A Journal of

Accepted Article

Title: Metal-Free Protocol for the Arylation-Lactonization Sequence of γ -Alkenoic Acids using Anilines as Aryl Radical Sources

Authors: Diego Felipe-Blanco and Jose Carlos Gonzalez-Gomez

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201901679

Link to VoR: <http://dx.doi.org/10.1002/ejoc.201901679>

Supported by

WILEY-VCH

FULL PAPER

Metal-Free Protocol for the Arylation-Lactonization Sequence of γ -Alkenoic Acids using Anilines as Aryl Radical Sources

Diego Felipe-Blanco,^[a] and Jose C. Gonzalez-Gomez^{*[a]}

Dedication ((optional))

Abstract: The presence of salicylic acid (10 mol-%) and H₂O (10 equiv) significantly improves the arylation-lactonization sequence of γ -alkenoic acids with *in situ* formed diazonium salts (from bench stable anilines). The reaction is finished in less than 5 h without thermal or photochemical activation, giving access to a variety of γ,γ -disubstituted butyrolactones. The protocol is user-friendly and can be used at gram-scale or adapted to transform alkenols into phthalanes. Control experiments revealed that aryl radicals participate in the reaction and a plausible mechanism is proposed to include this and other mechanistic investigations, for the catalyzed and the background reaction.

Introduction

One of the most common and recurrent motifs found in pharmaceutical and bioactive compounds is the γ -butyrolactone ring. The corresponding heterocyclic derivatives, natural and unnatural, have received significant attention due to their relevant bioactivities.^[1] For instance, Noscapine is a non-narcotic alkaloid extracted from the opium family, which is used as an antitussive (Figure 1). More recently, this compound has shown a variety of therapeutic applications, without showing side effects or addictive properties, and analogs of this compound have also been prepared and examined as bioactive compounds.^[2] Another example is Eplerenone, which is used in the treatment of heart failure or hydropic decompensation in patients with hepatic disease.^[3] Moreover, phthalanes which can be considered as derivatives of benzo- γ -butyrolactones, are also present in a variety of pharmacologically active compounds.^[4] Among these compounds are found Citalopram and Talopram (Figure 1), potent selective serotonin reuptake and norepinephrine transporters inhibitors, respectively.^[5]

Given their important bioactivities, intense efforts have been dedicated in recent years to the development of new methodologies to prepare γ -butyrolactone derivatives. Many of these methods rely on the direct intramolecular cyclization of γ,δ -unsaturated carboxylic acids, which are readily available starting materials.^[6] Important advances have been achieved in the hydrolactonization,^[7] halolactonization,^[8] trifluoromethyl-

lactonization,^[9] or aminolactonization,^[10] however, only a few examples of carbolactonizations have been reported.^[11] In this context, the arylation-lactonization of pent-4-enoic acids has been recently investigated to obtain the corresponding γ -butyrolactones.

Figure 1. Bioactive molecules bearing a γ -butyrolactone or phthalane ring.

For example, the group of Fagnoni reported in 2006 that aryl halides (or pseudohalides) with electron-donating groups react efficiently with pen-4-enoic acid derivatives under UV irradiation, through a triplet aryl cation, to give the corresponding γ -butyrolactones (Scheme 1a).^[12] In 2010 the Zhang group developed a gold-catalyzed protocol, where aryl boronic acids were added and Selectfluor was used as the terminal oxidant to obtain the key Ph-Au(III) intermediate that activates the alkene for the carbocyclization (Scheme 1b).^[13] More recently the use of arylboronic acids and stoichiometric amounts of Mn(OAc)₃ was also described. Mechanistically, it was proposed that the *in situ* formed aryl radicals adds to alkenoic acids, leading to a new radical that upon single-electron oxidation, undergo efficient cyclization (Scheme 1b).^[14] Moreover, the Xiao group reported that aryl diazonium salts can be photocatalytically reduced at -20 °C using a ruthenium catalyst, to obtain aryl radicals that were trapped by alkenoic acids, affording γ,γ -disubstituted butyrolactones after SET and cyclization (Scheme 1c).^[15] Most of these direct and well-designed carbolactonizations require either high energy UV light or noble-metal catalysts, which are often moisture or light-sensitive, expensive, and toxic. Furthermore, in most cases, heating or cooling the reaction mixture is necessary

[a] M.Sc. D. Felipe-Blanco, Prof. J. C. Gonzalez-Gomez
Instituto de Síntesis Orgánica (ISO) y Departamento de Química
Orgánica, Universidad de Alicante,
Apdo. 99, 03080 Alicante, Spain
E-mail: josecarlos.gonzalez@ua.es
<http://iso.ua.es>

Supporting information for this article is given via a link at the end of the document. ((Please delete this text if not appropriate))

FULL PAPER

to obtain the best results, with the consequent energetic cost, especially to run the reactions at large scale.

a) UV-promoted (limited to electron rich aryl substrates)

b) Transition-metal-mediated

c) Photoredox catalysis with visible light

d) **This work:** Metal-free organocatalysis

Scheme 1. Preparation of γ -butyrolactones by arylation-lactonization of pent-4-enoic acids.

Inspired by the work of Carrillo and co-workers,^[16] we have recently developed the hydrodeamination of *in-situ* formed diazonium salts, catalyzed by salicylic acid (SA) and using THF as the hydrogen donor.^[17] We also used this simple and environmentally friendly generation of aryl radicals to obtain α -aryl ketones from enol acetates and anilines.^[18] As part of our ongoing program, we describe herein the first example of metal-free organocatalyzed arylation-lactonization of 4-alkenoic acids to obtain γ,γ -disubstituted butyrolactones at 20 °C (Scheme 1d).

Results and Discussion

To test our hypothesis, we selected 2-(1-phenylvinyl)benzoic acid (**1a**) and 4-chloroaniline (**2a**) as model substrates to examine the arylation-lactonization and optimize reaction conditions (Table 1). To our surprise, the background reaction proceeded in significant extension in the absence of any catalyst or additive, affording the product **3aa** (entry 1). As previously found by other authors in a similar arylation-lactonization sequence,^[15] the addition of H₂O to the solvent mixture had a positive impact on the reaction yield, being acetonitrile better solvent than acetone (entries 2-4). Following our previous works,^[17,18] we examined the addition of 10 mol-% of SA (entry 5), obtaining superior yields when 10 equivalents of H₂O were also added (entries 6 and 7). Aware by

the work of other authors that the transformation of *in-situ* formed diazonium salts into aryl radicals^[19] could also be promoted by inorganic bases,^[20] we examined the influence of sodium carbonate, potassium carbonate and potassium acetate (entries 8-10). Since all these promoters were examined in stoichiometric amounts, we added 100 equivalents of H₂O to improve their solubility in the reaction media, but the reaction yields were lower than with substoichiometric amounts of SA (entry 7). Increasing the amount of aniline **2a** up to 3 equivalents resulted in a similar reaction yield, but with a significant increase in the formation of biphenyls and other byproducts (entry 11). Additionally, it was demonstrated that the formation of the diazonium salt *prior* to the addition of **1a** was not beneficial for the performance of the reaction (entry 12). It is worth mentioning that the oxyarylation of styrenes with diazonium salts is well preceded. However, slow addition of diazonium salts, high temperatures and a large excess of styrenes are required to minimize the unselective attack of aryl radicals onto unconverted diazonium salts.^[21] Knowing that the decomposition of arene diazonium salts to give aryl radicals can be promoted by the light ($\lambda > 360$ nm),^[22] we also demonstrated that the ambient light was not playing any important role in this reaction (entry 13).

Table 1. Optimization of the reaction conditions.

Entry	Solvent	Promoter (mol-%)	Additive (equiv)	Yield (%) ^[a]
1	CH ₃ CN	-	-	30
2	CH ₃ CN	-	H ₂ O (10)	42
3	CH ₃ CN	-	H ₂ O (100)	45
4	acetone	-	H ₂ O (100)	35
5	CH ₃ CN	SA (10)	-	54 (50)
6	CH ₃ CN	SA (10)	H ₂ O (100)	42
7	CH ₃ CN	SA (10)	H ₂ O (10)	60 (57)
8	CH ₃ CN	Na ₂ CO ₃ (100)	H ₂ O (100)	45
9	CH ₃ CN	K ₂ CO ₃ (100)	H ₂ O (100)	52
10	CH ₃ CN	KOAc (200)	H ₂ O (100)	52
11 ^[b]	CH ₃ CN	SA (10)	H ₂ O (10)	60
12 ^[c]	CH ₃ CN	SA (10)	H ₂ O (10)	40
13 ^[d]	CH ₃ CN	-	-	32

^[a] Determined by GC, using adamantane as the internal standard. In parentheses are the yields of isolated pure **3aa**. ^[b] Using 3 equivalents of **2a**, higher amounts of byproducts were observed. ^[c] Preforming the diazonium salt 15 minutes before the addition of **1a**. ^[d] Protected from light.

FULL PAPER

With the optimized conditions in hand, we first explored the reactivity of various anilines with 2-(1-phenylvinyl)benzoic acid (**1a**) as the reaction partner. Importantly, all alkenoic acids used (**1a** – **1l** and **1p**) were readily prepared in two steps by Friedel-Crafts acylation of arenes with the corresponding carboxylic anhydrides, followed by a Wittig reaction with a phosphonium ylide (details are given in the SI). As depicted in Scheme 2, different electron-withdrawing groups such as nitro, halogens, trifluoromethyl, ester, or nitrile in *para*-position of the aromatic ring of the aniline, were very well tolerated affording the corresponding products (**3aa** to **3af**) in yields from moderate-to-good. Moreover, some of these substituents were also examined at different positions of the aniline, affording the corresponding products (**3aj** and **3ak**) in similar good yields. Importantly, using the same reaction conditions, compound **3ak** was obtained in gram-scale with excellent yield. Interestingly, unsubstituted anilines or with electron-donating substituents, were also suitable substrates under our reaction conditions, affording the corresponding products (**3ag**, **3ah** and **3ai**) in synthetically useful yields, despite the reported lower reactivity for their corresponding diazonium salt intermediates.^[23] Disubstituted anilines and heteroaromatic amines gave the corresponding lactones (**3al** and **3am**) in moderate yields. The suitability of iodine-bearing aniline **2l** with this protocol is relevant because iodine transfer is well established in radical chemistry^[24] and provides a handle for further transformation of **3al** using palladium coupling chemistry. It is worth noting that we have also checked the positive impact of the salicylic acid in the formation of compounds **3ak** and **3am**. In addition, the arylation-lactonization reaction was also applicable to a variety of alkenoic acids, bearing either electron-donating or electron-withdrawing groups on both aromatic rings. Regardless of the electronic nature of substituents on aromatic rings-A or B of the alkenoic acids, the corresponding products (**3bb** – **3jb**) were obtained in good yields. Notably, benzoic acid **1b** with a greater steric demand due to a methyl group in *ortho*-position also afforded the product **3gb** in good yield. It is worth noting that the previous starting materials are 1,1-diphenylethylenes, which are well suited to trap an aryl radical. However, when alkenoic acids without an aromatic ring-B were employed as starting materials, the reaction also took place to give the corresponding lactones in moderate-to-good yields (**3kb**, **3lb**). Interestingly, the structure of compound **3kb** (with three contiguous stereogenic centers), was unambiguously elucidated by X-ray diffraction analysis, confirming the epimerization of the CH adjacent to the ester group during the preparation of **1k**.^[25] Notably, the Weinreb-amide **1m** was also successfully transformed into the imide **3mb** through a chemoselective O-cyclization. Importantly, alcohols were also suitable substrates to carry out the arylation-cyclization sequence to obtain the corresponding phthalanes. In this case, the protocol was more efficient for the tertiary alcohol **1n** than for primary **1o**, most likely because the two methyl groups favored the cyclization according to the Thorpe-Ingold effect.^[26] Moreover, the internal alkenoic acid **1p** was also a suitable substrate, obtaining the product **3pb** in a low yield, but with excellent relative stereocontrol of the two contiguous stereocenters formed.

Scheme 2. Scope of the reaction. Yields are reported for isolated pure products.

^[a] The reaction was run in the absence of SA. ^[b] It was prepared in gram-scale (1.38 g) from 5 mmol of **1a**. ^[c] Only one diastereoisomer observed by ¹H-NMR.

To gain insight into the reaction pathway, some control experiments were conducted. As shown in Scheme 3a, we replaced H₂O by H₂O¹⁸ to investigate the source of the oxygen atom in the lactone ring, observing no incorporation of O¹⁸ in the product **3ab**, according to GC-MS. To validate the radical pathway, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added into the catalytic system. The reaction was totally inhibited, and we could isolate TEMPO-captured compound **4** in 62% yield, which clearly

FULL PAPER

supports the formation of the aryl radical. Moreover, for a better understanding of the reactivity of these aryl radicals, some competition experiments were carried out. One experiment was conducted with a 1:1 mixture of *p*-nitroaniline (**2b**) and aniline (**2i**) under standard conditions, and the reaction was stopped after 1 h to ensure low conversion. A similar competition experiment was carried out using an equimolar mixture of *p*-anisidine and aniline. The results shown in Scheme 3c suggest that electron-withdrawing substituents in the aniline ring accelerate the studied reaction, which is in accordance with a decrease of a positive charge during the generation of aryl radicals from a cationic intermediate.^[23] Finally, when we submitted the **ester-1a** to react with aniline **2a** under our optimized conditions, we also obtained the lactone **3aa** in moderate yield. However, when the same experiment was run in the absence of salicylic acid, only product **5** was isolated in a rather low yield (Scheme 3d). These experiments suggest that the SA might also accelerate the final cyclization step.

Scheme 3. Mechanistic investigation.

According to our mechanistic investigations and considering other previously reported studies in similar transformations,^{[14-18], [21], [27]} we propose the mechanism depicted in Scheme 4. On one hand,

the nucleophilic addition of the salicylic acid to the *in-situ* formed aryl diazonium salt **A** could afford the aryl diazobenzoate **B** (pathway A).^[28] The N-O homolytic bond cleavage of this intermediate might be facilitated by the formation of stable N₂ and the H-bond stabilized salicyloyl radical, leading also to the aryl radical **C**. On the other hand, the background reaction might proceed through nucleophilic addition of the alkenoic acid **1** to the diazonium salt to give the aryl diazobenzoate **I** (pathway B). Fragmentation of this intermediate might occur in a similar way to the one proposed for **B**, providing the aryl radical **C** and radical intermediate **II**, which could rapidly be transformed into starting material **1** by hydrogen atom abstraction ($k \approx 10^7 \text{ M}^{-1}\text{s}^{-1}$).^[29] The addition of the electrophilic aryl radical **C** to alkenoic acid **1** should give the benzyl radical **D** (Meerwein arylation), which could be oxidized to the benzylic cation **E**, either *via* SET to the salicyloyl radical in a closed catalytic cycle, or by the diazonium salt **A** to propagate a radical chain reaction. The final cyclization should be followed by deprotonation to give the product **3**. The positive impact of H₂O in the reaction might be associated with better solvation of cations **A** and **E**. A reversible addition/elimination of H₂O to intermediate **E** could also favor the cyclization step, which is also consistent with no incorporation of O-atoms from H₂O in the lactone ring.^[30]

Conclusions

We have developed a metal-free protocol that provides direct access to sterically hindered benzo- γ -butyrolactone derivatives from bench stable anilines, without photochemical or thermal activation. The reaction is completed in less than 5 h at 20 °C, using only 10 mol-% of inexpensive and benign salicylic acid and H₂O (10 equiv) as additives. Under these mild reaction conditions, a wide range of substituted alkenoic acids and anilines are tolerated, as well as alkenols to give phthalanes or amides to obtain imidates. Remarkably, the protocol is operationally very simple and can be used to obtain the desired products in gram-scale.

FULL PAPER

Scheme 4. Plausible mechanism.

Experimental Section

General Remarks: Commercial chemicals were used as obtained from Sigma-Aldrich, TCI Europe or Alfa-Aesar. The preparation of starting material not obtained from commercial sources is detailed below. TLCs were performed on silica gel 60 F254, using aluminum plates and visualized by exposure to ultraviolet light. Flash chromatographies were carried out on hand-packed columns of silica gel 60 (230–400 mesh). Infrared (IR) spectra were recorded with a spectrophotometer equipped with an ATR component; wavenumbers are given in cm^{-1} . Product yields were determined by GC-FID (6890 Agilent, HP-5 30 m column) using adamantane as the internal standard. LRMS were obtained using a mass spectrometer coupled with a gas chromatograph (GC); the mobile phase was helium (2 mL min^{-1}); HP-1 column of 12 m was used; temperature program starts at 80°C for 3 min, then up to 270°C at a rate of $15^\circ\text{C min}^{-1}$, and 15 min at 270°C (unless other conditions are indicated). ^1H -NMR spectra were recorded at 300 or 400 MHz for ^1H -NMR and 75 or 101 MHz for ^{13}C -NMR, using CDCl_3 as solvent and TMS as an internal standard (0.00 ppm). HRMS analyses were also carried out in the electron impact mode (EI) at 70 eV using a quadrupole mass analyzer or in the electrospray ionization mode (ESI) using a TOF analyzer. The data are reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br s = broad signal, coupling constant(s) in Hz, integration). ^{13}C -NMR spectra were recorded with ^1H -decoupling at 101 MHz and referenced to CDCl_3 at 77.16 ppm.

General procedure for the arylation-lactonization reaction: The corresponding alkenoic derivative (0.30 mmol), the substituted aniline (0.60 mmol) and the salicylic acid (4.14 mg, 0.03 mmol) were added into an oven dried Schlenck. The system was evacuated and filled with argon (three times) before the solvent MeCN (2.5 mL) and the additive H_2O (56 μL , 3.0 mmol) were added. The reaction mixture was stirred vigorously until a homogeneous solution was obtained (1–5 min). At this point, *tert*-butylnitrite (100 μL , 86 mg, 0.75 mmol) was added (the solution turned from orange to deep red after some minutes) and the stirring continued for 5 h, keeping the temperature at 20°C with an external water bath. At this time, EtOAc (25 mL) was added and the organic layer were collected and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give the desired product.

3-(4-Chlorobenzyl)-3-phenylisobenzofuran-1(3H)-one (3aa): Following the general procedure with substrates **1a** and 4-chloroanilines (**2a**), compound **3aa** was obtained after column chromatography (from 90:10 to 80:20 hexane/EtOAc) as an orange oil (57.3 mg, 0.17 mmol, 57%). TLC (hexane/EtOAc 80:20): $R_f = 0.44$; ^1H -NMR (300 MHz, CDCl_3): $\delta = 7.69$ (ddd, $J = 7.7, 6.7, 1.1$ Hz, 2H), 7.65 – 7.53 (m, 3H), 7.47 – 7.31 (m, 4H), 7.05 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 2H), 3.68 (d, $J = 14.0$ Hz, 1H), 3.55 (d, $J = 14.0$ Hz, 1H) ppm; ^{13}C -NMR (75 MHz, CDCl_3): $\delta = 169.6$ (CO), 151.4 (C), 140.0 (C), 134.1 (CH), 133.1 (C), 132.5 (C), 132.0 (2xCH), 129.4 (CH), 128.9 (2xCH), 128.6 (CH), 128.2 (2xCH), 126.04 (C), 125.94 (CH), 125.4 (2xCH), 122.7 (CH), 89.41 (C), 45.8 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{21}\text{H}_{16}\text{O}_2\text{Cl}$ [$\text{M}^+ + \text{H}$] 335.0839, found 335.0828; IR (ATR): $\nu = 1772, 1286, 1230, 1063, 778, 669 \text{ cm}^{-1}$.

FULL PAPER

3-(4-Nitrobenzyl)-3-phenylisobenzofuran-1(3H)-one (3ab): Following the general procedure with substrates **1a** and 4-nitroaniline (**2b**), compound **3ab** was obtained after column chromatography (from 90:10 to 70:30 hexane/EtOAc) as a yellow solid (85 mg, 0.25 mmol, 82%). TLC (hexane/EtOAc 70:30): R_f = 0.35; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.94 (d, J = 8.7 Hz, 2H), 7.74 – 7.64 (m, 3H), 7.59 – 7.53 (m, 2H), 7.46 (ddd, J = 8.1, 7.0, 1.3 Hz, 1H), 7.42 – 7.30 (m, 3H), 7.19 – 7.10 (J = 8.7 Hz, 2H), 3.84 (d, J = 13.9 Hz, 1H), 3.66 (d, J = 13.9 Hz, 1H) ppm; $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ = 169.1 (CO), 151.1 (C), 147.0 (C), 141.7 (C), 139.5 (C), 134.3 (CH), 131.5 (2xCH), 129.6 (CH), 128.93 (2xCH), 128.68 (CH), 126.0 (CH), 125.7 (C), 125.1 (2xCH), 123.0 (2xCH), 122.5 (CH), 88.8 (C), 46.1 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{21}\text{H}_{16}\text{NO}_4$ [M^+ + H] 346.1079, found 346.1072; IR (ATR): ν = 1779, 1582, 1448, 1352, 1170 cm^{-1} .

3-(4-Bromobenzyl)-3-phenylisobenzofuran-1(3H)-one (3ac): Following the general procedure with substrates **1a** and 4-bromoaniline (**2c**), compound **3ac** was obtained after column chromatography (from 90:10 to 80:20 hexane/EtOAc) as an orange oil (67.1 mg, 0.18 mmol, 59%). TLC (hexane/EtOAc 80:20): R_f = 0.40; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.71 (dt, J = 7.6, 1.0 Hz, 1H), 7.66 (td, J = 7.5, 1.1 Hz, 1H), 7.61 – 7.53 (m, 3H), 7.44 (td, J = 7.4, 1.0 Hz, 1H), 7.41 – 7.29 (m, 3H), 7.20 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 3.66 (d, J = 14.0 Hz, 1H), 3.53 (d, J = 14.0 Hz, 1H) ppm; $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ = 169.5 (CO), 151.4 (C), 140.0 (C), 134.1 (CH), 133.0 (C), 132.4 (2xCH), 131.1 (2xCH), 129.4 (CH), 128.9 (2xCH), 128.6 (CH), 126.06 (C), 125.98 (CH), 125.36 (2xCH), 122.7 (CH), 121.3 (C), 89.3 (C), 45.3 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{21}\text{H}_{16}\text{O}_2\text{Br}$ [M^+ + H] 379.0334, found 379.0325; IR (ATR): ν = 1778, 1592, 1488, 1448, 1405, 1168 cm^{-1} .

4-((3-Oxo-1-phenyl-1,3-dihydroisobenzofuran-1-yl)methyl)benzonitrile (3ad): Following the general procedure with substrates **1a** and 4-aminobenzonitrile (**2d**), compound **3ad** was obtained after column chromatography (from 90:10 to 70:30 hexane/EtOAc) as an off white solid (83.2 mg, 0.26 mmol, 85%). TLC (hexane/EtOAc 80:20): R_f = 0.32; M.P. (hexane/EtOAc 90:10): 125–127 °C; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.75 – 7.65 (m, 2H), 7.63 (dt, J = 7.8, 1.0 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.47 (td, J = 7.5, 1.1 Hz, 1H), 7.42 – 7.29 (m, 5H), 7.08 (d, J = 8.2 Hz, 2H), 3.78 (d, J = 13.9 Hz, 1H), 3.61 (d, J = 13.9 Hz, 1H) ppm; $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ = 169.2 (CO), 151.3 (C), 139.66 (C), 139.63 (C), 134.3 (CH), 131.8 (2xCH), 131.5 (2xCH), 129.7 (CH), 129.0 (2xCH), 128.8 (CH), 126.12 (CH), 125.87 (C), 125.3 (2xCH), 122.6 (CH), 118.8 (C), 111.2 (CH), 89.0 (C), 46.5 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{22}\text{H}_{16}\text{NO}_2$ [M^+ + H] 326.1181, found 335.1173; IR (ATR): ν = 1779, 2225, 1582, 1448, 1352, 1170 cm^{-1} .

Methyl 4-((3-oxo-1-phenyl-1,3-dihydroisobenzofuran-1-yl)methyl)benzoate (3ae): Following the general procedure with substrates **1a** and methyl 4-aminobenzoate (**2e**), compound **3ae** was obtained after column chromatography (from 95:5 to 80:20 hexane/EtOAc) as pale yellow solid (66.6 mg, 0.19 mmol, 62%). TLC (hexane/EtOAc 80:20): R_f = 0.44; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.75 (d, J = 8.3 Hz, 2H), 7.66 (td, J = 7.3, 1.1 Hz, 2H), 7.61 (dt, J = 7.1, 1.2 Hz, 1H), 7.59 – 7.55 (m, 2H), 7.45 – 7.30 (m, 4H), 7.03 (d, J = 8.4 Hz, 2H), 3.84 (s, 3H), 3.76 (d, J = 13.9 Hz, 1H), 3.63 (d, J = 13.8 Hz, 1H) ppm; $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ = 169.4 (CO), 167.0 (CO_2Me), 151.4 (C), 139.95 (C), 139.36 (C), 134.1 (CH), 130.8 (2xCH), 129.43 (CH), 129.24 (2xCH), 128.91 (2xCH + C), 128.61 (CH), 126.00 (C), 125.93 (CH), 125.35 (2xCH), 122.8 (CH), 89.3 (C), 52.1 (CH_3), 46.5 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{23}\text{H}_{19}\text{O}_4$ [M^+ + H] 359.1283, found 359.1279; IR (ATR): ν = 1780, 1767, 1603, 1537, 1437, 1416, 1257, 1191 cm^{-1} .

3-Phenyl-3-(4-(trifluoromethyl)benzyl)isobenzofuran-1(3H)-one (3af): Following the general procedure with substrates **1a** and 4-

(trifluoromethyl)aniline **2f**, compound **3af** was obtained after column chromatography (from 95:5 to 80:20 hexane/EtOAc) as grey solid (87.3 mg, 0.24 mmol, 79%). TLC (hexane/EtOAc 80:20): R_f = 0.52; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.72 – 7.63 (m, 3H), 7.60 – 7.56 (m, 2H), 7.44 (td, J = 7.3, 1.3 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.36 – 7.31 (m, 3H), 7.08 (d, J = 8.0 Hz, 2H), 3.78 (d, J = 13.9 Hz, 1H), 3.63 (d, J = 14.0 Hz, 1H) ppm; $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ = 169.4 (CO), 151.3 (C), 139.7 (C), 138.1 (C), 134.2 (CH), 131.0 (2xCH), 129.4 (CH), 129.16 (q, J = 32.5 Hz) (C), 128.9 (2xCH), 128.6 (CH), 125.9 (CH), 125.8 (C), 125.2 (2xCH), 124.79 (q, J = 3.8 Hz) (CH), 124.05 (q, J = 272.0 Hz) (CF_3), 122.6 (CH), 89.1 (C), 46.1 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{22}\text{H}_{16}\text{F}_3\text{O}_2$ [M^+ + H] 369.1102, found 369.1108; IR (ATR): ν = 1777, 1604, 1510, 1448, 1418, 1224, 1160 cm^{-1} .

3-(4-Methoxybenzyl)-3-phenylisobenzofuran-1(3H)-one (3ag): Following the general procedure with substrates **1a** and *p*-anisidine (**2g**), compound **3ag** was obtained after column chromatography from 95:5 to 80:20 hexane/EtOAc) as an off white solid (46.5 mg, 0.14 mmol, 47%). TLC (hexane/EtOAc 80:20): R_f = 0.37; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.70 – 7.66 (m, 1H), 7.65 – 7.62 (m, 1H), 7.60 – 7.55 (m, 3H), 7.43 (dd, J = 7.5, 1.0 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.35 – 7.30 (m, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.61 (d, J = 8.7 Hz, 2H), 3.69 (s, 3H), 3.64 (d, J = 14.1 Hz, 1H), 3.55 (d, J = 14.1 Hz, 1H) ppm; $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ = 169.9 (CO), 158.7 (C), 151.8 (C), 140.4 (C), 134.0 (C), 131.9 (2xCH), 129.3 (CH), 128.9 (2xCH), 128.5 (CH), 126.4 (C), 126.02 (C), 125.9 (CH), 125.6 (2xCH), 123.0 (CH), 113.5 (2xCH), 89.9 (C), 55.3 (CH_3), 45.84 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{22}\text{H}_{19}\text{O}_3$ [M^+ + H] 331.1334, found 331.1333; IR (ATR): ν = 1775, 1611, 1513, 1448, 1247, 1178 cm^{-1} .

3-(4-Methylbenzyl)-3-phenylisobenzofuran-1(3H)-one (3ah): Following the general procedure with substrates **1a** and *p*-toluidine **2h**, compound **3ah** was obtained after column chromatography (from 95:5 to 80:20 hexane/EtOAc) as a white solid (48.2 mg, 0.15 mmol, 51%). TLC (hexane/EtOAc 90:10): R_f = 0.40; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.70 – 7.62 (m, 2H), 7.59 (dq, J = 7.0, 1.4 Hz, 3H), 7.44 – 7.35 (m, 3H), 7.35 – 7.29 (m, 1H), 6.88 (d, J = 7.9 Hz, 2H), 6.82 (d, J = 8.0 Hz, 2H), 3.66 (d, J = 14.0 Hz, 1H), 3.57 (d, J = 14.0 Hz, 1H), 2.20 (s, 3H) ppm; $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ = 169.8 (CO), 151.7 (C), 140.4 (C), 136.6 (C), 133.8 (CH), 130.78 (C), 130.66 (2xCH), 129.14 (CH), 128.81 (2xCH), 128.70 (2xCH), 128.42 (CH), 126.26 (C), 125.76 (CH), 125.48 (2xCH), 122.9 (CH), 89.8 (C), 46.2 (CH_2), 21.1 (CH_3) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{22}\text{H}_{19}\text{O}_2$ [M^+ + H] 315.1385, found 315.1381; IR (ATR): ν = 1777, 1602, 1514, 1495, 1448, 1167 cm^{-1} .

3-Benzyl-3-phenylisobenzofuran-1(3H)-one (3ai): Following the general procedure with substrates **1a** and aniline (**2i**), compound **3ai** was obtained after column chromatography (from 90:10 to 80:20 hexane/EtOAc) as an off white solid (57.3 mg, 0.17 mmol, 53%). TLC (hexane/EtOAc 80:20): R_f = 0.45; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 7.66 (ddd, J = 8.5, 7.2, 1.1 Hz, 2H), 7.62 – 7.57 (m, 3H), 7.46 – 7.30 (m, 4H), 7.09 (dd, J = 5.0, 2.0 Hz, 3H), 6.95 (td, J = 4.9, 4.3, 3.1 Hz, 2H), 3.72 (d, J = 13.9 Hz, 1H), 3.60 (d, J = 13.9 Hz, 1H) ppm; $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ = 169.7 (CO), 151.6 (C), 140.3 (C), 133.94 (C), 133.91 (CH), 130.80 (2xCH), 129.2 (CH), 128.8 (2xCH), 128.5 (CH), 128.0 (2xCH), 127.1 (CH), 126.2 (C), 125.74 (CH), 125.47 (2xCH), 122.9 (CH), 89.7 (C), 46.6 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{21}\text{H}_{17}\text{O}_2$ [M^+ + H] 301.1229 found 301.1219; IR (ATR): ν = 1778, 1598, 1492, 1448, 1409, 1168, 787 cm^{-1} .

3-Phenyl-3-(3-(trifluoromethyl)benzyl)isobenzofuran-1(3H)-one (3aj): Following the general procedure with substrates **1a** and 3-(trifluoromethyl)aniline (**2j**), compound **3aj** was obtained after column chromatography (from 90:10 to 80:20 hexane/EtOAc) as a dark orange oil (67.3 mg, 0.18 mmol, 61%). TLC (hexane/EtOAc 80:20): R_f = 0.38; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.63 – 7.58 (m, 2H), 7.57 – 7.53 (m, 1H), 7.53

FULL PAPER

– 7.48 (m, 2H), 7.39 – 7.32 (m, 2H), 7.32 – 7.23 (m, 4H), 7.19 – 7.16 (m, 2H), 6.96 (s, 1H), 3.68 (d, $J = 14.0$ Hz, 1H), 3.55 (d, $J = 14.0$ Hz, 1H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): $\delta = 169.4$ (CO), 151.2 (C), 139.7 (C), 134.9 (C), 134.28 (C), 134.19 (CH), 130.15 (q, $J = 32.1$ Hz) (C), 129.5 (CH), 128.96 (2xCH), 128.68 (CH), 128.51 (CH), 127.34 (q, $J = 3.9$ Hz) (CH), 126.02 (C), 125.94 (CH), 125.35 (2xCH), 123.94 (q, $J = 272.4$ Hz) (CF_3), 123.93 (q, $J = 4.0$ Hz) (C), 122.7 (CH), 89.2 (C), 46.3 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{22}\text{H}_{16}\text{O}_2\text{F}_3$ [$\text{M}^+ + \text{H}$] 369.1102, found 335.1103; IR (ATR): $\nu = 1787, 1623, 1492, 1468, 1383, 1279, 1174, 1135$ cm^{-1} .

3-(2-Nitrobenzyl)-3-phenylisobenzofuran-1(3H)-one (3ak): Following the general procedure with substrates **1a** and 2-nitroaniline (**2k**), compound **3ak** was obtained after column chromatography (from 90:10 to 70:30 hexane/EtOAc) as a yellow solid (1.384 g, 4.00 mmol, 80%). TLC (hexane/EtOAc 70:30): $R_f = 0.39$; ^1H -NMR (300 MHz, CDCl_3): $\delta = 7.68$ – 7.60 (m, 4H), 7.60 – 7.53 (m, 2H), 7.45 – 7.31 (m, 6H), 7.29 – 7.21 (m, 1H), 4.38 (d, $J = 14.5$ Hz, 1H), 4.11 (d, $J = 14.5$ Hz, 1H) ppm; ^{13}C -NMR (75 MHz, CDCl_3): $\delta = 169.1$ (CO), 150.8 (C), 150.1 (C), 139.7 (C), 134.6 (CH), 134.2 (CH), 132.5 (CH), 129.51 (CH), 128.97 (2xCH), 128.93 (C), 128.7 (CH), 128.37 (CH), 125.70 (CH), 125.52 (C), 125.12 (2xCH), 124.8 (CH), 122.8 (CH), 89.2 (C), 41.4 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{21}\text{H}_{16}\text{NO}_4$ [$\text{M}^+ + \text{H}$] 346.1079, found 346.1073; IR (ATR): $\nu = 2952, 1762, 1602, 1520, 1345, 1170, 776$ cm^{-1} .

3-Iodo-4-((3-oxo-1-phenyl-1,3-dihydroisobenzofuran-1-yl)methyl)benzonitrile (3al): Following the general procedure with substrates **1a** and 4-amino-3-iodobenzonitrile (**2l**), compound **3al** was obtained after column chromatography (from 90:10 to 70:30 hexane/EtOAc) as a yellow solid (70.4 mg, 0.17 mmol, 52%). TLC (hexane/EtOAc 80:20): $R_f = 0.32$; ^1H -NMR (400 MHz, CDCl_3): $\delta = 7.98$ (d, $J = 1.7$ Hz, 1H), 7.78 (ddd, $J = 7.0, 1.9, 1.1$ Hz, 2H), 7.69 (td, $J = 7.5, 1.1$ Hz, 1H), 7.59 – 7.53 (m, 2H), 7.50 (td, $J = 7.5, 0.9$ Hz, 1H), 7.41 – 7.31 (m, 4H), 7.22 (d, $J = 8.1$ Hz, 1H), 4.02 (d, $J = 14.7$ Hz, 1H), 3.84 (d, $J = 14.7$ Hz, 1H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): $\delta = 169.0$ (CO), 151.0 (C), 143.25 (CH), 142.61 (CH), 139.2 (C), 134.2 (CH), 131.11 (CH), 131.06 (CH), 129.7 (CH), 128.94 (2xCH), 128.7 (CH), 125.9 (CH), 125.4 (C), 125.2 (2xCH), 123.3 (CH), 116.7 (C), 112.6 (CN), 102.6 (C), 89.2 (C), 50.0 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{22}\text{H}_{15}\text{INO}_2$ [$\text{M}^+ + \text{H}$] 452.0147, found 452.0159; IR (ATR): $\nu = 2952, 2225, 1762, 1602, 1520, 1242, 1170, 776$ cm^{-1} .

Methyl 3-((3-oxo-1-phenyl-1,3-dihydroisobenzofuran-1-yl)methyl)thiophene-2-carboxylate (3am): Following the general procedure with substrates **1a** and methyl 3-aminothiophene-2-carboxylate (**2m**), compound **3am** was obtained after column chromatography (from 95:5 to 80:20 hexane/EtOAc) as a yellow solid (57 mg, 0.16 mmol, 52%). TLC (hexane/EtOAc 80:20): $R_f = 0.43$; ^1H -NMR (400 MHz, CDCl_3): $\delta = 7.69$ – 7.60 (m, 4H), 7.54 (td, $J = 7.6, 1.2$ Hz, 1H), 7.41 – 7.33 (m, 4H), 7.32 – 7.27 (m, 1H), 7.25 (d, $J = 5.1$ Hz, 1H), 7.01 (d, $J = 5.1$ Hz, 1H), 4.52 (d, $J = 14.4$ Hz, 1H), 4.06 (d, $J = 14.4$ Hz, 1H), 3.80 (s, 3H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): $\delta = 169.8$ (CO), 163.0 (CO_2Me), 151.7 (C), 142.8 (C), 140.2 (C), 133.7 (CH), 131.7 (CH), 130.3 (CH), 129.2 (CH), 128.79 (2xCH), 128.51 (C), 128.38 (CH), 125.44 (C), 125.41 (CH), 125.16 (2xCH), 123.2 (CH), 90.0 (C), 51.9 (CH_3), 38.3 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{21}\text{H}_{17}\text{O}_4\text{S}$ [$\text{M}^+ + \text{H}$] 365.0848, found 365.0845; IR (ATR): $\nu = 3061, 3029, 2995, 1780, 1707, 1603, 1537, 1437, 1416, 1257, 1191$ cm^{-1} .

3-(4-Nitrobenzyl)-3-(p-tolyl)isobenzofuran-1(3H)-one (3bb): Following the general procedure with substrates **1b** and 4-nitroaniline (**2b**), compound **3bb** was obtained after column chromatography (from 90:10 to 70:30 hexane/EtOAc) as a pale yellow solid (82.6 mg, 0.23 mmol, 75%). TLC (hexane/EtOAc 70:30): $R_f = 0.38$; ^1H -NMR (400 MHz, CDCl_3): $\delta =$

7.94 (d, $J = 8.7$ Hz, 2H), 7.69 (td, $J = 7.0, 1.2$ Hz, 2H), 7.65 – 7.62 (m, 1H), 7.49 – 7.39 (m, 3H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.14 (d, $J = 8.7$ Hz, 2H), 3.83 (d, $J = 13.9$ Hz, 1H), 3.64 (d, $J = 13.9$ Hz, 1H), 2.34 (s, 3H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): $\delta = 169.3$ (CO), 151.4 (C), 147.1 (C), 141.9 (C), 138.7 (C), 136.5 (C), 134.4 (CH), 131.6 (2xCH), 129.68 (2xCH), 129.60 (CH), 126.06 (CH), 125.8 (C), 125.2 (2xCH), 123.1 (2xCH), 122.6 (CH), 89.0 (C), 46.1 (CH_2), 21.1 (CH_3) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{22}\text{H}_{18}\text{NO}_4$ [$\text{M}^+ + \text{H}$] 360.1236, found 360.1223; IR (ATR): $\nu = 3052, 1768, 1576, 1542, 1415, 1335, 1190, 778$ cm^{-1} .

3-(4-Methoxyphenyl)-3-(4-nitrobenzyl)isobenzofuran-1(3H)-one (3cb): Following the general procedure with substrates **1c** and 4-nitroaniline (**2b**), compound **3cb** was obtained after column chromatography (from 90:10 to 70:30 hexane/EtOAc) as a yellow sticky oil (92.3 mg, 0.25 mmol, 82%). TLC (hexane/EtOAc 70:30): $R_f = 0.35$; ^1H -NMR (300 MHz, CDCl_3): $\delta = 7.93$ (d, $J = 8.7$ Hz, 2H), 7.74 – 7.66 (m, 2H), 7.60 (dt, $J = 8.0, 0.9$ Hz, 1H), 7.49 – 7.41 (m, 3H), 7.13 (d, $J = 8.7$ Hz, 2H), 6.89 (d, $J = 8.9$ Hz, 2H), 3.82 (d, $J = 14.0$ Hz, 1H), 3.79 (s, 3H), 3.62 (d, $J = 13.9$ Hz, 1H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): $\delta = 169.2$ (CO), 159.8 (C), 151.4 (C), 147.1 (C), 141.9 (C), 134.3 (CH), 131.60 (2xCH), 131.40 (C), 129.6 (CH), 126.8 (2xCH), 126.07 (CH), 125.9 (C), 123.1 (2xCH), 122.6 (CH), 114.3 (CH), 88.9 (C), 55.5 (CH_3), 46.2 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{21}\text{H}_{18}\text{NO}_5$ [$\text{M}^+ + \text{H}$] 376.1179, found 376.1177; IR (ATR): $\nu = 3098, 1777, 1596, 1539, 1398, 1345, 1190, 1002, 767$ cm^{-1} .

3-(4-Chlorophenyl)-3-(4-nitrobenzyl)isobenzofuran-1(3H)-one (3db): Following the general procedure with substrates **1d** and 4-nitroaniline (**2b**), compound **3db** was obtained after column chromatography (from 90:10 to 70:30 hexane/EtOAc) as a yellow solid (80.9 mg, 0.21 mmol, 71%). TLC (hexane/EtOAc 70:30): $R_f = 0.36$; ^1H -NMR (400 MHz, CDCl_3): $\delta = 7.98$ – 7.94 (m, 2H), 7.71 (ddd, $J = 7.4, 6.4, 1.3$ Hz, 2H), 7.63 (d, $J = 7.9$ Hz, 1H), 7.52 – 7.47 (m, 3H), 7.39 – 7.33 (m, 2H), 7.14 (d, $J = 8.7$ Hz, 2H), 3.80 (d, $J = 13.9$ Hz, 1H), 3.62 (d, $J = 13.9$ Hz, 1H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): $\delta = 168.9$ (CO), 150.8 (C), 147.2 (C), 141.3 (C), 138.2 (C), 134.9 (C), 134.58 (CH), 131.6 (2xCH), 129.93 (CH), 129.25 (2xCH), 126.73 (2xCH), 126.32 (2xCH), 125.7 (C), 123.3 (2xCH), 122.4 (CH), 88.4 (C), 46.2 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{21}\text{H}_{15}\text{NO}_4\text{Cl}$ [$\text{M}^+ + \text{H}$] 380.0690, found 380.0683; IR (ATR): $\nu = 1782, 1596, 1545, 1405, 1342, 1190, 1010, 778$ cm^{-1} .

3-(4-Nitrobenzyl)-3-(thiophen-2-yl)isobenzofuran-1(3H)-one (3eb): Following the general procedure with substrates **1e** and 4-nitroaniline (**2b**), compound **3eb** was obtained after column chromatography (from 90:10 to 70:30 hexane/EtOAc) as a pale yellow solid (66.5 mg, 0.19 mmol, 63%). TLC (hexane/EtOAc 70:30): $R_f = 0.38$; ^1H -NMR (400 MHz, CDCl_3): $\delta = 7.96$ (d, $J = 8.7$ Hz, 2H), 7.75 – 7.68 (m, 2H), 7.61 (dt, $J = 7.7, 0.9$ Hz, 1H), 7.50 (td, $J = 7.5, 0.9$ Hz, 1H), 7.33 (dd, $J = 5.1, 1.2$ Hz, 1H), 7.15 (d, $J = 8.7$ Hz, 2H), 7.09 (dd, $J = 3.6, 1.2$ Hz, 1H), 6.99 (dd, $J = 5.1, 3.6$ Hz, 1H), 3.91 (d, $J = 13.8$ Hz, 1H), 3.67 (d, $J = 13.9$ Hz, 1H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): $\delta = 168.6$ (CO), 150.4 (C), 147.2 (C), 142.8 (C), 141.2 (C), 134.5 (CH), 131.6 (2xCH), 130.1 (CH), 127.3 (CH), 126.54 (CH), 126.15 (CH), 125.93 (C), 125.66 (CH), 123.2 (2xCH), 122.6 (CH), 87.0 (C), 47.0 (CH_2) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{19}\text{H}_{14}\text{NO}_4\text{S}$ [$\text{M}^+ + \text{H}$] 352.0644, found 352.0635; IR (ATR): $\nu = 1780, 1603, 1537, 1345, 1250, 1183, 778$ cm^{-1} .

7-Methyl-3-(4-nitrobenzyl)-3-phenylisobenzofuran-1(3H)-one (3fb): Following the general procedure with substrates **1f** and 4-nitroaniline (**2b**), compound **3fb** was obtained after column chromatography (from 90:10 to 70:30 hexane/EtOAc) as an off white solid (77.6 mg, 0.22 mmol, 72%). TLC (hexane/EtOAc 70:30): $R_f = 0.46$; ^1H -NMR (300 MHz, CDCl_3): $\delta = 7.96$ (d, $J = 8.7$ Hz, 2H), 7.60 – 7.49 (m, 3H), 7.46 (dt, $J = 7.7, 0.8$ Hz, 1H), 7.44 – 7.27 (m, 3H), 7.21 (d, $J = 7.4$ Hz, 1H), 7.16 (d, $J = 8.7$ Hz, 2H), 3.81 (d, $J = 13.9$ Hz, 1H), 3.63 (d, $J = 13.9$ Hz, 1H), 2.54 (s, 3H) ppm; ^{13}C -NMR

FULL PAPER

(75 MHz, CDCl₃): δ = 169.4 (CO), 151.8 (C), 147.1 (C), 142.1 (C), 140.28 (C), 139.97 (C), 134.0 (CH), 131.6 (2xCH), 131.3 (CH), 129.0 (2xCH), 128.6 (CH), 125.2 (2xCH), 123.21 (C), 123.12 (2xCH), 119.9 (CH), 87.7 (C), 46.3 (CH₂), 17.5 (CH₃) ppm; HRMS (ESI-TOF) m/z calculated for C₂₂H₁₈NO₄ [M⁺ + H] 360.1236, found 360.1229; IR (ATR): ν = 2998, 1759, 1585, 1545, 1345, 1212, 1001, 767 cm⁻¹.

7-Fluoro-3-(4-nitrobenzyl)-3-phenylisobenzofuran-1(3H)-one (3gb):

Following the general procedure with a 1:2 molar mixture of **1g**:**1h** and 4-nitroaniline (**2b**), compound **3gb** was obtained after column chromatography (from 95:5 to 70:30 hexane/EtOAc) as a pale yellow solid (21.4 mg, 0.06 mmol, 59% yield respect to the initial amount of **1g**). TLC (hexane/EtOAc 80:20): R_f = 0.36; ¹H-NMR (300 MHz, CDCl₃): δ = 7.97 (d, J = 8.7 Hz, 2H), 7.70 (ddd, J = 8.3, 7.6, 4.6 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.45 (dd, J = 7.7, 0.6 Hz, 1H), 7.42 – 7.31 (m, 3H), 7.17 (d, J = 8.7 Hz, 2H), 7.10 (td, J = 8.5, 0.6 Hz, 1H), 3.84 (d, J = 14.0 Hz, 1H), 3.66 (d, J = 14.0 Hz, 1H). ppm; ¹³C-NMR (75 MHz, CDCl₃): δ = 165.19 (d, J = 2.6 Hz) (CO), 159.56 (d, J = 266.5 Hz) (CF), 153.9 (C), 147.3 (C), 141.4 (C), 139.1 (C), 136.97 (d, J = 7.9 Hz) (C), 131.6 (2xCH), 129.2 (2xCH), 129.0 (CH), 125.2 (2xCH), 123.3 (2xCH), 118.6 (d, J = 4.5 Hz) (CH), 116.8 (d, J = 18.7 Hz) (CH), 113.7 (d, J = 14.2 Hz) (CH), 88.7 (C), 46.1 (CH) ppm; HRMS (ESI-TOF) m/z calculated for C₂₁H₁₅FNO₄ [M⁺ + H] 364.0985, found 364.0982; IR (ATR): ν = 1795, 1567, 1349, 1222, 1162, 784 cm⁻¹.

4-Fluoro-3-(4-nitrobenzyl)-3-phenylisobenzofuran-1(3H)-one (3hb):

Following the general procedure with a 1:2 molar mixture of **1g**:**1h** and 4-nitroaniline (**2b**), compound **3hb** was obtained after column chromatography (from 95:5 to 70:30 hexane/EtOAc) as a pale yellow oil (45.1 mg, 0.12 mmol, 62% yield respect to the initial amount of **1h**). TLC (hexane/EtOAc 80:20): R_f = 0.48; ¹H-NMR (400 MHz, CDCl₃): δ = 7.97 (d, J = 8.7 Hz, 2H), 7.63 – 7.57 (m, 4H), 7.51 (dt, J = 7.4, 0.9 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.44 – 7.34 (m, 4H), 7.28 (d, J = 8.7 Hz, 2H), 3.91 (d, J = 14.0 Hz, 1H), 3.82 (d, J = 14.1 Hz, 1H) ppm; ¹³C-NMR (101 MHz, CDCl₃): δ = 167.8 (d, J = 5.3 Hz), 156.6 (d, J = 251.5 Hz) (CF), 147.3 (C), 141.8 (C), 138.7 (C), 136.6 (d, J = 16.6 Hz) (C), 132.4 (d, J = 6.8 Hz) (CH), 131.2 (2xCH), 129.14 (CH), 129.08 (2xCH), 125.7 (d, J = 3.5 Hz) (CH), 123.4 (2xCH), 122.3 (d, J = 3.8 Hz) (CH), 121.6 (d, J = 20.6 Hz) (CH), 88.87 (d, J = 3.3 Hz), 44.1 (CH₂) ppm; HRMS (ESI-TOF) m/z calculated for C₂₁H₁₅FNO₄ [M⁺ + H] 364.0985, found 364.0979; IR (ATR): ν = 1795, 1567, 1349, 1222, 1165, 793 cm⁻¹.

5-Fluoro-3-(4-nitrobenzyl)-3-phenylisobenzofuran-1(3H)-one (3ib):

Following the general procedure with a 1:2 molar mixture of **1i**:**1j** and 4-nitroaniline (**2b**), compound **3ib** was obtained after column chromatography (from 95:5 to 70:30 hexane/EtOAc) as a pale yellow solid (20.3 mg, 0.06 mmol, 56% yield respect to the initial amount of **1i**). TLC (hexane/EtOAc 80:20): R_f = 0.36; ¹H-NMR (400 MHz, CDCl₃): δ = 7.98 (d, J = 8.7 Hz, 2H), 7.71 (dd, J = 8.4, 4.8 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.45 – 7.34 (m, 3H), 7.32 (dd, J = 7.8, 2.1 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 7.15 (dd, J = 8.6, 2.1 Hz, 1H), 3.84 (d, J = 14.0 Hz, 1H), 3.65 (d, J = 14.0 Hz, 1H) ppm; ¹³C-NMR (101 MHz, CDCl₃): δ = 166.71 (CO), 166.51 (d, J = 257.6 Hz) (CF), 154.04 (d, J = 9.3 Hz) (C), 147.1 (C), 141.3 (C), 138.9 (C), 131.5 (2xCH), 129.11 (2xCH), 128.93 (CH), 128.43 (d, J = 10.3 Hz) (CH), 124.9 (2xCH), 123.2 (2xCH), 121.7 (d, J = 1.5 Hz) (C), 117.82 (d, J = 24.0 Hz) (CH), 109.86 (d, J = 24.6 Hz) (CH), 88.13 (d, J = 2.6 Hz) (C), 45.9 (CH₂) ppm; HRMS (ESI-TOF) m/z calculated for C₂₁H₁₅FNO₄ [M⁺ + H] 364.0985, found 364.0983; IR (ATR): ν = 1789, 1560, 1340, 1199, 1165, 776 cm⁻¹.

6-Fluoro-3-(4-nitrobenzyl)-3-phenylisobenzofuran-1(3H)-one (3jb):

Following the general procedure with a 1:2 molar mixture of **1i**:**1j** and 4-nitroaniline (**2b**), compound **3jb** was obtained after column chromatography (from 95:5 to 70:30 hexane/EtOAc) as a pale yellow solid (43.6 mg, 0.12 mmol, 60% yield respect to the initial amount of **1h**). TLC

(hexane/EtOAc 80:20): R_f = 0.38; ¹H-NMR (300 MHz, CDCl₃): δ = 7.98 (d, J = 8.7 Hz, 2H), 7.62 (ddd, J = 8.4, 4.2, 0.6 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.46 – 7.31 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 3.83 (d, J = 13.9 Hz, 1H), 3.65 (d, J = 13.9 Hz, 1H) ppm; ¹³C-NMR (75 MHz, CDCl₃): δ = 167.9 (d, J = 3.8 Hz) (CO), 163.3 (d, J = 251.6 Hz) (CF), 147.3 (C), 146.82 (d, J = 2.3 Hz) (C), 141.5 (C), 139.3 (C), 131.7 (2xCH), 129.17 (2xCH), 128.99 (CH), 128.03 (d, J = 9.1 Hz) (C), 125.2 (2xCH), 124.33 (d, J = 8.6 Hz) (CH), 123.3 (2xCH), 122. (d, J = 24.0 Hz) (CH), 112.5 (d, J = 23.6 Hz) (CH), 89.0 (C), 46.3 (CH₂) ppm; HRMS (ESI-TOF) m/z calculated for C₂₁H₁₅FNO₄ [M⁺ + H] 364.0985, found 364.0981; IR (ATR): ν = 1789, 1562, 1342, 1213, 1168, 786 cm⁻¹.

(3R*,3aR*,7aR*)-3-(4-nitrobenzyl)-3-phenylhexahydroisobenzofuran-1(3H)-one (3kb):

Following the general procedure with substrates **1k** and 4-nitroaniline (**2b**), compound **3kb** was obtained after column chromatography (from 95:5 to 70:30 hexane/EtOAc) as a colorless solid (54.8 mg, 0.16 mmol, 52%). TLC (hexane/EtOAc 80:20): R_f = 0.35; ¹H-NMR (400 MHz, CDCl₃): δ = 7.94 (d, J = 8.8 Hz, 2H), 7.29 – 7.22 (m, 5H), 7.05 (d, J = 8.7 Hz, 2H), 3.37 (d, J = 14.2 Hz, 1H), 3.28 (d, J = 14.2 Hz, 1H), 2.43 (tt, J = 11.0, 3.4 Hz, 1H), 2.33 – 2.25 (m, 2H), 2.08 (ddd, J = 13.7, 12.0, 3.0 Hz, 1H), 2.02 – 1.85 (m, 2H), 1.68 (qd, J = 11.9, 3.6 Hz, 1H), 1.40 – 1.20 (m, 3H) ppm; ¹³C-NMR (101 MHz, CDCl₃): δ = 175.65 (CO), 146.9 (C), 143.0 (C), 142.1 (C), 131.5 (2xCH), 128.71 (2xCH), 127.94 (CH), 124.22 (2xCH), 123.0 (2xCH), 88.9 (C), 54.0 (CH₂), 44.7 (CH₂), 40.2 (CH₂), 27.1 (CH₂), 25.90 (CH₂), 25.64 (CH₂), 25.62 (CH₂) ppm; HRMS (ESI-TOF) m/z calculated for C₂₁H₂₂NO₄ [M⁺ + H] 352.1549, found 352.1542; IR (ATR): ν = 3052, 1764, 1596, 1545, 1345, 1190, 1010, 778 cm⁻¹.

5-(4-Nitrobenzyl)-5-phenyldihydrofuran-2(3H)-one (3lb):^[15]

Following the general procedure with substrates **1l** and 4-nitroaniline (**2b**), compound **3lb** was obtained after column chromatography (from 90:10 to 70:30 hexane/EtOAc) as pale yellow solid (38.2 mg, 0.14 mmol, 45%). TLC (hexane/EtOAc 70:30): R_f = 0.36; ¹H-NMR (300 MHz, CDCl₃): δ = 8.03 (d, J = 8.7 Hz, 2H), 7.36 – 7.28 (m, 3H), 7.25 – 7.20 (m, 2H), 7.15 (d, J = 8.7 Hz, 2H), 3.35 (d, J = 14.0 Hz, 1H), 3.30 (d, J = 14.0 Hz, 1H), 2.63 – 2.48 (m, 2H), 2.45 – 2.37 (m, 2H) ppm; ¹³C-NMR (75 MHz, CDCl₃): δ = 175.9 (CO), 147.2 (C), 142.8 (C), 141.8 (C), 131.5 (2xCH), 128.78 (2xCH), 128.25 (CH), 124.89 (2xCH), 123.3 (2xCH), 88.4 (C), 48.5 (CH₂), 34.5 (CH₂), 28.6 (CH₂) ppm; IR (ATR): ν = 1765, 1602, 1520, 1345, 1188, 1171, 776 cm⁻¹.

3-(4-Nitrobenzyl)-3-phenylisobenzofuran-1(3H)-one O-methyl oxime (3mb):

Following the general procedure with substrates **1m** and 4-nitroaniline (**2b**), compound **3mb** was obtained after column chromatography (from 90:10 to 80:20 hexane/EtOAc) as a pale yellow oil (72.9 mg, 0.20 mmol, 65%). TLC (hexane/EtOAc 70:30): R_f = 0.36; ¹H-NMR (400 MHz, CDCl₃): δ = 7.94 (d, J = 8.8 Hz, 2H), 7.56 – 7.52 (m, 2H), 7.44 (dd, J = 7.7, 3.9 Hz, 2H), 7.38 (t, J = 7.7 Hz, 3H), 7.35 – 7.27 (m, 2H), 7.17 (d, J = 8.7 Hz, 2H), 3.94 (s, 3H), 3.85 (d, J = 13.8 Hz, 1H), 3.66 (d, J = 14.0 Hz, 1H) ppm; ¹³C-NMR (101 MHz, CDCl₃): δ = 154.6 (CNOMe), 147.0 (C), 145.5 (C), 142.3 (C), 140.7 (C), 131.7 (2xCH), 130.9 (CH), 129.24 (CH), 128.93 (2xCH), 128.63 (CH), 128.59 (C), 125.3 (2xCH), 123.0 (2xCH), 122.3 (CH), 121.9 (CH), 93.4 (C), 62.9 (OMe), 46.0 (CH₂) ppm; HRMS (ESI-TOF) m/z calculated for C₂₂H₁₉NO₄ [M⁺ + H] 375.1345, found 375.1344; IR (ATR): ν = 3052, 1653, 1565, 1345, 1212, 776 cm⁻¹.

1,1-Dimethyl-3-(4-nitrobenzyl)-3-phenyl-1,3-dihydroisobenzofuran (3nb):

Following the general procedure with substrates **1n** and 4-nitroaniline (**2b**), compound **3nb** was obtained after column chromatography (from 90:10 to 80:20 hexane/EtOAc) as a white solid (83.0 mg, 0.23 mmol, 77%). TLC (hexane/EtOAc 80:20): R_f = 0.32; M.P. (hexane/EtOAc 90:10): 147–149 °C; ¹H-NMR (400 MHz, CDCl₃): δ = 7.96 (d, J = 8.7 Hz, 2H), 7.64 – 7.60 (m, 3H), 7.55 (dt, J = 7.6, 0.9 Hz, 1H), 7.39 – 7.26 (m, 4H), 7.25 – 7.20 (m, 1H), 7.16 (d, J = 8.7 Hz, 2H), 7.00 (dt, J =

FULL PAPER

7.4, 0.9 Hz, 1H), 3.52 (d, J = 13.6 Hz, 1H), 3.45 (d, J = 13.6 Hz, 1H), 1.37 (s, 3H), 1.24 (s, 3H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): δ = 147.1 (C), 146.6 (C), 146.0 (C), 145.2 (C), 141.7 (C), 132.0 (2xCH), 128.4 (CH), 128.3 (2xCH), 127.53 (CH), 127.16 (CH), 125.4 (2xCH), 122.78 (CH), 122.61 (2xCH), 121.05 (CH), 89.7 (C), 85.6 (C), 49.8 (CH₂), 30.2 (CH₂), 29.5 (CH₃) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{23}\text{H}_{22}\text{NO}_3$ [M^+ + H] 360.1600, found 360.1584; IR (ATR): ν = 3052, 1565, 1345, 1009, 776 cm^{-1} .

1-(4-Nitrobenzyl)-1-phenyl-1,3-dihydroisobenzofuran (3ob): Following the general procedure with substrates **1o** and 4-nitroaniline (**2b**), compound **3ob** was obtained after column chromatography (from 90:10 to 80:20 hexane/EtOAc) as a colorless oil (58.6 mg, 0.18 mmol, 59%). TLC (hexane/EtOAc 80:20): R_f = 0.36; ^1H -NMR (400 MHz, CDCl_3): δ = 7.95 (d, J = 8.7 Hz, 2H), 7.57 – 7.51 (m, 2H), 7.45 – 7.40 (m, 1H), 7.37 – 7.30 (m, 3H), 7.30 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 7.07 (dt, J = 7.5, 1.0 Hz, 1H), 5.08 (d, J = 12.2 Hz, 1H), 4.79 (d, J = 12.3 Hz, 1H), 3.61 (d, J = 13.5 Hz, 1H), 3.54 (d, J = 13.5 Hz, 1H) ppm; ^{13}C -NMR (75 MHz, CDCl_3): δ = 146.7 (C), 144.96 (C), 144.69 (C), 143.0 (C), 139.0 (C), 131.6 (2xCH), 128.5 (2xCH), 128.1 (CH), 127.58 (CH), 127.48 (CH), 125.3 (2xCH), 122.7 (2xCH), 122.3 (CH), 121.3 (CH), 91.38 (C), 72.5 (CH₂), 47.8 (CH₂) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{21}\text{H}_{16}\text{NO}_3$ [M^+ - H] 330.1130, found 330.1138; IR (ATR): ν = 3052, 1563, 1257, 1344, 1010, 787 cm^{-1} .

(*R*,*R*)-3-(1-(4-Nitrophenyl)ethyl)-3-phenylisobenzofuran-1(3H)-one (3pb): Following the general procedure with substrates **1b** and 4-nitroaniline (**2b**), compound **3pb** was obtained after column chromatography (from 95:5 to 70:30 hexane/EtOAc) as a yellow solid (37.7 mg, 0.11 mmol, 35%). TLC (hexane/EtOAc 70:30): R_f = 0.34; ^1H -NMR (300 MHz, CDCl_3): δ = 7.92 (d, J = 8.7 Hz, 2H), 7.73 – 7.69 (m, 2H), 7.68 – 7.63 (m, 1H), 7.62 – 7.57 (m, 1H), 7.56 – 7.51 (m, 1H), 7.48 – 7.41 (m, 2H), 7.39 – 7.35 (m, 1H), 7.34 – 7.30 (m, 1H), 7.29 – 7.24 (m, 2H), 3.98 (q, J = 7.0 Hz, 1H), 1.40 (d, J = 7.1 Hz, 3H) ppm; ^{13}C -NMR (75 MHz, CDCl_3): δ = 169.6 (CO), 152.1 (C), 147.3 (C), 147.0 (C), 139.7 (C), 134.3 (CH), 130.1 (2xCH), 129.4 (CH), 129.2 (2xCH), 128.5 (CH), 125.9 (CH), 125.0 (C), 124.7 (2xCH), 123.1 (2xCH), 122.2 (CH), 91.1 (C), 48.8 (CH), 16.2 (CH₃) ppm; HRMS (ESI-TOF) m/z calculated for $\text{C}_{22}\text{H}_{18}\text{NO}_4$ [M^+ + H] 360.1236, found 360.1237; IR (ATR): ν = 2952, 1762, 1602, 1520, 1345, 1170, 776 cm^{-1} .

Control experiment to investigate the source of the oxygen atom in the lactone: 2-(1-phenylvinyl)benzoic acid **1a** (22.4 mg, 0.10 mmol), 4-nitroaniline **2b** (27.6 mg, 0.20 mmol) and salicylic acid (1.38 mg, 0.01 mmol) were added into an oven-dried 3 mL-vial. The vial was capped with a septum and the system was evacuated and filled with argon (three times) after the solvent MeCN (0.83 mL) and the additive H_2O^{18} (18 μL , 1 mmol) were added. Then the reaction mixture was stirred vigorously over 5 min approx. until a homogeneous solution was obtained. At this point, *tert*-butylnitrite (33 μL , 28.7 mg, 0.25 mmol) was added (the solution turned orange after some minutes) and the reaction mixture was stirred for 5 h, keeping the temperature at 20 °C with an external water bath. After this time, the reaction mixture was diluted with EtOAc (2.5 mL) and the solution was injected directly in GC-MS. The tagged product with O^{18} was not observed.

Free radical capture experiment: 2-(1-phenylvinyl)benzoic acid **1a** (67.2 mg, 0.30 mmol), 4-nitroaniline **2b** (82.8 mg, 0.60 mmol), salicylic acid (4.14 mg, 0.03 mmol) and TEMPO (117.2 mg, 0.75 mmol) were added into an oven-dried Schlenck. The system was evacuated and filled with argon (three times) after the solvent MeCN (2.5 mL) and the additive H_2O (56 μL) was added. Then the reaction mixture was stirred vigorously over 5 min approx. until a homogeneous solution was obtained. At this point, *tert*-butylnitrite (100 μL , 86 mg, 0.75 mmol) was added (the solution turned orange after some minutes) and the reaction mixture was stirred for 5 h, keeping the temperature at 20 °C with an external water bath. At this time

EtOAc (25 mL) was added and the organic layer was collected and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc 95:5), giving compound **4** as a white crystalline solid (42.6 mg, 0.15 mmol, 51%). Compound **3ab** was not detected by TLC or GC.

2,2,6,6-Tetramethyl-1-(4-nitrophenoxy)piperidine (4): TLC (hexane/EtOAc 90:10): R_f = 0.65; ^1H -NMR (400 MHz, CDCl_3): δ = 8.14 (d, J = 9.5 Hz, 2H), 7.30 (br s, 2H), 1.65 – 1.56 (m, 5H), 1.45 – 1.42 (m, 1H), 1.24 (s, 6H), 0.98 (s, 6H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): δ = 168.8 (C), 141.2 (C), 125.6 (CH), 114.2 (CH), 61.0 (C), 39.8 (CH₂), 32.4 (CH₃), 20.6 (CH₃), 17.0 (CH₂) ppm; LRMS (EI-DIP) m/z (%): 278 (M^+ , 11), 263 (43), 149 (20), 125 (100), 97 (40); IR (ATR): ν = 1588, 1507, 1332, 1254, 1227, 1109, 853 cm^{-1} .

Competition experiment A: 2-(1-Phenylvinyl)benzoic acid **1a** (67.2 mg, 0.30 mmol), 4-nitroaniline **2b** (41.4 mg, 0.30 mmol), aniline (27.3 μL , 27.9 mg, 0.30 mmol), and salicylic acid (4.14 mg, 0.03 mmol) were added into an oven-dried Schlenck. The system was evacuated and filled with argon (three times) after the solvent MeCN (2.5 mL) and the additive H_2O (56 μL) were added. Then the reaction mixture was stirred vigorously over 5 min approx. until a homogeneous solution was obtained. At this point, *tert*-butylnitrite (100 μL , 86 mg, 0.75 mmol) was added (the solution turned orange after some minutes) and the reaction mixture was stirred for 5 h, keeping the temperature at 20 °C with an external water bath. At this time EtOAc (25 mL) was added and the organic layer was collected and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (from 95:5 to 70:30 hexane/EtOAc) affording product **3ab** (17.6 mg, 0.047 mmol, 17%) and product **3ai** (8.1 mg, 0.027 mmol, 9%).

Competition experiment B: Following the same procedure than in experiment A, but using *p*-anisidine **2g** (36.9 mg, 0.30 mmol) and aniline (27.3 μL , 27.9 mg, 0.30 mmol). The residue was purified by flash column chromatography on silica gel (from 95:5 to 80:20 hexane/EtOAc), affording product **3ag** (11.9 mg, 0.036 mmol, 12%) and product **3ai** (12.6 mg, 0.042 mmol, 14%).

Reaction of ester-1a with 2g in the presence salicylic acid: Methyl 2-(1-phenylvinyl)benzoate (67.2 mg, 0.30 mmol) and 4-chloroaniline **2g** (76.5 mg, 0.60 mmol) and salicylic acid (4.14 mg, 0.03 mmol), were added into an oven-dried Schlenck. The system was evacuated and filled with argon (three times) after the dry MeCN (2.5 mL) was added. Then the reaction mixture was stirred vigorously over 5 min approx. until a homogeneous solution was obtained. At this point, *tert*-butylnitrite (100 μL , 86 mg, 0.75 mmol) was added (the solution turned orange after some minutes) and the reaction mixture was stirred for 5 h, keeping the temperature at 20 °C with an external water bath. At this time EtOAc (25 mL) was added and the organic layer was collected and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (from hexane 100% to 70:30 hexane/EtOAc), affording product **3aa** (51.2 mg, 0.15 mmol, 51%).

Reaction of ester-1a with 2g in the absence of salicylic acid: Methyl 2-(1-phenylvinyl)benzoate (67.2 mg, 0.30 mmol) and 4-chloroaniline **2g** (76.5 mg, 0.60 mmol) were added into an oven-dried Schlenck. The system was evacuated and filled with argon (three times) after the dry MeCN (2.5 mL) was added. Then the reaction mixture was stirred vigorously over 5 min approx. until a homogeneous solution was obtained. At this point, *tert*-butylnitrite (100 μL , 86 mg, 0.75 mmol) was added (the solution turned orange after some minutes) and the reaction mixture was stirred for 5 h, keeping the temperature at 20 °C with an external water bath. At this time EtOAc (25 mL) was added and the organic layer was collected and concentrated *in vacuo*. The residue was purified by flash

FULL PAPER

column chromatography on silica gel (from hexane 100% to 90:10 hexane/EtOAc), affording product **5** (28.2 mg, 0.08 mmol, 27%, 10:1 *EZ* mixture).

Methyl 2-(2-(4-chlorophenyl)-1-phenylvinyl)benzoate (5): TLC (hexane/EtOAc 90:10): *R*_f = 0.70; ¹H-NMR (300 MHz, CDCl₃): δ = 7.99 – 7.94 (m, 1H), 7.46 (pd, *J* = 7.5, 1.7 Hz, 2H), 7.38 – 7.27 (m, 4H), 7.25 – 7.15 (m, 3H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.94 (s, 1H), 6.91 – 6.87 (m, 2H), 3.57 (s, 3H) ppm; ¹³C-NMR (75 MHz, CDCl₃): δ = 167.5 (CO₂Me), 143.3 (C), 142.6 (C), 141.2 (C), 135.9 (C), 132.59 (CH), 132.2 (CH), 131.6 (C), 131.0 (CH), 130.7 (2xCH), 128.39 (2xCH), 128.35 (2xCH), 128.00 (CH), 127.7 (CH), 126.93 (2xCH), 126.34 (CH), 52.1 (CH₃) ppm; LRMS (EI-DIP) *m/z* (%): 348 (M⁺, 100), 317 (24), 281 (32), 252 (41); HRMS (EI-TOF) *m/z* calculated for 348.0917, found 348.0921.

Acknowledgments

This work was generously supported by the Spanish Ministerio de Economía y Competitividad (MINECO; grant no. CTQ2017-88171-P) and the Generalitat Valenciana (GV; grant no. AICO/2017/007).

Keywords: sustainable chemistry • lactone synthesis • salicylic acid • aryl radicals • anilines

- [1] a) M. Jung, J. Ham, S. Jueun, *Org. Lett.* **2002**, *4*, 2763-2765; b) M. Seitz, O. Reiser, *Curr. Opin. Chem. Biol.* **2005**, *9*, 285-292; c) T. Janecki, E. Błaszczyk, K. Studzian, A. Janecka, U. Krajewska, M. Różalski, *J. Med. Chem.* **2005**, *48*, 3516-3521.
- [2] P. C. G. Rida, D. LiVecche, A. Ogden, J. Zhou, R. Aneja, *Med. Res. Rev.* **2015**, *35*, 1072-1096.
- [3] E. G. McMahon, *Curr. Opin. Pharmacol.* **2001**, *1*, 190-196.
- [4] a) X. Xu, F. Song, S. Wang, S. Li, F. Xiao, J. Zhao, Y. Yang, S. Shang, L. Yang, J. Shi, *J. Nat. Prod.* **2004**, *67*, 1661-1666; b) Y.-J. Kwon, M.-J. Sohn, C.-J. Kim, H. Koshino, W.-G. Kim, *J. Nat. Prod.* **2012**, *75*, 271-274.
- [5] a) J. N. N. Eildal, J. Andersen, A. S. Kristensen, A. M. Jorgensen, B. Bang-Andersen, M. Jorgensen, K. Stromgaard, *J. Med. Chem.*, **2008**, *51*, 3045-3048; b) J. Andersen, N. Stühr-Hansen, L. Zachariassen, S. Toubro, S. M. R. Hansen, J. N. N. Eildal, A. D. Bond, K. P. Bogoso, B. Bang-Andersen, A. S. Kristensen, K. Stromgaard, *Proc. Natl. Acad. Sci. U. S. A.*, **2011**, *108*, 12137-12142; c) For a recent synthetic approach, see: T. M. Ha, Q. Wang, J. Zhu, *Chem. Commun.* **2016**, *52*, 11100-11103.
- [6] For comprehensive reviews, see: a) R. R. A. Kitson, A. Millemaggi, R. J. K. Taylor, *Angew. Chem. Int. Ed.* **2009**, *48*, 9426-9451; b) A. Albrecht, I. Albrecht, Janecki, T., *Eur. J. Org. Chem.* **2011**, *2011*, 2747-2766.
- [7] a) D. S. Hamilton, D. A. Nicewicz, *J. Am. Chem. Soc.* **2012**, *134*, 18577-18580; b) H. Shigehisa, M. Hayashi, H. Ohkawa, T. Suzuki, H. Okayasu, M. Mukai, A. Yamazaki, R. Kawai, H. Kikuchi, Y. Satoh, A. Fukuyama, K. Hiroya, *J. Am. Chem. Soc.* **2016**, *138*, 10597-10604; c) L. Ferrand, Y. Tang, C. Aubert, L. Fensterback, V. Mouriès-Mansuy, M. Petit, M. Amatore, *Org. Lett.* **2017**, *19*, 2062-2065.
- [8] a) H. Nakatsuji, Y. Sawamura, A. Sakakura, K. Ishihara, *Angew. Chem. Int. Ed.* **2014**, *53*, 6974-6977; b) H. Egami, J. Asada, K. Sato, D. Hashizume, Y. Kwato, Y. Hamashima, *J. Am. Chem. Soc.* **2015**, *137*, 10132-10135; c) M. Wilking, C. G. Daniliuc, U. Hennecke, *Chem.-Eur. J.* **2016**, *22*, 18601-1807. d) S. E. Denmark, P. Ryabchuk, M. T. Burk, C. B. Gilbert, *J. Org. Chem.*, **2016**, *81*, 10411-10423; e) J. D. Griffin, C. L. Cavanaugh, D. A. Nicewicz, *Angew. Chem. Int. Ed.* **2017**, *56*, 2097-2100.
- [9] a) R. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2012**, *134*, 12462-12465; b) R. Zhu, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 12655-12658.
- [10] a) D. Karila, L. Leman, R. H. Dodd, *Org. Lett.* **2011**, *13*, 5830-583; b) B. N. Hemric, K. Shen, Q. Wang, *J. Am. Chem. Soc.* **2016**, *138*, 5813-5816; c) J. Xie, Y.-W. Wang, L.-W. Qi, B. Zhang, *Org. Lett.* **2017**, *19*, 1148-1151.
- [11] For recent examples, see: a) R. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 8069-8077; b) W. Sha, S. Ni, J. Han, Y. Pan, *Org. Lett.* **2017**, *19*, 5900-5903.
- [12] a) S. Protti, M. Fagnoni, A. Albini, *J. Am. Chem. Soc.* **2006**, *128*, 10670-10671; b) H. Qareya, C. Raviola, S. Protti, M. Fagnoni, A. Albini, *J. Org. Chem.* **2013**, *78*, 6016-6024.
- [13] G. Zhang, L. Cui, Y. Whang, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 1474-1475.
- [14] Y. Gao, J. Xu, P. Zhang, H. Fang, G. Tang, Y. Zhao, *RSC Adv.* **2015**, *5*, 36167-36170.
- [15] W. Guo, H.-G. Cheng, L.-Y. Chen, J. Xuan, Z.-J. Feng, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, *Adv. Synth. Catal.* **2014**, *356*, 2787-2793.
- [16] a) F. P. Crisóstomo, T. Martín, R. Carrillo, *Angew. Chem. Int. Ed.* **2014**, *53*, 2181-2185; b) M. D. Perretti, D. M. Monzón, F. P. Crisóstomo, V. S. Martín, R. Carrillo, *Chem. Commun.* **2016**, *52*, 9036-9039.
- [17] D. Felipe-Blanco, F. Alonso, J. C. Gonzalez-Gomez, *Adv. Synth. Catal.* **2017**, *359*, 2857-2863.
- [18] D. Felipe-Blanco, J. C. Gonzalez-Gomez, *Adv. Synth. Catal.* **2018**, *360*, 2873-2878.
- [19] For recent reviews on the formation of aryl radicals from aryldiazonium salts, see: a) M. R. Heinrich, *Chem. Eur. J.* **2009**, *15*, 820-833; b) D. P. Hari, B. König, *Angew. Chem. Int. Ed.* **2013**, *52*, 4734-4743; c) F. Mo, G. Dong, Y. Zhang, J. Wang, *Org. Biomol. Chem.* **2013**, *11*, 1582-1593; d) D. Koziakov, G. Wu, A. Jacobi von Wangelin, *Org. Biomol. Chem.* **2018**, *16*, 4942-4953.
- [20] a) C. Molinaro, J. Mowat, F. Gosselin, P. D. O'Shea, J.-F. Marcoux, R. Angeland, I. W. Davies, *J. Org. Chem.* **2007**, *72*, 1856-1858; b) D. M. Monzón, T. Santos, F. P. Crisóstomo, V. S. Martín, R. Carrillo, *Chem. Asian J.* **2018**, *13*, 325-333.
- [21] a) For a seminal report on the addition of aryl radicals to diazonium salts, see: F. Minisci, F. Coppa, F. Fontana, G. Pianese, L. Zhao, *J. Org. Chem.* **1992**, *57*, 3929-3933; b) For a recent thermally induced oxyarylation of styrenes with aryldiazonium salts, see: S. Kindt, K. Wicht, M. R. Heinrich, *Angew. Chem. Int. Ed.* **2016**, *55*, 8744-8747.
- [22] D. Cantillo, C. Mateos, J. A. Rincon, O. De Frutos, C. O. Kappe, *Chem.-Eur. J.* **2015**, *21*, 12894-12898.
- [23] Formally, an electron is accepted by the diazonium salt during the generation of aryl radicals, and this is less favored when electron-donating substituents are present. For a comprehensive study, see: R. M. Elofson, F. F. Gadallah, *J. Org. Chem.* **1969**, *34*, 854-857.
- [24] a) J. F. Bunnett, C. C. Waser, *J. Am. Chem. Soc.* **1966**, *88*, 5534-5537; b) D. L. Brydon, J. I. G. Cadogan, *J. Chem. Soc. C* **1968**, 819-824; c) T. J. Broxton, J. F. Bunnett, C. H. Paik, *J. Org. Chem.* **1977**, *42*, 643-649.
- [25] CCDC 1919481 contains the supplementary crystallographic data for **3kb**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [26] a) R. M. Beesley, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc., Trans.* **1915**, 107, 1080-1106; b) M. N. Levine, R. T. Raines, *Chem. Sci.* **2012**, *3*, 2412-2420.
- [27] a) M.-J. Bu, G.-P. Lu, C. Cai, *Synlett* **2015**, *26*, 1841-1846; b) M.-J. Bu, G.-P. Lu, C. Cai, *Org. Chem. Front.* **2016**, *3*, 630-634; c) F.-Q. Huang, G.-X. Zhou, X. Dong, L. W. Qi, B. Zhang, *Asian J. Org. Chem.* **2016**, *5*, 192-195.
- [28] It is known that acyloxydiazoyls decompose easily to generate aryl radicals. For selected examples, see: a) D. H. Hey and W. A. Waters, *J. Chem. Soc.*, **1948**, 882-885; b) R. Huisgen, G. Horeld, *Liebigs Ann. Chem.* **1949**, *562*, 137-162; c) C. Rüchardt, B. Freudenberg, *Tetrahedron Lett.* **1964**, *5*, 3623-3628; d) J. I. G. Cadogan, *Acc. Chem. Res.* **1971**, *4*, 186-192. In reference 17 we have checked that methyl salicylate does not promote the formation of aryl radicals from *in situ* formed diazonium

FULL PAPER

salts, therefore we support the formation of diazobenzoate **B** as intermediate.

- [29] J. Chateaufneuf, J. Luszytyk, K. U. Ingold, *J. Am. Chem. Soc.*, **1988**, *110*, 2886-2893.

- [30] For a similar proposal, although with some incorporation of O-atom from H₂O in the lactone ring, see: W. Sha, S. Ni, J. Han, Y. Pan, *Org. Lett.* **2017**, *19*, 5900-5903.

FULL PAPER

Entry for the Table of Contents (Please choose one layout)

Layout 2:

FULL PAPER

The presence of salicylic acid (10 mol-%) and H_2O (10 equiv) significantly improves the arylation-lactonization sequence of γ -alkenoic acids with *in situ* formed diazonium salts (from bench stable anilines). The reaction is finished in less than 5 h without thermal or photochemical activation, giving access to a variety of γ,γ -disubstituted butyrolactones.

*aryl radicals

Tandem Reactions*

Diego Felipe-Blanco, Jose C. Gonzalez-Gomez*

Page No. – Page No.

Metal-Free Protocol for the Arylation-Lactonization Sequence of γ -Alkenoic Acids using Anilines as Aryl Radical Sources