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Short Note

(*E*)-4-(3-Phenylisoxazol-5-yl)but-3-en-2-one

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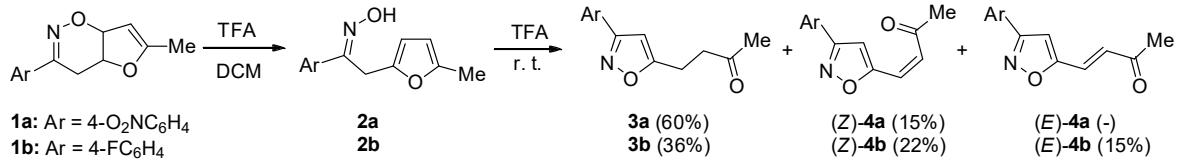
Abstract: *(E)*-4-(3-Phenylisoxazol-5-yl)but-3-en-2-one was synthesized via the oxidative ring opening reaction of 2-(5-methylfuran-2-yl)-1-phenylethanone oxime, followed by the iodine mediated isomerization.

Keywords: oxazole; furan; RORC reaction; (*E*,*Z*)-isomerization

1. Introduction

The isoxazole ring is a structural motif of numerous bioactive compounds, including several marketed drugs [1]. Substituted isoxazoles are known as promising anticancer [2–5], antifungal [6], antidepressant [7], antioxidant [8], and antituberculous agents [9]. Additionally, some of the isoxazoles demonstrate herbicidal [10] and insecticidal [11] properties.

In 2017, Pinho e Melo et al. described a new synthesis of isoxazoles from tetrahydrofurooxazines via the intermediate formation of oximes (Scheme 1) [12]. Main products of this acid-catalyzed reaction were substituted 4-(isoxazol-5-yl)butan-2-ones **3**. On the other hand, minor isoxazolylvinyl ketones (*E*)-**4** are of special interest, due to an active enone fragment, which can be utilized for the construction of linked isoxazoles [13] and other new complex structures containing an isoxazole subunit [14].

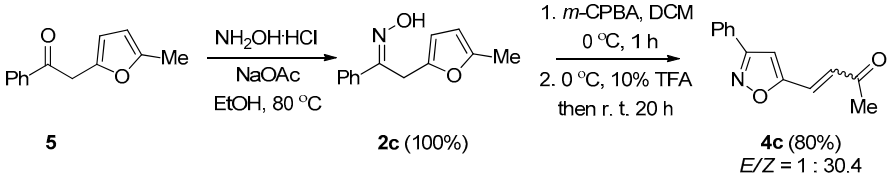


Scheme 1. Acid-catalyzed formation of isoxazolylvinyl ketones as minor products.

Herein, we describe an easy approach to (*E*)-4-(3-phenylisoxazol-5-yl)but-3-en-2-one **4c**, and its characterization by 1D and 2D NMR spectroscopy.

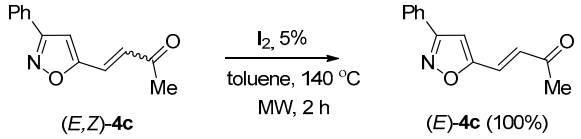
2. Results and Discussion

Oxime **2c** was synthesized via the reaction of furfuryl ketone **5** with hydroxylamine hydrochloride, and sodium acetate in ethanol. The subsequent furan ring opening–isoxazole ring closure reaction of **2c** under oxidative conditions [15,16] provided the target 4-(3-phenylisoxazol-5-yl)but-3-en-2-one **4c** in high yield as a mixture of (*E*,*Z*)-isomers (Scheme 2).



Scheme 2. Synthesis of compound **4c**.

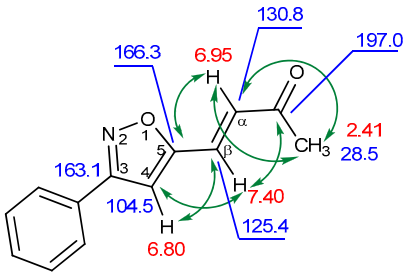
Isoxazole (*E*)-**4c** was obtained in a pure form through iodine-mediated isomerization [17] and fully characterized (Scheme 3).



Scheme 3. Isomerization (*E*,*Z*)-**4c**→(*E*)-**4c**.

The structure of compound **4c** was confirmed by 1H and 2D nuclear magnetic resonance spectroscopy: ^{1}H-^{1}H correlation spectroscopy (COSY), ^{1}H-^{13}C heteronuclear single-quantum correlation spectroscopy (HSQC), and ^{1}H-^{13}C heteronuclear multiple-bond correlation spectroscopy (HMBC) (Figures 1–3). In the ^{1}H NMR spectrum of (*E*)-**4c**, signals of the vinyl protons α-H and β-H are observed at δH = 6.95 and 7.40 ppm, respectively, and have a coupling constant of 16.2 Hz, which indicates a (*E*)-configuration (Figure S1). In the ^{1}H-^{13}C HMBC spectrum, there are cross-peaks between the α-H proton and C-atom of the methyl group (δC 28.5 ppm) and isoxazole C(5) atom (δC 166.3 ppm). The β-H proton correlates with carbonyl carbon atom at δC 197.0 ppm and isoxazole C(4) atom at δC 104.5 ppm. Cross-peaks between the proton H(4) at δH 6.80 ppm and β-C atom of the acetyl vinyl fragment at δC 125.4 ppm, and between protons of the methyl group at δH 2.41 ppm and α-C atom of the acetyl vinyl fragment at δC 130.8 ppm are observed as well. All key cross-peaks are presented in Table 1.

Table 1. Cross-peaks in heteronuclear single-quantum correlation and heteronuclear multiple-bond correlation spectra of compound *(E)*-**4c**.



^{1}H, δ, ppm	^{13}C, δ, ppm	
	HMQC	HMBC
7.40 (β-H)	125.4	104.5, 130.8, 166.3, 197.0 (C=O)
6.95 (α-H)	130.8	28.5, 125.4, 166.3, 197.0 (C=O)
6.80 (H_{Iso})	104.5	125.4, 163.1, 166.3
2.41 (CH_3)	28.5	130.8, 197.0 (C=O)

In summary, we have suggested an effective route to (*E*)-4-(3-phenylisoxazol-5-yl)but-3-en-2-one employing oxidative RORC reaction of furfuryl ketone oxime. The exploration of the reaction scope is underway in our laboratory.

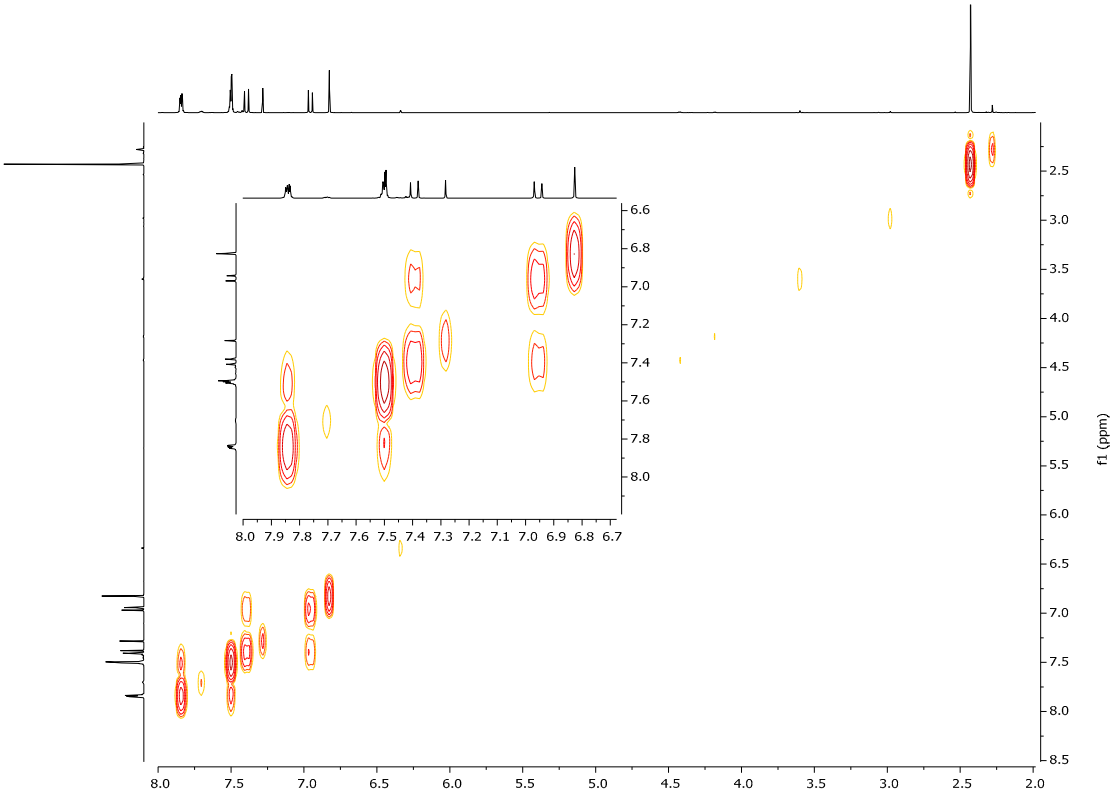


Figure 1. Data of ^{1}H-^{1}H correlation spectroscopy for compound *(E)*-**4c** ($CDCl_3$).

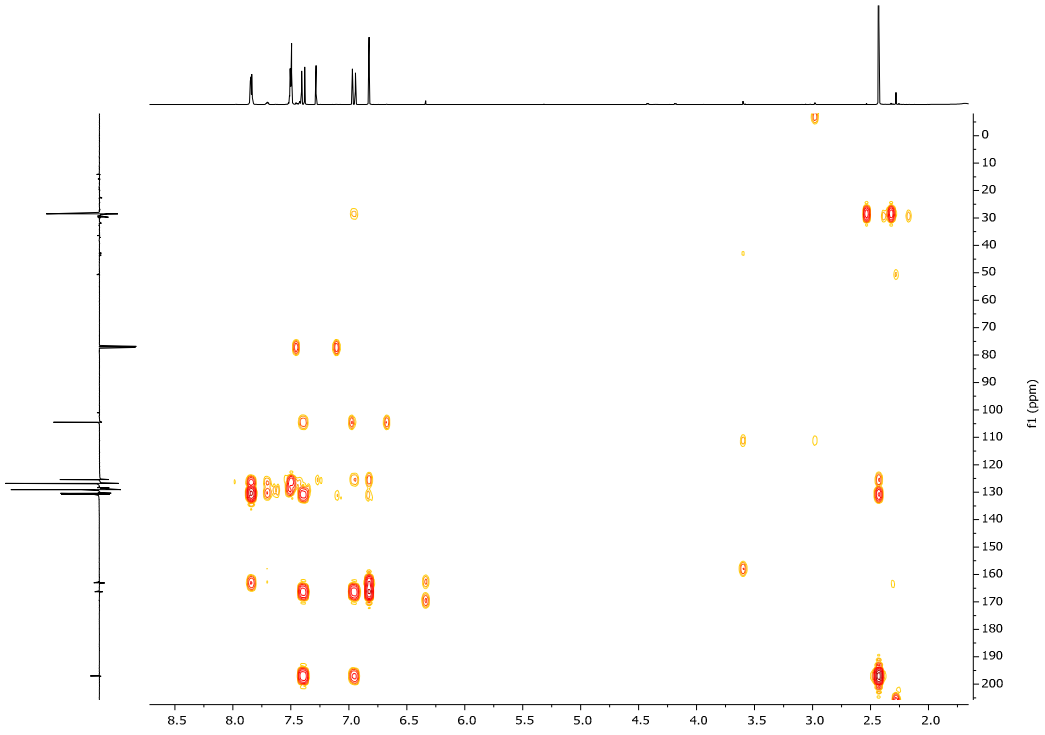


Figure 2. Data of ^{1}H-^{13}C heteronuclear multiple-bond correlation spectroscopy for compound *(E)*-**4c** ($CDCl_3$).

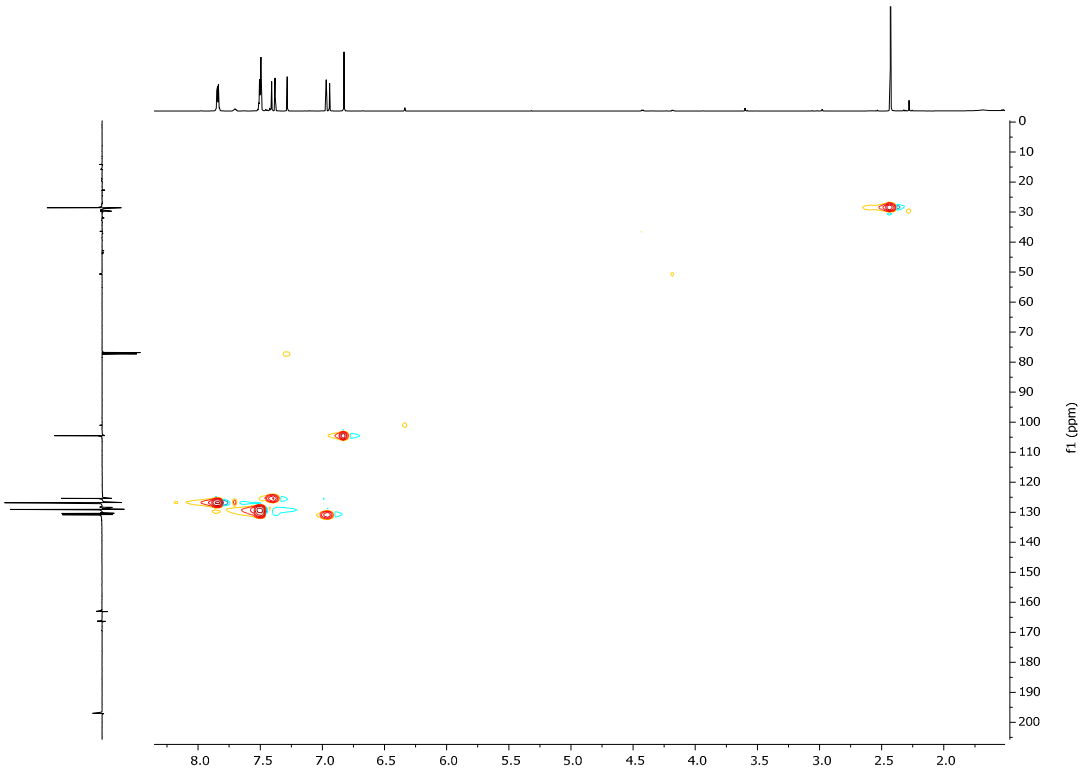


Figure 3. Data of ^{1}H-^{13}C heteronuclear single-quantum correlation spectroscopy for compound *(E)*-**4c** ($CDCl_3$).

3. Materials and Methods

All commercial products and solvents were used without further purification (Fisher Scientific, Loughborough, UK). All reactions were run under the air unless noted otherwise.

The reactions under microwave irradiation were conducted in Microwave Synthesis Reactor «Biotage® Robot Eight» (Biotage AB, Uppsala, Sweden) using sealed microwave reaction vessels. TLC analyses were performed on Merck 60 F254 aluminum plates in combination with UV detection (254 nm). Flash chromatography was performed on silica gel 200–300 mesh (Merck, Darmstadt, Germany) using mixture EtOAc/*i*-hexane as eluents. Melting points were determined on a Mel-Temp II Laboratory Devices apparatus (Triad Scientific Manasquan, Manasquan, NJ, USA); the values are uncorrected. NMR spectra were recorded on a Bruker AV-600 (^{1}H NMR at 600 MHz and ^{13}C NMR at 151 MHz,) and Bruker AV-400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 101 MHz) spectrometers (Bruker GmbH, Mannheim, Germany). Proton chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS), with the solvent resonance employed as the internal standard ($CDCl_3$ δ = 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets), coupling constants (*J*) and integration. Coupling constants (*J*) are reported in Hertz (Hz). Carbon chemical shifts are reported in ppm from tetramethylsilane (TMS), with the solvent resonance as the internal standard ($CDCl_3$ δ = 77.16 ppm).

IR spectra were measured on PerkinElmer Spectrum BX spectrophotometer (NaCl plates, PerkinElmer LAS GmbH, Rodgau, Germany). HRMS-ESI spectra were recorded at The Mass Spectroscopy Laboratory, Chair of Organic Chemistry, Friedrich-Alexander University of Erlangen-Nuremberg.

Starting furfuryl ketone **5** was obtained according to the published procedure [18].

*2-(5-Methylfuran-2-yl)-1-phenylethan-1-one oxime (***2c***)*

Hydroxylamine hydrochloride (2 mmol) and anhydrous NaOAc (4 mmol) were added to a solution of furfuryl ketone **5** (2 mmol) in ethanol (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 EtOAc/*i*-Hex as eluents.

Yield 0.61 g (100%). White solid. M.p. 90–92 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.69–7.67 (m, 2H), 7.37–7.36 (m, 3H), 5.92 (d, *J* = 3.0 Hz, 1H), 5.83 (m, 1H), 4.13 (s, 2H), 2.24 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.2, 150.9, 147.9, 135.3, 129.4, 128.5, 126.4, 107.5, 106.3, 25.5, 13.6 ppm. IR (NaCl): 3241, 2922, 1568, 1495, 1461, 1321, 1168, 1016, 960 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{13}H_{13}NO_2$ $[M\text{-}H]^+$: 214.0868; found: 214.0862.

*(E,Z)-4-(3-Phenylisoxazol-5-yl)but-3-en-2-one ((E,Z)-***4c***)*

m-CPBA (77% w/w, 0.135 g, 0.6 mmol) was added to a solution of oxime **2c** (0.5 mmol) in DCM (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 three times, and then with brine. DCM was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to give a pure (*E,Z*)-**4**.

*(Z)-4-(3-Phenylisoxazol-5-yl)but-3-en-2-one ((Z)-***4c***)*

In a mixture with *(E)*-isomer. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.87–7.86 (m, 2H), 7.69 (s, 1H), 7.48–7.44 (m, 3H), 6.74 (d, *J* = 12.8 Hz, 1H), 6.43 (d, *J* = 12.8 Hz, 1H), 2.37 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.8, 166.0, 163.2, 130.8, 130.4, 130.1, 128.9, 126.8, 123.5, 106.0, 31.5 ppm.

*Isomerization (E,Z)-***4**→*(E)-***4**

Microwave reaction vessel was charged with (*E,Z*)-**4c** (0.2 mmol), I_2 (0.0034 g, 0.013 mmol), and toluene (5 mL). The reaction mixture was stirred at 140 °C in a microwave reactor for 2 h. After completion of the reaction, toluene and iodine were removed under reduced pressure to afford pure (*E*)-**3a**.

*(E)-4-(3-Phenylisoxazol-5-yl)but-3-en-2-one) (E)-***4c***)*

Yield 0.034 g (80%). White solid. M.p. 130–132 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.83–7.81 (m, 2H), 7.49–7.47 (m, 3H), 7.40 (d, *J* = 16.2 Hz, 1H), 6.95 (d, *J* = 16.2 Hz, 1H), 6.80 (s, 1H), 2.41 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 197.0, 166.3, 163.1, 130.8, 130.4, 129.1, 128.4, 126.8, 125.4, 104.5, 28.5 ppm. IR (NaCl): 1664 (C=O), 1560, 1439, 1268, 983, 952, 769 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{13}H_{11}NO_2$ $[M + H]^+$: 214.0868; found: 214.0861.

Supplementary Materials: The following are available online, Figure S1: ^{1}H NMR spectrum of compound **2c**, Figure S2: ^{13}C NMR spectrum of compound **2c**, Figure S3: ^{1}H NMR spectrum of compound (*E*)-**4c**, Figure S4: ^{13}C NMR spectrum of compound (*E*)-**4c**, Figure S5: ^{1}H NMR spectrum of compound (*Z*)-**4c**, Figure S6: ^{13}C NMR spectrum of the compound (*Z*)-**4c**.

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Conflicts of Interest: The authors declare no conflict of interest.

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