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Selective cross-dehydrogenative C–O coupling of *N*-hydroxy compounds with pyrazolones. Introduction of the diacetyliminoxyl radical into the practice of organic synthesis†

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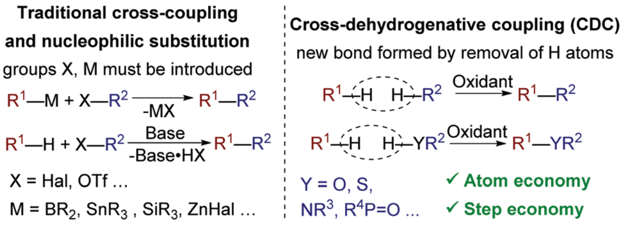
Oxidative C–O coupling of pyrazolones with *N*-hydroxy compounds of different classes (*N*-hydroxyphthalimide, *N*-hydroxybenzotriazole, oximes) was achieved; both one-electron oxidants ($Fe(ClO_4)_3$, $(NH_4)_2Ce(NO_3)_6$) and two-electron oxidants ($PhI(OAc)_2$, $Pb(OAc)_4$) are applicable, and the yields reach 91%. Apparently, the coupling proceeds *via* the formation of *N*-oxyl radicals from *N*-hydroxy compounds. One of the *N*-oxyl intermediates, the diacetyliminoxyl radical, was found to be exclusively stable in solution in spite of being sterically unhindered; it was isolated from an oxidant and used as a new reagent for the synthesis and mechanism study. The products of C–O coupling of pyrazolones with *N*-hydroxyphthalimide can be easily transformed into aminooxy compounds, valuable substances for combinatorial chemistry.

Introduction

The development of C–C and C–heteroatom cross-dehydrogenative coupling (CDC) methods is one of the major trends in modern organic synthesis and green chemistry. Such methods avoid prefunctionalization of coupling partners (with -Hal, -OTf, $-SnBu_3$, $-B(OH)_2$, and other groups) and thus afford high atom and step economy (Scheme 1).[1]



Scheme 1 Traditional and cross-dehydrogenative coupling.

C–O bonds are abundant in natural and synthetic organic compounds, which makes the development of C–O cross-dehydrogenative coupling (C–O CDC) desirable. Nevertheless, C–O CDC remains one of the most challenging types of oxidative couplings[1c–f] due to the ease of side oxidation processes. Usually a new C–O bond between two molecules is formed *via* reductive elimination in a metal catalyzed process or as a result of the reaction of an O-nucleophile with a C-electrophile (Scheme 2).[1c] O-Reagents are frequently used in excess amounts to maintain the selectivity, which limits the scope of O-reagents to simple molecules. To overcome the mentioned limitations and open new coupling possibilities, we focused our attention on O-radicals as intermediates for C–O bond formation. *N*-Oxyl radicals derived from the *N*-hydroxy compounds proved to be useful for intramolecular cyclizations,[2] C=C bond functionalization,[3] oxidation,[4] C–O CDC with alkylarenes,[5a,b] β-dicarbonyl compounds,[5c,d] and aldehydes.[5e,f]

Nevertheless, structural diversity of C-reagents for the coupling and *N*-oxyl intermediates remains limited. In the present study we demonstrated the applicability of *N*-oxyl radicals for

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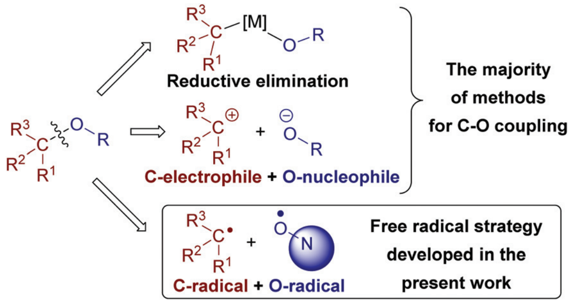


Scheme 2 Strategies for C–O coupling.

oxidative coupling with heterocyclic compounds. Pyrazolones were chosen as heterocycle representatives because they are both challenging substrates for radical coupling due to the easiness of their oxidation and oxidative dimerization[6] and important compounds for medicinal chemistry.

Pyrazolin-5-ones and pyrazolidine-3,5-diones are known as anti-inflammatory drugs (Chart 1), neuroprotectants and antioxidants (Edaravone), antiviral,[7] antitumor,[8] fungicidal and bactericidal[9] compounds, HNO donors,[10] agonists of farnesoid X receptor,[11a] AT1 angiotensin II receptor antagonists,[11b] and Dyrk1A[11c] and UDP-*N*-acetylenolpyruvyl glucosamine reductase[11d] inhibitors.

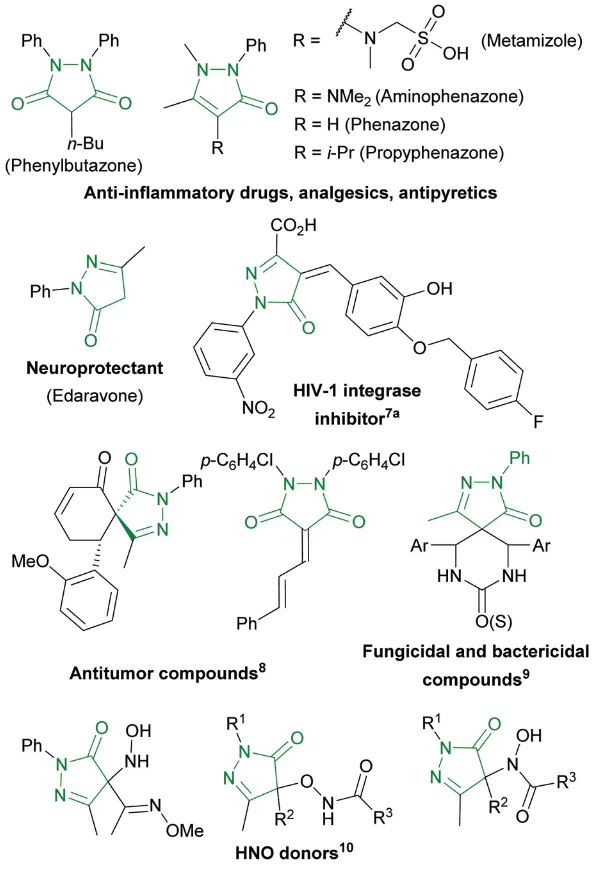
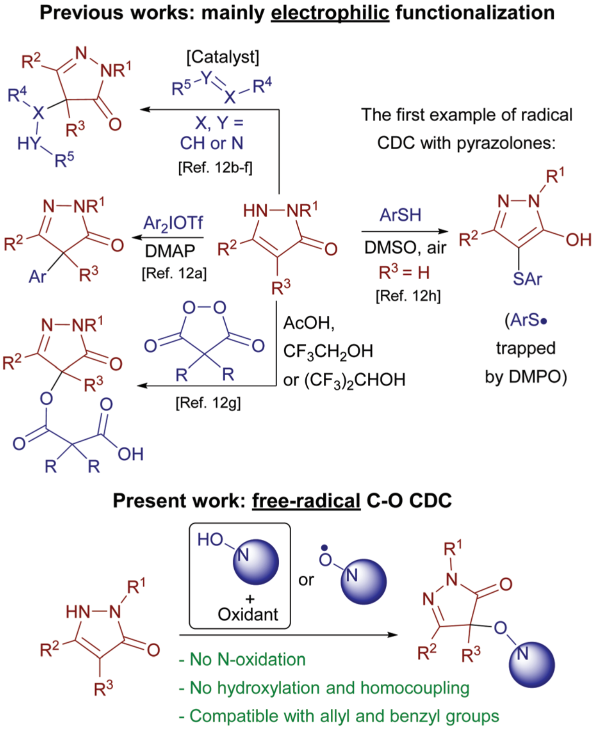


Chart 1 Examples of bioactive compounds and drugs with pyrazolone moiety.



Scheme 3 Methods for oxidative functionalization of pyrazolones.

Methods for pyrazolone functionalization have been intensively developed in the last few years, but almost all of them are conceptually based on the same principle, namely, electrophilic attack on position 4 of the heterocycle (Scheme 3).

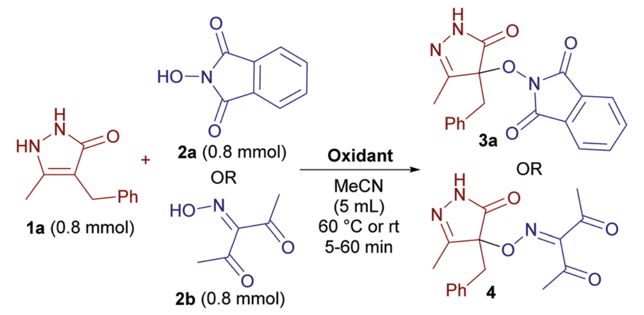
Diaryliodonium salts,[12a] nitroalkenes,[12b] 4-oxo-4-arylbutenoates,[12c] alkynones,[12d] azodicarboxylates,[12e] isatin-derived *N*-Boc ketimines[12f] and diacyl peroxides[12g] were used as electrophiles. A rare example of free-radical oxidative C–S coupling of pyrazolones with thiophenols was reported recently (Scheme 3).[12h] In the present study free-radical oxidative C–O coupling of pyrazolones with *N*-hydroxy compounds is reported (Scheme 3). Typical problems for O-centered radicals, harsh generation conditions and low selectivity, were successfully circumvented. A substantial insight into the nature of a free-radical coupling mechanism was achieved by the discovery of a new free-radical reagent, the diacetyliminoxyl radical, which previously was known as the only plausible intermediate.[5d]

Results and discussion

With 4-benzyl-3-methylpyrazolin-5-one **1a**, *N*-hydroxyphthalimide (NHPI) **2a** and 3-(hydroxyimino)-2,4-pentanedione **2b** as the model substrates, the influence of reaction parameters on the yield of C–O coupling products **3a** and **4** was studied (Table 1).

In contrast to the previously reported coupling of NHPI with β-dicarbonyl compounds,[5c] the reaction with pyrazolones

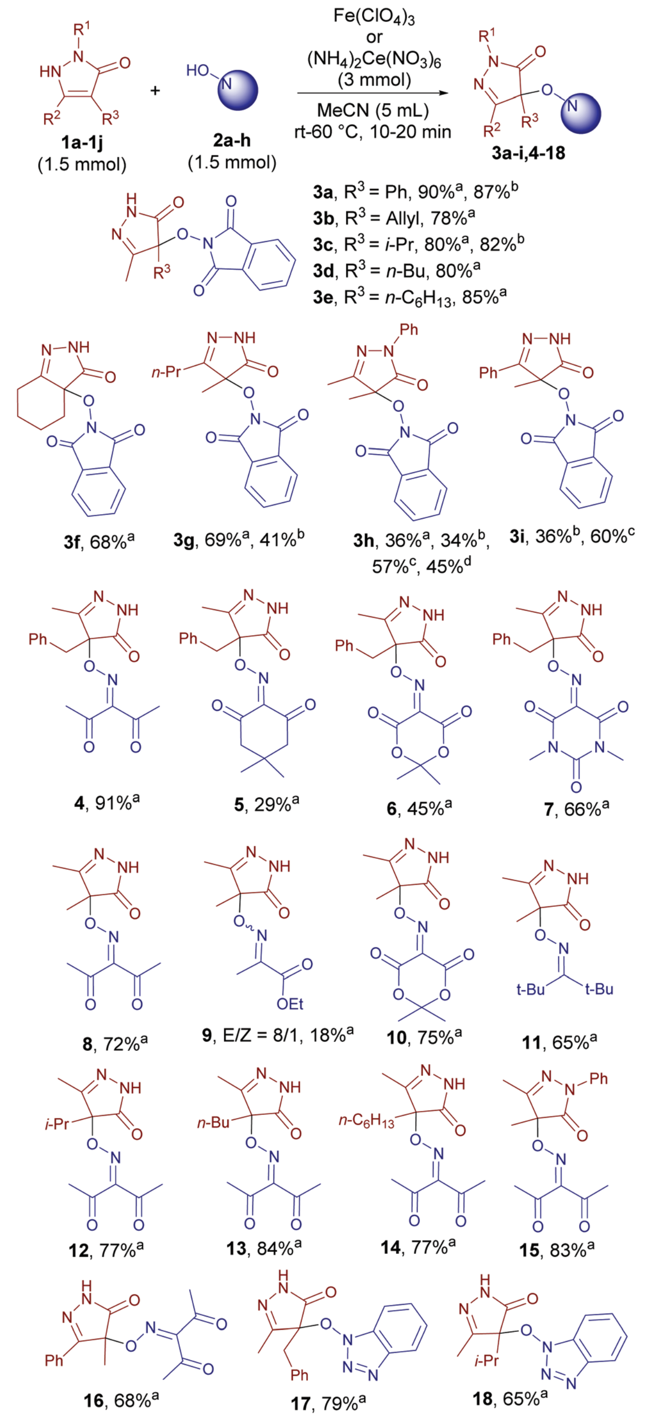
Table 1 Oxidant screening for the C–O coupling of pyrazolone **1a** with NHPI **2a** or oxime **2b**



Run	Oxidant (mol/mol of **1a**)	Time (min)	*T* (°C)	Yield (%)
Oxidative C–O coupling of 1a with NHPI 2a				
1	$Fe(ClO_4)_3 \cdot nH_2O$ (2)	10	60	90
2	$Fe(ClO_4)_3 \cdot nH_2O$ (2)	20	rt	72
3	$Fe(NO_3)_3 \cdot 9H_2O$ (2)	20	60	<5
4	$FeCl_3$ (2)	20	60	15
5	$(NH_4)_2Ce(NO_3)_6$ (2)	20	rt	87
6	$Pb(OAc)_4$ (1)	20	60	84
7	$PhI(OAc)_2$ (1)	20	60	69
8	$Cu(ClO_4)_2 \cdot 6H_2O$ (2)	20	60	24
9	$Mn(OAc)_3 \cdot 2H_2O$ (2)[a]	20	60	9
10	$KMnO_4$ (0.4)[a]	20	60	35
Oxidative C–O coupling of 1a with oxime 2b				
11	$Fe(ClO_4)_3 \cdot nH_2O$ (2)	10	60	91
12	$Fe(ClO_4)_3 \cdot nH_2O$ (2)	20	rt	90
13	$Fe(ClO_4)_3 \cdot nH_2O$ (2)	5	rt	69
14	$KMnO_4$ (0.4)[a]	10	60	85
15	$Mn(OAc)_3 \cdot 2H_2O$ (2)[a]	10	60	52
16	$Mn(OAc)_3 \cdot 2H_2O$ (2)	60	60	20
17	$Cu(ClO_4)_2 \cdot 6H_2O$ (2)	10	60	36
18	$(NH_4)_2Ce(NO_3)_6$ (2)	10	60	24
19	$Pb(OAc)_4$ (1)	10	60	43
20	$PhI(OAc)_2$ (1)	10	60	30

[a] AcOH was used as the solvent.

Table 2 The scope of pyrazolones **1** and *N*-hydroxy compounds **2** for oxidative C–O coupling



[a] $Fe(ClO_4)_3$ was added to a stirred mixture of pyrazolone and *N*-hydroxy compound at 60 °C, reaction time was 10 min [b] $(NH_4)_2Ce(NO_3)_6$ was added to a stirred mixture of pyrazolone and NHPI at room temperature, reaction time was 20 min [c] Mixing order changed: pyrazolone **1h–i** was added portion wise to the stirred mixture of NHPI and $(NH_4)_2Ce(NO_3)_6$ in MeCN at room temperature. [d] Mixing order changed: pyrazolone **1h** was added portion wise to the stirred mixture of NHPI and $Fe(ClO_4)_3$ in MeCN at 60 °C.

proceeds under the action of either single-electron oxidants ($Fe(ClO_4)_3$, $(NH_4)_2Ce(NO_3)_6$, runs 1, 2, and 5) or two-electron oxidants ($Pb(OAc)_4$, $PhI(OAc)_2$, runs 6 and 7). The highest yield was obtained with $Fe(ClO_4)_3$ (run 1, 90%), whereas iron(III) chloride and nitrate were inefficient (entries 3 and 4). Low yields were observed with $Cu(ClO_4)_2$ and manganese based oxidants (runs 8–10).

When oxime **2b** was used instead of NHPI **2a**, a different order of oxidant efficacy was observed (runs 11–20), $Fe(ClO_4)_3$ being still the best. In the case of $(NH_4)_2Ce(NO_3)_6$, the low yield of **4** can be attributed to the instability of iminoxyl radicals derived from oxime **2b** in the presence of $(NH_4)_2Ce(NO_3)_6$.[5d]

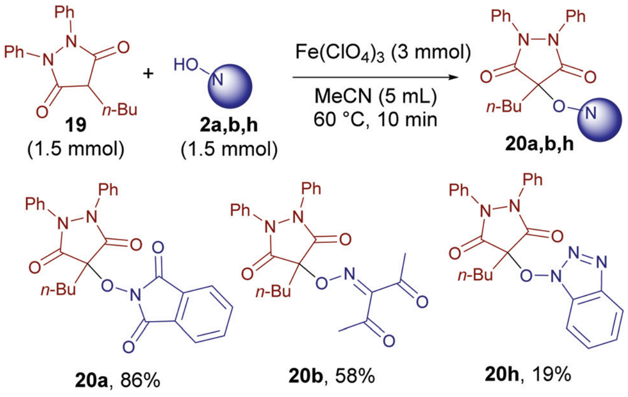
With the optimized conditions in hand we tested the scope of the discovered coupling (Table 2). Under universal reaction conditions ($Fe(ClO_4)_3$ as the oxidant, 60 °C, 10 min) pyrazolin-5-ones **1** reacted smoothly with *N*-hydroxy compounds of different classes: NHPI (products **3a–3i**), oximes (products **4–16**), and *N*-hydroxybenzotriazole (products **17–18**). Lower yields were obtained in the reaction of NHPI with pyrazolones containing a phenyl substituent (products **3h** and **3i**). We proposed that these pyrazolones are oxidized faster than NHPI with the formation of side products. Indeed, when the reagent addition order was changed and NHPI was mixed with an oxidant to generate *N*-oxyl radicals before the addition of pyrazolones, the yields of products **3h** and **3i** substantially increased (Table 2, yields with notes c and d).

In the row of *N*-hydroxy compounds the yield depends on the stability of the corresponding *N*-oxyl radicals. The lowest yield was obtained with the oxime of ethyl pyruvate (18%, product **9**).

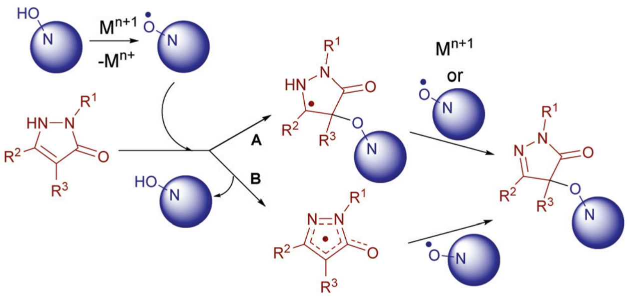
Pyrazolidine-3,5-dione **19**, known as the anti-inflammatory drug phenylbutazone, reacts with NOH-compounds **2** analogously to pyrazolin-5-ones **1** (Scheme 4).

A plausible mechanism of the oxidative coupling of pyrazolones with *N*-hydroxy compounds is depicted in Scheme 5. *N*-Oxyl radicals are generated from *N*-hydroxy compounds under the action of an oxidant. Then two sequences are possible: the attack of an *N*-oxyl radical on pyrazolone (**A**) followed by oxidation or oxidation of pyrazolone (**B**) followed by the addition of the radical.

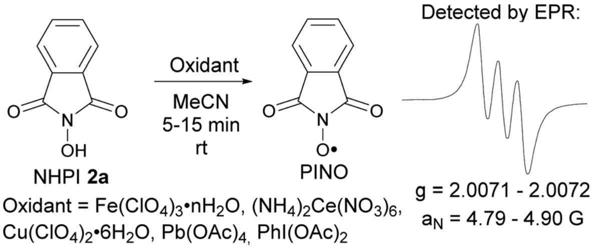
The formation of *N*-oxyl radicals from NHPI under the action of used oxidants was confirmed by EPR spectroscopy (Scheme 6 and ESI†). The formation of iminoxyl radicals from oxime **2b** under analogous conditions was reported earlier.[5d]



Scheme 4 The oxidative C–O coupling of pyrazolidine-3,5-dione **19** with *N*-hydroxy compounds **2a**, **b**, and **h**.



Scheme 5 Possible pathways of the oxidative C–O coupling of pyrazolones with *N*-hydroxy compounds.



Scheme 6 Generation of phthalimide-*N*-oxyl radicals (PINO) from NHPI.

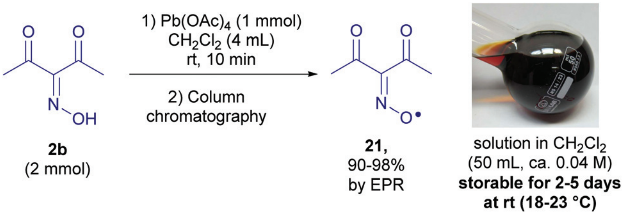
Diacetyliminoxyl free radical

The detection of a free radical under the reaction conditions does not prove its participation in the process and does not reveal its exact role. It is desirable to directly observe the "individual" reactivity of radicals in the absence of other reagents, such as oxidants used for their generation, which is usually impossible due to the high reactivity of free radicals, including sterically unhindered *N*-oxyl radicals with acceptor groups. To solve this problem, a method for the synthesis of diacetyliminoxyl radical **21**,[13] a plausible intermediate, was developed (Scheme 7).

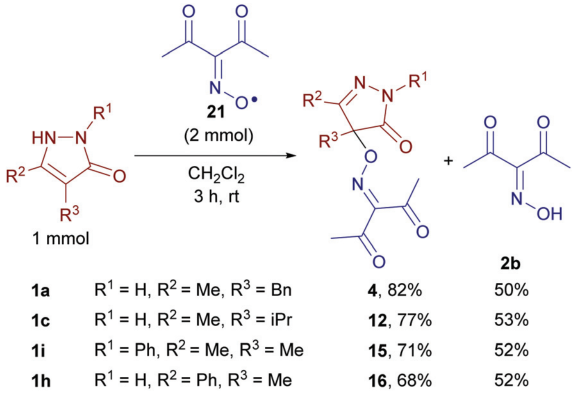
Oxidation of **2b** with $Pb(OAc)_4$ gave rise to oxime radical **21** with almost quantitative yield based on EPR (see the ESI†). Radical **21** turned out to be surprisingly stable despite being sterically unhindered; it tolerated column chromatography on silica gel and the resulting dark red solution of **21** in CH_2Cl_2 (*ca.* 0.04 M) was stored at room temperature for 2–5 days without a significant decomposition detectable by EPR or FTIR spectroscopy. As far as we know it is record stability for the unhindered oxime radical that was not reported previously.[13]

Oxime radical **21** reacted with pyrazolones **1a**, **c**, **i**, and **h** giving C–O coupling products **4**, **12**, **15**, and **16**, respectively, and oxime **2b** (Scheme 8). Apparently, one equivalent of **21** formed the product and another one played the role of the oxidant. The yields are close to that obtained with *in situ* generation of iminoxyl radicals using $Fe(ClO_4)_3$ (see Table 2). These results are convincing evidence in favor of the mechanism depicted in Scheme 5.

It should be noted that the structure of the synthesized radical **21** has little in common with known stable *N*-oxyl radicals (Chart 2). The majority of the stable *N*-oxyl radicals are amine-*N*-oxyl radicals. Only some representatives of this extensive type of radicals are depicted. This class includes both



Scheme 7 Synthesis of diacetyliminoxyl radical **21**.



Scheme 8 The reaction of diacetyliminoxyl radical **21** with pyrazolin-5-ones.

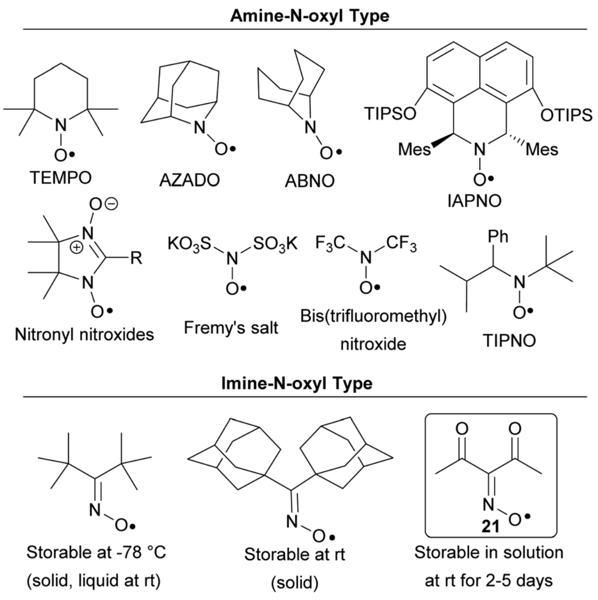
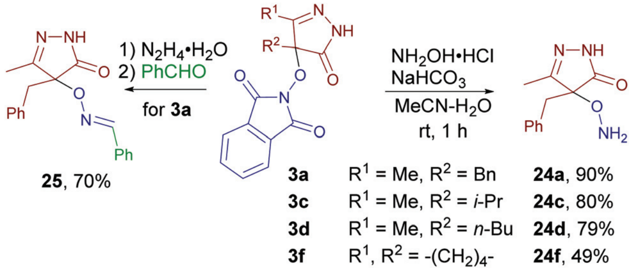


Chart 2 Examples of known stable *N*-oxyl radicals and synthesized radical **21**.

cyclic structures (TEMPO,[14] AZADO,[15] ABNO,[16] IAPNO,[17] nitronyl nitroxides[18]) and acyclic structures (Fremy's salt,[19] bis(trifluoromethyl)nitroxide,[20] TIPNO and others[21]). These *N*-oxyl radicals found wide use in various fields[22a,b] including oxidation processes,[15b,16a,17,22a–d] "living" radical polymerization,[21b,c,22a] spin-labeling[22e] and synthesis of magnetic materials.[18b,c,22f] Stable oxime radicals (imine-*N*-oxyl type) are very rare and highly hindered, examples are di-*tert*-butyliminoxyl radical and di(1-adamantyl)iminoxyl radical (Chart 2).[23] An important feature of radical **21** is its synthetic accessibility: the parent oxime can be prepared in one simple step from acetylacetone, $NaNO_2$ and H_2SO_4.[24]

Synthetic application of the coupling products

Finally, the synthetic utility of some of the synthesized products was tested (Scheme 9). Novel O-substituted hydroxylamines **24a**, **c**, **d**, and **f** were synthesized from products **3a**, **c**, **d**, and **f** without the need for chromatographic purification. In the case of the product **3a** one-pot deprotection/condensation sequence was demonstrated to obtain oxime ether **25**.



Scheme 9 The synthetic utility of the synthesized oxidative C–O coupling products.

Conclusions

In conclusion, a new type of oxidative C–O coupling was realized, the method was applied to a wide range of *N*-hydroxy compounds and pyrazolones. *N*-Oxyl radicals are identified as key intermediates that selectively add to position 4 of the pyrazolone ring. The first method for the synthesis of the diacetyliminoxyl radical in solution was proposed. This radical can be used as an easily available reagent and a model radical for mechanistic studies.

Experimental

Iron(III) perchlorate hydrate reagent grade (Alfa Aesar, anhydrous basis purity *ca.* 65%), $Fe(NO_3)_3\cdot 9H_2O$ 99+%, $FeCl_3$ 98% anhydrous, $(NH_4)_2Ce(NO_3)_6$ 99%, $Pb(OAc)_4$ 95%, $PhI(OAc)_2$ 98%, $Cu(ClO_4)_2\cdot 6H_2O$ 98%, $Mn(OAc)_3\cdot 2H_2O$ 95%, $KMnO_4$ 99%, *N*-hydroxyphthalimide 98%, *N*-hydroxybenzotriazole hydrate 98% (11–26% H_2O), 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) 98%, benzaldehyde 98+%, $N_2H_4\cdot H_2O$ (64% hydrazine), 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione (phenylbutazone) 99+%, $NH_2OH\cdot HCl$ 99%, and $NaHCO_3$ 99% were used as is from commercial sources. CH_2Cl_2 was distilled prior to use. MeCN and EtOAc were distilled over P_2O_5. Glacial acetic acid was used as is from commercial sources. Preparation of the starting pyrazolones and oximes is described in the ESI.†

General reaction conditions for oxidative C–O coupling of 1a with NHPI 2a (Table 1)

To a mixture of 4-benzyl-3-methylpyrazolin-5-one **1a** (150 mg, 0.797 mmol), *N*-hydroxyphthalimide **2a** (130 mg, 0.797 mmol) and solvent (5 mL) stirred at given temperature, an oxidant (50.4–874 mg, 0.4–2 mol/mol of **1a**) was added for 5–20 seconds; stirring was continued at the same temperature for 20 min

The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and water (20 mL) and shaken.

The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and all organic extracts were combined. In the case of an intensive color of extract indicative of the presence of metal complexes, it was additionally washed with an aqueous solution of $Na_2S_2O_4$ (200 mg in 20 mL of water). Organic extract was washed with water (2 × 20 mL), dried over Na_2SO_4, and rotary evaporated under water-jet vacuum. C–O coupling product **3a** was isolated by column chromatography on silica gel using the EtOAc/CH_2Cl_2 eluent; the volume part of EtOAc was gradually increased from 0 to 20%.

4-Benzyl-3-methyl-4-(phthalimide-*N*-oxy)pyrazolin-5-one 3a. White powder, mp = 176–177 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 8.18 (bs, 1H), 7.93–7.82 (m, 2H), 7.82–7.72 (m, 2H), 7.32–7.15 (m, 5H), 3.55 (d, J = 13.1 Hz, 1H), 3.43 (d, J = 13.1 Hz, 1H), 2.27 (s, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 171.0, 163.8, 157.5, 135.0, 131.2, 130.0, 128.9, 128.8, 127.9, 124.1, 87.8, 38.3, 14.7. IR (KBr) ν(cm^{-1}): 3200, 3108, 1802, 1751, 1370, 1359, 1342, 1309, 1187, 1070, 1015, 1002, 952, 872, 745, 700, 566, 558, 520. Elemental analysis calcd (%) for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03. Found: C, 65.14; H, 4.31; N, 11.94.

General reaction conditions for oxidative C–O coupling of 1a with oxime 2b (Table 1)

To a mixture of 4-benzyl-3-methylpyrazolin-5-one **1a** (150 mg, 0.797 mmol), 3-(hydroxyimino)-2,4-pentanedione **2b** (103 mg, 0.797 mmol) and solvent (5 mL) stirred at 60 °C, an oxidant (50.4–874 mg, 0.4–2 mol/mol **1a**) was added for 5–20 seconds; stirring was continued at 60 °C for 10 min. The coupling product **4** was isolated as described above for **3a**.

3-(((4-Benzyl-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)oxy)imino)pentane-2,4-dione 4. White powder, mp = 139–140 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 8.26 (bs, 1H), 7.35–7.22 (m, 3H), 7.22–7.09 (m, 2H), 3.26 (d, J = 13.4 Hz, 1H), 3.17 (d, J = 13.4 Hz, 1H), 2.41 (s, 3H), 2.28 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 197.0, 193.5, 173.4, 158.7, 158.3, 131.0, 130.0, 128.8, 128.1, 87.3, 38.0, 30.7, 25.9, 14.1. IR (KBr) ν(cm^{-1}): 3178, 3114, 1734, 1692, 1366, 1298, 1049, 1017, 1009, 942, 755, 700. Elemental analysis calcd (%) for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.91; H, 5.39; N, 13.41.

General reaction conditions for Table 2 and Scheme 4

General procedure a (all experiments in Scheme 4 and experiments in Table 2 **with note** a**):** to a mixture of pyrazolone (1.5 mmol), *N*-hydroxy compound (1.5 mmol) and MeCN (5 mL) stirred at 60 °C, $Fe(ClO_4)_4 \cdot nH_2O$ (3 mmol) was added; stirring was continued for 10 min at 60 °C.

General procedure b (experiments in Table 2 with note b**):** to a mixture of pyrazolone (1.5 mmol), *N*-hydroxy compound (1.5 mmol) and MeCN (5 mL) stirred at room temperature, $(NH_4)_2Ce(NO_3)_6$ (3 mmol) was added; stirring was continued for 20 min at room temperature.

General procedure c (experiments in Table 2 with note c**):** to a mixture of *N*-hydroxyphthalimide (1.5 mmol) and MeCN (5 mL) stirred at room temperature, $(NH_4)_2Ce(NO_3)_6$ (3 mmol) was added for 5–10 seconds, stirring was continued for 4 min, and then pyrazolone (1.5 mmol) was added portion wise for 7–10 min; after the complete addition of pyrazolone, stirring was continued for 5 min at room temperature.

General procedure d (experiments in Table 2 **with note** d**):** to a mixture of *N*-hydroxyphthalimide (1.5 mmol) and MeCN (5 mL) stirred at 60 °C, $Fe(ClO_4)_4 \cdot nH_2O$ (3 mmol) was added for 5–10 seconds, and then pyrazolone (1.5 mmol) was added portion wise for 1 min; stirring was continued for 5 min at 60 °C.

The products **3a–i**, **4–18**, **20a**, **b**, and **h** were isolated as described for **3a** in experiment in Table 1.

4-Allyl-3-methyl-4-(phthalimide-*N*-oxy)pyrazolin-5-one 3b. White powder, mp = 154–155 °C. ^{1}H NMR (300.13 MHz, DMSO-d$_6$) δ: 11.29 (bs, 1H), 7.89 (m, 4H), 5.56–5.33 (m, 1H), 5.25 (d, J = 16.7 Hz, 1H), 5.15 (d, J = 10.3 Hz, 1H), 2.87 (dd, J_1 = 7.0 Hz, J_2 = 12.9 Hz, 1H), 2.74 (dd, J_1 = 7.0 Hz, J_2 = 12.9 Hz, 1H), 2.12 (s, 3H). ^{13}C NMR (75.47 MHz, DMSO-d$_6$) δ: 170.4, 163.3, 155.9, 135.2, 128.3, 123.6, 121.4, 86.1, 35.6, 13.8. IR (KBr) ν(cm^{-1}): 3374, 1795, 1750, 1732, 1367, 1350, 1308, 875, 711, 700. HR-MS (ESI): m/z = 322.0786, calcd for $C_{15}H_{13}N_3O_4 + Na^+$: 322.0798.

4-(Isopropyl)-3-methyl-4-(phthalimide-*N*-oxy)pyrazolin-5-one 3c. White powder, mp = 188–188.5 °C. ^{1}H NMR (300.13 MHz, DMSO-d$_6$) δ: 11.15 (bs, 1H), 7.87 (m, 4H), 2.43–2.22 (m, 1H), 2.13 (s, 3H), 1.08 (d, J = 6.7 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75.47 MHz, DMSO-d$_6$) δ: 170.4, 163.0, 156.7, 135.2, 128.1, 123.5, 90.3, 31.1, 15.9, 14.62, 14.57. IR (KBr) ν(cm^{-1}): 3297, 1796, 1748, 1731, 1467, 1375, 1349, 1188, 1055, 992, 874, 708. Elemental analysis calcd (%) for $C_{15}H_{15}N_3O_4$: C, 59.80; H, 5.02; N, 13.95. Found: C, 59.51; H, 5.09; N, 14.07.

4-(Butyl)-3-methyl-4-(phthalimide-*N*-oxy)pyrazolin-5-one 3d. White powder, mp = 168–168.5 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 8.48 (bs, 1H), 7.88–7.78 (m, 2H), 7.78–7.70 (m, 2H), 2.25–2.11 (m, 1H), 2.22 (s, 3H), 2.03 (td, J_t = 12.5, J_d = 4.9, 1H), 1.45–1.26 (m, 2H), 1.26–0.98 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 171.4, 163.8, 158.3, 134.9, 129.0, 124.0, 87.8, 31.4, 24.4, 22.7, 14.0, 13.8. IR (KBr) ν(cm^{-1}): 3303, 1794, 1752, 1467, 1377, 1351, 1314, 1188, 1017, 1001, 944, 876, 707, 650, 630, 606, 562, 520. Elemental analysis calcd (%) for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.93; H, 5.40; N, 13.18.

4-(Hexyl)-3-methyl-4-(phthalimide-*N*-oxy)pyrazolin-5-one 3e. White powder, mp = 121–122 °C. ^{1}H NMR (300.13 MHz, DMSO-d$_6$) δ: 11.27 (bs, 1H), 7.88 (m, 4H), 2.10 (s, 3H), 2.04–1.91 (m, 2H), 1.38–1.13 (m, 6H), 1.13–0.91 (m, 2H), 0.84 (t, J = 6.4 Hz, 3H). ^{13}C NMR (75.47 MHz, DMSO-d$_6$) δ: 170.9, 163.3, 156.5, 135.1, 128.3, 123.5, 87.2, 30.9, 30.8, 28.4, 21.8, 21.7, 13.8, 13.5. IR (KBr) ν(cm^{-1}): 3219, 2961, 2929, 1799, 1740, 1468, 1456, 1439, 1363, 1346, 1303, 1188, 1075, 1016, 994, 939, 874, 753, 707, 563, 521. HR-MS (ESI): m/z = 366.1417, calcd for $C_{18}H_{21}N_3O_4 + Na^+$: 366.1424.

2-((3-Oxo-2,3,4,5,6,7-hexahydro-3aH-indazol-3a-yl)oxy)isoindoline-1,3-dione 3f. White powder, mp = 180–182 °C. ^{1}H NMR (300.13 MHz, DMSO-d$_6$) δ: 11.25 (bs, 1H), 7.87 (m, 4H), 2.73–2.40 (m, 2H), 2.40–2.20 (m, 1H), 2.17–1.90 (m, 2H), 1.81–1.62 (m, 1H), 1.62–1.25 (m, 2H). ^{13}C NMR (75.47 MHz, DMSO-d$_6$) δ: 171.6, 163.3, 159.0, 135.2, 128.3, 123.6, 82.8, 32.5, 27.3, 27.0, 19.7. IR (KBr) ν(cm^{-1}): 3187, 1796, 1739, 1713, 1363, 1347, 1308, 1187, 1104, 1015, 1000, 956, 875, 791, 748, 705, 676, 606, 563, 521. HR-MS (ESI): m/z = 300.0988, calcd for $C_{15}H_{13}N_3O_4 + H^+$: 300.0979.

2-((4-Methyl-5-oxo-3-propyl-4,5-dihydro-1*H*-pyrazol-4-yl)oxy)isoindoline-1,3-dione 3g. White powder, mp = 156.5–157.5 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 8.61 (bs, 1H), 7.94–7.64 (m, 4H), 2.77–2.61 (m, 1H), 2.51–2.35 (m, 1H), 1.85–1.68 (m, 2H), 1.65 (s, 3H), 1.03 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 172.2, 163.9, 161.6, 134.9, 129.0, 124.0, 84.3, 29.7, 18.6, 18.1, 14.0. IR (KBr) ν(cm^{-1}): 3270, 1795, 1742, 1709, 1468, 1368, 1355, 1311, 1187, 1162, 1109, 1076, 975, 874, 752, 702, 671, 650, 607, 588, 565, 520. Elemental analysis calcd (%) for $C_{15}H_{15}N_3O_4$: C, 59.80; H, 5.02; N, 13.95. Found: C, 59.83; H, 4.93; N, 13.90.

3,4-Dimethyl-1-phenyl-4-(phthalimide-*N*-oxy)pyrazolin-5-one 3h. White powder, mp = 133–136 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 7.91–7.78 (m, 4H), 7.78–7.68 (m, 2H), 7.36 (t, J = 7.9 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H), 2.37 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 168.0, 163.9, 158.5, 137.6, 134.9, 129.0, 125.5, 124.1, 118.9, 86.6, 18.4, 13.7. IR (KBr) ν(cm^{-1}): 1792, 1747, 1720, 1595, 1499, 1465, 1399, 1364, 1311, 1186, 1146, 1121, 1080, 1065, 962, 876, 763, 751, 704, 690, 573, 519. HR-MS (ESI): m/z = 372.0942, calcd for $C_{19}H_{15}N_3O_4 + Na^+$: 372.0955.

4-Methyl-3-phenyl-4-(phthalimide-*N*-oxy)pyrazolin-5-one 3i. White powder, mp = 206–208 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 11.91 (bs, 1H), 8.09–7.94 (m, 2H), 7.94–7.79 (m, 4H), 7.62–7.39 (m, 3H), 1.75 (s, 3H, CH_3). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 171.8, 163.4, 154.7, 135.1, 130.3, 129.5, 128.8, 128.4, 126.1, 123.5, 83.7, 19.3. IR (KBr) ν(cm^{-1}): 3281, 1743, 1733, 1720, 1372, 1362, 1349, 1188, 1083, 970, 876, 771, 696, 649, 520. HR-MS (ESI): m/z = 358.0794, calcd for $C_{18}H_{13}N_3O_4 + Na^+$: 358.0798.

2-(((4-Benzyl-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)oxy)imino)-5,5-dimethylcyclohexane-1,3-dione 5. Slightly yellow powder, mp = 145–147 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 8.22 (s, 1H), 7.29 (m, 5H), 3.44–3.09 (m, 2H), 2.92–2.43 (m, 4H), 1.95 (s, 3H), 1.18 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 192.4, 190.3, 173.8, 158.9, 151.2, 131.6, 130.2, 128.7, 127.9, 88.3, 55.2, 54.3, 38.2, 30.5, 29.6, 27.7, 14.3. IR (KBr) ν(cm^{-1}): 3356, 3321, 1735, 1693, 1620, 1570, 1255, 1213, 1030, 1006, 989, 957, 758, 730, 699, 632, 598, 578, 571, 555. Elemental analysis calcd (%) for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.82. Found: C, 63.98; H, 5.78; N, 11.72.

5-(((4-Benzyl-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)oxy)imino)-2,2-dimethyl-1,3-dioxane-4,6-dione 6. Slightly yellow powder, mp = 150–152 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 8.27 (bs, 1H), 7.40–7.15 (m, 5H), 3.49–3.28 (m, 2H), 1.98 (s, 3H), 1.83 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 172.9, 157.9, 155.8, 150.7, 136.7, 131.0, 130.2, 128.8, 128.2, 116.7, 106.5, 89.5, 38.0, 28.8, 27.7, 14.3. IR (KBr) ν(cm^{-1}): 3231, 1782, 1756, 1730, 1577, 1395, 1385, 1301, 1268, 1240, 1227, 1201, 1085, 1044, 1020, 976, 932, 891, 758, 729, 702. Elemental analysis calcd (%) for $C_{17}H_{17}N_3O_6$: C, 56.82; H, 4.77; N, 11.69. Found: C, 56.71; H, 4.70; N, 11.59.

5-(((4-Benzyl-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)oxy)imino)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 7. White powder, mp = 164–166 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 11.10 (s, 1H), 7.52–7.10 (m, 5H), 3.49–3.05 (m, 2H), 3.17 (s, 3H), 3.15 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 173.0, 157.2, 156.7, 152.7, 150.4, 137.2, 132.0, 130.1, 128.2, 127.4, 88.6, 36.9, 28.4, 27.9, 13.7. IR (KBr) ν(cm^{-1}): 3308, 1740, 1692, 1676, 1450, 1419, 1378, 1292, 1051, 1011, 927, 749. Elemental analysis calcd (%) for $C_{17}H_{17}N_5O_5$: C, 54.98; H, 4.61; N, 18.86. Found: C, 54.90; H, 4.63; N, 18.83.

3-(((3,4-Dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)oxy)imino)pentane-2,4-dione 8. White powder, mp = 106–107 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 11.25 (bs, 1H), 2.33 (s, 3H), 2.21 (s, 3H), 1.96 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 197.6, 193.1, 173.8, 158.5, 157.3, 83.6, 30.1, 25.4, 16.9, 12.6. IR (KBr) ν(cm^{-1}): 3322, 1742, 1716, 1687, 1364, 1298, 1204, 1190, 1125, 1067, 964, 929, 681, 619, 583, 564. Elemental analysis calcd (%) for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.48; N, 17.57. Found: C, 50.08; H, 5.20; N, 17.48.

Ethyl 2-(((3,4-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)oxy)imino)propanoate 9. Mixture of *E* and *Z* isomers, *E*/*Z* = 8/1; configuration was determined by NOESY, NMR signal assignment was made based on the HMBC NMR experiment (see the ESI†). White powder, mp = 82–85 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): major *E* isomer δ: 11.07 (bs, 1H, NH), 4.24–4.13 (m, 2H, OCH_2), 2.04 (s, 3H, $\underline{CH_3}$–C═N–O), 1.89 (s, 3H, $\underline{CH_3}$–C═N–NH), 1.40 (s, 3H, $\underline{CH_3}$–C–O–N), 1.21 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$–CH_2); minor *Z* isomer δ: 11.02 (bs, 1H, NH), 4.37–4.24 (m, 2H, OCH_2), 1.95 (s, 3H, $\underline{CH_3}$–C═N–O), 1.88 (s, 3H, $\underline{CH_3}$–C═N–NH), 1.27 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$–CH_2), 1.26 (s, 3H, $\underline{CH_3}$–C–O–N). ^{13}C NMR (75.47 MHz, DMSO-d_6): major *E* isomer δ: 174.6 (HN–$\underline{C}$═O), 162.4 (O–$\underline{C}$═O), 159.2 ($\underline{C}$═N–NH), 152.0 ($\underline{C}$═N–O), 82.6 ($\underline{C}$–O–N), 61.5 (O$\underline{C}H_2$), 17.4, 13.9, 12.5, 11.6 (CH_3); minor *Z* isomer δ: 17.1, 16.2, 12.4. IR (KBr) ν(cm^{-1}): 3222, 1717, 1432, 1374, 1329, 1308, 1204, 1178, 1151, 1124, 1006, 932, 863, 754, 673, 570. Elemental analysis calcd (%) for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.71; H, 6.25; N, 17.40.

5-(((3,4-Dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)oxy)imino)-2,2-dimethyl-1,3-dioxane-4,6-dione 10. White powder, mp = 143–146 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 11.31 (bs, 1H), 1.95 (s, 3H), 1.71 (s, 3H), 1.70 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 173.5, 158.2, 156.0, 150.5, 137.1, 105.9, 85.4, 27.6, 27.4, 16.9, 12.6. IR (KBr) ν(cm^{-1}): 3330, 1778, 1738, 1570, 1399, 1387, 1373, 1314, 1296, 1271, 1244, 1197, 1157, 1110, 1057, 1036, 984, 952, 911, 894, 794, 638, 629, 568. Elemental analysis calcd (%) for $C_{11}H_{13}N_3O_6$: C, 46.65; H, 4.63; N, 14.84. Found: C, 46.40; H, 4.43; N, 14.80.

4,5-Dimethyl-4-(((2,2,4,4-tetramethylpentan-3-ylidene)amino)oxy)-2,4-dihydro-3*H*-pyrazol-3-one 11. White powder, mp = 143–144 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 8.22 (bs, 1H), 1.96 (s, 3H), 1.44 (s, 9H), 1.39 (s, 3H), 1.12 (s, 9H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 176.7, 171.2, 162.3, 82.1, 40.7, 38.8, 29.9, 29.8, 17.6, 13.1. IR (KBr) ν(cm^{-1}): 3215, 3104, 3010, 2991, 2975, 2956, 2931, 2872, 1710, 1625, 1482, 1448, 1433, 1392, 1381, 1369, 1311, 1195, 1122, 1075, 1024, 970, 892, 868, 746, 673, 574. Elemental analysis calcd (%) for $C_{14}H_{25}N_3O_2$: C, 62.89; H, 9.43; N, 15.72. Found: C, 62.83; H, 9.56; N, 15.55.

3-(((4-Isopropyl-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)oxy)imino)pentane-2,4-dione 12. Slightly yellow viscous gum. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 8.64 (bs, 1H), 2.38 (s, 3H), 2.33–2.15 (m, 1H), 2.27 (s, 3H), 1.98 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 197.0, 193.6, 173.7, 159.2, 158.1, 89.4, 31.0, 30.5, 25.8, 16.0, 14.6, 14.1. IR (thin layer) ν(cm^{-1}): 3280, 2975, 2940, 2923, 1727, 1696, 1609, 1469, 1421, 1392, 1364, 1295, 1192, 1089, 1051, 1004, 944, 756, 718, 690, 678, 629, 615, 569, 548. Elemental analysis calcd (%) for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.80; H, 6.48; N, 15.68.

3-(((4-Butyl-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)oxy)imino)pentane-2,4-dione 13. White powder, mp = 42–43 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 8.30 (bs, 1H), 2.38 (s, 3H), 2.28 (s, 3H), 2.04–1.89 (m, 1H), 2.00 (s, 3H), 1.87–1.72 (m, 1H), 1.44–1.10 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 197.0, 193.6, 174.0, 159.5, 158.1, 87.2, 31.1, 30.6, 25.9, 23.8, 22.7, 13.8, 13.4. IR (KBr) ν(cm^{-1}): 3267, 2961, 2934, 2874, 1729, 1697, 1421, 1364, 1293, 1185, 1082, 1047, 1008, 982, 936, 697, 620, 586, 567. Elemental analysis calcd (%) for $C_{13}H_{19}N_3O_4$: C, 55.51; H, 6.81; N, 14.94. Found: C, 55.25; H, 6.97; N, 14.70.

3-(((4-Hexyl-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)oxy)imino)pentane-2,4-dione 14. White powder, mp = 62–63 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 8.44 (bs, 1H), 2.37 (s, 3H), 2.27 (s, 3H), 2.05–1.89 (m, 1H), 2.00 (s, 4H), 1.86–1.71 (m, 1H), 1.39–1.12 (m, 8H), 0.86 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 197.0, 193.6, 174.0, 159.5, 158.1, 87.2, 31.43, 31.37, 30.6, 29.2, 25.9, 22.5, 21.7, 14.1, 13.4. IR (KBr) ν(cm^{-1}): 3204, 3120, 2955, 2932, 2860, 1729, 1696, 1459, 1427, 1385, 1363, 1293, 1183, 1082, 1062, 1050, 1021, 1003, 935, 767, 717, 620, 591, 563, 542. Elemental analysis calcd (%) for $C_{15}H_{23}N_3O_4$: C, 58.24; H, 7.49; N, 13.58. Found: C, 58.10; H, 7.55; N, 13.49.

3-(((3,4-Dimethyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)oxy)imino)pentane-2,4-dione 15. Slightly yellow gum. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 7.92–7.84 (m, 2H), 7.48–7.37 (m, 2H), 7.25–7.17 (m, 1H), 2.40 (s, 3H), 2.20 (s, 3H), 2.15 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 197.0, 193.5, 170.2, 159.8, 158.1, 137.7, 129.1, 125.6, 118.8, 86.0, 30.6, 25.9, 17.8, 13.0. IR (thin layer) ν(cm^{-1}): 1728, 1697, 1596, 1502, 1398, 1367, 1312, 1293, 1239, 1194, 1151, 1119, 1090, 1066, 1023, 968, 929, 907, 759, 692. HR-MS (ESI): *m*/*z* = 338.1112, calcd for $C_{16}H_{17}N_3O_4 + Na^+$: 338.1111.

3-(((4-Methyl-5-oxo-3-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)oxy)imino)pentane-2,4-dione 16. White powder, mp = 112–113 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 8.93 (bs, 1H), 7.84–7.70 (m, 2H), 7.52–7.34 (m, 3H), 2.43 (s, 3H), 2.20 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 197.0, 193.7, 174.5, 158.0, 157.8, 131.0, 129.2, 129.1, 126.2, 84.4, 30.8, 25.9, 19.7. IR (KBr) ν(cm^{-1}): 3200, 3120, 1736, 1708, 1691, 1630, 1359, 1297, 1216, 1118, 982, 754, 723, 695, 635, 618, 552, 516. HR-MS (ESI): *m*/*z* = 324.0952, calcd for $C_{15}H_{15}N_3O_4 + Na^+$: 324.0955.

4-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)oxy)-4-benzyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one 17. Slightly yellow powder, mp = 158–161 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 11.09 (s, 1H), 8.08–8.01 (m, 1H), 7.91–7.83 (m, 1H), 7.71–7.61 (m, 1H), 7.52–7.43 (m, 1H), 7.39–7.24 (m, 5H), 3.65 (d, *J* = 12.9 Hz, 1H), 3.50 (d, *J* = 12.9 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 170.6, 156.0, 142.1, 131.0, 130.0, 128.8, 128.5, 127.8, 127.7, 125.4, 119.5, 110.3, 90.8, 36.8, 14.4. IR (KBr) ν(cm^{-1}): 3294, 1743, 1711, 1081, 993, 769, 754, 744, 731, 697, 672, 637, 569. Elemental analysis calcd (%) for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79. Found: C, 63.16; H, 4.38; N, 21.50.

4-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)oxy)-4-isopropyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one 18. White powder, mp = 110–111 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 8.28 (bs, 1H), 7.95–7.86 (m, 1H), 7.84–7.75 (m, 1H), 7.54–7.43 (m, 1H), 7.40–7.29 (m, 1H), 2.66–2.46 (m, 1H), 2.42 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 171.1, 158.5, 143.0, 128.6, 125.1, 119.9, 110.5, 92.7, 31.9, 16.1, 15.1, 14.5. IR (KBr) ν(cm^{-1}): 3309, 3124, 2973, 1734, 1726, 1704, 1467, 1445, 1379, 1281, 1240, 1196, 1157, 1100, 1073, 1042, 996, 784, 766, 745, 687, 638, 622, 573, 545, 431. Elemental analysis calcd (%) for $C_{13}H_{15}N_5O_2$: C, 57.13; H, 5.53; N, 25.63. Found: C, 57.03; H, 5.48; N, 25.58.

2-((4-Butyl-3,5-dioxo-1,2-diphenylpyrazolidin-4-yl)oxy)isoindoline-1,3-dione 20a. Slightly yellow powder, mp = 156–158 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 7.89–7.80 (m, 2H), 7.80–7.72 (m, 2H), 7.43–7.14 (m, 10H), 2.52–2.34 (m, 2H), 1.54–1.33 (m, 4H), 0.93 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 165.3, 163.4, 135.0, 134.8, 129.2, 128.9, 127.7, 124.0, 123.6, 83.7, 33.0, 24.9, 22.8, 13.8. IR (KBr) ν(cm^{-1}): 1794, 1762, 1741, 1726, 1594, 1493, 1372, 1353, 1319, 1295, 1265, 1188, 1175, 1125, 980, 877, 755, 744, 708, 691, 523. Elemental analysis calcd (%) for $C_{27}H_{23}N_3O_5$: C, 69.07; H, 4.94; N, 8.95. Found: C, 68.69; H, 5.01; N, 8.91.

4-Butyl-4-(((2,4-dioxopentan-3-ylidene)amino)oxy)-1,2-diphenylpyrazolidine-3,5-dione 20b. Slightly yellow powder, mp = 47–49 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 7.45–7.31 (m, 8H), 7.30–7.20 (m 2H), 2.41 (s, 3H), 2.25 (s, 3H), 2.22–2.12 (m, 2H), 1.54–1.30 (m, 4H), 0.91 (t, *J* = 6.7 H, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 196.0, 193.0, 168.0, 157.9, 135.4, 129.3, 127.5, 122.5, 83.8, 32.8, 30.6, 26.0, 24.3, 22.7, 13.7. IR (KBr) ν(cm^{-1}): 2960, 2932, 1768, 1732, 1696, 1596, 1488, 1460, 1420, 1360, 1292, 1176, 1104, 1084, 1048, 1024, 1004, 928, 760, 740, 716, 692, 636, 624, 556, 500. HR-MS (ESI): *m*/*z* = 458.1676, calcd for $C_{24}H_{25}N_3O_5 + Na^+$: 458.1686.

4-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)oxy)-4-butyl-1,2-diphenylpyrazolidine-3,5-dione 20h. Slightly yellow powder, mp = 130–131 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 8.01–7.91 (m, 1H), 7.78–7.70 (m, 1H), 7.57–7.45 (m, 1H), 7.42–7.10 (m, 11H), 2.57–2.43 (m, 2H), 1.73–1.41 (m, 4H), 0.99 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 165.6, 143.3, 134.5, 129.2, 128.8, 127.9, 125.2, 123.7, 120.0, 110.0, 86.3, 33.6, 24.4, 22.8, 13.8. IR (KBr) ν(cm^{-1}): 2960, 2928, 2872, 2860, 1760, 1728, 1596, 1488, 1460, 1440, 1380, 1348, 1312, 1280, 1236, 1172, 1156, 1080, 1052, 780, 760, 744, 692. HR-MS (ESI): *m*/*z* = 464.1685, calcd for $C_{25}H_{23}N_5O_3 + Na^+$: 464.1693.

Generation of phthalimide-*N*-oxyl radical from *N*-hydroxyphthalimide (experimental details for Scheme 6)

An oxidant (quantities are given below) was added to a 0.002 M solution of *N*-hydroxyphthalimide in MeCN (20 mL) at room temperature (18–23 °C), and the mixture was shaken until the complete dissolution of the oxidant; the EPR spectrum of the solution was registered 5–15 min after mixing. Following oxidants were used: $(NH_4)_2Ce(NO_3)_6$ (21.9 mg, 0.04 mmol), $Fe(ClO_4)_3 \cdot nH_2O$ (*ca.* 35% H_2O, 21.8 mg, 0.04 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$ (14.8 mg, 0.04 mmol), $Pb(OAc)_4$ (8.9 mg, 0.02 mmol), $PhI(OAc)_2$ (6.4 mg, 0.02 mmol). The triplet EPR spectrum characteristic of the phthalimide-*N*-oxyl radical was observed in all cases (see the ESI† for details).

Generation and characterization of diacetyliminoxyl radical 21 (experimental details for Scheme 7)

All experiments with diacetyliminoxyl radical **21** were conducted at room temperature (18–23 °C).

Diacetyl oxime **2b** (258 mg, 2 mmol) was dissolved in CH_2Cl_2 (4 mL) at 18–23 °C, and then $Pb(OAc)_4$ (467 mg, 1 mmol) was added with vigorous stirring. The mixture immediately turned dark red, stirring was continued for 10 min, and then the mixture was transferred to the chromatographic column, prepared by suspending the silica gel (12 g) in excess of CH_2Cl_2. CH_2Cl_2 was used as an eluent, and the fraction corresponding to the dark-red spot was collected, so that the volume of the fraction was 50 mL. The obtained solution of diacetyliminoxyl radical **21** in CH_2Cl_2 (50 mL, $C \approx 0.04$ mmol mL^{-1} according to quantitative EPR measurement, see the ESI†) was used for experiments described below. The stability and purity of **21** in solution was confirmed by EPR, FT-IR spectroscopy and ICP-MS (to confirm separation from the lead compounds); for spectral data and discussion, see the ESI.†

Reactions of diacetyliminoxyl radical 21 with pyrazolin-5-ones 1a, 1c, 1h, and 1i (experimental details for Scheme 8)

To a stirred solution of diacetyliminoxyl radical **21** in CH_2Cl_2 (50 mL, *ca.* 0.04 mol L^{-1}, ≈2 mmol, prepared as described above), pyrazolin-5-one (1 mmol; **1a**: 188.2 mg; **1c**: 140.2 mg; **1h**: 188.2 mg; **1i**: 174.2 mg) was added at room temperature (18–23 °C). Stirring was continued for 3 h, and gradual dissolution of pyrazolin-5-one and the decrease in the intensity of the red color of the solution were observed. The mixture was rotary evaporated under water-jet vacuum, an aliquot (20 mg) of the residue was analyzed by ^1H and ^{13}C NMR, and the rest was transferred to a silica gel chromatographic column and eluted with EtOAc/CH_2Cl_2 (EtOAc content was increased gradually from 0 to 30 vol%) to isolate the reaction products. In the case of pyrazolin-5-one **1h**, an additional experiment was performed with a reaction time of 24 h (instead of 3 h), and the same product yields were observed.

The ^1H and ^{13}C NMR spectra of the reaction mixtures of diacetyliminoxyl radical **21** with pyrazolones **1a**, **c**, **h**, and **i** are given in the ESI.† Signals were assigned to the coupling products (**4**, **12**, **15** and **16**) and oxime **2b** by comparing the spectra of reaction mixtures with the spectra of individual compounds. No significant impurity signals were observed.

Experimental details for Scheme 9

General procedure for the synthesis of hydroxylamines 24. The product of C–O coupling **3** (180–210 mg, 0.6 mmol), $NH_2OH \cdot HCl$ (83.4 mg, 1.2 mmol), MeCN (3 mL) and H_2O (0.5 mL) were placed in a 10 mL round-bottom flask. Then $NaHCO_3$ (101 mg, 1.2 mmol) was added with vigorous stirring at room temperature; stirring was continued for 1 h. The mixture was rotary evaporated to dryness, and the residue was extracted with CH_2Cl_2 (3 × 7 mL). Combined extracts were washed with $NaHCO_3$ (2 × 3 mL), dried over $MgSO_4$, and rotary evaporated. Et_2O (1–2 mL) was added to the residue to cause crystallization, and then was rotary evaporated. Hydroxylamines **24a**, **c**, **d**, and **f** were obtained as white powders.

4-(Aminooxy)-4-benzyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one 24a. White powder, mp = 55–57 °C. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 8.60 (bs, 1H), 7.36–7.19 (m, 3H), 7.19–7.04 (m, 2H), 5.63 (bs, 2H), 3.05 (d, J = 13.3 Hz, 1H), 2.96 (d, J = 13.3 Hz, 1H), 2.02 (s, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 175.6, 160.4, 132.3, 130.0, 128.5, 127.6, 88.0, 38.6, 14.2. IR (KBr) ν(cm^{-1}): 3313, 3247, 3174, 3107, 1717, 1455, 1435, 1147, 1072, 757, 737, 701, 640, 577, 562. HR-MS (ESI): m/z = 220.1082, calcd for $C_{11}H_{13}N_3O_2 + H^+$: 220.1081.

4-(Aminooxy)-4-isopropyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one 24c. White powder, mp = 100–102 °C. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 10.74 (s, 1H), 6.23 (s, 2H), 1.96–1.80 (m, 1H), 1.93 (s, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.78 (d, J = 7.1 Hz, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 175.5, 159.4, 88.7, 30.4, 16.1, 14.6, 13.9. HR-MS (ESI): m/z = 172.1074, calcd for $C_7H_{13}N_3O_2 + H^+$: 172.1081. IR (KBr) ν(cm^{-1}): 3296, 3226, 3150, 1730, 1591, 1293, 1282, 1161, 1083, 1069, 732, 667, 559.

4-(Aminooxy)-4-butyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one 24d. White powder, mp = 89–90 °C. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 8.68 (bs, 1H), 5.49 (bs, 2H), 2.03 (s, 3H), 1.84–1.66 (m, 1H), 1.65–1.48 (m, 1H), 1.41–1.00 (m, 4H), 0.86 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 176.1, 161.3, 87.6, 31.7, 24.1, 22.8, 13.8, 13.5. IR (KBr) ν(cm^{-1}): 3299, 3233, 2961, 2926, 1731, 1595, 1248, 1166, 1080, 1072, 1059, 757, 748, 692, 643, 580, 562. HR-MS (ESI): m/z = 186.1239, calcd for $C_8H_{15}N_3O_2 + H^+$: 186.1237.

3a-(Aminooxy)-2,3a,4,5,6,7-hexahydro-3*H*-indazol-3-one 24f. White powder, mp = 111–112 °C. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 9.10 (bs, 1H), 5.53 (bs, 2H), 2.74–2.54 (m, 1H), 2.54–2.33 (m, 1H), 2.26–1.98 (m, 2H), 1.84–1.54 (m, 2H), 1.53–1.30 (m, 2H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 176.5, 164.5, 83.4, 33.9, 28.9, 27.4, 20.3. IR (KBr) ν(cm^{-1}): 3288, 3175, 2943, 2925, 1719, 1677, 1619, 1225, 1171, 1146, 1111, 1024, 1008, 741, 683, 651, 595, 574. HR-MS (ESI): m/z = 192.0745, calcd for $C_7H_{11}N_3O_2 + Na^+$: 192.0743.

(*E*)-Benzaldehyde-*O*-(4-benzyl-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)oxime 25. $N_2H_4 \cdot H_2O$ (32.2 mg, 0.644 mmol) and MeCN (3 mL) were placed in a 10 mL round-bottom flask, then

2-((4-benzyl-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)oxy)isoindoline-1,3-dione **3a** (150 mg, 0.429 mmol) was added with intensive stirring, that was continued for 40 min at room temperature, and precipitate formation was observed. Benzaldehyde (182 mg, 1.72 mmol) was added, and the precipitate gradually dissolved. Stirring was continued for 2 h at room temperature, and then the mixture was rotary evaporated to dryness. The product was isolated by column chromatography on silica gel using a EtOAc/CH_2Cl_2 mixture as the eluent with a gradual change in the ratio of solvents from 0 to 1/10. (*E*)-Benzaldehyde-*O*-(4-benzyl-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)oxime **25** was obtained as a white powder (93 mg, 0.303 mmol, 70%). Signal assignment in ^{1}H and ^{13}C NMR spectra, as well as defining configuration of the C=N bond was performed with the aid of 2D NMR experiments, HMBC and NOESY (see the ESI†). Mp = 120–121 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 10.88 (bs, 1H, NH), 8.46 (s, 1H, HC=N), 7.58–7.50 (m, 2H, ArH), 7.47–7.37 (m, 3H, ArH), 7.33–7.17 (m, 5H, ArH), 3.21 (d, J = 12.9 Hz, 1H, CH_2), 3.09 (d, J = 12.9 Hz, 1H, CH_2), 1.97 (s, 3H, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 174.2 (CONH), 158.1 (C=N–N), 151.8 (C=N–O), 132.3, 130.9, 130.7, 129.9, 128.9, 128.2, 127.2 (Ph), 86.0 (C–O–N), 37.2 (CH_2), 13.7 (CH_3). IR (KBr) ν(cm^{-1}): 3417, 3221, 3065, 1732, 1702, 1455, 1377, 1161, 1076, 1016, 921, 758, 749, 697, 628, 570, 519, 510. Elemental analysis calcd (%) for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.31; H, 5.62; N, 13.59.

Conflicts of interest

There are no conflicts of interest to declare.

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