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A concise aqueous phase supramolecular synthesis of 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one derivatives

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ABSTRACT

2-Phenyl-2,3-dihydroquinazolin-4(1*H*)-one derivatives were synthesized for the first time in water under neutral conditions by the reaction of aldehyde, and anthranilamide mediated by β-cyclodextrin in high yields. β-Cyclodextrin can be recovered and reused with a small loss of catalytic activity.

Heterocyclic compounds acquired significance, as these are associated with a wide range of potential biological and pharmaceutical activities.[1] These N-containing heterocyclic compounds play a crucial role in the context of drug scaffolds, synthetic organic chemistry, and medicinal chemistry as well as material sciences.[2] 2,3-Dihydroquinazolinone derivatives act as important intermediates in the synthesis of drug molecules, and natural products.[3] These also exhibit various activities such as anti-cancer, anti-tumor, diuretic, herbicidal, as well as plant growth regulation.[4] Moreover, these derivatives can be easily oxidized to their quinazolin-4(3*H*)-one analogues,[5] which occur in several natural products.[6] Numerous protocols have been developed for the synthesis of 2,3-dihydroquinazolinones, using silica sulfuric acid,[7] montmorillonite K-10,[8] Amberlyst-15,[9] molecular iodine,[10] zinc(II) perfluorooctanoate [$Zn(PFO)_2$],[11] gallium(III) triflate,[12] $KAl(SO_4)_2 \cdot 12H_2O$,[13] $Al(H_2PO_4)_3$,[14] MCM-41-SO_3H,[15] and 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4).[16a] Recently Wang and co-workers demonstrated the eco-friendly synthesis of 2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones from anthranilamide and different aldehydes/ketones in water.[16b] These methods suffer from one or more disadvantages such as the use of hazardous organic solvents, low yields, strongly acidic conditions, expensive moisture-sensitive catalysts, and tedious work-up conditions. There are some drugs with quinazolinone skeleton (Fig. 1). In continuation of our efforts toward the development of novel environ-friendly methodologies,[17–27] herein, we report a mild and efficient one-pot protocol for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives by a two component reaction, involving aromatic/aliphatic aldehydes and anthranilamide mediated by recyclable β-CD in water (Scheme 1). Presently organic reactions in aqueous phase have attracted the attention of researchers because of the added advantages of water, as an environmentally benign and economically affordable solvent. However, the fundamental problem in performing the reactions in water is that many organic substrates are hydrophobic and are insoluble in water. Cyclodextrins, possessing hydrophobic cavities, are well known supramolecular catalysts, which by reversible formation of host–guest complexes, activate the organic molecules and catalyze the reactions. As part of our ongoing program toward the development of greener chemical approaches for the synthesis of novel reaction intermediates and heterocyclic moieties, we report herein the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by the reaction of aromatic/aliphatic aldehydes and anthranilamide, using β-cyclodextrin, as a recyclable supramolecular catalyst, in aqueous medium.

In this study, a model reaction was conducted by reacting benzaldehyde, and anthranilamide in water medium at room temperature to obtain the corresponding 2,3-dihydroquinazolin-4(1*H*)-one in low yields (55%). The poor solubility of benzaldehyde in water at elevated temperatures resulted in the formation of undesired products. When the same reaction was conducted using β-CD at room temperature the product was obtained in moderate yield (68%). However by a controlled experiment using β-CD, as a supramolecular catalyst, at 55–60 °C the product was obtained in excellent yield (86%) (Scheme 1). In general, all the reactions were

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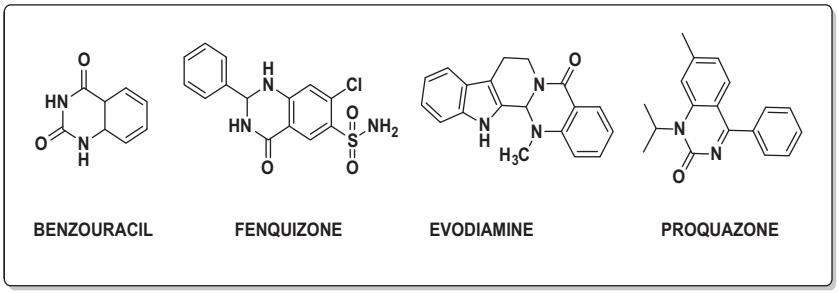
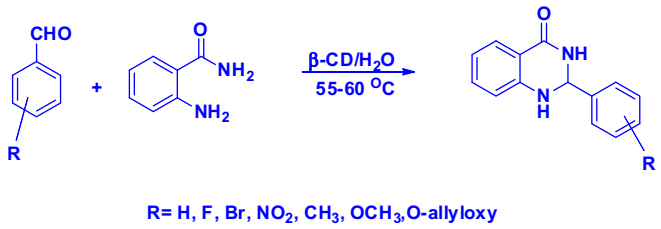


Figure 1. Some marketed drugs with quinazolinone skeleton.



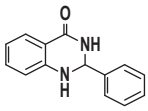
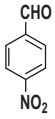
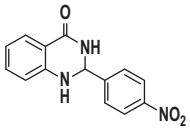
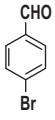
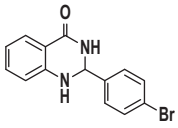
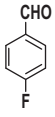
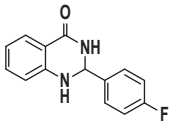
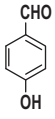
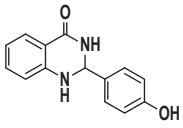
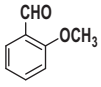
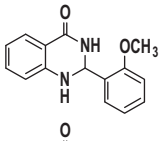
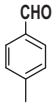
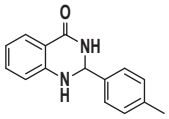
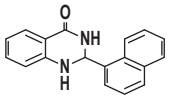
Scheme 1. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

Table 1
Recyclability of the catalyst[a]

Cycles	Yield[b] (%)	Catalyst recovered (%)
Fresh	86	95
1	85	94
2	83	92
3	80	90

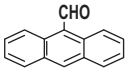
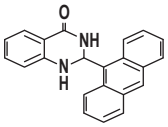
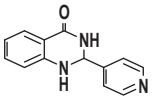
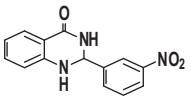
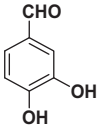
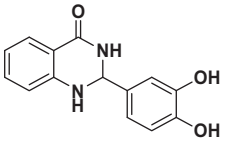
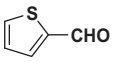
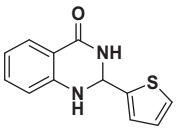
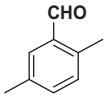
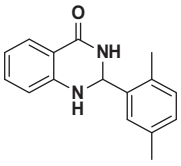
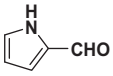
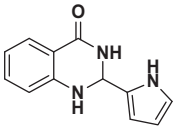
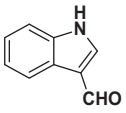
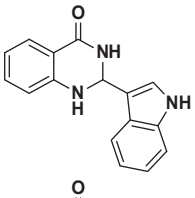
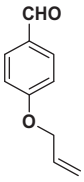
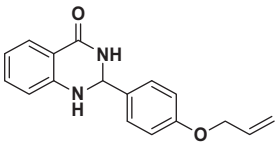
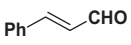
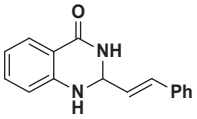
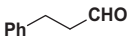
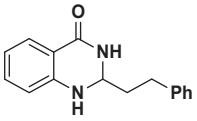
[a] Reaction conditions: Benzaldehyde (1.0 mmol), Anthranilamide (1.0 mmol), β-Cyclodextrin (10 mol %), 55–60 °C, 1.5 h.
[b] Isolated yield.

Table 2
Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones[a]

Entry	Aldehyde	Product	Yield[b] (%)
1			86
2			92
3			89
4			88
5			85
6			87
7			86
8			83

(*continued on next page*)

Table 2 (*continued*)

Entry	Aldehyde	Product	Yield[b] (%)
9			85
10			82
11			88
12			84
13			81
14			85
15			82
16			80
17			84
18			78
19			79

[a] Reaction conditions: aromatic aldehyde (1.0 mmol), anthranilamide (1.0 mmol), β-cyclodextrin (10 mol %), 55–60 °C, 1.5–7 h.
[b] Isolated yield.

clean, and the 2,3-dihydroquinazolin-4(1*H*)-ones were obtained in excellent yields (78–92%) (Table 2). All the products were characterized by ^{1}H, ^{13}C NMR, IR, and mass spectrometry.[29,30] The catalytic activity of the β-CD was established by the fact that 2,3-dihydroquinazolin-4(1*H*)-one formation was observed in low yields in the absence of β-cyclodextrin. The evidence of the formation of 2,3-dihydroquinazolin-4(1*H*)-one in the presence of β-CD was supported by ^{1}H NMR studies of the inclusion complex between benzaldehyde and β-CD.[28] All the reactions were carried out with a catalytic amount (10 mol %) of β-CD in water. β-CD

was observed to be recoverable in these reactions. After the reaction, the reaction mass was cooled to room temperature and β-CD was filtered and washed with ice-cold water and dried. The recovered β-CD was further used in the reaction with the same substrates and checked for the yields and the catalytic activity of the recovered catalyst
(β-CD), as shown in Table 1. It was observed that the yields of 2,3-dihydroquinazolin-4(1*H*)-ones diminished slightly after two to three recycles.

In summary, we have developed an eco-friendly method to synthesize 2,3-dihydroquinazolin-4(1*H*)-ones in excellent yields under neutral conditions in one-pot involving catalysis by β-cyclodextrin in water.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.029.

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29. *General experimental procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones using β-cyclodextrin:* β-Cyclodextrin (10 mol %) was dissolved in water (15 ml), and to this clear solution, benzaldehyde (1.0 mmol) was added, and stirred for 15 min, followed by the addition of anthranilamide (1.0 mmol). The reaction mixture was heated at 55–60 °C until completion of the reaction as indicated by TLC. The reaction mixture was cooled to 5 °C and β-cyclodextrin was filtered. The aqueous layer was extracted with ethyl acetate (4 × 10 ml). The combined organic layers were washed with water, saturated brine solution, and dried over anhydrous Na_2SO_4. The combined organic layers were evaporated under reduced pressure and the resulting crude product was purified by column chromatography by using ethyl acetate and hexane mixture (3:7) as an eluent. The identity and purity of the product were confirmed by ^1H, ^{13}C NMR, and mass spectra.
30. Data of representative examples synthesized compounds.
2-Phenyl-2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 1)[1]; IR: 3302, 3184, 3061, 2924, 1658, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.95 (d, 1H, *J* = 7.5 Hz), 7.60–7.57 (m, 2H), 7.48–7.45 (m, 2H), 7.36–7.30 (m, 1H), 7.27 (s, 1H), 6.92 (t, 1H, *J* = 6.7 Hz), 6.65 (d, 1H, *J* = 7.5 Hz), 5.92 (s, 1H), 5.79 (s, 1H, br), 4.38 (s, 1H, br); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 164.75, 147.22, 138.51, 134.02, 130.16, 129.12, 128.72, 127.39, 119.67, 114.55, 69.07; MS (ESI): *m*/*z* = 225 $[M+H]^+$.
2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 2)[1]; IR: 3278, 3174, 3032, 2922, 2855, 1647, 1608, 1520, 1461, 1345 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.32 (d, 1H, *J* = 8.3 Hz), 7.97 (m, 1H), 7.84–7.80 (m, 2H), 7.42–7.36 (m, 1H), 7.28 (s, 1H), 6.99–6.91 (m, 1H), 6.71 (d, 1H, *J* = 7.5 Hz), 6.16 (s, 1H, br), 6.04 (s, 1H), 4.42 (s, 1H, br); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 162.97, 147.61, 146.51, 145.96, 132.45, 126.79, 126.50, 122.26, 116.71, 113.72, 64.88; MS (ESI): *m*/*z* = 270 $[M+H]^+$.