



Oxoammonium salt-mediated oxidative nitriles synthesis from aldehydes with ammonium acetate



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ABSTRACT

An efficient and scalable route for the synthesis of nitriles was developed by oxoammonium salt (4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate) mediated oxidative conversion of aldehydes with NH₄OAc. A variety of aliphatic aldehydes as well as benzaldehydes were converted into the corresponding nitriles in high yields. The nitroxyl radical which is the reduced species of the used oxoammonium salt was recovered by simple acid-base extraction for the recycling.

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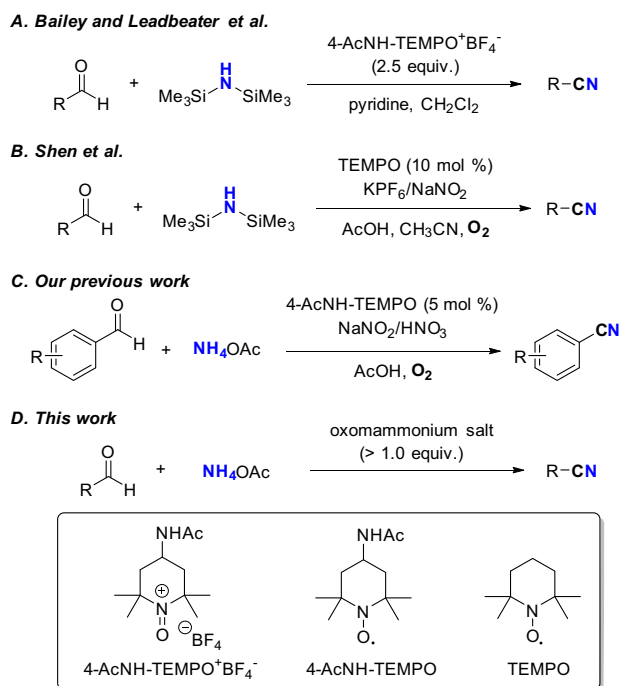
The nitrile moiety is a highly important functional group in organic synthesis, because it could be employed as a versatile intermediate for the synthesis of various functional groups as well as heterocycles.¹ Besides, the nitrile moiety itself plays a crucial role in numerous fruitful compounds such as pharmaceuticals, agrochemicals, and functional materials.² The most traditional methods for the preparation of nitriles are substitution reactions³ such as Sandmeyer reaction⁴ and Rosenmund-von Braun reaction⁵ using metal cyanide. In order to avoid the use of toxic metal cyanides, several organic cyanide sources have been investigated.⁶ Functional group transformations from nitrogen-containing functionalities to nitriles are another pathways that no direct incorporation of cyano groups are necessary. Such transformations are including double oxidation of primary amines⁷ and dehydration of amides⁸ or aldoximes.⁹ These approaches sometimes require harsh reaction conditions and showed several limitations in substrate scope and scalability. Recently, the oxidative transformations of aldehydes or alcohols with a nitrogen source have received much attention. A variety of oxidants including (*n*-Bu₄-N)₂S₂O₈, I₂, NaCl₂, PhI(OH)OTs have been stoichiometrically employed for the synthesis of nitriles.¹⁰ In addition, aerobic oxidative nitrile synthesis using oxygen as a terminal oxidant have been developed,¹¹ although the safety issue should be considered in plant scale.

Oxoammonium salts are interesting oxidants with three oxidation states; oxoammonium salts, nitroxyl radicals, and hydroxyl amines.¹² In metal-free conditions, the oxoammonium salt acts as an oxidant and the hydroxyl amine is produced (two-electrons redox).¹³ On the other hand, it was proposed that the one-electron redox between the nitroxyl radical and the hydroxyl amine facilitated the oxidation in the presence of transition metal co-catalyst such as Cu.¹⁴ The redox system between oxoammonium salts and hydroxyl amines is attractive because they are metal-free and recyclable.¹⁵ In addition, these systems provide highly selective oxidations under mild conditions. Therefore, diverse oxidative transformations such as alcohol oxidation, amine oxidation, oxidative esterification, oxidative cleavage of ether, cross dehydrogenative coupling (CDC reaction), silyl enol conversion, and cycloaddition synthesis have been accomplished stoichiometrically¹⁶ or catalytically.¹⁷ However, few examples of metal-free aldehydes to nitriles transformations mediated by oxoammonium salt were reported.^{18,19}

In 2015, Bailey and Leadbeater et al. reported that 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (4-AcNH-TEMPO⁺BF₄⁻, Bobbitt's Salt) mediated oxidative nitriles synthesis from aldehydes and alcohol using hexamethyldisilazane (HMDS) (Scheme 1, A).^{18a} Although this protocol showed good substrate scope and functional group tolerance in mild conditions, the requirement of toxic HMDS as a nitrogen source made this protocol less attractive. In 2016, Shen group developed an oxidative aldehydes to nitriles transformation using catalytic

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Scheme 1. Previously reported oxoammonium salt-mediated nitriles synthesis from aldehydes.

amount of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), but the use of HMDS was still required (Scheme 1, B).^{18c} Recently, our group reported 4-acetamido-2,2,6,6-tetramethylpiperidine-*N*-oxyl (4-AcNH-TEMPO) catalyzed aerobic oxidative conversions of aldehydes to nitriles using easily accessible NH₄OAc (Scheme 1, C).^{18b} In this catalytic system, various benzonitriles having electron-donating groups or electron-withdrawing group were obtained in good yields, however, the oxidative conversions of aliphatic aldehydes were problematic. In the context of our interests in oxidation,²⁰ we envisioned that the use of stoichiometric amount of oxoammonium salt with NH₄OAc would provide a synthetic route for the aliphatic nitriles synthesis.

We examined oxoammonium salt-mediated oxidative nitriles synthesis with octanal as a model substrate (Table 1). First of all,

we tested our previously reported conditions^{18b} with a stoichiometric amount of 4-AcNH-TEMPO⁺BF₄⁻. Gratifyingly, the formation of octanenitrile was observed in 50% yield (entry 1). The use of TEMPO⁺BF₄⁻ instead of 4-AcNH-TEMPO⁺BF₄⁻ showed worse yield (entry 2). The oxidative nitriles synthesis was carried out in different solvents such as CH₃CN, CH₂Cl₂, DMF, and DMSO, but none of them were superior to acetic acid (entries 3–5).²¹ The use of other ammonium salts such as NH₄Cl and aqueous NH₃ showed poor results (entries 6 and 7). The acceptable yields were obtained when the reaction temperature and the amount of ammonium salt were increased (entries 8–10). The reduction of 4-AcNH-TEMPO⁺BF₄⁻ gave the octanenitrile product in moderate yield (entry 11).

With the optimized conditions in hands (Table 1, entry 10), the substrate scope of aliphatic aldehydes was investigated (Table 2). Both linear aldehydes including octanal, decanal, and 6-chlorohexanal and branched aldehyde such as 2-ethylhexanal showed good yields (entries 1–4). Interestingly, the aldehydes which have no alpha proton exhibited better reactivity and produced the corresponding nitriles in high yields (entries 5–7). Although cyclohexanecarboxaldehyde and its derivatives showed full conversions, the product yields were poor (entries 8 and 9). The double bond in 3-cyclohexene-1-carboxaldehyde was tolerable in the present oxidative nitrile synthesis (entry 10). Hydrocinnamaldehyde derivatives were converted to the corresponding nitriles albeit moderate yields (entries 11–13).

The developed method was applied to the benzaldehydes for the synthesis of benzonitriles (Table 3). Benzaldehydes which have substituents at para position showed good reactivities regardless of electronic environments (entries 1–7). Although 3-methyl benzaldehyde showed a moderate yield (entry 8), the oxidative transformation of 2-methyl benzaldehyde (entry 9) was successful with high yield. Piperonylnitrile was synthesized by the developed oxidative method with good yield and functional group tolerance (entry 10), however, the oxidative nitriles synthesis of mesitaldehyde showed poor conversion and yield presumably due to steric reason (entries 11). Not only vinyl aldehyde such as cinnamaldehyde but also polyaromatic aldehyde such as 1-naphthaldehyde underwent the developed oxidative transformation smoothly (entries 12–13). In addition, heteroaromatic nitrile was also synthesized (entry 14). Interestingly, 1,3-dicyanobenzene was produced by the oxidation of isophthalaldehyde (entry 15).²²

Table 1
Optimization for oxoammonium salt-mediated octanal to octanenitrile transformation.^a

Entry	Oxoammonium salt	Solvent	NH ₄ X (equiv)	Yield (%) ^b
1	4-AcNH-TEMPO ⁺ BF ₄ ⁻	AcOH	NH ₄ OAc (2.4)	50
2	TEMPO ⁺ BF ₄ ⁻	AcOH	NH ₄ OAc (2.4)	38
3	4-AcNH-TEMPO ⁺ BF ₄ ⁻	CH ₃ CN	NH ₄ OAc (2.4)	40
4	4-AcNH-TEMPO ⁺ BF ₄ ⁻	CH ₂ Cl ₂	NH ₄ OAc (2.4)	20
5	4-AcNH-TEMPO ⁺ BF ₄ ⁻	DMF	NH ₄ OAc (2.4)	33
6	4-AcNH-TEMPO ⁺ BF ₄ ⁻	AcOH	NH ₄ Cl (2.4)	13
7	4-AcNH-TEMPO ⁺ BF ₄ ⁻	AcOH	NH ₃ (aq) (2.4)	38
8 ^c	4-AcNH-TEMPO ⁺ BF ₄ ⁻	AcOH	NH ₄ OAc (2.4)	48
9 ^d	4-AcNH-TEMPO ⁺ BF ₄ ⁻	AcOH	NH ₄ OAc (2.4)	60
10 ^d	4-AcNH-TEMPO ⁺ BF ₄ ⁻	AcOH	NH ₄ OAc (4.0)	73
11 ^{d,e}	4-AcNH-TEMPO ⁺ BF ₄ ⁻	AcOH	NH ₄ OAc (4.0)	47

^a Reaction conditions: octanal (0.3 mmol), oxoammonium salt (2.0 equiv), NH₄X in solvent (0.6 mL) under N₂ balloon at 50 °C for 12 h.

^b Yield determined by ¹H NMR spectroscopy (internal standard: 1,1,2,2-tetrachloroethane).

^c At room temperature.

^d at 70 °C.

^e 1.0 equiv of oxoammonium salt was used.

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