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Regioselective synthesis of new EWG-Bearing 3-benzoyl-2-phenylbenzofurans by one-pot intramolecular acylation/thermal cyclization of phosphoranes and their CB1 antagonist activity☆

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ABSTRACT

(Benzoylmethylene)triphenylphosphoranes are useful intermediates in the synthesis of 3-benzoyl-2-phenylbenzofurans. Under Wittig conditions, they allow the simultaneous preparation of two 3-acyl regioisomers. Starting from the *o*-[(benzoyloxy)benzylidene]triphenylphosphonium salt bearing electron withdrawing groups (EWGs) on the *ortho*-benzoyloxy ring (nitro, cyano and trifluoromethyl groups), we developed an improved regioselective synthetic strategy, *via* tandem ylide acylation and thermal cyclization of the acyl ylide intermediate. Using our optimized method, only one 3-acyl regioisomer was obtained and the yields were highly improved (up to 92 %) comparing to the previously reported method, expanding the scope of synthesis to a wide variety of new EWG-containing 3-benzoyl-2-phenylbenzofurans. The synthesized compounds were evaluated for their activity on CB1 receptors. In particular, some of these compounds displayed activity as CB1 antagonists.

1. Introduction

Cannabinoid receptors, type 1 (CB1) and type 2 (CB2), are G-protein-coupled receptors (GPCRs) that respond to a wide range of endogenous and exogenous natural and synthetic cannabinoids [1,2]. The CB1 receptor is the most abundant GPCR in the central nervous system [3] and its activation directly inhibits neurotransmitters release, synapse formation, nociception, and appetite [4,5]. Research in CB1 receptor may lead to the development of new potentially useful drugs for the treatment of a series of diseases and syndromes, including pain, addiction, energy metabolism, diabetes, movement and eating disorders, multiple sclerosis, and other neurodegenerative and psychiatric conditions [6].

3-Benzoylbenzofurans represent an important class of heterocycles that display potent biological activities of pharmacological interest. Representative examples of marketed drug include amiodarone, LY-320135, benzbromarone, dronedarone and SKF-64346 (Fig. 1) [7–11]. Therefore, many methods for the synthesis of 3-acylbenzofurans have been developed. However, most of them are only suitable for the preparation of 3-benzoyl-2-phenylbenzofurans bearing electron-donating groups (EDG) [12–17].

3-Benzoyl-2-phenylbenzo[*b*]furans carrying strong EWGs may be convenient precursors in the preparation of more complex compounds [18,19]. Moreover, EWGs such as NO_2, CN, and CF_3 are widely used in drug discovery programs, since they can work as pharmacophores themselves, due to their ability to form polar interactions or hydrogen bonds with the receptors, as well as modulate the pharmacodynamic and pharmacokinetic properties of active compounds [20,21]. Despite their relevance in the discover of new pharmaceuticals, preparation of derivatives bearing an EWG on the 2-phenyl ring has received little attention, with most of the emphasis devoted to the preparation of halogenated compounds [15–17,22,23].

To the best of our knowledge, approaches to strongly deactivated 3-benzoyl-2-phenylbenzofurans are limited to only a few methods. The Friedel–Crafts acylation of the 2-(4-nitrophenyl)benzofuran leads to mixtures of regioisomeric aroylbenzofurans, and the expected 3-acyl derivative is formed as a minor product (Scheme 1a) [24,25]. More

☆ [☆] EWG = Electron withdrawing group

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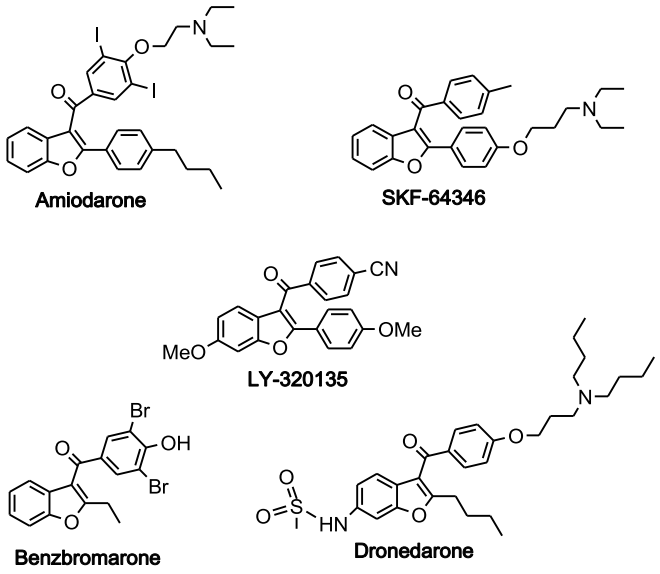


Fig. 1. Bioactive compounds containing the 3-benzoylbenzofuran scaffold.

specifically, aroylation occurred predominantly at 4 (39% yield) and 6 positions (13%) of the heterocycle, whereas the desired 3-acyl isomer was obtained in very low yields (7%). Doi and Sato reported the nickel catalyzed cascade C–O bond cleavage/cyclization of *ortho*-alkylphenol ester to construct 3-acylbenzofurans. Although the method proved to be effective for the synthesis of a variety of functionalized 3-acylbenzofurans, derivatives carrying a strong EWG (*i.e.* CF_3) on the 2-phenyl ring gave a poor yield (10%) (Scheme 1b) [17].

In a previous study, we described the preparation of 3-benzoyl-2-phenylbenzofurans using phenolic phosphonium salts as starting materials, in aprotic solvent. The method proved to be effective for the synthesis of deactivated derivatives. However, it was limited to the preparation of benzofurans carrying identical substituents on the 2-phenyl and on the 3-benzoyl rings (Scheme 1c) [26,27].

The present study was initiated from the results obtained during our previous study. We unexpectedly observed that when the starting phenolic derivatives were replaced with the phenol ester, the reaction with benzoyl chlorides affords, beside the 2-phenylbenzofuran, a mixture of two isomeric 3-acylbenzofurans formed by two competitive routes: benzoyl group intramolecular migration followed by phenolic oxygen esterification (Route A), and direct acylation of the ylide carbon atom (Route B - Scheme 1d) [28]. This interesting behavior encouraged us to further optimize the reaction conditions to obtain selectively a unique EWG-bearing 3-acyl regioisomer in order to get better yields and avoid the formation of the 2-phenylbenzofuran derivative, despite the common intermediacy of **III** (Scheme 1e and Scheme 2).

2. Results and discussion

At the outset of our investigation, the reaction conditions were optimized by using the phosphonium salt **1** (EWG = NO_2) as model substrate and the benzoyl chloride (**2a**) (Scheme 2). In fact, preliminary results showed that a unique regioisomer (Scheme 1d - Route A) was formed only when the starting phosphonium salt **1** bears an EWG [28]. Therefore, it occurred to us that by an appropriate choice of the R substituent, the reactivity of the ylide intermediate **II** could be improved and form the basis of the selective migration of the benzoyl group. However, in toluene at 110 °C, the 3-acyl regioisomer **4** was recovered in very low yields and still in mixture with the correspondent 2-phenylbenzofuran **3**, which unfortunately was the major product.

We then examined the reaction in an aprotic solvent but at lower temperature, *i.e.* in toluene at 40 °C (Table 1). However, under these conditions, we were not able to find even traces of the expected 3-acyl product **4**, even after a long-time reaction (24 h). Instead, we isolated a unique reaction product, that, after NMR and HRMS-ESI analysis (See Supporting Information for detail), turned out to be the α-acylated phosphonium ylide **VIa.** It has previously been reported that phosphorus ylides containing a carbonyl group at the ylide carbon atom can be isolated in a free state and stored under ordinary conditions [29], due to the stabilizing effect of the carbonyl group. Therefore, it is not surprising that ylide **VIa** is also stable under such conditions. It should be noted, even if the carbon atom of the acyl ylide, as well as the oxygen of the alfa acyl group, can both constitute the center of a further acylation reaction [29,30], under these conditions the secondary acylation of the acyl ylide **VIa** does not occur. To our surprise, despite the HRMS-ESI analysis showed the protonated molecular ion of **VIa** ($[M+H]^+$, *m/z* 622.1781), the GC/MS analysis instead showed two peaks in the chromatogram: the first peak (retention time, r.t = 16.7 min) corresponds to the mass spectrum of triphenylphosphine oxide (Ph_3PO) ($M^{+\cdot}$ *m/z* 278) and the second peak (r.t. = 19.8 min) to the 3-benzoyl isomer **4** ($M^{+\cdot}$*m/z* 343) [24,28]. These data suggest that the phosphoranylidene **VIa** undergoes thermal extrusion of Ph_3PO and cyclization to **4** in the GC injector of the mass spectrometer (Fig. S1 Supporting Information). We therefore hypothesized that the phosphoranylidene **VIa** constitutes a possible intermediate that cyclizes to the 3-acylbenzofuran **4** when the reaction is conducted at higher temperature (Scheme 2). Therefore, we next tested the effect of different solvents on the formation of the intermediate **VIa**. The reaction performed in toluene at 40 °C gave low yields of **VIa** (25% Table 1, entry 1), reasonably because apolar solvents favor the route that leads to the 2-phenylbenzofuran derivatives [31]. Study of different polar aprotic solvents showed that acetonitrile (ACN) and dichloromethane (DCM) favor the formation of the acylated ylide **VIa** (75% Table 1, entries 2 and 3). It should also be noted that when a benzoyl chloride of lower reactivity was used, *i.e.* the 4-methoxybenzoyl chloride (**2b**) (Table 1, entries 4–6), a different trend was observed. The yields of the corresponding ylide **VIb** dropped from 54% to 30% when ACN was used instead of DCM (Table 1, entries 5 and 6), revealing that DCM is the best suited solvent. These results also suggest that, using benzoyl chlorides possessing an EDG, the reaction still occurs, even if with a decreasing in the yields (75% vs 54%).

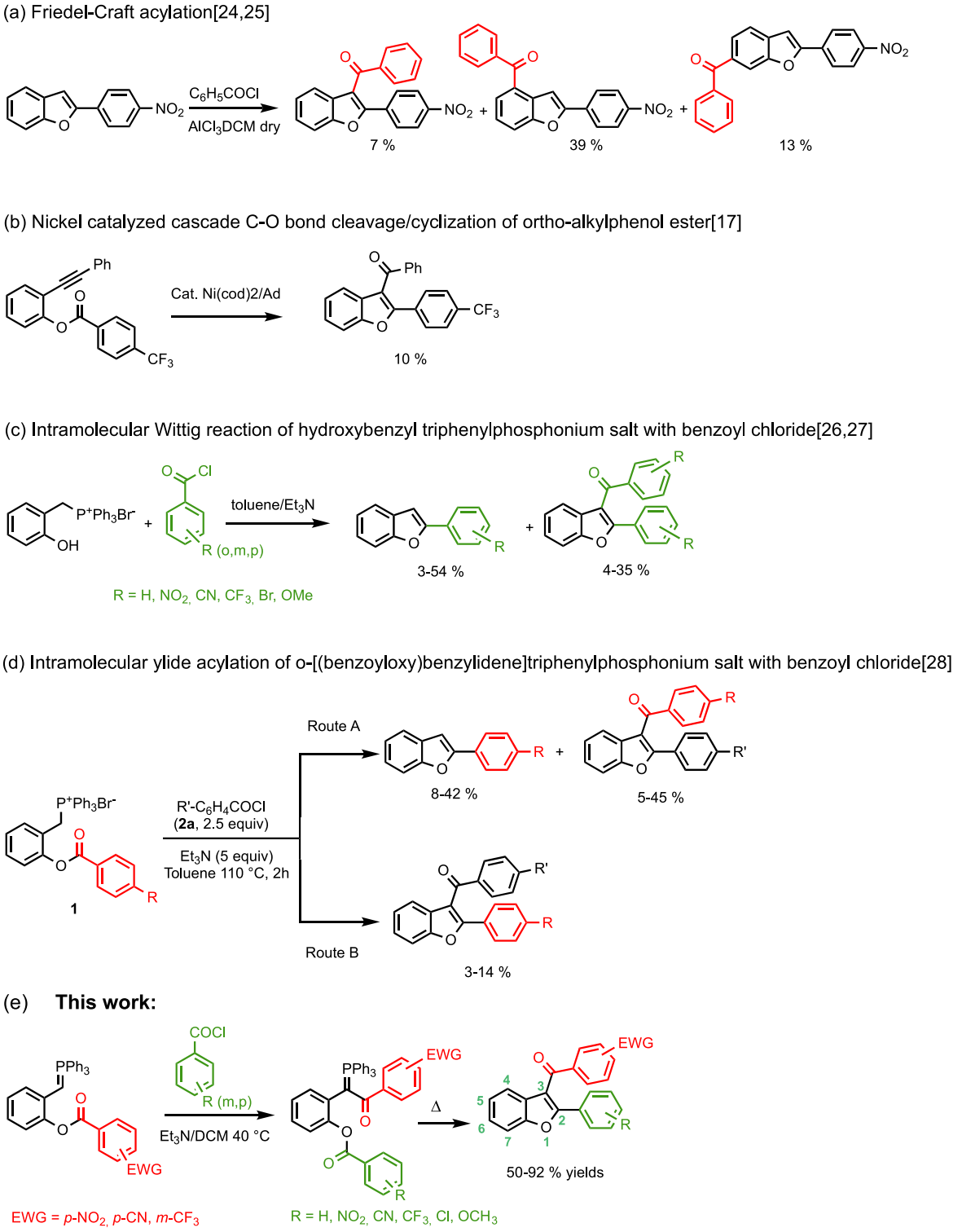
In an attempt to verify the optimal cyclization temperature, phosphorane **VIa** was heated in a range of temperatures from 40 to 180 °C, for different reaction times, and the reaction progress was monitored by thin-layer chromatography (TLC). Our results demonstrate that phosphorane **VIa** was completely converted to the 3-acyl derivatives after 1 h at 160 °C. Higher temperatures did not lead to better yields, not even to a higher rate of cyclization. It is important to point out that thermal extrusion of Ph_3PO from phosphorous ylides was also observed using flash vacuum pyrolysis (FVP), operating at reduced pressure and at higher temperature (500 and even 700 °C), furnishing a variety of alkynes [32].

With the selected temperature conditions of cyclization in hand, we then progressed to test if a one pot procedure, which avoid the isolation and purification of the resulted ylide intermediate, was feasible. We firstly investigate the use of a unique solvent (Table 2). The use of dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) under reflux did not lead to the desired 3-acyl derivative **4**, not even under prolonged heating (entries 1 and 2). When the reaction was performed at 110 °C in toluene (entry 3), the major pathway was the conversion of intermediate **III** into **3** (42%), whereas the desired 3-acyl isomer **4** was obtained only in a 15% yield. The reaction conducted in chlorobenzene (CB) at 140 °C (entry 5) led to a mixture of **3** (38%) and **4** (53%), whereas in *ortho*-dichlorobenzene (*o*-DCB) at 180 °C (entry 7), **4** was obtained as the only product, in a yield of 80%. Next, we surveyed a one-pot tandem approach combining the use of DCM at 40 °C for 2 h (*vide supra*) for the ylide acylation, followed by the addition of *o*-DCB, at reflux temperature (180 °C) for further 1 h, to achieve the thermal cyclization of **VIa**. Using DCM/*o*-DCB, the yield of **4** was further increased to 85% (entry 8).

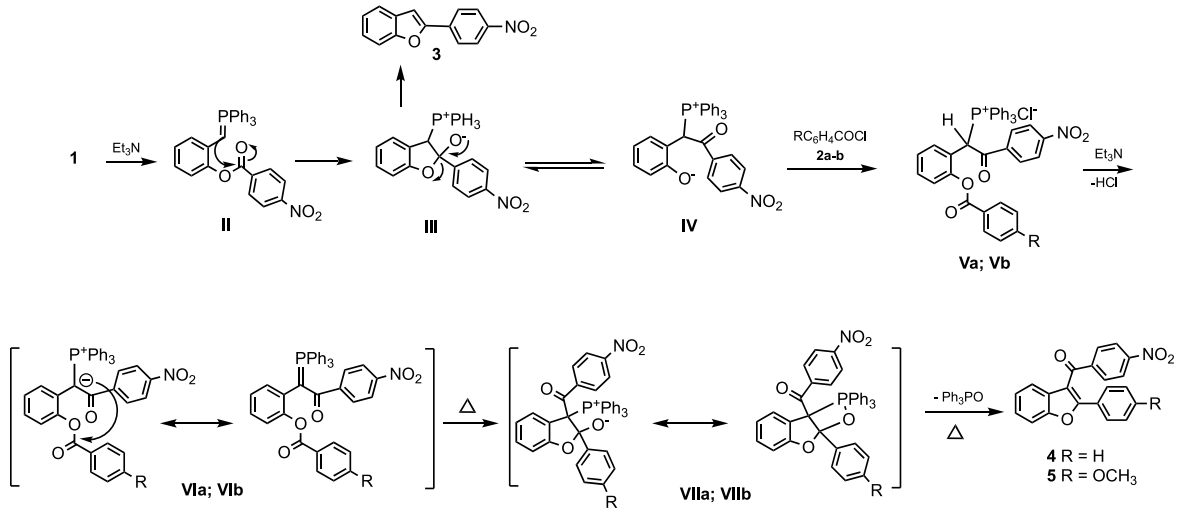
Finally, in order to avoid the use of high boiling solvent difficult to remove, the reaction was conducted in DCM at 40 °C for 2 h, and subsequently the temperature was gradually increased and kept at 160 °C for one more hour without any solvent. Under these conditions, **4** was still obtained with a very good yield (85%; entry 9).

Analogous experiments were conducted using the less reactive 4-methoxybenzoyl chloride (**2b**) (Table 2, entry 10–13). As observed, using DCM and subsequently heating the reaction mixture to 160 °C for 1 h, **5** was obtained with a further increase of the yield (**5**, 56%) whereas **3** decreased to 5% (entry 13).

Afterwards, we extended our optimized reaction conditions to the synthesis of a series of 3-acyl benzofurans **4**–**20**. Specifically, we tested

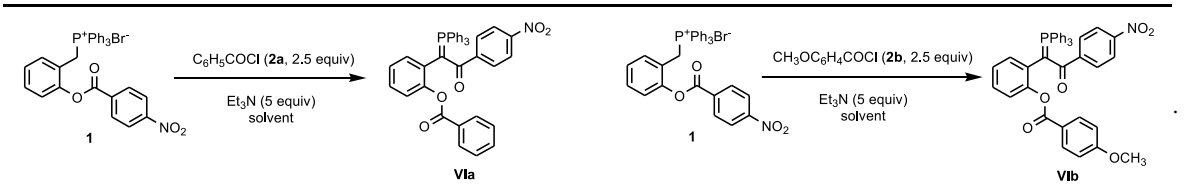


Scheme 1. Previous methods and currently work on EWG-bearing 2-phenyl-3-acylbenzofurans.



Scheme 2. Possible mechanism of formation of compound **3**, and the 3-acyl derivatives **4** and **5** *via* intermediates **VIa-b**.

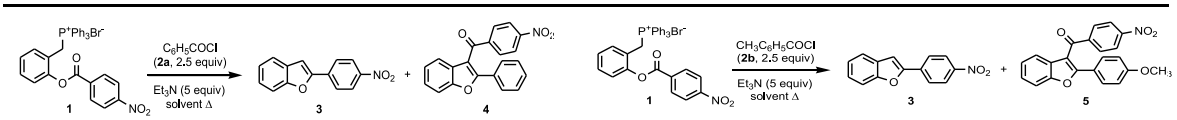
Table 1
Optimization of the reaction conditions for intermediates **VIa** and **VIb**.



entry	solvent	temperature(°C)	VIa (%)[a]	entry	solvent	temperature (°C)	VIb (%)[a]
1	toluene	40	25	4	*o*-DCB	40	N. D.
2	ACN	40	75	5	ACN	40	30
3	DCM	40	75	6	DCM	40	54

[a] Isolated yields.

Table 2
Optimization of the reaction conditions for the 3-acyl derivatives **4** and **5**.



entry	solvent	time (h)	temperature (°C)	3 (%)[a]	4 (%)[a]	entry	solvent	time (h)	temperature (°C)	3 (%)[a]	5 (%)[a]
1	DMF	24	160	0	0	10	*o*-DCB	3	180	27	29
2	DMSO	24	180	0	0	11	ACN^/o-DCB**	3	80–180	7	25
3	Toluene	3	110	42	15	12	DCM*/o-DCB**	3	40–180	8	53
4	CB	3	110	30	45	13	DCM***	3	40–160	5	56
5	CB	3	140	38	53						
6	*o*-DCB	3	140	13	68						
7	*o*-DCB	3	180	0	80						
8	DCM*/o-DCB**	3	40–180	0	85						
9	DCM***	3	40–160	0	85						

[^] 2 h at 80 °C.
[a] Isolated yields.
[*] 2 h at 40 °C.
[**] 1 h at 180°C after removing DCM.
[***] 2 h at 40 °C, 1h at 160 °C after removing DCM.

the reactivity of phosphonium salt **1**, **1′** and **1″**, prepared from *ortho*-cresol, as previously reported [28], with highly reactive benzoyl chlorides (R═NO_2, CN, CF_3, Cl, 2,6-di-Cl). The scope of the reaction is reported in Schemes 3–5.

We noticed that the reaction gave better results when phosphonium salts bearing an EWG on the benzoyloxy ring reacted with highly reactive benzoyl chlorides. Under these conditions, the phosphonium salt undergoes benzoyl group migration, acylation and thermal cyclization to furnish the single 3-acyl isomer in good to very good yields, even when the EWG was located in the *meta* position.

The generality of the reaction was also tested using less reactive benzoyl chlorides **2b** (R═OCH_3). In this case, the 3-acyl isomers were isolated in acceptable yields (Scheme 3, **5** 56%; Scheme 4, **11** 50%) together with few amounts of the 2-phenylbenzofuran derivative. Steric factors make intramolecular acylation difficult. When 2,6-dichlorobenzoyl chloride **2g** was used, the regioisomer arising from intramolecular acylation was not detected whereas the regioisomer arising from direct acylation was detected in very low yield (Scheme 3, **9** 3%), reasonably because of steric hindrance by the two chlorine atoms. However, it cannot be excluded that using the less hindered 2-chlorobenzoyl chloride the desired reaction can occur at some extent. Studies to verify the versatility of this method, when applied to aliphatic acyl chlorides, are underway in our laboratory.

2.1. Biological results

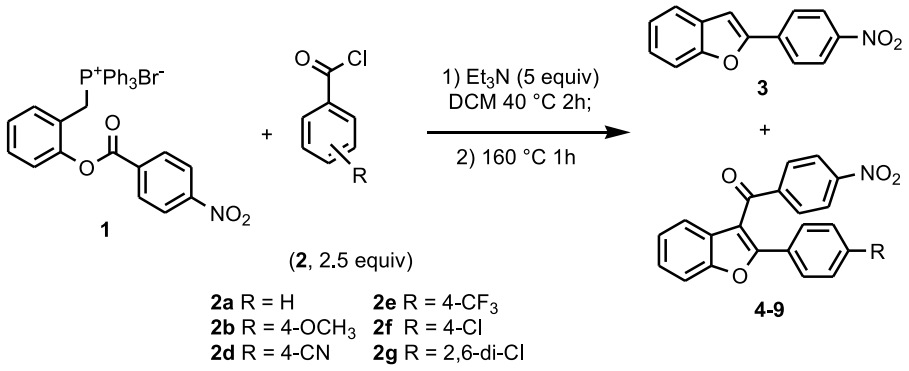
The functionality at CB1 receptors was studied for benzofurans *para*-substituted on the 3-benzoyl ring **4**–**8**, **10**, **11**, **13**, **14**, **15**–**17** by using [^{35}S]GTPγ*S* binding assay, a well validated functional assay for GPCRs, using membranes from rat brain cortex, as previously reported [33–35]. To verify if the compounds act as CB1 receptor agonists or antagonists, compounds were tested alone or in the presence of 5 μM WIN-55,212-2 (WIN) at two different concentrations (0.1 and 1 μM). WIN, the full CB1 receptor agonist, was used as the reference compound. As expected, WIN at 5 μM stimulated [^{35}S]GTPγ S binding to approximately 122.0 ± 5.3% of the basal activity.

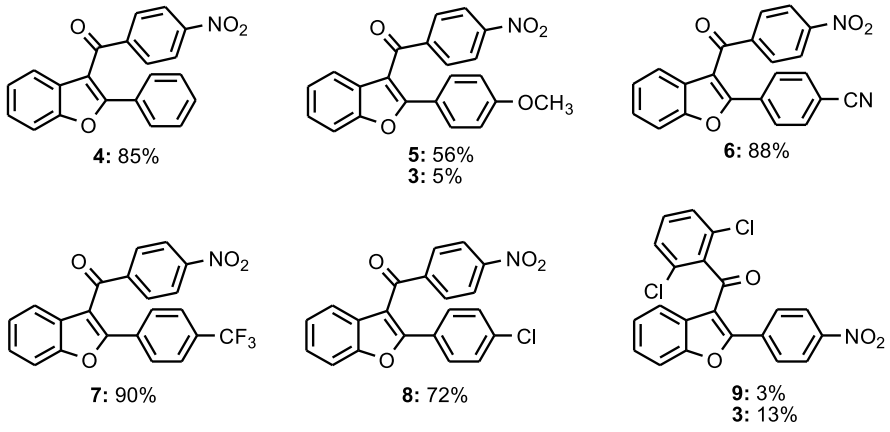
As shown in Table 3, the well-known antagonist AM251 inhibited both WIN-stimulated and constitutive GTPγS binding, which confirms its inverse agonist activity. All tested compounds, except **4** and **5**, reduced the basal [^{35}S]GTPγS binding to rat cortical membranes, showing inverse agonist activity. Specifically, at the highest tested concentration, they induced a weak decrease of basal [^{35}S]GTPγS ranging from −11 till −22 %, respect to basal values.

Of note, compounds **7**, **14**, **8**, **4**, **13** and **11** inhibited in a concentration-dependent manner WIN-stimulated GTPγS activity (−43 to −31 %) displaying an antagonist activity. The other compounds were less or much less active.

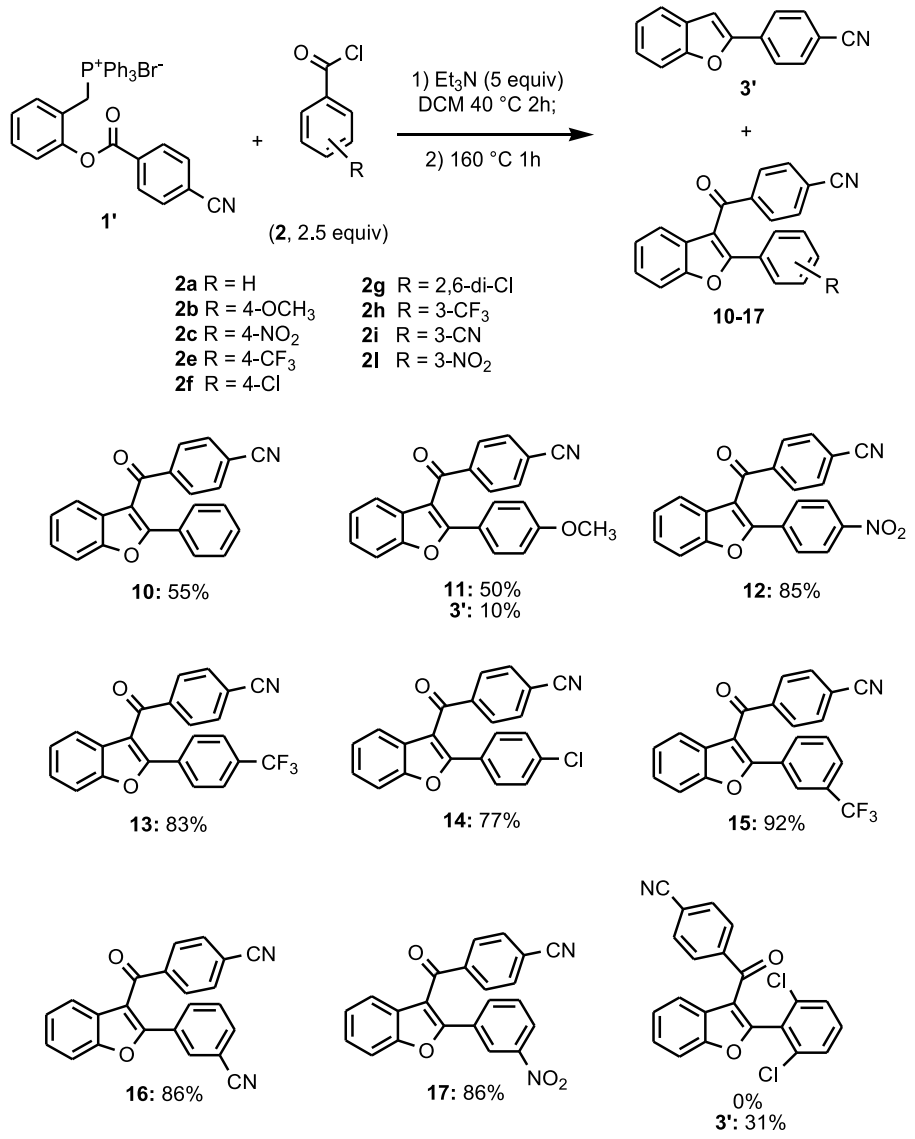
3. Conclusion

In summary, we have developed a regioselective, efficient, and low-cost synthetic procedure for the rapid preparation of new 3-benzoyl-2-phenylbenzofurans bearing a variety of EWGs on the 2-phenyl ring. The method relies on an intramolecular migration of a benzoyl group in





Scheme 3. Migration/acylation/cyclization of **1** with various benzoyl chlorides **2**.



Scheme 4. Migration/acylation/cyclization of **1′** with various benzoyl chlorides **2**.

o-acyloxybenzylidenephosphoranes upon the action of benzoyl chlorides in refluxing DCM; the thermal cyclization under solvent-free conditions of the acyl ylide intermediate gives selectively the desired 3-benzoyl-2-arylbenzofurans in good to very good yields. Beside the several advantages offered by this approach (mild reaction conditions, simple operation and catalysts and metals free), the method allows a modular assembly of target products from *o*-cresol and two different benzoyl chlorides providing opportunities for diversified synthesis of large product libraries. Therefore, we believe that the present method can be considered as a complementary procedure to those already known, which are however suitable only for EDG-substituted 3-acyl analogues. The method may have wide applications in both organic and medicinal chemistry as it allows the access to novel NO_2, CN and CF_3-containing 3-acy-2-phenylbenzofurans, which otherwise can be difficult to prepare. Moreover, some of the new synthesized compounds displayed activity as CB1 antagonists. These results are particularly interesting since they might open the avenue to a new class of antagonists of the CB1 receptor, involved in a series of diseases and syndromes, including addiction, pain, eating disorders.

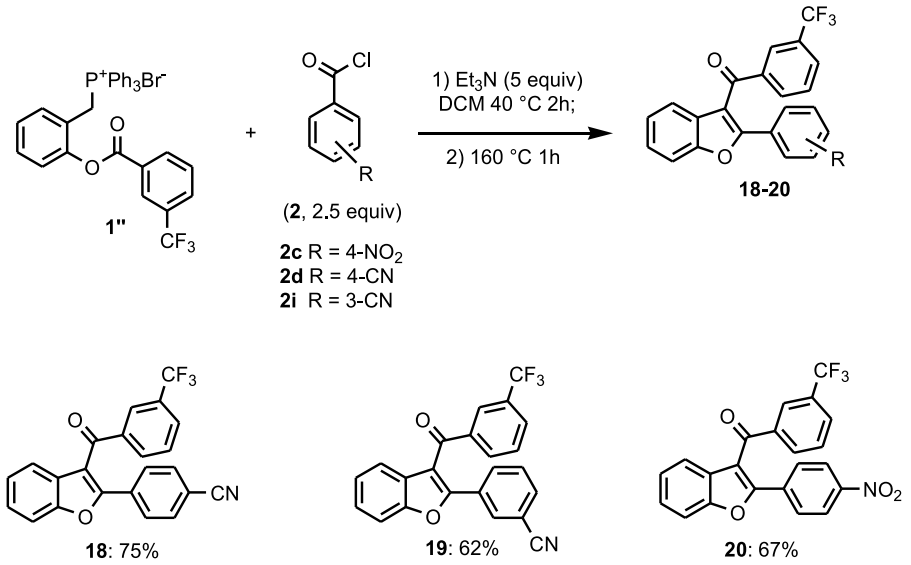
4. Experimental section

4.1. General procedure for migration/acylation/cyclization reaction

In a round bottom flask *o*-benzoyloxybenzyltriphenylphosphomium bromide **1**, **1′** or **1′′** (1.0 equiv.) and the proper benzoyl chloride (2.5 equiv.) were added and dissolved in dichloromethane (25 mL/mmol). Then triethylamine (5 equiv.) was added dropwise and the reaction mixture was stirred under reflux for 2 h. DCM was removed under reduced pressure, and the reaction mixture heated to 160 °C for further 1 h. The crude mixture was purified by column chromatography on silica gel in petroleum ether/ethyl acetate to furnish the desired products **4**–**20**.

CRediT authorship contribution statement

Michela Begala: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Michele Mancinelli:** Formal analysis, Data curation. **Rafaela Mostallino:** Formal analysis, Data curation. **Maria Paola Castelli:** Investigation, Formal analysis, Data curation. **Giovanna Lucia Delogu:** Supervision, Data curation, Conceptualization.



Scheme 5. Migration/acylation/cyclization of **1″** with various benzoyl chlorides **2**.

Table 3
Effects of compounds on the stimulation of [^{35}S]GTPγS binding *via* CB1 receptor.

Compound	Decrease (%) relative to basal		Decrease (%) relative to 5 μM WIN	
	0.1 μM	1 μM	0.1 μM	1 μM
7	−8.33 ± 1.76	−22.30 ± 1.20	−33.70 ± 2.91	−43.70 ± 0.88
14	−5.00 ± 2.00	−19.70 ± 0.33	−31.70 ± 4.70	−39.00 ± 2.31
8	−8.33 ± 2.40	−15.70 ± 1.45	−24.30 ± 2.40	−32.30 ± 2.67
4	−6.67 ± 2.91	−3.67 ± 6.98	−11.00 ± 5.51	−32.30 ± 5.55
13	−11.00 ± 4.73	−17.30 ± 2.19	−32.30 ± 5.55	−32.30 ± 5.55
11	−9.67 ± 2.19	−13.70 ± 2.33	−24.00 ± 5.86	−31.30 ± 3.93
15	−5.00 ± 2.31	−17.70 ± 1.33	−27.30 ± 2.03	−26.70 ± 0.33
10	−9.33 ± 3.93	−15.00 ± 0.58	−17.70 ± 5.36	−27.70 ± 5.67
6	−9.67 ± 2.33	−22.00 ± 0.58	−23.00 ± 4.04	−27.30 ± 6.97
17	−9.33 ± 3.71	−15.70 ± 3.84	−22.30 ± 6.17	−18.00 ± 4.62
16	−3.00 ± 1.53	−11.30 ± 2.85	−17.70 ± 1.45	−16.00 ± 4.58
5	−12.70 ± 3.71	−12.30 ± 2.19	−17.30 ± 5.04	−12.30 ± 2.19
AM 251	−8.00 ± 3.39	−14.10 ± 2.27	−77.60 ± 1.66	−86.90 ± 1.93

Data are the mean ± SEM of 3–4 experiments, each performed in triplicate. As the maximal effect of 5 μM WIN alone differed between experiments, data were normalized to the effect of 5 μM WIN (control, set as 0%).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Supplementary data to this article can be found online at. Change "Supplementary data to this article can be found online at. " with "Data will be made available on request"

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2024.133880.

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