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One step from nitro to oxime: a convenient preparation of unsaturated oximes by the reduction of the corresponding vinylnitro compounds

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ABSTRACT

A series of novel unsaturated oximes were conveniently prepared from the corresponding vinylnitro compounds by reduction with $SnCl_2 \cdot 2H_2O$. The structures of the oximes were characterized by ^1H and ^{13}C NMR, IR and HRMS, and X-ray crystallography analysis of 1-(6-chloro-pyridin-3-ylmethyl)-4,5-dihydro-1*H*-imidazole-2-carbaldehyde oxime **2a** reveals that, the hydroxyl group is arranged in a trans configuration. Some evidences from a brief investigation suggest that these oximes seem to be formed by reduction of the *aci* form of nitro aliphatic compounds.

1. Introduction

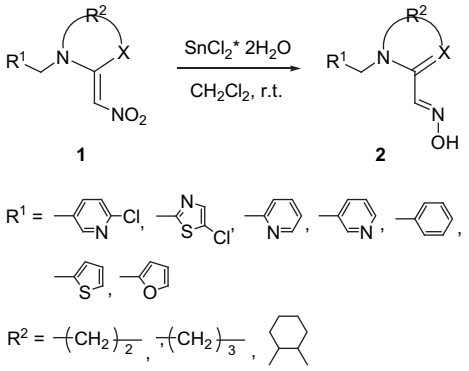
Oximes are of great interest as intermediates in organic synthesis,[1–6] for example, oxime ether, as one of the important oxime derivatives, has long been recognized in the fields of agrochemistry[7–11] and medicinal chemistry.[12–14] Furthermore for their own biological activities, oximes are particularly significant as antimicrobial agents,[15] insecticides,[16] vasodilators,[17] inhibitors of P450 17,[18] and antioxidants.[19]

Oximes are commonly prepared by three methods. The first is the most known method by the condensation of carbonyl compounds with hydroxylamine, however sometimes this method is not applicable for the preparation of unsaturated oximes.[20] The second is the often used method by *N*-oxides reaction with alkene,[21–23] and the third method is a practical one by treatment of precursors nitroalkanes with alkali.[24] In addition, there are a few reports that oximes can be obtained directly from nitro benzylic compounds by electrochemical reduction but no selectivity with simultaneous formation of hydroxylamine,[25] or by homogeneous catalyzed reduction of saturated nitro aliphatic compounds with the cuprous CO complexes as the catalyst but under rigorous reaction conditions.[26]

Recently in research of insecticide, we unexpectedly found that, reduction of cyclic vinylnitro compound CH-IMI(**1a**), a famous potential neonicotinoid pesticide, gave an unsaturated oxime, but not the corresponding hydroxylamine and/or amino compounds. The literature describing such structures, unsaturated oximes, is rather sparse and their preparation is of great difficulty.[27] Herein we wish to report the results regarding the preparation of unsaturated oxime from vinylnitro compounds by reduction with tin(II) chloride dihydrate ($SnCl_2 \cdot 2H_2O$).

2. Results and discussion

Compound **1a** was chosen as a model substrate in order to test the effectiveness of the reaction. In a typical experiment, placing **1a** and an excess of $SnCl_2 \cdot 2H_2O$ in dichloromethane resulted in the formation of the unsaturated oxime **2a** with complete consumption of the substrate in 5 h at room temperature (Scheme 1). In optimization of the reaction, it was found that other solvents, such as acetonitrile, ethyl acetate, methanol, and ethanol, were not suitable because of their poor solubility to the substrate. The optimal



Scheme 1. Synthesis of unsaturated cyclic oximes **2a–s** from vinylnitro compounds **1a–s**.

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Table 1
Reduction of nitro compounds **1** to the corresponding oximes **2**[a]

Substrate	R_1	R_2	Product	Yield (%)
1a		$-(CH_2)_2-$	**2a**	45
1b		$-(CH_2)_2-$	**2b**	43
1c		$-(CH_2)_2-$	**2c**	40
1d		$-(CH_2)_2-$	**2d**	40
1e		$-(CH_2)_2-$	**2e**	62
1f		$-(CH_2)_2-$	**2f**	58
1g		$-(CH_2)_2-$	**2g**	60
1h		$-(CH_2)_3-$	**2h**	48
1i		$-(CH_2)_3-$	**2i**	40
1j		$-(CH_2)_3-$	**2j**	65
1k		$-(CH_2)_3-$	**2k**	61
1l		$-(CH_2)_3-$	**2l**	64
1m			**2m**	68
1n			**2n**	65
1o			**2o**	60
1p			**2p**	58
1q			**2q**	75
1r			**2r**	72
1s			**2s**	72

[a] Optimal conditions: the amount of $SnCl_2 \cdot 2H_2O$ was 5.5 equiv of the substrate and dichloromethane as solvent.

amount of the reducing agent required for a satisfactory yield was proved to be 5.5 equiv with respect to the substrate.

In order to explore the scope of the reaction, a series of cyclic vinylnitro compounds **1b**–**s** (Scheme 1), which were synthesized by the method described previously,[28] were reduced under the optimal conditions and the results summarized in Table 1. In each case the corresponding oximes were obtained. Although the conversion of vinylnitro compounds to the corresponding oximes was complete within 5 h according to the TLC analysis, the yields of the isolated products were moderate, due to the so good solubility of the oximes in water that it is difficult to be extracted with dichloromethane in the work-up procedure.

The structures of the unsaturated oximes **2** were characterized by IR, ^1H, and ^{13}C NMR, HRMS, and X-ray crystallography. The IR spectra of compounds showed C=N, N–O and O–H stretching bands at 1630–1640 cm^{-1}, 920–940 cm^{-1} and 3420–3440 cm^{-1}, respectively, and O–H deformation vibration at 1300 cm^{-1}. The ^1H NMR of spectra of unsaturated oximes **2** showed a singlet at 7.70–7.79 ppm, which attributed to CH in the –*CH*=NOH, compared to the singlet at 6.60–6.66 ppm, which attributed to CH in the =*CH*–NO_2. Further, the structure of **2a** was determined by X-ray single-crystal diffraction analysis (Fig. 1) showing a non-planar framework and the hydroxyl group arranged in a trans configuration.

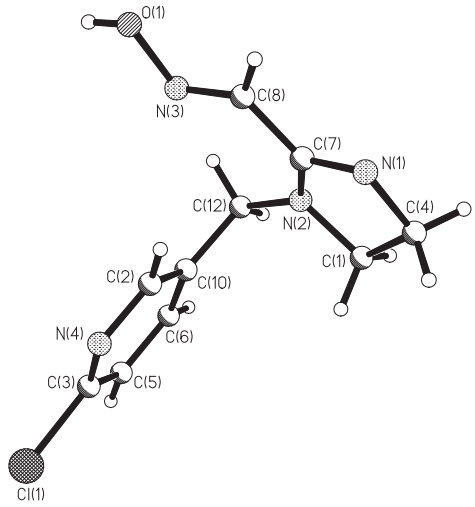
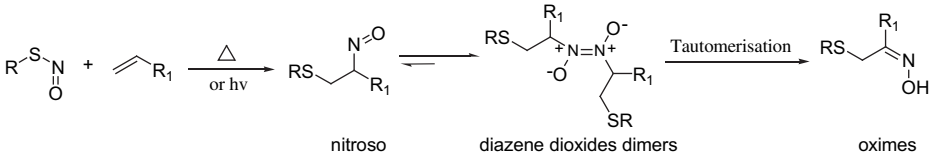


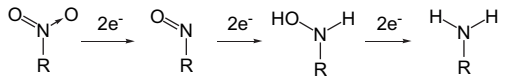
Figure 1. X-ray single-crystal structure of **2a**.

Motherwell et al. have ever reported that the oximes can be obtained by in situ tautomerization of the diazene dioxides dimers of the corresponding nitroso compounds (Scheme 2).[29] However Zuman and Shah think that the dimers are never formed in the reduction of nitro compounds,[30] due to the significant kinetic inhibition to the dimers formation or a higher rate of further reduction under the experiment conditions.[31] It is presumed that the unsaturated oximes **2** could not be formed through tautomerization of the corresponding dimers.

Reduction of nitro group to amino group under acidic conditions is usually as follows (Scheme 3): the nitro group is first reduced via two electrons to form the nitroso group, which accepts another two electrons to form hydroxylamine group and then converted to



Scheme 2. Tautomerization of the diazene dioxide dimers to the corresponding oximes.



Scheme 3. The general principle of nitro reduction to amino group.

amino group.[32] Nitroso compound is a highly reactive intermediate in the reduction conditions, which cannot be isolated and it can be reduced to the corresponding hydroxylamine, or amine further by control of the reduction conditions. Generally there is an equilibrium between *nitro* form and *aci* form in nitroalkanes, and the *aci* is less stable than the *nitro*.[33] In our case, the *aci* could be more stable because of formation of the strong conjugative interaction between the two C=N bonds. On the basis of the known reductive mechanism of nitro group and the above studies, two possible mechanisms path a and path b are proposed in the formation of oximes **2** (Scheme 4). In path a, the *nitro*-**1** is reduced via two electrons to form the *nitroso*, which is an unstable intermediate, the fast *nitroso* to *cis*-**2** prototropy may prevent the reduction of NO to NHOH, and then *cis*-**2** tautomerize to more stable *trans*-**2**.[34] In path b, the *nitro*-**1** could exist in *aci*-**1** and the *aci*-**1** is reduced via two electrons to form *cis*-**2**, which then tautomerize to *trans*-**2**.

reduction conditions. This indicated that NH in the cyclic and acyclic vinylnitro compounds **1** could make them form more stable *aci*-**1**, while O, S, and N of tertiary amine in **3**, **4**, and **5** could not lead to form stable *aci* form. The results imply that path b is more reasonable.

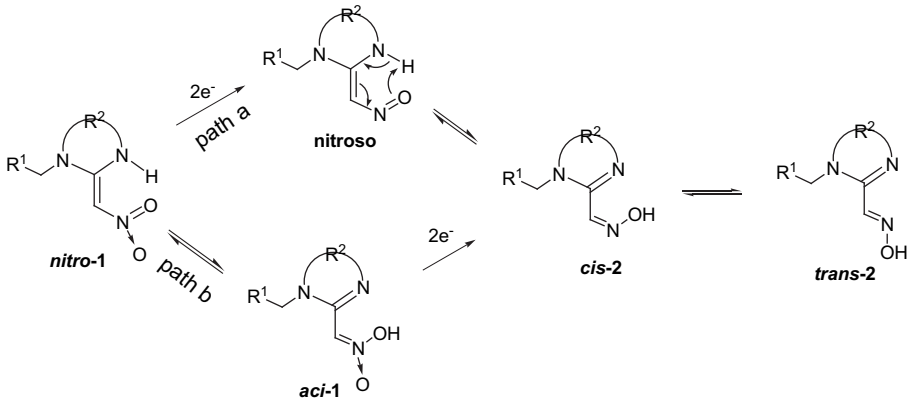
3. Conclusion

We have successfully synthesized a series of unsaturated oximes by reduction of the corresponding substituted vinylnitro compound using $SnCl_2 \cdot 2H_2O$ under mild conditions. The procedure is remarkably simple, and unique chem-selective without catalyst in preparing such oximes, which are usually difficult to be prepared by traditional methods. This is another example of direct conversion of nitro compounds to oximes and the research extends the application scope of nitro reduction.

4. Experimental

4.1. General

Melting points were obtained with an X-6 micro-melting point apparatus and are uncorrected. The infrared (IR) spectra



Scheme 4. Proposed mechanism for formation of oximes **2**.

In order to confirm which path more reasonable, a brief investigation into the scope of this reduction was performed. In controlled experiments, attempts to reduce the vinylnitro compounds **3**, **4** and **5** (Fig. 2) gave neither the corresponding oximes nor the corresponding hydroxylamine or amine with no conversion of the vinylnitro compound, while reducing acyclic vinylnitro compound **1t** (Fig. 2), a commercialized insecticide called nitenpyram, gave the corresponding oximes **2t** under the same

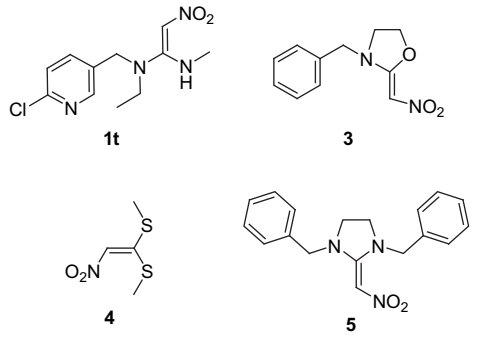


Figure 2. Structure of **1t**, **3**, **4** and **5**.

were recorded on a Nicolet 20DXB FR-IR spectrometer using potassium bromide pellets or films. The ^1H and ^{13}C NMR spectra were obtained on a Varian INOVA 400 MHz NMR spectrometer with DMSO-d_6 as the solvent and TMS as the internal standard. High-resolution mass spectra (HRMS) were obtained on HPLC-Q-Tof MS (Mcrio) spectrometer. X-ray single-crystal diffraction experiments were carried out on a Bruker Smart APEXII diffractometer. Flash chromatography was performed on silica gel. All the solvents were analytic grade. All chemicals or reagents and nitenpyram (**1t**) were purchased from standard commercial suppliers.

4.2. General procedure for substituted 2-nitromethylidene substrates 1a–e, 1h–j, and 1m–q

Compounds **1a**–**e**, **1h**–**j**, and **1m**–**q** were prepared according to the reported literature.[28] 2-Chloro-5-(chloromethyl) pyridine (1.62 g, 10 mmol) in acetonitrile (30 ml) was added dropwise to ethylenediamine (2.40 g, 40 mmol) in acetonitrile (20 ml) while stirring in an ice bath. After removing from the ice bath and stirring overnight at room temperature, the solvent was evaporated. Aqueous sodium hydroxide (1 M, 50 ml) was added to the residue,

which was then extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and evaporated to afford *N*-(2-chloro-pyridinylmethyl)ethylenediamine (1.39 g, 75% yield). *N*-(2-Chloro-pyridinylmethyl) ethylenediamine (0.93 g, 5 mmol) in ethanol (20 ml) was added dropwise to 1,1-bis(methylthio)-2-nitroethylene (0.83 g, 5 mmol) in ethanol (10 ml). The mixture was refluxed for 4 h. After evaporating the solvent, the residue was recrystallized from ethanol to afford 1-*N*-(2-chloro-pyridinylmethyl)-2-nitromethylene-imidazolidine **1a** (0.95 g, 75% yield). Compounds **1b–e**, **1h–j**, and **1m–q** were similarly prepared.

4.3. General procedure for substituted 2-nitromethylidene substrates 1f–g, 1k–l, and 1r–s

Compounds **1f–g**, **1k–l**, and **1r–s** were prepared according to the report.[35] A solution of ethylenediamine (2.4 g, 40 mmol) in methanol (20 ml) was stirred at 0 °C during the dropwise addition of 2-furaldehyde (0.96 g, 10 mmol). After the addition was completed, the solution was stirred and maintained at 0 °C while $NaBH_4$ (0.57 g, 15 mmol) was added cautiously in small portions. The reaction mixture was allowed to warm to ambient temperature and stirred for 2 h. The resulting cloudy solution was filtered, the filtrate was concentrated and the residual oil was partitioned between dichloromethane and H_2O. The dichloromethane layer was dried over magnesium sulfate and evaporated to afford *N*-(2-furalmethyl) ethylenediamine (1.02 g, 70% yield) and then *N*-(2-furalmethyl)ethylenediamine reacted with 1,1-bis(methylthio)-2-nitroethylene to afford **1f** in 70% yield. Compounds **1g**, **1k–l**, and **1r–s** were similarly prepared.

4.4. General procedure for preparation of unsaturated oximes 2a–t

A solution of **1a** (1.53 g, 6 mmol) in dichloromethane (100 ml) was treated with solid $SnCl_2 \cdot 2H_2O$ (7.4 g, 33 mmol). The mixture was stirred at ambient temperature under nitrogen for 5 h and then poured cautiously into saturated aqueous $NaHCO_3$. The resulting gelatinous emulsion was filtered through a pad of diatomite, and the biphasic filtrate was extracted with dichloromathane five times. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo, affording the oxime **2a** (0.64 g, 45% yield) that was purified by silica gel chromatography (CH_2Cl_2/CH_3OH=4:1, v/v).

*4.4.1. 1-(6-Chloro-pyridin-3-ylmethyl)-4,5-dihydro-1H-imidazole-2-carbaldehyde oxime (**2a**).* Yield 45%; white powders; mp 142.5–143.8 °C; IR (KBr, cm^{-1}): 3434, 1632, 1566, 1296, 929; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.54 (br, 1H), 7.73 (s, 1H), 7.60 (s, 1H), 4.84 (s, 2H), 3.67 (t, 2H, *J*=9.6 Hz), 3.33 (t, 2H, *J*=9.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 158.3, 149.0, 148.9, 142.1, 138.9, 124.1, 52.7, 50.6, 47.6; HRMS (ESI) calculated for $C_{10}H_{12}N_4OCl$ [M+H$^+$] 239.0700, found 239.0692.

*4.4.2. 1-(2-Chloro-thiazol-5-ylmethyl)-4,5-dihydro-1H-imidazole-2-carbaldehyde oxime (**2b**).* Yield 43%; white powders; mp 138.5–139.7 °C; IR (KBr, cm^{-1}): 3435, 1632, 1563, 1281, 922; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.76 (br, 1H), 8.33 (d, 1H, *J*=2.0 Hz), 7.77 (s, 1H), 7.75 (d, 1H, *J*=2.0 Hz), 7.51 (d, 1H, *J*=8.0 Hz), 4.71 (s, 2H), 3.70 (t, 2H, *J*=10.0 Hz), 3.31 (t, 2H, *J*=10.0 Hz); ^{13}C NMR (100 MHz DMSO-d_6) δ (ppm) 157.7, 150.0, 142.2, 140.0, 138.4, 52.7, 50.1, 43.3; HRMS (ESI) calculated for $C_8H_{10}N_4OSCl$ [M+H$^+$] 245.0264, found 245.0260.

*4.4.3. 1-Pyridin-2-ylmethyl-4,5-dihydro-1H-imidazole-2-carbaldehyde oxime (**2c**).* Yield 40%; gray powders; mp 125.6–127.1 °C; IR (KBr, cm^{-1}): 3416, 1636, 1556, 1295, 930; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.68 (br, 1H), 8.51 (d, 1H, *J*=4.4 Hz), 7.78 (t, 1H, *J*=8.0 Hz), 7.72 (s, 1H), 7.28 (t, 2H, *J*=7.2 Hz), 4.80 (s, 2H), 3.71 (t, 2H, *J*=10.0 Hz), 3.35 (t, 2H, *J*=10.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 158.8, 157.9, 149.1, 142.1, 136.7, 122.1, 121.3, 52.6, 52.0, 50.7; HRMS (ESI) calculated for $C_{10}H_{13}N_4O$ [M+H$^+$] 205.1089, found 205.1080.

*4.4.4. 1-Pyridin-3-ylmethyl-4,5-dihydro-1H-imidazole-2-carbaldehyde oxime (**2d**).* Yield 40%; gray powders; mp 144.4–145.6 °C; IR (KBr, cm^{-1}): 3430, 1637, 1556, 1276, 925; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.74 (br, 1H), 8.49 (s, 2H), 7.73 (s, 1H), 7.67 (d, 1H, *J*=7.6 Hz), 7.38 (t, 1H, *J*=7.6 Hz), 4.71 (s, 2H), 3.68 (t, 2H, *J*=6.0 Hz), 3.26 (t, 2H, *J*=6.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 158.5, 148.8, 148.3, 142.1, 135.1, 133.8, 123.5, 52.6, 50.5, 48.3; HRMS (ESI) calculated for $C_{10}H_{13}N_4O$ [M+H$^+$] 205.1089, found 205.1084.

*4.4.5. 1-Benzyl-4,5-dihydro-1H-imidazole-2-carbaldehyde oxime (**2e**).* Yield 62%; gray powders; mp 141.8–143.6 °C; IR (KBr, cm^{-1}): 3435, 1633, 1555, 1281, 928; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.85 (br, 1H), 7.74 (s, 1H), 7.34 (t, 2H, *J*=8.0 Hz), 7.26 (t, 3H, *J*=8.0 Hz), 4.70 (s, 2H), 3.67 (t, 2H, *J*=10.0 Hz), 3.24 (t, 2H, *J*=10.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 158.6, 141.9, 138.1, 128.4, 127.3, 127.0, 52.3, 50.4, 50.3; HRMS (ESI) calculated for $C_{11}H_{14}N_3O$ [M+H$^+$] 204.1137, found 204.1147.

*4.4.6. 1-Furan-2-ylmethyl-4,5-dihydro-1H-imidazole-2-carbaldehyde oxime (**2f**).* Yield 58%; white powders; mp 132.5–133.3 °C; IR (KBr, cm^{-1}): 3420, 1636, 1582, 1291, 958; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.90 (br, 1H), 7.70 (s, 1H), 7.59 (s, 1H), 6.40 (d, 1H), 6.26 (s, 1H), 4.68 (s, 2H), 3.64 (t, 2H, *J*=5.6 Hz), 3.28 (t, 2H, *J*=5.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 158.5, 147.8, 143.8, 135.1, 110.7, 110.0, 49.7, 43.1, 42.4; HRMS (ESI) calculated for $C_9H_{12}N_3O_2$ [M+H$^+$] 194.0930, found 194.0935.

*4.4.7. 1-Thiophen-2-ylmethyl-4,5-dihydro-1H-imidazole-2-carbaldehyde oxime (**2g**).* Yield 60%; white powders; mp 136.2–137.7 °C; IR (KBr, cm^{-1}): 3427, 1630, 1598, 1290, 927; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.88 (br, 1H), 7.75 (s, 1H), 7.44 (dd, 1H, *J*=4.0, 2.0 Hz), 7.00 (t, 2H, *J*=4.0 Hz), 4.88 (s, 2H), 3.65 (t, 2H, *J*=6.0 Hz), 3.26 (t, 2H, *J*=6.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 158.3, 142.1, 140.5, 126.7, 126.3, 125.5, 52.6, 49.9, 45.3; HRMS (ESI) calculated for $C_9H_{12}N_3O$ [M+H$^+$] 210.0701, found 210.0691.

*4.4.8. 1-(6-Chloro-pyridin-3-ylmethyl)-1,4,5,6-tetrahydro-pyrimidine-2-carbaldehyde oxime (**2h**).* Yield 48%; white powders; mp 153.1–154.3 °C; IR (KBr, cm^{-1}): 3447, 1630, 1586, 1299, 937; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.46 (br, 1H), 7.60 (s, 1H), 7.39 (s, 1H), 4.73 (s, 2H), 3.31–3.15 (m, 4H), 1.68 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 158.3, 149.0, 148.8, 138.7, 133.6, 124.1, 50.9, 46.0, 43.5, 20.8; HRMS (ESI) calculated for $C_{11}H_{14}N_4OCl$ [M+H$^+$] 253.0856, found 253.0846.

*4.4.9. 1-(2-Chloro-thiazol-5-ylmethyl)-1,4,5,6-tetrahydro-pyrimidine-2-carbaldehyde oxime (**2i**).* Yield 40%; white powders; mp 138.5–139.4 °C; IR (KBr, cm^{-1}): 3430, 1617, 1564, 1320, 939; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.26 (br, 1H), 8.30 (s, 1H), 7.73 (d, 1H, *J*=8.0 Hz), 7.51 (d, 1H, *J*=8.0 Hz), 7.44 (s, 1H), 4.66 (s, 2H), 3.32 (t, 2H, *J*=5.6 Hz), 3.12 (t, 2H, *J*=5.6 Hz), 1.72 (t, 2H, *J*=5.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 150.5, 150.1, 146.8, 140.1, 139.1, 47.2, 45.5, 44.0, 20.9; HRMS (ESI) calculated for $C_9H_{12}N_4OSCl$ [M+H$^+$] 259.0420, found 259.0415.

*4.4.10. 1-Benzyl-1,4,5,6-tetrahydro-pyrimidine-2-carbaldehyde oxime (**2j**).* Yield 65%; white powders; mp 125.8–127.1 °C; IR (KBr,

cm^{-1}): 3390, 1650, 1568, 1321, 933; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.58 (br, 1H), 8.33 (s, 1H), 741–7.29 (m, 5H), 4.87 (s, 2H), 3.49–3.35 (m, 4H), 1.69 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 151.9, 144.4, 138.0, 128.5, 127.0, 126.8, 53.8, 46.0, 42.8, 20.7; HRMS (ESI) calculated for $C_{12}H_{16}N_3O$ [M+H$^+$] 218.1293, found 218.1287.

*4.4.11. 1-Furan-2-ylmethyl-1,4,5,6-tetrahydro-pyrimidine-2-carbaldehyde oxime (**2k**).* Yield 61%; white powders; mp 151.8–153.4 °C; IR (KBr, cm^{-1}): 3433, 1649, 1571, 1297, 928; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.12 (br, 1H), 8.43 (s, 1H), 7.70 (s, 1H), 6.52 (d, 1H, J=3.2 Hz), 6.45 (d, 1H, J=3.2 Hz), 4.89 (s, 2H), 3.53 (t, 2H, J=5.6 Hz), 3.34 (t, 2H, J=5.6 Hz), 1.91 (t, 2H, J=5.6 Hz); ^{13}C NMR (100 MHz DMSO-d_6) δ (ppm) 153.9, 148.5, 144.4, 138.9, 111.2, 110.4, 48.1, 47.0, 38.3, 18.7; HRMS (ESI) calculated for $C_{10}H_{14}N_3O_2$ [M+H$^+$] 208.1086, found 208.1093.

*4.4.12. 1-Thiophen-2-ylmethyl-1,4,5,6-tetrahydro-pyrimidine-2-carbaldehyde oxime (**2l**).* Yield 64%; white powders; mp 154.2–156.0 °C; IR (KBr, cm^{-1}): 3426, 1646, 1566, 1315, 932; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.48 (br, 1H), 8.42 (s, 1H), 7.58 (s, 1H), 7.17 (s, 1H), 7.05 (s, 1H), 5.06 (s, 2H), 3.53–3.36 (m, 4H), 1.93 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 159.3, 156.2, 136.1, 129.5, 128.1, 127.7, 50.4, 44.3, 38.0, 18.3; HRMS (ESI) calculated for $C_{10}H_{14}N_3OS$ [M+H$^+$] 224.0858, found 224.0853.

*4.4.13. 1-(6-Chloro-pyridin-3-ylmethyl)-4,5,6,7,8,9-hexahydro-1H-benzoimidazole-2-carbaldehyde oxime (**2m**).* Yield 68%; white powders; mp 162.0–162.9 °C; IR (KBr, cm^{-1}): 3435, 1631, 1569, 1300, 920; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.04 (br, 1H), 7.70 (s, 1H), 7.60 (s, 1H), 4.89 (d, 1H, J=16.0 Hz), 4.74 (d, 1H, J=16.0 Hz), 2.89 (t, 1H, J=6.4 Hz), 2.56 (t, 1H, J=6.4 Hz), 2.13 (m, 2H), 1.71 (m, 2H), 1.28–1.21 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 158.0, 148.9, 148.8, 142.7, 138.8, 134.0, 124.0, 61.9, 60.7, 44.7, 28.3, 23.3, 20.8, 19.7; HRMS (ESI) calculated for $C_{14}H_{18}N_4OCl$ [M+H$^+$] 293.1169, found 293.1183.

*4.4.14. 1-(2-Chloro-thiazol-5-ylmethyl)-4,5,6,7,8,9-hexahydro-1H-benzoimidazole-2-carbaldehyde oxime (**2n**).* Yield 65%; white powders; mp 163.8–164.4 °C; IR (KBr, cm^{-1}): 3434, 1631, 1560, 1292, 922; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.84 (br, 1H), 8.33 (s, 1H), 7.75 (dd, 1H, J=8.0, 2.0 Hz), 7.70 (s, 1H), 7.50 (d, 1H, J=8.0 Hz), 4.81 (d, 1H, J=16.4 Hz), 4.60 (d, 1H, J=16.4 Hz), 3.75 (t, 1H, J=6.4 Hz), 3.35 (t, 1H, J=6.4 Hz), 1.72–1.41 (m, 4H), 1.71 (m, 2H), 1.21–1.16 (m, 4H); ^{13}C NMR (100 MHz DMSO-d_6) δ (ppm) 159.7, 150.6, 143.3, 140.9, 138.3, 70.8, 69.6, 42.5, 30.7, 28.7, 25.4, 24.2; HRMS (ESI) calculated for $C_{12}H_{16}N_4OSCl$ [M+H$^+$] 299.0733, found 299.0742.

*4.4.15. 1-Pyridin-2-ylmethyl-4,5,6,7,8,9-hexahydro-1H-benzoimidazole-2-carbaldehyde oxime (**2o**).* Yield 60%; white powders; mp 149.3–150.2 °C; IR (KBr, cm^{-1}): 3427, 1673, 1570, 1302, 928; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.69 (br, 1H), 8.48 (d, 1H, J=4.0 Hz), 7.76 (t, 1H, J=7.6 Hz), 7.71 (s, 1H), 7.35 (t, 1H, J=7.6 Hz), 7.25 (d, 1H, J=5.6 Hz), 4.82 (d, 1H, J=16.4 Hz), 4.71 (d, 1H, J=16.4 Hz), 2.94 (t, 1H, J=14.0 Hz), 2.65 (t, 1H, J=6.4 Hz), 2.14–1.63 (m, 4H), 1.31–1.20 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.0, 157.6, 149.6, 142.9, 137.3, 122.9, 121.8, 70.7, 70.2, 51.2, 29.8, 28.1, 24.3, 23.4; HRMS (ESI) calculated for $C_{14}H_{19}N_4O$ [M+H$^+$] 259.1559, found 259.1558.

*4.4.16. 1-Pyridin-3-ylmethyl-4,5,6,7,8,9-hexahydro-1H-benzoimidazole-2-carbaldehyde oxime (**2p**).* Yield 58%; white powders; mp 143.3–143.9 °C; IR (KBr, cm^{-1}): 3423, 1674, 1575, 1301, 931; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.76 (br, 1H), 8.51 (s, 1H), 8.46 (d, 1H, J=4.0 Hz), 7.74 (s, 1H), 7.68 (d, 1H, J=7.6 Hz), 7.37 (t, 1H, J=7.6 Hz), 4.91 (d, 1H, J=16.0 Hz), 4.51 (d, 1H, J=16.0 Hz), 2.94 (t, 1H, J=12.0 Hz), 2.62 (t, 1H, J=12.0 Hz), 2.14–1.65 (m, 4H), 1.30–1.22 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 160.1, 148.8, 148.2, 142.7, 135.2, 134.0, 123.4, 70.5, 70.3, 47.2, 30.4, 28.9, 24.9, 23.8; HRMS (ESI) calculated for $C_{14}H_{19}N_4O$ [M+H$^+$] 259.1559, found 259.1548.

*4.4.17. 1-Benzyl-4,5,6,7,8,9-hexahydro-1H-benzoimidazole-2-carbaldehyde oxime (**2q**).* Yield 75%; white powders; mp 148.3–149.9 °C; IR (KBr, cm^{-1}): 3434, 1631, 1561, 1303, 922; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.41 (br, 1H), 7.73 (s, 1H), 7.31 (d, 2H, J=6.8 Hz), 7.24 (t, 3H, J=6.8 Hz), 4.77 (d, 1H, J=16.0 Hz), 4.63 (d, 1H, J=16.0 Hz), 2.93 (t, 1H, J=11.2 Hz), 2.57 (t, 1H, J=11.2 Hz), 2.15–1.85 (m, 2H), 1.70–1.63 (m, 2H), 1.30–1.22 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 160.2, 142.6, 138.1, 128.2, 127.4, 126.9, 70.4, 69.7, 49.3, 30.4, 28.8, 24.9, 23.8; HRMS (ESI) calculated for $C_{15}H_{20}N_3O$ [M+H$^+$] 258.1606, found 258.1597.

*4.4.18. 1-Furan-2-ylmethyl-4,5,6,7,8,9-hexahydro-1H-benzoimidazole-2-carbaldehyde oxime (**2r**).* Yield 72%; white powders; mp 136.6–138.1 °C; IR (KBr, cm^{-1}): 3433, 1631, 1542, 1299, 928; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.89 (br, 1H), 7.73 (s, 1H), 7.58 (s, 1H), 6.38 (t, 1H, J=3.2 Hz), 6.26 (d, 1H, J=3.2 Hz), 4.97 (d, 1H, J=16.4 Hz), 4.40 (d, 1H, J=16.4 Hz), 2.93–2.86 (m, 1H), 2.49–2.44 (m, 1H), 2.14 (d, 1H, J=8.8 Hz), 2.06 (d, 1H, J=8.8 Hz), 1.72 (d, 2H, J=12.0 Hz), 1.34–1.23 (m, 4H); ^{13}C NMR (100 MHz DMSO-d_6) δ (ppm) 160.8, 151.5, 143.1, 142.7, 110.8, 108.9, 70.4, 69.3, 42.1, 30.8, 28.6, 25.4, 24.3; HRMS (ESI) calculated for $C_{13}H_{18}N_3O_2$ [M+H$^+$] 248.1399, found 248.1392.

*4.4.19. 1-Thiophen-2-ylmethyl-4,5,6,7,8,9-hexahydro-1H-benzoimidazole-2-carbaldehyde oxime (**2s**).* Yield 72%; white powders; mp 146.4–147.1 °C; IR (KBr, cm^{-1}): 3434, 1632, 1565, 1300, 918; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.98 (br, 1H), 7.74 (s, 1H), 7.42 (dd, 1H, J=4.0, 2.4 Hz), 6.98 (t, 2H, J=4.0 Hz), 5.14 (d, 1H, J=16.0 Hz), 4.65 (d, 1H J=16.0 Hz), 2.92 (t, 1H J=14.4 Hz), 2.55 (t, 1H, J=14.4 Hz), 2.15–2.06 (m, 2H), 1.72 (d, 2H, J=10.2 Hz), 1.36–1.22 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 160.3, 143.1, 139.9, 127.3, 127.2, 126.3, 70.5, 68.7, 44.0, 30.8, 28.7, 25.4, 24.3; HRMS (ESI) calculated for $C_{13}H_{18}N_3OS$ [M+H$^+$] 264.1171, found 264.1179.

*4.4.20. N-(6-Chloro-pyridin-3-ylmethyl)-N-ethyl-N′-methyl-acetamidine-2-carbaldehyde oxime (**2t**).* Yield 65%; white powders; mp 146.8–147.8 °C; IR (KBr, cm^{-1}): 3434, 1638, 1570, 1291, 916; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.63 (br, 1H), 8.30 (d, 1H, J=2.4 Hz), 7.90 (s, 1H), 7.72 (d, 1H, J=8.0 Hz) 7.45 (d, 2H, J=8.0 Hz), 4.49 (s, 2H), 3.20 (m, 2H), 2.93 (s, 3H), 0.98 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 153.4, 148.9, 148.5, 142.4, 138.9, 134.6, 123.8, 46.1, 42.3, 36.4, 13.3; HRMS (ESI) calculated for $C_{11}H_{16}N_4OCl$ [M+H$^+$] 255.1013, found 255.1008.

4.4.21. X-ray data. $C_{10}H_{11}Cl_1N_4O_1$ **2a**, unit cell parameters: a=11.3228(17), b=9.0996(14), c=10.9721(17), α=90.00, β=97.268(2), γ=90.00, space group $P2_1/c$.

The crystallographic data for the structure **2a** reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 734794 for compounds **2a**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44 1223 336033; email: deposit@ccdc.cam.ac.uk].

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