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ORIGINAL PAPER

Efficient conversion of aldoximes to nitriles using phosphoric acid diethyl ester 2-phenylbenzimidazol-1-yl ester

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Abstract Aromatic aldoximes were converted to the corresponding nitriles in good to excellent yields by employing phosphoric acid diethyl ester 2-phenylbenzimidazol-1-yl ester as reagent. The method was equally effective for oximes bearing electron-donating and electron-withdrawing substituents.

Keywords Aldehydes · Aldoximes · *N*-Hydroxy-2-phenylbenzimidazole · Nitriles

Introduction

The nitrile functionality is a key constituent of numerous natural products and also serves as an important synthetic intermediate for pharmaceuticals, agricultural chemicals, dyes, and material sciences [1–3]. One of the most general methods for synthesis of alkylnitriles is direct nucleophilic substitution of alkyl halides with inorganic cyanides, although the reaction is frequently accompanied by elimination of hydrogen halides, especially with bulky alkyl halides [4, 5]. α,β-Unsaturated nitriles can be prepared via a Wittig reaction of the corresponding aldehyde with cyanoalkyl phosphonate. However, it frequently results in an unbiased mixture of (*E*) and (*Z*)-isomeric nitriles [6]. Another means of preparation of nitriles is the conversion of aldehydes into oximes and dehydration of the latter to furnish the corresponding nitrile compounds. Unfortunately, common dehydrating agents are insufficient for this purpose and more active reagents are required. Several reagents have been described for this transformation, including dicyclohexyl carbodiimide in the presence of $CuCl_2$, [7] selenium dioxide in chloroform [8], chlorosulfonyl isocyanate [9], triphenylphosphine and carbon tetrachloride in acetonitrile [10], or the Burgess reagent [11]. There are some methods reported in literature for direct conversion of aldehydes to nitriles in a single-step procedure using hydroxylamine and various reagents, for example pyridine [12], selenium dioxide [13], phosphoric acid [14], or magnesium sulfate in presence of *p*-toluenesulfonic acid [15]. In addition, there are several reports describing methods of dehydration of aldoximes by the use of stoichiometric amounts of specific main or transition-metal complexes [16–20]. Despite recent progress, there is still a strong need for a preparative method for highly efficient and catalytic conversion of aldoximes to nitriles, because most methods include the use of corrosive, toxic, or expensive reagents. Recently, we have synthesized the coupling reagent phosphoric acid diethyl ester 2-phenylbenzimidazol-1-yl ester (**2**) and its applications were demonstrated for amide and peptide bond-forming reactions [21] and for the preparation of *O*-alkyl hydroxamic acids [22]. In continuation of our research work, application of the reagent **2** was extended for conversion of aldoximes to the corresponding nitrile compounds.

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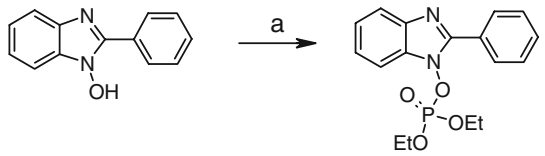
Results and discussion

Reagent **2** was synthesized according to the reported procedure [21, 22]. The procedure in brief includes synthesis

of *N*-hydroxy-2-phenylbenzimidazole (**1**) by coupling of *o*-nitroaniline with benzyl bromide using sodium hydride as base, followed by benzyl deprotection using 10% Pd/C. Compound **1** was treated with diethyl chlorophosphate and triethylamine in dichloromethane to afford reagent **2** (Scheme 1).

As a test reaction the single-step conversion of 4-bromobenzaldehyde to 4-bromobenzonitrile (**4e**) was examined using hydroxylamine hydrochloride and reagent **2** and various reaction conditions. Although variation of solvents, base, equivalents of reagents, and temperature were tried, the required compound was isolated in very poor yields (18% yield, reaction conditions: 4-bromobenzaldehyde (10 mmol), reagent **2** (14 mmol), 1,4-dioxane solvent (15 cm^3) and 100°C). Hence, a two step strategy was applied, in which first 4-bromobenzaldoxime was synthesized and then converted to 4-bromobenzonitrile (**4e**) under various reaction conditions. Using optimized reaction conditions (10 mmol aldoxime, 12 mmol **2**, 22 mmol triethylamine, acetonitrile, room temperature), compound **4e** was isolated in 98% yield. This method was applied for a range of aromatic aldoximes for conversion to the corresponding nitrile compounds, resulting in excellent yields (Scheme 2, Table 1). The method was equally effective for electron-donating and electron-withdrawing substituents. Reagent **2** was superior to previously reported methods in terms of yields and reaction times [23–26]. Compounds **4a**, **4b**, **4c**, and **4h** were isolated in 98, 97, 94, and 95% yields in 45 min reaction time while using a literature procedure [23–26] these compounds were isolated in 82, 85, 87, and 82% yields in 1 h reaction time. Compounds with electron-withdrawing substituents, for example 4-nitrobenzonitrile (**4i**), were also isolated in very good yield (91%) in 45 min reaction time, while a literature procedure [23–26] reports 87% yield in 35 h reaction time.



1 **2**

(a) $(EtO)_2P(O)Cl$, $(Et)_3N$, dichloromethane, 30 min, 0 °C.

Scheme 1

Using similar reaction conditions, α,β-unsaturated and aliphatic nitriles were also synthesized. The results are summarized in Table 2. Yields obtained were in the range 76–94%. All synthesized compounds were purified with column chromatography and characterized with MS and ^1H NMR. Melting points were compared with the reported literature values.

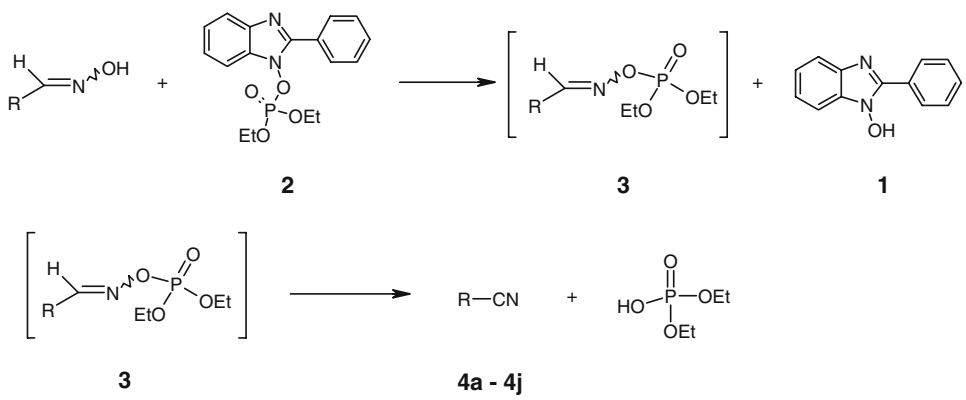
The probable reaction pathway for conversion of aldoxime to nitrile using reagent **2** is shown in Scheme 2. It includes reaction of the aldoxime with reagent **2** to form intermediate **3**, which consequently decomposes to afford the nitrile compound and diethylphosphoric acid.

In conclusion, reagent **2** was found to be a versatile reagent for efficient and simple conversion of aldoximes to the corresponding nitriles in good to excellent yields. Because reagent **2** can be easily prepared from inexpensive and commercially available starting materials, the method could also be useful for large-scale applications.

Experimental

Melting points were determined in capillary tubes. ^1H NMR spectra were recorded with a 400 MHz Varian–Gemini spectrometer. Mass spectra were recorded with a Micromass–Quattro-II mass spectrometer (Waters). HPLC was performed using a Zorbax SB-C18 reversed-phase column (0.46 × 25 cm^2) and a Shimadzu instrument equipped with an automatic injector and UV-PDA detector. Detection was carried out at 215 nm. The isocratic mobile phase was 0.05% TFA–acetonitrile (1:1, *v*/*v*). The products were eluted at a flow rate of 1 cm^3 min^{-1}. Flash column

Scheme 2



2 **3** **1**

3 **4a - 4j**

Table 1 Synthesis of nitrile compound from the corresponding aromatic aldoxime using reagent **2**

Entry no	R	Product	Reaction time (min)	Yield[a] (%)	Melting points (°C)	
					Found	Literature [Ref.]
1	Ph	**4a**	25	98	188–191	188–191 [27]
2	4-(CH_3)Ph	**4b**	20	97	25–27	26–28 [27]
3	4-ClPh	**4c**	30	94	221–223	223 [27]
4	2-ClPh	**4d**	25	96	45–47	43–46 [28]
5	4-BrPh	**4e**	25	95	234–236	235–237 [28]
6	2-BrPh	**4f**	35	98	249–251	251–253 [28]
7	2-(CH_3O)Ph	**4g**	20	96	–[b]	–[b]
8	4-(CH_3O)Ph	**4h**	25	95	57–59	57–60 [28]
9	4-(NO_2)Ph	**4i**	45	91	147–150	144–149 [27]
10	4-(CH_3)$_2$NPh	**4j**	30	96	72–75	70–76 [27]

[a] Isolated yields

[b] Oil

Table 2 Synthesis of nitriles from aliphatic aldoximes using reagent **2**

Entry no.	Aldoximes	Product	Reaction time (min)	Yield[a] (%)
1	PhCHCHCHNOH	PhCHCHCN (**5a**)	55	89
2	4-(CH_3O)PhCHCHCHNOH	4-(CH_3O)PhCHCHCN (**5b**)	45	92
3	CH_3CHCHCHNOH	CH_3CHCHCN (**5c**)	75	84
4	CH_3CH_2CHNOH	CH_3CH_2CN (**5d**)	60	76
5	*cyclo*-C_6H_{11}CHNOH	*cyclo*-C_6H_{11}CN (**5e**)	55	94

[a] Isolated yields

chromatography was performed using 300–400 mesh silica gel, and analytical thin-layer chromatography was performed on precoated silica gel plates (60F-254).

Typical procedure for conversion of aldoximes to the corresponding nitriles using reagent ***2***

To a mixture of 10 mmol aldoxime and 2.23 g triethylamine (22 mmol) in 15 cm^3 acetonitrile was added 4.16 g reagent **2** (12 mmol) at room temperature and the reaction mixture was stirred until completion of the reaction (monitored by TLC). The reaction mixture was the poured into ice water and extracted with ethyl acetate (2 × 25 cm^3). The combined organic extracts were dried over sodium sulfate and concentrated in vacuo. The crude material was purified via silica gel column chromatography to furnish the desired nitrile compound.

All synthesized compounds were characterized by ^{1}H NMR spectroscopy and mass spectrometry. The purity of synthesized compounds was determined by HPLC analysis. Melting points were compared with reported literature values.

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