

**CONVERSION OF OXIME AND TOSYL ALDOXIME TO NITRILES AS COMPETITIVE REACTION TO NUCLEOPHILIC RING CLOSURE****N. Chandan**Department of Chemistry, Siddharth College of Arts, Science and Commerce, Mumbai, MS, India  
nandkishorc@gmail.com**ABSTRACT**

The easily synthesized aldoximes from Michael adduct have been converted to the corresponding nitriles under very mild conditions by a simple reaction with *p*-Toluidine sulfonyl chloride with mild base triethylamine in CH<sub>2</sub>Cl<sub>2</sub>. A simple, mild, and practical process for direct conversion of aldehydes to nitriles was developed featuring a wide substrate scope and great functional group tolerability. This method allows for transformations of readily available, inexpensive, and abundant aldehydes to highly valuable nitriles in a pot, atom, and step-economical manner without transition metals. This protocol will serve as a robust tool for the installation of cyano-moieties to complicated molecules.

**Keywords:** Nitrile, Oxime, tosyl, pyrrolidine, mesyl, acroline etc.

**Introduction**

The Nitrile functional group is widely found in natural products, pharmaceuticals, agrochemicals, dyes, and herbicides. Moreover, because the nitrile group can be easily converted into various functional groups like carboxylic acids, amides, amines, aldehydes, ketones, tetrazoles, and other groups. Subsequently, the development of new methodologies for the synthesis of nitriles functional group from easy way was the significant interest. The traditional methods for their synthesis include Sandmeyer reactions<sup>1</sup>, Rosenmund–von Braun reactions<sup>2</sup>, as well as dehydration reactions of aldoximes<sup>3</sup> and amides. In recent years, numerous efforts have been devoted to transition metal catalyzed cyanation reactions<sup>4</sup> of aryl (pseudo)halides, organometallic reagents and aryl C–H bonds. A number of cyanating reagents have been explored for such transformations, including metal cyanides and organic nitrile group sources. The prevalence of nitrile-containing pharmaceuticals, and the continued stream of potential agents in the clinic, attests to the biocompatibility of the nitrile functionality.<sup>5</sup> The nitrile group is not particularly electrophilic toward free nucleophiles, even glutathione,<sup>6</sup> unless activated by adjacent structural elements such as electron withdrawing groups.<sup>7</sup> A caveat is the highly orchestrated activation–electrophilic additions such as those being exploited in several amino nitriles for diabetes and osteoporosis treatments

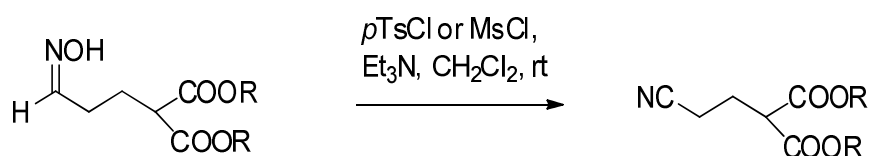
that feature a reversible electrophilic attack. The nitrile group is quite robust and, in most cases is not readily metabolized<sup>8</sup>. Metabolically, the nitrile group in most nitrile-containing drugs is passed through the body unchanged. The nitrile moiety is a highly important one not only due to its synthetic value as precursor to other functionalities but also due to its presence in a variety of natural products, pharmaceuticals and novel materials. Although there are several methods known for access to the nitrile functionality,<sup>9, 10</sup> but aldoximes to nitriles by using very simple reagent as *p*-Toluidine sulfonyl chloride with mild base triethylamine remains a convenient route as it was competitive reaction while synthesising the substituted pyrrolidines<sup>11</sup>. In this methodology we can easily convert oxime to nitrile as well tosyloxime to nitrile in quantitative yield. This paper reports our results on the development of a new method for the synthesis of nitriles from aldoximes.

**Result and Discussion**

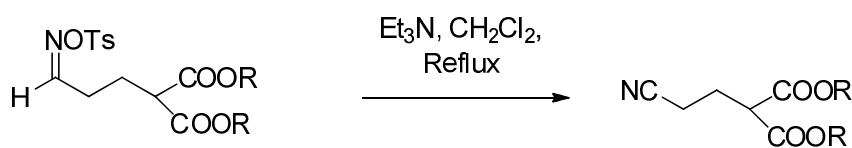
It has been reported that amides can be converted to nitriles via the use of PyBOP and (*iso*-Pr)<sub>2</sub>NEt in CH<sub>2</sub>Cl<sub>2</sub> at 40 °C<sup>12</sup>. This led us to consider whether aldoximes, that are generally more acidic than alcohols<sup>13</sup>, could undergo dehydrative reactions with commercially cheaply available *p*-Toluidine sulfonyl chloride and a base. Herein we report development of a simple dehydration of aldoximes using *p*-Toluidine sulfonyl chloride

and  $\text{Et}_3\text{N}$  in DCM. During the course of kaitocephalin synthesis and development of substituted pyrrolidine synthesis, we have also evaluated the use of *p*-Toluidine sulfonyl chloride and  $\text{Et}_3\text{N}$  to convert the oxime to nitrile. In Watanabe and Kitahara's synthesis of the proposed structure of kaitocephalin<sup>14</sup> and revision of stereochemistry, the unique strategy was used to configure the left-hand side of kaitocephalin using coupling of halide with nitrene. Similar to the nitrene, pyrroline **5** could be synthesised by following the same strategy developed above by varying the starting material from the  $\alpha,\beta$ -unsaturated ketone to acrolein. The required substrate **1** was directly prepared by conjugate addition of diethyl malonate with acrolein using mild basic conditions (anhydrous  $\text{K}_2\text{CO}_3$  in dry  $\text{CH}_2\text{Cl}_2$  heated to reflux for 15 hr) in 89% yield and this adduct was readily converted to the corresponding oxime **2** upon treatment with  $\text{NH}_2\text{OH}\cdot\text{HCl}$  and  $\text{Et}_3\text{N}$  in EtOH heated to reflux for 30 min in 91% yield. Subsequently the oxime **2** was treated with Na-metal in EtOH for 30 min, followed by addition of 2,4-dinitrofluorobenzene at 0 °C, and the reaction mixture clearly showed the molecular ion of oxime ether in mass spectra, but after

purification only a complex mixture containing the cyclised pyrroline **5** was isolated. It contained inseparable impurities evidenced by prominent  $^1\text{H}$  NMR spectra for the corresponding protons. The pyrroline **5** with impurities was used for reduction by H-Cube hydrogenation and gave pyrrolidine **6**; the molecular ion was observable and although the NMR spectra were messy, it contained the required peaks. To improve the results, oxime **2** was treated with *p*-toluenesulfonyl chloride and base ( $\text{Et}_3\text{N}$  in dry  $\text{CH}_2\text{Cl}_2$ ) and afforded the expected tosyl oxime **4** in low yield of 32% but the major product was the elimination product nitrile **3** in good yield 56% and surprisingly no trace of ring closure product pyrroline **5** was obtained, unlike the oxime ether approach. Furthermore, when the synthesis of the mesyl oxime was attempted, the same results was found and only elimination product **3** was formed (Scheme 3). When the oxime **2** was target to get the nucleophilic ring closure to achieve the pyrroline but undesired product **3** as nitrile was found in quantitative yield, hence we have developed the methodology to get the nitrile compounds as well the target right hand side of the kaitocephalin as natural product scheme-3.



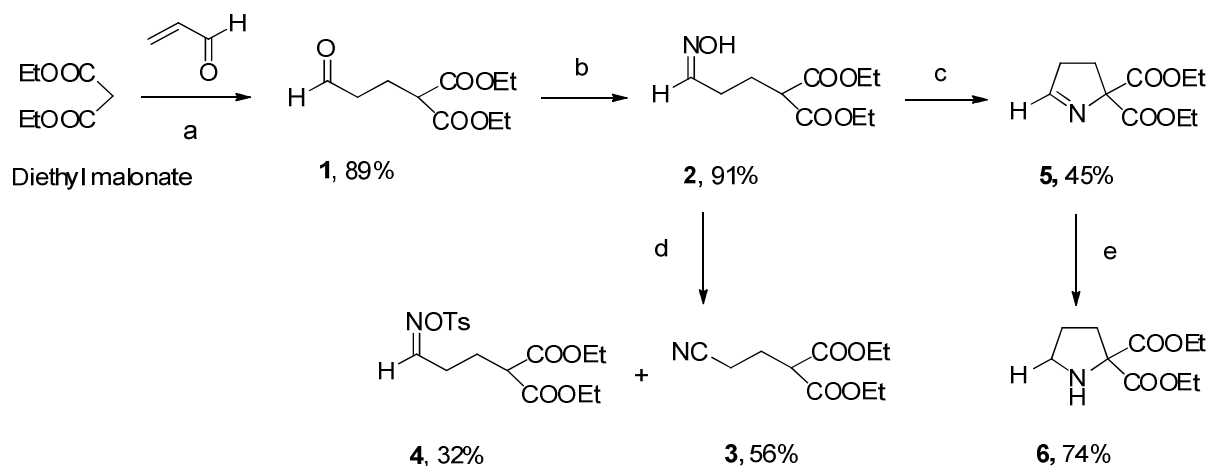
**Scheme 1** : Conversion of aldoxime to nitrile



**Scheme 2** : Conversion of Tosyloxime to nitrile

In the methodology developed oxime was treated with *p*-toluenesulfonyl chloride or methanesulfonyl chloride and base ( $\text{Et}_3\text{N}$  in dry  $\text{CH}_2\text{Cl}_2$ ) the oxime was directly converted into the nitrile product and the reaction was monitored with TLC and it as also noted that

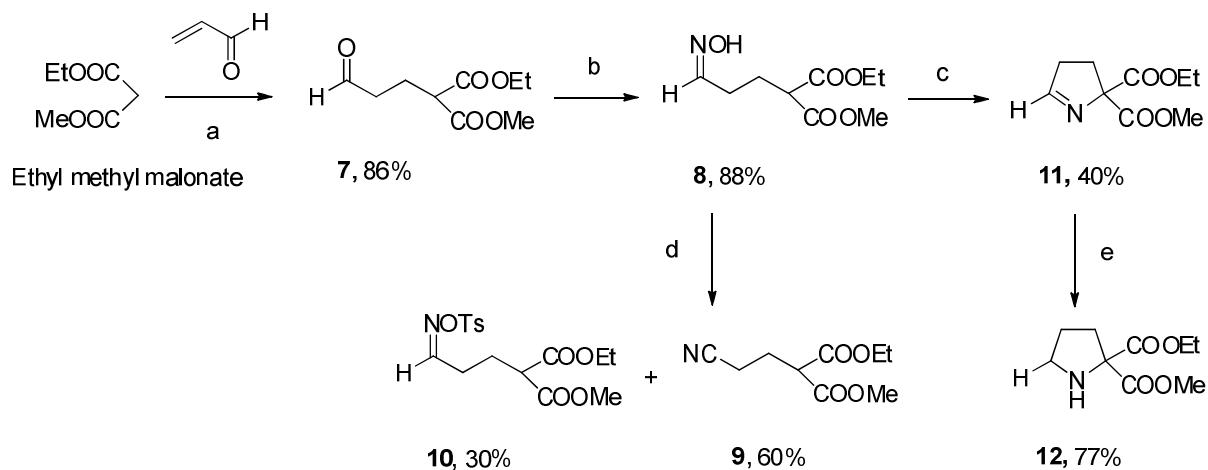
when the reaction temperature changes from rt to reflux the nitrile conversion rate as more scheme-1. It was also found that separated tosyl/mesyl oxime was completely converted to nitrile on reflux condition scheme-2.



**Scheme 3: Reagents and conditions** (a) anhydrous  $K_2CO_3$ ,  $CH_2Cl_2$ , reflux; (b)  $NH_2OH.HCl$ ,  $Et_3N$ , (c) Na-metal, EtOH, 2,4-dinitrofluorobenzene, rt; (d)  $pTsCl$  or  $MsCl$ ,  $Et_3N$ ,  $CH_2Cl_2$ , rt; (e) H-Cube hydrogenation Pd/C, EtOH,  $50^\circ C$ .

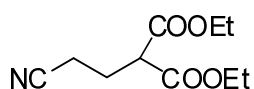
The methodology was tested with different substituents of Michael adduct by using ethyl methyl malonate with acrolein got the good yield 86% which was easily converted into oxime by using the standard conditions same used for the earlier oxime 2. When oxime 8 treated with *p*-toluenesulfonyl chloride and base ( $Et_3N$  in dry  $CH_2Cl_2$ ) at rt 60% of nitrile product was found and 30% tosyl oxime was

isolated. The formation of nitrile 9 product was modified by changing the reaction condition to reflux for 2 hrs and isolated tosyl oxime can be converted to nitrile 9 by reflux with  $Et_3N$  in dry  $CH_2Cl_2$ . Oxime 8 was treated with Na-metal in EtOH for 30 min, followed by addition of 2,4-dinitrofluorobenzene at  $0^\circ C$  gave the pyrroline 11 which was converted to pyrrolidine 12.



**Scheme 4: Reagents and conditions** (a) anhydrous  $K_2CO_3$ ,  $CH_2Cl_2$ , reflux; (b)  $NH_2OH.HCl$ ,  $Et_3N$ , (c) Na-metal, EtOH, 2,4-dinitrofluorobenzene, rt; (d)  $pTsCl$  or  $MsCl$ ,  $Et_3N$ ,  $CH_2Cl_2$ , rt; (e) H-Cube hydrogenation Pd/C, EtOH,  $50^\circ C$ .

### Diethyl 2-(2-cyanoethyl)malonate, 3

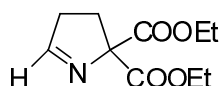


When oxime 2 (115mg, 0.49mmol) treated with *p*-toluenesulfonyl chloride (189mg, 0.99mmol) or  $MsCl$  (112mg, 0.99mmol) and

base  $Et_3N$  (148mg, 1.47mmol) in dry  $CH_2Cl_2$  at rt the undesired product as diester nitrile compound 3 was isolated with some tosylated product 4 which was later converted into diester nitrile.  $R_f = 0.58$  (EtOAc : petrol, 1:1);  $\nu_{max}(film)/cm^{-1}$  2938, 2360, 1730, 1436, 1234, 1155, 1048;  $\delta_H(400 MHz; CDCl_3; Me_4Si)$  1.26

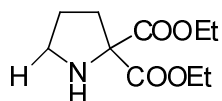
(6H, t,  $J$  7.1 Hz,  $2 \times \text{OCH}_2\text{CH}_3$ ), 2.22 (2H, m,  $\text{CH}_2\text{CH}_2\text{CH}$ ), 2.49 (2H, m,  $\text{CH}_2\text{CH}_2\text{CH}$ ), 3.48 (1H, t,  $J$  7.3 Hz,  $\text{CH}_2\text{CH}_2\text{CH}$ ), 4.20 (4H, q,  $J$  7.1 Hz,  $2 \times \text{OCH}_2\text{CH}_3$ );  $\delta_{\text{C}}$ (100 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 13.9 ( $2 \times \text{OCH}_2\text{CH}_3$ ), 15.0 ( $\text{CH}_2\text{CH}_2\text{CH}$ ), 24.4 ( $\text{CH}_2\text{CH}_2\text{CH}$ ), 50.1 ( $\text{CH}_2\text{CH}_2\text{CH}$ ), 61.8 ( $2 \times \text{OCH}_2\text{CH}_3$ ), 118 (CN), 168.0 ( $2 \times \text{COO}$ );  $m/z$  ( $\text{ESI}^+$ ) 236 ( $[\text{M}+\text{Na}]^+$ , 100%), HRMS ( $\text{ESI}^+$ )  $\text{C}_{10}\text{H}_{15}\text{NNaO}_4^+$  ( $[\text{M}+\text{Na}]^+$ ) requires 236.0893; found 236.0892.

#### Diethyl 3,4-dihydro-2H-pyrrole-2,2-dicarboxylate, 5



Oxime **2** (103 mg, 0.44 mmol) in EtOH (5 mL) sodium metal (11 mg, 0.49 mmol) was added and the mixture stirred at rt for 30 min followed by slow addition of 2,4-dinitrofluorobenzene (99 mg, 0.53 mmol) at 0 °C to give ring closure product instead the oxime ether which was purified by flash column chromatography to afford **5** (39 mg, 40%) as a colourless oil;  $R_f$  = 0.22 (EtOAc : petrol, 1:1);  $\nu_{\text{max}}$ (film)/ $\text{cm}^{-1}$  2987, 1733, 1542, 1495, 1253, 1202, 1121, 861;  $\delta_{\text{H}}$ (400 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 1.26 (6H, t,  $J$  7.1 Hz,  $2 \times \text{OCH}_2\text{CH}_3$ ), 2.24 (2H, m, C(4) $H_2$ ), 2.58 (2H, t,  $J$  7.3 Hz, C(3) $H_2$ ), 4.22 (4H, q,  $J$  7.1 Hz,  $2 \times \text{OCH}_2\text{CH}_3$ ), 7.85 (1H, t,  $J$  8.1 Hz, C(5) $H$ );  $\delta_{\text{C}}$ (100 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 14.0 ( $2 \times \text{OCH}_2\text{CH}_3$ ), 21.0 (C4), 27.1 (C3), 61.9 ( $2 \times \text{OCH}_2\text{CH}_3$ ), 75.5 (C2), 168.1 (C1), 168.9 ( $2 \times \text{COO}$ );  $m/z$  ( $\text{ESI}^+$ ) 427 ( $[\text{2M}+\text{H}]^+$ , 80%), 214 ( $[\text{M}+\text{H}]^+$ , 40%), HRMS ( $\text{ESI}^+$ )  $\text{C}_{10}\text{H}_{16}\text{NO}_4^+$  ( $[\text{M}+\text{H}]^+$ ) requires 214.1074; found 214.1080.

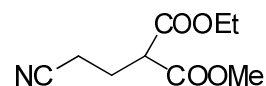
#### Diethyl pyrrolidine-2,2-dicarboxylate, 6



To the solution of pyrroline **5** (30 mg, 0.14 mmol) in MeOH (2 ml)  $\text{NaBH}_3\text{CN}$  (18 mg, 0.28 mmol) and 2 M HCl in MeOH (1 mL) was added at rt, to give crude product which was purified by flash column chromatography to afford pyrrolidine **6** (26 mg, 77%) as a colourless oil;  $R_f$  = 0.16 (EtOAc : petrol, 1:1);  $\nu_{\text{max}}$ (film)/ $\text{cm}^{-1}$  3378, 29738 1738, 1512, 1362, 1234, 1213, 1177, 1077, 836;  $\delta_{\text{H}}$ (400 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 1.26 (6H, t,  $J$  7.1 Hz,  $2 \times$

$\text{OCH}_2\text{CH}_3$ ), 2.31 (1H, m, C(4) $HH$ ), 2.44 (1H, m, C(4) $HH$ ), 2.60 (1H, m, C(3) $HH$ ), 2.71 (1H, m, C(3) $HH$ ), 2.93 (1H, m, C(5) $HH$ ), 3.04 (1H, m, C(5) $HH$ ), 4.22 (4H, q,  $J$  7.1 Hz,  $2 \times \text{OCH}_2\text{CH}_3$ ), 6.38 (1H, bs,  $NH$ );  $\delta_{\text{C}}$ (100 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 13.9, 14.0 ( $2 \times \text{OCH}_2\text{CH}_3$ ), 27.9 (C4), 29.3 (C3), 50.1 (C5), 61.9 ( $2 \times \text{OCH}_2\text{CH}_3$ ), 67.9 (C2), 168.6 ( $2 \times \text{COO}$ );  $m/z$  ( $\text{ESI}^+$ ) 429 ( $[\text{2M}+\text{H}]^+$ , 100%), 216 ( $[\text{M}+\text{H}]^+$ , 15%), HRMS ( $\text{ESI}^+$ )  $\text{C}_{10}\text{H}_{18}\text{NO}_4^+$  ( $[\text{M}+\text{H}]^+$ ) requires 216.1230; found 216.1235.

#### 1-Ethyl 3-methyl 2-(2-cyanoethyl) malonate, 9



When oxime **8** (100mg, 0.46mmol) treated with *p*-toluenesulfonyl chloride (175mg, 0.92mmol) or MsCl (105mg, 0.92mmol) and base  $\text{Et}_3\text{N}$  (139mg, 1.38mmol) in dry  $\text{CH}_2\text{Cl}_2$  at rt the undesired product as diester nitrile compound **9** was isolated with some tosylated product **10** which was later converted into diester nitrile.  $R_f$  = 0.56 (EtOAc : petrol, 1:1);  $\nu_{\text{max}}$ (film)/ $\text{cm}^{-1}$  2939, 2363, 1735, 1433, 1235, 1166 1049;  $\delta_{\text{H}}$ (400 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 1.24 (3H, t,  $J$  7.0 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.20 (2H, m,  $\text{CH}_2\text{CH}_2\text{CH}$ ), 2.41 (2H, m,  $\text{CH}_2\text{CH}_2\text{CH}$ ), 3.51 (1H, t,  $\text{CH}_2\text{CH}_2\text{CH}$ ), 4.03 (3H, s,  $\text{OCH}_3$ ), 4.21 (2H, q,  $J$  7.0 Hz,  $\text{OCH}_2\text{CH}_3$ );  $\delta_{\text{C}}$ (100 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 13.7 ( $\text{OCH}_2\text{CH}_3$ ), 15.3 ( $\text{CH}_2\text{CH}_2\text{CH}$ ), 24.7 ( $\text{CH}_2\text{CH}_2\text{CH}$ ), 50.5 ( $\text{CH}_2\text{CH}_2\text{CH}$ ), 60.2 ( $\text{OCH}_3$ ), 61.9 ( $\text{OCH}_2\text{CH}_3$ ), 119 (CN), 168.6, 168.9 ( $\text{COO}$ );  $m/z$  ( $\text{ESI}^+$ ) 222 ( $[\text{M}+\text{Na}]^+$ , 100%), HRMS ( $\text{ESI}^+$ )  $\text{C}_9\text{H}_{13}\text{NNaO}_4^+$  ( $[\text{M}+\text{Na}]^+$ ) requires 222.0883; found 222.0896.

#### Conclusion

In summary, we have developed effective methodology to synthesise nitriles compounds from aldehydes. Whereas through this methodology we can easily graft the cyano-functional group on substrate with polyfunctional compounds with very good yield. This methodology was developed as the by-product formed in the attempt of nucleophile ring closer of tosyloxime/oxime ether in basic condition on reflux expecting the substituted pyrrolidines.

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