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Direct oxidative conversion of alkyl halides into nitriles with molecular iodine and 1,3-diiodo-5,5-dimethylhydantoin in aq ammonia

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ABSTRACT

Various benzylic halides were smoothly and directly converted into the corresponding aromatic nitriles in high yields using molecular iodine and 1,3-diiodo-5,5-dimethylhydantoin, respectively, in aq ammonia. Similarly, primary alkyl halides were also converted into corresponding nitriles in moderate to good yields using molecular iodine and 1,3-diiodo-5,5-dimethylhydantoin in aq ammonia, although a long reaction time was required. The present reaction is a new method for the preparation of aromatic nitriles from benzylic halides and a new method for the conversion of alkyl halides into corresponding nitriles with retention of the number of carbon atoms.

1. Introduction

Molecular iodine is one of the simplest oxidants currently available. It is highly affordable and has relatively low toxicity. Considered to be an environmentally benign oxidizing agent for organic synthesis, molecular iodine is used in various organic reactions, including the oxidation of alcohols or aldehydes to esters, the oxidation of sulfides to sulfoxides, the oxidation of cyclohexenones to benzene rings, the introduction of protecting groups, the deprotection of protecting groups, iodocyclization, carbon–carbon bond formation, and the formation of heterocycles.[1] Synthetic studies of 1,3-diiodo-5,5-dimethylhydantoin (DIH) are extremely limited,[2] although its structure is similar to that of *N*-iodosuccinimide (NIS). However, as DIH (MW=380) has two N–I bonds, it can be expected that 1 equiv of DIH has the same oxidative ability as 2 equiv of molecular iodine (MW=254) or NIS (MW=225). Thus, DIH is highly efficient and economical. On the other hand, nitriles are one of the most important synthetic transformation precursors because they can be easily converted into esters, amides, carboxylic acids, amines, and nitrogen-containing heterocycles, particularly tetrazoles that have potent biological activity,[3] and have been used as synthetic intermediates for agricultural chemicals, pharmaceuticals, and functional materials.[4] The most typical preparation method of nitriles is the reaction of alkyl halides with highly toxic metal cyanide via a nucleophilic pathway. However, this reaction induces one-carbon homologation. Consequently, nitriles are generally prepared by the dehydration of amides with $SOCl_2$, TsCl/Py, P_2O_5, $POCl_3$, $COCl_2$, $(EtO)_3P/I_2$, or Ph_3P/CCl_4, by the condensation of carboxylic acids with NH_3/silica gel or NH_3/ethyl polyphosphate, and by the reaction of esters with Me_2AlNH_2.[5] Nitriles can also be easily obtained by the oxidation of primary amines using AgO, $Pb(OAc)_4$, cobalt peroxide, $Na_2S_2O_8$ or $(Bu_4N)_2S_2O_8$ with metals, NaOCl, $K_3Fe(CN)_6$, Cu(I) or Cu(II) with oxygen, $RuCl_3$ or related Ru reagents, PhIO, and trichloroisocyanuric acid with TEMPO.[6] However, to the best of our knowledge, the direct oxidative conversion of alkyl halides into corresponding nitriles with retention of the number of carbon atoms has never been reported.[7] As part of our ongoing studies on the use of molecular iodine and DIH for organic synthesis,[8] we would like to report the direct oxidative conversion of benzylic halides and primary alkyl halides into corresponding aromatic nitriles and aliphatic nitriles with molecular iodine and DIH, respectively, in aq ammonia.

2. Results and discussion

2.1. Direct oxidative conversion of benzylic halides and alkyl halides into corresponding nitriles with molecular iodine in aq ammonia[7]

Recently, we reported the direct, efficient, practical, and less toxic oxidative conversion of primary alcohols and amines into

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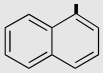
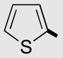
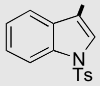
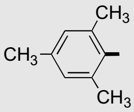
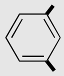
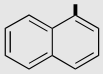
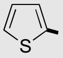
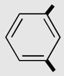
corresponding nitriles using molecular iodine in aq ammonia.[9] Based on the results of that study, we planned to perform the direct oxidative conversion of primary alkyl halides into corresponding nitriles using molecular iodine in aq ammonia. Primary alkyl halides should react with ammonia via the S_N2 nucleophilic pathway to form corresponding primary amines that can be smoothly oxidized to corresponding nitriles by molecular iodine in a one-pot manner. Practically, the reaction was carried out by treating benzyl chloride (1 mmol) with molecular iodine (2.1 mmol, 2.1 equiv) smoothly in aq ammonia (28–30%, 3 mL) at 60 °C in a standard reactor under an empty balloon to provide benzonitrile in good yield, as shown in Table 1 (entry 1). *p*-Chlorobenzyl, *p*-nitrobenzyl, *p*-methylbenzyl, *p*-methoxybenzyl, and 1-naphthylmethyl chlorides could be also converted into corresponding nitriles in good yields under the same conditions (entries 2–6). Benzyl, *p*-chlorobenzyl, *p*-nitrobenzyl, *p*-methylbenzyl, *p*-methoxybenzyl, and 1-naphthylmethyl bromides could be also converted into corresponding nitriles in good yields under the same conditions using 2.4 mmol of molecular iodine (entries 11–16). The same treatment of benzyl iodide provided benzonitrile in good yield (entry 19). 3-Chloromethyl-1-tosylindole and 2,4,6-trimethylbenzyl chloride could also be converted into corresponding nitriles in good yields under the same conditions (entries 8 and 9). When the same reaction was carried out with 2-halomethylthiophene as substrate, the yield of 2-cyanothiophene was low. However, after treating 2-halomethylthiophene with aq ammonia for 2 h at rt, adding molecular iodine to the reaction mixture, and warming the obtained mixture at 60 °C, 2-cyanothiophene was obtained in moderate yields (entries 7 and 17). One of the reasons why the yield of 2-cyanothiophene was lower than that of the other aromatic nitriles may be the low boiling point of 2-cyanothiophene. Treatment of 1,3-bis(chloromethyl)benzene and 1,3-bis(bromomethyl)benzene with molecular iodine (4.2 equiv and 4.8 equiv) in aq ammonia gave 1,3-dicyanobenzene in good yields (entries 10 and 18).

Table 1
Conversion of benzylic halides into aromatic nitriles with I_2 in aq NH_3

$$\text{Ar}{-}\text{CH}_2\text{X} \xrightarrow[60\ ^\circ\text{C}]{\mathbf{I_2},\ \text{aq.NH}_3\ (3.0\ \text{mL})} \text{Ar}{-}\text{CN}$$

Entry	X	Ar	I_2 (equiv)	Time (h)	Yield[a] (%)
1	Cl	C_6H_5	2.1	4	73
2	Cl	*p*-ClC_6H_4	2.1	10	73
3	Cl	*p*-$O_2NC_6H_4$	2.1	4	92
4	Cl	*p*-$CH_3C_6H_4$	2.1	2	82
5	Cl	*p*-$CH_3OC_6H_4$	2.1	4	88
6	Cl		2.1	4	83
7	Cl		2.1	4[b]	60
8	Cl		2.1	4	61
9	Cl		2.1	4	86
10	Cl		4.2	4	81
11	Br	C_6H_5	2.4	4	78
12	Br	*p*-ClC_6H_4	2.4	8	78
13	Br	*p*-$O_2NC_6H_4$	2.4	4	88
14	Br	*p*-$CH_3C_6H_4$	2.4	4	88
15	Br	*p*-$CH_3OC_6H_4$	2.4	4	84
16	Br		2.4	4	87
17	Br		2.4	4[b]	49
18	Br		4.8	4	74
19	I	*p*-ClC_6H_4	2.4	8	78

[a] Isolated yield.
[b] I_2 was added after 2 h.

Clearly, the present reaction is a good method for the preparation of aromatic nitriles from benzylic halides directly. That means we do not need to use the Sandmeyer reaction of diazonium with toxic CuCN or the dehydration of aromatic amides with dehydrating agents.

When the same reaction was carried out under the same conditions with 1-iodododecane (1 mmol) as substrate, corresponding lauronitrile was not formed at all and the starting material was quantitatively recovered. Then, we examined the effect of additives as cosolvent, such as THF, dioxane, DMSO, or DMF, on promoting the nucleophilic reaction of ammonia with 1-iodododecane, and after several trials, we found that the addition of a small amount of DMF in a screw-capped glass vial (10 mL), instead of the use of a standard reactor under a balloon, improved the yield of lauronitrile. We believe that the evolution of ammonia gas from the reaction mixture under the present conditions is restrained by using a screw-capped glass vial, since the reaction of aliphatic primary alkyl halides with ammonia proceeds rather slowly compared with that of benzylic halides with ammonia. Thus, DMF (0.01 mL) was added to a mixture of 1-iodododecane in aq ammonia (1 mL) in a screw-capped glass vial, and the obtained mixture was warmed at 60 °C for 72 h. Then, molecular iodine (3 equiv) and aq ammonia (6 mL) were added to the reaction mixture and again the mixture was warmed at 60 °C for 4 h to provide lauronitrile in 75% yield (entry 1). Based on these results, 1-bromododecane and 1-chlorododecane were also treated with molecular iodine in aq ammonia and a small amount of DMF to form corresponding lauronitrile in good to moderate yields under the same conditions (entries 2 and 3). The reactivity depends on the alkyl halides, i.e., primary alkyl chlorides are less reactive than primary alkyl bromides and iodides. On the other hand, other primary alkyl-chain halides, such as 3-phenylpropyl halides, 4-phenylbutyl halides, 5-phenylpentyl halides, and 11-haloundecanoic acids, were efficiently converted into corresponding nitriles in good yields without DMF (entries 9–17). 1,10-Diiododecane and 1,10-dibromodecane provided the corresponding sebaconitrile in moderate yields by using 6 equiv of molecular iodine under the same conditions (entries 7 and 8). In contrast, cyclohexylmethyl halides were less reactive and adamantylmethyl halides did not react at all due to steric hindrance of the initial conversion into corresponding amines via the S_N2 reaction pathway with ammonia (entries 4–6) (Table 2).

As a result, the present reaction is a novel means to convert alkyl halides into the corresponding nitriles, with retention of the number of carbon atoms.

2.2. Direct oxidative conversion of benzylic halides and alkyl halides into corresponding nitriles with DIH in aq ammonia

The use of 1,3-diiodo-3,3-dimethylhydantoin (DIH) in the iodination of aromatics was first reported in 1965.[2] However, to the best of our knowledge, it has been never used in organic synthesis. We have reported the direct, efficient, practical, and less toxic oxidative conversion of primary alcohols and amines into corresponding nitriles using DIH in aq ammonia.[9c] Thus, based on the