7 and 8). Moreover, we observed that alkyl enals and trisubstituted enones are transformed to the respective nitriles in equally high yields (86% and 92%, entries 9 and 10). We also wanted to assess if this method was compatible with oxyaldehydes with acid-sensitive protecting groups; unfortunately, we observed that 3-*t*-butyldiphenylsilyloxy propanal provided the respective nitrile in very low yield along with many impurities. Other protected oxyaldehydes failed to provide the nitrile in efficient yields.

The nitrile synthesis scope for aliphatic and conjugated aldehydes has proven to be highly successful. Lastly, we wanted to investigate the scope of aromatic aldehydes with a large array of substitution patterns (Table 3). Aromatic aldehydes bearing substituents on the *para* position provided the respective nitrile in