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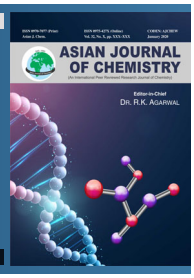

β-Cyclodextrin Mediated Multicomponent Synthesis of Spiroindole Derivatives in Aqueous Medium

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An efficient β-cyclodextrin catalyzed multicomponent synthetic protocol has been developed for the synthesis of spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione from isatoic anhydride, isatin and primary amine in aqueous medium. This methodology offers a convenient method for the synthesis of spiroindole quinazolines in excellent yields. To extend synthetic utility of protocol some dihydro quinazolines have been also synthesized.

Keywords: Spirooxindole, β-Cyclodextrin, Supramolecular, Water, Quinazoline.

INTRODUCTION

Water is the most safe, abundant, sustainable and cost effective solvent for chemical synthesis [1]. Development of environment benign syntheses with eco-friendly solvents are the real challenges in modern chemistry to reduce the increasing waste worldwide [2]. These concerns have led to quest for green solvent like water, ionic liquids and supercritical CO_2. Water is the solvent for majority of biotic reactions and also considered as 'nature solvent' or solvent of life. Use of water as solvent in organic syntheses is taken more seriously after the pioneer work of Breslow "in water" and Sharpless "on water" [3,4] strategy further enhances interest in this area. However, from last few decades, water as solvent for organic reaction has been explored more. The poor solubility is the major hurdle while working with water as a solvent, which restricts chemists from using water for synthesis [5]. Stability of most of the metal catalysts is also a key drawback of using water for metal catalytic system and make it uncompatible synthetic methodology. Water is also known to hamper organocatalyst activity due to disruption of hydrogen bonding or other interactions. These problems are more prominent in multicomponent reactions (MCRs) due to use of many reactants, organocatalysts and metal catalysts [6]. Hence to develop an environmentally benign synthetic protocol using sustainable catalyst and solvent is of considerable interest.

Quinazolines and indoles are itself considered as privileged structures for synthesis of biologically active nucleuses [7-10]. Oxindole moiety is also very prominant in large number of compounds of pharmaceutical interest, such as growth hormone secretagogues, analgesic, antiinflammatory compounds and CNS active agents (serotonergics and the anti-Parkinson drug ropirinole [11]). Various natural products of biological importance are known to hold the sterically forced spiro structure which generates interest in the development of synthetic methodologies to frame new spiro compounds for different biological activity. Spirooxindole is a key structural element in several bioactive natural products [12], including the antifungal ascidian metabolite cynthichlorine, the cell cycle inhibitor spirotryprostatin, the antibiotic speradine, the MDR inhibitor and antimicrotubule agent welwistatin [13,14]. Some spiropyrrolidines have shown potential antileukaemic, anticonvulsant, antiviral and local anesthetic activities [15,16]. Therefore due to various beneficial effects associated with spiro compounds a number of synthetic protocols have been reported for synthesis of this class of heterocycles but most of them are suffer with synthesis in harsh acidic medium or in refluxing conditions [17,18] which drag our interest in developing an efficient synthesis of spiro[indoline-3,2'-quinazoline] in aqueous medium.

Cyclodextrins are glyco macromolecules having cyclic glucose oligomers with cylindrical shapes in such a manner

that the primary hydroxyl groups are located at the more restricted rim of the cylinder. The cyclodextrins are known to catalyze reactions by supramolecular catalysis involving reversible formation of host–guest complexes by non-covalent bonding as seen in enzymes [19,20]. Cyclodextrins bind substrates by molecular recognition and catalyze reactions in a selective manner. These particular properties of cyclodextrin make them a good choice in supramolecuar catalysis. Molecular recognition depends on the size, shape and hydrophobicity of the guest molecule. The biochemical selectivity in supramolecular catalysis allows only certain regions of molecule for favourable attack, is superior to chemical selectivity where attack is due to intrinsic activity of substrate [21]. Cyclodextrin once used can be recovered after completion of reaction. Previously, an improved synthesis of various tryptanthrin derivatives can be achieved with β-cyclodextrins catalysis in water is also reported [22].

Motivated by these facts and keeping our goal to develop a new catalytic system to reveal the catalytic potential of β-cyclodextrins, here we plan our strategy to use β-cyclodextrin, a cyclic carbohydrate and water soluble catalyst for multicomponent reaction to synthesize spirooxindole derivatives. Cyclodextrins are proved to be a remarkable catalyst in many of the oxidation reactions [23-25]. However at best of our prediction the area of multicomponent synthesis is almost untouched by using cyclodextrin as a catalyst, as only few spiro heterocyclic structure have been generated using MCRs.

EXPERIMENTAL

All the reactions were carried out at room temperature that is 28-32 °C, unless otherwise specified. All the reagents were purchased from Sigma-Aldrich Chemical Co, Lancaster and were used directly without any further purification. NMR spectra were obtained using the Brucker DRX 200 and 300 MHz spectrometer. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. IR spectra were taken on VARIAN FT-IR spectrometer as KBr pellets (when solid). Elemental analysis was performed using a Perkin Elmer Autosystem XL Analyzer. Melting points were measured using a COMPLAB melting point apparatus. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light.

General procedure for synthesis of compound (4a-r): β-Cyclodextrin (30 mol %), isatoic anhydride (1.0 mol eq.) and substituted isatin (1.0 mol eq.), were mixed in 8 mL water followed by stirring for 0.5 h at room temperature. Then primary amine (1.0 mol eq.) was added and reaction mixture was stirred vigorously upto disappearance of reactants on TLC (monitored by silica TLC). After completion reaction mixture was extracted by ethyl acetate and evaporated under reduced pressure. Solid residue was further crystallized by methanol and filtrate was kept for catalyst recovery.

In order to develop a green catalyst for multicomponent reaction we planned our strategy of utilizing cyclodextrin as a catalyst, for synthesis of oxindole nucleus. The three most common cyclodextrins are α, β and γ-species having 6, 7 and 8 sugar molecules respectively in the ring system [20]. During the course of the screening of the type and amount of the catalyst among all the three forms α, β and γ-cyclodextrins were screened. For optimization of the catalyst, the reaction of isatoic anhydride (**1**), isatin (**2**) and aniline (**3**) was taken as the model reaction. After screening of all the three forms of cyclodextrin very good result was obtained by using β-cyclodextrin as a catalyst, whereas products were formed in very low yield by using α-cyclodextrin and γ-cyclodextrin (Table-1). No product formation was detected without using cyclodextrin, it showed that cyclodextrin plays an essential role in catalyzing the reaction. The enhanced activity of β-CD may be attributed by its lowest water solubility among all of the CDs and appropriate size of its cavity. Due to low solubility its hydroxyl group is more available for the formation of host-guest complex [24,25]. Hence, β-cyclodextrin was selected as catalyst for the reaction.

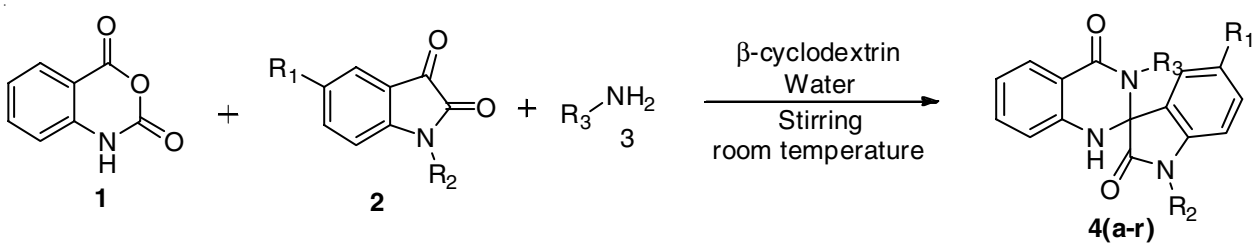
TABLE-1
SUMMARY OF DIFFERENT CATALYST USED

Entry	Catalyst	Solvent	Time (h)	Yield[a] (%)
1	α-CD	Water	13	21
2	β-CD	Water	3	89
3	γ-CD	Water	11	19
4[b]	–	Water	–	–

[a]% yield of purified fractions, [b]reaction was done in absence of any catalyst.

Multicomponent synthesis of spiroindole quinazoline derivatives: Subsequently to verify the general procedure of reaction, various types of isatin derivatives and substituted primary amines were tested under the optimized reaction conditions (**Scheme-I**), the results are summarized in Table-2.

Reaction was carried out by dissolving cyclodextrin in water, followed by addition of isatoic anhydride, amine and isatin. Reaction mixture was stirred vigorously at room temperature to give the desired product in high yield. Reaction goes smoothly without the formation of any side products. The reaction was carried out for appropriate time duration at room temperature. Further in order to incorporate substrate variation to support our developed protocol, we used differently substituted benzaldehydes in place of isatin for above multicomponent reaction in same reaction condition (**Scheme-II**). It is

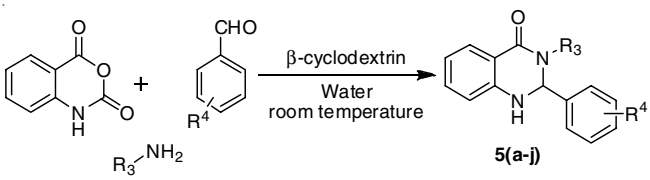


Scheme-I: Synthesis of different spiroindole quinazolines derivatives

TABLE-2
SYNTHESIS OF DIFFERENT SPIROOXINDOLE DERIVATIVES

Compound	R^1	R^2	R^3	Time (h)	Yield (%)[a]
4a	H	Ethyl	C_6H_5	4	81
4b	H	Propyl	C_6H_5	4	88
4c	H	H	Cyclohexyl	7	86
4d	H	Benzyl	3-Cl, 4-$NO_2C_6H_4$	6	84
4e	H	H	C_6H_5	4	92
4f	H	Benzyl	Cyclohexyl	7	86
4g	H	Benzyl	C_6H_5	5	84
4h	H	Benzyl	4-OHC_6H_4	5	87
4i	H	Benzyl	4-Cl C_6H_4	5	84
4j	H	Benzyl	4- OCH_3 C_6H_4	6	91
4k	H	Benzyl	3-OCH_3, 4-NO_2 C_6H_3	5	86
4l	Br	H	H	5	88
4m	F	H	H	6	90
4n	NO_2	H	H	7	83
4o	H	H	H	4	92
4p	H	H	4-$CH_3C_6H_4$	5	91
4q	H	H	4-BrC_6H_4	4	86
4r	H	H	4- OCH_3 C_6H_4	5	86

[a]% yield of purified fractions.



Scheme-II: Synthesis of different dihydro quinazolines derivatives

found that with bezaldehydes in place of isatin increases the rate of reaction. Results are summarized in Table-3. Progress of reaction was monitored by TLC.

TABLE-3
SYNTHESIS OF DIFFERENT SPIROOXINDOLE DERIVATIVES

Compd.	R^3	R^4	Time (h)	Yield (%)[a]
5a	C_6H_5	3-CH_3	3	85
5b	C_6H_5	2,3-dimethoxy	3	81
5c	C_6H_5	3,4-dimethoxy	3	88
5d	C_6H_5	2,3,4-trimethoxy	3	86
5f	C_6H_5	3,4,5-trimethoxy	3	84
5g	C_6H_5	3-Br	3	92
5h	4-CH_3	4-OCH_3	4	86
5h	4-Cl	4-OCH_3	3	84
5i	4-CH_3	4-F	3	87
5j	4-OCH_3	3-CH_3	3	84

[a]% yield of purified fractions.

After completion of reaction, reaction mixture was extracted with ethyl acetate. Organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. Residue was purified by column chromatography using ethyl-acetate:hexane as an eluent, to get the final product in excellent yield. Aqueous layer was left over at 4 °C for catalyst recovery. All the products were characterized from spectroscopic (^{1}H NMR and ^{13}C NMR) and spectrometric (ESMS) data.

Catalyst reusability: The advantage of using cyclodextrin as a catalyst is that it is reusable after the reaction. The catalyst reusability was studied five times including the use of fresh catalyst. After completion of reaction, reaction mixture was extracted with ethyl acetate. Aqueous layer was left overnight at temperature of 50 °C. Due to its low solubility β-CD precipitated at lower temperature β-CD precipitated. After precipitation β-CD is filtered off, dried and reused for next batch as such.

RESULTS AND DISCUSSION

The fact that these reactions do not take place in absence of cyclodextrin indicates the essential role of cyclodextrins as a catalyst. We tried to explain the possible pathway for the reactions base on observations. The mechanistic protocol (Fig. 1) explained below shows role of cyclodextrin appears to activate the carbonyl carbon in isatoic anhydride leading to cleavage of anhydride ring opening and formation of intermediate (**6**). Intermediate (**6**) then react with ketonic group of isatin to form the product (**8**).

Evidence for association between isatoic anhydride and cyclodextrin is supported by ^{1}H NMR spectroscopy. The studies were undertaken with isatoic anhydride. A comparison of ^{1}H NMR spectra (D_2O solutions) of β-CD, β-CD-isatoic anhydride complex and freeze-dried reaction mixture after 2 h was undertaken. It is evident from ^{1}H NMR study that there is an upfield shift of H-3 (0.034 ppm) and H- 5(0.058 ppm) of cyclodextrin in the complex in comparison to β-cyclodextrin indicating the formation of an inclusion complex of isatoic anhydride with β-cyclodextrin. NMR spectra taken at different times, reveals that in reaction mixture complex retains the upfield character of H-3 and H-5 during reaction showing retention of complex during reaction. Thus the role of cyclodextrin is not only to catalyze the reaction, but also providing a new mechanistic pathway to reaction. Catalyst was reused in next batch without any treatment. There was inevitably loss of catalyst during recovery process. The actual amount used in the next batch is almost (20 %) less than the previous batch and thus the loss in yield is mainly due to smaller quantity of catalyst used. On a large scale perhaps a better idea of catalyst reusability will be evident.

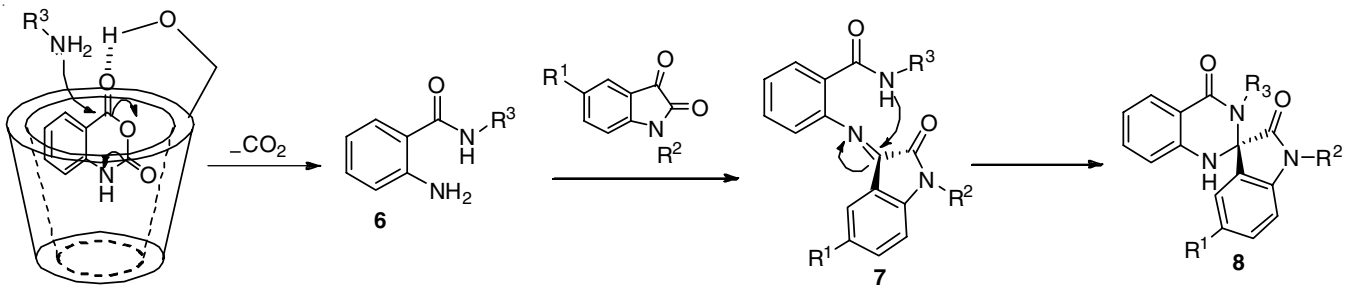


Fig. 1. Plausible mechanistic pathway for reaction for synthesis of spiroindole nucleus

Conclusion

In conclusion we have demonstrated the untapped potentials associated with the β-cyclodextrin as a catalyst in multicomponent reaction for the synthesis of 1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione derivatives using water as a solvent. The cost and environmentally benign nature of catalyst and solvent made the greenness of the process used here to synthesize valuable spiro heterocycles.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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