POLYETHYLENE GLYCOL SUPPORTED PHOSPHORUS CHLORIDE: AN EFFICIENT AND RECYCLABLE CATALYST FOR THE PREPARATION OF NITRILES FROM ALDOXIMES

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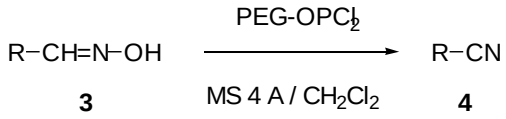
Abstract

Polyethylene glycol (PEG) supported phosphorus chloride has been developed and used as an efficient and recyclable catalyst for dehydration of various aldoximes into the corresponding nitriles. This protocol has many advantages such as high conversion, high selectivity, short reaction time, mild reaction conditions, and simple experimental procedure.

Graphical Abstract



Keywords

PEG-supported phosphorus chloride; nitrile**;** aldoxime**;** dehydration**;** catalytic synthesis

INTRODUCTION

Nitriles are important synthetic intermediates for pharmaceuticals, pesticides, dyes, and material sciences.[1–3] Moreover, the nitrile group is a versatile functional group in organic synthesis and can be easily transformed into a variety of groups such as acids, esters, aldehydes, amines, amides, imidoesters, benzamidines and nitrogen-containing heterocycles.[4,5] The classical methods for the preparation of nitriles include Kolbe nitrile synthesis,[6] ammoxidation of aldehydes,[7] hydrocyanation of alkenes,[8] Sandmeyer reaction of diazonium salts,[9] and Rosenmund–von Braun reaction of aryl halides.[10] In recent years, numerous methods for their synthesis have been reported in the literature,[11] such as the metal-catalyzed cyanation of aryl halides,[12] dehydration of amides[13,14] or oximes,[15] Schmidt reaction of aldehydes,[16] oxidation of azides[17] and alcohols.[18] Among these, the dehydration of oximes into nitriles is one of the most suitable and attractive strategies for the preparation of nitriles owing to the availability of starting material and the avoidance of very toxic cyanide ion. To date, many different reagents and conditions have been established for the dehydration of aldoximes to give nitriles.[19–30] Although many of these methods possess synthetic value, the search for a simple, rapid, mild, environmentally friendly, and universally applicable synthetic strategy for the conversion of aldoximes into nitriles is still an attractive subject. In the past years, there has been a considerable growth in interest in the use of soluble polymer-supported catalysts and reagents in organic synthesis because of their low cost, easy of preparation, simple workup and recoverablity

of catalysts.[31–33] Polyethylene glycol (PEG), as a inexpensive polymer, is an ideal soluble support since it is soluble in many organic solvents, such as CH_2Cl_2, DMF, toluene or CH_3OH at room temperature and can be precipitated from a solution by addition of diethyl ether, *tert*-butyl methyl ether, hexane or propan-2-ol.[34] Furthermore, the PEG-bound products can be adequately characterized by using routine analytical techniques such as TLC, IR and ^{1}H NMR.[35] Herein, we present our efforts to develop a novel facile method for the preparation of nitriles from aldoximes using PEG-supported phosphorus chloride as an efficient and recyclable catalyst under mild conditions. To the best of our knowledge, the conversion of aldoximes into nitriles using this new reagent has not been reported.

RESULTS AND DISCUSSION

By considering the solubility profile and loading capacity of the polymer derivatives, commercially available dihydroxy functionalised polyethylene glycol (PEG) of average molecular weight 4000 was chosen as the polymer support for the synthetic protocol. As shown in **Scheme 1**, the phenol was attached to the PEG 4000 support by esterification of PEG with 4-hydroxybenzoic acid in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in anhydrous CH_2Cl_2 at room temperature for 24 h. Subsequently, the PEG-supported phenol (PEG-OC_6H_4-OH-*p*) **1** was converted to phosphorus chloride **2** by treating with excess phosphorus trichloride. The reaction went to completion over 5 h and gave the corresponding PEG-supported phosphorus chloride (PEG-$OPCl_2$) **2** after the

release of hydrogen chloride gas. The reaction mixture was then isolated by addition of degassed diethyl ether into the reaction mixture, followed by filtration and sequential washing of the polymeric precipitate with diethyl ether to afford the reagent **2** in 95 % yield, based on the weight of polymer isolated. The progress of the PEG supported reaction was monitored by ^{1}H NMR and IR analysis. The ^{1}H NMR spectra of PEG-bound **1** and **2** were presented **Figure 1**, which indicated the conversion of terminal hydroxyl groups on PEG to be complete and quantitative. In addition, the aromatic protons of PEG-OC_6H_4-OH-*p* **1** appearing at 7.80 and 6.80 ppm shifted to 7.69 and 6.89 ppm respectively after condensation with phosphorus trichloride. Besides, the IR spectra of PEG, PEG-bound **1** and **2** were shown in **Figure 2**. The complete disappearance of the hydroxyl stretch at 3426 cm^{-1} plus the disappearance bands of 1280 cm^{-1} as well as the appearance of weak P–Cl band absorption at 585 cm^{-1}, indicated the PEG-$OPCl_2$ **2** formation. The loading capacity of **2** was calculated by elemental analyses and found to be 0.90 mmol Cl/g.

With the PEG attached phosphorus chloride **2** in hand, the viability and efficiency of the dehydration reactions of aldoximes catalyzed by this new regent was explored. To optimize the reaction conditions, a model reaction of benzaldehyde oxime with the catalyst **2** to afford benzonitrile was investigated and the results are summarized in **Table 1**. Several solvents including polar and non-polar solvents were tested for the reaction. From the results in **Table 1**, it is evident that some solvents such as DMSO, MeCN, THF and CH_2Cl_2 are all applicable for

this conversion. Considering the ease of product separation, CH_2Cl_2 was selected to be the solvent of choice. Additionally, after further varying the other reaction conditions such as amount of catalyst, reaction temperature and time, the better result for this conversion was conveniently achieved in 92 % yield through the dehydration reaction of benzaldehyde oxime in the presence 20 mol % of PEG-$OPCl_2$ in CH_2Cl_2 at refluxing temperature (entry 6). Interestingly, it was found that the reaction rate and selectivity could be significantly increased when the reaction was carried out in the presence of molecular sieves (4 Å, 2 weight equiv to oxime) (entry 9). It should be pointed out that the reaction was complete within 30 min in the presence of molecular sieves while it took 1 h to achieve a full conversion in the absence of molecular sieves (entries 6–8), whereas no conversion was observed by the action of molecular sieves alone (10 weight equiv to oxime) without the catalyst **2** even after 24 h under reflux.

The plausible mechanism of the nitrile formation is depicted in **Scheme 3**. For the synthesis of nitriles, 4Å molecular sieves were used to absorb the water produced in the conversion of aldoximes into the corresponding nitriles and prevent the hydrolysis of the catalyst **2**.

To explore the generality and scope of this method, the optimized reaction conditions were applied to a variety of aldoximes. As can be observed from **Table 2**, it is clear that this catalyst system of PEG-$OPCl_2$/molecular sieves is highly efficient and useful for aromatic (entries 1–15) and aliphatic aliphatic (entries 19 and 20) aldoximes. Excellent results were obtained for aryl aldoximes with different substituents at the *meta* and/or *para* positions; relatively low yields of

nitriles were obtained for *ortho*-substituted aromatic aldoximes (entries 6, 8 and 11–12) and the reaction time needs to be slightly prolonged, probably owing to the stereo-hindrance effect of the *ortho*-substituted groups. It should be noted that *trans*-cinnamaldoxime was also conveniently converted to the corresponding nitrile in good yield with stereochemical retention of the double bond (entry 18). Besides, various heteroaromatic aldoximes turned out to be compatible with the employed reaction conditions (entries 16 and 17). Furthermore, a substrate bearing bis-aldoxime was also uneventfully dehydrated to give 1,4-dicyanobenzene in excellent yield (entry 21).

As depicted in **Table 2**, the recovery and reuse of PEG-$OPCl_2$ catalyst was examined by considering the model reaction under the same conditions (entries 1–4). After the completion of the reaction, the PEG-$OPCl_2$ was precipitated from the reaction mixture with dried diethyl ether for the subsequent run of the reaction. The efficiency of the PEG-$OPCl_2$ catalyst on the dehydration of benzaldoxime **3a** was maintained up to four runs in this case, and then it took slightly longer to get a complete conversion. Meanwhile, the yield of the product **4a** slight decreased gradually.

In summary, a new PEG-supported phosphorus chloride catalyst has been prepared, and has been employed here for the first time as an efficient dehydration agent for the conversion of the wide range of aldoximes to the corresponding nitriles. This protocol has many advantages such as the availability and reusability of this dehydration agent, high efficiency and selectivity, as well as mild reaction conditions, short reaction times, and simple work-up procedure. The further

application based on PEG-supported phosphorus chloride is currently underway.

EXPERIMENTAL

Melting points were determined with an X_4 melting point apparatus and were not corrected. The ^{1}H NMR spectra were recorded with a Bruker Avance (400 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as an internal standard. The FTIR spectra were measured with a Perkin-Elmer SP One FTIR spectrophotometer. Mass spectra (EI, 70eV) were recorded on a HP5989B mass spectrometer. Aldoximes **3a–3r** were prepared from hydroxylamine hydrochloride with the corresponding aldehydes by standard methods.[26] The other chemicals were obtained from commercial suppliers and used without purification.

Preparation of PEG-supported Phosphorus Chloride (PEG-$OPCl_2$) 2

4-Hydroxybenzoic acid (1.38 g, 10 mmol), 1,3-dicyclohexylcarbodiimide (DCC) (2.06 g, 10 mmol) and 4-(dimethylamino)pyridine (DMAP) (305 mg, 2.5 mmol) were added to PEG (5g, 2.5 mmol) in CH_2Cl_2 (20 mL) and the mixture was stirred at room temperature for 24 h. The precipitate was removed by filtration and the filtrate was diluted with *i*-PrOH (200 mL). CH_2Cl_2 was removed under reduced pressure and the residue was cooled to –10 ^{o}C. The white precipitate was collected and washed several times with *i*-PrOH and Et_2O. After drying in vacuum, the PEG-bound phenol **1** was obtained as white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 1 H), 7.80 (d, J = 8.0 Hz, 2 H), 6.80 (d, J = 8.0 Hz, 2 H), 3.82–3.47 (m, PEG backbone, OCH_2CH_2O); IR (KBr): ν_{max} = 3365, 2990, 1680, 1500, 1342, 1242, 1100, 827 cm^{-1}.

To phosphorus trichloride (10 mL) in a three-necked flask equipped with a condenser, the above PEG-bound phenol **1** was added in portions under stirring. HCl gas was gradually released from the reaction vessel. After the addition, the mixture was stirred for 5 h at room temperature. Then, excess phosphorus trichloride was evaporated off and the crude product was dissolved in CH_2Cl_2 (20 mL). After this, diethyl ether (200 mL) was added to the mixture with vigorous stirring, and then cooled to –10 ^oC. The resulting precipitate was collected by filtration, washed with diethyl ether (3 × 20 mL) and then dried under high vacuum to give the desired PEG-$OPCl_2$ **2** as a white solid (5.3 g, 95.5 % based on polymer recovery). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.4 Hz, 2 H), 6.89 (d, J = 8.4 Hz, 2 H), 3.81–3.46 (m, PEG backbone, OCH_2CH_2O); IR (KBr): ν_{max} = 2992, 1682, 1502, 1342, 1243, 1113, 828, 585 cm^{-1}. The catalyst loading capacity was determined by elemental analysis to be about 0.90 mmol Cl/g.

Preparation of Nitriles (4a–4r): General Procedure

To a stirred solution of aldoxime **3** (1.0 mmol) in CH_2Cl_2 (5 mL) was added PEG-$OPCl_2$ (0.20 mmol, 220 mg) and molecular sieves 4 Å (2 wt equiv to aldoxime), the reaction mixture stirred at refluxing temperature for the given time in **Table 2**. After completion of the reaction (TLC), diethyl ether (100 mL) was added to the reaction mixture with vigorous stirring and then cooled to 0 ^oC. The recovered white precipitate, along with molecular sieves 4 Å was collected by filtration, washed with cold diethyl ether (2 × 20 mL) for reuse. The combined filtrate was concentrated in a rotary evaporator, and the residue was purified by through a pad of silica gel

column (10–20 % ethyl acetate in hexane) to give pure product, which was characterized by comparison of its IR and ^{1}H NMR spectra or melting point with published [13,14, 16, 18, 26, 28, 30] values. The analytical data for the obtained products **4a–4r** are together with their ^{1}H and ^{13}C NMR spectra are presented in the Supplemental Materials (Figures S 1 – S 36)

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Table 1. Catalytic conversion of benzaldehyde oxime to benzonitrile [a]

Entry	Solvent	Time	Yield (%) [b]
1	MeCN	4 h	78
2	THF	3 h	86
3	DMF	3 h	90
4	$PhCH_3$	3 h	89
5	CH_2Cl_2	2.5 h	90
6 [c]	CH_2Cl_2	1 h	92
7 [d]	CH_2Cl_2	1 h	90
8 [e]	CH_2Cl_2	1 h	92
9 [f]	CH_2Cl_2	30 min	98

[a]Benzaldehyde oxime (1.0 mmol), PEG-$OPCl_2$ (220 mg, 0.20 mmol), solvent (5 mL)

[b]Isolated yield

[c]At refluxing temperature

[d]PEG-$OPCl_2$ (170 mg, 0.15 mmol) was used under refluxing temperature without additional molecular sieves

[e]PEG-$OPCl_2$ (275 mg, 0.25 mmol) was used under refluxing temperature without additional molecular sieves

[f]The reaction was carried out in the presence of PEG-$OPCl_2$ (220 mg, 0.20 mmol) and molecular sieves (4 Å, 2 weight equiv to aldoxime) under refluxing temperature.

Table 2. PEG-$OPCl_2$ catalytic dehydration of various aldoximes to nitriles [a]

Entry	Substrate **(3)**	Time (min)	Nitrile **(4)** [b]	Yield (%) [c]
1	Benzaldehyde oxime **(3a)**	30	**4a**	98
2 [d]	Benzaldehyde oxime **(3a)**	30	**4a**	94 [e]
3 [d]	Benzaldehyde oxime **(3a)**	35	**4a**	93 [f]
4 [d]	Benzaldehyde oxime **(3a)**	40	**4a**	90 [g]
5	4-Methoxybenzaldehyde oxime **(3b)**	35	**4b**	98
6	2-Methylbenzaldehyde oxime **(3c)**	40	**4c**	84
7	3-Methylbenzaldehyde oxime **(3d)**	30	**4d**	97
8	2-Hydroxybenzaldehyde oxime **(3e)**	45	**4e**	85
9	4-Hydroxybenzaldehyde oxime **(3f)**	40	**4f**	95
10	4-Chlorobenzaldehyde oxime **(3g)**	30	**4g**	92
11	2-Chlorobenzaldehyde oxime **(3h)**	40	**4h**	84
12	2,4-Dichlorobenzaldehyde oxime **(3i)**	45	**4i**	82
13	4-Bromobenzaldehyde oxime **(3j)**	30	**4j**	94
14	4-Nitrobenzaldehyde oxime **(3k)**	45	**4k**	91

15	3-Nitrobenzaldehyde oxime **(3l)**	45	**4l**	93
16	2-Furaldehyde oxime **(3m)**	35	**4m**	90
17	2-Thenaldehyde oxime **(3n)**	35	**4n**	95
18	Cinnamaldehyde oxime **(3o)**	35	**4o**	85
19	Phenylacetaldehyde oxime **(3p)**	30	**4p**	92
20	Heptaldehyde oxime **(3q)**	40	**4q**	87
21	Terephthalaldehyde oxime **(3r)**	30	**4r**	97

[a]Reaction of aldoxime (1.0 mmol) in CH_2Cl_2 (5 mL) at refluxing temperature in the presence of PEG-$OPCl_2$ (220 mg) and molecular sieves 4 Å (2 wt equiv to aldoxime)

[b]All products are known compounds, and were characterized by comparison of their mp, IR and ^{1}H NMR data with those of authentic samples

[c]Isolated yield

[d]No additional molecular sieves were added during the recycles

[e]PEG-$OPCl_2$ was used for the 2nd run

[f]PEG-$OPCl_2$ was used for the 3rd run

[g]PEG-$OPCl_2$ was used for the 4th run.

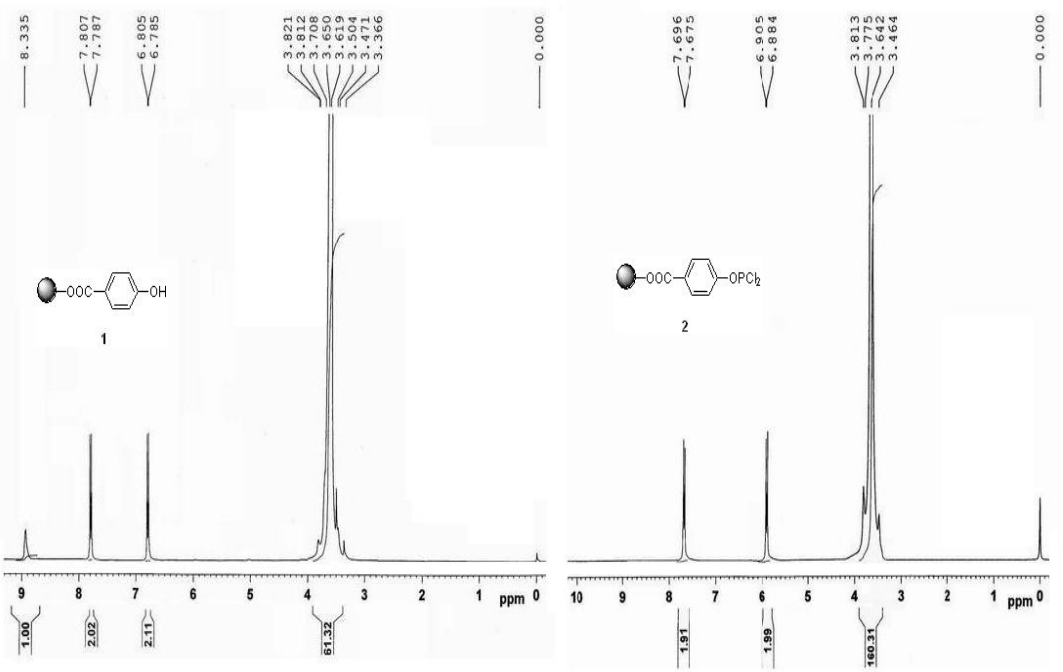


Figure 1. ^{1}H NMR spectra of PEG-C_6H_4OH-*p* (**a**) and PEG-$OPCl_2$ (**b**).

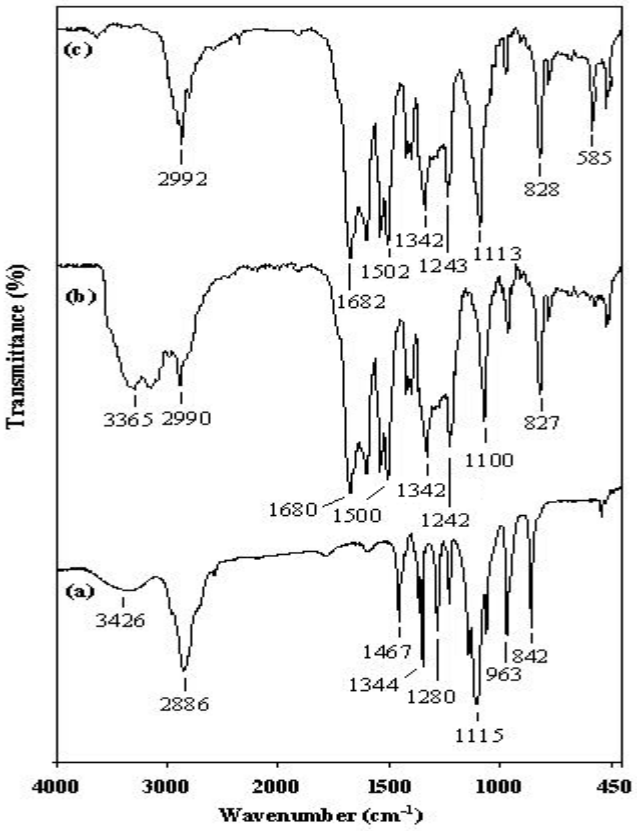
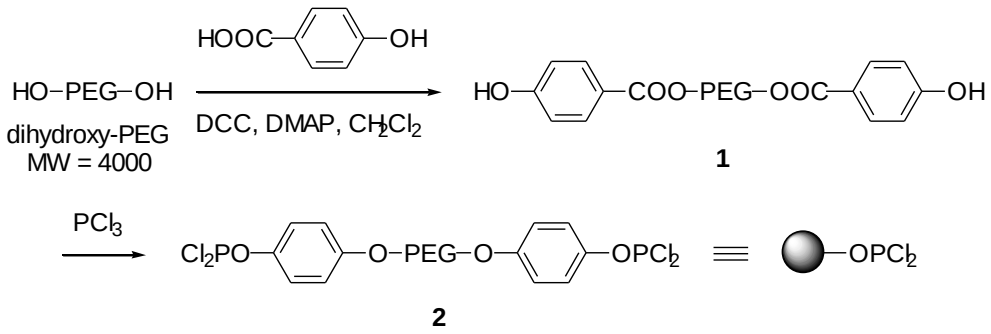
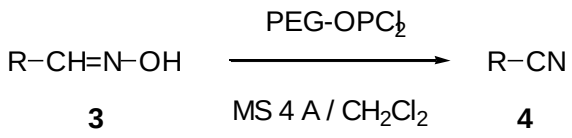


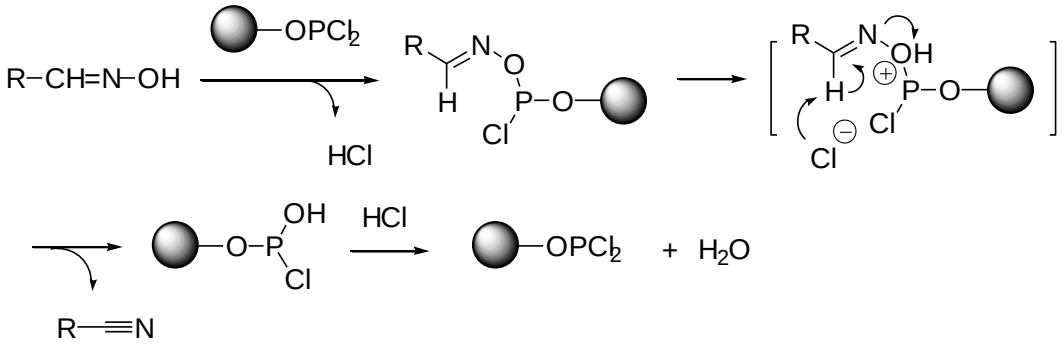
Figure 2. IR spectra of PEG (**a**), PEG-C_6H_4OH-*p* (**b**) and PEG-$OPCl_2$ (**c**).



Scheme 1. Preparation of PEG-supported phosphorus chloride **2**.



Scheme 2. PEG-$OPCl_2$ catalyzed conversion of aldoximes to nitriles.



Scheme 3. Possible mechanism of the nitrile formation.