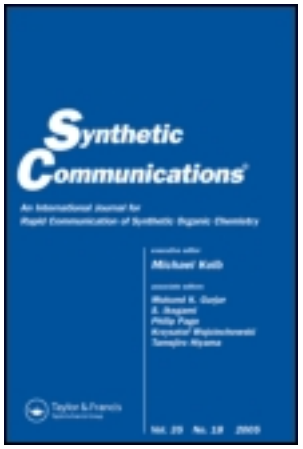

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DIRECT SYNTHESIS OF NITRILES FROM ALCOHOLS OR ALDEHYDES USING H_5IO_6/KI IN AQUEOUS AMMONIA

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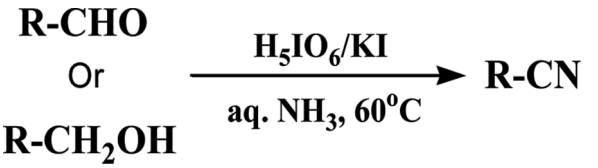
GRAPHICAL ABSTRACT



Abstract *The oxidative conversion of alcohols or aldehydes to the corresponding nitriles in moderate to good yields was easily achieved by treatment of H_5IO_6 and KI in aqueous NH_3. This simple and one-pot system provides easy workup and separation of the product.*

Keywords Alcohol; aldehyde; ammonia; nitrile; periodic acid; potassium iodide

INTRODUCTION

Nitriles are useful functional groups in synthetic organic chemistry. Organic nitriles are versatile synthetic intermediates that can easily be converted into a variety of other functional groups.[1] Hydrolysis of nitriles is useful for the production of hydroxy analogs of methionine derivatives that could have an interest in cattle feeding and for the transformation of compounds containing other acid- or base-sensitive groups.[2] Nitrile groups are of interest in the cyclopropanation process.[3] This group is a facilitator for electron-transfer chain-substitution processes.[4] Several methods are known for the synthesis of nitriles. The most common and well-known procedure for the preparation of nitriles is the nucleophilic displacement of substrates with suitable leaving groups such as halogen compounds.[5] The other reported methods are dehydration of amides or aldoximes,[6,7] conversion of aldehydes,[8] alcohols,[9] or carboxylic acids[10] into nitriles using various reagents, and the direct conversion of amines into nitriles.[11] Some of these reported procedures often suffer from several drawbacks such as tedious workup procedure, poor yields

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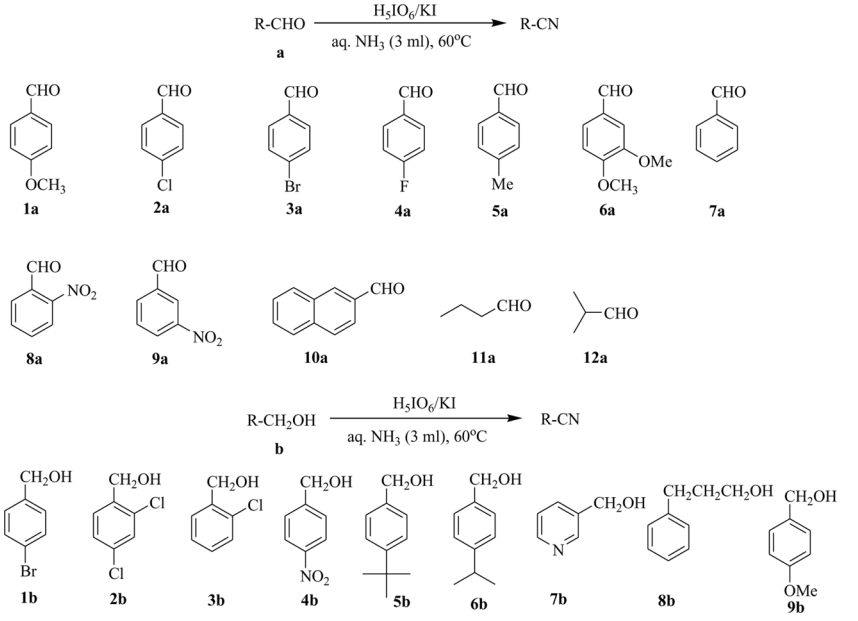
of products, and expensive reagents and catalysts. To overcome these limitations, oxidative methods involving the direct conversion of aldehydes and alcohols to the nitriles using commercially available aqueous ammonia could be a viable alternative and clean route. Ammonia is one of the most attractive sources of nitrogen for the synthesis because of its low cost and wide availability.[12] The oxidative synthesis directly from alcohols or aldehydes with NH_3 as a nitrogen source is a good candidate for the "green nitrile synthesis."[13] However, direct synthesis (especially from alcohols) is very difficult and reported procedures (such as I_2/NH_3,[8] *o*-iodoxybenzoic acid/NH_3,[14] $Ru(OH)_x/Al_2O_3/NH_3$,[15] KI/I_2-TBHP/NH_3,[16] etc.) require the use of toxic and expensive reagents and catalysts.

Therefore, as a part of our studies we became interested in a new, simple, and facile protocol for the direct conversion of alcohols and aldehydes to the corresponding nitriles using periodic acid (H_5IO_6) and potassium iodide (KI) in aqueous ammonia at 60 °C.

RESULTS AND DISCUSSION

In continuation of our ongoing program on the functionalization of organic compounds, we decided to design a new oxidative system for the direct conversion of aldehydes and alcohols to the nitriles. In this light, a variety of aromatic or aliphatic aldehydes and alcohols (Scheme 1) were transformed into nitriles smoothly via reaction with aqueous ammonia in the presence of periodic acid (H_5IO_6) and potassium iodide (KI) at 60 °C. The results of these transformations are summarized in Table 1.



Scheme 1. Oxidative conversion of alcohols and aldehydes into corresponding nitriles.

Table 1. Oxidative conversion of aldehydes (**a**) and alcohols (**b**) to the corresponding nitriles with H_5IO_6/KI[a] in aqueous NH_3 at 60 °C

Entry	Substrate	Time (min)	Yield (%)[b]	Mp (°C) (observed)	Mp (°C) (reported)	Ref.
1	**1a**	90	97	58–61	59	[17]
2	**1a**	90	52[c,d]	—	—	—
3	**1a**	180	No reaction[e]	—	—	—
4	**2a**	90	97	93.5–94.5	94	[17]
5	**3a**	90	93	113–115	110–111	[14]
6	**4a**	90	60	36–37.7	33–35	[14]
7	**5a**	90	99	26–28	25	[13a]
8	**6a**	90	92	68.3–70.6	62.5	[18]
9	**7a**	60	78	Oil	Oil	[14]
10	**8a**	30	80	106–108	104–106	[19]
11	**9a**	90	92	110–112	112	[19]
12	**10a**	90	88	65–67	65–66	[20]
13	**11a**	90	73	Oil	Oil	[14]
14	**12a**	90	78	Oil	Oil	[21a]
15	**1b**	180	75[f]	112–115	110–111	[14]
16	**2b**	180	55[g]	59–61	55–58	[19]
17	**3b**	180	50[f]	41–43	42	[7a]
18	**4b**	180	70[f]	147–149	149–150	[20]
19	**4b**	180	20[e,f]	147–149	149–150	[20]
20	**5b**	180	76[g]	Oil	Oil	[21b]
21	**6b**	180	70[g]	Oil	Oil	[21c]
22	**7b**	180	45[g]	51–53	47	[22]
23	**8b**	180	11[g]	Oil	Oil	[21d]
24	**9b**	180	88[f]	58–59	59	[17]
25	**9b**	180	16[c,d]	—	—	—

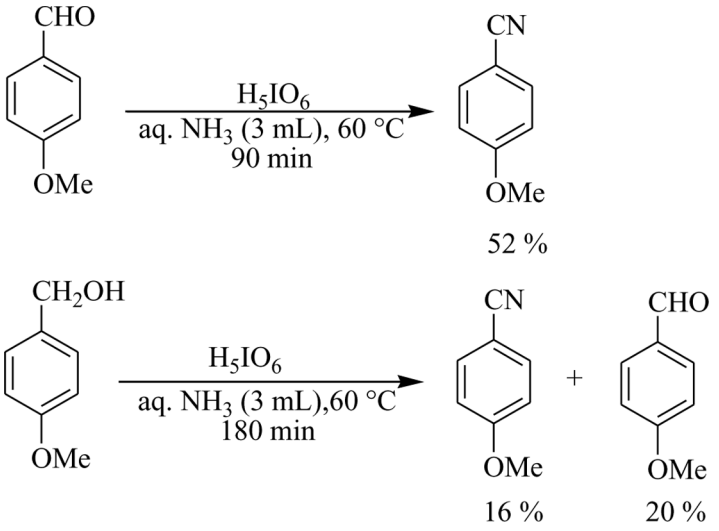
[a]Aldehyde/H_5IO_6/KI = 1:2:0.05; alcohol/H_5IO_6/KI = 1:3:0.8.
[b]Isolated yield.
[c]In the absence of KI.
[d]Yield determined by ^{1}H NMR.
[e]Reaction performed at room temperature.
[f]Yield determined by preparative TLC.
[g]GC yield.

All nitrile synthetic reactions were performed in a sealed tube and conversion of aldehydes and alcohols was indicated by thin-layer chromatography (TLC).

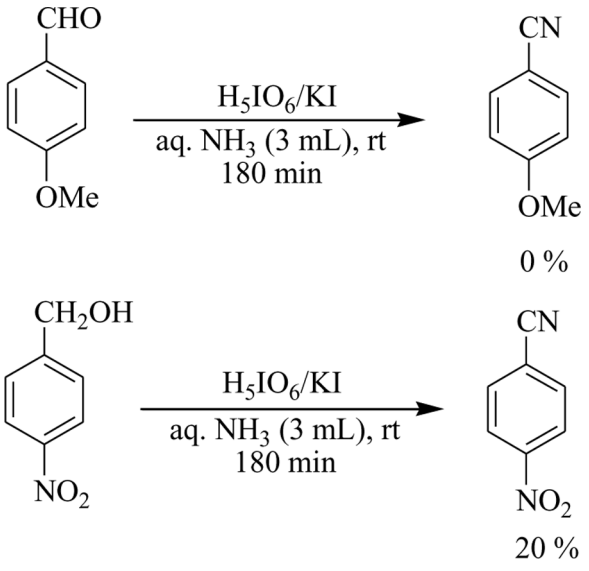
To investigate the role of potassium iodide (KI), 4-methoxybenzaldehyde, and 4-methoxybenzyl alcohol (as a representative samples) were subjected to the oxidative conversion to the corresponding nitrile in the absence of KI. Surprisingly the reactions did not complete (Scheme 2, entries 2 and 25, Table 1).

Also, the effect of temperature in outcome of reaction was examined via doing reaction in the ambient temperature. As can be seen from Table 1 (entries 3 and 20), the temperature is necessary for both conversion of aldehydes and alcohols into nitriles. This result is outlined in Scheme 3.

A proposed mechanism for these transformations is outlined in Scheme 4. In the case of alcohol, formation of aldehyde could be an intermediate, which can be

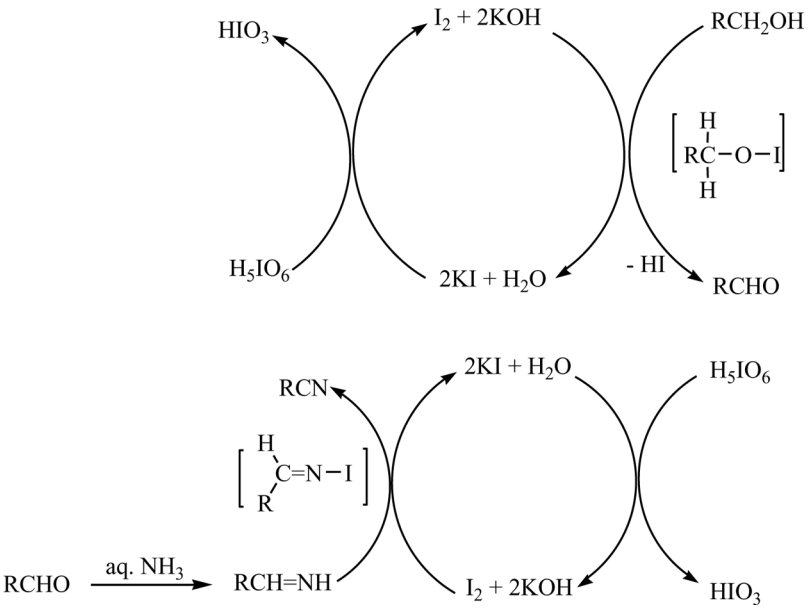


Scheme 2. Conversion of 4-methoxybenzaldehyde and 4-methoxybenzyl alcohol into 4-methoxybenzonitrile in the absence of KI.



Scheme 3. Influence of temperature on the synthesis of nitriles.

achieved via oxidation of alcohol by H_5IO_6 and KI. In the next step aldehyde reacts with ammonia to form an imine, which further reacts with iodine (that formed from H_5IO_6/KI) to form N-iodo aldimine, which eventually oxidized into corresponding nitrile.



Scheme 4. Mechanism of the conversion of alcohols and aldehydes into nitriles.

CONCLUSION

In summary, a simple and convenient protocol has been delineated for the direct conversion of alcohols and aldehydes to their corresponding nitriles using KI in combination with H_5IO_6 in aqueous ammonia. The present method is mild, gives moderate to good yields of nitriles, and avoids the use of expensive and toxic metal catalysts and reagents. Moreover, the present nontransition metallic system also provides an easy scale-up and separation protocol.

EXPERIMENTAL

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. The nitrile products were characterized by comparison of their spectral (IR, ^{1}H NMR, and ^{13}C NMR) and physical data with authentic samples.

Conversion of 4-Methoxybenzylaldehyde to the 4-Methoxybenzonitrile

H_5IO_6 (455.8 mg, 2 mmol) and KI (8.3 mg, 0.05 mmol) were added to a mixture of 4-methoxybenzaldehyde (136 mg, 1 mmol) and aqueous NH_3 (3 mL) at room temperature. The resulting mixture was stirred in sealed tube at 60 °C. After 90 min, the reaction mixture was cooled down to room temperature diluted with water, and $Na_2S_2O_3$ (5 mmol) was added. Finally, the product was extracted with dichloromethane (20 mL), and the organic phase was dried over Na_2SO_4 (3 g) to give 4-methoxybenzonitrile in 97% yield.

Oxidation of 4-Bromobenzylalcohol to 4-Bromobenzonitrile

In a sealed tube a suspension of 4-bromobenzylalcohol (171 mg, 1 mmol), H_5IO_6 (683.7 mg, 3 mmol), and KI (132.8 mg, 0.8 mmol) in aqueous ammonia (3 mL) was stirred at 60 °C. After 180 min, the reaction mixture cooled down to room temperature and was diluted with water, and $Na_2S_2O_3$ (5 mmol) was added. Then product was extracted with dichloromethane (20 mL), and the organic phase was dried over Na_2SO_4 (3 g). Finally the obtained residue was purified by preparative TLC to afford pure 4-bromobenzonitrile in 75% yield.

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