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Sulfamic acid as energy efficient catalyst for synthesis of flurophores, 1-*H*-spiro [isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-diones

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Abstract. An energy efficient synthesis of 1-*H*-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-diones has been expediently accomplished by a reaction of isatin(s) / cyclic ketone and anthranilamide in ethanol at ambient temprature. Excellent yields of the products in short time duration, operational simplicity, and simple work-up procedure are the attractive features of the present protocol. Synthesized 1-*H*-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-diones were found to be fluorescent with absorption in UV region (302, 362 nm) and emission in visible region (413-436 nm) with Stokes shift of 44-72 nm.

Keywords. Cyclo-condensation; energy efficient synthesis; fluorescence spectroscopy; spiro compounds.

1. Introduction

Environmental and economic concerns have recently directed strong attention towards achieving synthesis of useful pharmacophores under eco-benign conditions. Quinazolinones have emerged as *important* structural motifs due to their wide biological and pharmaceutical activities, such as analgesic, anticancer, antifertility, antibacterial, diuretic, and herbicide activities.[1–7] On the other hand, spiro-oxindole framework is found to be the core structure in many pharmacological agents and natural alkaloids.[8] In particular, 3-substituted indolin-2-one derivatives have received extensive biological scrutiny.[9–12] Recently, extensive and versatile pharmacological properties have been reported for some isatin-derived spiro-2,3-dihydroquinazolinones[13–15] (figure 1). In this context, the synthesis of spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-dione is of prime importance.

In contrast to the widely studied 2,3-dihydroquinazolinones,[16–29] sporadic literature is available[30–34] for the synthesis of 1-*H*-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-diones. They are generally synthesized by multi-component reaction of isatoic anhydride, amine and carbonyl compounds or two component cyclocondensation of anthranilamide with carbonyl compounds. Amongst these two routes, scanty reports are available for latter which involve reflux condition using organic asymmetric catalyst CPA,[35] KAl $(SO_4)_2.12H_2O$ (alum)[36] and Amberlyst-15 under ultrasound irradiation.[37] Therefore, an energy efficient method for the synthesis of 1-*H*-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-diones is highly desirable.

Sulfamic acid (SA, H_2NSO_3H) is a solid inorganic acid with mild acidity. The properties like nonvolatile, noncorrosive, stable, low-cost, easy commercial availability, etc., have triggered their use as catalyst of choice in number of organic transformations.[38–41] In recent years, we have reported SA as an effective catalyst for the synthesis of 1,2,4-triazole-3-thiones, spiroindoloquinoxaline, and substituted-5-deazaoxaflavins.[42–44] Our earlier experience with SA and interest in the synthesis of heterocycles, prompted us to explore SA for the synthesis of 1-*H*-spiro[indoline-3,2′-quinazoline]-2,4-(3-*H*)-diones. In the current work, we disclose an efficient methodology for synthesis of 1-*H*-spiro [indoline-3,2′-quinazoline]-2,4-(3-*H*)-diones by ring closure of anthranilamide with a carbonyl derivative in the presence of catalytic amount of sulfamic acid in ethanol media at room temperature (scheme 1).

2. Experimental

2.1 *Materials and characterization*

Various substituted isatins and anthranilamide (Sigma-Aldrich), sulfamic acid (Spectrochem) were used as received. Melting points were recorded by open capillary method and are uncorrected. NMR spectra were recorded on Bruker AC-300/400 (300/400 MHz for ^{1}H NMR and 75/100 MHz for ^{13}C NMR) spectrometer in DMSO-d_6 using TMS as an internal standard and δ values are expressed in ppm. Mass spectra were recorded on SHIMADZU LCMS 2020, UV - Visible

*For correspondence

absorption spectra were recorded on Specord 210 plus UV Visible-spectrometer and the emission spectrum was recorded on a spectrofluorometer- Jasco, Model-F.P-8300 in DMSO solvent with concentration of 0.03 mg/mL and path length 1 cm.

2.2 *General procedure for synthesis of 1-H-spiro [isoindoline-1,2′-quinazoline]-3,4′(3′H)-diones*

To a mixture of isatin(s)/acenaphthoquinone/cyclic ketone(s) (1 mmol) and anthranilamide (1 mmol) in ethanol (96%, 2 mL), sulfamic acid (0.2 mmol) was added. The reaction mixture was stirred at ambient temperature for the time mentioned in table 2 until completion of reaction, as monitored by TLC. After the completion of reaction, the precipitated products was just filtered. The confirmation of isolated products was done by spectral techniques such as ^{1}H, ^{13}C NMR, IR and mass spectrometry.

3. Results and Discussion

In the initial stages of the present work, screening of catalysts was carried out for cyclocondensation of anthranilamide (1 mmol) and isatin (1 mmol) in ethanol at room temperature to enable optimization of the reaction conditions. Catalysts such as *p*-TSA, sulfamic acid, L-proline, EPZ-10, EPZ-G(solid supported Lewis acids) and $AlCl_3$ were employed for the model reaction and results are summarized in table 1. It is evident from table 1 that sulfamic acid is the best catalyst in terms of yield of desired product and time required for its formation. Effect of amount of sulfamic acid was also studied for model reaction and delightfully, we got the expected product in excellent yield with 20 mol% of sulfamic acid within 40 min (scheme 1).

As desired product gets precipitated from the reaction mixture, isolation was done by simple filtration after adding cold water. Confirmation of final product was done by physical constant (M.P.) and spectral techniques such as, ^{1}H, ^{13}C NMR, IR and mass spectra.

Comparison of efficiency of SA with that of earlier reported catalysts for the present transformation is summarized in table 2. The outcome displays outstanding efficacy of SA in terms of time as well as yield.

A plausible mechanism of the reaction is proposed in scheme 2. Initially, isatin (1) was activated by sulfamic acid, then the carbonyl unit of the isatin (**1**′) undergo nucleophilic attack by amine of anthranilamide (**2**) to

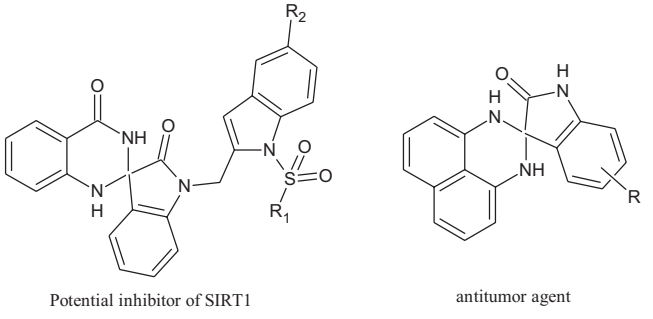
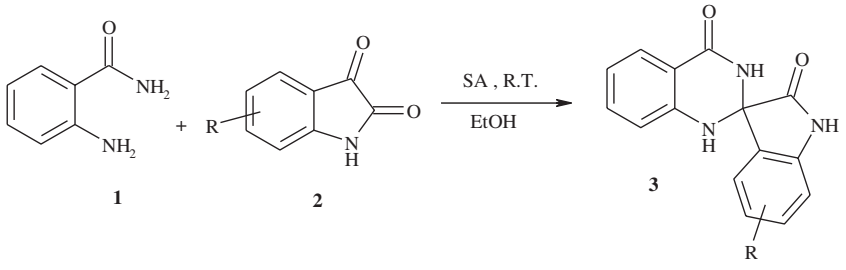


Figure 1. Some biologically important spiro-2,3-dihydroquinoxalinones.

Table 1. Optimization of the reaction conditions for synthesis of 1-*H*-spiro [indoline-3,2′- quinazoline]-2,4-(3-*H*)-diones.

Entry	Catalyst	Catalyst load (mol%)	Temp.	Time min	Yield %[a]
1	*L*-Proline	20	RT	60	65
2	*p*-TSA	20	RT	60	70
3	EPZ-10	20	RT	80	43[b]
4	EPZ-G	20	RT	80	38[b]
5	$AlCl_3$	20	RT	60	62
6	Sulfamic acid	20	RT	40	92
7	Sulfamic acid	05	RT	50	53
8	Sulfamic acid	10	RT	50	60
9	Sulfamic acid	15	RT	40	83
10	Sulfamic acid	30	RT	40	92

*Reaction conditions: Isatin (1mmol), anthranilamide (1 mmol), Solvent = 2 mL, 96% ethanol; room temperature; [a]Isolated yields; [b]As the catalyst is insoluble in alcohol, extraction of reaction mixture with ethyl acetate was carried out for isolation of product.



Scheme 1. Efficient synthesis of 1-*H*-spiro [isoindoline-1,2′-quinazoline]-3,4′(3′H)-diones.

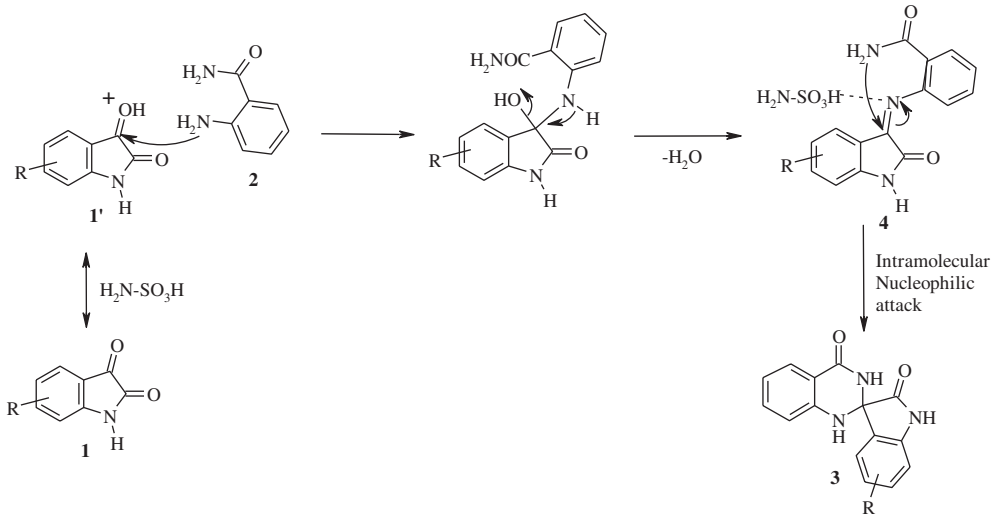
produce an imine intermediate **4**, which subsequently undergoes intramolecular cyclization involving nucleophilic attack by $–CONH_2$ moiety on –C=N– affording the desired product (**3**) (scheme 2).

Encouraged by the initial success in the synthesis of 1-*H*-spiro[indoline-3,2′-quinazoline]-2,4-(3-*H*)-diones and to investigate the general scope and versatility of current strategy, different substituted isatins (entries 1-7, table 3), acenaphthylene-1,2-dione (entry 10, table 3), cyclohexanone (entry 8, table 3) and cyclopentanone (entry 9, table 3) were examined under optimized conditions. Excitingly, corresponding substituted 1-*H*-spiro [indoline-3,2′-quinazoline]-2,4-(3-*H*)-diones were successfully and smoothly obtained, and the results are listed in table 3.

Finally, the absorption and fluorescence spectra of synthesized 1-*H*-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-diones (SIIQ), **3a–j** were recorded in DMSO solvent (0.03 mg/mL and path length 1 cm) (figure 2). The calculated values of the absorption maxima (λ_{max}),

Table 2. Efficiency of SA and comparison with earlier reported catalysts.

Entry	Catalyst	Catalyst load (mol%)	Solvent	Temp.	Time h	Yield %[a]	Ref
1	$KAl(SO_4)_2.\ 12H_2O$	20	EtOH	Reflux	6	92	36
2	CPA	10	Ethylene dichloride	30°C	12	56	35
3	Sulfamic acid	20	EtOH	RT	0.67	92	This work



Scheme 2. Plausible mechanism for the synthesis of 1-*H*-spiro [isoindoline-1,2′-quinazoline]-3,4′(3′H)-diones.

Table 3. Sulfamic acid catalyzed synthesis of a wide array of 1-*H*-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-diones.

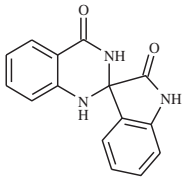
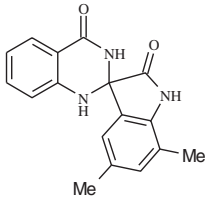
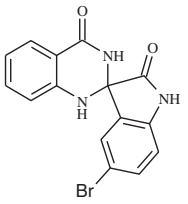
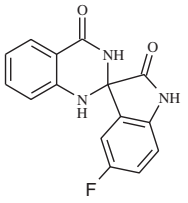
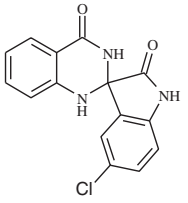
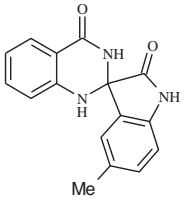
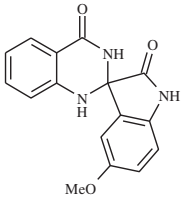
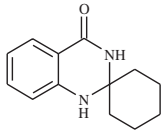
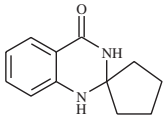
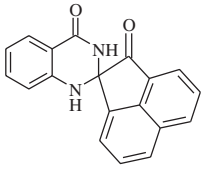
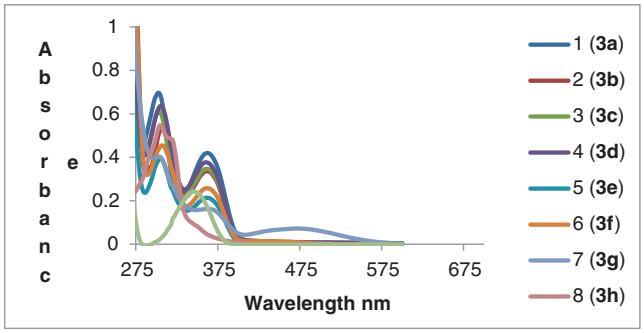
Entry		Product	Time min	Yield*%[a]
1	**3a**		40	92
2	**3b**		30	90

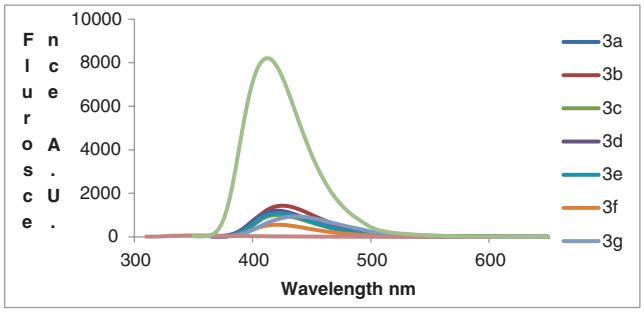
Table 3. (continued)

Entry		Product	Time min	Yield*%[a]
3	**3c**		50	86
4	**3d**		60	78
5	**3e**		45	86
6	**3f**		40	76
7	**3g**		40	87
8	**3h**		20	90
9	**3i**		25	85
10	**3j**		30	78

*Reaction condition: Isatin(s) (1 mmol), anthranilamide (1 mmol), Sulfamic acid 20 mol %, Solvent -2 mL, 96 % ethanol; room temperature; [a]Isolated yield.



(a) UV absorption spectra of 3a-j



(b) Fluorescence's spectra of 3a-j

Figure 2. Absorption and emission spectra of SIIQ. (a) UV absorption spectra of **3a-j** and (b) Fluorescence spectra of **3a-j**.

Table 4. Photophysical data of the synthesized compounds, **3a-3j** in DMSO as solvent.

Sr. No.	Product code	Absorbance Maximum (λ_{max}) nm	Fluorescence Maximum (λ_{em}) nm	Stokes Shift (ss) nm
1	**3a**	302, 362	425	63
2	**3b**	308, 362	424	62
3	**3c**	304, 362	422	60
4	**3d**	306,360	421	61
5	**3e**	306, 362	422	60
6	**3f**	308, 362	421	59
7	**3g**	304, 364	436	72
8	**3h**	346	413	67
9	**3j**	304	348	44

*Fluorescence spectra of the synthesized compounds monitored at the excitation wavelength (λ_{max} = 360-365 nm for **3a-3g**; concentration = 0.03 mg/mL, path length = 1 cm).

emission maxima (λ_{em}), Stokes shift (ss) are listed in table 4.

The absorption and emission maxima appear due to $\pi - \pi^*$ and n- π^* transition resulting from electron delocalization of the aromatic quinazolinone and isatin ring. The compounds **3a-g** exhibited two absorption maxima due to $\pi - \pi^*$ and n- π^* transition, whereas compounds **3h** and **3j** exhibit a single absorption maxima due to the $\pi - \pi^*$transition. The effects of substituents have a negligible role in the absorption spectra, whereas in the emission spectra, considerable Stokes shift was observed (72 nm) for 5-methoxy substituent (**3g**). When isatin is replaced by acenaphthaquinone **(3j)**, intensity of emission spectrum considerably decreased with Stokes shift of 67 nm, which may be due to loss of conjugation, while in the case of **3h**, intensity of emission spectra increased (about eight times) with less Stokes shift of 43 nm.

4. Conclusions

In conclusion, we have developed an energy efficient sulfamic acid catalyzed method for the cyclocondensation of carbonyl compounds with anthranilamide leading to 1-*H*-spiro [isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-diones. The Synthesized compounds were found to be flurophores with considerable Stokes shift of 44-72 nm, even though there is negligible effect of substituent in absorption and emission spectra. Further detailed study will certainly explore the analytical applications of such spiroquinazolinones. The method possesses following advantages: (a) inexpensive sulfamic acid as the catalyst; (b) environment friendly ethanol as the solvent; (c) high reaction yields; (d) short time duration; (e) ambient temperature; (f) water as the only by-product; and (g) wide substrate scope.

Supplementary Information (SI)

Experimental details, procedures and spectral data *viz.,* IR, ^{1}H, ^{13}C NMR and Mass spectra of synthesized compounds are provided as supplementary file. Supplementary information is available at www.ias.ac.in/chemsci.

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