Green chemistry approach for the synthesis of bioactive heterocycles

F. 43-197/2014(SR)

Final report

Prof. S.G. Tilve
Department of Chemistry
Goa University

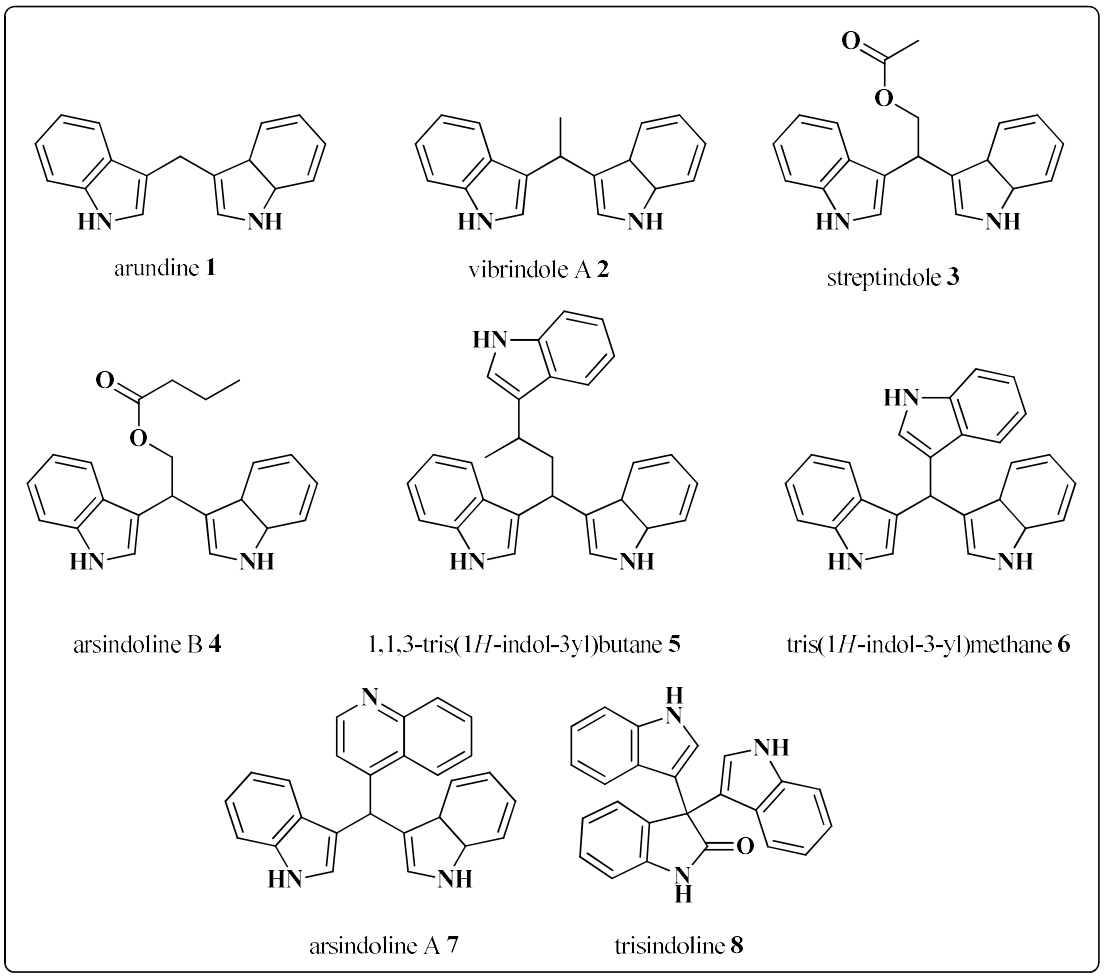
Enclosure 1

Title: Green chemistry approach for the synthesis of bioactive heterocycles

The focus of green chemistry lies on reducing environmental pollution by designing benign reaction processes, avoiding waste generation and saving time and energy. Recently as a part of our programme in green chemistry we have demonstrated use of iodine and graphite as catalyst for the synthesis of important heterocyclic motifs. As an extension to this we are also presently exploring solvent free, catalyst free and mechanochemical synthesis (Ball Mill)

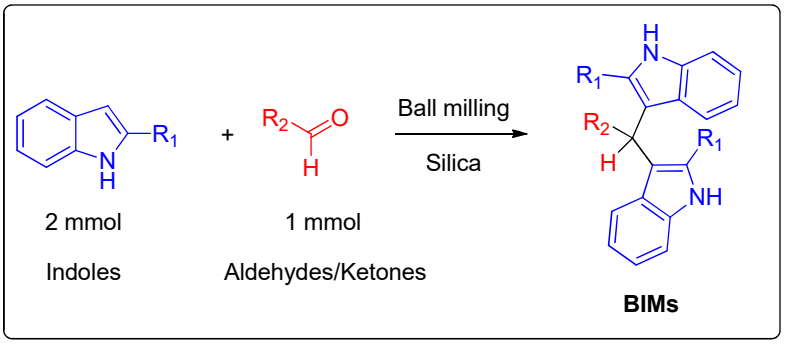
1. A greener approach towards the synthesis of *bis*(indolyl)methanes under solvent free conditions using ball milling technique.

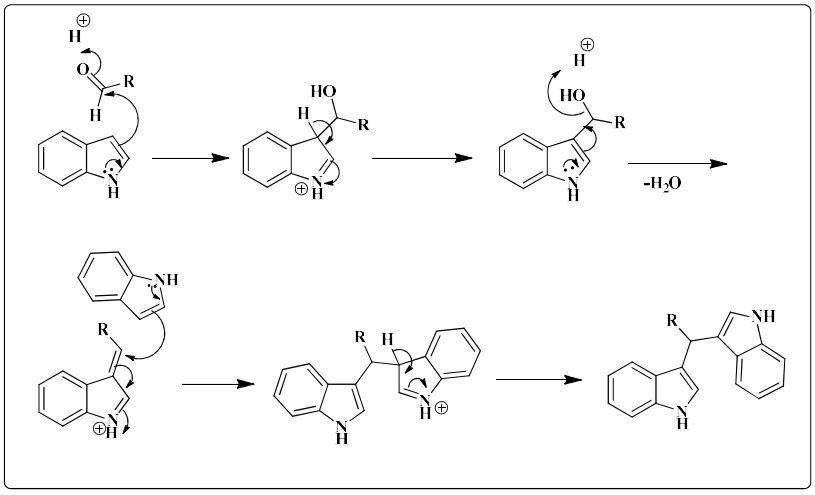
<u>Naturally occurring bis(indolyl)methanes.</u>



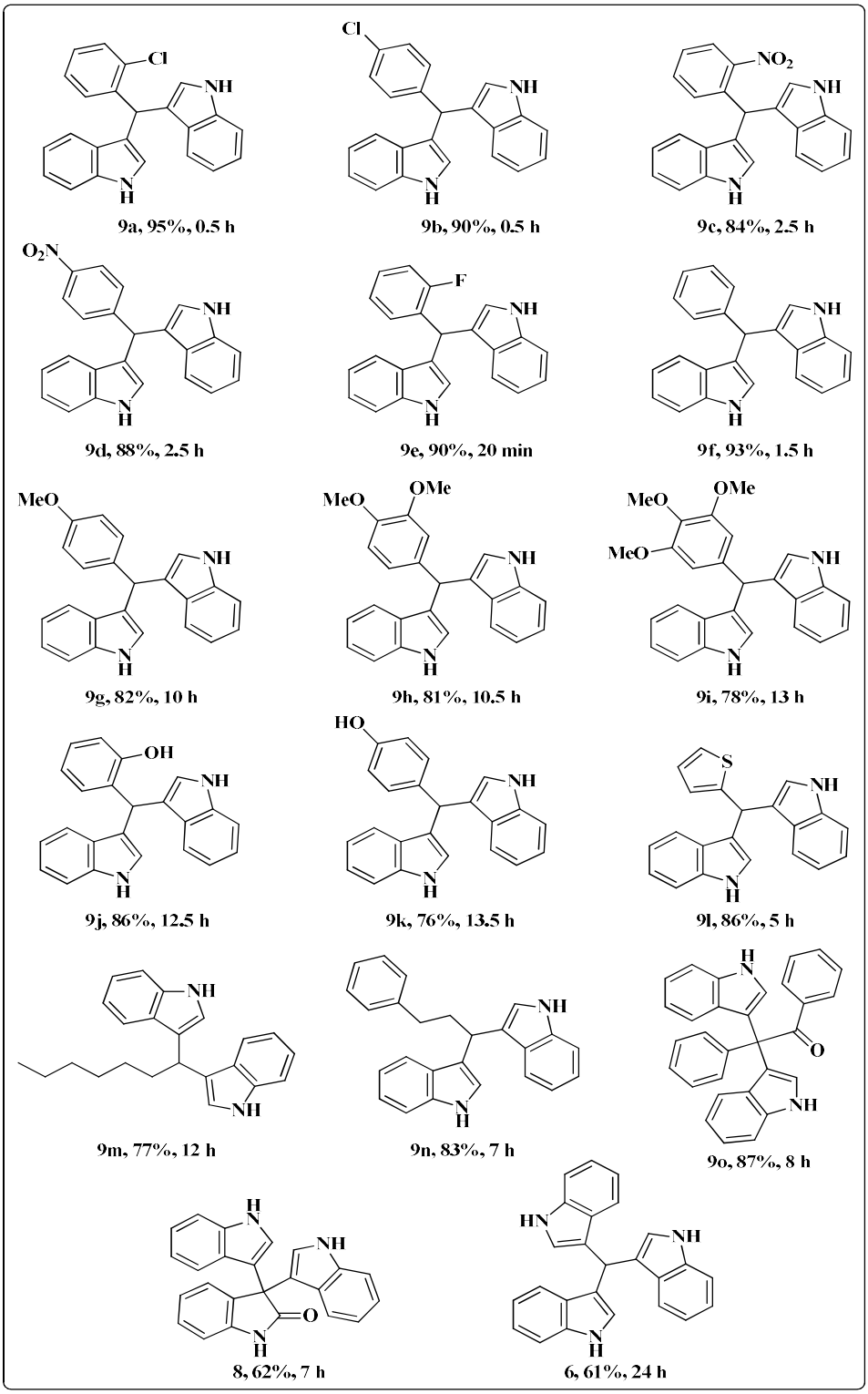
Mechanochemically promoted organic reactions have shown considerable attention due to their advantages of high reaction rates and solventless procedures. Bis(indolyl)methanes (**BIMs**) have been attractive targets to develop green methodologies because of their wide range of biological, industrial and synthetic applications. These compounds have proven to be of importance as they exhibit anticancer and antimicrobial activities. Encouraged by the need for environmental friendly practices, we have carried out C-alkylation of indoles with aromatic aldehydes to achieve the synthesis of **BIMs** using a high speed planetary ball milling machine. Silica was chosen as a support for carrying out the reactions.

Synthesis of bis(indolyl)methanes (BIMs)



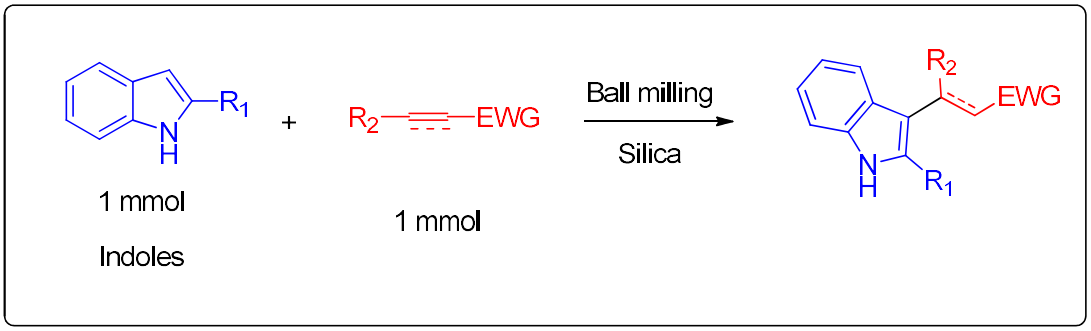


Probable mechanism for the formation of BIMs

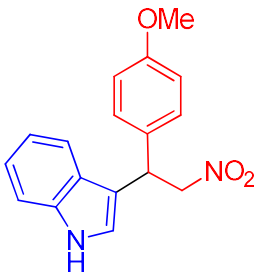


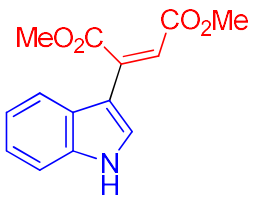
In conclusion, we have successfully demonstrated ball-milling technique as an efficient technique for the synthesis of BIMs using silica as a support material. The utility of this technique was demonstrated by synthesizing library of 17 BIMs including two natural products. The normally less reactive electron rich aryl aldehydes, aliphatic aldehydes and selective ketones were found to be amenable for this technique.

2. A greener approach towards the alkylation and alkenylation of indole under solvent free conditions using ball milling technique



Alkylation and alkenylation reaction on indole was also initiated using the ball milling technique. Successful alkylation with nitrostyrene and acetylene dicarboxylate took place. However alkylation with chalcone failed in our hands. More examples of nitrostyrenes and indoles are to be studied.

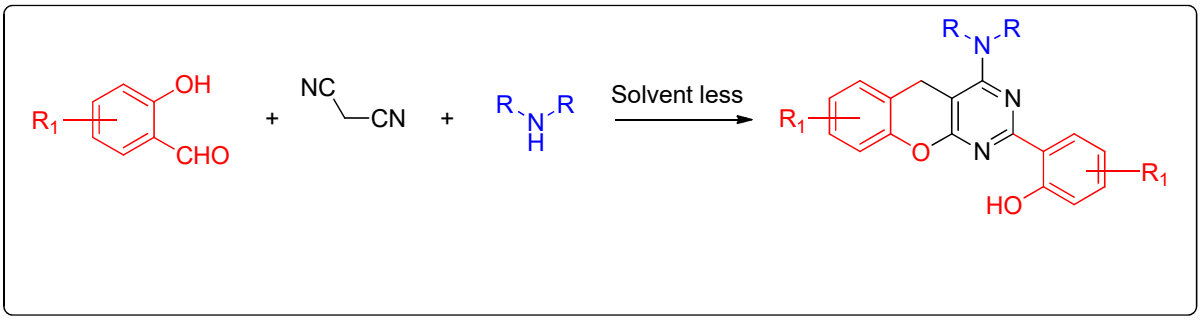


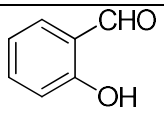
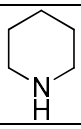
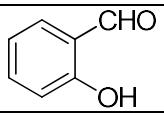
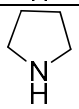
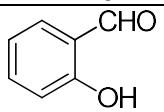
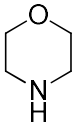
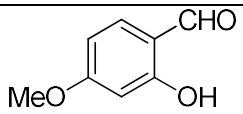
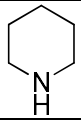
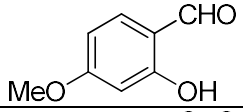
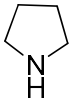
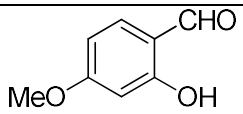
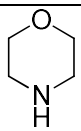
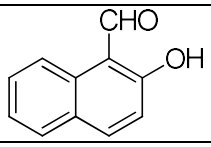
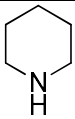
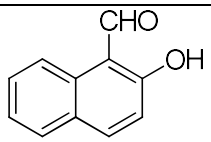
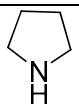
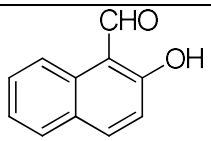
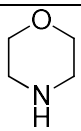


3. **Solvent less Synthesis of Chromeno[2,3-d]pyrimidines**

With the emergence of high throughput screening the demand for new drug molecules has increased manifold. Combinotorial chemistry and parallel automated synthesis has met this demand to a certain extent. However, these methods have certain limitations particularly in providing diverse molecules. The one of the emerging fields in this regard is the multicomponent synthesis. The 55 year old Ugi four component reactions and the Biginelli reaction have attracted considerable attention. These multicomponent reactions provide considerable diversity particularly providing nitrogen heterocycles.

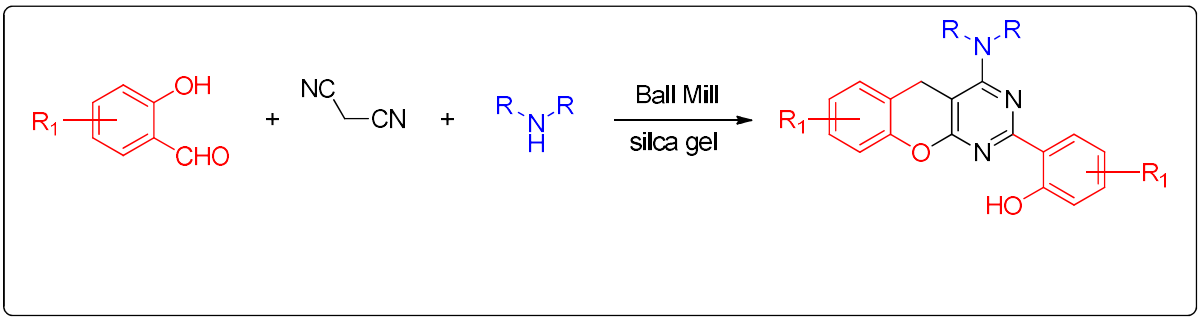
Functionalized nitrogen-hetrocycles are attractive targets in medicinal chemistry. The importance of pyrimidine scaffold in nature needs no mention. Pyrimidine compounds are known as antibacterial antiviral and antitumor agents. Fused pyrimidine displays interesting pharmacological profiles. Pyridopyrimidines acts as analgesics and CNS depressants. Benzopyranopyrimidines shows anti-inflammatory, analgesic and *in vitro* anti-aggregating activities. Fused molecules sharing benzopyran moiety have shown platelet anti-aggregative activity comparable to that of acetylsalicylic acid. As a part of continuing research interest of our group to develop green approaches to biologically relevant molecules we were interested in synthesizing Benzopyrano[2,3-*d*]pyrimidine. We have developed a solvent free, catalyst free protocol for the synthesis Chromeno[2,3-d]pyrimidines.

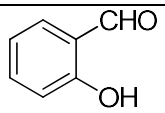
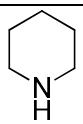
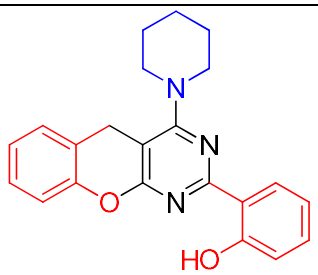
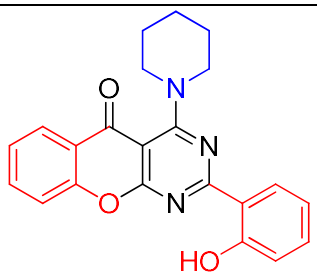
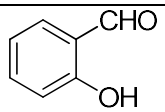
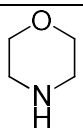
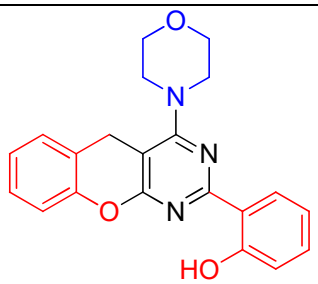
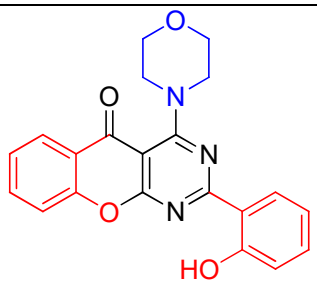
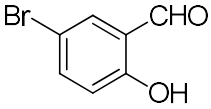
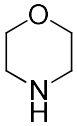
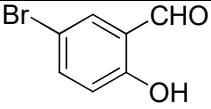
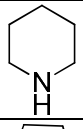
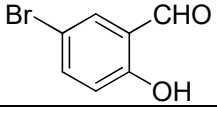
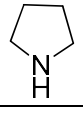


Entry	1	3	Yield % 4
a			89
b			87
c			89
d			88
e			75
f			85
g			87
h			87
i			84

It is observed that the salicylaldehyde derivatives whose melting points were higher the reaction protocol could not be attempted. Hence it is decided that Mechanochemical synthesis using ball mill to be tried.

Mechanochemical solvent less synthesis of Chromeno[2,3-d]pyrimidines

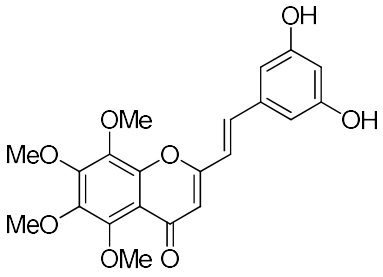


Entry	1	3	Yield %	Yield%
a			 40%	 40%
b			 44%	 40%
c			Complex mixture	
d			Complex mixture	
e			Complex mixture	

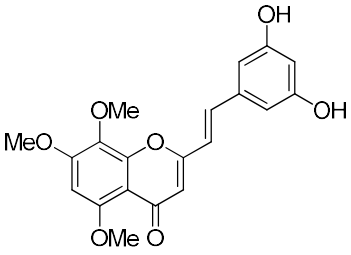
During the studies it was observed that instead of exclusive formation of expected product an additional oxidized product was also obtained. Efforts to get exclusive oxidized product has so far not succeeded.

4. **Synthesis of styrylchromones**

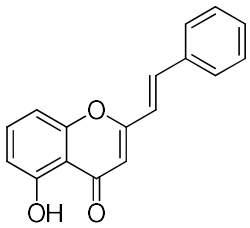
Styrylchromones are a class of chromone (1-benzopyrone-4-one; 1,4-benopyrone; 4-oxo-4H-1-bezopyran)derivatives characterized by the presence of a styryl group at the 2-position of the chromone structure. Biological activities of natural and synthetic 2-styrylchromones have been tested in different biological systems, and it is found that they exhibits activities with potential therapeutic applications such as antiallergic, antitumor, affinity and selectivity for adenosine receptors, antiviral, antioxidant and anti-inflammatory. The presence and postion of hydroxyl substituent particularly on ring A tunes the activity of these compounds. The presence of a styryl group enhances the antioxidant activity.
Harmothamnione and 6-desmethoxy harmothamnione are the first two naturally occurring 2-styrylchromones isolated from the marine cryptophytes *Chrysophaeum taylor*. Harmothamnione show cytototoxic activity against P388 lymphocytic leukemia and HL-60promyyelocytic leukemia lines in vitro. It is also a selective inhibitor of RNA synthase. 6-desmethoxy harmothamnione shows cytotoxic activity against 9KB cell lines. 5-Hydroxy-2-styrylchromone was isolated from *Imperara cylidica* in 2006. More recently the isolation of six new derivatives was reported:4',6-dihyroxy-3-methoxy-2-strylchromone from the resinous wood of *Aqualaria* resinous and 4',5,7-trihydroxy-2-stuyrylchromone with four other derivatives names platachromones A-D from Platanus xacerifolia. However, total synthesis of the recently discovered plateachromones A-D is yet to be reported.



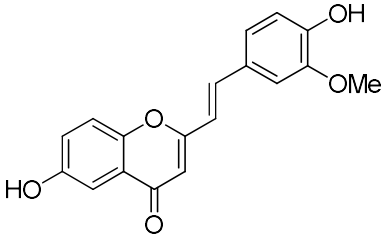
Harmothamnione



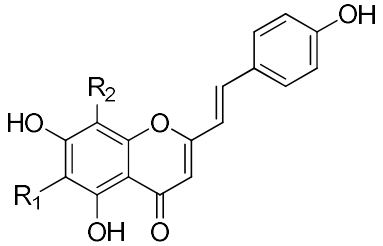
6-desmethoxy harmothamnione



5-Hydroxy-2-styrylchromone



4',6-dihyroxy-3-methoxy-2-strylchromone



$R_1 = R_2 = H$

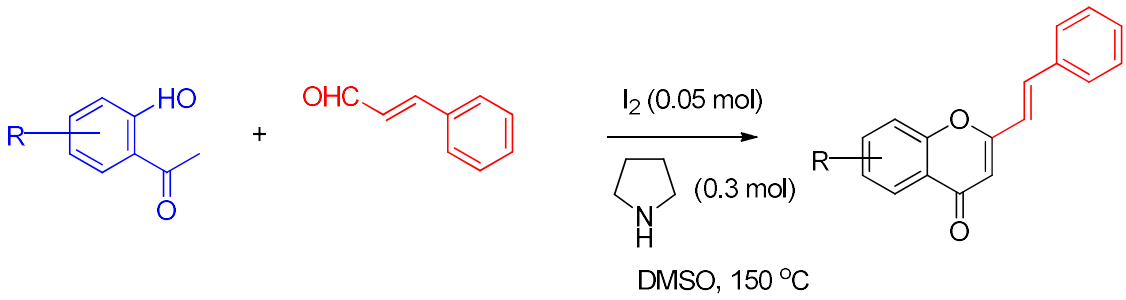
$R_1 = H, R_2 = CH_2CH{=}CMe_2$

$R_1 = CH_2CH{=}CMe_2,\ R_2 = H$

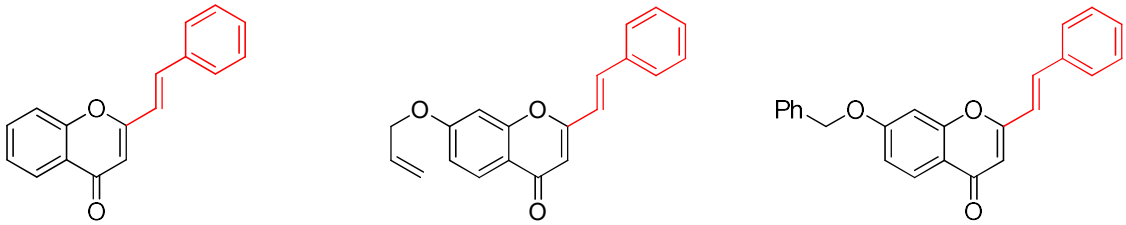
$R_1 = CH(OH)CH{=}CMe_2,\ R_2 = H$

$R_1 = H, R_2 = CH(OH)CH{=}CMe_2$

We had developed earlier a convenient dual catalysis by iodine and pyrrolidine catalyzed synthesis of flavones. We have now evaluated this methodology for the synthesis of styrylchromones.

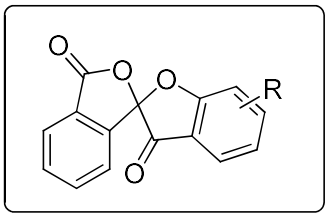


So far we have synthesized three derivates shown below of styrylchromones in good yields and further work is needed to generalize the method including a synthesis of a natural product to demonstrate the utility of this method.

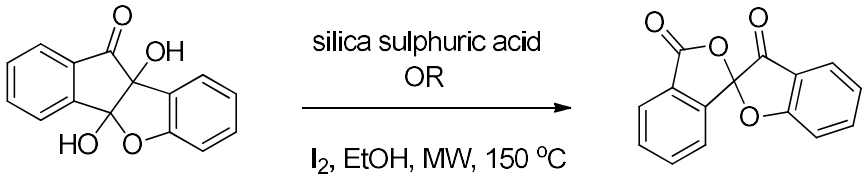


5. **Green synthesis of 4b,9b-dihydroxy-4b,9b-dihydro-5-oxa-indeno[2,1-*a*]indene-10-ones using mechanochemical technique under solvent free conditions.**

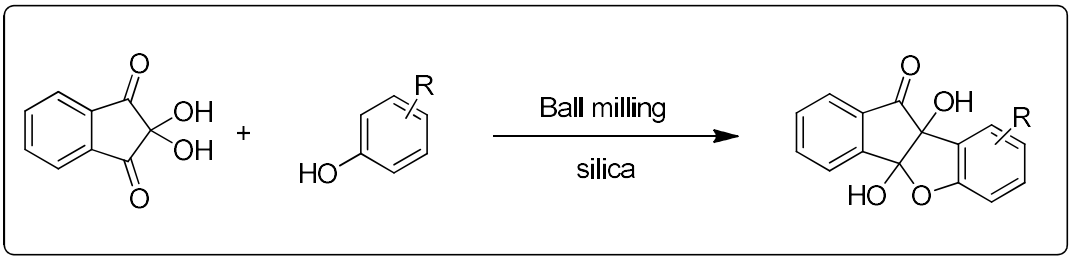
Spiro compounds having cyclic structures are of recent interest due to their interesting conformational features and their structural results on biological systems. The most common methodologies for the synthesis of spirocyclic compounds involve alkylation methods, rearrangement based approaches or cycloaddition reactions. Spiro substructures have immense importance not only in the field of medicinal chemistry but also in the material science for the preparation of organic LED.

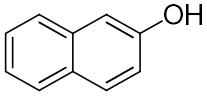
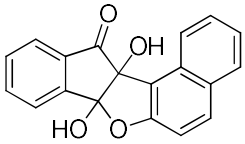
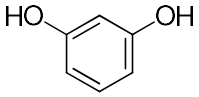
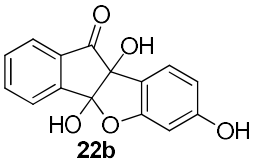
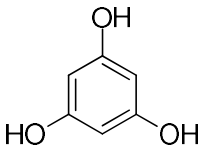
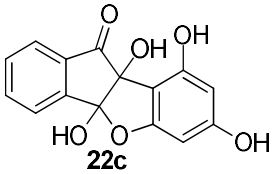
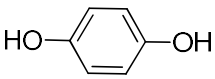
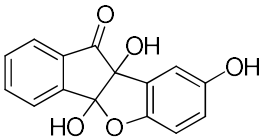
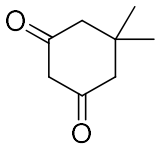
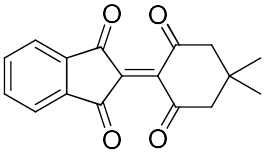


The spiro substructure shown above has shown biological activities as an inhibitor of influenza virus infection. This motif has been synthesized from the corresponding hydroxyl indinones as shown below.



We have developed a protocol for the synthesis of such hydroxyindinones (4b,9b-dihydroxy-4b,9b-dihydro-5-oxa-indeno[2,1-*a*]indene-10-ones) by Mechanochemical synthesis. Further work is in progress to make more derivatives.



SUBSTRATE	PRODUCT	REACTION TIME IN BALL MILL	YIELD
	 **22a**	20 min	90
	 **22b**	10 min	91
	 **22c**	10 min	88
	 **22d**	10 min	87
	 **23**	6 min	74