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ORIGINAL PAPER

p-TSA-catalyzed synthesis of spiroquinazolinones

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Abstract *p*-Toluene sulfonic acid-catalyzed one-pot reaction of anthranilamide with ketones resulted in very good yields of novel spiroquinazolinones. The reaction worked well with a wide variety of ketones in shorter reaction times. The products were characterized using different spectral techniques.

Keywords Spiroquinazolinones · *p*-Toluene sulfonic acid (*p*-TSA) · Anthranilamide (ATA) · Ketones

Introduction

The quinazolinone skeleton remains as a building block for natural purine base [1], a few alkaloids, many biologically active compounds, and intermediates in organic synthesis [2]. Quinazolinone derivatives exhibit potential biological and pharmaceutical properties such as antiinflammatory [2], antihypertensive [3], anticancer [4], antitumor [5], anticonvulsant [6–8], and antibacterial activities [9]. Due to their importance in various fields, the development of environmentally benign, high-yielding clean synthetic methods for the disubstituted dihydroquinazolin-4(1*H*)-ones are in great demand.

One-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones has been achieved by the reductive cyclization of *o*-nitrobenzamide or *o*-azidobenzamide with aldehydes and ketones in the presence of metallic samarium and a catalytic amount of iodine or SmI_2 [10, 11] and low-valent titanium reagent [12–14]. A number of literature reports are available for the condensation of 2-aminobenzamides with aldehydes/ketones including those in the presence of *p*-TsOH/DDQ [15], I_2 [16], $FeCl_3$ [17], $CuCl_2$ [18], $TiCl_4$/Zn [19], chiral phosphoric acid [20, 21], ionic liquid/water [22], PPA-SiO_2 [23], $Sc(OTf)_3$ [24], $Ga(OTf)_3$ [25], zirconium(IV) chloride [26, 27], and heteropoly acids [28]. Multicomponent synthesis of dihydroquinazolinone has been reported from isatoic anhydride, aromatic aldehydes and ammonium acetate or amine catalyzed by L-proline [29], montmorillonite K-10 [30], vitamin B_1 [31], 2,2,2-trifluoroethanol [32], silica-bonded N-propylsulfamic acid [33], alum [34], and silica-bonded S-sulfonic acid [35].

Synthesis of 2-substituted quinazolinones from 2-aminobenzamide and various aldehydes has been known for a long time [36]. But the synthesis of 2,2-disubstituted quinazolinones from 2-aminobenzamides with ketones, cyclic ketones, and 1,2-dicarbonyl compounds has not yet been familiarized. Most of the synthetic protocols of spiroquinazolinone [37, 38] reported so far suffer from harsh reaction conditions, prolonged reaction time, use of high catalyst loading, and expensive methods, and also yields are often low due to poor selectivity in such conditions. Hence, better procedures for the synthesis of spiroquinazolinones are still awaited.

Experimental methods

Isatin, 5-chloroisatin, 5-nitroisatin, acenaphthenequinone, norcamphor, cyclohexanone, cyclopentanone, 1,4-cyclohexadione, *p*-benzoquinone, and all the catalysts used were purchased from Sigma-Aldrich and used as such without further purification. The melting points of all compounds were determined with an electrothermal apparatus

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using a capillary tube and are uncorrected. The purities of the compounds were checked by TLC using precoated silica gel plates with hexane:ethyl acetate (6:4) as eluent. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrophotometer at 400/100 MHz, respectively, using TMS as reference. High-resolution mass spectra of representative compounds were recorded on maXis 10138 Mass spectrometer at 70 eV. Elemental microanalyses were carried out on a Perkin-Elmer elemental analyzer Model 240C and a Thermo Finnigan analyzer series Flash EA1112.

General procedure for the synthesis of spiroquinazolinones (3a–3j)

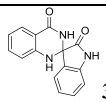
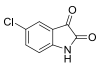
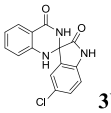
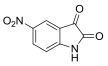
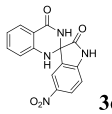
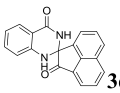
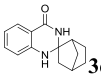
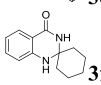
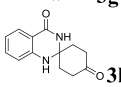
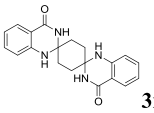
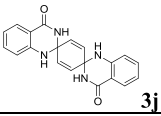
20 mol % of *p*-TSA was added to the 1:1 mixture of anthranilamide (1 mmol) and ketone (1 mmol) in 10 ml of ethanol and allowed to reflux for the appropriate time as shown in Table 1. The solid product formed from the reaction was separated by simple filtration and washed with water to remove *p*-TSA for obtaining the pure compound.

*1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3a**):* Colorless solid; mp: 260–262 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.29 (s, CONH), 8.35 (s, CONH), 7.60 (d, 1H, $J = 7.6$ Hz), 7.47 (d, 1H, $J = 7.2$ Hz), 7.32 (t, 1H, $J = 7.6$ Hz), 7.28 (s, 1NH), 7.22 (t, 1H, $J = 7.6$ Hz), 7.05 (t, 1H, $J = 7.6$ Hz), 6.85 (d, 1H, $J = 7.6$ Hz), 6.68 (t, 1H, $J = 7.6$ Hz), 6.61 (d, 1H, $J = 8$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.4, 164.3, 147.2, 142.5, 133.7, 131.2, 129.9, 127.3, 125.8, 122.7, 117.6, 114.7, 114.3, 110.5, 71.4; LCMS ($M^+ +1$) calcd for $C_{15}H_{11}N_3O_2$: 266.09, found 266.0.

*5-Chloro-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3b**):* Colorless solid; mp: 280–282 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.43 (s, CONH), 8.39 (s, CONH), 7.60 (d, 1H; $J = 7.2$ Hz), 7.49 (s, 1H), 7.37 (d, 1H, $J = 6.4$ Hz), 7.33 (s, 1NH), 7.23 (t, 1H), 6.85 (d, 1H, $J = 8$ Hz), 6.69 (t, 1H), 6.60 (d, 1H, $J = 8$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.8, 164.0, 147.8, 142.7, 133.8, 131.0, 127.3, 126.6, 125.8, 117.8, 114.3, 112.1, 71.5; HRMS (ESI) m/z calcd for $C_{15}H_{10}ClN_3O_2$ ($M^+ +1$): 300.15, found 300.05.

*5-Nitro-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**3c**):* Colorless solid; mp: 292–294 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.04 (s, CONH), 8.45 (s, CONH), 8.31 (d, 1H, $J = 2.4$ Hz), 8.29 (s, 1H), 7.63 (d, 1H, $J = 8$ Hz), 7.41 (s, NH), 7.28 (t, 1H, $J = 8.8$ Hz), 7.06 (d, 1H, $J = 8.8$ Hz), 6.73 (t, 1H, $J = 7.4$ Hz), 6.62 (d, 1H, $J = 8$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.8, 164.0, 149.1, 146.7, 142.9, 134.1, 130.8, 128.3, 127.4, 121.2, 118.2, 114.6, 114.5, 111.0, 71.1; HRMS (ESI) m/z calcd for $C_{15}H_{10}N_4O_4$ ($M^+ +1$): 311.07, found 311.07.

Table 1 *p*-TSA-catalyzed synthesis of spiroquinazolinones

S.No	Ketone	Time (min)	Yield (%)[a]	Product
1		30	82	 **3a**
2		60	80	 **3b**
3		60	79	 **3c**
4		60	81	 **3d**
5		10	85	 **3e**
6		10	86	 **3f**
7		10	86	 **3g**
8		10	85	 **3h**
9[b]		10	83	 **3i**
10[b]		60	82	 **3j**

Reactions were performed with 1 mmol of anthranilamide and 1 mmol of ketone with 20 mol % of *p*-TSA in ethanol under reflux conditions

[a] Isolated yield

[b] Anthranilamide:ketone in a 2:1 ratio

*1′H,2H-spiro[acenaphthylene-1,2′-quinazoline]-2,4′(3′H)-dione (**3d**):* Colorless solid; mp: 238–240 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.49 (s, CONH), 8.37 (d, 1H, $J = 8$ Hz), 8.14 (d, 1H, $J = 7.6$ Hz), 8.01 (d, 1H, $J = 7.2$ Hz), 7.90 (m, 3H), 7.67 (d, 1H, $J = 7.2$ Hz), 7.46 (s, NH), 7.24 (t, 1H, $J = 7.6$ Hz), 6.73 (t, 1H, $J = 7.2$ Hz), 6.57 (d, 1H, $J = 8$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 200.8, 164.1, 147.1, 141.2, 138.4, 133.9, 132.6, 130.3, 129.7, 129.5, 128.8, 127.4, 126.8, 123.0, 122.1, 117.8, 114.8, 114.1, 74.4; HRMS (ESI) m/z calcd for $C_{19}H_{12}N_2O_2$ ($M^+ +1$): 301.08 found 301.09.

*1′H-spiro[bicyclo[2.2.1]heptane-2,2′-quinazolin]-4′(3′H)-one (**3e**):* Colorless solid; mp: 194–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.19 (s, CONH), 7.56 (t, 1H, $J = 4.4$ Hz), 7.20 (s, NH), 6.85 (d, 1H, J = 6.8 Hz),

6.76 (d, 1H, $J = 6.4$ Hz), 6.62 (t, 1H; $J = 4$ Hz), 2.07 (m, 2H), 1.27 (m, 8H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 147.9, 133.5, 127.7, 116.9, 115.8, 114.5, 75.5, 46.4, 45.7, 35.1, 35.6, 28.1, 22.5; HRMS (ESI) m/z calcd for $C_{14}H_{16}N_2O$ ($M^+ +1$): 229.19, found 229.13; Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.48; H, 7.12; N, 12.15.

*1′H-spiro[cyclohexane-1,2′-quinazolin]-4′(3′H)-one (**3f**):* Colorless solid; mp: 220–222 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.93 (s, CONH), 7.57 (d, 1H, $J = 8$ Hz), 7.22 (t, 1H, $J = 8$ Hz), 6.81 (d, 1H, $J = 8$ Hz), 6.62 (m, 2H), 1.74 (m, 2H), 1.55 (m, 6H), 1.43 (m, 1H), 1.25 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 147.2, 133.5, 127.5, 116.9, 115.0, 114.8, 68.2, 37.6, 25.1, 21.3; DEPT ^{13}C NMR (135 MHz, DMSO-d_6): δ CH_2 H's: 37.61, 25.10, 21.34; HRMS (ESI) m/z calcd for $C_{13}H_{16}N_2O$ ($M^+ +1$): 217.13, found: 217.13; Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46 N, 12.95. Found: C, 72.31; H, 7.41; N, 12.85.

*1′H-spiro[cyclopentane-1,2′-quinazolin]-4′(3′H)-one (**3g**):* Colorless solid; mp: 264–266 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.09 (s, CONH), 7.56 (d, 1H, $J = 7.6$ Hz), 7.20 (t, 1H, $J = 7.2$ Hz), 6.73 (s NH), 6.68 (d, 1H, $J = 8$ Hz), 6.62 (t, 1H, $J = 5.2$ Hz), 1.65 (d, 8H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.9, 148.0, 133.4, 127.7, 117.0, 115.0, 114.8, 77.5, 22.4; LCMS ($M^+ +1$) calcd for $C_{12}H_{14}N_2O$: 203.13, found: 203.0; Anal. Calcd. For $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.32; H, 6.91; N, 13.96.

*1′H-spiro[cyclohexane-1,2′-quinazoline]-4,4′(3′H)-dione (**3h**):* Colorless solid; mp: >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.68 (s, CONH), 7.57 (d, 1H, $J = 7.6$ Hz), 7.24 (t, 1H, $J = 6.8$ Hz), 6.77 (d, 1H, $J = 8$ Hz), 6.66 (t, 1H, $J = 8$ Hz), 6.53 (s, NH), 2.07 (s, 4H), 1.86 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.3, 172.2, 147.2, 132.5, 126.4, 116.1, 113.7, 69.2, 32.4.

*1′′,3′′-Dihydrospiro[1′,3′-dihydrospiro[cyclohexane-1,2′-quinazolin]-4′-one-4,2′′-quinazolin]-4′′-one (**3i**):* Colorless solid; mp:>300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.67 (s, 2CONH), 7.57 (t, 2H, $J = 6.4$ Hz), 7.26 (d, 2H, $J = 6.8$ Hz), 6.78 (t, 2ArH, $J = 6.6$ Hz), 6.65 (d, 2ArH, $J = 7.2$ Hz), 6.54 (s, 2NH), 1.87 (s, 8H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.2, 146.5, 133.3, 127.3, 117.0, 114.9, 114.7, 66.7, 32.0. LCMS ($M^+ +1$) expected: 349.21, found 349.0; Anal. Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.75; N, 16.17. Found: C, 69.05; H, 5.71; N, 16.17.

(*3j*) Colorless solid; mp:>300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.87 (s, 2CONH), 8.23-7.59 (m, 8H), 7.27 (s, 2NH), 6.04 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.9, 170.1, 145.3, 138.0, 132.4, 129.7, 125.8, 124.5, 122.1, 97.7; Anal. calcd for $C_{20}H_{16}N_4O_2$: C: 69.76 H: 4.68 N: 16.27 Found: C: 69.68, H: 4.61, N: 16.18.

Results and discussion

Nowadays, biologically active compounds have been synthesized via one-pot multicomponent reactions in a combinatorial fashion. Operationally simple organic transformations with inexpensive and readily available catalysts are attractive approaches for organic as well as medicinal chemists. Herein, we report the one-pot synthesis of some novel spiroquinazolinones using *p*-toluene sulfonic acid (*p*-TSA) as catalyst (Fig. 1).

Initially, we tried to carry out the synthesis of disubstituted quinazolinone, by taking anthranilamide and isatin as a model reaction with various catalysts such as acetic acid, sulfuric acid, alum, and *p*-TSA, and also in the absence of a catalyst. The yields were poor in the absence of a catalyst and also with catalysts other than *p*-toluene sulfonic acid. While optimizing the mol % of the catalyst to be used, we found that 20 mol % of *p*-TSA was better and there were no more enhancements in the yield by increasing the mol % of *p*-TSA. Hence, we have planned to apply 20 mol % of *p*-TSA catalyst for further reactions.

The mechanism of the reaction may be visualized as follows: protonation of 1,2-dicarbonyl compounds or other ketones takes place using *p*-toluene sulfonic acid, followed by the addition of anthranilamide leading to the formation of an imine (**A**). The cyclization reaction occurs by the attack of the amide $–NH_2$ group on the double bond of imine forming spiroquinazolinone after the H^+ shift (Fig. 2).

A series of spiroquinazolinone derivatives (**3a–3j**) were obtained from anthranilamide with different ketones such as isatin, 5-chloroisatin, 5-nitroisatin, acenaphthenequinone, norcamphor, cyclohexanone, cyclopentanone, 1, 4-cyclohexadione, and *p*-benzoquinone, by simple refluxing with *p*-TSA in ethanol. Because of the formation of a solid product in the reaction vessel, simple washing with distilled water was enough to get the pure product.

The reaction was widely applicable to diketones such as isatin, 5-substituted isatins, acenaphthenequinone, and various aliphatic cyclic ketones. The reactions were completed within an hour for the diketones and within 10 min for the cyclic ketones as shown in Table 1. When the reaction was

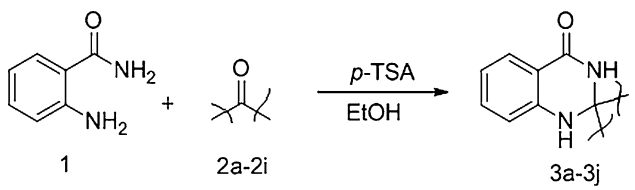


Fig. 1 General reaction scheme for the synthesis of spiroquinazolinones

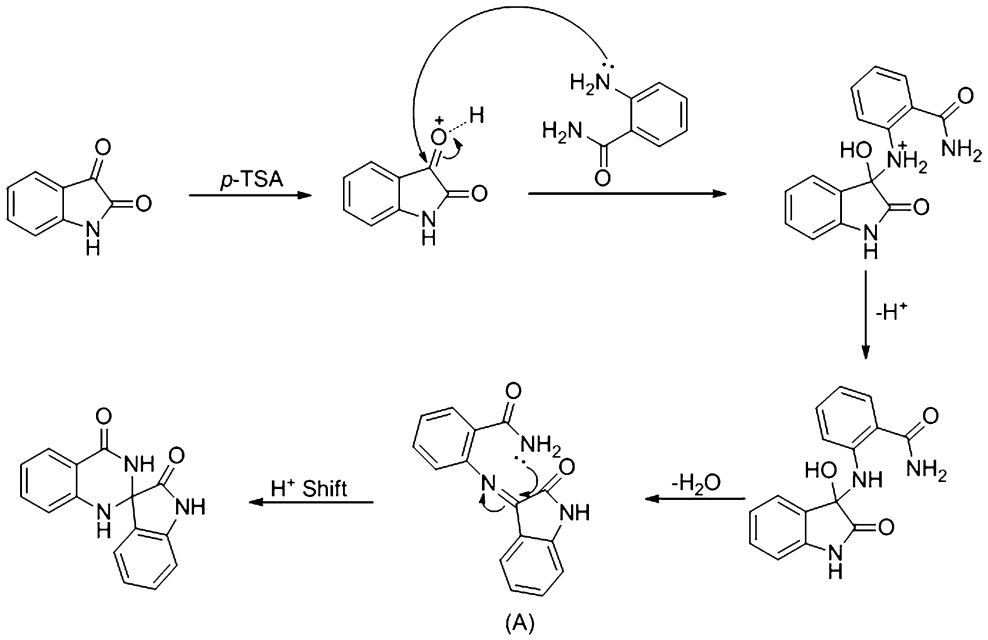


Fig. 2 Plausible mechanism for the synthesis of spiroquinazolinones

carried out with anthranilamide:1,4-cyclohexadione in 1:1 ratio, we found that the spiro compound was formed only on the single side of the ketone (Table 1, entry-8); if conducted with a 2:1 ratio, the dispiro compound formed (Table 1, entries 9, 10) was evidenced from the ^{1}H, ^{13}C NMR spectra and LCMS. Similarly, the reaction with *p*-benzoquinone also resulted in the formation of the dispiro compound. Unfortunately, this reaction does not work well for camphor and also for the cyclic 1,3-diketones such as dimedone, 1,3-cyclohexadione and Meldrum's acid, which may be due to the presence of steric strain in the expected spiroquinazolinone product.

Conclusions

An efficient protocol for the synthesis of spiroquinazolinones has been developed, which offered several advantages such as use of green solvent, easy separation of the product without any chromatographic techniques, mild reaction conditions, use of inexpensive and commercially available starting materials, and shorter reaction time.

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