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Direct Conversion of Aldehydes into Nitriles *via* *O*-Phenylcarbamoylated Aldoximes

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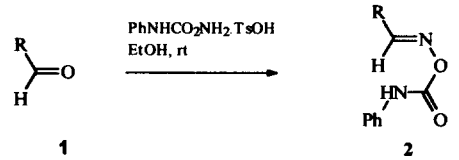
Abstract: *O*-Arylcarbamoylated hydroxylamine tosylate reacts with aldehydes at room temperature to give the corresponding *O*-carbamoylated oximes. The reaction of carbamoylated hydroxylamine with aromatic aldehydes in THF or in toluene at reflux affords the corresponding nitriles and anilinium tosylate in high yield. Attempts to cyclize compounds **2** in the presence of AcCl lead again to the formation of nitriles.

The most widely applicable and often the most convenient methods for carbon-nitrogen triple bond formation involve eliminative processes. Some examples are aldoxime dehydration, *O*-acyloxime pyrolysis, base catalysed decomposition of aldoxime *O*-2,4-dinitrophenyl ethers, elimination of amines from aldehyde hydrazones or hydrazonium salts *etc.*[1] Using dimethyldioxirane, the conversion of aldehyde *N,N*-dimethylhydrazones into the corresponding nitriles under mild conditions was recently reported.[2] In all of these methods the starting material is an isolated oxime, *O*-substituted oxime, or aldehyde hydrazone derivative. Nitrile syntheses at the other extreme involve the *in situ* formation and dehydration of the oxime.[1,3]

We have planned to exploit *O*-phenylcarbamoylated hydroxylamines, easily available by the method which we have recently reported,[4] in the synthesis of *O*-carbamoylated oximes and convert them into 1,2,4-oxadiazol-5-ones. The analgesic Anidoxime structure[5,6] is an example of a drug possessing an *O*-phenylcarbamoylated oxime structure.

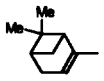


1 2

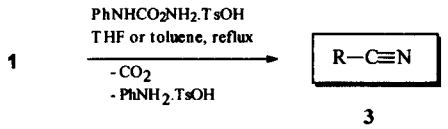
Scheme 1

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00692-4

Table. Carbamoylated Oximes **2a-j** and Nitriles **3a-l**.

1-3	R	Yield of 2[c] (%)	Mp (°C)	Lit mp *syn*	Lit mp *anti*	Yield of 3(%) Meth .A[d]	Yield of 3(%) Meth. B[c]	Mp of 3	Lit mp
a	Ph	67	135	77[9,10]	136[9,10]	91	90	oil	[e]
b	2-$MeOC_6H_4$	93	105-106	107[14]		93	95	oil	[e]
c	3-$MeOC_6H_4$	87	94.4-94.7			89	91	oil	[e]
d	4-$MeOC_6H_4$	90	82-82.5	82[9]	103[9]	90	93	57-58	60[11]
e	2,3-$(MeO)_2C_6H_3$	86	117-117.6			92	93	47	47[e]
f	3,4-(-OCH_2O-)C_6H_3	85	125-126	127[12]	82[12]	91	95	91-92	91[12,13]
g	3,4-$(MeO)_2C_6H_3$	89	129[16]		129[10]	96	97	67-68	67-68[e]
h	2-$NO_2C_6H_4$	80	115-117	119[14]		90	95	105-107	109-110[13]
i	2-ClC_6H_4	95	101-102			93	95	40-41	42-43[13]
j		92	104-105			95	90[a]	oil	
k	Me						87[b]		
l	Et						89[b]		

[a] The compound obtained by methods A and B was identical with the corresponding (*R*)-nitrile prepared from the reaction of (*R*)-aldoxime with acetic anhydride. [b] Yields determined by GC. [c]based on **1**. [d]based on **2**. [e]The compounds were identified by comparing their ir spectra with those of commercially available compounds.



Scheme 2

We herein report the synthesis of *O*-phenylcarbamoylated aldoximes[7] by the reaction of aldehydes with *O*-carbamoylated hydroxylamine as well as the reaction of the same reactants in refluxing THF or toluene[8] leading to nitriles (Method B). The reaction of aldehydes **1** with *O*-phenylcarbamoylhydroxylamine in EtOH at room temperature proceeded smoothly to give the corresponding *O*-carbamoylated oximes **2** in high yield

(Scheme 1). The isolation of compounds **2** was performed by adding water to the reaction mixture which lead to the crystallization of the product. Compounds **2** were treated with an equimolar amount of TsOH to give the corresponding nitriles (Method A). To prove the structure of compounds **2** they were prepared by a routine method starting from corresponding aldoxime and phenyl isocyanate. The compounds obtained in this way were identical with those obtained by the reaction of **1** with *O*-phenylcarbamoylhydroxylamine. We then refluxed compounds **1** and carbamoylated hydroxylamine in THF expecting that *in situ* formed **2** would undergo cyclization to the corresponding oxadiazolone structure in the presence of TsOH. However, the products obtained were characterized as the corresponding nitriles **3** and anilinium tosylate. The reaction of aldehydes **1b,d,f,g** in THF is complete within 2 h and the yields are as given in the table. The reaction of **1a,c,e,h-l** under the same reaction conditions and reaction times gave unsatisfactory conversion, therefore they were converted into the corresponding nitriles by refluxing them in toluene in the presence of *O*-carbamoylated hydroxylamine tosylate for 0.5 h. Compound **2d** was heated in THF in the presence of AcCl for 18 h in order to induce cyclization *via* iminium species but the products isolated were 4-methoxybenzonitrile and acetanilide. The method developed is a simple one step procedure for the direct conversion of aldehydes to nitriles in high yields. Moreover the isolation of the product involves only the filtration of the anilinium tosylate formed, which crystallizes at the end of the reaction in the reaction mixture. The evaporation of the filtrate gave nearly pure nitrile which is further purified by recrystallization or flash column chromatography. The prepared nitriles **3a-j** were identified by comparison of their physical constants and spectral characteristics with those of commercially available samples.

EXPERIMENTAL

Melting points were determined on a Electrothermal Digital melting point apparatus. IR spectra were recorded on a Mattson 1000 FTIR. ^{1}H NMR spectra were recorded on a Varian 200 MHz spectrometer. The aldehydes used were commercial products purchased from Aldrich. Freshly prepared *O*-phenylcarbamoylhydroxylamine tosylate[4] was used in the reactions performed.

***O*-Phenylcarbamoylated oximes. General Procedure**:- To a solution of aldehyde (0.5 mmol) **1** in EtOH (3 mL) *O*-phenylcarbamoylhydroxylamine tosylate (0.162 g, 0.5 mmol) was added and the reaction mixture stirred at room temperature for an hour. The stirring was stopped and water (2 mL) was added slowly to the reaction mixture. Upon standing at room temperature crystallisation occured. The crystals were filtered and washed with ethanol-water (1 : 3, 2 x 0.5 mL). The product was dried under vacuum at room temperature.

***O*-Phenylcarbamoylbenzaldoxime (2a).** See table for the mp and lit mp of the *syn* and *anti* isomers. Yield 67%. IR (KBr) ν_{NH} 3351 cm^{-1}; ν_{co} 1719 cm^{-1}. ^1H NMR $CDCl_3$ δ ppm 7.06-7.85 (10H, m), 8.15 (1H, brs, NH), 8.46 (1H, s);
Anal. Calcd for $C_{14}H_{12}N_2O_2$ (240.26): C, 69.98; H, 5.04; N, 11.66. Found: C, 69.90; H, 5.08; N, 11.70.

***O*-Phenylcarbamoyl-2-methoxybenzaldoxime (2b).** Yield 93%. IR (KBr) ν_{NH} 3236 cm^{-1}; ν_{co} 1719 cm^{-1}. ^1H NMR $CDCl_3$ δ ppm 3.90 (3H, s), 6.92-7.85 (9H, m), 8.21 (1H, brs, NH), 8.83 (1H, s);
Anal. Calcd for $C_{15}H_{14}N_2O_3$ (270.26): C, 66.66; H, 5.22; N, 10.37. Found: C, 66.70; H, 5.15; N, 10.30.

***O*-Phenylcarbamoyl-3-methoxybenzaldoxime (2c).** Yield 87%. Mp 94.4-94.7 °C. IR (KBr) ν_{NH} 3351 cm^{-1}; ν_{co} 1719 cm^{-1}. ^1H NMR $CDCl_3$ δ ppm 3.86 (3H, s), 7.05-7.65 (9H, m), 8.10 (1H, brs, NH), 8.40 (1H, s);
Anal. Calcd for $C_{15}H_{14}N_2O_3$ (270.26)): C, 66.66; H, 5.22; N, 10.37. Found: C, 66.69; H, 5.25; N, 10.35.

***O*-Phenylcarbamoyl-4-methoxybenzaldoxime (2d).** See table for the mp and lit mp of the *syn* and *anti* isomers. Yield 90%. IR (KBr) ν_{NH} 3351 cm^{-1}; ν_{co} 1719 cm^{-1}. ^1H NMR $CDCl_3$ δ ppm 3.91 (3H, s), 6.95-7.83 (9H, m), 8.21 (1H, brs, NH), 8.43 (1H, s);
Anal. Calcd for $C_{15}H_{14}N_2O_3$ (270.26)): C, 66.66; H, 5.22; N, 10.37. Found: C, 66.59; H, 5.19; N, 10.28.

***O*-Phenylcarbamoyl-2,3-dimethoxybenzaldoxime (2e).** Yield 86%. Mp 117-117.6 °C. IR (KBr) ν_{NH} 3300 cm^{-1}; ν_{co} 1730 cm^{-1}. ^1H NMR $CDCl_3$ δ ppm 3.91 (6H, s), 7.02-7.60 (8H, m), 8.16 (1H, brs, NH), 8.79 (1H, s);
Anal. Calcd for $C_{16}H_{16}N_2O_4$ (300.31): C, 63.99; H, 5.37; N, 9.33. Found: C, 63.90; H, 5.35; N, 9.27.

***O*-Phenylcarbamoyl-3,4-methylenedioxybenzaldoxime (2f).** See table for the mp and lit mp of the *syn* and *anti* isomers. Yield 85%. IR (KBr) ν_{NH} 3351 cm^{-1}; ν_{co} 1740 cm^{-1}. ^1H NMR $CDCl_3$ δ ppm 6.05 (2H, s), 6.64-7.64 (8H, m), 8.11 (1H, brs, NH), 8.32 (1H, s);
Anal. Calcd for $C_{15}H_{12}N_2O_4$ (284.27): C, 63.37; H, 4.26; N, 9.86. Found: C, 63.30; H, 4.20; N, 9.91.

***O*-Phenylcarbamoyl-3,4-dimethoxybenzaldoxime (2g).** See table for the mp and lit mp of the *anti* isomer. Yield 89%. IR (KBr) ν_{NH} 3350 cm^{-1}; ν_{co} 1740 cm^{-1}. ^1H NMR $CDCl_3$ δ ppm 3.90 (6H, s), 7.05-7.60 (8H, m), 8.16 (1H, brs, NH), 8.79 (1H, s);
Anal. Calcd for $C_{16}H_{16}N_2O_4$ (300.31): C, 63.99; H, 5.37; N, 9.33. Found: C, 63.90; H, 5.40; N, 9.41.

***O*-Phenylcarbamoyl-2-nitrobenzaldoxime (2h).** See table for the mp and lit mp of the *syn* isomer. Yield 80%. IR (KBr) ν_{NH} 3280 cm^{-1}; ν_{co} 1720 cm^{-1}. ^1H NMR $CDCl_3$ δ ppm 7.05-8.30 (10H, m), 9.00 (1H, s);

Anal. Calcd for $C_{14}H_{11}N_3O_4$ (285.25): C, 58.94; H, 3.89; N, 14.73. Found: C, 58.97; H, 3.89; N, 14.72.

***O*-Phenylcarbamoyl-2-chlorobenzaldoxime (2i)**. Yield 95%. Mp 101-102 °C. IR (KBr) ν_{NH} 3280 cm^{-1}; ν_{co} 1725 cm^{-1}. ^1H NMR $CDCl_3$ δ ppm 7.06-8.0 (10H, m), 8.90 (1H, s).
Anal. Calcd for $C_{14}H_{11}N_2O_2Cl$ (274.70): C, 61.21; H, 4.04; N, 10.20. Found: C, 61.25; H, 4.08; N, 10.15.

***(R)*-*O*-Phenylcarbamoylmyrtenaldoxime (2j)** Yield 92%. Mp 104-105°C. $[\alpha]_D^{20}$ +18 (C = 0.18, $CHCl_3$); IR (KBr) ν_{NH} 3280 cm^{-1}; ν_{co} 1725 cm^{-1}. ^1H NMR $CDCl_3$ δ ppm 0.83 (3H, s), 1.18 (1H, d, J = 10 Hz) 1.41 (3H, s), 2.18 (1H, s), 2.50 (3H, m), 2.87 (1H, m), 6.23 (1H, s), 7.05-7.60 (5H, m), 7.98 (1H, brs, NH), 8.05 (1H, s);
Anal. Calcd for $C_{17}H_{20}N_2O_2$ (284.35): C, 71.80; H, 7.09; N, 9.85. Found: C, 71.74; H, 7.15; N, 9.80.

***O*-Phenylcarbamoylated oximes from the reaction of aldoximes with phenyl isocyanate. General Procedure**:- To a solution of aldoxime (0.5 mmol) in chloroform (5 mL) phenyl isocyanate (0.5 mmol) was added and the reaction mixture stirred at room temperature for 3 h. The solvent was evaporated and the residue dissolved in ethanol (3 mL). Water (2 mL) was added slowly to the reaction mixture. Upon standing at room temperature crystallisation occurred; the products obtained after filtration and drying in a vacuum oven were identical to those obtained by the reaction of aldehydes with *O*-phenylcarbamoylhydroxylamine tosylate.[15]

Nitriles. Method A. General Procedure:- To a solution of *O*-phenylcarbamoylated aldoxime **2** (0.5 mmol) in toluene (5 mL) toluenesulphonic acid monohydrate (0.0946 g, 0.5 mmol) was added and the mixture stirred at reflux for 0.5 h. The solvent was evaporated under vacuum and water (15 mL) was added to the residue then extracted with chloroform (2 x 15 mL). The combined extracts were dried (anh. Na_2SO_4), filtered and the solvent evaporated. The mixture was passed thorough a short silica gel column using chloroform as eluent.

Nitriles. Method B. General Procedure:- To a solution of aldehyde **1** (0.5 mmol) in THF[8] (5 mL) *O*-phenylcarbamoylhydroxylamine tosylate (0.162 g, 0.5 mmol) was added and the mixture stirred at reflux for 2 h. The mixture was cooled and the crystalline anilinium tosylate formed was separated by filtration. The filtrate was evaporated under vacuum and the residue was extracted with dry ether (2 x 15 mL). The combined extracts were filtered and the solvent evaporated. The product obtained was chromatographically pure nitrile. The other product remaining after the ethereal extraction was dissolved in THF at reflux and left to crystallize at room temperature. The white needles obtained were identical with the product obtained from the reaction of aniline with TsOH. All nitriles prepared are literature known and were identified by comparing their physical and ir spectral data (see table).

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REFERENCES AND NOTES

1. Barton, D.; Ollis, W. D. In *Comprehensive Organic Chemistry*; Pergamon: Oxford, UK, **1979**, Vol 2, Chapter 8, pp 532-535.
2. Altamura, A.; D'Accolti, L.; Detomaso, A.; Dinoi, A.; Fiorentino, M.; Fusco, C.; Curci, R., *Tetrahedron Lett.*, 39, **1998**, 2009-2012.
3. March, J. In *Advanced Organic Chemistry*; John Wiley and Sons: N.Y. **1985**, Ch 16, pp 806-807
4. Coşkun, N., *Tetrahedron*, 55, **1999**, 475-484.
5. Grainger, D.J., Gawley, T.H., and Dundee, J.W., *Br. J. Anaesth.*, **1977**, 49, 257-258.
6. Watzman, N., Buckley, J.P., *J. Pharm. Sci.*, **1980**, 69, 225-226.
7. The known *O*-phenylcarbamoylated aldoximes are prepared by the reaction of corresponding *syn* and *anti* oximes with arylisocyanates.[9,10] The carbamoylated *anti* oximes have been shown to decompose easily to the corresponding nitriles in the presence of amines while the *syn* forms remain unchanged or gave the corresponding *syn* oximes at the same conditions.[11,12]
8. Compounds **3a,c,e,h-l** were prepared from the reaction of corresponding aldehydes and carbamoylated hydroxylamine tosylate at reflux in toluene for 0.5 h.
9. Goldschmidt, H.; Rietschoten, W.H., *Chem. Ber.*,**1893**, 26, 2087-2100.
10. Brady, O.L.; Dunn, F.P., *J. Chem. Soc.*, **1916**, 109, 650-681.
11. Hauser, C.R.; Jordan, E., *J. Am. Chem Soc.*, **1936**, 58, 1772-1776.
12. Rainsford, A.E.; Hauser, C.R., *J. Org. Chem.*, **1939**, 4, 480-492.
13. Hauser, C.R.; Jordan, E., *J. Am. Chem.* Soc., **1935**, 57, 2450-2456.
14. Brady, O.l.; McHuch, G.P., *J. Chem. Soc.*, **1925**, 127, 2414-2427.
15. Compounds **2a,d,g** were obtained by this method.
16. The compound did not crystallize from ethanol water. The recrystallization was performed from chloroform-petroleem ether. If all of the literature assignments for the known carbamoylated oximes are true the compounds obtainable by our method are mainly *syn*.