Simple and Efficient Synthesis of Various Dibenzofuran Carbaldehydes

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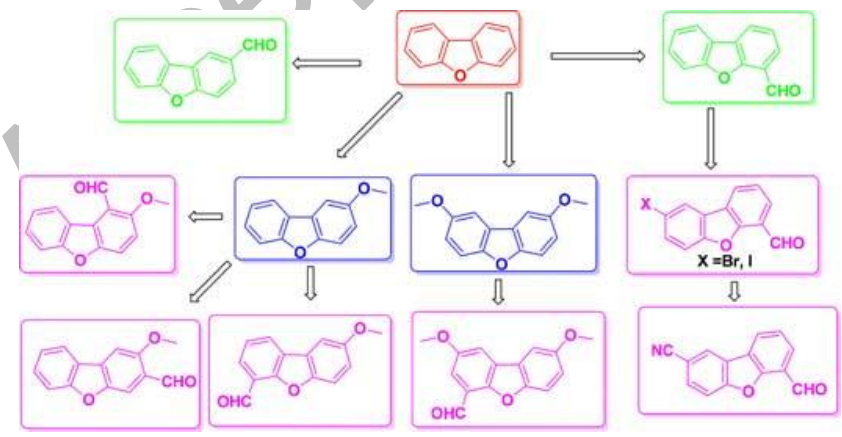
Abstract

We herein report simple and efficient methods for the synthesis of various formyl derivatives of dibenzofuran. The aldehydes reported are prepared in at most three steps and in yields greater than 60% from commercially available dibenzofuran, with one exception where isomers must be separated. The protocols described involve either formylation of previously functionalized dibenzofuran derivatives or the initial introduction of the formyl group and subsequent further functionalization under standard reaction conditions as described. We have also reported an efficient and simple method for the synthesis of key methoxydibenzofurans in high yield (65% overall for two steps).

Graphical Abstract:



KEYWORDS: Dibenzofuran carbaldehydes, efficient protocols, formylation, methoxy derivatives, bromo derivatives.

INTRODUCTION

Dibenzo[*b,d*]furan (**1**) is a tricyclic heterocyclic compound consisting of two benzene rings fused to one central furan ring. Dibenzofuran is a minor but relatively inexpensive constituent of coal tar and also a structural unit which is not widespread in nature, but seems to be largely confined to particular groups of organisms such as lichens, fungi and some higher plants.[1] Although several literature studies have revealed the synthesis of substituted furans and few dibenzofuran derivatives using various cyclization processes, these require costly metal catalysts. [2] The chemistry of dibenzofuran has attracted the interest of scientists over the past decade because of its promising applications in various areas like biological and medicinal chemistry, and materials science. Many natural and synthetic dibenzofuran derivatives have been tested for various activities,[3] such as antibacterial, antifungal, antiviral and cytotoxic, and some have proved to be quite potent.

In organic chemistry the synthesis of molecules having aldehyde functional groups [4] is vital because of the significant involvement of this functionality in various chemical transformations. The applications of aldehydes are central in many named reactions and not limited to Wolff–Kishner reduction, oxo-Diels–Alder reaction, Wittig reaction, Takai reaction, hydroacylation, Corey–Fuchs reactions, Ohira–Bestmann reaction, Johnson–Corey–Chaykovsky reaction, decarbonylation, etc.[5] All these chemical modifications are used for the synthesis of numerous active molecules and for various applications, making

the introduction of a formyl group on a complex moiety a pivotal step in modern organic synthesis. The literature reports a limited number of aldehydic dibenzofuran-containing natural products (e.g. hypostrepsilic acid,[6] penioflavin,[7]) (Figure 1). Although the introduction of a formyl group on the dibenzofuran skeleton would seem to be a straightforward proposition, only dibenzofuran 2-carbaldehyde (**2**) and dibenzofuran 4-carbaldehyde (**3**) have been reported as products of the application of efficient, regioselective synthetic procedures with moderate to good yields.[8,9] Thus, electrophilic attack of the bulky dichloromethyl methyl ether – Lewis acid complex occurs preferentially at the less hindered C-2, *para* to the dibenzofuran oxygen atom, while lithiation with *n*-butyl lithium shows a strong preference for C-4, *ortho* to the directing group. In view of the significance of the aldehyde functional group in organic chemistry and also considering the growing interest of the dibenzofuran nucleus over the past few years, we decided to synthesize various dibenzofuran carbaldehydes as intermediates for use in a range of chemical modifications.

RESULTS AND DISCUSSION

Our present approach started with the formylation of the dibenzofuran nucleus in which one or two electron-donating oxygen atoms had already been introduced. Thus, 2-methoxy and 2,8-dimethoxydibenzofuran (**8** and **9**) were prepared from the previously reported 2-bromo and 2,8-dibromo dibenzofuran (**6** and **7**). The bromo derivatives were synthesized according to the literature procedures [10] and used without further purification. The required methoxy derivatives were then conveniently prepared from the corresponding bromo derivatives by reaction with NaOMe in the presence of CuBr

(Scheme 1). These methoxy derivatives, **8** and **9**, were purified by silica gel chromatography and characterized by ^{1}H and ^{13}C NMR spectral analysis. Although the synthesis of key intermediate 2-methoxy dibenzofuran (**8**) was reported in an earlier communication starting from dibenzofuran (**1**) *via* the synthesis of dibenzofuran-2-carbaldehyde (**2**) and dibenzofuran-2-ol (**10**),[11] it involved three column purifications resulting in a relatively low yield. Here we report an efficient and simple synthesis of compound **8** from 2-bromodibenzofuran (**6**) (in 65% overall yield) which only required a single chromatographic purification. Efficient syntheses of **8** were reported recently by ring closure of 2-(4-methoxy)phenoxyphenol tosylate or mesylate, but an expensive catalyst was necessary and the precursors had to be prepared.[12] A similar synthesis of **9** only achieved 65% yield from 2-(2-chloro-4-methoxy)phenoxybenzonitrile.[13] Formylation of 2-methoxy dibenzofuran (**8**) with α,α-dichloromethyl methyl ether and $SnCl_4$ has already been shown to afford dibenzofuran carbaldehydes **4** and **5** in 92% yield, in a 35:65 ratio. Aldehydes **4** and **5** were separated chromatographically and fully characterized by their standard analytical data.[14]

A set of new dibenzofuran aldehydes **11**, **12** and **13** were synthesized according to the previous literature protocol,[9] using *n*-BuLi and dry DMF (Scheme 2). Under these reaction conditions, aldehydes **11**, and **12** were obtained in moderate yields starting from the dibenzofuran derivatives **8**, and **9** respectively. Phenolic aldehyde **13** was synthesized from dibenzofuran-2-ol (**10**),[10] using a larger excess of *n*-BuLi (3 equivalents). All these derivatives were properly characterized by using ^{1}H and ^{13}C NMR and mass spectral analysis.

As expected, an aldehyde group deactivates the ring that bears it towards electrophilic substitution. However, in the case of dibenzofuran-4-carbaldehyde, the other aromatic ring is sufficiently reactive for facile bromination or iodination at C-8, *para* to the dibenzofuran oxygen. Thus, the halo derivatives (**14** and **15**) of aldehyde **3** were obtained in good yields (75% and 70% isolated after recrystallization, respectively) by treatment with bromine or with iodine monochloride in acetic acid (Scheme 3). Unexpectedly, attempts to obtain aldehyde **15** using *N*-iodosuccinimide were not fruitful. These halo aldehydes were fully characterized with their spectral data.

Several attempts were made to synthesize 2-cyanodibenzofuran-6-carbaldehyde starting from the bromo derivative **14** according to protocols described in the literature for halogen substitution using CuCN, and $Zn(CN)_2$ as CN group sources, even in presence of Pd catalysts. In contrast, the iodo derivative **15** underwent ready substitution with CuCN (Scheme 4). The structure of aldehyde **16** was confirmed by its spectral data. An alternative approach, *via* lithiation of 2-cyanodibenzofuran (**17**),[15] prepared from 2-bromodibenzofuran (**4**), proved unsuccessful.

2-Bromodibenzofuran-6-carbaldehyde **14** was inert to substitution of the bromine atom by different amines such as ethylamine, morpholine or imidazole, even after modifying the aldehyde functional group to an acetal. However, aldehyde **11** could be obtained from aldehyde **14** after derivatizing the formyl group with trimethyl orthoformate, followed by methoxylation with NaOMe (Scheme 5).

CONCLUSION

We have succeeded in developing useful and efficient protocols for the synthesis of new substituted dibenzofuran carbaldehydes starting from reported analogues. Thus, in addition to the previously reported dibenzofuran-2- and 4-carbaldehydes (**2** and **3**) and 2-methoxy-1- and 3-carbaldehydes (**4** and **5**), methoxy, dimethoxy and hydroxyl dibenzofurans were formylated efficiently to yield different new aldehydes. Also, dibenzofuran-4-carbaldehyde was halogenated and its bromo and iodo derivatives were subjected to further modifications. These one- or two-step processes led to the reported aldehydes in good to excellent yields. We have also developed a novel method for the preparation of 2-methoxydibenzofuran (**8**) and 2,8-dimethoxydibenzofuran (**9**) starting from dibenzofuran, in satisfactory yields and using cheap, readily available reagents. All the new analogues are in the process of further utilization for the synthesis of novel, potentially bioactive molecules.

EXPERIMENTAL SECTION

General Remarks*:* Dibenzofuran and α,α-dichloromethyl methylether were purchased from Merck Chile, and n-BuLi, NaOMe and $SnCl_4$ were from Sigma Aldrich. Solvents were purchased commercially and dried prior to use according to the standard protocols. Melting points were measured with a Stuart SMP 10 melting point apparatus and are uncorrected. NMR spectra were recorded on 300 (Bruker), 400 (Bruker) and 500 MHz (Varian) spectrometers in appropriate solvents using TMS as internal standard and the chemical shifts are shown in the δ scale. High-resolution mass spectra was obtained by EI ionization for compound **14** and ESI-MS High resolution mass spectrometer *Exactive*™

Plus Orbitrap, Thermo Fisher Scientific (Bremen, Germany) was used for the other dibenzofuran formyl derivatives. IR spectra were recorded in KBr pellets and the wave numbers are shown in cm^{-1}. All the experiments were monitored by analytical thin layer chromatography (TLC) performed on silica gel GF_{254} pre-coated plates and silica gel finer than 200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

***Procedure for the synthesis of methoxy dibenzofurans 8** and **9**:* To a solution of compound **6** or **7** (1 eq.) in dry toluene, an excess of NaOMe (25% v/v in MeOH) (>10 eq.), CuBr (1.2 eq.) and a small volume of ethyl acetate was added at RT to improve solubility. Then the deep blue colored solution was refluxed overnight under a nitrogen atmosphere. After completion of the reaction (TLC), water was carefully added and the reaction mixture extracted with dichloromethane. The combined organic layers were dried with anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. Purification of the crude reaction mixture (using hexane/dichloromethane mixtures as eluent) afforded the title compounds **8** and **9** in good yields. Usually the pure products were isolated along with other methoxy derivatives (mono-/di-) and dibenzofuran in smaller quantities (<5%).

Procedure for the synthesis of aldehydes* 11-13:*** To a solution of compound **8**/**9**/**10** (20 mmol) in dry THF (15 mL) *n*-BuLi (2.0 M in hexane, 30 mmol or 60 mmol in the case of compound **10**) was added at 0 °C and stirring was continued at RT for 3 h. Afterwards,

dry DMF (~5 mL) was added at 0 °C and stirring was continued further at RT for 2 h. After completion of the reaction, it was quenched with 1M HCl carefully at 0 °C and then the reaction mixture was extracted with CH_2Cl_2 and water. The combined organic layer was then treated with brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification of this crude material over silica gel (EtOAc:hexane, various ratios not exceeding 30:70) afforded the new dibenzofuran 4-carbaldehydes with good yields.

ACKNOWLEDGEMENTS

Authors (TY and BKC) are grateful to CONICYT (Chile) for providing funds through FONDECYT postdoctoral grant 3150474.

SUPPORTING INFORMATION

Full experimental detail, including the analytical data and copies of ^{1}H and ^{13}C NMR spectra, ESI-HRMS were included. This material can be found *via* the "Supplementary Content" section of this article's webpage.

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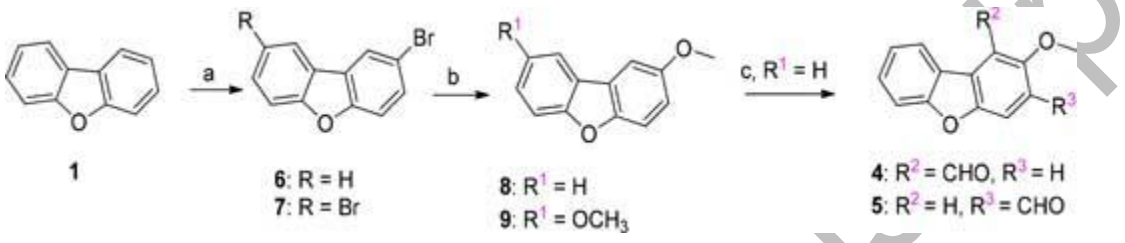
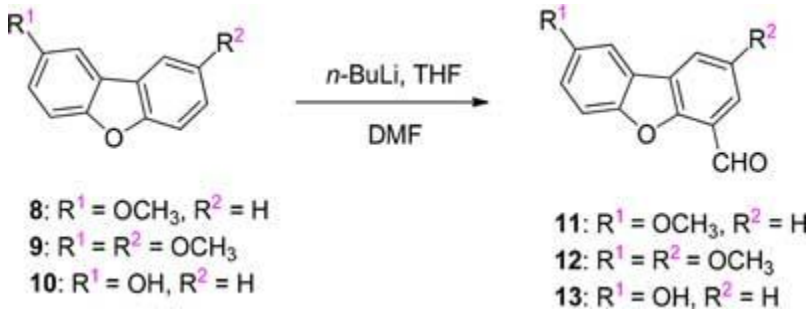
Scheme 1. Preparation of 2-methoxy- and 2,8-dimethoxydibenzofurans **8** and **9**. *Reagents and Conditions*: (a) Br_2, AcOH, RT. (b) NaOMe (25% v/v in MeOH), toluene, EtOAc (small amounts), CuBr, reflux, 16h, overall yield 65% for compound **8** and 70% for compound **9.** (c) $SnCl_4$, α,α-dichloromethyl methyl ether, DCM, RT, 2 h, 92% yield with 35:65 ratio of aldehydes **4** and **5**.



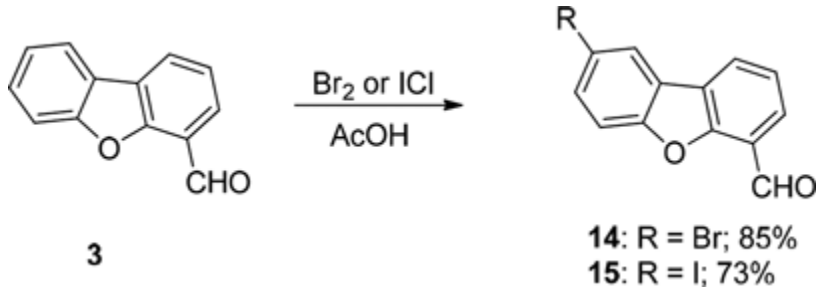
Scheme 2. Synthesis of 2-methoxy, 2,8-dimethoxy and 8–hydroxy dibenzofuran-4-carbaldehydes **11, 12** and **13**. *Reagents and Conditions*: (a) *n*-BuLi/THF, 0 °C to RT (3 h), DMF at 0 °C to RT, 2 h, 65% for **11**, 68% for **12**, 60% for **13**.



8: $R^1 = OCH_3$, $R^2 = H$
9: $R^1 = R^2 = OCH_3$
10: $R^1 = OH$, $R^2 = H$

11: $R^1 = OCH_3$, $R^2 = H$
12: $R^1 = R^2 = OCH_3$
13: $R^1 = OH$, $R^2 = H$

Scheme 3. Synthesis of 8-halo dibenzofuran-4-carbaldehydes **14** and **15**.



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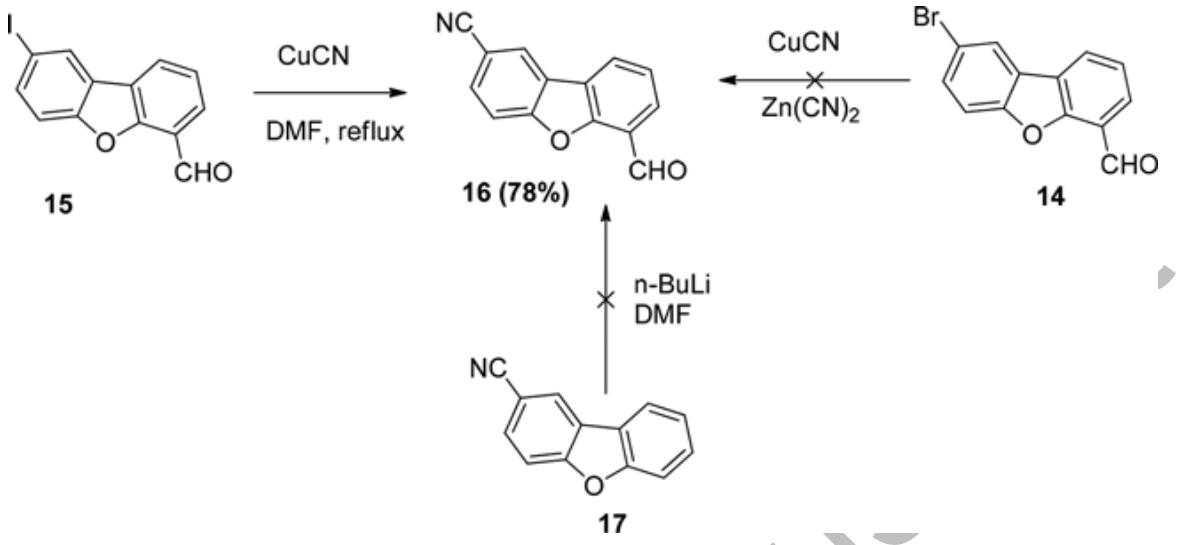
14: R = Br; 85%
15: R = I; 73%

Scheme 4. Synthesis of 8-cyano dibenzofuran-4-carbaldehyde **16**.



Scheme 5. Alternative method for the synthesis of 8-methoxy-4-carbaldehyde **11**. *Reagents and Conditions*: (a) $CH(OMe)_3$, acetone, RT, overnight. (b) NaOMe (25% v/v in MeOH), CuBr, EtOAc (small amounts), toluene, reflux, 16 h. (c) *p*-TSA, acetone, reflux, 3 h, 45% (overall yield).

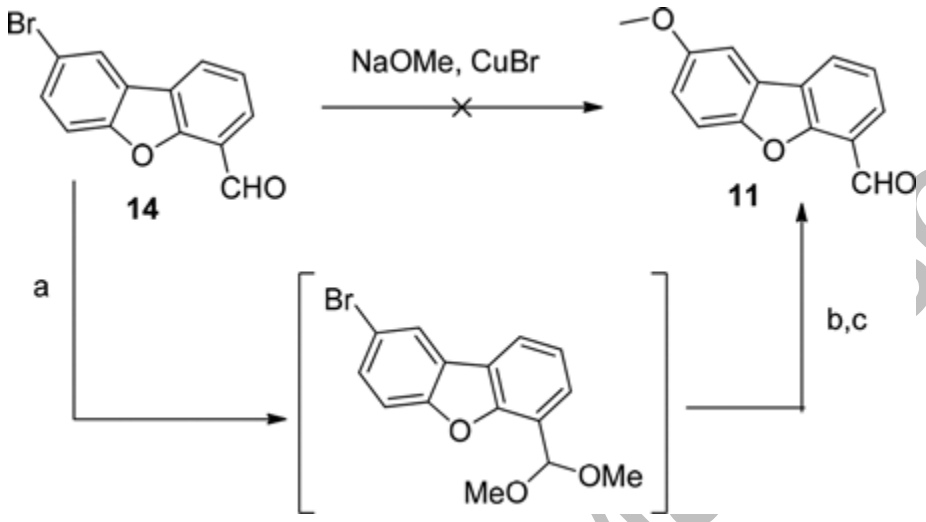
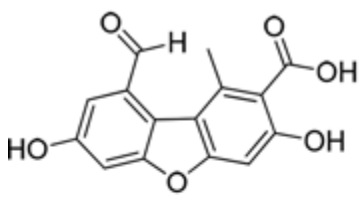
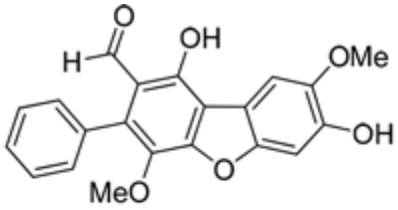


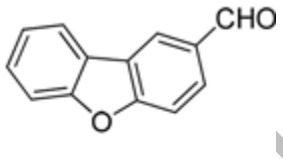
Figure 1. Examples of natural dibenzofurans with aldehyde functional group and previously reported dibenzofuran aldehydes.



Hypostrepsilic acid



Penioflavin



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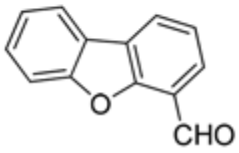

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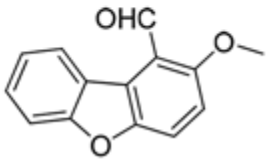

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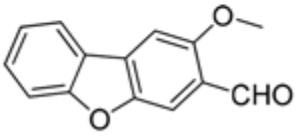

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