

Short Communication: Acetic Acid Catalyzed Synthesis of Benzo[h]quinazoline-2(3H)-thione Derivatives Using Polyethylene glycol-400 as Green Reaction Medium



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ABSTRACT

In this present investigation, an efficient protocol for the synthesis of a bundle of novel substituted benzo[h]quinazoline-2(3H)-thione derivatives was reported. The acetic acid catalyzed benzo[h]quinazoline-2(3H)-thione derivatives were prepared from 2-(substituted arylidene)-1-tetralones, thiourea, and green solvent polyethylene glycol-400 with efficient and milder reaction conditions. All the novel scaffolds were confirmed by the spectroscopic methods (IR, ¹H NMR, Mass, and elemental analysis). The superiority of the present method was operational simplicity, easy purification; high yields, easily available catalyst, environmental-friendly solvent.

Introduction

Heterocyclic compounds have a broad range of scope in the major class of compounds and their application in the medicinal uses with decent advantages. The compound having hetero atoms are significantly important in the biochemical process as well as their presence in the widerange of chemicals, pigments, paints, and

pharmaceutical drugs therefore they have high demands in the chemical industries such as medicinal/pharmaceutical, paint, packing, and textile. Quinazoline ring is an important heterocyclic skeleton in drug research [1]. The scaffold of quinazoline having nitrogen atoms play important role in their moiety and shows numerous universal concerns due to their wide and distinct pharmaceutical activities [2]. Quinazoline was the most commonly found

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heterocyclic moiety in medicinal research, due to its wide spectrum of pharmacological potential and a huge amount of its derivatives are referred to be structural synthons of numerous physiological relevance and pharmaceutical applications [4]. The compounds containing quinazoline-2(1*H*)-thione moieties were showed important classes of bioactive molecules such as anti-bacterial, anti-viral, and anti-inflammatory activities [5]. Quinazoline derivatives were also found to the inhibitory activity of various forms of cellular phosphorylation, while certain derivatives demonstrated significant central nervous system activity through acting as a ligand [6]. *N*-allylated quinazoline-2,4-diones and derivatives also possess different pharmacological activities like anti-tumor, anti-plasmodium, anti-virus, anti-hypertensive, and anti-convulsant [7-14]. 2-Pentylquinazolin-4(3*H*)-one (thione)quinazoline derivatives were considered as tremendous target molecules for the medicinal chemists, due to the fact that they are the scaffold of potent anti-proliferative and anticancer drugs [15]. Keeping in mind, such a broad spectrum of applications of quinazoline derivatives; we here planned the synthesis of some new substituted benzo[*h*]quinazoline-2(3*H*)-thione derivatives from 2-(substituted arylidene)-1-tetralones with thiourea using acetic acid as catalyst in PEG-400 as a green reaction solvent.

Experimental

Materials and methods

Melting points were determined by an open capillary method and were uncorrected. The

Table 1. Physico-chemical data of synthesized 2-(substituted arylidene)-1-tetralones **1(a-f)**

Entry	Substitution (Ar)	Mol. Formula	M.P.(°C)	Yield(%) ^a
1a	4-OMe-benzaldehyde	C ₁₈ H ₁₆ O ₂	110	92
1b	4-Cl-benzaldehyde	C ₁₇ H ₁₃ OCl	132	94
1c	4-OH-benzaldehyde	C ₁₇ H ₁₄ O ₂	124	92
1d	Benzaldehyde	C ₁₇ H ₁₄ O	98	86
1e	3-OMe-4-OH-benzaldehyde	C ₁₈ H ₁₆ O ₃	128	90
1f	2-Thiophenaldehyde	C ₁₅ H ₁₂ OS	116	88

^aIsolated Yields.

*Experimental procedure for the synthesis of benzo[*h*]quinazoline-2(3*H*)-thiones 3(a-f)*

chemicals and solvents were used laboratory-grade and purified. The purity of synthesized products was monitored by thin-layer chromatography (TLC) on a microscopic slide with silica Gel-G layers. TLC spots were visualized in the UV/ iodine chamber. The structures of these products were confirmed based on spectral analysis. IR spectra were recorded on Shimadzu spectrophotometer (in KBr pellets). ¹H NMR spectra were recorded (in DMSO-*d*₆) on Avance-300 MHz spectrometer using trimethylsilane (TMS) as an internal standard. The mass was recorded on the EI-Shimadzu-GC-MS spectrometer.

Experimental procedure for the synthesis of 2-(substituted arylidene)-1-tetralone (1a-f)

The mixture of 1-tetralone (α-tetralone) (1 mmol) and aldehyde (1 mmol) in 20 mL polyethylene glycol-400 was mixed in the 100 mL round bottom flask. Then, nearly 3 mL dilute KOH solution (40%) was added to the round bottom flask. The progress of the reaction was monitored by TLC with constant stirring. Once TLC shows the completion of the reaction, the reaction mixture was poured into 50 mL ice-cold water, the solid was formed, filtered over filter paper, dried and recrystallized from the suitable solvent. The yield and physical constant (M.P.) of the product was noted carefully. Similarly, all the compounds were synthesized by the same procedure.

The physical and analytical data of the prepared compounds were mentioned in **Table 1**.

In a 50 mL round bottom flask, the mixture of 2-(substituted arylidene)-1-tetralones **1(a-f)** (1

Mmol.) and thiourea(**2**) (1.5Mmol) were taken in 20 mL PEG-400 as a reaction solvent. The 1 mL of acetic acid was added as catalyst into the same flask. A small porcelain piece was kept in the flask. The whole mixture was heated to reflux on the water bath for an hour. The progress of the reaction was monitored by TLC. Once the TLC shows the completion of the reaction. The whole reaction mixture was

poured into nearly 50 mL ice-cold water. The formed solid compound was filtered, dried, and recrystallized with an appropriate solvent. The yield and physical constant (M.P.) of the product was noted in the open capillary method. Similarly, all the compounds were synthesized by the same procedure. The physical and analytical data of the prepared compounds were mentioned in **Table 2**.

Table 2. Physico-chemical data of synthesized benzo[h]quinazoline-2(3H)-thione3(a-f)

Entry	Substitution (Ar)	Mol. Formula	M. P (°C)	Yield (%) ^a
3a	4-OMe-benzaldehyde	C ₁₉ H ₁₈ N ₂ OS	136	94
3b	4-Cl-benzaldehyde	C ₁₈ H ₁₅ ClN ₂ S	152	92
3c	4-OH-benzaldehyde	C ₁₈ H ₁₆ N ₂ OS	145	90
3d	Benzaldehyde	C ₁₈ H ₁₆ N ₂ S	116	88
3e	3-OMe-4-OH-benzaldehyde	C ₁₉ H ₁₈ N ₂ O ₂ S	164	90
3f	2-Thiophenaldehyde	C ₁₆ H ₁₄ N ₂ S ₂	128	86

^aIsolated Yields.

Spectral data selected compound-3a

4,4a,5,6-tetrahydro-4-(4-methoxyphenyl) benzo[h]quinazoline-2(3H)-thione (3a)

IR (KBr, cm⁻¹): 3200, 2980, 1615; ¹H NMR (DMSO-*d*₆, δ ppm): 1.71-2.60 (m, 5H, CH₂-CH₂-CH), 3.21 (m, 1H, -CH), 5.11 (s, 1H, NH), 3.68 (s, 3H, OCH₃), 6.95-8.12 (m, 8H, Ar-H); EIMS (*m/z*): 322 (M⁺); Anal. Calcd. For C₁₉H₁₈N₂OS: C, 70.78; H, 5.63; N, 8.69; Found C, 70.71; H, 5.72; N, 8.61.

Results and Discussion

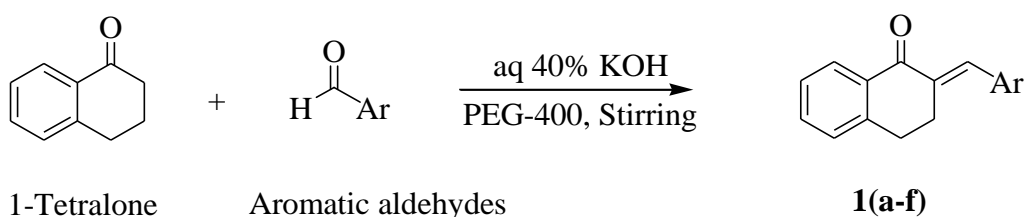
Solvents play an imperative task in organic synthesis. The selection of proper solvent is very important for the desired output of synthesis. The aromatic solvents like chlorobenzene, benzene, toluene, etc. are routinely used in organic transformation and have major disadvantages over environmental hazards. The major drawback of these solvents is their toxic nature, effervescent, expensive, and non-recovery. Therefore, the use of such hazardous solvents causes various side effects on living things includes humans and the environment. To minimize such drawbacks, different attempts have been made to develop methods of solvent-free chemistry and few successful transformations have been made in the literature [16]. However, the majority of

organic transformations solvents play an important role in making the reaction homogeneous and allowing molecular interactions to be more easy and efficient. The main key principle of green chemistry was the removal of toxic solvents in chemical processes or the replacement of hazardous solvents with environmentally friendly solvents [17]. The advantages of water as an eco-friendly medium have been well esteemed; however, the practical operation is bounded because of the lyophobic (hydrophobic) nature of organic materials and the moisture-sensitive catalyst [18].

In general, polyethylene glycol (PEG) is a greener alternative reaction medium over toxic organic solvents due to its biodegradable material, inexpensive, non-toxic, thermally stable, and possibly recyclable and reusable nature. Recently, the tremendous usage of PEG as an eco-friendly, novel, alternative source in the development of various organic chemical transformations has been observed [19]. Presently, the reporting of new eco-friendly friendly synthetic routes with polyethylene glycol (PEG-400) as a reaction solvent for the synthesis of biologically active compounds have been reported [20-21]. Herein, we report to attempt the synthesis of some substituted benzo[h]quinazoline-2(3H)-thione derivatives

by the acetic acid-catalyzed condensation reaction of 2-(substituted arylidene)-1-tetralones and thiourea in polyethylene glycol-400 solvent. The starting compounds 2-(substituted arylidene)-1-tetralones **1(a-f)** were synthesized by the classical CS condensation protocol in the PEG-400 as an ecofriendly reaction solvent. The mixture of α -tetralone (1 mmol) and substituted aryl aldehyde (1 mmol) was mixed in 20 mL polyethylene glycol-400 as reaction solvent taken in 100 mL conical flask. The brine solution of KOH (Approx. 2 mL of 40%) was added to the reaction mixture. The solution

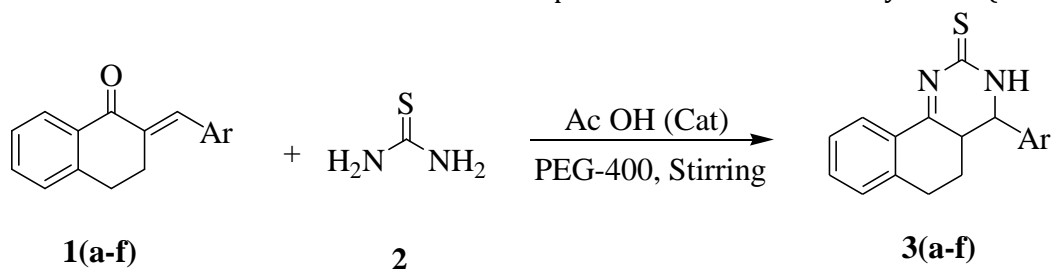
changes its color to reddish-brown. Stirred the obtained solution on magnetic stirrer for half an hour at room temperature. The progress of the reaction was monitored by thin-layer chromatography (TLC). Once the TLC shows the completion of the reaction; the solution of the reaction mixture was poured into 50 mL ice-cold water. The corresponding solid product was obtained in the beaker was separated and filtered. The crude product was recrystallized from a suitable solvent. The synthesis of 2-(substituted arylidene)-1-tetralones **1(a-f)** was represented in Scheme 1.



Scheme 1. Synthesis of 2-(substituted arylidene)-1-tetralones using KOH in PEG-400

Further, the synthesis of target compounds benzo[h]quinazoline-2(3H)-thione derivatives **3(a-f)** can be achieved by the cyclic condensation reaction of 2-(substituted arylidene)-1-tetralones **1(a-f)** (1mmol.) with thiourea (1.5mmol) in PEG-400 using acetic acid as catalyst at water bath temperature. In the beginning, we started our synthesis with 2-(4-methoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**1a**) and thiourea (**2**) (1.5mmol) in PEG-400 reaction solvent using acetic acid as catalyst at water bath temperature. The corresponding product (**3a**) was obtained in 1 hour with an excellent

yield (94%)(Scheme 2, Table-2). For the process optimization, we have performed the same reaction in various solvents such as Ethanol, CH₃CN, DCM, and PEG-400 as summarized in **Table3**. We found that polyethylene glycol-400 becomes an efficient reaction solvent in terms of reaction time as well as yield (94%). Promoting by these results, we next turned our attention towards different 2-(substituted arylidene)-1-tetralones **1(b-f)** (1Mmol.) with thiourea (**2**) (1.5Mmol) in PEG-400 using acetic acid as catalyst at water bath temperature to give the corresponding products in excellent yields (Scheme 2).



Scheme 2. Synthesis of benzo[h]quinazoline-2(3H)-thione derivatives using acetic acid in PEG

Table3. Solvent effect on the reaction of 2-(4-methoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one(**1a**) and thiourea(**2**) using AcOH as catalyst at water bath temperature

No	Solvent	Time (hrs)	Yield (%)
1	Ethanol	6	68
2	Dichloromethane	6.5	65
3	CH ₃ CN	8	58
4	PEG-400	1 (60 min)	94

Structures of all newly synthesized benzo[h]quinazoline-2(3H)-thione derivatives were confirmed by the spectral analysis. The IR spectra of the products were showed a presence of characteristic stretching frequency 3310 cm⁻¹ referring to N-H stretch. Further, the IR spectra of the products were also showed characteristic stretching frequency 1610-1620 cm⁻¹ confirms the presence of -C=N bond in benzo[h]quinazoline-2(3H)-thione. The absorption bands associated with other functionalities appeared in the expected regions. The ¹HNMR spectra of benzo[h]quinazoline-2(3H)-thione derivatives showed a multiplet pattern in the region δ 1.71-2.66 region corresponding to the -CH₂-CH₂-CH protons. The characteristic -NH proton appeared as a singlet near δ 5.1-5.6 δ ppm. The aromatic hydroxyl (phenolic) proton appeared as a singlet near δ 10.2-11.6 δ ppm, while the remaining aromatic and aliphatic protons were observed at expected regions. The mass spectra of the newly synthesized benzo[h]quinazoline-2(3H)-thiones **3(a-f)** were also revealed molecular ion peaks corresponding to their molecular formula.

Conclusion

In summary, we have reported a simple, efficient, and eco-friendly method for the synthesis of some new substituted benzo[h]quinazoline-2(3H)-thione derivatives. The reaction of 2-(substituted arylidene)-1-tetralones and thiourea with glacial acetic acid as catalyst in polyethylene glycol (PEG-400) as an efficient reaction solvent at mild reaction conditions was described. In the comparative study of reaction solvent on the synthesis of benzo[h]quinazoline-2(3H)-thione derivatives; it was observed that PEG-400 is an efficient reaction solvent in terms of reaction time as well as yield. In the end, this procedure offers

many advantages like mild reaction conditions, good yield of target products, minimum environmental impact, operational simplicity, and ease to perform. The use of PEG-400 as an alternative green reaction solvent was the main advantage of this methodology. These synthesized compounds can be studied for biological evaluation and may use as drug molecules.

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