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A facile and high efficient synthesis of nitriles from aldoximes and primary amides with a mixture of triphenylphosphine/2, 3-dichloro-5, 6-dicyanobenzoquinone (PPh_3/DDQ) under neutral conditions

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Aldoximes are immediately converted to their corresponding nitriles with a mixture of triphenylphosphine and 2,3-dichloro-5,6-dicyanobenzoquinone in dichloromethane under neutral conditions at room temperature., Nitriles are also formed from the reaction of primary amides with this reagent in refluxing acetonitrile under neutral conditions.

Keywords: Triphenylphosphine, 2,3-dichloro-5,6-dicyanobenzoquinone, oximes, primary amides, nitriles.

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Several methods have been reported for preparation of nitriles by dehydration of aldoximes using selenium dioxide-chloroform[1], diphosphorus tetraiodide[2], trifluoroacetic anhydride-pyridine[3], chlorosulphonyl isocyanate[4], 4,6-dipheny-2-methylthio-pyriliumtetrafluoro borate[5], copper (II) acetate-acetonitrile[6], trichloroacetyl chloride-triethylamine[7], triphenylphosphine/carbontetrachloride (PPh_3/CCl_4) in acetonitrile[8], montmorillonite KSF[9] and Envirocat EPZG^{R}[10]. Unfortunately, many of these reagents have limitations in forms of their economy and lack of availability, use of great excess of reagents, vigorous reaction conditions, longer reaction times and tedious work-up. Reagents such as triethylamine/sulfur dioxide[11] and sulfuryl chloride fluoride[12] allow the rapid and mild dehydration of aldehyde oximes but the preparation of the reagents is inconvenient (at -78°C). Dehydration with zeolite (CsX) suffers from high temperatures (350°C)[13] and reagents like phosgene[14], diphosgene[15] and triphosgene[16] are hazardous to use.

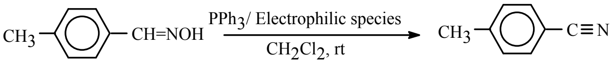
Some methods have been reported for the conversion of amides into nitriles such as Vilsmeir reagent[17], cyanoric chloride/DMF[18], triethoxydiiodophosphorane[19], and trifluoroacetic anhydride[20]. However, these reagents still have some disadvantages regarding difficulty in handling or unsatisfactory yields. Consequently, there is a need for the development of new and mild methods for this transformation.

Results and Discussion

A convenient synthesis of nitriles from aldoximes and primary amides by using triphenylphosphine in the presence of N-chlorosuccinimide (PPh_3/NCS) as dehydrating agent was reported earlier[21] and now in continuation of our work on triphenylphosphine/2, 3-dichloro-5,6-dicyanobenzoquinone (PPh_3/DDQ)[22a,22b], the high efficiency of this reagent system is reported in conversion of aldoximes and primary amides to nitriles (Equation 1).

$$\begin{matrix} \mathrm{RCH{=}NOH} \\ \text{or} \\ \mathrm{RCONH_2} \end{matrix} \xrightarrow[\mathrm{CH_2Cl_2}\ \text{or}\ \mathrm{CH_3CN}]{\mathrm{PPh_3/DDQ}} \mathrm{RC{\equiv}N} \qquad \ldots (1)$$

First, the reaction of *p*-methylbenzaldehydeoxime was studied with PPh_3 in the presence of different electrophilic halogenes such as NCS, Br_2, N-bromosuccinimide (NBS), 2, 4, 4, 6-tetrabromo-2,5-cyclohexadienone (TABCO)[23], I_2 and also DDQ at room temperature (Equation 2). The results are shown in **Table I**.



1 2

… (2)

Table I — Conversion of *p*-methylbenzaldehydeoxime **1** to *p*-methylbenzonitrile **2** with PPh_3 in the presence of different electrophilic species in dichloromethane as solvent at room temperature

Entry	Reagent system	Molar ratio[a]	Time (min)	Yield (%)[b]
1	PPh_3/Br_2	1:1.4:3	5	74
2	PPh_3/NBS	1:1.4:1.4	immediately	70
3	PPh_3/TABCO[c]	1:1.4:1.4	immediately	65
4	PPh_3/NCS	1:1.4:1.4	immediately	77
5	PPh_3/I_2	1:1.4:1.4	60	82[d]
6	PPh_3/DDQ	1:1.2:1.2	immediately	97

[a] The molar ratio is related to oxime: PPh_3: electrophilic species. [b] Isolated yield.
[c] 2, 4, 4, 6-Tetrabromo-2, 5-cyclohexadienone was prepared according to the literature[23].
[d] This reaction was carried out in the reflux conditions.

Table I shows that the use of PPh_3 in the presence of DDQ as an electrophilic species is more efficient than using PPh_3/Br_2, PPh_3/NBS, PPh_3/TABCO, PPh_3/NCS and PPh_3/I_2 and the best result was obtained with this reagent system so that in treatment of *p*-methylbenzaldehydeoxime **1** with the mixture of PPh_3 and DDQ in dichloromethane as solvent, *p*-methylbenzonitrile **2** was immediately produced at room temperature in excellent yield (**Table I**, Entry 6). However, the same reaction using PPh_3/Br_2, PPh_3/NBS, PPh_3/TABCO, PPh_3/NCS and PPh_3/I_2 instead of PPh_3/DDQ produced *p*-methylbenzonitrile **2** in 74, 70, 65, 77 and 82% yields respectively and also in the cases of PPh_3/I_2 or Br_2 was not immediately occurred. Therefore, this procedure (**Table I**, Entry 6) was selected and applied for the conversion of other aldoximes to their corresponding nitriles (**Table II**). As shown in **Table II**, aldoximes are immediately converted to nitriles under mild reaction conditions in excellent yields. Dehydration of primary amides which are more difficult to dehydrate than aldehyde oximes was unsuccessful with this reagent system at room temperature. For example, in treatment of benzamide and propanamide with PPh_3/DDQ (1.2:1.2) in dichloromethane at room temperature, the related nitriles were not obtained after 6 and 12 hr respectively. However, primary amides were dehydrated to nitriles in refluxing acetonitrile with this reagent. For example, in treatment of benzamide, propanamide and phenylacetamide with PPh_3/DDQ (1.2:1.2) in refluxing acetonitrile, the corresponding nitriles were obtained after 7-9 hr in 73-88% yields (**Table II**, entries 9-11).

Table II — Conversion of aldoximes and primary amides to nitriles using PPh_3/DDQ [a,b]

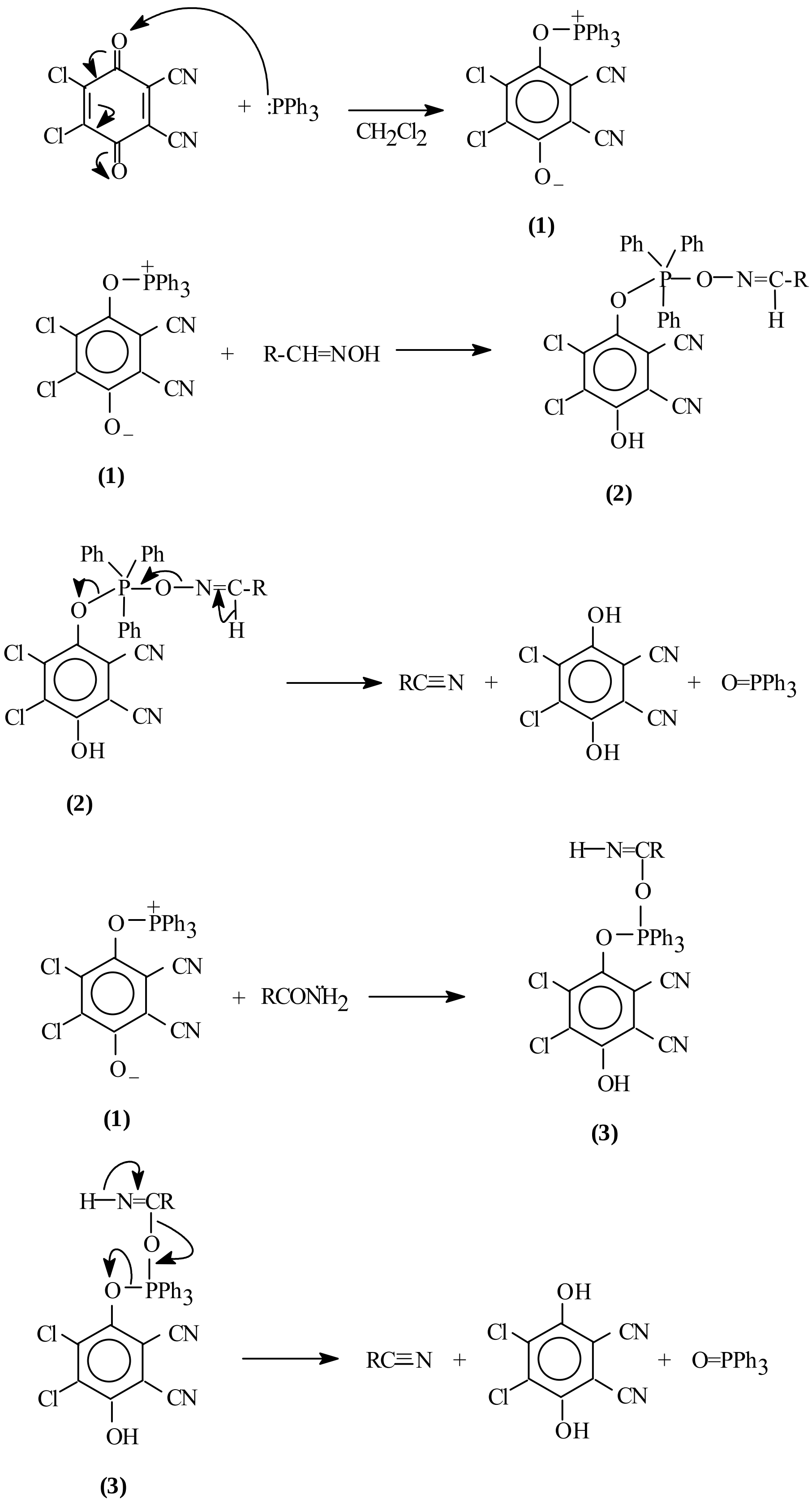
Entry	Substrate	Product	Yield (%)[c]
1	PhCH=NOH	PhCN	87
2	*p*-O_2NPhCH=NOH	*p*-O_2NPhCN	96
3	*o*-O_2NPhCH=NOH	*o*-O_2NPhCN	94
4	*p*-ClPhCH=NOH	*p*-ClPhCN	96
5	*o*-ClPhCH=NOH	*o*-ClPhCN	94
6	*p*-CH_3PhCH=NOH	*p*-CH_3PhCN	97
7	*p*-BrPhCH=NOH	*p*-BrPhCN	92
8	*p*-CH_3OPhCH=NOH	*p*-CH_3OPhCN	90
9	$PhCONH_2$	PhCN	73
10	$CH_3CH_2CONH_2$	CH_3CH_2CN	88[d]
11	$PhCH_2CONH_2$	$PhCH_2CN$	84

[a] The molar ratio of oxime or amide:PPh_3:DDQ is 1:1.2:1.2 in these reactions.
[b] These reactions are immediately carried out at room temperature for aldoximes in CH_2Cl_2 and in refluxing acetonitrile for 7-9 h for primay amides. [c] Isolated yield. [d] Yield is based on GC analysis using *n*-octane as internal standard.

Although the mechanism of the reaction is not clear, on the basis of the reports on the reaction of PPh_3 with sterically hindered quinone of high oxidation-reduction potential[24] as shown in **Scheme I** it is assumed that first complex **1** is formed from the reaction of PPh_3 and DDQ and then aldoxime reacts with **1** to form the intermediate **2** which later undergoes the elimination reaction to produce the corresponding nitriles, triphenylphosphineoxide and reduced DDQ. Also, primary amide is treated with **1** to produce the intermediate **3** which undergoes the elimination reaction and leads to formation of the same products. The aromatization of DDQ and the formation of $OPPh_3$ are assumed as the major driving forces for this reaction.

Experimental Section

All oximes were prepared from aldehydes according to the literature[25]. All products are known compounds and were characterized by comparison of their physical data with those of known samples. FT-IR spectra were recorded on a Perkin-Elmer RXI spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-250 spectrometer. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX instrument. The products were purified by column chromatography using petroleum ether/ethyl acetate as eluent.



Scheme 1

General procedure for the conversion of aldoxime to nitrile:

Aldoxime (1 mmole) was added to a stirring mixture of PPh_3 (0.314 g, 1.2 mmole) and DDQ (0.272 g, 1.2 mmolee) in dichloromethane as solvent at room temperature. Immediate completion of the reaction was shown by TLC monitoring. After filtration and evaporation of the solvent, the crude product was purified by short column chromatography using petroleum ether/ethyl acetate as eluent to give the corresponding nitrile (**Table II**).

p-Chlorobenzonitrile: ^1H NMR ($CDCl_3$, 250 MHz): δ 7.33-7.36 (m, 2H), 7.47-7.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 111.12, 118.33, 129.00, 133.29, 139.80; IR (KBr): 3100 (m), 2235 (s), 1600 (m), 1480 (s), 1410 (w), 1093 (s), 1020 (m), 835 (s) cm^{-1}, m.p. 90-91°C, Lit.[2] 91-93 ° C.

p-Bromobenzonitrile: ^1H NMR ($CDCl_3$, 250 MHz): δ 7.48-7.54 (m, 2H), 7.58-7.64 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 111.58, 118.44, 128.36, 133.00, 133.82 ppm; IR (KBr): 3095 (w), 2230 (s), 1590 (s), 1485 (s), 1070 (s), 1020(s), 830(s) cm^{-1}; Mass spectra m/e 181(M, 76.6%), 183(M+2, 74%), 102 (M-Br, 100%).

Typical procedure for the conversion of phenylacetamide to phenylacetonitrile:

Phenylacetamide (0.135 g, 1 mmole) was added to a stirring mixture of PPh_3 (0.314 g, 1.2 mmole) and DDQ (0.272 g, 1.2 mmole) in acetonitrile as solvent. The reaction mixture was stirred under reflux conditions and completed (9 hr) based on TLC monitoring. After evaporation of solvent, the crude product was purified by short column chromatography using petroleum ether/ethyl acetate as eluent to give phenylacetonitrile, 0.1 g, 84% yield.

Conclusion

In conclusion, PPh_3/DDQ is a mild and efficient reagent for the conversion of aldoximes to nitriles under neutral conditions. Short reaction times, high yields, simple work-up, availability of the reagent and occurrence of the reactions at room temperature can also be considered as advantages of the present method. Also, primary amides are conveniently converted to the related nitriles under non-acidic conditions in high yields by this reagent.

Acknowledgements

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