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Novel Synthesis of 2-thienylcarbonyl-cyclohexane-1,3-dione as Building Block for Indazolones and Isoxazolones

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A new synthetic methodology using ultrasonic treatment was applied to the *C*-acylation of 1,3-cyclohexanedione with thiophene-2-carbonyl chloride to afford 3-hydroxy-2-(2-thienylcarbonyl)cyclohex-2-en-1-one (**5**). This compound was used as a building block to prepare different bicyclic systems: tetrahydro-4*H*-indazol-4-ones (**7a**–**c** and **9a**,**b**,**d**), and 6,7-dihydrobenzisoxazole (**11**) by reaction with different hydrazines and hydroxylamine, respectively. Structural elucidation of all compounds was thoroughly achieved by NMR spectroscopy.

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Introduction

2-Acyl-cycloalkane-1,3-diones and their derivatives have widely been known for their widespread biological activity. Particularly, it has been reported that some derivatives have antityrosinemic activity, working as inhibitors of 4-hydroxyphenylpiruvate dioxygenase (4-HPPD) activity in the treatment of a hereditary disease called tyrosinemia type I.[1] Moreover, many articles describe herbicide agents containing the β-triketone structure or its derivatives.[2] In addition, these carbonylic compounds are also attractive because they can be used as building blocks in the synthesis of various heterocycles.[3]

A general approach to the synthesis of acyl-cycloalkanediones has been developed.[4] According to this method, the cycloalkanediones are converted into the mono-*O*-enol acyl derivatives by the reaction of acyl chlorides as precursors and pyridine as base. In the next step, these enol esters undergo *O*-*C* isomerization to give the target β-triketones in the presence of Lewis acids ($AlCl_3$ or $ZnCl_2$). This reaction can also proceed either using phase-transfer catalysis in the presence of a tertiary amine in an inert organic solvent or through the interaction of a β-diketone sodium salt with acyl chlorides or carboxylic anhydrides.[5] Another method to prepare β-triketones with aromatic and also non-aromatic side chains involves the isomerization reaction of the *O*-acylderivative to the *C*-acylisomer in the presence of cyanide ion sources.[6,7]

Our particular focus here is the synthesis of a thienyl-carbonyl derivative of cyclohexane-1,3-dione, because the presence of an heterocyclic system and specifically the sulfur heteroatom could alter the metabolic effect and perhaps improve the therapeutic properties of these type of compounds. Even that it is known that potent HPPD inhibitors have the aryl-acylcyclohexanedione nucleus, heteroaryl-acylcyclohexanediones are also potential candidates of active substances. Hence, it is not surprising that the thiophene structure either as the central ring or as part of a central fused ring system plays an important role in pharmaceutical and medicinal applications and drug discovery.[8] The classical bioisosteric equivalence between benzene and thiophene prompted us to study an alternative way to synthesize a thienyl-acylcyclohexanedione compound. Whereas 2-benzoyl-cycloalkane-1,3-diones are commonly found in the literature, heteroaroyl-cycloalkane-1,3-diones are scarce and only few examples of pyridinyl, furanyl, pyrrolyl and thienyl derivatives can be found.[7,9,10]

In this work we report a new synthetic route to obtain 3-hydroxy-2-(2-thienylcarbonyl)cyclohex-2-en-1-one (**5**) (Fig. 1), from thiophene-2-carbonyl chloride (**1**) and cyclohexane-1,3-dione (**2**) using an efficient 'one pot' methodology applying ultrasound irradiation to promote the reaction as a clean, useful and alternative protocol.

We also describe the synthesis of tetrahydro-4*H*-indazol-4-ones (**7a**–**c** and **9a**,**b**,**d**) and 6,7-dihydrobenzisoxazol-4-ones (**11** and **12**), which were synthesized from **5**, through the reaction with different hydrazines and hydroxylamine, respectively (Fig. 1). These bicyclic compounds have pharmaceutical interest, thus, 1,5,6,7-tetrahydro-4*H*-indazol-4-ones present analgesic,[11] anti-inflammatory,[12] broncholytic, antibiotic,[13] and antiviral activity.[14] In addition, 6,7-dihydrobenzisoxazol-4(5*H*)-ones have been identified as effective anti-psychotic and analgesic agents.[15]

Results and Discussion

In a first approach, compound **5** was prepared according to the previous reported protocol.[7,10] Thus, the reaction of thiophene-2-carbonyl chloride (**1**) with cyclohexane-1,3-dione (**2**) gave the enol ester **3**, which was properly isolated from the reaction mixture by column chromatography in 53% yield (Pathway A, Scheme 1). In the second step, preparation of **5** was

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accomplished by the cyanide-catalyzed isomerization of this enol using triethylamine as a base in acetonitrile. It is believed that an initial attack of cyanide ion to the *O*-acylated compound would promote the cleavage of the enol ester and the subsequent formation of a cyclohexanedione anion and acyl cyanide (**4**).

Then, both intermediates may recombine to give the *C*-acylated product. Following this route, thienyl derivative **5** was obtained in low yield (28%).

In order to improve the yield of the expected compound **5**, we modified the above methodology. Thus, a new strategy was developed, based on the preparation of acylcyanide **4** as a key intermediate (Pathway B, Scheme 1). In the first part of the reaction, the acyl chloride **1** was treated with dried potassium cyanide in anhydrous acetonitrile under ultrasound irradiation at 50°C. It has been reported that the presence of a small quantity of water accelerates the heterogeneous reaction between acyl chlorides and potassium cyanide in acetonitrile.[16] It has been assumed that the role of a small amount of water is to attack the crystal lattice of the solid potassium cyanide. Based on the fact that ultrasound may play the same role of a small quantity of water, and taking into account the advantages of heterogeneous sonochemistry in many organic processes,[17] we applied this alternative source of irradiation to obtain **4**. The reaction was monitored by TLC to ensure completion. GC-MS analysis of the crude after 3 h indicated the presence of acylcyanide **4** as the exclusive product. Compound **4** was pure enough to be used in the next step without purification. Then, triethylamine and cyclohexane-1,3-dione were added to the same flask (in situ procedure) and the mixture was stirred overnight at room temperature to give 2-thienylcarbonyl-cyclohexanedione (**5**), achieving a remarkable yield of 88%. After extraction workup, **5** was satisfactory to be used in the next derivatization step without additional purification. While this compound has been prepared in the literature using the conventional methodology, this 'one pot' method was a significant improvement in terms of yields and simplicity.[10]

Although the first effective drug treatment for tyrosinemia has been discovered, that is, 3-hydroxy-2-[2-nitro-4-(trifluoromethyl)benzoyl]cyclohex-2-en-1-one (NTBC), a triketone-type compound (Fig. 2), its mode of action, based on HPPD inhibition, remains unclear. In order to provide insights into this inhibition, it has been studied in previous works that the favoured keto-enol form mimics the keto-acid functionality present in the substrate and is capable of binding strongly to the ferric ion in the active site.[18] Although 2-acyl-cyclohexane-1,3-diones have up to eight possible keto-enol and enol-enol tautomeric forms, recent evidences, which include X-ray structures[19] and molecular modelling studies,[20] suggest that the exocyclic carbonyl moiety of NTBC is coplanar and conjugated with the cyclohexanedione ring system by an intramolecular hydrogen bond of the hydroxyl hydrogen to the oxygen atom of C-3 carbonyl group. It is known that if one of the carbonyl groups in the triketone is modified, the inhibition potency of the resulting compound decreases substantially and the enol at the C-3 position is an essential feature for potent 4-HPPD inhibition in NTBC derivatives.[19] In addition, it was found by theoretical calculations for NTBC derivatives that the enol with the

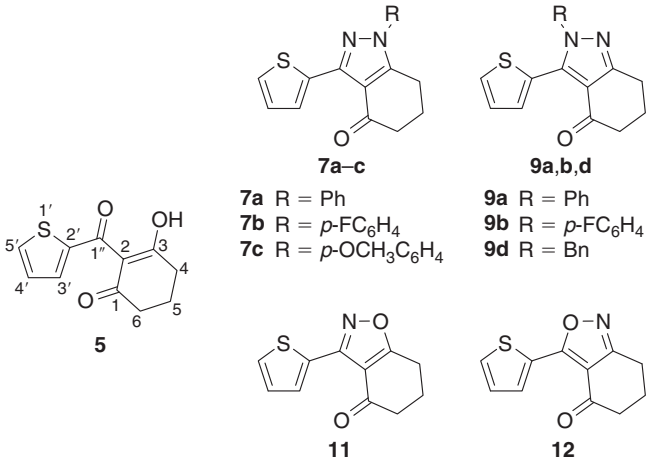


Fig. 1. Thienyl derivatives synthesized in this research.

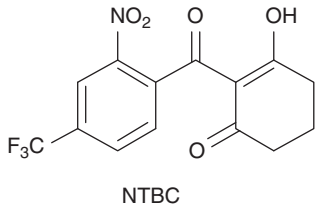
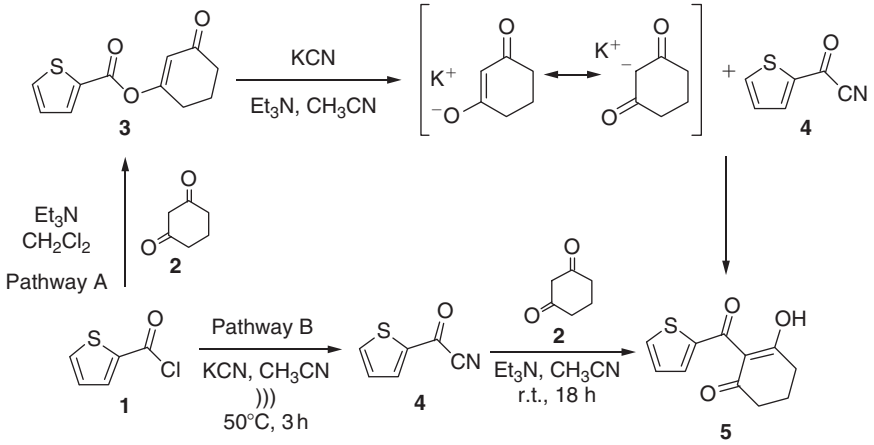
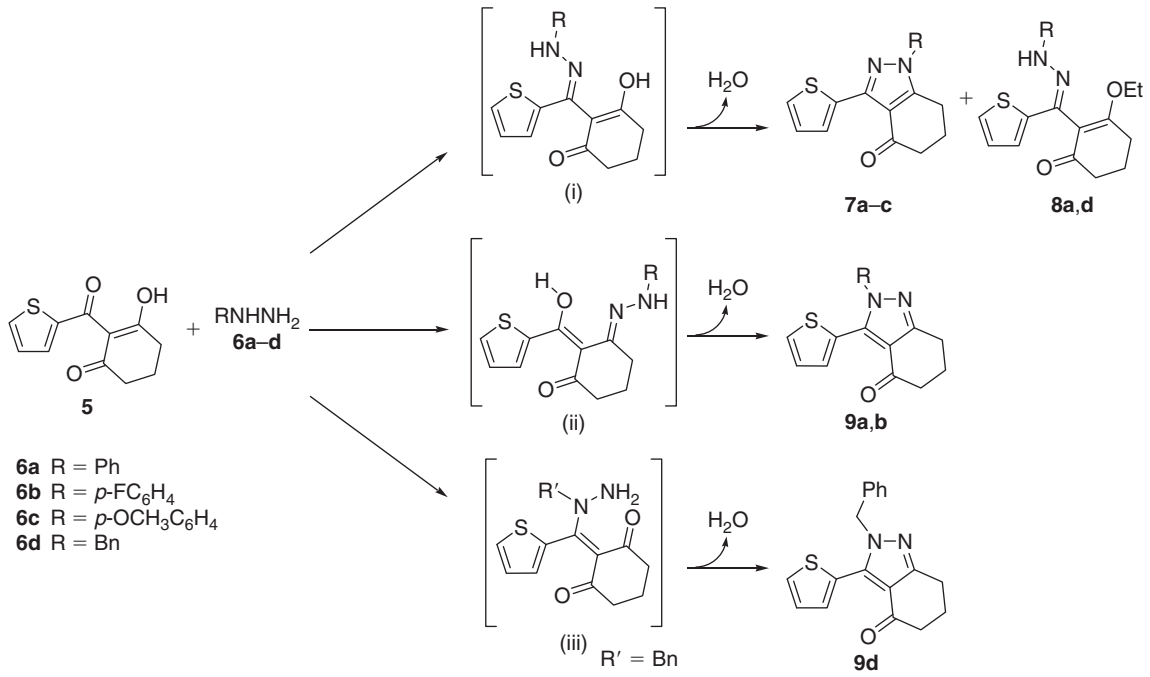


Fig. 2. Structure of NTBC, an inhibitor of 4-HPPD activity.



Scheme 1.



Scheme 2.

endocyclic double bond (between C-2 and C-3 in our case) was the dominant conformation.[20]

In our case, we could confirm the keto-enol structure of **5** by ^{1}H NMR spectroscopy, considering a highly deshielded signal at 17.29 ppm corresponding to the enol hydrogen at C-3 position. This deshielding is in agreement with the same signal of similar acylcyclohexenone derivatives.[19,21] The identification of all carbons was done on the basis of two-dimensional HSQC and HMBC spectroscopic experiments. The corresponding to the carbonyl groups were assigned at 187.37 (C-1″ HMBC connectivity with H-3′) and 194.48 ppm (C-1, HMBC connectivity with H-5 and H-6).

Compounds **3** and **5** were also tested with a ferric chloride assay to observe the colorimetric change. Only **5** gave a positive characteristic purple colour, which suggests this derivative can bind tightly with enzyme-bound ferric ions via the enol tautomer of the triketone.[19]

Beyond their importance as herbicidal and anti-tyrosinemic agents, 2-acyl-cyclohexane-1,3-diones are of significant interest as potential synthons of natural products and of others of biologically active heterocycles owing to their high degree of functionalization and their high reactivity.[4] Among these heterocycles, both 1,5,6,7-tetrahydroindazol-4-one and 6,7-dihydrobenzisoxazol-4-one nuclei form part of the skeleton of many biologically active products with both simple and rather complex structures. Examples of the first group are antipyretic, analgesic and antiphlogistic agents[11] and among those of the second group are antipsychotic agents.[14]

Focussing on the indazole chemistry and the synthetic approaches to prepare them, we can mention the utilization of cyclohexanone enamines and appropriate bidentate nucleophiles as starting materials, where a wide array of pyrazole and indazole derivatives could be prepared.[22] These known procedures require complex purification of the final products and also prove to be unsatisfactory for the synthesis of different analogues. In some cases, these difficulties were overcome with microwave irradiation, promoting the conversion of enaminoketones into a variety of indazoles.[23]

In particular, the synthesis of the 1,5,6,7-tetrahydro-4*H*-indazol-4-one derivatives could also be performed on the most widely used method for constructing the pyrazole ring from the condensation of β-dicarbonyl compounds with hydrazines.[24] Following this simple methodology, we decided to deal with the synthesis of tetrahydroindazole derivatives **7a**–**c**, in a more straightforward, mild and broadly applicable approach (Scheme 2). A stepwise procedure, comprising nucleophilic addition of hydrazine to the exocyclic carbonyl group (C-1″), followed by intramolecular cyclocondensation was proposed.

Thus, **5** was treated with arylhydrazines **6a**–**c** to afford indazoles **7a**–**c** and with benzylhydrazine **6d** to give indazole **9d** as the major products in moderate to very good yields (Scheme 2 and Table 1). This synthetic methodology was versatile and it permitted the formation of compounds not previously described in literature (**7a**–**c**, **8d** and **9a**,**b**,**d**) in moderate to good yields.

Many reaction conditions were evaluated, thus, indazoles **7a** and **7c** were obtained in good yields when DMF was used as the solvent, while **7b** was obtained with better yield when ethanol and sodium hydroxide were used. Analyzing the effect of the hydrazine source in the formation of **7a** in ethanol, the use of hydrochloride salt following by neutralization with NaOAc improved the yield. However, in DMF reactions, using free hydrazine quantitative amounts of **7a** could be obtained.

A particular situation was observed in the reaction when benzylhydrazine **6d** was used, where the expected indazole **7d** was never formed. Thus, hydrazone **8d** was isolated as main product when the reaction solvent was ethanol and the isomeric indazole **9d** was isolated as main product when DMF was used. In this case, the double bond geometry of hydrazone **8d** was not established and the two isomers may be present.

Even a little amount of the isomeric indazoles (**9a**,**b**) were obtained in the reactions of **5** with hydrazines **6a**,**b**; using

Table 1. Reagents and conditions for the synthesis of indazolones

Hydrazine	Conditions[A]	Product yield [%]		
		7	**8**	**9**
6a·HCl **6a** **6a**[D]	NaOAc, H_2O, EtOH EtOH[C] DMF	38[B] 26[B] 87[B]	<5	<5
6b·2HCl **6b**·2HCl	Na_2CO_3, DMF, H_2O NaOH, EtOH	28[E] 40[E]	–	13[E]
6c·HCl	Na_2CO_3, DMF	41[E]	–	–
6d·HCl **6d**·HCl	EtOH, H_2O DMF	–	24[B]	30[E]

[A]Ratio of **5**:**6** equal to 1:1.1.
[B]Yield of isolated products after purification by recrystalization from EtOH/H_2O.
[C]One drop of HCl was added.
[D]Freshly distilled.
[E]Yield of isolated products after purification by chromatographic column.

benzylhydrazine **6d**, the formation of **9d** was the most important reaction.

In these reactions, hydrazone intermediates **i** were not isolated and indazolones **7a**–**c** were directly obtained by intramolecular cyclization. However, in the reactions when ethanol was used as solvent, the *O*-ethylated hydrazones **8a**,**d** were detected by GC-MS as minor products. The formation of these compounds may be explained in terms of a nucleophilic attack of the solvent towards cyclohexanedione carbonyl group in the intermediate **i**.

It is reported in the literature that the regioselectivity of the reaction of acylcyclohexanediones and hydrazines leads exclusively to the formation of the 1-aryl isomer like **7**.[25] In our case, the $-NH_2$ group of the hydrazine reacts with the exocyclic carbonyl group of the 2-thienyl-cyclohexane-1,3-dione **5** with subsequent intramolecular cyclization of the hydrazones intermediates **i**, affording tetrahydroindazolones **7a**–**c** as main products.[26] However, in the condensation of **5** with **6a** and **6b**, the unexpected formation of isomeric 2-aryl-3-(2-thienyl)-2,5,6,7-tetrahydro-4*H*-indazol-4-ones **9a** and **9b** was obtained in <5 and 13% yield, respectively. The existence of these compounds could be rationalized by the reaction of the hydrazine with the endocyclic cyclohexanedione enol group to form intermediate **ii**, followed by cyclization (Scheme 2).

When benzylhydrazine **6d** was employed in DMF, **9d** was the only product. In this case, we believe that intermediate **iii** is more feasible to form than **i**, due to a higher nucleophilic character on the secondary amino group of **6d**, which at first reacts with the exocyclic carbonyl group of **5**. This type of regioselectivity in reactions of benzylhydrazine and carbonylic compounds was previously observed in the synthesis of pyrazolo-derivatives.[27]

To corroborate the reactivity of the different carbonyl groups of **5**, charge distributions were calculated via the Hartree Fock approach using the 6–31+G(d,p) method. It has been found that the highest positive charge of **5** was localized in the C-1″, indicating that this position was the preferred site of attack of the nucleophile, as it was experimentally corroborated.

A complete elucidation of the structures was achieved by spectroscopic techniques of 1-D NMR, 2-D NMR HSQC and HMBC and NOE experiments. Distinction between the regioisomeric indazoles was ascertained on the basis of NOESY, ^1H and ^{13}C NMR experiments. Irradiation of the methylene protons H-7 of compounds **7a**–**c** mutually induces NOE on the aryl proton H-2″ (Fig. 3). Indeed, the same irradiation on isomers **9a**,**b**,**d** did not induce NOE on the aryl proton. Another indication was that protons H-3′ of compounds **7a**–**c** presented higher chemical shifts than compounds **9a**,**b**,**d**, since in the latter the thienyl group has

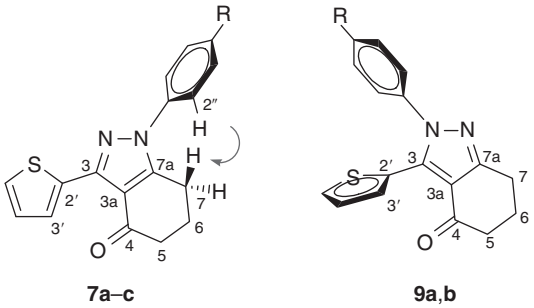


Fig. 3. Atom numbering of indazoles **7a**–**c** and **9a**,**b**.

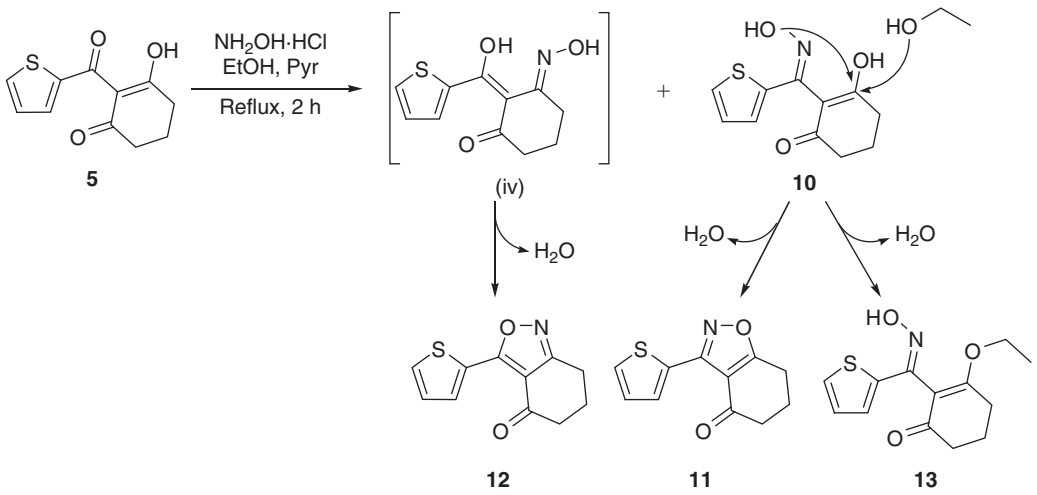
Table 2. ^1H and ^{13}C NMR chemical shifts [ppm] of indazoles 7a–c and 9a,b,d in $CDCl_3$

Compound	H-3′	C-2′	C-3	C-3a	C-7a
7a	8.49	134.44	146.49	116.18	150.78
7b	8.49	134.38	146.66	116.27	150.93
7c	8.48	134.68	146.29	115.93	150.87
9a	7.49	128.34	137.76	116.77	157.42
9b	7.52	128.04	137.90	116.74	157.45
9d	7.51	127.79	137.42	116.86	156.89

an inclination with respect to the molecular plane. The cause of this effect might be the steric hindrance with the phenyl group. The chemical shifts of the quaternary carbons C-2′, C-3, C-3a and C-7a are representative of these compounds (Table 2).

Theoretical calculations of geometries of compounds **7a** and **9a** have been made at the HF/6–31+G(d,p) level of theory and it was found that in **7a**, the distance of protons H-2″ and H-7 was 2.5 Å, whereas in **9a** this distance is increased to 3.87 Å. These results were in agreement with our experimental NMR findings.

As part of our continuing work, dihydrobenzisoxazolone **11** was synthesized from cyclocondensation of **5** with hydroxylamine. There are two general methods for the synthesis of isoxazoles: (a) the reaction of hydroxylamine with a three-carbon atoms system, such as a 1,3-diketone or a α,β-insaturated ketone;[28] and (b) the reaction of a nitrile oxide with an alkene or alkyne.[29] In order to obtain 3-(2-thienyl)-6,7-dihydro-benzisoxazol-4-ones (**11**), we found the first method more convenient. Thus, 2-acyl-1,3-cyclohexanedione **5** was treated with hydroxylamine hydrochloride in the presence of base, to give **11** as the main product.



Scheme 3.

Table 3. Reaction conditions for the synthesis of benzisoxazolones

Conditions[A]				Product yield[B] [%]			
Solvent	Base	Temperature	Reaction time [h]	**10**	**11**	**12**	**13**
H_2O	NaOMe	r.t.	24	–	31	–	–
EtOH	Pyridine	80°C	9	27	42	10	2
EtOH	–	80°C	2	10	3	–	3

[A]Ratio of **5**:NH_2OH·HCl equal to 1:2.
[B]Yield of isolated products.

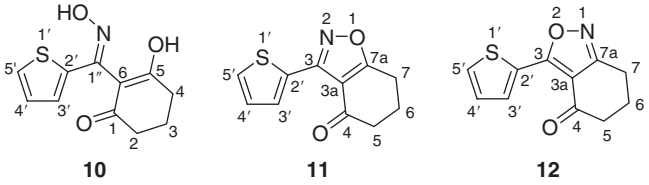


Fig. 4. Atoms numbering of compounds **10**, **11** and **12**.

Table 4. ^{13}C NMR chemical shifts [ppm] of compounds 10–12 in $CDCl_3$

Isoxazole	C-2′	C-3	C-3a	C-7a
11	128.83	165.46	111.86	166.03
12	129.20	154.29	113.25	183.47
Oxime	C-2′	C-1″	C-6	C-5
10	130.41	160.33	108.00	150.51

Using sodium methoxide as base and water as solvent, **11** was obtained as the only product, but in low yield. When the reaction was carried out with pyridine in ethanol, the yield of **11** was increased; nevertheless, oxime **10** and isoxazole **12** were obtained. Traces of the *O*-ethylated oxime **13** were identified by GC-MS analysis when ethanol was used as solvent. The reaction with hydroxylamine hydrochloride without base resulted in very low yields. Reaction conditions and the formation of products are described in Scheme 3 and Table 3. It should be pointed out that compounds **10**, **11**, **12** and **13** have not been previously described in literature.

According to the literature data[30] and the previous results obtained here in the preparation of tetrahydroindazoles, the formation of both oximes intermediates **iv** and **10** as precursors of isoxazoles **12** and **11**, respectively, was expected. Several attempts to obtain quantitatively benzoisoxazolones **11** and/or **12** were carried out, however they were unsuccessful. Thus, in the best reaction conditions (EtOH/pyridine), not only were both regioisomeric isoxazoles were obtained, but the oxime **10** could be also isolated (Table 3). This finding may reflect the greater stability of the oxime intermediate compared with the hydrazone intermediates (**i**–**iii**) proposed in the synthesis of tetrahydroindazoles. It should be noted that the double bond geometry of oxime **10** was not determined.

Characterization of compounds **10**, **11** and **12** was ascertained by spectroscopic analysis (^{1}H, ^{13}C, COSY, HSQC, HMBC) and mass spectrometry. Structure elucidation of the regioisomeric products **11** and **12**, achieved by ^{13}C NMR and mass spectra is also reported. The mass spectrum of **11** showed dominant ions at *m/z* 111, which is consistent with the loss of the thiophene-2-carbonitrile fragment. This pattern was not observed in the mass spectrum of **12**. In this case, the base peak corresponds to the molecular ion and the fused ring cleavage is the main fragmentation (*m/z* 149).

The assignment of carbons C-3 and C-7a was accomplished by comparison of their NMR spectra (Fig. 4, Table 4). The analysis of the HMBC spectra led us to attribute the signal at 183.47 ppm to the quaternary carbon at position 7a in compound **12**, due to an interaction with protons H-7 and H-6. The assignment of C-3 (154.29 ppm) was achieved by correlation with proton H-3′. Although the C=N bond usually resonates upfield compared with the C–O single bond in fused isoxazoles,[31] interestingly, in this case we found the other way around.

Conclusions

In summary, we have established a new efficient methodology for the synthesis of thienylcarbonyl-cyclohexanedione (**5**), using ultrasound irradiation as a novel approach.

In addition, a straightforward synthesis of 1,5,6,7-tetrahydro-4*H*-indazol-4-ones (**7a**,**b**,**c**) was developed. Unexpectedly, isomers 2-phenyl-3-(2-thienyl)-2,5,6,7-tetrahydro-4*H*-indazol-4-ones (**9a**,**b**,**d**) were also obtained. Furthermore, benzisoxazolone-type compounds **11** and **12** were synthesized.

Experimental

General

All chemicals were of reagent grade and were used without further purification. All solvents were distilled. Melting points were determined in open capillary tubes and are uncorrected. FT-IR spectra were obtained with a Nicolet 55XC-FTIR. Mass spectra were measured at an ionizing voltage of 70 eV. All ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded at 400.16, 376.48 and 100.56 MHz, respectively (Bruker Avance II, BBI probe, *Z*-gradient spectrometer). Chemical shifts (δ) are reported in ppm values and coupling constants (*J*) in Hz. The internal standard was TMS. ^{13}C assignments were confirmed by 2D HSQC and HMBC experiments.

Preparative thin-layer chromatography was carried out with Merck silica gel plates (60 DGF_{254}) and column chromatography with Merck silica gel (70–230 mesh).

Computational Methods

All geometries and energy calculations were performed at the HF/6–31+G(d,p) level of theory by using the *Gaussian 03*[32] suite of programs. All stationary points were confirmed as true minima by harmonic vibrational frequency calculations at the same computational level.

Synthesis of 3-Oxocyclohex-1-en-1-yl Thiophene-2-carboxylate **3** and 3-Hydroxy-2-(2-thienylcarbonyl) cyclohex-2-en-1-one **5** (Pathway A)

Thiophene-2-carbonyl chloride **1** (0.304 g, 2.0 mmol) was added dropwise to a cooled (−10°C) stirred solution of cyclohexane-1,3-dione **2** (0.300 g, 2.7 mmol) and triethylamine (0.35 mL) in anhydrous CH_2Cl_2 (12 mL). The mixture is left for 10 min at −10°C and then for another 12 h at room temperature.

A solution of **3** (0.250 g, 1.126 mmol), triethylamine (0.34 mL), potassium cyanide (1.1 mg, 16.9 µmol, 1.5% mol) in acetonitrile (2.8 mL) was stirred for 12 h at room temperature. The solution was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and 1 M HCl. The triketone **5** was then extracted from the organic layer into aqueous sodium bicarbonate. Neutralization and extraction with ether gave, after drying and concentration, the crude product that was chromatographed.[15]

Synthesis of 3-Hydroxy-2-(2-thienylcarbonyl)cyclohex-2-en-1-one **5** (Pathway B)

A mixture of thiophene-2-carbonyl chloride **1** (0.500 g, 3.400 mmol), potassium cyanide (dried at 150°C under reduced pressure and powdered; 0.245 g, 3.75 mmol), and acetonitrile (5 mL) is placed in a 100-mL round-bottom flask, which is immersed in a laboratory ultrasonic cleaner (TestLab, 80 W, 40 KHz) thermostated at 50°C. After ultrasonic treatment for 3 h, anhydrous Et_3N (1 mL) and cyclohexane-1,3-dione (0.420 g, 3.750 mmol) were added and the mixture was stirred at room temperature overnight. The isolation methodology used was identical to Pathway A, nevertheless, no further purification was needed. Spectral data agrees with literature.[10]

3-Oxocyclohex-1-en-1-yl Thiophene-2-carboxylate **3**

White crystals, mp 41–44°C. Yield 55.7% (0.335 g). ν_{max}(KBr)/cm^{-1} 3092, 2951, 2886, 2866, 1733, 1674, 1410, 1249, 1123, 735. δ_H ($CDCl_3$) 2.12 (quintuplet, *J* 6.2, 2H, H-3), 2.46 (t, *J* 6.2, 2H, H-2), 2.68 (t, *J* 6.2, 1.1, 2H, H-4), 6.06 (t, *J* 1.1, 1H, H-6), 7.17 (dd, *J* 5.0, 3.8, 1H, H-4′), 7.69 (dd, *J* 5.0, 1.2, 1H, H-5′), 7.91 (dd, *J* 3.8, 1.2, 1H, H-3′). δ_C ($CDCl_3$) 21.45 (C-3), 28.54 (C-2), 36.92 (C-4), 117.85 (C-6), 128.39 (C-4′), 132.02 (C-2′), 134.54 (C-5′), 135.48 (C-3′), 158.63 (C-1‴), 169.75 (C-1), 199.59 (C-5). *m/z* [%] 113 (5), 112 (6), 111 (100), 83 (7), 69 (3), 57 (2), 42 (3).

3-Hydroxy-2-(2-thienylcarbonyl)cyclohex-2-en-1-one **5**

Yellow crystals. Yield 88.5% (0.6766 g). ν_{max}(KBr)/cm^{-1} 3092, 2952, 2925, 2861, 1666, 1555, 1406, 1351, 1255, 721. δ_H ($CDCl_3$) 2.05 (quintuplet, *J* 6.2, 2H, H-3), 2.57 (t, *J* 6.2, 2H, H-2), 2.72 (t, *J* 6.2, 2H, H-4), 7.11 (dd, *J* 5.0, 4.0, 1H, H-4′), 7.70 (dd, *J* 5.0, 1.1, 1H, H-5′), 8.08 (dd, *J* 4.0, 1.1, 1H, H-3′), 17.28 (s, 1H, OH-5). δ_C ($CDCl_3$) 19.02 (C-3), 32.97 (C-4), 38.45 (C-2), 112.78 (C-6), 127.63 (C-4′), 135.49 (C-5′), 136.38 (C-3′), 141.07 (C-2′), 187.37 (C-1″), 194.48 (C-1), 196.44 (C-5). *m/z* [%] 223 (12), 222 $[M]^+$ (62), 221 (89), 194 (15), 166 (57), 138 (31), 111 (100), 84 (19), 83 (11), 69 (16), 42 (11). *m/z* (HR-EI) calcd. for $C_{11}H_{10}O_3S$ 222.0351 $[M]^{+\bullet}$; found 222.0361.

Synthesis of 3-(2-Thienyl)-1,5,6,7-tetrahydro-4H-indazol-4-ones **7a,c**

A mixture of 3-hydroxy-2-(2-thienylcarbonyl)cyclohex-2-en-1-one **5** (0.318 g, 1.436 mmol) and the corresponding hydrazine in DMF (3 mL) was heated to reflux for 5 h. The reaction progress was monitored by TLC. Water was added dropwise to the mixture; after cooling, the precipitate was collected by filtration. The mother liquor was further purified by extraction with ether (3 × 10 mL), the combined organic extracts were dried with anhydrous $MgSO_4$ and evaporated. The residue (**7c**) was purified by column chromatography with ether as eluent and then recrystallized from acetone/water.

1-Phenyl-3-(2-thienyl)-1,5,6,7-tetrahydro-4H-indazol-4-one **7a**

Pale yellow solid, mp 146.8–147.5°C. Yield 87.0% (0.3674 g). ν_{max}(KBr)/cm^{-1} 3092, 3071, 2941, 2923, 2846, 1665, 1497, 1468, 948, 698 cm^{-1}. MS: *m/z* [%] 295 (20), 294 $[M]^+$ (100), 267 (12), 266 (61), 265 (52), 133 (13), 89 (10), 77 (30), 51 (9). δ_H ($CDCl_3$) 2.17 (quintuplet, *J* 6.2, 2H, H-6), 2.63 (t, *J* 6.2, 2H, H-5), 2.97 (t, *J* 6.2, 2H, H-7), 7.12 (dd, *J* 5.0, 3.7, 1H, H-4′), 7.33 (dd, *J* 5.0, 1.0, 1H, H-5′), 7.43 (tt, *J* 7.0, 1.7, 1H, H-4″), 7.52–7.59 (m, 2H, H-2″ and H-6″), 7.52–7.59 (m, 2H, H-3″ and H-5″), 8.49 (dd, *J* 3.7, 1.0, 1H, H-3′). δ_C ($CDCl_3$) 23.23 (C-6), 23.82 (C-7), 38.98 (C-5), 116.18 (C-3a), 124.19 (C-3″,5″), 126.55 (C-5′), 127.62 (C-4′), 128.43 (C-4″), 129.41 (C-2″,6″), 129.91 (C-3′), 134.44 (C-2′), 138.41 (C-1″), 146.49 (C-3), 150.78 (C-7a), 192.65 (C-4). *m/z* (HR-EI) calcd. for $C_{17}H_{14}N_2OS$ 294.0827 $[M]^{+\bullet}$; found 294.0822.

1-(4-Methoxyphenyl)-3-(2-thienyl)-1,5,6,7-tetrahydro-4H-indazol-4-one **7c**

Pale brown solid, mp 160.7–162.6°C dec. Yield 41.1% (0.0609 g). δ_H ($CDCl_3$) 2.15 (quintuplet, *J* 6.2, 2H, H-6), 2.61 (t, *J* 6.2, 2H, H-5), 2.90 (t, *J* 6.2, 2H, H-7), 3.86 (s, 3H, H-1‴), 7.00 (m, 2H, H-3″,5″), 7.11 (dd, *J* 5.0, 3.7, 1H, H-4′), 7.31 (dd, *J* 5.0, 1.0, 1H, H-5′), 7.43 (m, 2H, H-2″,6″), 8.48 (dd, *J* 3.7, 1.0, 1H, H-3′). δ_C ($CDCl_3$) 23.29 (C-6), 23.68 (C-7), 39.10 (C-5), 55.77 (C-1‴), 114.63 (C-3″,5″), 115.93 (C-3a), 125.86 (C-2″,6″), 126.53 (C-5′), 127.71 (C-4′), 129.89 (C-3′), 131.59 (C-1″), 134.68 (C-2′), 146.29 (C-3), 150.87 (C-7a), 159.71 (C-4″), 192.71 (C-4). *m/z* [%] 325 (29), 324 $[M]^+$ (100), 323 (47), 297 (10), 296 (50),

216 (10), 135 (26), 133 (12), 107 (29), 77 (15). *m/z* (HR-EI) calcd. for $C_{18}H_{16}N_2O_2S$ 324.0932 $[M]^{+\bullet}$; found 324.0936.

*Synthesis of 1-(4-Fluorophenyl)-3-(2-thienyl)-1,5,6,7-tetrahydro-4*H*-indazol-4-one* ***7b***

Compound **5** (0.105 g, 0.475 mmol) was dissolved in ethanol (2 mL) and 4-fluorophenylhydrazine hydrochloride **6d** (0.080 g, 0.493 mmol) and NaOH (0.022 g, 0.552 mmol) were added. The reaction mixture was heated at reflux temperature for 6 h. The residue was evaporated to dryness under reduced pressure, dissolved with $CHCl_3$ (10 mL) and extracted with HCl (0.1 M, 3 × 10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The solid residue obtained was purified by column chromatography with $CHCl_3$/Hexane/EtOH (3.5:0.1:0.05) as eluent.

*1-(4-Fluorophenyl)-3-(2-thienyl)-1,5,6,7-tetrahydro-4*H*-indazol-4-one* ***7b***

Pale yellow solid. Yield 39.4% (0.0553 g). δ_H ($CDCl_3$) 2.17 (quintuplet, *J* 6.3, 2H, H-6), 2.62 (t, *J* 6.3, 2H, H-5), 2.93 (t, *J* 6.3, 2H, H-7), 7.12 (dd, *J* 5.1, 3.7, 1H, H-4′), 7.18–7.23 (m, 2H, H-3″ and H-5″), 7.33 (dd, *J* 5.1, 1.1, 1H, H-5′), 7.50–7.54 (m, 2H, H-2″,6″), 8.49 (dd, *J* 3.7, 1.1, 1H, H-3′). δ_C ($CDCl_3$) 23.27 (C-6), 23.77 (C-7), 39.03 (C-5), 116.27 (C-3a), 116.50 (J_{CF} 22.9, C-3″,5″), 126.24 (J_{CF} 8.8, C-2″,6″), 126.75 (C-5′), 127.77 (C-4′), 130.13 (C-3′), 134.38 (C-2′), 134.64 (J_{CF} 3.2, C-1″), 146.66 (C-3), 150.93 (C-7a), 162.32 (J_{CF} 248.7, C-4″), 192.62 (C-4). δ_F ($CDCl_3$) −112.27 (ddd, *J* 12.4, 7.9, 4.8, F-4″). *m/z* [%] 313 (20), 312 $[M]^+$ (100), 285 (13), 284 (62), 283 (53), 133 (20), 95 (26), 89 (11), 75 (9). *m/z* (HR-EI) calcd. for $C_{17}H_{13}FN_2OS$ 312.0733 $[M]^{+\bullet}$; found 312.0734.

2-[(Benzylhydrazono)(2-thienyl)methyl]-3-ethoxycyclohex-2-en-1-one ***8d***

Brown solid. Yield 24.3% (0.0432 g). *m/z* [%] 354 $[M]^+$ (15), 309 (11), 268 (12), 267 (67), 254 (12), 217 (12), 189 (12), 163 (15), 91 (100), 65 (9). *m/z* (HR-EI) calcd. for $C_{20}H_{22}N_2O_2S$ 354.1402 $[M]^{+\bullet}$; found 354.1392.

*2-Phenyl-3-(2-thienyl)-2,5,6,7-tetrahydro-4*H*-indazol-4-one* ***9a***

Yellow solid. Yield <5% (0.007 g). δ_H ($CDCl_3$) 2.20 (quintuplet, *J* 6.3, 2H, H-6), 2.59 (t, *J* 6.3, 2H, H-5), 2.96 (t, *J* 6.3, 2H, H-7), 6.99 (dd, *J* 5.0, 3.7, 1H, H-4′), 7.31–7.33 (m, 2H, H-2″ and H-6″), 7.38 (dd, *J* 5.0, 1.2, 1H, H-5′), 7.37–7.41 (m, 2H, H-3″ and H-5″), 7.37–7.41 (m, 1H, H-4″), 7.49 (dd, *J* 3.7, 1.2, 1H, H-3′). δ_C ($CDCl_3$) 23.44 (C-6), 23.66 (C-7), 40.07 (C-5), 116.77 (C-3a), 126.55 (C-2″,6″), 126.93 (C-4′), 128.34 (C-2′), 129.05 (C-5′), 129.05 (C-1″), 129.31 (C-3″,5″), 132.02 (C-3′), 137.76 (C-3), 139.44 (C-4″), 157.42 (C-7a), 193.93 (C-4). *m/z* [%] 295 (20), 294 $[M]^+$ (100), 293 (67), 267 (10), 266 (65), 186 (11), 133 (36), 105 (23), 77 (50), 51 (11). *m/z* (HR-EI) calcd. for $C_{17}H_{14}N_2OS$ 294.0827 $[M]^{+\bullet}$; found 294.0825.

*2-(4-Fluorophenyl)-3-(2-thienyl)-2,5,6,7-tetrahydro-4*H*-indazol-4-one* ***9b***

Pale yellow solid. Yield 12.8% (0.018 g). δ_H ($CDCl_3$) 2.19 (quintuplet, *J* 6.3, 2H, H-6), 2.59 (t, *J* 6.3, 2H, H-5), 2.94 (t, *J* 6.3, 2H, H-7), 7.01 (dd, *J* 5.0, 3.7, 1H, H-4′), 7.09 (collapsed dd, *J* 9.2, 5.0, 2H, H-3″,5″), 7.31 (dd, *J* 9.2, 5.0, 2H, H-2″ and H-6″), 7.39 (dd, *J* 5.0, 1.1, 1H, H-5′), 7.52 (dd, *J* 3.7, 1.1, 1H, H-3′). δ_C ($CDCl_3$) 23.36 (C-6), 23.58 (C-7), 40.02 (C-5), 116.32 (J_{CF} 22.9, C-3″,5″), 116.74 (C-3a), 127.03 (C-4′), 128.04 (C-2′), 128.42 (J_{CF} 9.2, C-2″,6″), 129.17 (C-5′), 132.12 (C-3′), 135.44 (J_{CF} 3.0, C-1″), 137.90 (C-3), 157.45 (C-7a), 162.63 (J_{CF} 250.0, C-4″), 193.86 (C-4). δ_F ($CDCl_3$) −111.43 (ddd, *J* 12.3, 8.0, 4.3, F-4″). *m/z* [%] 313 (20), 312 $[M]^+$ (100), 311 (66), 285 (11), 284 (63), 204 (16), 133 (54), 123 (18), 95 (40), 89 (13), 75 (13). *m/z* (HR-EI) calcd. for $C_{17}H_{13}FN_2OS$ 312.0733 $[M]^{+\bullet}$; found 312.0743.

*2-Benzyl-3-(2-thienyl)-2,5,6,7-tetrahydro-4*H*-indazol-4-one* ***9d***

Pale yellow solid, mp 166.3–168.2°C dec. Yield 29.9% (0.0430 g). δ_H ($CDCl_3$) 2.15 (quintuplet, *J* 6.2, 2H, H-6), 2.52 (t, *J* 6.2, 2H, H-5), 2.89 (t, *J* 6.2, 2H, H-7), 5.35 (s, 2H, H-1‴), 7.09–7.11 (m, 2H, H-2″,6″), 7.10 (dd, *J* 5.0, 3.7, 1H, H-4′), 7.25 (dd, *J* 3.7, 1.0, 1H, H-5′), 7.25–7.33 (m, 2H, H-3″ and H-5″), 7.25–7.33 (m, 1H, H-4″), 7.51 (dd, *J* 5.0, 1.0, 1H, H-3′). δ_C ($CDCl_3$) 23.46 (C-6), 23.46 (C-7), 39.67 (C-5), 53.34 (C-1‴), 116.86 (C-3a), 126.96 (C-2″,6″), 127.17 (C-4′), 127.79 (C-2′), 127.88 (C-5′), 128.78 (C-3″,5″), 128.85 (C-4″), 130.61 (C-3′), 136.38 (C-1″), 137.42 (C-3), 156.89 (C-7a), 193.66 (C-4). *m/z* [%] 309 (22), 308 $[M]^+$ (100), 307 (27), 280 (16), 279 (25), 231 (17), 217 (12), 189 (28), 133 (27), 91 (77), 89 (19), 65 (19). *m/z* (HR-EI) calcd. for $C_{18}H_{16}N_2OS$ 308.0983 $[M]^{+\bullet}$; found 308.0983.

*Synthesis of 3-(2-Thienyl)-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one* ***12***

To a solution of **5** (0.100 g, 0.450 mmol) in ethanol (3 mL), hydroxylamine hydrochloride (0.344 g, 0.495 mmol) and pyridine (0.1 mL) were added. The mixture was heated to reflux in a water bath for 6 h. The solvent was evaporated to dryness, and the residue was dissolved with water, extracted with ethyl acetate and dried with anhydrous $MgSO_4$. The residue was purified by thin-layer chromatography with $CHCl_3$/hexane/EtOH (3:1:0.05) as eluent.[33]

3-Hydroxy-2-[(hydroxyimino)(2-thienyl)methyl]cyclohex-2-en-1-one ***10***

Pale yellow solid, mp 189°C dec. Yield 26.9% (0.0287 g). ν_{max}(KBr)/cm^{-1} 3085, 3063, 2916, 2873, 1716, 1628, 1591, 1404, 941, 892, 710. δ_H (CD_3CN) 1.90 (quintuplet, *J* 6.2, 2H, H-3), 2.75 (t, *J* 6.2, 2H, H-4), 2.78 (t, *J* 6.2, 2H, H-2), 7.21 (dd, *J* 5.0, 3.8, 1H, H-4′), 7.67 (dd, *J* 5.0, 1.1, 1H, H-5′), 8.44 (dd, *J* 3.8, 1.1, 1H, H-3′), 9.10 (s, 1H, OH-5). δ_C (CD_3CN) 21.56 (C-3), 22.20 (C-4), 23.58 (C-2), 108.00 (C-6), 128.80 (C-4′), 130.41 (C-2′), 131.08 (C-5′), 131.78 (C-3′), 150.51 (C-5), 160.33 (C-1″), 163.85 (C-1). *m/z* [%] 237 $[M]^+$ (1), 235 (15), 234 (100), 233 (33), 217 (27), 120 (25), 111 (76), 110 (12), 83 (17), 45 (14), 41 (16).

*3-(2-Thienyl)-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-one* ***11***

White solid, mp 137–139.5°C. Yield 42.4% (0.0418 g). ν_{max}(KBr)/cm^{-1} 3111, 3090, 2948, 2912, 2847, 1729, 1676, 1575, 1480, 1427, 1296, 745. δ_H (CD_3CN) 2.13 (quintuplet, *J* 6.2, 2H, H-6), 2.56 (t, *J* 6.2, 2H, H-5), 2.91 (t, *J* 6.2, 2H, H-7), 7.28 (t, *J* 5.0, 1H, H-4′), 7.81 (d, *J* 5.0, 1H, H-5′), 8.54 (d, *J* 3.7, 1H, H-3′). δ_C (CD_3CN) 21.94 (C-7), 22.89 (C-6), 39.95 (C-5), 111.86 (C-3a), 128.83 (C-2′), 129.41 (C-4′), 133.53 (C-3′), 133.62 (C-5′), 165.46 (C-3), 166.03 (C-7a), 193.68 (C-4). *m/z* [%] 220 (16), 219 $[M]^+$ (99), 190 (22), 163 (10), 162 (28), 136

(12), 135 (55), 112 (11), 111 (100), 83 (21), 41 (15). *m/z* (HR-EI) calcd. for $C_{11}H_9NO_2S$ 219.0354 $[M]^{+\bullet}$; found 219.0352.

3-(2-Thienyl)-6,7-dihydro-1,2-benzisoxazol-4(5H)-one ***12***

White solid. Yield 10.2% (0.0108 g). ν_{max}(KBr)/cm^{-1} 3096, 3068, 2959, 2914, 2854, 1720, 1679, 1579, 1456, 1269, 1119, 1068. δ_H (CD_3CN) 2.21 (quintuplet, *J* 6.4, 2H, H-6), 2.56 (t, *J* 6.4, 2H, H-5), 3.04 (t, *J* 6.4, 2H, H-7), 7.19 (dd, *J* 5.1, 3.7, 1H, H-4′), 7.59 (dd, *J* 5.1, 1.1, 1H, H-5′), 8.45 (dd, *J* 3.7, 1.1, 1H, H-3′). δ_C (CD_3CN) 21.45 (C-6), 22.82 (C-7), 38.16 (C-5), 113.25 (C-3a), 127.95 (C-4′), 128.51 (C-5′), 129.20 (C-2′), 132.70 (C-3′), 154.29 (C-3), 183.47 (C-7a), 192.59 (C-4). *m/z* [%] 220 (15), 219 $[M]^+$ (100), 163 (12), 162 (30), 150 (14), 149 (77), 136 (18), 135 (13), 123 (25), 82 (15), 45 (15), 42 (42), 41 (13). *m/z* (HR-EI) calcd. for $C_{11}H_9NO_2S$ 219.0354 $[M]^{+\bullet}$; found 219.0353.

3-Ethoxy-2-[(hydroxyimino)(2-thienyl)methyl]cyclohex-2-en-1-one ***13***

Pale yellow solid. Yield 2.1% (0.0025 g). ν_{max}(KBr)/cm^{-1} 3070, 2952, 2926, 2854, 1724, 1457, 1283, 1118, 1062, 738. δ_C ($CDCl_3$) 1.23 (t, *J* 7.2, 3H), 2.00 (quintuplet, *J* 7.5, 2H), 2.40 (t, *J* 7.5, 2H), 2.74 (t, *J* 7.5, 2H), 4.09 (q, *J* 7.2, 2H), 7.20 (dd, *J* 5.1, 3.7, 1H), 7.60 (dd, *J* 3.7, 1.0, 1H), 7.69 (dd, *J* 5.1, 1.0, 1H), 10.51 (s, 1H). *m/z* [%] 265 $[M]^+$ (18), 220 (28), 179 (11), 178 (100), 177 (9), 165 (46), 111 (38), 45 (11), 41 (13). *m/z* (HR-EI) calcd. for $C_{13}H_{15}NO_3S$ 265.0773 $[M]^{+\bullet}$; found 265.0771.

Accessory Publication

General procedure for the synthesis of these new compounds and their ^1H, ^{13}C and 2D NMR spectra, are available on the Journal's Website.

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