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Triple domino reaction for the synthesis of pyrazole/indoline linked chromenes

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ABSTRACT

A simple and convenient method towards the synthesis of highly diversified chromenopyrazole/indoline frameworks in excellent yields *via* iodine promoted triple domino reaction involving Michael addition followed by intramolecular cyclization and dehydrogenation sequence has been described for the first time.

1. Introduction

The development of highly efficient synthetic methods towards functionalized heterocyclic entities with interesting biological activities remains to be an important endeavor in modern organic synthesis.[1] In the arena of various heterocyclic systems, chromene ring is one of the versatile and most exploited scaffolds for several synthetic manipulations due to its various biological importance. The chromene moiety is a basic skeleton for an array of bioactive compounds, natural products, and dye pigments. Numerous reports are available in the literature for the utility of chromene moieties concerning with their bioactivities like antifungal, antimicrobial, antiviral, antioxidant, antitumor, cytotoxic and radical scavengers.[2] Members of this family are well known for several applications such as pharmaceuticals, food additives, cosmetics, fragrances, agrochemicals, termiticides, dispersal fluorescent optical brightening agents and tunable dye lasers.[3] Some of the representative examples of their derivatives such as Chrysosplenol C (**I**), Matteuorien (**II**), Nymphaeol C (**III**) and Quercetin-3-O-rutinoside (**IV**) are shown in Fig. 1.[4] Hence, the rapid synthesis of chromene tethered heterocycles is a highly useful and interesting aspect in organic chemistry.

Pyrazole[5] and their derivatives are found in a variety of bioactive molecular entities and natural products. Pyrazole annulated compounds are known as a stimulating unit in pharmaceuticals and are active components in promising drugs such as Celebrex (treatment against osteoarthritis, rheumatoid arthritis). In fact, 3-methyl-1-phenyl-1*H*-pyrazol-5-one is widely known as potential neuroprotective agent for recovery of acute brain ischemia.[6]

To be precise, several research groups devoted their effort for the construction of pyrazole tethered molecular entities owing to their bioactivities and utility in pharmaceutical chemistry such as antioxidant, antimalarial, anticoagulant, antitubercular and anti-HIV activities.[7]

Since chromene, pyrazole and indoline units are well screened for their interesting biological applications, we envisaged that the diversified chromene tethered pyrazole/indoline hybrid molecules also may exhibit similar kind of biological properties, which will be interesting from medicinal point of view.

2. Results and discussion

Due to the significance of chromene and related frameworks, we were provoked to construct chromene tethered pyrazole/indoline derivatives through a triple domino reaction involving Michael addition followed by intramolecular cyclization and dehydrogenation. This type of triple domino reaction for the synthesis of chromene tethered pyrazole/indoline derivatives is not known so far in the literature. In continuation of our work towards the construction of hybrid heterocyclic frameworks,[8] herein we report an efficient protocol for the synthesis of highly diversified chromenopyrazole/indoline derivatives from hydroxychalcones and

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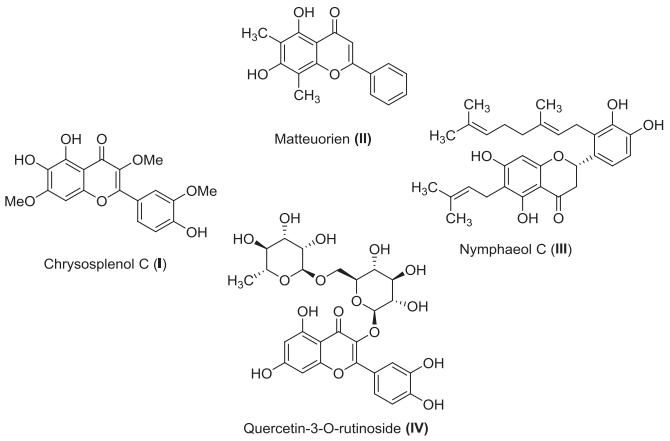
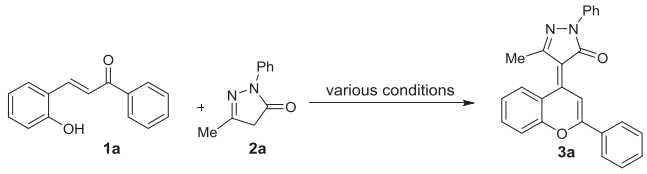


Fig. 1. Representative examples of chromene containing scaffolds.

various cyclic amides. The requisite precursor *i.e.* substituted *trans*-2-hydroxy chalcones were prepared according to the reported procedure.[9] To execute our idea, we first selected *(E)*-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one **(1a)** and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **(2a)** as substrates for optimizing the reaction. Initially we treated the substrates under the catalytic influence of $FeCl_3$ (20%) in toluene under reflux condition over a period of 5 h which led to the formation of desired chromenopyrazole **(3a)** only in 10% yield (entry 1, Table 1).

In order to improve the yield, we have carried out the reaction under various reaction conditions (entry 2–13, Table 1). Among all the reaction conditions, we have obtained the maximum yield (93%, entry 12, Table 1) by carrying out the reaction with 40 mol % of Iodine in chlorobenzene under reflux condition over a period of 30 min. Increasing the I_2 catalyst loading to 50 mol % did not increase the yield further (entry 13, Table 1). Therefore, the reaction was carried out with 40 mol % I_2 in C_6H_5Cl under reflux condition

Table 1
Optimization conditions for the formation of chromenopyrazole **(3a)** under various conditions.[a,b,c]



Entry	Catalyst	mol%	Solvent	Temp	Time(h)	Yield(%)
1.	$FeCl_3$	20	Toluene	reflux	5	10
2.	Iodine	20	THF	reflux	2	nr
3.	Iodine	20	DCE	reflux	0.5	33
4.	Iodine	20	MeCN	reflux	0.5	nr
5.	Iodine	20	*p*-Dioxane	reflux	1	nr
6.	Iodine	20	DCM	reflux	0.5	nr
7.	Iodine	20	Toluene	reflux	1	62
8.	Iodine	20	$CHCl_3$	reflux	0.5	9
9.	Iodine	10	C_6H_5Cl	reflux	0.5	74
10.	Iodine	20	C_6H_5Cl	reflux	0.5	78
11.	Iodine	30	C_6H_5Cl	reflux	0.5	88
12.	Iodine	40	C_6H_5Cl	reflux	0.5	93
13.	Iodine	50	C_6H_5Cl	reflux	0.5	93

[a] All reactions were carried out with 1 mmol scale.
[b] Isolated yield of the pure product obtained after column chromatography purification.
[c] nr = No reaction.

over a period of 30 min which was found to be the optimal condition for the triple domino reaction.

Prompted by this result, we have employed several 2-hydroxy chalcones **(1b-l)** with 5-methyl-2-phenyl-2,4-dihydro-3*H*- pyrazol-3-one **(2a)** using the above mentioned condition which smoothly afforded the variety of chromeno pyrazoles **(3b-l)** in 84–94% yields and the results are summarized in Table 2.

By following the similar procedure described above, we have synthesized a variety of chromenopyrazoles **(3m-u)** in excellent yields (78–92%) using 2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one **(2b)** *via* Michael addition followed by intramolecular cyclization according to Table 3.

The structure of the molecules **3a** and **3m** were further confirmed by single crystal X-ray diffraction analyses and the ORTEP diagram of compounds **3a** and **3m** are shown in Fig. 2.

To enhance the scope of the reaction further, we also used indolinone **(4)** in the domino reaction. The treatment of the chalcones **(1a, 1c-d, 1f, 1j, 1t, 1v, 1w** and **1 x)** with indolinone **(4)** in chlorobenzene solvent under the influence of Iodine at reflux temperature smoothly led to the wide variety of chromenoindolines **(5a-i)** in excellent yields (83–92%) as shown in Table 4.

Although detailed mechanistic studies were not carried out for this protocol, a plausible mechanism for the formation of chromeno pyrazole using 2-hydroxy chalcone and pyrazole involving two different pathways is shown in Scheme 1. The reaction is initiated by the activation of the carbonyl group by iodine followed by the Michael addition of pyrazole to form intermediate **A** which immediately transformed into an intermediate **B** through intramolecular cyclization. Loss of water and iodine molecule gives intermediate **C** which undergoes aerial oxidation to form product **3a**. The other pathway involves the coordination of the double bond in intermediate **C** with iodine forming an iodonium ion **D**, which is subsequently opened through the nucleophilic attack by iodide anion leading to the intermediate **E**. Subsequent elimination of two molecules of HI gives the product **3a**.

3. Conclusion

In conclusion, we have developed an efficient and general protocol for the construction of chromenopyrazoles and chromenoindoline derivatives from hydroxychalcones and cyclic amides *via* molecular iodine promoted triple domino reaction involving Michael addition followed by intramolecular cyclization and dehydrogenation sequence for the first time. A library of cyclic amide tethered chromene frameworks were synthesized in excellent yields. This protocol also opens new avenues for the construction of libraries of chromene-tethered scaffolds for further biological screening.

4. Experimental section

4.1. General remarks

Commercial reagents were used without further purification. Melting points are uncorrected. IR spectra were recorded on a Perkin Elmer-FTIR spectrometer using solid samples as KBr plates. For compounds ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in deuterochloroform ($CDCl_3$) on a Bruker 400 MHz spectrometer using tetramethylsilane (TMS, $\delta = 0$) as an internal standard at room temperature unless otherwise stated. Mass spectra were recorded on Agilent 1200 LC/MS-6110 mass spectrometer. Spectral data of ^1H, ^{13}C NMR and ESI-HRMS of all compounds are listed below.