Efficient synthesis and biological evaluation of dibenzo[b,e]oxepin-11(6H)-ones as potential anthelmintic agents

Jimena Scoccia,[a] M. Julia Castro,[a,b] M. Belén Faraoni,[a] Cecilia Bouzat,[b] Víctor S. Martín,[c] Darío C. Gerbino*,[a]

[a]Instituto de Química del Sur, INQUISUR (CONICET-UNS), Departamento de Química, Universidad Nacional del Sur, Avenida Alem 1253, 8000 Bahía Blanca, Argentina. E-mail: dgerbino@uns.edu.ar
[b]Instituto de Investigaciones Bioquímicas de Bahía Blanca, INIBIBB (CONICET-UNS), Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur, Camino La Carrindanga km 7, 8000 Bahía Blanca, Argentina.
[c]Instituto Universitario de Bio-Orgánica, IUBO, Departamento de Química Orgánica, Universidad de La Laguna, C/Astrofísico Francisco Sánchez 2, 38206 La Laguna, Tenerife, Spain.

Abstract

The first systematic study for the construction of a small library dibenzo[b,e]oxepin-11(6H)-ones by direct intramolecular acylation from readily available 2-(phenoxymethyl)benzoic acids was developed. For this purpose, a novel and efficient cooperative system consisting of $SnCl_2$ and Cl_2CHOCH_3 is presented. This methodology show be compatible with a wide variety of functional groups in good to excellent yields and high regioselectivity. The generality of new protocol was applied to the scalable and reproducible synthesis of tricyclic antidepressant doxepin. The synthesized dibenzo[b,e]oxepins were evaluated for their biological activities using free-living nematode *Caenorhabditis elegans* as effective and cost-efficient model system for anthelmintic discovery.

Keywords: synthesis, dibenzo[b,e]oxepin-11(6H)-one, intramolecular acylation, *Caenorhabditis elegans*, anthelmintic activity.

Introduction

Helminthiasis, also known as worm infection, is a serious problem worldwide resulting in high human morbidity and enormous economic losses in livestock [1], especially in tropical and sub-tropical countries. Anthelmintic drugs are used for the control of parasitic infections caused by helminths. The search for new and effective anthelmintics has grown sustainably in recent years, as synthetic drugs currently used in the control of helminths are expensive, and most of them have lost their effectiveness due to problems of resistance to these drugs [2]. *Caenorhabditis elegans* is a free-living nematode naturally found in soils of temperate climate, which has become a model organism for parasitic nematode research and an excellent system for the screening of compounds with potential anthelmintic activity, because it is inexpensive, readily available, and easy to work [3]. In addition, the use of *C. elegans* in assays to investigate nematode behavior, locomotion, reproduction and death is uncomplicated and reliable [4].

Natural products play an important role in drug development particularly in anticancer, antibiotics and antiparasitic drugs [5]. Its structural diversity is a source of inspiration for drug discovery and the preparation of analogs as simplified, synthetically more accessible and stable models are broadly described in the literature [6]. In this context, the tricyclic dibenzo[b,e]oxepin-11(6H)-one scaffold also know “doxepinone” emerges as an interesting synthetic target because a large number of compounds having this privileged structure present relevant biological activities; such as antidepressant, anxiolytic, anticholinergic, antihistaminic [7], antipsychotic [8] and also analgesic, antipyretic, anti-inflammatory [9] and antitumor [10]

(Figure 1). The dibenzo[b,e]oxepin-11(*6H*)-one motif containing natural products, such as chaetones I and II showed remarkable cytotoxic and antimicrobial activities [11].

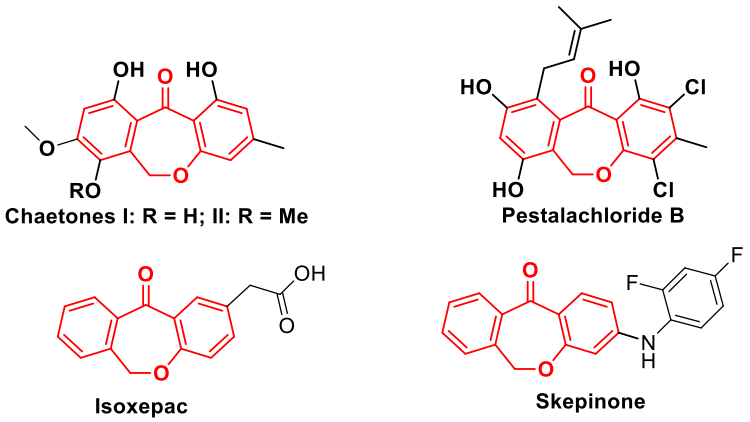


Figure 1. Representative structures of dibenzo[b,e]oxepinones of biological interest.

Interestingly, chaetone II also exhibited antitumor activity against gastric cancer cells BGC823 [12]. Moreover, the metabolite pestalachloride B displayed significant antifungal activities against different plant pathogens [13]. Dibenzo[b,e]oxepinones, isoxepac and skepinone of synthetic origin were identified as potential therapeutic agents for the treatment of inflammatory diseases, such as rheumatoid arthritis (RA), psoriasis, and Crohn's disease [14]. In addition, these pharmacophores units are very important in medicinal chemistry due their proved therapeutic properties. Biological versatility exhibited by dibenzo[b,e]oxepinones and their congeners makes them very attractive targets for synthetic chemists. Accordingly, the development of efficient methodologies for the construction of dibenzo[b,e]oxepinone unit has represented a considerable synthetic challenge in the field of organic synthesis. Even though the synthesis of this framework represents a growing field due to the requirements of medicinal chemistry researches, a limited number of approaches for their synthesis have been developed to date [15]. Among them, the two most common approaches for the synthesis of dibenzo[b,e]oxepinones are: (a) intramolecular C-O bond formation via Williamson ether synthesis [16] and (b) cyclodehydration or intramolecular Friedel–Crafts acylation reaction of intermediates with a preformed aryl benzyl ether bond [17]. However, they often suffer from a variety of disadvantages, such as, poor yields, severe side reactions, high reaction temperature, prolonged reaction time, requirement of expensive reagents, low tolerance of functional groups [15a,18] and poor regioselectivity. Similarly, other protocol under much milder reaction in the presence of trifluoroacetic anhydride was developed [19]. More recently, a new Parham cyclization methodology has been developed for the preparation of dibenzo[b,e]oxepinones. This strategy involves the generation of functionalized aryllithiums by bromine–lithium exchange, followed by intramolecular cyclization onto an electrophilic nitrile functional group [20].

Herein, we describe the development of a novel an efficient synthetic strategy for the generation of a small library of dibenzo[b,e]oxepinones by direct intramolecular acylation of 2-(phenoxymethyl)benzoic acids by using $SnCl_2$ and Cl_2CHOCH_3. To the best of our knowledge this is the first report of the construction of seven membered oxygen heterocycles employing tin and dichloromethyl methyl ether as cooperative system. In this research, all obtained dibenzo[b,e]oxepinones were evaluated for their anthelmintic activities using the experimental model nematode *C. elegans*.

Experimental section

1. General experimental details

All operations were performed under an argon atmosphere using standard Schlenk techniques. Solvents were dried and distilled in accordance with standard procedure [21]. Reactions were monitored by thin-layer chromatography on silica gel plates (60F-254) visualized under UV light and/or using 5% phosphomolybdic acid in ethanol. All ^{1}H and ^{13}C NMR spectra were recorded at room temp. in $CDCl_3$ or DMSO-d_6 on a Bruker Avance ARX-300 spectrophotometer. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane (TMS) using the residual solvent resonance ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR, Acetone-d_6: 2.09 ppm for ^{1}H NMR, 30.60 and 205.87 ppm for ^{13}C NMR; DMSO-d_6: 2.54 ppm for ^{1}H NMR and 39.50 ppm for ^{13}C NMR). Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; brs = broad signal). IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer in the ATR mode at room temp. Melting points were determined using a Büchi 510 apparatus and are not corrected. Mass spectra (EI) were obtained at 70 eV on an Agilent CG-78903 instrument equipped with a MS-5977A MSD selective mass detector. The purity of volatile compounds and the chromatographic analyses (GC) were determined with a GC Shimadzu (GC-14B) with a flame ionization detector equipped with a HP-5MS column (30 m × 0.25 mm × 0.25 µm) using nitrogen as carrier gas. High resolution mass spectra were recorded on Thermo Fisher LTQ Orbitrap XL, (for EI) and a Finnigen MAT 95 (for ESI). Flash column chromatography was performed using Macherey Nagel MN Kieselgel 60M (0.040-0.063 mm / 230-240 mesh ASTM). All starting materials were of the best available grade (Aldrich, Merck, Acros or TCI) and were used without further purification.

*2. General procedure for synthesis of dibenzo[b,e]oxepin-11(6H)-ones (**1a-1i**)*

2-(phenoxymethyl)benzoic acids derivatives (1.0 mmol), $SnCl_2$ (0.6 equiv.), dichloromethyl methyl ether (10 equiv.), and CH_2Cl_2 (10 mL) were added to a Schlenk tube under argon. The resulting solution was stirred at room temperature until the completion of the reaction. The progress of the reaction was monitored by TLC and GC-MS. The reaction was quenched by addition of water. The mixture was extracted with CH_2Cl_2, washed with aqueous saturated $NaHCO_3$ and then the combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using silica gel 60 or recrystallized in ethanol.

*3. General procedure for synthesis of 2-(phenoxymethyl)benzoic acids (**2a-2g**) - Method A*

Substituted phenol (16 mmol) was added to a stirred suspension of sodium hydride (24 mmol) in anhydrous DMF (20 mL). Upon cessation of dihydrogen evolution, phthalide (15 mmol), dissolved in the minimum amount of benzene (CAUTION) and the mixture heated under reflux for 24 h. The cooled solution was poured into ice water (50 mL) and acidified with conc. HCl. The formed precipitate was filtered, washed with water and subsequently dissolved in dichloromethane (50 mL). The organic layer was washed successively with 20% aq. Na_2CO_3 (3 × 20 mL) and water (3 × 20 mL), and dried over Na_2SO_4. The solvent was distilled off to give a solid. The crude product was used in the next step without further purification.

*4. General procedure for synthesis of 2-(phenoxymethyl)benzoic acids (**2h-2i**) - Method B*

To a solution of 6.0 g (0.04 mol) of methyl 2-methylbenzoate in 38 ml of chloroform, 7.5 g (0.042 mol) of *N*-bromosuccinimide and 0.078 g of benzoyl peroxide were added and carefully warmed up to 65 °C until reaction started. Then the mixture was refluxed for 5 h. After cooling down to room temperature, the deposit of succinimide was filtered. The solvent was evaporated under reducer pressure and the crude product was used in the next step without further purification.

To a solution of methyl 2-(bromomethyl)benzoate (6.55 mmol), substituted phenol (8.5 mmol), K_3PO_4 (16.4 mmol) and toluene 20 ml were added to Schlenk under argon. The resulting solution was stirred to 110°C for 5 h. The progress of the reaction was monitored by TLC. The mixture was extracted with EtOAc, washed with water, brine and the combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification.

To the solution of the ester (0.015 mol) in MeOH (73 mL), was added 13 mL aqueous KOH (20%) and refluxed at 80°C for 5 h. MeOH was removed and the aqueous phase was washed with DCM. After acidifying with HCl (10%) the deposit was collected and washed with water.

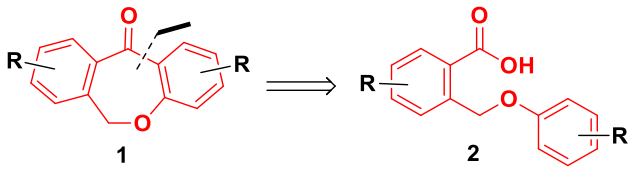
5. Anthelmintic assays using C. elegans

The *C. elegans* wild-type (Bristol variety) strain was obtained from the Caenorhabditis Genetic Center, which is funded by the NIH National Center for Research Resources (NCRR). Nematodes were raised at 21°C under standard laboratory conditions on agar plates cultured with Escherichia coli (OP50) [22]. Thrashing assays were used to measure worm motility essentially as described before [23]. Worms were synchronously grown to early adult stage. Individual young adult *C. elegans* were placed in 100 µl of M9 buffer (3 g/L KH_2PO_4, 6 g/L Na_2HPO_4, 5 g/L NaCl, 0.25 g/L $MgSO_4.7H_2O$) in the absence or presence of the compound under study (1 mM/DMSO 1%) in a 96-well microlitre plate. After 10 minutes, the number of thrashes were counted for 30 s. A single thrash was defined as a complete change in the direction of bending at the mid body. The experiments were repeated 3 times for each condition (20 worms tested each time). All assays were blind and carried out at 20-22°C. Data are shown as mean ±S.D. Statistical comparisons were done using the oneway ANOVA with Bonferroni's multiple comparison posttest. Thrashing rates lower than those of control worms with $p < 0.05$ were considered significant. The half-inhibition concentration, IC_{50}, was obtained from the curve resulting from the percentage of thrashes/ min in the presence of compound **1a** respect to the buffer condition.

Results and Discussion

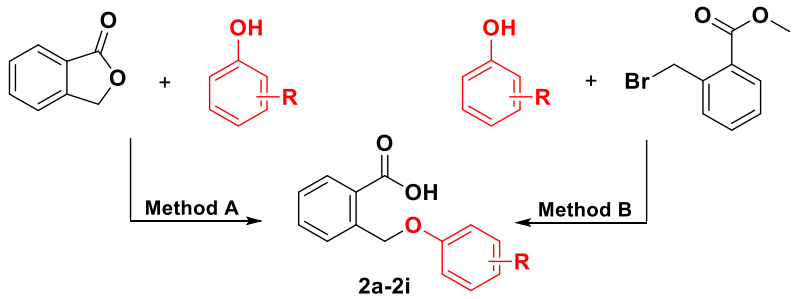
In recent studies, Jiang and co-workers [24] established an interesting intramolecular acylation of benzyl esters by using the combined system of $FeCl_3$ with Cl_2CHOCH_3. This novel reactive system offered an efficient approach to the privileged structure xanthone [25], which is structurally closely related to our target dibenzo[b,e]oxepinone. However, this protocol is subjected to some limitations, such as non-availability of starting materials and low tolerance of electron-withdrawing functional groups. Inspired by this work, and with the aim to develop an operationally simple synthesis of the dibenzo[b,e]oxepinone core, we decided to study the course of the direct intramolecular acylation of readily available 2-(phenoxymethyl)benzoic acids

by using different Lewis acids and dichloromethyl methyl ether (DCME). The strategic concept of our synthesis is summarized in Scheme 1.



Scheme 1. Retrosynthetic analysis for dibenzo[b,e]oxepinone framework.

The required starting materials for the synthesis of dibenzo[b,e]oxepinones **1a-1i** can easily be obtained by treatment of phthalide with different sodium phenoxides derivatives in DMF by modifications to known procedures (see ESI for experimental details) [15a,f]. An alternative synthetic route to access the substrates **2a-2i** involves a Williamson synthesis between methyl 2-(bromomethyl)benzoate with substituted phenoxides followed by acid hydrolysis (Scheme 2).

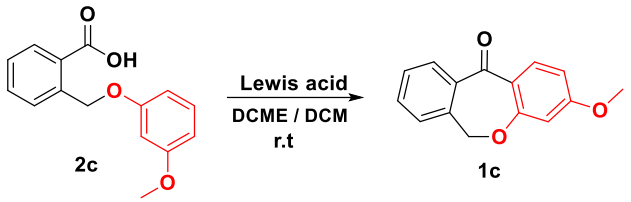


Scheme 2. Preparation of 2-(phenoxymethyl)benzoic acids **2a-2i**. *Method A*: NaH (1.5 eq.), DMF, reflux, 24 h; then 1 N NaOH, 1 M HCl; *Method B*: K_3PO_4 (2 eq.), toluene, reflux, 5 h; then KOH, methanol, reflux.

We started our study by choosing 2-((3-methoxyphenoxy)methyl)benzoic acid (**2c**) as model substrate to optimize the reaction conditions. These results are shown in Table 1.

As part of our interest in the area of green catalysis, we first focused our research in the direct intramolecular acylation of **2c** in the presence of environmentally friendly $FeCl_3$ and DCME, following the protocol reported by Jian and co-workers [24]. It was observed that the reaction did not initiate at room temperature or even heating at reflux by using the cooperative system $FeCl_3$ with DCME in the presence of dichloromethane as solvent (Table 1, entries 1, 2 and 3). However, to our surprise the reaction initiated when the amount of DCME was increased to 10 equivalents for 24 h, the desired dibenzo[b,e]oxepinone **1c** was obtained with a poor yield of only 10% in the presence of anhydrous $FeCl_3$ (Table 1, entry 4). Unfortunately, increasing the loading of catalyst to 1 equivalent was ineffective for the present transformation, recovering the starting material **2c** (Table 1, entry 5). Based on these results, we decided carry out a systematic screening of the reaction conditions by treating the model substrate **2c** with various Lewis acid [26] in the presence of DCME in dichloromethane at room temperature (Table 1). As shown in the Table, we found that $SnCl_2$ and $ZnCl_2$ gave the best results (Table 1, entries 11 and 12) while other commercially available catalysts including FeO, $CuCl_2$, $AlCl_3$, $MgCl_2$ and $SnCl_4$ showed less or no efficiency in terms of chemical yields (Table 1, entries 6-9).

Table 1. Optimization of the reaction conditions[a]

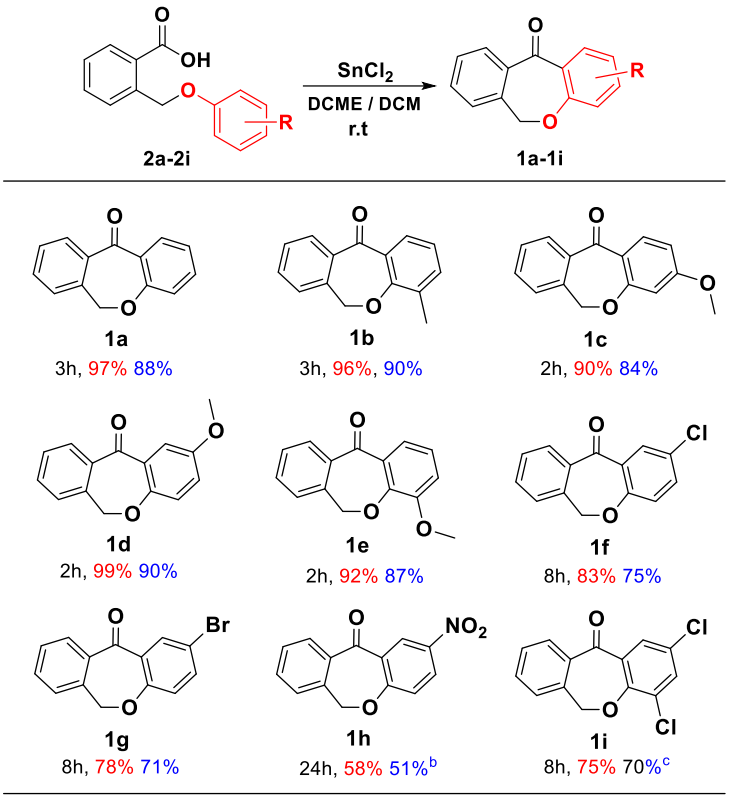


Entry	Lewis acid (eq.)	DCME (eq.)	Time (h)[b]	Yield (%)[c]
1	$FeCl_3$ (0.6)	1.0	24	n. r
2	$FeCl_3$ (0.6)	1.0	24[d]	n. r
3	$FeCl_3$ (1.0)	1.0	24	n. r
4	$FeCl_3$ (0.6)	10	24	10
5	$FeCl_3$ (1.0)	10	24	n. r
6	$SnCl_4$ (0.6)	10	24	n. r
7	$AlCl_3$ (0.6)	10	24	10
8	$CuCl_2$ (0.6)	10	3	42
9	FeO (0.6)	10	3	52
10	$MgCl_2$ (0.6)	10	24	n. r
11	$ZnCl_2$ (0.6)	10	2	80
12	**$SnCl_2$ (0.6)**	**10**	**2**	**90**
13	$SnCl_2$ (0.6)	--	24	n. r
14	--	10	24	48
15	$SnCl_2$ (0.6)	8.0	5	91
16	$SnCl_2$ (0.6)	6.0	5	43
17	$SnCl_2$ (0.4)	10	5	40
18	$SnCl_2$ (0.8)	10	2	80

[a] **Reaction conditions**: substrate **2c** (1 mmol), dichloromethyl methyl ether (DCME), in dichloromethane (0.1 M) at room temperature under argon. [b] Time reaction monitored by TLC. [c] Determined by GC using internal standard. [d] Reaction was conducted in DCM at reflux.

Taking into account the results summarized in Table 1, we choose the Lewis acid $SnCl_2$ for being the most efficient catalyst for the desired transformation. Control experiments were performed to prove the necessity of the coexistence of the catalyst $SnCl_2$ and the promoter Cl_2CHOCH_3. The experimental results showed that the presence of DCME is crucial to the success of the reaction (entry 13). Furthermore, the absence of catalyst $SnCl_2$ led to a significant decrease in reaction yield (entry 14). When the amount of DCME was decreased from 8.0 to 6.0 equiv., a pronounced decrease was observed (i.e., 91%, 43%, Table 1, entries 15–16). Both the increase and the decrease of catalyst loading were not effective in improving yields of the desired transformation (entries 17 and 18). From the amount of $SnCl_2$, it could be found that 0.6 equiv. of $SnCl_2$ was the optimal choice (Table 1, entries 12 and 15). These combined studies demonstrated that 0.6 equiv. of anhydrous $SnCl_2$ by using 10 equiv. of DCME in the presence of dichloromethane at room temperature exhibited the highest efficiency for the direct intramolecular acylation from **2c**. In order to extend the scope and the general efficiency of our methodology, we also applied this protocol to the synthesis of functionalized dibenzo[b,e]oxepinones **1a–1i** under the optimized conditions (Table 2).

Table 2. Scope for the synthesis of functionalized dibenzo[b,e]oxepinones[a]



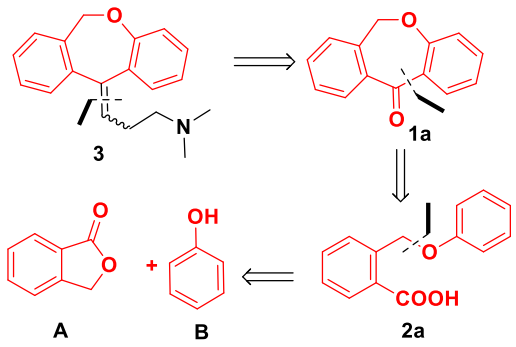
[a] **Reaction conditions:** substrates **2a-2i** (1 mmol), $SnCl_2$ (0.6 eq.), DCME (10 eq.), in dichloromethane (0.1 M) at room temperature under argon. Time reaction monitored by TLC. [b] Reaction was conducted in 1,2-dichloroethane at reflux in the presence of $SnCl_2$ (2 eq.). [c] Reaction was conducted in 1,2-dichloroethane in the presence of $SnCl_2$ (1 eq.) Determined by GC using internal standard. Isolated yield after purification.

The results shown in Table 2 indicate that the present methodology is compatible with the presence of a variety of functional groups in the starting phenols, including nitro, bromo, chlorine, methoxy and alkyl group, affording a set of substituted dibenzo[b,e]oxepinones **1a–1i** in good to excellent yields. With regard to the electronic properties of the substituents, the presence of electron-donating groups on the aromatic ring of the starting phenols led to better yields of the cyclization products **1b-1e** at room temperature. It should be noted, that by using our protocol allowed the synthesis of tricyclic fused rings starting from phenols bearing electron-withdrawing groups **1f-1i** thus overcoming one of the limitations reported by other authors [15a,f]. The product **1h** was formed very slowly in the presence of only $SnCl_2$ (0.6 eq.), but the reaction yield was improved to 51% by an increase in catalyst loading (2 eq.) and in the presence of 1,2-dichlorethane at reflux. In this case, we think that the need to use an excess of Lewis acid could be related to the first equivalent is preferably coordinated with the strong *meta*-director NO_2, leaving the second available to react with the corresponding substrate, thus generating carbocation, which promotes intramolecular acylation desired [27]. Surprisingly, treatment of compound **2i** bearing two electron-withdrawing groups Cl, afforded **1i** in good yield. In addition, the acylation showed total regioselectivity for the substrate containing a meta-substituent in the phenolic ring, and the reaction could occur at the less sterically hindered *ortho*-C–H bond of the carboxylic acid **1c**.

Although the detailed mechanism for the formation of dibenzo[b,e]oxepinone scaffold is not very definitive, it is conceivable that this reaction is a Friedel–Crafts type reaction [26], where initially, dichloromethyl

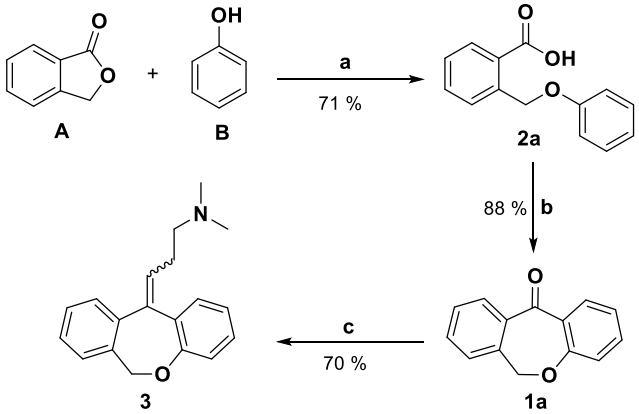
methyl ether (DCME) would promote the conversion of 2-(phenoxymethyl)benzoic acid to corresponding acid chloride acid [28] through a process of nucleophilic-elimination addition with generation of methyl formate (detected by ^{1}H-NMR from crude product). Finally, an intramolecular *ortho*-acylation catalysed by $SnCl_2$ would lead to the target **1**.

Having proven the efficiency and reliability of our methodology to access the dibenzo[b,e]oxepin-11(*6H*)-one framework, we decided to apply the described protocol to the total synthesis of known tricyclic drug doxepin. Simplified retrosynthetic analysis of doxepin **3** is summarized in Scheme 3. As a key consideration, we proceed to assemble the dibenzo[b,e]oxepin-11(6H)-one (**1a**) scaffold through a direct intramolecular acylation from 2-(phenoxymethyl)benzoic (**2a**) acid mediated by $SnCl_2$ and DCME.



Scheme 3. Retrosynthetic pathway to access the doxepin (**3**).

The target 3-(dibenzo[b,e]oxepin-11(6H)-ylidene)-*N,N*-dimethyl propan-1-amine (**3**) was synthesized in three stages. In the first stage, the 2-(phenoxymethyl) benzoic acid (**2a**) was easily prepared by treating the commercial available isobenzofuran-1(*3H*)-one (**A**) with sodium phenoxide, which was obtained by reacting phenol (**B**) with NaH in the presence of DMF at reflux. The carboxylic acid **2a** was precipitated using a mineral acid solution. The key intermediate **1a** was cyclized by intramolecular acylation from **2a** by using $SnCl_2$ and dichloromethyl methyl ether (DCME) as cooperative system in the presence of dichloromethane at room temperature. Finally, the target molecule **3** was synthesized by reacting **1a** with 3-dimethylaminopropylmagnesium chloride and the subsequent dehydration of the resulting tertiary alcohol by hydrochloric acid at reflux in good yield (Scheme 4).



Scheme 4. Total synthesis of doxepin (**3**). Conditions: NaH (1.5 eq), DMF, reflux, 24 h; then conc. HCl; b) $SnCl_2$ (0.6 eq.), DCME (10 eq.), DCM (0.1 M), r.t, 3 h; c) 3-(*N,N*-dimethylamino)propylmagnesium chloride, toluene, 65 °C, 2h; then conc. HCl, 1 h, reflux.

The proportion between *E* and *Z*-isomers in the crude product was 4 to 1. The structure elucidation of **3** was proved by its GC-MS, ^{1}H, and ^{13}C NMR spectra analysis.

This synthesis of **3** involves only 3 steps and proceeds with an overall yield of 44% starting from commercially available phthalide (**A**), thus overcoming the best chemical yields reported by other authors [29e,f] until now. Notably, most intermediates are crystalline solids and only one of the three steps required chromatographic purification. In this way, the synthesis of **3** could be performed on a multigram scale enabling us to also investigate some aspects of the reactivity.

Some xanthones (dibenzo-γ-pirones), structurally related to our target dibenzo[b,e]oxepinone, have been shown to have antiparasitic actions [30]. In this context, and considering the experience of our group in biological assays associated with this type of activity, we sought to determine if our synthesized tricyclic scaffolds act as antiparasitic drugs. To this end, we used *C. elegans* as a model of helminthic parasites and measured their rapid effects on *C. elegans* mobility by the thrashing assay method. The thrashing rate of wild-type N2 worms in M9 buffer (plus 1 % DMSO) is 204 ± 9.3/ min. After a 10-min incubation period with compounds **1a-1i** and **3** (1 mM), a slight albeit statistically significant reduction in the thrashing rate was observed (Figure 2).

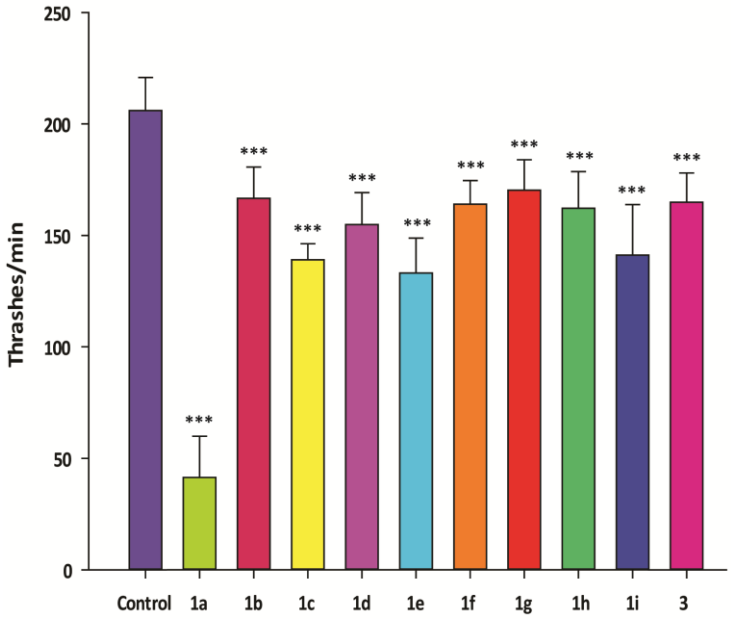


Figure 2. Thrashing rates after 10 min in M9 solution with the compounds at 1 mM. Assays were performed on three separate days. For each drug, 20 animals were assayed. **P* < 0.05; ***P* < 0.01; ****P* < 0.001.

For these compounds, the thrashing rates varied between 60-84 % with respect to the control condition. Interestingly, compound **1a** produced a much more significant effect on worm mobility, leading to a reduction of 80% of the thrashes/ min at 1 mM after a 10-min exposure (Figure 2). When analysed at a range of concentrations (30 µM to 1.5 mM), compound **1a** produced a concentration-dependent decrease of the trashing rate, with an IC_{50} value of 389 ± 50 µM (Figure 3). Increasing the incubation period to 20 min in the presence of 1 mM compound **1a** produced complete paralysis of worms.

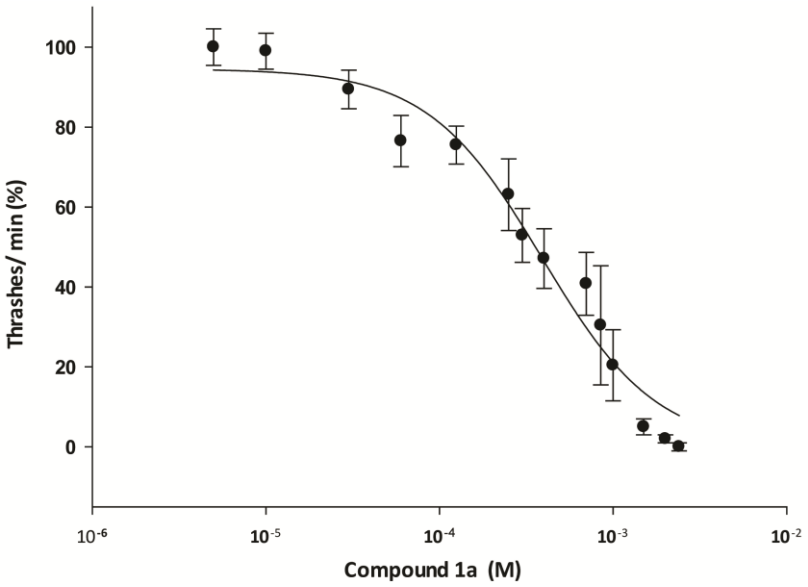


Figure 3. Dose-response curve for dibenzo[b,e]oxepin-11(*6H*)-one **1a**. Thrashing rates were plotted as a percentage of the control condition in the absence of the drug. Values are mean percentages ± SD derived from three trials performed on separate days. All experiments were performed at 20-22 °C.

Thrashing assays are useful to demonstrate short-term and rapid effects of compounds on the high-frequency *C. elegans* locomotion. In these assays, common anthelmintic drugs, such as levamisole, morantel and pyrantel (1 mM), have been shown to affect significantly the thrashing rates after 5 –10 min in M9 solution, leading to a 90% reduction and producing paralysis of the majority of animals [31]. We showed that dibenzo[b,e]oxepin-11(*6H*)-one **1a** produces similar effects as those mediated by widely-used anthelmintic drugs.

Conclusions

In conclusion, we have developed a new and complementary methodology for the easy construction of dibenzo[b,e]oxepin-11(6H)-ones from readily available 2-(phenoxymethyl)benzoic acids by using $SnCl_2$ and Cl_2CHOCH_3 as an efficient cooperative system. Due to the modularity, operational simplicity, and reliability it is likely that the method will find future exploitation in the synthesis of compound libraries in the context of investigations related to the field of medicinal chemistry. To probe the general feasibility of our protocol, we elaborated a short and scalable synthesis of tricyclic antidepressant doxepin from commercial available phthalide. The scalability of the process and the simple reaction conditions, combined with the low cost of the starting materials makes this new total synthesis transferable to pharmaceutical industry. The synthetic accessibility and significant antiparasitic activity exhibited by dibenzo[b,e]oxepinone **1a** might be a promising lead in the search for novel anthelmintic drugs. It is noteworthy that is the first report of anthelmintic activity of this class of oxygenated tricyclic compounds. Future studies may be directed to identify its mechanism of action.

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