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ORIGINAL PAPER

An improved catalytic method for the synthesis of 3,3-di(indolyl)oxindoles using Amberlyst 15 as a heterogeneous and reusable catalyst in water

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Abstract Amberlyst 15 efficiently catalyzed the electrophilic substitution reaction of indoles with isatin derivatives to afford 3,3-di(indolyl)oxindoles in water. An important feature of this protocol is the reaction of 3-methyl-1*H*-indole with isatins to give the corresponding 3,3-diaryloxindole derivatives in high yields. The catalyst exhibited remarkable reusable activity.

Keywords 3,3-Di(indolyl)oxindoles · Amberlyst 15 · Water · Isatin · Indole

Introduction

Indoles are important compounds in organic chemistry because of their widespread occurrence in nature and diversified biological and pharmacological activities [1, 2]. The oxindole framework is a privileged heterocyclic motif that constructs the core of a large family of bioactive natural products and a series of pharmaceutically active compounds [3–10]. Several methods have been developed for the synthesis of oxindoles, including approaches based on the condensation of arenes with isatins in different reaction conditions [11–23].

Recently, great attention has also been focused from both environmental and economical points on the use of heterogeneous solid acid catalysts for various organic transformations [24, 25]. The solid acids generally have high turnover numbers that can be easily separated from reaction mixtures [26]. Amberlyst 15, a macro reticular sulfonic acid-based polystyrene cation exchange resin, is an insoluble polymeric catalyst that can replace most soluble strong acids. During recent years, Amberlyst 15 has attracted much attention as an easily available and non-hazardous catalyst, or an effective promoter that can enhance the reactivity and selectivity of various organic reactions [27–31].

With an increasing awareness of the need for more sustainable strategies for synthetic chemistry across academic laboratories and industry, several eco-friendly strategies have been recognized: to carry out solvent-free reactions, to replace the use of stoichiometric reagents with catalysts, to use biocatalytic processes, and finally to perform reactions in aqueous media or other nonclassical reaction solvents [32, 33]. With this emphasis on the use of cleaner green chemistry processes, recently the uses of organic reactions in water have received considerable attention. Being abundant, economical and safe, water has naturally become a benign solvent in organic synthesis [34, 35].

Results and discussion

In connection with our ongoing work on oxindoles [36–38], we report an efficient and clean route for the synthesis of some new oxindole derivatives from isatins and indoles using Amberlyst 15 as a green and reusable catalyst in water (Scheme 1).

Initially, when the reaction of indole (1 mmol) and isatin (0.5 mmol) with a catalytic amount of Amberlyst 15 (0.3 g) was heated in water at 70 °C as a simple model

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Scheme 1

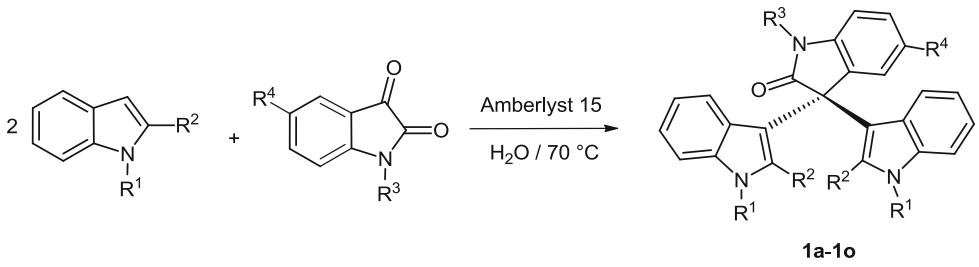


Table 1 The reaction of isatins with 2-substituted indoles catalyzed by Amberlyst 15 in water (Scheme 1)

Prod.	R^1	R^2	R^3	R^4	Yield[a]/%	M.p./°C	Lit. m.p./°C
1a	H	H	H	H	94, 91, 89[b]	311–313	312–314 [27]
1b	H	H	H	NO_2	89	297–298	298–299 [27]
1c	H	H	H	Br	90	309–310	310–311 [27]
1d	H	H	$PhCH_2$	H	91[c]	287–289	288–289 [27]
1e	H	H	Me	H	92	291–292	292–293 [27]
1f	H	Me	H	H	93	301–302	300–301 [27]
1g	H	Me	Me	H	91	272–274	272–273 [27]
1h	H	Me	$PhCH_2$	H	92[c]	212–213	212–214 [27]
1i	Me	H	H	H	95	334–336	>300 [28]
1j	Me	H	Me	H	90	331–333	232-234 [29]
1k	Me	H	H	NO_2	88	331–332	332–333 [36]
1l	Me	H	H	Br	92	325–326	324–325 [36]
1m	Me	H	$PhCH_2$	H	90[c]	223–225	223–224 [36]
1n	H	Me	H	NO_2	89	241–244	–
1o	H	Me	H	Br	92	201-203	–

[a] Yields of pure isolated product based on isatin

[b] The same Amberlyst 15 was used for each of the three runs

[c] Reaction conducted in water/acetone (4/1)

substrate, the reaction proceeded rapidly to give the corresponding 3,3-di(indolyl)oxindole in high yield after a relatively short reaction time.

To clarify the generality of this reaction, several isatin derivatives were treated with different indoles in water to afford the corresponding 3,3-di(heteroaryl)oxindoles **1**. The results are shown in Table 1. All known compounds were characterized by comparison of their physical and spectroscopic data with authentic samples. We found that the presence of electron-withdrawing groups on the aromatic ring of isatin or electron-donating groups on the isatin nitrogen did not affect the reaction time and yields.

Since only a few reports on the reaction of isatin with 3-substituted indoles have so far appeared in the literature [5, 7], we examined the effect of 3-methyl-1*H*-indole on this conversion. We were pleased to find that the reaction of 3-methyl-1*H*-indole with isatin in the presence of Amberlyst 15 in water proceeded to give the corresponding 3,3-di(heteroaryl)oxindole in excellent yield (Scheme 2). Encouraged by this result, we extended the reaction of 3-methyl-1*H*-indole with 5-bromo and 5-nitroisatin under similar conditions, and all of the new products were characterized by ^{1}H, ^{13}C NMR, IR, and mass spectral data.

It is noteworthy that the ^{1}H NMR spectrum of 3,3-bis(3-methylindolyl)oxindole (**2a**) showed a singlet at $\delta = 1.94$ ppm for two methyl groups of the indole rings, and one signal at 8.66 ppm appeared for two NHs of the indole moieties. In contrast to **2a**, in the ^{1}H NMR spectrum of 3,3-bis(3-methylindolyl)-5-bromooxindole (**2b**), two different signals appeared for two NHs at 9.73 and 10.20 ppm, and two signals at 1.70 and 1.98 ppm appeared for two methyl groups of the indole rings. Similarly, the ^{1}H NMR spectrum of 3,3-bis(3-methylindolyl)-5-nitrooxindole (**2c**) showed two different signals for two NHs as well as for two methyl groups (^{1}H, ^{13}C). Presumably, the appearance of two different signals for two NHs and methyl groups in compounds **2b** and **2c** results from the steric hindrance (methyl-bromine or methyl-nitro interaction), which restrained the free rotation of the diastereotopic indole rings around carbon–carbon bonds. The reaction of 3-methyl-1*H*-indole with isatin derivatives required a longer time to produce comparable yields with respect to compounds **1** (Table 2).

The reaction of isatin with pyrrole was also studied under the reaction conditions, but a black compound was obtained that was shown to be a mixture of mono- and disubstituted oxindoles in 37% yield together with 67% of the unreacted isatin.

The catalyst can be easily recycled by filtering and reused at least three times without significant loss of yield and reactivity (Table 1). However, when the reaction of isatin and indole was conducted in the absence of the catalyst under the same reaction conditions, no product was formed, and only the starting materials were collected. In general, the suggested mechanism for the reaction of indoles with isatin derivatives is patterned in Scheme 3.

In summary, we have described a simple, convenient, and environmental protocol for the preparation of 3,3-di(indolyl)oxindoles from different indoles and isatins using Amberlyst 15 in water. The notable features of this method are mild reaction conditions, simplicity in operation, cleaner reaction profiles, low cost, and reusability of the catalyst, which make it an attractive and very useful process for the synthesis of important biological oxindoles.

Scheme 2

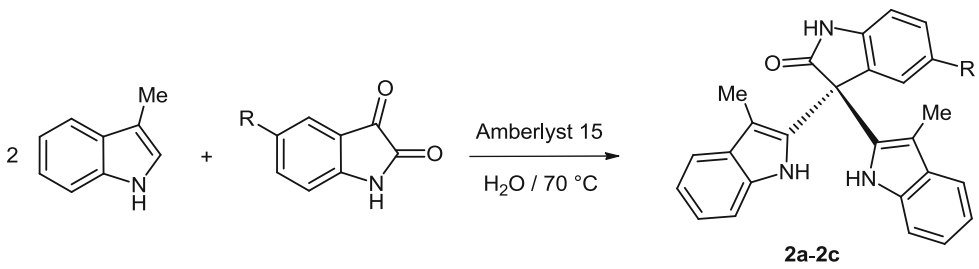


Table 2 The reaction of isatins with 3-methyl-1*H*-indole catalyzed by Amberlyst 15 in water (Scheme 2)

Prod.	R	Time/h	Yield[a]/%	M.p./°C
2a	H	8	93	300–302
2b	Br	12	89	260–265
2c	NO_2	12	88	283–286

[a] Yields of pure isolated product based on isatin

Experimental

Chemicals were obtained from Fluka and Merck, and used without further purification. All known products were identified by comparison of their physical and spectral data with those of authentic samples. Melting points were measured on an Electrothermal 9100 apparatus. Infrared spectra were recorded on a Shimadzu IR-8300 series FT–IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 MHz instrument in $CDCl_3$ with TMS as a standard. Mass spectra were recorded on a Jeol DX303 HF mass spectrometer.

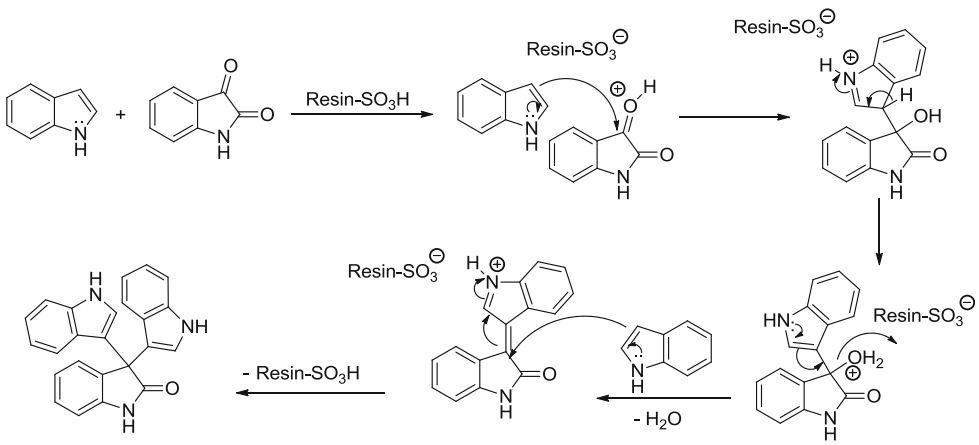
General procedure for the preparation of 3,3-di(heteroaryl)oxindoles

A mixture of indole (1 mmol) and isatin (0.5 mmol) in 10 cm^3 water in the presence of 0.3 g Amberlyst-15 was stirred at 70 °C for 0.5 h (for reaction times for compounds **2**, see Table 2). After completion of the reaction, as indicated by TLC, the precipitated solid and the Amberlyst were filtered off and washed with water (2 × 20 cm^3). To the residue under the filter was added 20 cm^3 acetone, and after dissolution of the product, the resin was removed by filtration, and the resulting solution was evaporated under reduced pressure. The pure product was obtained by recrystallization from ethanol. The catalyst could be recovered after filtration. The residue was then washed with acetone, dried at 130 °C for 1 h, and reused in another reaction. The recycled catalyst was used for three consecutive reactions without observation of appreciable loss in its catalytic activities.

3,3-Bis(2-methyl-1H-indol-3-yl)-5-nitrooxindole (**1n**, $C_{26}H_{20}N_4O_3$)
M.p.: 241–244 °C; IR (KBr):$\bar{\nu}$ = 1,698, 3,383 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.99 (s, 3H, Me), 2.17 (s, 3H, Me), 6.53 (d, J = 7.6 Hz, 1H), 6.73 (d, J = 7.8 Hz, 2H), 6.88 (d, J = 7.8 Hz, 1H), 7.00 (m, 3H), 7.23 (bs, 2H), 8.10 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H), 8.78 (s, 1H, NH), 8.82 (s, 1H, NH), 10.18 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.84, 14.04, 53.32, 108.58, 109.78, 110.81, 111.54, 111.58, 119.28, 119.47, 119.75, 120.79, 121.04, 121.09, 126.28, 127.53, 128.24, 133.01, 135.20, 135.81, 135.91, 137.15, 142.32, 142.74, 148.61, 180.23 ppm; MS: m/z = 436 (M^+).

3,3-Bis(2-methyl-1H-indol-3-yl)-5-bromooxindole (**1o**, $C_{26}H_{20}BrN_3O$)
M.p.: 201–203 °C; IR (KBr):$\bar{\nu}$ = 1,718, 3,403 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.98 (s, 3H, Me), 2.12

Scheme 3



(s, 3H, Me), 6.53 (d, $J = 7.9$ Hz, 1H), 6.73 (d, $J = 8.1$ Hz, 1H), 6.82 (t, $J = 6.7$ Hz, 2H), 6.98 (d, $J = 8.0$ Hz, 1H), 7.05 (d, $J = 6.7$ Hz, 2H), 7.22 (d, $J = 7.7$ Hz, 2H), 7.30 (t, $J = 8.4$ Hz, 1H), 7.42 (s, 1H), 7.86 (s, 1H, NH), 7.93 (s, 1H, NH), 8.69 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 13.87$, 14.07, 53.76, 109.48, 110.68, 110.77, 110.98, 111.84, 115.53, 119.81, 119.90, 120.19, 120.47, 121.25, 121.48, 127.64, 128.45, 129.56, 131.37, 132.05, 135.02, 135.39, 135.45, 137.61, 139.37, 180.52 ppm; MS: $m/z = 469$ (M^+).

3,3-Bis(3-methyl-1H-indol-2-yl)oxindole
(**2a**, $C_{26}H_{21}N_3O$)
M.p.: 300–302 °C; IR (KBr):$\bar{\nu} = 1{,}719$, 3,297 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 1.94$ (s, 6H, Me), 6.88–7.26 (m, 10H), 7.42 (d, $J = 7.6$ Hz, 2H), 8.66 (s, 2H, NH), 10.03 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 9.51$, 55.27, 109.92, 110.93, 111.44, 118.80, 119.46, 122.25, 122.97, 126.34, 129.39, 130.13, 130.46, 131.48, 135.45, 141.83, 177.36 ppm; MS: $m/z = 391$ (M^+).

3,3-Bis(3-methyl-1H-indol-2-yl)-5-bromooxindole
(**2b**, $C_{26}H_{20}BrN_3O$)
M.p.: 260–265 °C; IR (KBr):$\bar{\nu} = 1{,}657$, 3,423 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 1.70$ (s, 3H, Me), 1.98 (s, 3H, Me), 6.33 (s, 1H), 6.56 (d, $J = 8.1$ Hz, 1H), 6.76 (m, 2H), 6.87 (t, $J = 7.3$ Hz, 1H), 6.92 (m, 2H), 7.00 (t, $J = 7.3$ Hz, 1H), 7.07 (t, $J = 7.3$ Hz, 1H), 7.20 (d, $J = 7.6$ Hz, 1H), 7.36 (d, $J = 7.6$ Hz, 1H), 9.73 (s, 1H, NH), 10.20 (s, 1H, NH), 11.80 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 9.04$, 22.91, 52.79, 95.29, 109.15, 110.78, 110.9, 111.78, 113.76, 118.50, 119.43, 121.94, 123.20, 123.31, 123.33, 125.22, 125.98, 128.70, 129.82, 130.34, 135.60, 135.66, 137.44, 141.28, 166.82, 171.49 ppm; MS: $m/z = 469$ (M^+).

3,3-Bis(3-methyl-1H-indol-2-yl)-5-nitrooxindol
(**2c**, $C_{26}H_{20}N_4O_3$)
M.p.: 283–286 °C; IR (KBr):$\bar{\nu} = 1{,}658$, 3,408 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 1.66$ (s, 3H, Me), 2.00 (s, 3H, Me), 6.72 (d, $J = 8.5$ Hz, 1H), 6.82 (t, $J = 7.3$ Hz, 2H), 6.96 (t, $J = 6.8$ Hz, 3H), 7.08 (t, $J = 7.5$ Hz, 1H), 7.15 (d, $J = 7.4$ Hz, 1H), 7.30 (bs, 1H), 7.40 (d, $J = 6.3$ Hz, 1H), 7.60 (d, $J = 8.4$ Hz, 1H), 10.38 (s, 1H, NH), 10.43 (s, 1H, NH), 11.81 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 8.83$, 22.62, 94.75, 108.85, 110.94, 112.09, 115.88, 118.18, 119.23, 120.03, 121.86, 123.34, 123.49, 123.68, 128.69, 130.02, 135.88, 141.00, 142.01, 142.32, 142.74, 148.60, 167.84, 171.50 ppm; MS: $m/z = 436$ (M^+).

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