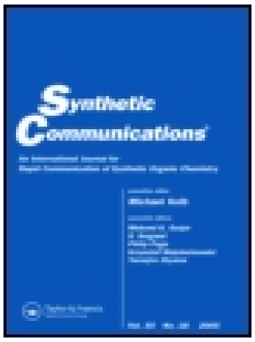

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Seralite SRC-120 resin catalyzed synthesis of bis(indolyl)methanes using indoles and low/high boiling point carbonyl compounds under solvent free conditions

Harish K. Indurthi[a], Reena Virdi[b], Papita Koli[a], Desaboini Nageswara Rao[c], and Deepak K Sharma[a]

[a]Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology-Banaras Hindu University, Varanasi, India; [b]Overseas Healthcare Pvt Ltd, Phillaur, India; [c]Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA, USA

ABSTRACT

A highly inexpensive, and operationally simple seralite SRC-120 (strongly acidic cation exchange resin) catalyzed synthesis of 3,3′-bis(indolyl)methanes (BIMs) from indoles and low/high boiling point carbonyl compounds under solvent-free condition is reported. Synthesis of BIMs with low boiling point carbonyls at room temperature takes prolonged reaction time and give low yields at high temperature. The reported method overcomes these limitations and works remarkably well with low/high boiling point aldehydes/ketones in shorter reaction times (5–10 min) under microwave irradiation conditions and provides moderate to excellent yields (65–94%). Moreover, the recyclability of the catalyst for at least five times without notable loss in activity makes the whole process attractive and green protocol.

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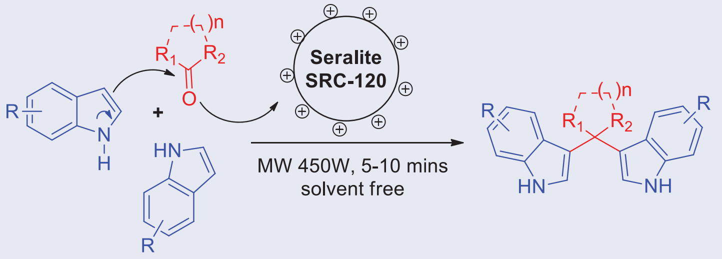
KEYWORDS
Bis(indolyl)methane; breast cancer; microwave irradiation; NGD-16; seralite SRC-120

GRAPHICAL ABSTRACT



Introduction

3,3′-bis(indolyl)methane (BIM) is a condensation product of indole-3-carbinol (I3C) obtained from cruciferous plants.[1] BIM scaffolds are also present in various natural

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CONTACT Desaboini Nageswara Rao ✉ nageswararao.desaboini@umassmed.edu Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA 01655-0112, USA; Deepak K Sharma ✉ deepak.phe@itbhu.ac.in Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology-Banaras Hindu University, Varanasi, Uttar Pradesh 221005, India.

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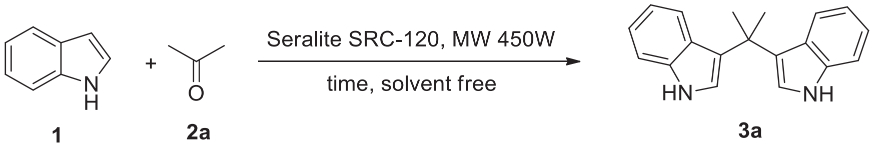
products derived from marine and terrestrial microorganisms (Fig. 1), e.g., bisindole sulfate (*Arcyria denudate*),[2] vibrindole A (*Vibrio parahaemolyticus*),[3] arsindoline B (*Aeromonas Sp.*),[4] rebeccamycin (*Lechevalieria aerocolonigenes*),[5] and staurosporines (*Streptomyces Sp.*).[6] BIMs exhibit a wide range of biological activities such as anticancer,[7] antileishmanial,[8] antioxidant,[9] antibacterial,[10] and antiinflammatory.[11] Due to its varied pharmacological activities, there is continuous interest in simple, cost-effective, and green approaches in BIMs synthesis.

In general, synthesis of symmetrical and unsymmetrical BIMs[12] occurs by electrophilic substitution reaction of indoles with carbonyl compounds in the presence of Lewis or Bronsted acids,[13] protic acids,[14] solid acid catalysts,[15] organocatalyst,[16] and metal catalyst.[17] The reusable ionic liquids and heterogeneous catalysts for the synthesis of BIMs have been developed and overcome some of the limitations caused by the above developed methods.[18] However, the high cost and acute toxicity of ionic liquids and the use of organic solvents in heterogeneous catalysts for the synthesis of BIMs are some of the existing limitations. There are some reports of using water as a medium,[19] but long-chain alkyl aldehydes give a lower yield of BIMs because of poor miscibility in water. In recent years, Zhang et al.[20] performed the visible light-induced aerobic oxidative cross-coupling of glycine derivatives with indoles to synthesize BIMs in the presence of rhodamine 6 G (Rh-6G) as photocatalyst in dichloromethane, whereas Qiu and coworkers[21] have demonstrated the UV-light-Induced Friedel – Crafts alkylation of indoles with carbonyl compounds in the presence of CF_3SO_2Na in toluene for synthesizing BIMs. The use of recyclable Fe/Al pillared clay[22] and hyper-cross-linked microspheres[23] as catalysts under solvent-free conditions followed green protocol for the synthesis of BIMs. However, these methods require high temperature hence not useful for low boiling point aldehydes and ketones. Also, the preparation and characterization of these catalysts are tedious processes. Based on our previous experience working with BIM formation from carbonyl compounds in solvent-free reaction conditions, we have observed that ketones need longer time and high temperatures because of steric hindrance.[22] Thus, the focus of our current method is the rapid, scalable, and economical synthesis of BIMs under solvent-free conditions applicable for low to high boiling point alkyl aldehydes or ketones.

In our previous work, we performed a structure-activity relationship study of BIMs and observed that BIMs synthesized from 5-bromoindole and alkyl aldehydes are potent inhibitors of cancer cell proliferation in comparison to the aryl aldehydes.[24] Due to their importance as potent inhibitors of cancer, and to overcome the limitations of their synthesis, we have developed a robust and greener protocol for the synthesis of BIMs. Herein, we demonstrate the microwave-assisted synthesis of BIMs[25] from indoles and carbonyl compounds by seralite SRC-120. The reason for selecting microwave-assisted synthesis is a remarkable decrease in reaction time for the products, which required high temperature and longer time for synthesis.[26] Hence, we speculated that for low boiling point ketones/aldehydes, microwave-assisted is a useful technique. The seralite SRC-120 is a commercially available low-cost strongly acidic cation exchange resin that will act as a catalyst and support for reactants in the microwave. In literature, seralite SRC-120 used for esterification of ethylene glycol,[27] preparation of resin immobilized CuO nanoparticles for alcohol oxidation,[28] epoxidation of linseed oil.[29] These

Table 1. Standardization of reaction condition for synthesis of compound **3a**.[a]



Entry	Seralite SRC-120	Time (min)	% Yield[b]
1	59 mg (0.5-fold)	5	28
2	117 mg (1-fold)	5	60
3	234 mg (2-fold)	5	75
4	234 mg (2-fold)	10	79
5[c]	–	5	np[d]

[a]Reaction conditions: indole **1** (1 mmol, 117 mg), acetone **2a** (0.5 mmol, 37 µL), seralite SRC-120 (0.5 to 2-fold with respect to indole), MW 450 W, 5–10 min. [b]Isolated yield of **3a**. [c]No seralite SRC-120. [d]No product formation.

reported reactions stimulated us to check the applicability of seralite SRC-120 for the synthesis of BIMs.

Results and discussions

A test reaction was performed with indole (**1**, 1 mmol) and low boiling point ketone, i.e., acetone (**2a**, 0.5 mmol) in the presence of seralite SRC-120 (0.5 fold to the weight of **1**) in the microwave for 5 mins for the synthesis of 3,3′-(propane-2,2-diyl)bis(1H-indole) (**3a**). The product **3a** was obtained in low yield (28%, Table 1, entry 1) because of less quantity of resin support. Next, the amount of resin was increased by 1 and 2 folds to the weight of indole **1**, and the yield of compound **3a** obtained was 60% and 75% (Table 1, entry 2, and 3), respectively. After that, the reaction time was increased, which resulted in a minor improvement in yield (79%, Table 1, entry 4). The formation of compound **3a** was not observed in the absence of a catalyst (Table 1, entry 5), indicating its crucial role in the synthesis of BIM.

After the standardization of reaction conditions, the scope of various sterically hindered alkyl and aryl ketones (Scheme 1) was checked. Alkyl ketones, like cyclopentanone and cyclohexanone, gave compounds **3b** and **3c** in 68% and 65% yields, respectively. Aryl ketones, such as acetophenone and 4-bromo acetophenone, gave **3d** and **3e** in 72% and 74% yields. The substrate scope of indoles was also tested, as 5-bromo indole and 5-methoxy indole reacted smoothly with acetone to get compounds **3f** and **3g** in 82% and 68% yield.

Further, the scope of alkyl and aryl aldehydes was checked to synthesize BIMs (Scheme 2). 5-bromoindole reacted with low boiling point propionaldehyde and butyraldehyde under standardized reaction condition, which produced compound **3h** in 86%, and **3h** in 85% yield, respectively. High boiling point aldehyde, octanal resulted in compounds **3j** in 81% yield. BIMs synthesized from benzaldehyde and aromatic aldehydes with electron-withdrawing and electron-donating groups attached, such as 4-chlorobenzaldehyde and 4-methoxybenzaldehyde produced compounds **3k** in 92%, **3l** in 94% and **3m** in 88% yield, respectively, indicating that electron-withdrawing groups give slightly higher yield in comparison to electron-donating groups. It was also observed that BIMs

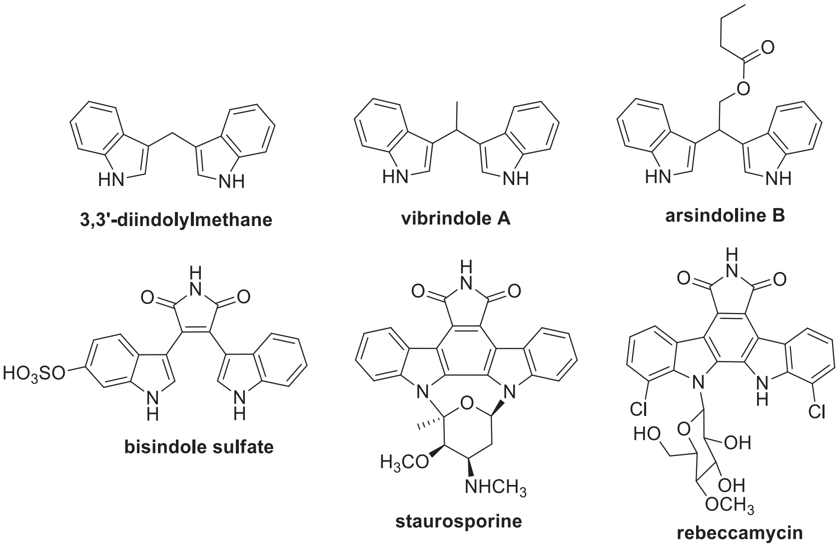


Figure 1. Bis(indolyl)methanes obtained from plants and microorganisms.

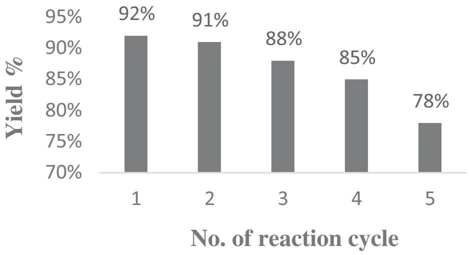
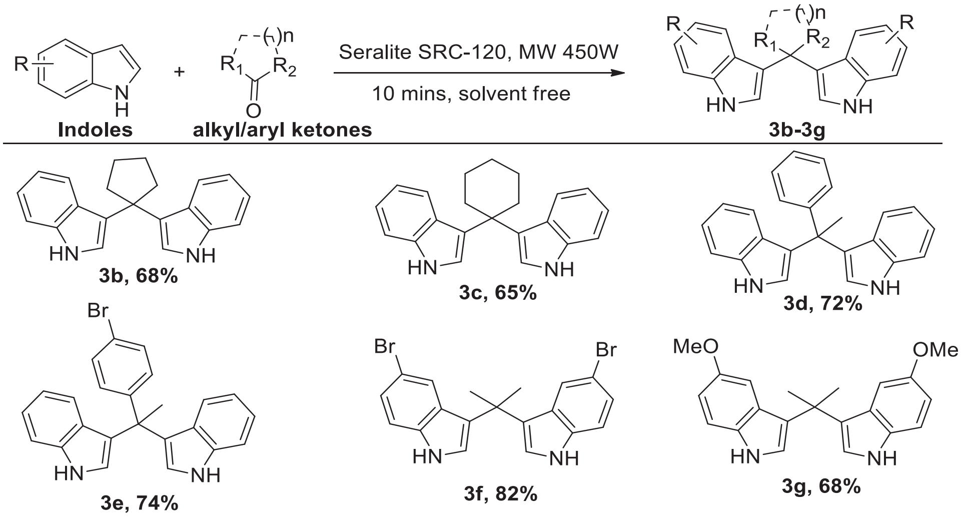


Figure 2. Effect of recyclability of the seralite SRC-120 catalyst on the yield of the compound **3k**.

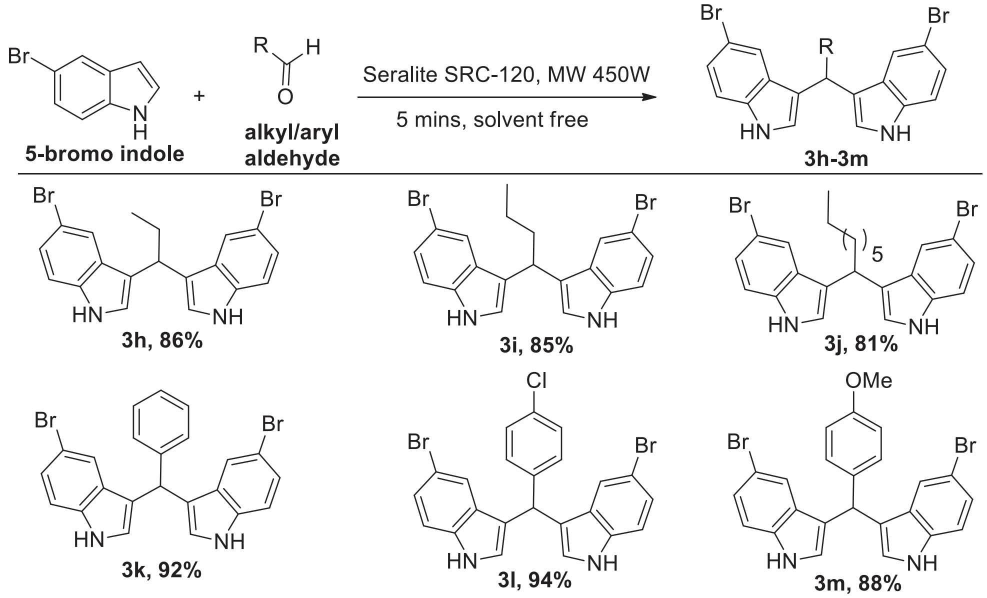
synthesized from aldehydes are more reactive and give a higher yield than the ketones. Synthesis of compounds **3f** and **3h** was also performed at room temperature conditions, which takes 18 h and 1 h for its conversion, and yields obtained as 74% and 85%, respectively (see Supporting information for details).

The recyclability of the seralite SRC-120 catalyst was also investigated. The catalyst was recovered by adding dichloromethane to the reaction mixture, filtering and washing with ethyl acetate, and finally dried under a vacuum. The recyclability of the catalyst was examined for five-run (Fig. 2). We have observed less than 15% loss in efficacy in terms of yield for the compound **3k**. The loss in catalytic efficiency was most likely due to loss of $-H^+$ during reaction, workup, handling, and morphological change of the catalyst, which needs to be studied and reported in due course.

Finally, a small scale and gram-scale synthesis was performed for compound **3o** (Scheme 3) to demonstrate the practical application of the standardized reaction conditions. Compound **3o** is a precursor for the **NGD-16**, which is the most potent anticancer compound against breast cancer cell line (MCF-7), as reported in our previous work. **NGD-16** enhances the expression of proapoptotic protein Par4 and concomitantly decreases the expression of pro-survival protein GRP78 and resulted in apoptosis.[27]

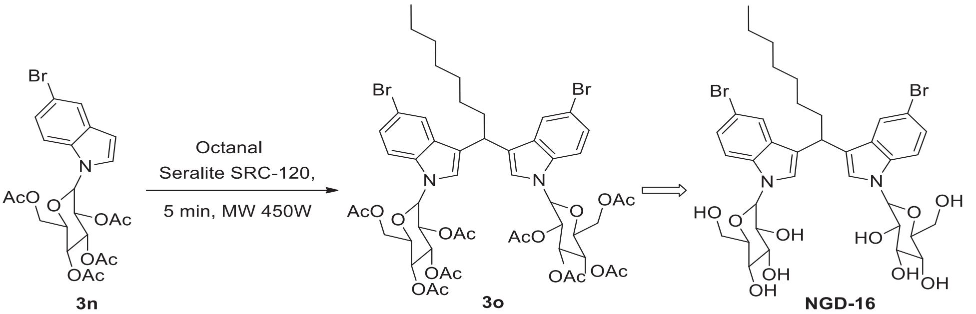


Scheme 1. Substrates Scope in synthesis of BIMs from alkyl/aryl ketones with indoles. ^{a}Reaction conditions: indoles (1 mmol), ketones (0.5 mmol), seralite SRC-120 (2-folds to the weight of indole or substituted indole), MW 450W, 10 min; Isolated yields.

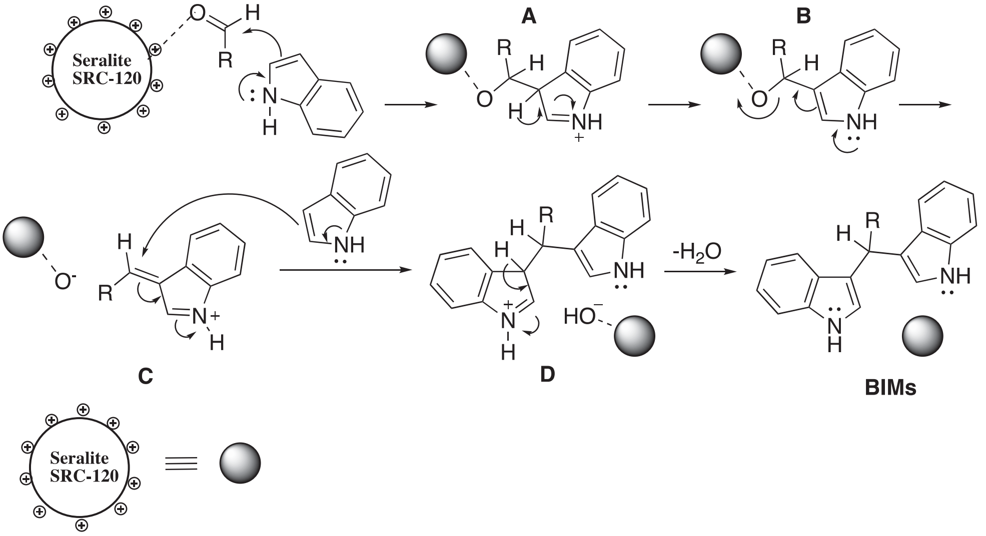


Scheme 2. Substrates Scope in synthesis of BIMs from alkyl/aryl aldehydes with 5-bromoindole. ^{a}Reaction conditions: 5-bromoindole (1 mmol), aldehydes (0.5 mmol), seralite SRC-120 (2 folds to the weight of indoles), MW 450W, 5 min; Isolated yields.

The desired product **3o** was obtained with 83% yield in small scale reaction (0.25 mmol scale, method A, Scheme 3) whereas 85% yield of **3o** was isolated under gram scale reaction (1 mmol, method B, Scheme 3). This indicated that the current reaction was working very well under gram scale reaction as well.



Scheme 3. Gram scale synthesis of most potent anti-cancer inhibitor **NGD-16. Method A (small scale)** ^{a}Reaction conditions: **3n** (262 mg, 0.5 mmol), octanal (40 µL, 0.25 mmol), seralite SRC-120 (524 mg), MW 450W, 5 min; 83% isolated yield of **3o**. **Method B (Gram scale)** ^{a}Reaction conditions: **3n** (1.05g, 2 mmol), octanal (160 µL, 1 mmol), seralite SRC-120 (2 g), MW 450W, 5 min, 85% isolated yield of **3o**.



Scheme 4. Proposed mechanism for the synthesis of BIMs in the presence of seralite SRC-120.

A plausible reaction mechanism for the seralite SRC-120 catalyzed synthesis of BIMs proposed in Scheme 4. First, resin activates the carbonyl group of the aldehyde/ketones because of the highly cationic nature of the resin. Next, the nucleophilic attack of indole occurs at activated carbonyl, leading to the formation of an intermediate **A**. This intermediate **A** undergoes deprotonation of indole 3rd-position to produce intermediate **B,** followed by rearrangement to produce highly reactive intermediate **C**. Now, second equivalent of indole attacks to the highly reactive intermediate **C,** and forms bis(indolyl)methane intermediate **D**. Which further undergoes deprotonation of 3rd-position of another indole to produce desired bis(indolyl)methanes. In this whole process water was eliminated as a byproduct and the resin was reusable for another reaction.

Finally, a comparison is made between previously known methods (entry 1–12, Table 2) and our current method for the synthesis of compound **3a** (entry 13, Table 2). It was

Table 2. Comparison of the previously reported methods with the current method.

Entry	Catalyst	Reaction conditions	Yield (%)	Ref.[a]
1	CF_3SO_2Na	O_2/air, U. V., toluene, r. t., 24 h	81	[21]
2	$(C_4F_9SO_2NHCO)_2C_6H_4$	H_2O, 30 °C, 1 h	80	[30]
3	PEG_{1000}-DAIL	solvent free, r. t., 50 min	73	[31]
4	Nanocomposite of MoS_2-RGO	H_2O, 30 °C, 4–24 h	54	[32]
5	Hydrated ferric sulfate	EtOH, 6 h, 50 °C	72	[33]
6	TBAHS	EtOAc, 12 h, 60 °C	45	[34]
7	$[TEOA][HSO_4]$	Solvent free, r. t., 30 min	70	[35]
8	Povidone-phosphotungstic acid	CH_2Cl_2, 1 h, 25 °C	90	[36]
9	Br_2	CH_3CN, 50 °C, 24 h	74	[37]
10	BF_3-Et_2O	Et_2O, r. t., 29 h	56	[38]
11	1,3-Dibromo-5,5-dimethylhydantoin	Solvent free, 50 °C, 2.20 h	80	[39]
12	Triphenylphosphine-m-sulfonate/Carbon Tetrabromide	Solvent free, r. t., 4 h	83	[40]
13	Seralite SRC-120	Solvent free, MW 450 W, 10 min	79	cm[b]

[a]References. [b]Current method.

found that the present method is better compared to the other methods in terms of the properties of catalyst (reusable, low cost, easy to handle, and stable), reaction conditions (solvent-free and less time), and yield.

Conclusion

In conclusion, we have used readily available, low cost and highly stable seralite SRC-120 as an active catalyst for the microwave-assisted solvent-free synthesis of a variety of BIM compounds. In literature, BIM synthesis with low boiling point ketones at room temperature required longer reaction time and at a higher temperature under solvent-free conditions gives poor yield. This simple and convenient operation works very well for low/high boiling point ketones/aldehydes and provides moderate to excellent yields. The recyclability of the seralite SRC-120 catalyst without notable loss in catalytic activity for at least five times, further adds in the worthiness of this process. These all significant features make this whole process a greener, attractive and alternative synthetic route for the preparation of BIMs.

General

Chemical reagents and solvents were purchased from SRL, spectrochem, Sigma Aldrich, or TCI and used as received. Flash column chromatography was carried out on a CombiFlash RF automated chromatography system using silicycle columns. Thin-layer chromatography (TLC) was performed using silica gel (60 F-254) coated aluminum plates (EMD Millipore), and spots were visualized by exposure to ultraviolet light (UV). NMR spectra were acquired on Bruker Avance III HD 400 and 500 MHz NMR instruments. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Orbitrap Velos Pro mass spectrometer coupled with a Thermo Scientific Accela 1250 UPLC and an autosampler using electrospray ionization (ESI) in the positive mode. Reactions were carried out using Raga's Scientific Microwave Synthesis System (Model: RG34L). Seralite SRC-120 was purchased from Sisco Research Laboratory Pvt. Ltd. (product No. 14891).

General procedure for microwave assisted reaction (3a–3m and 3o)

To a reaction vial, indoles (1.0 mmol), aldehydes/ketones (0. 5 mmol), and seralite SRC-120 (2 folds to the weight of indoles) were added and mixed well. The sealed reaction vial was irradiated at 450 W in microwave for an appropriate time (5–10 mins). After cooling, dichloromethane was added to the reaction mixture, filtered and washed with dichloromethanes (2 × 20 mL), and finally dried under vacuum to recover the catalyst. The filtrate was purified by flash column chromatography (Silicycle column, gradient elution with 0–60% EtOAc/Hexanes).

Notes

(a) alkyl aldehydes/ketones are liquid at room temperature. So, it is easy to mix them with indoles and adsorb on the resin. (b) In the case of low molecular weight alkyl ketone and aldehyde, like acetone and propanal, we have added few dichloromethane drops to make homogeneous solutions with high molecular weight 5-bromoindole. After that, we have adsorbed the mixture on the resin. (c) In case both reactants are solid, we have dissolved reactant mixture in dichloromethane and then adsorbed on the resin. (d) We have recovered solvent after adsorption on vacuum drying. (e) aldehydes take 5 min, and ketone takes 10 min for the formation of BIM.

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IHK and Reena contributed equally in this work.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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