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Nitrosocarbonyl release from *O*-substituted hydroxamic acids with pyrazolone leaving groups

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This article is dedicated to Professor Gary H. Posner in appreciation of his career contributions to organic chemistry

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ABSTRACT

A new class of nitrosocarbonyl precursors, *O*-substituted hydroxamic acids with pyrazolone leaving groups (OHPY), is described. These compounds generate nitrosocarbonyl intermediates, which upon hydrolysis release nitroxyl (azanone, HNO) under physiologically relevant conditions. Pyrazolones have been used to confirm the generation of nitrosocarbonyls by competitive trapping to form isomeric *N*-substituted hydroxamic acids (NHPY) via an *N*-selective nitrosocarbonyl aldol reaction. The rate of nitrosocarbonyl release from OHPY donors is impacted by donor substituents, including the pyrazolone leaving group.

1. Introduction

Nitroxyl (azanone, HNO), the one-electron reduced and protonated form of nitric oxide, has been shown to improve both vasorelaxation and myocardial contractility, making HNO donors ideal candidates for drug development.[1–9] HNO is a reactive molecule that spontaneously dimerizes to produce hyponitrous acid (HON=NOH), which then dehydrates to give nitrous oxide (N_2O).[10] Due to this inherent reactivity, HNO must be generated in situ through the use of donor compounds.

Angeli's salt ($Na_2N_2O_3$, AS, Fig. 1) is a well-known donor that generates HNO under physiological conditions with a short half-life.[11] Derivatization of this inorganic salt has been unsuccessful to date, thus preventing modification for tunable HNO release. Piloty's acid (PA) derivatives and acyloxy nitroso compounds (AcON) represent other types of HNO donors that have been developed with tunable half-lives.[12–17] Our group has recently reported two new series of HNO donors with half-lives that can be varied from minutes to hours under physiological conditions: (hydroxylamino) pyrazolone (HAPY) and (hydroxylamino)barbituric acid (HABA) derivatives.[18–20] In addition to these examples, the continued development of efficient HNO donors is important to expand the research tools available to understand the potential role of HNO in biological processes.

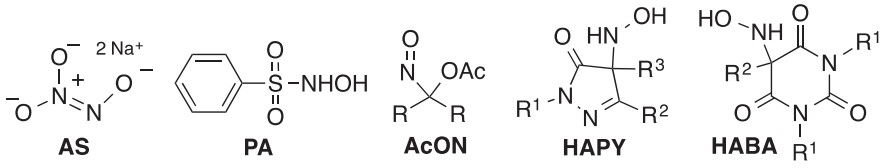

Fig. 1. Some previously reported HNO donors.

Another strategy to release HNO is based on the hydrolysis of nitrosocarbonyl intermediates.[21,22] Nitrosocarbonyls are highly

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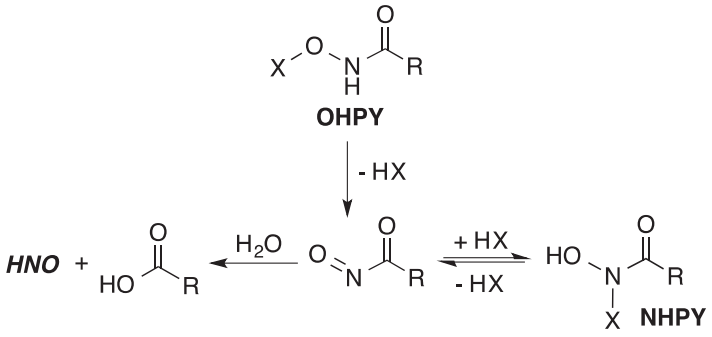
reactive species that can react with nucleophiles including water to generate HNO. Oxidation of hydroxamic acids and thermal decomposition of 9,10-dimethylanthracene adducts represent common approaches to nitrosocarbonyl generation.[23–25] The photolysis of nitrodiazo compounds, nitronates with alpha leaving groups, and 1,2,4-oxadiazole-4-oxides have also been shown to generate nitrosocarbonyls efficiently.[26–28] Recently, the aerobic oxidation of hydroxamic acids by metal catalysts under mild conditions has been developed as an efficient strategy for nitrosocarbonyl generation.[29–46] In general, however, the above methods are not suitable for HNO generation under physiological conditions.

Herein, we report a novel class of nitrosocarbonyl donors that upon deprotonation and loss of the leaving group (Scheme 1, HX=pyrazolone) generate nitrosocarbonyl intermediates that can hydrolyze to release HNO under physiological conditions. As has been demonstrated in recent reports,[33,35,36,40–42,45] nitrosocarbonyls can react with nucleophiles through an *N*-selective nitrosocarbonyl aldol reaction to produce *N*-substituted hydroxamic acid adducts. We have recently found that pyrazolones are efficient traps for nitrosocarbonyl intermediates to generate *N*-substituted hydroxamic acid derivatives with pyrazolone leaving groups (NHPY) in a reversible manner.[47] In the current work, we observe OHPY decomposition to generate nitrosocarbonyls which further react with pyrazolones to produce isomeric NHPY compounds (Scheme 1). We have synthesized and studied NHPY compounds independently, and have recently demonstrated the efficient formation of nitrosocarbonyl intermediates upon decomposition of these compounds.[47]

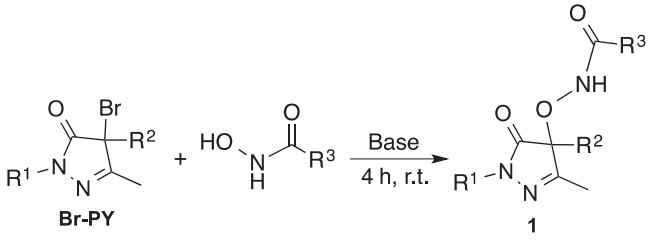


Scheme 1. Reactivity of OHPY nitrosocarbonyl precursors.

2. Results and discussion

2.1. Synthesis

OHPY compounds **1** have been synthesized by formation of the corresponding bromide (Br-PY) followed by reaction with hydroxamic acids (Scheme 2). Initially, OHPY **1a** was synthesized without the need for chromatographic purification, and its structure was confirmed by X-ray crystallography (Supplementary data). The other precursors were purified using column chromatography.



Scheme 2. Synthesis of OHPY derivatives.

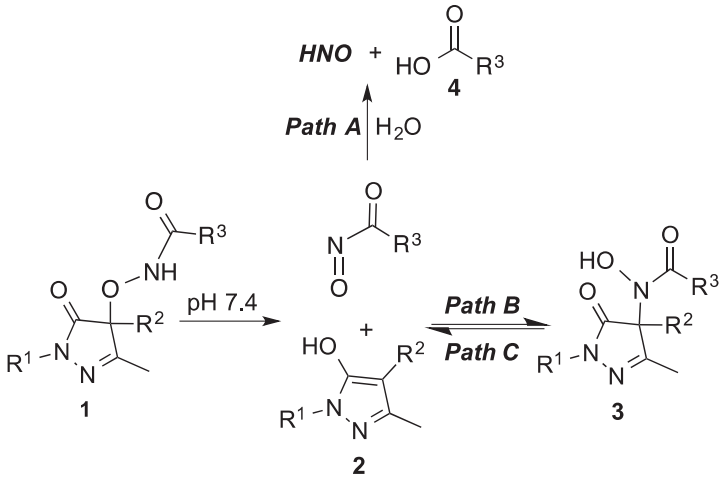
The OHPY and NHPY isomers can obviously be distinguished by X-ray crystallography. An analysis of ^{13}C NMR data and available crystal structures (Supplementary data), reveal that OHPY and NHPY compounds have distinctive chemical shifts for their quaternary carbons (δ=87.6–90.2 ppm for OHPY vs δ=68.4–76.5 ppm for NHPY). Thus, ^{13}C NMR spectroscopy conveniently allows the two isomers to be distinguished if crystal structures cannot be obtained.

2.2. Decomposition of OHPY compounds

Nitrosocarbonyl formation following OHPY decomposition under physiological conditions was studied. As described above, the reaction of nitrosocarbonyls and pyrazolones to produce NHPY compounds can be efficient. Upon nitrosocarbonyl generation from OHPY precursors **1**, therefore, a competition exits between hydrolysis to generate HNO and carboxylic acid **4** (Scheme 3, *Path A*) and trapping by the pyrazolone byproduct **2** to produce NHPY compounds **3** (Scheme 3, *Path B*). NHPY compounds subsequently can also release nitrosocarbonyl intermediates with half-lives that depend on R^1, R^2, and R^3 (Scheme 3, *Path C*).[47]

^1H NMR spectroscopy was used to examine the decomposition of OHPY donors and measure relative product yields in aqueous solution (Table 1).[19,20] Pyrazolone **2**, NHPY **3**, and carboxylic acid **4** are cleanly formed as the only observable organic products. Because NHPY compounds **3a**, **3c**, and **3d** all have half-lives on the order of days,[47] *Path C* in Scheme 3 does not contribute to the observed chemistry for OHPY donors **1a**, **1c**, and **1d**. Thus, the relative yields of pyrazolone **2** and carboxylic acid **4** compared with that for NHPY compound **3** in Table 1 reflect the competition between *Path A* and *Path B* for these donors.

OHPY decomposition was also monitored by UV–vis spectroscopy to measure donor half-lives at pH 7.4 and 37 °C (Table 1). Based on the chemistry of related HNO donors,[19,20] we propose that the first step of decomposition is deprotonation which leads to release of nitrosocarbonyl plus pyrazolone. If the barrier to dissociation from anionic OHPY is very small, observed half-lives should correlate with donor pK_a and the pyrazolone leaving group.[19,20] Pyrazolone **2a** (R^1=Ph, R^2=(C(=NOMe)Me, pK_a=6) is a better leaving group than pyrazolone **2b** (R^1=Ph, R^2=Me, pK_a=7.6),[19] consistent with the much shorter half-life for OHPY **1a** ($t_{1/2}$=25 min) compared with **1b** (stable). Exchanging the R^1 group from phenyl to methyl (OHPY **1c** vs **1d**) increases the half-life by a factor of two, consistent with that previously reported for analogous HAPY and NHPY donors.[19,47] A comparison of the known pK_a values of the related



Scheme 3. Reactivity of OHPY donors **1**.

Table 1
Product yields and half-lives for OHPY donors

OHPY	R^1	R^2	R^3	%2[a]	%3[a]	%4[a]	$t_{1/2}$ (min)[b]
1a	Ph	C(=NOMe)Me	Me	74	26	73	25
1b	Ph	Me	Me				Stable[c]
1c	Ph	C(=NOMe)Me	MeO	28	72	27	0.6
1d	Me	C(=NOMe)Me	MeO	14	86	14	1.2
1e	Ph	C(=NOMe)Me	*t*-BuO	[d]	[d]	[d]	[d]

[a] Relative yields determined from ^{1}H NMR analysis of the complete decomposition of 0.5 mM of the OHPY donor in 10% DMSO-d_6, 10% D_2O, and 80% H_2O, phosphate buffer (0.25 M) containing 0.2 mM of the metal chelator, diethylenetriaminepentaacetic acid (DTPA), pH 7.4 at 37 °C under argon.
[b] Determined by UV–vis spectroscopy.
[c] Less than 5% decomposition after 2 days.
[d] Not Determined due to low solubility.

compounds, PhC(O)NHOH (8.8) and PhOC(O)NHOH (10.0),[48] indicates that the pK_a of OHPY **1a** is likely lower than that of OHPY **1c**. Although these two donors have the same pyrazolone leaving group, the longer half-life for OHPY **1a** ($t_{1/2}$=25 min) compared with **1c** ($t_{1/2}$=0.6 min) suggests that the barrier to dissociation may also affect the observed half-lives. In the case of NHYP donors, the dissociation barrier was found to be strongly dependent on the R^3 group.[47] The origin and impact of the R^3 group on OHPY dissociation requires further investigation.

HNO generation was examined by gas chromatographic (GC) headspace analysis to quantify the amount of its dimerization product, N_2O, formed following decomposition of OHPY donors in pH 7.4 phosphate buffer solutions at 37 °C (Table 2). The amount of HNO release was measured relative to standard HNO donor, Angeli's salt. As expected, HNO yields from OHPY donors are consistent with the corresponding yields of pyrazolone **2** and carboxylic acid **4** observed under the same conditions.

Table 2
HNO yields for OHPY donors at different concentrations

OHPY	% HNO[a]		
	500 μM	100 μM	20 μM
1a	70	75	91
1b	[b]	[b]	[b]
1c	20	29	41
1d	8	17	29
1e	[c]	26	35[d]

[a] HNO yields are measured after complete decomposition of the donor and are reported relative to the standard HNO donor, Angeli's salt, as determined by N_2O headspace analysis (SEM±5%; n=3).
[b] Stable.
[c] Not determined due to low solubility.
[d] $t_{1/2}$=3.2 min (measured using UV–vis spectroscopy).

The competition between nitrosocarbonyl hydrolysis to HNO (*Path* A) and pyrazolone trapping (*Path* B) depends on the relative concentration of pyrazolone. Lower concentrations of pyrazolone **2** following decomposition of lower concentrations of OHPY **1** will disfavor NHPY formation and correspondingly increase the yield of HNO. Determination of HNO yields at different concentrations of donors (Table 2), confirms that the yield of HNO is impacted as expected.

2.3. Mechanistic studies

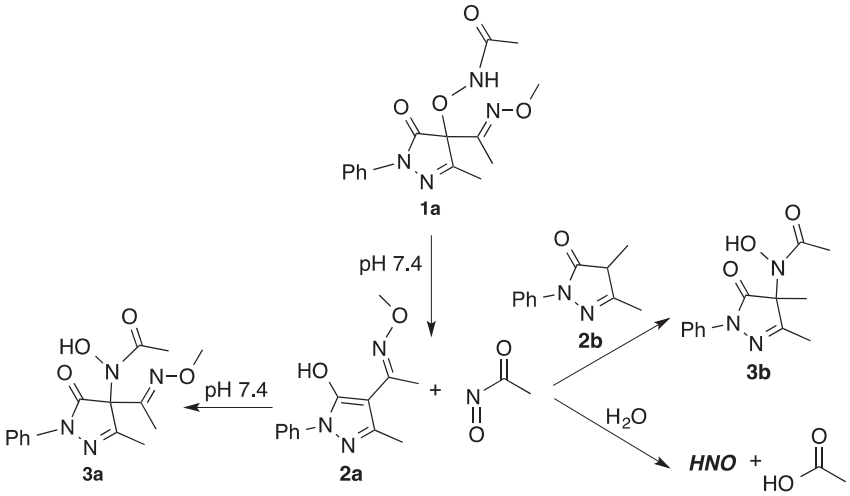
Our proposed mechanism for OHPY decomposition involves deprotonation followed by initial formation of a nitrosocarbonyl intermediate. Pyrazolone **2b** has recently been demonstrated to be an efficient trap for nitrosocarbonyls under physiological conditions.[47] To confirm the formation of nitrosocarbonyls upon OHPY decomposition, we incubated OHPY **1a** (0.5 mM) in presence of pyrazolone **2b** (0.5 mM) in pH 7.4 phosphate buffer at 37 °C (Scheme 4). Upon decomposition of donor **1a** under these conditions, we observe quantitative formation of NHPY **3b** (Supplementary data), strong evidence for nitrosocarbonyl formation.

In the absence of pyrazolone **2b**, the decomposition of OHPY **1a** provides NHPY **3a** (26%) (which has a half-life of 5 days), and HNO (70%) and acetate (73%) (Scheme 4 and Tables 1 and 2). The stability of NHPY **3a**, along with the observation that it is not formed in the presence of pyrazolone **2b**, also argues against the possibility of a direct intramolecular rearrangement from anionic OHPY **1a** to NHPY **3a** without involvement of a nitrosocarbonyl intermediate.

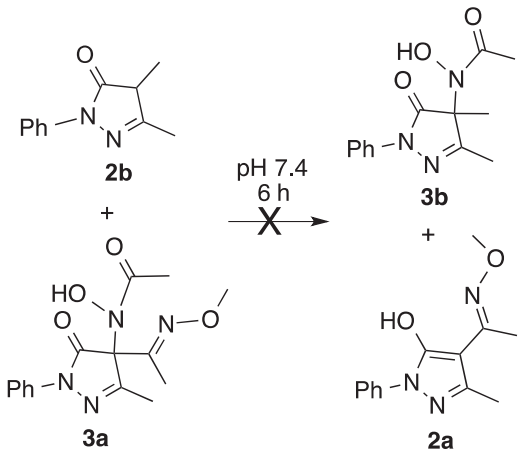
Based on reactivity studies of bis-heteroatom-substituted amides,[49] the formation of NHPY **3b** may be possible through the direct attack of pyrazolone **2b** on the amide nitrogen of the hydroxamic acid moiety of NHPY **3a** (Scheme 5). To examine this possibility, NHPY **3a** was incubated with pyrazolone **2b** and its stability was confirmed by ^{1}H NMR spectroscopy at pH 7.4 and 10. The pK_a of NHPY **3a** has recently been measured to be 10.0 and its stability at or above pH 10 suggests a relatively high barrier for nitrosocarbonyl formation from this NHPY donor even when deprotonated.[47]

3. Conclusions

The OHPY class of nitrosocarbonyl precursors efficiently generates these intermediates under physiological conditions following



Scheme 4. Reactivity of OHPY **1a** in the presence of pyrazolone **2b**.



Scheme 5. The possible reaction of NHPY **3a** with pyrazolone **2b**.

deprotonation and loss of pyrazolone. The nitrosocarbonyl produced is subsequently hydrolyzed to HNO in competition with trapping by the pyrazolone byproduct via an *N*-selective nitrosocarbonyl aldol reaction to form an isomeric NHPY compound. The rate of nitrosocarbonyl release from OHPY compounds in aqueous solution is dependent on the pyrazolone leaving group. This rate is also influenced by the R^3 substituent, an effect that is under current investigation.

4. Experimental section

4.1. Method and materials

All starting materials were of reagent grade and used without further purification. *N*-hydroxy-*N*-(4-(acetyl-*O*-methoxyoxime)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)-*N*-acetamide (NHPY **3a**), *N*-hydroxy-*N*-(4-(acetyl-*O*-methoxyoxime)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)-*N*-methylcarbamate (NHPY **3c**), *N*-hydroxy-*N*-(*4*-(acetyl-*O*-methoxyoxime)-1,3-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)-*N*-methylcarbamate (NHPY **3d**),[47] 4-(acetyl-*O*-methoxyoxime)-3-methyl-1-phenyl-pyrazolone **2a**, 3,4-dimethyl-1-phenyl-pyrazolone **2b**, 4-(acetyl-*O*-methoxyoxime)-1,3-dimethylpyrazolone **2c**,[19] 4-(acetyl-*O*-methoxyoxime)-4-bromo-3-methyl-1-phenyl-pyrazolone, 4-bromo-3,4-dimethyl-1-phenyl-pyrazolone, 4-(acetyl-*O*-methoxyoxime)-4-bromo-1,3-dimethyl-pyrazolone,[18] *C*-methoxycarbohydroxamic acid, and *tert*-butylhydroxycarbamate[50] were prepared according to literature procedures. Acetohydroxamic acid was purchased and used without further purification. NMR spectra were obtained on a 400 MHz FT-NMR spectrometer. All chemical shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ (7.26 ppm for ^1H, 77.23 ppm for ^{13}C). High-resolution mass spectra were collected on a magnetic sector mass spectrometer working in fast atom bombardment (FAB) mode. Gas chromatography (GC) headspace analysis was performed on the instrument equipped with ECD detection and a molecular sieve packed column. Ultraviolet–visible (UV–vis) absorption spectra were collected using a diode array spectrophotometer.

4.2. Synthesis

*4.2.1. General procedure for the synthesis of N-((4-(acetyl-O-methoxyoxime)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)oxy)-acetamide (OHPY **1a**) and N-((3,4-dimethyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)oxy)-acetamide (OHPY **1b**).* To a solution of acetohydroxamic acid (1 mmol) in dimethylformamide (3 mL) at room temperature was added sodium hydride, 60% (1.1 mmol), and the reaction stirred for one hour. This solution was added to a solution of 1 mmol of brominated pyrazolone (4-(acetyl-*O*-methoxyoxime)-4-bromo-3-methyl-1-phenyl-pyrazolone for the synthesis of OHPY **1a** and 4-bromo-3,4-dimethyl-1-phenyl-pyrazolone for the synthesis of OHPY **1b**) in dimethylformamide (2 mL), and the reaction proceeded at room temperature for 3 h. The reaction was diluted with ether (20 mL) and washed with ammonium chloride, water, and brine. The organic phase was collected, dried over magnesium sulfate ($MgSO_4$), and concentrated in vacuo. Recrystallization from dichloromethane and hexane gave the product OHPY **1a** (25% yield) and, following purification by flash chromatography (30% ethylacetate/hexane) on silica gel, OHPY **1b** (28% yield).

*4.2.2. General procedure for the synthesis of N-((4-(acetyl-O-methoxyoxime)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)oxy)-methylcarbamate (OHPY **1c**), N-((4-(acetyl-O-methoxyoxime)-1,3-dimethyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)oxy)-methylcarbamate (OHPY **1d**), and N-(4-(acetyl-O-methoxyoxime)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)oxy)-tert-*

*butylcarbamate (OHPY **1e**).* To a solution of 1 mmol of hydroxamic acid (*C*-methoxycarbohydroxamic acid for the synthesis OHPY **1c** and **1d**, and *tert*-butylhydroxycarbamate for the synthesis of OHPY **1e**) in acetonitrile (3 mL) at room temperature was added triethylamine (1 mmol), and the reaction stirred for one hour. This solution was added to a solution of 1 mmol of brominated pyrazolone 4-(acetyl-*O*-methoxyoxime)-4-bromo-3-methyl-1-phenyl-pyrazolone for the synthesis of OHPY **1c** and **1e**, and 4-(acetyl-*O*-methoxyoxime)-4-bromo-1,3-dimethyl-pyrazolone for the synthesis of OHPY **1d**) in acetonitrile (2 mL), and the reaction proceeded at room temperature for 3 h. The reaction mixture was concentrated via rotary evaporation, redissolved in dichloromethane, and washed with water and brine. The organic phase was collected, dried over $MgSO_4$, and concentrated in vacuo. The compound was purified by flash chromatography (20% ethylacetate/hexane) on silica gel to give OHPY **1c**, **1d**, and **1e** with yields of 34%, 28%, and 37%, respectively.

*4.2.3. Synthesis of N-hydroxy-N-(3,4-dimethyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-N-acetamide (NHPY **3b**).* To a solution of acetohydroxamic acid (210 mg, 2.80 mmol) and pyrazolone **2b** (105 mg, 0.56 mmol) in 50% aqueous ethanol (7 mL), was added potassium carbonate (12 mg, 0.09 mmol) to adjust the pH to 7–8. Sodium periodate (599 mg, 2.80 mmol) was added to the reaction mixture, which was sonicated for 10 min, and then stirred for 3 h at room temperature. The reaction mixture was diluted with ethanol (12 mL) and the solid was filtered. The filtrate was concentrated via rotary evaporation and the resulting solid was redissolved in ethylacetate (50 mL) and washed three times with a saturated solution of ammonium chloride (30 mL). The organic phase was collected, dried over $MgSO_4$, and concentrated in vacuo. Recrystallization from dichloromethane and hexane gave the title compound (73% yield).

4.3. Compound characterization

*4.3.1. N-((4-(Acetyl-O-methoxyoxime)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)oxy)-acetamide (OHPY **1a**).* Colorless crystals, mp 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, s, OH), 7.85–7.83 (2H, m, arom), 7.41–7.38 (2H, m, arom), 7.22–7.20 (1H, m, arom), 3.90 (3H, s, Me), 2.34 (3H, s, Me), 2.06 (3H, s, Me), 1.92 (3H, s, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.5, 158.1, 156.7, 150.8, 137.8, 129.1, 125.7, 119.1, 90.2, 62.5, 20.0, 16.4, 10.2. HRMS (FAB): found *m/z*=319.14094 (MH^+); calcd for $C_{15}H_{19}N_4O_4$: 319.14063.

*4.3.2. N-((3,4-Dimethyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)oxy)-acetamide (OHPY **1b**).* White solid, mp 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.07 (1H, s, OH), 7.90–7.88 (2H, m, arom), 7.44–7.41 (2H, m, arom), 7.23–7.25 (1H, m, arom), 2.34 (3H, s, Me), 1.92 (3H, s, Me), 1.56 (3H, s, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 161.3, 158.1, 137.5, 129.1, 125.6, 118.4, 87.6, 20.4, 18.5, 13.2. HRMS (FAB): found *m/z*=262.11949 (MH^+); calcd for $C_{13}H_{15}N_3O_3$: 262.11917.

*4.3.3. N-((4-(Acetyl-O-methoxyoxime)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)oxy)-methylcarbamate (OHPY **1c**).* White solid, mp 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92–7.90 (2H, m, arom), 7.50 (1H, s, OH), 7.41–7.44 (2H, m, arom), 7.20–7.22 (1H, m, arom), 3.90 (3H, s, Me), 3.77 (3H, s, Me), 2.38 (3H, s, Me), 2.08 (3H, s, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.8, 158.8, 157.3, 151.3, 137.4, 129.2, 125.3, 118.7, 89.8, 62.8, 53.8, 14.9, 10.0. HRMS (FAB): found *m/z*=335.13496 (MH^+); calcd for $C_{15}H_{19}N_4O_5$: 335.13554.

*4.3.4. N-((4-(Acetyl-O-methoxyoxime)-1,3-dimethyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)oxy)-methylcarbamate (OHPY **1d**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (1H, s, OH), 3.89 (3H, s, Me), 3.79 (3H, s, Me), 3.28 (3H, s, Me), 2.27 (3H, s, Me), 2.03 (3H, s, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.6, 158.3, 157.6, 151.1, 88.9, 62.5, 53.3, 31.4, 15.0, 10.3. HRMS (FAB): found *m/z*=273.12013 (MH^+); calcd for $C_{10}H_{17}N_4O_5$: 273.11989.

*4.3.5. N-((4-(Acetyl-O-methoxyoxime)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)oxy)-tert-butylcarbamate (OHPY **1e**).* White solid, mp 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94–7.92 (2H, m, arom), 7.43–7.40 (2H, m, arom), 7.31 (1H, s, OH), 7.23–7.21 (1H, m, arom), 3.91 (3H, s, Me), 2.36 (3H, s, Me), 2.06 (3H, s, Me), 1.46 (1H, s, C(Me)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.3, 159.4, 156.1, 151.2, 137.8, 129.2, 125.3, 118.4, 89.8, 82.9, 62.4, 28.0, 15.1, 10.2. HRMS (FAB): found *m/z*=377.18180 (MH^+); calcd for $C_{18}H_{25}N_4O_5$: 377.18250.

*4.3.6. N-Hydroxy-N-(3,4-dimethyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-N-acetamide (NHPY **3b**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.08 (1H, s, OH), 7.87–7.85 (2H, m, arom), 7.45–7.43 (2H, m, arom), 7.24–7.22 (1H, m, arom), 2.18 (3H, s, Me), 2.10 (3H, s, Me), 1.68 (3H, s, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 159.0, 157.2, 137.5, 127.9, 125.8, 119.5, 72.3, 22.5, 19.2, 12.4. HRMS (FAB): found *m/z*=262.11917 (MH^+); calcd for $C_{13}H_{15}N_3O_3$: 262.11981.

Acknowledgements

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Supplementary data

Supplementary data (Crystallographic data of OHPY **1a** (CCDC 1495947) and NHPY **3b** (CCDC 1495948) have been deposited at the Cambridge Crystallographic Database Centre. These data can be obtained for free via https://www.ccdc.cam.ac.uk/) related to this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.08.016.

References and notes

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