A Facile and Efficient One-Pot Synthesis of Nitriles from Aldehydes Using Hypervalent Iodine(III) Reagents in Aqueous Ammonium Acetate

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Abstract: A facile procedure for the direct oxidation of aldehydes to the corresponding nitriles using either the hypervalent iodine(III) reagent $PhI(OAc)_2$ or a polymer-supported hypervalent iodine(III) reagent $poly{4-[bis(acetoxy)iodo]}$ styrene as oxidant is reported. The oxidation proceeded in water at 70 °C in the presence of sodium dodecylsulfate using ammonium acetate as nitrogen source. The reaction was complete in four hours for the oxidation of benzylic and allylic aldehydes, and gave more than 90% yield in most cases. For the oxidation of aliphatic aldehydes, moderate to excellent yields of nitriles were also obtained after prolonged reaction times.

Key words: aldehydes, hypervalent iodine, nitriles, oxidations, polymers

The conversion of aldehydes into the corresponding nitriles is an important functional group transformation both in laboratory synthesis and industrial production due to the extensive use of nitrile compounds in synthetic chemistry.¹ Moreover, cyanides play a crucial role because they can be easily converted into a variety of functional groups such as acids, amides, ketones, oximes and amines.² Numerous methods involving aldoxime dehydration in a two-step process have been traditionally employed to accomplish this transformation.³ Direct conversion of aldehydes into nitriles without isolation of nitrogencontaining intermediates has also been explored.⁴ Of those one-pot preparative methods developed in recent years, the use of ammonia combined with an appropriate oxidant, such as the systems of NH₃/O₂/CuCl₂·H₂O/MeO-Na,⁵ NH₃/Pb(OAc)₄,⁶ NH₃/I₂/MeONa,⁷ NH₃/S₈/NaNO₂,⁸ NH₃/H₂O₂/CuCl,⁹ NH₃/I₂,¹⁰ NH₃/CAN,¹¹ NH₃/NBS,¹² or NH₃/TBHP/KI(I₂),¹³ is considered to be an expedient method for this transformation. However, volatile ammonia has an undesirable smell and is harmful to the environment. In addition, ammonia is a common contaminant in waste water and biomass cultivation media. The adverse effects of ammonia have promoted the development of various techniques for its removal.¹⁴ Previously, ammonium acetate has also been developed as a good cyanide source in the system of ammonium acetate and molecular iodine.¹⁵ One of the limitations of this procedures is the requirement to use more than stoichiometric amounts of iodine, which could lead to the generation of large amounts of salt as a by-product during work-up.

SYNTHESIS 2010, No. 18, pp 3121–3125 Advanced online publication: 07.07.2010 DOI: 10.1055/s-0030-1258162; Art ID: F06510SS © Georg Thieme Verlag Stuttgart · New York On the other hand, hypervalent iodine reagents have recently received much attention for their mild and highly chemoselective oxidizing properties.¹⁶ For example, widely used pentavelent iodine reagents such as Dess-Martin periodinane (DMP) and its precursor 2-iodoxybenzoic acid (IBX) are widely known as mild and highly selective reagents for the oxidation of alcohols. However, these iodine(V) reagents are potentially explosive and the regenerated iodine(III) species from the oxidations are usually not utilized. Thus, readily available and stable iodine(III) oxidants such as bis(acetoxy)iodobenzene and iodosobenzene is attracting much attention. Recently, Akamanchi and co-workers have reported a mild procedure for the direct oxidative conversion of aldehydes into nitriles using IBX in aqueous ammonia.¹⁷ To the best of our knowledge, there is no report on the use of hypervalent iodine(III) reagents as oxidants for the preparation of nitriles.

In a continuation of our interest in exploring systems for the oxidation of organic compounds,¹⁸ here, we would like to report a facile procedure for the direct oxidation of aldehydes to the corresponding nitriles with PhI(OAc)₂ in the presence of catalytic amounts of sodium dodecylsulfate (SDS) using NH₄OAc as the nitrogen source (Scheme 1).

Scheme 1 Oxidation of aldehydes by $PhI(OAc)_2/SDS$ in aqueous ammonium acetate

Initial experiments were carried out using 4-chlorobenzaldehyde as a model substrate. First, a range of hypervalent iodine reagents, such as: PhIO, PhI(OCOCF₃)₂, PhICl₂, $PhIO_2$ or $PhI(OAc)_2$ were used as oxidant in the reaction at 50 °C, however, all of them were unsatisfactory except for PhI(OAc)₂ (Table 1, entries 1–5). Ammonium salts other than NH₄OAc could also be used as nitrogen source, but lower yields were obtained (Table 1, entries 6-8). When the reaction was allowed to proceed at different temperatures, an optimal yield of 84% was obtained at 70 °C (Table 1, entries 5 and 9-11). However, addition of ZnO or 3 Å molecular sieves to accelerate the dehydration of aldimine, which is formed in situ, to nitrile in the reaction medium had no obvious advantage (Table 1, entries 12 and 13). Use of acetonitrile as a co-solvent to dissolve the aldehyde and PhI(OAc)₂ also did not improve the reaction (Table 1, entry 14). It is well known that in aqueous-phase reactions, addition of surfactants can improve the reactions by solubilization or micelle formation effects. In order to improve the yield and selectivity of the oxidation of aldehydes, we examined the effects of a variety of anionic, cationic and nonionic surfactants (Table 1, entries 15–19). Among the surfactants examined, sodium dodecylsulfate (SDS), an anionic surfactant, was found to be the most effective. The reaction proceeded faster and the yields of nitriles were remarkably increased by addition of SDS to the reaction mixture. In the presence of 20 mol% SDS, the reaction was complete within four hours at 70 °C with 100% conversion of the reactant and about 95% isolated yield of the corresponding 4-chlorobenzonitrile (Table 1, entry 19).

In order to evaluate the versatility of this novel catalytic system, we applied the procedure to the oxidation of a wide range of aldehydes. As shown in Table 2, most aldehydes underwent oxidation to afford the corresponding nitriles in excellent yield. Benzylic aldehydes underwent smooth oxidation (Table 2, entries 1–7). Allylic aldehydes, such as cinnamyl aldehyde (Table 1, entry 8), were

also oxidized efficiently without any observable reaction at the double bond functionality. Even for the oxidation of 2-furaldehyde, a heterocyclic aldehyde, excellent yield was also obtained (Table 1, entry 9). The electronic properties of the substituents in the aromatic ring had a remarkable influence on the rate of the oxidation of aldehydes. Strong electron-withdrawing groups, such as nitro groups, improve the oxidation of the aldehyde (Table 2, entry 4). Strong electron-donating groups, such as a methoxy group, lowered the reaction rate (Table 2, entry 6). This differs from previously reported procedures where the presence of methoxy groups favors aldehyde oxidation.^{11,13} Additionally, steric effects had only a relatively minor influence on the oxidation of aldehydes (Table 2, entries 4 and 5). It is worth mentioning that, together with the good results obtained with benzylic alcohols, the yields obtained from the oxidation of aliphatic aldehydes under the same conditions were also quite high after prolonged reaction times (Table 2, entries 10-12). In view of the fact that the oxidation of aliphatic aldehydes is much more difficult than that of benzylic aldehydes, the

Table 1 Oxidation of 4-Chlorobenzaldehyde^a

Entry	Oxidant	NH ₃	Temp (°C)	Additive	Yield (%) ^b
1	PhIO	NH ₄ OAc	50	_	_
2	$PhI(OCOCF_3)_2$	NH ₄ OAc	50	_	_
3	PhIO ₂	NH ₄ OAc	50	_	27
4	PhICl ₂	NH ₄ OAc	50	_	-
5	PhI(OAc) ₂	NH ₄ OAc	50	_	58
6	PhI(OAc) ₂	NH ₄ Cl	50	_	19
7	PhI(OAc) ₂	NH ₄ HCO ₃	50	-	-
8	PhI(OAc) ₂	$HCOONH_4$	50	_	34
9	PhI(OAc) ₂	NH ₄ OAc	r.t.	_	16
10	PhI(OAc) ₂	NH ₄ OAc	70	_	84
11	PhI(OAc) ₂	NH ₄ OAc	90	_	76
12	PhI(OAc) ₂	NH ₄ OAc	70	ZnO	77
13	PhI(OAc) ₂	NH ₄ OAc	70	3 Å MS	80
14	PhI(OAc) ₂	NH ₄ OAc	70	MeCN	82
15	PhI(OAc) ₂	NH ₄ OAc	70	TBAB	88
16	PhI(OAc) ₂	NH ₄ OAc	70	TEBAC ^c	25
17	PhI(OAc) ₂	NH ₄ OAc	70	Tween80 ^c	63
18	PhI(OAc) ₂	NH ₄ OAc	70	CTAB ^c	52
19	PhI(OAc) ₂	NH ₄ OAc	70	SDS	95

^a Reaction conditions: 4-chlorobenzaldehyde (1 mmol), PhI(OAc)₂ (2 mmol), aq NH₄OAc (3 mL, 30 mmol), additive (0.2 mmol), 70 °C, 5 h, unless otherwise noted.

^b GC yield.

^c TEBAC = benzyltriethylammonium chloride; Tween80 = sorbitan monooleate ethoxylate; CTAB = hexadecyltrimethylammonium bromide.

results obtained in the present procedure were also satisfactory.

We then modified this system by using a polymer-supported hypervalent iodine(III) reagent to develop a practical and clean procedure for the oxidation of aldehydes. Poly{4-[bis(acetoxy)iodo]}styrene (PBAIS) has recently attracted much attention because of its similar reactivity to PhI(OAc)₂ but with the additional advantages of simple workup procedure and easy recovery and recycling.¹⁹ The use of PBAIS instead of PhI(OAc)₂ in the oxidation of aldehydes led to similar results, albeit after longer reaction times. At the end of the reaction, the polymer species were recovered by precipitation from diethyl ether, filtration from the reaction medium, and regeneration by treatment with peracetic acid. The polymer was successfully recycled three times (Table 2, entry 1).

A plausible mechanism for this reaction is depicted in Scheme 2. First, the aldehyde reacts with NH_4OAc to form an aldimine, which then undergoes oxidation by $PhI(OAc)_2$ to afford N–I(OAc)Ph aldimine. Elimination of PhI and HOAc from the aldimine gives the final product nitrile. Iodobenzene was detected at the end of the reaction.

Table 2	Oxidation of Aldehydes to Nitr	les with PhI(OAc) ₂ , SDS	S and Aqueous Ammonium	Acetate ^a
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Entry	Substrate	Product	PhI(OAc) ₂	PhI(OAc) ₂		PhI(OAc) ₂	
			Yield (%) ^b	Time (h)	Yield (%) ^b	Time (h)	
1	СНО	CN	93	2	90 (1st) 88 (2nd) 91 (3rd)	4 4 4	
2	CHO	CI	95	4	93	7	
3	Br	Br	93	4	91	7	
4	O ₂ N CHO	O ₂ N CN	95	4	94	7	
5	CHO	NO ₂ CN	92	4	93	7	
6	МеО	MeO	85	6	81	8	
7	но	HO	80	6	76	8	
8	СНО	CN	98	2	95	4	
9	СНО	CN CN	90	1	83	3	
10	СНО	CN	81	5	75	7	
11	Me(CH ₂) ₆ CHO	Me(CH ₂) ₆ CN	83°	8	78°	12	
12	<i>n</i> -C ₁₁ H ₂₃ CHO	n-C ₁₁ H ₂₃ CN	76 ^c	8	63°	12	
13	СНО	CN	79°	8	71°	12	

^a Reaction conditions: aldehyde (1 mmol), aq NH₄OAc (3 mL, 30 mmol), PhI(OAc)₂ (2 mmol), SDS (0.2 mmol), 70 °C.

^b Yields of isolated products unless otherwise noted.

^c Yields were determined by GC.



Scheme 2 A plausible reaction pathway

In conclusion, a simple and efficient method for the oxidation of aldehydes to the corresponding nitriles with $PhI(OAc)_2$ in the presence of catalytic amounts of SDS using NH_4OAc as the nitrogen source has been developed. A key feature of the oxidation protocol is its inherent simplicity; there is no need for rigorous exclusion of air or moisture to effect a clean oxidation and, in most cases, a simple pass through a plug of silica is enough to obtain highly pure products.

All chemicals (AR grade) were obtained from commercial sources and used without further purification. Poly{4-[bis(acetoxy)io-do]}styrene (PBAIS) was prepared according to a literature procedure.^{19b} Column chromatography was performed using Silicycle (40–60 μ m) silica gel.

4-bromobenzonitrile, 2-nitrobenzonitrile, 4-hydroxybenzonitrile, 2furonitrile, octane nitrile and lauronitrile were identified with commercially available authentic samples and determined by GC–MS. Other products were analyzed by ¹H NMR and GC–MS.

Oxidation of Aldehydes with $\mbox{PhI}(\mbox{OAc})_2/\mbox{SDS/aq}\ \mbox{NH}_4\mbox{OAc};$ Typical Procedure

To a solution of aldehyde (1 mmol), aq NH₄OAc (3 mL, 30 mmol) and SDS (60 mg, 0.2 mmol), was added PhI(OAc)₂ (640 mg, 2 mmol). The mixture was stirred at 70 °C for several hours, while checking the reaction progress by gas- or thin-layer chromatography. After completion, aqueous sodium thiosulfate (50 mL) and Et₂O (20 mL) were sequentially added to the residue and the mixture was stirred vigorously for 10 min. The organic layer was separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined ether phase was concentrated under vacuum and the crude product was purified by column chromatography (petroleum ether–EtOAc, 10:1) to provide the analytically pure product.

Oxidation of Aldehydes with PBAIS/SDS/aq $\rm NH_4OAc;$ Typical Procedure

To a solution of aldehyde (1 mmol), aq NH₄OAc (3 mL, 30 mmol) and SDS (60 mg, 0.2 mmol), was added PBAIS (1.0 g, 2 mmol). The mixture was stirred at 70 °C for several hours, while checking the reaction progress by gas- or thin-layer chromatography. After completion, Et₂O (30 mL) was added and the mixture was filtered to remove the polymer. The organic extract from the filtrate was dried and evaporated. The residue was purified by column chromatography to give pure products, which were analyzed by ¹H NMR and GC/MS. Recovered polymer species poly(4-iodostyrene) was reoxidized by peracetic acid (30% H₂O₂ and Ac₂O) to give PBAIS and reused.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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