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A Sustainable Synthesis of Oximes, Hydrazones and Thiosemicarbazones under Mild Organocatalyzed Reaction Conditions

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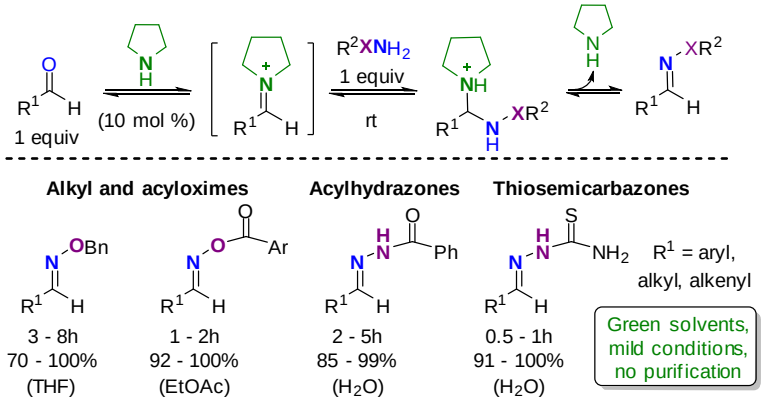
ABSTRACT: Pyrrolidine catalyzes very efficiently, presumably *via* iminium activation, the formation of acyloximes, acylhydrazones and thiosemicarbazones derived from aromatic and aliphatic aldehydes using equimolar amounts of reagents and green solvents. Experimental simplicity and excellent yields after a simple filtration are the main advantages of the method, being an alternative to those currently available especially for the acyl derivatives, which do not work under uncatalyzed conditions. Its application to the synthesis of acyloximes by direct condensation between aldehydes and acylhydroxylamines is unprecedented.



Hydroxylamines and hydrazines are commonly referred as α-nucleophiles, showing a distinctive enhanced reactivity towards electrophiles compared to amines. The origin of this α-effect probably relies on the presence of one or more nonbonding electron pairs in the atom adjacent to the reaction center.[1] Oximes and hydrazones are usually much more stable than other C=N functionalized compounds such as imines.[2] This higher stability is currently exploited in the emerging field of dynamic covalent chemistry[3] as well as in the preparation of bioconjugates.[4] In addition, these functionalities appear on several classes of biologically relevant products (Figure 1).[5,6]

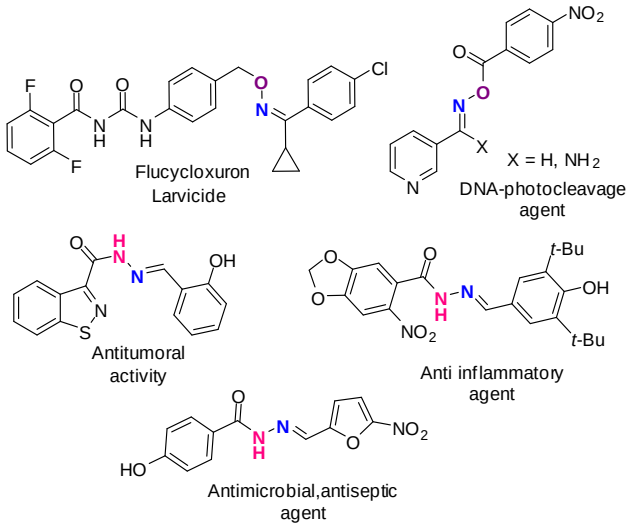
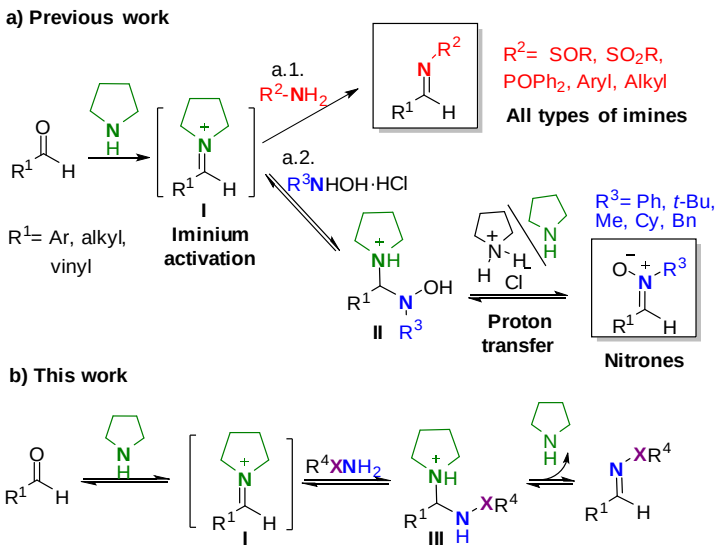


Figure 1. Oximes and hydrazones as important biological compounds.

Among the different approaches for the synthesis of oximes and hydrazones, the shortest method involves the direct condensation between a carbonyl compound and the corresponding α-nucleophile.[7] The importance of creating this type of bonds is clearly established in the relevant work by Dawson and co-workers, where oxime ligation could be efficiently promoted by aniline derivatives at neutral pH,[8] and the subsequent efforts to find other less toxic and water-soluble catalysts able to effect this transformation.[9,10]

We recently demonstrated that secondary amines might serve as efficient aminocatalysts in the preparation of imine derivatives, achieving optimal results when using pyrrolidine.[11] This metal-free process occurred through iminium ion (**I**) formation under mild reaction conditions, leading to a wide variety of imines in outstanding yields in the presence of a catalytic amount (10 mol %) of pyrrolidine (Scheme 1a, path a.1). Following the same methodology, we also developed a very efficient, simple, general and reliable protocol to prepare nitrones in a matter of minutes starting from differently *N*-substituted hydroxylamine hydrochlorides (Scheme 1a, path a.2).[12] In this case, the use of 1.2 equiv of pyrrolidine allows the complete liberation of the free hydroxylamine (which consumes 1 equiv of pyrrolidine), and also increases the electrophilicity of the carbonyl group through the formation of iminium ion **I**. In addition, nitrone formation is prompted because elimination of pyrrolidine from aminal **II** is very favored as it is easily protonated thanks to its basic character. Moreover, the simultaneous formation of pyrrolidinium chloride (1 equiv) turned out to be beneficial since the pyrrolidine/pyrrolidinium system acts as proton transfer favoring some steps of the catalytic cycle without hampering the nucleophilicity of the *N*-substituted hydroxylamine by protonation.

Scheme 1. Pyrrolidine catalysis *via* iminium activation ion and cooperative pyrrolidine/pyrrolidinium catalysis.



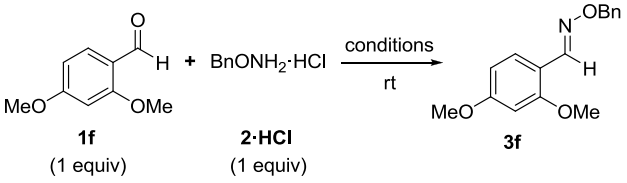
According to these results, we envisioned that the use of pyrrolidine could also have a beneficial effect on the preparation of oximes, hydrazones and derivatives (Scheme 1b). As in the formation of nitrones, the high reactivity of the corresponding α-nucleophile would produce a fast attack to either the aldehyde or to the iminium ion. Nevertheless, a positive role of pyrrolidine would be expected in the second step of the catalytic cycle, where the elimination of pyrrolidine from the resulting protonated aminal intermediate **III** could be very favored.[13] Furthermore, we can predict a more marked influence of pyrrolidine in the preparation of the more biologically relevant *N*-acyloximes[14] and *N*-acylhydrazones,[15] which present higher synthetic difficulties because of the lower nucleophilic character of the corresponding α-nucleophiles. Particularly, *N*-benzoyloximes have been prepared almost exclusively through indirect methods,[16] as their access by direct condensation affords very low yields as a consequence of the easy evolution towards the corresponding nitriles.[17]

Therefore, we present herein a systematic study to evaluate the role of pyrrolidine in the condensations of aldehydes with nucleophiles of type **R-X-NH2** where X = NH, O and R = aryl, alkyl, -COR, -SO_2R, -C(=S)NH_2; in order to provide a general method especially competitive to prepare substrates exhibiting higher synthetic difficulties as well as biological interest. In all

cases, both water and organic solvents have been tested. Yields and conditions have been compared with those of the best methods described so far in the literature.

We started by testing the role of pyrrolidine in the preparation of oxime ethers from *O*-alkylhydroxylamine hydrochlorides. According to the literature, this transformation usually requires a large excess of base, typically pyridine or NaOAc, in order to release the free hydroxylamine. Furthermore, polar protic solvents, excess of reagent, heat, extended reaction times and tedious purifications are usually needed to attain high yields of the final product.[18] Contrasting with this information, we have found that the condensation between equimolecular amounts of 2,4-dimethoxybenzaldehyde (**1f**) and *O*-benzylhydroxylamine hydrochloride (**2**·HCl) occurred in the absence of any base at room temperature in aqueous media, and hence *O*-benzyloxime **3f** was obtained at 70% conversion after 30 min (Table 1, entry 1), requiring 4 h to reach full conversion (entry 2). This behavior could be due to the fast dissociation of hydrochloride **2**·HCl in water and the high reactivity of the free hydroxylamine. The addition of 0.1 equiv of pyrrolidine to the reaction mixture slightly increases the reaction rate (compare entries 1 and 3), which is more marked by using higher amounts of pyrrolidine (compare entries 2 with 4-6), being possible the substantial reduction of the time for obtaining quantitative yields of **3f**. This moderate catalytic effect of pyrrolidine in aqueous media could be mainly attributed to its influence as a base in accelerating the liberation of the free hydroxylamine from its hydrochloride (**2**·HCl), demonstrating that the effect of pyrrolidine was very similar to that observed by addition of NaOAc, a representative base employed in oxime synthesis, in both stoichiometric and catalytic amounts (entries 7-8).

Table 1. Optimization of the Reaction Conditions to Form *O*-Benzyloxime 3f from Aldehyde 1f and Hydroxylamine 2·HCl[a]



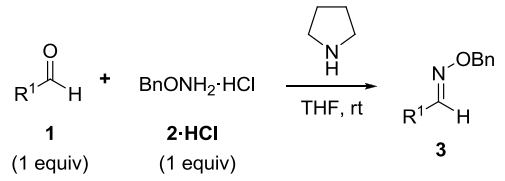
entry	base (equiv)	solvent	*t* (h)	conv. (%)[b]
1	none	H_2O	0.5	70
2	none	H_2O	4	100
3	pyrrolidine (0.1)	H_2O	0.5	88
4	pyrrolidine (1.0)	H_2O	2	100 (99)[c]
5	pyrrolidine (1.1)	H_2O	1	100 (93)[c]
6	pyrrolidine (1.1)	H_2O	0.5	97
7	NaOAc (1.1)	H_2O	0.5	100
8	NaOAc (0.1)	H_2O	0.5	88
9	none	CH_2Cl_2	0.5	13
10	NaOAc (0.1)	CH_2Cl_2	0.5	30
11	pyridine (0.1)	CH_2Cl_2	0.5	47
12	pyrrolidine (0.1)	CH_2Cl_2	0.5	55
13	pyridine (0.1)	THF	0.5	37
14	pyrrolidine (0.1)	THF	0.5	54
15	pyrrolidine (0.1)	THF	4	100 (100)[c]

[a]0.2 mmol scale. [b]Measured by integration in the ^{1}H NMR crude spectra. [c]In parentheses, isolated yield of pure product after filtration through basic celite.

The preparation of oxime **3f** was also studied in organic solvents, where the dissociation of hydrochloride **2**·HCl producing the free hydroxylamine is more difficult than in water, determining a much slower formation of the oxime **3f**. Thus, the conversion observed after 30 min in CH_2Cl_2 without any base was only 13% (entry 9), much lower than that in water (entry 1). The influence produced by the addition of catalytic amounts of bases is now more significant (entries 10-12). Pyrrolidine resulted to be efficient in CH_2Cl_2, as well as in THF (compare entries 13 and 14), where full conversion was reached after 4 h, being oxime **3f** isolated in quantitative yield after removing pyrrolidine by a simple filtration through basic celite (entry 15). The higher conversion obtained in the presence of pyrrolidine with respect to other commonly used bases (compare entries 13 and 14) suggests, even with the highly reactive hydroxylamines, an effect of pyrrolidine beyond of the simple liberation of the hydrochloride **2**·HCl.

The latter pyrrolidine-catalyzed conditions were extended to a variety of aromatic and aliphatic aldehydes to render the corresponding oxime ethers **3** in excellent yields. Thus, electron-donating or electron-withdrawing groups were well tolerated in several benzaldehyde derivatives, although in some cases the amount of pyrrolidine should be raised to 0.2 equiv for achieving a better yield (Table 2, entries 1-7). The process was also suitable for preparing the *O*-benzyloximes derived from 2-formylpyridine (entry 8), and the more challenging enals (entry 9) or aliphatic aldehydes (entries 10-12).

Table 2. Synthesis of *O*-Benzyloximes 3 from Aldehydes 1[a]



entry	R^1 (aldehyde)	pyrrolidine (equiv)	*t* (h)	**3** (yield, %)[b]
1	Ph (**1a**)	0.2	5.5	**3a** (84)
2	4-$MeOC_6H_4$ (**1b**)	0.2	6	**3b** (80)
3	4-$NO_2C_6H_4$ (**1c**)	0.2	6	**3c** (96)
4	4-ClC_6H_4 (**1d**)	0.2	6	**3d** (96)
5	2-ClC_6H_4 (**1e**)	0.1	6	**3e** (92)
6	2,4-di-$MeOC_6H_4$ (**1f**)	0.1	4	**3f** (100)
7	3,4,5-tri-$MeOC_6H_4$ (**1g**)	0.1	7.5	**3g** (100)
8	2-pyridyl (**1h**)	0.1	3	**3h** (85)
9	PhCH=CH (**1i**)	0.2	8	**3i** (92)
10	*i*-Bu (**1j**)	0.1	2	**3j** (100)
11	cyclohexyl (**1k**)	0.1	1.5	**3k** (91)
12	*t*-Bu (**1l**)	0.2	4	**3l** (70)

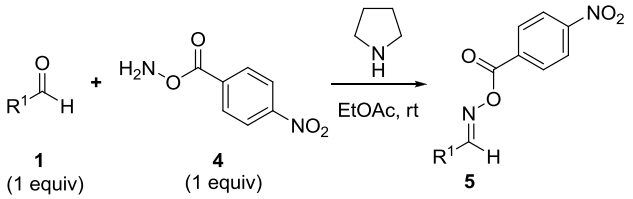
[a]0.2 mmol scale. [b]Isolated yield of pure product after filtration through basic celite.

The yields of the *O*-benzyloximes collected in Table 2 are similar or higher than those reported in the literature, most of them requiring high temperatures and excess of nucleophile and base (in some cases is used as solvent), which implies the use of extraction operations, chromatographic columns and/or recrystallization techniques to isolate and purify the oximes.[18]

In this sense, our method proved superior in terms of simplicity (room temperature, short reaction times and ease of purification). Other strategies commonly employed consist of the alkylation of the corresponding aldoximes or the use of radical or oxidative methods, procedures which imply several reaction steps and a lower atomic economy (see Table S5 in the SI for more details).

O-Benzoyloximes are interesting compounds because of their higher biological relevance compared to the parent oxime ethers.[14] They are generally synthesized from the corresponding aldehydes through a two-step protocol (formation of oximes and further acylation) that usually entails relatively harsh reaction conditions,[16,19,20] because the methods for their preparation through direct condensation between aldehydes and *O*-acylhydroxylamines normally afford mixtures of the *O*-benzoyloxime and the corresponding nitrile.[17] These features converted benzoyloxime derivatives **5** in special goals for testing our synthetic method. The results obtained in the reaction of aromatic and aliphatic aldehydes with *O*-(4-nitrobenzoyl)hydroxylamine (**4**) are depicted in Table 3. The established optimal conditions implied using 10-20 mol % of pyrrolidine in EtOAc as solvent, which allowed us to obtain very high yields within 1-2 h. Partial decomposition of the aromatic benzoyloximes into their corresponding nitriles was observed when using protic solvents (H_2O or MeOH), higher catalyst loadings or under extended reaction times. Again, purification was easily carried out by filtration through celite. We must remark the excellent results obtained in the synthesis of the 4-nitrobenzoyloxime derived from 2-formylpyridine, **5h** (entry 5), which was recently designed for interacting and cleaving DNA by the action of light ("photo-cleaver"), with potential applications in both treatment of solid tumors and as a diagnostic tool for the detection of cancer.[14a]

Table 3. Synthesis of *O*-Benzoyloximes 5 from Aldehydes 1[a]



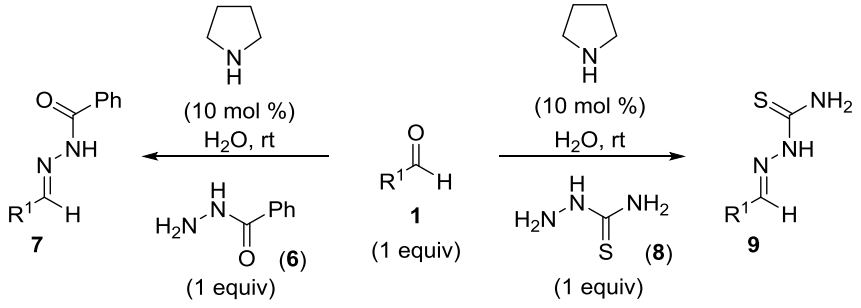
entry	R^1 (aldehyde)	pyrrolidine (equiv)	*t* (h)	**5** (yield, %)[b]
1	Ph (**1a**)	0.2	2	**5a** (100)
2	4-$MeOC_6H_4$ (**1b**)	0.1	1	**5b** 95
3	4-$NO_2C_6H_4$ (**1c**)	0.2	2	**5c** (99)
4	4-ClC_6H_4 (**1d**)	0.2	2	**5d** (93)
5	2-pyridyl (**1h**)	0.1	1	**5h** (93)
6	*i*-Bu (**1j**)	0.1	2	**5j** (100)

[a]0.2 mmol scale. [b]Isolated yield of pure product after filtration through celite.

Next, we turned our attention to the synthesis of the parent aryl- and sulfonylhydrazones, which are versatile synthetic intermediates.[21] The high reactivity of arylhydrazines determines that their reactions with aldehydes were completed in a matter of minutes, both in H_2O or THF, being the presence of pyrrolidine practically irrelevant (for more information, see Tables S1 and S2 in SI). However, our method proved to be very practical when applied to the synthesis of *N*-acylhydrazones **7** and thiosemicarbazones **9** from the corresponding acylhydrazines **6** and thiosemicarbazides **8**, respectively, much less nucleophilic than arylhydrazines (Table 4). Therefore, the reported methods for preparing this type of compounds in high yields and reasonable times involve the use of microwaves, acid catalysis, reflux temperature or excess of reagents, which impose the use of purification processes (see Table S6 in SI for detailed information). By contrast, the coupling of equimolar quantities of aldehydes **1** with

benzohydrazide **6** proceeded smoothly at room temperature in the presence of catalytic pyrrolidine in H_2O, providing the final acylhydrazones **7** in high yields under much milder reaction conditions compared to those previously described.[22] In comparison, the non-catalyzed reaction did not afford any amount of the target *N*-acylhydrazones after similar reaction times (see Tables S3 and S4 in SI). The scope of the process included differently substituted aromatic aldehydes as well as aliphatic ones. The fact that these reactions work under aqueous conditions is a noteworthy point as they are relevant as pharmacophoric moieties[15] and synthetic intermediates. [21] The process could be scaled-up providing multigram amounts of the final *N*-acylhydrazones in comparable chemical yields and reaction times (Table 4, entry 8).

Table 4. Synthesis of *N*-Acylhydrazones 7 and Thiosemicarbazones 9 from Aldehydes 1[a]



entry	R^1 (aldehyde)	*N*-acylhydrazones		thiosemicarbazones	
		t (h)	**7** (yield, %)[b]	*t* (min)	**9** (yield, %)[b]
1	Ph (**1a**)	2	**7a** (98)	40	**9a** (99)
2	4-$MeOC_6H_4$ (**1b**)	4	**7b** (91)	50	**9b** (91)
3	4-$NO_2C_6H_4$ (**1c**)	5	**7c** (90)	30	**9c** (99)
4	4-ClC_6H_4 (**1d**)	2	**7d** (93)	35	**9d** (95)
5	2-ClC_6H_4 (**1e**)	3	**7e** (85)	60	**9e** (92)

6	*i*-Bu (**1h**)	2	**7j** (95)	35	**9j** (98)
7	cyclohexyl (**1k**)	2	**7k** (99)	35	**9k** (100)
8[c]	Ph (**1a**)	3	**7a** (94)		

[a]0.2 mmol scale. [b]Isolated yield of pure product after filtration through celite. [c]Performed on 10 mmol scale.

Analogously, the parent semithiocarbazones **9** were prepared under identical reaction conditions by treatment of aldehydes **1** with thiosemicarbazide **8**, proceeding even faster than in the case of acylhydrazones (Table 4). Once again, synthetic protocols previously described for the preparation of compounds **9** that provided high yields demanded either heat, longer reaction times, excess of reagents or the use of acidic catalysts and a recrystallization process to purify the products (see Table S7 in SI for more detailed information).[23]

In conclusion, pyrrolidine is also an excellent catalyst for the efficient synthesis of substituted oximes, hydrazones and thiosemicarbazones through iminium ion activation and with minimal experimental manipulation and waste. Its usefulness is especially important when applied to the preparation of the more challenging and biologically relevant acyl derivatives. *N*-Acyloximes were not previously accessible through the direct condensation between aldehydes and acylhydroxylamines and cannot be prepared under uncatalyzed conditions, whereas *N*-acylhydrazones had been prepared only through impractical protocols. These mild and acid-free reaction conditions required are amenable for further implementation in the synthesis of oxime- and hydrazone-containing biomolecules while preserving their structural integrity.

EXPERIMENTAL SECTION

General Experimental Methods. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with 300 MHz spectrometers in $CDCl_3$, THF-d_6, acetone-d_6 or DMSO-d_6 with the residual solvent peak as an internal standard. Chemical shifts (δ) are given in parts per million, and coupling constants are given as absolute values expressed in hertz. Positive electrospray ionization (ESI) or electron impact ionization (EI) mass spectra were collected using a TOF analyzer system. Obtained data are expressed in mass/charge (m/z) units. Values between parentheses indicate relative intensities with regard to the base peak. Silica gel pore 60 Å, 40-63 μm, Celite® 512 medium and (Hyflo® Super Cel®) were used for filtration. All solvents were used without previous treatment. EtOAc and THF were used in analytical grade. Although we have proven that tap water can be used, the results presented herein have been obtained using deionized water. All starting materials were purchased from commercial suppliers. Aldehydes were washed with aqueous saturated $NaHCO_3$ to remove acids traces. Pyrrolidine > 99.5% pure was used.

*General procedure for the synthesis of O-benzyloximes **3***. To a 0.33 M solution of *O*-benzylhydroxylamine hydrochloride (**2**·HCl) (32 mg, 0.2 mmol) and the corresponding aldehyde **1** (1 equiv) in THF, a freshly prepared 0.2 M solution of pyrrolidine in THF (10 or 20 mol %) was added. The mixture was stirred at room temperature during the time indicated in each case. Then, the reaction was filtered through a short pad of basic celite (Hyflo® Super Cel®) using a glass frit with EtOAc to obtain the final oximes **3** without any further purification. *O*-benzyloximes **3** were obtained as a mixture of diastereomers *E/Z*.

*Benzaldehyde O-benzyl oxime (**3a**).* From benzaldehyde (**1a**) (21.2 mg, 0.2 mmol) and 20 mol % of pyrrolidine, after 5.5 h the title compound was obtained in 84% yield (35.5 mg) as a

colourless oil (*E/Z* ratio 87:13). Data of the mayor diastereomer (*E*): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.77–7.67 (m, 2H), 7.62–7.39 (m, 8H), 5.37 (s, 2H). Spectroscopic data matched those previously reported.[18a]

*4-Methoxybenzaldehyde O-benzyl oxime (**3b**).* From 4-methoxybenzaldehyde (**1b**) (27.2 mg, 0.2 mmol) and 20 mol % of pyrrolidine, after 6 h the title compound was obtained in 80% yield (38.6 mg) as a colourless oil (*E/Z* ratio 83:17). Data of the mayor diastereomer (*E*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.38–7.20 (m, 5H), 6.80 (d, *J* = 8.8 Hz, 3H), 5.11 (s, 2H), 3.73 (s, 3H). Spectroscopic data matched those previously reported.[24]

*4-Nitrobenzaldehyde O-benzyl oxime (**3c**).* From 4-nitrobenzaldehyde (**1c**) (30.2 mg, 0.2 mmol) and 20 mol % of pyrrolidine, after 6 h the title compound was obtained in 96% yield (49.2 mg) as a colourless oil (*E/Z* ratio 86:14). Data of the mayor diastereomer (*E*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30–8.19 (m, 3H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.54–7.35 (m, 5H), 5.32 (s, 2H). Spectroscopic data matched those previously reported.[25]

*4-Chlorobenzaldehyde O-benzyl oxime (**3d**).* From 4-chlorobenzaldehyde (**1d**) (28.1 mg, 0.2 mmol) and 20 mol % of pyrrolidine, after 6 h the title compound was obtained in 96% yield (47 mg) as a colourless oil (*E/Z* ratio 81:19). Data of the major diastereomer (*E*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.36–7.18 (m, 7H), 5.12 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9 (CH=N), 132.4 (C), 130.9 (C), 129.1 (2 x CH), 128.8 (C), 128.6 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 128.1 (C), 76.7 (CH_2). MS (EI): *m*/*z* 245 (M^+, 4), 139 (12), 137 (32), 102 (14), 91 (100), 77 (12). HRMS (EI): calcd for $C_{14}H_{12}NOCl$ (M^+): 245.0607; found: 245.0596.

*2-Chlorobenzaldehyde O-benzyl oxime (**3e**).* From 2-chlorobenzaldehyde (**1e**) (28.1 mg, 0.2 mmol) and 10 mol % of pyrrolidine, after 6 h the title compound was obtained in 92% yield (45

mg) as a colourless oil (*E/Z* ratio >95:5). Data of the major diastereomer (*E*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.80 (d, *J* = 7.3 Hz, 1H), 7.44–7.04 (m, 8H), 5.15 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2 (CH=N), 137.4 (C), 134.0 (C), 130.9 (CH), 130.1 (C), 129.94 (CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.2 (CH), 127.3 (CH), 127.0 (C), 76.8 (CH_2). MS (EI): *m*/*z* 210 (M^+-Cl, 12), 137 (16), 91 (100). HRMS (EI): calcd for $C_{14}H_{12}NO$ (M^+-Cl): 210.0919; found: 210.0896.

*2,4-Dimethoxybenzaldehyde O-benzyl oxime (**3f**).* From 2,4-dimethoxybenzaldehyde (**1f**) (33.2 mg, 0.2 mmol) and 10 mol % of pyrrolidine, after 4 h the title compound was obtained in quantitative yield (54.2 mg) as a colourless oil (*E/Z* ratio >95:5). Data of the major diastereomer (*E*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.39–7.17 (m, 5H), 6.39 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 5.09 (s, 2H), 3.71 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (C-OCH_3), 159.0 (C-OCH_3), 145.2 (CH=N), 138.0 (C), 128.5 (2 x CH), 128.4 (2 x CH), 127.9 (CH), 127.5 (CH), 113.9 (C), 105.6 (CH), 98.3 (CH), 76.2 (CH_2), 55.6 (OCH_3), 55.50 (OCH_3). MS (EI): *m*/*z* 271 (M^+, 15), 163 (100), 149 (17), 134 (69), 91 (53). HRMS (EI): calcd for $C_{16}H_{17}NO_3$ (M^+): 271.1208; found: 271.1197.

3,*4,5-Trimethoxybenzaldehyde O-benzyl oxime (**3g**).* From 3,4,5-trimethoxybenzaldehyde (**1g**) (39.2 mg, 0.2 mmol) and 10 mol % of pyrrolidine, after 7.5 h the title compound was obtained in quantitative yield (60.2 mg) as a colourless oil (*E/Z* ratio 88:12). Data of the major diastereomer (*E*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.37–7.19 (m, 5H), 6.72 (s, 2H), 5.13 (s, 2H), 3.78 (s, 6H), 3.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5 (CH=N), 148.9 (2 x C-OCH_3), 139.8 (C-OCH_3), 137.6 (C), 128.5 (2 x CH), 128.4 (2 x CH), 128.0 (CH), 127.7 (C), 104.3 (2 x CH), 76.4 (CH_2), 60.9 (OCH_3), 56.3 (2 x OCH_3). MS (EI): *m*/*z* 301 (M^+, 25), 193

(100), 178 (99), 150 (31), 135 (41). HRMS (EI): calcd for $C_{17}H_{19}NO_4$ (M^+): 301.1314; found: 301.1302.

*Picolinaldehyde O-benzyl oxime (**3h**).* From 2-formylpyridine (**1h**) (21.4 mg, 0.2 mmol) and 10 mol % of pyrrolidine, after 3 h the title compound was obtained in 85% yield (36 mg) as a colourless oil (*E/Z* ratio >98:2). Data of the mayor diastereomer (*E*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.8 Hz, 1H), 8.28 (s, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.52–7.34 (m, 5H), 7.33–7.25 (m, 1H), 5.31 (s, 2H). Spectroscopic data matched those previously reported.[18a]

*Cinnamaldehyde O-benzyl oxime (**3i**).* From cinamaldehyde (**1i**) (26.4 mg, 0.2 mmol) and 20 mol % of pyrrolidine, after 8 h the title compound was obtained in 92% yield (43.6 mg) as a colourless oil (*E/Z* ratio 71:29). Data of diastereomer *(E):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 9.5 Hz, 1H), 7.38–7.22 (m, 10H), 6.81 (dd, *J* = 16.0, 9.5 Hz, 1H), 6.69 (d, *J* = 16.0 Hz, 1H), 5.13 (s, 2H). Spectroscopic data matched those previously reported.[26]

*3-Methylbutanal O-benzyl oxime (**3j**).* From 3-methylbutanal (**1j**) (17.2 mg, 0.2 mmol) and 10 mol % of pyrrolidine, after 2 h the title compound was obtained in quantitative yield (38.2 mg) as a colourless oil (*E/Z* ratio 61:39). Spectroscopic data matched those previously reported.[18b]

*Cyclohexanecarbaldehyde O-benzyl oxime (**3k**).* From cyclohexanecarbaldehyde (**1k**) (22.4 mg, 0.2 mmol) and 10 mol % of pyrrolidine, after 1.5 h the title compound was obtained in 91% yield (39.5 mg) as a colourless oil (*E/Z* ratio 76:24). Spectroscopic data matched those previously reported.[18b]

*Pivalaldehyde O-benzyl oxime (**3l**).* From pivalaldehyde (**1l**) (17.2 mg, 0.2 mmol) and 20 mol % of pyrrolidine, after 4 h the title compound was obtained in 70% yield (26.7 mg) as a colourless

oil (*E/Z* ratio 100:0). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.29 (m, 5H), 5.10 (s, 2H), 1.15 (s, 9H). Spectroscopic data matched those previously reported.[18f]

*General procedure for the synthesis of O-benzoyloximes **5***. To a 0.33 M solution of *O*-(4-nitrobenzoyl)hydroxylamine (**4**) (36.4 mg, 0.2 mmol) and the corresponding aldehyde **1** (1 equiv) in EtOAc, a freshly prepared 0.2 M solution of pyrrolidine in EtOAc (10 or 20 mol %) was added. The mixture was stirred at room temperature during the time indicated in each case. Then, the reaction was filtered through a short pad of celite using a glass frit with EtOAc to obtain the final *O*-benzoyloximes **5** without any further purification. *O*-Benzoyloximes derived from aromatic aldehydes show a fast decomposition process at room temperature toward the corresponding nitrile, hampering in some cases their full characterization.

*(E)-Benzaldehyde O-(4-nitrobenzoyl)oxime (**5a**).* From benzaldehyde (**1a**) (21.2 mg, 0.2 mmol) and 20 mol % of pyrrolidine, after 2 h the title compound was obtained in quantitative yield (54 mg). ^{1}H NMR (300 MHz, acetone-d_6) δ 8.75 (s, 1H), 8.35–8.21 (m, 4H), 7.83–7.69 (m, 2H), 7.55–7.34 (m, 3H). Spectroscopic data matched those previously reported.[17b]

*(E)-4-Methoxybenzaldehyde O-(4-nitrobenzoyl)oxime (**5b**).* From 4-methoxybenzaldehyde (**1b**) (27.2 mg, 0.2 mmol) and 10 mol % of pyrrolidine, after 1 h the title compound was obtained in 95% yield (57 mg) as a yellow solid. ^{1}H NMR (300 MHz, THF-d_8) δ 8.60 (s, 1H), 8.40–8.24 (m, 4H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, THF-d_8) δ 164.0 (C=O), 162.4 (C), 158.0 (CH=N), 152.0 (C), 134.8 (C), 131.6 (2 x CH), 131.0 (2 x CH), 124.6 (C), 115.8 (2 x CH), 115.4 (2 x CH), 55.9 (CH_3). MS (ESI^+): *m*/*z* 323 (M^++Na) (100), 173 (56), 139 (44). HRMS (ESI^+): calcd for $C_{15}H_{12}N_2O_5Na$ (M^++Na): 323.0638; found: 323.0638.

*(E)-4-Nitrobenzaldehyde O-(4-nitrobenzoyl)oxime (**5c**).* From 4-nitrobenzaldehyde (**1c**) (30.2 mg, 0.2 mmol) and 20 mol % of pyrrolidine, after 2 h the title compound was obtained in 99% yield (63 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.09 (d, *J* = 9.2 Hz, 2H), 8.30 (d, *J* = 9.0 Hz, 2H), 8.38 (d, *J* = 9.2 Hz, 2H), 8.42 (d, *J* = 9.0 Hz, 2H), 9.16 (s, 1H); (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.35–8.20 (m, 6H), 7.95 (d, *J* = 8.7 Hz, 2H). Spectroscopic data matched those previously reported.[17b]

*(E)-4-Chlorobenzaldehyde O-(4-nitrobenzoyl)oxime (**5d**).*[19] From 4-chlorobenzaldehyde (**1d**) (28.1 mg, 0.2 mmol) and 20 mol % of pyrrolidine, after 2 h the title compound was obtained in 93% yield (57 mg). ^{1}H NMR (300 MHz, acetone-d_6) δ 8.90 (s, 1H), 8.49–8.35 (m, 4H), 7.91 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H). MS (ESI$^+$): *m*/*z* 327 (M^++Na) (15), 209 (93), 173 (50), 139 (29). HRMS (ESI$^+$): calcd for $C_{14}H_9N_2O_4NaCl$ (M^++Na): 327.0143; found: 327.0151.

*(E)-Picolinaldehyde O-(4-nitrobenzoyl) oxime (**5h**).* From 2-formylpyridine (**1h**) (21.4 mg, 0.2 mmol) and 10 mol % of pyrrolidine, after 1 h the title compound was obtained in 93% yield (50.4 mg) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.8 Hz, 1H), 8.69 (s, 1H), 8.40–8.30 (m, 4H), 8.20 (d, *J* = 7.8 Hz, 1H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.47–7.39 (m, 1H). Spectroscopic data matched those previously reported.[14a]

*(E)-3-Methylbutanal O-(4-nitrobenzoyl)oxime (**5j**).* From 3-methylbutanal (**1j**) (17.2 mg, 0.2 mmol) and 10 mol % of pyrrolidine, after 2 h the title compound was obtained in quantitative yield (50 mg) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36–8.17 (m, 4H), 7.93 (t, *J* = 6.8 Hz, 1H), 2.36 (t, *J* = 6.8 Hz, 2H), 2.03–1.89 (m, 1H), 1.02 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (C=O), 160.6 (CH=N), 150.8 (C), 134.4 (C), 130.9 (2 x CH), 123.9 (2 x CH), 38.1 (CH_2), 26.7 (CH), 22.5 (2 x CH_3). MS (ESI$^+$): *m*/*z* 273 (M^++Na) (100), 251 (M^++H) (27). HRMS (ESI$^+$): calcd for $C_{12}H_{14}N_2O_4Na$ (M^++Na): 273.0845; found: 273.0835.

*General procedure for the synthesis of N-acylhydrazones **7**.* To a solution of benzohydrazide (**6**) (27.2 mg, 0.2 mmol) and the corresponding aldehyde **1** (1 equiv) in 0.5 mL of deionized H_2O, a freshly prepared 0.2 M solution of pyrrolidine in deionized H_2O (100 µL, 10 mol %) was added. The mixture was stirred at room temperature during the time indicated in each case. Then, the reaction was filtered through a short pad of celite using a glass frit with EtOAc to obtain the final *N*-acylhydrazones **7** without any further purification.

(E)-N'-Benzylidenebenzohydrazide (**7a**). From benzaldehyde (**1a**) (21.2 mg, 0.2 mmol), after 2 h the title compound was obtained in 98% yield (44 mg) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (s, NH), 8.48 (s, 1H, CH=N), 7.93 (d, *J* = 7.23 Hz, 2H), 7.74 (d, *J* = 6.3 Hz, 2H), 7.53−7.32 (m, 6H). Spectroscopic data matched those previously reported.[22a]

*(E)-N'-(4-Methoxybenzylidene)benzohydrazide (**7b**).*[22c-d] From 4-methoxybenzaldehyde (**1b**) (27.2 mg, 0.2 mmol), after 4 h the title compound was obtained in 91% yield (46.3 mg) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (bs, 1H), 8.39 (s, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.60–7.42 (m, 3H), 6.98 (d, *J* = 8.7 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.9 (C=O), 160.8 (C), 147.7 (CH=N), 133.5 (C), 131.5 (C), 128.6 (2 x CH), 128.4 (2 x CH), 127.5 (2 x CH), 126.9 (CH), 114.3 (2 x CH), 55.2 (CH_3). MS (EI): *m*/*z* 252 (M^+ - 2H) (100), 181 (31), 135 (76), 105 (41). HRMS (EI): calcd for $C_{15}H_{12}N_2O_2$ (M^+ - 2H): 252.0899; found: 252.0899.

*(E)-N'-(4-Nitrobenzylidene)benzohydrazide (**7c**).*[27] From 4-nitrobenzaldehyde (**1c**) (30.2 mg, 0.2 mmol), after 5 h the title compound was obtained in 90% yield (48.4 mg) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.15 (bs, 1H), 8.57 (s, 1H), 8.32 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.94 (d, *J* = 7.3 Hz, 2H), 7.73–7.39 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.4 (C=O), 147.8 (CH=N), 145.2 (C), 140.6 (2 X CH), 133.1 (C), 131.9 (C), 128.5 (2 X CH),

127.9 (2 X CH), 127.7 (CH), 124.0 (2 X CH). MS (ESI^+): m/z 270 ($M^+ + 1$) (100). HRMS (ESI^+): calcd for C14H12N3O3 ($M^+ + 1$): 270.0873; found: 270.0882.

*(E)-N'-(4-Chlorobenzylidene)benzohydrazide (**7d**).*[28] From 4-chlorobenzaldehyde (**1d**) (28.1 mg, 0.2 mmol), after 2 h the title compound was obtained in 93% yield (48 mg) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89 (bs, NH, 1H), 8.44 (s, 1H), 7.90 (d, *J* = 7.4 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.63–7.39 (m, 5H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.1 (C=O), 146.0 (CH=N), 134.5 (C), 133.2 (C), 131.8 (C), 128.9 (3 x CH), 128.6 (2 x CH), 128.4 (2 x CH), 127.6 (2 x CH). MS (ESI^+): *m*/*z* 259 ($M^+ + 1$) (100). HRMS (ESI^+): calcd for $C_{14}H_{12}N_2OCl$ ($M^+ + 1$): 259.0632; found: 259.0633.

*(E)-N'-(2-Chlorobenzylidene)benzohydrazide (**7e**).* From 2-chlorobenzaldehyde (**1e**) (28.1 mg, 0.2 mmol), after 3 h the title compound was obtained in 85% yield (44 mg) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.12 (bs, NH 1H), 8.93 (s, CH=N), 8.12–7.82 (m, 3H), 7.61–7.25 (m, 6H). Spectroscopic data matched those previously reported.[22c]

*(E)-N'-(3-Methylbutylidene)benzohydrazide (**7j**).* From 3-methylbutanal (**1j**) (17.2 mg, 0.2 mmol), after 2 h the title compound was obtained in 95% yield (39 mg) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.85–7.72 (m, 3H), 7.59–7.41 (m, 3H), 2.15 (t, *J* = 5.7 Hz, 2H), 1.84 (m, 1H), 0.94 (m, 6H). Spectroscopic data matched those previously reported.[22a]

*(E)-N'-(Cyclohexylmethylene)benzohydrazide (**7k**).* From cyclohexanecarbaldehyde (**1k**) (22.4 mg, 0.2 mmol), after 2 h the title compound was obtained in 99% yield (45.6 mg) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.38 (bs, 1H), 7.83 (d, *J* = 7.7 Hz, 2H), 7.66 (d, *J* = 5.0 Hz, 1H), 7.58–7.38 (m, 3H), 2.35–2.13 (m, 1H), 1.84–1.53 (m, 5H), 1.40–1.06 (m, 5H). Spectroscopic data matched those previously reported.[22b]

*Large-scale procedure for the synthesis of N-acylhydrazone **7a**.* To a solution of benzohydrazide (**6**) (1.46 g, 10.74 mmol) and benzaldehyde (**1a**) (1.14 g, 10.74 mmol) in 27 mL of deionized H_2O, pyrrolidine (88 µL, 1.07 mmol) was added. The mixture was stirred at room temperature for 3 h, and then filtered off using a glass frit washing the solid with cold H_2O (4 x 30 mL) to give *N*-acylhydrazone **7a** in 94% yield (2.27 g) without any further purification.

*General procedure for the synthesis of thiosemicarbazones **9**.* To a solution of thiosemicarbazide (**8**) (18.2 mg, 0.2 mmol) and the corresponding aldehyde **1** (1 equiv) in 0.5 mL of deionized H_2O, a freshly prepared 0.2 M solution of pyrrolidine in deionized H_2O (100 µL, 10 mol %) was added. The mixture was stirred at room temperature during the time indicated in each case. Then, the reaction was filtered through a short pad of celite using a glass frit with EtOAc to obtain the final thiosemicarbazones **9** without any further purification.

*(E)-2-Benzylidenehydrazine-1-carbothioamide (**9a**).* From benzaldehyde (**1a**) (21.2 mg, 0.2 mmol), after 40 min the title compound was obtained in 99% yield (35.4 mg) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 8.15 (s, 1H), 7.79–7.70 (m, 2H), 7.42–7.33 (m, 3H). Spectroscopic data matched those previously reported.[23a]

*(E)-2-(4-Methoxybenzylidene)hydrazine-1-carbothioamide (**9b**).* From 4-methoxybenzaldehyde (**1b**) (27.2 mg, 0.2 mmol), after 50 min the title compound was obtained in 91% yield (38 mg) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 7.99 (s, 1H), 7.60 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.70 (s, 3H). Spectroscopic data matched those previously reported.[23a]

*(E)-2-(4-Nitrobenzylidene)hydrazine-1-carbothioamide (**9c**).* From 4-nitrobenzaldehyde (**1c**) (30.2 mg, 0.2 mmol), after 30 min the title compound was obtained in 99% yield (44.3 mg) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.71 (s, 1H, NH), 8.41 (s, 1H, CH=N), 8.26 and

8.38 (2s, 2H, NH_2), 8.22 (d, *J* = 8.2 Hz, 2H), 8.07 (d, *J* = 8.2 Hz, 2H). Spectroscopic data matched those previously reported.[23b]

*(E)-2-(4-Chlorobenzylidene)hydrazine-1-carbothioamide (**9d**).* From 4-chlorobenzaldehyde (**1d**) (28.1 mg, 0.2 mmol), after 35 min the title compound was obtained in 95% yield (40.5 mg) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 8.18 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H). Spectroscopic data matched those previously reported.[23c]

*(E)-2-(2-Chlorobenzylidene)hydrazine-1-carbothioamide (**9e**).* From 2-chlorobenzaldehyde (**1e**) (28.1 mg, 0.2 mmol), after 60 min the title compound was obtained in 92% yield (39.3 mg) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 8.59 (s, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 7.52–7.27 (m, 3H). Spectroscopic data matched those previously reported.[23d]

*(E)-2-(3-Methylbutylidene)hydrazine-1-carbothioamide (**9j**).* From 3-methylbutanal (**1j**) (17.2 mg, 0.2 mmol), after 35 min the title compound was obtained in 98% yield (31.2 mg) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.99 (s, 1H, NH), 7.32 (t, *J* = 6.3 Hz, 1H), 7.08 and 6.46 (bs, NH_2), 2.13 (t, *J* = 6.0 Hz, 2H), 1.93–1.80 (m, 1H), 0.95 (d, *J* = 6.3 Hz, 6H). Spectroscopic data matched those previously reported.[23e]

*(E)-2-(Cyclohexylmethylene)hydrazine-1-carbothioamide (**9k**).* From cyclohexanecarbaldehyde (**1k**) (22.4 mg, 0.2 mmol), after 35 min the title compound was obtained in quantitative yield (37 mg) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 7.48 (d, *J* = 6.4 Hz, 1H, CH=N), 2.30–2.15 (m, 1H), 1.83–1.61 (m, 5H), 1.35–1.18 (m, 5H). Spectroscopic data matched those previously reported.[23f]

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Additional optimization studies, comparison of conditions previously reported for the prepared compounds and copies of NMR spectra of each compound (PDF).

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Notes

The authors declare no competing financial interest.

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