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Novel chemoenzymatic oxidation of amines into oximes based on hydrolase-catalysed peracid formation

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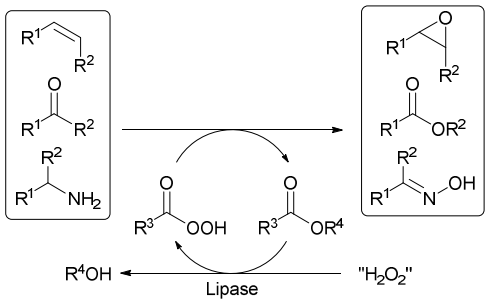
The efficient transformation of benzylamines into the corresponding oximes has been described by means of a chemoenzymatic process. This strategy is based on a two-step sequence developed in one-pot at 30 °C and atmospheric pressure. First, the formation of a reactive peracid intermediate occurs by means of a lipase-catalysed perhydrolysis reaction, then this peracid acts as chemical oxidising agent of the amines. A total of nine ketoximes were isolated in high purity after a simple extraction protocol (90-98% isolated yield), while for the eleven synthesised aldoximes a further column chromatography purification was required (71-82% isolated yield). In all cases excellent selectivities were attained, offering a practical method for amine oxidation in short reaction times (1 hour). The environmental impact of the process was analysed and compared with a recently published alternative chemical synthesis, finding for this metric a good *E*-factor value.

Introduction

Oximes are valuable organic compounds since they serve as building blocks for the synthesis of amines, nitriles oxides and lactams by means of oxidative, reductive and acidic hydrolytic protocols, respectively. In recent years oxime applications in organic chemistry have attracted considerable attention due to their use as directing groups[1] and metal ligands.[2,3] In addition, they are present or allow the introduction of key functionalities in a wide range of products with application in medicinal and fine chemistry industries.[4-8]

Oxidation of primary amines is limited to the amine sensitivity. Nowadays aerobic conditions are considered the most recurrent strategy for their conversion into oximes.[9] In this context multiple catalysts and reaction conditions have been described, including the use of organocatalysts,[10,11] transition metals,[12] both at the same time[13,14] or inclusively the application of enzymes.[15] Very recently, Shankarling and coworkers have reported a metal-free oxidation of primary amines using *m*-chloroperbenzoic acid (*m*-CPBA) as oxidant and ethyl acetate as solvent. A wide range of oximes might be obtained with complete conversion in short reaction times (20 minutes), and in general with high selectivity (>90%). The corresponding nitriles, aldehydes and imines were observed in some cases as by-products, requiring a column chromatographic purification for the isolation of the oximes in 78-94% isolated yield.[16]

Biocatalysis provides an efficient access to multiple classes of organic compounds.[17] Hydrolases and mainly lipases catalyse hydrolytic but also reverse reactions such as esterification, transesterification, aminolysis and ammonolysis, among others.[18] Interestingly, lipases have expanded their versatility in synthetic chemistry taking advantage of their key role in global redox transformations.[19] These transformations are possible based on a hydrolase-catalysed perhydrolysis reaction over a carboxylic acid or ester, resulting in the formation of a reactive peracid intermediate able to oxidise alkenes[20-26] or ketones[27-32] into epoxides or esters, respectively (Scheme 1). From all the tested enzymes, *Candida antarctica* lipase type B (CAL-B) has usually displayed the best activities under different reaction conditions. The proper selection of the oxidising agent, peracid precursor and solvent type represent the key items for the development of an efficient chemoenzymatic oxidative protocol. The urea-hydrogen peroxide complex (UHP) provides a good solution in these oxidative processes since it allows the progressive liberation of H_2O_2 in the reaction medium, avoiding the presence of an excess of free hydrogen peroxide that can produce the fast inactivation of the enzyme.



Scheme 1. Chemoenzymatic oxidation of alkenes, ketones (previous work) and amines (this work) mediated by CAL-B.

As mentioned before, the chemoenzymatic oxidation of alkenes and esters is well documented,[20-32] while other hydrolase-mediated oxidative transformations are less explored, especially with nitrogenated compounds as starting materials. In fact, just the oxidation of *N*-alkylimines and anilines into *N*-alkyloxaziridines[33] and azoxybenzenes,[34] respectively, have been reported. In these cases the best conditions were also found with CAL-B and UHP as reactants. Herein, we wish to report for the first time a novel one-pot two-step chemoenzymatic protocol for the conversion of primary amines into oximes (Scheme 1), searching for adequate and mild reaction conditions for the enzymatic production of a peracid intermediate, which will be later responsible of the oxidation of the studied amines.

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Electronic Supplementary Information (ESI) available: Analytical conditions, additional enzymatic screening studies, EATOS calculations and NMR spectra of synthesised oximes appear in the ESI.
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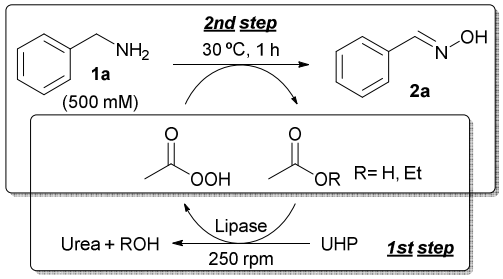
Table 1. Chemoenzymatic oxidation of benzylamine (**1a**, 500 mM) using 2 equiv. of UHP, a lipase (25 mg enzyme/mmol amine) and ethyl acetate as solvent and peracid precursor after 1 h at 30 °C and 250 rpm.



Entry	Lipase	Yield **2a** (%)[a]
1	----	----
2	*Candida antarctica* type A	2
3	*Candida antarctica* type B	88
4	*Candida rugosa*	9
5	*Rhizomucor miehei*	4
6	*Pseudomonas cepacia*	7
7	*Pseudomonas fluorescens*	3
8	*Pseudomonas stutzeri*	10

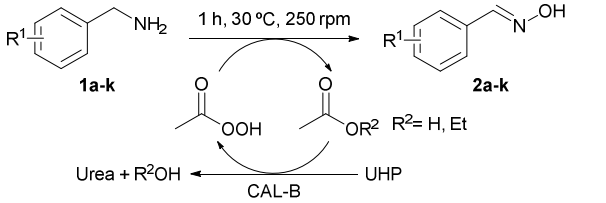
[a] Percentage of (*E*)-benzaldehyde oxime (**2a**) in the reaction medium.

Initially, a set of hydrolases were tested in the oxidation of benzylamine (**1a**) using 2 equivalents of the UHP complex, and ethyl acetate (EtOAc) as both solvent and peracid precursor. In these conditions ethanol and water are released as innocuous by-products. The selected lipases were the ones from *Candida antarctica* types A and B, *Candida rugosa*, *Rhizomucor miehei, Pseudomonas fluorescens*, *Pseudomonas cepacia*, and *Pseudomonas stutzeri* (Table 1). Except for CAL-B, conversions up to 10% were found after 1 h at 30 °C, while CAL-B led to a 88% conversion into the (*E*)-benzaldehyde oxime (**2a**, entry 3).

Once selected CAL-B for further optimisation, two different oxidative conditions were employed. These are the use of ethyl acetate (EtOAc) as both solvent and peracid precursor,[30] and alternatively the combination of lauric acid as peracid precursor and acetonitrile (MeCN) as solvent.[21] For simplicity, benzylamine (**1a**) was again selected as model substrate, finding in all cases the oxime **2a** as the main product (Scheme 2). Concomitant formation of benzaldehyde (**3a**), benzonitrile (**4a**) and *N*-benzylidenebenzylamine (**5a**) was also detected. Oxidation side products **3a** and **4a** were observed in almost negligible proportion (<1%) by GC analyses, while significant amounts of **5a** were attained (5-9%). This imine product comes from the chemical reaction of the formed benzaldehyde (**3a**) with the remaining benzylamine (**1a**). In addition, we performed the reaction at different temperatures. On the one hand, the reaction at 20 °C also led to a highly favoured formation of the oxime **2a**. On the other hand, the reaction was carried out at higher temperatures (37 and 45 °C), but in these conditions the formation of **5a** was highly favoured. For simplicity, we continued our study selecting 30 °C as an appropriate temperature. Data from an exhaustive enzymatic study can be found in the Supplementary material (Tables S2 and S3). In the best conditions, the aldoxime **2a** was obtained in 88% conversion starting with a 500 mM amine concentration using EtOAc as peracid precursor. The formation of the desired aldoxime increased within the time, finding a conversion of 40% and 76% of **2a** at 20 and 40 minutes, respectively. Finally, the development of a column chromatography purification was required for the isolation of the pure product (80%).

At this point, the methodology was extended to other benzylamines **1b-k** bearing different pattern substitutions in the aromatic ring (Table 2). The (*E*)-aldoximes **2b-k** were selectively obtained in a range between 80 and 93% after only 1 h at 30 °C, recovering the final products in excellent purity and good isolated yields (71-82%) after column chromatography (Table 2).

Table 2. Chemoenzymatic oxidation of benzylamines **1a-k** (500 mM) using 2 equiv. of UHP and CAL-B (25 mg enzyme/mmol amine) in ethyl acetate after 1 h at 30 °C and 250 rpm.



Entry	Benzylamine **1**	R^1	Yield **2a-k** (%)[a]
1	**1a**	H	88 (80)
2	**1b**	4-Me	86 (78)
3	**1c**	4-Cl	90 (82)
4	**1d**	4-F	90 (80)
5	**1e**	4-^{t}Bu	93 (74)
6	**1f**	4-CF_3	92 (78)
7	**1g**	3-CF_3	91 (79)
8	**1h**	C_3-OCH_2O-C_4	80 (73)
9	**1i**	4-OMe	83 (71)
10	**1j**	3-OMe	93 (82)
11	**1k**	2-OMe	93 (80)

[a] Yields of aldoximes **2a-k** after liquid-liquid extraction, while in brackets appear the isolated yields after column chromatography.

Searching for the application of this strategy to the production of ketoximes, α-methylbenzylamines (**1l-t**, 500 mM) were assayed in the chemoenzymatic system composed by CAL-B as enzyme, UHP as chemical oxidant and EtOAc as both peracid precursor and solvent (Table 3). Similarly, an excellent reactivity was found under the same experimental conditions (30 °C, 1 h and 250 rpm). The target ketoximes **2l-t**, bearing different substitutions such halogen atoms, alkyl or ether moieties, were selectively obtained in excellent purity after a simple extraction protocol, then the purification by column chromatography was not required.

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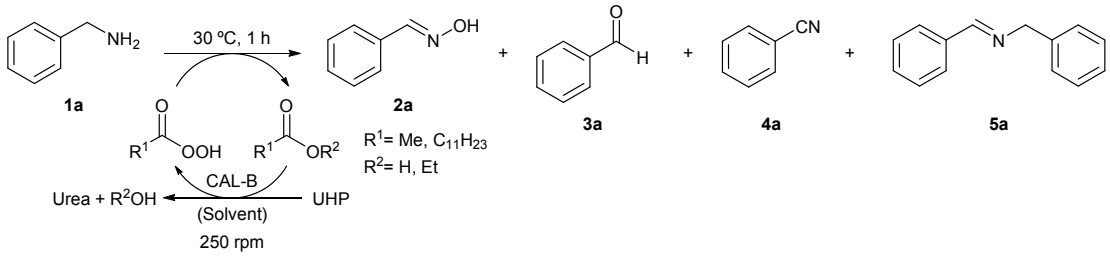
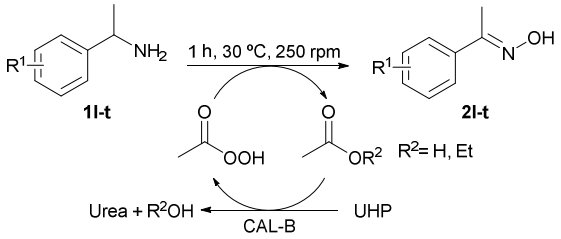


Scheme 2. CAL-B mediated oxidation of benzylamine (**1a**) using ethyl acetate or lauric acid and the urea-hydrogen complex.

Table 3. Chemoenzymatic oxidation of α-methylbenzylamines **1l-t** (500 mM) using 2 equiv. of UHP and CAL-B (25 mg enzyme/mmol amine) in ethyl acetate after 1 h at 30 °C and 250 rpm.



Entry	α-Methylbenzylamine **1**	R^1	Isolated yield **2l-t** (%)[a]
1	**1l**	H	96
2	**1m**	4-Me	90
3	**1n**	4-Cl	95
4	**1o**	4-F	98
5	**1p**	4-CF_3	96
6	**1q**	3-CF_3	91
7	**1r**	4-OMe	93
8	**1s**	3-OMe	96
9	**1t**	2-OMe	91

[a] Isolated yields of pure ketoximes **2l-t** after liquid-liquid extraction.

Finally, we compared this methodology with the previously described using *m*-CPBA[16] in terms of environmental impact since both protocols are similar and allow synthesising the oximes in a simple manner. To achieve this, we performed a quantification of the *E*-factor[35] for both processes. The EATOS tool[36] was used focusing on the impact of the reaction conditions regarding the reagents, catalysts and solvents employed, and taking into account the waste generated. As can be seen in the Supplementary material, using the oxidation of benzylamine as model substrate, both systems are highly appealing as very low *E*-factor values were attained (2.0 for this system and 4.7 for the *m*-CPBA-mediated method, excluding solvents). Obviously, when solvents are taking into account, the values increased (88 for our chemoenzymatic reaction and 304 for the chemical system), but it must be kept in mind that at big scale the recycling of organic solvents is a common applied technique. Therefore these numbers could be further optimised.

Conclusions

A practical and straightforward chemoenzymatic method has been described for the oxidation of a panel of twenty primary amines into oximes under very mild conditions. The strategy is based on a two-step process that occurs in one-pot. *Candida antarctica* lipase type B was found as the most active biocatalyst in the perhydrolysis of ethyl acetate for the formation of active peracetic acid. This peracid reacted with benzyl- and α-methylbenzylamines bearing different pattern substitutions in the aromatic ring for the selective production of the corresponding oximes in good to excellent yields (71-98%). The final ketoxime products were isolated after an extraction purification, the use of column chromatography purification being necessary for the synthesised aldoximes. Calculations using the EATOS tool demonstrated the favorable ecological impact of the lipase/UHP oxidation protocol as just urea and water are released as main by-products.

Experimental section

Materials and methods

Candida antarctica lipase type B (CAL-B, Novozym-435, 7300 PLU/g) was kindly donated by Novo-Nordisk. All the chemicals and solvents were used as received from commercial sources: acetonitrile from VWR Chemicals, ethyl acetate and hexane from Merck and the urea-hydrogen complex from Aldrich.

NMR spectra were recorded on a Bruker AV-300 or a Bruker DPX-300 spectrometer (300.13 MHz for ^{1}H, 75.5 MHz for ^{13}C and 282 MHz for ^{19}F). All chemical shifts (δ) are given in parts per million (ppm) and referenced to the residual solvent signal as internal standard. All coupling constants (*J*) are reported in Hz. Melting points were taken on samples in open capillary tubes and are uncorrected. Gas chromatography (GC) analyses were performed on a Hewlett Packard 6890 Series chromatograph equipped with FID. Conditions and retention times are given in the ESI. Thin-layer chromatographies (TLC) were conducted with Merck Silica Gel 60 F_{254} precoated plates and visualised using a UV lamp and/or potassium permanganate stain. Column chromatographies were performed using Merck Silica Gel 60 (230-400 mesh).

General procedure for chemoenzymatic oxidation of amines 2a-t. The urea-hydrogen peroxide complex (UHP, 94.1 mg, 1.0 mmol) and

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CAL-B (12.5 mg) were added over a solution of the corresponding amine **1a-t** (0.5 mmol) in EtOAc (1 mL). The suspension was shaken for 1 h at 30 °C and 250 rpm. After this time the reaction was stopped by addition of water (1 mL) and the enzyme filtered off. The solution was extracted with EtOAc (3 × 1 mL). An aliquot of the organic phase was taken for GC analyses. The resulting organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to obtain the corresponding (*E*)-oximes **2a-t**. For aldoximes **2a-k** a column chromatography on silica gel (20% EtOAc/hexane) was necessary to achieve the final products in high purity.

(*E*)-Benzaldehyde oxime (**2a**). Yield (80%, 48.5 mg). R_f (20% EtOAc/ Hexane) 0.61. White solid. mp: 32-33 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.24 (s, 1H), 7.65-7.62 (m, 2H), 7.44-7.42 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 150.5 (CH), 131.8 (C), 130.1 (CH), 128.8 (CH), 127.1 (CH).

(*E*)-4-Methylbenzaldehyde oxime (**2b**). Yield (78%, 52.7 mg). R_f (20% EtOAc/ Hexane) 0.60. White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.15 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 150.2 (CH), 140.3 (C), 129.5 (CH), 129.2 (C), 126.9 (CH), 21.5 (CH_3).

(*E*)-4-Chlorobenzaldehyde oxime (**2c**). Yield (82%, 63.8 mg). R_f (20% EtOAc/ Hexane) 0.52. White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.53 (s, 1H), 8.13 (s, 1H), 7.52 (d, *J* = 5.0, 2H), 7.36 (d, *J* = 5.0, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 149.2 (CH), 135.9 (C), 130.5 (C), 129.0 (CH), 128.1 (CH).

(*E*)-4-Fluorobenzaldehyde oxime (**2d**). Yield (80%, 55.7 mg). R_f (20% EtOAc/ Hexane) 0.54. White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.25 (s, 1H), 8.15 (s, 1H), 7.59 (dd, *J* =8.5, 5.5 Hz, 2H), 7.10 (t, *J* = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 163.5 (d, *J* = 250 Hz, C), 149.2 (CH), 128.8 (d, *J* = 8.5 Hz, CH), 128.2 (C), 116.1 (d, *J* = 22.0 Hz, CH).

(*E*)-4-(*tert*-Butyl)benzaldehyde oxime (**2e**). Yield (74%, 65.6 mg). R_f (20% EtOAc/ Hexane) 0.50. White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.16 (s, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 153.4 (C), 150.1 (CH), 129.1 (C), 126.8 (CH), 125.7 (CH), 34.8 (C), 31.2 (CH_3).

(*E*)-4-(Trifluoromethyl)benzaldehyde oxime (**2f**). Yield (78%, 73.8 mg). R_f (20% EtOAc/ Hexane) 0.62. White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.77 (br s, 1H), 8.21 (s, 1H), 7.75-7.63 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 149.2 (CH), 135.2 (C), 131.8 (q, *J* = 32.8 Hz, C), 127.2 (CH), 125.7 (q, *J* = 3.7 Hz, C), 123.8 (q, *J* = 272 Hz, C). ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) 63.2.

(*E*)-3-(Trifluoromethyl)benzaldehyde oxime (**2g**). Yield (79%, 74.7 mg). R_f (20% EtOAc/ Hexane) 0.61. Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.94 (s, 1H), 8.24 (s, 1H), 7.87 (s, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 149.0 (CH), 132.7 (C), 131.3 (q, *J* = 32.7 Hz, C), 130.0 (CH), 129.3 (CH), 126.6 (q, *J* = 3.8 Hz, CH) , 123.8 (q, *J* = 3.8 Hz, CH), 123.7 (q, *J* = 272 Hz, C). ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) 62.5.

(*E*)-Benzo[d][1,3]dioxole-5-carbaldehyde oxime (**2h**). Yield (73%, 60.6 mg R_f (20% EtOAc/ Hexane) 0.40. Yellow solid.). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) δ 8.06 (s, 1H), 7.19 (d, *J* = 1.6 Hz, 1H), 6.98 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.00 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 149.9 (CH), 149.3 (C), 148.2 (C), 126.2 (C), 108.3 (CH), 105.6 (CH), 101.4 (CH_2).

(*E*)-4-Methoxybenzaldehyde oxime (**2i**). Yield (71%, 53.7 mg R_f (20% EtOAc/ Hexane) 0.56. Brown solid.). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.12 (s, 1H), 7.54-7.51 (d, *J* = 8.8 Hz, 2H), 6.93-6.90 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 161.0 (C), 149.7 (CH), 128.5 (CH), 124.6 (C), 114.1 (CH), 55.3 (CH_3).

(*E*)-3-Methoxybenzaldehyde oxime (**2j**). Yield (82%, 62.0 mg). R_f (20% EtOAc/ Hexane) 0.54. Brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.15 (s, 1H), 7.35-7.30 (m, 1H), 7.19-7.13 (m, 2H), 6.98-6.96 (m, 1H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 157.6 (C), 146.6 (CH), 131.1 (CH), 127.3 (CH), 120.7 (CH), 120.6 (C), 111.1 (CH), 55.5 (CH_3).

(*E*)-2-Methoxybenzaldehyde oxime (**2k**). Yield (80%, 60.5 mg). R_f (20% EtOAc/ Hexane) 0.58. Brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.15 (s, 1H), 7.35-7.30 (m, 1H), 7.16-7.12 (m, 2H), 6.98-6.95 (m, 1H), 3.85 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 159.8 (C), 150.1 (CH), 133.2 (C), 129.8 (CH), 120.0 (CH), 116.4 (CH), 111.2 (CH), 55.3 (CH_3).

(*E*)-Acetophenone oxime (**2l**). Yield (96%, 64.9 mg). R_f (20% EtOAc/ Hexane) 0.61. White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.67-7.64 (m, 2H), 7.42-7.40 (m, 3H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 156.0 (C), 136.5 (C), 129.2 (CH), 128.5 (CH), 126.0 (CH), 12.2 (CH_3).

(*E*)-1-(*p*-Tolyl)ethanone oxime (**2m**) Yield (90%, 67.1 mg). R_f (20% EtOAc/ Hexane) 0.59. White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.55 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 2.40 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 155.9 (C), 139.3 (C), 133.6 (C), 129.2 (CH), 125.9 (CH), 21.3 (CH_3), 12.3 (CH_3).

(*E*)-1-(4-Chlorophenyl)ethanone oxime (**2n**). Yield (95%, 80.6 mg). R_f (20% EtOAc/ Hexane) 0.55. White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.58 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 155.1 (C), 135.3 (C), 134.9 (C), 128.7 (CH), 127.3 (CH), 12.1 (CH_3).

(*E*)-1-(4-Fluorophenyl)ethanone oxime (**2o**). Yield (98%, 75.0 mg). R_f (20% EtOAc/ Hexane) 0.57. White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.63 (dd, *J* = 9.0, 5.3 Hz, 2H), 7.09 (t, *J* = 9.0, 2H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 163.4 (d, *J* = 250 Hz, C), 155.1 (C), 132.6 (C), 127.9 (d, *J* = 8.7 Hz, CH), 115.5 (d, *J* = 21.7 Hz, CH), 12.3 (CH_3).

(*E*)-1-[4-(Trifluoromethyl)phenyl]ethanone oxime (**2p**). Yield (96%, 97.5 mg). R_f (20% EtOAc/ Hexane) 0.60. White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.76 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 155.1 (C), 139.8 (C), 131.1 (q, *J* = 32.7 Hz, C), 126.3 (CH), 125.5 (q, *J* = 3.7 Hz, CH), 123.9 (q, *J* = 272.3 Hz, C), 12.2 (CH_3).

(*E*)-1-[3-(Trifluoromethyl)phenyl]ethanone oxime (**2q**). Yield (91%, 92.4 mg). R_f (20% EtOAc/ Hexane) 0.62. White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.91 (s, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 154.9 (C), 137.3 (C), 130.9 (q, *J* = 32.4 Hz), 129.2 (CH), 129.0 (CH), 125.8 (q, *J* = 3.8 Hz, CH), 124.3 (q, *J* = 273 Hz, C), 122.9 (C), 12.0 (CH_3).

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(*E*)-1-(4-Methoxyphenyl)ethanone oxime (**2r**). Yield (93%, 76.8 mg). R_f (20% EtOAc/ Hexane) 0.59. Brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.59 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 160.8 (C), 155.9 (C), 129.4 (C), 127.7 (CH), 114.3 (CH), 55.7 (CH_3), 12.6 (CH_3).

(*E*)-1-(3-Methoxyphenyl)ethanone oxime (**2s**). Yield (96%, 79.3 mg). R_f (20% EtOAc/ Hexane) 0.57. Brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.35-7.33 (m, 1H), 7.30-7.21 (m, 2H), 6.98-6.94 (m, 1H), 3.86 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 159.6 (C), 155.9 (C), 137.9 (C), 129.5 (CH), 118.6 (CH), 115.1 (CH), 111.3 (CH), 55.3 (CH_3), 12.4 (CH_3).

(*E*)-1-(2-Methoxyphenyl)ethanone oxime (**2t**). Yield (91%, 75.2 mg). R_f (20% EtOAc/ Hexane) 0.61. Brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.39-7.32 (m, 2H), 7.00-6.93 (m, 2H), 3.86 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 157.4 (C), 157.0 (C), 130.3 (CH), 129.4 (CH), 126.5 (C), 120.6 (CH), 111.1 (CH), 55.5 (CH_3), 15.2 (CH_3).

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