Unexpected detection of 3-aryloxybenzofuran side products in the preparation of 2-arylbenzofurans: Identification, characterization, and comparison with chalcone's fragmentation patterns using EI/MSn

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Abstract
A gas chromatography-mass spectrometry study of the intramolecular Wittig reaction revealed, together with the expected 2-phenylbenzofuran, the formation of an unexpected side product that has not been reported until now. This study reports the identification of the by-product, i.e., the 3-benzoyl-2-phenylbenzofuran, on the base of its mass spectrometric behavior using a combination of electron ionization, exact mass measurement, multiple stage mass spectrometry, and labelled compounds. This study reports the common fragmentation pathways and discusses possible fragment structures of characteristic ions from a series of 3-aryloxy-2-arylbenzofuran derivatives obtained as by-product under Wittig conditions. Emphasis is laid on the formation and structure investigation of the [M-H]+ and [M-OH]+ ions. Our results showed interesting analogies with the mass spectrometric behavior of chalcones.

KEYWORDS
[M-OH]+, 3-aryloxybenzofurans, chalcone-like fragmentations, intramolecular Wittig reaction, MSn

1 | INTRODUCTION

2-Phenyl[b]benzofurans serve as core structures of many natural and artificial compounds of biological and medical importance. In the course of a program directed towards the synthesis of novel monoamine oxidase and butyrylcholinesterase inhibitors, we planned to synthesize 2-phenylbenzofurans using an intramolecular Wittig procedure due to the accessibility and simplicity of this methodology. In particular, compounds 4a-g were prepared from the appropriate triphenylphosphonium salt 2 and the commercially available aroyl chlorides 3a-g (Scheme 1).

The reaction mixtures were analyzed by gas chromatography (GC) coupled with mass spectrometry (MS) because the reaction products are susceptible to analysis by GC for their volatility and thermal stability. However, while developing this procedure, GC/MS analysis of the reaction mixture, obtained from the salt 2 and the benzoyl chloride 3a, revealed that, together with the desired product of cyclization 4a, the unexpected side-product 5a was present. The same trend was observed in the crude reaction mixtures of the main products 4b-g, obtained from the reaction of 2 with a variety of aroyl chlorides (3b-g). Although the Wittig reaction has been described in several papers regarding the preparation of 2-arylbenzofuran derivatives, the formation of secondary products was not mentioned.

Identification of unknown peaks is useful to permit discovery of novel or unexpected reaction products and play an important role in comprehending the reaction mechanism by which this reaction evolves. However, isolation and purification of sufficiently large quantities of by-product compounds for their unambiguous identification and characterization by different instrumental techniques, such as infrared spectroscopy and nuclear magnetic resonance, is a very complex and time-consuming process. Nowadays, GC-MS coupled to multiple stage mass spectrometry (MSn) is an invaluable tool for the rapid identification and structural characterization of unknown compounds, especially when low amount of analyte or not very pure samples are
available for the analysis. Hence, we have undertaken a detailed investigation on the unknown side products aimed to identify their structure and to elucidate their mass spectrometric behaviour. To this aim, EI-MS \(^n\) experiments were performed using a quadrupole ion trap (IT) analyser as it is very efficient multiple-stage mass spectrometers.\(^5\)

## 2 | EXPERIMENTAL

### 2.1 | MS analysis

All experiments were performed with a Varian Saturn 2000 IT mass spectrometer, operating under electron ionization (EI) conditions (electron energy 70 eV, emission current 20 nA, ion-trap temperature 200°C, manifold temperature 80°C, and automatic gain control target 21,000) with the IT operating in scan mode (scan range from \(m/z\) 40–400 at a scan rate of 1 scan/s), coupled with a Varian 3800 gas chromatograph (Varian, Walnut Creek, CA).

Collision-induced dissociation (CID) experiments were carried out by using helium as the collision gas (gas purity [He] was 99.9999%). For MS \(^n\) experiments, the supplementary rf voltage (45–55 V) was varied in such a way that the relative abundance of the surviving precursor ions was 5–15%. An isolation time of 10 milliseconds, excitation time of 40 milliseconds and an isolation width of 3 \(m/z\) for the precursor ion were used. Each MS/MS spectrum was an average of 5 scans.

Compounds 5a–g (1-µL aliquots of \(1.0 \times 10^{-5}\) M solutions in dichloromethane) were introduced into the gas chromatograph inlet. An Agilent J&W VF-5 ms low-bleed/MS GC capillary column (30 m, 0.25 mm i.d., 0.25-mm film thickness) (Agilent Technologies Inc., Wilmington, DE, USA) was used. The oven temperature was programmed from 150°C (held for 2 min) to 310°C at 30°C/minute (held for 2 min). The temperature was then ramped to 350 at 20°C/minute. The transfer line was maintained at 180°C and the injector port (30:1 split) at 290°C.

HRMS: MS analyses were performed on a Agilent 6520 LC-ESI(+)-QTOF-MS operated in the positive ion mode. Compounds (1 mg) were dissolved in acetonitrile (CH$_3$CN, 0.5 ml), and after injection mass spectral data were acquired in the range \(m/z\) of 100–1500 with an acquisition rate of 1.35 spectra/s, averaging 10,000 transients. The source parameters were adjusted as follows: drying gas temperature 250°C, drying gas flow rate 5 L/min, nebulizer pressure 45 psi, and fragmentor voltage 150 V.

### 2.2 | Materials and reagents

All reagents and solvents were purchased from Sigma-Aldrich (Sigma-Aldrich Srl, Milan, Italy) and Alfa Aesar (Thermo Fisher, Kandel, Germany) and used without further purification.

Compounds 4a and 5a were obtained by 2-benzyloxy-benzyl triphenyl phosphonium bromide 2 (1.1 mmol) and benzoyl chlorides (1.1 mmol) in the presence of Et$_3$N in toluene using the Wittig methodology described by Hercouet and Le Corre.\(^4,5\) Compounds 4b–g and 5b–g were prepared using an adaptation of this procedure.\(^6\)

2-(Hydroxydideuterium-methyl) phenol 1d$_f$ was prepared starting from the methyl 2-hydroxybenzoate in THF at 0°C using lithium aluminium deuteride, as described in literature.\(^7\)

The reference compound 3-benzoyl-2-phenyl-benzofuran was prepared by direct Friedel-Craft acylation of the 2-phenylbenzofuran 4a with benzoyl chloride using AlCl$_3$ as Lewis acid in anhydrous dichloromethane.\(^8\)

3-Benzoyl-2-phenyl-d$_4$-benzofuran 5ad$_f$ was synthesized in the same way as 3-benzoyl-2-phenyl-benzofuran starting from 2-phenylbenzofuran-d$_5$ 4ad$_5$.

2-Phenylbenzofuran-d$_5$ 4ad$_5$ and 3-benzoyl-d$_5$-2-phenyl-d$_5$-benzofuran 5ad$_{10}$ were prepared starting from 2-benzoyl-benzyl triphenyl phosphonium bromide 2 and benzoyl chloride-d$_5$ in toluene and Et$_3$N using the procedure reported elsewhere.\(^7\)

3-Phenyl-4H-chromen-4-one 6 (isoflavone) was prepared by Suzuki-Miyaura cross-coupling of 3-iodochromene with benzenboronic acid catalysed by Pd(O)/C.\(^10,11\)

## 3 | RESULTS AND DISCUSSION

### 3.1 | Identification of the by-product 5a

A typical gas chromatogram of the reaction mixture from the triphenylphosphonium salt of 2-hydroxybenzyl alcohol and the benzoyl chloride is presented in Figure 1. As can be seen, together with the desired 2-phenylbenzofuran 4a (TR 9.2 min) and the triphenylphosphine oxide (TR 12.5 min), one further peak is present at higher retention time (TR 12.6 min), corresponding to the unexpected product 5a.

By comparing the data obtained from the EI mass spectra of compounds 4a and 5a (Figures 1 and 2A), it was enabled to define which part of the molecule of 2-phenylbenzofuran 4a was also present in the structure of the unknown compound 5a. In particularly, we focused
our attention on the diagnostic ion at m/z 193 in the mass spectrum of 5a (Figure 2A). This ion most likely corresponds to the intact 2-phenylbenzofuran molecule deprived of a H atom. In fact, under MS/MS experiments, m/z 193 exhibits the loss of CO typical of the benzofuran nucleus to give the ion at m/z 165, which is also observed in the EI and MS/MS mass spectra of the 2-phenylbenzofuran 4a (M⁺).
m/z 194.12-14 As the sum of m/z value of the fragment ions at m/z 193 and m/z 105, absent in the mass spectrum of 4a, is equal to m/z M–(m/z 298), these two ions could be complementary ions, representing two parts of the molecule; the rest of the structure was determined by comparison of the data achieved from the identification of the ion at m/z 105, with that from accurate mass measurement of the unknown compound 5a. Under CID experiments, the m/z 105 ion decomposes into ions at m/z 77 and 51 thus indicating the presence of a benzoyl group (C_{6}H_{5}CO) in the structure of 5a.15 Accordingly, accurate mass measurement for the side product 5a reveals a C_{21}H_{14}O_{2} (calc. 299.1066 exp. 299.1066) composition, showing that the mass difference between 5a and the 2-phenylbenzofuran 4a (C_{14}H_{10}O) was in seven carbon atoms, four hydrogen atoms, and one oxygen (104 Da) suggesting the addition of a benzoyl group to the main product 4a.

Even more, when the reaction was performed using the labelled benzoyl chloride-d5 3Ad5 in place of the benzoyl chloride 3a, we found that the molecular ion shifted from m/z 298, for compound 5a, to m/z 308, for the labelled compound 5Ad10, thus confirming that two molecules of the labelled acyl chloride contribute to the structure of the side product (Figure 2B). The general structure of acylated 2-phenylbenzofuran was then proposed for the unknown compound 5a.

The position of the acyl group was then investigated using the 2-hydroxybenzyl alcohol-d2 1d2 as starting reagent. The Wittig reaction so performed leads to the unlabelled acyl benzofuran 5a at m/z 298. These data clearly show the lack of methine hydrogen in the furan ring of compound 5a, thus demonstrating that the benzoyl group is attached to the C-3 position of the benzofuran nucleus. Our results indicate, therefore, that the side products 5a most likely have the 3-arylbenezofuran structure depicted in Scheme 1. The model 3-benzoyl-2-phenylbenzofuran was prepared by Friedel-Craft acylation of the 2-phenylbenzofuran 4a and was analysed by MS, as a final confirmation of the proposed structure for 5a. A detailed study aimed to provide a much deeper insight into the reaction mechanism that lead to the 3-arylbenezofuran have been reported elsewhere.7

These findings are of particular interest since the 3-arylbenezofuran scaffold constitutes the core of many pharmaceutical drug candidates such as amiodarone,16 LY 320135,17 benzbrromarone,18 and SKF-64346.19 Moreover, from synthetic viewpoint, this procedure represents a new regioselective and versatile synthetic approach to 3-acyl derivatives.7 However, to the best of our knowledge, mass spectrometric investigation of 3-arylbenezofuran has received only little attention with most of emphasis devoted to the plasma and urine detection of few biologically active compounds, i.e., amiodarone, benziodarone, desethylamiodarone,20,21 and benzbrromarone.22

A detailed study dealing with the fragmentation of aroyl benzofuran has also appeared; however, it only covered the ESI MS/MS behaviour of 2-aryl derivatives.23

Therefore, as a material for further investigations, we present a systematic and detailed study on the El-induced fragmentation of 3-benzoyl-2-phenylbenzofuran. To this aim, we selected several ring substituted 3-acyl derivatives obtained by our procedure and subjected them to El MS experiments using an IT mass spectrometer.

### 3.2 Fragmentation typical for 3-arylb-2-arylbenzofurans

The El mass spectra of compounds 5a-g are depicted in Table 1. We divided the structure into three parts: the benzofuran scaffold, the aroyl group (ring A), and the aryl group (ring B) (see Scheme 2 referred to compound 5a, Ar = C_{6}H_{5}J). Two sets of acylation ions were observed resulting from the two competing α-cleavages next to the carbonyl group, i.e., the [M–Ar]+ ions a and the ArC=O+ ions b. Both types of acylation ions under MS/MS conditions undergo the typical loss of CO to generate, respectively, the 2-phenylbenzofuran fragment ions c (complementary to ion b) and the phenylion ions d (complementary to ion a), which, therefore, allow an easy identification of the original intact molecule (vide supra). The only exception to this trend was observed for the nitro derivatives 5b. Under CID experiments, each of the acylation ions from 5b, i.e., the [M–Ar]+ ion of m/z 266 and the 4-nitrobenzoxylation of m/z 150, does not show the direct losses of CO. Instead, they both form characteristic fragment ions at m/z 236 and 220 and at m/z 120 and 104, respectively, due to the losses of NO and of NO2, which only subsequently lose CO molecule (see the Supporting Information).

We also examined how the intensity of ions b is influenced by substituents on rings B or by heteroaromatic rings, for instance, furyl and thieryl moieties. Concerning compounds 5b-e, we found that the intensity of the acylation ions b is strongly influenced by the nature of the substituent on the benzoyl group (Table 1). In the mass spectrum of compound 5e, bearing the methoxy group on the ring B, the p-methoxybenzoyl cation (m/z 135) is particularly intense (relative abundance, R.A. 36%). This behaviour can be explained with the ability of the p-methoxy group to exert resonance stabilization of the p-methoxybenzoyl cation. The mass spectra of the heteroaryl compounds 5f and 5g exhibit the ArC=O+ ions rather intense (R.A. 44 and 37%) reasonably because the 2-furyl and 2-thienyl substituents have electronic effect comparable with that of p-anisyl group, well recognized as an overall electron-donating system.

In the case of compounds 5b-d bearing electron withdrawing groups, NO2, CN, and CF3, the formation of the ArC=O+ ions is strongly suppressed (R.A. 4–16%) in favour of the [M–Ar]+ ions (R.A.34–63%). Moreover, the stronger the electron-withdrawing effect on the ring B, the lower is the relative abundance of the benzoyl cation b.

The [M–Ar]+ acylation ions a constitute the most prominent fragment ions in the mass spectra of all compounds (R.A. 34–66%), with the only exception of compounds 5e-g, for which the formation of ion b is the most favoured process (vide supra). A possible representation of the [M–Ar]+ ions is the resonance-stabilized oxonium structure j depicted in Scheme 2, which could account for the high intensities observed. We therefore thought of interest to compare the CID mass spectrum of the [M–Ar]+ ions from 5a with that of the oxonium ion at m/z 221 formed in the El mass spectrum of isoflavone 6 (m/z 222),25 used as reference ion (Figure 3). As can be seen, the CID mass spectra are very similar, proving that the cyclization to structure j occurs to some extents. There is, however, a difference in the relative intensity.
### TABLE 1  El (70 eV) mass spectra of compounds 5a-g

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<th>5ad₁₀</th>
<th>5ad₂</th>
<th>5b</th>
<th>5c</th>
<th>5d</th>
<th>5e</th>
<th>5f</th>
<th>5g</th>
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Abbreviation: El: electron ionization.

### SCHEME 2  Main proposed fragmentation pathways for compound 5a on the basis of MS² and MS³ spectra. Possible structures for ions at m/z 221
of the m/z 193 ion. This ion that we assign to the CO loss is more abundant for the compound 5a (45% vs 4%). These data can be rationalized by the fact that part of the m/z 221 ion population of 5a possesses the open structure a, which undergoes easier this fragmentation.

In addition to the α-cleavages, characteristic for carbonyl compounds, some further interesting losses were observed under EI-MS and MS/MS experiments, ie, the losses of H- and of OH- radicals from the molecular ion.

3.3 | Elimination of a hydrogen radical

The EI mass spectra of the 3-benzoyl-benzofurans 5a-e show intense [M-H]+ ions (Table 1). In the MS/MS spectra, the H loss was even more pronounced (Figure 4). Only for compounds 5b and 5e, the H- loss occurred together with the loss of the substituent or of part of it as they show the total loss of 47 and 16 amu from the molecular ion. We suggest that the first step is the loss of a hydrogen atom and that NO2 or CH3 are lost from the even-electron ion so formed. Thus, the high abundant ions at m/z 341 and m/z 342 were attributed to the [M-H-NO2]+ and the [M-H-CH3]+ for compounds 5b and 5e, respectively (Figures 4B and 4E).

To get insight into the structure of the [M-H]+ specie, we first investigated the origin of the H- lost. To this aim, the MS/MS spectrum of the unsubstituted compound 5a (m/z 298; Figure 4A) was compared with that of its deuterium labelled analogue 5ad10 (rings A and B = C6D5; m/z 308. Figure 2C). Under this condition, 5a formed the stable ion at m/z 297, with a R.A. of 100%. The loss of 2 amu (m/z 306) from the molecular ion of the labelled derivatives 5ad10 (m/z 308) clearly indicates that the source of the H- eliminated is the phenyl group in position 2 (ring A) and/or the aroyl group in position 3 (ring B). MS/MS experiments on the 3-benzoyl-2-phenyl-ds-benzo furan 5ads (Figure 5B) has helped to further elucidate the origin of the H- loss. Under MS2 experiments the molecular ion of the labelled derivative 5ads (ring A = C6D5; m/z 303) shows the preferential loss of deuterium radical from the ring A (m/z 301 R. A. 100%), rather than the loss of H- from the benzoyl group (ring B; m/z 302 R. A. 25%). This result indicates that the former process requires less energy than the latter and consequently is more favoured. In fact, MSn experiments performed using an IT, privilege processes with the lowest critical energies.26 Accordingly, a different trend was observed in the full-scan EI mass spectrum of 5ads, which displayed the ions at m/z 302 and 301 with similar intensities (R.A. 29 and 34%; Figure 5A).

We supposed that the driving force for the loss of the aromatic hydrogen radical preferentially from ring A lay in the formation of a highly resonance-stabilized ion, ie, the oxonium ion k reported in

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**FIGURE 3** (A) Electron ionization mass spectrum of isoflavone 6. Collision-induced dissociation of the m/z 221 ions of (B) isoflavone 6 and (C) compound 5a.
Scheme 3. A possible mechanism consists in an intramolecular aromatic substitution reaction; this might occur through the interaction of the carbonyl group with the 2′ position of the phenyl ring A to form a six-membered ring and consequent hydrogen radical loss that would result in restoration of aromaticity to ring A. Analogous rearrangement process was also postulated to occur by Ronayne and co-workers and by Van de Sande and co-workers for chalcones and led to the formation of an oxonium ion. In fact, 3-benzoyl-2-phenylbenzofurans
**SCHEME 3**  Proposed mechanism of radical H loss from compound 5a and similarity with chalcone (bold part of the structures)

**SCHEME 4**  Proposed mechanism of OH loss for 5a

**SCHEME 5**  Chalcones-like mechanism of OH loss for 3-benzoyl-2-phenylbenzofurans (benzofuran-chalcones hybrids)

**FIGURE 6**  (A) MS², (B) MS³, and (C) MS⁴ of the M+ ion of compound 5c (m/z 388)
can be considered as benzofuran-chalcones hybrids, where the C2-C3 double bond of the benzofuran nucleus fixes in the cis disposition the chalcones-type double bond (bold part of the ions in Scheme 3). It must be point out that the aromatic oxonium ion \( k \) could further rearrange to the structure \( k_1 \), as demonstrated to occur in chalcones and 3-flavene by Traldi and co-workers.\(^{29}\) Unfortunately, unlike chalcones, CID experiments on the \([M-H]^+\) ion lead to the losses of \( \text{CHO} \) and \( \text{CO} \) that agree with both structures \( k \) and \( k_1 \).

### 3.4 Elimination of hydroxyl radical: 3-aryl-2-arylbenzofurans vs chalcones

All compounds under investigation exhibit unusual and fairly small \([M-17]\) peaks (Table 1). With the only exception of compounds 5a, 5c, and 5d, this behaviour is somewhat increased in intensity under MS/MS conditions (R.A. 2-30\%: Figure 4). The deuterium labelling results using the simplest 3-benzoyl-benzofuran 5a indicate that a deuterium was involved in this process. As can be seen, in the mass spectrum, the deuterated analogue \( 5a_{d10} \) (Figure 2B), ions at \( m/z \) 281 shifted to \( m/z \) 290 reflecting the loss of OD from the molecular ion. The most reasonable inference is that the oxygen involved in the OH loss arises from the carbonyl group. In fact, compounds 5a, as well as compounds 5f and 5g, have no additional substituents, which could themselves produce \([M-OH]^+\) ion. To the best of our knowledge, only few papers have been reported on the involvement of a carbonyl oxygen atom in the formation of dehydroxylated ions. Bowie and White described the formation of \([M-H_2O]^+\) and \([M-OH]^+\) ions in the mass spectra of aromatic carbonyl compounds, which contain an ortho (or peri) methoxy-substituent.\(^{30}\) More recently, Zenchevich and Pushkareva reported that compounds bearing -CO-CH=CH-N\((\text{CH}_3)_2\) structural fragments exhibit unusual peaks of \([M-OH]^+\) ions formed by a rearrangement with the migration of a hydrogen atom.\(^{31}\)

To get insight into the mechanism of formation of the \([M-OH]^+\) ion, further experiments were performed on the labelled compound \( 5a_{d5} \). In the MS/MS mass spectrum of \( 5a_{d5} \), the formation of ion at \( m/z \) 285 \([M-OD]^+\) clearly indicates that the hydrogen lost derives from ring A (Figure 5B).

One of the possible mechanisms rationalizing these results is reported in Scheme 4. The carbonyl undergoes loss of a hydroxyl radical after abstraction of the hydrogen from ring A by McLafferty type rearrangement\(^{32,32}\); the ionic species so generated is plausibly represented as the ion with the structure \( y \), which contains a new five-membered ring.

In the case of \( p \)-nitro-derivative 5b, some considerations have to be done. Compound 5b has two nitro groups in the para positions of ring-A and B, respectively, which may be themselves involved in a M-OH process. The OH loss is commonly observed in nitro-aromatic derivatives, due to an ortho effect.\(^{32,33}\) However, the proximity effect described in these studies occurs between aromatic nitro function and a group in its proximity, ie, in ortho or peri positions, and, therefore, appears unlikely for \( p \)-nitro-compound 5b where the distances between the \( NO_2 \) substituents and the phenyl rings are rather much greater.

Interestingly, Baldas and Porter\(^{38}\) reported that the spectra of 3- and 4-nitrochalcones display the loss of hydroxyl radical and that this fragmentation is initiated by the transfer of a hydrogen atom from the 2-position of the phenyl ring to the nitro group via a cyclized intermediate.

Considering the striking analogy between chalcone and 5a (vide supra), we expected, for \( p \)-NO\(_2\) derivative 5b, a similar mechanism to that reported for nitrochalcones,\(^{38}\) that involves the nitro group rather than the carbonyl. A chalcone-like mechanism was therefore proposed for compound 5b (Scheme 5).

This behaviour is in agreement with the collisional experiments performed on compound 5b (Figure 6). Under MS\(^3\) experiments, the \([M-OH]^+\) ion \((m/z 371)\) loses NO\(_2\) to form the \( m/z 341 \). MS\(^4\) experiments reveal that the \( m/z 341 \) ion fragments by the loss of a nitro radical \((m/z 295)\) and of NO\(_2\) \((m/z 311)\). However, the sequential losses of NO and NO\(_2\) from the \([M-OH]^+\) ion is also consistent with the mechanism that involves the carbonyl group (Scheme 4), which, therefore, cannot be ruled out for the nitro derivative 5b.

### 4 CONCLUSIONS

Electron ionization and collision-induced dissociation tandem mass spectrometry have proved to be highly effective for a complete structure assignment of 3-benzoyl-2-phenylbenzofuran, a side product formed in the preparation of 2-phenylbenzofurans under Wittig conditions. Our study showed that beside the alpha cleavages typical of carbonyl compounds, the usual losses of H and of OH constitute diagnostic fragmentations. These losses were attributed to the interaction between the carbonyl of the 3-acyl group and the 2-phenyl ring, thus reflecting their proximity in the structure of the benzofuran nucleus. We also evidenced that 3-aryl-2-arylbenzofurans can be considered as benzofuran-chalcones hybrids and that their EI fragmentation routes have strong similarities compared with those of chalcones. However, some differences were also underlined. In particular, we found that the OH loss from the molecular ion of 3-aryl-2-arylbenzofurans involves the carbonyl group in position 3. Only nitro-chalcones were reported to show the \([M-OH]^+\) ion, and it was suggested that the source of the OH loss was exclusively the nitro group. In the case of the analogous 3-benzoyl-2-phenylbenzofuran derivatives bearing the NO\(_2\) group, MS\(^3\) experiments demonstrated that a nitro-chalcone-like mechanism cannot be excluded.

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REFERENCES


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