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Synthesis of pyridazinones via molecular-iodine-mediated cleavage of 4-bromomethylcoumarin precursors

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ABSTRACT
A facile and an efficient protocol for the synthesis of pyridazinones via molecular-iodine-mediated cleavage of 4-bromomethylcoumarin precursors in the presence of I₂ in ethanol at 70 °C is reported. The present approach replaced the basic condition (K₂CO₃) with Lewis acidic condition.

GRAPHICAL ABSTRACT

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KEYWORDS
4-Bromomethylcoumarins; coumarin; iodine; pyridazine; pyridazinones; ring transformation

Introduction
Nitrogen-containing heterocycles are of biological importance, and the design of newer strategies for their synthesis is an important area of research in organic chemistry. [1–4] Pyridazines and pyridazinones are important structures in the development of new bioactive compounds and several of them have been used in the treatment of many human pathologies.[5,6] Pyridazinones have attracted much attention in synthetic and medicinal chemistry because of their useful biological activities and exceptional pharmacological properties.[7] A large number of compounds bearing pyridazinone scaffolds have entered preclinical and clinical tests over the past few years. Many commercially available drugs (Fig. 1), including Zardaverine (phosphodiesterase inhibitor),[8,9] Emorfazone (the efficacy of this drug on post-surgical dental pain and inflammation is lacking),[10] and CEP-26401 (Irdabisant, potent histamine H₃ receptor (H₃R) antagonist/inverse agonist with drug-like properties),[11] are derived from 1,2-pyridazin-3-one core entities.

Pyridazinone-based compounds have been associated with valuable biological activities such as antiviral,[12] anti-inflammatory,[13] antinociceptive,[14] antiplatelet,[15] anticancer,[16] antiangiogenic agents,[17] and acetylcholinesterase inhibitors.[18] Hence, the synthesis of pyridazinones has evoked much attention, as a result of which a variety of synthetic
methodologies have been reported. The most important approaches are (i) from chiral β-methy-√ketocarboxylic acid,[19] (ii) retro-ene-assisted palladium-catalyzed synthesis of 4,5-disubstituted-3(2H)-pyridazinones,[20] (iii) concise synthesis of ω-fluoralkylated ketoesters, a building block for the synthesis of six-, seven-, and eight-membered fluoroalkyl substituted 1,2-diaza-3-one heterocycles,[21] (iv) cyclocondensation of arylhydrazine with 1,4-difunctionalized compound,[22] and (v) from coumarins and hydrazine. Other methods have also been developed within the past three decades.[23] The recent method developed by Kulkarni et al. is based on a base catalyst such as K₂CO₃, and has its own limitations such as use of excess amount of toxic, metal carbonate base and moderate yields. Thus, development of a convenient and efficient strategy to establish pyridazinone entities is still interesting in the realm of synthetic and medicinal organic chemistry. To the best of our knowledge, this is the first report on the use of Lewis acid condition to synthesize the pyridazinones.

In recent years, molecular iodine, a mild Lewis acid, has been used in plethora of functional group transformations in organic synthesis. The mild Lewis acidity associated with iodine has enhanced its usage in organic synthesis to realize several organic transformations using catalytic amounts to stoichiometric levels. Owing to numerous advantages associated with iodine, it has been explored as a powerful catalyst for various organic transformations. Molecular iodine has emerged as an inexpensive, nontoxic, nonmetallic, readily available, and environmentally benign catalyst for various organic transformations, which have been reviewed recently.[24–27]

Results and discussion

4-Bromomethylcoumarins are prepared as per literature reports.[28–34] During the course of our initial investigations, the reaction of 4-bromomethyl-6-ethylcoumarin (1d) and benzohydrazide (2) was used as a model reaction for the optimization of the reaction conditions (Scheme 1). The control experiment in the absence of catalyst was first carried out for 48 h and the target compound (3d) was not obtained because of poor reactivity of benzohydrazide. We hypothesized that iodine catalyzes the reaction. A preliminary examination showed that I₂ in ethanol among several solvents effectively catalyzed the model reaction. Next, the catalyst loading was investigated and it was found that 10 mol% of iodine was enough for the model reaction to obtain the target compound (3d) in an excellent yield of 96%. Thus, 10 mol% of iodine was selected as an optimal catalyst loading for further investigations.

To determine the optimum reaction conditions, the effect of other reaction parameters such as the solvent, temperature, and reaction time were investigated. Several other solvents including acetonitrile, dichloromethane (DCM), tetrahydrofuran (THF),
dimethylformamide (DMF), toluene, chloroform, dimethylsulfoxide (DMSO), and 1,4-dioxane were screened but lower yields were obtained (Table 1, entries 5–12). So in this reaction, ethanol was used as a solvent. In addition, the effect of temperature and reaction time were also studied (Table 1, entries 1–4 and 13–15). It was found that neither increasing nor decreasing the reaction time and temperature could enhance the yield. Therefore, this reaction could be best carried out with 10 mol% of iodine as catalyst in ethanol at 70 °C for 12 h. This remarkable activation in reaction rate prompted us to explore the potential of this protocol for the synthesis of series of 2-benzoyl-5-(2-hydroxyphenyl)-pyridazin-3(2H)-ones. All the aforementioned reactions proceeded expeditiously and delivered good to excellent yields. The overall yield ranged from 96% of 2-benzoyl-5-(5-ethyl-2-hydroxyphenyl)-pyridazin-3(2H)-one (3d) to 83% of 2-benzoyl-5-(5-fluoro-2-hydroxyphenyl)-pyridazin-3(2H)-one (3l).

Mechanism

A reasonable mechanism for the formation of 2-benzoyl-5-(2-hydroxyphenyl)-pyridazin-3(2H)-one is illustrated (Scheme 2), which is similar to the established mechanism.[35] Nucleophilic attack of benzohydrazide on the methylene group followed by an intramolecular nucleophilic attack of the nitrogen lone pairs on the lactone carbonyl results in the intermediate, which undergo in situ dehydrogenation to give 2-benzoyl-5-(2-hydroxyphenyl)-pyridazin-3(2H)-one.
Conclusion

In conclusion, we have developed a facile and an efficient procedure for the synthesis of novel 2-benzoyl-5-(2-hydroxyphenyl)-pyridazin-3(2H)-ones from 4-bromomethylcoumarins and benzohydrazide in the presence of iodine as a catalyst. This method provides biologically interesting pyridazinone derivatives in good to excellent yields.

Experimental

Commercially available reagents were used without further purification. The melting points were measured with an electric melting point apparatus and were not corrected. The infrared (IR) spectra were recorded on a Shimadzu-8400S FT-IR spectrophotometer (KBr disks). $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded in CDCl$_3$/DMSO-d$_6$ as solvent with a Bruker spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts were expressed in parts per million (ppm). The high-resolution mass spectrum (HRMS) was recorded at IISC, Bangalore. Elemental analysis for C, H, and N were performed with an Elemental Vario Micro Cube CHN Rapid Analyzer. All the compounds gave satisfactory elemental analysis.

General procedure for the synthesis of 2-benzoyl-5-(5-ethyl-2-hydroxyphenyl)-pyridazin-3(2H)-one (3d)

Iodine (10 mol%) was added to a stirring solution of benzohydrazide (0.5 g, 3.6 mmol) in ethanol (10 ml), which was heated to 70 °C in an oil bath. Later 6-ethyl-4-bromomethylcoumarin (0.98 g, 3.6 mmol) was added and refluxing was continued for 12 h. After

Scheme 2. Reasonable mechanism for the synthesis of novel pyridazinone derivatives.
completion of the reaction, ethanol was removed under reduced pressure. The residue left out was dissolved with ethyl acetate and added aqueous Na$_2$S$_2$O$_3$ solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic phase was washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel [eluent: hexane and ethyl acetate (7:3)] to afford the product as a colorless solid.

**2-Benzoyl-5-(5-ethyl-2-hydroxyphenyl)-pyridazin-3(2H)-one (3d)**

Yield 96%; colorless solid; mp 225 °C; IR (KBr, cm$^{-1}$): 1679, 1726 (C =O), 3402 (OH); $^1$H NMR (400 MHz, CDCl$_3$): δ 1.25 (t, 3H, CH$_3$ of ethyl group, $J_{1,2} = 7.6$ Hz), 2.61 (q, 2H, CH$_2$ of ethyl group, $J_{1,2} = 7.6$ Hz), 6.78 (s, 1H, Ar-H), 6.89 (s, 1H, Ar-H), 7.36–7.90 (m, 8H, Ar-H), 9.17 (s, 1H, OH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 13.7, 33.0, 113.3, 116.6, 116.7, 122.0, 123.8, 127.1, 127.2, 130.8, 132.7, 132.8, 144.7, 148.6, 150.5, 151.3, 159.5, 161.9, 163.5 ppm; HR-MS: [M$+$Na] 343.0000. Anal. calcd. for C$_{19}$H$_{16}$N$_2$O$_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.19; H, 4.98; N, 8.68.

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