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An efficient one-pot synthesis of octahydroquinazolinone derivatives using catalytic amount of H_2SO_4 in water

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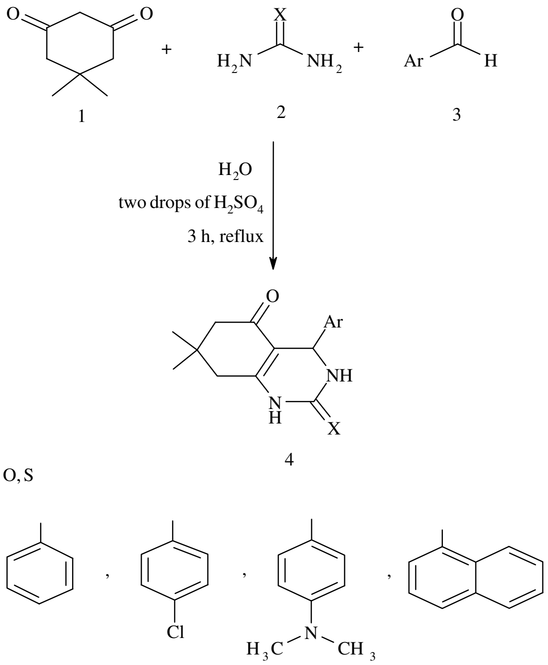
Abstract—In this investigation, a practical green chemistry procedure for synthesis of octahydroquinazolinone according to the Biginelli reaction using 5,5-dimethyl-1,3-cyclohexanedione, urea or thiourea, and appropriate aromatic aldehydes in the presence of two drops of concentrated H_2SO_4 as a catalyst is described in water. This methodology is of interest due to the use of water as a solvent without use of any organic solvent and toxic metals as catalyst, thus minimizing the cost, the operational hazards, and environmental pollution. Also this modified route provides much higher yields and simple work-up procedure of products.

Octahydroquinazolinone derivatives have attracted considerable attention since they exhibit potent antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*,[1] and calcium antagonist activity.[2,3]

Several methods have been developed for the preparation of quinazolinone derivatives. These routes usually involved reaction of aldehydes with $SOCl_2$ and pyridine, then with 2-aminobenzylamine in a refluxing solvent such as benzene or xylene with azeotropic water removal,[4] refluxing in ethanol/acetic acid mixtures[5] and by reaction in alkali media, but all have resorted to harsh condition such as low yield, use of expensive and hazardous chemical material with side reactions. More recently, the Biginelli reaction has been employed for the synthesis of octahydroquinazolinones in absolute ethanol but with low yields of products (19–69%).[2] In general, Biginelli reactions are simple one-pot procedures which have been employed for the synthesis of dihydropyrimidinones using low-yielding condensations of β-dicarbonyl compounds with aldehydes and urea, in the presence of Lewis acids, such as $Mn(OAc)_3$, LiBr, VCl_3, $La(OTf)_3$, $ZrCl_4$, and $InBr_3$, as a catalyst.[6–14]

However, many of these reagents or catalysts are expensive, harmful, and difficult to handle especially on a large scale (Scheme 1).



Scheme 1.

In view of the above observation and as part of our program that involves the synthesis of heterocyclic compounds,[15–17] we now wish to report a simple and an efficient route according to the Biginelli reaction for the synthesis of octahydroquinazolinone derivatives using urea or thiourea, dimedone, and an appropriate

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Keywords: Octahydroquinazolinones; Dimedone; Biginelli reaction.

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Table 1.

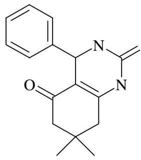
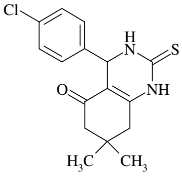
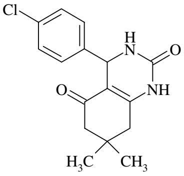
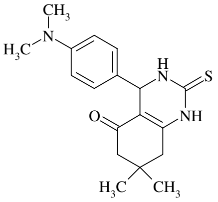
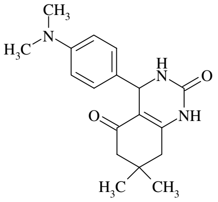
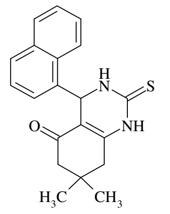
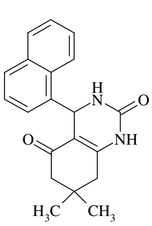
Compound	Structure	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)	Yield (%)	mp (°C)
4a		0.97 (3H, s, CH_3), 1.09 (3H, s, CH_3), 2.16 and 2.22 (2H, AB q, J = 16.3 Hz, CH_2), 2.46 (2H, s, CH_2), 4.75 (1H, s, CH), 7.08–7.30 (5H, m, arom), 7.26 (2H, broad band, NH)	27.32 and 29.23 (2CH_3), 31.84 (C), 32.16 (CH_2), 40.88 (CH_2), 50.77 (CH), 115.66 (C^{sp2}), 126.32 (C^{ortho}), 128.00 (C^{meta}), 128.37 (C^{para}), 128.80 (C), 144.12 (C^{sp2}), 162.29 (C=S), 196.32 (C=O)	98	160–162
4b		0.97 (3H, s, CH_3), 1.09 (3H, s, CH_3), 2.15 and 2.22 (2H, AB q, J = 16.3 Hz, CH_2), 2.46 (2H, s, CH_2), 4.70 (1H, s, CH), 7.16–7.23 (4H, m, arom), 7.28 (2H, broad band, NH)	27.28 and 29.22 (2CH_3), 31.47 (C), 32.15 (CH_2), 40.84 (CH_2), 50.71 (CH), 115.24 (C^{sp2}), 128.16 (C^{ortho}), 129.77 (C^{meta}), 129.73 (C), 131.98 (C^{ipso}), 142.75 (C^{sp2}), 162.43 (C=S), 196.22 (C=O)	93	219–221
4c		0.96 (3H, s, CH_3), 1.07 (3H, s, CH_3), 2.13 and 2.20 (2H, AB q, J = 16.3 Hz, CH_2), 2.46 (2H, s, CH_2), 4.69 (1H, s, CH), 7.14-7.22 (4H, m, arom), 7.25 (2H, broad band, NH)	27.26 and 29.22 (2CH_3), 31.47 (C), 32.14 (CH_2), 40.82 (CH_2), 50.71 (CH), 115.19 (C^{sp2}), 128.13 (C^{ortho}), 129.78 (C^{meta}), 129.80 (C), 131.93 (C^{ipso}), 142.79 (C^{sp2}), 162.49 (C=O), 196.24 (C=O)	95	>250
4d		0.99 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.15 and 2.20 (2H, AB q, J = 16.2 Hz, CH_2), 2.44 (2H, s, CH_2), 2.84 (6H, s, 2CH_3), 4.65 (1H, s, CH), 6.58–7.14 (4H, m, arom), 7.27 (2H, broad band, NH)	27.45 and 29.26 (2CH_3), 30.66 (C), 32.16 (CH_2), 40.69 (CH_2), 40.87 (2CH_3), 50.84 (CH), 112.49 (C^{ortho}), 115.99 (C^{sp2}), 128.94 (C^{meta}), 128.96 (C^{ipso}), 132.73 (C), 148.98 (C^{sp2}), 161.85 (C=S), 196.40 (C=O)	94	212–214
4e		0.99 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.15 and 2.20 (2H, AB q, J = 16.3 Hz, CH_2), 2.45 (2H, s, CH_2), 2.85 (6H, s, 2CH_3), 4.65 (1H, s, CH), 6.59–7.14 (4H, m, arom), 7.27 (2H, broad band, NH)	27.46 and 29.26 (2CH_3), 30.95 (C), 32.15 (CH_2), 40.69 (CH_2), 40.88 (2CH_3), 50.84 (CH), 112.51 (C^{ortho}), 115.99 (C^{sp2}), 128.94 (C^{meta}), 128.96 (C^{ipso}), 132.75 (C), 148.97 (C^{sp2}), 161.83 (C=O), 196.38 (C=O)	95	223–225
4f		0.96 (3H, s, CH_3), 1.11(3H, s, CH_3), 2.11 and 2.20 (2H, AB q, J = 16.3 Hz, CH_2), 2.52 (2H, s, CH_2), 5.54 (1H, s, CH), 7.21–7.77 (7H, m, arom), 8.84 (2H, broad band, NH)	27.31 and 29.25 (2CH_3), 32.10 (C), 32.15 (CH_2), 40.63 (CH_2), 50.62 (CH), 116.88 (C^{sp2}), 124.77 (CH), 125.13 (C), 125.54 (CH), 125.81 (CH), 127.30 (CH), 127.32 (CH), 127.35 (CH), 128.06 (CH), 131.67 (C), 133.55 (C), 143.55 (C^{sp2}), 161.99 (C=S), 196.45 (C=O)	94	225–227

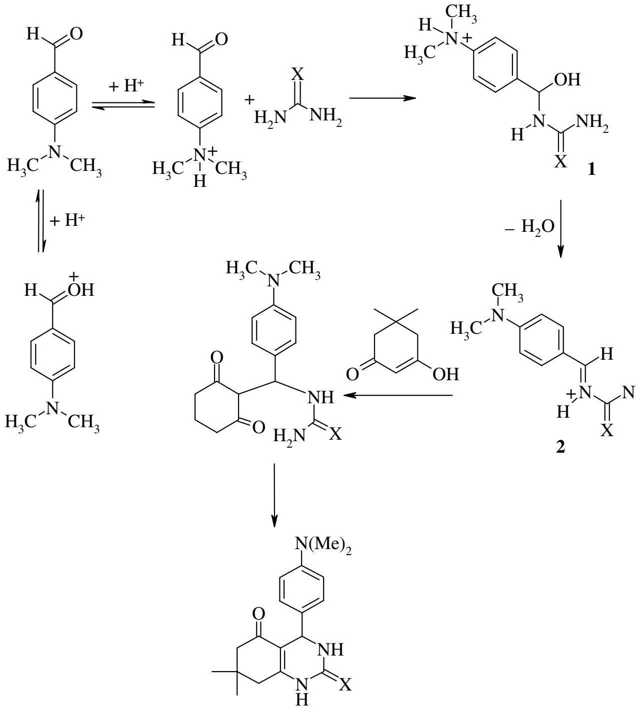
Table 1 (*continued*)

Compound	structure	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)	Yield (%)	mp (°C)
4g		0.82 (3H, s, CH_3), 0.95(3H, s, CH_3), 2.01 and 2.18 (2H, AB q, J = 16.3 Hz, CH_2), 2.55 (2H, s, CH_2), 5.55 (1H, s, CH), 7.21–9.27 (7H, m, arom), 9.04 (2H, broad band, NH)	26.72 and 29.65 ($2CH_3$), 32.27 (C), 32.33 (CH_2), 40.06 (CH_2), 50.79 (CH), 114.38 (C^{sp2}), 124.83 (CH), 125.36 (C), 125.62 (CH), 126.87 (CH), 126.98 (CH), 127.94 (CH), 128.54 (CH), 129.06 (CH), 130.55 (C), 133.77 (C), 149.51 (C^{sp2}), 162.51 (C=O), 196.16 (C=O)	90	>250

aromatic aldehyde in excellent yields (90–98%) in water as a solvent in the presence of two drops of concentrated H_2SO_4 without use of any aromatic solvent and in the absence of any salt of heavy metals.

As a representative example, the reaction of benzaldehyde (10 mmol), 5,5-dimethyl-1,3-cyclohexanedione (10 mmol), and thiourea (15 mmol) in the presence of two drops of concentrated H_2SO_4 was found to be complete within 3 h, as indicated by TLC, in refluxing H_2O (50 mL) and 4-phenyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **4a** in 98% yield precipitated from the reaction mixture on cooling to room temperature. Thus, a series of octahydroquinazolinones and octahydrothioquinazolinones were prepared in excellent yields as summarized in Table 1. The results presented in Table 1 indicate the scope and generality of this method, which is efficient, not only for urea, but also for thiourea. An important feature of this method is that the excellent electron-releasing group such as $(CH_3)_2NH$ at para position of benzaldehyde and withdrawing group give excellent yields in high purity.

It is pertinent to note that a literature search showed that, three compounds **4a–c** have previously been reported, while compounds **4d–g** were unknown. All compounds were characterized on the basis of their spectroscopic data such as ^{1}H NMR, ^{13}C NMR, and IR spectra and physical data. All these data are consistent with the proposed structures (Table 1). It is worthy to mention that in condensation of an aldehyde with urea or thiourea, it is necessary that the aldehyde must be active whereas, *p*-dimethyl aminobenzaldehyde containing an excellent electron-releasing group at para position has reacted with urea or thiourea as well as other aromatic aldehydes to form corresponding octahydroquinazolinones via intermediates **1** and **2**.[18–20] The reason for this behavior is not clear to us, but we think the amino group was protonated first in the reaction mixture and the resulted ammonium group might play an important role as an electron-withdrawing group in this reaction (Scheme 2).



Scheme 2.

In conclusion, we showed that the condensation of aromatic aldehydes with urea or thiourea and dimedone in the presence of catalytic amount of concentrated H_2SO_4 efficiently occurred in water to provide a convenient and rapid synthesis of octahydroquinazolinones and octahydrothioquinazolinones **4a–g** in excellent yields.[21] Water was chosen as a solvent due to some advantages, including its low cost, no inflammability, and, the most important, low toxicity of such a solvent.

Acknowledgment

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21. Typical procedure for the preparation of 4-phenyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **4a**. A mixture of dimedone (1.40 g, 10 mmol), benzaldehyde (1.01 g, 10 mmol) and thiourea (1.12 g, 15 mmol) in water (50 mL) was heated under reflux in the presence of two drops of concentrated H_2SO_4 for 3 h. After completion of the reaction, as monitored by TLC, the crude product, which precipitated on cooling, was filtered and washed with H_2O and recrystallized from ethanol. Yield: 98%, 2.80 g, mp: 160–162 °C; IR (KBr) (ν_{max}, cm^{-1}): 3252 (NH), 1709 (C=O), 1680 (C=S). 4-(4-Chlorophenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **4b**. Yield 93%, 3.00 g, mp: 219–221 °C; IR (KBr) (ν_{max}, cm^{-1}): 3325 (NH), 1709 (C=O), 1660 (C=S). 4-(4-Chlorophenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2, 5-dione **4c**. Yield 95%, 2.90 g, mp > 250 °C; IR (KBr) (ν_{max}, cm^{-1}): 3324 (NH), 1709 (C=O), 1685 (C=O). 4-(4-(Dimethylamino)phenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **4d**. Yield 94%, 3.10 g, mp: 212–214 °C; IR (KBr) (ν_{max}, cm^{-1}): 3325 (NH), 1705 (C=O), 1660 (C=S). 4-(4-(Dimethylamino)phenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione **4e**. Yield 95%, 2.98 g, mp: 223–225 °C; IR (KBr) (ν_{max}, cm^{-1}): 3325 (NH), 1709 (C=O), 1685 (C=O). 4-(Naphthalene-1-yl)-7,7-dimethyl-1,2,3,4,5, 6,7,8-octahydroquinazoline-2-thione **4f**. Yield 94%, 3.15 g, mp: 225–227 °C; IR (KBr) (ν_{max}, cm^{-1}): 3320 (NH), 1716 (C=O), 1691 (C=S). 4-(4-Naphthalene-1-yl)-7,7-dimethyl-1,2,3,4,5,6, 7,8-octahydroquinazoline-2, 5-dione **4g**. Yield 90%, 2.88 g, mp > 250 °C; IR (KBr) (ν_{max}, cm^{-1}): 3329 (NH), 1714 (C=O), 1690 (C=O).