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Synthesis of Quinazolinone Derivatives through Multicomponent/Click Reactions

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Quinazolinones were synthesized through the one-pot three-component reaction of aromatic aldehydes, isatoic anhydride, and urea under solvent-free conditions using sulfonic acid functionalized mesoporous silica (SBA-Pr-SO_3H). The propargyl ether containing 2,3-dihydroquinazolin-4(1*H*)-ones were reacted with sodium azide in the presence of CuI to gain the new triazole-quinazolinone products.

Keywords: Dihydroquinazolinone, Quinazolinone, SBA-Pr-SO_3H, Click reaction, Isatoic anhydride

INTRODUCTION

Quinazoline (Fig. 1) is a natural product which was firstly separated from the Chinese plant aseru (*Dichroa febrifuga* Lour) [1,2]. In 1903, Gabriel synthesized it for the first time [3]. This heterocyclic compound contains two fused six member aromatic rings including benzene and pyrimidine ring. 2,3-Dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones are two kinds of such heterocycles and have a wide spectrum of biological and pharmacological activities as antibacterial [4-6], tyrosine kinase inhibitory [7], anti-inflammatory [8], diuretic [9], antitumor [10] and antiparkinsonian agents [11].

Synthesis of quinazolinone derivatives is a demanding task due to their great biological activities. Reductive cyclization of 2-nitrobenzamide or condensation of 2-aminobenzamide [12,13] with aldehydes or ketones using Brønsted or Lewis acid catalysts are conventional methods for the synthesis of quinazolinone compounds [14-18]. Moreover, three-component condensation of isatoic anhydride, aldehydes or ketones, and primary amines, is another method being performed in the presence of various catalysts such as gallium triflate [19], silica sulfuric acid [20], $SrCl_3.6H_2O$ [21], *p*-TsOH [22], $Bi(NO_3)_3.5H_2O$ [23], ethylenediamine diacetate [24] and ionic liquids [Bmim]Br [25]. Most of these procedures have certain drawbacks such as the use of non-recyclable, toxic or expensive catalyst, strong acidic conditions, hazardous organic solvents, requirement of high reaction temperature, and low yield of the products. Therefore, there is a need for a simple and cost effective method and an efficient acidic catalyst to overcome these indecency and limitations. To this end, in continuation of our research [26-29], herein, the catalytic activity of sulfonic acid functionalized mesoporous silica (SBA-Pr-SO_3H) as a highly efficient heterogeneous acid catalyst is examined in the multi-component synthesis of quinazolinones. Furthermore, some new prepared quinazolinone products containing C-C triple bond are subjected to the Click reaction to gain new quinazolinone including 1,2,3-triazole.

EXPERIMENTAL

General

Chemicals were purchased from the Merck Company and were used as received. FT-IR spectra were recorded on KBr disks using a FT-IR Bruker Tensor 27 instrument. Melting points were determined through the capillary tube method using an electro thermal 9200 apparatus. The ^1H NMR (300 and 500 MHz) and ^{13}C NMR (75 and 125 MHz) spectra were recorded on a Bruker DPX and tetramethylsilane (TMS) was used as the internal standard

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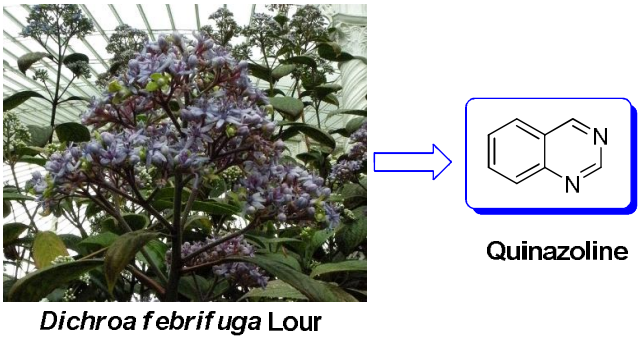


Fig. 1. Quinazoline structure and its natural source.

in DMSO-d_6 solution. Mass spectrometry (MS) analysis was run on a model 5973 mass-selective detector (Agilent).

General Procedure for the Preparation of Propargyl Ether Including Benzaldehydes 2e-f

Salicylaldehyde derivative (5 mmol), propargyl bromide 6 (6 mmol, 0.41 ml) and K_2CO_3 (5 mmol, 0.69 g) in DMF (10 ml) were stirred for the corresponding time described in Table 3 at room temperature. After completion of the reaction (monitored by TLC), cold distilled water was gradually added to the reaction mixture until no more precipitation was formed and then it was filtered off. The crude product was recrystallized in a mixture of EtOH and H_2O (3:1) and then characterized.

General Procedure for the Preparation of 2,3-Dihydroquinazolin-4(1*H*)-one 4a-f and Quinazoline-4(3*H*)-one Derivatives 5a-c

The SBA-Pr-SO_3H (0.02 g) was firstly activated under reduced pressure at 100 °C and after cooling to room temperature, isatoic anhydride 1 (1 mmol, 0.163 g), aromatic aldehyde 2a-f (1.1 mmol) and urea 3 (1.1 mmol) were added. The mixture was heated under solvent free condition at 115 °C for an appropriate time. Completion of the reaction was followed by means of TLC (*n*-Hexane: EtOAc, 2:1). The resulting crude product was dissolved in hot methanol, filtered to remove the heterogeneous catalyst, and then, the filtrate was cooled to give the pure product. Characterization data for the sample products:

NH) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): 55.4, 66.4, 78.3, 79.3, 114.4, 114.6, 114.9, 117.2, 127.4, 128.3, 133.3, 134.1, 134.2, 148.0, 148.1, 157.3, 163.7 ppm. MS (m/e): 278 (M^+, 50%), 277 (80%), 147 (100%), 120 (90%).

2-(3-Methoxy-2-(prop-2-ynyloxy)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one 4f. m.p.: 271-273 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H = 3.56 (s, 1H, acetylene CH), 3.81 (s, 3H, CH_3), 4.78 (AB quartet, 2H, CH_2), 6.16 (s, 1H, NH-CH-NH), 6.67-6.78 (m, 3H, ArH), 7.04-7.15 (m, 3H, ArH and NH), 7.23 (t, *J* = 7.2 Hz, 1H, ArH), 7.64 (d, *J* = 7.6 Hz, 1H, ArH), and 8.01 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): 55.9, 59.9, 61.4, 78.6, 79.7, 112.9, 114.6, 114.8, 117.3, 118.9, 124.6, 127.4, 133.4, 134.9, 143.5, 148.0, 152.0, 163.8 ppm.

General Procedure for the Preparation of 1,2,3-Triazole Containing 2,3-Dihydroquinazolin-4(1*H*)-ones 7a-b

2,3-Dihydroquinazolin-4(1*H*)-one 4e-g (0.5 mmol), CuI (0.02 g) and NaN_3 (1 mmol, 0.06 g) was dissolved in DMF and stirred vigorously at ambient temperature. After completion of the reaction (traced with TLC), cold distilled water (10 ml) was added to the reaction mixture to precipitate a green solid. The crude product was filtered off and recrystallized in ethanol.

2-(4-((1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one 7a. m.p.: 248-249 °C, FT-IR (KBr): υ_{max} = 3192, 3080, 2919, 1673, 1603 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H = 5.09 (s, 2H, CH_2), 5.69 (s, 1H, NH-CH-NH), 6.68 (m, 1H, ArH), 6.99 (d, *J* = 8.6 Hz, 1H, ArH), 7.12-7.22 (m, 2H, NH and ArH), 7.41-7.49 (dd, *J* = 7.8 Hz, 2H, ArH), 7.60 (d, *J* = 7.3, 1H, ArH), 7.69 (d, *J* = 7.6 Hz, 1H, ArH), 7.80 (d, *J* = 6.8 Hz , 1H, ArH), 7.93-8.19

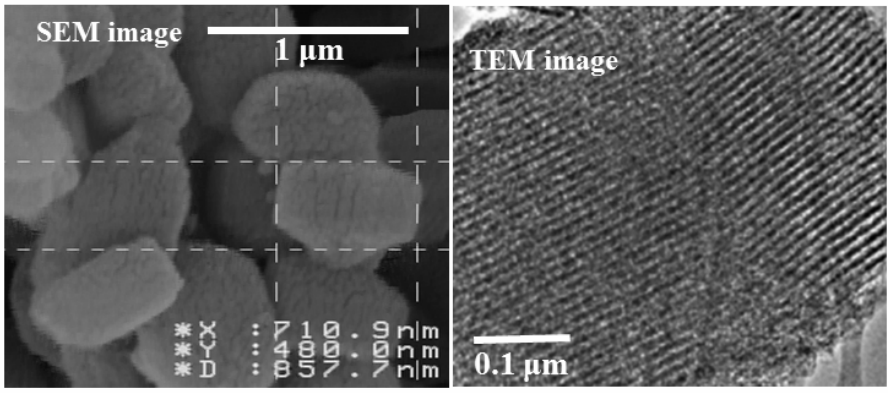
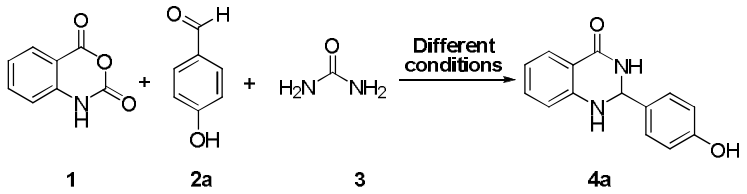


Fig. 2. SEM (Left) and TEM (Right) images of SBA-Pr-SO_3H.

Table 1. Optimization of the Reaction Conditions for the Synthesis of 2,3-Dihydro-quinazolin-4(1*H*)-one 4a

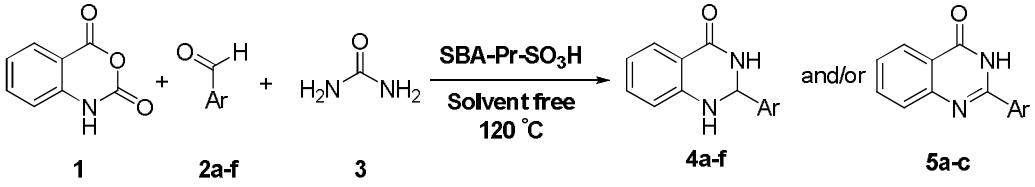


Entry	Solvent (3 ml)	Catalyst (0.02 g)	Condition	Time (h)	Yield (%)
1	EtOH	SBA-Pr-SO_3H	Reflux	6	93
2	H_2O	SBA-Pr-SO_3H	Reflux	12	-
3	MeOH	SBA-Pr-SO_3H	Reflux	8	60
4	-	SBA-Pr-SO_3H	120 °C	30 min	95
5	-	-	120 °C	7	55

(m, 3H, NH, ArH) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): 70.2, 75.9, 114.4, 114.5, 114.8, 117.2, 125.8, 126.3, 127.4, 128.4, 129.5, 134.6, 159.4, 162.3 ppm.

RESULTS AND DISCUSSIONS

In this research, SBA-Pr-SO_3H was initially produced through the reaction of SBA-15 with 3-mercaptopropyl-triethoxysilane following oxidation treatment of the grafted thiol groups by the use of hydrogen peroxide [30]. Then, it was analyzed and characterized using different analysis methods. Accordingly to BET, surface area of SBA-Pr-SO_3H was examined as 440 $cm^2\ g^{-1}$ with pore diameter of 3.0 nm. Additionally, SEM and TEM images showed the rod-like morphology and internal channels of the catalysts, respectively, which the channels were not collapsed during



Scheme 1. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones/quinazoline-4(3*H*)-ones (4 and/or 5)

SBA-15 modification (Fig. 2).

Afterward, a simple method was developed for the synthesis of quinazolinones through the one-pot three-component reaction. It was necessary at first to find the optimum reaction conditions for the formation of products; therefore, the reaction of isatoic anhydride 1 (1 mmol), 4-hydroxybenzaldehyde 2a (1.1 mmol) and urea 3 (1.1 mmol) was studied in different solvents including H_2O, MeOH, EtOH as well as solvent free systems (Table 1). The results showed that the solvent free system in the presence of SBA-Pr-SO_3H (0.02 g) under heating at 120 °C is the best condition giving the product 4a with high yield within short reaction time (30 min). To confirm the catalyst efficiency, this reaction was repeated under the optimized conditions in the absence of SBA-Pr-SO_3H, and so, the product was obtained in lower yield after 7 h. This emphasizes that SBA-Pr-SO_3H plays a significant role to catalyze this reaction.

Therefore, to investigate generality of these conditions, different aromatic aldehydes were applied to this reaction (Scheme 1) and it was found that two different substituted 2,3-dihydroquinazolin-4(1*H*)-ones and quinazoline-4(3*H*)-ones may be obtained (Table 2). As shown in Table 2, entries 1-8, aldehydes including 4-OH, 4-F, 4-Cl, 2-Me, 2-OH-4-OMe and propargyl ether substituents gave non-oxidized products 4a-f, while 4-NMe_2, 4-OMe, and 2,4-dimethoxy benzaldehyde derivatives gave the oxidized products 5a-c. There is no rule to explain the reality of this phenomenon.

The new products were characterized by melting points, FT-IR, GC–MS, and NMR spectral data. Furthermore, the propargyl ether containing aldehydes were synthesized through the reaction of salicylaldehyde derivatives and propargyl bromide under basic condition (Scheme 2, Table 3).

By the propargyl ether containing products 4e-f in hand, Click reactions were preceded as shown in Scheme 3. Accordingly, compounds 4e-f were treated with sodium azide in the presence of CuI to gain triazole containing 2,3-dihydroquinazolin-4(1*H*)-ones 7a-b in good to high yields (Table 4).

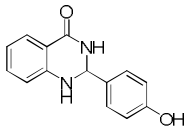
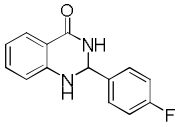
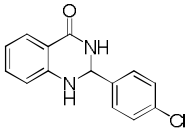
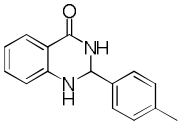
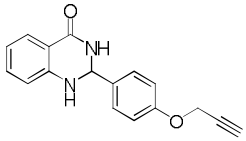
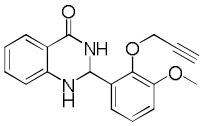
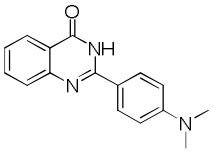
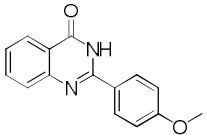
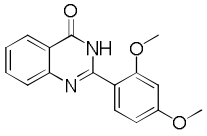
The most probable mechanism for this reaction is shown in Scheme 4. The carbonyl group of isatoic anhydride 1 is firstly protonated by the solid acid catalyst to give intermediate 1'. This intermediate can be easily attacked by nitrogen atom of urea 3 as a nucleophile, followed by a decarboxylation to produce 2-amino-*N*-carbamoyl-benzamide 8. Then, the amino group of the latter reacts with the protonated aromatic aldehyde 2' to give the imine 9 which undergoes an intramolecular cyclization to obtain intermediate 10. Ultimately, the cleavage of (N-C=O)-bond affords the desired product 4, although some of the products (5a-c) were produced through an automatic oxidation process under air atmosphere. Herein, SBA-Pr-SO_3H acted as a mesoporous catalyst where the reaction occurs easily in its nanopores.

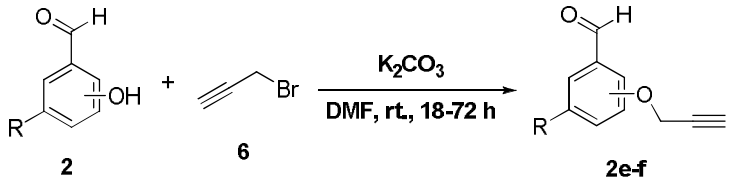
In order to investigate the catalytic efficiency of SBA-Pr-SO_3H, the reaction results were compared with the other published research as shown in Table 5. Naidu and coworkers (2014) synthesized quinazolinone compounds *via* directing the current reaction in the absence of catalyst in refluxing EtOH within 6 h, while Azizian and coworkers (2003) preformed the same reaction using microwave irradiation in the presence of *N*,*N*-dimethylacetamide. Correspondingly, the present methodology reduced the reaction time by the use of a recyclable catalyst [40] under green condition.

CONCLUSIONS

In summary, SBA-Pr-SO_3H was employed as an effective catalyst in the one-pot multicomponent synthesis of quinazolinone derivatives. Due to the applicability of this

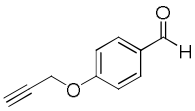
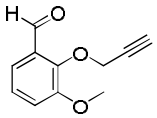
Table 2. Derivatives of 2,3-Dihydroquinazolin-4(1*H*)-ones/quinazoline-4(3*H*)-ones (4 or 5) Prepared in the Presence of SBA-Pr-SO_3H

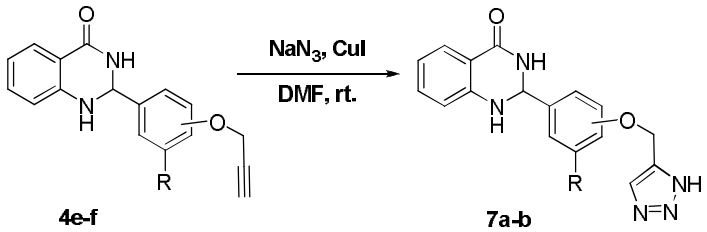
Entry	No.	Product	Time (min)	Yield (%)	m.p. (°C)	m.p. (°C) [Lit.]
1	4a		30	92	277-278	278-280 [31]
2	4b		40	78	279-281	279-280 [32]
3	4c		60	80	206-208	205-208 [33]
4	4d		120	73	219-221	220-221 [34]
6	4e		90	99	209-211	New
8	4f		65	95	271-273	New
9	5a		35	91	239-241	240-242 [35]
10	5b		15	98	245-248	245-248 [36]
11	5c		11	85	184-185	184-186 [37]



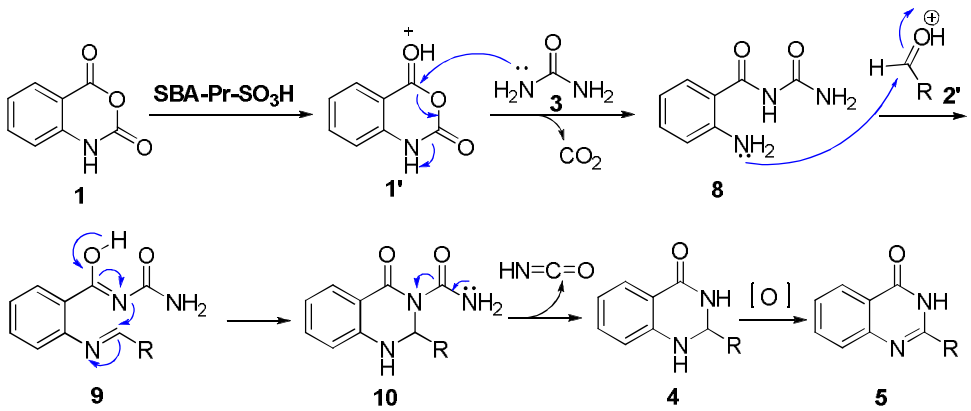
Scheme 2. Preparation of propargyl ether containing benzaldehydes

Table 3. Derivatives of Propargyl Ether Containing Benzaldehydes

Entry	No.	Product	Time (h)	Yield (%)	m.p. (°C)	m.p. [Lit.]
1	2e		30	95	79-80	80-81 [38]
3	2f		48	85	49-51	49-51 [39]



Scheme 3. Preparation of 1,2,3-triazole containing 2,3-dihydroquinazolin-4(1*H*)-ones



Scheme 4. A proposed mechanism for the formation of products 4 and 5.

Table 4. Derivatives of 1,2,3-Triazole Containing 2,3-Dihydroquinazolin-4(1*H*)-ones 7a-b Prepared Using ClickR

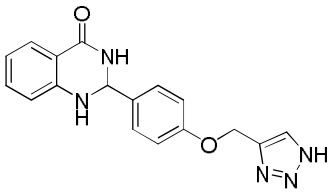
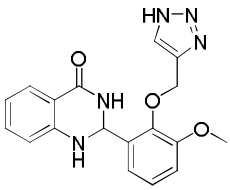
Entry	No.	Product	Time (h)	Yield (%)	m.p. (°C)
1	7a		12	91	248-249
2	7b		18	87	232-234

Table 5. Comparing the Reaction Conditions in the Synthesis of Quinazolin-4(1*H*)-ones 4

Entry	Catalyst	Solvent	Condition	Time (min)	Yield (%)
1	SBA-Pr-SO_3H	-	120 °C	11-120	73-98
2	-	EtOH	Reflux	6 h	83-92 [41]
3	*N*,*N*-dimethylacetamide	-	MW[a]	10	72-93 [42]

[a]Microwave irradiation.

method, some new propargyl ethers containing quinazolinones 4e-f were produced and subjected to the Click reaction. Correspondingly, new 1,2,3-triazole containing quinazolinones were produced.

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