Chemo-/regioselective synthesis of 6-unsubstituted dihydropyrimidinones, 1,3-thiazines and chromones *via* novel variants of Biginelli reaction†

Jie-Ping Wan and Yuan-Jiang Pan*

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A novel and facile cascade Biginelli-like assembly employing enaminone, aldehyde and urea/thiourea has been developed, which provides a highly chemo- and regioselective synthesis of new dihydropyrimidinones, 1,3-thiazines and chromones by altering particular functional groups in the reactants.

The first three-component reaction using aromatic aldehydes, β-keto esters and urea to synthesize functionalized 3,4-dihydropyrimidinones (DHPMs) was reported by Biginelli over one century ago.[1] Over recent decades, there has been increasing focus on DHPMs as potential lead structures in drug discovery based on both simple DHPM molecules and the study of bioactive natural products.[2] Various biological activities such as antihypertensive,[3] antibacterial,[4] antiviral[5] as well as calcium channel modulating[6] activities *etc.* have been discovered in suitably functionalized DHPMs and a large number of DHPM-based scaffolds have already been developed into drugs or lead compounds. For instance, monastrol is the first discovered cell-permeable small molecule which specifically inhibits mitotic kinesis Eg5.[7a] Recent research has demonstrated that (*R*)-mon-97 has much more potent antitumor activity than monastrol,[7b] and (*R*)-SQ 32, 926 is an antihypertensive agent with potent oral activity (Fig. 1).[2a] The great potential of DHPMs in biological and pharmaceutical fields has accordingly triggered growing interest in their synthetic study.[8]

In the last two decades, the work of Kappe's group has considerably broadened both the application and understanding of the classical Biginelli reaction.[9] Despite a large body of work on the Biginelli reaction reported in the literature, including seminal work by Atwal and Overman,[10] few accounts so far have focused on extending its substrate scope. Recently, Bussolari[11a] and co-workers developed a protocol for the synthesis of 5-unsubstituted DHPMs by employing oxalacetic acid as the active methylene donor, and aromatic ketones have also been applied as reaction partners to yield 5-unsubstituted DHPMs in some cases.[11b–d] However, unlike the success in the synthesis of 5-unsubstituted DHPMs, few systematic methods have been established to synthesize 6-unsubstituted DHPMs until Booker-Milburn's[12a] recent work on a $BF_3{\cdot}Et_2O$ catalyzed three-component reaction involving two aldehydes and an *N*- or *N*,*N*′-substituted urea (or sulfamide). An advancement though it is in DHPM synthesis, this methodology suffers from intolerance to unsubstituted urea and thiourea. Therefore, searching for more facile and practical synthetic routes to 6-unsubstituted DHPMs is still a significant task.[12b] Multicomponent reaction is now one of the most desirable methodologies in constructing functional heterocyclic scaffolds based on its properties of high efficiency and broad product structural diversity, which caters for the urgent requirement of building up huge molecule libraries in modern drug discovery.[13]

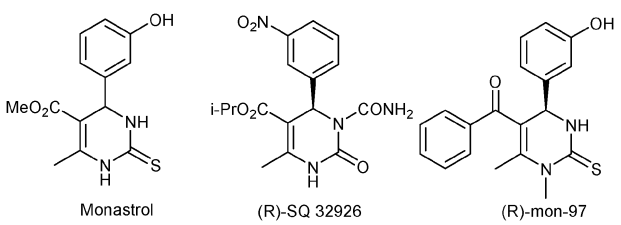

Fig. 1 Pharmacologically active DHPMs.

Based on our progressive endeavors in exploring novel and practical multicomponent reactions to synthesize useful heterocyclic compounds,[14] we present herein the results of some new three-component cascade reactions for the selective synthesis of 6-unsubstituted DHPMs and 1,3-thiazines as well as chromones using enaminone.[15]

Initially, enaminone **3a** was selected to react with thiourea and benzaldehyde in the presence of 50 mol% TFA. The target DHPM **4a** was obtained in 80% yield. In order to improve the reaction efficiency, the reaction conditions were optimized (Table 1). A study designed to optimize yields showed TMSCl (1.5 mol eq.) to be superior to TFA. No reaction took place when acetic acid was used as a promoter. Non-polar solvents, such as toluene (entry 9), led to an intractable paste due to issues with low solubility. Conducting the reaction at a lower temperature (entry 8) resulted in incomplete conversion.

After screening the reaction parameters, we turned to examining the reaction scope with the optimized conditions (entry 5, Table 1). Various aromatic aldehydes, enaminones and urea/thiourea were subjected to the protocol (Table 2). As expected, corresponding DHPMs were afforded in satisfactory yield regardless of the substitution pattern in the arene groups in both the aldehyde and enaminone substrates with the exception of 2-OH in enaminone (Table 5). Both urea and thiourea turned out to be good reaction partners.

The structures of the DHPMs were clearly assigned by both abundant spectral analysis and X-ray single crystal diffraction

Department of Chemistry, Zhejiang University, Hangzhou, 310027, P.R. China. E-mail: panyuanjiang@zju.edu.cn; Fax: 86 571 87951629; Tel: 86 571 87951264

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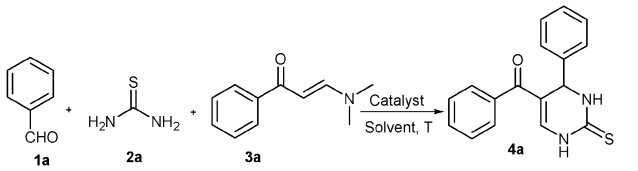
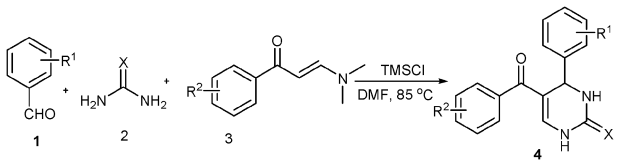
Table 1 Different conditions for the synthesis of DHPMs[a]



Entry	Catalyst (eq.)	Solvent	T/°C	Yield (%)[b]
1	TFA (0.5)	DMF	85	80
2	AcOH (0.5)	DMF	85	Trace
3	TMSCl (0.5)	DMF	85	86
4	TMSCl (1.0)	DMF	85	91
5	TMSCl (1.5)	DMF	85	95
6	TMSCl (2.0)	DMF	85	93
7	TMSCl (1.5)	DMF	100	95[c]
8	TMSCl (1.5)	DMF	70	Mixture
9	TMSCl (1.5)	Toluene	85	Paste

[a] Reaction condition: 0.3 mmol **1a**, 0.35 mmol **2a** and 0.3 mmol **3a** stirred for 10 h. [b] Isolated yield based on aldehyde. [c] Average yield of two identical run.

Table 2 Synthesis of 6-unsubstituted DHPMs from various aromatic substrates[a]



Entry	R^1	R^2	X	Product	Yield (%)[b]
1	H	H	S	**4a**	95
2	4-Me	H	S	**4b**	91
3	4-OMe	H	S	**4c**	86
4	4-Cl	H	S	**4d**	95
5	4-Br	H	S	**4e**	89
6	4-CF_3	H	S	**4f**	96
7	4-OH	H	S	**4g**	82
8	4-NO_2	H	S	**4h**	93
9	4-NMe_2	H	S	**4i**	79
10	2-OMe	H	S	**4j**	80
11	2-F	H	S	**4k**	77
12	3,4-$(OMe)_2$	H	S	**4l**	61
13	4-Cl	4-Me	S	**4m**	90
14	4-Me	4-Me	S	**4n**	92
15	4-Me	4-NO_2	S	**4o**	87
16	3-NO_2	4-NO_2	S	**4p**	90
17	H	H	O	**4q**	89
18	4-Me	H	O	**4r**	86
19	4-OMe	H	O	**4s**	85
20	4-F	H	O	**4t**	86
21	4-NO_2	H	O	**4u**	92
22	3-NO_2	H	O	**4v**	82
23	H	4-Me	O	**4w**	93
24	4-OMe	4-OMe	O	**4x**	90
25	4-Cl	4-OMe	O	**4y**	96

[a] Reaction conditions: 0.3 mmol **1**, 0.35 mmol **2** and 0.3 mol **3** mixed in 2 mL DMF, 1.5 eq. mol TMSCl, stirred at 85 °C for 10 h. [b] Isolated yield based on aldehyde.

on the product **4d** (Fig. 2).† It is notable that these DHPMs bear high structural resemblance to the lead compound mon-97 as shown in Fig. 1.

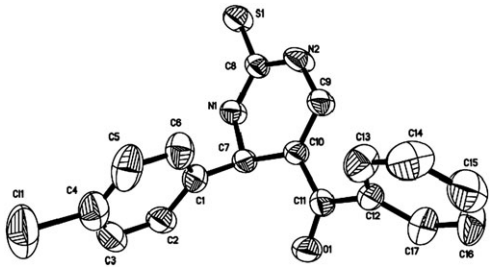
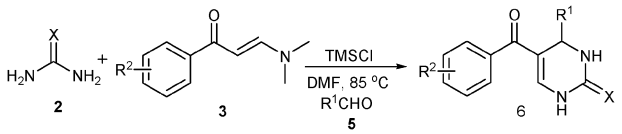


Fig. 2 X-Ray structure of **4d**.

Encouraged by the good results acquired from aromatic aldehydes, we attempted to expand the scope of this three-component reaction to aliphatic aldehydes. To our delight, good results were obtained from these reactions although the DHPMs were afforded in modest yield (Table 3). These results also highlighted the eminent compatibility of this novel synthetic system.

The reactions of *N*-substituted urea and thiourea were subsequently investigated (Table 4). *N*1-Methyl DHPMs **7** were isolated exclusively when *N*-methyl urea was employed; surprisingly, unprecedented regioselectivity in the classical Biginelli reaction was observed when *N*-methyl thiourea was subjected to the same reaction: instead of DHPM, the isomer 1,3-thiazine **8** was found to be the major product (see ESI† for

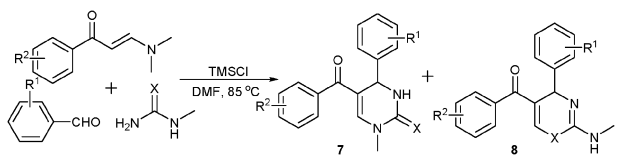
Table 3 Synthesis of 6-unsubstituted DHPMs from aliphatic aldehydes[a]



Entry	R^1	R^2	X	Product	Yield (%)[b]
1	CH_3CH_2	H	S	**6a**	72
2	$CH_3(CH_2)_2$	H	S	**6b**	69
3	$CH_3(CH_2)_5$	H	S	**6c**	74
4	$(CH_3)_2CHCH_2$	H	S	**6d**	70
5	CH_3CH_2	4-OMe	O	**6e**	65
6	$CH_3(CH_2)_2$	4-OMe	O	**6f**	62

[a] Identical conditions as Table 2. [b] Isolated yield based on aldehyde.

Table 4 Regioselective formation of DHPMs and 1,3-thiazines[a]

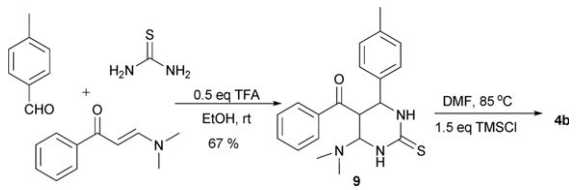


Entry	R^1	R^2	X	Product	Yield (**7**/**8**%)[b]
1	4-CH_3	4-OMe	O	**7a**	62
2	4-NO_2	H	O	**7b**	66
3	H	4-OMe	S	**7c**/**8c**	19/60
4	4-NO_2	H	S	**7d**/**8d**	20/63
5	4-CH_3	H	S	**8e**	71

[a] Identical conditions as Table 2. [b] Isolated yield based on aldehyde.

characterization) while corresponding DHPMs were isolated as minor products.

Unlike the classical Biginelli reaction, the above reactions plausibly proceeded *via* the Hofmann elimination of THPM **9**. Therefore, we managed to synthesize **9** under less drastic catalyst conditions (eqn (1)). Hence, THPM **9** was subjected to the aforementioned standard conditions, and it was smoothly converted to DHPM **4b** in almost quantitative yield (98%), which suggested **9** as the key intermediate in the reaction process.

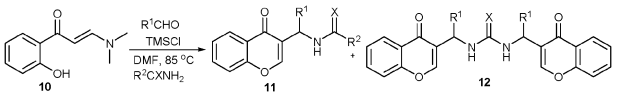


(1)

The understanding of the reaction process promoted us to explore the reaction using enaminones with nucleophilic groups at the *ortho* position of the benzene ring, which was expected to trigger the generation of a further fused product. To our surprise, when 2-hydroxylphenyl enaminone **10** was used, 3-substituted chromones **11** were selectively furnished (Table 5), while the dimers **12** were occasionally formed as side products. The results represent a formally Baylis–Hillman-type reaction, but what is interesting is that the acidic conditions in this reaction are significantly different from the basic conditions in the classical Baylis–Hillman reaction. It is noteworthy that doubling the amount of aldehyde, enaminone and the catalyst does not increase the yield of **12**, which demonstrated the good chemoselectivity of this reaction.

In summary, we have developed several new variants of the Biginelli reaction. In contrast to the traditional Biginelli reaction, the present method bears specific novelty not only because of the 6-unsubstituted DHPMs, but also because of the manipulable synthesis of other important heterocyclic systems, such as 1,3-thiazines and chromones. A plausible mechanism has been demonstrated based on the synthesis of THPM **9** and its transformation to the corresponding DHPM. The methodology provides an important supplement to the classical Biginelli reaction in terms of preparing structurally novel DHPMs and related heterocyclic isomers.

Table 5 Selective synthesis of 3-substituted chromones[a]



Entry	R^1	R^2	X	Product	Yield (%)[b]
1	4-MeC_6H_4	NH_2	S	**11a** (**12a**)	61 (16)
2	4-ClC_6H_4	NH_2	S	**11b** (**12b**)	70 (13)
3	3-$MeOC_6H_4$	NH_2	S	**11c**	83
4	$(CH_3)_2CHCH_2$	NH_2	S	**11d**	62
5	4-$NO_2C_6H_4$	NH_2	O	**11e**	77
6	4-$MeOC_6H_4$	NH_2	O	**11f**	68
7	4-FC_6H_4	CH_3	O	**11g**	85

[a] Identical conditions as Table 2. [b] Isolated yield based on aldehyde.

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