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One-pot multi-component synthesis of tetrahydroquinazolinones via Biginelli condensation using molecular iodine as a catalyst

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ABSTRACT

Tetrahydroquinazolinone derivatives were synthesized in moderate to high yields via one-pot three component Biginelli reaction of dimedone, urea or thiourea and corresponding aromatic aldehydes in the presence of molecular iodine as an efficient catalyst, in ethanol under reflux conditions. This protocol offers several advantages including good yields of products and easy experimental work-up procedure.

1. Introduction

Multi-component, one-pot synthesis has received considerable attention because of its wide range of applications in pharmaceutical chemistry for the creation of structural diversity and combinatorial libraries for drug discovery.In recent years, the Biginelli reaction has been employed for the synthesis of dihydropyrimidines and tetrahydroquinazolinones, which used cyclic β-diketones and open-chain dicarbonyl compounds [1-3]. These tetrahydroquinazolinone derivatives have been widely employed since they exhibit potent antibacterial activity against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa [4] and calcium antagonist activity [5,6].

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 [7], refluxing in ethanol/acetic acid mixture [8], refluxing in water/sulfuric acid [9], silica/sulfuric acid [10] and by reaction in alkali media [11]. However, many of these procedures suffer from one or more disadvantages such as high temperature reaction conditions, prolonged time period, poor yields, and use of hazardous and expensive catalysts. So, the development of a clean, high-yielding, and environmentally friendly approach is still desirable.

Because of global environmental concern and social sustainable development, green synthesis is a current hot topic [12].Molecular iodine as an inexpensive, nontoxic, readily available catalyst has been used successfully in the Biginelli reaction [13,14] affording the corresponding products in excellent yields with high selectivity [13-16]. The mild Lewis acidity associated with iodine enhanced its usage in organic synthesis to realize several organic transformations using stoichiometric levels to catalytic amounts. Owing to numerous advantages associated with this eco-friendly element, iodine has been explored as a powerful catalyst for various organic transformations [17,18]. As the tetrahydroquinazolinones are important biologically active compounds, which have profound medical applications, development of a reaction that uses catalytic amounts of mild toxic and readily available iodine should greatly contribute to the creation of environmentally benign processes.

In view of these observations and also due to our interest in the synthesis of heterocycles [19], we wish to report a convenient method for synthesis of tetrahydroquinazolinones using molecular iodine as an inexpensive, nontoxic and readily available catalyst.

2. Experimental

2.1. Instrumentation

The uncorrected melting points were determined on a Gallenkamp apparatus. Elemental analyses were obtained on a Carlo Erba 1106 CHN analyzer, while the IR spectra (potassium bromide) were recorded on a Shimadzu 470 spectrophotometer. The 400 MHz ^1H and 100 MHz ^{13}C NMR spectra were observed on a Bruker WM 400 instrument with TMS as the internal standard using dimethylsulfoxide-d_6 as solvent. The ^{13}C signals were assigned on the basis of DEPT 135/90 spectra. The mass spectra (70 eV, electron impact mode) were recorded on AMD 604 instrument.

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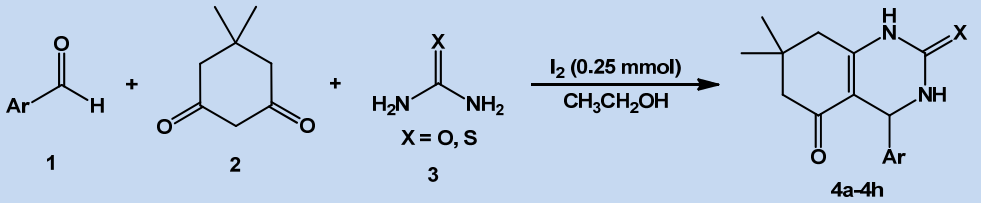
Table 1. Iodine catalyzed synthesis of tetrahydroquinazoline derivatives (THQZ) under optimized reaction conditions [a].



1 2 3 4a-4h

Entry	THQZ	Ar	X	Time (h)	Yield [b] (%)	M.p. (°C)	
						Measured	Reported
1	**4a**	C_6H_5	O	3	96	287-290	290-291 [5]
2	**4b**	C_6H_5	S	5	93	280-283	284-285 [22]
3	**4c**	4-ClC_6H_4	O	4	95	> 300	> 300 [5]
4	**4d**	4-ClC_6H_4	S	5	88	217-219	219-221 [22]
5	**4e**	4-HOC_6H_4	O	6	86	> 300	300-332 [22]
6	**4f**	4-$CH_3C_6H_4$	S	6	90	270-272	273-275 [22]
7	**4g**	4-$CH_3OC_6H_4$	O	3	93	240-242	241-243 [5]
8	**4h**	4-$CH_3OC_6H_4$	S	4	97	273-275	275-276 [23]

[a] The reaction was carried out using aldehyde (1.0 mmol), 5,5-dimethylcyclohexane-1,3-dione (2.0 mmol), urea or thiourea (2.0 mmol), and iodine (0.25 mmol) in refluxing EtOH.
[b] Isolated yields.

2.2. General procedure for the condensation reaction of 4a-4h

A 25 mL round-bottomed flask charged with aldehyde, **1**, (1.0 mmol), 5,5-dimethylcyclohexane-1,3-dione, **2**, (0.280 g, 2.0 mmol), urea or thiourea, **3**, (2.0 mmol), and iodine (0.064 g, 0.25 mmol) followed by few drops (5-6 drops) of ethanol. The mixture was then refluxed until the reaction was completed 3-6 h, monitored by TLC. The reaction mixture was treated with aqueous solution of sodium thiosulfate, extracted with ethyl acetate. The ethyl acetate layer was further washed with a dilute solution of sodium thiosulfate, followed by water and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left a residue, which on recrystallization from ethanol yielded a crystalline product. The obtained products **4a-h** were identified by comparison with authentic samples.

7,7-Dimethyl-4-phenyl-3,4,7,8-tetrahydroquinazoline-2,5(1H, 6H)-dione (**4a**): Color: White. Yield: 96%. M.p.: 287-290 °C. FT-IR (KBr, ν, cm^{-1}): 3259 (N-H), 1713 (C=O, C-5), 1647 (C=O, C-2). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 0.88 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.10 (q, 2H, CH_2-8), 2.38 (q, 2H, CH_2-6), 5.16 (d, 1H, *J* = 2.80 Hz, H-4), 7.24-7.30 (m, 5H, Ar-H), 7.76 (s, 1H, N_3-H), 9.46 (s, 1H, N_1-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 26.88, 28.70, 32.22, 39.58, 49.74, 52.11, 107.43, 126.25, 127.14, 128.34, 144.69, 151.90, 152.40, 192.88. MS (EI, *m/z* (%)): 270 (M^+, 100).

4-(4-Chlorophenyl)-7,7-dimethyl-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione (**4c**): Color: White. Yield: 96%. M.p.: > 300 °C. FT-IR (KBr, ν, cm^{-1}): 3248 (N-H), 1710 (C=O, C-5), 1645 (C=O, C-2). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 0.89 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 2.02 (q, 2H, CH_2-8), 2.33 (q, 2H, CH_2-6), 5.16 (d, 1H, *J* = 2.80 Hz, H-4), 7.30 (m, 4H, Ar-H), 7.80 (s, 1H, N_3-H), 9.50 (s, 1H, N_1-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 26.84, 28.71, 32.27, 39.49, 49.78, 51.49, 107.04, 128.14, 128.35, 131.38, 143.56, 151.76, 152.69, 192.84. MS (EI, *m/z* (%)): 306 ($[M + 2]^+$, 31), 304 (M^+,100).

3. Results and discussion

Tetrahydroquinazolinones, **4a-h** were synthesized by reaction of 5,5-dimethylcyclohexane-1,3-dione (dimedone) and corresponding aromatic aldehyde with urea (or thiourea) in the presence of catalytic amount of molecular iodine (0.25 mmol) in refluxing ethanol. The yield of products was good to excellent. The results are summarized in Table 1.

When attempts were made to carry out the model reaction of benzaldehyde, dimedone, and urea at room temperature in ethanol as a mild solvent, formation of solid product (**4a**) was observed, but in low yield (15%) after 24 h. The TLC of reaction mixture indicated the presence of starting materials. However, under reflux conditions the yield of product (**4a**) was improved significantly (96%). This clearly demonstrates that temperature has important effect on the reaction and the best results were obtained at reflux temperature in ethanol. Thus, we have selected the optimized reaction conditions to examine the generality of this reaction.

The effect of molecular iodine was found to be an effective catalyst in terms of conversion. Though, the reaction proceeds even with 0.25 mmol of I_2, the products were obtained in high yields (86-97% over 3-6 h). Moreover, our investigation showed that the best results were observed when the molar ratio of aldehyde, dimedone and urea (or thiourea) was 1:2:2. In addition, it was found that the yields were not obviously affected by different amount of iodine.

Based on literature reviews [20,21], we speculate that the reaction proceeds *via* an acyl imine intermediate formed from condensation of the aldehyde and urea. Subsequent addition of the diketone, followed by cyclization and dehydration afforded the tetrahydroquinazolinone.

4. Conclusion

In conclusion, the present procedure provides an efficient and improved modification of the Biginelli reaction for preparation of tetrahydroquinazolinones using catalytic amounts of readily available iodine. This procedure is associated with some advantages such as high yields, ease of workup and mildly toxic catalyst.

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