Electrochemical Synthesis of Sulfinic Esters from Alcohols and Thiophenols

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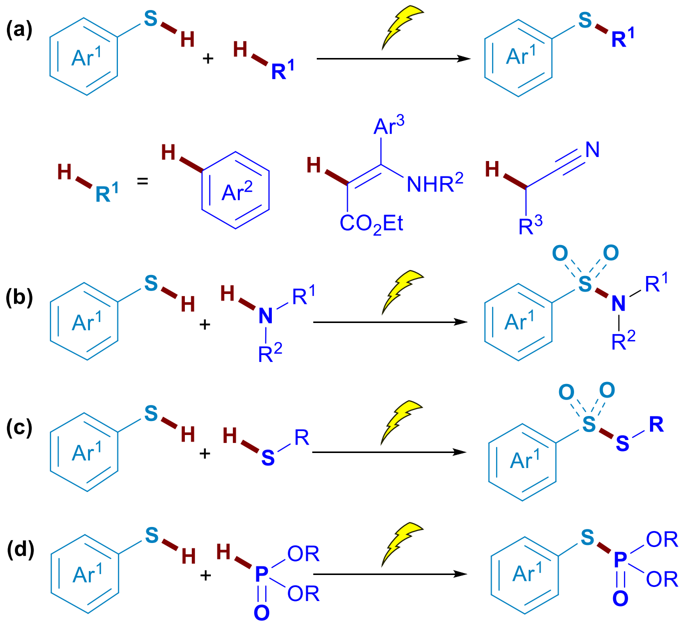
ABSTRACT. Electrochemical oxidative couplings between S–H and O–H bonds are achieved herein directly from readily-available alcohols and thiophenols, affording a series of diverse sulfinic esters. This strategy can take advantage of 6 equivalents of alcohol, relative to thiophenol, to achieve moderate to good yields, without the assistance of any metallic catalysts, bases, and additional oxidants.

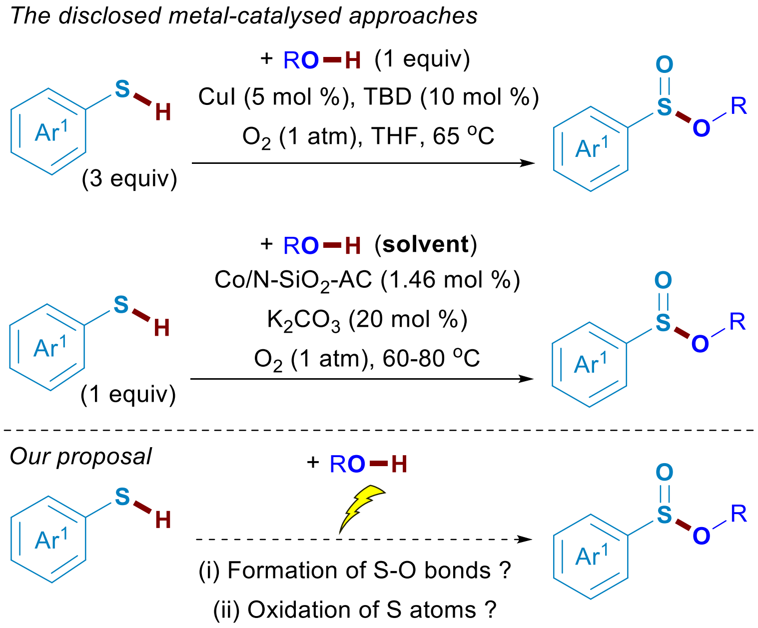
Sulphur-containing structural units are widely present in synthetic intermediates, natural products and bioactive molecules, such as agrochemicals and pharmaceuticals.[1] Therefore, the development of approaches to construct and transform the sulphur-containing skeleton has always been an attractive research topic of academic and industrial interest in organic chemistry. In particular, among the established strategies to build up the S–C and S–X (X = N, O, P, S) bonds, the direct oxidative dehydrogenative coupling between S–H bonds in thiols/thiophenol and C–H or X–H bonds may represent the most straightforward one, since such processed bypass the incorporation of leaving groups and require no pre-functionalization steps.[2-3] However, the requirement of the oxidants also renders the control of sulphur's oxidation state a tough nut to crack, since thiols/thiophenols are easily over-oxidised in the presence of oxidants. In the pursuit of more efficient approaches to realize the oxidative coupling of S–H bonds, electrochemical anodic oxidation has proved its utility and received increasing attention.



Scheme 1. Electrochemical dehydrogenative oxidative couplings of thiophenols.

Organic electrosynthesis has been developed for a long history and is currently gaining its renaissance under the background of pursuing greener synthetic strategies.[4-8] It is considered to be environmentally friendly because it provides an environment where electrons can interact with the nucleus directly, thus avoiding the use of chemical oxidants or reductants and reducing waste and pollution.[9] Furthermore, such an electrochemical process can be precisely controlled via the variation of voltage or current. More specifically, when it comes to electrochemical transformations of S–H bonds, a series of fruitful achievements have been made in the past three years. As shown in **Scheme 1**, starting from thiophenols, dehydrogenative oxidative couplings between thiophenols (S–H) and (hetero)arenes (C–H, **Scheme 1a**),[10-11] enamines (C–H, **Scheme 1a**),[12] acetonitrile (C–H, **Scheme 1a**),[13] amines (N–H, **Scheme 1b**),[14] thiols (S–H, **Scheme 1c**),[15-16] thiophenols (S–H, **Scheme 1c**)[17], aryl sulfinic acids (**Scheme 1c**)[18] or phosphonate (P–H, **Scheme 1d**)[19-20] have been achieved with the assistance of electricity.[21] Generally, no additional oxidants or catalysts were required for such transformations, and S–H bonds could be cleaved with retention of sulphur's oxidation state. More recently, the following oxidation of sulphur atoms was also realized under the electrochemical environment, which could merge well with the foregoing dehydrogenative couplings. For instance, sulfonamides (**Scheme 1b**)[22] and thiosulfonates (**Scheme 1c**)[17] could be obtained from two consecutive oxidations of sulfonamide and disulfides that were *in situ* generated via oxidative couplings of S–H bonds in the same vials, respectively. Despite such progress, electrochemical oxidative couplings between S–H bonds of thiophenols and O–H bonds of alcohols have not been disclosed, to the best of our knowledge.

On the other hand, as an important class of organosulphur compounds, sulfinic esters with umpolung reactivity can serve as both electrophiles and nucleophiles in organic synthesis to access other types of sulphur-containing molecules.[23] Therefore, their synthesis also received considerable attention. Traditionally, sulfinic esters can be prepared from sulfinyl halides,[24-27] sulfinic acids,[28] sodium sulfonates,[29-30] sulfonyl hydrazides or disulfides.[31] More recently, the direct oxidative couplings of thiophenols and alcohols have been realized to afford sulfinic esters via two independent metal-catalysed reaction systems (**Scheme 2**).[32-33] With this in mind, we speculate it feasible to access sulfinic esters via electrochemical oxidative couplings of the same two commodity chemicals. Such transformations would avoid the use and preparation of catalysts and would be particularly useful, given the inexpensive and readily available starting materials and electricity. However, as mentioned above, electrochemical oxidative couplings of S–H/O–H bonds remained unknown at present.[34] In addition, a suitable control of oxidation state of the sulphur atoms to suppress the over-oxidised by-products is also key to the success of such transformations. Herein, we report our preliminary efforts on this subject.

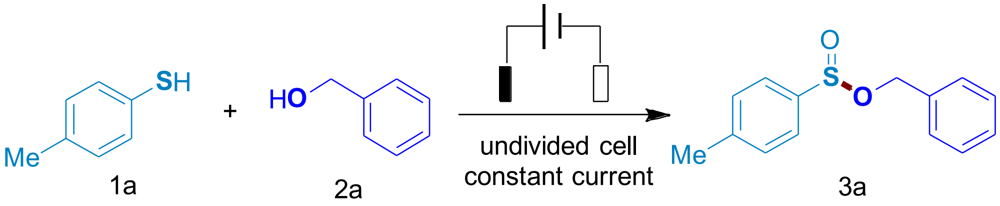


Scheme 2 Dehydrogenative oxidative couplings of thiophenols and alcohols.

We commenced the studies using 4-methylthiophenol (**1a**) and benzyl alcohol (**2a**) as reaction components (**Table 1**). After extensive experiments, 67% of target sulfinic ester **3a** could be obtained, when **1a** and 6.0 equivalents of **2a** were stirred in aerobic MeCN for 10 hours at room temperature, with the constant current being 6 mA, Pt/Pt as the electrodes and Bu_4NCl as the electrolyte (**Entry 8**). Variants from these parameters more or less decreased the yield of **3a**. Increasing or reducing the amount of **2a** by 2.0 equiv gave 46% (**Entry 13**) and 58% (**Entry 12**) yields of **3a**, respectively. Furthermore, changing the Bu_4NCl to another commonly used electrolyte Bu_4NClO_4 induced 17% less yield (**Entry 3**). The test of other electrolytes also did not give better results. Stronger or weaker electrical current were both detrimental to the reaction

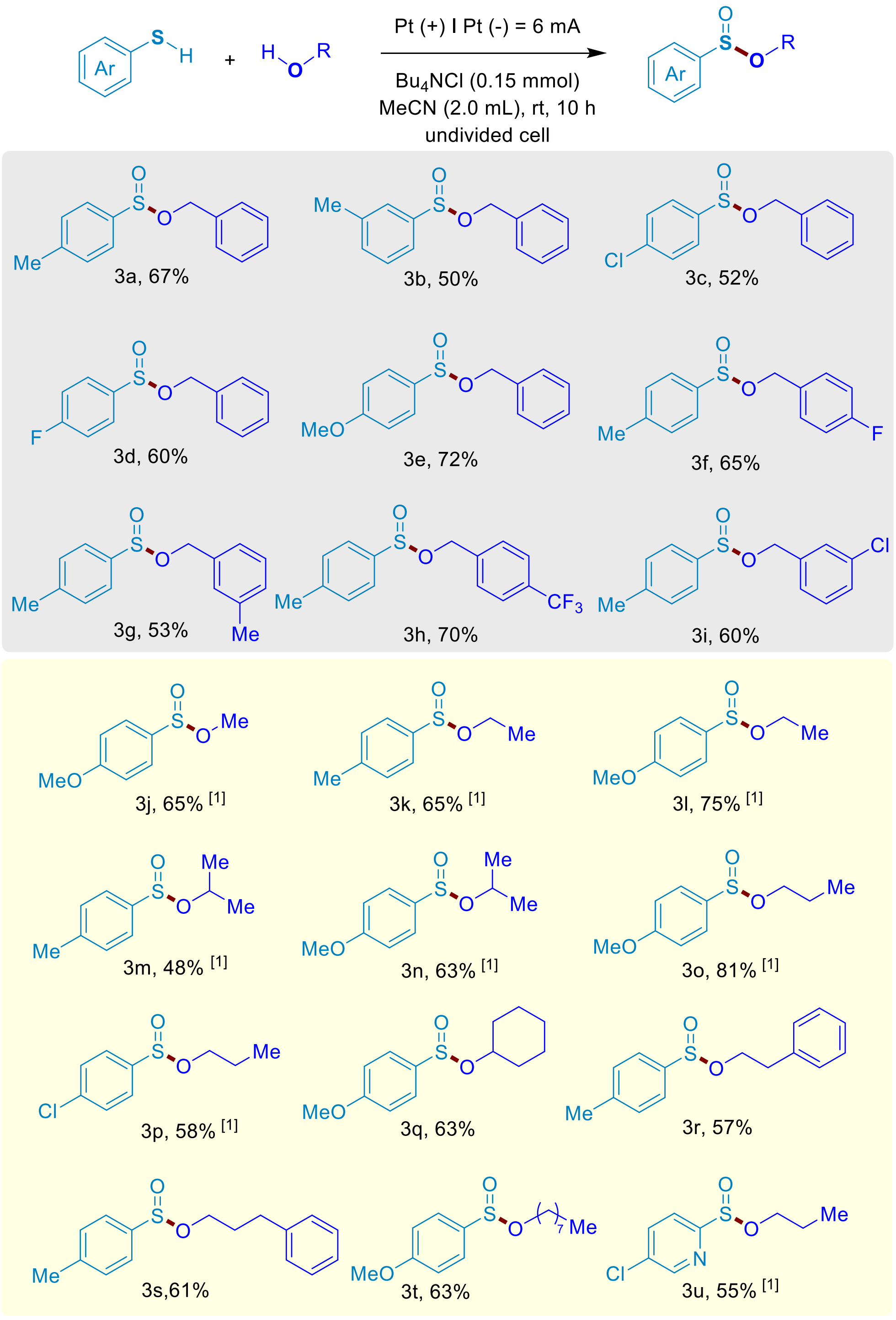
(**Entry 5, 6, 7**). Increasement of the current to 10 mA induced 10% less yield, however, further increment to 14 mA would dramatically reduce the yield to 16%, which might be attributed to the rising side reactions caused by the strong current. As for electrodes, Pt/C and C/C electrode pairs gave 49% (**Entry 9**) and 55% yield (**Entry 11**) of product, respectively.

Table 1. Optimization of reaction conditions[a]



Entry	**2a**	Anode	Solvent	Electrolyte	Current	Yields
1	6	Pt/Pt	DMF	Bu_4NCl	10	None
2	6	Pt/Pt	MeCN	PivONa	10	41
3	6	Pt/Pt	MeCN	Bu_4NClO_4	10	50
4	6	Pt/Pt	MeCN	AcOK	10	Trace
5	6	Pt/Pt	MeCN	Bu_4NCl	10	57
6	6	Pt/Pt	MeCN	Bu_4NCl	14	16
7	6	Pt/Pt	MeCN	Bu_4NCl	4	43
8	**6**	**Pt/Pt**	**MeCN**	**Bu_4NCl**	**6**	**67**
9	6	Pt/C	MeCN	Bu_4NCl	6	49
10	6	Pt/RVC	MeCN	Bu_4NCl	6	20
11	6	C/C	MeCN	Bu_4NCl	6	55
12	4	Pt/Pt	MeCN	Bu_4NCl	6	58
13	8	Pt/Pt	MeCN	Bu_4NCl	10	46

[a] Reaction conditions of Entry 8: Pt/Pt electrodes, constant current = 10 mA, 0.4 mmol of 1a (1.0 equiv), 2.4 mmol of 2a (6.0 equiv), Bu_4NCl (0.15 mmol) in MeCN (2.0 mL), rt, air, 10 h. [b] Isolated yield.

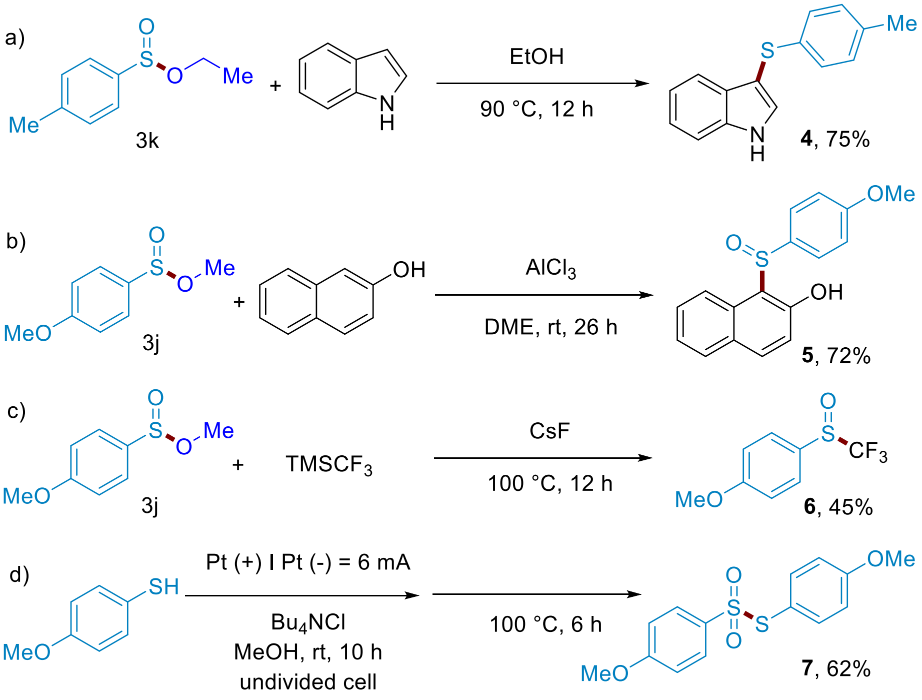


Scheme 3. Substrate scope of the electrochemical oxidative couplings of alcohols and thiophenols.

[1] alcohol as the solvent.

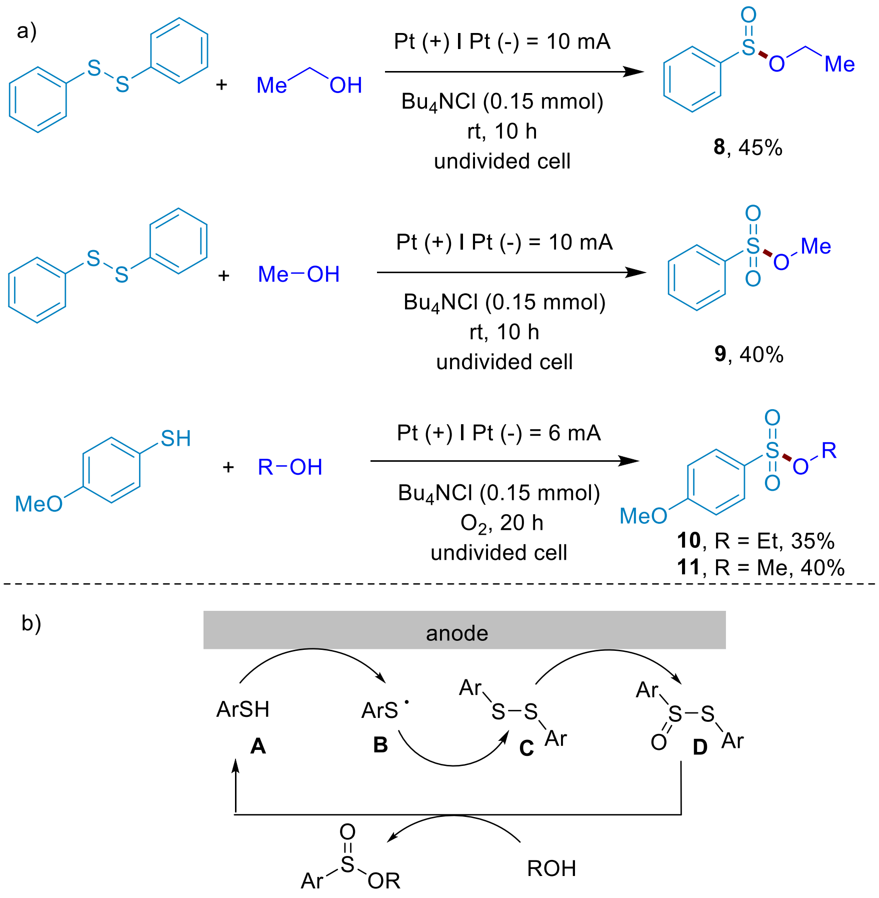
With the optimized reaction conditions in hand, we further explored the substrate scope of this electrochemical transformation (**Scheme 3**). Thiophenols with different substituents were treated with 6.0 equiv of benzyl alcohol at first. The electron-donating group on thiophenols rendered better yields, since methoxy group substituted thiophenol (**3e**, 72%) gave a better yield than the methyl (**3a**, 67%; **3b**, 50%), fluorine (**3d**, 60%) or chlorine (**3c**, 52%) substituted ones. Then, variation from benzyl alcohol was explored. It seemed that the electronic property of this counterpart had a limited effect on the outcome of the reaction. The application of 4-trifluoromethyl benzyl alcohol in this transformation resulted in 70% yield of the corresponding product **3h**. Fluorine and chlorine were also suitable substituents for the benzyl alcohol, affording **3f** and **3i** in 65% and 60% yields, respectively. The compatibility with the halides on both of the counterparts, especially chlorine (**3c**, **3i**), provided the opportunity for the further elaboration of the obtained sulfinic esters. Several other types of alcohols were also competent starting materials for this transformation, resulting in the formation of the corresponding sulfinic esters in approximately 60% yields (**3q** and **3t**). This list included the cyclic secondary alcohol cyclohexanol (**3q**), primary alcohols with appending phenyl group 2-phenylethan-1-ol (**3r**) and 3-phenylpropan-1-ol (**3s**) and long chain primary alcohol octan-1-ol (**3t**). It should be noted that all the above-mentioned reactions were performed with 6.0 equiv of alcohol involved.

When it came to the short chain alkyl alcohols, such as methanol and ethanol, which were much cheaper and more available than the long chain alcohols and benzyl alcohol, the direct application of the above-mentioned conditions resulted in limited success. A brief further optimization was carried out (see Supporting Information for details). It turned out that using these alcohols as the reaction solvents could gave comparative yields, relative to the above reaction system. Based on this, several commonly used alcohol solvents were applied in the reaction, affording the products in 48-81 yields. Similarly, in these cases, electron-donating group on thiophenols rendered better yields (**3k**, -Me, 65% vs. **3l**, -OMe, 75%; **3m**, -Me, 48% vs. **3n**, -OMe, 63%; **3o**, -OMe, 81% vs. **3p**, -Cl, 58%). As anticipated, secondary alcohol gave less product than the primary ones, probably due to the bulky steric effect during approaching the coupling counterpart.



Scheme 4. Derivatization of the obtained sulfinic esters to other sulphur-containing structures

Taking advantage of the obtained sulfinic esters, other sulphur-containing structures could be readily accessible (**Scheme 4**). When **3k** was treated with indole in ethanol, indole thioether **4** was isolated in 75% yield.[35] Diaryl sulfoxides **5** could be prepared by virtue of the Friedel-Crafts type reaction between **3j** and 2-naphthol, in 72% yield.[36] Trifluoromethyl sulfoxide **6** could also be obtained via the reaction between **3j** and $TMSCF_3$.[37] In addition, after the preparation of **3j**, simple removal of the electrodes and heating the reaction mixture at 100 °C for 6 hours would afford thiosulfonate **7** in 62% yield.



Scheme 5. A proposed reaction mechanism.

To gain more insight into the reaction mechanism, several control experiments were performed (**Scheme 5a**). First, addition of 1.0 equiv of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) to the standard reaction conditions, which would lead to **3a** or **3k**, obstructed the formation of target products. Then, the direct use of 1,2-diphenyldisulfane in the reaction with ethanol resulted in the formation of sulfinic ester **8** in 45% yield, which implied the involvement of disulfane in the reaction mechanism. Interestingly, under the same conditions, the interaction between 1,2-diphenyldisulfane and methanol would generate sulfonate **9**, the product that might derive from further oxidation of the sulfinic ester. To demonstrate this, a reaction between 4-methoxybenzenethiol and ethanol/methanol was performed under O_2 atmosphere. Such change resulted in sulfonate **10** and **11** in 35% and 40% yields, separately, which also demonstrated the key role of O_2 in the oxidation of sulphur atom.[38-39]

Based on the experimental results and previous literature reports.[5-14] A preliminary reaction mechanism is proposed in **Scheme 5b**. The thiol radicals **B**, which could be generated via oxidation and deprotonation of thiophenol **A** on the anode, dimerize to form disulfane **C**. The following oxidation of **C** by O_2 would lead to the generation of thiosulfinates **D**, which would go through the nucleophilic substitution process with alcohol to access target product. In the meanwhile, the regenerated thiophenol should take part in the next reaction cycle.

In conclusion, the electrochemical oxidative coupling between alcohols and thiophenols has been achieved, providing direct access to sulfinic esters in moderate to good yields. This electrosynthesis process bypassed the use of any metallic catalyst, base, and additive oxidant and was able to take advantage of 6.0 equiv of alcohol as the coupling counterpart. Detailed mechanism exploration and further derivation of this electrochemical system are on the way in our lab.

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

Compound characterization, ^{1}H and ^{13}C NMR spectra (PDF)

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Author Contributions

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