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Research Article

Chemistry for New drug discovery

Oligosaccharides as Green Catalyst for One-Pot Multicomponent Synthesis of Spirooxindole Derivatives in Water

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Abstract: A one pot synthetic methodology has been developed towards multicomponent synthesis of spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione from isatoic anhydride, isatin and primary amines in aqueous medium via supramolecular catalysis. An untapped potential of β-Cyclodextrin to mediate multicomponent reactions in aqueous medium has been revealed. Developed protocol was further verified by extrapolating the synthetic protocol using different isatin derivatives and amine analogues. In other synthetic scheme, some compounds were synthesized by reaction of various substituted benzaldehydes, Isatoic anhydride and primary amines. Synthesized library of compounds were further characterized using various spectroscopic techniques. During all the synthetic process, the catalytic efficiency of cyclodextrin was exploited. Efficiency of all the three forms of cyclodextrins were tested to find the best reaction for synthesis of spiro compounds. The usefulness of β-cyclodextrin was proved by showing its reusability. The essential role of β-cyclodextrin in the synthetic methodology is further proved by doing the control experiments which showed that no product was formed in the absence of catalyst. The attachment of reactant molecule was also proved by doing 1H NMR of reaction mixture at different time interval in D_2O. On the basis of observation, a plausible mechanistic pathway of reaction was proposed. Other two forms of cyclodextrins were also eliminated on the ground of their insuitability in the formation of desired product. Catalyst reusability was studied and it was shown that our catalytic system is useful without any significant loss in catalytic potential even after 5 cycles. Catalyst recovery procedure was established and was used without any significant loss of catalytic activity upto 5 times.

Keywords: Green Chemistry, Spirooxindole, β-Cyclodextrin, Green Catalysis, Water, Quinazoline, Oligosaccharides

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1. INTRODUCTION

Water is the most abundant, safe, environment friendly 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 a solvent in organic syntheses is taken more seriously after the pioneer work of Breslow "in water".[3] Recently, Sharpless "on Water"[4] strategy further initiated interest in this area. However, from the last few decades, water as solvent for organic reaction has been explored more. The major problem associated with water as a solvent is the poor solubility of either the reactants or catalysts or both,[5] lack of water compatible catalytic methodology because most metal catalysts are unstable in water. Water can also 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]Keeping these things in mind, here we plan our strategy to explore β-cyclodextrin, a cyclic carbohydrate and water soluble catalyst for multicomponent reaction to synthesize Spiro[indoline-3,2'-quinazoline] derivatives.Cyclodextrins are proved to be a remarkable catalyst in many of the oxidation reactions.[7] However as 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. Multicomponent reactions have very special place in synthetic medicinal chemistry due to their great utility in assembling pharmacologically important structures in one pot synthesis.[8]Quinazolines and indoles are themself considered as biologically active nucleus[9] The presence of sterically constrained spiro structure in various natural products generates interest in the investigations of spiro compounds for different biological activity.[10] Oxindole moiety is also present in large number of compounds of pharmaceutical interest, such as growth hormone secretagogues, analgesic, anti-inflammatory compounds, and CNS active agents (serotonergics and the anti-Parkinson drug ropirinole[11]). Spirooxindole is a key structural element in several bioactive natural products,[12] including the antifungal ascidian metabolite cynthichlorine, the cell cycle inhibitor spiro tryprostatin, the antibiotic speradine, the MDR inhibitor and antimicrotubule agent welwistatin.[13-14] Some spiropyrrolidines have shown potential anti leukaemic, anticonvulsant, antiviral and local anesthetic activities.[15]Syntheses of these heterocycles have been reported in harsh acidic medium and in refluxing conditions.[16-18] This has attracted our attention to develop an efficient synthesis of spiro[indoline-3,2'- quinazoline] in aqueous medium.

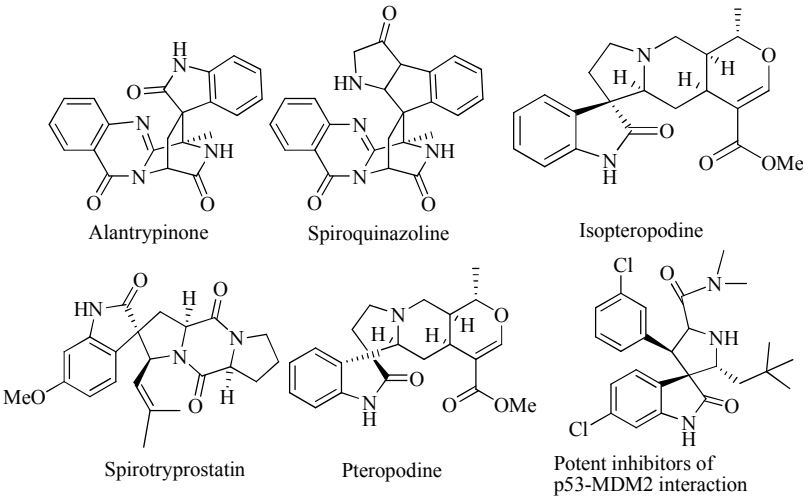

Fig 1.Representatives of spirooxindole bioactive compounds

Cyclodextrins are cyclic glucose oligomers with cylindrical shapes having the primary hydroxyl groups at the more restricted rim of the cylinder. They catalyze reactions by supramolecular catalysis involving reversible formation of host–guest complexes by noncovalent bonding as seen in enzymes.[19-20] Cyclodextrins bind substrates by molecular recognition and catalyze reactions in a selective manner. Recognition depends on the size, shape and hydrophobicity of the guest molecule. The biochemical selectivity in supramolecular catalysis allows only certain regions 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. We have recently reported that synthesis of various tryptanthrin derivatives can be achieved with β-cyclodextrins in water. Here we have described an efficient and convenient synthesis of spiroindolequinazolines using β-cyclodextrins as catalyst in water at room temperature via multicomponent protocol.

2. MATERIAL AND METHODS

All the reactions were carried out at a room temperature of 28-32^{0}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 Bruker DRX 200 and 300MHz spectrometer. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. IR spectra were taken on VARIAN FT-IR spectrometers 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.[22]

2.1 General procedure for synthesis of spiro[indoline-3,2'- quinazoline]-2,4'(3'H)-dione derivatives:

Substituted isatin (1 mmol, 1eq.), isatoic anhydride (162mg, 1 mmol., 1eq.) and substituted primary amine (1mmol., 1eq.) was taken in 8ml water. β-cyclodextrin (30 mol%) was added. Reaction mixture was allowed to stir at room temperature. Reaction was monitored by TLC. After completion of reaction mixture was extracted by ethyl acetate and evaporated under reduced pressure. Solid residue was further crystallized by methanol.

2.2 Catalyst recovery procedure

After completion of reaction, reaction mixture was extracted with ethyl acetate. Aqueous layer was left overnight at a temperature of 50^{0}C. Due to its low solubility β-CD precipitated at lower temperature. Cyclodextrin precipitated filtered off, dried and reused for the next batch as such.[22]

3. RESULTS AND DISCUSSIONS

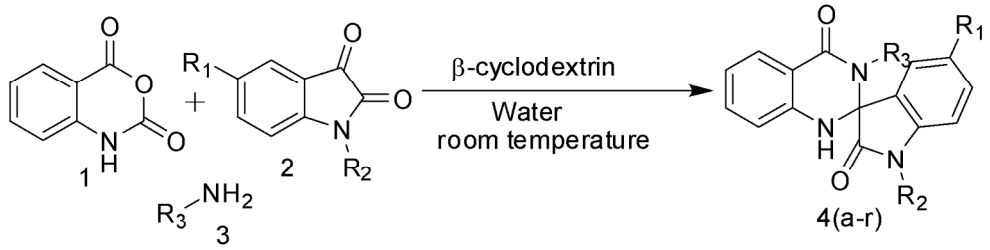

Fig 2. Synthesis of different spiro indole quinazolines derivatives.

In order to develop a green catalyst for multicomponent reaction, we planned our strategy of utilizing cyclodextrin as a catalyst, to synthesize indole 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 a variety of reaction conditions such as solvent, reaction temperature, the amount of the catalyst, and all the three forms α, β and γ-cyclodextrins, we found that the use of water as a solvent was essential for the efficient formation of spiroindolequinazolines derivatives. For optimization of the catalyst, the reaction of isatoic anhydride (1), isatin (2) and aniline (3) were taken as the model reaction. We concluded that very interesting result was obtained by using β-cyclodextrin as a catalyst. Whereas yields of products were very low with α and γ-cyclodextrin (Table 1). No product formation was detected without using cyclodextrin, it showed that cyclodextrin plays an essential role in catalysing 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.[21]Hence β-cyclodextrin was selected as catalyst for the reaction. 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 1), the results have been summarized in (Table 2).

Table 1. Summary of different catalyst used

Entry	Catalyst	Solvent	Time (Hrs.)	Yield[a] (%)
1	α- CD	Water	13	21
2	β- CD	Water	3	93
3	γ- CD	Water	11	19
4[b]	-	Water	-	-

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

Table 2. Synthesis of different spirooxindole derivatives

compound	R^1	R^2	R^3	Time[a]	Yield(%)[b]
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]= time in hrs, [b]= % yield of purified fractions.

Reaction was carried out by dissolving cyclodextrin in water, followed by addition of isatoic anhydride, amine and isatin.[21] Reaction mixture was stirred vigorously at room temperature to give the desired compound 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. It was observed the with benzaldehyde rate of reaction was fast with that of with Isatin. Results are summarized in table 3. Progress of reaction was monitored by TLC.

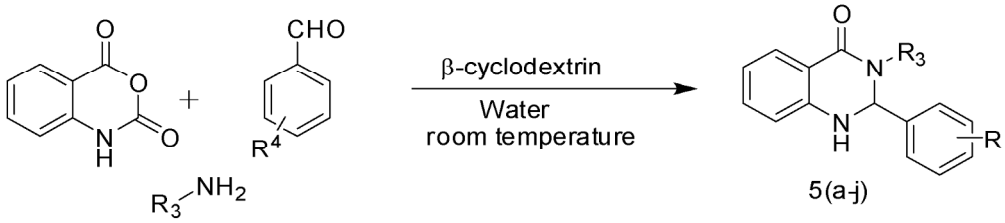

Fig 3. Synthesis of different spiro indole quinazolines derivatives.

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 mobile phase, to get the final product in excellent yield. Aqueous layer was left over at 4^0C for catalyst recovery. All the products were characterized from spectroscopic (^{1}H NMR and ^{13}C NMR) and spectrometric (ESMS) data.

Table 3. Synthesis of different spirooxindole derivatives

Compound	R^3	R^4	Time[a]	Yield(%)[b]
5a	C_6H_5	3-CH3	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]= time in hrs, [b]= % yield of purified fractions.

The fact that these reactions do not take place in absence of cyclodextrin indicates the essential role of cyclodextrins as a catalyst. The mechanistic protocol explained below shows the 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 reacts with a ketonic group of isatin to form the product (7).

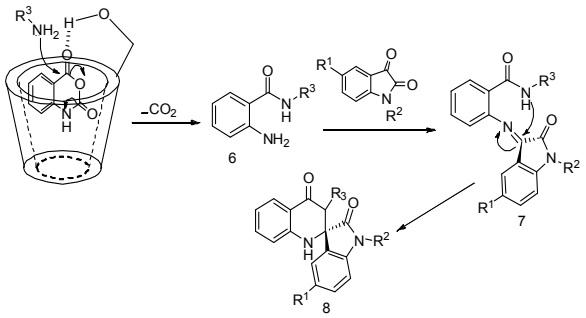

Fig 4. Plausible mechanistic pathway for reaction

Evidence for association between isatoic anhydride and cyclodextrin is supported by 1HNMR spectroscopy. The studies were undertaken with isatoic anhydride. A comparison of 1HNMR 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 the

figure 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.[22] 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. At this stage we have concluded that the cyclodextrin does not only work as catalyst but also turn the reaction pathway towards a new direction. The reusability of catalyst make it very useful for synthesis of spiro compounds. There was inevitably loss of catalyst during the 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 the smaller quantity of catalyst used. On a large scale perhaps a better idea of catalyst reusability will be evident.

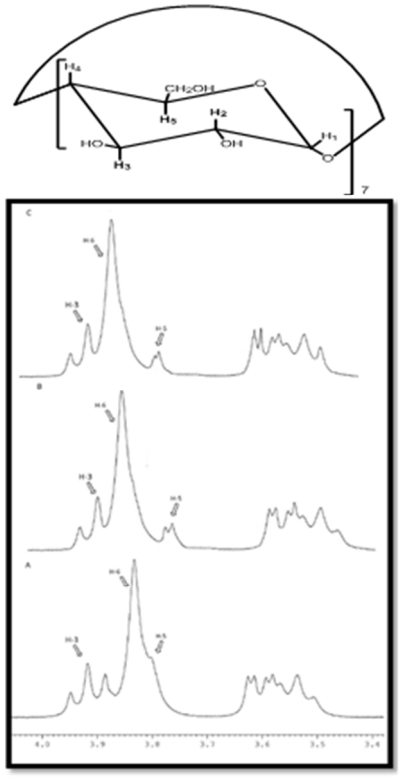

Fig 5. HNMR spectra of A) β-CD B) β-CD isatoic anhydride complex. C) Freeze-dried reaction mixture after 2 hrs.

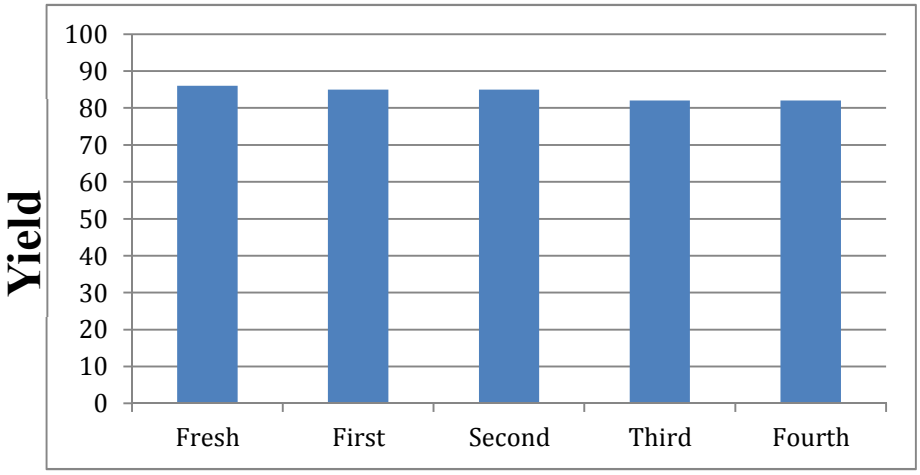

Fig 6. Catalyst (β-cyclodextrin) recyclability data.

3.1 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 (Figure 6). After completion of reaction, reaction mixture was extracted with ethyl acetate. Aqueous layer was left overnight at a temperature of 50^{0}C. Due to its low solubility β-CD precipitated at lower temperature. Cyclodextrin precipitated filtered off, dried and reused for the next batch as such.[22]

4. 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 spiroheterocycles.

5. ACKNOWLEDGEMENT

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6. AUTHORS CONTRIBUTION STATEMENT

Dr. A. M. Jha worked for planning and execution of all the work and Dr. N. Jha contributed in drafting the manuscript.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

8. REFERENCES

1. Hangarge R V, Sonwane SA, Jarikote D V, Shingare MS. No Title. Green Chem. 2001;3(6):310–2. Doi: 10.1039/b106871g
2. Feng X, Zhai J, Jiang L. The Fabrication and Switchable Superhydrophobicity of TiO2 Nanorod Films. Angew Chemie Int Ed . 2005;44(32):5115–8. Doi: 10.1002/anie.200501337
3. Klijn JE, Engberts JBFN. Fast reactions 'on water.' Nature.2005;435(7043):746–7. Doi: 10.1038/435746a
4. Chanda A, Fokin V V. Organic Synthesis "On Water." Chem Rev. 2009;109(2):725–48. Doi: 10.1021/cr800448q
5. Feng X-W, Li C, Wang N, Li K, Zhang W-W, Wang Z, et al. Lipase-catalysed decarboxylative aldol reaction and decarboxylative Knoevenagel reaction. Green Chem. 2009;11(12):1933. Doi: 10.1039/b914653a
6. Nepogodiev SA, Stoddart JF. Cyclodextrin-Based Catenanes and Rotaxanes†. Chem Rev. 1998;98(5):1959–76. Doi: 10.1021/cr970049w
7. Takahashi K. Organic Reactions Mediated by Cyclodextrins. Chem Rev . 1998;98(5):2013–34. Doi: 10.1021/cr9700235
8. Breslow R, Dong SD. Biomimetic Reactions Catalyzed by Cyclodextrins and Their Derivatives. Chem Rev. 1998;98(5):1997–2012. Doi: 10.1021/cr970011j
9. Touré BB, Hall DG. Natural Product Synthesis Using Multicomponent Reaction Strategies. Chem Rev. 2009;109(9):4439–86. Doi: 10.1021/cr800296p
10. Abdel-Rahman AH, Keshk EM, Hanna MA, El-Bady SM. Synthesis and evaluation of some new spiro indoline-based heterocycles as potentially active antimicrobial agents. Bioorg Med Chem. 2004;12(9):2483–8. Doi: 10.1016/j.bmc.2003.10.063
11. Ryng S, Machoń Z, Wieczorek Z, Zimecki M, Mokrosz M. Synthesis, immunomodulating effects and structure-activity relationships of new N-phenyl-5-amino-3-methylisoxazole-4-carboxamides. Eur J Med Chem . 1998;33(10):831–6. Doi: 10.1016/s0223-5234(99)80035-x
12. Skibo EB, Islam I, Heileman MJ, Schulz WG. Structure-activity studies of benzimidazole-based DNA-cleaving agents. Comparison of benzimidazole, pyrrolobenzimidazole, and tetrahydropy ridobenzimidazole analogs. J Med Chem. 1994;37(1):78–92. Doi: 10.1021/jm00027a010
13. Lacy C, Scheuer PJ. New Moloka'iamine Derivatives from an Undescribed Verongid Sponge. J Nat Prod . 2000;63(1):119–21. Doi: 10.1021/np9902643
14. Raj AA, Raghunathan R, SrideviKumari MR, Raman N. Synthesis, Antimicrobial and Antifungal Activity of a New Class of Spiro pyrrolidines. Bioorg Med Chem. 2003;11(3):407–19. Doi: 10.1016/s0968-0896(02)00439-x
15. Ranjith Kumar R, Perumal S, Senthilkumar P, Yogeeswari P, Sriram D. A facile synthesis and antimycobacterial evaluation of novel spiro-pyrido-pyrrolizines and pyrrolidines. Eur J Med Chem . 2009;44(9):3821–9. Doi: 10.1016/j.ejmech.2009.05.010
16. Silva JFM da, Garden SJ, Pinto AC. The chemistry of isatins: a review from 1975 to 1999. J Braz Chem Soc. 2001;12(3):273–324. Doi: 10.1590/s0103-50532001000300002
17. Lepage F, Tombret F, Cuvier G, Marivain A, Gillardin JM. New N-aryl isoxazolecarboxamides and N-isoxazolylbenzamides as anticonvulsant agents. Eur J Med Chem . 1992;27(6):581–93. Doi: 10.1016/0223-5234(92)90137-p
18. Mohammadi AA, Dabiri M, Qaraat H. A regioselective three-component reaction for synthesis of novel 1′H-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′H)-dione derivatives. Tetrahedron. 2009;65(18):3804–8. Doi: 10.1016/j.tet.2009.02.037
19. Wenz G. Cyclodextrins as Building Blocks for Supramolecular Structures and Functional Units. Angew Chemie Int Ed English . 1994;33(8):803–22. Doi: 10.1002/anie.199408031
20. Surendra K, Krishnaveni NS, Rao KR. Direct Barbier-type allylation of aromatic acetals and dioxolanes in the presence of β-cyclodextrin in water. Tetrahedron Lett. 2006;47(13):2133–6. Doi: 10.1016/j.tetlet.2006.01.125
21. Odashima K, Itai A, Iitaka Y, Koga K. Host-guest complex formation between a water-soluble polyparacyclophane and a hydrophobic guest molecule. J Am Chem Soc. 1980;102(7):2504–5. Doi: 10.1021/ja00527a083
22. Kumar A, Tripathi VD, Kumar P. β-Cyclodextrin catalysed synthesis of tryptanthrin in water. Green Chem . 2011;13(1):51–4. Doi: 10.1039/c0gc00523a
23. Khalafi-Nezhad A, Panahi F. Immobilized palladium nanoparticles on a silica–starch substrate (PNP–SSS): as an efficient heterogeneous catalyst for Heck and copper-free Sonogashira reactions in water. Green Chem . 2011;13(9):2408. Doi: 10.1039/c1gc15360a
24. Szejtli J. Introduction and General Overview of Cyclodextrin Chemistry. Chem Rev. 1998; 98(5):1743–54. Doi: 10.1021/cr970022c
25. Chen G, Jiang M. Cyclodextrin-based inclusion complexation bridging supramolecular chemistry and macromolecular self-assembly. Chem Soc Rev. 2011;40(5):2254. Doi: 10.1039/c0cs00153h