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ORIGINAL ARTICLE

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

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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.

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 thiazolodine 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 β-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), $VOSO_4$ (Reddy et al., 2009), conc. H_2SO_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}H and ^{13}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 Na_2SO_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}H NMR, ^{13}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-octahydroquinazoline-2,5-dione (entry **4a**)*

IR (KBr) cm^{-1} = 3261 and 3178 (N–H str.), 1620 (C=C str.); ^{1}H NMR (DMSO-d_6): δ = 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 CH_3 at C-7), 0.87 (s, 3H, CH_3 at C-7); ^{13}C NMR (DMSO-d_6): δ = 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 (*C*H_3 at C-7), 26.9 (*C*H_3 with at C-7). Anal. Calcd for $C_{16}H_{18}N_2O_2$: 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-octahydroquinazoline-2,5-dione (entry **4e**)*

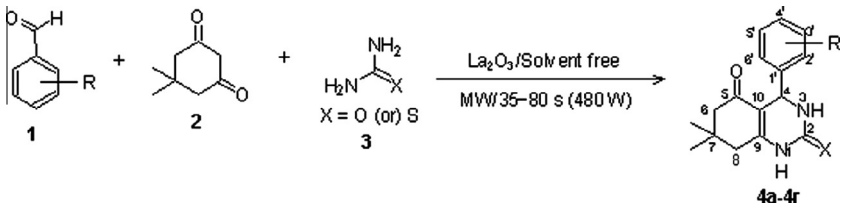
IR (KBr) cm^{-1} = 3276 and 3025 (N–H str.), 1638 (C=C str.); ^{1}H NMR (DMSO-d_6) δ = 9.23 (s, 1H, H-1), 7.07 (s, 1H, H-3), 7.06 (d, J = 6.5 Hz, 2H, Ar-H), 6.72 (d, J = 7 Hz, 2H, Ar-H), 4.76 (s, 1H, H-4), 3.67 (s, 3H, OCH_3), 2.44 (d, J = 17 Hz, 1H, H-6), 2.32 (d, J = 17 Hz, 1H, H-6), 2.16 (d, J = 16 Hz, 1H, H-8), 1.99 (d, J = 16.5 Hz, 1H, H-8), 1.02 (s, 3H, CH_3 at C-7), 0.89 (s, 3H, CH_3 at C-7); ^{13}C NMR (DMSO-d_6) δ = 194.81 (CO), 157.56 (O*C*H_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 (O*C*H_3 at C-4′), 50.77 (C-4), 40.53 (C-6), 32.58 (C-8), 32.35 (C-7), 29.6 (*C*H_3 at C-7), 26.98 (*C*H_3 at C-7). Anal. Calcd for $C_{17}H_{20}N_2O_3$: 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-octahydroquinazoline-2-thione (entry **4j**)*

IR (KBr) cm^{-1} = 3231 and 3115 (N–H str.), 1651 (C=C str.), 1329 and 1285 (C=S str.); ^{1}H NMR (DMSO-d_6): δ = 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, CH_3 at C-7), 0.89 (s, 3H, CH_3 at C-7); ^{13}C NMR (DMSO-d_6): δ = 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 (*C*H_3 at C-7), 27.24 (*C*H_3 at C-7). Anal. Calcd for $C_{16}H_{18}N_2OS$: 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-octahydroquinazoline-2-thione (entry **4n**)*

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



Scheme 1 Synthesis of octahydroquinazoline derivatives via Biginelli reaction under microwave irradiation.

Table 1 Synthesis of octahydroquinazolinone derivatives catalyzed by lanthanum oxide under microwave-irradiation and solvent-free condition.

Entry	R	X	Time[a] (s)	Product	Yield[b] (%)	M.p. (°C)	
						Found	Reported
1	C_6H_5	O	35	**4a**	96	292–295	290–291 (Yarim et al., 2003)
2	3-(Cl)–C_6H_4	O	36	**4b**	92	279–281	282–283 (Yarim et al., 2003)
3	3-(NO_2)–C_6H_4	O	33	**4c**	98	297–299	300–301 (Kantevari et al., 2006)
4	4-(Cl)–C_6H_4	O	32	**4d**	96	318–320	> 300 (Kantevari et al., 2006)
5	4-(CH_3O)–C_6H_4	O	62	**4e**	92	274–276	–
6	4-(NO_2)–C_6H_4	O	32	**4f**	96	302–304	304–305 (Kantevari et al., 2006)
7	4-(F)–C_6H_4	O	35	**4g**	93	138–140	134–136 (Lin et al., 2007)
8	C_6H_5–CH=CH	O	38	**4h**	94	150–152	–
9	3,4,5-(CH_3O)–C_6H_2	O	68	**4i**	91	140–142	139–140 (Kantevari et al., 2006)
10	C_6H_5	S	47	**4j**	93	286–288	284–285 (Kantevari et al., 2006)
11	3-(Cl)–C_6H_4	S	49	**4k**	90	272–274	275–276 (Yarim et al., 2003)
12	3-(NO_2)–C_6H_4	S	42	**4l**	97	281–283	–
13	4-(Cl)–C_6H_4	S	44	**4m**	92	288–290	–
14	4-(CH_3O)–C_6H_4	S	70	**4n**	90	278–280	272–275 (Kantevari et al., 2006)
15	4-(NO_2)–C_6H_4	S	42	**4o**	94	288–290	–
16	4-(F)–C_6H_4	S	46	**4p**	92	260–262	–
17	C_6H_5–CH=CH	S	43	**4q**	91	172–174	–
18	3,4,5-(CH_3O)–C_6H_2	S	80	**4r**	90	134–136	–

[a] Reaction was continued until the TLC shown the starting materials had disappeared.
[b] Isolated yield.

Table 2 Comparison of results using La_2O_3 with results obtained by other workers for the synthesis of **4a**.

Entry	Catalyst	Condition	Time (h)	Yield (%)	Reference
1	Nafion-H	EtOH/reflux	10	70	(Lin et al., 2007)
2	Silica sulfuric acid	EtOH/reflux	4	90	(Mobinikhaledi et al., 2010)
3	Con. H_2SO_4	H_2O/reflux	3	95	(Hassani et al., 2006)
4	TMSCl	CH_3CN/DMF reflux	1.5	95	(Kantevari et al., 2006)
5	Ionic liquid	[tbmim]Cl_2/$AlCl_3$ ultrasound assistance	40 min	91	(Niralwad et al., 2010
6	La_2O_3	MW/solvent free at 480 W	35 s	96	Present work

Table 3 Reusability of the catalyst for synthesis of **4a** under microwave irradiation.

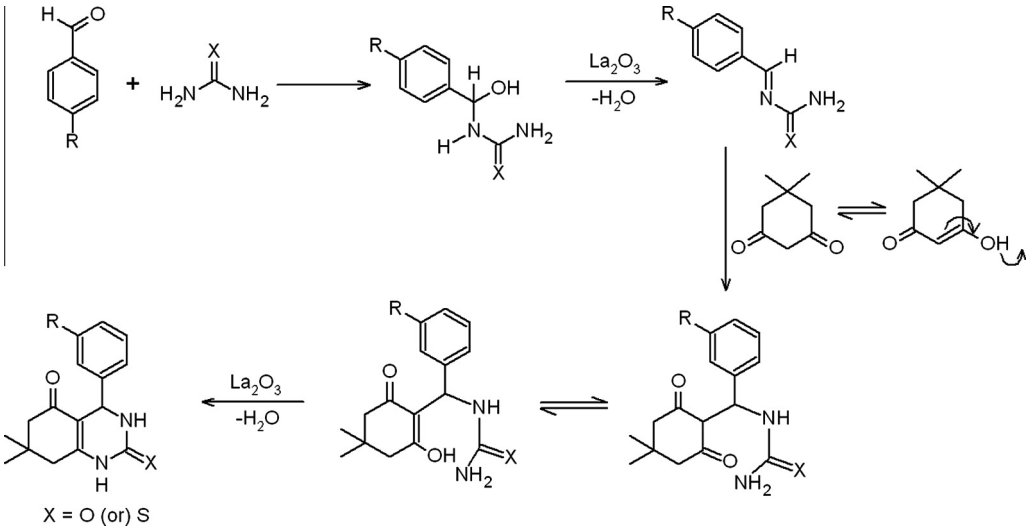
Run	1	2	3	4	5
Yield (%)[a]	96	94	91	87	84

[a] Isolated yield.

1H, H-1), 9.4 (s, 1H, H-3), 7.20 (d, J = 6 Hz, 2H, Ar-H), 6.79 (d, J = 6 Hz, 2H, Ar-H), 5.15 (s, 1H, H-4), 3.74 (s, 3H, OCH_3), 2.40 (d, J = 17 Hz, 1H, H-6), 2.32 (d, J = 17 Hz, 1H, H-6), 2.15 (d, J = 16 Hz, 1H, H-8), 2.02 (d, J = 16 Hz, 1H, H-8), 1.09 (s, 3H, CH_3 at C-7), 0.97 (s, 3H, CH_3 at C-7); ^{13}C NMR (DMSO-d_6) δ = 194.0 (C=O), 174.9 (C-2), 159.2 (OCH_3 at C-4′), 148.9 (C-9), 144.6 (C-1′), 136.2 (C-2′ and C-6′), 128.3 (C-3′ and C-6′), 114.4 (C-10), 55.6 (OCH_3 at C-4′), 50.9 (C-4), 40.4 (C-6), 32.9 (C-8), 32.4 (C-7), 29.8 (CH_3 at C-7), 27.1 (CH_3 at C-7). Anal. Calcd for $C_{17}H_{20}N_2O_3$S: C, 61.44; H, 6.02; N, 8.43. Found: C, 61.48; H, 6.09; N, 8.51.

5. Results and discussion

Initially, in order to optimize the reaction parameters, we investigated the reaction of benzaldehyde with dimedone in the presence of La_2O_3 under different conditions. We found that the best result was obtained with benzaldehyde (10 mmol),



Scheme 2 Plausible mechanism for the formation of octahydroquinazolinone.

dimedone (10 mmol) urea/thiourea (15 mmol) and La_2O_3 (10 mol%) at 480 W (Scheme 1). Whereas, the yield of the product reduced by decreasing the amount of the catalyst. When the same reaction was performed in the absence of the catalyst, the corresponding product was obtained in only 28% yield.

Encouraged by this result, a series of aldehydes were examined under optimized conditions and the results are shown in Table 1. It is seen that several aromatic aldehydes carrying either electron-releasing or withdrawing substituents in *meta* and *para*-positions afford high yield of the product. Another important feature of this procedure is the survival of variety of functional groups under this reaction conditions. Here, we have found that the reaction of aromatic aldehydes having electron-withdrawing groups was rapid as compared to the reaction of aldehydes having electron donating groups. It was observed that the reaction of aromatic aldehydes with urea is very fast as compared to thiourea. Table 2 compares the efficiency of present work with the efficiency of other methods in the synthesis of compound **4a**. It clearly indicates that this method is better than the previously reported methods for the synthesis of octahydroquinazolinone derivatives. The reusability of the catalyst was investigated, the obtained results show that the catalyst activity slightly decreases for each run (Table 3). We have not tried this method for aliphatic aldehydes.

On the basis of all our experimental results, together with literature reports, we have proposed the plausible mechanism for the formation of octahydroquinazolinone in the presence of La_2O_3 and shown in Scheme 2. The reaction is believed to proceed through the formation of an *N*-acyliminium ion intermediate from the urea or thiourea and aldehyde precursors in the presence of La_2O_3, the addition of β-cyclic ketone to the iminium ion and subsequent dehydration leading to the formation of octahydroquinazolinone.

6. Conclusion

In conclusion, lanthanum oxide is a readily available, inexpensive, and efficient catalyst for the synthesis of octahydroquinazolinone derivatives. Present methodology offers very attractive features such as reduced reaction times, higher yields, ease of product isolation, economic variability of the catalyst, when compared with conventional method as well as with other catalysts which will have wide scope in organic synthesis. This simple procedure and solvent free conditions combined with easy recovery and reuse of this catalyst make this method economically and environmentally benign process. We believe that this procedure is convenient, economic and ecofriendly for the synthesis of octahydroquinazolinone derivatives of biological and medicinal importance.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jscs.2011.11.014.

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