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Stereoselective Construction of Functionalized Tetra and Pentacyclic Coumarinopyranpyrazole / Pyrimidinedione / Coumarin Scaffolds Using Solid State Melt Reaction

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An assembly of tetra and pentacyclic hybrid scaffolds has been established using a solid state melt reaction (SSMR) for the first time. These hybrid heterocyclic entities were accomplished in a stereoselective fashion in 86-98% yield under catalyst-, solvent-, work up- and column chromatography free conditions.

Introduction

Heterocyclic frameworks are ubiquitous in nature and found to be an integral part of vast number of biologically active components.[1] In general, multistep involved to construct complex heterocycles; however the number of steps can be intensely reduced while using domino / cascade reactions.[2] The domino reaction in organic synthesis which enhances the selectivity and efficiency, particularly for fused heterocyclic architectures. Similarly, the domino Knoevenagel-hetero-Diels-Alder reaction[2-3] substantially increase the molecular complexity and high levels of convergence in synthesis. Indeed, these reactions minimizes the laboratory equipment, chemical and solvent usage for the synthesis of various heterocyclic motifs,[4] in which coumarin, pyrazole and pyrimidinedione containing hybrid pyranochromenone frameworks are important due to their key units in many natural products pertaining to their interesting medicinal properties.

Recently, significant numbers of reports are appearing in the literature towards the coumarin, pyrazole and pyrimidine fused heterocyclic derivatives[5] due to their aforementioned properties. Accordingly, the pyrazole centered ring system, in particular the pyranopyrazole units have shown molluscicidal, antimicrobial, anti-inflammatory activities, besides active ingredients in prominent drugs *viz.*, Viagra®, Celebrex® etc.[6a-f] Coumarin scaffolds display a broad range of applications like optical brightening agents, pharmaceuticals, food additives, cosmetics, agrochemicals and tunable dye lasers.[6g-h] In addition, they also possess a broad spectrum of biological activities such as anthelmintic, anticoagulants, hypnotic and insecticidal properties.[7] Whereas, the pyrimidine moieties exhibiting antiviral and anti-HIV activities.[8] Some of the representative examples for coumarin, pyrazole, pyrimidinedione, and coumarinopyran motif[9a-d] containing natural products and potential bioactive molecules are shown in Figure 1. The wide ranges of biological applications have intrigued considerable attention of synthetic chemists to find newer and more economic protocol to attain them in a strategically attractive manner.

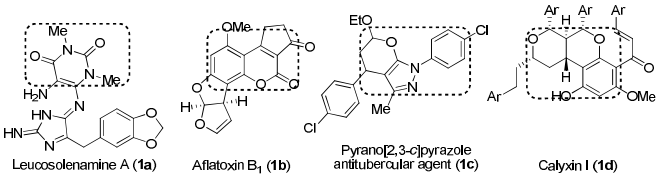


Figure 1. Natural products and bioactive molecules embodying the coumarin, pyrazole, pyrimidinedione and chromenopyran units

In continuation of our studies,[2c, 2h, 9e-f, 10] we explored the solid state melt reaction (SSMR) for the synthesis of novel heterocyclic frameworks particularly chromeno / quinolino pyranpyrimidinedione, pyrazoles and coumarins. Furthermore, this novel SSMR was utilized for the construction of benzo-heterocyclic frameworks and other useful motifs.[10] The successful outcome of this protocol intrigued us to synthesis various compounds through the domino transformations via multiple bond-forming processes. Thus, we have undertaken a research program for the construction of various hybrid compounds using domino Knoevenagel hetero Diels-Alder reaction via SSMR strategy.

Consequently, we envisaged that the privileged tetra / pentacyclic hybrid pyrazole, pyrimidine and coumarin annulated coumarinopyran frameworks can be effectively constructed using solid state melt reaction (SSMR) through domino Knoevenagel hetero Diels-Alder reaction according to the retrosynthetic analysis shown in Scheme 1.

. To execute our idea, initially we treated cinnamoyl chloride with salicylaldehyde in presence of potassium carbonate in acetonitrile as a solvent at room temperature for about 1 h which led to the requisite precursor *i.e.* 2-formylphenyl cinnamate (**2a**) in 74% yield. After obtaining the 2-formylphenyl cinnamate (**2a**), initially we tried the reaction with *N*,*N*-dimethyl barbituric acid under various reaction conditions, however the best result was obtained when the substrate **2a** was melted with *N*, *N*-dimethyl barbituric acid (**3a**) at 180 °C under solvent- and catalyst- free condition over a

period of 1 h which successfully provided the complex angularly fused tetracyclic coumarinopyranpyrimidinedione (**5a**) in excellent yield (98%). Interestingly, this novel reaction creates coumarin ring and coumarinopyran ring in a highly diastereoselective fashion with the conservation of high atom economy.

Scheme 1. Retrosynthetic strategy for the synthesis of tetra and pentacyclic frameworks

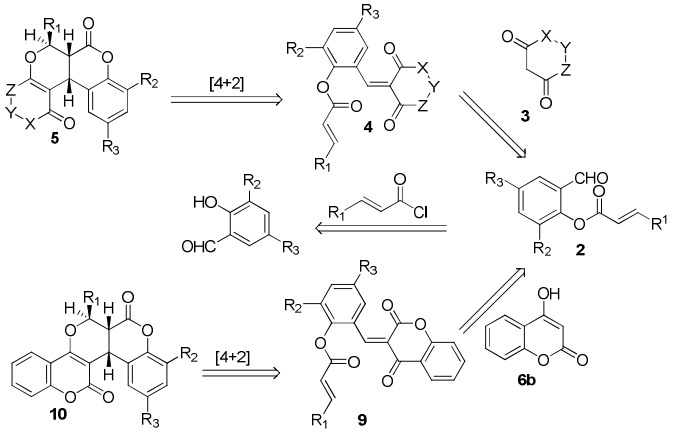
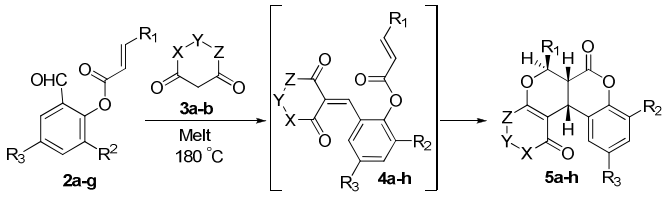
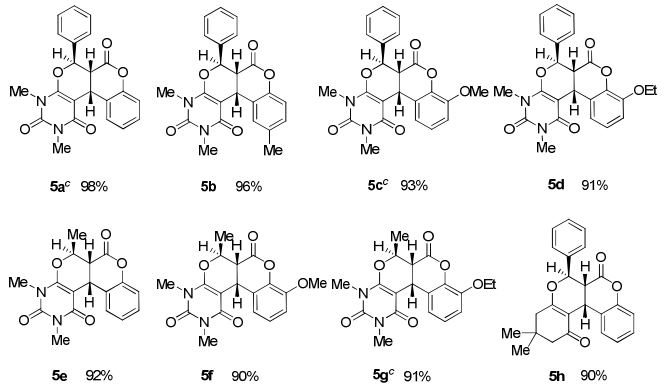


Table 1. Synthesis of tetracyclic coumarinopyranpyrimidine diones / dimethylcyclohexanones (**5a-h**)[a,b] using 2-formylaryl cinnamate / crotonate derivatives (**2a-g**)

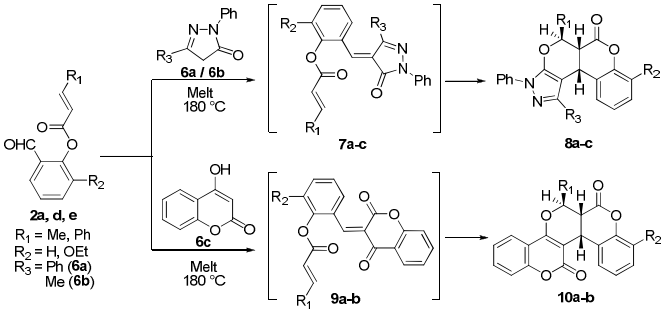


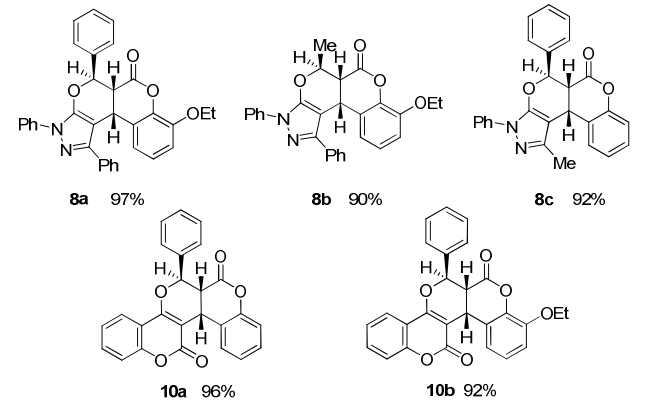


[a]All reactions were carried out on 1 mmol scale of 2-formylaryl cinnamates (**2a-g**) with 1 mmol of *N,N*-dimethyl barbituric acid / 5, 5-dimethylcyclohexane-1,3-dione (**3a / 3b**) under melt condition at 180 ºC for 1 h. [b]Isolated yields of **5a-h**. [c]Structures of the molecule were further confirmed by single-crystal X-ray data.[11]

Encouraged by this result, we have utilized cinnamoyl / crotonyl chlorides with various salicyaldehyde derivatives under basic condition for the preparation of various 2-formylaryl cinnamate and crotonate derivatives (**2b-g**). Further reaction of the substrates **2b-g** with *N,N*-dimethyl barbituric acid (**3a**) / 5, 5-dimethylcyclohexane-1,3-dione (**3b**) under similar condition smoothly led to the tetracyclic coumarinopyran annulated pyrimidinedione / cyclohexenone frameworks (**5b-h**) in excellent yields (90-96%), and the results are summarized in Table 1. It is important here that reaction is not only diastereoselective but also chemoselective in nature which was confirmed by NMR and single crystal X-ray studies.

Table 2. Synthesis of tetra / pentacyclic coumarinopyran pyrazoles (**8a-c**) / coumarinopyrancoumarins (**10a-b**)[a,b] using 2-formylarylcinnamate / crotonate derivatives (**2a, d-e**)



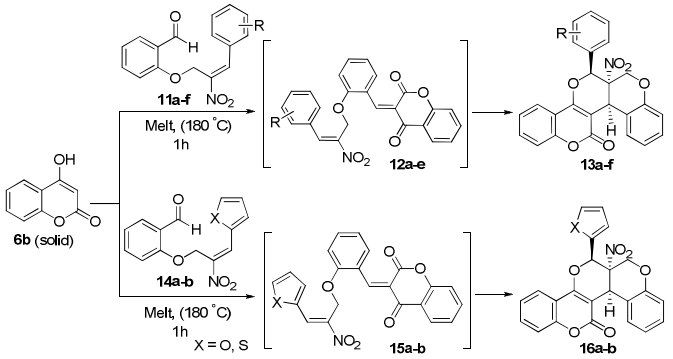


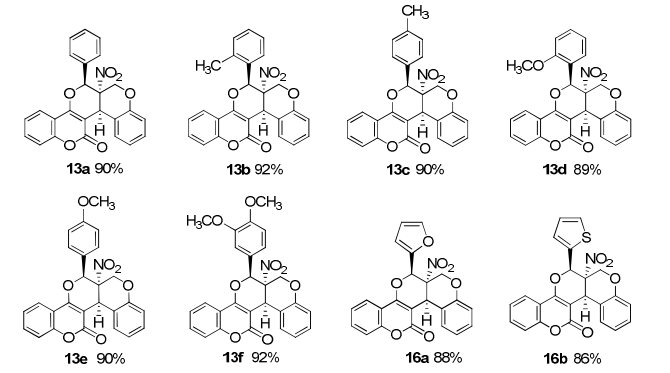
[a]All reactions were carried out on 1 mmol scale of 2-formylaryl cinnamate / crotonate derivatives (**2a, d-e**) with 1 mmol of 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (**6a**) / 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**6b**), 4-hydroxy-2*H*-chromen-2-one (**6c**) under melt condition at 180 ºC for 1 h. [b]Isolated yields of **8a-c** and **10a-b**.

To check the generality of the reaction, we have treated various 2-formylaryl cinnamate derivatives (**2a, d-e**) with diverse active methylenes such as 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (**6a**) / 3-methyl-1-phenyl-1*H*-pyrazol-5(4H)-one (**6b**) and 4-hydroxy-2H-chromen-2-one (**6c**) under aforementioned synthetic procedure which successfully provided the anticipated tetra and pentacyclic hybrid coumarinopyranpyrazole/coumarin scaffolds (**8** / **10**) in 92-97% yields as shown in Table 2. In order to broaden the scope of this protocol, we have decided to construct various polycyclic frameworks using similar method with nitro functionality. Accordingly, on treatment of salicylaldehyde with several Baylis-Hillman bromides containing nitro functionality

under basic condition led to the requisite precursors **11** and **14**. Furthermore, we have melted the 4-hydroxy-2*H*-chromen-2-one (**6b**) with various Baylis-Hillman derivatives (**11a-e**), (**14a-b**) derived from nitro olefins which efficiently led to the pentacyclic hybrid coumarinopyrancoumarins (**13a-e** / **16a-b**) possessing nitro functionality at the angular position in very good yields (86-92%) and the results are presented in Table 3.

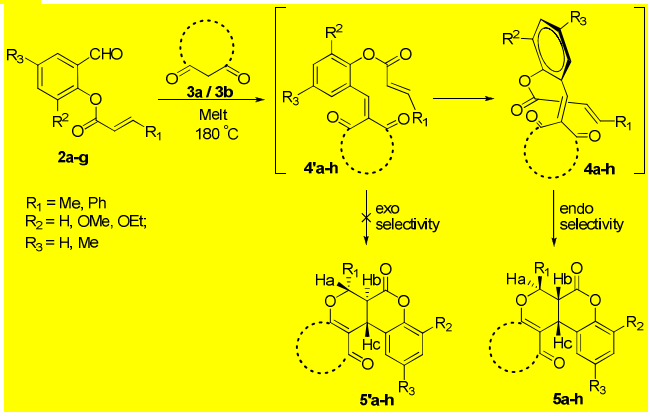
Table 3. Synthesis of pentacyclic coumarinopyrancoumarins (**13a-e** / **16a-b**)[a,b] possessing nitro functionality at angular position using *O*-alkylated derivatives (**11a-e & 14a-b**)





[a]All reactions were carried out on 1 mmol scale of *O*-allylated compounds (**11a-e** & **14a-b**) with 1 mmol of 4-hydroxy-2H-chromen-2-one (**6b**) under melt condition at 180 ºC for 1 h. [b]Isolated yields of the products **13a-e** & **16a-b**.

Scheme 2. A plausible mechanistic pathway for the synthesis of **5a-h**



The plausible mechanistic pathway for the formation of **5a-h** is shown in Scheme 2 in which the active methylenes such as *N*, *N*-dimethyl barbituric acid (**3a**) / 5, 5-dimethylcyclohexane-1,3-dione (**3b**) undergo a Knoevenagel condensation with aldehydes (**2a-g**) to afford the heterodienes **4′a-h** which in turn may lead to the compounds (**4a-h**) with another orientation. The geometrical nature and attack of dienophiles are the controlling factors for the stereochemistry of the tetracyclic frameworks formed in the reaction. The *exo* transition state leads an adduct with *trans* fusion in the ring junction. Whereas the *endo* transition state leads to adducts **5a-h** with *cis* fusion in the ring junction. The *cis* fusion of the ring junction was further confirmed by coupling constants of Hb and Hc protons (J = 3.9-5.1 Hz). Furthermore the stereochemistry of the compounds (**5a**, **5c** & **5g**) was established by single crystal X-ray analysis.[11]

Conclusions

We have successfully developed a simple and novel protocol for the facile synthesis of complex angularly substituted tetra and pentacyclic hybrid molecular frameworks containing a coumarinopyranpyrazole / pyrimidinedione and coumarin ring systems using cinnamate, crotonate and *O*-allyl derivatives *via* a solid-state melt reaction (SSMR) through a domino process. Noteworthy features include the following: (a) Avoidance of catalysts and solvents even for solid reactants; (b) the products are obtained in a high diastereo- and chemoselective fashion; (c) column chromatography purification is not required to obtain the pure products; and (d) products are obtained with excellent yields. Therefore, this method will be highly useful to organic chemists both in academia as well as industrial sector. Furthermore, the highly remarkable SSMR strategy is valuable additional tool box for the production of various complex hybrid polyheterocyclic scaffolds.

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Notes and references

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Electronic Supplementary Information (ESI) available: Representative experimental procedures with all spectral data of **5a-h**, **8a-b**, **10a-b**, **13a-f** and **16a-b**. See DOI: 10.1039/c000000x/

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