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OVERVIEW

Iodine supported poly(4-vinylpyridine): Efficient and recoverable catalyst for the synthesis of 3,3-diheteroaromatic oxindoles.

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Abstract

An efficient methodology for the synthesis of 3,3-diheteroaromatic oxindole derivatives has been demonstrated by coupling indole-2,3-dione (isatin) with differently substituted indoles and pyrrole in the presence of iodine-supported on poly(4-vinylpyridine) under neutral and solvent-free conditions. The products were obtained in a short time and good to excellent yields.

Keywords: Iodine, Poly(4-vinylpyridine), 3,3-Diheteroaromatic oxindole, Solvent-free, Green chemistry

1. Introduction

Iodine has been employed solely, mixed, or supported with other chemicals as a catalyst in organic synthesis, due to its unique properties compared with other halogens, including the mild oxidant activity and electrophile property [1]. Iodine has been used as a Lewis-acid catalyst and exhibits superiority over metallic catalysts. Iodine is insensitive to humidity and water, low cost, and environmentally benign. Iodine showed high catalytic activity in a dilute solution and solvent-free conditions. Both features are particularly vital conditions according to the 12 principles of green chemistry. [2].

Oxindole core is known as a vital endogenous hetero-aromatic scaffold in biological compound designing. Some of the oxindoles displayed anticancer, antitubercular, antimicrobial, antiviral, antimicrobial, α-glucosidase inhibitory, antileishmanial, antioxidative, tyrosinase inhibitory, PAK4 inhibitory, antirheumatic, and intraocular pressure reducing activities [3]. Therefore, there are many reports in the literature on the synthesis of oxindole derivatives due to their extensive biological activities [4-6]. In current work, iodine-supported poly(4-vinylpyridine) I2/P(4-VP) exhibited an efficient catalytic activity for the preparation of 3,3-diindolyl and 3,3-dipyrrolyl oxindole derivatives through the treatment of the substituted indoles or pyrrole with isatin under metal-free, neutral medium, and solvent-free conditions. The stereo-selective reaction proceeded smoothly, and the desired products were obtained in high yields.

2. Experimental

All yields refer to isolated products. IR spectra were recorded on a Perkin Elmer 781 spectrometer. NMR spectra were recorded on a Bruker DPX 300 MHz spectrometer. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX. All analyses were performed on a Shimadzu GC-16A instrument with a flame ionization detector using silicon DC-200 or Carbowax 20M columns. TLC plates were used to determine the purity of the products and reaction monitoring.

1.1. Procedure for preparation of the molecular iodine supported on poly(4-vinylpyridine) {I_2/P(4-VP)}

Poly (4-vinylpyridine) (100 mg) was added to a solution of iodine (252 mg, 0.99 mmol) in diethyl ether (10 ml). The resulting suspension was stirred for 24 hr at room temperature. The mixture was filtered and the resulting solid was washed several times with ether to remove the excess iodine. The light brown solid was dried in a vacuum. The capacity of the reagent was found, by titration with $Na_2S_2O_3$ solution, to be 3.62 mmol iodine per gram of polymer.

1.2. Typical procedure for the reaction of epoxides with alcohol in the presence I_2/P(4-VP)

Iodine/P(4-VP) (20 mg, 3.6 mol%) was added to a mixture of isatin (2 mmol) and different derivatives of indole and pyrrole (2 mmol). The reaction mixture was stirred at room temperature under solvent-free conditions. After the appropriate time (Table 2) when the reactions were complete, as indicated by TLC, the product was extracted with 2 × 15 mL of cold diethylether. The ethereal solution was evaporated at reduced pressure and the remaining solid was recrystallized from ethanol (95.5%) to afford the pure products. After the extraction of products, the catalyst was recycled in the next run.

3. Results and Discussion

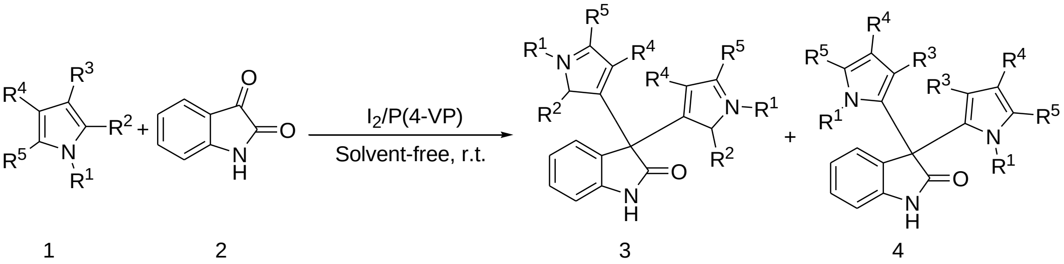
At first, the condensation of isatin (**1**) with indole (**2**) was carried out at room temperature in the presence of various catalyst loadings. No product was detected after 6 h in the absence of the catalyst, whereas it proceeded smoothly upon the addition of the catalyst (Table 1). Also, two control condensation of isatin (**1**) with indole (**2**) were conducted using molecular iodine in the absence of P(4-VP) and P(4-VP) in the absence of iodine (Table 1, entries 1 and 2). The results showed that 20 mg of I_2/P(4-VP) (I_2 = 3.6 mol %) was optimal catalyst loading to conduct the reaction quantitatively to give 3,3-diindolyl oxindole as the sole product in 96% yield (Table 1, entry 3).

Table 1. Comparison of the results obtained for the condensation of isatine with indole catalyzed with iodine, P(4-VP), and I_2/P(4-VP) at room temperature.

Entry	Catalyst	Amount of catalyst	Time (min)	Yield (%)[a]
1	Iodine in 2-propanol	5 mol%	15	96
2	Poly(4-vinylpyridine)	20 mg	1 day	34
3	I_2/P(4-VP), solvent-free	20 mg	7	96

[a] Yields refer to GC yields.

The substrate scope and generality of the method was investigated by the condensation of isatine with differently substituted indoles and pyrrole were performed under optimized reaction conditions (Scheme 1), which afforded 3,3-diindolyl and 3,3-dipyrrolyl oxindoles in 90-98% isolated yield within 10-80 min (Table 2, entries 1-9).



Scheme 1. The coupling isatine with different indoles and pyrroles.

The corresponding bisindolyl oxindoles were isolated through the coupling isatin with 1- or 2-substituted indoles (Table 1, entries 3, 5, and 6). The reaction proceeded within a longer reaction time for 5-methoxy indole. The reaction was completed faster when the catalyst loading was increased up to 40 mg (Table 1, entry 4). Reactions took a longer time (30-60 min) for 3-substituted indoles (Table 1, entries 7 and 8). Furthermore, 3,3-dipyrrolyl-2-oxindole **4c** was successfully obtained through the coupling pyrrole with isatin under optimized reaction conditions (Scheme 1, Table 1, entry 9). The chemical structure of isolated products was confirmed by comparing the spectroscopic data (NMR and Mass) with the data reported in the literature [7-9].

Table 2: I_2/P(4-VP) catalyzed synthesis of oxindole derivatives (**3** and **4**) from isatin (**2**).

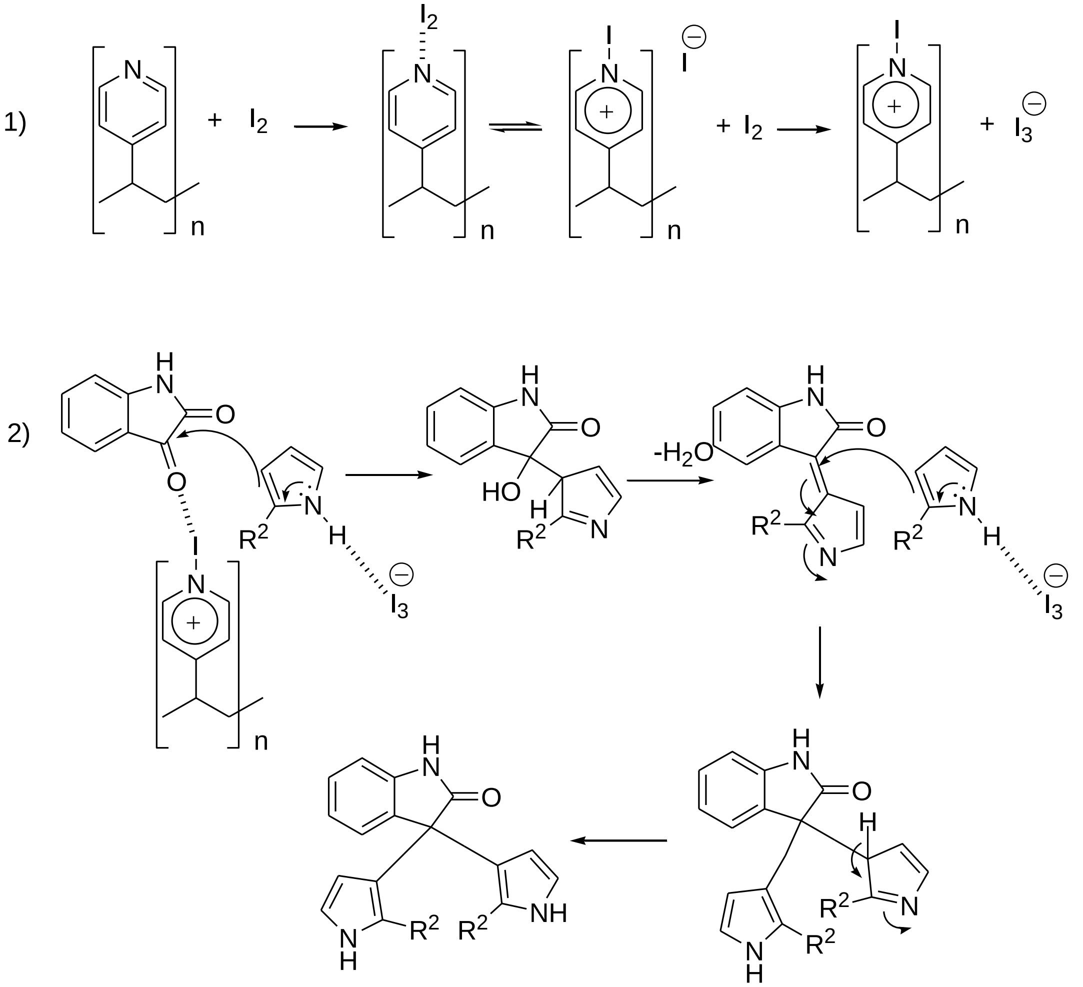
Entry	Substrate				Product[a]	Time(min)	Yield(%)[b]
	R^1	R^2	R^3	R^4, R^5			
1	H	H	H	CH=CH-CH=CH	3a	10	98
2	H	H	H	CH=C(Br)-CH=CH	3b	10	96
3	H	OCH_3	H	CH=CH-CH=CH	3c	15[c]	95
4	H	H	H	CH=C(OCH_3)-CH=CH	3d	80	90
5	CH_3	H	H	CH=CH-CH=CH	3e	10	92
6	H	COOH	H	CH=CH-CH=CH	3f	15	94
7	H	H	CH_3	CH=CH-CH=CH	4a	30	90
8	H	H	CH_2COOH	CH=CH-CH=CH	4b	60	90
9	H	H	H	H, H	4c	10	94

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

[b] Isolated yields.

[c] I_2/P(4-VP) = 40 mg

A plausible mechanism proposed for the formation of 3,3-diheteroaromatic oxindoles, as shown in Scheme 2. The first step, a contact ion pair of $[P(4\text{-}VP)I]^+[I_3]^-$ is formed between P(4-VP) and iodine. Therefore, P(4-VP) promotes the transformation of molecular iodine to a nucleophilic halide species. As-formed cation and anion participate in the coupling reaction of isatin and indole, including the nucleophilic addition of the indole onto the carbonyl group and dehydration of adduct to give the azafulvaline intermediate, as shown in Scheme 2. The reaction proceeds through the second nucleophilic addition of indole molecule onto the azafulvaline intermediate, followed by the dehydration.



Scheme 2. A plausible mechanism for the reaction.

The mentioned steps above occur continuously until all of the isatine and indole are consumed. After workup, the catalyst could be easily recycled five times.

Conclusion

In conclusion, the synergistic effect of I_2 and P(4-VP) and catalytic efficiency of of I_2/P(4-VP) was demonstrated for the coupling of isatin and different indole and pyrrole derivatives and the corresponding 3,3-disubstituted oxindole derivatives were isolated in good to high yields. Iodine-supported P(4-VP) is non-volatile and less toxic, and it showed high stability. The commercial availability, mild conditions and simple procedure, high recyclability, and good to high yields of products can be mentioned as some merits of the current development.

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