



ORIGINAL ARTICLE

# Rapid and efficient one-pot synthesis of octahydroquinazolinone derivatives using lanthanum oxide under solvent-free condition



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## KEYWORDS

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**Abstract** A simple, efficient and cost-effective method for the synthesis of octahydroquinazolinone derivatives using dimedone, urea/thiourea and aromatic aldehydes using lanthanum oxide as a catalyst under solvent free condition in microwave irradiation is reported. The present method does not involve any hazardous organic solvents. This catalyst has promising features for the reaction response such as the shortest reaction time, excellent product yields, simple work-up procedure and purification of products by non-chromatographic methods.

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## 1. Introduction

Octahydroquinazolinone derivatives have attracted considerable attention in recent years, owing to their potential antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* (Yarim et al., 2002) and also as a calcium antagonist activity (Yarim et al., 2003). A number of these bioactive heterocycles also function as analgesic and anti-inflammatory agents (Nigam et al., 1990). The corresponding thiazolidine moiety also possesses antibacterial and antifungal activities (Ladani et al., 2009). In 1893, Italian

chemist Pietro Biginelli reported on the acid catalyzed cyclocondensation reaction of an aldehyde, ethylacetoacetate and urea, a procedure known as Biginelli reaction (Biginelli, 1893). More recently, the Biginelli reaction has been employed for the synthesis of octahydroquinazolinones, which used cyclic  $\beta$ -diketones instead of open chain dicarbonyl compounds (Hassani et al., 2006). Literature survey reveals that the synthesis of octahydroquinazolinone derivatives using Trimethylsilylchloride (TMSCl) (Kantevari et al., 2006), Nafion-H (Lin et al., 2007),  $\text{VO}_4$  (Reddy et al., 2009), conc.  $\text{H}_2\text{SO}_4$  (Hassani et al., 2006), conc. HCl (Ladani et al., 2009), ionic liquid (Niralwad et al., 2010) and silica sulfuric acid (Mobinikhaledi et al., 2010) as catalysts. However, many of these procedures suffer from one or more disadvantages such as harsh reaction conditions, prolonged time period, poor yields with formation of many side products and use of large quantity of volatile organic solvents. So, the development of a clean, high yielding and eco-friendly approach is still desirable.

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In recent years, the use of lanthanide(III) compounds as catalysts or promoters in organic synthesis has attracted great interest from chemists (Imamoto, 1994). Lanthanide additive or complexes can enhance the reactivity such as reduction (Nishino et al., 2002), carbon-carbon bond formation (Kobayashi, 1999), aldol condensation (Kobayashi et al., 1993), Fridel-Crafts acylation (Kawada et al., 1994), aza Diels-Alder reaction (Makioka et al., 1995), Michael addition reaction (Veldurthy et al., 2005) and have of broad applications.

As environmental consciousness increases in chemical research and industry, the challenge for a sustainable environment calls for clean procedures to avoid harmful organic solvents. It is well known that chemical synthesis can be dramatically promoted using microwave irradiation. Not only can it reduce chemical reaction times from hours to minutes or seconds but can also reduce the side reactions, increase the yields, and improve reproducibility compared with conventional methods (Kappe et al., 1999). Reactions in dry media or under solvent-free conditions are especially appealing, as they provide an opportunity to work with an open vessel, thus avoiding the risk of high internal pressure development and with the possibility of scaling-up the reactions to larger scale (Kappe, 2004). Under these conditions, the yields were significantly raised and the reaction time was shortened for synthesizing octahydroquinazolinone derivatives using easily separable solid catalyst. Herein, we wish to report a simple and efficient method for the synthesis of octahydroquinazolinone derivatives under solvent free conditions using lanthanide oxide as a catalyst.

## 2. Experimental

Benzaldehyde and substituted benzaldehydes (Aldrich chemicals) were used as received. Dimedone (AnalaR grade), urea/thiourea and lanthanum oxide were purchased from Merck and used as such. All melting points were measured in open capillaries and are uncorrected. IR spectra were recorded using an Avatar-330 FT-IR spectrophotometer using KBr pellets.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a BRUKER AVIII FT-NMR 500 MHz spectrometer in DMSO- $d_6$  using TMS an internal standard. Elemental analyses were carried out in Perkin Elmer 240 CHN elemental analyzer. Microwave LG MS-1947C AC - 230 V/50 Hz model was used.

## 3. General procedure for the synthesis of octahydroquinazolinone derivatives

A mixture of aromatic aldehydes (**1**) (10 mmol), dimedone (**2**) (10 mmol) and urea/thiourea (**3**) (15 mmol) with the catalysts (10 mol%) without solvent in a beaker (capacity 50 mL) placing the reaction mixture at the center of the microwave oven (480 W) and irradiation for a period of 10 s at a time. After every irradiation, the reaction vessel was removed from the microwave oven for a period of 10 s and stirred the reaction mixture. The completion of the reaction was checked by TLC (ethylacetate/hexane, 7:3). The total period of microwave irradiation was 35–80 s. The reaction mixture was then extracted with ethyl acetate and the catalyst was separated by the filtration. The organic layer then washed with water and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Organic solvent was evaporated under reduced pressure and solid compound was

crystallized from absolute ethanol to afford the pure corresponding octahydroquinazolinone derivatives (**4a–4r**) in excellent yields. The structure of the pure products was confirmed by FT-IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and elemental analysis.

## 4. Spectral data and elemental analysis for selected compounds

### 4.1. 4-Phenyl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazolinone-2,5-dione (entry **4a**)

IR (KBr)  $\text{cm}^{-1}$  = 3261 and 3178 (N–H str.), 1620 (C=C str.);  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 9.28 (s, 1H, H-1), 7.18 (s, 1H, H-3), 7.15–7.02 (m, 5H, Ar-H), 4.83 (s, 1H, H-4), 2.46 (d,  $J$  = 17 Hz, 1H, H-6), 2.34 (d,  $J$  = 17 Hz, 1H, H-6), 2.17 (d,  $J$  = 16 Hz, 1H, H-8), 2.01 (d,  $J$  = 16 Hz, 1H, H-8), 1.07 (s, 3H  $\text{CH}_3$  at C-7), 0.87 (s, 3H,  $\text{CH}_3$  at C-7);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 194.8 (CO), 149.8 (C-2 and C-9), 147.61 (C-1'), 128.1–125.9 (aromatic carbons), 111.95 (C-10), 50.8 (C-4), 40.53 (C-6), 33.31 (C-7), 32.6 (C-8), 29.6 ( $\text{CH}_3$  at C-7), 26.9 ( $\text{CH}_3$  with at C-7). Anal. Calcd for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2$ : C, 71.11; H, 6.66; N, 10.37. Found: C, 71.20; H, 6.59; N, 10.31.

### 4.2. 4-(4-Methoxyphenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazolinone-2,5-dione (entry **4e**)

IR (KBr)  $\text{cm}^{-1}$  = 3276 and 3025 (N–H str.), 1638 (C=C str.);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 9.23 (s, 1H, H-1), 7.07 (s, 1H, H-3), 7.06 (d,  $J$  = 6.5 Hz, 2H, Ar-H), 6.72 (d,  $J$  = 7 Hz, 2H, Ar-H), 4.76 (s, 1H, H-4), 3.67 (s, 3H,  $\text{OCH}_3$ ), 2.44 (d,  $J$  = 17 Hz, 1H, H-6), 2.32 (d,  $J$  = 17 Hz, 1H, H-6), 2.16 (d,  $J$  = 16 Hz, 1H, H-8), 1.99 (d,  $J$  = 16.5 Hz, 1H, H-8), 1.02 (s, 3H,  $\text{CH}_3$  at C-7), 0.89 (s, 3H,  $\text{CH}_3$  at C-7);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  = 194.81 (CO), 157.56 ( $\text{OCH}_3$  at C-4'), 149.5 (C-2 and C-9), 140.0 (C-1'), 128.9 (C-2' and C-6'), 113.4 (C-3' and C-5'), 112.2 (C-10), 55.3 ( $\text{OCH}_3$  at C-4'), 50.77 (C-4), 40.53 (C-6), 32.58 (C-8), 32.35 (C-7), 29.6 ( $\text{CH}_3$  at C-7), 26.98 ( $\text{CH}_3$  at C-7). Anal. Calcd for  $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_3$ : C, 68.0; H, 6.66; N, 9.33. Found: C, 67.84; H, 6.73; N, 9.30.

### 4.3. 4-Phenyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolinone-2-thione (entry **4j**)

IR (KBr)  $\text{cm}^{-1}$  = 3231 and 3115 (N–H str.), 1651 (C=C str.), 1329 and 1285 (C=S str.);  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 10.5 (s, 1H, H-1), 9.67 (d,  $J$  = 1 Hz, 1H, H-3), 7.35–7.20 (m, 5H, Ar-H), 5.19 (d,  $J$  = 3.5 Hz, 1H, H-4), 2.50 (d,  $J$  = 17 Hz, 1H, H-6), 2.40 (d,  $J$  = 17 Hz, 1H, H-6), 2.36 (d,  $J$  = 16 Hz, 1H, H-8), 2.25 (d,  $J$  = 16 Hz, 1H, H-8), 1.03 (s, 3H,  $\text{CH}_3$  at C-7), 0.89 (s, 3H,  $\text{CH}_3$  at C-7);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 194.0 (C=O), 175.13 (C-2), 149.1 (C-9), 143.83 (C-1'), 129.09–126.64 (aromatic carbons), 108.6 (C-10), 52.66 (C-4), 50.32 (C-6), 32.7 (C-7), 31.70 (C-8), 29.25 ( $\text{CH}_3$  at C-7), 27.24 ( $\text{CH}_3$  at C-7). Anal. Calcd for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3$ : C, 67.13; H, 6.29; N, 9.79. Found: C, 67.17; H, 6.31; N, 9.77.

### 4.4. 4-(4-Methoxyphenyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolinone-2-thione (entry **4n**)

IR (KBr)  $\text{cm}^{-1}$  = 3265 and 2953 (N–H str.), 1664 (C=C str.), 1362 and 1258 (C=S str.);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 10.3 (s,

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