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# Deprotonative Metallation of Benzofuran and Benzothiophene Derivatives for the Formation of Tetracyclic and Pentacyclic Heteroaromatic Compounds

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**Abstract:** *N,N*-dialkylbenzofuran- and *N,N*-dialkylbenzothiophene-2-carboxamides were readily prepared from bare benzofuran and benzothiophene by deprotocupration followed by trapping with *N,N*-dialkylcarbonyl chlorides. They were reacted with 2-benzofuryl- and 2-benzothiényllithiums to form symmetrical and unsymmetrical diarylketones, or underwent deprotolithiation-electrophilic trapping sequences at their 3 position. From 3-iodinated derivatives, copper-catalysed *N*-arylation of azoles was performed, followed by lithium amide-promoted cyclisation, to give 'tripentone' analogues. The diarylketones were also iodinated at their 3,3' positions and then engaged in the copper-promoted double *N*-arylation of anilines, giving rise to a family of original pentacyclic derivatives. A preliminary assessment of their electrochemical and biological properties was carried out, showing promising results against the proliferation of melanoma cells.

## Introduction

While benzo[*b*]furan<sup>[1]</sup> and benzo[*b*]thiophene<sup>[2]</sup> are present in many biologically active compounds and in organic materials for different applications,<sup>[3]</sup> derivatives in which they are fused with other heterocyclic rings are far less common.<sup>[4]</sup>

In addition, although these aromatic heterocycles can be easily functionalised,<sup>[1,5]</sup> notably by deprotometallation-electrophilic trapping sequences<sup>[6]</sup> and C-H functionalisation,<sup>[7]</sup> the use of substrates prone to nucleophilic attack is rarely studied. Nevertheless, we can cite the C3 deprotometallation of 2-(4-chlorobenzoyl)-6-methoxybenzothiophene using TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidino) in THF

(THF = tetrahydrofuran) at –30 °C.<sup>[8]</sup> Similarly, benzothiophene-3-carboxaldehyde was chemoselectively deprotometallated at C2 using the zinc amide base TMPZnOPiv·Mg(OPiv)Cl·LiCl (OPiv = pivalate) in THF at room temperature (rt).<sup>[9]</sup>

In the present study, our first objective was to access sensitive benzofuran- and benzothiophene-2-carboxamides from bare heterocycles, using deprotocupration-arylation sequences as key steps. These derivatives proved to be perfectly suitable substrates for accessing symmetrical di-2-benzothiényl ketone and unsymmetrical 2-benzofuryl 2-benzothiényl ketone. The sensitive carboxamides and ketones were then functionalised using a lithium-zinc base, and the iodides formed after iodolysis were involved in copper-mediated coupling reactions to access new polycyclic scaffolds whose properties were evaluated.

## Results and Discussion

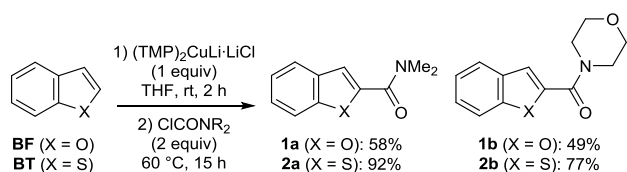
### Synthesis of Sensitive Benzofuran- and Benzothiophene-2-carboxamides

*N,N*-dimethylbenzofuran- and *N,N*-dimethylbenzothiophene-2-carboxamide (**1a** and **2a**) can be prepared from the corresponding 2-carboxaldehydes and dimethylamine in the presence of 1,3-diiodo-5,5-dimethylhydantoin and potassium carbonate in tetrachloromethane.<sup>[10]</sup> They can also be obtained by amination of the corresponding 2-carboxylic acids, promoted by potassium *tert*-butoxide, using *N,N*-dimethylformamide (DMF).<sup>[11]</sup>

While the 2-(morpholinocarbonyl) derivatives **1b** and **2b** were prepared using the first approach,<sup>[10]</sup> **1b** can also be

obtained from ethyl benzofuran-2-carboxylate *via* nickel-catalysed amide bond formation using morpholine in toluene.<sup>[12]</sup> Finally, 2-(morpholinocarbonyl)benzothiophene has also been prepared by amidation of the 2-carboxylic acid using morpholine in the presence of 1-hydroxybenzotriazole and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide,<sup>[13]</sup> or from 2-benzothienoyl chloride.<sup>[14]</sup>

Our aim here was to develop direct access to **1** and **2** from benzofuran and benzothiophene. Back in 2009 we showed that ketones could be introduced into the 2-position of furan and thiophene by consecutive treatment with (TMP)<sub>2</sub>CuLi·LiCl and aryl chlorides in THF.<sup>[15]</sup> Thus, when benzofuran (**BF**) was treated successively by (TMP)<sub>2</sub>CuLi·LiCl (1 equiv) in THF at rt for 2 h, and *N,N*-dimethylcarbamoyl chloride or *N*-morpholinocarbonyl chloride (2 equiv) at 60 °C overnight, the expected carboxamides **1a** and **1b** were obtained in 58 and 49% yield, respectively. Perhaps due to its slightly lower p*K*<sub>a</sub> value at C2 (32.4 vs. 33.2),<sup>[16]</sup> benzothiophene (**BT**) led to the corresponding carboxamides **2a** and **2b** in higher yields (92 and 77%, respectively; Scheme 1).

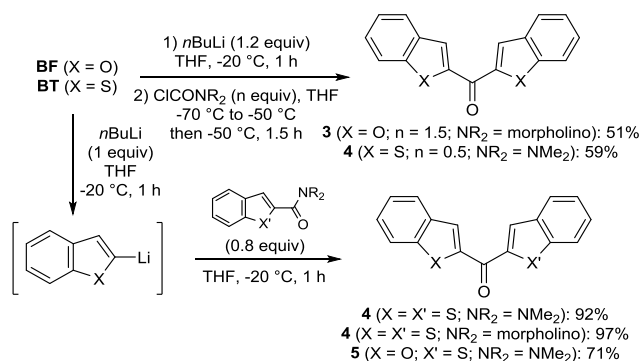


**Scheme 1.** Synthesis of benzofuran-2-carboxamides (**1a,b**) and benzothiophene-2-carboxamides (**2a,b**) by deprotocupration-trapping sequences from benzofuran (**BF**) and benzothiophene (**BT**), respectively.

### Synthesis of Sensitive Benzofuran- and Benzothiophene-based Ketones

As already observed in the synthesis of ketones, the use of (TMP)CuLi·LiCl avoids any addition of the arylcuprates formed to the carboxamides produced. On the other hand, if (TMP)CuLi·LiCl is replaced by *n*-butyllithium during the deprotometallation step, even at -20 °C, 2-benzofuryl- and 2-benzothiophenyllithium react with the sensitive carboxamides formed to produce di-2-benzofuryl and di-2-benzothiophenyl ketones **3** and **4** in 51 and 59% yields, respectively (Scheme 2, top). The reaction giving **4** (70% yield) had already been demonstrated in diethyl ether in 2012 by Nenajdenko and co-workers.<sup>[17]</sup> Concerning ketone **3**, it had already been isolated by Togo and co-workers by attempting to intercept 2-benzofuryllithium with ethyl chloroformate (40% yield), in addition to the expected ester.<sup>[18]</sup>

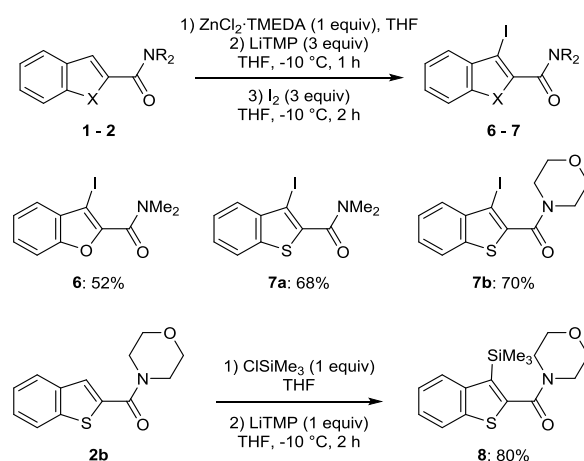
As we now had benzothiophene-2-carboxamides **2a** and **2b**, we reacted them with 2-benzothiophenyllithium (formed by reacting **BT** with *n*-butyllithium in THF at -20 °C for 1 h) to give ketone **4**, isolated in 92 and 97% yields, respectively. Interestingly, the unsymmetric 2-benzofuryl 2-benzothiophenyl ketone **5** was selectively formed, and isolated in 71% yield, by reacting 2-benzofuryllithium (formed from **BF** and *n*-butyllithium in THF at -20 °C for 1 h) with **2a** in THF at -20 °C for 1 h (Scheme 2, bottom).



**Scheme 2.** Synthesis of di-2-benzofuryl, di-2-benzothiophenyl and 2-benzofuryl 2-benzothiophenyl ketones (**3-5**) by deprotolithiation-trapping sequences from benzofuran (**BF**) or benzothiophene (**BT**).

### Functionalisation at C3 of Sensitive Benzofuran- and Benzothiophene-2-carboxamides

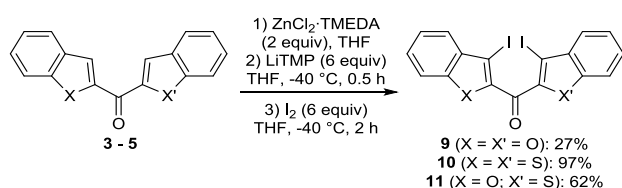
The C3 functionalisation of furan-2-carboxamides **1a** and **1b** was only documented in 2020 by reductive silylation.<sup>[19]</sup> In the thiophene-2-carboxamides series, only morpholinocarbonyl **2b** has been functionalised at C3, by iridium-catalysed dehydrogenative cross-alkynylation.<sup>[20]</sup> It was therefore interesting to study their functionalisation. Because of their sensitivity to nucleophiles, we employed the hindered lithium amide LiTMP, with the chelate ZnCl<sub>2</sub>·TMEDA (TMEDA = *N,N,N',N'*-tetramethylethylenediamine) as an *in situ* trap<sup>[21]</sup> to prevent the addition of the heteroaryllithium formed onto the function. Thus, carboxamides **1** and **2** were treated with LiTMP (3 equiv) at -10 °C in the presence of ZnCl<sub>2</sub>·TMEDA (1 equiv) in THF for 1 h. After iodolysis, the expected 3-iodinated derivatives **6** and **7** were obtained in yields of 52-70% (Scheme 3, top and middle). A similar approach, this time using chlorotrimethylsilane (1 equiv) as an electrophilic trap with LiTMP (1 equiv), led to the 3-silylated derivative **8** in 80% yield (Scheme 3, bottom).



**Scheme 3.** Synthesis of 3-substituted benzofuran-2-carboxamides and benzothiophene-2-carboxamides by deprotolithiation in the presence of electrophilic traps.

## Functionalisation at C3 and C3' of Sensitive Benzofuran- and Benzothiophene-based Ketones

We then turned our attention to the previously unreported functionalisation of ketones **3-5** in position 3. We had previously shown that different ketones could be functionalised using the same lithium-zinc tandem base.<sup>[22]</sup> We considered the double functionalisation of these substrates because having two iodine atoms at C3/C3' would provide access to novel heterocyclic pentacycles. They were treated with an excess of LiTMP (6 equiv) in the presence of ZnCl<sub>2</sub>·TMEDA (2 equiv) at -40 °C for 0.5 h. After iodolysis, the corresponding diiodinated derivatives **9-11** were isolated in yields ranging from 27 to 97% (Scheme 4; Figure 1). It is interesting to note that, as above, the reaction is easier in the thiophene 3-position than in the furan 3-position.

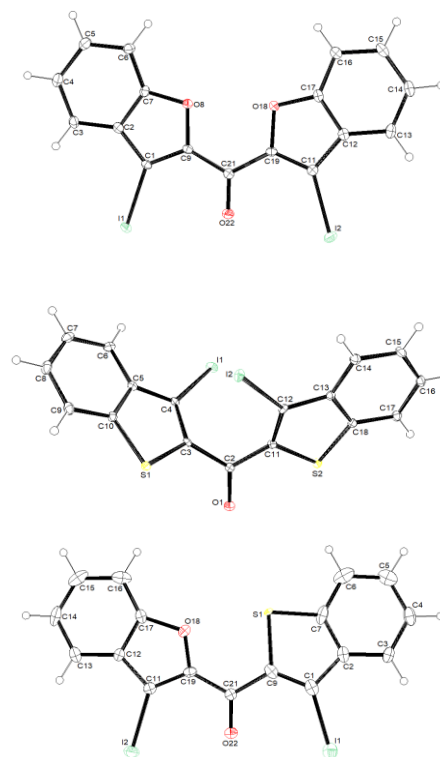


**Scheme 4.** Synthesis of 3,3'-diiodinated di-2-benzofuryl, di-2-benzothiophenyl and 2-benzofuryl 2-benzothiophenyl ketones by deprotonation in the presence of an electrophilic trap.

## N-Arylation of Azoles using the 3-iodinated Benzofuran- and Benzothiophene-2-carboxamides and Access to New Heterocycles Containing a Pyrrolizone Core

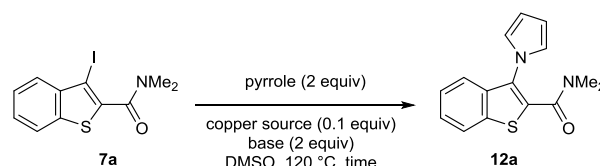
In order to progress towards new heterocycles, we then studied the behaviour of 3-iodinated benzofuran- and benzothiophene-2-carboxamides in the copper-catalysed *N*-arylation of azoles. Such reactions have only been claimed from 2-iodobenzothiophenes in moderate yields, either under palladium catalysis<sup>[23]</sup> or in the presence of copper sulphate at very high temperatures.<sup>[24]</sup> We therefore first carried out a short optimisation of the copper-catalysed *N*-arylation of pyrrole using **7a** (Table 1). A comparison of two copper sources, copper(I) iodide (entries 1-3) and copper(I) oxide (entries 4-6), showed the superiority of the latter. Of the two bases tested, caesium carbonate (entries 4 and 5) and potassium phosphate (entry 6), the former proved to be the best. After 32 h of reaction with pyrrole (2 equiv) in the presence of copper(I) oxide (0.1 equiv) and caesium carbonate (2 equiv) in dimethylsulfoxide (DMSO) at 120 °C, product **12a** was isolated in 74% yield (entry 5). Similar results have been reported previously by Teo and co-workers for the coupling of various azoles with iodopyridines under these conditions.<sup>[25]</sup>

These reaction conditions also worked in the case of morpholino carboxamide **7b** (product **12b**) and proved suitable for the *N*-arylation of indoles (products **13** and **14**). In the case of 3-iodinated benzofuran **6**, the expected products **15** and **16** could also be isolated, albeit in lower yields (Scheme 5).



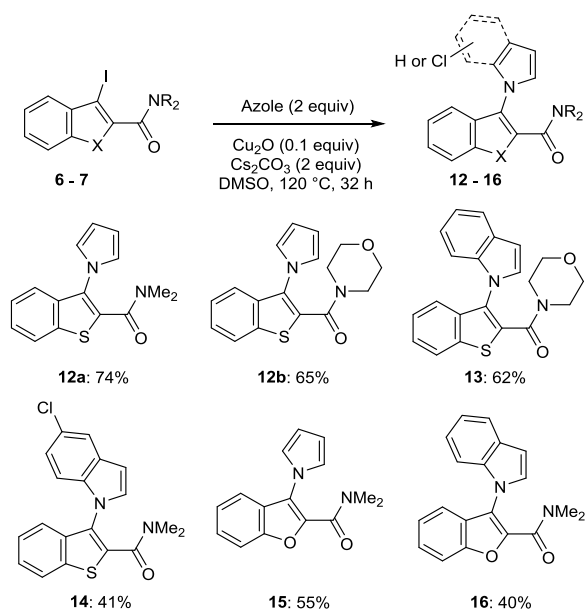
**Figure 1.** ORTEP diagrams (30% probability) of **9** (top), **10** (middle) and **11** (bottom).<sup>[26]</sup>

**Table 1.** Short optimisation of the reaction conditions giving *N,N*-dimethyl-3-(*N*-pyrrolyl)benzothiophene-2-carboxamide (**12a**) from the iodide **7a**.



Entry	Copper source	Base	Time	Yields (%) <sup>[a]</sup>		
				<b>12a</b>	<b>7a</b>	<b>2a</b>
1 <sup>[b]</sup>	CuI	Cs <sub>2</sub> CO <sub>3</sub>	20 h	22	48	29
2 <sup>[c]</sup>	CuI	Cs <sub>2</sub> CO <sub>3</sub>	32 h	33	9	6
3 <sup>[c]</sup>	CuI	K <sub>3</sub> PO <sub>4</sub>	32 h	18	30	34
4 <sup>[b]</sup>	Cu <sub>2</sub> O	Cs <sub>2</sub> CO <sub>3</sub>	20 h	36	7	11
5 <sup>[c]</sup>	Cu <sub>2</sub> O	Cs <sub>2</sub> CO <sub>3</sub>	32 h	74	0	20
6 <sup>[c]</sup>	Cu <sub>2</sub> O	K <sub>3</sub> PO <sub>4</sub>	32 h	26	25	49

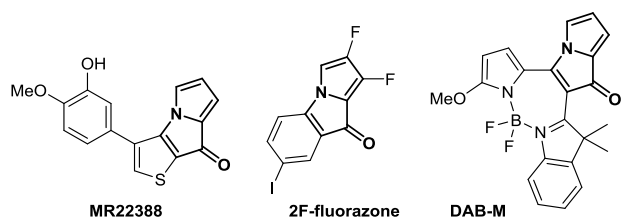
[a] Yield after purification (see experimental part). [b] Work-up: addition of a saturated aqueous solution of ammonium chloride and extraction using ethyl acetate. [c] Work-up: filtration over Celite<sup>®</sup> and washing using ethyl acetate.



**Scheme 5.** Synthesis of 3-substituted benzofuran- and benzothiophene-2-carboxamides by *N*-arylation of azoles using the corresponding 3-iodinated precursors.

### Conversion to 'Triptone' Analogues

Heterocycles containing the pyrrolizone motif can exhibit a wide range of bioactivities.<sup>[27]</sup> For example, 'triptone' **MR22388**, which is a thieno[2,3-*b*]pyrrolizin-8-one acting as a tubulin polymerisation inhibitor, has shown significant cytotoxicity (in the submicromolar to nanomolar range) against various cancer cell lines.<sup>[28]</sup> In addition, pyrrolizone can impart specific physicochemical properties to organic materials<sup>[29]</sup> (Figure 2).

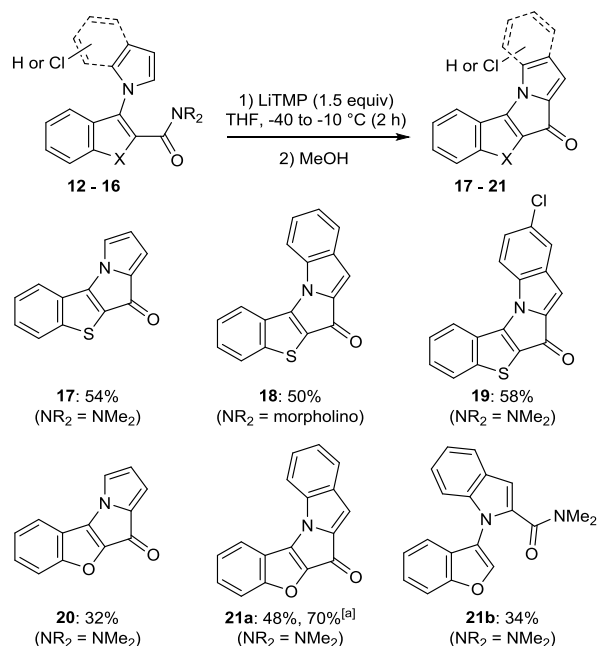


**Figure 2.** Molecules of interest containing a pyrrolizone core.

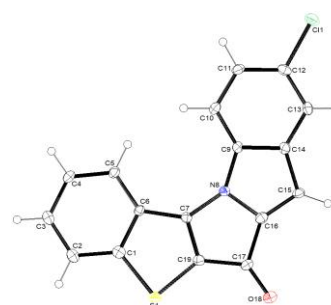
Thus, we wished to involve the 3-substituted benzofuran- and benzothiophene-2-carboxamides prepared above in a cyclisation step towards 'triptone' analogues. Due to our interest in hindered lithium amide-mediated cyclisation,<sup>[30]</sup> precursors **12-16** were subjected to the action of LiTMP (1.5 equiv) in THF at  $-40$  to  $-10$  °C. Under these conditions, the benzothiophene derivatives **17-19** were isolated in yields of 50-58% (Scheme 6, top and middle; Figure 3).

However, in the benzofuran series, lower yields were recorded for **20** and **21a**, with more complex crude reaction mixtures. Indeed, migration of the carboxamide from the 2-position of the benzofuran to the 2-position of the azole can also

occur, as evidenced by the formation of 1-(3-benzofuryl)-*N,N*-dimethylindole-2-carboxamide (**21b**; 34% yield) from **16**. We thought that maintaining the temperature at  $-40$  °C might have a beneficial effect on the outcome of the reaction, by preventing the ketone formed from being attacked by lithium diethylamide also present in the reaction mixture; as expected, **21a** was obtained in a better 70% yield under these conditions (Scheme 6, bottom).



**Scheme 6.** Cyclisation of 3-substituted benzofuran-2-carboxamides and benzothiophene-2-carboxamides mediated by LiTMP. [a] Reaction mixture kept at  $-40$  °C for 2 h before addition of methanol; estimated yield (see Supporting information).



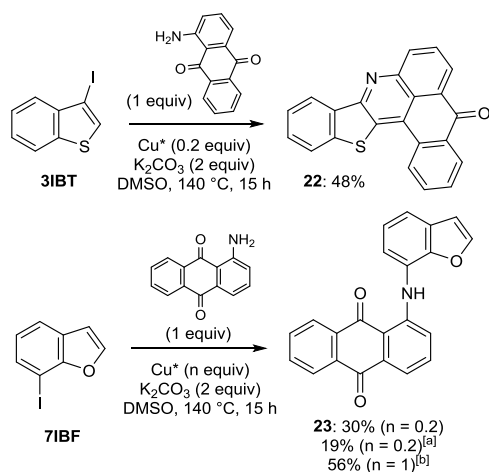
**Figure 3.** ORTEP diagrams (30% probability) of **19**.<sup>[26]</sup>

### Access to New Heterocyclic Pentacycles by Double *N*-Arylation of Anilines using the 3,3'-diiodinated Benzofuran- and Benzothiophene-based Ketones

In the past, we have successfully used Ullman-type *N*-arylation to obtain original polycyclic structures,<sup>[31]</sup> which is why we then investigated the possibility of performing a double *N*-arylation of this type using our original diiodinated derivatives. Inspired by coupling reactions between aromatic amines and halides,<sup>[32]</sup> we

chose to use activated copper<sup>[33]</sup> according to the protocol recommended in Vogel's Textbook of Practical Organic Chemistry.<sup>[34]</sup> Regarding the choice of solvent, it is possible to use either dibutyl ether as in the original articles, or DMSO as demonstrated more recently.<sup>[31e,35]</sup>

We first performed single *N*-arylations from 3-iodobenzothiophene (**3IBT**) and 7-iodobenzofuran (**7IBF**) using 1-aminoanthraquinone as the coupling partner, and observed that the reactions already took place with a sub-stoichiometric amount of activated copper (0.2 equiv). In the case of **3IBT**, we only isolated the cyclised derivative **22** (Scheme 7, top), already obtained by Tsuchimoto and co-workers *via* the indium-catalysed annulation of 1-aminoanthraquinone with 3-methoxybenzothiophene. We have also identified a substantial advantage of using a stoichiometric amount of copper, added in several steps,<sup>[36]</sup> as shown in the synthesis of **23** (Scheme 7, bottom).

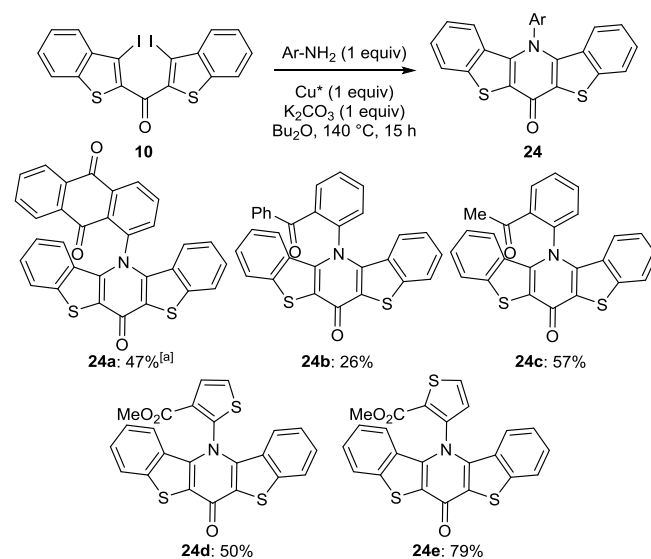


**Scheme 7.** *N*-arylation of 1-aminoanthraquinone using 3-iodobenzothiophene or 7-iodobenzofuran. [a] Using nonactivated copper. [b] Using 5 x 0.2 equiv of activated copper added every 2 h.

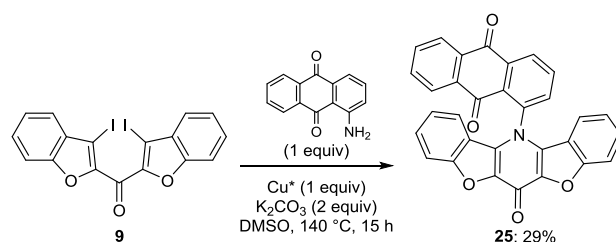
The first double *N*-arylation reactions were carried out on thiophene-based diiodide **10**. The use of different anilines (1-aminoanthraquinone, 2-aminobenzophenone, 2-aminoacetophenone, methyl 2-aminothiophene-3-carboxylate and methyl 3-aminothiophene-2-carboxylate) led to the expected *N*-substituted benzothieno[3,2-*b*]benzothieno[2,3-*e*]pyridin-6-ones **24**. However, as these compounds unfortunately proved to be poorly soluble in common organic solvents, purifications were difficult, leading to variable yields ranging from 26 to 79% (Scheme 8).

Hartwig and co-workers observed, in related palladium-catalysed coupling reactions,<sup>[37]</sup> that 3-iodobenzofurans were less reactive than 3-iodobenzothiophenes. Similarly, copper-catalysed *N*-arylation reactions should be favoured in the case of less electron-rich aryl groups as follows:<sup>[36]</sup> 3-benzofuryl (C2 Mulliken charge<sup>[38]</sup> = -0.235) < 3-benzothienyl (-0.14). This could explain why compound **25** was only isolated in 29% yield from ketone **9** and 1-aminoanthraquinone (Scheme 9). Unfortunately, the use of other coupling partners such as 2-

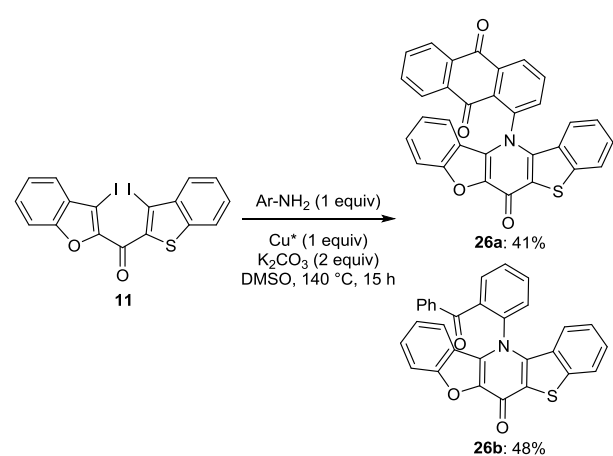
aminoacetophenone and 2-aminobenzophenone did not improve the results, as only traces of the expected products were detected in the crude reaction mixtures.



**Scheme 8.** Double *N*-arylation of anilines using 3,3'-diiodinated di-2-benzothiophenyl ketones. [a] Using only 0.1 equiv of activated copper.



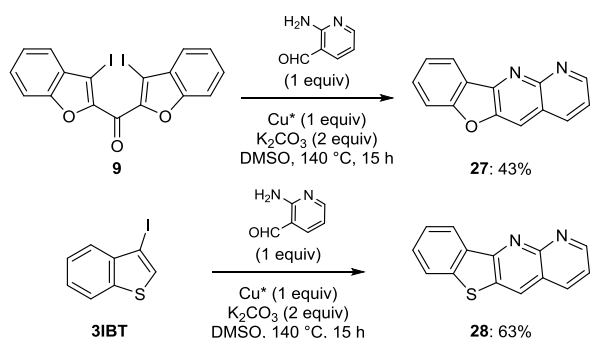
**Scheme 9.** Double *N*-arylation of 1-aminoanthraquinone using 3,3'-diiodinated di-2-benzofuryl ketone.



**Scheme 10.** Double *N*-arylation of 1-aminoanthraquinone and 2-aminobenzophenone using 3,3'-diiodinated 2-benzofuryl 2-benzothiophenyl ketone.

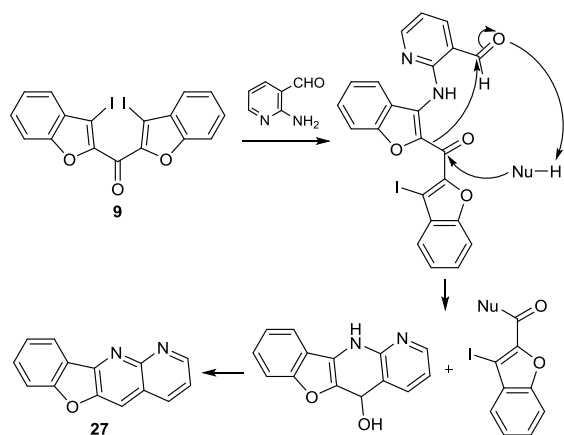
Interestingly, when the reaction was carried out using ketone **11**, the pentacycles **26a** and **26b** were isolated in higher yields of 41 and 48%, respectively (Scheme 10). As *N*-arylation is easier in the case of 3-iodobenzothiophene, it could be the first step in the sequence, perhaps facilitating the subsequent intramolecular reaction with the 3-iodobenzofuran moiety.

When diiodide **11** was treated with 2-aminonicotinaldehyde as the coupling partner, the expected bis-coupled product was not obtained. Instead, among the various products formed during the reaction, we identified benzofuro[3,2-*b*][1,8]naphthyridine (**27**) and benzothieno[3,2-*b*][1,8]naphthyridine (**28**). When we repeated the reaction using the symmetrical ketone **9** as a substrate, this also led to the tetracycle **27** (an isomer of the previously prepared benzofuro[2,3-*b*][1,8]naphthyridine<sup>[39]</sup>), isolated in 43% yield. To confirm the structure of **28**, benzothieno[3,2-*b*][1,8]naphthyridine was prepared unambiguously from **3IBT** and 2-aminonicotinaldehyde in 63% yield (Scheme 11).



**Scheme 11.** Unexpected products formed during *N*-arylation of 2-aminonicotinaldehyde using 3,3'-diiodinated di-2-benzofuryl ketone and 2-benzofuryl 2-benzothieryl ketone.

To explain the formation of compound **27** from diiodide **9** in the reaction with this aminopyridine bearing a reactive carbonyl group, we can propose a nucleophilic attack on the sensitive ketone function, triggering cyclisation and subsequent aromatisation (Scheme 12). Compound **28** can be formed in the same way, either from symmetrical diiodide **10** or from unsymmetrical diiodide **11**.



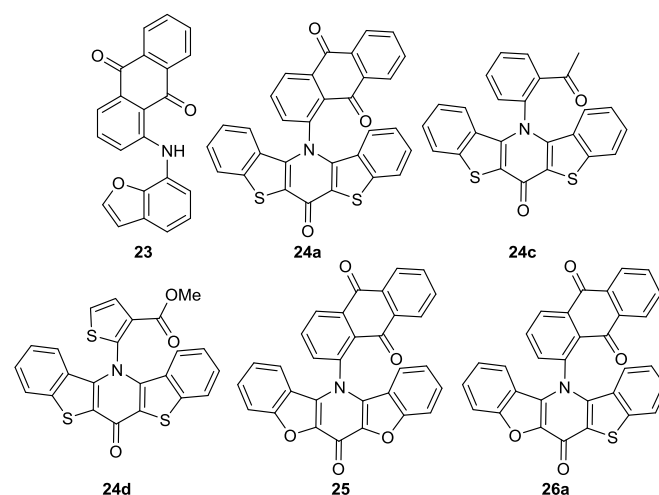
**Scheme 12.** Proposed mechanism to rationalise the formation of compound **27** using 2-amino-3-formylpyridine.

## Electrochemical Properties

As very few related structures have been reported,<sup>[40]</sup> we decided to examine the electrochemical properties of compounds **23**, **24a, c, d**, **25** and **26a**. Indeed, polycyclic aromatic systems have shown good potential for electronic applications such as organic field transistors and light-emitting diodes.<sup>[41]</sup> Anthraquinone-based molecules are also attractive structures for energy storage.<sup>[42]</sup> They are also capable of interacting with biological structures, enabling electrochemical detection of DNA, for example.<sup>[43]</sup>

The compounds were studied by cyclic voltammetry (CV) and differential pulse voltammetry (DPV) in degassed DMF, using Ag/AgCl as the reference electrode. The main data are shown in Table 2.

**Table 2.** Electrochemical data (in V) of selected compounds.<sup>[a]</sup>



Compound	1 <sup>st</sup> reduction			2 <sup>nd</sup> reduction				
	$E_{pc}^{[b]}$	$E_{pa}^{[b]}$	$i_{pc}/i_{pa}^{[b]}$	$E_{1/2}^{[c]}$	$E_{pc}^{[b]}$	$E_{pa}^{[b]}$	$i_{pc}/i_{pa}^{[b]}$	$E_{1/2}^{[c]}$
<b>23</b>	-0.81	-0.73	1.00	-0.75	-1.42	-1.34	1.00	-1.37
<b>24a</b>	-0.63	-0.56	0.94	-0.58	-1.34	-1.28	1.53	-1.31
<b>24c</b>	-1.65	-1.58	0.91	-1.60	-1.97	-[d]	-[e]	-1.83
<b>24d</b>	-1.74	-1.66	1.91	-1.70	-1.97	-[d]	-[e]	-1.91
<b>25</b>	-0.63	-0.57	1.00	-0.59	-[e]	-[e]	-[e]	-[e]
<b>26a</b>	-0.64	-0.57	0.95	-0.60	-1.33	-1.27	1.35	-1.30

[a] Potentials values in DMF (1 mM) given relative to Ag/AgCl, scan rate = 100 mV·s<sup>-1</sup>. [b] From CV experiments. [c] From DPV experiments. [d] Irreversible. [e] Not determined.

With the exception of the derivative **24d**, all the first reduction peaks corresponding to the formation of the radical anion were found to be reversible, with an  $i_{pc}/i_{pa}$  ratio close to unity. Compared with the bare anthraquinone, for which the first and second reduction potentials are recorded at  $-0.85$  and  $-1.50$  V respectively, the introduction of a 7-furylamino group in position 1 (compound **23**) shifts the values anodically by 100 and 130 mV respectively. This differs from the introduction of an electron-donating amino group at the same position on the anthraquinone, which leads instead to cathodic shifts in the reduction potentials. This result is not surprising, however, as anodic shifts have already been observed with the introduction of electron-donating substituents. One example is 1-hydroxyanthraquinone, where stabilisation of the anthraquinone radical species by the adjacent substituent has been proposed.<sup>[44]</sup>

When the 7-furylamino group of **23** was replaced by 6-oxobis(benzothieno)[3,2-*b*:2',3'-*e*]-1,4-dihydro-12-pyridyl (compound **24a**), a greater anodic shift was observed for the first reversible reduction peak of the anthraquinone moiety ( $-0.85$  V for bare anthraquinone,  $-0.75$  V for **23** and  $-0.58$  V for **24a**). A similar effect on the first reduction potential of the anthraquinone was noticed in the presence of the 6-oxobis(benzofuro)[3,2-*b*:2',3'-*e*]-1,4-dihydro-12-pyridyl group (compound **25**;  $-0.59$  V) and the 6-oxobenzofuro[2,3-*e*]benzothieno[3,2-*b*]-1,4-dihydro-12-pyridyl group (compound **26a**;  $-0.59$  V).

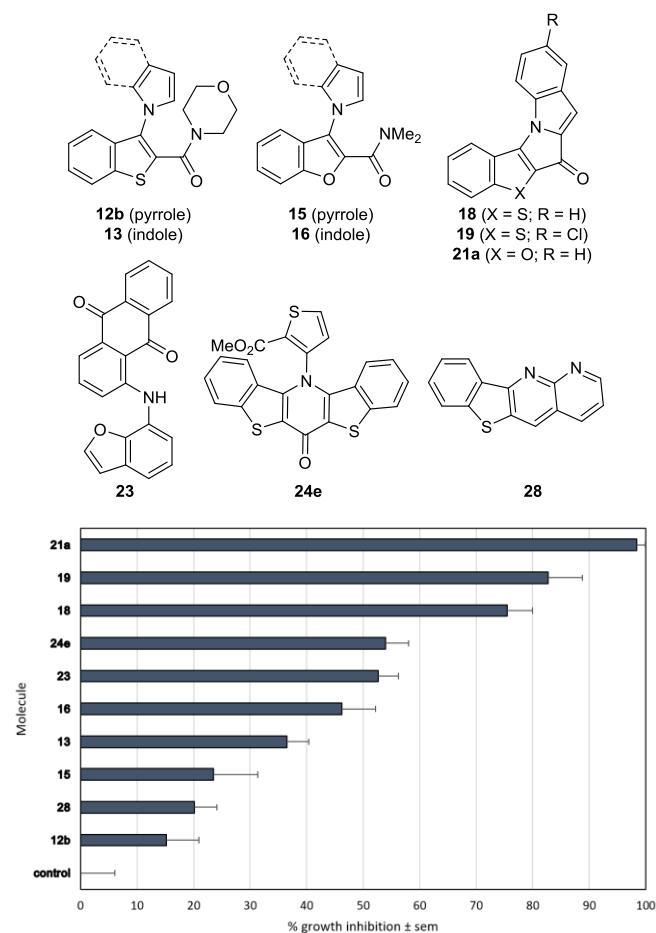
Due to the presence of the electron-donating nitrogen in their ring and the loss of a carbonyl group, bis(benzothieno)[3,2-*b*:2',3'-*e*]pyrid-6-ones should be more difficult to reduce than anthraquinones. As expected, the first reduction peaks of derivatives **24c** and **24d** were recorded at  $-1.60$  and  $-1.70$  V, respectively, and were found to be quasi-irreversible. In addition, other irreversible systems were recorded at  $-1.83$  and  $-1.91$  V. However, it remains unclear whether the loss of reversibility can be attributed to the coupling of the radical anion or is the result of an ECE mechanism due to the presence of a proton donor or residual water.

We then chose derivatives **24a** and **25** as model compounds to study their oxidation by CV in DMF. For both, an irreversible process was recorded at  $+1.06$  V, suggesting that the oxidation process occurs first at the nitrogen atom, as for *N*-arylated acridones.<sup>[45]</sup> In addition, oxidation of the benzothiophene ring seems to be excluded as it has been shown that benzothiophenes substituted with electron-withdrawing groups such as an ester are generally oxidised at approximately  $+1.35$  V (SCE).<sup>[46]</sup> In search of another oxidation process, investigations were carried out up to  $+1.5$  V, but without revealing any additional oxidation peak (solvent oxidation was, however, noted from  $+1.6$  V). Interestingly, a similar trend was observed for the derivatives **24c,d**.

### Biological Evaluation on Melanoma Cells

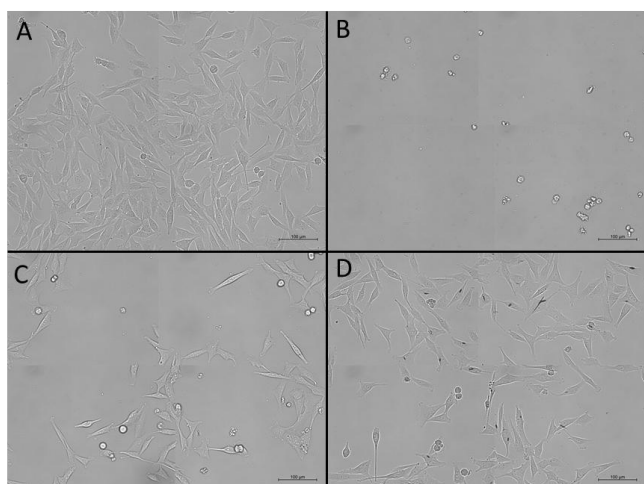
Finally, the antiproliferative activity of ten compounds (**12b**, **13**, **15**, **16**, **18**, **19**, **21a**, **23**, **24e** and **28**) was tested against A2058 human melanoma cells, as previously described by our group.<sup>[47]</sup> As shown in Figure 4, while low to very high growth inhibition

was measured at  $10^{-5}$  M after 72 h, compounds **18**, **19** and **21a** proved to be the most potent, with  $> 70\%$  antiproliferative activity against these metastatic and chemoresistant melanoma cells. Compound **21a** in particular performed remarkably well, inducing total cell death at  $10 \mu\text{M}$ ; this high cytotoxicity is consistent with the appearance of the culture broth, since only cell debris resembling apoptotic bodies was observed (Figure 5).



**Figure 4.** Antiproliferative activity (% growth inhibition) of the compounds **12b**, **28**, **15**, **13**, **16**, **23**, **24e**, **18**, **19** and **21a**. 2000 A2058 human melanoma cells were treated for 72 h with  $10^{-5}$  M of compound. Control cells were treated with an equivalent dose of DMSO (solvent of the tested compounds).





**Figure 5.** Antiproliferative activity of compounds **21a** (B), **19** (C) and **18** (D). 2000 A2058 human melanoma cells were treated for 72 h with  $10^{-5}$  M of compound. Control cells (A) were treated with an equivalent dose of DMSO (solvent of the tested compounds).

Without an in-depth study, it is not easy to predict the biological targets of **21a** that would explain the high activity observed. Indeed, prior to this study, molecules with the benzofuro[2',3':4,5]pyrrolo[1,2-a]indol-11-one skeleton had never been described. The closest molecules are the 'tripentones', which have a thieno[2,3-*b*]pyrrolizin-8-one core, such as the compound **MR22388** (Figure 2). Biological studies carried out to understand its antitumor activity on cancer cell lines have shown that it acts as a pro-apoptotic agent. This activity was associated with an anti-tubulin effect and weak cyclin-dependent kinase inhibitory activity.<sup>[28]</sup> The structure-activity relationships of benzothiophenes **18**, **19**, and benzofuran **21a** highlight the importance of the pentacyclic angular structure. This structural feature can improve molecular recognition and specificity in interactions with target proteins or DNA. The presence of five rings in these compounds contributes to increasing their molecular surface area, facilitating broader or multipoint interactions with biological targets, which may improve their cytotoxic efficacy.

As kinases may be targets responsible for the observed activity, compound **21a** was then tested against a panel of eight cancer-related protein kinases: cyclin-dependent kinase 9 (*HsCDK9/Cyclin T*), proto-oncogene kinase *HsPIM1*, dual specificity tyrosine phosphorylation regulated kinase 1A (*RnDYRK1A*), glycogen-synthase kinase-3 (*HsGSK3* isoforms  $\alpha$  and  $\beta$ ), dual specificity cdc-like kinase *MmCLK1*, mitotic kinase *HsHaspin*, and vascular endothelial growth factor receptor 2 tyrosine kinase *HsVEGFR2*. However, no inhibition was noticed. This suggests a potential action by other mechanisms.

Further examination of apoptosis, caspase activation and mitochondrial dysfunction, as well as necroptosis or ferroptosis, would be useful to clarify the mechanisms by which compound **21a** induces cell death. Moreover, given the angular heterocyclic structure of **21a**, a study of interactions with DNA and related enzymes such as topoisomerases, or DNA and RNA

polymerases, should also be considered. Finally, molecular docking simulations to explore potential interactions of compound **21a** with various cytoskeletal targets could prove instructive.

## Conclusion

Here, we have shown how the facile introduction of a carboxamide into the 2-position of benzofuran and benzothiophene can promote subsequent functionalisation towards valuable products. This was demonstrated by the synthesis of iodinated and diiodinated derivatives, successfully engaged in copper-promoted Ullman-type cross-coupling to give novel analogues of 'tripentones' as well as new pentacyclic structures. Their electrochemical and biological properties were assessed, revealing the ability of some of them to counter the *in vitro* proliferation of melanoma cells and demonstrating the potential of these compounds.

To learn more about the mode of action of compound **21a**, the most potent, it would be interesting to broaden the scope of targets to include a wider spectrum of kinases or other potentially relevant enzymes. In addition, techniques such as cellular pathway analysis, proteomics and gene expression profiling could help identify the pathways most affected by compound **21a**.

## Experimental Section

General information including crystallography and electrochemical measurements; Compound synthesis, analyses, and X-ray crystallographic details; ORTEP diagrams of **1a,b**, **2a,b**, **3**, **4**, **9-11** and **19**; NMR spectra of **2a,b**, **3**, **5**, **6**, **7a,b**, **8-11**, **12a,b**, **13-20**, **21a,b**, **22**, **23**, **24a-e**, **25**, **26a,b**, **27** and **28**; Voltammograms for compounds **23**, **24a,c,d**, **25** and **26a**.

The authors have cited additional references within the Supporting information.<sup>[48]</sup>

## Acknowledgements

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

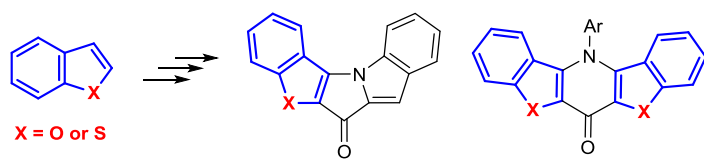
The data that support the findings of this study are available in the supporting information of this article.

**Keywords:** benzofuran • benzothiophene • bimetallic base • polycyclic compound • copper

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## Entry for the Table of Contents



Benzofuran and benzothiophene were elaborated to access original heteroaromatic scaffolds possessing specific electrochemical and biological properties.

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