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A new efficient method for the conversion of aldehydes into nitriles using ammonia and hydrogen peroxide

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Abstract

Aldehydes were converted into the corresponding nitriles by a homogeneous reaction with ammonia and aqueous hydrogen peroxide in the presence of copper salts or complexes under mild conditions. © 2000 Elsevier Science Ltd. All rights reserved.

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The conversion of aldehydes (1) into the corresponding nitriles (2) is a functional group transformation of significant practical importance, especially in the fine chemical industry. The most widely used general method is based on the dehydration of aldoximes, and although numerous protocols already exist, new variants continue to appear.^{1–5} A few methods are known which involve various transformations of other *N*-substituted azomethine derivatives of aldehydes, such as *N*,*N*-dialkylhydrazones,^{6,7} *O*-2,4-dinitrophenyloximes,⁸ imines with 1-amino-4,6-diphenyl-2-pyridone.⁹ The relatively high cost of hydroxylamine, substituted hydrazines, etc. has stimulated development of methods based on the oxidative dehydrogenation of ammonia-derived azomethines (3) using persulfates,^{10,11} nickel peroxide,¹² iodine,¹³ and oxygen in the presence of Cu catalysts^{14–17} as oxidants under relatively mild conditions (Scheme 1).

1a-h	-120	3a-h	[-=2]	2a-h
RCHO		RCH=NH		RCN
	NLL		ovidant	

Scheme 1. (a) $R = Me_2C = CHCH_2CH_2CMe = CH-$; (b) PhCH = CH-; (c) Ph-; (d) p-MeOPh-; (e) 3,4-methylenedioxyphenyl; (f) MeCH = CH-CH = CH-; (g) $Me_2C = CHCH_2CH_2CH_2CH_2CH_2-$; (h) $n-C_{10}H_{21}-$

From economic and environmental standpoints, the oxygen-based methods^{14–17} seem more attractive than the others,^{10–13} although they have technical drawbacks which limit their practical applicability. For example, some reports^{14,15} use molar ratio copper:substrate of 1:1 or greater. Other procedures^{16,17} use a large excess of ammonia and very dilute solutions.

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Hydrogen peroxide is another environmentally friendly and inexpensive oxidant. However, we found no indication in the literature that hydrogen peroxide can be used for this transformation. Moreover, unsuccessful attempts to use hydrogen peroxide have been described.^{18–28} For example, it is known that aldehydes react with ammonia and hydrogen peroxide to form aminohydroperoxides or aminoperoxides, not nitriles.^{18,19} Nitriles themselves react readily with hydrogen peroxide in the presence of bases giving amides in high yields (the Radziszewski reaction).^{20–23} Both a, β -unsaturated aldehydes and nitriles can be epoxidized by hydrogen peroxide.^{24,25} In the presence of nitriles, hydrogen peroxide epoxidizes non-activated double bonds (the Payne epoxidation).^{26,27} Also, some amounts of the Baeyer–Villiger oxidation products could always be expected on contacting aldehydes and hydrogen peroxide.²⁸

Our primary goal was the conversion of citral (1a) into geranyl nitrile (2a)—a case where all the above mentioned reactions could be anticipated—and chances to obtain nitrile (2a) seemed extremely poor. Nevertheless, dropwise addition of 50% aqueous hydrogen peroxide (CAUTION! strong oxidizer)¹⁸ to a mixture of aldehyde (1a), 29.4% aqueous ammonium hydroxide, and a catalytic

Cu-catalyzed conversion of aldenydes to manes with annihila and 50% hydrogen peroxide in P11011									
Entry	Substrate	R	Method	Catalyst	Product ^b	Conversion, %	Yield, % ^c		
1	1a ^d	Me ₂ C=CHCH ₂ CH ₂ CMe=CH-	А	CuCl	$2a^d$	98	87		
2	1a	Me ₂ C=CHCH ₂ CH ₂ CMe=CH-	А	CuBr	2a	100	80		
3	1a	Me ₂ C=CHCH ₂ CH ₂ CMe=CH-	А	CuOAc	2a	98	79		
4	1a	Me ₂ C=CHCH ₂ CH ₂ CMe=CH-	А	$CuCl_2$	2a	100	80		
5	1a	Me ₂ C=CHCH ₂ CH ₂ CMe=CH-	А	Cu ₂ O	2a	99	78		
6	1a	Me ₂ C=CHCH ₂ CH ₂ CMe=CH-	А	$Cu(AcAc)_2$	2a	99	84		
7	1a	Me ₂ C=CHCH ₂ CH ₂ CMe=CH-	А	Cu powder	2a	99	77		
8	1 a	Me ₂ C=CHCH ₂ CH ₂ CMe=CH-	В	CuCl	2a	99	85		
9	1b	PhCH=CH-	А	$CuCl_2$	2b	100	72		
10	1b	PhCH=CH-	В	CuCl	2b	96	76		
11	1c	Ph-	А	$CuCl_2$	2c	95	24 ^e		
12	1c	Ph-	В	CuCl	2c	96	32		
13	1d	p-MeOPh-	А	$CuCl_2$	2d	83	46 ^e		
14	1d	p-MeOPh-	В	CuCl	2d	83	48		
15 ^f	1e	3,4-Methylenedioxyphenyl	А	$CuCl_2$	2e	82	38 ^g		
16 ^f	1e	3,4-Methylenedioxyphenyl	В	CuCl	2e	92	51 ^g		
17	1f	МеСН=СНСН=СН-	А	$CuCl_2$	2f	98	54		
18	1g	Me ₂ C=CH(CH ₂) ₂ CHMeCH ₂ -	А	$CuCl_2$	2g	87	8 ^e		
19	1h	$n-C_{10}H_{21}-$	А	$CuCl_2$	2h	43	14 ^e		

 Table 1

 Cu-catalyzed conversion of aldehydes to nitriles with ammonia and 50% hydrogen peroxide in *i*-PrOH^a

^a Satisfactory yields of nitrile (**2a**) were also obtained in a variety of other water-miscible solvents: alcohols, glycols, glycol ethers (especially 1-methoxy-2-propanol), DMSO, N-methylpyrrolidone, etc.

^b All products were identified by comparison with authentic samples (GLC).

^c Distilled yields based on reacted substrate.

^d Isomer ratio 2-E/2-Z about 2.5/1.

^e By GLC.

^f In these entries, amount of hydrogen peroxide used was 5.2 moles.

^g Recrystallized from heptane.

amount of cuprous chloride in DMF or *i*-PrOH gave nitrile (2a) in about 10% yield. A significant improvement (50% yield) was observed when both hydrogen peroxide and ammonium hydroxide were added dropwise simultaneously to the other reagents.

Yet better results (Table 1, method A) were obtained when starting aldehyde (1a) (0.38 mol) was also added parallel with hydrogen peroxide (1.4 mol) and ammonium hydroxide (0.44–0.49 mol) to a stirred mixture of copper catalyst (0.01 mol) and 300 ml of *i*-PrOH at 17–30°C (the reaction was noticeably exothermic, so some cooling was necessary). Importantly, the addition rates were selected so as to always maintain low concentrations of all starting reagents and intermediate azomethine (3a) in the course of the reaction. Specifically, ammonium hydroxide was added for about 3 hours, and the addition of aldehyde (1a) and hydrogen peroxide commenced almost simultaneously with ammonium hydroxide and was finished in 2.5 and 4 hours, respectively. Other aldehydes (1b–h) were converted similarly. After a conventional work-up, the products were purified by distillation or crystallization.

In method B, gaseous ammonia (2.5–2.8 mol) was passed for 3 hours into a solution of 4 g of cuprous chloride in 800 ml of *i*-PrOH, while 1.5 mol of aldehyde (1), and 3.35 mol of 50% hydrogen peroxide were added dropwise for 2.5 and 4 hours, respectively. Both procedures A and B were optimized with respect to the conversion of aldehyde (1a) into nitrile (2a) only, which explains the relatively lower yields of other α,β -unsaturated and aromatic nitriles. Poor yields of aliphatic nitriles (2g,h) may be due to the slow rate of oxidative dehydrogenation of the corresponding azomethines (3g,h).

In the case of α,β -unsaturated aldehydes, the formation of small amounts of retro-aldol by-products was observed by GLC, for instance 6-methyl-5-hepten-2-one from aldehyde (1a) or benzaldehyde (and benzonitrile) from (1b). Also, small amounts of carboxylic acids and acetone were formed due to the direct oxidation of starting aldehydes and *i*-PrOH solvent, respectively.

The requirement for a significant excess of hydrogen peroxide over the aldehyde raised a legitimate suspicion that the real oxidant is oxygen formed in the copper-catalyzed decomposition of hydrogen peroxide. However, control experiments starting with aldehyde (1a) and using air or oxygen instead of hydrogen peroxide gave practically no nitrile (2a), so hydrogen peroxide remains the most likely actual oxidant. There is not enough data yet to discuss the mechanistic aspects of the reaction, and even the intermediacy of azomethines (3) has not been proven. The reaction certainly deserves more detailed study.

Regardless of its mechanism, the reaction of aldehydes with ammonia and hydrogen peroxide in the presence of copper catalysts presents a new, convenient and efficient method for obtaining nitriles.

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