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Multicomponent Reaction of Z-chlorooximes, Isocyanides and Hydroxylamines as Hyper-nucleophilic Traps. A One-pot Route to Aminodioximes and Their Transformation into 5-amino-1,2,4-oxadiazoles by Mitsunobu-Beckmann Rearrangement

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Multicomponent Reaction of *Z*-chlorooximes, Isocyanides and Hydroxylamines as Hyper-nucleophilic Traps. A One-pot Route to Aminodioximes and Their Transformation into 5-amino-1,2,4-oxadiazoles by Mitsunobu-Beckmann Rearrangement.

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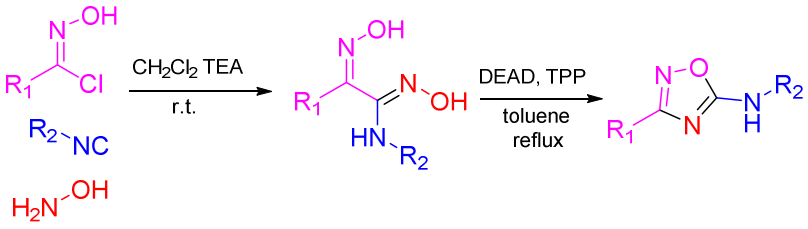


ABSTRACT

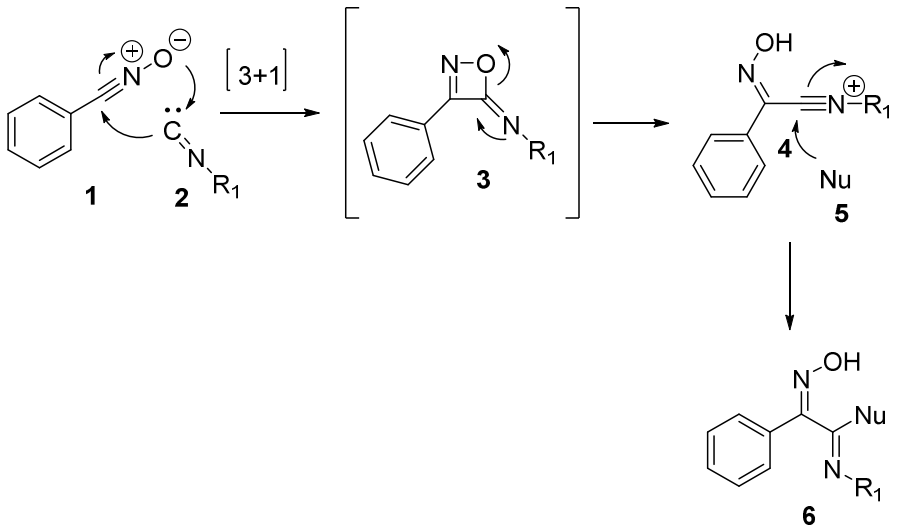
Synthetically useful aminodioximes are prepared *via* a novel three-component reaction among *Z*-chlorooximes, isocyanides and hydroxylamines by exploiting the preferential attack of isocyanides to nitrile-*N*-oxides *via* a [3+1] cycloaddition reaction. The results of quantum mechanical studies of the reaction mechanism are also discussed. Furthermore the one-pot conversion of aminodioximes to 1,2,3-oxadiazole-5-amines *via* Mitsunobu-Beckmann rearrangement is reported for the first time.

INTRODUCTION

Our recent discovery that, at room temperature, nitrile-*N*-oxides are excellent electrophilic partners for isocyanides,[1] able to trigger a multicomponent reaction, it opened up a new chapter in the already rich history of the chemistry of isocyanides.[2] The exploitation of this novel reactivity, led to the discovery of three new multicomponent reaction[1,3] and a novel way to synthesize pharmaceutical relevant ketoamide amides.[4] Independently from the strength of the nucleophile used as third component: carboxylate, phenate and primary and secondary amines (in order of increasing nucleophilicity), we observed that the reaction between isocyanides and nitrile *N*-oxides always overruled the possible attack of the nucleophile to the nitrile *N*-oxide.[5] The unexpected nitrile *N*-oxide behavior prompted us to re-examine the reaction mechanism. Indeed, it should be logic to consider that nitrile *N*-oxides[6] are better electrophilic partners for phenates and amines than isocyanides which are usually considered as poor nucleophiles.[7] It follows that the reaction between nitrile *N*-oxides and isocyanides cannot be interpreted as a simple nucleophilic addition. However, if we consider the isocyanides involved in these transformations in their carbenic nature and not in their ionic resonance form, a concerted [3+1] cycloaddition reaction between isocyanide and nitrile *N*-oxide could take place to give an oxazetidine ring.[8] A recent paper corroborates this hypothesis, demonstrating that isocyanides exist predominantly in the carbenic form.[9] Although [3+1] cycloaddition reactions between isocyanides and azomethine imines, nitrile ylides, and azomethine ylides[10] have already been reported, there are no examples for a [3+1] cycloaddition reaction between nitrile *N*-oxides and isocyanides.[11] Nitrile *N*-oxides (**1**), as well as all the 1,3-dipolar species, are ambiphilic dipoles characterized by a low energy difference between their HOMO or LUMO frontier orbitals[12] and they can hence react both with electron-rich or electron-poor dipolarophiles, as in this case the isocyanide (**2**) in its carbenic nature.

A four-membered ring should be obtained from this [3+1] cycloaddition (**3**), which readily opens, in order to relieve the ring strain, affording the nitrilium intermediate (**4**) which could now be attacked by a third nucleophile (**5**) finally forming the novel product (**6**) (Scheme 1).

Scheme 1. Proposed mechanism for the chemoselective addition of isocyanides to nitrile *N*-oxides in the presence of a third stronger nucleophile.



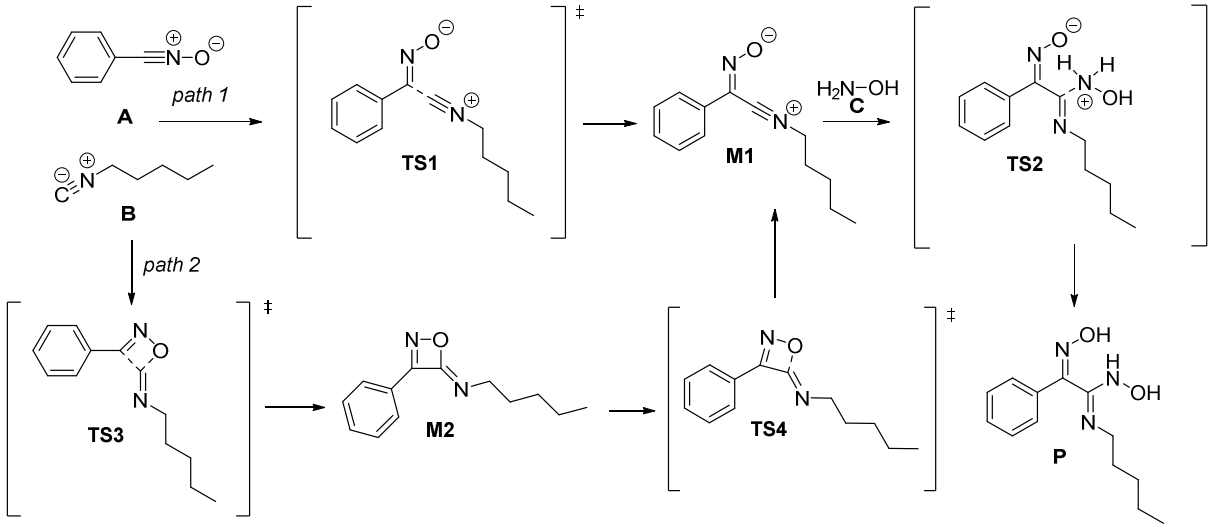
Stimulated by this hypothesis, we envisaged a novel multicomponent reaction using a hyper-nucleophile like hydroxylamine as third component even though literature reports on the isocyanide-mediated multi-component processes involving hydroxylamine were somehow discouraging. The reactive nature of hydroxylamine, due to its three nucleophile sites, renders poor yields and several side products in the Ugi reaction.[13] Moreover, hydroxylamines have been shown to react very fast with the nitrile *N*-oxides and low temperatures are necessary to give satisfactory yields.[14]

RESULTS AND DISCUSSION

In order to verify this hypothesis, *ab initio* calculations were performed to compare the energies involved in either the [3+1] cycloaddition or the ionic addition between the isocyanide and the nitrile *N*-oxide, and in the reaction between the nucleophile (hydroxylamine) and the nitrile *N*-oxide. The model reaction between phenyl nitrile oxide **A**, pentyl isocyanide **B**, and hydroxylamine **C**, which generates product **P** was chosen for this theoretical investigation. The detailed reaction mechanisms were interpreted using density functional theory (DFT), widely employed to study

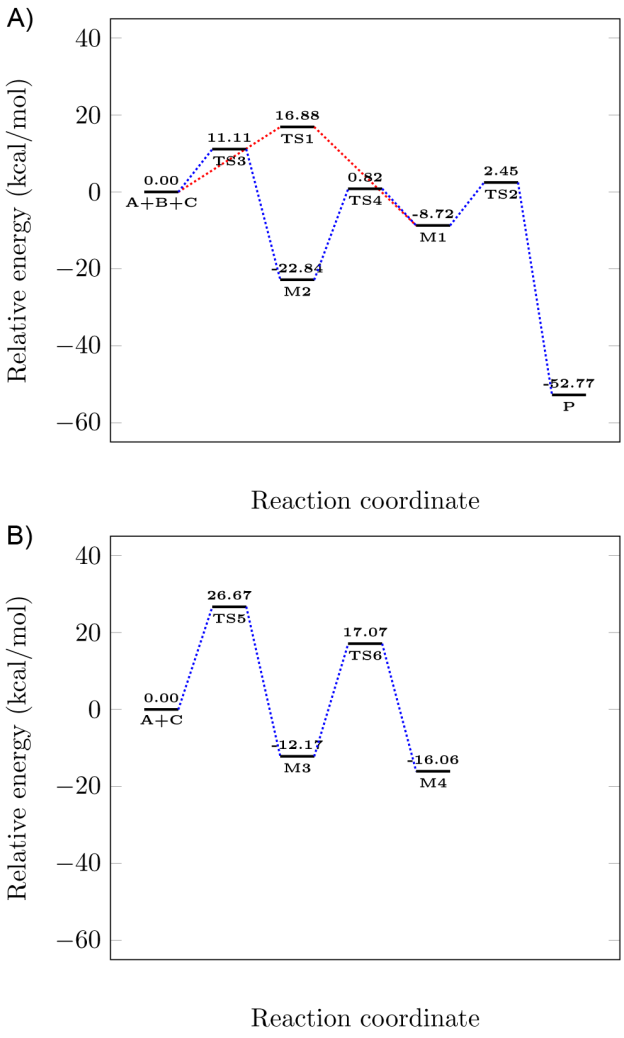
organic reaction mechanisms.[15] Two possible reaction pathways were investigated in detail (Scheme 2).

Scheme 2. The possible reaction pathways.



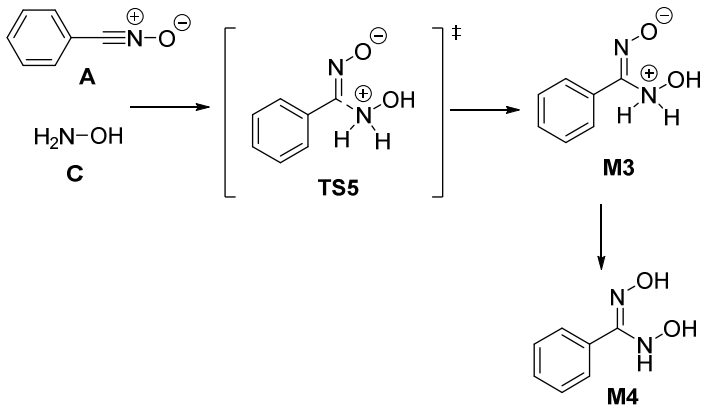
In reaction path 1 the isocyanide carbon atom behaves as a nucleophile attacking the nitrile *N*-oxide species to generate intermediate **M1**. In the second step, the nitrilium ion is attacked by the nitrogen atom of hydroxylamine. Subsequently, a protrotropic exchange gives the final compound **P**. We set the energies of the three reactants (**A** + **B** + **C**) as 0.00 kcal/mol as reference in the energy profile. The calculated energy barrier for traversing **TS1** was 16.88 kcal/mol (depicted in Figure 1A). In reaction path 2, the isocyanide behaves as carbene giving a [3+1] cycloaddition with the nitrile *N*-oxide species in the first step. Subsequently, the resulting oxatedine ring opens due to ring strain via the transition state **TS4** to generate intermediate **M1**. The calculated energy barrier for path 2 for traversing **TS3** was 11.11 kcal/mol, while the rate limiting step is traversing **TS4** that need 23.66 kcal/mol (depicted in Figure 1A).

Figure 1. The energy profile of reactions at the M06-2X/6-31G(d, p) level in dichloromethane (unit: kcal/mol). The energy reference is the sum of the reactant energies computed separately. A) Pathway 1 and 2 are depicted in red and blue respectively. B) Pathway 3.



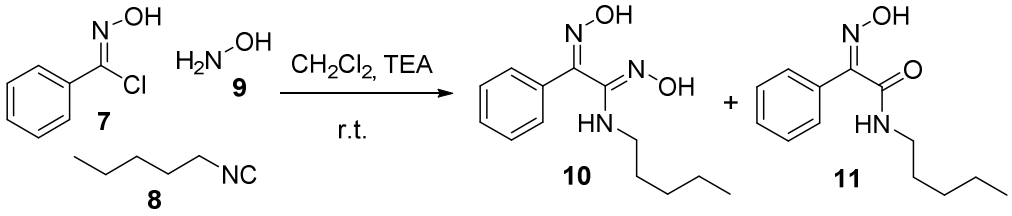
In addition to paths 1 and 2, we also evaluated the direct attack of hydroxylamine **C** to the phenyl nitrile oxide **A** (Pathway 3, Scheme 3). The energy barrier for traversing **TS5** was 26.67 kcal/mol (Figure 1B), which indicates that reactant **C** cannot compete with the isocyanide **B** in the reaction with nitrile *N*-oxides.

Scheme 3. The competitive reaction channel investigated (pathway 3).



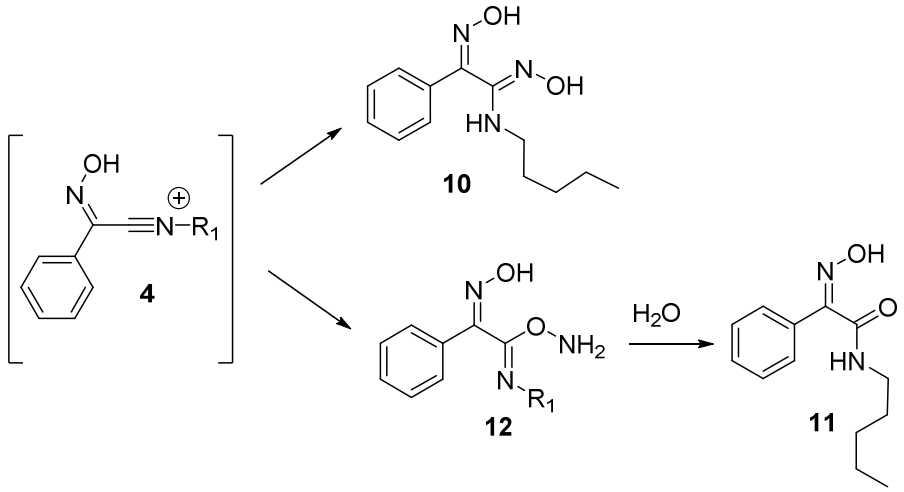
Summarizing, the energy barriers of entire pathways 1, 2, and 3 are 16.88, 11.11, and 26.67 kcal/mol, respectively, indicating that path 2 is the most energetically favorable. Moreover, the energy barrier of path 2 is not too high to be accessible under room temperature reaction conditions. In order to demonstrate the untamed nature of the reaction between hydroxylamine and nitrile *N*-oxides at room temperature, we carried out a two component reaction between *Z*-phenychlorooxime and hydroxylamine in dichloromethane in the presence of TEA. The result was a plethora of spots on TLC and we were able to isolate only trace amounts of the desired compound. After this preliminary results, we then set up a three component reaction among *Z*-phenylchlorooxime (**7**), pentylisocyanide (**8**) and hydroxylamine as free base[16] (**9**) in dichloromethane using 1 eq of TEA at room temperature. We observed a clean reaction and the smooth formation of two products. ^{1}H NMR analysis revealed the formation of the desired aminodioxime **10** in 45 % yield, and the amide **11** in 15 %. (Scheme 4). The success of this novel multicomponent reactions lies in the faster [3+1] cycloaddition reaction between isocyanides and nitrile *N*-oxides.

Scheme 4. The novel three component reaction.



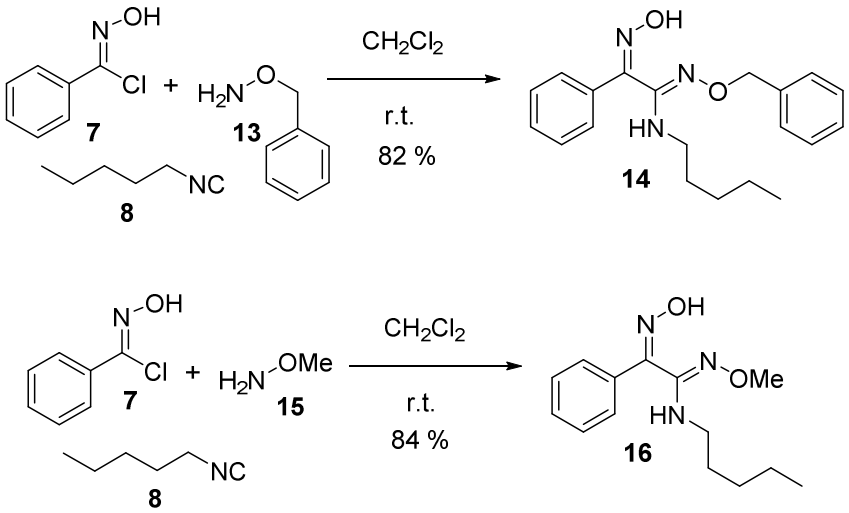
We rationalized the formation of the amide **11** due to the reaction between the nitrilium ion and the hydroxyl group of hydroxylamine to give an unstable imidate (**12**) prone to undergo hydrolysis to the amide (Scheme 5).

Scheme 5. Proposed mechanism for the formation of amide **11**.



In order to verify this hypothesis the reaction was run using either *O*-benzylhydroxylamine (**13**) or *O*-methylhydroxylamine (**15**). The corresponding aminodioxime (**14**) and (**16**) were obtained in 82 and 84 % yield respectively without observable formation of the amide by-product (Scheme 6).

Scheme 6. Multicomponent reaction using *O*-benzylhydroxylamine (**13**) or *O*-methylhydroxylamine (**15**).



Motivated by these preliminary results, and with the goal to suppress/reduce the formation of the undesired amide, and hence decrease the formation of the alcholate of hydroxylamine, we decided to screen different bases in dichloromethane. The results are shown in Table 1.

Table 1. Optimization of the reaction conditions.

Entry	Base	Equivalents	Yield (**10**)	Yield (**11**)
1	*N*-methyl morpholine	1	65 %	11 %
2	TEA	2	47 %	10 %
3	Imidazole	1	67 %	8.4 %
4	$NaHCO_3$	1	72 %	10 %
5	2,6-Lutidine	1	52 %	9 %

We observed that the use of the less basic sodium bicarbonate (entry 4) was able to reduce the formation the amide probably due to the reduced ionization to the corresponding alcoholate and it increased the yield of aminodioxime to 72 %.

The ^{1}H and ^{13}C NMR spectra of the aminodioximes **10**, recorded in DMSO-d_6, revelead the presence of an equilibrium between the imino and the amino forms, which is shifted prevalently towards the amino tautomer.[17] On the basis of the proposed reaction mechanism (Scheme 3), and considering that the transition from one oxime geometrical isomer to another requires either high temperature or acid or base catalysis or ultraviolet light,[18] it is reasonable to assume that the first oxime retains the *syn* configuration, while the amidoxime moiety can in principle exist as a mixture of tautomers. As one major isomer is always formed, it is reasonable to think that it is the more stable *amphi* form (*Z*,*Z*).

With such optimized conditions in hand we explored the scope of this novel multicomponent reaction using different *Z*-chlorooximes (**7**, **17-24**) and isocyanides (**8**, **25-27**) (Figure 2). The library of compounds synthesized is shown in Figure 3.

Figure 2. Building blocks used.

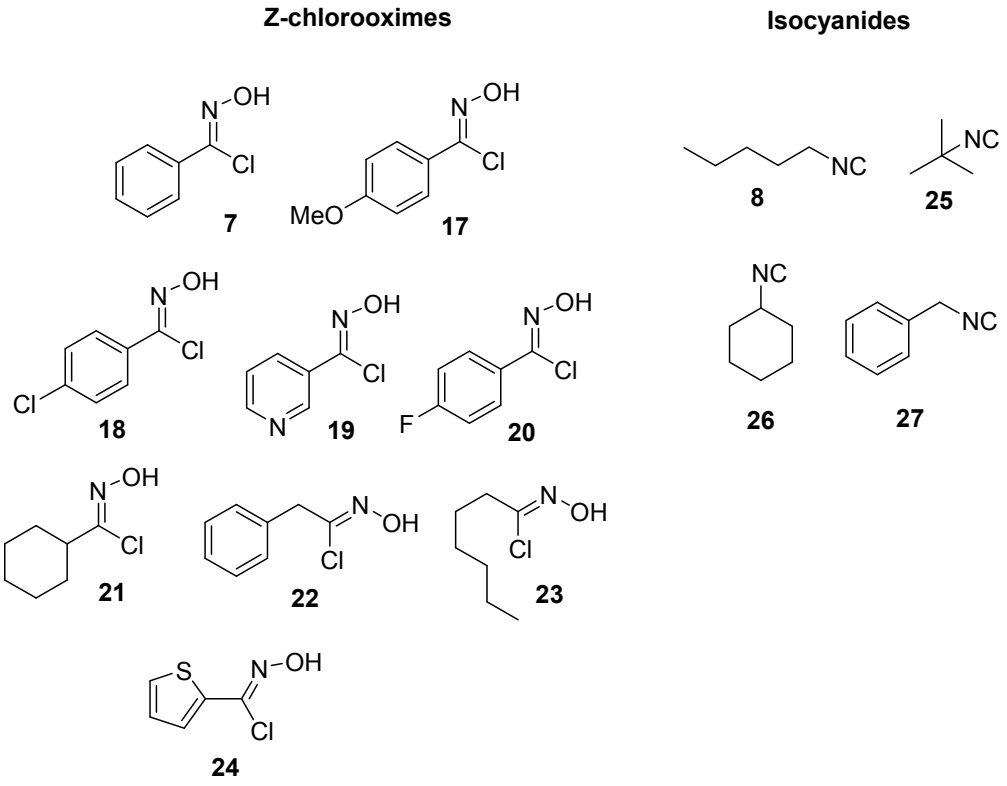
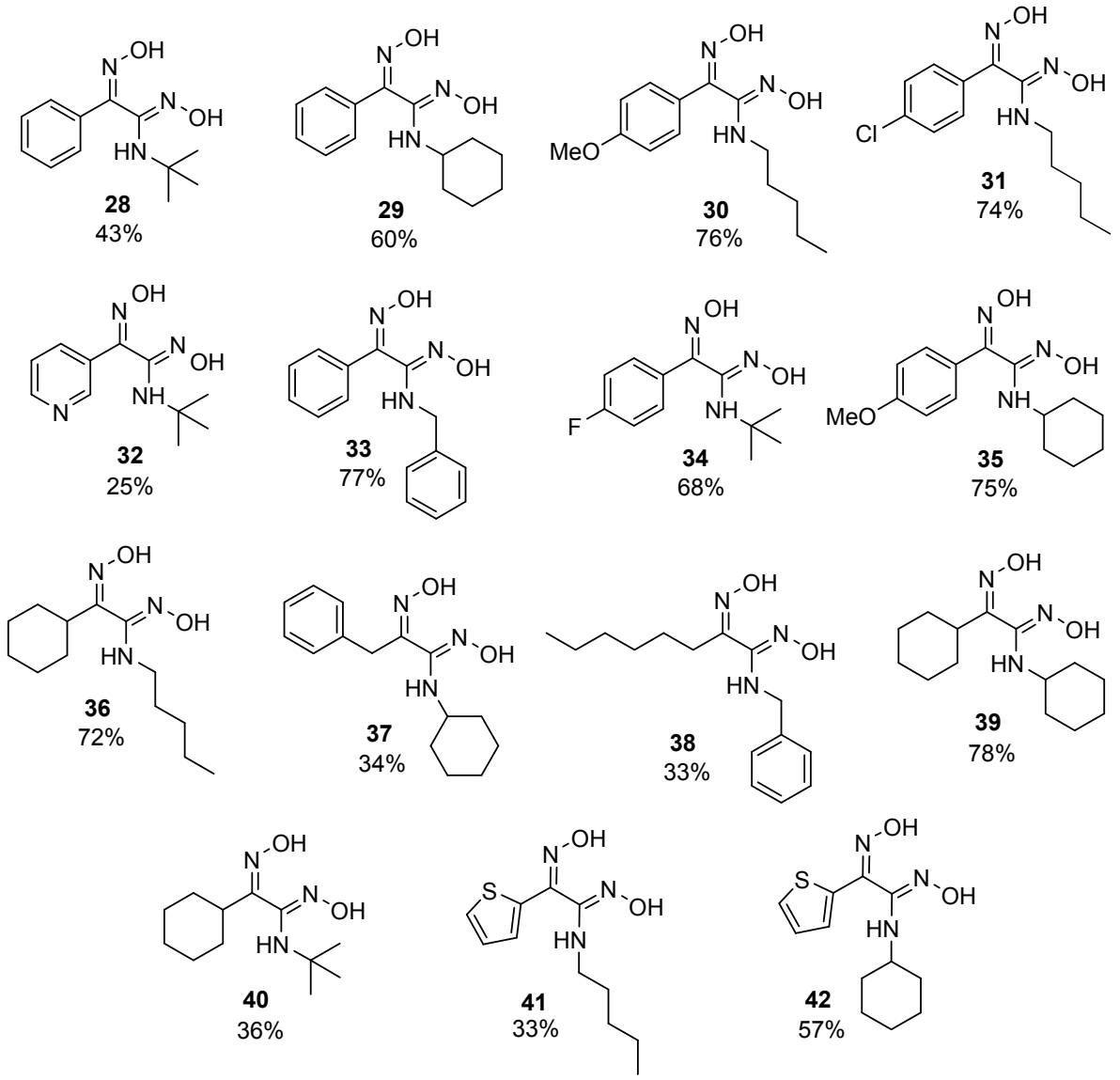


Figure 3. Aminodioximes synthesized (Amide by-product was always isolated in less than 10%).



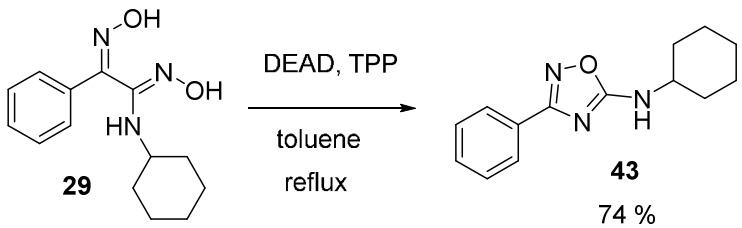
As shown Figure 3, the reaction is quite general: primary, secondary, tertiary isocyanides are all able to initiate the multicomponent process via [3+1] cycloadditon with nitrile *N*-oxides, while the reaction fails with the less reactive aromatic isocyanides. Aromatic, heteroaromatic and aliphatic *Z*-chlorooximes were successfully used as precursors of the nitrile *N*-oxide species. In all the examples reported a predominant isomer (> 90 %), the *amphi* form, was obtained. Only when the *tert*-butyl isocyanide was used (examples **28**, **32**, **34, 40**) a 1:1 mixture of imino-amino tautomers was detected (see spectra in the supporting information).

In order to unambiguously establish the stereochemistry of the aminodioximes synthesized, a single-crystal X-ray diffraction analysis on derivative **28** was carried out; its crystallographic structure and the discussion is presented in the supporting information.

Apart for their undisputed role in analytical chemistry, the obtained aminodioximes (also known as vic-dioximes) are an important class of ligands able to form complexes with several transition metals. Such complexes have been shown to be useful in different fields of chemistry,[19] and some were also found to exhibit semiconducting properties.[20] Their preparation by means of a one-pot multicomponent reaction constitutes a significant improvement on the previous methods, which typically require at least 4-6 reaction/purification steps when starting from acetophenones.[21]

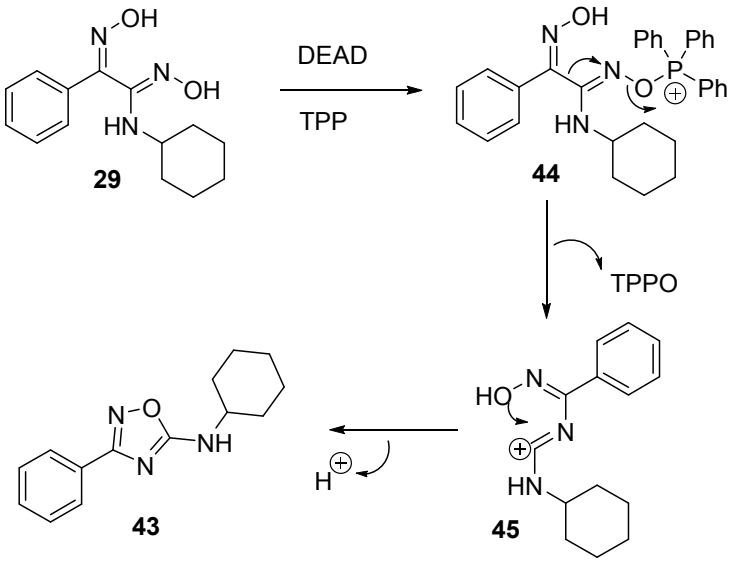
Aminodioxines are also pivotal reagent for the synthesis of 2-aminofurazans[22] under dehydrative conditions (4 M NaOH). Depending on the substrate functionalization such strong basic conditions are not always viable, rendering this transformation poor in scope. We recently demonstrated that for sensitive substrates mild dehydrative conditions using the Mitsunobu reaction on vicinal bis-oximes can afford furazans.[23] We therefore decided to employ the same dehydrative conditions with the newly formed aminodioximes. In particular, we tried dehydrative Mitsunobu conditions on the compound **29**. Serendipitously, we did not obtain the expected 2-aminofurazan, but the corresponding 5-amino-1,2,4-oxadiazole (**43**) in 74 % yield (Scheme 7). The reaction was completely chemoselective as no other isomers were detected.[24]

Scheme 7. Formation of the 5-amino-1,2,4-oxadiazole **43** starting from the aminodioxime **29.**



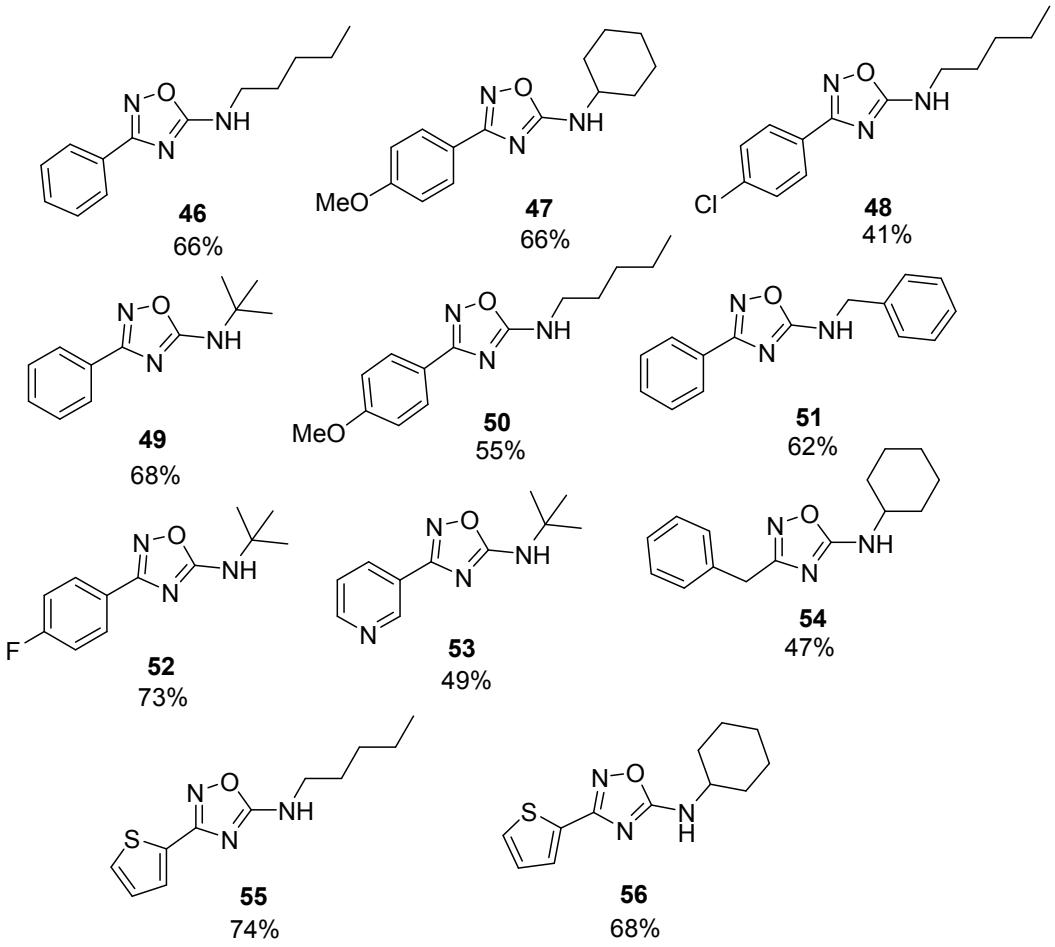
To explain this result, we propose the following mechanistic scenario. The TPP-DEAD Morrison-Brunn-Huisgen betain extracts the proton of the aminooxime. Subsequently, the resulting alcoholate reacts with the TPP-DEAD adduct to give the intermediate **44**, which spontaneously undergoes a Beckmann rearrangement with the concomitant expulsion of TPPO. Finally the hydroxyl group of hydroxylamine, properly positioned, quenches the carbocationic species affording the 1,2,4-oxadiazole nucleus (Scheme 8).[25]

Scheme 8. Proposed mechanism for the formation of 5-amino-1,2,4-oxadiazoles starting from aminodioxides using Mitsunobu conditions.



We applied this novel transformation to synthesize a small library of 5- amino-1,2,4-oxadiazoles (**46**-**56**) (Figure 4).

Figure 4. 5-amino-1,2,4-oxadiazoles synthesized.



The reaction appears to be general in scope irrespective of which isomer prevail on the synthesized amidoximes.

The unprecedented transformation of aminodioximes into 5-amino-1,2,4-oxadiazoles through a Beckmann rearrangement was also confirmed by a few reports where 3,5-diaryl-1,2,4-oxadiazoles were prepared form symmetrical 1,2-aryldioximes of α-aryldiketones.[26]

CONCLUSIONS

In conclusion, we reported a straightforward synthetic route to aminodioximes and 5-aminosubstituted 1,2,4-oxadiazoles important class of compounds in several branches of

chemistry[27] which, until now, required long syntheses. The stereochemistry of aminodioximes was confirmed by single-crystal X-ray diffraction analysis. Quantum mechanical studies supported by experimental data highlighted a [3+1] cycloaddition mechanism for the reaction of nitrile *N*-oxides with isocyanides, further validating the use of such 1,3-dipolar species in isocyanide-mediated multicomponent processes.

EXPERIMENTAL SECTION

General Methods. Commercially available reagents and solvents were used without further purification. Dichloromethane was dried by distillation from P_2O_5 and stored over activated molecular sieves (4 Å). When necessary the reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen. Melting points were determined in open glass capillaries and are uncorrected. All the compounds were characterized by IR. ^{1}H and ^{13}C APT NMR were recorded on a 300 MHz. High-resolution ESI-MS spectra were performed on a LTQ Orbitrap XL mass spectrometer. The spectra were recorded by infusion into the ESI source using MeOH as the solvent. Chemical shifts (δ) are reported in part per million (ppm) relative to the residual solvent peak. Column chromatography was performed on silica gel 70–230 Mesh ASTM or silica gel 230–400 Mesh ASTM. Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Silica gel 60 F_{254}). When necessary they were developed with $KMnO_4$.

General preparation of hydroxylamine solution.

Hydroxylamine hydrochloride (15 mmol) in methanol (10 mL), was added to a stirred solution of potassium hydroxide (15 mmol) in methanol (4 mL) at 0 °C. The mixture was stirred for 30 min at room temperature and the precipitate potassium chloride was removed and the filtrate was used as such.[16]

General preparation of aminodioximes (10, 14, 16, 28-42)

The *Z*-chlorooxime (1 eq.) was dissolved in dry dichloromethane. Isocyanide (1 eq.), hydroxylamine (solution 1M in methanol, 1.2 eq.) and sodium bicarbonate (1 eq.) were added and the reaction was stirred at room temperature under a nitrogen atmosphere until all the *Z*-chlorooxime was consumed (typically 16 hours as judged by TLC). The reaction mixture was concentrated under reduced pressure and the crude material was purified by column chromatography.

General preparation of 1,2,3-oxadiazole-5-amines (43, 46-56)

To a cooled (0 °C) suspension of aminodioxime (1 eq.) in dry toluene was added triphenylphosphine (2 eq.). Diethyl azodicarboxylate (DEAD, 2 eq.) was then added dropwise and the resulting solution was heated at reflux under a nitrogen atmosphere. When reagents was consumed (typically 16 hours as judged by TLC) the reaction mixture was concentrated under reduced pressure and the crude material was purified by column chromatography.

(1Z,2Z)-*N*'-hydroxy-2-(hydroxyimino)-*N*-pentyl-2-phenylacetimidamide (10)

(Z)-*N*-hydroxybenzimidoyl chloride 100 mg (0.643 mmol), 1-pentil isocyanide 0.081 mL (0.643 mmol), hydroxylamine 0.720 mL (solution 1M in methanol, 0.772 mmol), sodium bicarbonate 54 mg (0.643 mmol), DCM dry 1 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 6:4) to give the product as white solid (114 mg, yield 71.6 %).

Signals are referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.67 (s, OH), 9.38 (s, OH), 7.60 (m, 2H), 7.37 (m, 3H), 5.89 (t, NH, J = 6.4 Hz), 2.77 (br q, 2H) 1.31 (m, 2H), 1.09 (m, 4H), 0.73 (t, 3H, J = 6.7 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 148.8, 148.4, 135.0, 129.7, 128.9, 126.5, 42.4, 30.6, 28.8, 22.7, 14.3; IR (KBr) 3265, 1653, 1442, 1409, 948, 897, 691 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+Na)^+$ Calcd for $C_{13}H_{19}N_3NaO_2$: 272.1375; Found: 272.1370 $[M+Na]^+$.

(*Z*)-2-(hydroxyimino)-*N*-pentyl-2-phenylacetamide (11)

White solid; yield 11.5 %; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.45 (s, OH), 8.44 (t, NH, J = 5.5 Hz), 7.62 (m, 2H), 7.39 (m, 3H), 3.21 (br q, 2H) 1.46 (m, 2H), 1.30 (m, 4H), 0.87 (t, 3H, J = 6.7 Hz);

^{13}C-NMR (75 MHz, DMSO-d_6) δ 163.9, 153.5, 133.0, 129.9, 129.2, 126.2, 40.1 (peak overlaps with DMSO-d_6), 38.7, 29.1, 22.3, 14.5; IR (KBr) 3330, 2955, 1633, 1560, 1430, 1258, 946 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{13}H_{19}N_2O_2$: 235.1446; Found: 235.1466 $[M+H]^+$.

(1Z,2Z)-*N*'-(benzyloxy)-2-(hydroxyimino)-*N*-pentyl-2-phenylacetimidamide (14)

(Z)-*N*-hydroxybenzimidoyl chloride 100 mg (0.643 mmol), 1-pentyl isocyanide 0.081 mL (0.643 mmol), *O*-benzylhydroxylamine 0.720 mL (solution 1M in methanol, 0.772 mmol), sodium bicarbonate 54 mg (0.643 mmol), DCM dry 1 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 8:2) to give the product as white solid (179 mg, yield 82%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.78 (s, OH), 7.50-7.30 (m, 10H), 6.33 (br t, NH), 4.93 (s, 2H), 2.78 (m, 2H), 1.30 (m, 2H), 1.07 (m, 4H), 0.71 (br t, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 149.1, 148.1, 139.8, 134.6, 129.8, 128.9, 128.6, 128.4, 127.8, 126.4, 74.7, 43.2, 30.6, 28.8, 22.2, 14.3; IR (KBr) 3110, 1630, 1439, 1053, 955, 944, 726 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{20}H_{26}N_3O_2$: 340.2025; Found: 340.2011 $[M+H]^+$.

(1Z,2Z)-2-(hydroxyimino)-*N*'-methoxy-*N*-pentyl-2-phenylacetimidamide (16)

(Z)-*N*-hydroxybenzimidoyl chloride 100 mg (0.645 mmol), 1-pentyl isocyanide 0.086 mL (0.645 mmol), methoxyl amine 0.772 mL (solution 1M in methanol, 0.772 mmol), sodium bicarbonate 54 mg (0.645 mmol), DCM dry 1 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 8:2) to give the product as white solid (141.8 mg, yield 84%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.78 (s, OH), 7.61 (m, 2H), 7.40 (m, 3H), 6.18 (br t, NH), 3.65 (s, 3H), 2.78 (m, 2H), 1.30 (m, 2H), 1.09 (m, 4H), 0.75 (br t, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 148.5, 148.1, 134.7, 129.8, 129.0, 126.4, 61.0, 43.2, 30.5, 28.8, 22.2, 14.3; IR (KBr) 3137, 1630, 1439, 1414, 1052, 955, 693 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+Na)^+$ Calcd for $C_{14}H_{21}N_3NaO_2$: 286.1531; Found: 286.1518 $[M+Na]^+$.

(1Z,2Z)-*N*-(tert-butyl)-*N*'-hydroxy-2-(hydroxyimino)-2-phenylacetimidamide (28)

(Z)-*N*-hydroxybenzimidoyl chloride 250 mg (1.61 mmol), *tert*-butyl isocyanide 0.182 mL (1.61 mmol), hydroxylamine 1.8 mL (solution 1M in methanol, 1.93 mmol), sodium bicarbonate 135 mg (1.61 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 7:3, 6:4) to give the product as white solid (162.5 mg, yield 43%).

Signals are referred to one isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.72 (s, OH), 9.79 (s, OH), 7.65 (br d, 2H), 7.38 (m, 3H), 5.36 (s, NH), 1.08 (s, 9H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 150.3, 146.3, 135.4, 128.8, 128.6, 126.4, 51.3, 31.3; IR (KBr) 3062, 1638, 1404, 1370, 949, 900, 694 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+Na)^+$ Calcd for $C_{12}H_{17}N_3NaO_2$: 258.1218; Found: 258.1219 $[M+Na]^+$.

(1Z,2Z)-*N*-cyclohexyl-*N*'-hydroxy-2-(hydroxyimino)-2-phenylacetimidamide (29)

(Z)-*N*-hydroxybenzimidoyl chloride 250 mg (1.61 mmol), cyclohexyl isocyanide 0.200 mL (1.61 mmol), hydroxylamine 1.8 mL (solution 1M in methanol, 1.93 mmol), sodium bicarbonate 135 mg (1.61 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 7:3, 6:4) to give the product as white solid (250.5 mg, yield 60%).

Signals are referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.66 (s, OH), 9.40 (s, OH), 7.65 (m 2H), 7.37 (m, 3H), 5.73 (br d, NH), 2.71 (m, 1H), 1.64 (m, 4H), 1.44 (m, 1H), 1.19 (m, 2H), 1.00 (m, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 148.3, 146.9, 134.6, 129.2, 128.5, 125.9, 51.8, 40.1 (peak overlaps with DMSO-d_6), 34.5, 24.9; IR (KBr) 3263, 1660, 1449, 1412, 950, 903, 694 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{14}H_{20}N_3O_2$: 262.1555; Found: 262.1542 $[M+H]^+$.

(1Z,2Z)-*N*′-hydroxy-2-(hydroxyimino)-2-(4-methoxyphenyl)-*N*-pentylacetimidamide (30)

(*Z*)-*N*-hydroxy-4-methoxybenzimidoyl chloride 250 mg (1.34 mmol), 1-pentyl isocyanide 0.168 mL (1.34 mmol), hydroxylamine 1.5 mL (solution 1M in methanol, 1.61 mmol), sodium bicarbonate 113 mg (1.34 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 5:5, 4:6) to give the product as white solid (286 mg, yield 76 %).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.40 (s, OH), 9.34 (s, OH), 7.55 (d, J = 8.8 Hz, 2 H, AA′XX′), 6.97 (d, J = 8.8 Hz, 2 H, AA′XX′), 5.85 (br t, NH), 3.77 (s, 3H), 2.78 (m, 2H), 1.31 (m, 2H), 1.10 (m, 4H), 0.74 (br t, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 160.7,

148.6, 148.4, 129.9, 127.5, 114.4, 55.8, 42.9, 30.7, 28.8, 22.3, 14.3; IR (KBr) 3274, 1652, 1255, 1182, 947, 899, 833 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{14}H_{22}N_3O_3$: 280.1661; Found: 280.1646 $[M+H]^+$.

(1*Z*,2*Z*)-2-(4-chlorophenyl)-*N*'-hydroxy-2-(hydroxyimino)-*N*-pentylacetimidamide (31)

(*Z*)-4-chloro-*N*-hydroxybenzimidoyl chloride 250 mg (1.31 mmol), cyclohexyl isocyanide 0.166 mL (1.31 mmol), hydroxylamine 1.46 mL (solution 1M in methanol, 1.57 mmol), sodium bicarbonate 110 mg (1.31 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 7:3, 6:4) to give the product as white solid (274 mg, yield 74 %).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.86 (br s, OH), 9.48 (br s, OH), 7.62 (d, *J* = 8.6 Hz, 2H, AA′XX′), 7.49 (d, *J* = 8.6 Hz, 2H, AA′XX′), 6.01 (br s, NH), 2.77 (m, 2H), 1.27 (m, 6H), 0.75 (m, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 148.1, 147.9, 134.4, 133.9, 129.2, 128.1, 42.9, 30.7, 28.8, 22.2, 14.3; IR (KBr) 3292, 1640, 1493, 1449, 1093, 946, 832 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{13}H_{19}ClN_3O_2$: 284.1165; Found: 284.1142 $[M+H]^+$.

(1Z,2Z)-*N*-(tert-butyl)-*N′*-hydroxy-2-(hydroxyimino)-2-(pyridin-3-yl)acetimidamide (32)

(*Z*)-*N*-hydroxynicotinimidoyl chloride 200 mg (1.28 mmol), *tert*-butyl isocyanide 0.145 mL (1.28 mmol), hydroxylamine 1.4 mL (solution 1M in methanol, 1.53 mmol), sodium bicarbonate 107.5 mg (1.28 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 6:4, 5:5) to give the product as white solid (75.4 mg, yield 25 %).

Signals referred to one isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.46 (s, OH), 9.95 (s, OH), 8.63 (s, 1H), 8.55 (br d, 1H), 7.84 (br d, 1H), 7.43 (m, 1H), 5.26 (s, NH), 1.32 (s, 9H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 149.5, 149.1, 147.0, 145.2, 132.9, 129.4, 123.6, 50.8, 28.5; IR (KBr) 3137, 1642, 1504, 1415, 1243, 961, 918 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{11}H_{17}N_4O_2$: 237.1351; Found: 237.1349 $[M+H]^+$.

(1Z,2Z)-*N*-benzyl-*N*'-hydroxy-2-(hydroxyimino)-2-phenylacetimidamide (33)

(*Z*)-*N*-hydroxybenzimidoyl chloride 250 mg (1.6 mmol), benzyl isocyanide 0.197 mL (1.6 mmol), hydroxylamine 1.77 mL (solution 1M in methanol, 1.9 mmol), sodium bicarbonate 134 mg (1.6 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 7:3) to give the product as white solid (331.1 mg, yield 77 %).

Signals are referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.77 (s, OH), 9.55 (s, OH), 7.53 (m, 2H), 7.32 (m, 4H), 7.17 (m, 4H), 6.41 (t, NH, *J* = 6.7 Hz), 4.04 (d, 2H, *J*= 6.7 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 148.7, 148.3, 140.7, 135.0, 129.6, 128.8, 128.5, 127.6, 127.2, 126.4, 46.8; IR (KBr) 3265, 1658, 1494, 1452, 1093, 944, 902 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{15}H_{16}N_3O_2$: 270.1242; Found: 270.1240 $[M+H]^+$.

(1Z,2Z)-*N*-(tert-butyl)-2-(4-fluorophenyl)-*N′*-hydroxy-2-(hydroxyimino)acetimidamide (34)

(*Z*)-4-fluoro-*N*-hydroxybenzimidoyl chloride 250 mg (1.4 mmol), *tert*-butyl isocyanide 0.158 mL (1.4 mmol), hydroxylamine 1.6 mL (solution 1M in methanol, 1.7 mmol), sodium bicarbonate 118 mg (1.4 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 7:3) to give the product as white solid (248.1 mg, yield 68 %).

Signals referred to one isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.75 (s, OH), 9.84 (s, OH), 7.66 (m, 2H), 7.25 (m, 2H), 5.36 (br s, NH), 1.08 (s, 9H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 163.1 (d, *J* = 244.5 Hz), 150.2, 146.2, 132.3 (d, *J* = 2.8 Hz), 128.8 (d, *J* = 8 Hz), 116.0 (d, *J* = 21.2 Hz), 51.2, 31.4; ^{19}F (282 MHz, $CDCl_3$) -126.02; IR (KBr) 3226, 1643, 1513, 1265, 1224, 953, 834 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+Na)^+$ Calcd for $C_{12}H_{16}FN_3NaO_2$: 276.1124; Found: 276.1114 $[M+Na]^+$.

(1Z,2Z)-*N*-cyclohexyl-*N′*-hydroxy-2-(hydroxyimino)-2-(4-methoxyphenyl)acetimidamide (35)

(*Z*)-*N*-hydroxy-4-methoxybenzimidoyl chloride 250 mg (1.3 mmol), cyclohexyl isocyanide 0.161 mL (1.3 mmol), hydroxylamine 1.5 mL (solution 1M in methanol, 1.6 mmol), sodium bicarbonate 109 mg (1.35 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 5:5, 4:6) to give the product as white solid (286.2 mg, yield 75 %).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.39 (s, OH), 9.35 (s, OH), 7.56 (d, *J* = 8.6 Hz, 2 H, AA′XX′), 6.97 (d, *J* = 8.6 Hz, 2 H, AA′XX′), 5.67 (br d, NH), 3.81 (s, 3H),

2.69 (m, 1H), 1.60 (m, 4H), 1.44 (m, 1H), 1.21 (m, 2H), 1.01 (br s, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 160.1, 148.0, 147.2, 127.4, 127.2, 114.0, 55.3, 51.8, 40.2 (peak overlaps with DMSO-d_6), 34.6, 25.0; IR (KBr) 3118, 1643, 1514, 1259, 1247, 1178, 944 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{15}H_{22}N_3O_3$: 292.1661; Found: 292.1659 $[M+H]^+$.

(1Z,2Z)-2-cyclohexyl-*N′*-hydroxy-2-(hydroxyimino)-*N*-pentylacetimidamide (36)

(*Z*)-*N*-hydroxycyclohexanecarbimidoyl chloride 350 mg (2.16 mmol), 1-pentyl isocyanide 0.271 mL (2.16 mmol), hydroxylamine 2.4 mL (solution 1M in methanol, 2.59 mmol), sodium bicarbonate 181 mg (2.16 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 7:3) to give the product as white solid (400.1 mg, yield 72%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.83 (s, OH), 9.20 (s, OH), 5.45 (br t, NH), 2.80 (m, 2H), 2.24 (m, 1H), 1.84 (m, 2H), 1.69 (m, 4H), 1.22 (m, 10H), 0.85 (t, 3H, *J* = 6.9 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 153.5, 149.9, 43.2, 43.1, 39.7 (peak overlaps with DMSO-d_6), 30.7, 30.5, 29.9, 26.3, 22.5, 14.4; IR (KBr) 3105, 1643, 1467, 1451, 964, 917, 887 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{13}H_{26}N_3O_2$: 256.2025; Found: 256.2019 $[M+H]^+$.

(1Z,2Z)-*N*-cyclohexyl-*N′*-hydroxy-2-(hydroxyimino)-3-phenylpropanimidamide (37)

(*Z*)-*N*-hydroxy-2-phenylacetimidoyl chloride 350 mg (2.1 mmol), cyclohexyl isocyanide 0.261 mL (2.1 mmol), hydroxylamine 2.3 mL (solution 1M in methanol, 2.5 mmol), sodium bicarbonate 176 mg (2.1 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 7:3, 6:4) to give the product as white solid (194.9 mg, yield 34%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.06 (s, OH), 9.35 (s, OH), 7.30-7.18 (m, 5H), 5.22 (br d, NH), 3.57 (2H, peaks overlap with DMSO-d_6), 2.44 (br s, 1H), 1.45 (br s, 3H), 1.15 (br s, 2H), 0.92 (m, 5H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 149.1, 148.5, 136.5, 129.4, 128.5, 126.7, 52.2, 40.7, 34.5, 25.3, 25.0; IR (KBr) 3064, 1642, 1424, 997, 941, 723, 697 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{15}H_{22}N_3O_2$: 276.1712; Found: 276.1707 $[M+H]^+$.

(1Z,2Z)-*N*-benzyl-*N′*-hydroxy-2-(hydroxyimino)octanimidamide (38)

(*Z*)-*N*-hydroxyheptanimidoyl chloride 350 mg (2.14 mmol), benzyl isocyanide 0.261 mL (2.14 mmol), hydroxylamine 2.4 mL (solution 1M in methanol, 2.57 mmol), sodium bicarbonate 180 mg (2.14 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 6:4) to give the product as white solid (195.3 mg, yield 33%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.96 (s, OH), 9.42 (s, OH), 7.35-7.18 (m, 5H), 6.20 (t, NH), 4.07 (d, 2H, J = 4.9 Hz), 1.98 (t, 2H, J = 7.5 Hz), 1.29 (m, 3H), 1.20-1.09 (m, 5H), 0.81 (br t, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 150.0 (2C), 141.4, 128.7, 127.6, 127.2, 46.5, 34.4, 30.1, 28.8, 25.9, 22.5, 14.4; IR (KBr) 3307, 1695, 1461, 1455, 1350, 921, 697 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{15}H_{24}N_3O_2$: 278.1868; Found: 278.1856 $[M+H]^+$.

(1Z,2Z)-*N*,2-dicyclohexyl-*N′*-hydroxy-2-(hydroxyimino)acetimidamide (39)

(*Z*)-*N*-hydroxycyclohexanecarbimidoyl chloride 300 mg (1.86 mmol), cyclohexyl isocyanide 0.231 mL (1.86 mmol), hydroxylamine 2.1 mL (solution 1M in methanol, 2.23 mmol), sodium bicarbonate 156 mg (1.86 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 7:3) to give the product as white solid (388.5 mg, yield 78%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.81 (s, OH), 9.19 (s, OH), 5.40 (br d, NH), 2.69 (m, 1H), 2.22 (m, 1H), 1.85-1.08 (m, 20H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 153.2, 148.4, 51.9, 42.7, 39.5 (peak overlaps with DMSO-d_6), 34.8, 30.1, 25.9, 25.7, 25.1; IR (KBr) 3208, 1627, 1449, 1413, 969, 933, 892 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{14}H_{26}N_3O_2$: 268.2025; Found: 268.2013 $[M+H]^+$.

(1Z,2Z)-*N*-(tert-butyl)-2-cyclohexyl-*N′*-hydroxy-2-(hydroxyimino)acetimidamide (40)

(*Z*)-*N*-hydroxycyclohexanecarbimidoyl chloride 300 mg (1.86 mmol), *tert*-butyl isocyanide 0.210 mL (1.86 mmol), hydroxylamine 2.1 mL (solution 1M in methanol, 2.23 mmol), sodium bicarbonate 156 mg (1.86 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 7:3) to give the product as white solid (161.5 mg, yield 36%).

Signals referred to one isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.84 (s, OH), 9.69 (s, OH), 5.01 (s, NH), 2.29 (m, 1H), 1.91 (m, 4H), 1.62 (m, 6H), 1.25 (s, 9H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 155.3, 148.1, 51.2, 40.5, 31.1, 30.1, 29.2, 26.5; IR (KBr) 3276, 1647, 1508, 1449, 1364, 969, 953 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+Na)^+$ Calcd for $C_{12}H_{23}N_3NaO_2$: 264.1688; Found: 264.1684 $[M+Na]^+$.

(1Z,2E)-*N′*-hydroxy-2-(hydroxyimino)-*N*-pentyl-2-(thiophen-2-yl)acetimidamide, (41)

(*Z*)-*N*-hydroxythiophene-2-carbimidoyl chloride 300 mg (1.8 mmol), 1-pentyl isocyanide 0.226 mL (1.8 mmol), hydroxylamine 2.0 mL (solution 1M in methanol, 2.16 mmol), sodium bicarbonate 151 mg (1.8 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 6:4) to give the product as white solid (157.3 mg, yield 33%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.63 (s, OH), 9.50 (s, OH), 7.50 (br d, 1H), 7.09 (m, 2H), 5.87 (br t, NH), 2.80 (m, 2H), 1.29 (m, 2H), 1.11 (m, 4H), 0.73 (br t, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 148.1, 145.3, 139.2, 128.4, 127.9 (2C), 42.9, 30.7, 28.8, 22.2, 14.3; IR (KBr) 3209, 1546, 1438, 1340, 1231, 912, 701 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{11}H_{18}N_3O_2S$: 256.1119; Found: 256.1111 $[M+H]^+$.

(1Z,2E)-*N*-cyclohexyl-*N′*-hydroxy-2-(hydroxyimino)-2-(thiophen-2-yl)acetimidamide, (42)

(*Z*)-*N*-hydroxythiophene-2-carbimidoyl chloride 250 mg (1.5 mmol), cyclohexyl isocyanide 0.186 mL (1.5 mmol), hydroxylamine 1.7 mL (solution 1M in methanol, 1.8 mmol), sodium bicarbonate 126 mg (1.5 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 6:4) to give the product as white solid (238.1 mg, yield 57%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.63 (s, OH), 9.54 (s, OH), 7.51 (br d, 1H), 7.09 (m, 2H), 5.64 (br d, NH), 2.72 (m, 1H), 1.62 (m, 4H), 1.44 (m, 1H), 1.18 (m, 2H), 1.02 (m, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 147.2, 145.4, 139.4, 128.3, 128.0, 127.4, 52.4, 40.3 (peak overlaps with DMSO-d_6), 35.0, 25.4; IR (KBr) 3275, 1658, 1442, 1008, 919, 905, 891 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{12}H_{18}N_3O_2S$: 268.1119; Found: 268.1104 $[M+H]^+$

***N*-cyclohexyl-3-phenyl-1,2,4-oxadiazol-5-amine, (43)**

Aminodioxime 100 mg (0.383 mmol), triphenylphosphine 200.9 mg (0.766 mmol), diethyl azodicarboxylate 0.120 mL (0.766 mmol), toluene dry 1 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as white solid (69.2 mg, yield 74%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.9 Hz, 2H,), 7.43 (m, 3H), 5.63 (br d, NH), 3.66 (m, 1H), 2.08 (m, 2H), 1.71 (m, 2H), 1.63 (m, 1H), 1.36 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.7, 168.5, 130.8, 128.7, 127.8, 127.3, 53.0, 33.3, 25.4, 24.7; IR (KBr) 3242, 1647, 1491, 1444, 1390, 1098 ν_{max}/cm^{-1}; m.p. 126.7-127.7 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{14}H_{18}N_3O$: 244.1449; Found: 244.1444 $[M+H]^+$.

_N_-pentyl-3-phenyl-1,2,4-oxadiazol-5-amine (46)

Aminodioxime 70 mg (0.281 mmol), triphenylphosphine 81 mg (0.308 mmol), diethyl azodicarboxylate 0.048 mL (1.11 mmol), toluene dry 1 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1) to give the product as white solid (43 mg, yield 66%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 8.0 Hz, 2H), 7.43 (m, 3H), 6.17 (br s, NH), 3.42 (q, 2H, J = 7.0 Hz), 1.61 (m, 2H), 1.32 (m, 4H), 0.87 (br t, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.5, 168.5, 130.9, 128.7, 127.7, 127.3, 43.8, 29.5, 28.8, 22.3, 14.0; IR (KBr) 3244, 1654, 1527, 1462, 1386, 1301 ν_{max}/cm^{-1}; m.p. 68.1-69.0 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{13}H_{18}N_3O$: 232.1449; Found: 232.1451 $[M+H]^+$.

_N_-cyclohexyl-3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-amine (47)

Aminodioxime 150 mg (0.515 mmol), triphenylphosphine 270.2 mg (1.03 mmol), diethyl azodicarboxylate 0.162 mL (1.03 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 85:15) to give the product as yellow solid (93 mg, yield 66%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 8.8 Hz, 2 H, AA′XX′), 6.92 (d, J = 8.8 Hz, 2 H, AA′XX′), 5.82 (br d, NH), 3.81 (s, 3H), 3.62 (m, 1H), 2.02 (m, 2H), 1.68 (m, 2H), 1.45 (m, 1H),

1.42-1.10 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.5, 168.1, 161.6, 128.8, 120.2, 114.0, 55.4, 52.9, 33.2, 25.3, 24.7; IR (KBr) 3307, 1634, 1390, 1259, 1177, 839 ν_{max}/cm^{-1}; m.p. 110.6-111.0 °C; MS (ESI) *m/z* $(M+Na)^+$ Calcd for $C_{15}H_{19}N_3NaO_2$: 296.1375; Found: 296.1360 $[M+Na]^+$.

3-(4-chlorophenyl)-*N*-pentyl-1,2,4-oxadiazol-5-amine (48)

Aminodioxime 144 mg (0.507 mmol), triphenylphosphine 266 mg (1.014 mmol), diethyl azodicarboxylate 0.159 mL (1.014 mmol), toluene dry 2 mL. The crude material was purified by column chromatography eluents: PE/EtOAc 95:5, 9:1) to give the product as white solid (55 mg, yield 41%).

^{1}H-NMR (300 MHz, $CDCl_3$δ 7.90 (d, *J* = 8.8 Hz, 2 H, AA′XX′), 7.42 (d, *J* = 8.8 Hz, 2 H, AA′XX′), 5.82 (br s, NH), 3.44 (q, *J* = 7.0 Hz, 2H), 1.55 (m, 2H), 1.32 (m, 4H), 0.90 (br t, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.4, 167.6, 136.9, 129.0, 128.6, 126.2, 43.9, 29.5, 28.8, 22.3, 14.0; IR (KBr) 3232, 1637, 1413, 1099, 1013, 841 ν_{max}/cm^{-1}; m.p. 105.0-106.3 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{13}H_{17}ClN_3O$: 266.1060; Found: 266.1071 $[M+H]^+$.

***N*-(tert-butyl)-3-phenyl-1,2,4-oxadiazol-5-amine (49)**

Aminodioxime 100 mg (0.425 mmol), triphenylphosphine 223 mg (0.850 mmol), diethyl azodicarboxylate 0.290 mL (0.850 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as white solid (62.7 mg, yield 68%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.43 (m, 3H), 5.59 (br s, NH), 1.45 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.5, 168.3, 130.9, 128.8, 128.0, 127.4, 52.9, 29.2; IR (KBr) 3263, 1622, 1379, 1219, 1141, 751 ν_{max}/cm^{-1}; m.p. 87.1-88.3 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{12}H_{16}N_3O$: 218.1293; Found: 218.1279 $[M+H]^+$.

3-(4-methoxyphenyl)-*N*-pentyl-1,2,4-oxadiazol-5-amine (50)

Aminodioxime 60 mg (0.215 mmol), triphenylphosphine 112.8 mg (0.430 mmol), diethyl azodicarboxylate 0.067 mL (0.430 mmol), toluene dry 2 mL. The crude material was purified by

column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as yellow solid (30.7 mg, yield 55%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.8 Hz, 2 H, AA′XX′), 6.95 (d, *J* = 8.8 Hz, 2 H, AA′XX′), 5.89 (br s, NH), 3.84 (s, 3H), 3.42 (q, *J* = 6.7 Hz, 2H), 1.62 (m, 2H), 1.33 (m, 4H), 0.90 (br t, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.3, 168.2, 161.7, 128.9, 120.2, 114.1, 55.5, 43.9, 29.6, 28.9, 22.4, 14.1; IR (KBr) 3244, 1655, 1393, 1257, 1175, 846 ν_{max}/cm^{-1}; m.p. 72.6-73.5 °C; MS (ESI) *m/z* $(M+Na)^+$ Calcd for $C_{14}H_{19}N_3NaO_2$: 284.1375; Found: 284.1355 $[M+Na]^+$.

***N*-benzyl-3-phenyl-1,2,4-oxadiazol-5-amine (51)**

Aminodioxime 110 mg (0.408 mmol), triphenylphosphine 114.3 mg (0.817 mmol), diethyl azodicarboxylate 0.128 mL (0.817 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as white solid (63.6 mg, yield 62%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 6.8 Hz, 2H), 7.43 (m, 3H), 7.34 (m, 5H), 6.71 (br s, NH), 4.63 (d, *J* = 6.1 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.4, 168.5, 137.2, 130.9, 128.9, 128.7, 128.1, 127.6, 127.5, 127.3, 47.7; IR (KBr) 3242, 1655, 1494, 1446, 1398, 1350 ν_{max}/cm^{-1}; m.p. 115.5-116.0 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{15}H_{14}N_3O$: 252.1136; Found: 252.1135 $[M+H]^+$.

***N*-(tert-butyl)-3-(4-fluorophenyl)-1,2,4-oxadiazol-5-amine (52)**

Aminodioxime 110 mg (0.434 mmol), triphenylphosphine 227.8 mg (0.868 mmol), diethyl azodicarboxylate 0.136 mL (0.868 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 98:2, 95:5) to give the product as white solid (74.6 mg, yield 73%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.10 (m, 2H), 5.58 (br s, NH), 1.44 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.4, 167.5, 164.0 (d, *J* = 248.5), 129.4 (d, *J* = 8.6), 124.1, 115.8 (d, *J* = 21.7), 52.8, 29.0 (3C); ^{19}F (282 MHz, $CDCl_3$) -109.24; IR (KBr) 3302, 1632, 1410, 1374, 1222, 840

ν_{max}/cm^{-1}; m.p. 108.1-109.2 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{12}H_{15}FN_3O$: 236.1199; Found: 236.1185 $[M+H]^+$.

_N_-(tert-butyl)-3-(pyridin-3-yl)-1,2,4-oxadiazol-5-amine (53)

Aminodioxime 60 mg (0.254 mmol), triphenylphosphine 133 mg (0.508 mmol), diethyl azodicarboxylate 0.080 mL (0.508 mmol), toluene dry 1 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 7:3) to give the product as white solid (27 mg, yield 49%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.31 (br s, 1H), 8.73 (br s, 1H), 8.40 (br d, 1H), 7.50 (m, 1H), 5.71 (br s, NH), 1.50 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.8, 166.4, 151.5, 148.9, 134.7, 124.5, 123.7, 53.0, 29.2; IR (KBr) 3210, 2987, 1750, 1372, 1276, 1226, 1101 ν_{max}/cm^{-1}; m.p. 140.8-141.7 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{11}H_{15}N_4O$: 219.1245; Found: 219.1246 $[M+H]^+$.

3-benzyl-_N_-cyclohexyl-1,2,4-oxadiazol-5-amine (54)

Aminodioxime 100 mg (0.383 mmol), triphenylphosphine 200 mg (0.765 mmol), diethyl azodicarboxylate 0.120 mL (0.765 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as white solid (46.6 mg, yield 47%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 3H), 7.30 (m, 2H), 5.65 (br d, NH), 3.87 (s, 2H), 3.52 (m, 1H), 1.98 (m, 2H), 1.74-1.57 (m, 3H), 1.41-1.20 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.6, 169.7, 136.0, 129.0, 128.7, 127.0, 52.7, 33.3, 32.7, 25.3, 24.7; IR (KBr) 3211, 3088, 1636, 1537, 1397, 718 ν_{max}/cm^{-1}; m.p. 90.9-91.7 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{15}H_{20}N_3O$: 258.1606; Found: 258.1601 $[M+H]^+$.

_N_-pentyl-3-(thiophen-2-yl)-1,2,4-oxadiazol-5-amine (55)

Aminodioxime 110 mg (0.39 mmol), triphenylphosphine 205 mg (0.78 mmol), diethyl azodicarboxylate 0.122 mL (0.78 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as yellow solid (68.3 mg, yield 74%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, 1H, *J* = 3.8, 1.2 Hz), 7.42 (dd, 1H, *J* = 4.9, 1.2 Hz), 7.10 (dd, 1H, *J* = 4.9, 3.8 Hz), 6.27 (br s, NH), 3.43 (q, 2H, *J* = 6.7 Hz), 1.61 (m, 2H), 1.31 (m, 4H), 0.87 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.2, 164.4, 129.3, 128.8, 128.6, 127.8, 43.8, 29.5, 28.8, 22.3, 14.0; IR (KBr) 3255, 2951, 1654, 1434, 1389, 1319 ν_{max}/cm^{-1}; m.p. 75.8-76.6 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{11}H_{16}N_3OS$: 238.1014; Found: 238.0989 $[M+H]^+$.

***N*-cyclohexyl-3-(thiophen-2-yl)-1,2,4-oxadiazol-5-amine (56)**

Aminodioxime 120 mg (0.449 mmol), triphenylphosphine 235 mg (0.898 mmol), diethyl azodicarboxylate 0.141 mL (0.898 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as yellow solid (76.7 mg, yield 68%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, 1H, *J* = 3.8, 1.2 Hz), 7.43 (dd, 1H, *J* = 4.9, 1.2 Hz), 7.11 (dd, 1H, *J* = 1.2, 3.8 Hz), 5.33 (br d, NH), 3.66 (m, 1H), 2.04 (m, 2H), 1.71 (m, 3H), 1.45-1.10 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.5, 164.5, 129.3, 128.8, 128.5, 127.7, 52.9, 33.2, 25.3, 24.6; IR (KBr) 3229, 2932, 1640, 1554, 1508, 1433, 1389, 1317 ν_{max}/cm^{-1}; m.p. 131.9-132.5 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{12}H_{16}N_3OS$: 250.1014; Found: 250.1008 $[M+H]^+$.

Computational Methods. All theoretical calculations were performed using the GAMESS (US) program.[28] All structures were optimized at the M06-2X/6-31G(d, p) level.[29] The corresponding vibrational frequencies were calculated at the same level to take account of the zero-point vibrational energy (ZPVE). We confirmed that all the reactants, intermediates, and product have no imaginary frequencies, and each transition state has one, and only one, imaginary frequency. The intrinsic reaction coordinate (IRC)[30] calculations were performed at the same level of theory to ensure that the transition states led to the expected reactants and products. All given energies are free Gibbs energies (in kcal mol^{-1}), all reported energetic values refer to standard conditions such as 298 K and 1 atm pressure. Solvent corrected geometries and energies were calculated with C-PCM as implemented in GAMESS (US).[31] In this model, the species of interest are embedded in a cavity of molecular shape surrounded by a polarizable continuum, whose field modifies the energy and

physical properties of the solute. The solvent reaction field is described by polarization charges distributed on the cavity surface. This procedure is known to reproduce experimental solvation energies reasonably well. Parameters for dichoromethane (DCM) were chosen since this was the solvent used for the experimental investigations. 3D pictures were made in Avogadro.[32]

ASSOCIATED CONTENT

Supporting information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. X-ray data for **28** (CIF). Cartesian coordinates (in Å), total energy (in a.u.), and imaginary frequencies (in cm^{-1}) of all structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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