Malaysian Catalysis-An International Journal

Malay. Catal. Int.J Vol 3, Issue 1 (2023) 07-15

OVERVIEW

Poly(4-vinylpyridine)iodonium triiodide: A new efficient catalyst for the synthesis of 3,3-diheteroaromatic oxindole analogues

Received 19th June 2023,
Accepted 04th Jul 2023.

DOI: 10.22452/mcij.vol3no1.2

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Abstract

The synthesis of a series of 3,3-diheteroaromatic oxindoles has been effectively produced through treatment of indole-2,3-dione (isatin) with various indoles and pyrroles using quaternized poly(4-vinylpyridine)iodinium iodide , under solvent-free condition and neutral medium. The reaction proceeds rapidly with excellent yields. This catalyst has been shown to be stable and highly recyclable.

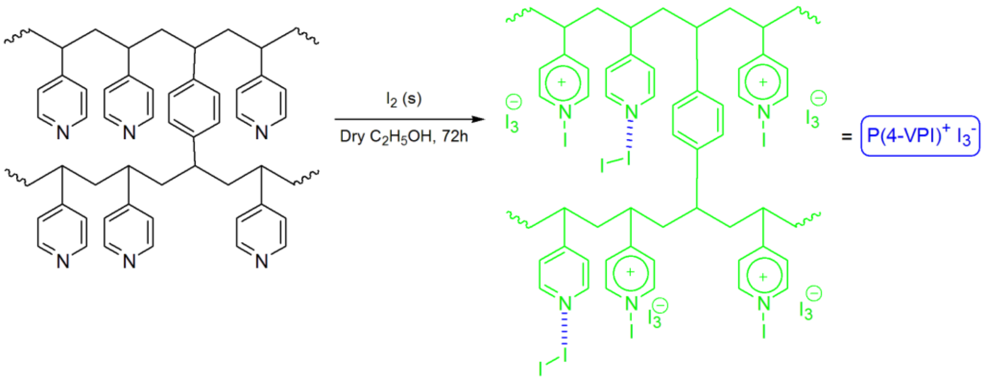
Keywords: Iodine; Poly(4-vinylpyridine); Functionalized polymer; 3,3-Diheteroaromatic oxindole

1. Introduction

Functionalized polymers as macromolecules containing same or different functional groups attract great attention due to some advantages over their functional monomers [1]. The most important benefit of the functionalized polymer in the reactions is their easy separation from the reaction medium. Additionally, supported reagents can be applied in excess to speed up the reactions without increasing work-up costs. Furthermore, these polymeric materials can be highly recyclable. It has been demonstrated that the structural properties of the polymeric support and the nature and extent of cross-linking can influence on the activity of functional groups linked either covalently or ionically to the polymeric support, through modifying polarity, swell ability, and etc [1–3].

Iodine has received a great attention because it is the least effective oxidant and a weak electrophile; therefore, it frequently requires the aid of a strong oxidizer or acid [4]. Compared to most acidic metal-based catalysts, iodine has numerous advantages. With an interestingly wide catalytic potential, it is a cost-effective chemical that is moisture tolerant. Iodine also has considerable catalytic efficiency in low concentration solutions, highly concentrated reaction conditions (HCRC), and solvent-free reaction conditions (SFRC), which is another distinguishing feature of iodine. The subsequent reaction conditions are especially crucial for green chemistry since they reduce waste generation, health risks, and operating costs. Iodine has long been regarded in carbohydrate chemistry as an effective reagent and catalyst [5,6]. Numerous aspects of the chemistry of iodine, such as its usage as a catalyst and its role in protection/deprotection chemistry have also been explored and published [7–9].

Oxindoles have been granted patents as PR (progesterone receptors) agonists and have been revealed antibacterial, antiprotozoal, and anti-inflammatory properties [10,11]. It has been shown convolutamydine, an oxindole found in nature, has been proven to exhibit significant impacts on the differentiation of HL-60 human plomyelocytic leukemic cells. The wide range of biological properties of oxindole scaffolds and the anti-spermatogenic potential of indole derivatives have drawn synthetic chemists to a variety of synthetic techniques [12,13]. Although they were presented as highly effective, most of the techniques relied on the condensation of arenes with isatins in acidic media and have certain drawbacks in terms of cost, time of reaction, operational conditions, selectivity, and yield [14,15]. Thus, it is vital in synthetic organic chemistry to develop methodologies using newer reagents that are more effective, simpler to use, have softer reaction conditions, and have a larger yield percentage.



Scheme 1. The formation of the quaternized poly(4-vinylpyridine)iodonium triiodide.

In this current work, the preparation and application of polymer-supported iodine, which is based on quaternized poly(4-vinylpyridine) and is referred to as $[P(4\text{-}VPI)]^+$ $[I_3]^{-}$, are reported as part of our proposed work the polymer-supported reagents reactivity (Scheme 1). It can act as a promising catalyst for the straightforward production of 3,3-diindolyl and 3,3-dipyrrolyl oxindoles without the requirement for a metal-based catalyst when incorporated with substituted indoles or pyrrole under neutral and solvent-free conditions. The key benefit was that the problem with iodine handling and sublimation was solved by achieving high yields of the products.

2. Results and Discussion

2.1 Structural confirmation of the poly(4-vinylpyridine)iodonium triodide

Figure **1** shows P(4-VP) and P(4-VPI)$^+$ I^{3-} FTIR spectra. In the spectra of P(4-VP), the $\nu_{C=C}$ and $\nu_{C=N}$ stretching vibrations in the pyridine ring appeared at 1598.88, 1554.52, 1496.66, and 1413.72 cm^{-1} [16]. The [P(4-VPI)]$^+$ cation, on the other hand, exhibited a completely different FTIR spectrum due to the addition of an iodine atom to the nitrogen atom of the pyridine rings [17]. In addition to the predicted P(4-VP) vibrations, a second distinct set of shifts was observed, frequently red- or blue-shifted and reflecting those of the P(4-VP) polymer, but with bigger absolute shifts (Figure 1). Based on a comparison with reported spectra in the literature, these peaks were attributed to poly(4-vinylpyridinium)-iodonium cation, [P(4-VPI)]$^+$ [18,19]. The bands at 1554.52 and 1413.72 cm$^{−1}$ disappeared; whereas, a strong peak at 1639.38 cm$^{−1}$ appeared, assigning to the formation of poly(4-vinylpyridine)iodonium cation through treating P(4-VP) with an ethanolic solution of iodine.

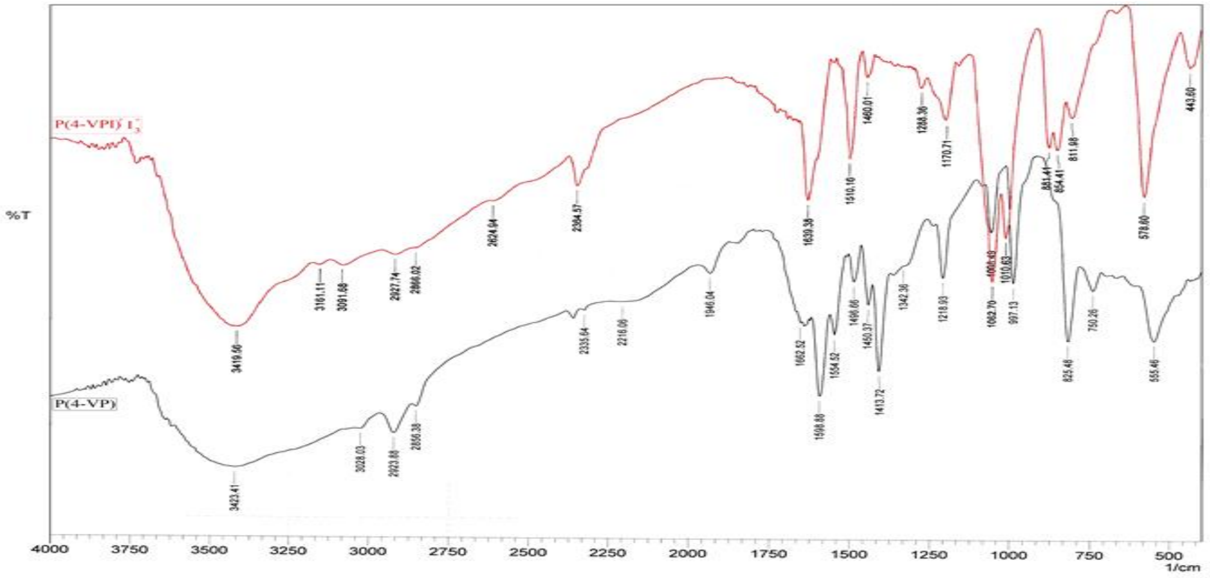


Figure 1. FTIR spectra of P(4-VP) and [P(4-VPI]$^+$ [I$_3$]$^-$.

UV-visible absorption spectrum of iodine, P(4VP), and $[P(4\text{-}VPI]^+ [I_3]^-$ in dichloromethane is shown in Figure 2. The strong absorbance values at 294 and 363 nm are assigned to the triiodide anion.

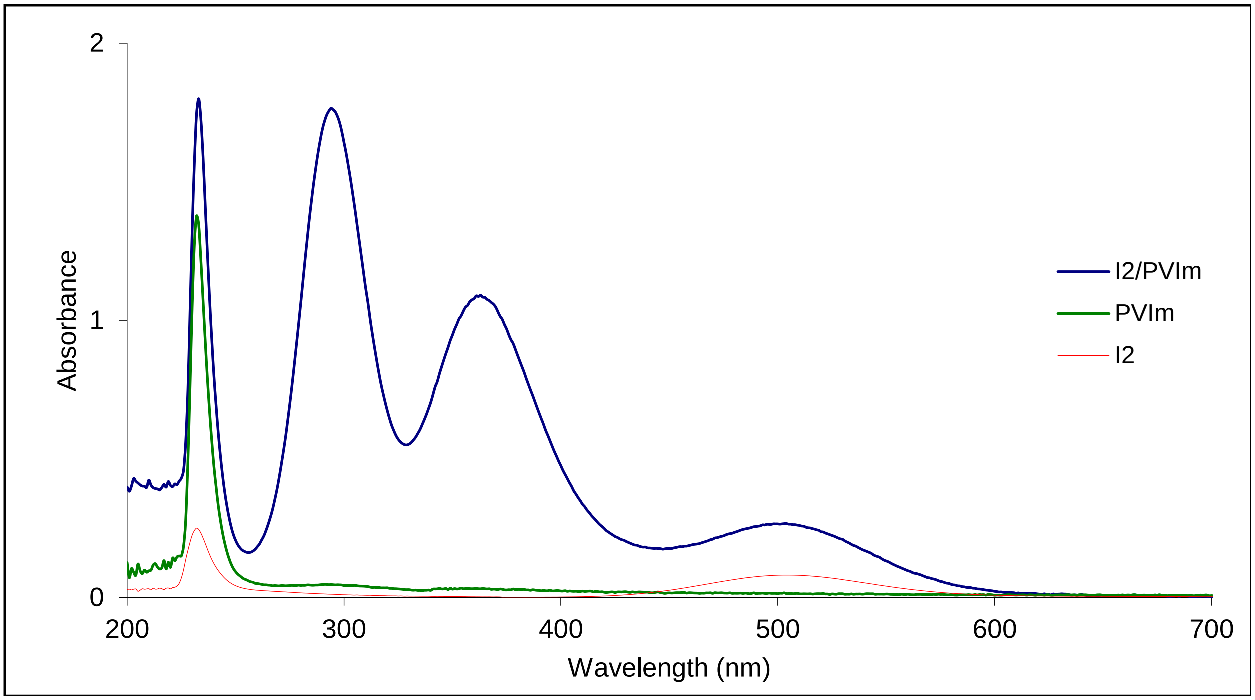


Figure 2. UV-visible absorption spectra of iodine, P(4VP), and $[P(4\text{-}VPI]^+[I_3]^-$ in dichloromethane.

Reid and Mullikan indicated that the pyridine-iodine complex absorbance in pure pyridine originated from charge-transfer complex (outer complex) transforms into an inner complex [20]. The reactions between pyridine and elemental iodine, including (pyridine) + I_2 → $[(\text{pyridine})I]^+ + I^-$, or 2(pyridine) + I_2 → $[(\text{pyridine})2I]^+ + I_3^-$ were also easily observed in binary pyridine-iodine combinations in polar solvents, but not as easy in non-polar solvents [21]. It is indicated that the production of polyiodide anions, $[I^{2n+1}]^-$, in the interlayer of the polymer media was one of the stimulants for the ionic reaction and our research group is now conducting further experiments on the above-mentioned phenomenon.

2.2 3,3-Diheteroaromatic oxindole analogues synthesis

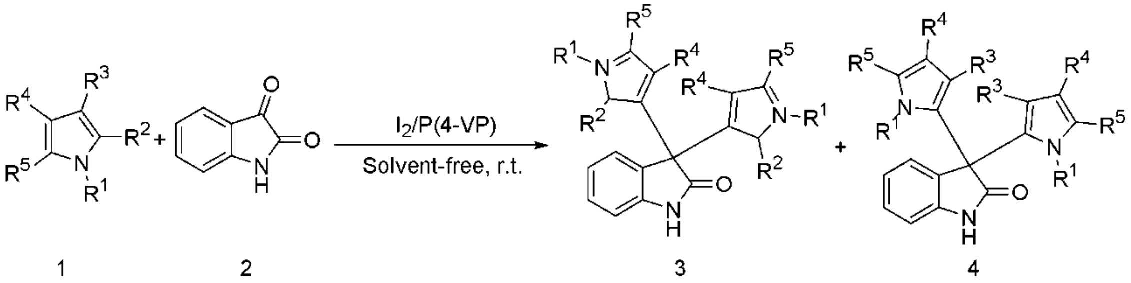
The condensation reaction of isatin (**1**) and indole (**2**) was initially investigated at room temperature with different catalyst concentrations. Though the reaction failed to give the corresponding product without a catalyst even after 6 hours, it was successfully proceed after adding the catalyst. The condensation of isatin (**1**) with indole (**2**) was also studied in the presence of only elemental iodine or P(4-VP)(Table 1, entries 1 and 2). The yields of the di-indolyl oxindole using the current methodology were quite good, as shown in Table 1.

Table 1. Catalytic efficiency of iodine, P(4-VP) and $[P(4\text{-}VPI)]^+[I_3]^-$ in the condensation of isatin with indole.[a]

Entry	Catalyst	Amount of catalyst (mg)	Time (min)	Yield (%)[b]
1	Iodine	10	45	76
2	Poly(4-vinylpyridine)	10	1 day	34
3	I_2/P(4-VP), solvent-free	10	5	98

[a]Reaction conditions: isatin (1 mmol), indole or pyrrole (2 mmol), at room temperature and solvent-free conditions.
[b]Yields refer to GC yields.

It was found that the 3,3-diindolyl and 3,3-dipyrrolyl oxindoles in 98 and 94% yield, respectively, were afforded as the only products using optimal loading of $[P(4\text{-}VPI)]^+[I_3]^-$ (10 mg, 3.6 mol%) (Table 2, entries 1 and 9). To demonstrate the versatility of the method, the condensation of indole with various indoles and pyrrole was carried out using $[P(4\text{-}VPI)]^+[I_3]^-$. The optimal catalyst amounts were used to perform these reactions under mild, solvent-free conditions. These reactions produced 3,3-diindolyl and 3,3-dipyrrolyl oxindoles in 90-98% isolated yield within 7 to 60 minutes (Table 2, entries 1–9) (Scheme 2).



Scheme 2. The coupling isatin with different indoles and pyrrole.

It is worth mentioning that isatin was smoothly coupled with 1- or 2-substituted indoles to produce the bisindolyl oxindoles in excellent yields of 3c, 3e, and 3f (Table 2, entries 3, 5, and 6). By spectroscopic investigation, including NMR and Mass, as well as by comparison with the reported spectroscopic data in the literature, the products were identified [22–25]. In the case of 5-methoxy indole **3d**, the reaction took place at a slower rate. (Table 2, entry 4). However, the reaction time was reduced by increasing the catalyst loading from 10 mg to 20 mg. The completion of reactions with 3-substituted indoles took longer (20–45 min) which can be explained by steric hindrance effect (Table 2, entries 7 and 8). The spectroscopic analysis confirmed the production of 3,3-di-indolyl-2-oxindoles.

To date, a few numbers of articles were reported on the reaction of isatin with 3-substituted indoles [26–28]. Additionally, under the same conditions, pyrrole and isatin also efficiently reacted to produce 3,3-dipyrrolyl-2-oxindole 4c (Scheme 2, Table 1, entry 9).

Table 2. Synthesis of oxindole derivatives (**3** and **4**) through condensation of different indoles and pyrrole with isatin (**2**) catalysed by poly(4-vinylpyridine)iodonium triiodide via Scheme 2.

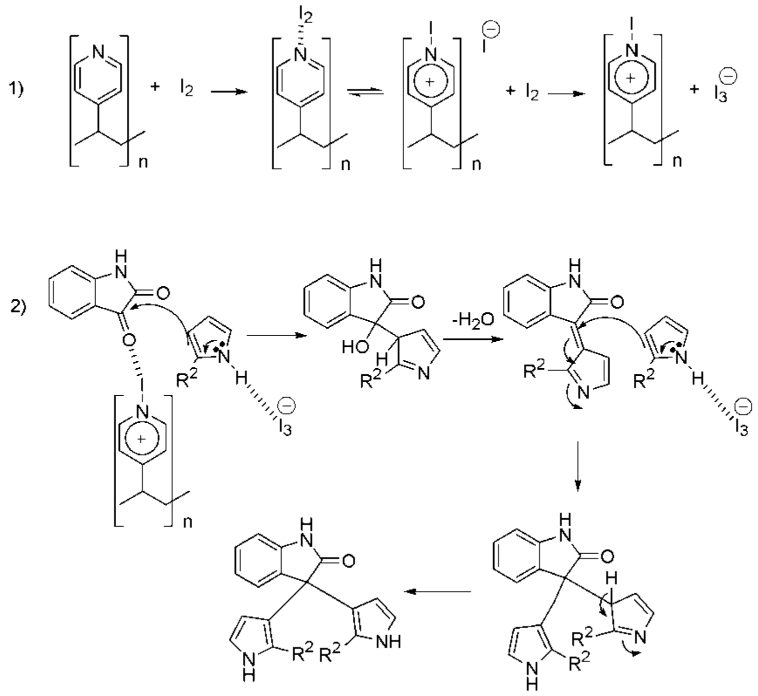
Entry	Substrate				Product[a]	Time (min)	Yield (%)[b]
	R^1	R^2	R^3	R^4, R^5			
1	H	H	H	CH=CH-CH=CH	3a	7	98
2	H	H	H	CH=C(Br)-CH=CH	3b	7	96
3	H	OCH_3	H	CH=CH-CH=CH	3c	10	95
4	H	H	H	CH=C(OCH_3)-CH=CH	3d	60	90
5	CH_3	H	H	CH=CH-CH=CH	3e	8	92
6	H	COOH	H	CH=CH-CH=CH	3f	10	94
7	H	H	CH_3	CH=CH-CH=CH	4a	20	90
8	H	H	CH_2COOH	CH=CH-CH=CH	4b	45	90
9	H	H	H	H, H	4c	7	94

[a] All products were identified by comparison of their physical and spectral data with those of authentic samples.

[b] Yields refer to GC yields.

The possible mechanistic pathway for the coupling of isatin and indoles or pyrrole, which explains the synthesis of products, was described in Scheme 3 even though further investigation is required to determine the specific mechanism of the reaction. According to published research, the generation of a 1:1 molecular complex between P(4-VP) and elemental iodine (outer complex) is the first step in the process [31–33]. Further dissipation of this complex was accomplished in order to release the triiodide anion and poly(4-vinylpyridine)iodonium cation (inner complex). Therefore, molecular iodine was transformed into polyiodide anion $[I_{2n+1}]^-$ in the presence of P(4-VP), which promoted the condensation reaction of isatin and indole.

The condensation of indole with isatin was more effectively explained through progressively adding indole by nucleophilic addition to the carbonyl group and dehydrating the addition product to yield the intermediate azafulvaline. The second indole molecule was then nucleophilically added to the azafulvaline intermediate to complete the reaction. After work-up, the catalyst could be readily regenerated and employed in the next runs.



Scheme 3. A plausible mechanism for the reaction.

3. Conclusions

In conclusion, the formation of $[P(4\text{-}VPI)]^+[I_3]^-$ was demonstrated by FTIR and UV-Vis spectra analysis of reactants and product. It was employed as a neutral catalyst for the reaction between isatin and various indoles and pyrrole, affording the high yields of the 3,3-disubstituted oxindole derivatives. Poly(4-vinylpyridine)iodonium triiodide is highly stable, nonvolatile, and has significantly lower toxicity. It is demonstrated that heterogeneous polymer supported catalysts have a new synthetic use in organic synthesis due to their accessibility, ease of use, highly recyclable, mild reaction conditions, and excellent yields.

Conflicts of interest

There are no conflicts to declare.

Acknowledgment

This work was supported by the IIRG004A-2022FNW a Grant from Ministry of Higher Education (MOHE)-Top 100, Universiti Malaya, Malaysia and the IF008-2023 from Nippon Sheet Glass Foundation for Materials Science and Engineering, Japan.

References

1. Akelah A, Sherrington DC. Application of functionalized polymers in organic synthesis. Chem Rev 1981;81:557–87.

2. Akelah A, Sherrington DC. Recent developments in the application of functionalized polymers in organic synthesis. Polymer (Guildf) 1983;24:1369–86.

3. Vidal F, Jäkle F. Functional Polymeric Materials Based on Main-Group Elements. Angew Chemie - Int Ed 2019;58:5846–70.

4. Rosenfeld L. Discovery and Early Uses of Iodine. J Chem Educ 2000;77:984.

5. Ishihara K. Concepts in Iodine Catalysis. Iodine Catal. Org. Synth., Wiley; 2022, p. 11–26.

6. Singh F V., Shetgaonkar SE, Krishnan M, Wirth T. Progress in organocatalysis with hypervalent iodine catalysts. Chem Soc Rev 2022;51:8102–39.

7. Togo H, Iida S. Synthetic Use of Molecular Iodine for Organic Synthesis. Synlett 2006;2006:2159–75.

8. Banerjee AK, Vera W, Mora H, Laya MS, Bedoya L, Cabrera E V. Iodine in Organic Synthesis. ChemInform 2006;37:299–308.

9. Wang X, Yan F, Wang Q. Molecular iodine: Catalysis in heterocyclic synthesis. Synth Commun 2021;51:1763–81.

10. Khetmalis YM, Shivani M, Murugesan S, Chandra Sekhar KVG. Oxindole and its derivatives: A review on recent progress in biological activities. Biomed Pharmacother 2021;141:111842.

11. Sharma S, Monga Y, Gupta A, Singh S. 2-Oxindole and related heterocycles: synthetic methodologies for their natural products and related derivatives. RSC Adv 2023;13:14249–67.

12. Saraswat P, Jeyabalan G, Hassan MZ, Rahman MU, Nyola NK. Review of synthesis and various biological activities of spiro heterocyclic compounds comprising oxindole and pyrrolidine moities. Synth Commun 2016;46:1643–64.

13. Sakla AP, Kansal P, Shankaraiah N. Syntheses and Applications of Spirocyclopropyl Oxindoles: A Decade Review. European J Org Chem 2021;2021:757–72.

14. Kaur M, Singh M, Chadha N, Silakari O. Oxindole: A chemical prism carrying plethora of therapeutic benefits. Eur J Med Chem 2016;123:858–94.

15. Boddy AJ, Bull JA. Stereoselective synthesis and applications of spirocyclic oxindoles. Org Chem Front 2021;8:1026–84.

16. Grzyb B, Machnikowski J, Weber JV. Mechanism of co-pyrolysis of coal-tar pitch with

polyvinylpyridine. J Anal Appl Pyrolysis 2004;72:121–30.

17. Khaligh NG. Investigation of the catalytic activity of poly(4-vinylpyridine) supported iodine as a new, efficient and recoverable catalyst for regioselective ring opening of epoxides. RSC Adv 2012;2:3321.
18. Jones B, Moody GJ, Thomas JR. N-iodopyridinium dichloroiodate(I). Inorg Chem 1970;9:114–9.
19. Nguyen HT, Nguyen DD, Spanget-Larsen J. Ionic reaction products of iodine with pyridine, 4-methylpyridine, and 4-tert-butylpyridine in a polyethylene matrix. A FTIR polarization spectroscopic investigation. Chem Phys Lett 2019;716:119–25.
20. Reid C, Mulliken RS. Molecular Compounds and Their Spectra. IV. The Pyridine-Iodine System 1. J Am Chem Soc 1954;76:3869–74.
21. Tassaing T, Besnard M. Ionization Reaction in Iodine/Pyridine Solutions: What Can We Learn from Conductivity Measurements, Far-Infrared Spectroscopy, and Raman Scattering? J Phys Chem A 1997;101:2803–8.
22. Yadav J, SubbaReddy B, Gayathri K, Meraj S, Prasad A. Bismuth(III) Triflate Catalyzed Condensation of Isatin with Indoles and Pyrroles-: A Facile Synthesis of 3,3-Diindolyl- and 3,3-Dipyrrolyl Oxindoles. Synthesis (Stuttg) 2006;2006:4121–3.
23. Varun, Sonam, Kakkar R. Isatin and its derivatives: a survey of recent syntheses, reactions, and applications. Medchemcomm 2019;10:351–68.
24. Nain S, Mathur G, Anthwal T, Sharma S, Paliwal S. Synthesis, Characterization, and Antibacterial Activity of New Isatin Derivatives. Pharm Chem J 2023:1–8.
25. Subba Reddy BV, Rajeswari N, Sarangapani M, Prashanthi Y, Ganji RJ, Addlagatta A. Iodine-catalyzed condensation of isatin with indoles: A facile synthesis of di(indolyl)indolin-2-ones and evaluation of their cytotoxicity. Bioorg Med Chem Lett 2012;22:2460–3.
26. Paira P, Hazra A, Kumar S, Paira R, Sahu KB, Naskar S, et al. Efficient synthesis of 3,3-diheteroaromatic oxindole analogues and their in vitro evaluation for spermicidal potential. Bioorganic Med Chem Lett 2009;19:4786–9.
27. Azizian J, Mohammadi AA, Karimi N, Mohammadizadeh MR, Karimi AR. Silica sulfuric acid a novel and heterogeneous catalyst for the synthesis of some new oxindole derivatives. Catal Commun 2006;7:752–5.
28. Wang SY, Ji SJ. Facile synthesis of 3,3-di(heteroaryl)indolin-2-one derivatives catalyzed by ceric ammonium nitrate (CAN) under ultrasound irradiation. Tetrahedron 2006;62:1527–35.