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HALOLACTONIZATION OF γ –ACETYLENIC ACIDS: SYNTHESIS OF NOVEL SPIROISOINDOLE HALOBUTYROLACTONES

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Abstract –γ-Acetylenic carboxylic acids are cyclized to spirohalo butyrolactones, in the presence of NBS or NIS and K_2CO_3. The corresponding 5(*E*)-haloalkylidene-spirobutyrolactones were isolated in high yields, and this process constitutes an easy and efficient route to analogous structures of natural products of biological interest.

INTRODUCTION

In recent years, increasing attention has been focused on exocyclic enol lactones synthesis[1-7] due their structural implication in biological systems.[8] For example, enol lactones bearing an halogen at the vinylic position are usually prepared by halolactonization of alkynoic acids and known as potential mechanism-based enzyme inactivators (suicide inactivators) of serine proteases.[9]

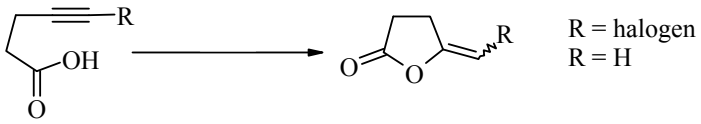


Figure 1

On the other hand, spiro compounds, which are molecules containing one carbon atom common to two rings, are frequently occurring motifs in biological systems.[10-12] For example, spirocyclic isoindolin-1-one **I** [13] was described as an aldose reductase inhibitor and antihyperglycemic agent. A wide range of biological activities are also displayed by 3-spiroisoindoles of general formula **II.**[11]

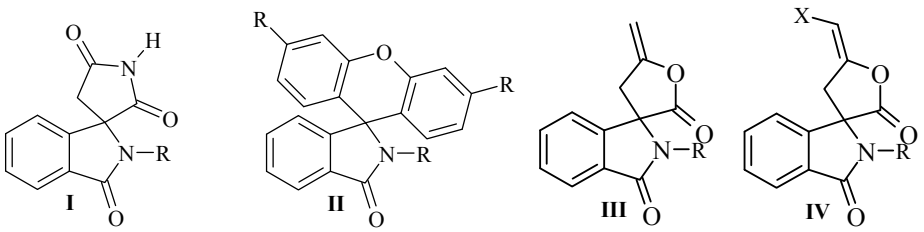


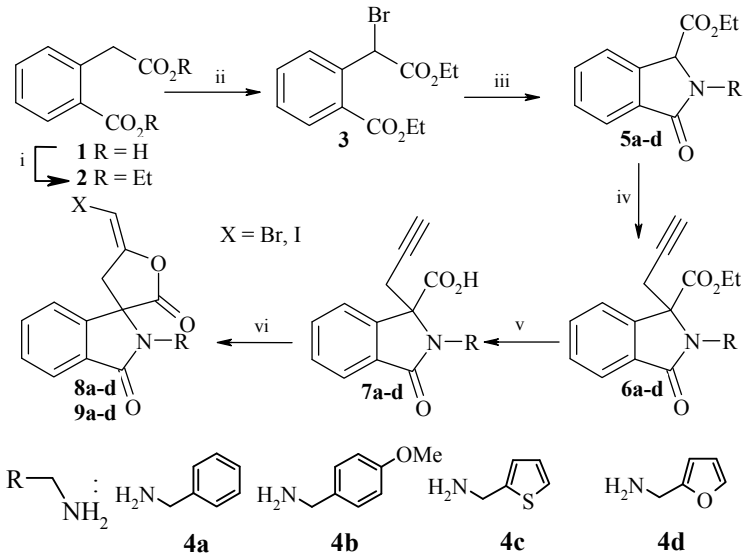
Figure 2

As apart of an on going research project devoted to the synthesis of biologically relevant nitrogenated and oxygenated compounds,[14,15] we recently reported that spiroisoindole-γ-methylene-γ-butyrolactones of type **III** are regioselectively obtained in high yields when γ-acetylenic carboxylic acids **7** (Scheme 1) are reacted with a catalytic amount of silver carbonate (5 mol%).[15a]

Now, we wish to report the synthesis of new spirolactones of type **IV** bearing a halogen at the vinylic position through halolactonization of acids **7** with NBX (X: I, Br) as the key step to form the five membered ring.

RESULTS AND DISCUSSION

Commercially available homophthalic **1**, which we used as a starting material for the synthesis of the γ-acetylenic carboxylic acids of general formula **7**, was converted in quantitative yield into the corresponding crude diethyl homophthalate **2** by esterification with HCl in refluxing EtOH.[15] Compound **2** without purification was then converted into diethyl α-bromohomophthalate **3** in 85% yield as previously described by our group.[15d] Treatment of bromide **3** with the required primary amines **4a-d** for 8 h in acetonitrile at room temperature afforded the phthalimidines **5a-d** in good yields (84-92%).[15]

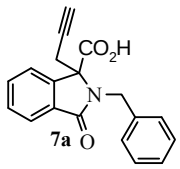
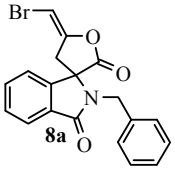
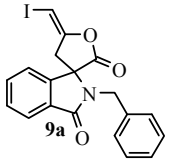
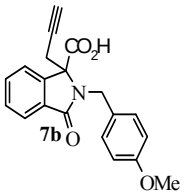
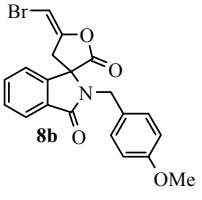
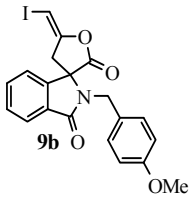
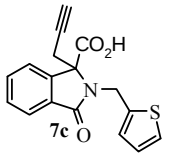
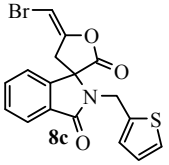
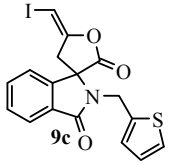
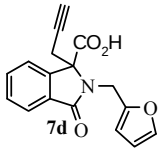
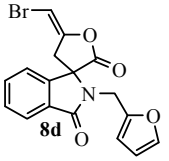
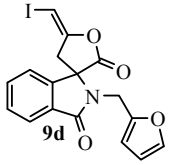


Scheme 1. Reagents and conditions: (i) HCl, EtOH, 0 °C, 4 h then reflux, 4 h; (ii) NBS, AIBN, CCl_4, reflux, 12 h; (iii) amines **4a-d**, MeCN, rt, 8 h; (iv) K_2CO_3, propargyl bromide, MeCN, reflux, 12 h; (v) a. NaOH, EtOH/H_2O, rt, 2 h; b. aqueous 1M HCl, 0 °C; (vi) K_2CO_3, NBS or NIS, CH_2Cl_2, 0 °C.

Next, acids **7a-d** were prepared by alkylation of phthalimidines **5a-d** with 1.2 equiv of propargyl bromide and 1 equiv of K_2CO_3 in MeCN followed by basic saponification of the resulting alkylated phthalimidines esters **6a-d**. Finally, the acetylenic carboxylic acids **7a-d** were submitted to the halolactonization reaction with *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) and K_2CO_3 in CH_2Cl_2 at 0 °C, furnishing

the spiro halobutyrolactones **8a-d** (**9a-d)** in good yields. Silica gel columnn chromatography was used to remove the succinimide, and the results are summarized in Table 1.

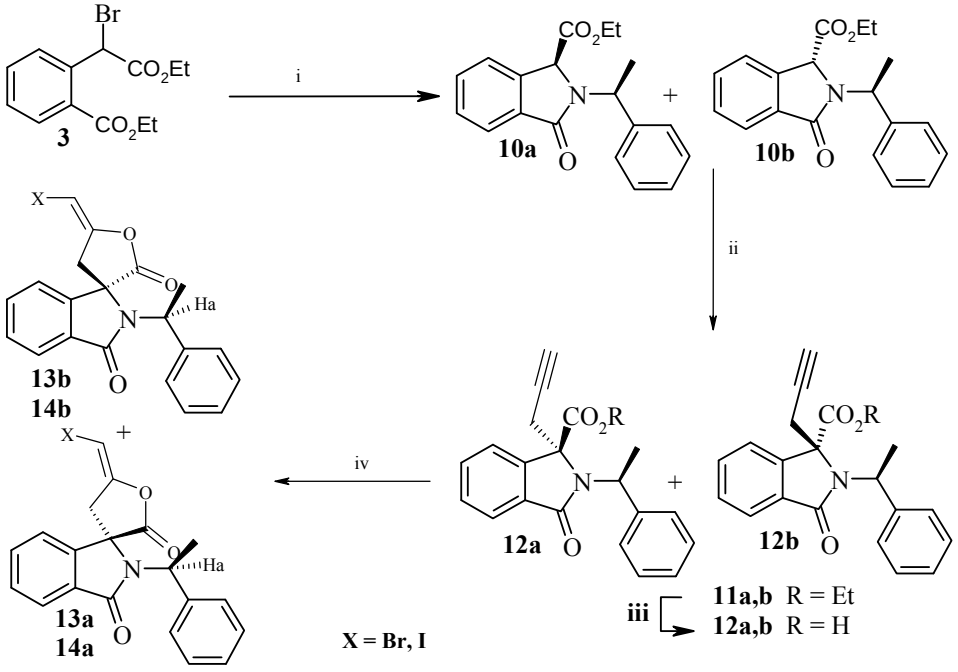
Table 1. Halocyclization produced via Scheme 1

Entry	Substrate	X^+	Product	Yield%	X^+	Product	Yield%
1		NBS		82	NIS		74
2				75			78
4				95			87
6				0			69

The assignement of these structures was made on the basis of their IR, and NMR spectroscopies (^{1}H, ^{13}C and DEPT experiments). So, the ^{1}H NMR spectra of **8a-d** (**9a-d**) showed the methylene group of the –N-CH_2- functionalities as an AB system due to the diastereotopic effect with a coupling constant of J = 15-16 Hz characteristic of *gem* protons. Also, each proton H_4 appears as a doublet of doublet (J = 18 Hz characteristic of *gem* protons and $J_{H4\text{-}Ha}$ = 2.3 Hz). Importantly, in all cases, the haloctonization is completely stereoselective and results in exclusive formation of the *E* olefin. This implicates a discrete halonium ion intermediate which undergoes attack by the carboxylate exclusively with inversion. The *E* stereochemistry of these compounds was assigned from the chemical shift of their vinylic protons (a triplet at $\delta \approx 6.1$ ppm with a coupling constant of J = 2.3 Hz due to the coupling with the two protons H_4) and by comparison with known products (for the *E* isomer, this proton is found near $\delta \approx 6.0$ ppm, whereas for the *Z* isomer it is at approximately $\delta \approx 5.4$ ppm).[9] It is noteworthy that, although a variety of reaction temperatures (0 °C, -30 °C, -78 °C), solvant (CH_2Cl_2, THF, MeCN) and NBS ratios were explored, the formation of spirolactone **8d** was not accomplished but complete degradation occurred.

Synthesis of chiral spirobutyrolactone derivatives

Having successfully established the feasibility of the working plan, we extended the halo spirobutyrolactonization strategy to the synthesis of chiral non racemic spiro-γ-methylene-γ-butyrolactones. The *S*-α-methylbenzylamine was chosen as example for this study.



Scheme 2. Reagents and conditions: (i) (*S*)-α-methylbenzylamine, MeCN, rt, 8 h; (ii) K_2CO_3, propargyl bromide, MeCN, reflux, 12 h; (iii) a. NaOH, EtOH/H_2O, rt, 2 h; b. aqueous 1M HCl, 0 °C; (iv) K_2CO_3, NBS or NIS, CH_2Cl_2, 0 °C.

The key starting material for this synthesis was the compound **10**, the synthesis of which has been described previously by us.[15a] Next, alkylation of **10** followed by saponification of **11** under the same operating methods previously used to obtain acids **7** afforded a mixture of non separable products in 71% overall yield for the two stages.

Finally, the spirocyclization of carboxylic acids **12a,b** with NBS/NIS in the presence of K_2CO_3, gave a 2:1 mixture of diastereomers (**13a/13b** with NBS) and (**14a/14b** with NIS) that were readily separated by column chromatography in yields of 78% and 72%, respectively (Scheme 2). The relative position in the ^{1}H NMR spectra of the proton H_a provided the necessary information to assign the relative configuration of these adducts by analogy with previously reported compounds (the resonance of the proton of the α-methylbenzylamine in the diastereomer in which we have established that the relative configuration of the spirocentre is R* appears at 5.75 ppm, while that of the other diastereomer appears upfield at 4.46 ppm).[15a]

CONCLUSION

In summary, a highly efficient spirohalocyclization reaction of γ-acetylenic carboxylic acids was developed in the isoindolone series by using X^+ (NBS or NIS) and K_2CO_3. The carboxylic substrates were very easily prepared from simple precursors and the cyclization reactions selectively afforded the corresponding 5(*E*)-haloalkylidene-spirobutyrolactones. Further investigations will be devoted to the synthesis of halo γ-spirolactones, as well as applications in analogous natural product syntheses.

EXPERIMENTAL

General

All melting points were measured on a Boetius micro hotstage and are uncorrected. ^1H and ^{13}C NMR spectra were recorded respectively at 200 (300) and 50 (75) MHz on a Brucker AC-200 and Brucker AVANCE 300 spectrometers. The infrared spectra were recorded on a Perkin-Elmer FT-IR paragon 1000 spectrometer. Thin-layer chromatography (TLC) was performed with aluminum plates (0.20 mm) precoated with fluorescent silica gel, using EtOAc/hexanes as eluent. Reaction components were then visualized under UV light and dipped in a Dragendorff solution. Silica gel (230-400 mesh) was used for flash chromatography separations. Some reactions were performed under an inert atmosphere. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mt St Aignan, France. Abbreviations: dd = doublet of doublets, m = multiplet, s = singlet, d = doublet, q = quartet, t = triplet, DCM = dichloromethane. Tetrahydrofuran was dried by distillation from sodium/benzophenone. Dichloromethane was dried by distillation from calcium hydride and acetonitrile was dried by distillation from P_2O_5.

Typical procedure of primary amine condensation. Products **5** and **10** are prepared according our previous work.[15]

Alkylation with propargyl bromide. Products **6** and **11** are prepared according our previous work.[15]

Preparation of acids 7and **12.** Products **7** and **12** are prepared according our previous work.[15]

Typical procedure of the spirohalolactonization reaction.

A mixture of acetylenic acid **7** (1 mmole), K_2CO_3 (1.1 equiv) and *NBS* or *NIS* (1.2 equiv) in degassed CH_2Cl_2 (5 mL) was stirred under argon atmosphere at 0 °C. After the completion of the reaction indicated by TLC analysis, solvent was evaporated under reduced pressure and the crude mixture was purified by silica gel flash chromatography (cyclohexane/EtOAc, 60/40) to give the corresponding lactones **8, 9, 13** or **14**.

2'-Benzyl-5(*E*)-bromomethylidene-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (8a). White solid; yield: 82%; mp 157-159 °C; IR (ν, cm^{-1}, $CHCl_3$) 1678, 1709; ^1H NMR (300 MHz, $CDCl_3$, 25 °C)

δ 3.00 (dd, *J* = 18.0, *J* = 2.3 Hz, 1H), 3.12 (dd, *J* = 18.0, *J* = 2.3 Hz, 1H), 4.26 (d, *J* = 15.6 Hz, 1H), 5.24 (d, *J* = 15.6 Hz, 1H), 6.20 (t, *J* = 2.3 Hz, 1H,), 7.30-7.40 (m, 6H), 7.53-7.64 (m, 2H), 7.91-7.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 34.6 (CH_2), 44.4 (CH_2), 68.5 (Cq), 88.1 (CH), 120.4 (CH), 124.6 (CH), 127.9 (2CH), 128.1 (CH), 129.0 (2CH), 130.3 (CH), 130.4 (Cq), 133.2 (CH), 136.1 (Cq), 143.8 (Cq), 148.1 (Cq), 168.5 (C=O), 170.9 (C=O). Anal. Calcd for $C_{19}H_{14}BrNO_3$ (384.23): C, 59.39; H, 3.67; N, 3.65. Found: C, 59.42; H, 3.65; N, 3.68.

2'-(4-Metoxybenzyl)-5(*E*)-bromomethylidene-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (8b). White solid; yield: 75%; mp 123-125 °C; IR (ν, cm^{-1}, $CHCl_3$) 1687, 1721; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 3.03 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 3.17 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 3.79 (s, 3H), 4.28 (d, *J* = 15.6 Hz, 1H), 5.15 (d, *J* = 15.6 Hz, 1H), 6.21 (t, *J* = 2.3 Hz, 1H), 6.83-6.86 (m, 2H), 7.19-7.25 (m, 2H), 7.34-7.39 (m, 1H), 7.55-7.64 (m, 2H), 7.91-7.96 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 34.6 (CH_2), 43.9 (CH_2), 55.3 (CH_3), 68.3 (Cq), 88.0 (CH), 114.3 (2CH), 120.4 (CH), 124.6 (CH), 127.9 (Cq), 129.3 (2CH), 130.2 (CH), 130.4 (Cq), 133.1 (CH), 143.6 (Cq), 148.1 (Cq), 159.4 (Cq), 168.4 (C=O), 170.3 (C=O). Anal. Calcd for $C_{20}H_{16}BrNO_4$ (414.26): C, 57.99; H, 3.89; N, 3.38. Found: C, 57.94; H, 3.91; N, 3.40.

2'-(Thiophen-2-ylmethyl)-5(*E*)-bromomethylidene-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (8c). White solid; yield: 95%; mp 84-86 °C; IR (ν, cm^{-1}, $CHCl_3$) 1677, 1710; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 3.12 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 3.25 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 4.56 (d, *J* = 15.6 Hz, 1H), 5.32 (d, *J* = 15.6 Hz, 1H), 6.27 (t, *J* = 2.3 Hz, 1H), 6.87-7.06 (m, 2H), 7.28-7.42 (m, 2H), 7.52-7.69 (m, 2H), 7.85-7.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 34.7 (CH_2), 39.5 (CH_2), 68.3 (Cq), 88.4 (CH), 120.4 (CH), 124.7 (CH), 127.3 (CH), 127.4 (CH), 129.6 (CH), 129.8 (Cq), 130.4 (CH), 133.4 (CH), 140.4 (Cq), 143.4 (Cq), 147.9 (Cq), 168.1 (C=O), 170.0 (C=O). Anal. Calcd for $C_{17}H_{12}BrNO_3S$ (390.26) : C, 52.32; H, 3.10; N, 3.59. Found: C, 52.36; H, 3.11; N, 3.54.

2'-(1-Phenylethyl)-5(*E*)-bromomethylidene-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (13a). yield: 78%; Min: White solid; mp 95-97 °C; IR (ν, cm^{-1}, $CHCl_3$) 1677, 1702; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.01 (d, *J* = 7.0 Hz, 3H), 3.20 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 3.34 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 4.62 (q, *J* = 7.0 Hz, 1H), 6.26 (t, *J* = 2.3 Hz, 1H), 7.27-7.49 (m, 6H), 7.51-7.65 (m, 2H), 7.81-7.98 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 19.8 (CH_3), 34.5 (CH_2), 50.3 (CH), 67.2 (Cq), 88.2 (CH), 120.0 (CH), 124.3 (CH), 126.8 (2CH), 127.8 (CH), 128.8 (2CH), 130.2 (Cq), 130.3 (CH), 132.9 (CH), 140.2 (Cq), 144.5 (Cq), 148.1 (Cq), 170.7 (C=O), 170.8 (C=O). Anal. Calcd for $C_{20}H_{16}BrNO_3$ (398.26): C, 60.32; H, 4.05; N, 3.52. Found: C, 60.28; H, 4.07; N, 3.49.

2'-(1-Phenylethyl)-5(*E*)-bromomethylidene-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (13b).

Maj: White solid; mp 116-118 °C; IR (ν, cm^{-1}, $CHCl_3$) 1672, 1702; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.78 (d, *J* = 7.0 Hz, 3H), 2.84 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 2.97 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 5.80 (q, *J* = 7.0 Hz, 1H), 6.14 (d, *J* = 2.3 Hz, 1H), 7.28-7.49 (m, 5H), 7.51-7.67 (m, 3H), 7.84-7.98 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 17.2 (CH_3), 34.2 (CH_2), 50.4 (CH), 67.3 (Cq), 87.8 (CH), 119.8 (CH), 124.5 (CH), 126.9 (2CH), 128.0 (CH), 128.9 (2CH), 130.1 (CH), 130.2 (Cq), 133.1 (CH), 140.3 (Cq), 144.4 (Cq), 148.0 (Cq), 168.5 (C=O), 171.7 (C=O). Anal. Calcd for $C_{20}H_{16}BrNO_3$ (398.26): C, 60.32; H, 4.05; N, 3.52. Found: C, 60.30; H, 4.03; N, 3.55.

2'-Benzyl-5-methylidene-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (9a). White solid; yield: 74%; mp 149-152 °C; IR (ν, cm^{-1}, $CHCl_3$) 1663, 1708; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 3.00 (dd, *J* = 2.3, *J* = 18.0 Hz, 1H), 3.11 (dd, *J* = 2.3, J = 18.0 Hz, 1H), 4.27 (d, *J* = 15.6 Hz, 1H), 5.26 (d, *J* = 15.6 Hz, 1H), 6.12 (t, *J* = 2.3 Hz, 1H), 7.33-7.39 (m, 6H), 7.56-7.66 (m, 2H), 7.94-7.98 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 37.0 (CH_2), 44.4 (CH_2), 56.2 (CH), 69.3 (Cq), 120.4 (CH), 124.6 (CH), 127.8 (2CH), 128.1 (CH), 129.0 (2CH), 130.2 (CH), 130.3 (Cq), 133.2 (CH), 136.0 (Cq), 143.5 (Cq), 149.9 (Cq), 168.4 (C=O), 170.9 (C=O). Anal. Calcd for $C_{19}H_{14}INO_3$(431.23) : C, 52.92; H, 3.27; N, 3.25. Found: C, 52.95; H, 3.28; N, 3.29.

2'-(4-Metoxybenzyl)-5(*E*)-iodomethylidene-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (9b). White solid; yield: 78%; mp 137-139 °C; IR (ν, cm^{-1}, $CHCl_3$) 1691, 1747; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 2.98 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 3.13 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 3.79 (s, 3H), 4.27 (d, *J* = 15.6 Hz, 1H), 5.14 (d, *J* = 15.6 Hz, 1H), 6.09 (t, *J* = 2.3 Hz, 1H), 6.81-6.89 (m, 2H), 7.18-7.25 (m, 2H), 7.31-7.39 (m, 1H), 7.52-7.66 (m, 2H); 7.88-7.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 44.1 (CH_2), 45.6 (CH_2), 55.2 (CH_3), 55.3 (CH), 68.4 (Cq), 114.0 (2CH), 122.1 (CH), 124.2 (CH), 129.3 (2CH), 129.6 (CH), 129.8 (Cq), 130.1 (Cq), 130.9 (Cq), 132.3 (CH), 143.4 (Cq), 158.8 (Cq), 169.1 (C=O), 169.9 (C=O). Anal. Calcd for $C_{20}H_{16}INO_4$ (461.26): C, 52.08; H, 3.50; N, 3.04. Found: C, 52.11; H, 3.48; N, 3.06.

2'-(Thiophen-2-ylmethyl)-5(*E*)-iodomethylidene-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (9c). White solid; yield: 87%; mp 164-166 °C; IR (ν, cm^{-1}, $CHCl_3$) 1662, 1709; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 3.08 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 3.22 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 4.55 (d, *J* = 15.6 Hz, 1H), 5.33 (d, *J* = 15.6 Hz, 1H), 6.14 (t, *J* = 2.3 Hz, 1H), 6.94-7.05 (m, 2H), 7.27-7.41 (m, 2H), 7.55-7.67 (m, 2H), 7.90-7.98 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 37.1 (CH_2), 39.2 (CH_2), 56.2 (CH), 69.1 (Cq), 120.4 (CH), 124.6 (CH), 126.5 (CH), 127.0 (CH), 127.3 (CH), 130.0 (Cq), 130.2 (CH), 133.3 (CH), 138.5 (Cq), 143.6 (Cq), 150.0 (Cq), 168.0 (C=O), 170.7 (C=O). Anal. Calcd for $C_{17}H_{12}INO_3S$ (437.26): C, 46.70; H, 2.77; N, 3.20. Found: C, 46.74; H, 2.75; N, 3.24.

2'-(Furan-2-ylmethyl)-5(*E*)-iodomethylidene-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (9d). White solid; yield: 69%; mp 99-101 °C; IR (ν, cm^{-1}, $CHCl_3$) 1681, 1708; ^1H NMR (300 MHz,

$CDCl_3$, 25 °C) δ 3.10 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 3.24 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 4.56 (d, *J* = 16.2 Hz, 1H), 5.01 (d, *J* = 16.2 Hz, 1H), 6.13 (t, *J* = 2.3 Hz, 1H), 6.35-6.38 (m, 2H), 7.33-7.40 (m, 2H), 7.53-7.63 (m, 2H), 7.87-7.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 36.6 (CH_2), 36.8 (CH_2), 55.9 (CH), 68.7 (Cq), 110.2 (CH), 111.0 (CH), 120.3 (CH), 124.5 (CH), 130.0 (Cq), 130.1 (CH), 133.2 (CH), 142.8 (CH), 143.9 (Cq), 148.4 (Cq), 150.2 (Cq), 168.0 (C=O), 170.6 (C=O). Anal. Calcd for $C_{17}H_{12}INO_4$ (421.19): C, 38.48; H, 2.87; N, 3.33. Found: C, 38.50; H, 2.90; N, 3.37.

2'-(1-Phenylethyl)-5(*E*)-iodomethylidene-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (14a). yield: 72%; Min: White solid; mp 126-128 °C; IR (ν, cm^{-1}, $CHCl_3$) 1662, 1707; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.02 (d, *J* = 7.0 Hz, 3H), 3.17 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 3.21 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 4.62 (q, *J* = 7.0 Hz, 1H), 6.14 (t, *J* = 2.3 Hz, 1H), 7.27-7.40 (m, 4H), 7.41-7.51 (m, 2H), 7.52-7.65 (m, 2H), 7.83-7.93 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 17.2 (CH_3), 36.7 (CH_2), 50.5 (CH), 56.4 (CH), 68.2 (Cq), 120.1 (CH), 124.2 (CH), 127.0 (2CH), 128.0 (CH), 128.9 (2CH), 130.2 (CH), 131.5 (Cq), 133.0 (CH), 140.2 (Cq), 144.5 (Cq), 149.9 (Cq), 168.3 (C=O), 172.3 (C=O). Anal. Calcd for $C_{20}H_{16}INO_3$ (445.26): C, 53.95; H, 3.62; N, 3.15. Found: C, 53.93; H, 3.63; N, 3.12.

2'-(1-Phenylethyl)-5(*E*)-iodomethylidene-4,5-dihydrospiro[furan-1',3-isoindol-3'-one]-2-one (14b). Maj: White solid; mp155-157 °C; IR (ν, cm^{-1}, $CHCl_3$) 1661, 1707; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.78 (d, *J* = 7.0 Hz, 3H), 2.83 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H),2.97 (dd, *J* = 2.3 Hz, *J* = 18 Hz, 1H), 5.80 (q, *J* = 7.0 Hz, 1H), 6.08 (t, *J* = 2.3 Hz, 1H), 7.28-7.49 (m, 5H), 7.51-7.67 (m, 3H), 7.84-7.98 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 19.8 (CH_3), 37.0 (CH_2), 55.6 (CH), 56.0 (CH), 70.7 (Cq), 119.8 (CH), 124.4 (CH), 127.1 (2CH), 127.8 (CH), 128.8 (2CH), 130.1 (CH), 130.3 (Cq), 133.1 (CH), 140.8 (Cq), 143.3 (Cq), 150.0 (Cq), 168.5 (C=O), 171.4 (C=O). Anal. Calcd for $C_{20}H_{16}INO_3$ (445.26): C, 53.95; H, 3.62; N, 3.15. Found: C, 53.92; H, 3.64; N, 3.18.

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