Tetrahedron xxx (2015) 1–7

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Iron-catalyzed four-member multicomponent reaction for assembly of (*E*)-6-arylvinyl-3,4-dihydropyrimidin-2(1*H*)-ones

Zhiguo Zhang *, Lianqiang Zhang, Xinyu Duan, Xiangqian Yan, Yan Yan, Qingfeng Liu, Tongxin Liu, Guisheng Zhang *

Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, PR China

ARTICLE INFO

Article history:
Received 3 June 2015
Received in revised form 11 July 2015
Accepted 14 July 2015
Available online xxx

Keywords:
Four-component reaction
Biginelli-type reaction
Aldol condensation reaction
Iron-catalyzed
Vinylogous aldol condensation

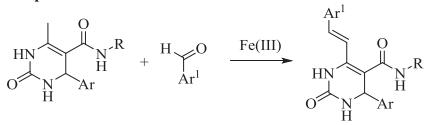
ABSTRACT

A novel iron-catalyzed one-pot multi-component tandem reaction of acetoacetamide, urea, and two molecules of aryl aldehydes has been developed. This reaction provides a general, straightforward, practical and useful method for the preparation of potential bioactive (*E*)-6-arylvinyl-3,4-dihydropyrimidin-2(1*H*)-ones. They are also versatile precursors leading to diverse drug-like dihydropyrimidin-2(1*H*)-one derivative. The characters of avoiding protonic acid and using a single inexpensive and environmentally benign catalyst make this method more valuable.

1. Introduction

3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) are identified a broad range of biological activities, such as antitumor,[1] antihypertensive,[2] antiHIV,[3] antimicrobials, antiinflammatory, antibacterial, antifungal, and anthelmintic activities.[4] 6-Arylvinyl DHPMs are not only potential bioactive compounds, but also potential versatile precursors of preparing diverse drug-like DHMP derivatives, e.g., pyrido[4,3-*d*]pyrimidines,[5] through conjugate-addition, intermolecular and intramolecular cycloadditions, halogenations, hydrogenations, hydrations, oxidations, and other reactions based on the newly formed carbon–carbon double bond. It is well-known that DHPMs can be obtained from the classical Biginelli reaction or Biginelli-like reaction,[6] but, highly functional DHPM derivatives[7] including 6-arylvinyl DHPMs[5] have to be prepared by a derivatization of Biginelli products although it would be a better choice to obtain them from one-pot multi-component Biginelli-type reaction.[8] Very recently, we achieved an iron-catalyzed vinylogous aldol condensation of Biginelli products with aldehydes for the synthesis of 6-arylvinyl DHPMs (Eq. 1),[5] which inspired us to hypothesize that a Lewis acid catalyzed one-pot four-component strategy for assembly of 6-arylvinyl DHPMs should be feasible (Eq. 2).

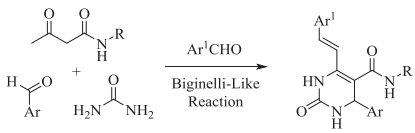
Our previous work:



(1)

R = Aryl, Alkyl; Ar^1 = Ar or $Ar^1 \neq$ Ar

This work:



(2)

R = Aryl, Alkyl; Ar^1 = Ar or $Ar^1 \neq$ Ar

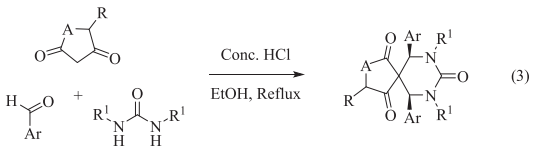
A literature review disclosed that only three papers had focused on the four-component Biginelli-like multi-component reactions (MCRs) (with one molecule of β-dicarbonyl compounds, one molecule of urea and two molecules of aldehyde) since Biginelli reaction was discovered. In 2000, Byk and co-works found that a five-member ring β-keto ester (lactone) could react with one molecule of urea and two of aldehyde to give a new family of spiro heterobicyclic aliphatic rings in good yields without traces of the expected DHMP (Biginelli) products.[9] Soon after, they extended the four-component Biginelli-type reaction to the condensation between cyclic β-keto lactams with two molecules of aldehyde and urea, and the reaction produced exclusively *syn* spiro-fused pyrimidine isomers in a 1:1 mixture.[10] And similar spiro-fused ring syntheses

* Corresponding authors. Fax: +86 373 332 5250; e-mail addresses: zhangzg@htu.edu.cn (Z. Zhang), zgs6668@yahoo.com (G. Zhang).

http://dx.doi.org/10.1016/j.tet.2015.07.039
0040-4020/

could also be obtained when annular cyclopentane-1,3-dione and dimethylbarbituric acid (or their analogues) were used as the special 1,3-dicarbonyl compounds.[11] However, it must be noted that all of these MCR methods[9–11] afforded a spiro compound instead of the 6-arylvinyl DHMPs (Eq. 3). Herein, we report an effective and practical iron-catalyzed one-pot four-component Biginelli-type condensation for the straightforward assembly of 6-arylvinyl DHPMs from acetoacetamide, urea, and two molecules of aldehyde.

The known four-component Biginelli-like reactions:



(3)

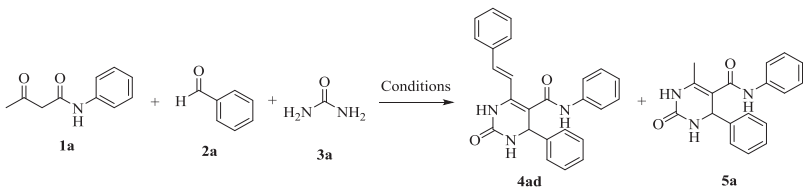
A = O, NR^1; R = H, Me, Bn; R^1 = H, Benzyloxycarbonyl.

2. Results and discussion

Over the past decade, iron-catalyzed MCRs have drawn much attention due to the nontoxicity, low cost, sustainability, ready availability, stability, and environmentally friendly properties.[12] Several literature have successfully achieved the iron-catalyzed Biginelli reactions.[6e-l] Combined with our recent work on the synthesis of 6-arylvinyl DHPMs,[5] iron salts were selected as the catalyst for the effective and practical preparation of π-conjugated 6-arylvinyl DHPMs. Some key results of the conditions screening are summarized in Table 1. Our initial investigation focused on the effect of solvents on the four-component coupling reactions of **1**, **2**, and **3**. Initially, several solvents were screened in a model reaction of acetoacetanilide (**1a**) (0.5 mmol),[13] benzaldehyde (**2a**) (1.5 mmol), and urea (**3a**) (0.5 mmol) by using $FeCl_3·6H_2O$ (0.05 mmol) as catalyst, and CH_3CN was found to be the most suitable media for this multicomponent condensation (Table 1, entry 1). The use of EtOH resulted in the formation of **4ad** in 29% yield together with 47% **5a**, and the yield of **4ad** could not be further increased by prolonging the reaction times (Table 1, entry 2). In solvents CH_2Cl_2 and DMSO, the desired product **4ad** was not obtained, especially in DMSO, the only isolated compound was Biginelli product **5a** (82%) (Table 1, entries 3 and 4). The temperature has a great influence on the reaction. It was found that the yield of **4ad** would decrease significantly along with the decreased temperature (Table 1, entries 5 and 6). At reflux, increasing or decreasing the amount of the $FeCl_3·6H_2O$ would only provide a slightly lower yield of **4ad** (Table 1, entry 1 vs. entries 7,8). Interestingly, we did not obtain a satisfied result when 2.0 equiv of **2a** was used for the reaction, although it seems it is enough for the protocol (Table 1, entry 9). Moreover, the experimental results disclosed that increasing the amount of **2a** to 4.0 equiv entirely could not improve the yield of the **4ad** (Table 1, entry 10). In addition, iron salts screening showed that the multicomponent coupling reaction could be catalyzed by Fe^{III} salts or Fe^{II} salts, such as $FeCl_3·6H_2O$, $Fe_2(SO_4)_3·xH_2O$, anhydrous $FeCl_3$, $Fe(NO_3)_3·9H_2O$, and $FeSO_4·7H_2O$, in the absence of any acid (such as HCl) (Table 1, entries 1, 11–14). But it is obvious that $FeCl_3·6H_2O$ was the most effective catalyst for the reaction (Table 1, entry 1). More importantly, this tandem reaction is very efficient, compared with the stepwise reaction of Biginelli reaction (**5a**: 92% yield) and vinylogous aldol condensation (**4ad**: 88% yield) (total yield: 81%),[5] the yield of **4ad** can be obtained up to 86% in the presence of sole $FeCl_3·6H_2O$ via the one-pot strategy (Table 1, entry 1). It is noteworthy that, according to the ^1H NMR data, the C=C double bond at the 6-position was assigned as an *E* configuration based on the magnitude of the coupling constant (16.4 Hz).[9]

The optimized reaction condition was established (Table 1, entry 1), the scope of this protocol was investigated next (Table 2). We first explored the scope of the reaction by using various acetoacetanilides (**1a**–**h**) and **2a**. As expected, **1a**–**h** worked well and gave

Table 1
Survey of reaction conditions[a]

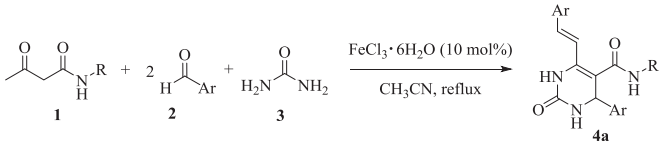


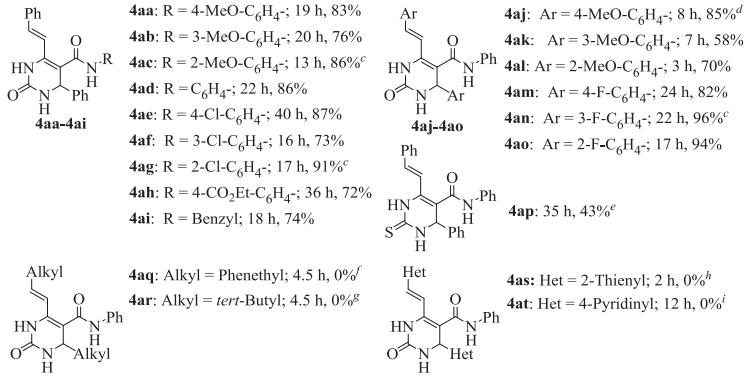
Entry	Catalyst	*T*/°C	Time/h	Products	Yield[b]/%
1	$FeCl_3·6H_2O$	Reflux	22	**4ad**	86
2[c]	$FeCl_3·6H_2O$	Reflux	24	**4ad**+**5a**	29+47
3[d]	$FeCl_3·6H_2O$	Reflux	20	**4ad**+**5a**	0+0
4[e]	$FeCl_3·6H_2O$	82	6	**5a**	82
5	$FeCl_3·6H_2O$	60	24	**4ad**+**5a**	47+46
6	$FeCl_3·6H_2O$	40	4	**5a**	90
7[f]	$FeCl_3·6H_2O$	Reflux	46	**4ad**	74
8[g]	$FeCl_3·6H_2O$	Reflux	21	**4ad**	72
9[h]	$FeCl_3·6H_2O$	Reflux	12	**4ad**	11
10[i]	$FeCl_3·6H_2O$	Reflux	23	**4ad**	88
11	$Fe_2(SO_4)_3·xH_2O$	Reflux	33	**4ad**	84
12	$FeCl_3$	Reflux	36	**4ad**	73
13	$Fe(NO_3)_3·9H_2O$	Reflux	3	**4ad**+**5a**	Trace+79
14	$FeSO_4·7H_2O$	Reflux	40	**4ad**	76

[a] Unless otherwise indicated, all reactions were carried out with **1a** (0.5 mmol), **2a** (1.5 mmol), and **3a** (0.5 mmol) in CH_3CN (3.0 mL) in the presence of 0.1 equiv iron salt.
[b] Isolated yield.
[c] Reaction was performed in EtOH.
[d] Reaction was performed in CH_2Cl_2.
[e] Reaction was performed in DMSO.
[f] $FeCl_3·6H_2O$ (0.05 equiv) was used.
[g] $FeCl_3·6H_2O$ (0.2 equiv) was used.
[h] Compound **2a** (2.0 equiv) was used and 85% of **5a** was obtained.
[i] Compound **2a** (4.0 equiv) was used.

Please cite this article in press as: Zhang, Z.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.07.039

Table 2
Four-component one-pot condensation strategy for the synthesis of **4a**[a,b]





[a] Unless otherwise indicated, all reactions were carried out with **1** (0.5 mmol), **2** (1.5 mmol), **3** (0.5 mmol) and $FeCl_3 \cdot 6H_2O$ (10 mol%) in CH_3CN (3.0 mL).

[b] Isolated yield.

[c] 4.0 Equiv of aldehyde was used.

[d] 4.0 Equiv of aldehyde **2** and 0.2 equiv $FeCl_3 \cdot 6H_2O$ was used.

[e] 0.1 Equiv of $Fe_2(SO_4)_3 \cdot xH_2O$ was used, 38% of **5p** was obtained, and prolonged reaction time could not improve the yield of **4ap**.

[f] 54% of **5q** was obtained.

[g] 73% of **5r** was obtained.

[h] 53% of **5s** was obtained along with the recovered **1a** 40%.

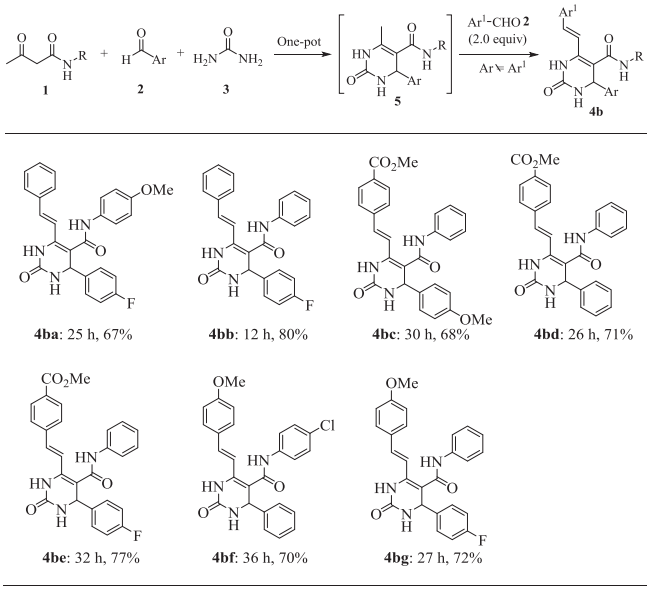
[i] 59% of 3-oxo-*N*-phenyl-2-(pyridin-4-ylmethylene)butanamide was obtained.

the target products **4aa**–**h** in good to excellent yields (72–91%) regardless of the electronic nature of the diverse substituents and the position of the substituents. In these cases, it took a little longer time for the substrates **1e** and **1h** with electron-withdrawing groups (EWG) (−Cl, $-CO_2Et$) on the *ortho*-position of the benzene ring to afford compounds **4ae** (40 h) and **4ah** (36 h), respectively. Additionally, the use of *N*-aliphatic substituted acetoacetamide **1i** resulted in a slightly lower yield of target product **4ai** (74%). Next, the electronic effects of various aromatic aldehydes with an electron-donating groups (EDG) (OMe) or EWG (−F, −COOEt) were examined, and the experimental data showed that all tested aromatic aldehydes were transformed into the highly substituted π-conjugated 3,4-dihydropyrimidin-2(1*H*)-one analogues **4aj**–**o** very well except for the 3-methoxybenzaldehyde, which only gave a moderate yield of **4ak** (58%) for some reasons. The expansion of urea seemed to be limited, only 43% **4ap** was obtained under the optimized condition. Finally, although the yield of **4ap** could be obtained in 43% by using the catalyst of $Fe_2(SO_4)_3 \cdot xH_2O$ (0.1 equiv), it could not be further improved by prolonging the reaction times or increasing the amount of aldehyde. It only afforded the Biginelli products **5q** (54%) and **5r** (73%) instead of the desired 6-arylvinyl DHPMs **4aq** and **4ar** when aliphatic aldehydes **1q** and **1r** were used. Similarly, heteroaryl aldehydes 2-thenaldehyde (**1s**) and isonicotinaldehyde (**1t**) also did not convert to the expected 6-arylvinyl DHPMs **4as** and **4at**, respectively.

In order to enlarge the available drug-like library of the diverse **4** (using different aldehydes **2** at the two stages of Biginelli reaction and vinylogous aldol condensation) for the bioactivity screening as well as verify the universality of the approach, one-pot stepwise strategy for the synthesis of **4b** was performed by using several randomly selected **1**, **2**, and **3**. To our delight, a series of π-conjugated 3,4-dihydropyrimidin-2(1*H*)-one analogues (**4ba**–**g**) with a variety of different substituent groups could be achieved in 67–80% yield via the multi-step one-pot process (Table 3). It worth noting that the amount of the aldehydes **2** should not be added more than 1.1 equiv at the first step in the synthesis of **5**, otherwise, it would give the yield of **4a** more than 5%. It is noteworthy that as one of the most important applications, very recently, we have used compounds **4** to prepare potential bioactive pyrido[4,3-*d*]pyrimidines **6** in the presence of NaOH in EtOH at reflux.[5]

This chemistry was also extended to the other β-dicarbonyl compounds such as ethyl acetoacetate (**1u**) and acetylacetone (**1v**), but they only gave the corresponding Biginelli products **5u** and **5v** in 85% and 81% yields, respectively (Eq. 4). Even we increased the

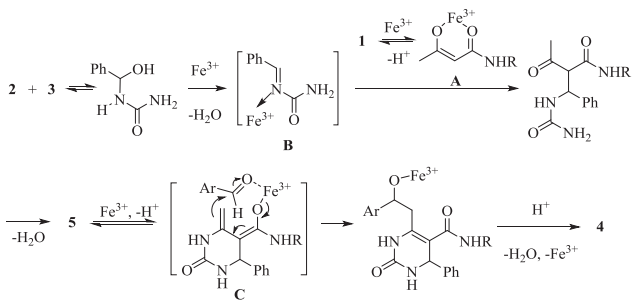
Table 3
One-pot stepwise strategy for the synthesis of **4b**[a,b]



[a] Unless otherwise indicated, the first step were carried out with **1** (0.5 mmol), **2** (0.55 mmol), **3** (0.75 mmol) and $FeCl_3 \cdot 6H_2O$ (10 mol%) in CH_3CN (2.0 mL) and another different aldehydes **2** (1.0 mmol) was added to the mixture at the second step.

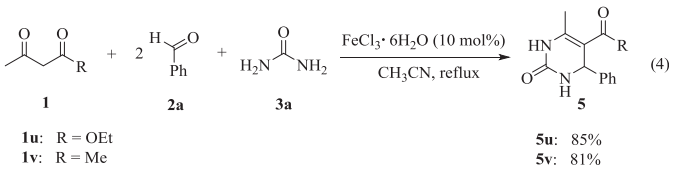
[b] Isolated yield.

amount of the benzaldehyde to 3 equiv or carried out the reactions in the presence of molecular sieve under anhydrous condition. The Biginelli products bearing 5-ester or 5-acyl group are not the substrates of vinylogous aldol reaction under present conditions. These results indicate that the electron-rich amide moiety at the 5-position of DHPMs (**5**) is very important for this vinylogous aldol condensation reaction.[5] A possible mechanism of the tandem Biginelli reaction/vinylogous aldol condensation is proposed in Scheme 1. We proposed a mechanism for the first stage (**1** to **5**) similar to that of Folkers and Johnson,[6k] Kappe,[6j] Hu,[6i] and Lu[6d] for Biginelli reaction.[14] The first step in this reaction involves the formation of the highly reactive *N*-acyliminium species **B**, formed by the reaction of the aldehyde with urea and stabilized by either iron or proton (produced in situ). Subsequent addition of a π-nucleophile **A**, i.e., the enol tautomer of acetoacetamide **1** to the electron-deficient *N*-acyliminium species **B**, followed by the cyclization and dehydration, would produce the DHPMs **5**. For the vinylogous-aldol reaction stage, the vinylogous enolate **C**[12a,15] was firstly formed in the presence of $FeCl_3$. The nitrogen of the amide moiety contributed its lone-pair electrons to the conjugated system, which would enhance the nucleophilicity of the vinylogous enolate **C**.[5,16] The



Scheme 1. Proposed mechanism.

addition of the reactive species **C** to aldehydes **2** with the terminal carbon of its double-bond system (the γ-carbon/position), followed by dehydration to afford the products **4**.[16d,17]



In order to demonstrate the easy use of the multi-component condensation, a large-scale reaction of **1a**, **2a** with **3a** was conducted in CH_3CN. After vigorously stirring the mixture of **1a** (100 g, 0.565 mol), **2a** (172 mL, 1.695 mol), **3a** (33.9 g, 0.565 mol), and $FeCl_3 \cdot 6H_2O$ (15.3 g, 0.057 mol) in CH_3CN (1 L) for 48 h at reflux, the desired compound **4ad** was isolated as a white solid in 80% yield (179 g, 0.453 mol) without purification by silica gel column chromatography, and 0.9 L CH_3CN was recovered after distilled under reduced pressure.[18]

3. Conclusions

In summary, we have achieved an iron-catalyzed multi-component condensation reaction of β-keto amides, aldehydes and ureas for the synthesis of the useful 6-arylvinyl DHPMs in good to excellent yields via a tandem reaction of Biginelli reaction and vinylogous aldol condensation using a sole iron catalyst, four chemical bonds were constructed at once in this process, including two *C*–*N* bonds, one *C*–*C* single bond, and a *C*–*C* double bond. Protonic acid-free, and the use of sole $FeCl_3 \cdot 6H_2O$ as the catalyst in the tandem processes make the protocol more effective and practical. This straightforward strategy combines the advantages of both MCRs and tandem reactions, thus significantly enhance its green characteristic and the operational convenience. A variety of

Please cite this article in press as: Zhang, Z.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.07.039

cheap and readily available reactants, a wide range of substrate scopes, dense and flexible substituted patterns, significantly higher yields, and important synthetic potential of the products are advantages of the present method.

4. Experimental

4.1. General

All reagents were purchased from commercial sources and used without further treatment. All reactions were carried out under air atmosphere. The known compounds **4aa**–**4aj**, **4ap**, and **4b** were identified by comparison of their ^{1}H NMR with those of authentic samples.[5] The new compounds (**4ak**–**4ao**) listed in Table 2 were properly characterized by melting point, ^{1}H NMR, ^{13}C NMR, and HRMS. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer (^{1}H: 400 MHz, ^{13}C: 100 MHz at 25 °C). Coupling constants are reported in hertz (Hz). All high-resolution mass spectra (HRMS) were measured on a mass spectrometer by using electrospray ionization (ESI). Melting points were measured on a melting point apparatus equipped with a thermometer and were uncorrected. All reactions were monitored by TLC with GF_{254} silica gel coated plates. Flash chromatography was carried out on SiO_2 (silica gel 200–300 mesh).

4.2. General procedure for the synthesis of compounds 4a and 4b

*4.2.1. For **4a** (**4ad** as an example).* To a round-bottom flask (25 mL) equipped with a spherical condenser (40 cm length) were added 3-oxo-*N*-phenylbutanamide (89 mg, 0.5 mmol), urea (30 mg, 0.5 mmol), benzaldehyde (159 mg, 1.5 mmol), $FeCl_3\cdot 6H_2O$ (14 mg, 0.05 mmol), and CH_3CN (3 mL). Then, the mixture was well stirred under reflux for 22 h (The whole process was closely monitored by TLC.). After cooling off, water (3 mL) was added to the mixture. Then, the mixture was filtered and the insoluble material was purified by a short flash silica gel column chromatography to give oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid phenylamide **4ad** (169.8 mg, 86%) as white solid (eluent: dichloromethane/methanol=80:1).

*4.2.2. One-pot stepwise strategy for the synthesis of **4b** (**4ba** as an example).* In a three necked flask (50 mL) with a reflux condenser (40 cm), 4-fluorobenzaldehyde [186 mg, 0.55 mmol, dissolved in CH_3CN (2 mL) in a pressure equalizing dropping funnel] was dropwise added to a mixture of *N*-(4-methoxyphenyl)-3-oxobutanamide (104 mg, 0.5 mmol), urea (45 mg, 0.75 mmol), $FeCl_3\cdot 6H_2O$ (14 mg, 0.05 mmol), and CH_3CN (1 mL). The mixture was refluxed for 5 h before benzaldehyde (106 mg, 1.0 mmol) was added in. After 20 h at reflux, the mixture was cooled off, and water (3 mL) was added in, then the mixture was filtered and the insoluble material was purified by a short flash silica gel column chromatography to give (*E*)-4-(4-fluorophenyl)-*N*-(4-methoxyphenyl)-2-oxo-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide **4ba** (148 mg, 67%) as white solid (eluent: dichloromethane/methanol=80:1).

*4.2.3. (E)-N-(4-Methoxyphenyl)-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4aa**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=80:1) as a white solid (176.4 mg, 83%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.79 (s, 1H), 7.73 (s, 1H), 7.46 (d, J=8.8 Hz, 2H), 7.41–7.26 (m, 11H), 7.22 (d, J=16.8 Hz, 1H), 6.85 (d, J=8.8 Hz, 2H), 5.47 (d, J=2.4 Hz, 1H), 3.70 (s, 3H).

*4.2.4. (E)-N-(3-Methoxyphenyl)-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4ab**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=100:1) as a white solid (161.5 mg, 76%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 8.83 (s, 1H), 7.76 (s, 1H), 7.42–7.26 (m, 12H), 7.19–7.15 (m, 3H), 6.63 (td, J_1=7.6 Hz, J_2=2.0 Hz, 1H), 5.47 (d, J=2.8 Hz, 1H), 3.70 (s, 3H).

*4.2.5. (E)-N-(2-Methoxyphenyl)-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4ac**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=100:1) as a yellow solid (182.8 mg, 86%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.80 (s, 1H), 7.80–7.70 (m, 2H), 7.49 (t, J=7.2 Hz, 2H), 7.44–7.27 (m, 10H), 7.07 (t, J=7.6 Hz, 1H), 6.98 (d, J=8.0 Hz, 1H), 6.88 (t, J=7.6 Hz, 1H), 5.39 (s, 1H), 3.60 (s, 3H).

*4.2.6. (E)-2-Oxo-N,4-diphenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4ad**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=80:1) as a white solid (169.8 mg, 86%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.83 (s, 1H), 7.76 (s, 1H), 7.58 (d, J=8.0 Hz, 2H), 7.44–7.25 (m, 13H), 7.21 (d, J=16.4 Hz, 1H), 7.04 (t, J=7.2 Hz, 1H), 5.51 (s, 1H).

*4.2.7. (E)-N-(4-Chlorophenyl)-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4ae**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=80:1) as a white solid (186.6 mg, 87%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.87 (d, J=6.4 Hz, 1H), 7.78 (s, 1H), 7.62 (d, J=8.4 Hz, 2H), 7.47–7.23 (m, 13H), 7.20 (d, J=16.8 Hz, 1H), 5.50 (s, 1H).

*4.2.8. (E)-N-(3-Chlorophenyl)-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4af**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=80:1) as a white solid (156.6 mg, 73%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.88 (s, 1H), 7.79 (s, 1H), 7.78 (t, J=2.0 Hz, 1H), 7.47–7.26 (m, 13H), 7.18 (d, J=16.4 Hz, 1H), 7.09 (d, J=8.0 Hz, 1H), 5.48 (d, J=2.8 Hz, 1H).

*4.2.9. (E)-N-(2-Chlorophenyl)-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4ag**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=100:1) as a white solid (195.2 mg, 91%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.56 (s, 1H), 8.89 (s, 1H), 7.78 (s, 1H), 7.51–7.34 (m, 12H), 7.33–7.28 (m, 3H), 7.20 (t, J=8.0 Hz, 1H), 5.47 (d, J=2.4 Hz, 1H).

*4.2.10. (E)-Ethyl 4-(2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamido)benzoate (**4ah**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=80:1) as a white solid (168.2 mg, 72%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.91 (s, 1H), 7.88 (d, J=8.4 Hz, 2H), 7.81 (s, 1H), 7.73 (d, J=8.8 Hz, 2H), 7.51–7.16 (m, 12H), 5.51 (s, 1H), 4.27 (q, J=7.2 Hz, 2H), 1.30 (t, J=7.2 Hz, 3H).

*4.2.11. (E)-N-Benzyl-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4ai**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=60:1) as a white solid (151.3 mg, 74%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.56 (t, J=6.0 Hz, 1H), 7.65 (s, 1H), 7.37–7.25

Please cite this article in press as: Zhang, Z.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.07.039

(m, 14H), 7.20 (d, *J*=16.4 Hz, 1H), 7.13 (d, *J*=7.6 Hz, 2H), 5.37 (s, 1H), 4.39 (dd, *J*=14.8, 6.0 Hz, 1H), 4.20 (dd, *J*=14.8, 5.6 Hz, 1H).

*4.2.12. (E)-4-(4-Methoxyphenyl)-6-(4-methoxystyryl)-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4aj**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=60:1) as a white solid (193.3 mg, 85%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.72 (s, 1H), 7.66 (s, 1H), 7.57 (d, *J*=7.6 Hz, 2H), 7.34 (d, *J*=8.8 Hz, 2H), 7.29–7.21 (m, 5H), 7.11–7.01 (m, 2H), 6.95–6.88 (m, 4H), 5.42 (d, *J*=2.8 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H).

*4.2.13. (E)-4-(3-Methoxyphenyl)-6-(3-methoxystyryl)-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4ak**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=100:1) as a white solid (122.8 mg, 54%). Mp: 238–240 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H), 8.85 (s, 1H), 7.78 (s, 1H), 7.61 (d, *J*=7.6 Hz, 2H), 7.35 (d, *J*=16.8 Hz, 1H), 7.31–7.26 (m, 4H), 7.20 (d, *J*=16.4 Hz, 1H), 7.07–7.00 (m, 2H), 6.93–6.84 (m, 5H), 5.48 (d, *J*=2.4 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9, 159.6, 159.4, 153.0, 145.1, 139.1, 137.8, 136.2, 131.5, 130.1, 129.8, 128.7, 123.6, 119.9, 119.7, 119.3, 118.6, 114.2, 112.6, 112.5, 111.9, 110.1, 55.6, 55.04, 55.01. HRMS (ESI), *m*/*z* calcd for $C_{27}H_{25}N_3O_4$ ([M+Na]$^+$) 478.1737, found: 478.1734.

*4.2.14. (E)-4-(2-Methoxyphenyl)-6-(2-methoxystyryl)-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4 al**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=100:1) as a white solid (159.3 mg, 70%). Mp: 233–235 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 8.83 (s, 1H), 7.66 (d, *J*=8.4 Hz, 2H), 7.43 (d, *J*=16.8 Hz, 1H), 7.39–7.25 (m, 8H), 7.06–6.93 (m, 5H), 5.74 (d, *J*=2.4 Hz, 1H), 3.69 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 157.2, 156.1, 153.7, 139.4, 136.3, 130.9, 129.5, 128.7, 128.5, 128.0, 127.1, 127.0, 125.1, 123.1, 120.7, 120.6, 120.3, 119.4, 111.6, 111.04, 109.98, 55.4, 55.2, 50.1. HRMS (ESI), *m*/*z* calcd for $C_{27}H_{25}N_3O_4$ ([M+Na]$^+$) 478.1737, found: 478.1711.

*4.2.15. (E)-4-(4-Fluorophenyl)-6-(4-fluorostyryl)-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4am**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=60:1) as a white solid (176.7 mg, 82%). Mp: 237–239 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.81 (s, 1H), 7.75 (s, 1H), 7.57 (d, *J*=7.6 Hz, 2H), 7.46–7.36 (m, 5H), 7.29–7.13 (m, 7H), 7.04 (t, *J*=6.8 Hz, 1H), 5.52 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 163.0 (d, *J*=62.4 Hz), 160.6 (d, *J*=59.9 Hz), 152.6, 139.8 (d, *J*=1.8 Hz), 138.9, 136.3, 132.8 (d, *J*=3.3 Hz), 130.5, 128.6 (d, *J*=8.4 Hz), 128.5, 128.4, 123.5, 120.0, 119.2 (d, *J*=1.5 Hz), 115.8 (d, *J*=21.7 Hz), 115.3 (d, *J*=21.3 Hz), 109.7, 55.1. HRMS (ESI), *m*/*z* calcd for $C_{25}H_{19}F_2N_3O_2$ ([M+Na]$^+$) 454.1338, found: 454.1345.

*4.2.16. (E)-4-(3-Fluorophenyl)-6-(3-fluorostyryl)-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4an**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=60:1) as a white solid (206.9 mg, 96%). Mp: 252–254 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.98 (s, 1H), 7.91 (s, 1H), 7.61 (d, *J*=8.0 Hz, 2H), 7.45–7.39 (m, 3H), 7.32–7.20 (m, 6H), 7.17–7.12 (m, 3H), 7.07 (t, *J*=7.2 Hz, 1H), 5.55 (d, *J*=2.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 163.6 (d, *J*=22.5 Hz), 161.2 (d, *J*=22.8 Hz), 152.8, 146.3 (d, *J*=6.0 Hz), 139.0, 138.9 (d, *J*=7.8 Hz), 136.4, 131.0 (d, *J*=8.4 Hz), 130.7 (d, *J*=8.1 Hz), 128.7, 123.7, 123.1 (d, *J*=2.0 Hz), 122.6 (d, *J*=2.5 Hz), 120.9, 120.0, 115.3 (d, *J*=21.2 Hz), 114.5 (d, *J*=20.9 Hz), 113.3, 113.1, 112.8, 110.0, 55.2. HRMS (ESI), *m*/*z* calcd for $C_{25}H_{19}F_2N_3O_2$ ([M+Na]$^+$) 454.1338, found: 454.1318.

*4.2.17. (E)-4-(2-Fluorophenyl)-6-(2-fluorostyryl)-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4ao**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=60:1) as a white solid (202.6 mg, 94%). Mp: 249–251 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 9.02 (s, 1H), 7.67 (s, 1H), 7.55–7.45 (m, 3H), 7.41–7.13 (m, 11H), 7.03 (t, *J*=7.2 Hz, 1H), 5.76 (d, *J*=2.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 161.0 (d, *J*=68.8 Hz), 158.5 (d, *J*=65.9 Hz), 152.8, 139.0, 136.0, 130.2 (d, *J*=13.6 Hz), 129.8 (d, *J*=8.2 Hz), 128.9 (d, *J*=3.9 Hz), 128.7, 128.3 (d, *J*=3.2 Hz), 125.0, 124.8, 124.4, 124.0 (d, *J*=11.7 Hz), 123.5, 122.1 (d, *J*=5.9 Hz), 119.9, 119.5, 116.1 (d, *J*=21.5 Hz), 115.7 (d, *J*=21.7 Hz), 109.8, 50.5. HRMS (ESI), *m*/*z* calcd for $C_{25}H_{19}F_2N_3O_2$ ([M+Na]$^+$) 454.1338, found: 454.1316.

*4.2.18. (E)-N,4-Diphenyl-6-styryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4ap**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=500:1) as a yellow solid (88.4 mg, 43%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 9.95 (s, 1H), 9.65 (s, 1H), 7.58 (d, *J*=8.0 Hz, 2H), 7.50–7.25 (m, 13H), 7.15 (d, *J*=16.4 Hz, 1H), 7.05 (t, *J*=7.2 Hz, 1H), 5.48 (d, *J*=2.8 Hz, 1H).

*4.2.19. (E)-4-(4-Fluorophenyl)-N-(4-methoxyphenyl)-2-oxo-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4ba**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=80:1) as a white solid (148.4 mg, 67%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.82 (s, 1H), 7.74 (s, 1H), 7.46 (d, *J*=8.4 Hz, 2H), 7.43–7.32 (m, 7H), 7.30 (t, *J*=7.2 Hz, 1H), 7.24–7.14 (m, 3H), 6.86 (d, *J*=8.0 Hz, 2H), 5.48 (s, 1H), 3.71 (s, 3H).

*4.2.20. (E)-4-(4-Fluorophenyl)-2-oxo-N-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4bb**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=80:1) as a white solid (165.2 mg, 80%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.90 (s, 1H), 7.80 (s, 1H), 7.58 (d, *J*=8.0 Hz, 2H), 7.45–7.33 (m, 7H), 7.28 (t, *J*=8.0 Hz, 3H), 7.15–7.25 (m, 3H), 7.04 (t, *J*=7.2 Hz, 1H), 5.52 (s, 1H).

*4.2.21. (E)-Methyl 4-(2-(6-(4-methoxyphenyl)-2-oxo-5-(phenylcarbamoyl)-1,2,3,6-tetrahydropyrimidin-4-yl)vinyl)benzoate (**4bc**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=80:1) as a white solid (164.2 mg, 68%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.81 (s, 1H), 7.93 (d, *J*=8.4 Hz, 2H), 7.70 (s, 1H), 7.53 (t, *J*=8.4 Hz, 4H), 7.40 (d, *J*=16.4 Hz, 1H), 7.32 (d, *J*=16.8 Hz, 1H), 7.28–7.19 (m, 4H), 7.02 (t, *J*=7.2 Hz, 1H), 6.88 (d, *J*=8.8 Hz, 2H), 5.45 (d, *J*=2.8 Hz, 1H), 3.82 (s, 3H), 3.69 (s, 3H).

*4.2.22. (E)-Methyl 4-(2-(2-oxo-6-phenyl-5-(phenylcarbamoyl)-1,2,3,6-tetrahydropyrimidin-4-yl)vinyl)benzoate (**4bd**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=80:1) as a white solid (160.8 mg, 71%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.87 (s, 1H), 7.95 (d, *J*=8.0 Hz, 2H), 7.79 (s, 1H), 7.55 (t, *J*=8.4 Hz, 4H), 7.47–7.25 (m, 9H), 7.04 (t, *J*=7.2 Hz, 1H), 5.54 (s, 1H), 3.83 (s, 3H).

*4.2.23. (E)-Methyl4-(2-(6-(4-fluorophenyl)-2-oxo-5-(phenylcarbamoyl)-1,2,3,6-tetrahydropyrimidin-4-yl)vinyl)benzoate (**4be**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=80:1) as a white solid (181.5 mg, 77%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.89 (s, 1H), 7.94 (d, *J*=8.4 Hz, 2H), 7.79 (s, 1H), 7.54 (d, *J*=8.0 Hz, 4H), 7.43 (d, *J*=16.8 Hz, 1H), 7.38–7.25 (m, 5H), 7.19 (t, *J*=8.8 Hz, 2H), 7.05 (t, *J*=7.2 Hz, 1H), 5.52 (s, 1H), 3.84 (s, 3H).

*4.2.24. (E)-N-(4-Chlorophenyl)-6-(4-methoxystyryl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4bf**).* The product was isolated by flash chromatography (eluent:

Please cite this article in press as: Zhang, Z.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.07.039

dichloromethane/methanol=80:1) as a white solid (160.6 mg, 70%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.78 (s, 1H), 7.74 (s, 1H), 7.61 (d, J=8.8 Hz, 2H), 7.20–7.43 (m, 10H), 7.07 (d, J=16.4 Hz, 1H), 6.94 (d, J=8.4 Hz, 2H), 5.47 (s, 1H), 3.75 (s, 3H).

*4.2.25. (E)-4-(4-Fluorophenyl)-6-(4-methoxystyryl)-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4bg**).* The product was isolated by flash chromatography (eluent: dichloromethane/methanol=80:1) as a white solid (159.5 mg, 72%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.79 (s, 1H), 7.74 (s, 1H), 7.56 (d, J=7.2 Hz, 2H), 7.34 (s, 4H), 7.31–7.13 (m, 5H), 7.06 (d, J=17.2 Hz, 2H), 6.94 (d, J=7.6 Hz, 2H), 5.47 (s, 1H), 3.75 (s, 3H).

Acknowledgements

We thank the National Natural Science Foundation of China (21172056, 21272057, and 21372065), PCSIRT (IRT1061), China Postdoctoral Science Foundation funded project (2013M530339 and 2015M572109), the Program of Foundation and Frontier Technology Research of Henan Province (122300410296) and Innovation Scientists and Technicians Troop Construction Projects of Henan Province (134200510016).

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.07.039.

References and notes

1. (a) Abdel Hafez, O. M.; Amin, K. M.; Abdel-Latif, N. A.; Mohamed, T. K.; Ahmed, E. Y.; Maher, T. *Eur. J. Med. Chem.* **2009**, *44*, 2967–2974; (b) Reutrakul, V.; Leewanich, P.; Tuchinda, P.; Pohmakotr, M.; Jaipetch, T.; Sophasan, S.; Santisuk, T. *Planta Med.* **2003**, *69*, 1048–1051; (c) Kempen, I.; Papapostolou, D.; Thierry, N.; Pochet, L.; Counerotte, S.; Masereel, B.; Foidart, J. M.; Reboud-Ravaux, M.; Noel, A.; Pirotte, B. *Br. J. Cancer* **2003**, *88*, 1111–1118.
2. (a) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806–811; (b) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem.* **1992**, *35*, 3254–3263.
3. Okabe, M.; Sun, R. C.; Zenchoff, G. B. *J. Org. Chem.* **1991**, *56*, 4393–4395.
4. Ramesh, B.; Bhalgat, C. M. *Eur. J. Med. Chem.* **2011**, *46*, 1882–1891.
5. Zhang, L.; Zhang, Z.; Liu, Q.; Liu, T.; Zhang, G. *J. Org. Chem.* **2014**, *79*, 2281–2288.
6. (a) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2962–2967; (b) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 1317–1319; (c) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879–888; For recent iron-catalyzed Biginelli reactions, please see: (d) Lu, J.; Ma, H. *Synlett* **2000**, 63–64; (e) Martínez, S.; Meseguer, M.; Casas, L. S.; Rodríguez, E.; Molins, E.; Moreno-Mañas, M.; Roig, A.; Sebasftián, R. M.; Vallribera, A. *Tetrahedron* **2003**, *59*, 1553–1556; (f) Karimi-Jaberi, Z.; Moaddeli, M. S. *ISRN Org. Chem.* **2012**, 4, http://dx.doi.org/10.5402/2012/474626; (g) Safari, J; Gandomi-Ravandi, S. *RSC Adv.* **2014**, *4*, 11486–11492; (h) Starcevich, J. T.; Laughlin, T. J.; Mohan, R. S. *Tetrahedron Lett.* **2013**, *54*, 983–985; (i) Hu, E. H.; Sidler, D. R.; Dolling, U.-H. *J. Org. Chem.* **1998**, *63*, 3454–3457; (j) Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201–7204; (k) Folkers, K.; Johnson, T. B. *J. Am. Chem. Soc.* **1933**, *55*, 3784–3791; (l) Lu, J.; Bai, Y. *Synthesis* **2002**, 0466–0470.
7. (a) Singh, K.; Singh, S.; Mahajan, A. *J. Org. Chem.* **2005**, *70*, 6114–6117; (b) Couto, I.; Tellitu, I.; Domínguez, E. *J. Org. Chem.* **2010**, *75*, 7954–7957; (c) Dallinger, D.; Kappe, C. O. *Pure Appl. Chem.* **2005**, *77*, 155–161; (d) Khanetskyy, B.; Dallinger, D.; Kappe, C. O. *J. Comb. Chem.* **2004**, *6*, 884–892; (e) Perez, R.; Beryozkina, T.; Zbruyev, O. I.; Haas, W.; Kappe, C. O. *J. Comb. Chem.* **2002**, *4*, 501–510.
8. Suresh; Sandhu, J. S. *Arkivoc* **2012**, 66–133.
9. Byk, G.; Gottlieb, H. E.; Herscovici, J.; Mirkin, F. *J. Comb. Chem.* **2000**, *2*, 732–735.
10. Byk, G.; Kabha, E. *J. Comb. Chem.* **2004**, *6*, 596–603.
11. (a) Abelman, M. M.; Smith, S. C.; James, D. R. *Tetrahedron Lett.* **2003**, *44*, 4559–4562; (b) Shaabani, A.; Bazgir, A.; Bijanzadeh, H. R. *Mol. Divers.* **2004**, *8*, 141–145; (c) Shaabani, A.; Bazgir, A. *Tetrahedron Lett.* **2004**, *45*, 2575–2577; (d) Prajapati, D.; Bhuyan, D.; Gohain, M.; Hu, W. *Mol. Divers.* **2011**, *15*, 257–261.
12. (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254; (b) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624–629; (c) Correa, A.; Garcia Mancheno, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108–1117; (d) Sherry, B. D.; Furstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500–1511; (e) Diaz, D. D.; Miranda, P. O.; Padron, J. I.; Martin, V. S. *Curr. Org. Chem.* **2006**, *10*, 457–476.
13. Alvim, H. G. O.; Lima, T. B.; de Oliveira, A. L.; de Oliveira, H. C. B.; Silva, F. M.; Gozzo, F. C.; Souza, R. Y.; da Silva, W. A.; Neto, B. A. D. *J. Org. Chem.* **2014**, *79*, 3383–3397.
14. (a) Ramos, L. M.; Guido, B. C.; Nobrega, C. C.; Correa, J. R.; Silva, R. G.; de Oliveira, H. C.; Gomes, A. F.; Gozzo, F. C.; Neto, B. A. *Chem.—Eur. J.* **2013**, *19*, 4156–4168; (b) Ramos, L. M.; Ponce de Leon y Tobio, A. Y.; dos Santos, M. R.; de Oliveira, H. C. B.; Gomes, A. F.; Gozzo, F. C.; de Oliveira, A. L.; Neto, B. A. D. *J. Org. Chem.* **2012**, *77*, 10184–10193; (c) Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem.* **2002**, *68*, 587–590.
15. (a) Imhof, W.; Anders, E.; Göbel, A.; Görls, H. *Chem.—Eur. J.* **2003**, *9*, 1166–1181; (b) Wang, C.; Li, X.; Wu, F.; Wan, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 7162–7166; (c) Plietker, B. *Top. Organomet. Chem.* **2011**, *33*, 1–213.
16. (a) Kemnitz, C. R.; Loewen, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 2521–2528; (b) Bernabeu, M. C.; Chinchilla, R.; Nájera, C.; Rodríguez, M. A. *Tetrahedron Lett.* **1996**, *37*, 3595–3598; (c) Huang, Y.-Z.; Mo, X.-S. *Synlett* **1998**, 93–95; (d) Sarit, S. A.; Gurunath, R. *Arkivoc* **2006**, 152–161.
17. Bastida, D.; Liu, Y.; Tian, X.; Escudero-Adan, E.; Melchiorre, P. *Org. Lett.* **2013**, *15*, 220–223.
18. Please see Supplementary data for more information.