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Molecular Iodine Catalysed One Pot Synthesis of Spirooxindoles by Tandem Knoevenagel Cyclisation

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Abstract

Spirooxindoles are heterocycles found in various natural and synthetic products with potent bio-, physio-, and pharmaceutical activities. Heterocyclic fused phthalazines possess antimicrobial, antifungal, anticancer, anti-inflammatory, and cardiotonic activities. Hence, an efficient multi-component method has been developed for the synthesis of pyrazolophthalazinyl spirooxindoles through tandem Knoevenagel cyclisation from isatin, malononitrile and various phthalhydrazides in presence of readily available molecular iodine as a catalyst in ethanol solvent under ultrasonic condition to afford the products in very good yield within 15 mins. The method is simple, efficient, uses readily available commercial starting materials and gives good yield of product in short reaction time.

Keywords : Iodine, One-pot , Ultrasound, Spirooxindoles, Knoevenagel cyclisation, Multicomponent

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1. Introduction

Multi component reactions (MCRs) are significant type of organic reactions for the production of structurally complex organic molecules. MCR is a chemical reaction where three or more readily available starting materials react together to form a single product through one pot methodology. Compared to conventional linear type synthesis, the multicomponent reactions have been considered as an economic and environmental friendly method, due to its significant advantages such as saving energy, rapid and simple procedures [1]. It is considered as an ideal technique for the development of green chemistry methods.

Heterocyclic organic compounds mainly nitrogen and oxygen containing heterocycles have an important role in organic synthesis and medicinal chemistry fields. Geometrically distinct polycyclic structures are obtained by fusion of several rings, which lead to high functional specialization due to their ability to orient substituents in three dimensional spaces. The fused heterocyclic ring system stimulates the biological activity of the compounds. Therefore, development of efficient methodologies for the synthesis of fused heterocycles is always of interest to both organic and medicinal chemists. Spiro compounds have significant attraction towards the area of organic synthetic chemistry due to their unique structural and reactive nature. Spiro compounds are bicyclic or polycyclic organic compounds linked through one atom. The rings can be either identical or different in nature.

Among the spiro compounds, spirooxindole is a significant class of compounds widely present in many of the natural products as well as biologically active compounds [2-6]. Spirooxindole heterocycles have been widely studied because of their interesting structural properties along with high biological and medicinal activities [7,8]. Hence, we feel that, there is still a need for further development of synthetic methodologies with milder reaction conditions, shorter reaction durations and better yields, which can possibly be achieved using ultrasound as energy source.

In recent years, ultrasound assisted organic reactions have emerged as an environmentally benign method in organic synthesis [9-15]. It has several advantages over other conventional methods of organic

synthesis [15-20]. Some of the common advantages of ultrasound technique are high reaction yield, less effect on the environment, reduced reaction time and highly accelerated reaction rate. In the present work, we synthesized a new series of spiro compounds namely pyrazolophthalazinyl spirooxindoles in presence of simple and eco-friendly catalyst as I_2 using ultrasound technique.

2. Experimental

2.1. Instrumentation

All starting materials were commercial products and were used without further purification. Liquid aldehydes were distilled before use. TLC were used for monitoring the progress of the reaction. TLC was carried out on Merck made silica gel $60F_{254}$ plates with ethylacetate: hexane system. The product formation was confirmed by recording the melting points, IR and ^{1}H NMR spectra. Melting points were determined on Veego VMP-D melting point apparatus. IR spectra were recorded using Bruker Alpha-T ATR/FTIR spectrometer and nuclear magnetic resonance spectra were recorded on a 400 MHz Bruker AMX instrument in DMSO-d_6. All the reactions were studied using SIDILU, Indian make sonic bath working at 35 kHz maintained at 25-30 °C without mechanical stirring. Yields refer to isolated yields of the products.

2.2. Synthesis

A mixture of phthalhydrazide (2 mmol), malononitrile (2 mmol), substituted isatins (2 mmol) and iodine (30 mol%) in ethanol were sonicated in a sonic bath working at 35 kHz maintained at 25-30 °C. After completion of the reaction (monitored by TLC), product was dissolved in ethyl acetate (10 mL) and washed successively with $Na_2S_2O_3$ solution and then dried over anhydrous sodium sulphate to get the crude compound in almost pure form. The analytical grade of the product was obtained by column chromatography.

3. Results and discussion

For any successful synthesis optimizing the reaction conditions is of crucial importance. In order to optimize the reaction conditions, the reaction of isatin (2 mmol), malononitrile (2 mmol),

phthalhydrazide (2 mmole) was chosen as a model system. Initial investigations began with the conduct of model reaction in presence of different catalyst refluxing in ethanol and found that the reaction gave satisfying result in the presence of I_2 as an inexpensive and readily available catalyst.

To find a suitable synthetic methodology, three component reactions in the presence of I_2 in ethanol was carried out under both classical refluxing and ultrasound irradiation conditions. However, both conventional heating and the ultrasound irradiation afforded the desired product, but ultrasound irradiation prominently accelerated the reaction and afforded the product in very good yield within 15 mins. This is attributed to the fact that, liquids irradiated with ultrasound generate tiny bubbles that can undergo a violent collapse known as cavitation, which produces localized microscopic "hot spots" with transient high temperatures and pressures to bring about favourable reaction conditions. Sonication helps in efficient stirring of the reaction, which is also another reason for rate enhancement.

Entry	Catalyst/Methodology	Time (mins)	Yield(%)
1.	$ZnCl_2$/Reflux	30	58
2.	$ZnCl_2$/))))	15	60
3.	$CoCl_2$/Reflux	30	55
4.	$CoCl_2$/))))	15	60
5.	Amberlite-IR 120/Reflux	30	65
6.	Amberlite-IR 120/))))	15	70
7.	$FeCl_3$/Reflux	30	55
8.	$FeCl_3$/))))	15	65
9.	I_2/Reflux	30	75
10.	**I_2/))))**	15	90

Next attempt was to study the effect of amount of the catalyst, the reactions were carried out with different amounts of I_2 ranging from 10-30 mol%. It was noticed that increasing the amount of the catalyst from 10 to 20, and 30 mol%, the yields increased from 70 to 80 and 90%, respectively. 30 mol% I_2 in ethanol is ample to drive the reaction forward appreciably. Further addition did not improve the yield.

As already known, solvent plays a crucial role in ultrasonic assisted reactions. Screening of the solvent was done to find the ideal solvent for conducting the reaction. Therefore, the model reaction in presence of I_2 as catalyst was carried out in other solvents such as acetonitrile, chloroform, DCE and dichloromethane other than ethanol. It was noticed that the target product was obtained in good yield in ethanol as solvent (**Table 1**).

Table 1. Reaction of isatin (2 mmol), malononitrile (2 mmol), phthalhydrazide (2 mmole) to obtain pyrazolophthalazinyl spirooxindole in the presence of different solvents.

Entry	Solvent	% Yield [a]	Time (min)
1	CH_3CN	72	15
2	$CHCl_3$	70	15
3	DCM	65	15
4	DCE	68	15
5	Ethanol	90	15

Then, to delineate this approach (**Scheme 1**), particularly in regard to library construction, this methodology was evaluated by using different phthalhydrazides, corresponding pyrazolophthalazinyl spirooxindoles were obtained in very good yields (**Scheme 2**).

Scheme 1

Scheme 2

4. Conclusion

To conclude, we have successfully developed a simple and green catalytic procedure for the efficient synthesis of pyrazolophthalazinyl spirooxindoles under ultrasonic conditions. The easy work up procedure, high yield of products and energy efficient reaction conditions are the major advantages of the method.

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Graphical Abstract