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ZINC IODIDE: A MILD AND EFFICIENT CATALYST FOR ONE-POT MULTICOMPONENT SYNTHESIS OF 3-INDOLE DERIVATIVES AND STUDY OF ITS *IN-VITRO* ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT

An efficient and economical method was developed for the synthesis of 3-substituted indole zinc iodide catalysed condensation between aldehyde, malnonitrile and indole. The process was carried out in ethanol at refluxing temperature. This protocol provides broad applications due to its operation simplicity, shorter reaction time and low cost.

KEYWORDS: Zinc iodide, indole, Multicomponent reactions, aldehyde, anti-inflammatory (*in-vitro*).

INTRODUCTION

Multicomponent reactions means containing of two or more substrates react together to form organic compound containing elements of reactant. In recent year, catalytical conversion of one pot organic reactions in presence of readily available, non expensive, non toxic catalyst. These organic compounds having more importance in the field of medicinal, agrochemicals and agricultural chemistry. Now a days, researcher keep focus on multicomponent reactions to develop simple procedure, time saving ability and reduced chemical waste in synthesis of organic compounds.[1-2]

The indole is most essential moieties in organic chemistry found everywhere in nature. A huge number of natural and synthetic indole derivatives found in pharmaceuticals and medicinal applications. Among them 3-indole derivative attracted much more attention of researcher because they are found in natural products and it shows potent biological

activities. Since 3-indole derivative has various applications in organic chemistry, chemist shows special interest in synthesis of 3-indole derivative because they are key raw material in synthesis of therapeutic agents which exhibit pharmaceutical activities for this reason, synthesis of indole derivative at C-3 position have been active research area.[3-5]

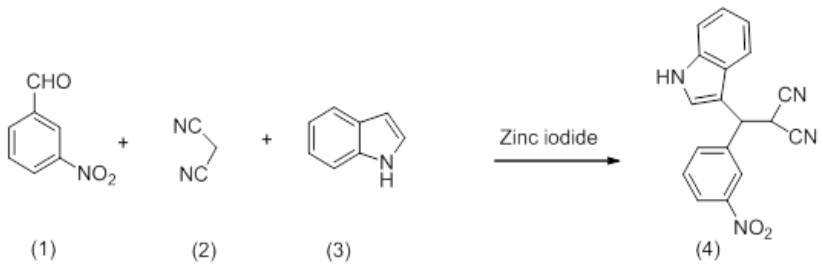
The three component reaction between aldehyde, malnonitrile and indole is a unique type of reaction for the synthesis of 3-substituted indole derivative. Literature survey reveals that, There are some reports about this reaction is that this reaction has been reported in presence of different catalyst and reagents such as In consideration of tetrabutylammonium fluoride,[6] sulfonato salen complex[7], L-proline[8], Glycine[9], Zn(II)/salen complexes as mediator in presence of base[10], Electrochemical approach[11], N, N 1-dioxide Zn(II) complex[12] and [TBA][Gly] ionic liquid[13]. In consideration of importance of three component reaction, there still remain necessity to develop new methodology to realize the importance of indole derivatives. We wish to report the synthesis of 3-substitured indole derivative via three component reaction of aldehyde, malnonitrile and indole in ethanol at refluxing condition, using zinc iodide is an efficient and inexpensive catalyst.

MATERIALS AND METHODS

All chemicals were used of laboratory grade and used without purification. Reactions were monitored by thin layer chromatography (TLC), visualizing with ultraviolet cabinet. Melting points were determined in open capillary tubes and are uncorrected. 1H NMR and 13C NMR spectra were recorded on a BRUKER AVANCE 400 MHz spectrometer using DMSO-d6 as solvent and TMS as an internal standard and given in δ units. Mass spectra were recorded on Thermo Finnigan LCQ Advantage Max Ion Trap Mass Spectrometer Hyphenated with Thermo finnigan Surveyor HPLC system using the EI technique at 70 eV.

General procedure for the synthesis of 3-substituted indole derivatives

A mixture of aromatic aldehydes (1 mmol), malononitrile (1 mmol), taken in 25 ml round bottom flask containing 10 ml of ethanol and 10mol% of zinc iodide was added and allow the reaction mixture to stir for 10 min at room temperature. After 10 minutes solid precipitation formed which specified that formation of knoevenagel condensation product. To that reaction mass indole(1mmol) was added and reaction mass refluxed for appropriate time. The progress of reaction was monitored on TLC. On completion of reaction, the mixture was poured into ice water, and the precipitate was filtered off, washed with cold water to remove the catalyst.



Scheme-1

Spectral data of selected compound

2-((1H-indol-3-yl) (3-nitrophenyl)methyl)malnonitrile. (4e)

^{1}H NMR (400MHz, DMSO-d6) δ = 11.34 (s, 1H), 8.44 (s, 1H), 8.17 (d,1H), 8.00 (d, 1H), 7.63-7373 (m, 2H), 7.50 (d, 1H), 7.40 (d, 1H), 7.09 (t, 1H), 6.96, (t, 1H), 6.00 (d,1H), 5.53, (d, 1H).; ^{13}C NMR (100 MHz, DMSO–d6) δ: 148.0, 141.4, 136.1, 135.0, 130.0, 126.3, 124.0, 123.3, 123.1, 112.4, 119.4, 118.9, 113.7, 112.3, 111.7, 42.2, 27.7. MS (ESIMS) (m/z): found 317.0(M+1).

RESULTS AND DISCUSSION

For initial optimization of the reaction conditions, the three component reaction of 3 nitro benzaldehyde, malnonitrile and indole was carried out as a model reaction. Initially, in order to optimize the role of solvent the model reaction was carried out in dimethylformamide as reaction media at room temp in presence of 10mol% of zinc iodide stirr for about 10 hrs the desired product formed 38% yield (Table1, entry1), when temperature of reaction is increased to about 80°c, no improvement in the yield was observed (Table1,entry2). Further, reaction was carried out different solvents like toluene, tetrahydrofuran, dichloromethane in presence of same concentration of catalyst found the product was obtained in poor to moderate yield (Table 1, entries 3,4,5).

Table 1: Study of zinc iodide catalyzed synthesis of 3 substituted indoles.[a]

Entry	Catalyst mol%	Solvent	Temperature(°c)	Time, h	Product
1	10	DMF	R.T	10	38
2	10	DMF	80	8	36
3	10	Toluene	75	5	25
4	10	THF	80	5	30
5	10	DCM	45	5	30
6	10	Ethanol	70	1	78
7	20	Ethanol	70	1	78
8	10	Ethanol	Reflux	1	91
9	10	Ethanol	R.T	10	45

[a]Reactions conditions: 3-nitro benzaldehyde(1mmol), malononitrile(1mmol) and indole (1mmol), zinc iodide (mol %), solvent 10 ml. [b]isolated yiels

Surprisingly, When the reaction was carried out in ethanol as a solvent,the rate of reaction improved significantly, leading to yield of product 78% at 70°c (Table 1,entry6). Increase the concentration of catalyst in same solvent system has no improvement of yield(Table1,entry 7). When the reaction was reflux for appropriate time the yield was improved to 91% whereas at room temperature poor yield was obtained(Table1 ,entries8,9).

Finally, a number of structurally different aldehyde were tested with indole under the optimized reaction conditions. as shown in the Table 2. aromatic aldehyde with electron withdrawing and neutral group to afford the product in good yield(Table2,entry 1-5),while the aromatic aldehyde with electron donating group gave the product in moderate yield(Table2,entry8-10).

Table 2: Synthesis of 3 substituted indole derivatives.[a]

Entry	Aldehyde	Time (min)	Product	Yield[b]
1	C_6H_5-CHO	60 min	4a	91
2	3- Cl C_6H_4-CHO	50 min	4b	92
3	4- Cl C_6H_4-CHO	75 min	4c	90
4	2- NO_2 C_6H_4-CHO	52 min	4d	92
5	3- NO_2 C_6H_4-CHO	70 min	4e	91
6	4- NO_2 C_6H_4-CHO	75 min	4f	93
7	4-F C_6H_4-CHO	60 min	4g	89
8	4-OCH_3 C_6H_4-CHO	90 min	4h	81
9	4-HO C_6H_4-CHO	90 min	4i	83
10	2-HO C_6H_4-CHO	85 min	4j	85

[a]Reactions conditions: 3-nitro benzaldehyde(1mmol), malononitrile(1mmol) and indole (1mmol), zinc iodide (mol %), solvent 10 ml. [b]isolated yiels

Biological activity

In-vitro anti-inflammatory activity[14-15]

The standard drug and synthesized compounds **(4a-i)** were dissolve in minimum amount of dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, pH 7.4). Final concentration of DMF in all solutions was less than 2.0%. Test solution (1 ml) containing different concentration of drugs was mixed with 1 ml of 1% mM albumin solution in phosphate buffer and incubated at 27±1°C in BOD incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 60±1 0C in water bath for 10 min. After cooling,

the turbidity was measured at 660nm (UV-Visible Elico Spectrophotometer. SL-159). Percentage of inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and average was taken. The ibuprofen was used as standard drug. Results are tabulated in **Table no. 3.**

$$\% \text{ of inhibition} = \left(\frac{Vt}{Vc} - 1 \right) \times 100$$

Where, Vt = Mean absorbance value of test group.

Vc = Mean absorbance value of control group.

Table 3: Anti-inflammatory activity of synthesized compounds (4a-j).

Sr No	Compounds	Mean absorbance value ± SEM	Inhibition of denaturation (in%)
1	Control	0.0850	-
2	Ibuprofen	0.162 ± 0.008	90.58
3	C_6H_5-CHO	0.112 ± 0.004	31.76
4	3-Cl C_6H_4-CHO	0.128 ± 0.007	50.58
5	4-Cl C_6H_4-CHO	0.121 ± 0.004	42.35
6	2-NO_2 C_6H_4-CHO	0.116 ± 0.003	36.47
7	3-NO_2 C_6H_4-CHO	0.109 ± 0.002	28.24
8	4-NO_2 C_6H_4-CHO	0.129 ± 0.006	51.76
9	4-F C_6H_4-CHO	0.144 ± 0.005	69.41
10	4-OCH_3 C_6H_4-CHO	0.129 ± 0.006	51.76
11	4-HO C_6H_4-CHO	0.149 ± 0.004	75.29
12	2-HO C6H4-CHO	0.151 ± 0.005	77.65

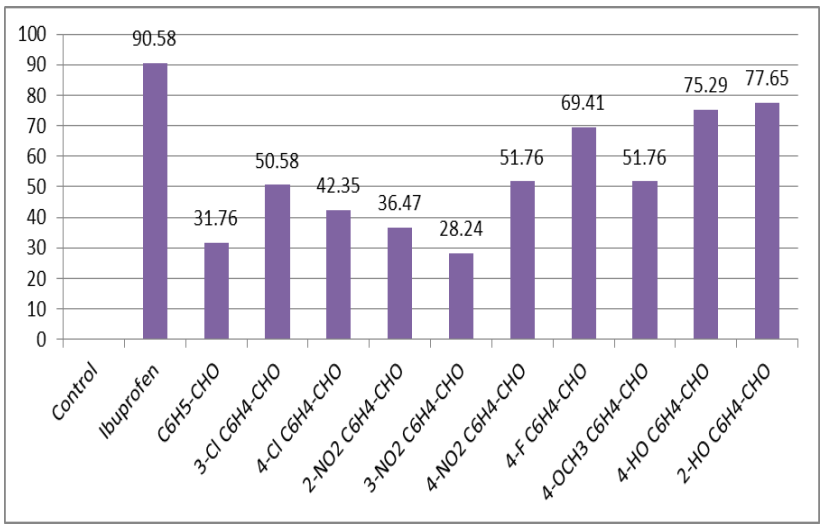


Fig. 1: Anti-inflammatory activity of synthesized compounds.

CONCLUSION

In summary, we have developed facile and advance protocol for one pot multicomponent synthesis of 3-substituted indole derivative by using aldehydes, malononitrile and indole in

presence of zinc iodide as a easily available catalyst. The key features of this protocol is operational simplicity, shorter reaction time, low cost of catalyst and higher product yield. The screening of anti-inflimmatory data reveales that most of the compounds shows good anti-inflimmatory activity.

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