

One-pot, three-component synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using *p*-toluenesulfonic acid–paraformaldehyde copolymer as an efficient and reusable catalyst

Ali Saffar-Teluri · Shiva Bolouk

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Abstract *p*-Toluenesulfonic acid–paraformaldehyde copolymer (copolymer-PTSA) catalyzes the three-component, one-pot condensation reaction of isatoic anhydride, ammonium salts or aromatic and aliphatic amines, and aldehydes in refluxing ethanol. The catalyst is reusable and could be recycled for several runs without any decrease in its efficiency.

Keywords 2,3-Dihydroquinazolin-4(1*H*)-ones · Heterogeneous catalyst · Copolymer-PTSA

Introduction

Quinazolinones are a class of N-heterocycles that has attracted much attention because of their broad range of pharmacological activities such as anticancer [1], anti-inflammatory [2], antidiuretic [3], and anticonvulsant [4] activities. 2,3-Dihydroquinazolin-4(1*H*)-ones in particular have various biological activities, and are also key intermediates for the synthesis of quinazolin-4(3*H*)-ones [5, 6]. Several methods have been reported for synthesis of quinazolinone and aryl-substituted quinazolinone compounds including cyclization of *o*-acylaminobenzamides [7], amidation of 2-aminobenzonitrile followed by oxidative ring closure [8], reduction of the azide functionality [9], preparation from isatoic anhydrides and Schiff bases [10], Lewis acid–surfactant combined catalysts under aqueous micellar media [11], and Pd-catalyzed heterocyclization of

nitroarenes [12]. All these procedures have certain limitations such as tedious processes, long reaction times, harsh reaction conditions, and low yields.

There has been growing interest in the catalytic application of functional polymers in organic synthesis. Several polymers having acidic or basic properties like polyanilines [13], polyvinyl pyridine [14], polyvinyl pyrrolidone [15], and cation and anion exchange resins [16–18] have been studied for use in a variety of chemical transformations. These solid catalysts have high acidity and alkalinity and often require a high degree of agitation, which causes rupture of the polymeric matrix. Hence, the development of a heterogeneous, active, and selective polymeric acid catalyst seems to be a challenging task.

In connection with our previous work on the synthesis of pharmaceutically important heterocyclic compounds [19], herein we report the one-pot condensation of isatoic anhydride, ammonium salts or aromatic and aliphatic amines, and aldehydes in the presence of *p*-toluenesulfonic acid–paraformaldehyde copolymer (copolymer-PTSA) in refluxing ethanol.

Results and discussion

To optimize the reaction conditions, we conducted the reaction of isatoic anhydride and benzaldehyde with ammonium carbonate or aniline in various solvents such as CH₃OH, CH₃CH₂OH, H₂O, CH₃CN, CH₂Cl₂, CHCl₃, and CCl₄. The results showed that the highest product yield was obtained in methanol and ethanol. However, because of the toxicity of methanol, all reactions were carried out in ethanol. Then the effect of amount of catalyst on the conversion rate of the reaction was studied by varying the amount of copolymer-PTSA under reflux (Table 1). It was

A. Saffar-Teluri (✉) · S. Bolouk
Department of Chemistry, Faculty of Material Science
and Engineering, Islamic Azad University-Najafabad Branch,
Najafabad, Iran
e-mail: a.saffar.t@iaun.ac.ir

Table 1 Optimization of the catalyst amounts for the synthesis of 2,3-dihydro-2-phenylquinazolin-4(1*H*)-one

Entry	Amount of copolymer-PTSA (g)	Time (h)	Yield (%) ^{a,b}
1	0	24	15
2	0.1	15	58
3	0.2	9	64
4	0.3	5	87
5	0.4	5	86
6	0.5	5	88

^a Reaction conditions: isatoic anhydride (1 mmol), ammonium carbonate (0.6 mmol), benzaldehyde (1 mmol), and ethanol (5 cm³), reflux

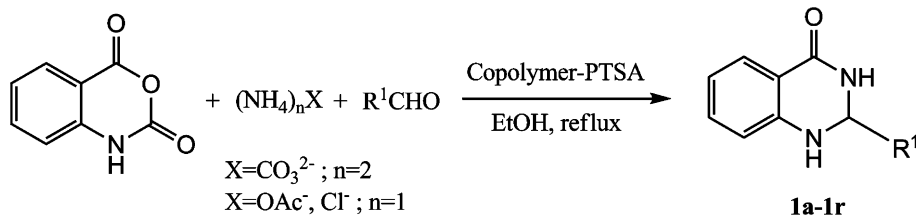
^b Isolated yields

found that 0.3 g of copolymer-PTSA was sufficient to carry out this reaction smoothly. An increase in the amount of copolymer-PTSA to more than 0.3 g showed no substantial improvement in the yield, whereas the yield was reduced by decreasing the amount of copolymer-PTSA to 0.2 and 0.1 g.

The use of ammonium salts as ammonia source in synthetic reactions has been well known for a long time [20–23]. In order to compare the efficiency of ammonium salts in the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones, the reactions were carried out using ammonium carbonate, acetate, and chloride under the same reaction conditions (Scheme 1). In all cases, monosubstituted 2,3-dihydroquinazolin-4(1*H*)-ones were produced in good yields. All of the products are known compounds and were identified by comparison of their physical and spectral data with those of authentic samples [24–27]. The results are summarized in Table 2.

Disubstituted derivatives of 2,3-dihydroquinazolin-4(1*H*)-one were also afforded in good yields by treatment of isatoic anhydride and aryl aldehydes with primary aromatic and aliphatic amines in the presence of copolymer-PTSA in refluxing ethanol (Scheme 2). The results are presented in Table 3.

The recyclability of the catalyst was investigated by using a model reaction between isatoic anhydride and benzaldehyde with ammonium carbonate or aniline in the presence of copolymer-PTSA. After completion of the reaction, the catalyst was filtered. The recycled catalyst was used for further runs and its activity did not show any significant decrease even after five runs (Table 2, **1a**; Table 3, **2i**).

Scheme 1**Table 2** Copolymer-PTSA-catalyzed synthesis of monosubstituted derivatives of 2,3-dihydroquinazolin-4(1*H*)-one

Product	R ¹	X	Time (h)	Yield (%) ^a	M.p. (°C)	Ref.
1a	Ph	CO ₃ ²⁻	5	87, 85, 86, 84, 83 ^b	219–221	[24]
1b	4-ClC ₆ H ₄	CO ₃ ²⁻	6	94	198–200	[24]
1c	2-CH ₃ OC ₆ H ₄	CO ₃ ²⁻	5.5	81	166–168	[25]
1d	4-CH ₃ OC ₆ H ₄	CO ₃ ²⁻	6.5	89	178–180	[24]
1e	4-CH ₃ C ₆ H ₄	CO ₃ ²⁻	6	82	234–236	[23]
1f	3,4-(CH ₃ O) ₂ C ₆ H ₃	CO ₃ ²⁻	5.5	83	209–211	[25]
1a	Ph	CH ₃ COO ⁻	5	77	219–221	[24]
1b	4-ClC ₆ H ₄	CH ₃ COO ⁻	6.1	82	198–200	[24]
1c	2-CH ₃ OC ₆ H ₄	CH ₃ COO ⁻	5.7	70	166–168	[25]
1d	4-CH ₃ OC ₆ H ₄	CH ₃ COO ⁻	6.7	78	178–180	[24]
1e	4-CH ₃ C ₆ H ₄	CH ₃ COO ⁻	6.5	71	234–236	[23]
1f	3,4-(CH ₃ O) ₂ C ₆ H ₃	CH ₃ COO ⁻	6	80	209–211	[25]
1a	Ph	Cl ⁻	5	79	219–221	[24]
1b	4-ClC ₆ H ₄	Cl ⁻	6.2	71	198–200	[24]
1c	2-CH ₃ OC ₆ H ₄	Cl ⁻	5.3	72	166–168	[25]
1d	4-CH ₃ OC ₆ H ₄	Cl ⁻	7	75	178–180	[24]
1e	4-CH ₃ C ₆ H ₄	Cl ⁻	6.1	74	234–236	[23]
1f	3,4-(CH ₃ O) ₂ C ₆ H ₃	Cl ⁻	6.2	77	209–211	[25]

^a Isolated yields

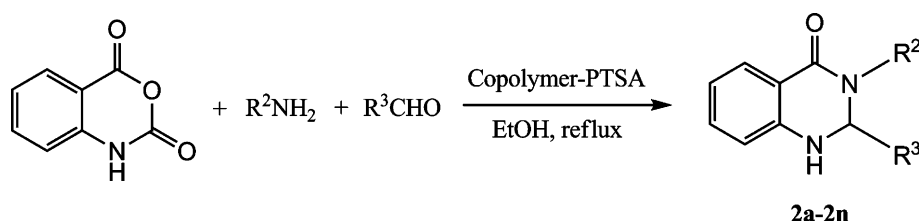
^b The catalyst was reused for five runs

In conclusion, we have successfully developed an efficient heterogeneous catalyzed (copolymer-PTSA) synthesis of quinazoline derivatives by the three-component, one-pot condensation of commercially available starting materials. The method offers several advantages including high yield of products, recyclability of the catalyst, and easy experimental work-up procedure.

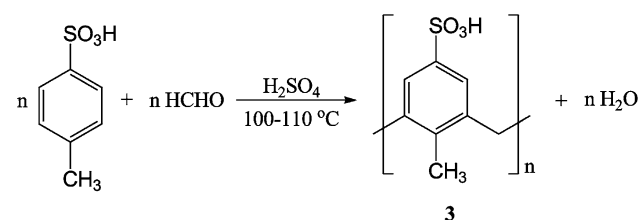
Experimental

All materials were of commercial reagent grade. Isatoic anhydride, aldehydes, ammonium salts, and primary amines were obtained from Merck. FT-IR spectra were obtained in the range 400–4,000 cm⁻¹ with a Nicolet Impact 400D spectrometer using potassium bromide pellets. ¹H NMR spectra were measured with a Bruker DRX-500 (500 MHz) using TMS (tetramethylsilane) as internal standard. Melting points were measured on a Mettler FPS. The catalyst (copolymer-PTSA) was synthesized by the reported procedure [28] (Scheme 3).

Scheme 2

**Table 3** Copolymer-PTSA-catalyzed synthesis of disubstituted derivatives of 2,3-dihydroquinazolin-4(1H)-one

Product	R ²	R ³	Time (h)	Yield (%) ^a	M.p. (°C)	Ref.
2a	Me	Ph	3.4	84	164–166	[10]
2b	Me	4-ClC ₆ H ₄	3.6	82	190–192	[10]
2c	Me	4-CH ₃ OC ₆ H ₄	3.2	85	145–147	[10]
2d	Et	Ph	3.7	83	134–137	[10]
2e	Et	4-ClC ₆ H ₄	4	82	132–135	[10]
2f	Et	4-O ₂ NC ₆ H ₄	3.3	89	159–161	[10]
2g	Et	3-O ₂ NC ₆ H ₄	3.4	90	176–178	[10]
2h	Et	4-CH ₃ OC ₆ H ₄	4.1	81	124–126	[10]
2i	Ph	Ph	6.5	82, 81, 79, 80, 78 ^b	205–207	[26]
2j	Ph	4-O ₂ NC ₆ H ₄	7	77	195–197	[26]
2k	Ph	4-ClC ₆ H ₄	6.5	79	214–217	[26]
2l	Ph	3-O ₂ NC ₆ H ₄	6	81	186–188	[26]
2m	Ph	4-BrC ₆ H ₄	6.5	81	221–224	[26]
2n	Ph	4-CH ₃ C ₆ H ₄	6.7	82	205–207	[26]

^a Isolated yields^b The catalyst was reused for five runs

Scheme 3

General procedure for the synthesis of mono- and disubstituted derivatives of 2,3-dihydroquinazolin-4(1H)-one

To a solution of isatoic anhydride (1 mmol), ammonium salt (ammonium carbonate 0.6 mmol, ammonium acetate 1.2 mmol, or ammonium chloride 1.2 mmol) or primary amine (1.2 mmol), and aldehyde (1 mmol) in 5 cm³ ethanol was added 0.3 g copolymer-PTSA. The mixture was heated at reflux for the appropriate time (Table 2; Table 3). After completion of the reaction as indicated by TLC (eluent: *n*-hexane/ethyl acetate 2:1), the mixture was filtered and the

residue was concentrated. The crude products were recrystallized from ethanol.

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