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ORIGINAL PAPER

Efficient synthesis of 6,6*a*-dihydroisoindolo[2,1-*a*]-quinazoline-5,11-dione derivatives catalyzed by functionalized nanoporous silica

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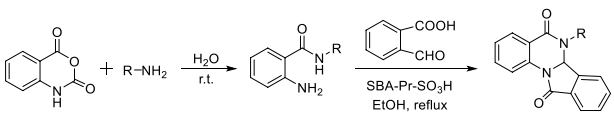
Abstract
An efficient and facile method has been developed for the synthesis of various 6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives, via a three-component reaction of 2-amino-*N*-(R)-benzamide derivatives with 2-formylbenzoic acid using sulfonic acid functionalized nanoporous silica as an efficient catalyst in ethanol under reflux. High yield of the desired products, reusability of the catalyst, and effortless workup step without using chromatography are the advantages of this method.

Graphic abstract



Keywords Isatoic anhydride · Amines · Nanoporous · HIV · Biological activity · SBA-pr-SO_3H

Introduction

Isoindolinones and their derivatives are important core structures in drug design and synthetic chemistry with a wide range of physiological and biological activities [1–5], such as antioxidant [6], antibiotic [7], antimicrobial [8], anticancer [9], and anti-inflammatory activities [10]. On the other hand, the 2,3-dihydroquinazolin-4(1*H*)-one-centered compounds play an important role in organic chemistry, as key structural units in many natural products as well as important pharmaceuticals [11, 12]. The most important pharmaceutics characteristic are antibacterial [13], antioxidant [14], anti-inflammatory [15, 16], antimalarial [17], antitumor [18], antiviral [19], antispermatogenic [20], antitubulin [21] ovarian cancer cell lines and are also EP4 receptor agonist in the treatment of pain [22], cytotoxicity and anti-HIV [23]. So the study of the synthesis and application of fusing two combinations of isoindolo-quinazolinone derivatives requires scientists' attention in recent years. Although different valuable synthetic procedures have been developed by researchers using different methods and catalysts to prepare these analogs such as the use of microwave irradiation [24], metal nanoparticle (CuO) [25] and iodine in ionic liquid [26], a number of handicaps still remain. For instance, these procedures usually include quite a few steps, low yields, and inorganic solvents. As a result, a simple, efficient, and green method to synthesize indoloquinazoline would be attractive.

On the other hand, utilizing nanomaterials has expanded substantially in recent years. Because of their large surface-to-volume ratio, which makes them efficient catalysts for chemical synthesis. SBA-15, as mesoporous silica was synthesized in 1998 [27]. After that, the internal surface of this catalyst was functionalized with different organic functional

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groups such as phosphonate [28], phenyl sulfonic acid [29], carboxylic [30], *N*,*N*-bis(salicylidene)ethylenediamine [31], and APTES [32]. In view of this, SBA-15 was modified as a solid acid catalyst with sulfonic acid functionalization (SBA-Pr-SO_3H) [33] and it was used as a highly active heterogeneous nanocatalyst with high thermal and physical stability in organic synthesis, environmental chemistry, and industry [34–37].

In the present manuscript, we utilized sulfonic acid functionalized SBA-15 (SBA-Pr-SO_3H) as recyclable heterogeneous catalyst development for the preparation of 6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives **5a–5j** via reaction of a variety of 2-amino-*N*-(R)-benzamides **3a–3j** and 2-formylbenzoic acid (**4**) under reflux condition in ethanol (Scheme 1).

Table 1 The optimization of the reaction conditions

Entry	Catalyst amount/g	Solvent	Temp	Time/h	Yield/%
1	0.1	CH_3CN	Reflux	8	43
2	0.1	CH_3OH	Reflux	8	58
3	0.1	C_2H_5OH	R.t	24	15
4	0.1	C_2H_5OH	50 °C	17	30
5	0.1	C_2H_5OH	Reflux	6	88
6	0.05	C_2H_5OH	Reflux	14	45
7	–	C_2H_5OH	Reflux	14	20
8	0.2	C_2H_5OH	Reflux	6	92
9	0.1	C_2H_5OH	Reflux	6	80

Reaction condition: 2-amino-*N*-(2-methoxybenzyl)benzamide (**3f**, 1 mmol), 2-formylbenzoic acid (**4**, 1 mmol) in 7 cm^3 solvent

Results and discussion

Initially, the catalyst was prepared by the synthesis and functionalization of SBA-15 mesoporous silica nanoparticles and then, characterized by FT-IR spectroscopy and thermal gravimetric analysis (TGA). Then, the condensation of 2-amino-*N*-(R)-benzamide derivatives **3** with 2-formylbenzoic acid (**4**) in the presence of SBA-Pr-SO_3H as a heterogeneous and reusable nanocatalyst for the synthesis of 6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives was studied (Scheme 1). For optimizing the reaction it was tested in different conditions. The results are listed in Table 1. The reaction between 2-amino-*N*-(2-methoxybenzyl)benzamide (**3f**) and 2-formylbenzoic acid was a model reaction.

To evaluate the effect of the solvent, reactions were carried out in various solvents. Acetonitrile, methanol, and ethanol afforded moderate yield 43, 58, and 92%, respectively. In this regard, ethanol was selected as a solvent in this study due to its higher yield (Table 1, entries 1, 2, 5). On the other hand, performing the reaction under reflux conditions was afforded the best yield of reaction (Table 1, entries 3, 4, 5). The result revealed that when the reaction was carried out in the absence of a catalyst, the product was formed in a very trace amount (Table 1, entries 6, 7). Also to study the recyclability of the catalyst, SBA-Pr-SO_3H recovered by simple filtration was reused and the reaction was afforded **3f** without affecting the yield significantly (Table 1, entry 9). At the end, it was found that the excellent result was obtained by 0.1 g catalyst, and reflux condition in ethanol as a solvent (Table 1, entry 5).

We focused the scope of this protocol on the synthesis of different 6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives by applying various substituted 2-aminobenzamides (Table 2). The reaction displayed high functional group tolerance and proved to be the best method for the synthesis of 6,6*a*-dihydroisoindolo[2,1-*a*]-quinazoline-5,11-diones. It was observed that 2-aminobenzamide with methoxy and methyl (benzene) substituents gave higher yields of the products due to higher nucleophilicity (Table 2, entries 9 and 10). Also the reaction proceeded well with a variety of aliphatic and cyclopropane amines which gave a good yield (Table 2, entries 1, 2, and 8). Different 2-amino-*N*-benzylbenzamid offered an excellent yield (Table 2, entry 4, 5, and 6). After the completion of the reaction, the products were separated by simple filtration and washed with hot ethanol. Then the structure of synthesized products was confirmed by melting points, IR, ^{1}H NMR, ^{13}C NMR, and mass analysis. The suggested mechanism for the synthesis of 6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives **5a–5j** was shown in Scheme 2.

Initially, the intermediate **A** was formed by the condensation of **4** with **3a–3j**, and then cyclization was converted to another intermediate **B**. Finally, the intermediate **B** gave isoindolo[2,1-*a*]quinazolines **5a–5j** by intermolecular dehydration.

Scheme 1

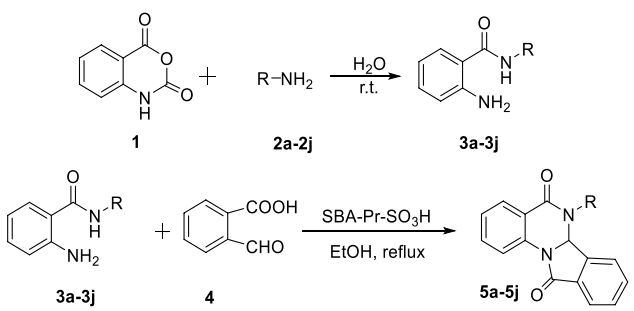
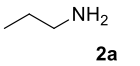
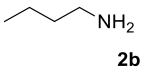
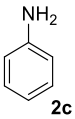
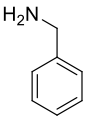
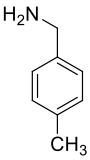
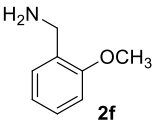
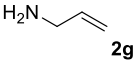
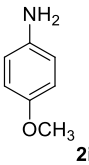
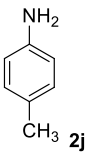


Table 2 Synthesis of 6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives in the presence of SBA-Pr-SO_3H (Scheme 1)

Entry	R-NH_2	Product	*t*/h	Yield/%[a]	M.p./°C (Ref.)
1	 **2a**	**5a**	7	90	134–135 (135–136 [26])
2	 **2b**	**5b**	7	87	140–141 (141–143 [26])
3	 **2c**	**5c**	8	80	186–188 (184–185 [38])
4	 **2d**	**5d**	6	90	154–156 (155–157 [38])
5	 **2e**	**5e**	6	85	203–204 (203–204 [26])
6	 **2f**	**5f**	6	88	187–188
7	 **2g**	**5g**	7	80	150–153
8	 **2h**	**5h**	8	85	158–161
9	 **2i**	**5i**	6	91	138–140 (135–137 [38])
10	 **2j**	**5j**	7	91	199–200 (199–200 [24])

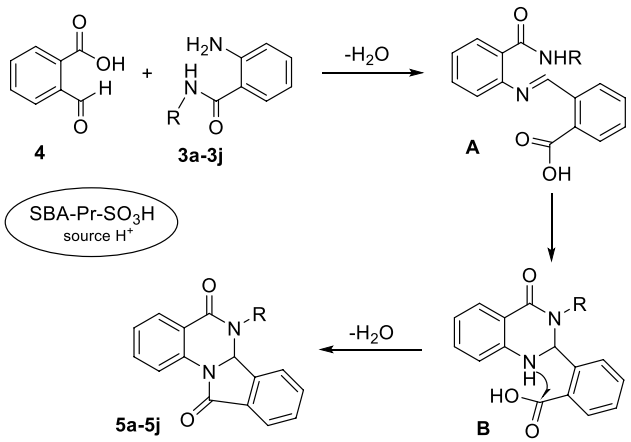
Reaction condition: 2-amino-*N*-(R)-benzamide **3a**–**3j** (1 mmol), 2-formylbenzoic acid (**4**, 1 mmol), 0.1 g SBA-Pr-SO_3H, reflux, 7 cm^3 ethanol

[a]Yield of isolated product

Conclusion

In conclusion, an efficient and facile method was reported for the synthesis of a series of 6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives by sulfonic acid functionalized nanoporous silica (SBA-Pr-SO_3H) as a reusable catalyst. This methodology is free from the use of any metal. On the other hand, one-pot, operational simplicity, good yield, and simple workup are the merits of this protocol.

Scheme 2



Experimental

All chemicals were obtained from the Sigma-Aldrich, Merck, and Fluka, they were used without further purification. All reactions were followed by thin-layer chromatography (TLC) with detection by UV light. Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a Perkin Elmer spectrophotometer (KBr). ^1H NMR and ^{13}C NMR spectra were obtained on Bruker 250 MHz spectrometer with DMSO-d_6 as a solvent. The thermogravimetric analysis (TGA) was performed using a TGA Q50 V6.3 build 189 instrument from ambient temperature to 1000 °C using 20 °C/min ramp rate.

General procedure for the synthesis of SBA-Pr-SO_3H

Preparation of SBA

At first, 4.0 g pluronic P123 was dissolved in 30 g water and 120 g HCl solution (2 M). Then, 8.5 g tetraethyl orthosilicate (TEOS) was added and the system was stirred at 40 °C for 8 h. Afterward, the suspension was transferred into the oven at 80 °C for 20 h without stirring, then was cooled to room temperature. The product was filtered, washed, and dried. The as-synthesized sample was calcinated at 550 °C for 6 h in air atmosphere for slow removal of the organic template.

Functionalization of the SBA-15 by organic groups

At first, 2 g SBA-15 silica and 10 cm^3 (3-mercaptopropyl)trimethoxysilane (MPTMS) in 20 cm^3 dry toluene was stirred

under reflux condition for 24 h. The product was filtered and extracted for 6 h in CH_2Cl_2 using a soxhlet apparatus, then dried under a vacuum. Then, the thiol groups were oxidized with H_2O_2 (excess) and one drop of H_2SO_4 in 20 cm^3 ethanol was stirred for 24 h at room temperature. The mixture was filtered and washed with H_2O and acetone. Then, the catalyst was dried and used [33].

The vibration characteristics of the functionalized SBA-Pr-SO_3H were measured by FT-IR. There are clearly visible characteristic peaks of the functional groups: Si–O–Si: 1100–1000 cm^{-1}, 785 cm^{-1}, and 470 cm^{-1}; S = O: 1177 cm^{-1} and 1080 cm^{-1}; and S–O: 616 cm^{-1}. Also, the thermal stability of SBA-Pr-SO_3H was investigated using thermogravimetry (TGA). Considering the weight reduction in the temperature between 200 and 800 °C (about 20% mass loss), the amount of organic group was calculated as 1.2 mmol/g.

General procedure for the synthesis of 6,6*a*-dihydroisoindolo[2,1-*a*]-quinazoline-5,11-dione derivatives 5a–5j

Synthesis of 2-amino-*N*-(R)-benzamide derivatives 3a–3j

Isatoic anhydride (1 mmol) and amine derivatives (1 mmol) were stirred in 5 cm^3 H_2O at room temperature. At the end of the reaction, the product was filtered, washed, and dried.

Synthesis of 6,6*a*-dihydroisoindolo[2,1-*a*]-quinazoline-5,11-dione derivatives 5a–5j

A mixture of 2-amino-*N*-(R)-benzamide derivatives (1 mmol), 2-formylbenzoic acid (1 mmol), and 0.1 g SBA-Pr-SO_3H as a catalyst in 7 cm^3 ethanol were stirred under reflux for 8 h. After reaction completion, the catalyst was removed and the product was obtained by recrystallization from ethanol.

6-(2-Methoxybenzyl)-6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione (5f, $C_{23}H_{18}N_2O_3$) Brown solid; m.p.: 187–188 °C; IR (KBr): $\overline{\nu}$ = 3001, 2921, 1718, 1602, 1414 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.82 (s, 3H), 4.84 (d, J = 17.50 Hz, 1H), 4.96 (d, J = 17.50 Hz, 1H), 6.68 (s, 1H), 6.70–8.06 (m, 12H) ppm; ^{13}C NMR (250 MHz, DMSO-d_6): δ = 55.85, 70.70, 111.04, 120.33, 120.65, 124.52, 125.01, 125.53, 125.79, 126.50, 128.39, 129.05, 130.93, 132.18, 133.26, 133.91, 137.15, 138.51, 156.38, 163.69, 164.81 ppm.

6-Allyl-6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione (5 g, $C_{18}H_{14}N_2O_2$) Brown solid; m.p.: 150–153 °C; IR (KBr): $\overline{\nu}$ = 2926, 1717, 1669, 1602, 1486 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.57–4.52 (m, 2H), 4.97 (d, J = 11 Hz, 2H), 5.69–5.80 (m, 1H), 6.59 (s, 1H), 7.32–8.01 (m, 8H) ppm; ^{13}C NMR (250 MHz, DMSO-d_6): δ = 44.81, 70.37, 116.1, 120.3, 120.53, 124.62, 125.49, 126.47, 128.98, 131.06, 132.26, 133.57, 133.82, 134.04, 137.02, 138.68, 163.15, 164.76 ppm.

6-Cyclopropyl-6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione (5 h, $C_{18}H_{14}N_2O_2$) White solid; m.p.: 158–161 °C; IR (KBr): $\overline{\nu}$ = 2920, 2851, 1726, 1601, 1466 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ = 0.56–1.24 (m, 4H), 3.37–3.60 (m, 1H), 6.47 (s, 1H), 7.26–8.08 (m, 8H) ppm; ^{13}C NMR (250 MHz, DMSO-d_6): δ = 10.58, 12.57, 27.40, 72.72, 120.64, 121.89, 125.16, 126.09, 128.79, 129.85, 131.66, 133.03, 133.71, 134.71, 138.13, 140.19, 165.74, 165.86 ppm.

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