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An efficient conversion of aldoximes to nitriles by diethyl hydrogen phosphonate-tetra methyl guanidine

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ABSTRACT

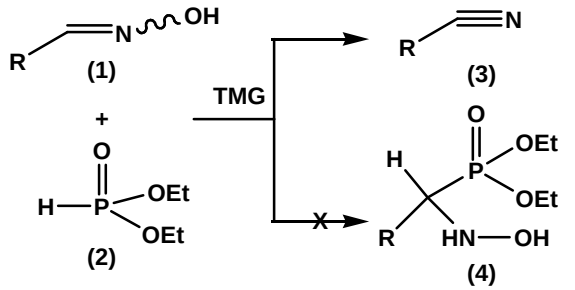
Aldoximes are almost converted quantitatively for the first time into their nitriles by reaction with diethyl phosphate in the presence of tetra methyl guanidine (TMG) in toluene at 65-75°C. The reaction is chemo selective and applicable to multi functionalized aldoximes.

KEYWORDS

Aldoxime;
Aromatic nitriles;
Diethyl hydrogen phosphate;
Tetramethylguanidine;
Toluene.

INTRODUCTION

Nitriles are useful substrates in organic synthesis. Among several methods available for the preparation of nitriles, dehydration of oximes is an elegant one. Apart from classical reagents such as $(CH_3CO)_2O$ and $C_6H_5SO_2Cl$[1], others like $RC(OEt)_3$[2], 2,4,6-trichloro[1,3,5] triazine-DMF[3], silicagel-$SOCl_2$[4], oxime-tosylate-MW[5], P_2O_5-SiO_2[6], DMF[7], Red-mud-MW[8] and PEG-SO_3H[9] are ideal for dehydration of oximes into nitriles. Organometallics



Scheme 1 : Conversion of aldoximes in to nitriles by DEHP-TMG

$TiCl_3(OTf)$[10], $[RuCl_2(b\text{-cymne})]_2$[11], $AlCl_3.6H_2O/KI/H_2O/CH_3CN$[12], $Na_2SO_3SOCl_2$[13], $Ga(OTf)_3$[14], W-Sn hydroxide[15], $Pd(OAc)_2$-PPh_3[16], and AIBN-

TABLE: 1 Optimization of reaction conditions

Entry	Base	Phosphate	Yields[%][a]	
			55-65°C	65-75°C
1	Et_3N[b]	DMHP[f]	-----	------
2	Et_3N	DEHP[g]	-----	------
3	Et_3N	DPHP[h]	-----	------
4	TMG[c]	DMHP	40	85
5	TMG	DEHP	55	99
6	TMG	DPHP	Trace	70
7	Py[d]	DMHP	-----	21
8	Py	DEHP	Trace	35
9	Py	DPHP	-----	16
10	NMP[e]	DMHP	20	55
11	NMP	DEHP	40	85
12	NMP	DPHP	Trace	46

No reaction up to 55°C, [a]Yield after purification, [b]Triethyl amine, [c]Tetra methyl guanidine, [d]Pyridine, [e]1,4-Dimethyl piperazine, [f] Dimethyl / [g] Diethyl / [h] Diphenyl hydrogen phosphonate

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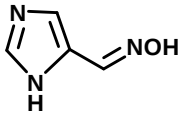
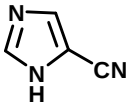
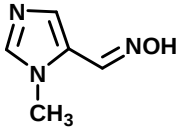
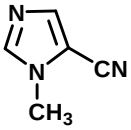
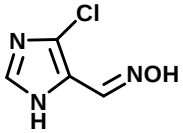
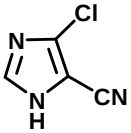
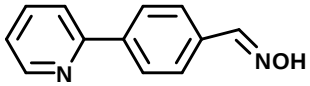
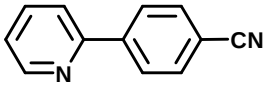
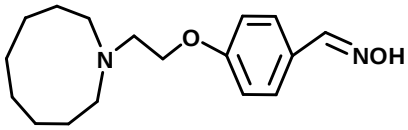
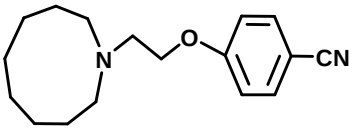
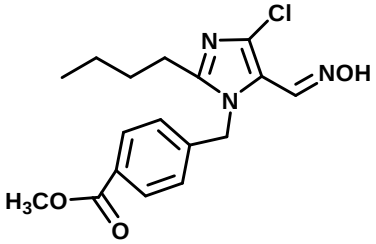
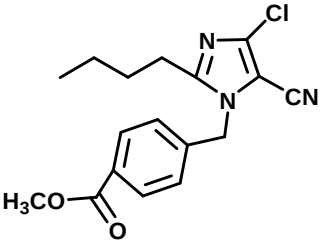
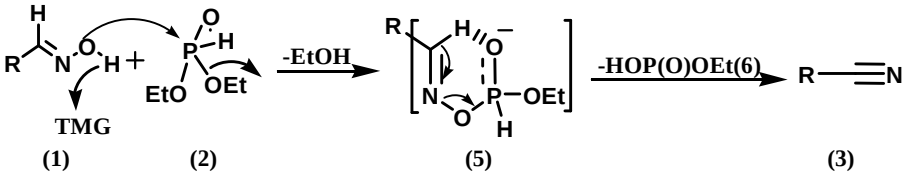
TABLE 2 : Conversion of aldoximes in to nitriles by DEHP-TMG

Entry	Substrate	Reaction time (Hrs)	Product	Yield[%][a]
1	$C_6H_5CH=NOH$	9	C_6H_5CN	95
2	$4\text{-}ClC_6H_5CH=NOH$	8	$4\text{-}ClC_6H_5CN$	97
3	$4\text{-}BrC_6H_5CH=NOH$	10	$4\text{-}BrC_6H_5CN$	98
4	$4\text{-}FC_6H_5CH=NOH$	7	$4\text{-}FC_6H_5CN$	98
5	$4\text{-}NO_2C_6H_5CH=NOH$	7	$4\text{-}NO_2C_6H_5CN$	97
6	$4\text{-}CNC_6H_5CH=NOH$	9	$4\text{-}CNC_6H_5CN$	98
7	$4\text{-}CH_3C_6H_5CH=NOH$	7	$4\text{-}CH_3C_6H_5CN$	98
8	$4\text{-}(CH_3)_2CHC_6H_5CHNOH$	11	$4\text{-}(CH_3)_2CHC_6H_5CN$	96
9	$4\text{-}(CH_3)_2NC_6H_5CH=NOH$	12	$4\text{-}(CH_3)_2NC_6H_5CN$	96
10	$4\text{-}CH_3OC_6H_5CH=NOH$	8	$4\text{-}CH_3OC_6H_5CN$	99
11	$4\text{-}(CH_3O)_3C_6H_5CH=NOH$	8	$4\text{-}(CH_3O)_3C_6H_5CN$	98
12	$4\text{-}HOC_6H_5CH=NOH$	10	$4\text{-}HOC_6H_5CN$	95
13	$4\text{-}PhOC_6H_5CH=NOH$	8	$4\text{-}PhOC_6H_5CN$	93
14	C_6H_5 CH=CHCH=NOH	9	$C_6H_5CH=CHCN$	95
15	$CH_3(CH_2)_2CH=NOH$	12	$CH_3(CH_2)_2CN$	94
16	$CH_3(CH_2)_5CH=NOH$	12	$CH_3(CH_2)_5CN$	92
17		13		94
18		14		93
19		10		95
20		11		97
21		12		95
22		12		93

[a]**Yield after purification**

Bu_3SnH[17] are another group of reagents utilized for this purpose. In an endevour to find better reagents for transformation of oximes into nitriles, some organophosphorus compounds like $RO_2P(O)Cl$[18,19], $ROP(O)\text{-}Cl_2$[20], $P_3N_3Cl_6$[21], $(Me_2N)_3P=O$[22], Ph_3PI_2[23] are also successful in performing this reaction. But most of these reagents are corrosive and toxic involving drastic experimental conditions besides cum-



Scheme 2 : Mechanism of conversion of aldoximes in to nitriles by DEHP-TMG

bersome procedures that also give poor yields. They include recently reported methodologies with $(EtO)_2P(O)ONR_2$[24], and BOP-DBU[25] which are not free from these draw backs.

In connection with the investigation on the synthesis of bioactive organophosphorus compounds, an attempt is made to prepare addition product **(4)** of the aldoxime **(1)** with dialkyl hydrogen phosphonate (DEPH) **(2)** in the presence of tetramethylguanidine (TMG) (Scheme 1). Contrarily, it reveals the formation of the nitrile **(3)** of the corresponding oxime instead of its addition product **(4)**. The reaction goes to prove that aldoxime conversion is almost quantitative and effective. Detailed studies of this reaction on several aldoximes conclusively prove that DEHP-TMG reagent system effectively dehydrates the aldoximes at 65-75°C to the corresponding nitriles in 92-99% yield (TABLE 2).

The reaction conditions are optimized by carrying it out with different alkyl/ aryl phosphonates, and various bases at different temperatures. DEHP-TMG in toluene at 65-75°C is found to be ideal for efficient conversion of aldoximes into nitriles (TABLE 1). On the other hand ketoximes failed to convert into corresponding nitriles under similar conditions.

EXPERIMENTAL

General procedure

The melting points are determined in open capillary tubes on a Mel-Temp apparatus and are left uncorrected. The IR spectra (ν_{max} in cm^{-1}) are recorded in KBr pellets on a Perkin Elmer 1000 unit. The ^1H, ^{13}C and ^{31}P NMR spectra are recorded on a Varian Gemini 300 and Varian AMX 400 MHz NMR spectrometers operating at 300 or 400 MHz for ^1H, and 100.57 MHz for ^{13}C respectively. All the compounds are dissolved in $CDCl_3$ or DMSO-d_6 and chemical shifts are referenced to TMS (^1H and ^{13}C). Micro analyses data obtained is from Central Drug Research Institute, Lucknow, India.

Experimental procedure

DEHP (0.1mmole) and TMG (0.1mmole) were added to the aldoxime (0.1mmole) solution in toluene (5mL) and the mixture was continuously stirred for 18-25hrs. the progress of the reaction was monitored by TLC using silica plates in 3:7 ethyl acetate-hexane mixture. After completion of the reaction, the solvent was removed in a rotaevaporator. The residue after treating with cold water (10ml) was stirred for 15 min to separate the product. The resultant solid products were collected by filtration and recrystallized from ethanol. The liquid products were directly purified by column chromatography using 100-200 mesh slicagel as adsorbent and 8:2 hexane: ethyl acetate as eluent. In both cases, the pure product with 92-99% yields was obtained. All the new nitriles were characterized by IR, ^1H, ^{13}C and Mass spectra. Known nitriles were confirmed by comparing with their physical and spectral data with that of their respective authentic samples.

SPECTRAL DATA

4-(pyridine-2-yl)benzonitrile (20)

IR(KBr, cm^{-1}) : 2225.22(CN) ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 2.29, 2.30 Hz, 1H), 8.12 (d, J = 8.07 Hz, 2H), 7.83-7.75 (m, 4H), 7.32(t, J=5.53, 5.30 Hz, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.09, 149.92, 143.32, 137.04, 132.46, 127.36, 123.25, 120.90, 118.70, 112.36. HRMS (EI) calcd for ($C_{12}H_8N_2$+H): 181.0766; found 181.0768.

4-[2-(1-azonanyl)ethoxy]benzonitrile (21)

IR (KBr, cm-1): 2224.66(CN) ^1H NMR (400 MHz, $CDCl_3$) δ 7.41(d, J=8.6Hz, 2H), 6.88(d, J=8.6Hz, 2H), 4.24(t, J=6.34Hz, 2H), 2.99(t, J=6.33Hz,), 2.86-2.79(m, 4H, $N(CH_2)_2$), 1.72-1.63(m, 12H, CH_2) ^{13}C

NMR (100MHz, $CDCl_3$) δ 159.81, 148.74, 128.12, 125.41, 114.72, 66.45, 56.03, 55.82, 27.35, 26.87, 26.75. MS (EI) m/z: 273($M^{+\cdot}$+1).

Methyl4-[(2-butyl-4-chloro-5-cyno-1H-1-imidazoly)methyl]benzoate (22)

IR (KBr, cm^{-1}): 2221.56 (CN) ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.043 (d, J = 8.2 Hz, 2H), 7.164 (d, J = 8.13 Hz, 2H), 5.21 (s, 1H, CH_3), 3.90(s, 3H, OCH_3), 2.59(t, J=7.6Hz, 2H), 1.66-1.61(m, 2H), 1.345-1.28(m, 2H), 0.86(t, J=7.30Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.07, 152.14, 140.42, 138.58, 130.48, 129.84, 126.42, 124.19, 109.84. MS (EI) m/z: 332($M^{+\cdot}$+1), 354 ($M^{+\cdot}$+Na).

RESULTS AND DISCUSSION

Conversion of the oximes **(1)** to the nitriles **(3)** is a base catalyzed and DEHP induced reaction (Scheme 2). Initial hydrogen abstraction by TMG from the oxime **(1)** renders its oxygen more nucleophilic and thus facilitates its nucleophilic attack on the P-atom of DEHP **(2)**. The low energy empty d-orbitals of the phosphonate phosphorus **(2)** allows oxime oxygen nucleophilic addition on it and forms the new P-O bond with simultaneous elimination of ethoxide as ethanol. This process is further facilitated due to the formation of a six memberd cyclic intermediate **(5)** stabilized by H-bonding with α-H of the oxime **(1)**. There is no reaction with ketoximes where α-proton is unavailable to form a H-bonded cyclic intermediate **(5)**, wich supports this assumption. Facile elimination of ethyl hydrogen phosphate from the cyclic intermediate **(5)** results in the formation of nitriles **(3)**. This reaction course in which conversion of DEHP **(2)** with ^{31}P ∂ 6.8 in the presence of TMG into the cyclic oxime phosphite intermediate **(5)** with ^{31}P ∂ 1.95 and elimination of ethyl hydrogen phosphite **(6)** with ^{31}P ∂ 26.18 is monitored by ^{31}P NMR.

CONCLUSION

A simple direct and highly efficient method for almost qantative conversion of aromatic aldoximes into nitriles by DEHP-TMG is reported for the first time. Significance of the reaction is its chemoselectivity and applicability to multifunctionalised aldoximes. The reaction is green for it works at moderate temperature with biodegradable non-toxic reagents.

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REFERENCS

[1] D.T.Mowry; Chem.Rev., **42**, 189 **(1947)**.
[2] M.M.Rogii, J.F.Van Peppen, K.P.Clain, T.R.Demmin; J.Org.Chem., **39(23)**, 3424 **(1974)**.
[3] L.D.Luca, G..Giacomelli, A.Porcheddu; J.Org. Chem., **67**, 6272 **(2002)**.
[4] F.Kazemi, A.R.Kiasat, E.Fadavipoor; Phosphorus, Sulfur and Silicon, **179**, 433 **(2004)**.
[5] H.A.Oskooie, M.M.Heravi, Z.Jaddi, M.Ghassemzadeh; Phosphorus, Sulfur and Silicon, **180**, 1993 **(2005)**.
[6] H.Eswghi, Z.Gordi; Phosphorus, Sulfur and Silicon, **180**, 2553 **(2005)**.
[7] P.Supsana, T.Liaskopoulos, P.G.Tsongas, G.Varvounis; Synlett., **17**, 2671 **(2007)**.
[8] S.H.Khezri, N.Azimi, M.M.Vali, B.E.Sis, M.M.Hashemi, M.H.Baniasadi, F.Teimouri; Arkivoc, **15**, 162 **(2007)**.
[9] X.C.Wang, L.Li, Z.T.Quan, H.P.Gong, H.L.Ye, X.F.Cao; Chin.Chem.Lett., **2**, 004 **(2009)**.
[10] N.Iranpoor, B.Zeynizadeh; Synth.Commun., **29(16)**, 2747 **(1999)**.
[11] S.H.Yang, S.Chang; Org.Lett., **3**, 4209 **(2001)**.
[12] M.Boruah, D.Konwar; J.Org.Chem., **67(20)**, 7138 **(2002)**.
[13] A.R.Kiasat, F.Kazemi, F.Khosravian; Phosphorus, Sulfur and Silicon, **178**, 1377 **(2003)**.
[14] P.Yan, P.Batamack, G.K.S.Prakash, G.A.Olah; Catalysis Letters, **101**, 141 **(2005)**.
[15] K.Yamaguchi, H.Fugiwara, Y.Ogasawara, M.Kotani, N.Mizuno; Angew, Chem.Int.Ed., **46**, 3922 **(2007)**.
[16] H.S.Kim, S.H.Kim, J.N.Kim; Tetrahedron Letters, **50**, 1717 **(2009)**.
[17] H.J.Peter de Lijser, C.R.burke, J.Rosenberg, J.Hunter; J.Org.Chem., **74**, 1679 **(2009)**.

[18] J.Patrick, Jr.Foley; J.Org.Chem., **34(9)**, 2805 **(1969)**.
[19] Z.Jie, V.Rammoorty, B.Fischer; J.Org.Chem., **67**, 711 **(2002)**.
[20] J.L.Zhu, F.Y.Lee, J.D.Wu, C.W.Kuo, K.S.Shia; Synlett., **8**, 1317 **(2007)**.
[21] G.Rosini, G.Baccolini, S.Cacchi; J.Org.Chem., **38(5)**, 1060 **(1973)**.
[22] N.O.Vesterager, E.B.Pedersew, S.O.Lawesson; Tetrahedron, **30**, 2509 **(1974)**.
[23] A.V.Narasaiah, D.Sreenu, K.Nagaiah; Synth. Commun., **36**, 137 **(2006)**.
[24] N.D.Kokare, D.B. Shinde; Monatsh.Chem., **140**, 185 **(2009)**.
[25] M.K.Singh, M.K.Lakshman; J.Org.Chem., **74(8)**, 3079 **(2009)**.