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Original article

Cu/SiO_2: A recyclable catalyst for the synthesis of octahydroquinazolinone

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ABSTRACT

A simple and one-pot method for the synthesis of octahydroquinazolinone is reported. Cu/SiO_2 in refluxing ethanol catalyzes this three-component condensation reaction to afford the corresponding quinazolinones in good yields.

1. Introduction

Multi-component reactions (MCRs) are of increasing importance in organic and medicinal chemistry, because the strategies of MCR offer significant advantages over conventional linear-type synthesis. MCRs leading to interesting heterocyclic scaffolds are particularly of use as drug-like molecules for biological screening, since the combination of three building blocks with a smaller molecular weight in a single operation leads to a high combinatorial efficacy [1].

Octahydroquinazolinone derivatives have attracted considerable attention in recent years owing to their potential antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* [2], and also as a calcium antagonist [3]. Synthesis of octahydroquinazolinone derivatives through condensation of dimedone, aldehyde and urea/thiourea using TMSCl has been reported [4].

Although various Lewis acid catalysts are employed [5,6] in the extension of the Biginelli reaction, they are expensive, harmful and especially difficult to handle on large scale.

Most of these procedures require longer reaction times, use strongly acidic conditions, give unsatisfactory yields and also suffer from the formation of many side products [7].

Recently, the use of Cu/SiO_2 as catalysts or promoters in organic synthesis has attracted great interest from many chemists [8]. Cu/SiO_2 has emerged as a powerful Lewis acid catalyst for synthesis of tetrahydrobenzo[α]xanthen-11-ones [9].

Here, we report our results obtained with Cu/SiO_2 composites as a catalyst in the synthesis of octahydroquinazolinone derivatives.

2. Experimental

In a round bottom flask a mixture of aromatic aldehyde (1 mmol), dimedone (1 mmol) and urea (1.5 mmol) was mixed with Cu/SiO_2 (0.09 g) in refluxing ethanol for an appropriate time. The progress of the reaction was monitored by TLC (ethyl acetate:hexane = 7:3). After completion of the reaction, the catalyst was removed by simple filtration. The solvent was evaporated under reduced pressure. The crude product was purified by recrystallization from ethanol. The recovered catalyst was firstly dried in vacuum at room temperature and then dried for 3 h in an oven at 100 °C, after which it was reused in a subsequent reaction.

Compound **4a**: Mp 168–170 °C; IR (KBr, cm^{-1}): ν 3323, 3258, 2925, 1710, 1677, 1241; ^1H NMR (500 MHz, DMSO-d_6): δ 0.94 (s, 3H, Me), 1.10 (s, 3H, Me), 2.16 (q, 2H, J = 16 Hz, CH_2), 2.37 (q, 2H, J = 16.5 Hz, CH_2), 5.24 (d, 1H, J = 2.5 Hz, CH), 7.31–7.19 (m, 5H, Ar), 7.43 (s, 1H, NH), 9.36 (s, 1H, NH); MS (m/z): 271 (M+1).

3. Results and discussion

In continuation of our synthesis of heterocycles [10], we report herein, for the first time, a simple and expeditious synthesis of octahydroquinazolinone derivatives in excellent yields employing Cu/SiO_2 (0.09 g) as catalyst in refluxing ethanol (Scheme 1).

In order to standardize the reaction, benzaldehyde (1 mmol), dimedon (1 mmol) and urea (1.5 mmol) were dissolved in ethanol

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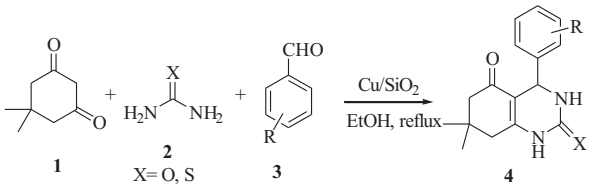

Scheme 1. Synthesis of octahydroquinazolinone.

Table 1
Optimization of amount of catalyst Cu/SiO_2.

Catalyst amount (g)	Time (min)	Yield (%)
0.03	55	83
0.05	45	90
0.07	40	94
0.09	35	96
0.11	36	96

Table 2
Synthesis of octahydroquinazolinone derivatives catalyzed by Cu/SiO_2.

Entry	X	R	Time (min)	Yield (%)[a]	Mp (°C) found (lit.)	Ref.
4a	O	H	35	96	168–170 (167–169)	[7]
4b	O	4-Cl	55	90	190–192 (196–198)	[11]
4c	O	4-Br	50	91	>300 (>300)	[3]
4d	O	4-F	45	91	134–135 (134–136)	[6]
4e	O	3-OMe	70	85	243–245 (248–249)	[11]
4f	O	3-NO_2	75	80	296–297 (298–300)	[11]
4g	S	H	45	83	160–161 (160–162)	[2]
4h	S	4-Cl	35	86	218–219 (218–220)	[2]
4i	S	4-Br	55	85	280–282 (282–283)	[11]
4j	S	3-OMe	65	80	235–237 237–239	[12]
4k	S	4-Me	70	75	>300 >300	[6]

[a] Isolated yield.

and stirred at room temperature for 24 h in the absence of the catalyst which led to very poor yields (only 20%, as obtained) of the octahydroquinazolinone. We also tried different solvents such as methanol, acetonitrile and chloroform under similar reaction conditions, but appreciable increment in product yield was not observed. Then it was thought worthwhile to study the reaction in the presence of catalyst like Cu/SiO_2, and use of 0.09 g of the catalyst produced maximum yield (96%). A further increase of the catalyst concentration does not increase the yield (Table 1).

On the contrary, the reaction slows down after adding more than 0.09 g of catalyst is conflicted with the data in Table 1. The standard reaction was also studied in the presence of Cu/SiO_2 (0.09 g), when the desired product was obtained only 96% isolated yield.

Encouraged by the above-mentioned results obtained for benzaldehyde, dimedon and urea, we investigated a number of other aromatic compounds (possessing both electron-donating and electron-withdrawing group). Here, we have found that the reactions of aromatic aldehydes having electron-withdrawing groups are very fast as compared with the reaction of aldehydes having electron donating groups. The results are shown in Table 2.

The isolated Cu/SiO_2 composite catalyst from the crude mixture was reused two times, and yields were comparable with the first run (with the yields of the product **4a** being 96%, 89%, and 85%, respectively).

All the products obtained were fully characterized by spectroscopic methods such as IR, ^1H NMR and mass spectroscopy and also by comparison with the reference compounds.

To investigate the re-usability of the catalyst, we performed the condensation of the aromatic aldehyde, dimedone and urea in the presence of Cu/SiO_2 in refluxing ethanol.

After completion of the reaction, the crude product obtained was filtered to yield a solid. The recovered solid catalyst can be reused at least two times without a significant loss of activity.

4. Conclusion

In summary, a simple procedure for the preparation of octahydroquinazolinone of the products in high yields has been reported. The short reaction time, simple work-up and isolation of the products in high yields with high purities and recyclability catalyst make this approach feasible and attractive for the generation of octahydroquinazolinone libraries as is demonstrated in Table 2.

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