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Polyethylene glycol (PEG-400) as an efficient and recyclable reaction media for one-pot synthesis of *2*-phenyl-*2, 3*-dihydroquinazolin-*4*(1*H*)-one derivatives under catalyst free conditions

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ABSTRACT

Polyethylene glycol (PEG-400) was found to be an effective reaction medium for one-pot synthesis of 2-phenyl-2, 3-dihydroquinazolin-4(1H)-one derivatives in good yields under mild reaction conditions. The use of PEG-400 is low, recyclable, and eco-friendly solvent.

Key words: Aldehydes, anthranilamide**,** *2*-phenyl-*2,3*-dihydroquinazolin-*4*(1*H*)-one, Catalyst-free conditions, Polyethylene glycol.

INTRODUCTION

Nitrogen containing heterocycles are an integral part of many drug molecules or physiologically active natural products and synthetic molecules. One such heterocycles is 2, 3-dihydroquinazolinone which contains a cyclic aminal chiral centre. 2, 3-dihydroquinazolinone is a privileged scaffold because of its extensive pharmacological activities such as antibacterial, ant fertility, antitumor, anti-fabricator, vasodilatory, antifungal, and analgesic efficacy.[1] In addition of 2,3-dihydroquinazolin-4(1*H*)-ones are an important class of heterocyclic compounds with a broad spectrum of pharmacological and biological activities, such as antifungal, and mono amine oxidise inhibitory activity.[2] Moreover, the quinazolinone core skeleton has been extensively utilized as a drug like template in medicinal chemistry.[3] These compounds can be easily oxidized to their quinazolin-4(3*H*)-one analogues,[4] which also include important pharmacologically active compounds.[5] Numerous protocols have been developed for the synthesis of 2,3- dihydroquinazolinones, by using silica sulfuric acid,[6] montmorillonite K-10,[7] Amberlyst-15,[8] molecular iodine,[9] zinc(II) perfluorooctanoate [$Zn(PFO)_2$],[10] gallium(III) triflate,[11] $KAl(SO4)_2$. $12H_2O$[12],$Al(H_2PO_4)_3$,[13] MCM-41-SO_3H,[14] and 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF4).[15] 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.[16] These above mentioned 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.

In recent years, the use of alternative solvents such as ionic liquids, polyethylene glycol and super critical fluids has gained importance as green reaction media in view of environmental perception.[17,18] Though water is a safe alternative, it is not always possible to use water as a solvent due to hydrophobic nature of the reactants and the sensivity of many catalysts to aqueous conditions, [19] In this context, PEG has become an alternative reaction media to perform organic synthesis due to its inherent advantages over toxic solvents. Furthermore, PEG is inexpensive, easy to handle, thermally stable, non-toxic and recyclable. [20]

In continuation of our efforts towards the synthesis of 2-phenyl-2, 3-dihydroquinazolin-*4*(1*H*)-one derivatives by using Polyethylene glycol from anthranilamide, aldehydes under catalyst-free conditions. PEG-400 as an eco-friendly and recyclable reaction media. To the best of our knowledge, there are no reports for the synthesis of 2-phenyl-2, 3-dihydroquinazolin-4(1*H*)-one derivatives using PEG-400 as a reaction medium under catalyst-free conditions (Scheme 1).

MATERIALS AND METHODS

In general, all the reactions were clean affording the 2, 3-dihydroquinazolin-4(1*H*)-one derivatives in high yields under the above conditions. Both electron rich and electron-deficient aldehyde derivatives gave the desired products (Table 1). The structures of all the products were determined from their spectral (IR, ^{1}H NMR, ^{13}C NMR and ESI-MS) data and also by direct comparison with authentic samples.[21]

The generality of this reaction was investigated with substituted aldehydes and anthranilamide and the results are presented in Table 1. A variety of aldehydes underwent smooth condensation with anthranilamide in PEG-400 at 85 ^{o}C to provide a diversified 2, 3-dihydroquinazolin-4(1*H*)-one derivatives (Table 1).

General procedure. synthesis of 2, 3-dihydroquinazolin-4(1*H*)-one derivative: A mixture of aldehyde and anthranilamide in 1:1 molar rations was taken in 5 mL polyethylene glycol-400. The resulting mixture was allowed to stir at 85 ^{o}C for the appropriate time. After completion of the reaction, as monitored by TLC, the reaction mass was poured into water and extracted with ethyl acetate. The organic layer was removed under reduced pressure, and the crude product was purified by column chromatography to yield the desired product.

The characteristic data of compounds are given below.

Compound (1). **2-(Pyridin-4-yl)-2,3-dihydroquinazolin-4(1H)-one** 1H NMR (300 MHz, $CDCl_3$) δ = 8.89 (d, 2H, *J* = 6.0 Hz), 8.57 (d, 2H, *J* = 7.5 Hz), 8.19 (d, 2H, *J* = 4.5 Hz), 7.97 (d, 2H, *J* = 3.0 Hz), 7.66-7.55 (m, 1H), 5.86 (s, 1H), 5.09 (s, 1H); 13C NMR (50 MHz, $CDCl_3$) δ = 160.99, 148.98, 145.87, 133.98, 127.34, 126.74, 125.56, 120.30, 69.05; MS (ESI): *m*/*z* = 226 [M + H]+.

Compound (2). **2-(3-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one** 1H NMR (300 MHz, $CDCl_3$) δ = 8.55 (s, 1H), 8.41 (d, 1H, *J* = 7.9 Hz), 7.88 (t, 2H, *J* = 7.9 Hz),7.77 (t, 1H, *J* = 7.9 Hz), 7.47(t, 1H, *J* = 6.9 Hz), 6.86 (t, 1H, *J* = 6.9 Hz), 6.81 (d, 1H, *J* = 7.9 Hz), 6.05 (s, 1H), 5.98 (s, 1H, br), 4.46 (s, 1H, br); 13C NMR (50 MHz, $CDCl_3$) δ = 163.32, 146.99, 146.19, 142.79, 132.59, 132.18, 128.61, 126.77, 122.35, 120.99, 116.88, 114.09, 113.78, 65.09; MS (ESI): *m*/*z* = 270 [M + H]+.

Compound (5). **2-(Thiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one** 1H NMR (300 MHz, $CDCl_3$) δ = 7.84 (d, 1H, *J* = 7.5 Hz), 7.51-7.42 (m, 2H), 7.32 (d, 1H, *J* = 3.7 Hz), 7.08 (t, 1H, *J* = 4.5 Hz), 6.82 (t, 1H, *J* = 7.5 Hz), 6.67 (d, 1H, *J* = 8.3 Hz), 6.29 (s, 1H), 6.19 (s, 1H, br), 4.46 (s, 1H, br); 13C NMR (50 MHz, $CDCl_3$) δ = 161.85, 132.43, 126.59, 125.29, 124.99, 124.86, 116.98, 113.92, 102.99, 62.38; MS (ESI): *m*/*z* = 231 [M + H].+

Compound (7). **2-(1H-Indol-3-yl)-2,3-dihydroquinazolin-4(1H)-one** 1H NMR (300 MHz, $CDCl_3$) δ = 10.018 (s, 1H), 8.83 (s, 1H), 8.35-8.32 (m, 3H), 7.75 (d, 2H, *J* = 3.0 Hz), 7.54 (t, 2H, *J* = 5.1 Hz), 7.36-7.33 (m, 2H), 5.89 (s,

1H), 4.85 (s, 1H, br); 13C NMR (50 MHz, $CDCl_3$) δ = 161.54, 151.62, 136.11, 133.85, 131.96, 131.19, 128.19, 127.22, 126.32, 115.89, 67.94; MS (ESI): *m/z* = 264 [M + H].+

Compound (8). **2-(1H-Pyrrol-2-yl)-2,3-dihydroquinazolin-4(1H)-one** 1H NMR (300 MHz, $CDCl_3$) δ = 8.44-8.33 (m, 1H), 8.16 (s, 2H), 7.95-7.85 (m, 1H), 7.67-7.55 (m, 2H), 7.46 (d, 1H, *J* = 1.5 Hz), 6.99 (t, 1H, *J* = 7. 8 Hz), 6.98 (s, 1H, br), 6.62 (s, 1H), 5.09 (s, 1H, br); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 160.56, 151.77, 147.54, 143,52, 132.81, 125.79, 125.55, 124.99, 62.88; MS (ESI): *m/z* = 214 $[M + H]^+$.

Compound (10). **2-(2-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.55-8.52 (m, 1H), 8.44-8.38 (m, 1H), 7.77-7.65 (m, 1H), 7.67-7.52 (m, 2H), 7.22 (t, 1H, *J* = 6.7 Hz), 7.10 (d, 1H, *J* = 6.7 Hz), 6.82-6.67 (m,1H), 6.75-6.53 (m,1H), 6.67 (t, 1H, *J* = 6.7 Hz), 4.57 (s, 1H, br), 4.15 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 170.58, 155.73, 148.42, 132.75, 131.14, 129.33, 127.65, 126.55, 125.88, 125.47, 124.65, 124.42, 119.41, 118.64, 112.58, 110.33, 109.74, 108.62, 70.27, 54.35, 53.68; MS (ESI): *m/z* = 255 $[M + H]^+$.

Compound (12). **2-(Naphthalen-1-yl)-2,3-dihydroquinazolin-4(1H)-one** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.14-8.06 (m, 2H), 8.08 (d, 1H, *J* = 1.5 Hz), 7.36 (t, 1H, *J* = 8.3 Hz), 7.26-7.16 (m, 3H), 7.22-7.11 (m, 3H), 6.76 (t, 1H, *J* = 8.3 Hz), 6.56 (d, 1H, *J* = 8.3 Hz), 6.21 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 164.12, 144.25, 132.85, 130.12, 128.85, 128.62, 128.45, 126.96, 125.74, 119.45, 114.85, 74.56; MS (ESI): m/z = 275 $[M + H]^+$.

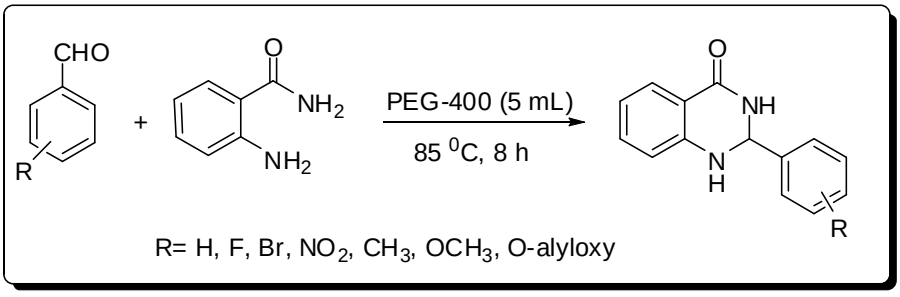
Compound (14). **2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.43 (d, 1H, *J* = 8.3 Hz), 7.97 (m, 1H), 7.93-7.85(m, 2H), 7.53-7.45 (m, 1H), 7.37 (s, 1H), 6.99-6.95 (m, 1H), 6.78 (d, 1H, *J* = 7.5 Hz), 6.19 (s, 1H, br), 6.06 (s, 1H), 4.63 (s, 1H, br); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 162.99, 147.72, 146.42, 144.96, 133.44, 125.89, 125.62, 121.27, 116.81, 113.76, 63.88; MS (ESI): *m/z* = 270 $[M + H]^+$.

Compound (16). **2-(4-Fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.85 (d, 1H, *J* = 8.9 Hz), 7.74-7.47 (m, 2H), 7.28-7.24 (m, 1H), 7.37 (t, 2H, *J* = 8.3 Hz), 6.85 (t, 1H, *J* = 8.3 Hz), 6.66 (d, 1H, *J* = 8.3 Hz), 5.95 (s, 1H), 5.87 (s, 1H, br), 4.45 (s, 1H, br); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 161.98, 158.78, 145.93, 133.66, 129.29, 129.19, 128.87, 118.94, 116.63, 115.35, 114.75, 66.48; MS (ESI): *m/z* = 243 $[M + H]^+$.

Compound (19). **(E)-2-Styryl-2,3-dihydroquinazolin-4(1H)-one;** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.97 (d, 1H, *J* = 8.2 Hz), 7.45-7.42 (m, 6H), 6.92 (t, 1H, *J* = 7.1 Hz), 6.68-6.54 (m, 3H), 6.39-6.35 (q, 1H, *J* = 16.4 Hz), 5.35 (d, 1H, *J* = 8.2 Hz), 4.45 (s, 1H, br); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 160.55, 155.11, 149.66, 147.98, 147.37, 146.99, 138.89, 136.96, 132.93, 127.33, 126.68, 125.99, 124.44, 124.33, 124.19, 119.38; MS (ESI): *m/z* = 251 $[M + H]^+$.

RESULTS AND DISCUSSION

Scheme 1.Synthesis of 2-phenyl-2, 3-dihydroquinazolin-4(1H)-one



In this study, a model reaction was conducted by reacting benzaldehyde, and thranilamide in water medium at room temperature to obtain the corresponding 2, 3-dihydroquinazolin-4(1*H*)-one in low yields (52%).

Table 1 Synthesis of 2, 3-dihydroquinazolin

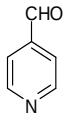
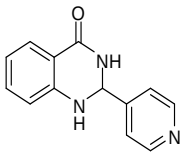
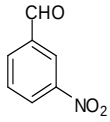
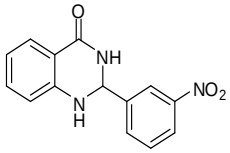
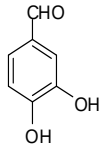
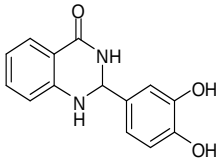
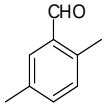
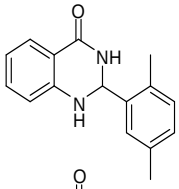
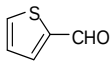
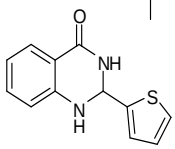
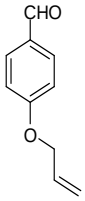
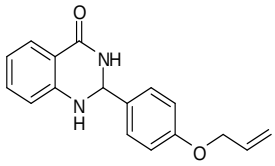
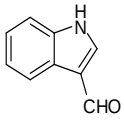
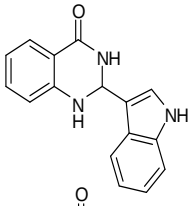
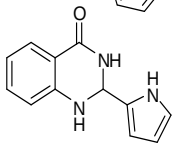
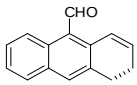
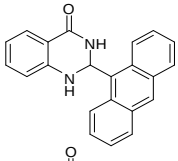
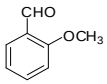
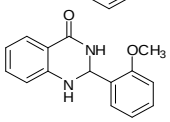
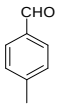
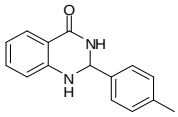
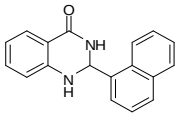
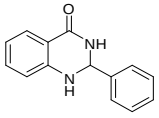
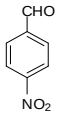
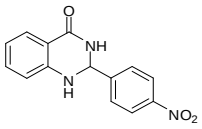
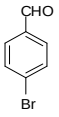
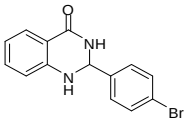
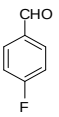
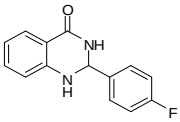
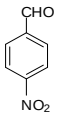
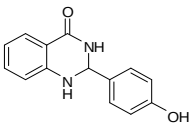
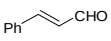
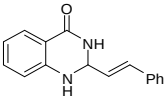
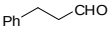
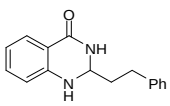
Entry	Aldehydes	Product	Time (h)	Yieldsb(%)
1			7	82
2			7	88
3			6	84
4			7	85
5			7	81
6			6	84
7			7	80
8			6	82

Table 1 (Continued)

Entry	Aldehyde	Product	Time (h)	Yields (%)
9			7	85
10			8	87
11			6	83
12			7	84
13			6	86
14			8	92
15			6	89
16			7	88
17			7	85
18			6	78
19			5	79

[a] Reaction conditions: aromatic aldehyde (1.0 mmol), PEG-400, 5mL) 85 ^{0}C 8h.
[b] Isolated yield.

The poor solubility of benzaldehyde in water at elevated temperatures resulted in the formation of undesired products. When the same reaction was conducted using PEG-400 at room temperature the product was obtained in moderateyield (69%). However by a controlled experiment using PEG-400, as a recyclable media, at 85 ^{o}C the product was obtained in excellent yield (89%) (Scheme 1) (Table 1)

CONCLUSION

In conclusion, we have developed an eco-friendly synthesis of 2-phenyl-2, 3-dihydroquinazolin-4(1*H*)-one derivatives by using PEG-400 as a recyclable reaction medium without the need of any additive or acid catalyst. The mild reaction conditions, inexpensive reaction medium, operational simplicity and high yields are the advantages of this protocol.

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