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Rongalite induced metal-free C(sp^2)−H functionalization of indoles: direct access to 3-(sulfonylmethyl) indoles†

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A rongalite-induced C(sp^2)−H functionalization reaction has been developed for the synthesis of 3-(phenyl-sulfonylmethyl) indole derivatives from indole and arylsulfonyl hydrazides. This regioselective C−H functionalization provides a wide range of C-3 sulfonylmethyl indoles with upto 90% yields. Here, rongalite functions as a C1 unit source and a single electron donor. The use of inexpensive rongalite (*ca.* $0.03 per 1 g), mild reaction conditions and gram-scale synthesis are some of the key features of this methodology.

Introduction

The development of new methods to synthesize complex molecules *via* a single-step and cost-effective strategy has been a long-standing challenge in organic synthesis. There has been significant progress in the development of multicomponent reactions (MCRs) as one of the most suitable approaches to address this challenge.[1] However, the product diversity of a MCR is limited as it mainly depends on the reactive functional groups, such as carbonyl, nitrile, isocyanides, *etc.*[2] Due to the ubiquitous nature of C−H functionalities in almost every molecular scaffold, multicomponent reactions involving direct reactions of a C−H bond (CH-MCR) would expand the molecular diversity.[3] Meanwhile, indoles are omnipresent in nature and play a pivotal role in organic chemistry and drug design.[4] Indole and its derivatives exhibit a wide range of pharmacological activities, such as antibacterial, anticonvulsant, antifungal, antimalarial, antidiabetic, antidepressant, anticancer, and antimicrobial activities.[5–8] Also, it is the core structure of several FDA-approved drugs that are widely used for treating various diseases.[9] The introduction of functionalization at the 3-position brings versatility in the indole system and is a common practice directed towards the synthesis of biologically active compounds.[10]

In particular, the sulfonylmethyl group is of significant interest due to its strong electron-withdrawing properties and capacity for further chemical modification making it an attractive target for incorporation into heterocyclic compounds,

such as indoles. The sulfonylmethyl group effectively alters the electron density and provides versatile sites for further functionalization, which can lead to the development of compounds with diverse pharmacological activities.[11] On the other hand, homologation chemistry represents a valid approach for incorporating a methylene group (−CH$_2$) into a given molecule.[12,13] This strategy brings significant changes in the physical and chemical properties of the organic skeleton.[14] Ideally, the homologation protocol would precisely introduce the methylene fragment between a C−H bond. A plethora of reagents were used for this strategy, *e.g.*, DMSO, DMF, tetramethylurea, and *N,N*-dimethylacetamide (DMA), with catalysts such as Ru, Ti, Cu, *etc.*[15] In recent years, one of the core research goals of chemists is to make existing chemical methods "greener" and 100% atom-efficient to ensure a sustainable and safe environment for future generations. Thus, the development of efficient C1 homologation has become a predominant field of research in synthetic chemistry.

Müller *et al.* were the first to report the synthesis of 3-(sulfonylmethyl) indoles from indoles and sulfinic acids in the presence of formalin solution.[16] In 2006, Petrini *et al.* introduced the Friedel–Crafts reaction and strategies using Reformatsky reagents for the synthesis of 3-(sulfonylmethyl) indoles (Scheme 1a).[17,18] Later, Zhu *et al.* reported the Fe-catalyzed C−H sulfonylmethylation of indoles using TosMIC as a sulfonyl source (Scheme 1b).[19]

Although the above method provides a good yield, it suffers from the use of expensive α-amidosulfones, TosMIC, and toxic formalin. Therefore, the development of a new methodology for the direct sulfonylmethylation of indoles in a single operation is a key area of research.

In this context, sodium hydroxymethanesulfinate dihydrate (SHM), commonly known as rongalite, is a commercially inexpensive (0.03$ per 1 g) industrial product and widely used in

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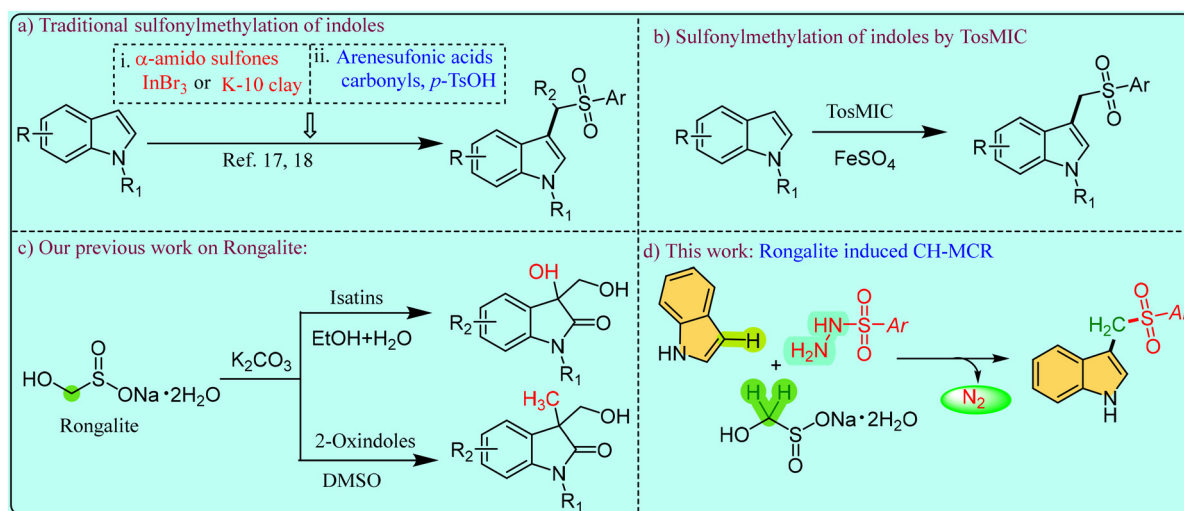
Scheme 1 Synthesis of sulfonylmethyl indoles.

organic synthesis.[20,21] It acts as a super electron donor,[22] source of the C1 unit and sulfoxylate dianion (SO_2^{2-}).[23] In continuation of our efforts on exploring the synthetic utility of rongalite as an electron source and in hydride-free reduction (Scheme 1c),[24] herein we report a one-pot CH-multicomponent reaction for sulfonylmethylation by exploring the C1 unit donating nature of rongalite (Scheme 1d).

Results and discussion

To validate our protocol for the synthesis of 3-(phenylsulfonyl-methyl) substituted indoles, we began with the reaction of indole **1a** (1.0 equiv.), *p*-toluenesulfonyl hydrazide **2a** (1.0 equiv.) and rongalite **3** (1.0 equiv.) in CH_3CN solvent (2 mL) at room temperature. Initially we did not observe any progress in the reaction which was monitored by TLC, even after stirring the reaction mixture at room temperature for 12 h. However, the starting material was consumed at 70 °C and gave the desired product 3-(tosylmethyl)-1*H*-indole **4a** in 30% yield (Table 1, entries 1–4). These results prompted us to optimize the reaction conditions to improve the product yield. Hence, we focused on the screening of various solvents. We conducted the reactions in chlorinated solvents such as dichloromethane and chloroform, but these solvents failed to give the desired product. This may be attributed to the low boiling points of these solvents (Table 1, entries 5 and 6). However, dichloroethane gave the target product in a low yield (Table 1, entry 7); this was not the case with toluene which failed to provide the desired end product (Table 1, entry 8).

We further screened polar aprotic solvents such as nitromethane, THF, TEG, DMSO, and DMF; except THF and DMF, everything else failed to afford the end product (Table 1, entries 9–13).

Finally, we tested the same reaction in polar protic solvents, *i.e.*, methanol and ethanol, which surprisingly gave good

Table 1 Optimization of the reaction conditions[a]

Entry	Solvent	Rongalite (equiv.)	Temperature (°C)	Time (h)	Yield[b] (%)
1	CH_3CN	1.0	rt	12	n.d.[c]
2	CH_3CN	1.0	50	12	20
3	CH_3CN	1.0	70	6	30
4	CH_3CN	1.0	80	6	30
5	CH_2Cl_2	1.0	45	12	n.d.
6	$CHCl_3$	1.0	60	12	n.d.
7	DCE	1.5	70	10	20
8	Toluene	1.0	70	6	n.d.
9	CH_3NO_2	1.0	70	10	n.d.
10	THF	1.0	70	12	10
11	TEG	1.0	90	12	n.d.
12	DMSO	1.0	90	12	n.d.
13	DMF	1.0	90	12	40
14	MeOH	1.0	70	12	40
15	EtOH	1.0	70	12	50
16	EtOH	1.5	70	8	70
17	EtOH	2.0	70	6	90
18	EtOH	2.5	70	6	90
19	H_2O	2.0	90	12	n.d.

[a] All the reactions were conducted on a 1 mmol scale of **1a** (1 mmol), **2a** (1 mmol) and **3** (2 mmol) in solvent (2 mL). [b] Yield where reported is of the isolated and purified product. [c] Not detected.

results (Table 1, entries 14 and 15). Next, we examined the stoichiometry of rongalite by varying its amount from 1.0 equivalent to 2.5 equivalents and found that 2 equivalents of rongalite is required to obtain better yields (Table 1, entries 16–18). Finally, we conducted the same reaction in water but failed to obtain the target product; this may be due to the solubility problem of substrates in water. The optimized conditions for the above reaction are as follows: indole **1a** (1.0 mmol), sul-

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fonyl hydrazide **2a** (1.0 mmol) and rongalite **3** (2.0 mmol) in ethanol (2 mL) at 70 °C for 6 h.

After optimizing the reaction conditions for the one-pot three-component synthesis of 3-(phenylsulfonylmethyl) substituted indoles (Table 1, entry 17), we focused on the scope of the substrates and reagents. Electron donating substitutions on indoles like Me, Ph, OH, OMe and OBn reacted with 4-methyl benzenesulfonohydrazide, affording the corresponding sulfonylmethyl indoles in good to excellent yields (Scheme 2, **4a–h**). Interestingly, electron-withdrawing groups such as NO₂, CHO, CN, and esters smoothly participated under the optimized reaction conditions to produce **4i–l**, albeit

in low yields. *N*-Methyl, *N*-benzyl and *N*-dodecyl groups on indoles did not alter the reaction yields (Scheme 2, **4m, 4n, 4u,** and **4v**).

Similarly, benzenesulfonohydrazide and 2,4,6-trimethylbenzenesulfonohydrazide reacted with different indoles and delivered the title products in good yields (Scheme 2, **4w–aa**). To our delight, aliphatic sulfonohydrazides containing isopropyl and cyclopropyl groups also reacted with rongalite and indole to furnish **4ab** and **4ac** in good yields. It is worth mentioning that electron withdrawing groups, *viz.*, NO₂ and CN, on sulfonohydrazides were unreactive under the optimized conditions.
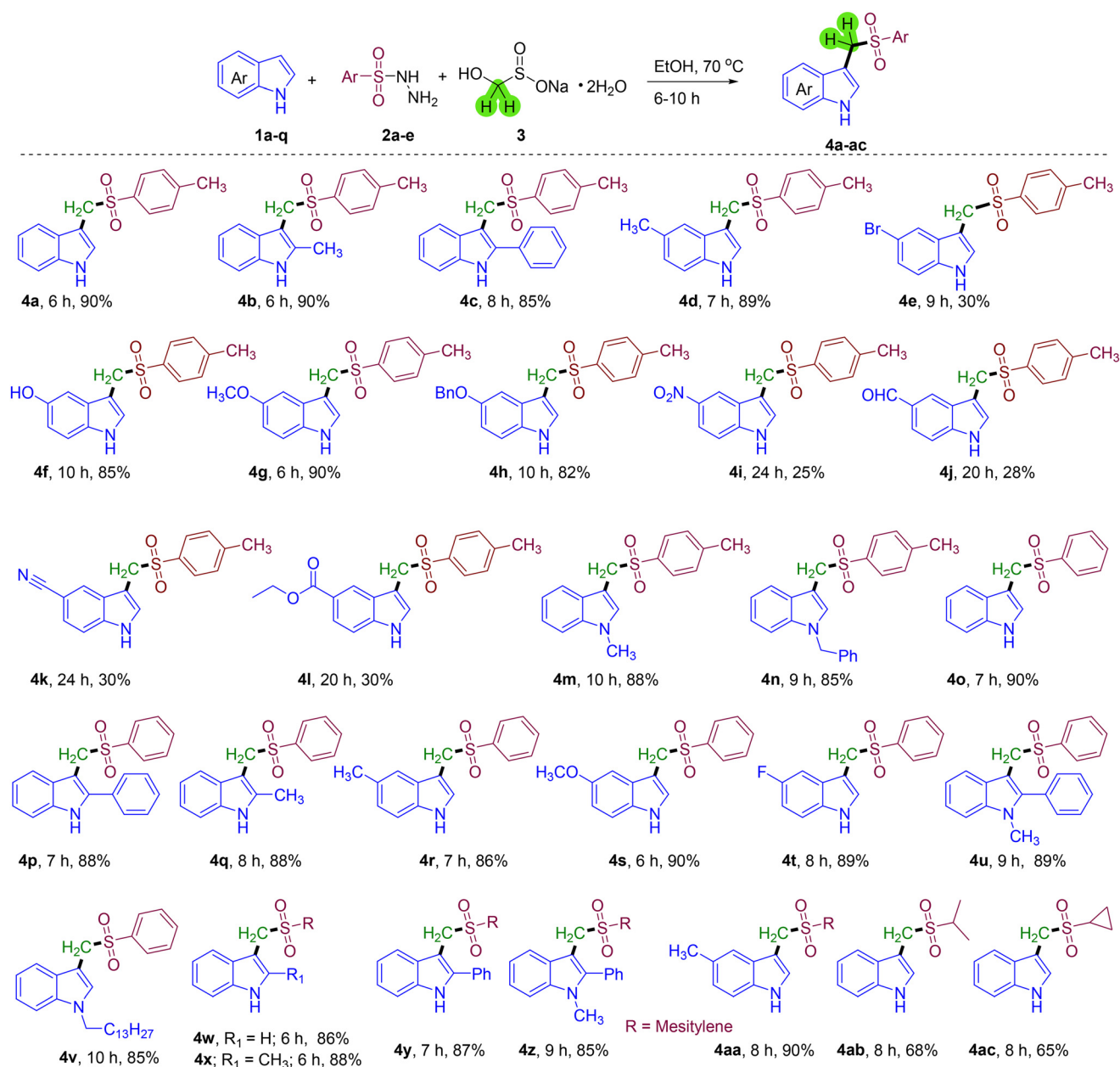

Scheme 2 Generality in the synthesis of 3-(phenylsulfonylmethyl) indole derivatives. Reactions were carried out using indoles **1a–q** (1.0 mmol), **2a–e** (1.0 mmol) and **3** (2.0 mmol) in ethanol (2 mL). Yields of isolated and purified products are reported.

All the synthesized compounds **4a–ac** were characterized by ^{1}H NMR, ^{13}C NMR and mass spectrometry. Finally, the structures of compounds **4g** and **4z** were confirmed by single crystal XRD (Fig. 1). The crystallographic data and refinement parameters of compounds **4g** and **4z** are presented in the ESI.†

To examine the scalability of the proposed method, we conducted a reaction using indole **1a** (1 g, 8.54 mmol), 4-methylbenzenesulfonohydrazide **2a** (2.38 g, 12.81 mmol) and rongalite **3** (1.35 g, 17.08 mmol) which were dissolved in EtOH solvent and stirred at 70 °C, and the target molecule **4a** was obtained in 84% yield (Scheme 3). This indicated that the method is also applicable for gram scale reactions.

To gain a mechanistic insight into the sulfonylmethylation, we conducted some control experiments (Scheme 4). Initially, the reaction conducted using indole **1a** (1.0 mmol) and 4-methylbenzenesulfonohydrazide **2a** (1.0 mmol) in the
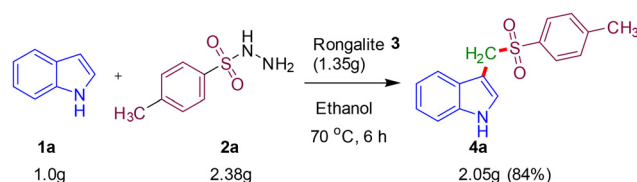
Scheme 3 Gram-scale synthesis of 3-(tosylmethyl)-1H-indole **4a**.
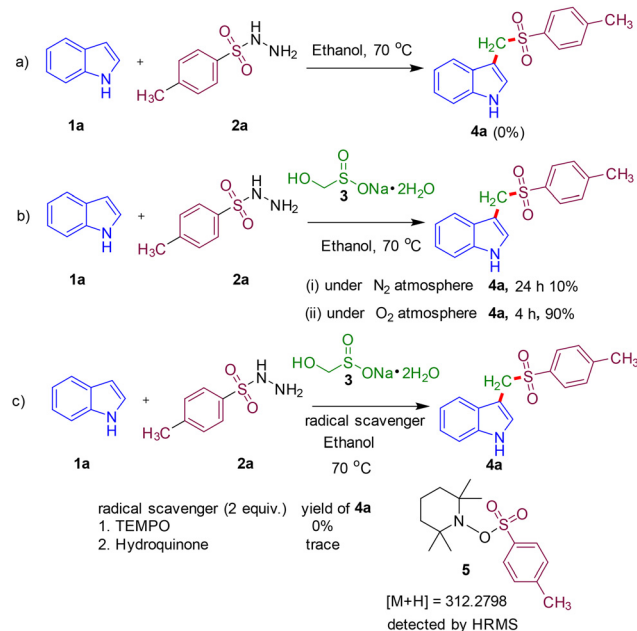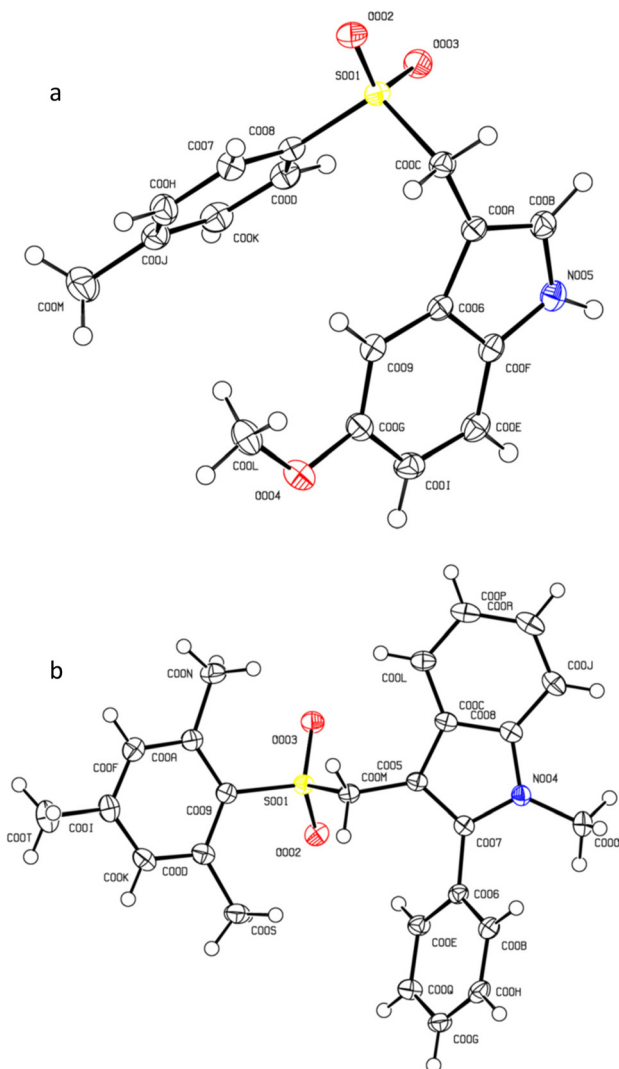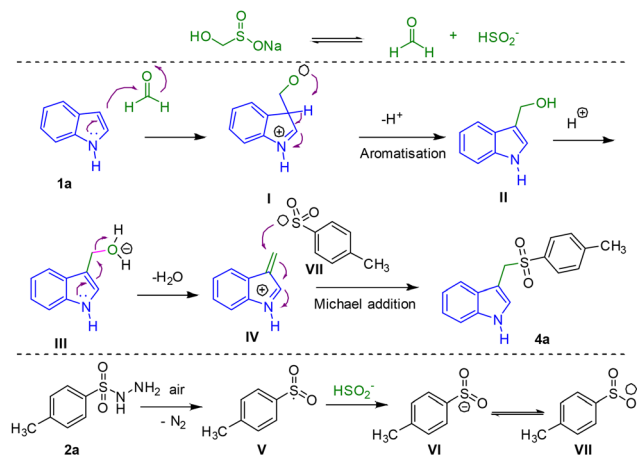

Scheme 4 Control experiments.

Fig. 1 ORTEP representations of X-ray crystal structures of (a) 5-methoxy-3-(tosylmethyl)-1H-indole **4g** and (b) 3-((mesitylsulfonyl)methyl)-1-methyl-2-phenyl-1H-indole **4z**. The thermal ellipsoids are drawn at a 50% probability level.

absence of rongalite **3** in ethanol (2 mL) at 70 °C failed to give the desired product **4a** (Scheme 4a). This result indicates that rongalite acts as a C1 synthon source. Later, the same reaction when conducted in the presence of rongalite under an inert atmosphere (N$_2$) gave only 10% of the target compound **4a**, which may be attributed to a small amount of dissolved oxygen (Scheme 4bi). However, the target product was observed in 90% yield in less time under an oxygen atmosphere (Scheme 4bii). These results suggest the involvement of oxygen in the reaction mechanism. Finally, the same reaction was repeated with radical scavengers such as TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl), DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) and hydroquinone (2 mmol) in ethanol (2 mL) at 70 °C. No progress of the reaction was observed to provide 3-(tosylmethyl)-1H-indole **4a** (Scheme 4c). The above results clearly indicate that the sulfonylmethylation of indoles by rongalite proceeds *via* a radical mechanism in the presence of oxygen. Additionally, the TEMPO adduct with *p*-toluenesulfonyl hydrazide was detected by HRMS analysis (see ESI, S54†).

A plausible reaction mechanism was proposed as shown in Scheme 5 based on the control experiments and literature reports.[24a,25,26]

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Scheme 5 Plausible reaction mechanism.

Firstly, indole **1a** reacts with *in situ* generated formaldehyde from rongalite to form intermediate (**I**) which further undergoes rearomatization and dehydration to yield intermediate (**IV**).

Finally, conjugate addition by the sulfonyl nucleophile (**VII**), generated *in situ* from sulfonohydrazide, gives the final compound **4a** *via* Michael addition. In this process, the sulfonyl nucleophile (**VII**) is generated from sulfonyl hydrazide **2a** and rongalite under an oxygen atmosphere.

Conclusions

In summary, this study successfully demonstrates the use of rongalite-induced C–H functionalization and multicomponent reactions to synthesize 3-(phenylsulfonylmethyl) indole derivatives. Utilizing indole and arylsulfonyl hydrazides, this method offers an efficient and straightforward pathway for sulfonylmethylation under mild conditions. The application of rongalite, known for its non-toxic and easy handling properties, provides operational simplicity, high yields, and environmental benefits. This technique serves as an attractive alternative to traditional sulfonylation methods, expanding the repertoire of synthetic approaches for producing valuable indole derivatives. The success of this method underscores the potential of rongalite in promoting sustainable and efficient synthetic practices in contemporary chemistry, with promising applications in the fields of pharmaceuticals and materials science.

Data availability

The data supporting this article have been included as part of the ESI.† Experimental procedures, characterization data, crystallographic data and copies of the ^{1}H, ^{13}C{1H} and HRMS spectra of all compounds are included.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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