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Solid-State Melt Reaction for the Domino Process: Highly Efficient Synthesis of Fused Tetracyclic Chromenopyran Pyrimidinediones Using Baylis−Hillman Derivatives†

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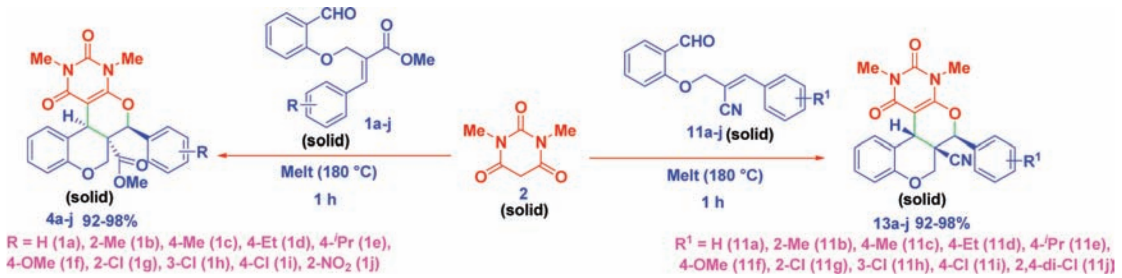
ABSTRACT



A solid-state melt reaction (SSMR) has been demonstrated via a domino process for the synthesis of tetracyclic chromenopyran pyrimidinedione frameworks using Baylis−Hillman derivatives through in situ formation of an olefin followed by an intramolecular [4 + 2] cycloaddition reaction sequence. The tetracyclic frameworks were obtained without using catalyst and solvent in a highly stereoselective and stereospecific fashion. The isolated yield is excellent and does not require column chromatography purification to obtain the pure product.

Synthesis of complex heterocyclic compounds is very challenging in the field of organic chemistry.[1] Usually, complex organic molecules are synthesized by a multistep reaction sequence. Recently, domino reactions have become very attractive and a useful strategy which minimizes the reaction steps to achieve the target complex organic compounds[2] with high yields. The domino Knoevenagel intramolecular hetero-Diels−Alder reaction is one of the most powerful synthetic routes for the synthesis of various heterocycles and natural products.[2a,c,3] The domino Knoevenagel intramolecular hetero-Diels−Alder reaction has also been extensively employed for the synthesis of polycyclic compounds, especially for the synthesis of chromenopyran pyrimidinedione ring systems.[2a,3b,d,f,4]

There has been a flurry of activity in the synthesis of pyrimidine derivatives due to their proven biological activity

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† Dedicated to Prof. D. Basavaiah.

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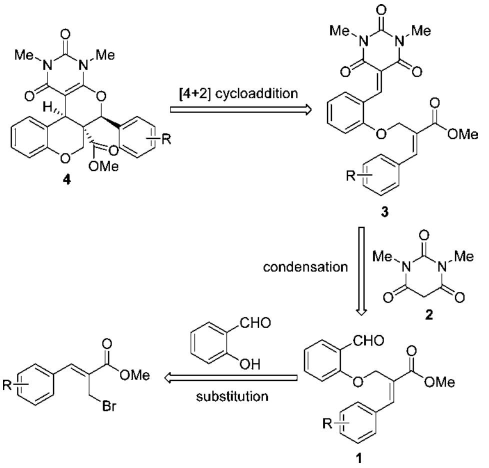
and medicinal utility. 5-Substituted uracils and their nucleosides are of immense biological significance because of their use in chemotherapy of cancer.[5a] Some of the pyrimidine derivatives also have anti viral and anti-HIV activities.[5b−e]

The Baylis−Hillman reaction is one of the most important reactions in the field of organic synthesis.[6] In fact, the Baylis−Hillman adducts and their derivatives are useful intermediates for the synthesis of many natural products and biologically active molecules.[6a−c,7] To the best of our knowledge, Baylis−Hillman derivatives have not been utilized for the domino Knoevenagel intramolecular hetero-Diels−Alder reaction to date. In continuation of our interest in the field of Baylis−Hillman chemistry,[8] herein for the first time we report a novel solid state melt reaction (SSMR) via a domino reaction for the synthesis of complex tetracyclic chromenopyran pyrimidinedione frameworks in a highly stereoselective and stereospecific fashion using Baylis−Hillman derivatives involving in situ formation of olefin followed by an intramolecular [4 + 2] cycloaddition reaction.

Generally domino Knoevenagel intramolecular hetero-Diels−Alder reactions are carried out with catalyst, solvent or microwave irradiation.[2a,c,d,9] We envisaged that the domino Knoevenagel intramolecular hetero-Diels−Alder reaction can be conducted without the above-mentioned essential reaction components/conditions which are very important criteria in green synthesis.

To execute our idea, first we selected methyl (2*Z*)-2-(bromomethyl)-3-arylprop-2-enoates, bromo derivatives of the Baylis−Hillman adducts and salicyladehyde to generate the required precursor (**1**) to obtain the desired tetracyclic chromenopyran pyrimidinedione compounds (**4**) via a tandem Knoevenagel intramolecular hetero-Diels−Alder reaction according to the retrosynthetic strategy shown in Scheme 1.

Scheme 1. Retrosynthetic Strategy for the Synthesis of Tetracyclic Frameworks with Angular Substitution



To prepare the desired tetracyclic chromenopyran pyrimidinedione compound (**4**), we first treated *N*,*N*-dimethylbarbituric acid and the Baylis−Hillman derivative **1a**[8a] with a catalytic amount of ethylenediammonium diacetate (EDDA) catalyst in toluene under reflux temperature for 6 h. However, the reaction did not provide the anticipated product (**4**). The reaction was carried out with other catalysts such as $AlCl_3$, $BF_3(OEt)_2$, and cerium(IV) ammonium nitrate (CAN), but they too failed to provide the desired product (Table 1, entries 1−4).

However, best results were obtained when the Baylis−Hillman derivative **1a** melted with *N*,*N*-dimethylbabituric acid (**2**) in a round-bottom flask at 180 °C for 1 h in solvent and catalyst-free conditions, yielding the desired angularly substituted (ester moiety) tetracyclic chromenopyran pyrimidinedione **4a** in 98% yield without column chromatography purification (pure product obtained after washing with ethylacetate and hexane mixture in a 1:49 ratio). Decreasing

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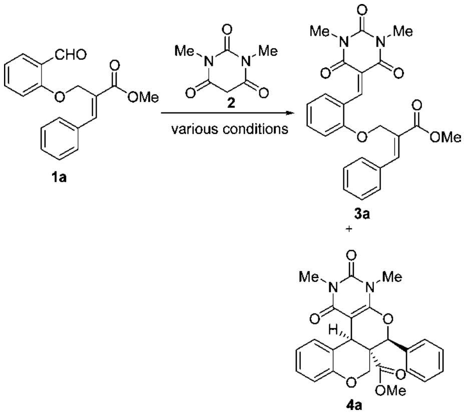
Table 1. Optimization for the Formation of Tetracyclic Compound Using Various Catalysts and Conditions



entry	catalyst (20 mol %)	T (°C)	solvent	time (h)	product[a] (%) 3a	4a
1	EDDA	110	toluene	6	57	
2	$AlCl_3$	110	toluene	6		
3	$BF_3(OEt)_2$	110	toluene	6		
4	CAN	110	toluene	6	29	
5		110	toluene	6	24	
6		100[b]		1	57	
7		120[b]		1	86	
8		140[b]		1	72	21
9		160[b]		1	23	72
10		**180**[b]		**1**		**98**

[a] Isolated yield of the pure product. [b] Solid reactants melted at the mentioned temperature without solvent.

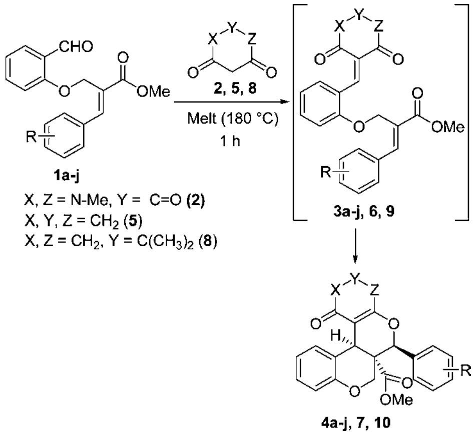
the reaction temperature from 180 °C led to incompletion of the reaction (Table 1, entries 6−9). It is worth mentioning that this is the first solid-state melt reaction (SSMR) for the domino Knoevenagel intramolecular hetero-Diels−Alder reaction. Utilization of the Baylis−Hillman derivatives for such domino hetero-Diels−Alder reactions is new in the field of Baylis−Hillman chemistry.

Encouraged by this result, we treated a variety of Baylis−Hillman derivatives (**1b**−**j**) with *N*,*N*-dimethylbarbituric acid which successfully yielded the desired fused tetracyclic chromenopyran pyrimidinedione derivatives **4b**−**j** in 92−98% yields (Table 2).

To understand the reaction further, we also melted cyclohexane-1,3-dione (**5**) and 5,5-dimethylcyclohexane-1,3-dione (**8**) with a Baylis−Hillman derivative (**1a**) in catalyst- and solvent-free conditions for 1 h at 180 °C, which successfully led to the corresponding fused tetracyclic chromenopyran pyrimidinedione compounds **7** and **10**, respectively, in excellent yields (96% and 95%).

To check the generality of the reaction, we melted the various Baylis−Hillman derivatives derived from acrylonitrile (**11a**−**j**)[8a] with *N*,*N*-dimethylbarbituric acid for 1 h at 180 °C which successfully provided the desired angularly substituted (cyano group) fused tetracyclic chromenopyran pyrimidinedione compounds **13a**−**j** in 92−98% yields. The isolated yields of the pure products (**13a**−**j**) are summarized in Table 3.

Table 2. Synthesis of Tetracyclic Frameworks Using *N*,*N*-Dimethylbarbituric Acid/Cyclohexane-1,3-dione/ 5,5-Dimethylcyclohexane-1,3-dione and Baylis−Hillman Derivatives **1a**−**j**



entry	substrate	R	product[a]	time (h)	yield[b,c] (%)
1	**1a**	H	**4a**[d]	1	98
2	**1b**	2-Me	**4b**	1	92
3	**1c**	4-Me	**4c**	1	98
4	**1d**	4-Et	**4d**	1	97
5	**1e**	4-^{i}Pr	**4e**	1	98
6	**1f**	4-OMe	**4f**	1	97
7	**1g**	2-Cl	**4g**	1	92
8	**1h**	3-Cl	**4h**	1	93
9	**1i**	4-Cl	**4i**	1	96
10	**1j**	$2-NO_2$	**4j**	1	94
11	**1a**	H	**7**	1	96
12	**1a**	H	**10**	1	95

[a] All reactions were carried out on a 1 mmol scale of O-alkylated compound (**1a**−**j**) with 1 mmol of *N*,*N*-dimethylbarbituric acid/cyclohexane-1,3-dione/5,5-dimethylcyclohexane-1,3-dione by melting at 180 °C for 1 h. [b] Isolated yield of the pure product. [c] All compounds were fully characterized (see the Supporting Information). [d] The structure of the molecule was further confirmed by single-crystal X-ray data (see the Supporting Information).[10]

It is worth mentioning that the highly stereoselective and stereospecific nature of the reaction was clearly evidenced by ^{1}H NMR data and X-ray crystal analyses. Comparison of the ^{1}H NMR spectra of the crude products and recrystallized products showed them to be identical, which confirms the highly stereoselective nature of the reaction. Furthermore, the stereochemistry of compound **4a** was confirmed by X-ray crystallographic analysis (Figure 1). The crystal structure of compound **4a** shows that the relative stereochemistry of the phenyl group and the adjacent ester moiety are in the *anti* orientation, which is presumably due to the initial *trans* geometry of the phenyl group and ester moiety present in the double bond at *vicinal* positions of compound **1a**, thus confirming the stereospecificity of the reaction. Similarly, the relative stereochemistry of compound **13a** was confirmed by X-ray crystallographic analysis (Figure 2). The crystal

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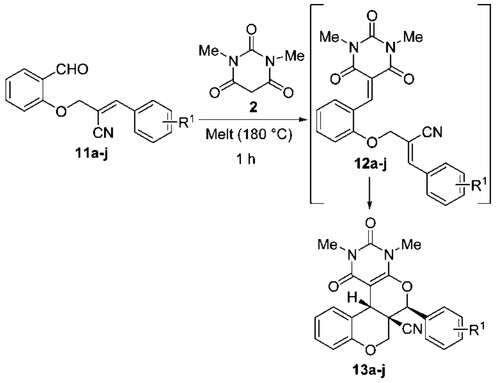
(10) Structures were confirmed by single-crystal X-ray data. CCDC numbers for **4a** and **13a** are 682089 and 682090, respectively.

Table 3. Synthesis of Tetracyclic Frameworks Using *N*,*N*-Dimethylbarbituric Acid and Baylis−Hillman Derivatives **11a−j**



entry	substrate	R^1	product[a]	time (h)	yield[b,c] (%)
1	**11a**	H	**13a**[d]	1	97
2	**11b**	2-Me	**13b**	1	98
3	**11c**	4-Me	**13c**	1	98
4	**11d**	4-Et	**13d**	1	96
5	**11e**	4-^{i}Pr	**13e**	1	95
6	**11f**	4-OMe	**13f**	1	98
7	**11g**	2-Cl	**13g**	1	94
8	**11h**	3-Cl	**13h**	1	92
9	**11i**	4-Cl	**13i**	1	93
10	**11j**	2,4-dichloro	**13j**	1	92

[a] All reactions were carried out on a 1 mmol scale of O-alkylated compound (**11a−j**) with 1 mmol of *N*,*N*-dimethylbarbituric acid by melting at 180 °C for 1 h. [b] Isolated yield of the pure product. [c] All compounds were fully characterized (see the Supporting Information). [d] The structure of the molecule was further confirmed by single-crystal X-ray data (see the Supporting Information).[10]

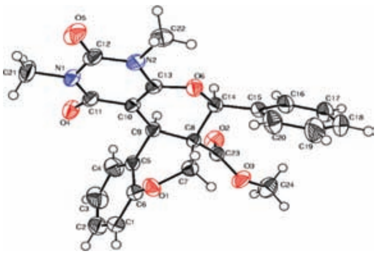


Figure 1. X-ray crystal structure of **4a**.

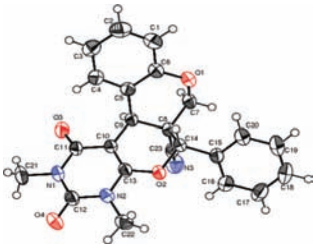


Figure 2. X-ray crystal structure of **13a**.

structure of compound **13a** shows that the phenyl group and adjacent nitrile moiety are in *syn* orientation which was presumably due to the initial *cis* geometry of the phenyl group and nitrile moiety present in the double bond at *vicinal* positions of compound **11a**, thus confirming the stereospecificity of the reaction. Hence, the starting material having a *trans* geometry (aryl and ester groups present in the *vicinal* positions of compound **1a**) led to the *anti* product and starting material having a *cis* geometry (aryl and nitrile moieties present in the *vicinal* positions of compound **11a**), which led to the *syn* product which clearly shows the high stereospecific nature of the reaction.

In conclusion, we have successfully developed a simple and novel protocol for the facile synthesis of complex angularly substituted tetracyclic frameworks containing a chromenopyran pyrimidinedione ring system via a solid-state melt reaction (SSMR) through a domino process using Baylis−Hillman derivatives. Notable features include the following: (a) catalyst and solvent are not required even for solid reactants; (b) the products are obtained in a highly stereoselective and stereospecific fashion; (c) column chromatography purification is not required to obtain the pure products; and (d) products are obtained with excellent yields. This strategy opens new opportunities for the preparation of libraries of a wide variety of chromenopyran pyrimidinedione derivatives for biological screening.

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Supporting Information Available: Experimental procedures (with all spectral data), ^{1}H and ^{13}C NMR spectra of all compounds **3a**, **4a−j**, **7**, **10**, and **13a−j**, CIF files, and ORTEP diagrams. This material is available free of charge via the Internet at http://pubs.acs.org.

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