

Reaction of Substituted Furan-2-carboxaldehydes and Furo[*b*]pyrrole Type Aldehydes with Hippuric Acid

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Abstract: 4-Heteroarylidene-2-phenyl-1,3-oxazol-5(4*H*)-ones were prepared by reactions of hippuric acid with substituted furan-2-carboxaldehydes or furo[*b*]pyrrole type aldehydes. The reactivity of various furan-2-carboxaldehyde derivatives in this reaction is discussed. The effect of microwave irradiation on some condensation reactions was compared with “classical” conditions. The results show that microwave irradiation shortens the reaction times while affording comparable yields. Elementary analysis, UV, IR and 1D NMR proved the structure of new synthesised compounds. 2D NMR spectroscopic measurements confirmed that the configuration at the carbon-carbon double bond corresponds to the pure *E* isomers of the products.

Keywords: 5-Arylfuran-2-carboxaldehydes; furo[3,2-*b*]pyrrole-2-carboxaldehydes; furo-[2,3-*b*]pyrrole-2-carboxaldehydes; hippuric acid; microwave irradiation; 1,3-oxazol-5(4*H*)-ones; furo[3,2-*b*]pyrrole-5-carboxylates; furo[2,3-*b*]pyrrole-5-carboxylates; ¹H- and ¹³C-NMR, COSY, NOESY, HSQC, HMBC.

Introduction

During the past few decades many results have been published in the area of the synthesis and the study of physical and chemical properties of heterocyclic compounds containing a furan ring connected to or fused with a benzene ring or with different heterocyclic systems. Substituted furans are ubiquitous structural units in natural products and pharmaceuticals [1] and have been widely used as synthetic intermediates [2,3].

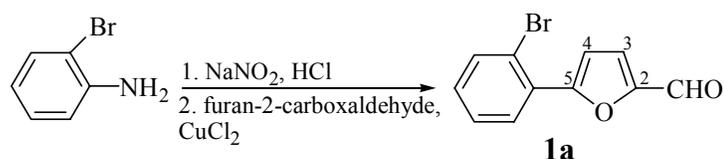
Substituted furan-2-carboxaldehydes **1a-e** and furo[*b*]pyrrole type aldehydes **2a-e**, **3a,b** are heteroaromatic compounds which possess a C2 carbonyl group that may act as a reactive centre for various condensation reactions. Many of the published condensation products are biologically active compounds [4,5] or can be used as intermediates in organic synthesis [6,7].

Reaction of aldehydes **1a-3b** with hippuric acid led to the products **4a-6b** containing a 1,3-oxazol-5(4*H*)-one ring. The use of 1,3-oxazol-5(4*H*)-ones as starting materials for synthesis is well known. They are used as convenient reagents for the synthesis of α,β unsaturated α -amino acids [8], cyclic analogues of natural amino acids [9] or as intermediates for the synthesis of new heterocyclic compounds [10]. The most common method for their preparation is the Erlenmeyer-Plöchl reaction, a cyclodehydration-condensation of the appropriate aldehyde and hippuric acid in dry acetic anhydride catalysed by acetate anion (using sodium or calcium acetate as a support/catalyst) [11-14]. The formation of the carbon-carbon double bond usually leads to the creation of 1,3-oxazol-5(4*H*)-ones as a mixture of *Z* and *E* isomers; for example, furan-2-carboxaldehyde and thiophene-2-carboxaldehyde [11,12] and also substituted benzaldehydes [13] give oxazolones as such mixtures of two isomers.

The aim of this study was to synthesise some new condensation products of **1a-e**, **2a-e** and **3a,b** by their reactions with hippuric acid (Schemes 2-4). We aimed to incorporate these heterocyclic biologically active moieties into new heterocyclic systems. We also wished to compare the “classical” method with the effect of microwave irradiation and to find conditions to increase the yield or the rate of condensations. Microwave irradiation is an unconventional method of chemical reaction activation indicated to be suitable for use in reactions of thermolabile compounds because it shortens the exposure of the reaction mixtures to high temperatures [15-18].

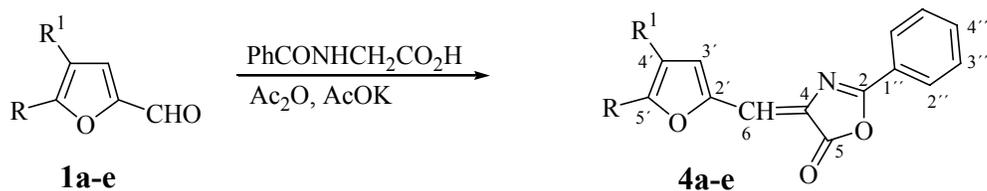
We also present the synthesis of 5-(2-bromophenyl)furan-2-carboxaldehyde (**1a**) by Meerwein’s method (Scheme 1). The starting material 5-(2-bromophenyl)furan-2-carboxaldehyde (**1a**) was prepared under the conditions of Meerwein’s reaction from 2-bromoaniline and furan-2-carboxaldehyde, as we used before in the case of various 5-aryl-2-carboxaldehydes [19]. Compound **1a** was obtained in 23% yield and its IR spectrum showed the characteristic band for the carbonyl group appearing at 1691 cm^{-1} . The signal for the aldehyde hydrogen was observed at 9.69 ppm in the $^1\text{H-NMR}$ spectra.

Scheme 1



The condensation products of aldehydes **1a-3b** with hippuric acid catalysed by potassium acetate [18] were prepared in dry acetic anhydride as shown in Schemes 2-4. The condensations of **1a-e** were also performed under microwave conditions, reducing the reaction times while affording yields comparable to those achieved in the reactions carried out under “classical” conditions (Table 1). Microwave irradiated procedures were performed using irradiation at a power output of 350W. Reaction times were only 1-2 minutes and work up was very easy. The reaction conditions were the same in both procedures except for the amounts of acetic anhydride and potassium acetate used (see Experimental). In the microwave assisted procedure the reaction mixture was fully dissolved after irradiation and the reaction started immediately upon dissolution. The reaction mixture was irradiated in 30 seconds intervals (TLC controlled) to prevent overheating which causes unselective reactions and for certain aldehydes more degradation products were also observed when the reaction times were longer than is listed in Table 1.

Scheme 2



	R	R ¹
a	2-BrC ₆ H ₄	H
b	3-NO ₂ C ₆ H ₄	H
c	3-CF ₃ C ₆ H ₄	H
d	CH ₃	CH ₃
e	CH=CH-CH=CH	

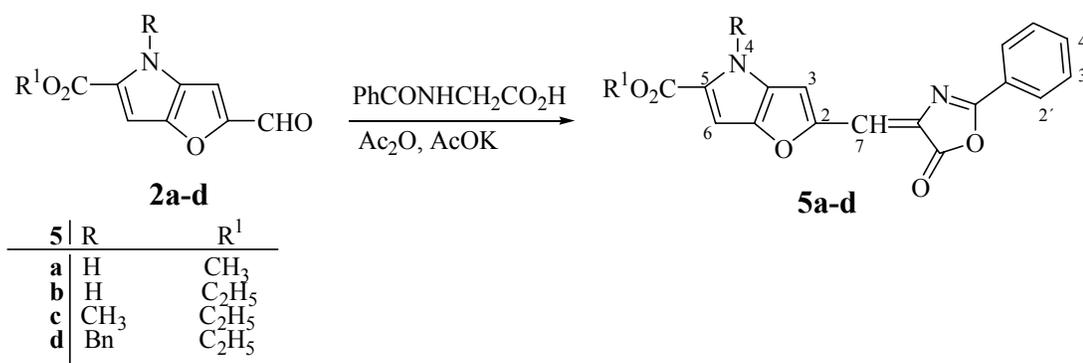
5-Arylfuran-2-carboxaldehydes **1a-c** reacted with hippuric acid giving (4*E*)-2-phenyl-4-[[5-(*R*-phenyl)-2-furyl]methylene}-1,3-oxazol-5(4*H*)-ones (**3a-c**) (Scheme 2) in high yields (70-83%) after short reaction times.

Table 1. Comparisons between “classical” and microwave procedures

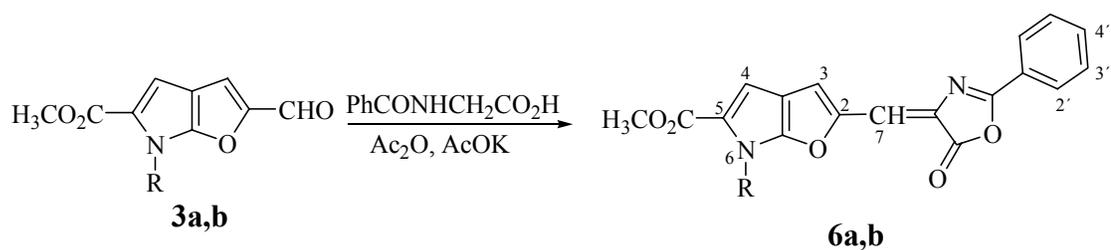
Compound	Classical conditions		MW reaction	
	Reaction time (min.)	Yield, %	Reaction time (min.)	Yield, %
4a	15	83	1	72
4b	30	70	1.5	74
4c	15	80	1.5	73
4d	60	62	2	67
4e	20	67	2	70

The yield of the other two condensation products, (4*E*)-2-phenyl-4-[(4,5-dimethylfuran-2-yl)methylene-1,3-oxazol-5(4*H*)-one (**3d**) and (4*E*)-2-phenyl-4-[(1-benzofuran-2-yl)methylene-1,3-oxazol-5(4*H*)-one (**3e**) (Scheme 2) was about 10-20% lower. The same situation was observed in the case of furo[3,2-*b*]pyrrole type aldehydes **2a-d** and furo[2,3-*b*]pyrrole type aldehydes **3a,b** (Schemes 3 and 4). The products, methyl-2-[(*E*)-(5-oxo-2-phenyl-1,3-oxazol-5(4*H*)-ylidene)methyl]furo[3,2-*b*]pyrrole-5-carboxylates (**5a-d**) and methyl-2-[(*E*)-(5-oxo-2-phenyl-1,3-oxazol-5(4*H*)-ylidene)-methyl]-furo[2,3-*b*]pyrrole-5-carboxylates (**6a,b**) were obtained in yields of 53-81%. During the reaction of both systems we found that 5-arylated furan-2-carboxaldehydes (**1a-c**) are more reactive than 4,5-dimethylfuran-2-carboxaldehyde (**1d**), benzofuran-2-carboxaldehyde (**1e**) and furo[*b*]pyrrole type aldehydes (**2a-3b**). Furo[*b*]type aldehydes are heterocyclic analogues of the pentalene dianion and their electron-rich system [20] makes the carbonyl group attached at C2 of the fused system less reactive than the carbonyl group in the 5-arylated furan-2-carboxaldehydes used in this reaction.

The reaction time of the condensation depends on both the solubility of the starting aldehydes and their properties. Substituted furan-2-carboxaldehydes **1a-e** are more soluble in acetic anhydride than furo[*b*]pyrrole type aldehydes **2a-3b**. Electron-withdrawing groups on the benzene ring of **1a-c** activate the C2 carbonyl group and the reactions are fast (reaction time max. 30 minutes). The carbonyl group at C2 of the aldehydes **1e**, **2a-3b** is less active in these reactions than in the case of **1a-c** and the reaction time is at least 60 minutes.

Scheme 3

Scheme 4



R for **a** = CH₃ **b** = MOM

All condensation products are stable solids, which are rather sparingly soluble in common solvents, and with high melting points. They display characteristic colours, a feature that is also observed in their corresponding UV-VIS spectra. The absorption maximum appears in the VIS area at around 400-470 nm. The characteristic bands found in the IR spectra correspond to the carbon-carbon double bond ($1650\text{-}1640\text{ cm}^{-1}$) and C=O lactone ($1790\text{-}1770\text{ cm}^{-1}$).

The ¹H-NMR spectra of the synthesised compounds **4a-6b** display the signals of the double bond H-5 in the 7.07-7.89 ppm range. The chemical shift of the C-5 double bond carbon in the ¹³C-NMR spectra of **4a-e** typically ranges from 116-118 ppm. The ¹H and ¹³C chemical shifts for compounds **4a-e** were assigned using gs (gradient selected)-H,H COSY (Correlated spectroscopy); 1D-gs-NOESY (Nuclear Overhauser spectroscopy); gs-HSQC (Heteronuclear Quantum Coherence spectroscopy) and HMBC (Heteronuclear Multiple Bond Correlation spectroscopy). H,H-COSY provided us proton-proton connectivity and 1D-NOESY showed through-space interactions of the olefinic proton H-6 and the furan H-3' β-proton. Determination of the actual position of the H-6 protons compared to the carbonyl group of the heterocyclic ring system was established by using the size of the scalar coupling between H-6 and the carbonyl carbon. It turns out that the coupling constant is 4.6 Hz. According to the literature [23] this size is indicative of a situation where the proton and the carbonyl are in a *Z* arrangement, which means that this compound exists as a pure *E* isomer. The other compounds **4a-e** behave similarly. The ¹³C chemical shifts assignment was straightforward using HSQC and HMBC spectra. ¹H-NMR spectra were measured for products **5a-6b**. These products are structural analogues of **4e** and their proton spectra are similar to that of **4e**. Based on this observation we can declare that products **5a-6b** also exist as a pure *E* isomers. The signal of the NH proton of **5a,b** and also the signals of the protons in methyl or ethyl group in the ester moieties were the same before [24-27] and after condensation, which proved that amino and ester group did not undergo any reaction with the hippuric acid. The complete chemical shifts for all synthesised compounds are listed in Experimental part.

Conclusions

The synthesis of 2-phenyl-4-(furan-2-yl)methylene-1,3-oxazol-5(4*H*)-ones, methyl-2-[(*E*)-(5-oxo-2-phenyl-1,3-oxazol-5(4*H*)-ylidene)methyl]furo[3,2-*b*]pyrrol-5-carboxylates and their [2,3-*b*]isomers showed the different reactivity of the starting aldehydes. The reactions of substituted furan-2-

carboxaldehydes, which were performed under “classical” conditions as well as using microwave irradiation, showed that the yields were almost the same, but the reactions in the microwave oven were noticeably faster. All synthesised compounds were characterised by spectroscopic measurements and were proven to be the pure *E* isomers.

Acknowledgements

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Experimental

General

The following starting compounds were prepared according to literature procedures: **1d** [21], **1e** [22], **2a-d**, and **3a,b** [24-27]. Melting points were determined using a Kofler hotplate apparatus and are uncorrected. All solvents were pre-distilled and dried appropriately prior to use. The terms “concentration and evaporation” refer to the removal of volatile materials under reduced pressure on a Buchi Rotovapor. Substances stated to be identical were so with respect to mps, mixed mps and IR spectra. Microwave assisted reactions were carried out in a Whirlpool domestic type microwave oven at 350 W. The apparatus was adapted for laboratory applications – *n*-heptane was used as coolant for the condenser. Elemental analyses were determined using a Carlo Erba CHNS-OEA 1108-Elemental Analyser. Infrared spectra were recorded on the following spectrophotometers: Magna IR-760 (Nicolet) (compounds **1a**, **4a-c**) and FTIR Galaxy 7020 (for **4d,e**) using KBr pellets (1 mg/300 mg KBr) with only major absorbencies being quoted. UV spectra were measured on a WPA UV/VIS Diode-Array spectrophotometer (Cambridge, UK) in methanol. Results are reported as λ_{\max} (log ϵ) (λ_{\max} in nm, ϵ in $\text{m}^2\text{mol}^{-1}$). ^1H (500 MHz)- and ^{13}C (125 MHz)-NMR spectra of compounds **4a-e** were measured at 320K on a BRUKER AVANCE spectrometer equipped with a 5mm broadband probe with z-gradients and a SGI computer. Two dimensional gs (gradient selected)-H,H-COSY; 1D-gs-NOESY; gs-HSQC, gs-HMBC techniques were measured using standard software programs provided by Bruker. The ^1H -NMR (400 MHz) spectra of compound **1a**, **5a-6b** were measured on a BRUKER B-ACS-60 instrument. The measurements were done using DMSO- d_6 as solvent with TMS as an internal standard reference. Coupling constants (J) are quoted to the nearest 0.1 Hz. Chemical shifts (δ -scale) are quoted in parts per million and following abbreviations are used: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad.

5-(2-Bromophenyl)furan-2-carboxaldehyde (1a)

2-Bromoaniline (21.5g, 0.136 mol) was dissolved in a mixture of concentrated HCl (33.7 mL) and H₂O (22.5 mL). The solution was cooled to 0°C and diazotized at 0-5°C with sodium nitrite (9.5 g, 0.138 mol) dissolved in H₂O (25 mL). The solution was stirred for another 10 min, filtered and then furan-2-carboxaldehyde (15.4 g, 0.16 mol) in H₂O (50 mL) was added along with a solution of CuCl₂·2H₂O (5 g, 0.04 mol) in H₂O (25 mL) at a temperature of 10-15 °C. The reaction mixture was slowly warmed up to 40°C and stirred at this temperature for 4h. The precipitate was filtered with suction, washed with water and an aqueous solution of sodium hydrogen carbonate (5%) and the steam distilled. After removing the volatiles the residue was separated by suction filtration, dried and crystallised. Yield: 9.2 g (23%), m.p. 80-82°C (*n*-heptane). For C₁₁H₇BrO₂ (249.96) calculated: 52.62% C, 2.81% H, 31.82% Br; found: 52.50% C, 2.84% H, 31.73% Br; IR $\nu_{\max}/\text{cm}^{-1}$ 1691 (C=O), 1377 (C-O); UV: 312, (3.49); ¹H-NMR δ_{H} : 9.69 (s, 1H, CH=O), 7.69 (d, 1H, *J* 3,4 3.74 Hz, H-3), 7.37 (d, 1H, *J* 3,4 3.74 Hz, H-4), 7.47-7.92 (m, 4H, ArH). ¹³C-NMR δ_{C} : 177.4 (CHO), 159.67 (C-5), 149.82 (C-2), 128.6 (C-4), 122.2 (C-3), 134.86, 130.68, 129.88, 119.48, 114.61.

(4E)-2-Phenyl-4-([5-(2-bromophenyl)-2-furyl]methylene)-1,3-oxazol-5(4H)-one (4a)

A mixture of 5-(2-bromophenyl)furan-2-carboxaldehyde (**1a**, 0.4 g, 2 mmol), hippuric acid (0.4 g, 2.4 mmol) and potassium acetate (0.3 g, 3 mmol) in acetic anhydride (10 mL) was refluxed with stirring for 15 min. (reaction progress was monitored by TLC using 3:1 isohexane-ethyl acetate as eluent). The mixture was then cooled down and neutralised by addition of solid potassium carbonate. The solid product was separated by filtration, dried and purified by crystallisation. Yield: 83%; m.p. 168-171°C (ethanol); For C₂₀H₁₂BrNO₃ (394.2) calculated: 60.93% C, 3.07% H, 20.27% Br, 3.55% N; found: 60.79% C, 3.12% H, 20.16% Br, 3.60% N; IR $\nu_{\max}/\text{cm}^{-1}$ 1791 (C=O), 1650 (C=C), 1327 (C-O furan), 1245 (C-O lactone), 1024 (C-H furan); UV: 419, (3.70); ¹H-NMR δ_{H} : 8.19-7.70 (m, 5H, H-2'', H-3'', H-4'', H-5'', H-6''), 8.05-7.68 (m, 4H, ArH), 7.76 (d, 1H, *J* 3',4' 3.7 Hz, H-4'), 7.55 (d, 1H, *J* 3',4' 3.7 Hz, H-3'), 7.31 (s, 1H, H-6); ¹³C-NMR δ_{C} : 166.68 (C-5), 162.54 (C-2), 154.67 (C-5'), 149.82 (C-2'), 133.64 (C-4''), 130.21 (C-4), 129.4 (C-3''), 128.6 (C-4'), 127.98 (C-2''), 125.22 (C-1''), 122.2 (C-3'), 116.88 (C-6), 134.86, 130.68, 129.88, 119.48, 114.61.

According to this same procedure the following compounds were prepared:

(4E)-4-([5-(3-Nitrophenyl)-2-furyl]methylene)-2-phenyl-1,3-oxazol-5(4H)-one (4b). Reaction time: 30 min. Yield: 70%; m.p. 223-227°C (ethanol); For C₂₀H₁₂N₂O₅ (360.3) calculated: 66.67% C, 3.36% H, 7.77% N; found: 66.64% C, 3.29% H, 7.72% N; IR $\nu_{\max}/\text{cm}^{-1}$ 1783 (C=O), 1654 (C=C), 1347 (C-O furan), 1243 (C-O lactone), 1028 (C-H furan); UV: 444, (3.77); ¹H-NMR δ_{H} : 8.32-7.82 (m, 4H, ArH), 8.25-7.70 (m, 5H, H-2'', H-3'', H-4'', H-5'', H-6''), 7.69 (d, 1H, *J* 3',4' 3.7 Hz, H-4'), 7.60 (d, 1H, *J* 3',4' 3.7 Hz, H-3'), 7.34 (s, 1H, H-6); ¹³C-NMR δ_{C} : 166.34 (C-5), 162.43 (C-2), 154.62 (C-5'), 150.45

(C-2'), 133.53 (C-4'), 130.42 (C-4), 129.25 (C-3'), 127.89 (C-2'), 125.14 (C-1'), 123.12 (C-4'), 116.51 (C-6), 149.59, 130.82, 130.42, 125.12, 118.57.

(4E)-2-Phenyl-4-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-oxazol-5(4H)-one (4c). The reaction time: 15 min. Yield: 80%; m.p. 172-174°C (ethanol); For C₂₁H₁₂F₃NO₃ (383.3) calculated: 65.80% C, 3.16% H, 3.65% N; found: 65.69% C, 3.22% H, 3.72% N; IR $\nu_{\max}/\text{cm}^{-1}$ 1785 (C=O), 1651 (C=C), 1331 (C-O furan), 1242 (C-O lactone), 1030 (C-H furan); UV: 419, (3.70). ¹H-NMR δ_{H} : 8.32-8.19 (m, 4H, ArH), 7.82-7.66 (m, 5H, H-2', H-3', H-4', H-5', H-6'), 7.71(d, 1H, *J* 3',4' 3.6 Hz, H-4'), 7.58 (d, 1H, *J* 3',4' 3.6 Hz, H-3'), 7.34 (s, 1H, H-6); ¹³C-NMR δ_{C} : 166.47 (C-5), 162.34 (C-2), 155.31 (C-5'), 150.32 (C-2'), 133.57 (C-4), 130.5 (C-4'), 129.96 (C-3'), 129.29 (C-2'), 125.19 (C-1'), 128.18 (C-4'), 123.01 (C-3'), 120.7 (q, CF₃), 116.62 (C-6), 130.41, 130.26, 129.83, 125.81, 112.02, 111.69.

(4E)-4-[4,5-Dimethyl-2-furyl]methylene]-2-phenyl-1,3-oxazol-5(4H)-one (4d). The reaction time: 60 min. Yield: 62%; m.p. 149-151°C (ethanol); For C₁₆H₁₃NO₃ (267.3) calculated: 71.90% C, 4.90% H, 5.24% N; found: 74.60% C, 3.88% H, 4.74% N; IR $\nu_{\max}/\text{cm}^{-1}$: 1789 (C=O (*E*)), 1767 (C=O (*Z*)), 1641 (C=C), 1329 (C-O furan), 1254 (C-O lactone), 1020 (C-H furan); UV 336, (3.32); ¹H-NMR δ_{H} : 8.07 (d, 2H, *J* 2',3' 7.35 Hz, H-2', H-6'), 7.74 (t, 1H, *J* 3',4' 7.29 Hz, H-4'), 7.60 (t, 2H, H-3', H-5'), 7.50 (s, 1H, H-3'), 7.07 (s, 1H, H-6), 2.3 (s, 3H, CH₃), 2.02 (s, 3H, CH₃); ¹³C-NMR δ_{C} : 167 (C-5), 161.4 (C-2), 155 (C-5'), 147.8 (C-2'), 133.4 (C-4'), 129.5 (C-3', C-5'), 128.2 (C-4), 127.9 (C-2', C-6'), 125.5 (C-1'), 124.8 (C-3'), 120.2 (C-4'), 117.8 (C-6), 12.3 (CH₃), 9.7 (CH₃).

(4E)-4-(1-Benzofuran-2-ylmethylene)-2-phenyl-1,3-oxazol-5(4H)-one (4e). The reaction time: 20 min. Yield: 67%; m.p. 183-186°C (ethanol); For C₁₈H₁₁NO₃ (289.3) calculated: 74.73% C, 3.83% H, 4.84% N; found: 74.60% C, 3.88% H, 4.72% N; IR $\nu_{\max}/\text{cm}^{-1}$: 1793 (C=O), 1644 (C=C), 1329 (C-O furan), 1255 (C-O lactone), 1000 (C-H furan); UV: 331, (3.76); ¹H-NMR δ_{H} : 8.17 (d, 2H, *J* 2',3' 7.78 Hz, H-2', H-6'), 8.03 (s, 1H, H-3'), 7.74 (t, 1H, *J* 3',4' 7.4 Hz, H-4'), 7.65 (t, 2H, H-3', H-5'), 7.32 (s, 1H, H-6), 7.81-7.34 (m, 4H, ArH); ¹³C-NMR δ_{C} : 166.5 (C-5), 163.8 (C-2), 155.8 (C-5'), 151.7 (C-2'), 134.3 (C-4'), 133.7 (C-4), 129.7 (C-3', C-5'), 128.7 (C-4'), 128.5 (C-2', C-6'), 125.3 (C-1'), 117.5 (C-6), 116 (C-3'); 127.8, 124.3, 123.0, 111.9.

Methyl 2-[(E)-(5-oxo-2-phenyl-1,3-oxazol-5(4H)-ylidene)methyl]-4H-furo[3,2-b]pyrrole-5-carboxylate (5a). The reaction time: 60 min. Yield: 53%; m.p. 305-311°C (ethanol); For C₁₈H₁₂N₂O₅ (336.3) calculated: 64.29% C, 3.60% H, 8.33% N; found: 64.39% C, 3.52% H, 8.22% N; UV: 463, (3.41); ¹H-NMR. δ_{H} : 12.1 (br s, 1H, NH), 8.11 (d, 2H, *J* 2',3' 8.0 Hz, H-2', H-6'), 7.71 (t, 1H, *J* 3',4' 8.0 Hz, *J* 4',5' 8.0 Hz, H-4'), 7.64 (d, 2H, *J* 2',3' 8.0 Hz, *J* 5',6' 8.0 Hz, H-3', H-5'), 7.59 (s, 1H, H-7), 7.23 (s, 1H, H-3), 6.87 (s, 1H, H-6), 3.84 (s, 3H, CO₂CH₃).

Ethyl 2-[(E)-(5-oxo-2-phenyl-1,3-oxazol-5(4H)-ylidene)methyl]-4H-furo[3,2-b]pyrrole-5-carboxylate (5b). The reaction time: 60 min. Yield: 74%; m.p. 295-300°C (ethanol); For C₁₉H₁₄N₂O₅ (350.3) calculated: 65.14% C, 4.03% H, 8.00% N; found: 64.94% C, 4.13% H, 7.95% N; UV: 463, (3.44); ¹H-NMR δ_H: 12.05 (br s, 1H, NH), 8.11 (d, 2H, *J*′,3′ 8.0 Hz, H-2′, H-6′), 7.72 (t, 1H, *J*′,4′ 8.0 Hz, *J*′,5′ 8.0 Hz, H-4′), 7.64 (t, 2H, *J*′,3′ 8.0 Hz, *J*′,5′,6′ 8.0 Hz, H-3′, H-5′), 7.60 (s, 1H, H-7), 7.23 (s, 1H, H-3), 6.84 (s, 1H, H-6), 4.32 (q, 2H, CO₂CH₂CH₃), 1.32 (t, 3H, CO₂CH₂CH₃).

Ethyl 4-Methyl-2-[(E)-(5-oxo-2-phenyl-1,3-oxazol-5(4H)-ylidene)methyl]furo[3,2-b]pyrrole-5-carboxylate (5c). The reaction time: 30 min. Yield: 90%; m.p. 174-177°C (ethanol); For C₂₀H₁₆N₂O₅ (364.4) calculated: 63.93% C, 4.43% H, 7.69% N; found: 63.88% C, 4.52% H, 7.84% N; UV: 463, (3.38); ¹H-NMR δ_H: 8.17 (d, 2H, *J*′,3′ 8.0 Hz, H-2′, H-6′), 7.89 (s, 1H, H-7), 7.70 (t, 1H, *J*′,4′ 8.0 Hz, *J*′,5′ 8.0 Hz, H-4′), 7.63 (t, 2H, *J*′,3′ 8.0 Hz, *J*′,5′,6′ 8.0 Hz, H-3′, H-5′), 7.22 (s, 1H, H-3), 6.87 (s, 1H, H-6), 4.28 (q, 2H, CO₂CH₂CH₃), 4.00 (s, 3H, NCH₃), 1.32 (t, 3H, CO₂CH₂CH₃).

Ethyl 4-Benzyl-2-[(E)-(5-oxo-2-phenyl-1,3-oxazol-5(4H)-ylidene)methyl]furo[3,2-b]pyrrole-5-carboxylate (5d). The reaction time: 30 min. Yield: 81%; m.p. 175-179°C (ethanol); For C₂₆H₂₀N₂O₅ (440.4) calculated: 70.90% C, 4.58% H, 76.36% N; found: 71.03% C, 4.52% H, 76.28% N; UV: 468, (3.89); ¹H-NMR δ_H: 8.12 (d, 2H, *J*′,3′ 8.0 Hz, H-2′, H-6′), 7.72 (t, 1H, *J*′,4′ 8.0 Hz, *J*′,5′ 8.0 Hz, H-4′), 7.65 (t, 2H, *J*′,3′ 8.0 Hz, *J*′,5′,6′ 8.0 Hz, H-3′, H-5′), 7.58 (s, 1H, H-7), 7.21-7.39 (m, 5H, ArH), 7.19 (s, 1H, H-3), 6.97 (s, 1H, H-6), 5.75 (s, 2H, NCH₂), 4.24 (q, 2H, CO₂CH₂CH₃), 1.26 (t, 3H, CO₂CH₂CH₃).

Methyl 6-Methyl-2-[(E)-(5-oxo-2-phenyl-1,3-oxazol-5(4H)-ylidene)methyl]furo[2,3-b]pyrrole-5-carboxylate (6a). The reaction time: 120 min. Yield: 66%; m.p. 255-260°C (ethanol); For C₁₉H₁₄N₂O₅ (350.3) calculated: 65.14% C, 4.03% H, 8.00% N; found: 65.04% C, 4.26% H, 8.05% N; UV: 453, (3.78); ¹H-NMR δ_H: 8.13 (d, 2H, *J*′,3′ 8.0 Hz, H-2′, H-6′), 7.80 (s, 1H, H-7), 7.70 (t, 1H, *J*′,4′ 8.0 Hz, *J*′,5′ 8.0 Hz, H-4′), 7.63 (t, 2H, *J*′,3′ 8.0 Hz, *J*′,5′,6′ 8.0 Hz, H-3′, H-5′), 7.27 (s, 1H, H-3), 7.01 (s, 1H, H-4), 3.97 (s, 3H, NCH₃), 3.81 (s, 3H, CO₂CH₃).

Methyl 6-Methoxymethyl-2-[(E)-(5-oxo-2-phenyl-1,3-oxazol-5(4H)-ylidene)methyl]furo[2,3-b]pyrrole-5-carboxylate (6b). The reaction time: 60 min. Yield: 70%; m.p. 165-168°C (ethanol); For C₂₀H₁₆N₂O₆ (380.3) calculated: 63.16% C, 4.24% H, 7.37% N; found: 63.01% C, 4.17% H, 7.28% N; UV: 444 (3.50); ¹H-NMR δ_H: 8.12 (d, 2H, *J*′,3′ 8.0 Hz, H-2′, H-6′), 7.80 (s, 1H, H-7), 7.71 (t, 1H, *J*′,4′ 8.0 Hz, *J*′,5′ 8.0 Hz, H-4′), 7.63 (t, 2H, *J*′,3′ 8.0 Hz, *J*′,5′,6′ 8.0 Hz, H-3′, H-5′), 7.26 (s, 1H, H-3), 7.11 (s, 1H, H-4), 5.79 (s, 2H, NCH₂), 3.81 (s, 3H, CO₂CH₃), 3.27 (s, 3H, OCH₃).

Compounds **4a-e** were also prepared using microwave irradiation according to the following procedure:

A mixture of substituted furan-2-carboxaldehyde **1a-e** (1 mmol), hippuric acid (1.2 mmol) and potassium acetate (a catalytic amount) in acetic anhydride (0.03 mmol, 3mL) was irradiated in a microwave tube for 1-2 min. at 350W (reaction progress monitored by TLC with 3:1 isohexane-ethyl acetate as eluent). After cooling down, the solid product was separated by filtration, dried and purified by crystallisation. The results of “classical” and microwave conditions are shown in Table 1.

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