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Synthesis of isoxazolylvinyl ketones from substituted furans

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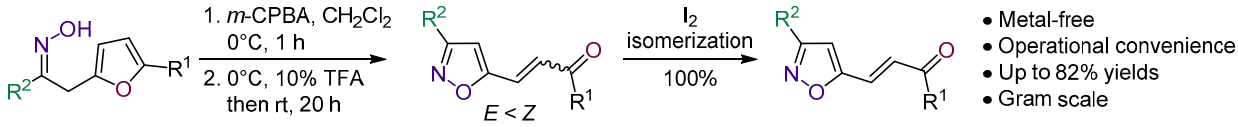


A new method for the preparation of isoxazolylvinyl ketones related to potential cytotoxic agents has been developed. In the first step, the reaction of furfuryl ketones with hydroxylamine hydrochloride affords the corresponding oximes. Further, the oxidative ring opening – ring closure reaction of oximes leads to isoxazoles with an α,β-unsaturated carbonyl motif. The developed procedure is metal-free and does not require expensive starting materials.

Keywords: chalcone, furan, isoxazole, ring opening – ring closure reaction.

Cancer is the second leading cause of death worldwide. In 2018, 18.1 million new cases and 9.6 million cancer deaths were reported according to the World Health Organization.[1] Despite of the huge breakthroughs in the development of anticancer drug therapy, some drawbacks, e.g., high toxicity of anticancer agents toward normal cells and the rise of multidrug resistance, remain. Therefore, the discovery of new effective cytotoxic agents is still highly desired.[2]

Isoxazole derivatives are known to reveal promising activity against breast cancer (MCF-7), prostate cancer (PC3),[3] the human central nervous system glioma (SNB-19),[4] lung adenocarcinoma (A549), colon cancer (Colo-205),[5] and other tumor cell lines.[6]

In medicinal chemistry, chalcones and their heterocyclic analogs bearing α,β-unsaturated fragments are known as important scaffolds with potent anticancer activity.[7] In particular, isoxazolylvinyl ketones and isoxazole-chalcones demonstrate activity against lung cancer cell lines H1792, H157, A549, Calu-1[8] and prostate DU-145 cancer cell lines (Fig. 1).[9]

Additionally, the enone motif in these structures can be further modified, giving access to various linked heterocycles. We have recently reviewed application of this concept to some related systems through functionalization of the enone fragment.[10] Since the common approach to heterocyclic chalcones is the Claisen–Schmidt condensation, the discovery of new cytotoxic agents based on chalcone scaffold has long been focused on easily available heterocyclic aldehydes and ketones.[8,9] To the best of our knowledge, the only isoxazole-chalcones that have been reported up to now are those depicted in Figure 1.

We suggested that easily available furfuryl ketones **1**[11] could serve as a starting point for the synthesis of isoxazolylvinyl ketones employing a ring opening – ring closure (RORC) strategy (Scheme 1). Recently, we have shown that compounds **1** afford pyrazole-chalcones upon the reaction with arylhydrazine hydrochlorides in a single step. The reported protocol does not require the use of expensive materials and metal catalysis, representing a valuable alternative to the Claisen–Schmidt condensation.[12] Herein, we describe a new synthesis of isoxazolylvinyl ketones from substituted furans.

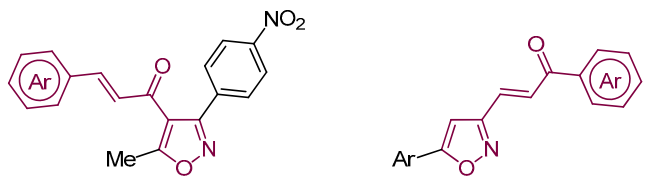
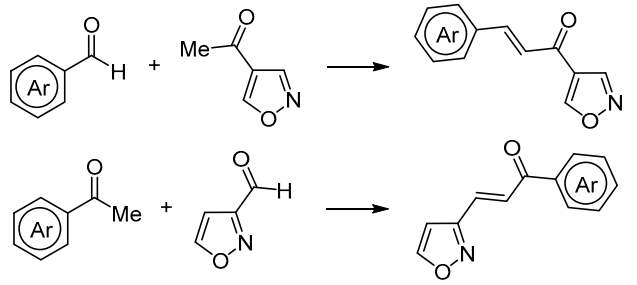
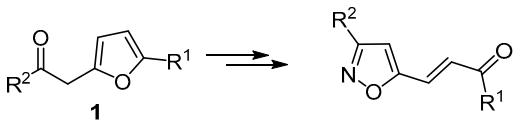


Figure 1. Common structures of reported isoxazole-chalcones and their anticancer activity.

Scheme 1. Possible pathways to isoxazolylvinyl ketones
a) Previous work:[8,9] Claisen–Schmidt condensation as the key step

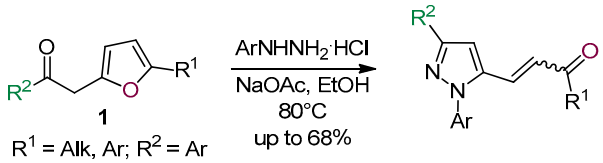


b) This work: RORC reaction as the key step



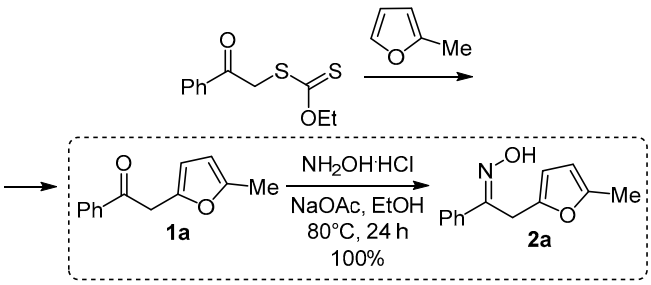
To prepare the target isoxazole derivatives, we decided to test the conditions established earlier for the synthesis of pyrazoles from furans.[11] Specifically, we have shown that treatment of furfuryl ketones **1** with hydrazine derivatives led to the corresponding pyrazoles in one step (Scheme 2).[11]

Scheme 2. Synthesis of pyrazole-chalcones from furans



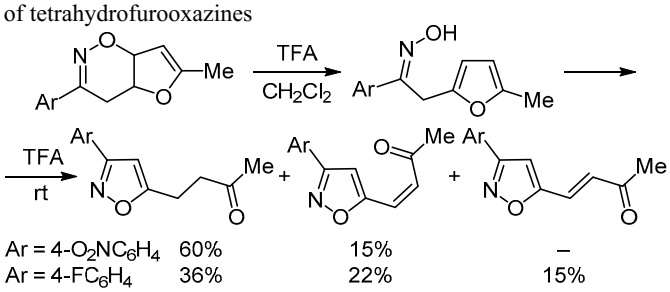
Accordingly, we have studied the reaction of furfuryl ketone **1a** with hydroxylamine hydrochloride and NaOAc in EtOH. However, prolonged heating (24 h) of ketone **1a** at 80°C led exclusively to oxime **2a** instead of the expected isoxazole, presumably due to the reduced nucleophilicity of the hydroxylamino group in compound **2a** (Scheme 3).

Scheme 3. Synthesis of ketone **1a** and its condensation with $NH_2OH·HCl$. Conditions: furfuryl ketone **1a** (2 mmol), $NH_2OH·HCl$ (2 mmol), NaOAc (4 mmol), EtOH (5 ml)



In 2017, Pinho e Melo et al. reported two examples of isoxazole synthesis from tetrahydrofurooxazines *via* the formation of corresponding oximes as intermediates (Scheme 4).[13] This acid-catalyzed reaction afforded a mixture containing substituted 4-(isoxazol-5-yl)butan-2-ones as major products. We aimed to obtain isoxazolylvinyl ketones as the major products and decided to study the transformation of compound **2a** under oxidative conditions.[14]

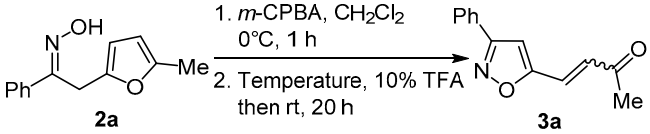
Scheme 4. Acid-catalyzed transformation of tetrahydrofurooxazines



The target isoxazole (*E*,*Z*)-**3a**[15] was obtained through the reaction of oxime **2a** with *m*-CPBA followed by treatment of the reaction mixture with TFA (Table 1). Product **3a** was isolated as a mixture of (*E*,*Z*)-isomers in moderate yield at room temperature. Importantly, adding TFA at low temperature (0°C (entry 2) and –10°C (entry 3)) allowed sufficient improvement of the yield of ketone **3a** along with much better stereoselectivity in favor of the (*Z*)-isomer. A quantitative isomerization of mixture (*E*,*Z*)-**3a** into the stable (*E*)-isomer (Fig. 2) was easily performed under heating with catalytic amount of I_2 (6.4 mol %).[16]

To illustrate the scope of the reaction, a series of oximes **2a**–**j** have been synthesized on a 2 mmol scale (Scheme 5) and subjected to the optimized reaction conditions (Table 1,

Table 1. Synthesis of isoxazolylvinyl ketone **3a** under oxidative conditions: a model reaction*



Entry	Temperature, °C	Yield, %	*E*/*Z* ratio**
1	rt	56	1:1.0
2	0	80	1:30.4
3	–10	79	1:30.0

* The reaction was carried out on 2 mmol scale.
** The *E*/*Z* ratio was determined by ^{1}H NMR spectroscopy.

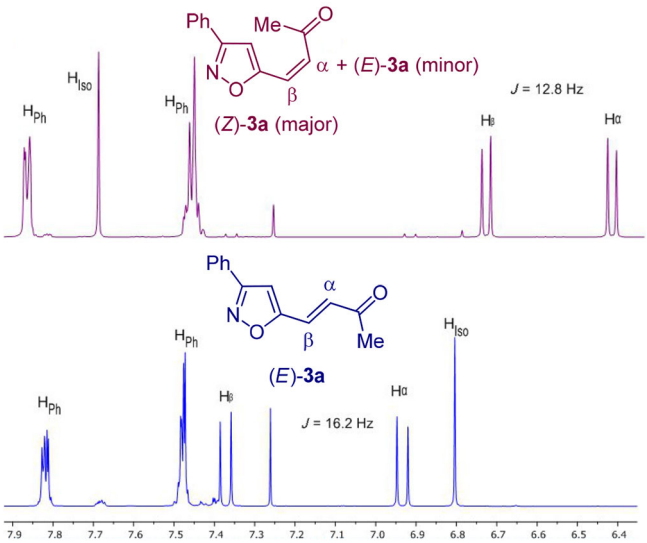
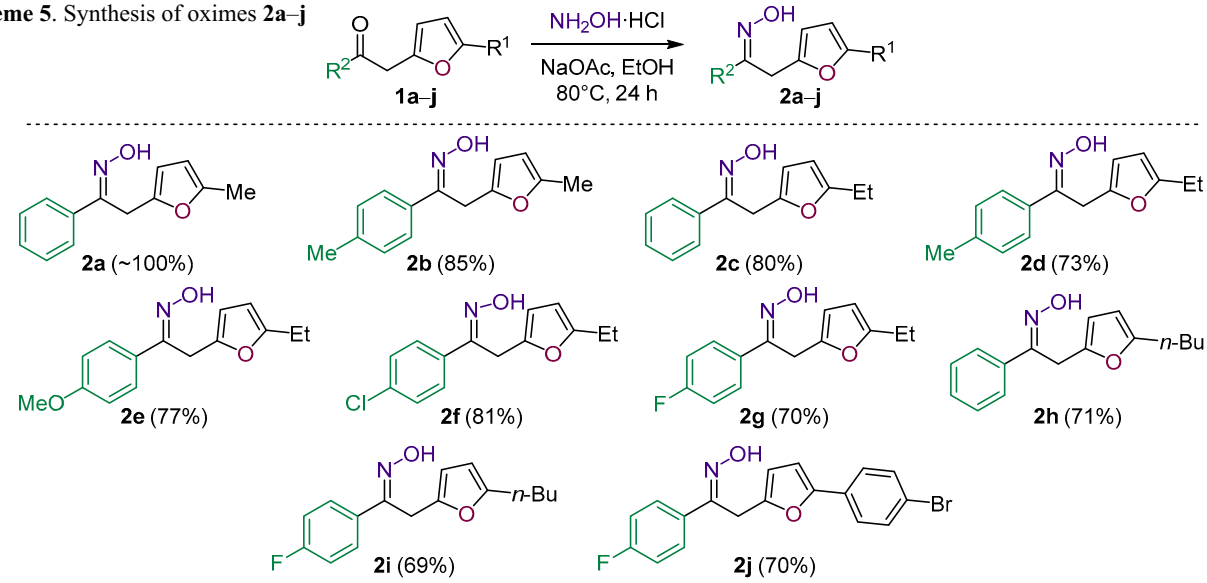


Figure 2. Monitoring of *E*/*Z* isomerization: selected sections of the ^{1}H NMR (600 MHz) spectra of compound (*E*)-**3a** (bottom) and mixture (*E*,*Z*)-**3a** (top) in $CDCl_3$.

Scheme 5. Synthesis of oximes **2a**–**j**



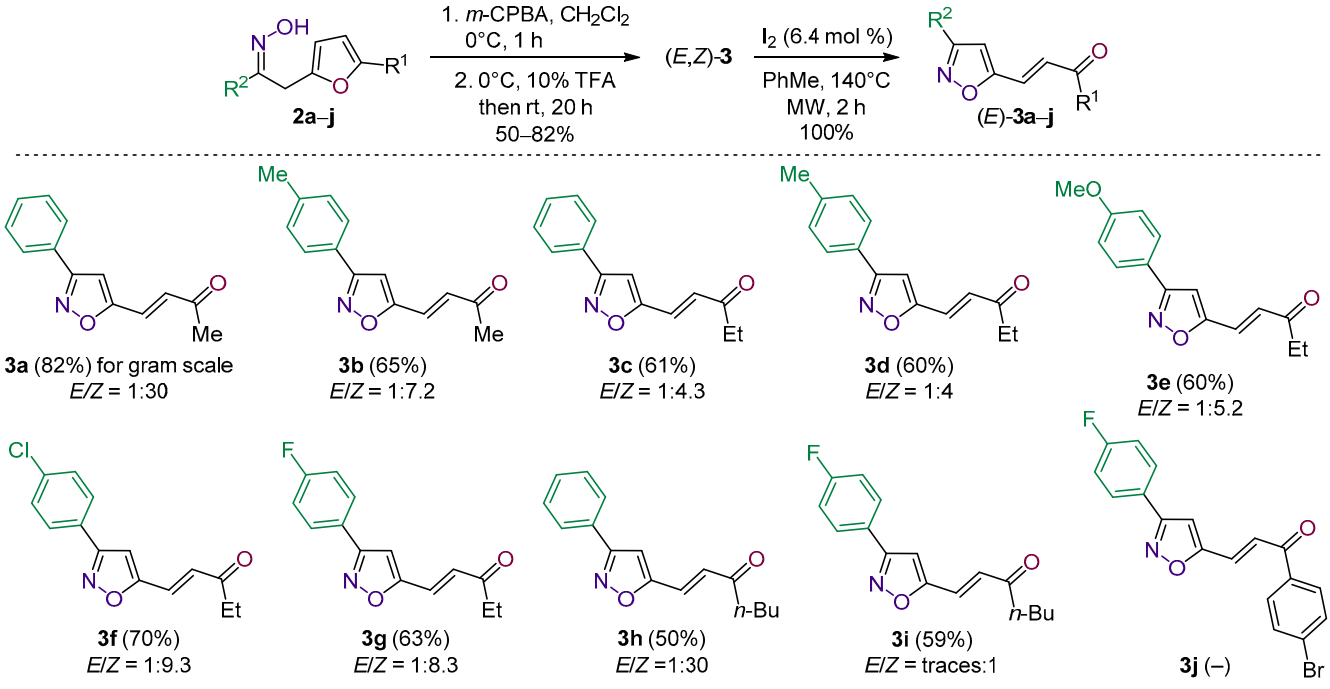
entry 2) with *m*-CPBA and TFA (Scheme 6). Each product **3a**–**j** was prepared on a 0.5 mmol scale in a pure (*E*)-form through the isomerization with I_2 and fully characterized.

The reaction worked well for substrates **2a**–**j** bearing electronically neutral hydrogen atom, electron-donating methyl and methoxy groups, and halogens in the aromatic ring of R^2 substituent. The corresponding isoxazoles **3a**–**i** were isolated in 50–82% yields. With respect to R^1 substituent, the methyl group was more favorable. The desired products **3a**,**b** were obtained in 82 and 65% yields, respectively. The reaction of oximes **2a**,**b** proceeded in a very clean manner, and products **3a**,**b** did not require any purification.

The NMR spectra of the crude reaction mixtures indicated the presence of only isomers of the target isoxazoles **3a**,**b**. The yields of compounds **3c**–**g** with ethyl group were comparable in the range of 60–70%. The same transformation of oximes **2h**,**i** containing butyl group proceeded in lower yields and gave mixtures of products that required further purification. When R^1 was a *p*-bromophenyl group, we could not isolate the target isoxazole **3j**. Probably, the aryl group can alter the regiochemistry due to steric and electronic reasons, and *m*-CPBA attacks the C=C double bond proximate to the oxime function, resulting in alternative reaction pathways (see also the mechanism, Scheme 7).

Importantly, the synthesis of isoxazolylvinyl ketones **3** can be performed on a gram-scale in high yields as it was demonstrated for compound **3a** (Scheme 6). The structure of isoxazole (*E*)-**3g** was confirmed by single crystal X-ray diffraction (Fig. 3).

Scheme 6. Synthesis of isoxazolylvinyl ketones **3a**–**i**. The *E*/*Z* ratio was determined by NMR spectra of crude products (*E*/*Z*)-**3a**–**i**



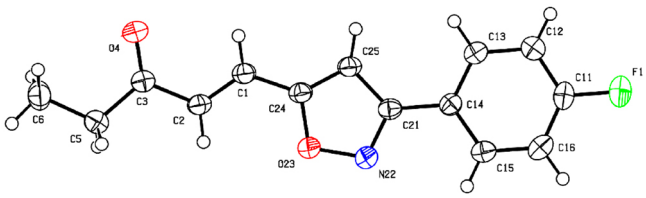
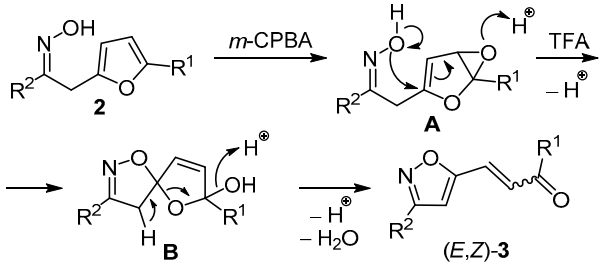


Figure 3. Molecular structure of compound (*E*)-**3g** with atoms represented as thermal vibration ellipsoids of 50% probability.

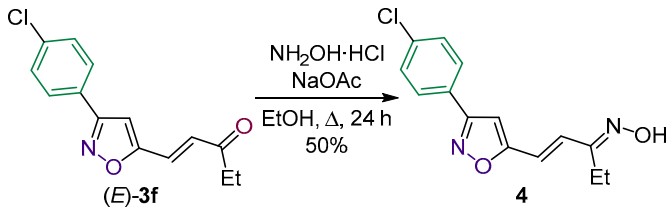
A proposed mechanism for the transformation of oximes **2** into isoxazoles **3** is presented in Scheme 7. The key step includes epoxidation of the furan double bond with *m*-CPBA resulting in the formation of bicyclic epoxide **A**. An intermediacy of similar oxidized products was reported earlier.[17] Further, the treatment with TFA induces intramolecular attack of nucleophilic hydroxylamine O atom onto C-2 atom of the furan ring with proton-assisted epoxide ring opening giving rise to the spirocyclic intermediate **B**. The subsequent ring opening of intermediate **B** and aromatization yield the final isoxazole **3**.

Scheme 7. Proposed mechanism for the transformation of oximes **2** into isoxazoles **3**



Since hetaryl-substituted isoxazoles that could be obtained from compounds **3** are known as the second generation RORγ inhibitors,[18] we decided to study the reaction of compound (*E*)-**3f** with hydroxylamine hydrochloride and NaOAc in EtOH to obtain a bisisoxazole. We have found that under conditions applied for the synthesis of oximes **2**, compound (*E*)-**3f** yielded the corresponding oxime **4** (Scheme 8). The ^{1}H NMR spectrum of compound **4** demonstrated two doublets of the vinylic protons at 6.80 and 6.98 ppm with J = 16.6 Hz. In the IR spectrum, we could not observe the signal of a carbonyl group. Instead, a new peak of the NOH group was detected at 3202 cm^{-1}. Further study of this reaction and synthesis of bisisoxazole from compounds **3** is underway.

Scheme 8. Synthesis of oxime **4**



In summary, we have developed a new method for the synthesis of isoxazolylvinyl ketones that are related to compounds with anticancer activity. We have demonstrated that oximes of furfuryl ketones undergo oxidative ring opening – ring closure (RORC) reaction under acidic conditions to produce new isoxazole with α,β-unsaturated fragment. The reaction worked well for substrates bearing diverse groups in aromatic ring, but strongly depends on the substituent in the furan ring. The best results were observed for substituted methylfurans. These experiments proceeded so clean that target isoxazoles did not required any purification.

Experimental

IR spectra were recorded on a PerkinElmer Spectrum BX spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-600 (600 and 151 MHz, respectively), Bruker AV-500 (500 and 126 MHz, respectively), or Bruker AV-400 (400 and 101 MHz, respectively) spectrometers in $CDCl_3$, using TMS or solvent residual peak (7.20 ppm and 77.2 ppm for ^{1}H and ^{13}C nuclei, respectively) as internal standard. High-resolution mass spectra were recorded on a Bruker micrOTOF-Q ESI-Qq-TOF mass spectrometer. TLC analyses were performed on Merck 60 F_{254} Aluminum silica gel plates in combination with UV detection (254 nm). Flash chromatography was performed on silica gel 200–300 mesh using *i*-hexane–EtOAc system as eluent. Melting points were determined on a Mel-Temp II Laboratory Devices apparatus. All commercial reagents and solvents were used without further purification. All reactions were run under air. The reactions under microwave irradiation were carried out in a Biotage® Robot Eight microwave synthesis reactor using sealed microwave reaction vessels.

Synthesis of furfuryl ketones 1a–j (General method).[11a,c] A solution of the corresponding xanthogenate[12] (12.5 mmol) and furan derivative (80 mmol for 2-methylfuran and 2-ethylfuran; 13 mmol for 2-butylfuran and 2-(4-bromophenyl)-furan) in DMSO (30 ml) was cooled (5–10°C) and treated with $FeSO_4 \cdot 7H_2O$ (1.74 g, 6.25 mmol). Then, 34% aqueous H_2O_2 (2.5 ml, 25 mmol) was dropwise added. After adding H_2O_2, the reaction mixture was stirred for 30 min at 5–10°C, then for 2 h at room temperature (TLC control). Once the reaction was complete, the mixture was poured into H_2O (300 ml), extracted with EtOAc (4×50 ml), the combined extracts were washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography using *i*-hexane–EtOAc, 8:1, as eluent.

2-(5-Methylfuran-2-yl)-1-phenylethan-1-one (1a). Yield 1.6 g (64%), pale-yellow oil.[19] IR spectrum (NaCl), ν, cm^{-1}: 784, 1021, 1220, 1597, 1693 (C=O). ^{1}H NMR spectrum (600 MHz), δ, ppm: 2.28 (3H, br. s, CH_3); 4.27 (2H, s, CH_2); 5.93–5.94 (1H, m, H Fur); 6.12–6.13 (1H, m, H Fur); 7.47–7.50 (2H, m, H Ph); 7.57–7.60 (1H, m, H Ph); 8.03–8.04 (2H, m, H Ph). ^{13}C NMR spectrum (101 MHz), δ, ppm: 13.6; 38.6; 106.6; 109.1; 128.7 (4C); 133.3; 136.3; 146.3; 151.7; 195.4. Found, *m*/*z*: 201.0752 $[M+H]^+$. $C_{13}H_{13}O_2$. Calculated, *m*/*z*: 201.0910.

2-(5-Methylfuran-2-yl)-1-(*p*-tolyl)ethanone (1b) was isolated as a mixture with 5% of starting xanthogenate and used further without additional purification. ^{1}H NMR spectrum (400 MHz), δ, ppm: 2.24 (3H, br. s, CH_3); 2.36 (3H, s, $C\underline{H}_3C_6H_4$); 4.20 (2H, s, CH_2); 5.88–5.90 (1H, m,

H Fur); 6.07–6.08 (1H, m, H Fur); 7.89–7.91 (2H, m, $CH_3C_6\underline{H}_4$); 7.23–7.24 (2H, m, $CH_3C_6\underline{H}_4$).

2-(5-Ethylfuran-2-yl)-1-phenylethan-1-one (1c). Yield 1.87 g (70%), brownish oil.[19] IR spectrum (NaCl), ν, cm^{-1}: 779, 1013, 1181, 1219, 1597, 1686 (C=O). ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 1.19 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 2.60 (2H, q, *J* = 7.5, $C\underline{H}_2CH_3$); 4.25 (2H, s, CH_2); 5.90–5.92 (1H, m, H Fur); 6.10–6.11 (1H, m, H Fur); 7.45–7.47 (2H, m, H Ph); 7.54–7.57 (1H, m, H Ph); 8.00–8.02 (2H, m, H Ph). ^{13}C NMR spectrum (151 MHz), δ, ppm: 11.9; 21.2; 38.4; 104.8; 108.6; 128.4 (2C); 128.5 (2C); 133.1; 136.2; 146.0; 157.2; 195.1. Found, *m*/*z*: 215.1065 $[M+H]^+$. $C_{14}H_{15}O_2$. Calculated, *m*/*z*: 215.1067.

2-(5-Ethylfuran-2-yl)-1-(*p*-tolyl)ethan-1-one (1d). Yield 1.42 g (50%), white solid, mp 42–44°C.[12] IR spectrum (NaCl), ν, cm^{-1}: 776, 1181, 1223, 1606, 1684 (C=O). ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 1.19 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 2.40 (3H, s, $C\underline{H}_3C_6H_4$); 2.60 (2H, q, *J* = 7.5, $C\underline{H}_2CH_3$); 4.22 (2H, s, CH_2); 5.89–5.91 (1H, m, H Fur); 6.08–6.10 (1H, m, H Fur); 7.25–7.26 (2H, m, $CH_3C_6\underline{H}_4$); 7.90–7.92 (2H, m, $CH_3C_6\underline{H}_4$). ^{13}C NMR spectrum (101 MHz), δ, ppm: 12.1; 21.4; 21.7; 38.6; 104.9; 108.7; 128.8 (2C); 129.3 (2C); 133.8; 144.2; 146.4; 157.4; 195.0. Found, *m*/*z*: 229.1220 $[M+H]^+$. $C_{15}H_{17}O_2$. Calculated, *m*/*z*: 229.1223.

2-(5-Ethylfuran-2-yl)-1-(4-methoxyphenyl)ethanone (1e). Yield 2.07 g (68%), brownish oil. IR spectrum (NaCl), ν, cm^{-1}: 799, 833, 1025, 1173, 1224, 1260, 1601, 1681 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.19 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 2.57–2.63 (2H, m, $C\underline{H}_2CH_3$); 3.87 (3H, s, OCH_3); 4.20–4.21 (2H, m, CH_2); 5.90–5.91 (1H, m, H Fur); 6.08–6.09 (1H, m, H Fur); 6.91–6.95 (2H, m, $CH_3OC_6\underline{H}_4$); 7.98–8.02 (2H, m, $CH_3OC_6\underline{H}_4$). ^{13}C NMR spectrum (101 MHz), δ, ppm: 12.1; 21.3; 38.4; 55.5; 104.9; 108.5; 113.7 (2C); 129.3; 131.0 (2C); 146.6; 157.3; 163.6; 193.9. Found, *m*/*z*: 245.1175 $[M+H]^+$. $C_{15}H_{17}O_3$. Calculated, *m*/*z*: 245.1172.

1-(4-Chlorophenyl)-2-(5-ethylfuran-2-yl)ethanone (1f). Yield 2.17 g (70%), pale-yellow oil. IR spectrum (NaCl), ν, cm^{-1}: 779, 833, 1012, 1092, 1219, 1399, 1589, 1688 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.19 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 2.54–2.67 (2H, m, $C\underline{H}_2CH_3$); 4.22 (2H, s, CH_2); 5.91–5.92 (1H, m, H Fur); 6.09–6.11 (1H, m, H Fur); 7.42–7.45 (2H, m, ClC_6H_4); 7.93–7.97 (2H, m, ClC_6H_4). ^{13}C NMR spectrum (101 MHz), δ, ppm: 12.1; 21.4; 38.7; 105.0; 108.9; 129.0 (2C); 130.1 (2C); 134.6; 139.8; 145.8; 157.6; 194.2. Found, *m*/*z*: 249.0679 $[M+H]^+$. $C_{14}H_{14}ClO_2$. Calculated, *m*/*z*: 249.0677.

2-(5-Ethylfuran-2-yl)-1-(4-fluorophenyl)ethan-1-one (1g). Yield 1.30 g (45%), brownish oil.[12] IR spectrum (NaCl), ν, cm^{-1}: 845, 1158, 1233, 1599, 1693 (C=O). ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 1.19 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 2.60 (2H, q, *J* = 7.5, $C\underline{H}_2CH_3$); 4.22 (2H, s, CH_2); 5.90–5.92 (1H, m, H Fur); 6.09–6.11 (1H, m, H Fur); 7.11–7.15 (2H, m, FC_6H_4); 8.02–8.06 (2H, m, FC_6H_4). ^{13}C NMR spectrum (151 MHz), δ, ppm (*J*, Hz): 12.1; 21.3; 38.7; 105.0; 108.9; 115.7 (d, *J* = 21.9, 2C); 131.4 (d, *J* = 9.5, 2C); 132.7 (d, *J* = 3.4); 145.9; 157.5; 165.8 (d, *J* = 255.1), 193.7.

2-(5-Butylfuran-2-yl)-1-phenylethanone (1h). Yield 1.30 g (43%), pale-yellow oil. IR spectrum (ATR), ν, cm^{-1}: 780, 1013, 1147, 1219, 1273, 1333, 1448, 1562, 1597 (C=O). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 0.90 (3H, t, *J* = 7.4, $CH_2CH_2CH_2C\underline{H}_3$); 1.29–1.34 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$); 1.55–1.61 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$); 2.56–2.59 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$); 4.25 (2H, s, CH_2); 5.90–5.91 (1H, m, H Fur); 6.09–6.10 (1H, m, H Fur); 7.44–7.48 (2H, m, H Ph); 7.55–7.56 (1H, m, H Ph); 8.00–8.02 (2H, m, H Ph). ^{13}C NMR spectrum (126 MHz), δ, ppm: 13.8; 22.2; 27.7; 30.1; 38.7; 105.6; 108.7; 128.6 (4C); 133.2; 136.3; 146.1; 156.2; 195.3. Found, *m*/*z*: 243.1379. $[M+H]^+$. $C_{16}H_{19}O_2$. Calculated, *m*/*z*: 243.1380.

2-(5-Butylfuran-2-yl)-1-(4-fluorophenyl)ethan-1-one (1i). Yield 1.33 g (41%), yellow oil.[12] ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 0.89 (3H, t, *J* = 7.3, $CH_2CH_2CH_2C\underline{H}_3$); 1.29–1.35 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$); 1.50–1.61 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$); 2.54–2.58 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$); 4.22 (2H, s, CH_2); 5.90–5.91 (1H, m, H Fur); 6.09–6.10 (1H, m, H Fur); 7.08–7.14 (2H, m, FC_6H_4); 8.01–8.06 (2H, m, FC_6H_4). ^{13}C NMR spectrum (101 MHz), δ, ppm (*J*, Hz): 13.8; 22.2; 27.7; 30.1; 38.7; 105.7; 108.8; 115.5 (d, *J* = 21.9, 2C); 131.3 (d, *J* = 9.5, 2C); 132.7 (d, *J* = 3.4); 145.9; 156.3; 165.8 (d, *J* = 255.1); 193.8.

2-[5-(4-Bromophenyl)furan-2-yl]-1-(4-fluorophenyl)-ethanone (1j). Yield 1.79 g (40%), yellow solid, mp 84–88°C. IR spectrum (ATP), ν, cm^{-1}: 817, 993, 1068, 1113, 1152, 1229, 1328, 1405, 1539, 1589, 1689 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 4.32–4.33 (2H, m, CH_2); 6.31–6.32 (1H, m, H Fur); 6.58–6.60 (1H, m, H Fur); 7.12–7.16 (2H, m, FC_6H_4); 7.43–7.47 (4H, m, BrC_6H_4); 8.02–8.07 (2H, m, FC_6H_4). ^{13}C NMR spectrum (101 MHz), δ, ppm (*J*, Hz): 38.6; 106.7; 110.7; 115.9 (d, *J* = 21.9, 2C); 120.9; 125.1 (2C); 129.6; 131.3 (d, *J* = 9.4, 2C); 131.7 (2C); 132.6 (d, *J* = 2.9); 148.1; 152.5; 165.9 (d, *J* = 255.6); 193.1. Found, *m*/*z*: 359.0079 $[M+H]^+$. $C_{18}H_{13}BrFO_2$. Calculated, *m*/*z*: 359.0078.

Synthesis of oximes 2a–j (General method). Hydroxylamine hydrochloride (139 mg, 2 mmol) and anhydrous NaOAc (32.8 mg, 4 mmol) were added to a solution of furfuryl ketone **1a**–**j** (2 mmol) in EtOH (5 ml), and the mixture was stirred for 24 h at 80°C (TLC and LC-MS control). Then, the reaction mixture was poured into H_2O (100 ml) and extracted with EtOAc (4×25 ml). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting crude product was purified by flash chromatography using *i*-hexane–EtOAc, 4:1, as eluent.

2-(5-Methylfuran-2-yl)-1-phenylethan-1-one oxime (2a).[15] Yield 610 mg (~100%), white solid, mp 90–92°C. IR spectrum (NaCl), ν, cm^{-1}: 960, 1016, 1168, 1321, 1461, 1495, 1568, 2922, 3241 (N–OH). ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 2.24 (3H, s, CH_3); 4.13 (2H, s, CH_2); 5.82–5.84 (1H, m, H Fur); 5.91–5.92 (1H, m, H Fur); 7.36–7.37 (3H, m, H Ph); 7.67–7.69 (2H, m, H Ph). ^{13}C NMR spectrum (101 MHz), δ, ppm: 13.6; 25.5; 106.3; 107.5; 126.4 (2C); 128.5 (2C); 129.4; 135.3; 147.9; 150.9; 155.2. Found, *m*/*z*: 214.0862 $[M–H]^-$. $C_{13}H_{13}NO_2$. Calculated, *m*/*z*: 214.0874.

2-(5-Methylfuran-2-yl)-1-(*p*-tolyl)ethanone oxime (2b). Yield 389 mg (85%), white solid, mp 84–86°C. IR spectrum (ATP), ν, cm^{-1}: 793, 915, 952, 1015, 1065, 1185, 1289, 1319, 1439, 1511, 1566, 2920, 1609, 3236, 3281 (N–OH).

^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.23 (3H, s, CH_3); 2.35 (3H, s, $C\underline{H}_3C_6H_4$); 4.12 (2H, s, CH_2); 5.82–5.83 (1H, m, H Fur); 5.90–5.91 (1H, m, H Fur); 7.16–7.17 (2H, m, $CH_3C_6\underline{H}_4$); 7.55–7.57 (2H, m, $CH_3C_6\underline{H}_4$); 9.00 (1H, br. s, NOH). ^{13}C NMR spectrum (101 MHz), δ, ppm: 13.5; 21.3; 25.4; 106.3; 107.4; 126.3 (2C); 129.2 (2C); 132.4; 139.4; 148.0; 150.8; 155.0. Found, *m*/*z*: 230.1178. $[M+H]^+$. $C_{14}H_{16}NO_2$. Calculated, *m*/*z*: 230.1176.

2-(5-Ethylfuran-2-yl)-1-phenylethanone oxime (2c). Yield 370 mg (80%), yellow solid, mp 52–55°C. IR spectrum (NaCl), ν, cm^{-1}: 966, 1012, 1180, 1366, 1446, 1497, 1563, 2973, 3292 (N–OH). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.20 (3H, t, *J* = 7.5, $CH_2C\underline{H}_3$); 2.61 (2H, qd, *J* = 7.5, *J* = 1.0, $C\underline{H}_2CH_3$); 4.17 (2H, d, *J* = 1.0, CH_2); 5.86–5.87 (1H, m, H Fur); 5.93–5.99 (1H, m, H Fur); 7.39–7.41 (3H, m, H Ph); 7.69–7.71 (2H, m, H Ph). ^{13}C NMR spectrum (101 MHz), δ, ppm: 12.1; 21.4; 25.6; 104.7; 107.3; 126.5 (2C); 128.5 (2C); 129.3; 135.4; 147.8; 155.3; 156.7. Found, *m*/*z*: 230.1174 $[M+H]^+$. $C_{14}H_{16}NO_2$. Calculated, *m*/*z*: 230.1176.

2-(5-Ethylfuran-2-yl)-1-(*p*-tolyl)ethanone oxime (2d). Yield 351 mg (73%), yellow oil. IR spectrum (NaCl), ν, cm^{-1}: 966, 1012, 1060, 1185, 1365, 1435, 1515, 1563, 1610, 2923, 2973, 3292 (N–OH). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.18 (3H, t, *J* = 7.5, $CH_2C\underline{H}_3$); 2.35 (3H, s, $C\underline{H}_3C_6H_4$); 2.55–2.61 (2H, m, $C\underline{H}_2CH_3$); 4.13 (2H, d, *J* = 1.0, CH_2); 5.85–5.87 (1H, m, H Fur); 5.94–5.95 (1H, m, H Fur); 7.18–7.21 (2H, m, $CH_3C_6\underline{H}_4$); 7.59–7.61 (2H, m, $CH_3C_6\underline{H}_4$). ^{13}C NMR spectrum (101 MHz), δ, ppm: 12.1; 21.3 (2C); 25.5; 104.6; 107.2; 126.3 (2C); 129.2 (2C); 132.5; 139.4; 147.9; 155.2; 156.6. Found, *m*/*z*: 244.1332 $[M+H]^+$. $C_{15}H_{18}NO_2$. Calculated, *m*/*z*: 244.1332.

2-(5-Ethylfuran-2-yl)-1-(4-methoxyphenyl)ethanone oxime (2e). Yield 399 mg (77%), yellow oil. IR spectrum (NaCl), ν, cm^{-1}: 836, 966, 1012, 1030, 1179, 1253, 1515, 1607, 2936, 2970, 3292 (N–OH). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.20 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 2.58–2.64 (2H, m, $C\underline{H}_2CH_3$); 3.84 (3H, s, CH_3O); 4.15 (2H, d, *J* = 1.0, CH_2); 5.86–5.87 (1H, m, H Fur); 5.95–5.96 (1H, m, H Fur); 6.89–6.93 (2H, m, $CH_3OC_6\underline{H}_4$); 7.65–7.68 (2H, m, $CH_3OC_6\underline{H}_4$). ^{13}C NMR spectrum (101 MHz), δ, ppm: 12.1; 21.4; 25.4; 55.3; 104.7; 107.2; 113.9 (2C); 127.9 (2C); 128.3; 147.9; 155.0; 156.6; 160.5. Found, *m*/*z*: 260.1282 $[M+H]^+$. $C_{15}H_{18}NO_3$. Calculated, *m*/*z*: 260.1281.

1-(4-Chlorophenyl)-2-(5-ethylfuran-2-yl)ethanone oxime (2f). Yield 426 mg (81%), white solid, mp 78–80°C. IR spectrum (NaCl), ν, cm^{-1}: 834, 967, 1012, 1094, 1180, 1291, 1315, 1494, 1563, 1595, 2937, 2973, 3292 (N–OH). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.17 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 2.55–2.61 (2H, m, $C\underline{H}_2CH_3$); 4.11–4.12 (2H, m, CH_2); 5.83–5.85 (1H, m, H Fur); 5.92–5.93 (1H, m, H Fur); 7.31–7.35 (2H, m, ClC_6H_4); 7.59–7.62 (2H, m, ClC_6H_4). ^{13}C NMR spectrum (101 MHz), δ, ppm: 12.1; 21.4; 25.4; 104.7; 107.5; 127.8 (2C); 128.7 (2C); 133.8; 135.4; 147.4; 154.5; 156.9. Found, *m*/*z*: 264.0788 $[M+H]^+$. $C_{14}H_{15}ClNO_2$. Calculated, *m*/*z*: 264.0786.

2-(5-Ethylfuran-2-yl)-1-(4-fluorophenyl)ethanone oxime (2g). Yield 340 mg (70%), yellow solid, mp 75–78°C. IR spectrum (NaCl), ν, cm^{-1}: 967, 1012, 1159, 1234, 1364, 1563, 1603, 2939, 2974, 3356 (N–OH). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.17 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 2.55–2.61 (2H, m, $C\underline{H}_2CH_3$); 4.11–4.13 (2H, m, CH_2); 5.87–5.88 (1H, dt, *J* = 3.1, *J* = 1.1, H Fur); 5.95–5.96 (1H, m, H Fur); 7.05–7.09 (2H, m, FC_6H_4); 7.67–7.70 (2H, m, FC_6H_4). ^{13}C NMR spectrum (101 MHz), δ, ppm (*J*, Hz): 12.1; 21.3; 25.5; 104.7; 107.4; 115.4 (d, *J* = 22.0, 2C); 128.4 (d, *J* = 8.5, 2C); 131.5 (d, *J* = 3.8); 147.5; 154.5; 156.8; 163.4 (d, *J* = 249.3). Found, *m*/*z*: 248.1083 $[M+H]^+$. $C_{14}H_{15}FNO_2$. Calculated, *m*/*z*: 248.1081.

2-(5-Butylfuran-2-yl)-1-phenylethanone oxime (2h). Yield 364 mg (71%), yellow oil. IR spectrum (ATP), ν, cm^{-1}: 949, 1012, 1061, 1175, 1287, 1445, 1561, 1607, 2864, 2928, 3242 (N–OH). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 0.89 (3H, t, *J* = 7.3, $CH_2CH_2CH_2C\underline{H}_3$); 1.56 (2H, quint, *J* = 7.5, $CH_2CH_2C\underline{H}_2CH_3$); 1.47–1.67 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$); 2.55 (2H, t, *J* = 7.6, $C\underline{H}_2CH_2CH_2CH_3$); 4.14 (2H, br. s, CH_2); 5.82–5.84 (1H, m, H Fur); 5.92–5.93 (1H, d, *J* = 3.1, H Fur); 7.31–7.44 (3H, m, H Ph); 7.66 (2H, m, H Ph). ^{13}C NMR spectrum (126 MHz), δ, ppm: 13.8; 22.2; 25.6; 27.7; 30.1; 105.4; 107.3; 126.5 (2C); 128.5 (2C); 129.3; 135.4; 147.7; 155.4 (2C). Found, *m*/*z*: 258.1492 $[M+H]^+$. $C_{16}H_{20}NO_2$. Calculated, *m*/*z*: 258.1489.

2-(5-Butylfuran-2-yl)-1-(4-fluorophenyl)ethanone oxime (2i). Yield 380 mg (69%), yellow solid, mp 64–65°C. IR spectrum (ATP), ν, cm^{-1}: 969, 1010, 1057, 1158, 1226, 1438, 1509, 1597, 2862, 2928, 3216 (N–OH). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 0.89 (3H, t, *J* = 7.4, $CH_2CH_2CH_2C\underline{H}_3$); 1.31–1.35 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$); 1.52–1.58 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$); 2.53–2.56 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$); 4.12 (2H, d, *J* = 1.0, CH_2); 5.83–5.84 (1H, m, H Fur); 5.92–5.93 (1H, m, H Fur); 7.02–7.06 (2H, m, FC_6H_4); 7.62–7.65 (2H, m, FC_6H_4); 8.85 (1H, br. s, NOH). ^{13}C NMR spectrum (126 MHz), δ, ppm (*J*, Hz): 13.8; 22.2; 25.6; 27.7; 30.1; 105.4; 107.4; 115.5 (d, *J* = 21.6, 2C); 128.5 (d, *J* = 8.3, 2C); 131.5 (d, *J* = 3.3); 147.4; 154.6; 155.6; 163.4 (d, *J* = 249.2). Found, *m*/*z*: 274.1245 $[M-H]^-$. $C_{16}H_{18}FNO_2$. Calculated, *m*/*z*: 274.1249.

2-[5-(4-Bromophenyl)furan-2-yl]-1-(4-fluorophenyl)-ethanone oxime (2j). Yield 522 mg (70%), white solid, mp 151–154°C. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 4.22 (2H, d, *J* = 1.0, CH_2); 6.14 (1H, dt, *J* = 3.3, *J* = 1.0, H Fur); 6.52–6.54 (1H, m, H Fur); 7.05–7.09 (2H, m, FC_6H_4); 7.42–7.47 (4H, m, BrC_6H_4); 7.67–7.71 (2H, m, FC_6H_4); 8.05 (1H, br. s, NOH). ^{13}C NMR spectrum (101 MHz), δ, ppm (*J*, Hz): 25.5; 106.5; 109.3; 115.6 (d, *J* = 21.8, 2C); 120.8; 124.9 (2C); 128.3 (d, *J* = 8.3, 2C); 129.7; 131.3 (d, *J* = 3.5); 131.8 (2C); 149.8; 151.9; 153.9; 163.5 (d, *J* = 249.7). Found, *m*/*z*: 374.0079 $[M+H]^+$. $C_{18}H_{14}BrFNO_2$. Calculated, *m*/*z*: 374.0187.

Synthesis of isoxazolylvinyl ketones 3a–i (General method). *m*-CPBA (77% w/w, 0.135 g, 0.6 mmol) was added to a solution of oxime **2a**–**i** (0.5 mmol) in CH_2Cl_2 (2 ml) at 0°C. The reaction mixture was stirred at the same temperature for 1 h. Then TFA (0.038 ml, 0.05 mmol) was added. The reaction mixture was allowed to reach room temperature and stirred for 20 h. Once the reaction was complete, the mixture was washed with $Na_2S_2O_3$ solution and then with brine. CH_2Cl_2 was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to give a pure respective product (*E*,*Z*)-**3a**–**i**.

Isomerization of compounds (*E*,*Z*)-3a–i into compounds (*E*)-3a–i (General method). Microwave reaction vessel was charged with compound (*E*,*Z*)-**3a–i** (0.2 mmol), I_2 (3.4 mg, 0.013 mmol), and PhMe (2 ml). The reaction mixture was stirred at 140°C in a microwave reactor for 2 h. After completion of the reaction, PhMe and I_2 were removed under reduced pressure. The resulting product was purified by flash chromatography using *i*-hexane–EtOAc, 4:1, as eluent.

(*E*)-4-(3-Phenylisoxazol-5-yl)but-3-en-2-one ((*E*)-3a).[15] Yield 87 mg (82%), white solid, mp 130–132°C. IR spectrum (NaCl), ν, cm^{-1}: 769, 952, 983, 1268, 1439, 1560, 1637 (C=C enone), 1664 (C=O). ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 2.41 (3H, s, CH_3); 6.80 (1H, s, H isoxazole); 6.95 (1H, d, *J* = 16.2, (O)CC<u>H</u>=CH); 7.40 (1H, d, *J* = 16.2, (O)CCH=C<u>H</u>); 7.47–7.49 (3H, m, H Ph); 7.81–7.83 (2H, m, H Ph). ^{13}C NMR spectrum (151 MHz), δ, ppm: 28.5; 104.5; 125.4; 126.8 (2C); 128.4; 129.1; 130.4 (2C); 130.8; 163.1; 166.3; 197.0. Found, *m*/*z*: 214.0861 $[M+H]^+$. $C_{13}H_{12}NO_2$. Calculated, *m*/*z*: 214.0863.

(*E*)-4-[3-(*p*-Tolyl)isoxazol-5-yl]but-3-en-2-one ((*E*)-3b). Yield 74 mg (65%), white solid, mp 133–136°C. IR spectrum (ATP), ν, cm^{-1}: 803, 963, 1162, 1256, 1299, 1355, 1424, 1523, 1557, 1624 (C=C enone), 1688 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.43 (3H, s, CH_3); 2.43 (3H, s, $C\underline{H}_3C_6H_4$); 6.80 (1H, s, H isoxazole); 6.94 (1H, d, *J* = 16.2, (O)CC<u>H</u>=CH); 7.28–7.32 (2H, m, $CH_3C_6\underline{H}_4$); 7.38 (1H, dd, *J* = 16.3, *J* = 0.4, (O)CCH=C<u>H</u>); 7.71–7.74 (2H, m, $CH_3C_6\underline{H}_4$). ^{13}C NMR spectrum (101 MHz), δ, ppm: 21.5; 28.5; 104.5; 125.5 (2C); 126.7 (2C); 129.7 (2C); 130.7; 140.6; 163.0; 166.1; 197.1. Found, *m*/*z*: 228.0970 $[M+H]^+$. $C_{14}H_{14}NO_2$. Calculated, *m*/*z*: 228.1019.

(*E*)-1-(3-Phenylisoxazol-5-yl)pent-1-en-3-one ((*E*)-3c). Yield 70 mg (61%), white solid, mp 127–130°C. IR spectrum (NaCl), ν, cm^{-1}: 764, 951, 981, 1297, 1403, 1562, 1632 (C=C enone), 1693 (C=O). ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 1.21 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$); 2.73 (2H, q, *J* = 7.3, $C\underline{H}_2CH_3$); 6.81 (1H, s, H isoxazole); 6.99 (1H, d, *J* = 16.1, (O)CC<u>H</u>=CH); 7.43 (1H, d, *J* = 16.1, (O)CCH=C<u>H</u>); 7.49–7.50 (3H, m, H Ph); 7.83–7.85 (2H, m, H Ph). ^{13}C NMR spectrum (151 MHz), δ, ppm: 7.9; 35.3; 104.5; 124.5; 126.8 (2C); 128.4; 129.0 (2C); 129.9; 130.3; 163.1; 166.5; 199.7. Found, *m*/*z*: 228.1021 $[M+H]^+$. $C_{14}H_{14}NO_2$. Calculated, *m*/*z*: 228.1019.

(*E*)-1-[3-(*p*-Tolyl)isoxazol-5-yl]pent-1-en-3-one ((*E*)-3d). Yield 72 mg (60%), white solid, mp 130–132°C. IR spectrum (NaCl), ν, cm^{-1}: 807, 948, 974, 1119, 1296, 1359, 1428, 1558, 1632 (C=C enone), 1696 (C=O). ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 1.18 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$); 2.41 (3H, s, $C\underline{H}_3C_6H_4$); 2.71 (2H, q, *J* = 7.3, $C\underline{H}_2CH_3$); 6.76 (1H, s, H isoxazole); 6.96 (1H, d, *J* = 16.1, (O)CC<u>H</u>=CH); 7.26–7.28 (2H, m, $CH_3C_6\underline{H}_4$); 7.40 (1H, d, *J* = 16.1, (O)CCH=C<u>H</u>); 7.70–7.71 (2H, m, $CH_3C_6\underline{H}_4$). ^{13}C NMR spectrum (151 MHz), δ, ppm: 7.9; 21.5; 35.3; 104.5; 124.5; 125.5; 126.7 (4C); 129.8; 140.6; 163.0; 166.3, 199.8. Found, *m*/*z*: 242.1177 $[M+H]^+$. $C_{15}H_{16}NO_2$. Calculated, *m*/*z*: 242.1176.

(*E*)-1-[3-(4-Methoxyphenyl)isoxazol-5-yl]pent-1-en-3-one ((*E*)-3e). Yield 77 mg (60%), pale-beige solid, mp 118–120°C. IR spectrum (NaCl), ν, cm^{-1}: 810, 842, 968, 1033, 1116, 1181, 1258, 1407, 1528, 1633 (C=C enone), 1690 (C=O). ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 1.18 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$); 2.70 (2H, q, *J* = 7.3, $C\underline{H}_2CH_3$); 3.86 (3H, s, OCH_3); 6.73 (1H, s, H isoxazole); 6.95 (1H, d, *J* = 16.1, (O)CC<u>H</u>=CH); 6.97–6.99 (2H, m, $CH_3OC_6\underline{H}_4$); 7.39 (1H, d, *J* = 16.1, (O)CCH=C<u>H</u>); 7.74–7.76 (2H, m, $CH_3OC_6\underline{H}_4$). ^{13}C NMR spectrum (151 MHz), δ, ppm: 7.9; 35.3; 55.4; 104.4; 114.4 (2C); 120.9; 124.6; 128.2 (2C); 129.7; 161.3; 162.6; 166.2; 199.8. Found, *m*/*z*: 258.1127 $[M+H]^+$. $C_{15}H_{16}NO_3$. Calculated, *m*/*z*: 258.1125.

(*E*)-1-[3-(4-Chlorophenyl)isoxazol-5-yl]pent-1-en-3-one ((*E*)-3f). Yield 91 mg (70%), yellow solid, mp 142–144°C. IR spectrum (NaCl), ν, cm^{-1}: 809, 832, 949, 972, 1092, 1020, 1120, 1258, 1428, 1557, 1633 (C=C enone), 1696 (C=O). ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 1.18 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$); 2.71 (2H, q, *J* = 7.3, $C\underline{H}_2CH_3$); 6.76 (1H, s, H isoxazole); 6.97 (1H, d, *J* = 16.1, (O)CC<u>H</u>=CH); 7.40 (1H, d, *J* = 16.1, (O)CCH=C<u>H</u>); 7.45–7.46 (2H, m, ClC_6H_4); 7.75–7.76 (2H, m, ClC_6H_4). ^{13}C NMR spectrum (151 MHz), δ, ppm (*J*, Hz): 7.8; 35.4; 104.2; 124.3; 126.9; 128.1 (2C); 129.3 (2C); 130.0; 136.4; 162.1; 166.8; 199.6. Found, *m*/*z*: 262.0631 $[M+H]^+$. $C_{14}H_{13}ClNO_2$. Calculated, *m*/*z*: 262.0629.

(*E*)-1-[3-(4-Fluorophenyl)isoxazol-5-yl]pent-1-en-3-one ((*E*)-3g). Yield 77 mg (63%), yellow solid, mp 139–140°C. IR spectrum (NaCl), ν, cm^{-1}: 810, 846, 1225, 1435, 1523, 1633 (C=C enone), 1694 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.18 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 2.71 (2H, q, *J* = 7.3, $C\underline{H}_2CH_3$); 6.76 (1H, s, H isoxazole); 6.96 (1H, d, *J* = 16.1, (O)CC<u>H</u>=CH); 7.14–7.19 (2H, m, FC_6H_4); 7.40 (1H, d, *J* = 16.1, (O)CCH=C<u>H</u>); 7.79–7.83 (2H, m, FC_6H_4). ^{13}C NMR spectrum (151 MHz), δ, ppm (*J*, Hz): 7.8; 35.3; 104.2; 116.2 (d, *J* = 22.2, 2C); 124.3; 124.6 (d, *J* = 3.8); 128.8 (d, *J* = 8.8, 2C); 130.0; 162.1; 164.0 (d, *J* = 250.5); 166.6; 199.6. Found, *m*/*z*: 246.0926 $[M+H]^+$. $C_{14}H_{13}FNO_2$. Calculated, *m*/*z*: 246.0925.

(*E*)-1-(3-Phenylisoxazol-5-yl)hept-1-en-3-one ((*E*)-3h). Yield 64 mg (50%), pale-beige solid, mp 113–116°C. IR spectrum (ATP), ν, cm^{-1}: 763, 979, 1056, 1127, 1294, 1397, 1461, 1557, 1628 (C=C enone), 1688 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 0.93 (3H, t, *J* = 7.3, $CH_2CH_2CH_2C\underline{H}_3$); 1.32–1.41 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$); 1.62–1.69 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$); 2.63–2.67 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$); 6.77 (1H, s, H isoxazole); 6.95 (1H, d, *J* = 16.1, (O)CC<u>H</u>=CH); 7.38 (1H, d, *J* = 16.1, (O)CCH=C<u>H</u>); 7.45–7.46 (3H, m, H Ph); 7.79–7.81 (2H, m, H Ph). ^{13}C NMR spectrum (101 MHz), δ, ppm: 13.9; 22.4; 26.1; 41.8; 104.5; 124.5; 126.8 (2C); 128.4; 129.1 (2C); 130.1; 130.4; 163.1; 166.5; 199.5. Found, *m*/*z*: 256.1336 $[M+H]^+$. $C_{16}H_{18}NO_2$. Calculated, *m*/*z*: 256.1332.

(*E*)-1-[3-(4-Fluorophenyl)isoxazol-5-yl]hept-1-en-3-one ((*E*)-3i). Yield 80.6 mg (59%), yellow solid, mp 117–119°C. IR spectrum (ATP), ν, cm^{-1}: 813, 929, 968, 1011, 1100, 1159, 1229, 1375, 1432, 1522, 1602 (C=C enone), 1655 (C=O). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 0.95 (3H, t, *J* = 7.4, $CH_2CH_2CH_2C\underline{H}_3$); 1.35–1.42 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$); 1.64–1.70 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$); 2.66–2.69 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$); 6.75 (1H, br. s, H isoxazole); 6.97 (1H, dd, *J* = 16.1, *J* = 0.4, (O)CC<u>H</u>=CH); 7.15–7.19 (2H, m, FC_6H_4); 7.39 (1H, dd, *J* = 16.1, *J* = 0.4,

(O)CCH=CH); 7.79–7.83 (2H, m, FC_6H_4). ^{13}C NMR spectrum (151 MHz), δ, ppm (*J*, Hz): 13.9; 22.4; 26.1; 41.9; 104.3; 116.2 (d, *J* = 21.8, 2C); 124.4; 124.6 (d, *J* = 3.3); 128.8 (d, *J* = 8.4, 2C); 130.2; 162.1; 164.0 (d, *J* = 250.6); 166.7; 199.4. Found, *m*/*z*: 274.1243 $[M+H]^+$. $C_{16}H_{17}FNO_2$. Calculated, *m*/*z*: 274.1238.

(1*E*)-1-[3-(4-Chlorophenyl)isoxazol-5-yl]pent-1-en-3-one oxime (4). Hydroxylamine hydrochloride (0.0132 g, 0.19 mmol) and anhydrous NaOAc (0.0311 g, 0.38 mmol) were added to a solution of isoxazole **3f** (0.05 g, 0.19 mmol) in EtOH (1 ml), and the mixture was stirred for 24 h at reflux (TLC control). Then, the reaction mixture was poured into H_2O (50 ml) and extracted with EtOAc (4×15 ml). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting crude product **4** was purified by flash chromatography. Yield 26 mg (50%), pale-yellow solid, mp 143–148°C. IR spectrum (ATP), ν, cm^{-1}: 788, 832, 959, 1080, 1185, 1295, 1375, 1429, 1557, 1602 (C=C enone), 2853, 2921, 3202 (N–OH). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.17 (3H, t, *J* = 7.6, CH_2CH_3); 2.63 (2H, q, *J* = 7.6, CH_2CH_3); 6.59 (1H, s, H isoxazole); 6.80 (1H, d, *J* = 16.6, (O)CCH=CH); 6.98 (1H, d, *J* = 16.6, (O)CCH=CH); 7.43–7.46 (2H, m, ClC_6H_4); 7.74–7.76 (2H, m, ClC_6H_4). ^{13}C NMR spectrum (101 MHz), δ, ppm: 10.9; 30.2; 100.1; 116.8; 124.5; 127.4; 128.1 (2C); 129.3 (2C); 131.3; 136.2; 160.7; 161.8. Found, *m*/*z*: 277.0739 $[M+H]^+$. $C_{14}H_{14}ClN_2O_2$ Calculated, *m*/*z*: 277.0738.

X-ray structural investigation of compound (*E*)-3g. Single colorless block-shaped crystals were recrystallized from a mixture of EtOAc and *i*-hexane by solvent layering. A suitable crystal 0.23 × 0.14 × 0.10 mm^3 was selected and mounted on a mylar loop in perfluoroether oil. The data were collected on an Agilent SuperNova diffractometer equipped with an Atlas dual CCD detector at 153.00(10) K using CuKa radiation. The crystal was kept at a steady 153.00(10) K during data collection. The complete crystallographic information on compound (*E*)-**3g** has been deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1943861).

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of the synthesized compounds and X-ray data of compound (*E*)-**3g** is available at the journal website at http://link.springer.com/journal/10593.

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