# Study of the Room-Temperature Synthesis of Oxime Ethers by using a Super Base

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In this study, we present a convenient method for the synthesis of oxime ethers by reacting oximes with various chlorides (alkyl, functionalized alkyl, and benzyl) and with the subsequent use of a super base—pulverized potassium hydroxide in DMSO. The reactions take place at room temperature and the products are obtained in high yields. The final products were received within 2 min to 3 h. In addition, the compounds do not require chromatographic separation. The structure elucidation of the titled compounds was performed by using $^{1}$H NMR and $^{13}$C NMR spectroscopy as well as mass spectrometry. The presented method of synthesis for oxime ethers is environmentally friendly, because neither water cooling or heating of the reaction mixture/solvents (necessary for chromatographic purification) is required. The synthesis can be carried out very easily on a large scale.

## 1. Introduction

Oxime ethers are compounds that are becoming increasingly popular. They are used in organic synthesis, providing valuable reagents to obtain *cis*-1.2-aminoalcohols,[1] hydroxyloamines,[2] enantioselective synthesis of the amines,[3] and, under specific conditions in cyclization reactions, can lead to the formation of substituted heteroaromatic compounds.[4,5] However, many oxime ethers are applicable as specified compounds with biological activity. They exhibit anticancer,[6] anti-aggregation,[7] antidepressant,[8,9] anticonvulsant,[10] antimicrobial,[11] antiviral,[12] acaricidal,[13] anti-protozoal,[14] and herbicidal[15] effects. There has also been research performed on the use of oxime ethers as fragrances.[16]

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Oxime ethers can be obtained from the aminohydroxylation reaction of ketones[17,18] and reactions of the oximes with alcohols with triphenylphosphine,[9,19] alkenes,[9] aryl halogens,[20,21] appropriate alkyl halogens, functionalized alkyl halogens, and benzyl halogens. For the synthesis of oxime ethers in latter method, bases in different solvents are usually used, for example $CH_3ONa$ in $CH_3OH$,[14] NaH in DMF,[22] $K_2CO_3$ in acetone/DMF,[6] $NaOH_{(aq)}$/toluene,[15] as the halogens used are cheap and readily available chlorides. However, the reaction of the chlorides with oximes generally requires heating, and the time of the reaction depends on the base and the solvent used. For example, *n*-butyl chloride reacts with 2-acetylthiophene oxime and $K_2CO_3$ in the presence of KI/18-crown-6 in toluene for 6 h at 100 °C.[23] In the reaction of acetophenone oxime with 2-chloro-*N*,*N*-dimethylethylamine hydrochloride and NaH in ethanol, the reaction is carried out for 48 h at reflux.[24] Reactive benzyl chlorides react faster with the oximes (NaH/DMF) and at lower temperatures.[25] For the reaction of alkyl bromides with oximes, the reactions may be carried out at room temperature (NaOH/benzene)[26] and some functionalized alkyl bromides require heating of the reaction mixture at reflux for 2 h ($K_2CO_3$/acetone + toluene).[27] Li et al.[28] presented a *one-pot* synthesis method for oxime ethers from benzaldehyde or acetophenone with reactive alkyl bromides, methyl iodide, or benzyl chloride in an aqueous solution of DMSO (2:5), with KOH and hydroxylamine hydrochloride. The reactions take place at 80 °C for 30–50 min, and a 20% excess of the halide to the carbonyl compound is taken into the process. The oxime is formed during the course of the reaction.[28] The authors emphasize clearly that alkyl chlorides do not undergo this reaction.

Presented examples for the synthesis of oxime ethers show that halogenated benzyl and alkyl bromides readily undergo the substitution reactions. Alkyl chlorides and their derivatives

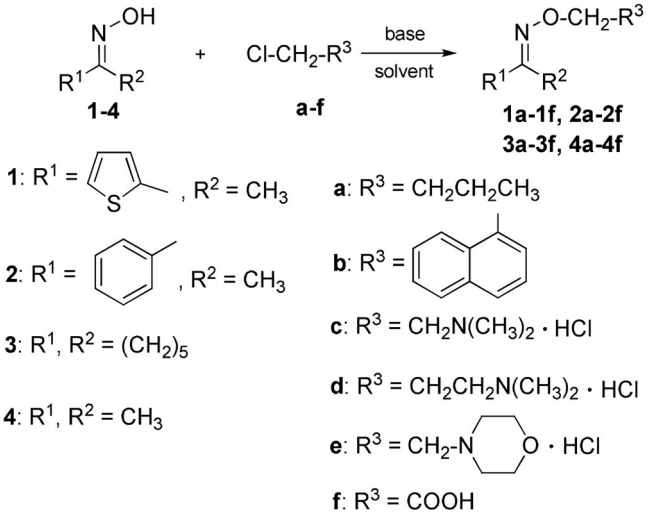
react with more difficulty, although the rate of the reaction depends on the process conditions. In general, the synthesis reaction of oxime ethers often requires long-lasting stirring and heating of the reaction mixture over at least several hours.

Herein, we present a quick and inexpensive method for the synthesis of oxime ethers in the reactions of oxime with an alkyl chloride, benzyl chloride, and functionalized alkyl chlorides in a stoichiometric amount of the chloride and the oxime. The use of chlorides is economically justified, because they are generally cheaper, albeit less reactive when compared to bromides. The presented method is straightforward, the final products are obtained in a pure form, and the yields are high. This method perfectly fits into the field of the green chemistry. The reactions take place at room temperature so that no water cooling is required and no electricity is needed to heat the reaction mixture. The final products do not require chromatographic purification and, therefore, the use of chromatography gel and the solvents are not required. These advantages determine the attractiveness of the developed method.

## 2. Results and Discussion

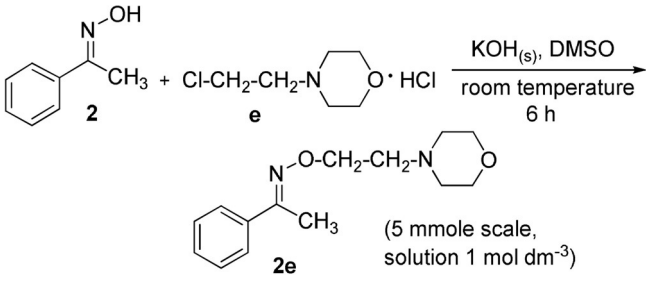
To obtain the alkylamine oxime ethers, we originally used a procedure that we had previously used to synthesize the *O*-benzyl ethers of 2-acetylbenzofuran and 2-acetylthiophene oximes with $K_2CO_3$ in acetone.[29,30] However, the reactions required long-lasting heating (72 h) and resulted in only partially converted substrates. During the subsequent investigations, we attempted to develop a new method for the synthesis of oxime ethers from cheap and readily available chlorides to reduce the reaction time without the need for prolonged heating. We wanted the above-mentioned reactions to be carried out at room temperature, and in a short time. We also tried to make the final products such that purification was simple.

We used oximes (**1**–**4**) and the following chlorides: alkyl (**a**), benzyl derivative (**b**) and functionalized derivatives (**c**–**f**) (Scheme 1). As a model reaction, we assumed the reaction of




**Scheme 1.** The general method of the reaction oximes **1**–**4** with chlorides **a**–**f**.

acetophenone oxime (**2**) with a stoichiometric amount of 4-(2-chloroethyl)morpholine hydrochloride (**e**) mixed in DMSO (1 mol $dm^{-3}$) with powdered KOH at room temperature (Scheme 2). The reaction time was 6 h. In a further stage of our




**Scheme 2.** The model reaction of the acetophenone oxime (**2**) with the 4-(2-chloroethyl)morpholine hydrochloride (**e**).

research, we modified the method to reduce the reaction time. Therefore, we have also analyzed the effect of selected parameters on the reaction time. The results presented in Table 1 show a significant effect of the selected parameters on the rate of the model reaction.

**Table 1.** The effect of the parameters on the rate of the model reaction.

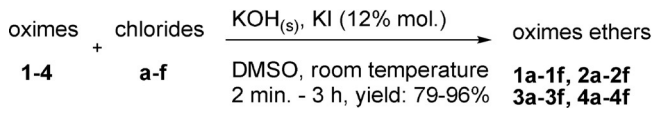
| Parameter: Reaction with… | Reaction time (TLC) [h] |
|---|---|
| 6 mol % KI | 3 |
| 12 mol % KI | 2 |
| a stoichiometric amount of KI | 6 |
| NaOH instead of KOH, with 12 mol % KI | 5 |
| $K_2CO_3$ instead of KOH, with 12 mol % KI | $>$7 days[a] |
| half the amount of DMSO, with 12 mol % KI | 5 |
| twice the amount of DMSO, with 12 mol % KI | 2.5 |
| 25 mM scale, with 12 mol % KI | 3 |

[a] Complete conversion was not achieved.

A catalytic addition amount of KI (6 mol % relative to the oxime and chloride) causes the reaction rate to double (3 h). However, the addition of 12 mol % KI accelerates the reaction rate three times compared to the model reaction (2 h). The addition of a stoichiometric amount of KI in relation to the oxime and chloride does not affect the reaction rate. The effect of the concentration of reagents and the base type was analyzed by using 12 mol % KI, because KI significantly increases the speed of the model reaction. Use of NaOH instead of KOH slows the reaction rate from 2 to 5 h. In turn, the use of the weaker base $K_2CO_3$ instead of KOH inhibits the reaction rate. After 7 days, unreacted oxime was still visible in the thin layer chromatography (TLC). Chaning the concentration of the sample to 2 mol $dm^{-3}$ changes the reaction speed from 2 to 5 h, owing to the higher density of the solution and the difficulty of mixing. Diluting the sample to a concentration of 0.5 mol $dm^{-3}$ only slightly slows the course of the reaction (2.5 instead of 2 h).

We also performed the reaction on a 25 mM scale with an addition of 12 mol % KI. The yield of the final product **2 e** for the model reaction is comparable to that of the 5 mM scale, but the reaction time is slightly longer, 3 h. The difficulty with mixing the larger volume of the reaction mixture results in a longer reaction time. This result demonstrates that the method can also be used for multiscale synthesis with a high product yield and process rate.

The results were used to develop a fast, simple, and efficient method for synthesis of the oxime ethers using inexpensive chlorides (Scheme 3).




**Scheme 3.** The conditions of the synthesis of the oxime ethers.

The reactions are carried out in a small capped flask (25 or 50 mL). In this method, to a solution of oxime and chloride (in molar 1:1) in DMSO (1 mol $dm^{-3}$) and 12 mol % KI, an excess of pulverized KOH is added. The reaction mixture is vigorously stirred at room temperature.

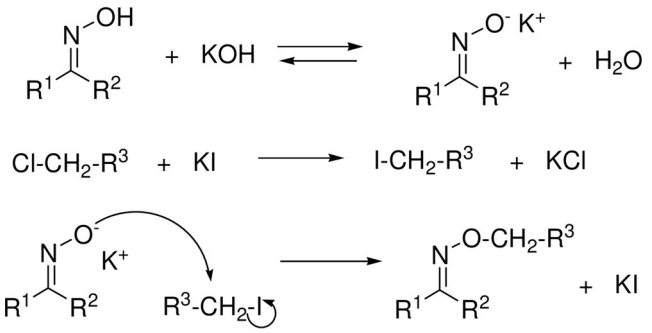
Developing the results has helped us to prepare 24 oxime ethers. For this, we used four different oximes (**1**–**4**) and six chlorides (**a**–**f**). The times of the reactions and yields of the final products are shown in Table 2.

**Table 2.** Reaction times for the formation of oxime ethers **1 a**–**4 f**, and their isolated yields.

| Oxime | Chloride | | | | | |
|---|---|---|---|---|---|---|
| | **a** | **b** | **c** | **d** | **e** | **f** |
| | Reaction time [min] (Yield [%]) | | | | | |
| **1** | 120 (92) | 2 (95) | 120 (93) | 60 (94) | 60 (91) | 60 (90) |
| **2** | 120 (90) | 2 (96) | 180 (93) | 60 (94) | 120 (92) | 60 (91) |
| **3** | 180 (86) | 4 (94) | 180 (91) | 120 (91) | 180 (90) | 60 (89) |
| **4** | 180 (84) | 2 (91) | 180 (85) | 60 (87) | 60 (86) | 60 (79) |

The conversion of substrates to the final products is completed and takes between 2 min and 3 h (chromatographic control with TLC). The compounds were isolated in a high yield, 79–96 %. The fastest reaction can be observed for the heteroaromatic oxime **1** (flat construction of the ring). Oxime **3** undergoes the slowest reaction (except for the reaction with chloroacetic acid **f**). The slowest reaction: *n*-butyl chloride (**a**) and 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (**c**) (2–3 h). The elongation of the reaction time of the oximes with chloride **c** is explained by the hypothetical hindrance of the nitrogen of the amino group. This effect is not observed when 3-chloro-*N*,*N*-dimethylpropylamine hydrochloride (**d**) is used, in which an additional methylene group is present. When both **d** and 4-(2-chloroethyl)morpholine hydrochloride (**e**) as well as chloroacetic acid (**f**) are used, the total conversion time of the substrates is 1 h (except chlorides **d** and **e** with oxime **3** and chloride **e** with oxime **2**). 1-(Chloromethyl)naphthalene (**b**) reacts very quickly as a benzyl derivative of a particular reactivity. Oximes **1**–**4** react with chloride **b** in 2–4 min.

The proposed reaction mechanism is shown in Scheme 4. We supposed that the increase in reaction rate is caused by the formation of the alkyl iodide in the reaction mixture, which then reacts with the potassium salt of the oxime to form the ether.




**Scheme 4.** The proposed mechanism of the oxime ethers synthesis.

Some of the obtained oxime ethers had been previously prepared by using other methods described in the literature.[20,21,29] Table 3 provides a comparison of the times and yields of the selected reactions described in the literature, as well as the method we have designed.

Syntheses that were previously carried out by other methods took a long time and were often carried out at high temperatures. Table 3 shows clearly that our newly-developed method is simpler, the reactions are faster, and the yields of the isolated products are higher.

An extremely important parameter in determining the reaction speed is the mixing intensity. The reactions are carried out in DMSO solution and the base is in a solid phase. Intensive mixing allows better contact of the solid phase with the solu-

**Table 3.** Comparison of the conditions shown in literature with conditions concerning the presented method.

| Literature method | | | | Presented method | | | |
|---|---|---|---|---|---|---|---|
| Oxime | Chloride | Conditions: time, temperature[a] | Yield [%] | Oxime | Chloride | Conditions: time, temperature[a] | Yield [%] |
| **2** | **a** | 13 h, 100 °C[21] | 52 | **2** | **a** | 2 h, RT | 90 |
| **3** | **e** | 1 h, 100 °C + 16 h, RT + 3 h, 60 °C[20] | 77.5 | **3** | **e** | 3 h, RT | 88 |
| **4** | **d** | 2 h, 78 °C + overnight, RT[29] | 47 | **4** | **d** | 1 h, RT | 87 |

[a] RT = room temperature.

tion. The strongly pulverized potassium base has the most developed surface and allows for better solvation of the $K^+$ ion by DMSO as well as $OH^-$ ion attack on the oxime molecule. The KOH–DMSO system is called a "super base" and exhibits exceptional reactivity.[32]

We also performed the synthesis reaction of oxime ethers in a KOH–DMF system, but we noticed that DMF undergoes the hydrolysis reaction with KOH.

Of the 24 oxime ethers obtained, 11 are new compounds that are not described elsewhere in the literature. $^1H$ and $^{13}C$ NMR analyses confirmed the structure of the final product. All compounds were obtained in a pure form, which was also confirmed by the NMR spectra. Mass spectra analysis confirmed the presence of the appropriate products. The final product solution is extracted four times with water (or brine). This is to completely remove the solvent (DMSO) from the organic solution after extraction.

## 3. Conclusions

The synthesis method for oxime ethers developed by us takes place at room temperature, using stoichiometric amounts of the reagents. The reaction time does not exceed 3 h. The final products are obtained in very high yields and purities. Among the main advantages of the presented method are the following: no water cooling, no need to heat the reaction mixture, and short reaction times. The final products do not require chromatographic purification.

## Experimental Section

Hydroxylamine hydrochloride, potassium hydroxide (85%), potassium iodide, magnesium sulfate, anhydrous ethanol, dimethylsulfoxide (DMSO), chloroform, ethyl acetate, *n*-hexane, triethylamine (Avantor, Poland), organic reagents, 1-(2-thienyl)ethan-1-one (>99%), *n*-butyl chloride (>99%), 1-(chloromethyl)naphthalene (>97%), 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (99%), 3-chloro-*N*,*N*-dimethylpropylamine hydrochloride (>96%), 4-(2-chloroethyl)morpholine hydrochloride (99%), chloroacetic acid (99%), cyclohexanone oxime (97%), acetone oxime (98%) (Sigma–Aldrich), and acetophenone oxime (98%) (Alfa-Aesar) were commercially available. The 1-(2-thienyl)ethan-1-one oxime was synthesized following the procedures described in the literature.[30]

All NMR spectra were recorded on a Bruker Avance III 400 MHz or 700 MHz spectrometer, using $CDCl_3$ as the solvent, with TMS as an internal standard. Mass spectra were recorded on a Shimadzu LC-MS 8030 spectrometer (triple quadrupole). HRMS spectra were recorded on QTOF (Impact HD, Bruker) spectrometer. Melting points were determined by using DigiMelt MPA161 digital melting point apparatus and were uncorrected. The reaction times were analyzed by TLC analysis. For non-absorbing compounds under a UV lamp (254 nm), TLC (vanillin, ethanol, sulfuric acid) was used.

### General Procedure for the Synthesis of Oxime Ethers 1 a–e, 2 a–e, 3 a–e, 4 a–e

In a flask (25 or 50 mL) equipped with a plug, to a solution of the oxime (**1**–**4**) (5.0 mmol) and DMSO (5 mL), an appropriate chloride (5.0 mmol), KI (0.10 g), and strongly pulverized KOH (10 mmol for the chlorides **a** and **b**, 20 mmol for the chlorides **c**-**e**) were added. The mixture was intensively stirred for between 2 min and 3 h at room temperature (monitored by TLC). Water (30 mL) and chloroform (30 mL) were added. The water phase was extracted with chloroform (30 mL). The combined organic layers were washed with water (4×25 mL) and dried ($MgSO_4$). Evaporation provided the oxime ethers.

### General Procedure for the Synthesis of Oxime Ethers 1 f, 2 f, 3 f, 4 f

In a flask (25 or 50 mL) equipped with a plug, to a solution of the oxime (**1**–**4**) (5.0 mmol) and DMSO (7 mL), chloroacetic acid (**f**) (5.0 mmol), KI (0.10 g), and strongly pulverized KOH (20 mmol) were added. The mixture becomes thick, but, after 10 min, stirring becomes easier. The mixture was intensively stirred for 1 h at room temperature (monitored by TLC). Water (20 mL), hydrochloric acid solution (2 M, 7.5 mL), and chloroform (40 mL) were added. The water phase was extracted with chloroform (40 mL). The combined chloroform solution was washed with water (**1 f, 2 f**) (3×20 mL) or brine (**3 f, 4 f**) and dried ($MgSO_4$). Evaporation provided the solid oxime ethers **1 f**-**4 f.**

#### *(E)-1-(Thiophen-2-yl)ethanone O-Butyl Oxime (1 a)*[23]

Following the general procedure starting from **1** (0.71 g, 5 mmol), oxime ether **1 a** was obtained as a colorless oil (0.91 g, 92%). $^1H$ NMR (700 MHz, $CDCl_3$): $\delta$ (ppm) 0.96 (t, $J$=7.0 Hz, 3H, $CH_{3\ but}$), 1.43 (tq, $J$=7.0 Hz, $J$=6.3 Hz, 2H, $CH_2$), 1.69 (tt, $J$=7.0 Hz, $J$=6.3 Hz, 2H, $CH_2$), 2.24 (s, 3H, $CH_3$), 4.17 (t, $J$=6.3 Hz, 2H, $OCH_2$), 7.01 (dd, $J$=4.9 Hz, $J$=3.5 Hz, 1H, CH), 7.20 (dd, $J$=3.5 Hz, $J$=1.4 Hz, 1H, CH), 7.25 (dd, $J$=4.9 Hz, $J$=1.4 Hz, 1H, CH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 12.87 ($CH_{3\ but}$), 13.94 ($CH_3$), 19.24 ($CH_2$), 31.33 ($CH_2$), 74.13 ($OCH_2$), 125.79 (CH), 126.47 (CH), 126.89 (CH), 140.83 (C), 150.08 ($C_{C=N}$). MS (ESI): *m/z* 198 $[M + H]^+$.

#### *(E)-1-(Thiophen-2-yl)ethanone O-Naphthalen-1-ylmethyl Oxime (1 b)*

Following the general procedure starting from **1** (0.71 g, 5 mmol), oxime ether **1 b** was obtained as a light yellow solid (1.33 g, 95%); mp: 73.5–75 °C. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 2.27 (s, 3H, $CH_3$), 5.69 (s, 2H, $OCH_2$), 7.04 (dd, $J$=5.2 Hz, $J$=3.6 Hz, 1H, CH), 7.24 (dd, $J$=3.6 Hz, $J$=1.2 Hz, 1H, CH), 7.29 (dd, $J$=5.2 Hz, $J$=1.2 Hz, 1H, CH), 7.51 (dd, $J$=8.4 Hz, $J$=6.4 Hz, 1H, CH), 7.54–7.58 (m, 2H, 2×CH), 7.61 (d, $J$=6.4 Hz, 1H, CH), 7.87 (d, $J$=8.4 Hz, 1H, CH), 7.91 (dd, $J$=8.8 Hz, $J$=1.2 Hz, 1H, CH), 8.21 (d, $J$=8.8 Hz, 1H, CH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 13.10 ($CH_3$), 74.84 ($CH_2$), 124.26 (CH), 125.32 (CH), 125.75 (CH), 126.23 (CH), 126.84 (CH), 126.96 (CH), 127.25 (CH), 128.54 (CH), 128.89 (CH), 130.72 (C), 132.00 (C), 133.24 (CH), 133.75 (C), 140.45 (C), 151.09 ($C_{C=N}$). HRMS (ESI): *m/z* calcd for $C_{17}H_{16}NOS$ $[M + H]^+$ 282.0953, found 282.0949.

#### *(E)-1-(Thiophen-2-yl)ethanone O-2-(Dimethylamino)ethyl Oxime (1 c)*

Following the general procedure starting from **1** (0.71 g, 5 mmol), oxime ether **1 c** was obtained as a yellow oil (0.99 g, 93%). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 2.26 (s, 3H, $CH_3$), 2.34 (s, 6H, 2×$CH_3$, $NCH_3$), 2.70 (t, $J$=5,6 Hz, 2H, $CH_2$), 4.30 (t, $J$=5.6 Hz, 2H, $OCH_2$), 7.02 (dd, $J$=5.2 Hz, $J$=3.6 Hz, 1H, CH), 7.22 (dd, $J$=3.6 Hz, $J$=1.2 Hz, 1H, CH), 7.27 (dd, $J$=5.2 Hz, $J$=1.2 Hz, 1H, CH). $^{13}C$ NMR

(100 MHz, $CDCl_3$): $\delta$ (ppm) 13.07 ($CH_3$), 45.93 (2×$CH_3$, $NCH_3$), 58.21 ($CH_2$), 72.49 ($OCH_2$), 126.02 (CH), 126.66 (CH), 126.92 (CH), 140.55 (C), 150.58 ($C_{C=N}$). HRMS (ESI): *m/z* calcd for $C_{10}H_{17}N_2OS$ $[M + H]^+$ 213.1062, found 213.1059.

### (E)-1-(Thiophen-2-yl)ethanone O-3-(Dimethylamino)propyl Oxime (1d)

Following the general procedure starting from **1** (0.71 g, 5 mmol), oxime ether **1d** was obtained as a pale-yellow oil (1.06 g, 94%). $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ (ppm) 1.92 (tt, $J$=7.7 Hz, $J$=6.3 Hz, 2H, $CH_2$), 2.26 (s, 3H, $CH_3$), 2.28 (s, 6H, 2×$CH_3$, $NCH_3$), 2.43 (t, $J$=7.7 Hz, 2H, $NCH_2$), 4.23 (t, $J$=6.3 Hz, 2H, $OCH_2$), 7.03 (dd, $J$=4.9 Hz, $J$=3.5 Hz, 1H, CH), 7.23 (dd, $J$=3.5 Hz, $J$=1.4 Hz, 1H, CH), 7.28 (dd, $J$=4.9 Hz, $J$=1.4 Hz, 1H, CH). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 12.87 ($CH_3$), 27.56 ($CH_2$), 45.49 (2×$CH_3$, $NCH_3$), 56.50 ($NCH_2$), 72.50 ($OCH_2$), 125.88 (CH), 126.58 (CH), 126.89 (CH), 140.70 (C), 150.30 ($C_{C=N}$). HRMS (ESI): *m/z* calcd for $C_{11}H_{19}N_2OS$ $[M + H]^+$ 227.1218, found 227.1218.

### (E)-1-(Thiophen-2-yl)ethanone O-2-Morpholinoethyl Oxime (1e)

Following the general procedure starting from **1** (0.71 g, 5 mmol), oxime ether **1e** was obtained as an orange oil (1.15 g, 91%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 2.25 (s, 3H, $CH_3$), 2.58 (t, $J$=4.8 Hz, 4H, 2×$CH_2$, $NCH_2$), 2.76 (t, $J$=6.0 Hz, 2H, $CH_2$), 3.75 (t, $J$=4.8 Hz, 4H, 2×$CH_2$, $OCH_2$), 4.33 (t, $J$=6.0 Hz, 2H, $CH_2$), 7.03 (dd, $J$=5.2 Hz, $J$=3.6 Hz, 1H, CH), 7.23 (dd, $J$=3.6 Hz, $J$=1.2 Hz, 1H, CH), 7.28 (dd, $J$=5.2 Hz, $J$=1.2 Hz, 1H, CH). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 13.07 ($CH_3$), 54.03 (2×$CH_2$, $NCH_{2\ mor.}$), 57.58 ($NCH_2$), 66.99 (2×$CH_2$, $OCH_{2\ mor.}$), 72.07 ($OCH_2$), 126.11 (CH), 126.76 (CH), 126.95 (CH), 140.43 (C), 150.68 ($C_{C=N}$). HRMS (ESI): *m/z* calcd for $C_{12}H_{19}N_2O_2S$ $[M + H]^+$ 255.1167, found 255.1169.

### (E)-2-(1-(Thiophen-2-yl)ethylideneaminooxy)acetic Acid (1f)

Following the general procedure starting from **1** (0.71 g, 5 mmol), oxime ether **1f** was obtained as an orange solid (0.90 g, 90%); mp: 102–103 °C. $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ (ppm) 2.33 (s, 3H, $CH_3$), 4.75 (s, 2H, $CH_2$), 7.02 (dd, $J$=4.9 Hz, $J$=4.2 Hz, 1H, CH), 7.27 (dd, $J$=4.2 Hz, $J$=1.4 Hz, 1H, CH), 7.31 (dd, $J$=4.9 Hz, $J$=1.4 Hz, 1H, CH), 9.0–10.7 (bs, OH, 1H). $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ (ppm) 12.92 ($CH_3$), 69.91 ($CH_2$), 126.64 (CH), 126.74 (CH), 127.13 (CH), 138.87 (C), 152.64 ($C_{C=N}$), 175.19 ($C_{COOH}$). HRMS (ESI): *m/z* calcd for $C_8H_{10}NO_3S$ $[M + H]^+$ 200.0381, found 200.0376.

### (E)-Acetophenone O-Butyl Oxime (2a)[23]

Following the general procedure starting from **2** (0.68 g, 5 mmol), oxime ether **2a** was obtained as a pale-yellow oil (0.86 g, 90%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 0.99 (t, $J$=7.2 Hz, 3H, $CH_{3\ but.}$), 1.46 (tq, $J$=7.2 Hz, $J$=6.4 Hz, 2H, $CH_2$), 1.74 (tt, $J$=7.2 Hz, $J$=6.4 Hz, 2H, $CH_2$), 2.26 (s, 3H, $CH_3$), 4.22 (t, $J$=6.4 Hz, 2H, $OCH_2$), 7.36–7.39 (m, 3H, 3×CH), 7.66–7.68 (m, 2H, 2×CH). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 12.66 ($CH_{3\ but.}$), 13.98 ($CH_3$), 19.28 ($CH_2$), 31.40 ($CH_2$), 74.02 ($OCH_2$), 126.01 (2×CH), 128.35 (2×CH), 128.85 (CH), 136.96 (C), 154.14 ($C_{C=N}$). MS (ESI): *m/z* 192 $[M + H]^+$.

### (E)-Acetophenone O-Naphthalen-1-ylmethyl Oxime (2b)

Following the general procedure starting from **2** (0.68 g, 5 mmol), oxime ether **2b** was obtained as a yellow oil (1.33 g, 96%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 2.27 (s, 3H, $CH_3$), 5.74 (s, 2H, $CH_2$), 7.38–7.41 (m, 3H, 3×CH), 7.48–7.62 (m, 4H, 4×CH), 7.69–7.71 (m, 2H, 2×CH), 7.87 (d, $J$=7.6 Hz, 1H, CH), 7.91 (dd, $J$=8.0 Hz, $J$=1.6 Hz, 1H, CH), 8.22 (d, $J$=8.0 Hz, 1H, CH). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 12.88 ($CH_3$), 74.74 ($CH_2$), 124.22 (CH), 125.34 (CH), 125.75 (CH), 126.13 (2×CH), 126.20 (CH), 127.07 (CH), 128.40 (2×CH), 128.57 (CH), 128.81 (CH), 129.09 (CH), 131.98 (C), 133.49 (C), 133.76 (C), 136.65 (C), 155.17 ($C_{C=N}$). HRMS (ESI): *m/z* calcd for $C_{19}H_{18}NO$ $[M + H]^+$ 276.1388, found 276.1384.

### (E)-Acetophenone O-2-(Dimethylamino)ethyl Oxime (2c)[24]

Following the general procedure starting from **2** (0.68 g, 5 mmol), oxime ether **2c** was obtained as a yellow oil (0.96 g, 93%). $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ (ppm) 2.24 (s, 3H, $CH_3$), 2.32 (s, 6H, 2×$CH_3$, $NCH_3$), 2.69 (t, $J$=5.6 Hz, 2H, $NCH_2$), 4.31 (t, $J$=5.6 Hz, 2H, $OCH_2$), 7.34–7.37 (m, 3H, 3×CH), 7.63–7.65 (m, 2H, 2×CH). $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ (ppm) 12.49, ($CH_3$), 45.66 (2×$CH_3$, $NCH_3$), 57.93 ($NCH_2$), 72.10 ($OCH_2$), 125.64 (2×CH), 127.97 (2×CH), 128.58 (CH), 136.35 (C), 154.22 (C). MS (ESI): *m/z* 207 $[M + H]^+$.

### (E)-Acetophenone O-3-(Dimethylamino)propyl Oxime (2d)

Following the general procedure starting from **2** (0.68 g, 5 mmol), oxime ether **2d** was obtained as a pale-yellow oil (1.03 g, 94%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 1.93 (tt, $J$=7.6 Hz, $J$=6.4 Hz, 2H, $CH_2$), 2.25 (s, 3H, $CH_3$), 2.27 (s, 6H, 2×$CH_3$, $NCH_3$), 2.42 (t, $J$=7.6 Hz, 2H, $NCH_2$), 4.26 (t, $J$=6.4 Hz, 2H, $OCH_2$), 7.36–7.39 (m, 3H, 3×CH), 7.65–7.67 (m, 2H, 2×CH). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 12.68 ($CH_3$), 27.63 ($CH_2$), 45.51 (2×$CH_3$, $NCH_3$), 56.58 ($NCH_2$), 72.40 ($OCH_2$), 126.01 (2×CH), 128.35 (2×CH), 128.91 (CH), 136.83 (C), 154.37 ($C_{C=N}$). HRMS (ESI): *m/z* calcd for $C_{13}H_{21}N_2O$ $[M + H]^+$ 221.1645, found 221.1654.

### (E)-Acetophenone O-2-Morpholinoethyl Oxime (2e)[33]

Following the general procedure starting from **2** (0.68 g, 5 mmol), oxime ether **2e** was obtained as an orange oil (1.14 g, 92%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 2.25 (s, 3H, $CH_3$), 2.59 (t, $J$=4.8 Hz, 4H, 2×$NCH_{2\ mor.}$), 2.78 (t, $J$=6.0 Hz, 2H, $NCH_2$), 3.75 (t, $J$=4.8 Hz, 4H, 2×$OCH_{2\ mor.}$), 4.37 (t, $J$=6.0 Hz, 2H, $OCH_2$), 7.38–7.41 (m, 3H, 3×CH), 7.65–7.67 (m, 2H, 2×CH). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 12.87 ($CH_3$), 54.09 ($CH_2$, 2×$NCH_{2\ mor.}$), 57.65 ($CH_2$, $NCH_2$), 67.01 ($CH_2$, 2×$OCH_{2\ mor.}$), 72.04 ($OCH_2$), 126.03 (2×CH), 128.39 (2×CH), 129.05 (CH), 136.63 (C), 154.72 ($C_{C=N}$). MS (ESI): *m/z* 249 $[M + H]^+$.

### (E)-2-(1-Phenylethylideneaminooxy)acetic Acid (2f)[34]

Following the general procedure starting from **2** (0.68 g, 5 mmol), oxime ether **2f** was obtained as an orange solid (0.88 g, 91%); mp: 93–94.5 °C; lit. mp: 97–98 °C.[34] $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 2.34 (s, 3H, $CH_3$), 4.81 (s, 2H, $CH_2$), 7.38–7.40 (m, 3H, 3×CH), 7.64–7.67 (m, 2H, 2×CH), 10.43 (bs, 1H, COOH. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 13.11 ($CH_3$), 70.30 ($CH_2$), 126.31 (2×CH), 128.45 (2×CH), 129.55 (CH), 135.83 (C), 157.25 (C), 175.63 (COOH). MS (ESI): *m/z* 194 $[M + H]^+$.

### *Cyclohexanone* O-*Butyl Oxime (3 a)*[26]

Following the general procedure starting from **3** (0.57 g, 5 mmol), oxime ether **3 a** was obtained as a pale-yellow oil (0.73 g, 86 %). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 0.95 (t, $J$ = 7.2 Hz, 3 H, $CH_3$), 1.40 (tq, $J$ = 7.2 Hz, $J$ = 6.8 Hz, 2 H, $CH_{2\ but.}$), 1.60–1.67 (m, 8 H, 3×$CH_{2\ cycl.}$ + $CH_{2\ but.}$), 2.21 (m, 2 H, $CH_{2\ cycl.}$), 2.45–2.52 (m, 2 H, $CH_{2\ cycl.}$), 4.01 (t, $J$ = 6.8 Hz, 2 H, $OCH_2$). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 13.95 ($CH_3$), 19.26 ($CH_{2\ but.}$), 25.26 ($CH_{2\ cycl.}$), 25.77 ($CH_{2\ cycl.}$), 25.87 ($CH_{2\ cycl.}$), 27.05 ($CH_{2\ cycl.}$), 31.17 ($CH_{2\ but.}$), 32.25 ($CH_{2\ cycl.}$), 73.00 ($CH_{2\ but.}$), 159.89 ($C_{C=N}$). MS (ESI): *m/z* 170 $[M + H]^+$.

### *Cyclohexanone* O-*Naphthalen-1-ylmethyl Oxime (3 b)*

Following the general procedure starting from **3** (0.57 g, 5 mmol), oxime ether **3 b** was obtained as a yellow oil (1.20 g, 94 %). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 1.58–1.71 (m, 6 H, 3×$CH_{2\ cycl.}$), 2.26 (m, 2 H, $CH_{2\ cycl.}$), 2.50 (m, 2 H, $CH_{2\ cycl.}$), 5.54 (s, 2 H, $OCH_2$), 7.45–7.57 (m, 4 H, CH), 7.83 (d, $J$ = 8.0 Hz, 1 H, CH), 7.88 (dd, $J$ = 8.0 Hz, $J$ = 1.6 Hz, 1 H, CH), 8.13 (dd, $J$ = 8.0 Hz, $J$ = 1.6 Hz, 1 H, CH). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 25.52 ($CH_2$), 25.82 ($CH_2$), 25.83 ($CH_2$), 27.09 ($CH_2$), 32.26 ($CH_2$), 73.73 ($OCH_2$), 124.21 (CH), 125.31 (CH), 125.67 (CH), 126.07 (CH), 126.67 (CH), 128.50 (CH), 128.58 (CH), 131.91 (C), 133.67 (C), 133.72 (C), 161.16 ($C_{C=N}$). HRMS (ESI): *m/z* calcd for $C_{17}H_{20}NO$ $[M + H]^+$ 254.1545, found 254.1540.

### *Cyclohexanone* O-*2-(Dimethylamino)ethyl Oxime (3 c)*

Following the general procedure starting from **3** (0.57 g, 5 mmol), oxime ether **3 c** was obtained as a pale-yellow oil (0.84 g, 91 %). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 1.57–1.70 (m, 6 H, 3×$CH_{2\ cycl.}$), 2.18–2.22 (m, 2 H, $CH_{2\ cycl.}$), 2.31 (s, 6 H, 2×$CH_3$, $NCH_3$), 2.47 (m, 2 H, $CH_{2\ cycl.}$), 2.62 (t, $J$ = 6.0 Hz, 2 H, $CH_2$, $NCH_2$), 4.13 (t, $J$ = 6.0 Hz, 2 H, $CH_2$, $OCH_2$). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 25.42 ($CH_2$), 25.73 ($CH_2$), 25.82 ($CH_2$), 27.02 ($CH_2$), 32.19 ($CH_2$), 45.91 (2×$CH_3$, $NCH_3$), 58.10 ($NCH_2$), 71.37 ($OCH_2$), 160.29 ($C_{C=N}$). HRMS (ESI): *m/z* calcd for $C_{10}H_{21}N_2O$ $[M + H]^+$ 185.1654, found 185.1651.

### *Cyclohexanone* O-*3-(Dimethylamino)propyl Oxime (3 d)*

Following the general procedure starting from **3** (0.57 g, 5 mmol), oxime ether **3 d** was obtained as a pale-yellow oil (0.90 g, 91 %). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 1.59–1.67 (m, 6 H, 3×$CH_{2\ cycl.}$), 1.83 (tt, $J$ = 7.6 Hz, $J$ = 6.4 Hz, 2 H, $CH_2$), 2.20 (m, 2 H, $CH_{2\ cycl.}$), 2.24 (s, 6 H, 2×$CH_3$, $NCH_3$), 2.36 (t, $J$ = 7.6 Hz, 2 H, $CH_2$), 2.46 (m, 2 H, $CH_{2\ cycl.}$), 4.04 (t, $J$ = 6.4 Hz, 2 H, $OCH_2$). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 25.26 ($CH_2$), 25.76 ($CH_2$), 25.85 ($CH_2$), 27.04 ($CH_2$), 27.40 ($CH_2$), 32.22 ($CH_2$), 45.46 (2×$CH_3$, $NCH_3$), 56.59 ($NCH_2$), 71.35 ($OCH_2$), 160.11 ($C_{C=N}$). HRMS (ESI): *m/z* calcd for $C_{11}H_{23}N_2O$ $[M + H]^+$ 199.1810, found 199.1808.

### *Cyclohexanone* O-*2-Morpholinoethyl Oxime (3 e)*[22]

Following the general procedure starting from **3** (0.57 g, 5 mmol), oxime ether **3 e** was obtained as a light red oil (1.02 g, 90 %). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 1.58–1.60 (m, 6 H, 3×$CH_{2\ cycl.}$), 2.19 (m, 2 H, $CH_2$), 2.45 (m, 2 H, $CH_{2\ cycl.}$), 2.54 (t, $J$ = 4.8 Hz, 4 H, 2×$NCH_{2\ mor.}$), 2.68 (t, $J$ = 6.0 Hz, 2 H, $NCH_2$), 3.73 (t, $J$ = 4.8 Hz, 4 H, 2×$OCH_{2\ mor.}$), 4.17 (t, $J$ = 6.0 Hz, 2 H, $OCH_2$). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 25.45 ($CH_2$), 25.76 ($CH_2$), 25.81 ($CH_2$), 27.04 ($CH_2$), 32.17 ($CH_2$), 54.02 ($CH_2$, 2×$NCH_{2\ mor.}$), 57.46 ($NCH_2$), 66.94 ($CH_2$, 2×$OCH_{2\ mor.}$), 71.00 ($OCH_2$), 160.46 ($C_{C=N}$). MS (ESI): *m/z* 227 $[M + H]^+$.

### *2-(Cyclohexylideneaminooxy)acetic Acid (3 f)*[35]

Following the general procedure starting from **3** (0.57 g, 5 mmol), oxime ether **3 f** was obtained as a pale yellow solid (0.77 g, 89 %); mp: 92.5–94 °C, lit. mp: 92–94 °C.[33] $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ (ppm) 1.59–1.69 (m, 6 H, 3×$CH_{2\ cycl.}$), 2.20 (m, 2 H, $CH_{2\ cycl.}$), 2.52 (m, 2 H, $CH_{2\ cycl.}$), 4.59 (s, 2 H, $OCH_2$), 10.26 (bs, 1 H, COOH). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 25.62 ($CH_2$), 25.64 ($CH_2$), 25.70 ($CH_2$), 26.91 ($CH_2$), 31.94 ($CH_2$), 69.56 ($OCH_2$), 163.37 ($C_{C=N}$), 175.13 (COOH). MS (ESI): *m/z* 172 $[M + H]^+$.

### *Propan-2-one* O-*butyl oxime (4 a)*

Following the general procedure starting from **4** (0.37 g, 5 mmol), oxime ether **4 a** was obtained as a pale-yellow oil (0.55 g, 84 %). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 0.95 (t, $J$ = 7.2 Hz, 3 H, $CH_3$), 1.42 (tq, $J$ = 7.2 Hz, $J$ = 6.4 Hz, 2 H, $CH_2$), 1.64 (tt, $J$ = 7.2 Hz, $J$ = 6.4 Hz, 2 H, $CH_2$), 1.88 (s, 3 H, $CH_3$), 1.91 (s, 3 H, $CH_3$), 4.05 (t, $J$ = 6.4 Hz, 2 H, $OCH_2$). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 13.93 ($CH_2$), 15.54 ($CH_3$), 19.23 ($CH_2$), 21.84 ($CH_3$), 31.24 ($CH_2$), 73.18 ($OCH_2$), 154.53 ($C_{C=N}$). HRMS (ESI): *m/z* calcd for $C_7H_{16}NO$ $[M + H]^+$ 130.1232, found 130.1227.

### *Propan-2-one* O-*Naphthalen-1-ylmethyl Oxime (4 b)*[36]

Following the general procedure starting from **4** (0.37 g, 5 mmol), oxime ether **4 b** was obtained as a yellow oil (0.97 g, 91 %). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 1.90 (s, 3 H, $CH_3$), 1.93 (s, 3 H, $CH_3$), 5.57 (s, 2 H, $OCH_2$), 7.45–7.58 (m, 4 H, CH), 7.84 (d, $J$ = 8.0 Hz, 1 H, CH), 7.90 (dd, $J$ = 8.0 Hz, $J$ = 2.0 Hz, 1 H, CH), 8.16 (dd, $J$ = 8.0 Hz, $J$ = 1.2 Hz, 1 H, CH). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 15.78 ($CH_3$), 21.92 ($CH_3$), 73.87 ($OCH_2$), 124.18 (CH), 125.31 (CH), 125.69 (CH), 126.10 (CH), 126.74 (CH), 128.52 (CH), 128.64 (CH), 131.91 (C), 133.62 (C), 133.73 (C), 155.53 ($C_{C=N}$). MS (ESI): *m/z* 214 $[M + H]^+$.

### *Propan-2-one* O-*2-(Dimethylamino)ethyl Oxime (4 c)*[37]

Following the general procedure starting from **4** (0.37 g, 5 mmol), oxime ether **4 c** was obtained as a yellow oil (0.61 g, 85 %). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 1.87 (s, 3 H, $CH_3$), 1.88 (s, 3 H, $CH_3$), 2.33 (s, 6 H, 2×$CH_3$, $NCH_3$), 2.64 (t, $J$ = 5.6 Hz, 2 H, $NCH_2$), 4.16 (t, $J$ = 5.6 Hz, 2 H, $OCH_2$).

$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 15.69 ($CH_3$), 21.83 ($CH_3$), 45.86 (2×$CH_3$, $NCH_3$), 58.14 ($NCH_2$), 71.38 ($OCH_2$), 154.79 ($C_{C=N}$). MS (ESI): *m/z* 145 $[M + H]^+$.

### *Propan-2-one* O-*3-(Dimethylamino)propyl Oxime (4 d)*[31]

Following the general procedure starting from **4** (0.37 g, 5 mmol), oxime ether **4 d** was obtained as a pale-yellow oil (0.69 g, 87 %). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 1.84 (t, $J$ = 6.4 Hz, 2 H, $CH_2$), 1.86 (s, 3 H, $CH_3$), 1.88 (s, 3 H, $CH_3$), 2.26 (s, 6 H, 2×$CH_3$, $NCH_3$), 2.39 (t, $J$ = 7.6 Hz, 2 H, $NCH_2$), 4.06 (t, $J$ = 6.4 Hz, 2 H, $OCH_2$). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 15.49 ($CH_3$), 21.84 ($CH_3$), 27.40 ($CH_2$), 45.38 (2×$CH_3$, $NCH_3$), 56.54 ($NCH_2$), 71.40 ($OCH_2$), 154.51 ($C_{C=N}$). MS (ESI): *m/z* 159 $[M + H]^+$.

### *Propan-2-one* O-*2-Morpholinoethyl Oxime (4 e)*[38]

Following the general procedure starting from **4** (0.37 g, 5 mmol), oxime ether **4 e** was obtained as a light red oil (0.80 g, 86 %). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 1.84 (s, 3 H, $CH_3$), 1.87 (s, 3 H,

$CH_3$), 2.53 (t, $J = 4.8$ Hz, 4H, $2\times NCH_{2\ mor.}$), 2.67 (t, $J = 6.0$ Hz, 2H, $NCH_2$), 3.72 (t, $J = 4.8$ Hz, 4H, $2\times OCH_{2\ mor.}$), 4.17 (t, $J = 6.0$ Hz, 2H, $OCH_2$). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 15.67 ($CH_3$), 21.79 ($CH_3$), 54.03 ($CH_2$), 57.54 ($CH_2$, $2\times NCH_{2\ mor.}$), 57.54 ($NCH_2$), 66.95 ($CH_2$, $2\times OCH_{2\ mor.}$), 71.11 ($OCH_2$), 154.82 ($C_{C=N}$). MS (ESI): *m/z* 187 $[M + H]^+$.

#### *2-(Propan-2-ylideneaminooxy)acetic Acid (4 f)[39]*

Following the general procedure starting from **4** (0.37 g, 5 mmol), oxime ether **4 f** was obtained as a pale-yellow solid (0.52 g, 79%); mp: 71–72.5 °C, lit. mp: 76-76.5 °C.[39] $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ (ppm) 1.89 (s, 3H, $CH_3$), 1.93 (s, 3H, $CH_3$), 4.60 ($OCH_2$), 9.90 (bs, 1H, COOH). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 15.83 ($CH_3$), 21.67 ($CH_3$), 69.61 ($OCH_2$), 157.82 ($C_{C=N}$), 175.18 (COOH). MS (ESI): *m/z* 132 $[M + H]^+$.

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## *Conflict of Interest*

*The authors declare no conflict of interest.*

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