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An expedient metal-free cascade route to chromonyl diene scaffolds: thermodynamic *vs.* kinetic control†

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A piperidine-catalyzed reaction between 3-formylchromone, 1,3-dimethyl barbituric acid, and ylidenemalononitriles is developed that offers chromonyl diene products in good yields. This cascade reaction proceeds *via* the insertion of ylidenemalononitriles between the Knoevenagel adduct obtained from 3-formylchromone and 1,3-dimethylbarbituric acid, where the pyrimidine-based enaminone is integrated with the chromone through the central diene linker. Similarly, introducing pyrimidine-based enaminone into the terminal part of the chromonyl diene scaffold gave an equilibrium mixture of rotational isomers in DMSO, which could be separated and isolated by crystallization. The computational analysis confirmed the role of barbiturate in directing the type of final chromonyl diene *via* kinetic or thermodynamic control. Moreover, computations revealed that one of these species, observed in the NMR spectra, is produced by the bond cleavage in the spirocyclic intermediate.

The barbituric acid derivatives have attracted extensive attention because of their unique therapeutic properties such as antioxidant,[1] antibacterial,[2] anti-proliferative,[3] antitubercular,[4] sedative,[5] antispasmodic,[6] anti-inflammatory,[7] anticonvulsant,[8] anticancer,[9] and hypnotic activities.[10] Although barbituric acid is, on its own, pharmacologically inactive, structural modification at its pyrimidinone C_5 atom allows potential biological activities[11] due to conjugated carbon–carbon double bonds.[12] Such 5-arylidene barbiturates are described as antimicrobials against different bacteria and fungi[13] and are potent tyrosinase inhibitors.[14] In addition, by adding the alkenylamine moiety to the structure, they can strongly chelate various metal ions in biological systems.[15] On the other hand, a naturally occurring oxygen-containing chromone nucleus has emerged as an essential pharmacophore of many biological compounds[16] including neuroprotective, anticancer, HIV-inhibitory, antioxidant activities, and are effective in inhibiting α-glucosidase.[17] From a pharmacological point of view, one route to modifying chromone is the introduction of barbituric acid derivatives, on which many biologically active compounds are based.[18] On the other hand, chromones bearing a functionalized conjugated dienes unit at the C3 position are potential intermediates for synthesizing biologically active molecules.[19] Furthermore, integrating one terminal chromone, one barbiturate, and a central diene linear linker can be an efficient way for the synthesis of π-conjugated compounds and a new strategy for biologically active product discovery (Fig. 1). Few reactions allow the direct synthesis of π-conjugated compounds through the formation of carbon–carbon bonds. The reported reactions of 1,3-butadiene derivatives containing chromone moiety have been prepared mainly using condensation of Wittig reagents[20] and Pd-catalyzed cross-coupling reaction.[21] Also, the aldol reaction of ylidenemalononitriles with 3-formylchromones led to the formation of electron-deficient dienes connected to the chromone moiety.[22] Along these lines, herein, we report the ylidenemalononitriles insertion reaction between the Knoevenagel adduct obtained from 3-formylchromone and 1,3-

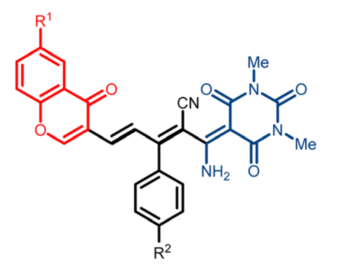

Fig. 1 The design of the proposed hybrid chromone-barbiturate linked by a central diene.

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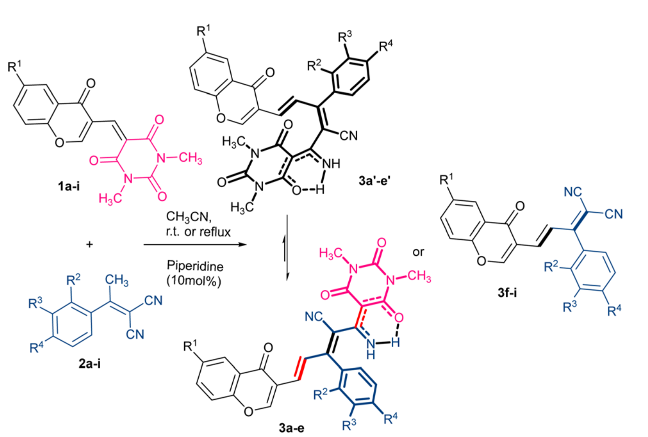
dimethylbarbituric acid in the synthesis of chromone-barbiturate hybrid structure linked by a linear diene (Scheme 1).

We began our study with model reactants chromonyl barbituric's acid **1b** and ylidenemalononitrile **2b** in the presence of a suitable base. The acetic acid-mediated synthesis involving Knoevenagel condensation of 3-formylchromone with 1,3-dimethylbarbituric acid in water is known.[23] We found that the resulting multifunctional synthon **1b** could *in situ* react with ylidenemalononitrile **2b**, which have been used extensively as vinylogous donors in Michael reactions.[24] Indeed, the chromonyl triene product containing barbiturate moiety **3b** was obtained in a 65% yield within 24 hours. Various bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), piperidine, Et_3N, and 1,4-diazabicyclo[2.2.2]octane (DABCO) were first evaluated in CH_3CN. Screening the amount of the selected base showed that the catalytic amount of piperidine (10 mol%) provided a good yield of **3b**. It is important to note that changing the CH_3CN solvent with EtOH led to inseparable reaction mixtures. Therefore, various solvents such as THF, DCM, CH_3CN, DMF, and toluene were examined, and the result showed that CH_3CN played a significant role in improving the product yield (Table 1). Electron-donating substituents (OMe and 2,3-di-OMe) at suitable positions of the phenyl ring were introduced, and the products **3b** and **3c** were afforded in excellent yields at room temperature. Note that electron-withdrawing chlorine atoms at both position 2 of the phenyl ring and within the chromone ring also worked well in this insertion process, so that, in the absence of chlorine of chromone, the chromonyl diene product **3f** was formed. Interestingly, the reaction provided the chromonyl diene product **3g** at room temperature and the desired chromonyl triene **3d** at reflux. To establish the scope and limitations, we found that in the case of 2,3-di-OMe and OMe substituents and 6-chloro-3-formylchromone, the reaction gave chromonyl diene products **3i** and **3h**, even at a reflux temperature. Also, in cases of 4-bromophenyl, 4-methylphenyl, 4-fluorophenyl and 4-chlorophenyl analogues, the reaction did not lead to desired products, and the formed yellow precipitate could not be analyzed due to its low solubility. Investigating spectral data of synthesized chromonyl trienes revealed two stereoisomers, which led us to assume that two *s-trans*,*s-trans*, and *s-trans*,*s-cis*-conformers exists as an equilibrium mixture in DMSO. In the ^{1}H NMR spectra of **3a**, the appearance of the singlet at δ 8.65 and 8.67 ppm indicated that the pyrone ring remained intact in both isomers. The chemical shifts of olefinic protons of major isomer at δ 6.26 and 7.97 ppm with the vicinal coupling constants $^3J = 15.7$–15.8 Hz revealed the *E*-configuration of chromonyl chalcone double bond. It is established that *cis* H-atoms with respect to the phenyl group appear in the higher field due to a long-range anisotropy effect of the non-coplanar benzene ring, which could be the reason for the shielding effect of olefinic H-11 proton.[25]



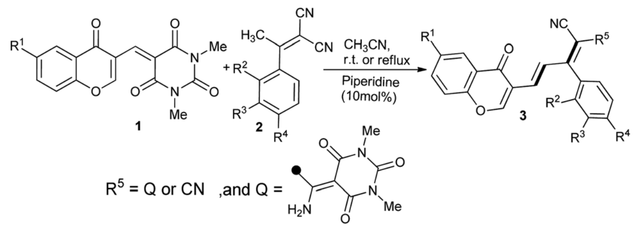
Scheme 1 One-pot sequential synthesis of substituted chromonyl triene barbiturate and chromonyl dienes.

The plausible mechanism of further transformations for all products can be readily rationalized from Scheme 2. It seems that the carbonyl groups of barbiturate in $\mathbf{In_{1a-1i}}$ provided two possible routes for the formation of final products by the [1,5]-H-transfer from the methylene substitution at the γ position of two carbonyl groups to the barbiturate moiety to form the intermediates $\mathbf{In_{2a-2e}}$, or the [1,3]-H-transfer with the same proton to barbiturate to from $\mathbf{In_{2f-2i}}$. After the H-transfer, the negative charge on the methylene site would liberate a barbiturate to generate the desired chromonyl diene products $\mathbf{P_{3f-3i}}$ through the formation of intermediates $\mathbf{In_{2f-2i}}$ (path A) or would take part in an annulation reaction to form $\mathbf{P_{3a-3e}}$ by passing from the intermediates $\mathbf{In_{2a-2e}}$ (path B).

Considering that two proton transfer mechanisms competed for the final product, we individually examined the affecting factors including thermodynamics and kinetics in this section. In comparing the energy barriers of hydrogen transfers, it was found that the transfer of [1,5] with an energy between 10 and 14 kcal mol^{-1} is kinetically faster than that of [1,3] (29–32 kcal mol^{-1}). However, the thermodynamic difference between the intermediates and transition state (0.5–1 kcal mol^{-1}) in [1,5]-H-transfer, indicated a possibility of reaction reversal.

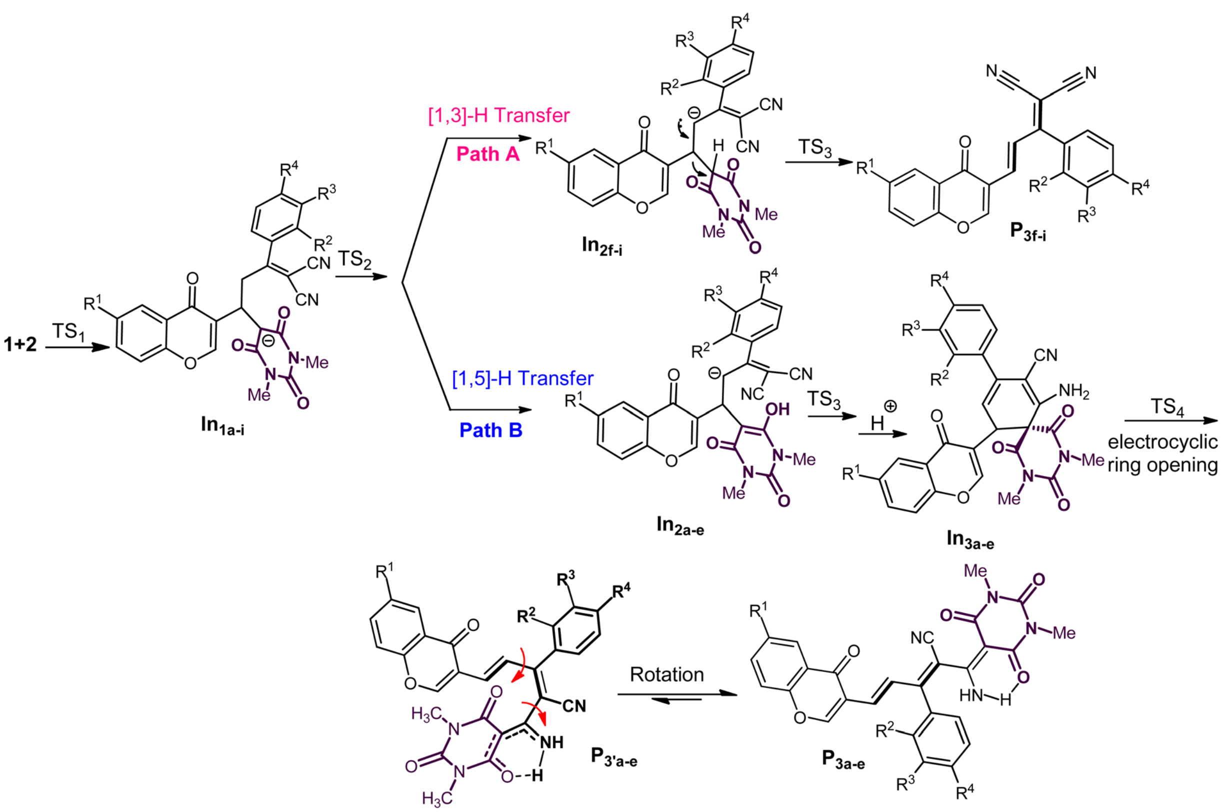
This issue could account for the formation of $\mathbf{P_{3f-3g}}$ in reflux conditions since the reflux condition not only provided the needed energy for [1,3]-H-transfer but also created more stable intermediates (Fig. 3). In order to verify that temperature can increase the instability of the intermediates $\mathbf{In_{2a-2i}}$, and promote the more favorable inverse pathway over the $\mathbf{In_{3a-3i}}$ formation, we selected **3d** as an example in reflux and the ambient temperature. The results showed that $\mathbf{In_{2d}}$ in path A had a significant instability among intermediates, and the reflux conditions have influenced on the reverse reaction more than passing the reaction through $\mathbf{TS_3}$ which was confirmed by experiments. In other words, unstable structures in reflux conditions tended to be at their optimal energy level, and favorable kinetic conditions could not influence the direction of reactivity. Thus, both sets of results confirmed that the decisive step in selecting the reaction pathway was related to proton transfer under thermodynamic control. Finally, breaking the spiro bond would proceed through 6π electrocyclic ring-opening due to the torsional strain of the formed spirocyclic $\mathbf{In_{3b}}$ (Fig. 2). It should be noted that the ^{1}C–^{2}C bond dissociation enthalpy ($\Delta H_R = -6.24$ kcal mol^{-1}, for details, see ESI†) of spirocyclic $\mathbf{In_3}$ confirms the 6π electrocyclic ring-opening.

Table 1 Scope of substituted chromonyl diene 3



Entry	R^1	R^2	R^3	R^4	R^5	Products	Temp.	Yield (%)
1	H	H	H	H	Q	**3a, 3′a**	r.t.	72 ($Z:E = 60:40$)
2	H	H	H	OMe	Q	**3b, 3′b**	r.t.	84 ($Z:E = 60:40$)
3	H	OMe	OMe	H	Q	**3c, 3′c**	r.t.	78 ($Z:E = 55:45$)
4	Cl	H	H	H	Q	**3d, 3′d**	80	67 ($Z:E = 60:40$)
5	Cl	Cl	H	H	Q	**3e, 3′e**	r.t.	63 ($Z:E = 60:40$)
6	H	Cl	H	H	CN	**3f**	80	75
7	Cl	H	H	H	CN	**3g**	r.t.	78
8	Cl	H	H	OMe	CN	**3h**	80	81
9	Cl	OMe	OMe	H	CN	**3i**	80	62

The experimental ^{1}H NMR evidence supported the existence of two products as an equilibrium mixture in DMSO in $\mathbf{P_{3a-3e}}$. According to the NMR computational data (for details, see ESI†), these are related to compounds $\mathbf{P_{3a'-3e}}'$, resulting from the ring-opening, and linear structures $\mathbf{P_{3a-3e}}$. In addition, the energy difference between $\mathbf{P_{3b}}$ and $\mathbf{P_{3b'}}$ is 0.45 kcal mol^{-1}, which shows that both stereoisomers could be in the equilibrium with each other. Considering the importance of the pyrimidine-based enaminone and chromonyl dienes and a unique orientation of the functional substituents on a rigid heterocyclic system, the highly selective cascade method for the synthesis of substituted chromonyl dienes in satisfactory yields has been described.



Scheme 2 The mechanistic proposal for the formation of chromonyl diene derivatives.

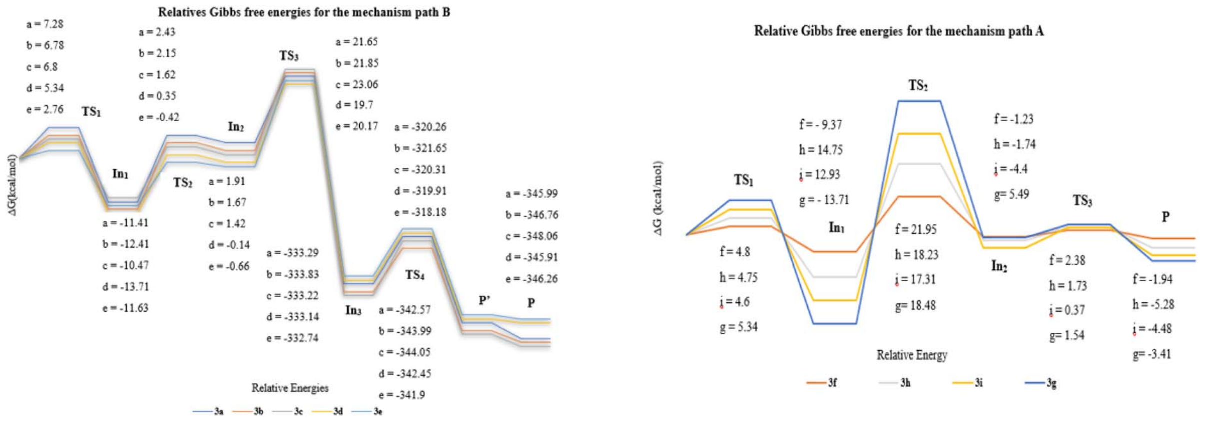


Fig. 2 Relative Gibbs free energies for the mechanism of path A and path B (all values in kcal mol^{-1}).

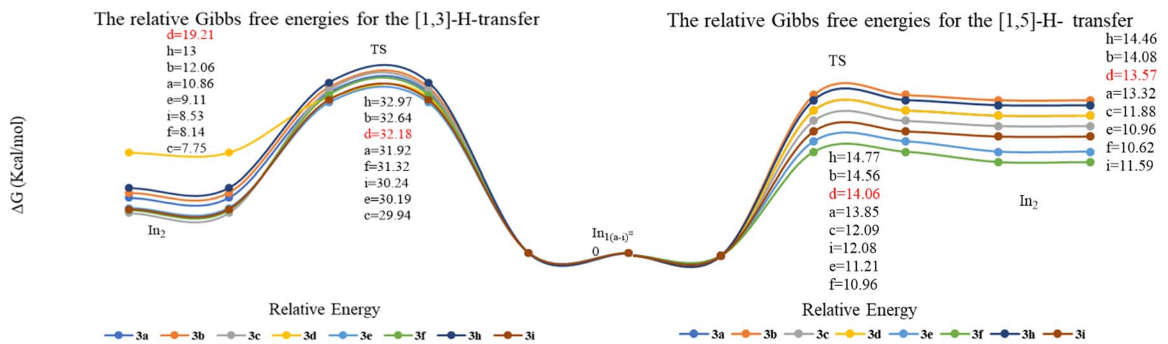


Fig. 3 Relative Gibbs free energies for the mechanism of [1,3] and [1,5] H-transfer (all values in kcal mol^{-1}).

This piperidine-catalyzed reaction proceeds *via* the ylidene-malononitrile insertion between the Knoevenagel adduct obtained from 3-formylchromone and 1,3-dimethylbarbituric acid, while the pyrimidine-based enaminone is integrated with the chromone through the central diene linker. Computations showed that the barbiturate unit can control the direction of reaction through a single bond rotation and can lead to the diversity of linear chromonyl diene products with and without a pyrimidine-based enaminone unit.

Conflicts of interest

There are no conflicts to declare.

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