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Efficient conversion of aldoximes into nitriles and ketoximes into amides using bis-morpholinophosphorylchloride

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Bis-morpholinophosphorylchloride (bmpc) has been identified as a new reagent to efficiently convert aldoxime into nitriles through dehydrogenation and ketoximes into amides through Beckmann rearrangement. When compared to other chlorophosphate reagents used earlier, which are liquids and irritating, bmpc is a non-irritating stable solid. In all the reactions, products are obtained in high yields and purity.

Keywords: Bis-morpholinophosphorylchloride, aldoxime, Ketoxime, Nitrile, Amide, Beckmann rearrangement

Nitrile is an important pharmacophore which is present in a large number of drug substances that are in the market and many are under clinical development[1]. It is a good bioisostere and acts as surrogate for the hydroxyl and carboxyl groups. Several cardiovascular drugs such as milrinone, olprinone; CNS drugs such as escitalopram, vilazodone; anti-diabetic drugs such as vildagliptin, saxagliptin and anti-HIV drugs such as etravirine, dapivirine are all nitrile derivatives[2]. Nitriles are also important class of compounds as they can be converted into carboxylic acids, aldehydes, amides, amines and ketones[3]. Various methods for the synthesis of nitrile have been reviewed[4].

Recently, we reported the preparation of nitriles from primary amides using bis-morpholinophosphoryl chloride (bmpc) (Fig. 1) as a novel dehydrating agent[5]. Another convenient method for the preparation of nitriles is by the dehydration of aldoximes. Hence, we extended our studies to aldoximes and have found that bmpc is also very efficient in dehydrating aldoximes into nitriles. Furthermore, bmpc also converted ketoximes into amides through Beckmann rearrangement.

Earlier, diethyl chlorophosphate[6], ethyl dichlorophosphate[7], and diethyl chlorophosphite[8], have been reported to dehydrate aldoximes into nitriles. Diethyl chlorophosphate[6], ethyl dichlorophosphate[7], and phenyldichlorophosphate[9] have been reported to convert ketoximes into amides. However, these reagents are corrosive and cause skin and eye irritation. Furthermore, being liquids at room temperature, these reagents are difficult to handle.

The chlorophosphoroimidate derivatives such as *N*,*N*-dimethyl phosphoramidic dichloride and bis(2-oxo-3-oxazolidinyl) phosphinic chloride (bop-cl) also have been studied earlier. While *N*,*N*-dimethyl phosphoramidic dichloride was found to be ineffective in converting ketoximes into amides[9], bop-cl was found to be very efficient in converting ketoximes into amides[10]. However, the purity of the commercially available bop-cl reagent is not satisfactory, and its preparation involves several steps[11]. In comparison, bmpc is a cream coloured solid which is stable under dry conditions. It is non-irritating and can be easily prepared in one step[12]. It has been used as phosphorylating agent[12, 13] and also as a condensing agent for peptidebond formation[14].

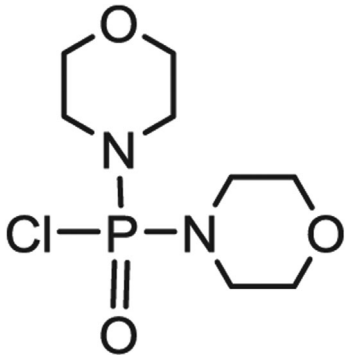


Fig. 1 — Structure of Bis-morpholinophosphorylchloride

Herein, we report bis-morpholinophosphorylchloride as a novel and efficient reagent for the conversion of aldoximes and ketoximes into nitriles and amides respectively.

Experimental Details

All the oximes used as starting materials, were prepared according to standard methods. All other chemicals used were obtained from commercial sources and used without further purification. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker instrument at 300, 75 and 121.5 MHz, respectively, with $CDCl_3$, CD_3OD or DMSO-d_6 as solvent. Mass spectra were recorded on a Thermo scientific LCQ Fleet spectrometer with ion trap mass spectrometer. Column chromatography was conducted over silica gel (100-200 mesh). Purity was determined by GC [Column: DB 624, 30 m x 0.32 mm dia.] and HPLC, performed on 'WATERS-2487' system controller and UV monitor as detector. Method: Purospher RP 18 (250 x 4.0 mm) column, 5 µm; eluent: sodium octane sulfonate buffer/acetonitrile (90:10); flow rate 1.5 mL/min; temp 45°C, detection at 215 nm.

Preparation of pyrrole-2-carbonitrile (2i)

A mixture of pyrrole-2-carbaoxaldoxime (**1i**, 5.0 g, 45.40 mmol) and dimethylformamide (25 mL) was stirred at room temperature for 10 min. To the mixture was added bis-morpholinophosphorylchloride (13.9 g, 54.50 mmol) and stirring continued for 15 min at 55-60°C. After cooling, the reaction mixture was poured into cold water (25 mL) and extracted with ethyl acetate (2 x 50 mL). The organic phase was washed with 10% aq. $NaHCO_3$ solution (20 mL), water (20 mL) and brine (20 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure and purification by distillation at bp. 93-95°C (10 mm Hg) [lit.[16] b.p. 122-123°C (15 mm Hg)]; pyrrole-2-carbonitrile (4.0g, 96% yield) obtained as a pale-yellow liquid with 99.65% GC purity. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.25 (br s, 1H), 7.15-7.14 (m, 1H), 6.91-6.90 (m, 1H), 6.23-6.21 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 125.03, 119.82, 115.35, 109.96, 100.08; MS (ESI): m/z 92.33 $[M]^+$. The other products **2a-n** were prepared and characterized in a similar manner.

Benzonitrile (2a): Yield: 90%; colourless liquid; b.p. 70-72°C (10 mm Hg) [lit.[16] bp. 76°C (15 mm Hg)]; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 7.86-7.83 (m, 2H), 7.76-7.70 (m, 1H), 7.62-7.56 (m, 2H); ^{13}CNMR (75 MHz, DMSO-d_6) δ (ppm) 133.75, 132.65, 129.91, 119.27, 111.83; MS (ESI): m/z 104.07 $[M+H]^+$.

3,4-Dimethoxybenzonitrile (2b): Yield: 88%, off white sold, m.p. 65-67°C (lit.[17] 65-66°C); ^{1}H NMR (300 MHz, DMSO-d_6):δ (ppm) 7.44-7.35 (m, 2H), 7.16-7.10 (m, 1H), 3.84 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 153.22, 149.38, 126.84, 114.80, 112.48, 103.05, 56.32, 56.24; MS (ESI): m/z 164.02 $[M+H]^+$.

3,4-Diethoxybenzonitrile (2c): Yield: 85%; white solid; m.p. 66-68°C (lit.[17] 67-68°C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 7.42-7.33 (m, 2H), 7.15-7.11 (m, 1H), 4.17-4.04 (m, 4H), 1.42-1.51 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 152.62, 148.65, 126.22, 119.41, 115.72, 112.64, 103.63, 64.91, 14.58, 14.55; MS (ESI): m/z 191.98 $[M+H]^+$.

4-Hydroxy-3-methoxybenzonitrile (2d): Yield: 83%; white solid; m.p. 86-88°C [lit.[17] 86-87°C]; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.37-7.34 (d, 1H), 7.31-7.24 (m, 1H), 6.92-6.89 (d,1H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 151.90, 148.40, 127.27, 120.05, 116.07, 115.66, 101.4156.35; MS (ESI): m/z 150.10 $[M+H]^+$.

2-Chlorobenzonitrile (2e): Yield: 65%; off-white solid; m.p. 42-44°C [lit.[6] 42°C]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.66 (m, 1H), 7.58-7.50 (m, 2H), 7.40-7.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.83, 134.02, 133.93, 130.06, 127.20, 115.97, 113.37; MS (APCI): m/z 137.92 $[M+H]^+$.

2-Hydroxybenzonitrile (2f): Yield: 82%; off-white solid; m.p. 91-93°C [lit.[16] 96-97°C]; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 11.04 (br s,1H) 7.61-7.58 (m, 1H), 7.53-7.46 (m, 1H), 7.03-7.00 (m, 1H), 6.98-6.90 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 160.58, 135.13, 133.67,119.99, 116.60, 99.31; MS (ESI): m/z 117.97 $[M-H]^+$.

3-Nitrobenzonitrile (2g): Yield: 84%; white solid; m.p. 117-118°C [lit.[6] 115°C]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55-8.46 (m, 2H), 8.02-7.99 (m, 1H), 7.79-7.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.22, 137.69, 130.75, 127.58, 127.23, 116.59, 114.08; MS (APCI): m/z 149.04 $[M+H]^+$.

4-Nitrobenzonitrile (2h): Yield: 86%; off-white solid; m.p. 148-149°C [lit.[16] 149-150°C]; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.29-8.24 (m, 2H), 7.67-7.62 (m, 2H), 4.26 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 147.44, 139.53, 129.90, 124.44, 118.84, 22.58; MS (APCI): m/z 149.07$[M+H]^+$.

2-Thiophenecarbonitrile (2j): Yield: 94%; pale yellow liquid; b.p. 110-112°C [lit.[16] bp 80°C (15 mm Hg)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.10-8.08 (dd, 1H), 7.99-7.97 (dd, 1H), 7.31-7.28 (m,1H); ^{13}CNMR (75 MHz, $CDCl_3$) δ (ppm) 139.37, 135.42, 128.77, 114.96, 108.77; MS (ESI): m/z 110.1 $[M+H]^+$.

2-Pyridinecarbonitrile (2k): Yield: 88%; colourless liquid; b.p. 112-117°C [lit.[18] 110-120°C (12 mm Hg)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.69-8.73 (dd, 1H), 7.86-7.74 (m, 1H), 7.70-7.65 (m, 1H), 7.49-7.53 (m, 1H); ^{13}CNMR (75 MHz, $CDCl_3$) δ (ppm) 151.08, 136.97, 134.00, 128.48, 126.86, 117.11; MS (ESI): m/z 104.97 $[M+H]^+$.

Isobutyronitrile (2l): Yield: 48%; colourless liquid; b.p. 177-110°C [lit.[16] bp 120°C]; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.77-2.63 (m, 1H), 1.34-1.32 (d, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 123.75, 19.877; MS (ESI): m/z 70.04 $[M+H]^+$.

Butyronitrile (2m): Yield: 52%; colourless liquid; b.p. 120-123°C [lit.[16] bp 138-139°C]; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.35-2.30 (t, 2H), 1.76-1.62 (m, 2H), 1.10-1.05 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 119.68, 19.06, 18.91, 13.18; MS (ESI): m/z 69.97 $[M+H]^+$.

Valeronitrile (2n): Yield: 65%; colourless liquid; b.p. 140-142°C [lit.[19] bp 140-141°C]; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.36-2.32 (t, 2H), 1.70-1.60 (m, 2H), 1.54-1.44 (m, 2H), 0.98-0.93 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 119.82, 27.29, 21.78, 16.76, 13.16; MS (ESI): m/z 84.07 $[M+H]^+$.

Preparation of N-phenylacetamide (4a)

Acetophenone oxime (**3a**, 10.0 g, 74.0 mmol) was added to toluene (100 mL) and the mixture was stirred for 10 min. To the mixture was added bis-morpholinophosphorylchloride (22.7 g, 88.8 mmol). After raising the temperature to 55-60°C, stirring was continued for 2 h. The reaction mixture was cooled and washed with 10% aq. NaOH solution (100 mL). The two layers were separated and the aqueous layer was re-extracted with toluene (50 mL). The combined organic layers were washed with water (100 mL), brine (100 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated to obtained 10.0 g solid with 98.5% HPLC purity. It was further purified by re-crystallization with ethyl acetate-hexane (1:4), to yield 9.8 g (98% yield) of **4a** as white solid. M.p. 112-114°C (lit.[6] 113°C) with 99.95% HPLC purity. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.51-7.48 (d, 2H), 7.33-7.26 (m, 2H), 7.12-7.07 (t, 1H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 169.17, 138.11, 128.90, 124.30, 120.25, 24.39; MS m/z 136.02 $[M+H]^+$. The other products given **4b-m** were prepared and characterized in a similar manner.

N-(4-Hydroxyphenyl) acetamide (4b): Yield: 90%; re-crystallization with water; white solid; m.p. 166-168°C (lit.[20] 167-168°C); ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 9.63 (s, 1H), 9.11 (s, 1H), 7.34-7.31 (m, 2H), 6.68-6.65 (m, 2H), 1.97 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 168.02, 153.60, 131.47, 121.32, 115.46, 24.18; MS m/z 152.05 $[M+H]^+$.

N-(4-Methoxyphenyl) acetamide (4c): Yield: 88%, re-crystallization with hexane-ethyl acetate (3:1); off-white solid; m.p.: 126-128°C (lit.[9] 127-129°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.39-7.36 (m, 2H), 6.86-6.81 (m, 2H), 3.78 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.88, 156.37, 131.20, 122.14, 114.03, 55.45, 24.12; MS m/z 166.06 $[M+H]^+$.

N-(4-Methylphenyl) acetamide (4d): Yield: 85%; re-crystallization with hexane-ethyl acetate (3:1); white solid; m.p. 149-150°C (lit.[6] 151°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.38-7.34 (d, 2H), 7.11-7.09 (d, 2H), 2.3 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.62, 135.74, 133.91, 129.45, 120.63, 24.51, 22.11. MS m/z 150.06 $[M+H]^+$.

N-(3-Hydroxyphenyl) acetamide (4e): Yield: 80%; white solid; m.p. 147-149°C (lit.[20] 148-149°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.30 (br s, 1H), 8.96 (s, 1H), 7.33 (s, 1H), 7.07-7.04 (t, 1H), 6.89-6.88 (d, 1H), 6.55-6.53 (d, 1H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 169.2, 157.5, 139.7, 129.3, 111.0, 110.3, 107.2, 24.1; MS m/z 152.02 $[M+H]^+$.

N-(2-Chlorophenyl) acetamide (4f): Yield: 72%; off-white solid; m.p. 90-92°C (lit.[21]90-91°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.34-8.32 (d, 1H), 7.69 (br s, 1H), 7.36-7.32 (m, 1H), 7.28-7.24 (m, 1H), 7.05-6.99 (t, 1H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.5, 135.2, 131.3, 130.07, 125.5, 124.7, 121.2, 24.8; MS m/z 170.15 $[M+H]^+$.

N-(3-Nitrophenyl) acetamide (4g): Yield: 75%; off-white solid; m.p. 155-156°C (lit.[20] 155-156°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.81 (s, 1H), 8.36 (s, 1H), 8.10-8.07 (t, 1H), 7.82-7.80 (d, 2H), 7.48-7.46 (d, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ (ppm) 170.0, 150.5, 140.8, 132.6, 129.5, 124.7, 121.4, 20.2; MS m/z 181.02 $[M+H]^+$.

Benzanilide (4h): Yield: 85%; white solid; m.p. 162-163°C (lit.[6] 162°C); ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 7.90 (br s, 1H), 7.85-7.83 (m, 2H), 7.62-7.60 (m, 2H), 7.54-7.48 (m 1H), 7.46-7.42 (m, 2H), 7.38-7.33 (m, 2H), 7.14-7.12 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 166.14, 139.24, 134.98, 131.61, 128.64, 128.18, 127.74, 123.72, 120.64; MS m/z 198.13 $[M-H]^+$.

ε-Caprolactam (4i): Yield: 79%; white solid; m.p. 69-71°C (lit.[20] 73-74°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.10 (br s, 1H), 3.15-3.10 (m, 2H), 2.40-2.35 (m, 2H), 1.67-1.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 179.53, 42.2, 36.9, 30.2, 29.5, 23.0; MS m/z 113.99 $[M+H]^+$.

δ-Valerolactam (4j): Yield: 82%; colour less liquid; b.p. 80-85°C (0.1mm Hg) (lit.[22]135-140°C at 11 mm Hg); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.44 (br s, 1H), 3.34-3.30 (m, 2H), 2.36-2.32 (m, 2H), 2.00-1.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 172.42, 42.0, 31.55, 22.41, 20.74; MS m/z 99.32 $[M]^+$.

N-methyl acetamide (4k): Yield: 70%; colour less liquid; b.p. 81-83°C (10 mm Hg) (lit.[23] 204-206°C at 760 mm Hg); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.88 (bs, 1H), 2.80-2.78 (d, 3H), 1.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 173.84, 26.23, 22.42; MS m/z 74.01 $[M+H]^+$.

N-ethyl acetamide (4l): Yield: 58%; colour less liquid; b.p. 60-65°C (1 mm Hg) (lit.[24] 97-98°C at 8 mm Hg); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.7 (br s, 1H), 3.27-3.25 (m, 2H), 1.97 (s, 3H), 1.15-1.13 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 170.66, 34.43, 23.03, 14.69; Mass: 86.1 $[M-H]^-$.

N-isobutyl acetamide (4m): Yield: 52%; yellowish liquid; b.p. 55-60°C (1 mm Hg) (lit.[25] 225°C at 760 mm Hg); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.13-3.11 (d, 1H), 2.36-2.33 (m, 1H), 1.81 (s, 3H), 0.83-0.86 (d, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 170.6, 46.9, 28.5, 23.5, 20.2; Mass: 116.1 $[M+H]^+$.

Results & Discussion

Conversion of aldoximes into nitriles

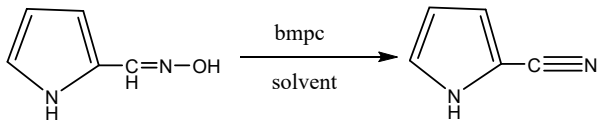
As a model reaction, pyrrole-2-carbaldoxime (**1i**) was reacted with 1.2 equivalents of bmpc in dimethylformamide (DMF) at 55-60°C. The reaction was completed in about 15 min and pyrrole-2-carbonitrile (**2i**) was obtained in 96% yield after normal workup. At room temperature, the reaction was completed in 60 min and at 100°C, impurities were observed. The reaction was studied in other solvents at 55-60°C. In acetonitrile, the reaction took about 30 min, in toluene about 60 min and in dichloromethane (at 35-40°C) about 180 min for completion. In solvents such as 2-methyl tetrahydrofuran and methyl *tert*-butyl ether, the reaction was incomplete even after 3 h (Table 1).

Using the above optimized conditions, various aldoximes were studied (Table 2). All the aldoximes used were of E- configuration. Reaction of unsubstituted benzaldoxime (**1a**) with bmpc in dmf at 55-60°C was completed in 30 min and gave benzonitrile (**2a**) in 90% yields. In general, any type of substitution, whether electron releasing or electron withdrawing group, at any position, resulted in lower yields and took longer time for the completion of the reaction. However, heterocyclic oxime, pyrrole-2-carbaldoxime (**1i**) was more reactive and gave pyrrole-2-nitrile in almost quantitative yields (96%). The pyrrole-2-carbonitrile (**2i**) is also an important intermediate in the preparation of remdesivir[15], a drug recently approved by FDA, for the treatment of covid 19 infection. Another heterocyclic oxime, thiophene-2-carbaldoxime (**1j**) also showed good reactivity giving thiophene-2-carbonitrile (**2j**) in high yields. Aliphatic aldoximes (**1l-n**) were generally showed low reactivity and gave low yields.

Beckmann rearrangement of ketoximes into amides

Bmpc was also found to be efficient in converting ketoximes into amides through Beckmann rearrangement. As a model reaction, acetophenone oxime (**3a**) was selected as substrate for optimizing

Table 1 — Dehydration of aldoximes to nitriles in the presence of bmpc*

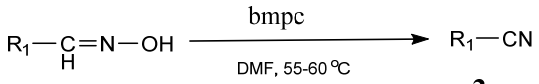


1i **2i**

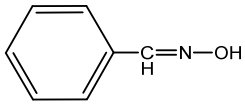
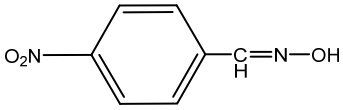
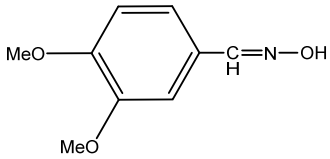
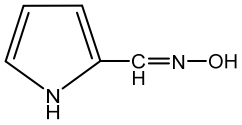
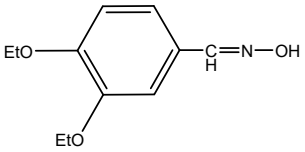
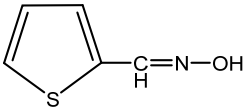
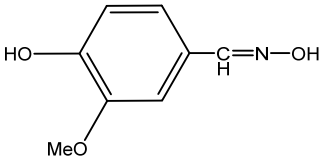
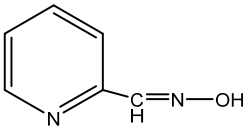
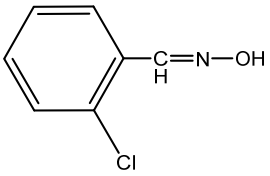
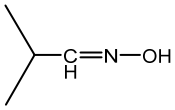
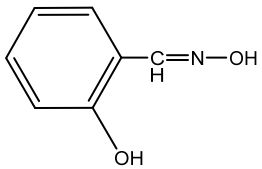
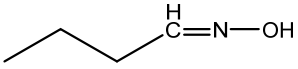
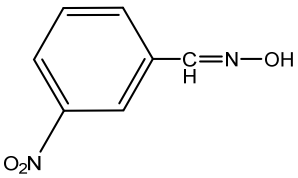
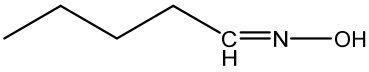
Solvent	Time (min)	Yield (%)[a]
Dimethylformamide	15	96
Acetonitrile	30	95
Toluene	60	89
Dichloromethane	180	91[b]
2-Methyltetrahydrofuran	180	60
Methyl tert-butyl ether	120	70

*Reaction condition: pyrrole-2-carbaldoxime (1.0 eq), bmpc (1.2 eqv.) in solvent at 55-60°C; [a]Isolated yield; [b]Reaction temperature at 35-40°C

Table 2 — Dehydration of aldoximes to nitriles in the presence of bmpc*



1 a-n **2 a-n**

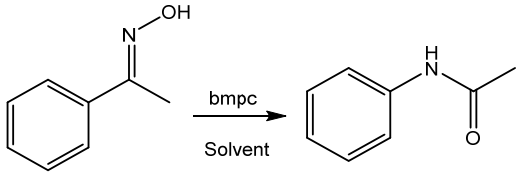
Entry	Substrate	Product[a]	Time (min)	Yield (%)[b]	Entry	Substrate	Product[a]	Time (min)	Yield (%)[b]
1		2a	30	90	8		2h	120	86
2		2b	90	88	9		2i	15	96
3		2c	90	85	10		2j	30	94
4		2d	120	83	11		2k	60	88
5		2e	150	65	12		2l	180	48
6		2f	180	82	13		2m	180	52
7		2g	180	84	14		2n	180	65

* Reaction condition: aldoxime (1.0 eqv.), bmpc (1.2 eqv.) in DMF at 55-60°C; [a]All the products are known; [b]yields are isolated

the reaction conditions (Table 3). When **3a** was reacted with 1.2 equivalent bmpc in toluene at 55-60°C, the reaction was completed in 2 h and the desired N-phenylacetamide (**4a**) was obtained in 98%. Decreasing bmpc to less than 1.0 equivalent resulted in incomplete reaction and 1.5 or 2.0 equivalent did not resulted in any further advantage. When the reaction was conducted at room temperature, **4a** lower yields were obtained. At reflux temperature (100°C), charring of the reaction mixture was observed and after 2 h, 40% product was obtained.

When acetonitrile was used as solvent, the reaction was slightly slower and 95% yield was obtained after 4 hours. Dimethylformamide (DMF) and N-methyl-2-pyrrolidone (NMP) also gave similar results (Table 3). In tetrahydrofuran, 1,4-dioxane, and dichloromethane

Table 3 — Optimisation of reaction conditions for Beckmann rearrangement of acetophenone oxime using bmpc

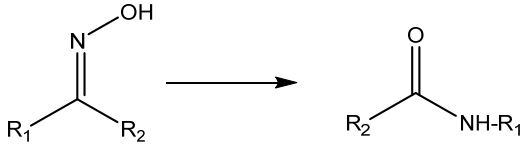


3a 4a

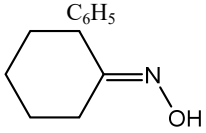
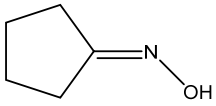
Entry	Solvent[a]	Temperature (°C)	Time (h)	Yield (%)
[b]1	Tolune	55-60	2	98
2	Tolune	25-30	24	34
3	Tolune	100-105	2	40
4	Acetonitrile	55-60	4	95
5	Acetonitrile	25-30	24	25
6	Dimethylformamide	55-60	3	85
7	Dimethylformamide	25-30	24	25
8	N-Methyl-2-pyrrolidone	55-60	4	82
9	Pyridine	55-60	12	NC[c]
10	Tetrahydrofuran	55-60	8	< 10
11	1,4-dioxane	55-60	10	< 10
12	Dichloromethane	35-40	10	< 10

[a]acetophenone oxime (7.40 mmol) reacted with bmpc (1.2 eqv.) in 10 mL solvent; [b]Isolated yield; [c]no conversion

Table 4 — Beckmann rearrangement of ketoximes to amides*



3a-m **4a-m**

Entry	R_1	R_2	Product[a]	Time (h)	Yield(%) [b]
1	C_6H_5	Me	4a	2	98
2	*p*-HOC_6H_5	Me	4b	6	90
3	*p*-$MeOC_6H_5$	Me	4c	3	88
4	*p*-MeC_6H_5	Me	4d	4	85
5	*m*-HOC_6H_5	Me	4e	8	80
6	*o*-ClC_6H_5	Me	4f	8	72
7	*m*-$O_2NC_6H_5$	Me	4g	8	75
8	C_6H_5	C_6H_5	4h	3	85
9			4i	5	79
10			4j	4	82
11	Me	Me	4k	6	70
12	Et	Me	4l	4	58
13	$(CH_3)_2CCH_2$	Me	4m	4	52

*Oxime (1.0 eqv) and bmpc (1.2 eqv) in toluene at 55-60°C; [a]All the products are known and are further characterised by NMR & Mass; [b] Isolated yield

very little product was obtained (<10%) and in pyridine no reaction occurred.

Using these optimised conditions, Beckmann rearrangement of various aromatic and aliphatic ketoximes was studied (Table 4). As shown in Table 4, the Beckmann rearrangement of the aromatic ketoximes bearing electron donating groups at *para* position to the phenyl ring (Entries 2-4) proceeded smoothly to give the corresponding amides in good to excellent yields. From 4-hydroxy acetophenone oxime (Entry 2), paracetamol was obtained in 90% yield. Presence of electron withdrawing groups

resulted in decreased yields (Entries 6 & 7). The aliphatic cyclic and acyclic ketones also underwent bmpc mediated Beckmann rearrangement to give corresponding lactams and amides (Entries 9-13). Although most of the asymmetric ketoximes studied were E-isomers, the methyl ethyl ketoxime and methyl isobutyl ketoxime (Entries 12 & 13) were E/Z mixtures in 1:3 ratio. However, both gave a single Beckmann product.

At present, the mechanism of bmpc mediated reaction with aldoximes and ketoxime is not clear. When the reaction of aldoxime with bmpc was monitored by ^{31}P-NMR, the initial signal of bmpc at δ 23.6 disappeared after about 30 min and a new signal at δ1.1 was observed (Fig. 2), suggesting a mechanism involving a phosphinic-oxime intermediate. Similarly, in the case of ketoxime reaction, the initial signal of bmpc at δ 24.0 disappeared after about one hour and a new signal at δ15.7 was observed (Fig. 3), suggesting a similar mechanism involving a phosphinic-oxime intermediate (Scheme 1).

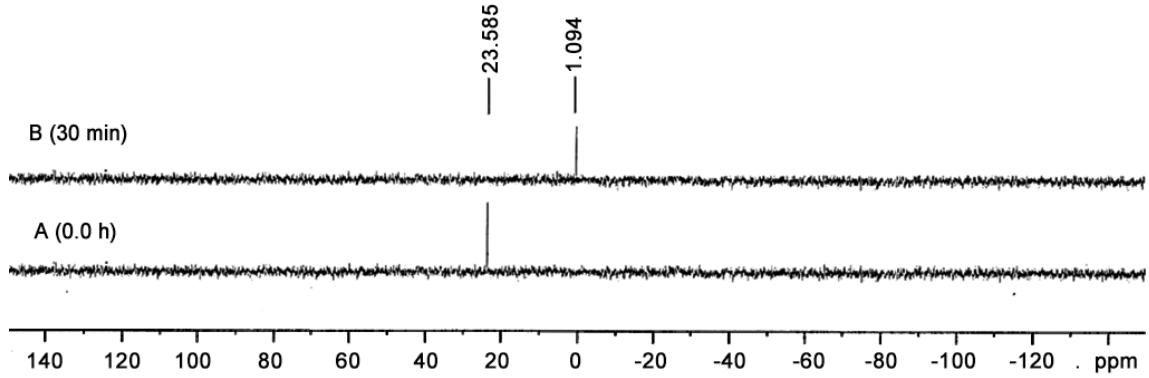


Fig. 2 — Monitoring of the reaction using ^{31}P NMR between **1i** and 1.2 molar eqv. of bmpc, in dmf; (A) **1i** and bmpc; (B) reaction mixture at 30 min

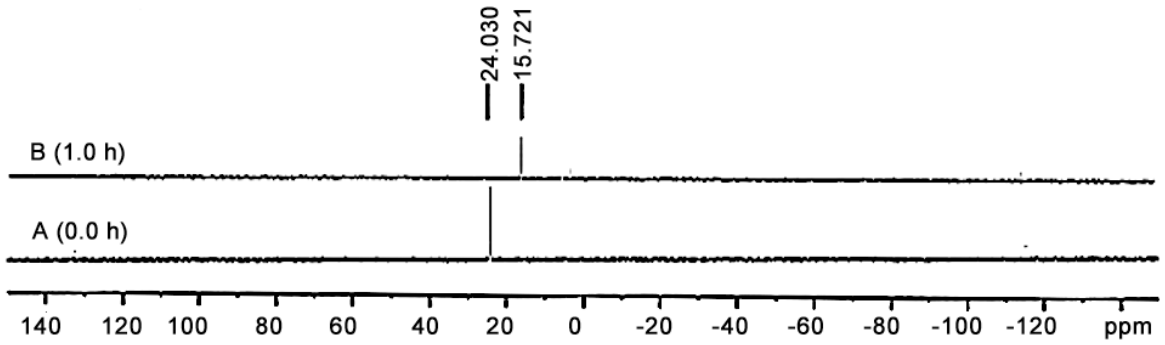
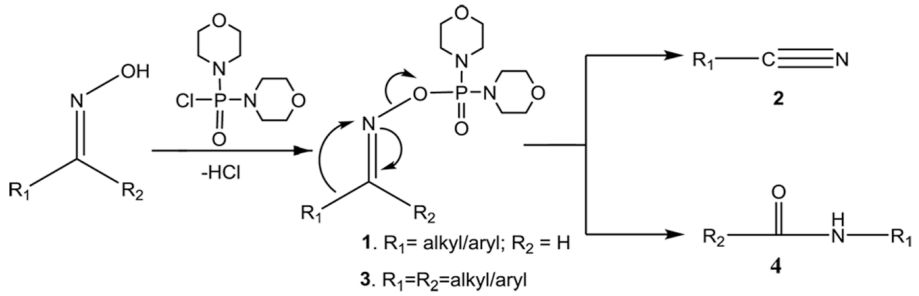


Fig. 3 — Monitoring of the reaction using ^{31}P NMR between **3a** and 1.2 molar eqv. of bmpc, in toluene; (A) **3a** and bmpc; (B) reaction mixture at 1 h



Scheme 1 — Proposed mechanism of bmpc mediated reaction with aldoximes and ketoximes

Conclusion

In summary, we have developed bmpc as a novel reagent for carrying out dehydration of aldoximes into nitriles and Beckmann rearrangement of ketoximes into amides. In most cases high to excellent yields were obtained. The reagent can be easily prepared and is a stable solid which is non-irritating unlike other reported chlorophosphate reagents.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

Acknowledgement

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