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Recyclable Amberlite IR 120 catalyzed synthesis of 3-substituted indoles

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Abstract: Indole reacts smoothly with chalcones in presence of catalytic amount of Amberlite IR120 acidic cation exchange resin. Various 3-substituted indoles were synthesized in good to excellent yields. The heterogeneous Amberlite polymer matrix resin can be easily recovered and reused further without loss of activity.

Keywords: 3-substituted indoles, Michael addition, Amberlite IR120, reusable heterogeneous catalyst.

Introduction

Indole and its derivatives are found to possess potential physiological properties [1]. The Michael addition of indole to chalcone gives 3-substituted indole, which exhibits numerous biological activities [2]. They are also used in the synthesis of natural products and therapeutic agents as important building blocks substructures [3]. However the conjugate addition of indole to α , β -unsaturated compounds has been known to promote in presence of catalytic and stoichiometric amounts of either Lewis acids or protic acids and requires careful prevention of side reactions such as polymerization or dimerization by control of acidity. Recently, few methods have been reported for the synthesis of 3-substituted indoles by using different

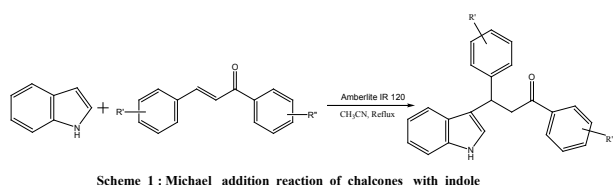
catalysts such as molecular iodine [4], CuBr_2 [5], InBr_3 [6], GaI_3 and GaCl_3 [7], $\text{CeCl}_3 \cdot 7 \text{H}_2\text{O}$ – NaI [8], SmI_2 [9], ZrCl_4 [10], CAN [11], ionic liquids [12], and sodium dodecyl sulphate (SDS) [13]. Use of lanthanide triflates [14] are better alternate to other acidic catalysts such as SnCl_4 , TiCl_4 , AlCl_3 but they are more expensive and their use on scale up level is a cause of concern.

Organic Synthesis is intensely promoted by catalysis and further by recyclability and reusability of the catalyst. Recyclable catalyst increases the cost effectiveness and productivity while minimized their environmental impact of chemical transformation. From this approach various works have been reported for the Michael addition reaction which includes graphite oxide [15], $\text{HClO}_4/\text{SiO}_2$ [16] and Al -

MCM-4[17]. In this consideration ion exchange resins have certain characteristic advantages over traditional acids and base catalysts. They are environmentally compatible since their recyclability allows them to be used again and again. After completion of the reaction, the resin can be easily separated by simple filtration and reused. Ion exchange resins have many applications as they are used in mining, food processing, pharmaceuticals, chemical processing and beverage processing [18]. In terms of clean and environmental friendly organic transformation, ion exchange resins found to have high applications in numerous works [19-25]. To the best of our knowledge Amberlite IR 120 catalyzed synthesis of 3-substituted indole by the reaction of indole with chalcones has not been reported till date. Amberlite IR 120 recyclable acidic resin is a sulfonic acid ($-\text{SO}_3\text{H}$) supported polystyrene divinylbenzene polymer.

Results and Discussion

In an initial endeavor to optimize the reaction conditions, we evaluated the amount of catalyst required for completion of the reaction. A model reaction using chalcone and indole was carried out using Amberlite 0.1 g as a catalyst.



We observed that increasing the amount of catalyst from 0.1g to 0.2g the yield increased from 70 to 90% (entry 2-3), further increasing catalyst amount (0.3g) improvement in neither the yield nor the reaction time were observed (entry 4). So 0.2g amount is sufficient to promote the reaction. Then, we examined the effect of different solvents at different temperature. When using acetonitrile, the reaction afforded the corresponding 3-Substituted indole with a modest yield after 10 hr reflux (Table 2, entry-3)

as compared to other solvents. (Table 2, entries 5-7). In the presence of ion exchange resins if the reaction medium is competently non polar, mechanistically the reaction takes place on resin particle surface. In a polar solvent such as acetonitrile, ethanol, the resin is count on to dissociate by releasing protons, which results in reaction arising in the liquid medium.

The reaction is highly influenced by effect of temperature, when reaction was executed at room temperature; its progress was much slower giving only 40% of product after 72 hrs of stirring (Table 1, entry 1). Eventually, the reaction conditions mentioned in Table 1, entry 3 were found to be optimum than all.

Table 1. Optimization of the reaction under different conditions.^a

Entry	Solvent	Catalyst	Temp (°C)	Time (hr)	Yield (%) ^b
1	CH ₃ CN	0.1g	RT	72	40
2	CH ₃ CN	0.1g	Reflux	12	70
3	CH ₃ CN	0.2g	Reflux	10	90
4	CH ₃ CN	0.3g	Reflux	10	90
5	EtOH	0.2g	Reflux	20	78
6	Toluene	0.2g	Reflux	20	40
7	THF	0.2g	Reflux	20	Trace
8	Solvent Free	0.2g	80°C	15	60

^aThe reactions were conducted by condensation of chalcone ($R', R''=H$) / 1 mmol, Indole / 1 mmol.
^bisolated yields.

The chalcones with different substituent's on the aromatic ring either electron withdrawing or releasing react readily giving excellent yields. (Table 2, entries 1-7). The protocol is very simple. Indole and different unsaturated ketones (1:1, 1 mmol scale) are mixed with Amberlite

IR120 in acetonitrile at reflux condition. After the specified time as mentioned in Table 2, the catalyst is isolated by simple filtration. Acetonitrile after evaporation under reduced pressure afforded the crude products which in most of the cases are sufficiently pure. All the reactions were clean and give the corresponding products in high yields without the generation of side products. Our main focus for this specific developed protocol is to reduce or minimize the formation of side products. The macro porous cation exchange resins have site isolation of sulphonic acid functional group due to which acidity is controlled. As this conjugate addition requires careful prevention of side reactions such as polymerization, dimerization or N-alkylation, the resin catalyzed protocol gave high purity and selectivity of the product due to no side reactions.

Table 2. Amberlite IR-120 catalyzed synthesis of 3-substituted indoles.^a

Entry	R'	R''	Time (hr)	Product	Yield (%) ^b	M.P °C	
						Observed	Reported
1	H	H	10	3a	90	130-132	127-128[12a]
2	4-OCH ₃	H	9	3b	92	128-130	130-131[7b]
3	H	4-OCH ₃	10	3c	91	172-174	174-177[12b]
4	4-Cl	4-OCH ₃	11	3d	90	201-203	202-205[12b]
5	H	4-OH	10	3e	89	122-126	—
6	4-Cl	H	12	3f	88	116-118	118-121[12b]
7	4-OCH ₃	H	11	3g	91	120-122	116-118[27]
8	4-CH ₃	4-OCH ₃	9	3h	90	180-182	183-186[12b]

^a Experimental conditions: Chalcones /1 mmol and Indole /1 mmol, Amberlite IR 120(0.2g) in 5ml Acetonitrile at reflux condition. ^bisolated yields.

For optimizing the reusability of amberlite IR-120 resin, experiments were performed over chalcone and indole. Fresh resin gave a yield of 90 % and it was observed that the catalyst could be reused many times without a significant loss in the product yield and catalytic activity. The results are summarized in Fig1.

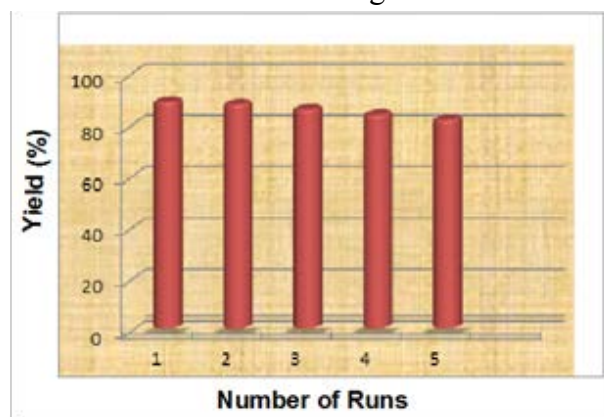


Figure 1. Reusability of Amberlite IR120 for the formation of 3-substituted indoles.

Experimental

Chemicals were purchased from SD Fine chemicals. All the products are known and their physical data is confirmed by comparison with those reported literature. NMR spectra were recorded on a Bruker advance DPX-250. Mass spectra were recorded on Waters GC-MS spectrophotometer. The progress of the reactions and the purity of the products were observed by TLC on silica-gel.

General procedure for the Amberlite IR120 catalyzed Michael addition of indoles with chalcones

Indole(1mmol) and chalcone(1mmol) are mixed with Amberlite IR120 (0.2g) in acetonitrile (5ml) and heated at reflux temperature. After completion of the reaction as monitored by TLC the catalyst is removed by simple filtration and the solvent after evaporation gives crude product which is purified by recrystallization from ethanol. The recovered catalyst is washed

with dichloromethane and used for the next run. analytical facilities.

Spectral data for representative compounds

3-(1H-indol-3-yl)-1,3-diphenylpropan-1-one (**3a**): M.P 130-132°C; ¹H NMR (400 MHz, CDCl₃): δ = 3.72 (dd, J = 7.6, 7.6 Hz, 1 H); 3.81 (dd, J = 6.8, 6.8 Hz, 1 H), 5.07 (t, J = 7.2 Hz, 1 H), 7.96 (s, 1 H), 7.01 (t, J = 7.4 Hz, 1 H), 7.14 (q, J = 7.2, 7.2 Hz, 2 H), 7.23–7.31 (m, 3 H), 7.35 (d, J = 7.2 Hz, 2 H), 7.40–7.44 (m, 3 H), 7.53 (t, J = 7.4 Hz, 1 H), 7.93 (d, J = 7.2 Hz, 2H), 7.97 (bs, 1 H); MS : m/z = 324.2.

3-(4-chlorophenyl)-3-(1H-indol-3-yl)-1-phenylpropan-1-on (**3f**); M.P 116-118°C; ¹H NMR (400 MHz, CDCl₃) δ 8.02 (br, s, 1H), 7.96 – 7.90 (m, 2H), 7.61 – 7.55 (m, 1H), 7.47 – 7.33 (m, 4H), 7.33 – 7.22 (m, 4H), 7.21 – 7.18 (m, 1H), 7.09 – 6.0 (m, 2H), 5.08 (t, J = 7.2 Hz, 1H) 3.84 (dd, J = 16.8, 6.3 Hz, 1H), 3.74 (dd, J = 16.8, 8.1 Hz, 1H); MS : m/z = 359.1.

Conclusion

In this study, we have strategically developed an efficient protocol with good selectivity of the catalyst. The method is operationally simple to furnish various 3-substituted indoles through Michael addition reaction promoted by Amberlite IR-120 cation exchange resin. Recyclability and reusability of the catalyst, simple workup procedures, maximum yields and no byproducts makes this protocol an attractive choice for the synthesis of 3-substituted indoles.

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