



Synthesis and Characterization of some Substituted Octa-hydroquinazoline using Ultrasound Technique

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Abstract

Ten derivatives of octahydro-quinazoline-2, 5-dione were synthesized using an ultrasound technique and using zirconium oxy nitrate hydrate as a new catalyst. The new compounds were proved upon elemental and spectroscopic analyses of FTIR, ¹H, and ¹³C-NMR together with their physical properties.

Keywords: Dimedone, Octahydroquinazoline, Ultrasound, Biginelli condensation

1. Introduction

Multicomponent chemical reactions are very important for preparation many heterocyclic compounds [1, 2] and this strategy has been used extensively in preparing important compounds in many fields [3, 4] which three or more reactants are combined in a single chemical step to produce products. Biginelli reaction involves acid-catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) using easily-accessible starting materials, namely, aldehyde, active methylene compound and (thio)urea. DHPMs have stimulated resurgence of interest in the past two decades due to their wide ranging pharmacological activities and presence of diverse natural products. [5, 6] This reaction witnessed developments to obtain a quantitative reaction as the reaction method changed, including the use of green chemistry methods [7, 8]. By reviewing the literature, it was found that a number of octahydroquinazolinone derivatives could be prepared by condensing Biginelli by using the interaction of dimedone compounds with urea or thiourea and with different aldehydes using in the presence of SiO₂-NaHSO₄ is reported. SiO₂-NaHSO₄ acts as an efficient mild [9, 10]. Also when using Biginelli Stimulation of condensation of dimethylene, urea, or thiourea and aromatic aldehydes substituted by (10 mol %) of thiamine (VB1) hydrochloride It has been studied in a solvent free condition under microwave irradiation, where the resulting ratio was good to excellent. It was characterized by the use of microwave irradiation, simple reaction conditions, and short reaction time [13-16]. While Biginelli condensation and thiamine hydrochloride were used as

an ultrasound catalyst, the reactions were efficiently performed in water in the absence of an organic solvent using ultrasound, it is characterized by simple conditions, purification and isolation, which made it is widely interesting from an environmental and economic perspective [17-19], also Biginelli reaction between substituted aldehydes, ethyl acetoacetate and urea, the corresponding dihydropyrimidinones (DHPMs) it was also obtained at satisfactory yields under It was also obtained at satisfactory yields under moderate reaction conditions [20] In addition, microwave irradiation was used to synthesis of octahydroquinazolinone derivatives. using lanthanum oxide as a catalyst [21-22]. According to above survey and as a part of our continuous interest in the Green chemistry, a series of new octahydro-quinazoline-2, 5-dione are synthesized using an ultrasound technique and using zirconium oxy nitrate hydrate as a new catalyst.

2. Experimental

2.1. Chemistry

Melting points were measured on SMP30 Melting Points Apparatus and are uncorrected. FTIR spectra were registered on FTIR.600 brot .tech engineering management spectrophotometer using KBr disc. NMR spectra were recorded on JEOL EEA400MHZ FT-NMR, by using TMS as an internal standard using DMSO-d₆ as a solvent. Ultrasonication irradiations were reactions on Unisonic PTY.LTD type F XP 12. Thin layer chromatography (TLC) plates prepared by silica gel and the plates were developed with iodine vapour, also were used to monitor the reactions as well as to confirm the purity of the synthesized compounds and to verify the purity

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Receive Date: 11 February 2022, Revise Date: 12 March 2022, Accept Date: 20 March 2022

DOI: 10.21608/EJCHEM.2022.121240.5439

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of commercial reagents. All reagents and chemicals were commercially available and were used as received from the suppliers.

2.2. General procedures of Synthesis of 4-(Substitutedphenyl)-7,7-dimethyl-4,6,7,8-tetrahydroquinazoline-2,5(1H,3H)-dione (4a-j)[23]

A mixture of aromatic aldehyde (0.001mole), dimedone (0.001 moles), urea or thiourea (0.0015) and a catalytic amount of zirconium oxy nitrate hydrate in ethanol (15 ml) was sonicated. The reaction temperature was raised to (25-30°C) after sonication for 0.5h. On completion of the reaction, leave the mixture to dry and recrystallize from hot ethanol to give the pure products 4a-j.

4-(4-Bromophenyl)-7,7-dimethyl-4,6,7,8-tetrahydroquinazoline-2,5(1H,3H)-dione 3(4a)

Compound 4a was separated as yellow crystals with Yield: 90%, mp. 297-299°C. (Lit.[24] mp >300 °C) IR (KBr, cm⁻¹): 3318, 3225 (2N-H), 3084 (C-H, Ar-H), 1690, 1654 (2 C=O), 1614 (C=Aliphatic), 1590 (C=Aromatic), 640 (=C-Br). ¹H-NMR (DMSO-d₆): 0.97 (s, 3H, CH₃), 1.00 (s, 3H, CH₃), 2.07 (s, 2H, CH₂), 2.25 (s, 2H, CH₂), 5.41 (s, 1H, CH), 7.12-7.85 (m, 5H, NH, ArH), 10.0 (s, 1H, NH). ¹³C-NMR (DMSO-d₆-400MHz) δ ppm: 26.98, 28.34, 29.09, 32.26, 32.26, 50.45, 114.38, 128.99, 130.81, 131.72, 131.72, 132.79, 132.79, 160.11, 163.54, and 196.55.

4-(4-Chlorophenyl)-7,7-dimethyl-4,6,7,8-tetrahydroquinazoline-2,5(1H,3H)-dione(4b)

Compound 4b was separated as gray crystals with Yield: 92%, mp. 315-317°C (Lit.[17], mp318-320°C). IR (KBr.cm⁻¹): 3325, 3190 (2N-H), 3080 (C-H, ArH), 1695, 16260 (2C=O), 1620 (C=C Aliphatic), 1606 (C=C, Aromatic), 730 (=C-Cl). ¹H-NMR (DMSO-d₆): 0.88 (s, 3H, CH₃), 0.99 (s, 3H, CH₃), 2.05 (s, 2H, CH₂), 2.21 (s, 2H, CH₂), 5.16 (s, 1H, CH), 7.18-7.96 (m, 4H, ArH), 9.45 (s, 1H, NH), 10.01 (s, 1H, NH). ¹³C-NMR (DMSO d₆, 400MHz) δ ppm: 28.09, 28.09, 29.16, 32.5, 50.26, 51.96, 107.52, 131.65, 131.65, 144.06, 144.06, 152.25, 153.03, 158.28, 160.0, and 192.60.

4-(Benzo[d][1,3]dioxol-4-yl)-7,7-dimethyl-4,6,7,8-tetrahydroquinazoline-2,5(1H,3H)-dione (4c)

Compound 4c was separated as yellow crystals with Yield: 85%, mp 254-256°C. IR (KBr, cm⁻¹): 3330, 3260 (2 NH), 3085 (C-H, Ar-H), 1650 (2 C=O), 1630 (C=Aliphatic), 1602 (C=Aromatic), 1330, 1242 (Asym., Sym. C-O-C): ¹H-NMR (DMSO-d₆): 0.92 (s,3H,CH₃), 1.01 (s, 3H, CH₃), 2.07 (s, 2H, CH₂), 2.12 (s, 2H, CH₂), 5.43 (s, 1H, CH), 5.98 (s, 2H, OCH₂O), 6.65-7.34 (m, 4H, NH, Ar-H), 9.81 (s, 1H, NH), ¹³C-NMR (DMSO-d, 400 MHz) δ ppm: 28.34, 28.34, 32.24, 32.33, 46.41, 101.10, 52.14, 106.88, 107.90,

109.12, 145.95, 148.84, 158.60, 160.50, 163.26, 164.89, 191.44.

4-(2,3-Dimethoxyphenyl)-7,7-dimethyl-4,6,7,8-tetrahydroquinazoline-2,5(1H,3H)-dione (4d)

Compound 4d was separated as golden yellow crystals with Yield: 80%, mp. 268-271°C. IR (KBr, cm⁻¹): 3340, 3198 (2 NH), 3088 (C-H), (Ar-H), 1680, 1655 (2C=O), 1635 (C=Aliphatic), 1605 (C=Aromatic), 1325, 1238 (Asym., Sym. C-O-C): ¹H-NMR (DMSO-d₆): 0.94 (s, 3H, CH₃), 1.01 (s, 3H, CH₃), 2.18 (s, 2H, CH₂), 2.34 (s, 2H, CH₂), 3.79 (s, 3H, OCH₃), 3.88 (s, 3H, OCH₃), 5.47 (s, 1H, CH), 6.68-7.48 (m, 3H, ArH), 9.43 (s,1H,NH) ,10.20 (s, 1H, NH). ¹³C-NMR (DMSO-d, 400 MHz) δ ppm: 28.42, 28.42, 29.14, 32.77, 47.77, 50.42, 56.14, 60.57, 107.01, 11231, 120.09, 124.18, 138.11, 146.36, 152.01, 152.86, 163.37, 196.34.

4-(4-Nitrophenyl)-7,7-dimethyl-4,6,7,8-tetrahydroquinazoline-2,5(1H, 3H)-dione(4e).

Compound 4e was separated as brown crystals with Yield: 80%, mp296-298°C.(Lit.[17] mp. 302-304°C. IR (KBr, cm⁻¹): 3355, 3220 (2 NH), 3075 (C-H, Ar-H), 1701, 1661 (2 C=O), 1622 (C=Aliphatic), 1598 (C=Aromatic), Asym. 1513, Sym. 1351 (NO₂), ¹H-NMR (DMSO-d₆): 0.09 (s, 3H, CH₃), 1.04 (s, 3H, CH₃), 2.06 (s, 2H, CH₂), 2.41 (s, 2H, CH₂), 5.31 (s, 1H, CH), 6.20-8.46 (m, 4H, ArH), 9.61 (s, 1H, NH), 10.21 (s, 1H, NH). ¹³C NMR (DMSO-d, 400 MHz) δ ppm: 28.31, 28.31, 32.34, 50.37, 56.51, 113.82, 123.44, 123.44, 127.15, 127.15, 131.12, 146.14, 160.10 (C₉), 163.94, 196.55.

4-(4-Bromophenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydroquinazolin-5(1H)-one(4f)

Compound 4f was separated as yellow crystals with yield: 88%, mp 303-305°C. (Lit.[25-27] mp >300 °C) IR (KBr, cm⁻¹): 3320, 3258 (2 NH), 3075 (C-H, Ar-H), 1695 (C=O), 1620 (C=Aliphatic), 1595 (C=Aromatic), 1175 (C=S), 646 (=C-Br). ¹H-NMR (DMSO-d₆): 0.98 (s, 3H, CH₃), 1.01 (s, 3H, CH₃), 2.10 (s, 2H, CH₂), 2.27 (s, 2H, CH₂), 5.29 (s, 1H, CH), 6.73-7.85 (m, 5H, NH, ArH), 10.00 (s, 1H, NH). ¹³C-NMR (DMSO-d₆, 400MHz) δ ppm: 28.21, 28.21, 32.33, 42.51, 50.77, 64.52, 101.43, 128.43, 130.97, 131.44, 132.79, 132.79, 135.56, 184.35, 198.31.

4-(4-Chlorophenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydroquinazolin-5(1H)-one(4g):

Compound 4g was separated as yellow crystals with Yield: 76%, mp 285-287°C. (Lit.[17] mp 288-290 °C) IR (KBr, cm⁻¹): 3335, 3265 (2 NH), 3068 (C-H,Ar-H), 1690 (C=O) ,1618 (C=Aliphatic), 1598 (C=C Aromatic), 1228 (C=S), 737 (=C-Br). ¹H-NMR (DMSO-d₆): 0.98 (s, 3H, CH₃), 1.01 (s, 3H, CH₃), 2.11 (s, 2H, CH₂), 2.26 (s, 2H, CH₂), 5.28 (s, 1H, CH), 7.09-7.95 (m, 5H, NH, ArH), 10.0 (s, 1H, NH). ¹³C-NMR (DMSO-d₆, 400MHz) δ ppm: 28.07, 28.07, 29.15,

32.3, 50.21, 51.93, 101.41, 128.42, 130.98, 131.42, 131.42, 132.7, 132.77, 135.59, 184.31, 198.30.

4-(Benzo[d][1,3]dioxol-4-yl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydroquinazolin-5(1H)-one(4h)

Compound 4h was separated as brown crystals with yield: 76%, mp 228-230°C. IR (KBr, cm^{-1}): 3310, 3245 (2 NH), 3082 (C-H, Ar-H), 1687 (C=O), 1621 (C=C-Aliphatic), 1601 (C=C-Aromatic), 1230 (C=S), Asym.1330, Sym.1240 (C-O-C). $^1\text{H-NMR}$ (DMSO- d_6): 0.91 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.06 (s, 2H, CH_2), 2.10 (s, 2H, CH_2), 5.41 (s, 1H, CH), 5.97 (s, 2H, OCH_2O), 6.66-7.32 (m, 4H, NH, Ar-H), 9.91 (s, 1H, NH) $^{13}\text{C-NMR}$ (DMSO- d_6), 400 MHz) δ ppm: 28.32, 28.31, 32.21, 32.34, 46.43, 101.11, 52.15, 106.99, 107.90, 109.25, 145.44, 148.62, 158.12, 160.25, 163.33, 164.11, 191.10.

4-(2,3-Dimethoxyphenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydroquinazolin-5(1H)-one(4i)

Compound 4i was separated as brown crystals with Yield: 79%, mp 223-225°C. IR (KBr, cm^{-1}): 3318, 3256 (2N-H), 3078 (C-H, ArH), 1698 (C=O), 1615 (C=C Aliphatic), 1600 (C=C Aromatic), 1235 (C=S), Asym.1328, Sym.1238 C-O-C). $^1\text{H-NMR}$ (DMSO- d_6): 0.94 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 2.1 (s, 2H, CH_2), 2.28 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.27 (s, 1H, CH), 7.13-7.40 (m, 4H, NH, ArH), 10.19 (s, 1H, NH). $^{13}\text{C-NMR}$ (DMSO- d_6) 400 MHz, δ ppm 28.20, 32.25, 32.54, 42.50, 50.76, 56.54, 62.41, 101.42, 118.81, 119.37, 124.85, 129.73, 152.59, 53.36, 163.36, 175.97, 190.43.

7,7-Dimethyl-4-(4-nitrophenyl)-2-thioxo-2,3,4,6,7,8-hexahydroquinazolin-5(1H)-one(4j)

Compound 4j was separated as yellow crystals with Yield: 77%, mp 283-285°C. (Lit. [17] mp 288-290 °C). IR (KBr, cm^{-1}): 3338, 3195 (2N-H), 3087 (C-H, Ar-H), 1700 (C=O), 1613 (C=C Aliphatic), 1595 (C=C

Aromatic), 1231 (C=S). $^1\text{H-NMR}$ (DMSO- d_6 , 400MHz.): 0.9 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 2.11 (s, 2H, CH_2), 2.26 (s, 2H, CH_2), 5.29 (s, 1H, CH), 7.38.43 (m, 5H, NH, ArH), 10.17 (s, 1H, NH). $^{13}\text{C-NMR}$ (DMSO- d_6), 400 MHz) δ ppm: 29.03, 29.03, 32.34, 32.34, 42.52, 50.37, 113.82, 124.75, 124.75, 127.22, 129.69, 131.12, 131.12, 146.24, 184.38, 192.54.

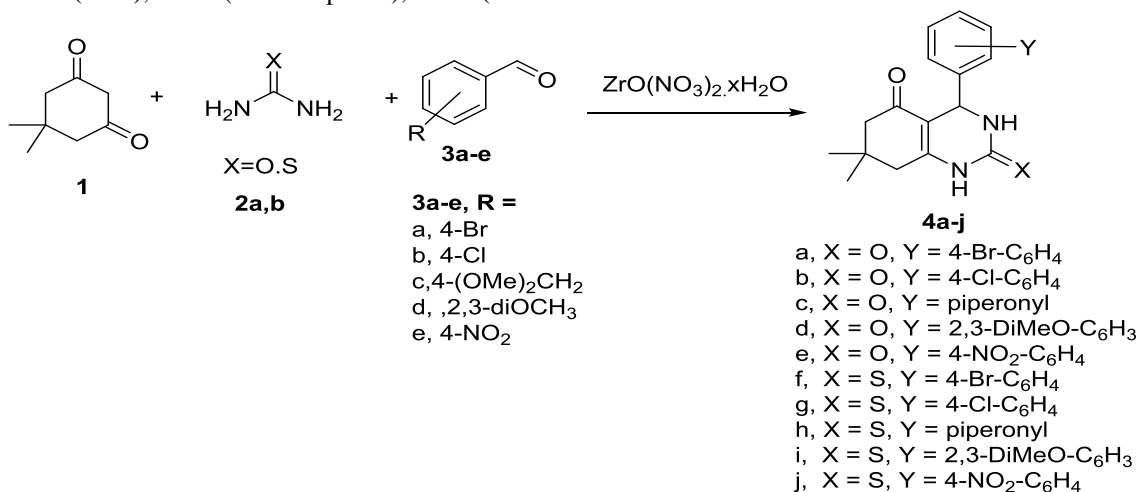
3. Results and Discussion

A cyclic diketone (Dimedone, 1) is reacted with urea or thiourea (2a,b) and benzaldehyde derivatives 3a-e in multicomponent reaction technique in the presence a catalytic amount of zirconium oxy nitrate hydrate in ethanol. This mixture was sonicated for 0.5h to afford tetrahydroquinazolin-2,5(1H,3H)-dione derivatives 4a-j in excellent yield (Scheme 1). The structures of new compounds 4a-j were elucidated upon elemental and spectroscopic analyses (cf. Experimental).

FT-I.R spectrum was characterized by absorptions at 3195-3338 cm^{-1} (NH). 1687-1700 (C=O and C=S), 1175-1235 cm^{-1} (C=C Aliphatic), 1613-1621 cm^{-1} and 1595-1601 cm^{-1} (C=C Aromatic).

$^1\text{H NMR}$ spectra in (DMSO- d_6) revealed two singlet peaks at 0.90-1.11 ppm due to CH_3 . Also, a two singlet peaks 2.06-2.28 ppm of 2 CH_2 , CH at appeared at 5.26-5.29 ppm and aromatic protons at δ 6.66-8.43 ppm as multiple bands. Finally, singlet peak at δ 9.45-9.61 ppm for NH (Figures 1,2).

The mechanism of Biginelli reaction is depicted in Scheme 2, it is a series of bimolecular reactions leading to the desired dihydropyrimidinone. Aryl aldehyde derivatives are reacted urea or thiourea to afford intermediate carbenium ion. The nucleophilic addition of urea gives the intermediate [A], which quickly dehydrates to give the desired product 4a-j (Scheme 2).



Scheme 1: synthesis of compounds 4a-j

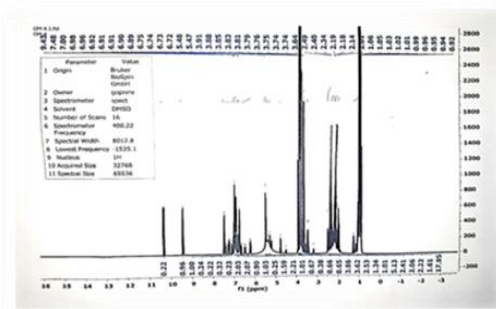
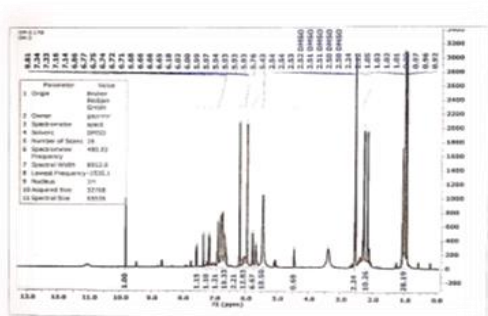


Figure 1: $^1\text{H-NMR}$ for compound (4a) and compound (4d)

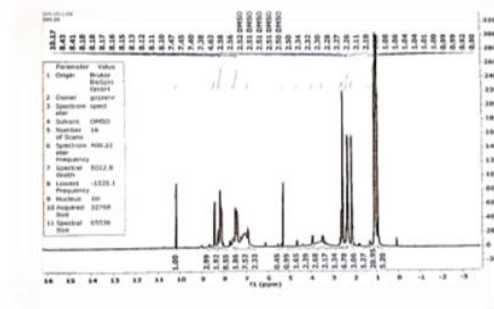
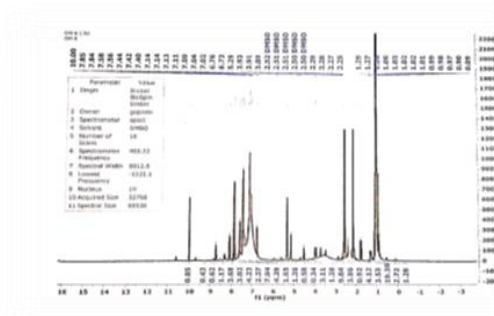
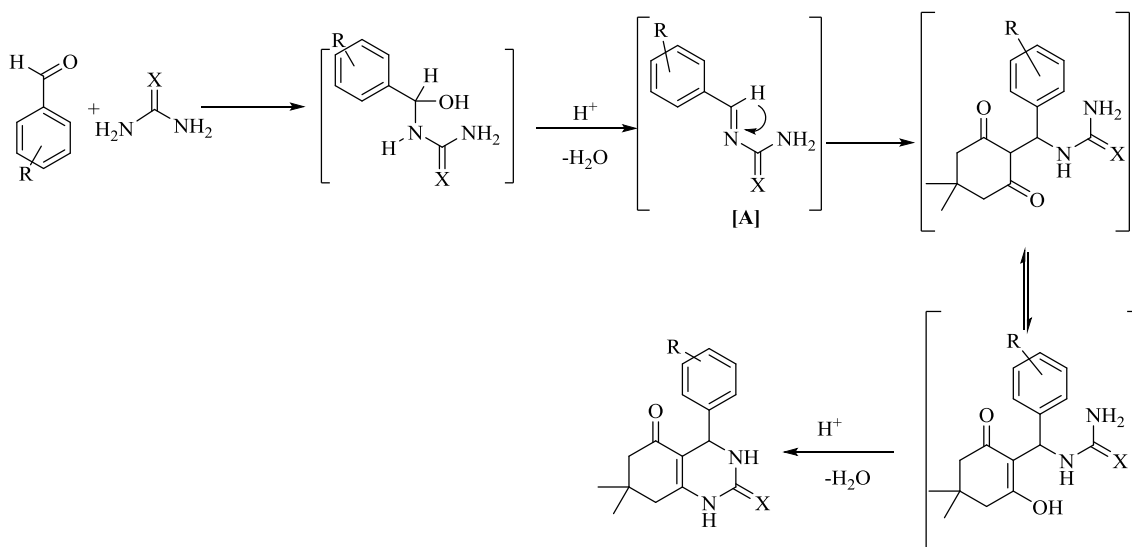


Figure 2: $^1\text{H-NMR}$ for compound (4e) and compound (4f)



Scheme 2

4. Conclusion

A new method of green chemistry of Beginelli condensation as under ultrasound using the three-component reaction of dimedone with urea (or thiourea) and substituted benzaldehyde in the presence of zirconium oxy nitrate hydrate as a new catalyst. The reaction is clean and rapid and affords the products in high yields.

5. Acknowledgment

The authors sincerely thank to Biochemistry department, College of Medicine, Mosul University

and Chemistry department, College of Science, University of Mosul for their support during this work.

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