Propylphosphonic Anhydride (T3P®): A Remarkably Efficient Reagent for the One-Pot Transformation of Aromatic, Heteroaromatic, and Aliphatic Aldehydes to Nitriles

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Abstract: Propylphosphonic anhydride has been demonstrated to be an efficient reagent for the transformation of aromatic, heteroaromatic, and aliphatic aldehydes to respective nitriles in excellent yields. This procedure offers simple and one-pot access to nitriles and highlights the synthetic utility of T3P® as a versatile reagent in organic chemistry.

Key words: propylphosphonic anhydride, dehydration, nitriles, aldoximes, electrophilic activation

The significant synthetic properties of the nitrile group have ensured long-standing studies of their utilization in organic synthesis[1] as they are useful precursors for the synthesis of amines, amides, amidines, ketones, carboxylic acids, and esters. Consequently, the formation of nitriles from the corresponding aldehydes has become an important functional-group transformation in organic chemistry.[2] Several methods involve the initial conversion of aldehydes into aldoximes, which are subjected to dehydration to give nitriles.[3] The use of ammonia combined with an appropriate oxidant is also a useful method for the transformation of aldehydes to their corresponding nitriles.[4] Direct conversion of aldehydes into nitriles without isolation of nitrogen-containing intermediates has also been explored.[5] Despite these, there is still scope for alternative reagent systems for the preparation of nitriles from aldehydes.

Propylphosphonic anhydride (T3P®) is a highly reactive *n*-propyl phosphonic acid cyclic anhydride, commonly used as a coupling agent and water scavenger with low toxicity.[6] Although T3P has been primarily used as a mild coupling reagent in peptide synthesis, new applications have recently been developed for this reagent.[7] There are quite a few examples, wherein, T3P is utilized in dehydration chemistry, for instance, for the conversion of carboxylic acids and amides into nitriles,[8] synthesis of heterocycles,[9] synthesis of isonitriles,[8] and synthesis of alkenes from alcohols.[10] Further, T3P offers several advantages over traditional reagents, such as broad functional-group tolerance, low epimerization tendency, easy workup due to water-soluble byproducts, and in particular it gives high yields and purity. These applications and nontoxic nature of T3P show its potential as a dehydration reagent in organic synthesis. However, T3P has not been studied and utilized as a reagent for the preparation of nitriles from aldehydes. Herein we report a mild, high-yielding, one-pot process for rapid access to nitriles by the reaction of aldehydes with hydroxylamine hydrochloride in the presence of T3P (Scheme 1).
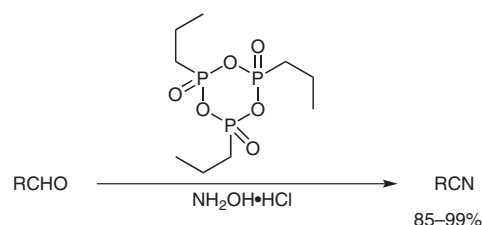

Scheme 1

A preliminary examination showed that T3P effectively mediated the conversion of 4-bromobenzaldehyde into 4-bromobenzonitrile as a model. When a DMF solution of 4-bromobenzaldehyde (1.0 equiv), hydroxylamine hydrochloride (1.1 equiv), Et₃N (1.1 equiv), and T3P (1.1 equiv; 50% solution in EtOAc) was stirred at 100 °C under nitrogen atmosphere, an initial turbidity was observed, and the reaction mixture became clear in 30 minutes. Upon heating for an additional 30 minutes, the desired product 4-bromobenzonitrile (**1**)[11] was produced in 98% yield (entry 1, Table 1). The above reaction conditions were appropriate for the transformation as lowering the reaction temperature to 70 °C (entry 3, Table 1) and decreasing the amount of T3P from 1.1 equivalents to 0.8 equivalents lowered the nitrile yield (entry 2, Table 1). However, performing the reaction in DMF using T3P (50% solution in DMF) at 120 °C drastically reduced the reaction time, but with no significant increase in the yield of **1** (entry 4, Table 1). Further, various bases such as Et₃N, DBU, DABCO, DIEA, and pyridine had comparable influence on the reaction except NaOAc (entry 8, Table 1).

Solvent effects on T3P-promoted one-pot dehydration were then investigated (Table 2). Of various organic solvents studied, DMF (entry 1, Table 2) and DMA (entry 8, Table 2) had superior solvent effects on this reaction. Thus, using T3P (1.1 equiv, 50% soln in EtOAc), hydroxylamine hydrochloride (1.1 equiv), and Et₃N (1.1 equiv) in

Table 1 Screening of Bases
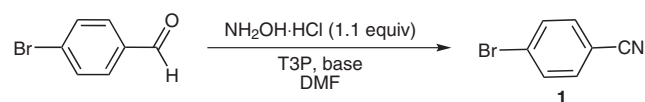
Entry	T3P (equiv)[a]	Base (1.1 equiv)	Temp (°C)	Time (h)	Yield (%)
1	1.1	Et₃N	100	1	98
2	0.8	Et₃N	100	2	82
3	1.1	Et₃N	70	4	71
4	1.1[b]	Et₃N	120	0.5	97
5	1.1	DABCO	100	1.5	83
6	1.1	DBU	100	1.5	81
7	1.1	pyridine	100	1.5	87
8	1.1	NaOAc	100	3	27
9	1.1	DIEA	100	1.5	93

[a] 50% soln in EtOAc.
[b] 50% soln in DMF.

Table 2 Screening of Solvents
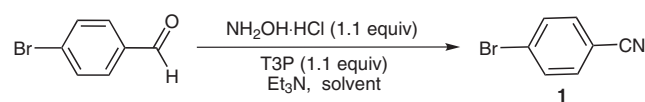
Entry	Solvent	Temp.(°C)	Time (h)	Yield (%)
1	DMF	100	1	98
2	EtOAc	80	5	88
3	1,4-dioxane	100	3	82
4	MeCN	70	3	73
5	toluene	100	3	65
6	DCE	80	4	72
7	nitromethane	80	3	67
8	DMA	100	1	95
9	THF	70	3	78

DMF at 100 °C proved to be optimal for the one-pot conversion of aldehydes into nitriles.

The mild and practical one-pot synthesis of nitriles from various aromatic aldehydes was examined under the conditions of entry 1 in Table 1. As depicted in Table 3, these reactions occurred in excellent yields, and the reaction conditions were compatible with various functional groups such as halo, hydroxy, methoxy, nitro, cyano, carboxylate, and boronate. However, for compounds bearing acid-sensitive functional groups such as boronate (entry 4, Table 3), an excess of base (3.0 equiv) was used to avoid any impediments arising out of acidic nature of T3P. It is worthy to note that benzene-1,4-dicarboxaldehyde exclu-

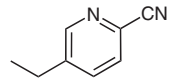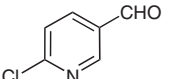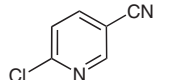**Table 3** Conversion of Aromatic Aldehydes into Nitriles Promoted by T3P
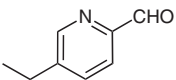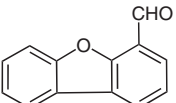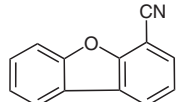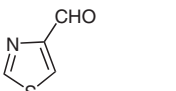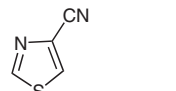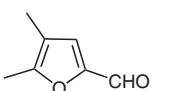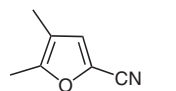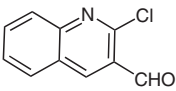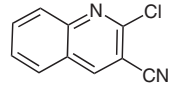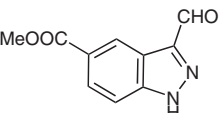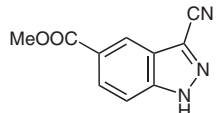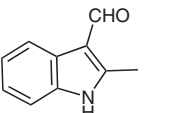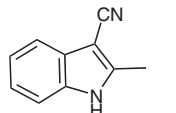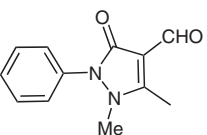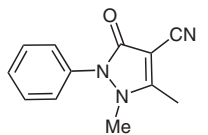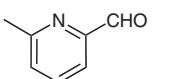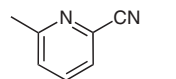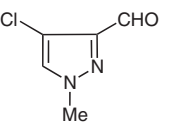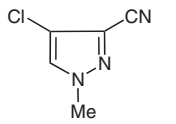
Entry	Aldehyde	Product	Yield (%)[a]
1		**1**	98
2		**2**	98
3		**3**	98
4		**4**	94[b]
5		**5**	96
6		**6**	99
7		**7**	94
8		**8**	98
9		**9**	97
10		**10**	96
11		**11**	95

[a] Isolated yields.
[b] Conditions: 3.0 equiv of base were used.

sively produced 4-cyanobenzaldehyde under the standard reaction conditions (entry 11, Table 3). Further, chromatographic separation of the products was not essential,

and an aqueous workup was adequate to isolate the products in good purity.

Table 4 Conversion of Heteroaromatic Aldehydes into Nitriles Promoted by T3P

Entry	Aldehyde	Product	Yield (%)[a]
1		**12**	95
2		**13**	96
3		**14**	99
4		**15**	95
5		**16**	97
6		**17**	98
7[b]		**18**	94
8		**19**	97
9		**20**	99
10		**21**	95
11		**22**	95

[a] Isolated yields.
[b] Aldehyde was prepared in-house following a literature protocol.[13]

Having achieved excellent results in one-pot transformation of aromatic aldehydes to nitriles using T3P, we proceeded to study the scope of this method and subsequently investigated the conversion of heteroaromatic aldehydes into their respective nitriles (Table 4). To our delight, a variety of heteroaromatic aldehydes, such as pyridine, thiazole, furan, dibenzofuran, quinoline, indole, pyrazole, and indazole, participated effectively in this reaction to yield respective nitriles in good yields (entries 1–11, Table 4).

We next examined the application of this protocol to aliphatic aldehydes (entries 1–10, Table 5). The reaction performed very well on all the substrates we attempted. However, phenylpropargyl aldehyde (entry 7, Table 5) gave a mixture of products, wherein the desired nitrile **29** was produced in 85% yield besides 5-phenylisoxazole[12] (11%) formed by the cyclization of intermediate aldoxime.

It is worthy to note that *N*-Boc-4-piperidine carboxaldehyde, a fairly sensitive molecule, reacted smoothly under the standard reaction conditions to provide the respective nitrile in good yield (entry 10, Table 5). However, an excess of base (3.0 equiv) was used to avoid the cleavage of *N*-Boc protection during the reaction.

We now account that the T3P-promoted one-pot transformation of aldehydes to nitriles is general in scope among the reactions we examined for aromatic, heteroaromatic, and aliphatic aldehydes. In general, the reaction of aldehydes and T3P (50% soln in EtOAc or DMF) in DMF containing hydroxylamine hydrochloride and Et$_3$N at 100 °C for one to three hours affords respective nitriles in excellent yields. A key feature of this reaction was its innate simplicity in producing nitriles directly from aldehydes.
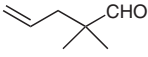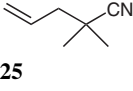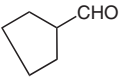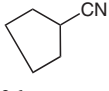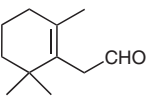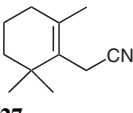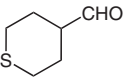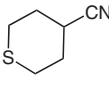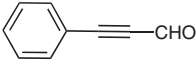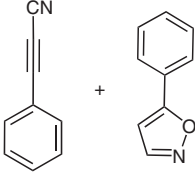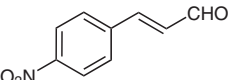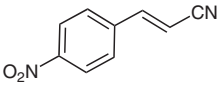
As T3P produces only water-soluble byproducts, in most cases, an aqueous workup was adequate to obtain pure products.

A plausible mechanism of nitrile synthesis is outlined in Scheme 2. The aldoxime generated in situ is transformed
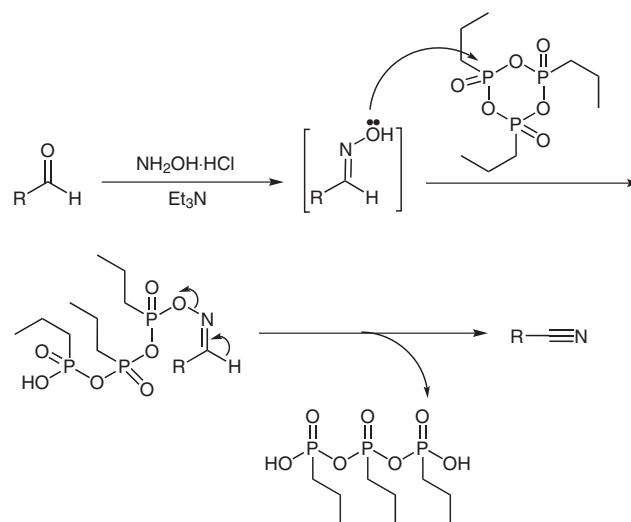
Scheme 2

Table 5 Conversion of Aliphatic Aldehydes into Nitriles Promoted by T3P

Entry	Aldehyde	Product	Yield (%)[a]
1	(CH₃)₂CH–CHO	**23** (CH₃)₂CH–CN	91
2	(CH₃)₃C–CHO	**24** (CH₃)₃C–CN	94
3	CH₂=CH–CH₂–C(CH₃)₂–CHO	**25** CH₂=CH–CH₂–C(CH₃)₂–CN	93[b]
4	cyclopentyl–CHO	**26** cyclopentyl–CN	95
5	dimethylcyclohexenyl–CH₂CHO	**27** dimethylcyclohexenyl–CH₂CN	97
6	tetrahydrothiopyranyl–CHO	**28** tetrahydrothiopyranyl–CN	94
7	Ph–C≡C–CHO	**29** Ph–C≡C–CN + 5-phenylisoxazole	85[c]
8	4-O₂N–C₆H₄–CH=CH–CHO	**30** 4-O₂N–C₆H₄–CH=CH–CN	94
9	cyclopentenyl–CH₂CHO	**31** cyclopentenyl–CH₂CN	95
10	Boc-piperidinyl–CHO	**32** Boc-piperidinyl–CN	93[d]

[a] Isolated yields.
[b] Product is highly volatile and extracted with pentane.
[c] Separated by chromatography.
[d] Conditions: 3.0 equiv of base were used.

into nitrile under conditions of electrophilic activation of the oxime hydroxy group to form the phosphonate intermediate, thus making it a better leaving group.

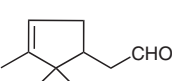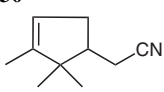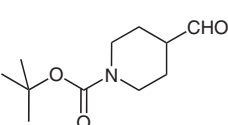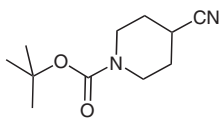In summary, T3P has been demonstrated to be a remarkably efficient reagent for the one-pot access to aromatic, heteroaromatic, and aliphatic nitriles from respective aldehydes.[14] The method seems to be convenient with respect to other reports and can be used as a valid alternative, thus avoiding tedious purifications or the use of more toxic reagents. This new procedure offers simple and easily reproducible technique for nitrile synthesis and highlights the synthetic utility of T3P as a versatile reagent in organic chemistry.

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(14) **General Procedure for the Synthesis of Nitriles from Aldehydes**

To a mixture of aldehyde (0.01 mol), hydroxylamine hydrochloride (0.011 mol), and Et_3N (0.011 mol) in DMF (10 mL) was added T3P (0.011 mol, 50% soln in EtOAc), and the mixture was stirred at 100 °C for 1–3 h. The completion of reaction was monitored by TLC (5% EtOAc in hexane). The mixture was cooled and carefully poured onto sat. aq $NaHCO_3$ solution (40 mL) and extracted with EtOAc (2 × 25 mL). The combined organic phase was washed with H_2O (1 × 25 mL), brine (1 × 25 mL), and dried over Na_2SO_4. On evaporating the solvent under vacuum, the nitrile was obtained in good yield and purity (Note: Aliphatic nitriles were extracted with Et_2O or pentane).

Characterization Data for Compound 18

Off-white solid; mp 194.2–195.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 14.65 (br s, 1 H), 8.37 (s, 1 H), 8.01 (dd, 1 H, J = 8.8, 1.2 Hz), 7.81 (d, 1 H, J = 8.8 Hz), 3.88 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.7, 141.5, 127.7, 125.0, 123.2, 121.1, 119.0, 113.4, 112.1, 52.3. IR (KBr): 3286, 2242 (CN), 1721, 1433, 1240, 738. ESI-MS (APCI, negative mode) for $C_{10}H_7N_3O_2$: *m/z* = 200 [M − H]⁺. Anal. Calcd (%) for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.76; H, 3.55; N, 20.82.

Characterization Data for Compound 27

Pale yellow liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.17 (s, 2 H), 1.94 (t, 2 H), 1.64 (s, 3 H), 1.55–1.49 (m, 2 H), 1.43–1.40 (m, 2 H), 0.98 (s, 6 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 132.2, 127.7, 119.6, 38.6, 34.5, 32.1, 27.2, 19.5, 18.6, 15.3. IR (liquid film): 2930, 2243 (CN), 1463, 1382 cm⁻¹. MS (GC) for $C_{11}H_{17}N$: *m/z* = 163 [M − H]⁺. Anal. Calcd (%) for $C_{11}H_{17}N$: C, 80.93; H, 10.50; N, 8.58. Found: C, 80.99; H, 10.57; N, 8.52.