A Practical Approach Towards Synthesis of Octahydroquinazolinone Derivatives in Water

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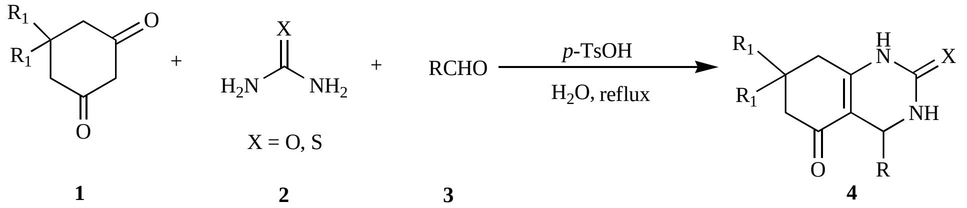
Abstract: A simple, efficient and green procedure has been developed for the synthesis of octahydroquinazolinone derivatives by Biginelli-type three-component cyclocondensation reactions of cyclic β-diketones, aldehydes and (thio)urea with *p*-TsOH catalysis in water.

Keywords: Octahydroquinazolinone, biginelli reaction, cyclic β-diketones, *p*-toluenesulfonic acid, synthesis, catalysis.

One-pot multicomponent reactions (MCRs) are attracting considerable interest for various reasons [1]. The production of dihydropyrimidinones *via* the well established Biginelli reaction certainly ranks as one of the most recognized and often used MCRs for the generation of novel pyrimidine scaffolds. This reaction involves the interaction of a β-ketoester, a urea, and an aldehyde [2]. Some of the interest in this heterocyclic synthesis is also due to the challenge of redesigning and improving an old but useful preparative method [3]. Very recently, the Biginelli reaction has been employed for the synthesis of octahydroquinazolinones, which used cyclic β-diketones instead of open-chain dicarbonyl compounds, but with low yields of products (19-69%) under catalystic amount of conc. HCl [4]. Additional scaffolds such as spiro-fused heterocycles and hexahydroxanthenes were formed in those reactions [5]. Moreover, octahydroquinazolinone derivatives exhibited potent antibacterial activity and calcium antagonist activity [4c, 6]. Therefore, improved procedures with better and milder conditions have been under attention for the novel Biginelli-like scaffold syntheses.

The toxicity and volatile nature of many organic solvents that are widely used in huge amounts for organic reactions have posed a serious threat to the environment. Water is a medium that is fully compatible with green chemistry [7]. In connection with our ongoing work on multicomponent reactions [8], we now wish to report a practical and simple approach for the synthesis of octahydroquinazolinone derivatives by the multicomponent reactions of cyclic β-diketones **1**, (thio)urea **2** and aldehydes **3** using *p*-toluenesulfonic acid (*p*-TsOH) as catalyst in water with good yields and selectivity (Scheme **1**).



Scheme 1.

In the present study we have selected benzaldehyde, 1,3-cyclohexanedione, and urea as model compounds using *p*-TsOH (10 mol%) as catalyst and have tested a variety of reaction conditions. In order to drive the reaction to completion, excess of 1,3-cyclohexanedione and urea has to be employed in the reaction. The best results were obtained with a 1.4:1.2:1 ratio of 1,3-cyclohexanedione, urea, and aldehyde. The effect of various solvents on the yield of the reaction was also studied. Results reported in Table **1** are quite surprising since similar yields were observed by carrying out the reaction in two solvents such as acetonitrile and water. Particularly impressive is the good yield observed in water despite the reaction requiring the elimination of two water molecules. Based on the reaction yields and environmental consideration, water was proved to be the best solvent among the other solvents such as acetonitrile, ethanol and toluene. Water insoluble solid products that separated out were easily purified by recrystallization. All these positive aspects make the reaction very compatible with green chemistry requirements.

With optimized protocol in hand, the condensation of cyclic β-diketones, (thio)urea and aldehydes afforded products **4** in good yield and purity [9]. The results are reported in Table **2**. A wide range of aromatic aldehydes either electron-donating or electron-withdrawing are

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Table 1. Solvent Effect for Reaction of 1,3-Cyclohexanedione 1 (2.8 mmol), Urea 2 (2.4 mmol) and Benzaldehyde 3 (2.0 mmol) Catalyzed by *p*-TsOH

Entry	Solvent	Time (h)	Yield of 4a (%)
1	Ethanol	8	62
2	Acetonitrile	8	77
3	Water	8	83
4	Toluene	8	Trace

Table 2. *p*-TsOH Catalyzed Synthesis of Octahydroquinazolinone Derivatives

Entry	R		R_1	X	Product	Yield (%)[a]
1	C_6H_5	**3a**	H	O	**4a**	83 (46)
2	4-$CH_3C_6H_4$	**3b**	H	O	**4b**	78 (43)
3	4-$CHF_2OC_6H_4$	**3c**	H	O	**4c**	85 (58 [8c])
4	4-$CH_3OC_6H_4$	**3d**	H	O	**4d**	84 (48)
5	4-$NO_2C_6H_4$	**3e**	H	O	**4e**	82 (46)
6	3-ClC_6H_4	**3f**	H	O	**4f**	86 (62)
7	4-ClC_6H_4	**3g**	H	O	**4g**	74 (54)
8	2-BrC_6H_4	**3h**	H	O	**4h**	68 (44)
9	3-BrC_6H_4	**3i**	H	O	**4i**	77 (45)
10	4-BrC_6H_4	**3j**	H	O	**4j**	75 (44)
11	4-FC_6H_4	**3k**	H	O	**4k**	85 (19) [5d]
12	3-FC_6H_4	**3l**	H	O	**4l**	79 (68) [8b]
13	2,4-$Cl_2C_6H_3$	**3m**	H	O	**4m**	84 (95) [3d]
14	4-ClC_6H_4	**3n**	CH_3	O	**4n**	72 (43) [2c]
15	4-FC_6H_4	**3o**	H	S	**4o**	70 (74) [5c], (30) [5d]
16	4-ClC_6H_4	**3p**	CH_3	S	**4p**	61 (93) [7b]

[a] Numbers in parentheses refer to reported yields in literature [4b] unless otherwise indicated.

tolerated in this procedure to provide a library of octahydroquinazolinones. Thiourea also works well to give the corresponding thio-derivatives. Compared to classical Biginelli method, one additional important feature of the present protocol is the ability to tolerate the variation in all the three components. Besides 1,3-cyclohexanedione, and 5,5-dimethyl-1,3-cyclohexanedione can also be employed. The three-component condensation reactions proceeded smoothly and were completed within 5-10 h. All the products were characterized on the basis of their spectroscopic data such as ^{1}H NMR, IR and EI-MS spectra and physical data.

In conclusion, this study has demonstrated that the synthesis of octahydroquinazolinone derivatives is achieved in good yields and selectivity using *p*-toluenesulfonic acid as catalyst to promote the Biginelli-type three component reactions of aldehydes, cyclic β-diketones and urea in water.

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[9] Typical procedure for the preparation of 4-(4-Difluoromethoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione **4c**. A mixture of cyclohexane-1,3-dione (1.57 g, 14 mmol), urea (0.72 g, 12 mmol), 4-(difluoromethoxy)-benzaldehyde (1.72 g, 10 mmol), and *p*-toluenesulfonic acid (0.17 g, 1 mmol) in water (40 mL) was refluxed for 7 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 (2.62 g, 85% yield). Data for **4c**: M.p. 266.3-266.6 ^{o}C; IR (KBr): 3221, 3121, 1699, 1649, 1606 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.81-1.95 (m, 2H), 2.19-2.26 (m, 2H), 2.44-2.51 (m, 2H), 5.17 (d, *J* = 3.0 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 2H), 7.18 (t, *J* = 74.3 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.76 (s, 1H), 9.50 (s, 1H); EI-MS: m/z (%) = 309 (26), 308 (M^{+}, 38), 307 (12), 252 (12), 251 (8), 241 (31), 240 (15), 165 (100). See X-ray crystal structure analysis of compound **4c** in literature [8c].