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Synthesis of disulfides by laccase-catalyzed oxidative coupling of heterocyclic thiols†

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A new method employing a laccase–mediator system as the catalyst and aerial oxygen as the oxidant has been developed for the oxidative coupling of heterocyclic thiols to the corresponding disulfides with yields up to 95% under mild reaction conditions.

Over the last few decades, the use of enzymes as catalysts in organic synthesis has received steadily increasing attention due to its economical and ecological advantages.[1] This holds particularly true for enzyme-catalyzed oxidations. Here, enzymes are being employed for the development of green oxidations, which are characterized by the use of nontoxic oxidants such as O_2 or H_2O_2, nontoxic solvents like H_2O, mild reaction conditions such as room temperature and atmospheric pressure and the formation of nontoxic side products like H_2O.[2]

Laccases (benzenediol: O_2 oxidoreductase; E.C. 1.10.3.2.) are easily available multicopper oxidases produced by fungi, plants and prokaryotes.[3] They catalyze the oxidation of organic molecules using molecular oxygen as the oxidant under mild conditions, *i.e.* in aqueous solvent systems at room temperature and at atmospheric pressure. As aerial oxygen is not only one of the cheapest oxidants available, but also regarded as an environmentally benign, sustainable oxidant, its application has become very popular over the last few years. In laccases, the substrate oxidation is accompanied by a reduction of oxygen to completely safe and nontoxic water.[4] The substrate range of laccases can be extended considerably by employing laccase–mediator systems which allow the oxidation of substrates with higher redox potentials.[5]

Meanwhile, laccases and laccase–mediator systems have been used for the oxidation of a number of functional groups, including activated methyl groups, alcohols, ethers and amines.[6] Other interesting transformations rely on oxidative aromatizations, like the transformation of 1,4-dihydropyridines to pyridines and the synthesis of 2-aryl-1*H*-benzimidazoles.[7] Laccases have also been used for the *in situ* generation of *o*- and *p*-quinones followed by Diels–Alder reactions[8] or nucleophilic additions of *C*-, *N*- and *S*-nucleophiles.[4c,9] Another interesting field is the laccase-catalyzed oxidative coupling of electron rich phenols[10] like sesamol type compounds,[10a,b] vanillidene derivatives,[10c] coniferyl alcohol,[10d,e] totarol,[10f] and hydroxystilbene derivatives.[10g]

Disulfides play a vital role in living systems with respect to the folding, stability and activity of numerous proteins[11] as well as their DNA-cleaving properties.[12] They are also of great interest as cleavable linkages for the design of drug delivery systems.[13] In organic chemistry, disulfides are used as intermediates for the synthesis of sulfinyl and sulfenyl compounds.[14] In industry, they are of great importance as vulcanizing agents.[15] In addition, it is known that different heterocyclic disulfides have interesting cytotoxic activity.[16] Therefore, the oxidation of thiols to the corresponding disulfides is of great interest both from a biological and a chemical point of view.

One of the most important methods for the preparation of symmetrical disulfides is the oxidative dimerization of the corresponding thiols (Scheme 1). Most procedures are based on the use of at least stoichiometric amounts of an inorganic oxidant, such as 2,6-dicarboxypyridinium chlorochromate,[17a] $(NH_4)_2Cr_2O_7$/silica chloride/50 wt% wet SiO_2,[17b] $KMnO_4$/$CuSO_4$,[17c] MnO_2,[17d] Br_2,[17e] HNO_3,[17f] I_2/DMSO[17g] and $Al(NO_3)_3 \cdot 9H_2O$/silica sulfuric acid.[17h]

Recently, a number of methods using O_2 as the oxidant have been developed for the oxidative dimerization. Typical examples include the oxidation of thiols with O_2 in the presence of 100 wt% of activated carbon,[18a] an excess of Al_2O_3,[18b] 1.5 equiv. of CsF on Celite[18c] and 38 mol% of a MOF [Fe(BTC)].[18d]

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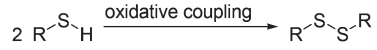
†Electronic supplementary information (ESI) available: Experimental data and copies of the ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/c3gc40106e



Scheme 1 Oxidative dimerization of thiols to disulfides.

In addition, the oxidative coupling of thiols with O_2 has been also achieved using a number of catalysts including 1 mol% diaryl tellurides under photosensitized conditions,[18e] 1 mol% Co(II)-Schiff base (Co-salophen),[18f] 10 mol% Mn(III)-Schiff base,[18g] 20 mol% NaI/10 mol% $FeCl_3$ [18h] and 15 mol% Ni-nanoparticles.[18i] The oxidative dimerization of thiols with O_2 was also possible in several ionic liquids[18j–l] or under sonication with Et_3N in DMF.[18m] Despite some progress, most of these methods suffer from a number of disadvantages, including the use of toxic and/or expensive oxidants or catalysts. Some of the reagents employed are commercially unavailable and their preparation is tedious. Also, some catalysts suffer from low catalytic efficiency. In addition, many of the methods reported require the use of volatile organic solvents. Another problem is that some reactions need to be run at high reaction temperatures. Against this background, it is a surprise that only little is known about the enzyme-catalyzed coupling of thiols using O_2 as the oxidant. So far, only horseradish peroxidase, mushroom tyrosinase[19a] and baker's yeast[19b] have been used for the oxidative dimerization of thiols.

Here, we report on the laccase-catalyzed oxidative coupling of heterocyclic thiols (Fig. 1) to the corresponding disulfides at room temperature using aerial oxygen at atmospheric pressure as the oxidant.

It is known that laccases differ with respect to their oxidation potentials and their optimal reaction conditions.[20] Laccases from *Trametes versicolor* (20 U mg^{-1})‡ and *Agaricus bisporus* (6 U mg^{-1})§ were chosen for this investigation. It has been reported that the optimum pH for the laccase from *T. versicolor* is around 4.4,[21a] while the optimum pH for the laccase from *A. bisporus* is around 6.0.[21b,c]

After some preliminary experiments with the laccases from *T. versicolor* and *A. bisporus* with regard to the amount of laccase, organic cosolvents and reaction time, selected thiols were reacted under the conditions given in Table 1 (Method A and Method B).

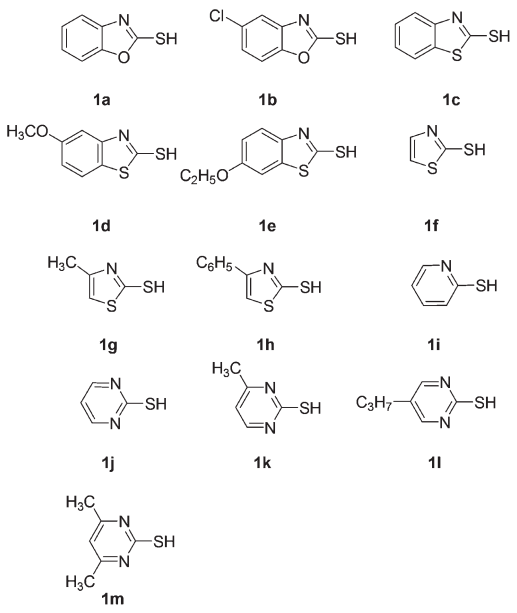
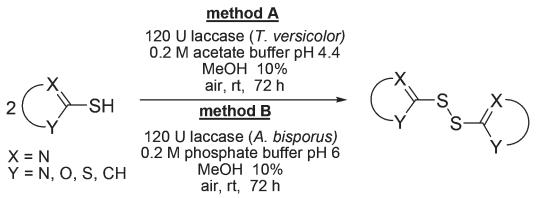
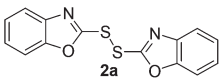
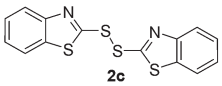
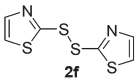
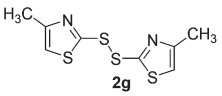
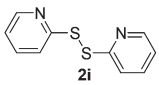
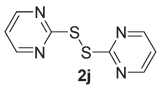
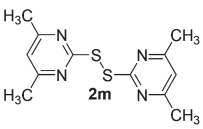


Fig. 1 Heterocyclic thiols employed as substrates.

Table 1 Laccase-catalyzed oxidative coupling of heterocyclic thiols **1** to disulfides **2** using different laccases[a]



Entry	1	Product	Method A Yield 2 (%)	Method B Yield 2 (%)
1	**1a**	 **2a**	5	—
2	**1c**	 **2c**	15	—
3	**1f**	 **2f**	26	25
4	**1g**	 **2g**	47	45
5	**1i**	 **2i**	27	18
6	**1j**	 **2j**	10	27
7	**1m**	 **2m**	11	50

[a] 1 mmol substrate was reacted.

Using laccase from *T. versicolor* (Method A), the disulfides **2** were formed exclusively with yields ranging from 5 to 47%. With the laccase from *A. bisporus* (Method B) the yields were in the range between 18 and 50%. However, with **1a** and **1c** as the substrates no product formation was observed with the *A. bisporus* laccase as the catalyst (Table 1, Method B, entries 1 and 2).

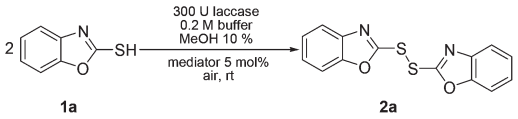
We wondered whether it is possible to improve the yields of the laccase-catalyzed oxidative dimerization by employing a laccase–mediator system. The oxidative coupling of **1a** to **2a** was chosen as a model reaction for the laccase-catalyzed oxidative coupling in the presence of different mediators (Table 2). 2-Mercaptobenzoxazole (**1a**) was oxidized with aerial O_2 in the presence of a combination of 300 U laccase from *T. versicolor* or *A. bisporus* and 5 mol% of a mediator (*vs.* substrate), such as ABTS, HOBT, TEMPO and violuric acid. The reactions with *T. versicolor* were performed at pH 4.4 while the transformations with *A. bisporus* were run at pH 6.0. It turned

out that ABTS was the most suitable mediator to serve this purpose. With *T. versicolor* as the enzyme and 5 mol% ABTS as the mediator, **2a** was isolated in 58% yield (Table 2, entry 1). Using a combination of laccase from *A. bisporus* and ABTS, the yield of **2a** amounted to 53% (Table 2, entry 2). With HOBT, TEMPO and violuric acid the yields of **2a** were considerably lower (Table 2, entries 3–8). In the absence of any mediator, the yield of **2a** dropped to 5% or traces (Table 2, entries 9 and 10 resp., see also Table 1, entry 1). As the yields with the laccase from *T. versicolor* were higher and because this enzyme is cheaper than the laccase from *A. bisporus*, all further experiments focused on the transformations with the combination *T. versicolor*–ABTS.

It is assumed that the reaction starts with the laccase-catalyzed oxidation of ABTS to the corresponding ABTS radicals, which is accompanied by the reduction of O_2 to water. This is followed by the oxidative dimerization of thiols **1** to give the corresponding disulfides **2**. This process is coupled with the reduction of ABTS radicals to ABTS (Scheme 2).

When the oxidation of **1a** to **2a** was repeated under the conditions given in Table 2, entry 1, but at 50 °C, the yield of **2a** was 56% (Table 3, entry 1). In order to increase the yield of **2a** and/or reduce the amounts of laccase and ABTS needed, the laccase-catalyzed transformation was run under the conditions given in Table 3. The best result was obtained when the transformation of **1a** to **2a** was run in the presence of 200 U laccase from *T. versicolor* and 2.5 mol% ABTS (Table 3, entry 4). A further reduction of the amount of laccase or ABTS did not pay off (Table 3, entries 5 and 6). When the reaction with 2.5 mol% ABTS was performed in the absence of any laccase, no formation of **2a** took place (Table 3, entry 7).

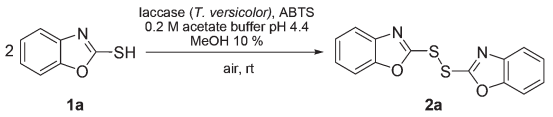
Table 2 Laccase-catalyzed oxidation of 2-mercaptobenzoxazole (**1a**) to disulfide **2a** using different laccases and different mediators[a]



Entry	Laccase	Buffer (pH)	Mediator	Time (h)	Yield of **2a** (%)
1	*T. versicolor*	Acetate (4.4)	ABTS	24	58
2	*A. bisporus*	Phosphate (6.0)	ABTS	24	53
3	*T. versicolor*	Acetate (4.4)	HOBT	48	33
4	*A. bisporus*	Phosphate (6.0)	HOBT	72	5
5	*T. versicolor*	Acetate (4.4)	TEMPO	48	13
6	*A. bisporus*	Phosphate (6.0)	TEMPO	48	4
7	*T. versicolor*	Acetate (4.4)	Violuric acid	48	17
8	*A. bisporus*	Phosphate (6.0)	Violuric acid	72	Traces
9	*T. versicolor*	Acetate (4.4)	—	24	5
10	*A. bisporus*	Phosphate (6.0)	—	24	Traces

[a] 1 mmol **1a** was reacted.

Table 3 Optimization of the laccase–ABTS-catalyzed oxidation of **1a** to disulfide **2a**[a]



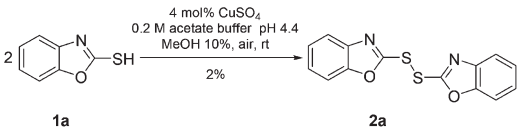
Entry	Laccase (U)	ABTS (mol%)	*T* (°C)	Time (h)	Yield of **2a** (%)
1	300	5	50	24	56
2	300	10	rt	24	57
3	200	5	rt	28	59
4	200	2.5	rt	30	59
5	200	1.25	rt	30	40
6	150	2.5	rt	30	48
7	—	2.5	rt	20	—

[a] 1 mmol **1a** was reacted.

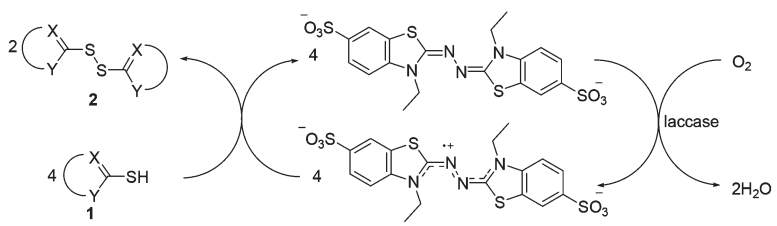
We also tried to replace the laccase–ABTS system by $CuSO_4$ as a simulation of laccase enzyme without protein backbone under the same experimental conditions. However, when the transformation of **1a** was run in the presence of 4 mol% $CuSO_4$, the yield of disulfide **2a** was very low (2%) (Scheme 3).

With the optimized conditions in hand (Table 3, entry 4),¶ the oxidative dimerization of a number of heterocyclic thiols including 2-mercaptobenzoxazoles **1a,b**, 2-mercaptobenzothiazoles **1c–e**, 2-mercaptothiazoles **1f–h**, 2-mercaptopyridine (**1i**) and 2-mercaptopyrimidines **1j–m** was studied. It was observed that all thiols could be oxidized smoothly. In all cases the disulfides **2a–m** were formed exclusively with yields ranging between 50 and 95% (Table 4). Noteworthy to mention is that no side products from overoxidation could be isolated.

The laccase-catalyzed oxidative coupling of thiols to disulfides presented here is in accordance with the principles of

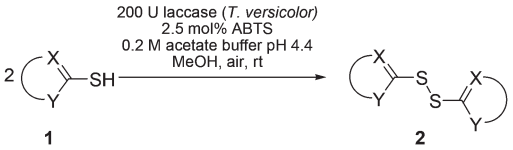


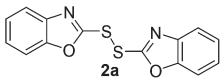
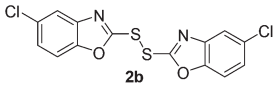
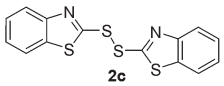
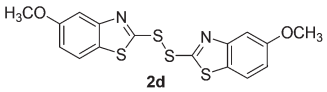
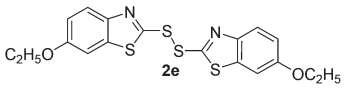
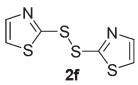
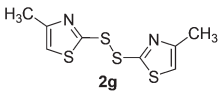
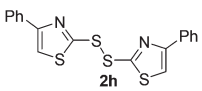
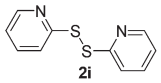
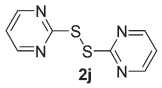
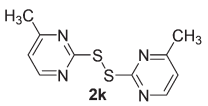
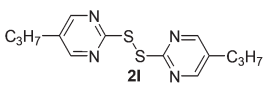
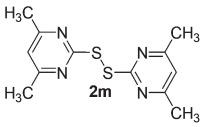
Scheme 3 Coupling of **1a** to **2a** with 4 mol% $CuSO_4$/air.



Scheme 2 Proposed mechanism of the laccase–ABTS catalyzed oxidation of heterocyclic thiols **1** to disulfides **2**.

Table 4 Scope of the laccase–ABTS catalyzed oxidation of **1** to **2**



Entry	1	Product	Time (h)	Yield 2 (%)
1[a]	**1a**	 **2a**	30	59
2[b]	**1b**	 **2b**	24	50
3[a]	**1c**	 **2c**	24	78
4[b]	**1d**	 **2d**	24	91
5[a]	**1e**	 **2e**	12	89
6[a]	**1f**	 **2f**	8	81
7[a]	**1g**	 **2g**	8	66
8[a]	**1h**	 **2h**	8	92
9[a]	**1i**	 **2i**	5	82
10[a]	**1j**	 **2j**	5	90
11[a]	**1k**	 **2k**	5	87
12[a]	**1l**	 **2l**	6	85
13[a]	**1m**	 **2m**	8	95

[a] 1 mmol substrate was reacted. [b] 0.5 mmol substrate was reacted.

green chemistry[22] for the following reasons: The reaction is a highly selective enzyme-catalyzed process that allows for a substantial reduction of waste. The oxidative dimerization of thiols **1** delivers analytically pure disulfides **2** in up to 95% yield. No toxic byproducts are formed. Aerial oxygen as the oxidant is converted into nontoxic water as the only byproduct of the conversion. Using the oxidative coupling of **1m** to **2m**‖ as an example, the *E*-factor (kg waste per kg product)[22c,d,23] of the overall process amounts to 8.08 kg kg^{-1}. This value compares well with the *E*-factors of other synthetic methods for the synthesis of disulfides.[17–19] The atom economy[22c,24] of the oxidative coupling of thiols to disulfides is very high; it amounts to 94%. The laccase-catalyzed process employs aerial oxygen as an oxidant and avoids the use of any toxic reagents like hazardous heavy metal catalysts/oxidants as well as other toxic reagents. The reactions were run in a mixture of acetate buffer (pH 4.4) and up to 17 vol% methanol, which is a safe and environmentally preferred solvent[25] as the reaction medium. Ethyl acetate, a preferred green solvent, was the solvent used in most cases for extraction. In contrast to other processes, the laccase-catalyzed oxidative dimerization can be carried out under mild reaction conditions, *i.e.* at room temperature, under air at atmospheric pressure, in an aqueous system at pH 4.4. The laccase-catalyzed disulfide synthesis is characterized by high turnover numbers. Using the dimerization of **1m** to **2m** as an example, it amounts to 9024. This value confirms the high catalytic efficiency of the process. The turnover frequencies of the process are also high; in the above mentioned example the TOF is 1128 h^{-1}. These values compare well with TONs and TOFs of other synthetic methods for the synthesis of disulfides. Unfortunately, the STY of the process is only 0.005 mol × h^{-1} × L^{-1}. However, it is expected that it could be improved by immobilization of laccase as CLEAs.[26] And last but not least, the laccase catalyst is isolated from renewable feedstock and is completely biodegradable. The same holds true for the acetic acid of the acetate buffer used.

The structures of all disulfides **2a–m** were either confirmed by comparing their physical and spectral data with their reference data or unambiguously elucidated by NMR spectroscopy and mass spectrometry.** Full assignment of the ^{1}H and ^{13}C chemical shifts were achieved by evaluating their gCOSY, gHSQC and gHMBC spectra.

For example, compound **2c** contains a coupled ^{1}H spin system consisting of aromatic protons 4-H, 5-H, 6-H and 7-H (Fig. 2). The sequence of the protons in the spin systems was determined by an analysis of the gCOSY spectrum. Determination of the chemical shifts of the quaternary carbons C-3a and C-7a was not unambiguous by ^{3}J-HMBC. Therefore, ^{13}C NMR chemical shifts were computed by quantum mechanical DFT calculations at the DFT GIAO mPW1PW91/6-311+G(2d,p)//mPW1PW91/6-31G(d) level of theory.[27] On the basis of the computationally calculated ^{13}C chemical shifts, the quaternary

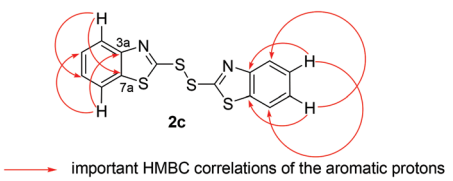


Fig. 2 Important HMBC correlations of **2c**.

carbons C-3a and C-7a were assigned at δ = 154.54 ppm (δ calcd = 152.58 ppm) and δ = 136.13 ppm (δ calcd = 140.04. ppm), resp. The remaining chemical shift at δ = 167.83 ppm was assigned at C-2 (δ calcd = 168.58 ppm).

To summarize, a laccase–mediator system has been employed to catalyze the oxidative coupling of heterocyclic thiols to the corresponding disulfides. The reactions make use of aerial oxygen at atmospheric pressure as the oxidant, proceed at room temperature in an aqueous solvent system at pH 4.4 and deliver the disulfides in good to excellent yields.

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Notes and references

‡Determination of the activity of laccase from *T. versicolor* according to ref. 28. A 0.1 M solution of ABTS (0.3 mL) in 0.2 M acetate buffer (pH 4.4) was diluted with 0.2 M acetate buffer (2.6 mL, pH 4.4) and treated with a solution of laccase in the same buffer (0.1 mL). The change in absorption was followed *via* UV-Vis spectroscopy (λ = 414 nm). One unit was defined as the amount of laccase that converts 1 μmol of ABTS per minute at pH 4.4 at rt.

§The activity of laccase from *A. bisporus* was taken as given by the supplier (6 U mg^{-1}).

¶General procedure for the laccase-catalyzed oxidation of heterocyclic thiols **1a–m** to the corresponding disulfides **2a–m**: A 50 or 100 mL round bottomed flask with a magnetic stirrer bar was charged with a solution or suspension of the heterocyclic thiol **1** (1 mmol) in methanol (3–6 mL). Acetate buffer (0.2 M, pH 4.4, 20–30 mL), laccase from *T. versicolor* (200 U, 10 mg) and ABTS diammonium salt (13.7 mg, 0.025 mmol) were added and the reaction mixture was stirred at rt for the time given. After extraction with EtOAc (3 × 30 mL) or CH_2Cl_2 (3 × 30 mL), the combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography on SiO_2.

‖Reaction was run using **1m** (1 mmol), methanol (1 mL), acetate buffer (0.2 M, pH 4.4, 10 mL), *T. versicolor* (200 U, 10 mg) and ABTS diammonium salt (13.7 mg, 0.025 mmol). After completion of the reaction, the crude product was extracted with EtOAc (3 × 3 mL) and purified by flash chromatography on SiO_2 to deliver **2m** in 131 mg, 94% yield.

Selected analytical data of bis(2-benzothiazolyl)disulfide (2c**): white powder (129 mg, 78%); mp 176–178 °C (lit.,[29] 178–179 °C); R_f = 0.61 (petroleum ether–EtOAc = 5 : 1); δ_H (300 MHz; $CDCl_3$) 7.36 (2H, ddd, $^3J_{5\text{-H},6\text{-H}}$ 7.5 Hz or 8.3 Hz, $^3J_{6\text{-H},7\text{-H}}$ 7.5 Hz or 8.3 Hz, $^4J_{4\text{-H},6\text{-H}}$ 1.2 Hz, 6-H), 7.47 (2H, ddd, $^3J_{4\text{-H},5\text{-H}}$ 7.2 Hz or 8.4 Hz, $^3J_{5\text{-H},6\text{-H}}$ 7.2 Hz or 8.4 Hz, $^4J_{5\text{-H},7\text{-H}}$ 1.2 Hz, 5-H), 7.78 (2H, dd, $^3J_{4\text{-H},5\text{-H}}$ 8.0 Hz, $^4J_{4\text{-H},6\text{-H}}$ 1.2 Hz, 4-H) and 7.94 (2H, dd, $^3J_{6\text{-H},7\text{-H}}$ 7.9 Hz, $^4J_{5\text{-H},7\text{-H}}$ 1.2 Hz, 7-H); δ_C (75 MHz; $CDCl_3$) 121.29 (C-4), 122.68 (C-7), 125.28 (C-6), 126.57 (C-5), 136.13 (C-7a), 154.54 (C-3a) and 167.83 (C-2).

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