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One-pot synthesis of spiro [indol- thiazolidinone]derivatives by three-component reaction of isatin, thioglycolic acid and amines catalyzed by oxalic acid

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ABSTRACT

Spiro-indolethiazolidinone derivatives are interesting heterocyclic compounds which show diverse biological and pharmacological properties. In this research spiro-indolethiazolidinone derivatives was prepared by one-pot condensation reaction of isatin, thioglycolic acid and a number of amines using oxalic acid as a catalyst at room temperature.

KEYWORDS

Three-component;
Spiro[indole-thiazolidinone];
Isatin;
Thioglycolic;
Oxalic acid.

INTRODUCTION

Thiazolidinone's ring bearing compounds show varied biological activities, so have displayed significant biological activity like anticancer[8-10], antibacterial, antifungal, antimicrobial, antihistaminic and antiviral[1-7].

Recent literature shows resurgence of interest in the chemistry and bioactivity of isatin derivatives leading to improvement in procedures of several already known reactions, development of stereoselective methodologies, and synthesis of isatin derivatives with various biological activities such as anticonvulsant, antimicrobial, antitumor, antiviral, anti-HIV, and ant tubercula[1]. The most fascinating application of isatins in organic synthesis is undoubtedly due to the highly reactive C-3 carbonyl group. The reactions of the C-3 carbonyl group of isatins, mostly by nucleophilicadditions or spiroannulation, transform it into 2-oxindole derivatives.

Thiazolidinone's ring bearing compounds show varied biological activities, so have displayed significant biological activity like anticancer[2-7], antibacterial, antifungal, antimicrobial, antihistaminic and antiviral[8-10].

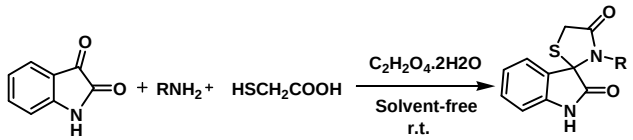
2-Oxindoles, especially those which are spiro-fused to other cyclic frameworks, have drawn tremendous interest of researchers in the area of synthetic organic chemistry and medicinal chemistry worldwide because they occur in many natural products like alkaloids, and have been reported to have various types of bioactivity such as progesterone receptor modulators, anti-HIV, anticancer, antitubercular and antimalaria[11-13].

Design of new substances based on privileged scaffolds is one of the successful directions in drug discovery. Combination of thiazolidinones and isatin in one molecule gives access to series of compounds with a broad spectrum of biological activity[14].

The most convenient method for the synthesis of 2,3-disubstituted-4-thiazolidinones is the one-pot three-component reaction of a primary amine, an oxo-compound and a thiolic agent. The different reaction conditions, such as long term heating with a dehydrant, using an acylation agent or microwave assistant organic synthesis were described[15-17]. Using isatin or its deriva-

tives in this reaction as oxo-compounds allowed to obtain spiro[indole-thiazolidinones]. The spiro[indole-thiazolidinone] system has been synthesized earlier conventionally by a two-step procedure using isatin-3-imines as key intermediate, which were synthesized from substituted isatins and aromatic amines[18-21]. However one-pot synthesis of these compounds has also been reported using ionic liquids[22], microwave irradiation[23] and acetic acid in anhydrous benzene[14]. Although this method has its own merits in comparison to a conventional two-step procedure but developing versatile approaches towards synthesis of spiro[indole-thiazolidinone] derivatives still remains a highly desired goal in organic synthesis.

During our quest to develop novel catalysts for multicomponent reactions[24-26], herein, we describe an efficient method for the synthesis of spiro[indole-thiazolidinone] derivatives through one-pot condensation reaction of isatin, thioglycolic acid and amines using citric acid as a catalyst (Scheme 1).



Scheme 1 : Synthesis of spiro[indole-thiazolidinone] derivatives

EXPERIMENTAL

General

Melting points were determined in open capillaries using an Electrothermal Mk3 apparatus. IR spectra were recorded using a Perkin-Elmer FT–IR 781 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-250 spectrometer. Purity of the compounds was checked by TLC.

General procedure for the synthesis of spiro[indole-thiazolidinone] derivatives

A mixture of isatin (1 mmol), amine (1 mmol), thioglycolic acid (1 mmol), and oxalic acid (0.1 g) was stirred at room temperature for the appropriate time indicated in TABLE 2. After completion of the reaction, as indicated by thin-layer chromatography (TLC; ethyl acetate=n-hexane 1=4), ethyl acetate (10 ml) was added and the catalyst was recovered by filtration. After evaporation of the solvent, the resulting solid residue was recrystalized from ethanol to obtain pure product.

TABLE 1 : Optimize the reaction condition

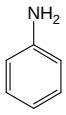
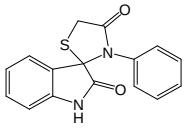
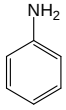
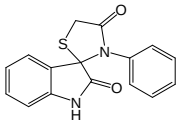
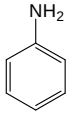
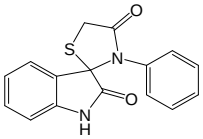
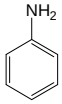
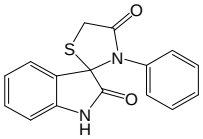
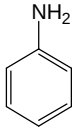
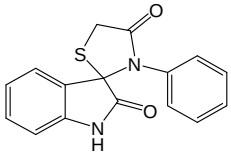
Entry	Aniline	Temperature	Product	Yield (%)	Time (min)
1		120°C		70	5
2		100°C		65	9
3		80°C		70	10
4		60°C		75	11
5		25°C		80	15

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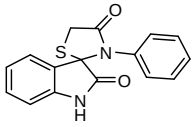
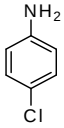
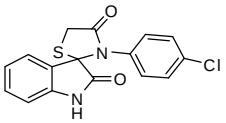
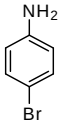
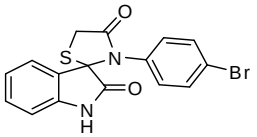
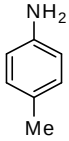
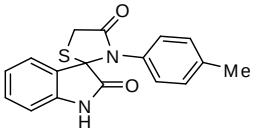
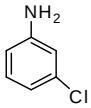
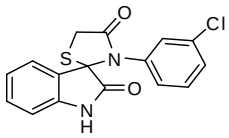
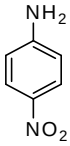
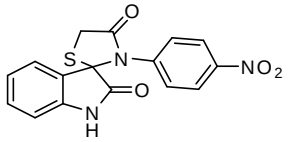
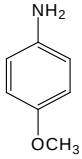
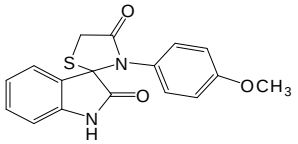
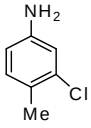
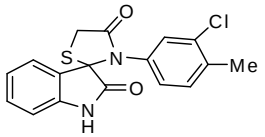
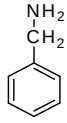
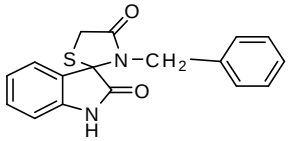
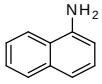
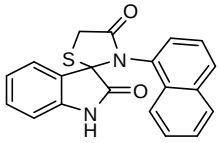
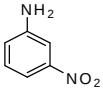
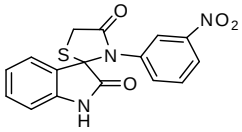
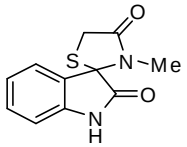
TABLE 2 : The results of one-pot reaction of isatin, thioglycolic acid and amines

Entry	amine	product	Time (min)	Yield (%)	m.p.(°C)[ref]
1			10	82	157 [18]
2			10	82	192-194 [12]
3			10	80	165-170 [18]
4			15	80	125 [19]
5			10	84	176-180 [23]
6			15	81	182-184 [23]
7			10	86	210-211 [21]
8			10	85	180-184 [20]
9			15	75	152-154 [21]
10			10	76	160-163 [20]
11			15	79	171-175 [20]
12	CH_3-NH_2		10	87	170-172 [21]

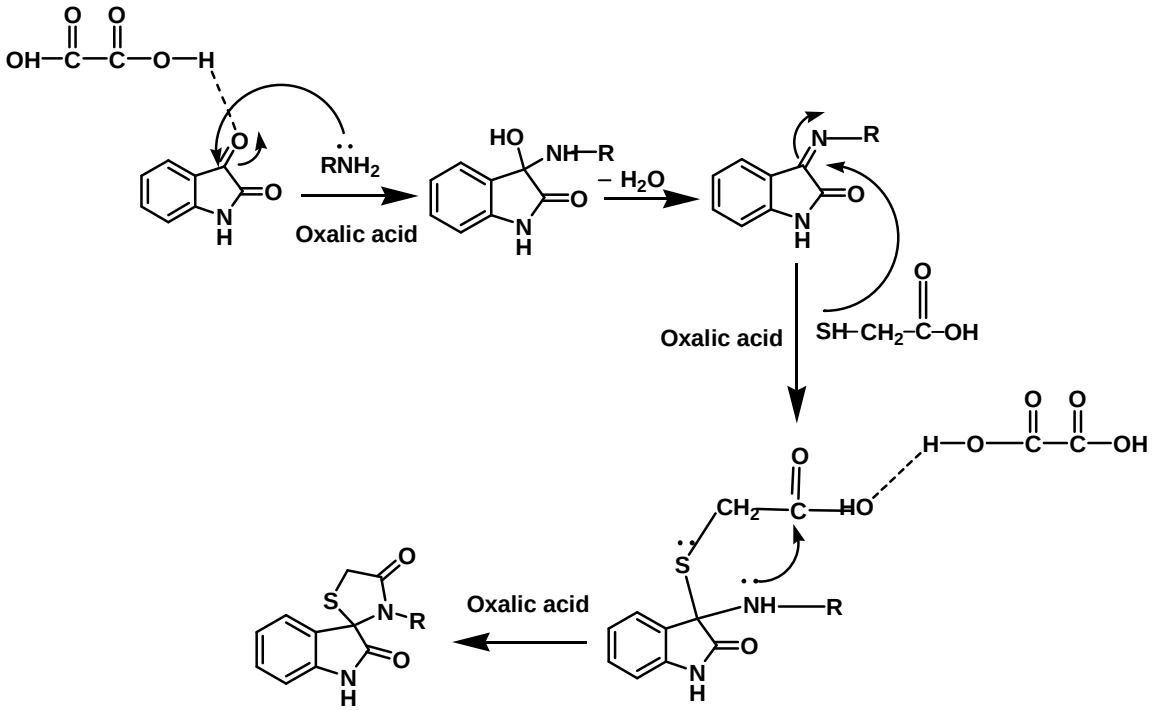
3'-(4-Methylphenyl)spiro[3H-indole-3,2'-thiazolidine]-2,4'(1H)-dione ($C_{17}H_{14}N_2O_2S$)

IR (KBr) 3,440, 2,926, 1,739, 1,680, 1,495, 1,363, 1,237, 932, 827, 757, 691, 629 cm^{-1}; ^1H NMR (250 MHz, DMSO-d6): δ = 2.23 (s, 3H, CH_3), 3.90 (d, J = 15.1 Hz, 1H), 4.15 (d, J = 15.1 Hz, 1H), 6.80 (m, 2H), 6.89 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.31 (m, 2H), 10.58 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d6): δ= 21.2, 32.3, 70.4, 112.1, 114.3, 115.9, 117.9, 118.4, 127.3, 130.6, 138.8, 152.3, 154.4, 171.8, 176.2 ppm

RESULTS AND DISCUSSION

Oxalic acid is a readily available and inexpensive reagent and can conveniently be handled and removed from the reaction mixture. Thus, the remarkable catalytic activities together with its operational simplicity make it the most suitable catalyst.

To optimize the reaction conditions, the reaction of isatin, thioglycolic acid and aniline was used as a model reaction. Reactions at different conditions and various molar ratios of substrates in the presence of oxalic acid revealed that the best conditions were solvent-free at



Scheme 2 : Proposed mechanism

room temperature (TABLE 1).

To show the generality of this method the optimized system was used for the synthesis of other spiro[indole-thiazolidinone] derivatives. The results are summarized in TABLE 2. Various functionalities present in the anilines, such as chloro, nitro, methyl groups were tolerated under these conditions at room temperature (TABLE 2).

The reaction can also proceed with aliphatic amine (TABLE 2, entry 12). In all these cases, the corresponding spiro[indole-thiazolidinone] were obtained in good yields. All products are known compounds and structures of them were confirmed by comparison with their known physical and spectral (NMR and IR) data.

The mechanism of this reaction is believed to proceed through condensation of isatin with amine to yield the corresponding imine. Then nucleophilic attack of the thiol group on the imine carbon–nitrogen double bond activated by acid catalyst underwent cyclization to form spiro[indole-thiazolidinone] derivatives, accompanied by loss of H_2O as shown in Scheme 2.

CONCLUSION

In conclusion, we describe a convenient and efficient process for the synthesis of spiro[indole-thiazolidinone] derivatives by one-pot reaction of isatin, thioglycolic acid and amines in the presence of oxalic

acid at room temperature. This method offers some advantages in terms of simplicity of performance, short reaction times and low cost, and it follows the guidelines of green chemistry. The catalyst is readily available and inexpensive, and it can be handled conveniently and removed from the reaction mixture. We believe that this is a convenient, economic, and user-friendly process for the synthesis of spiro[indole-thiazolidinone] derivatives of biological and medicinal importance.

ACKNOWLEDGEMENTS

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