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β-Cyclodextrin catalyzed synthesis of 2-oxoindolin-3-ylidene malononitrile derivatives in water

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ABSTARCT

Knoevenagel condensation of isatins with malononitrile has been carried using biomimetic catalyst, β-cyclodextrin in water at 60 ˚C and obtained 2-oxoindolin-3-ylidene malononitrile derivatives with excellent yields and shorter reaction times. The β-cyclodextrin can be recovered and reused a number of times without any loss of activity.

Keywords β-Cyclodextrin, Knoevenagel condensation, 2-oxoindolin-3-ylidene malononitrile derivatives.

INTRODUCTION

Water has emerged as a versatile solvent for organic chemistry in recent years [1] because it is a naturally occurring, cheap, and non-toxic eco-friendly solvent [2]. The types of organic reactions in water are broad including peri cyclic reactions [3], reactions of radicals and carbenes [4], oxidations-reductions [5] and *etc*. But the basic problem in performing reaction in water is that many organic compounds are hydrophobic and are insoluble in water. The development that has contributed to some extent to overcome this problem is the introduction of water-soluble catalysts such as β-cyclodextrin.

β-Cyclodextrin is cyclic oligosaccharide possessing hydrophobic cavities, which bind hydrophobic substrates into their cavities in water solution with selectively and catalyze chemical reactions with high selectivity. Reactions catalyzed by them involve supramolecular catalysis due to non-covalent bonding forming reversible complexes between substrates and β-cyclodextrin as seen in the enzymes [6]. β-Cyclodextrin-mediated organic reactions in aqueous medium are very useful both from economical and environmental point of view. β-Cyclodextrin apart from being nontoxic is considered to be metabolically safe [7].

2-Oxoindolin-3-ylidene malononitrile is especially important starting material or intermediate for the synthesis of various spiro compounds as a Michael acceptor [8] or activating double bond [9]. The most common methods for the synthesis of 2-oxoindolin-3-ylidene malononitrile are the

Knoevenagel condensation of isatins with malononitrile in the presence of a catalyst, such as piperidine [10], DBU [11], molecular iodine [12], sulfonic acid functionalized silica SBA-15 (SBA-Pr-SO_3H) [13], grinding in the presence of 1-5 equiv. of water [14]. However, those methods still have some disadvantages including long reaction time, hazardous organic solvents, reagents, catalyst for activation, commercially unavailable catalyst and low yield. Hence, in a quest for a new easy and ecofriendly procedure for the synthesis of 2-oxoindolin-3-ylidene malononitrile, we planned our strategy to exploit β-cyclodextrin as catalyst in aqueous medium.

MATERIALS AND METHODS

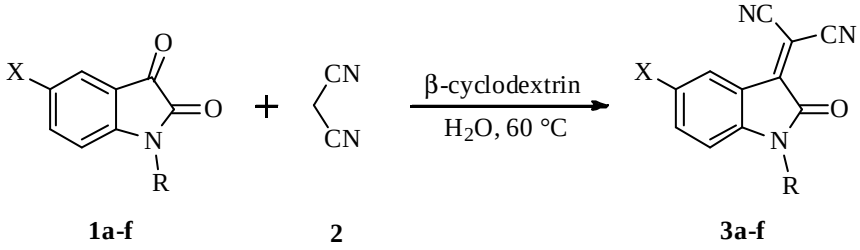
General. All chemicals were obtained commercially and used without further purification. Melting points were measured on a Electrothermal-9100 apparatus and are uncorrected.

General procedure for the preparation of 2-oxoindolin-3-ylidene malononitrile derivatives (3a-f):

β-Cyclodextrin (1mmol) was dissolved in water (10mL) with stirring at 60 ˚C. To this clear solution, isatins **1a-f** (1 mmol) and malononitrile 2 (1 mmol) were added. Then the reaction was stirred at 60 ˚C for the time reported in table **1** (the progress of the reaction being monitored by TLC and was used hexane/ethyl acetate as an eluent). After completion of the reaction, the reaction mixture was cooled to 40 ˚C and the solid was filtered, dried, and recrystallized from ethanol. The filtrate of the reaction mixture was cooled to 5 ˚C to recover β-cyclodextrin.

RESULTS AND DISCUSSIONS

Synthesis of compounds *via* a green, mild and simpler procedure, eliminating the use and generation of dangerous substances is the primary goal of green chemistry today. Herein, we report new applications of β-cyclodextrin a biomimetic catalyst for the synthesis of 2-oxoindolin-3-ylidene malononitrile. The synthesis of 2-oxoindolin-3-ylidene malononitrile was achieved under neutral conditions using β-cyclodextrin and water (Scheme **1**).



1a-f **2** **3a-f**

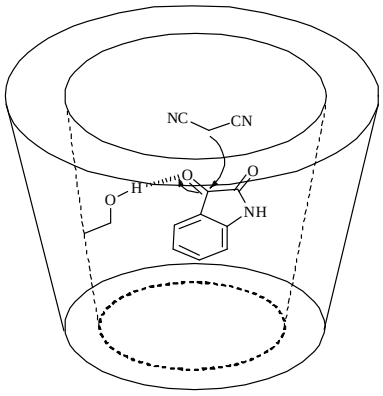
Scheme 1. Synthesis of 2-oxoindolin-3-ylidene malononitrile using β-cyclodextrin and water

The reaction of various isatin with malononitrile was carried out in water at 60 ˚C in the presence of β-cyclodextrin. Rapid reaction rates and high conversions were achieved and the results are presented in table **1**, all the products listed below are known compounds.

Table 1: Knoevenagel condensation of isatins with malononitrile in the presence of β-cyclodextrin in water at 60 ˚C

Compd. No.	X	R	Time (min)	Yield (%)	M.P. observed (°C)	M.P. reported (°C)
3a	H	H	5	93	237-239	239-240 [13]
3b	F	H	5	94	228-229	230-231 [12]
3c	Cl	H	5	93	225-227	228-230 [13]
3d	Br	H	5	92	235-236	236-238 [13]
3e	NO_2	H	5	94	259-261	262-264 [13]
3f	H	CH_3	5	95	232-234	234-235 [12]

The rate acceleration of this condensation can be attributed to complexation of isatins with β-cyclodextrin increases the reactivity of the carbonyl group because of intermolecular hydrogen bonding between outwardly hydroxyl groups of β-cyclodextrin and carbonyl oxygen of the isatins, which faciliting the Knoevenagel condensation isatins with malononitrile to form an 2-oxoindolin-3-ylidene malononitrile derivatives (Scheme **2**).



Scheme 2. Complexation of isatins with β-cyclodextrin

CONCLUSION

In summary, we have reported an efficient procedure for Knoevenagel condensation isatins with malononitrile, which leads to the synthesis of 2-oxoindolin-3-ylidene malononitrile derivatives. These reactions were carried out in the presence of β-cyclodextrin, in water at 60 ˚C. The procedure offers several advantages including high yields, short reaction times, operational simplicity, cost effectiveness and environmentally benign nature.

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