Tetrahedron xxx (2016) 1–6

Contents lists available at ScienceDirect

Tetrahedron

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

The synthesis of 3-sulfenylflavones *via* $FeCl_3$-promoted regioselective cyclization of alkynyl aryl ketones with *N*-arylthiobenzamides

Lin-Feng Shi, Xing-Guo Zhang, Xiao-Hong Zhang*

College of Chemical and Materials Engineering, Wenzhou University, Wenzhou 325035, China

ARTICLE INFO

Article history:
Received 28 September 2016
Received in revised form
8 November 2016
Accepted 14 November 2016
Available online xxx

Keywords:
$FeCl_3$-promoted
Cyclization
N-arylthiobenzamides
3-sulfenylflavones

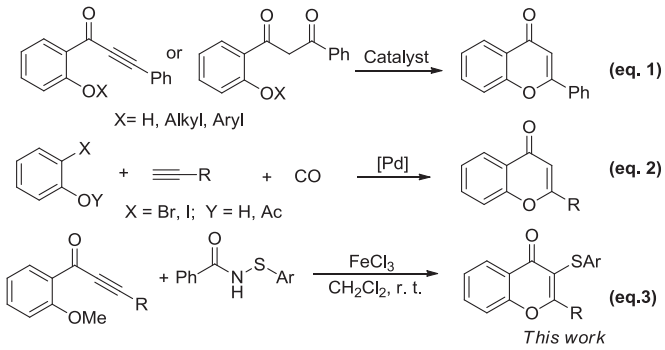
ABSTRACT

A $FeCl_3$-promoted regioselective cyclization of alkynyl aryl ketones with *N*-arylthiobenzamides had been developed for the synthesis of 3-sulfenylflavones derivatives. Various alkynyl aryl ketones and *N*-arylthiobenzamides with a number of functional groups were compatible in this reaction to afford the corresponding 3-sulfenylflavones in moderate to good yields. The mechanism was described in detail.

1. Introduction

Flavones are frequently found in numerous natural products[1] and are well known for their beneficial effects on human health.[2] Many flavone derivatives show a wide range of biological activities and have been already/potentially identified as tankyrase inhibitors,[3] aglucosidase inhibitors,[4] gastroprotective agents,[5] antihypertensive agents,[6] anti-inflammatory drugs,[7] anticancer agents[8] and so on.

These wide applications greatly promoted the development of several strategies for the construction of flavone derivatives.[9] At early time, Miranda and co-authors developed an esterification, rearrangement and the subsequent 6-endo-dig ring cyclization of phenylpropynoic acids with phenols to give flavones as well as the 5-exo-dig ring by-products.[10] Subsequently, Lewis acid-catalyzed,[11] LiOtBu/air-mediated[12] or ultrasonic-assisted[13] intramolecular annulations of 2-hydroxyphenyl carbonyl compounds or their equivalents[14] provided powerful methods for the construction of flavones (Scheme 1, eq. (1)). For example, Zeni and co-workers reported a $FeCl_3/(PhSe)_2$-promoted cyclization of alkynyl aryl ketones for the synthesis of 3-organoselenyl flavones.[15] Recently, the direct palladium-catalyzed carbonylative annulations of *o*-halogenphenols (or *o*-halogenphenol acetates) with terminal acetylenes had shown to be other efficient protocols for the synthesis of flavones (eq. (2)).[16] However, to the best of our knowledge, no 3-sulfenylflavones had been reported so far although the introduction of sulfur moiety can greatly enhance the biological activity. In the course of our ongoing efforts directed toward the synthesis of sulfenylated aromatic cyclics,[17] we wished to report a $FeCl_3$-promoted 6-endo-dig regioselective cyclization of alkynyl aryl ketones with *N*-arylthiobenzamides, leading to 3-sulfenylflavones in moderate to good yields under mild conditions (eq. (3)).



Scheme 1. Construction of flavones.

* Corresponding author.
E-mail address: kamenzxh@wzu.edu.cn (X.-H. Zhang).

http://dx.doi.org/10.1016/j.tet.2016.11.034
0040-4020/

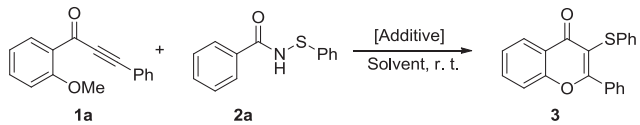
2. Results and discussion

The reaction between 1-(2-methoxyphenyl)-3-phenylprop-2-yn-1-one (**1a**) and *N*-(phenylthio)benzamide (**2a**) was chosen as a model reaction to optimize the reaction conditions, and the results were listed in Table 1. Initially, the reaction of substrate **1a** with *N*-(phenylthio)benzamide **2a** and 1.0 equiv $FeCl_3$ was performed in CH_2Cl_2 at room temperature, giving the desired 3-sulfenylflavone **3** in 40% yield (entry 1). When the amount of *N*-(phenylthio) benzamide **2a** was increased to 1.2 or 1.5 equiv, an obvious yield improvement can be observed (entries 2, 3). It was noted that the reagents **1a** and **2a** were kept intact in the absence of $FeCl_3$ (entry 4). The findings promoted us to explore the $FeCl_3$ amount and the results showed that 2.0 equiv $FeCl_3$ was enough to give a good yield (entries 5–7). Moreover, various promoters, such as $CuBr_2$, $AlCl_3$, $CuCl_2$, $Cu(OAc)_2$, $ZnCl_2$ and $FeBr_3$ were investigated, but all were less effective than $FeCl_3$ (entries 8–13). Subsequently, we further investigated the reaction conditions by examining different solvents, including DCE, THF, DMSO, $CHCl_3$, CCl_4, DMF, CH_3CN and dioxane (entries 14–21). The results showed that the reaction can undergo smoothly in some solvents bearing chlorine atom, such as CH_2Cl_2, DCE and $CHCl_3$. Meanwhile, trace of targeted molecule **3** was yielded possibly owing to the poor solubility of the reaction mixture in CCl_4 (entry 18). The solvent effect will be discussed in detail in the mechanism part. When the reaction temperature was enhanced to 50 °C or the reaction time was shortened to 15 h, the yield was reduced to 80% or 78%, respectively (entries 22–23). It is worth noting that only 35% and 45% yield were obtained when diphenyl disulfide or *N*-phenylthiosuccimimide was used as thiolation reagents (entries 24–26). The reaction of PhSSPh with I_2 was also evaluated, only giving compound **3** in 10% yield (entry 25). These results suggested that *N*-(phenylthio) benzamide **2a** with N–S bond was greatly superior to diphenyl disulfide and *N*-phenylthiosuccimimide in view of the 3-sulfenylflavone yields.

With the optimal conditions in hand, we next investigated the substrate scope of various alkynyl 2-methoxyaryl ketones and *N*-arylthiobenzamides (Table 2). Initially, a wide variety of *N*-arylthiobenzamides were tested, and the results demonstrated that *N*-arylthiobenzamides bearing both the electron-donating and electron-withdrawing groups on arylthio moiety underwent the cyclization reaction smoothly. In general, *N*-arylthiobenzamides with electron-rich groups gave the products in higher yields than those bearing electron-deficient groups. Methyl and methoxyl substituted benzamides afforded products **4** and **5** in 80% and 81% yield, respectively. Fluoride product **6** was isolated in 63% yield. *o, m, p*-(Chlorophenylthio) benzamides gave the corresponding products **7**–**9** in 54–80% yields while 3,5-dichloro product **10** was obtained in 42% yield. Substrate bearing a strong electron-withdrawing nitro group afforded product **11** only in 31% yield.

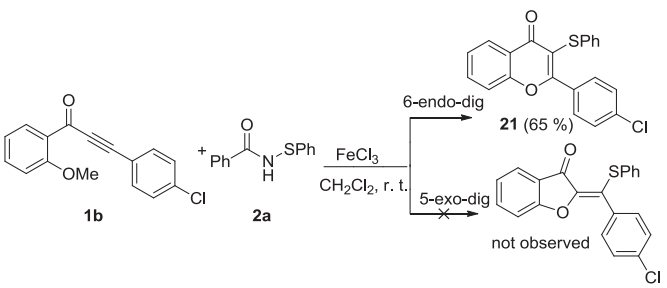
During the examination of substitution effect on alkynyl (R moiety), the results showed that the cyclization reaction seemed to be sensitive to the electronic effects of R group. For example, alkynyl 2-methoxyaryl ketones with methyl, ethyl, *n*-propyl, *n*-butyl and methoxyl moieties gave higher yields than their F, Cl, Br, NO_2 and CF_3 equivalents. Methyl, ethyl and *n*-propyl substituted 3-(phenylthio) flavones **12**–**15** were isolated in 85–87% yields except the lower yield of methoxyl derivative **17**. The alkynyl 2-methoxyaryl ketone with bulky *n*-butyl was also converted smoothly to product **16** in 87% yield. Fluoride, chloride and bromide products **18**–**23** were isolated in 41–81% yields under the optimal conditions. To determine whether the reaction proceeded *via* whether 6-endo-dig or 5-exo-dig cyclization process, 3-(4-chlorophenyl)-1-(2-methoxyphenyl)prop-2-yn-1-one **1b** was reacted with *N*-(phenylthio) benzamide **2a** under the standard conditions. The regioselective 6-endo-dig cyclization product **21** was isolated in 65% while the 5-exo-dig ring product was not observed. Moreover, the structure of product **21** was confirmed by X-ray crystallography (Scheme 2 and Fig. 1). However, alkynyl 2-methoxyaryl ketones bearing NO_2 and CF_3 underwent the cyclization reaction, giving their corresponding products **24**–**25** in 42% and 40% yields, respectively. It was notable that an acceptable 51% yield of **26** could be obtained when alkynyl was an aliphatic 1-hexyne.

Table 1
Screening conditions.[a]



Entry	Additive (equiv.)	2a (equiv.)	Solvent	Yield[b]
1	$FeCl_3$ (1.0)	1.0	CH_2Cl_2	40%
2	$FeCl_3$ (1.0)	1.5	CH_2Cl_2	46%
3	$FeCl_3$ (1.0)	1.2	CH_2Cl_2	47%
4	–	1.2	CH_2Cl_2	NR
5	$FeCl_3$ (1.5)	1.2	CH_2Cl_2	69%
6	$FeCl_3$ (2.0)	1.2	CH_2Cl_2	84%
7	$FeCl_3$ (2.5)	1.2	CH_2Cl_2	85%
8	$CuBr_2$ (2.0)	1.2	CH_2Cl_2	15%
9	$AlCl_3$ (2.0)	1.2	CH_2Cl_2	55%
10	$CuCl_2$ (2.0)	1.2	CH_2Cl_2	NR
11	$Cu(OAc)_2$(2.0)	1.2	CH_2Cl_2	NR
12	$ZnCl_2$ (2.0)	1.2	CH_2Cl_2	15%
13	$FeBr_3$ (2.0)	1.2	CH_2Cl_2	75%
14	$FeCl_3$ (2.0)	1.2	DCE	80%
15	$FeCl_3$ (2.0)	1.2	THF	NR
16	$FeCl_3$ (2.0)	1.2	DMSO	NR
17	$FeCl_3$ (2.0)	1.2	$CHCl_3$	79%
18	$FeCl_3$ (2.0)	1.2	CCl_4	trace
19	$FeCl_3$ (2.0)	1.2	DMF	NR
20	$FeCl_3$ (2.0)	1.2	CH_3CN	NR
21	$FeCl_3$ (2.0)	1.2	dioxane	NR
22	$FeCl_3$ (2.0)	1.2	CH_2Cl_2	80%[c]
23	$FeCl_3$ (2.0)	1.2	CH_2Cl_2	78%[d]
24	$FeCl_3$ (2.0)	–	CH_2Cl_2	35[e]
25	$FeCl_3$ (2.0)	–	CH_2Cl_2	10[f]
26	$FeCl_3$ (2.0)	–	CH_2Cl_2	45[g]

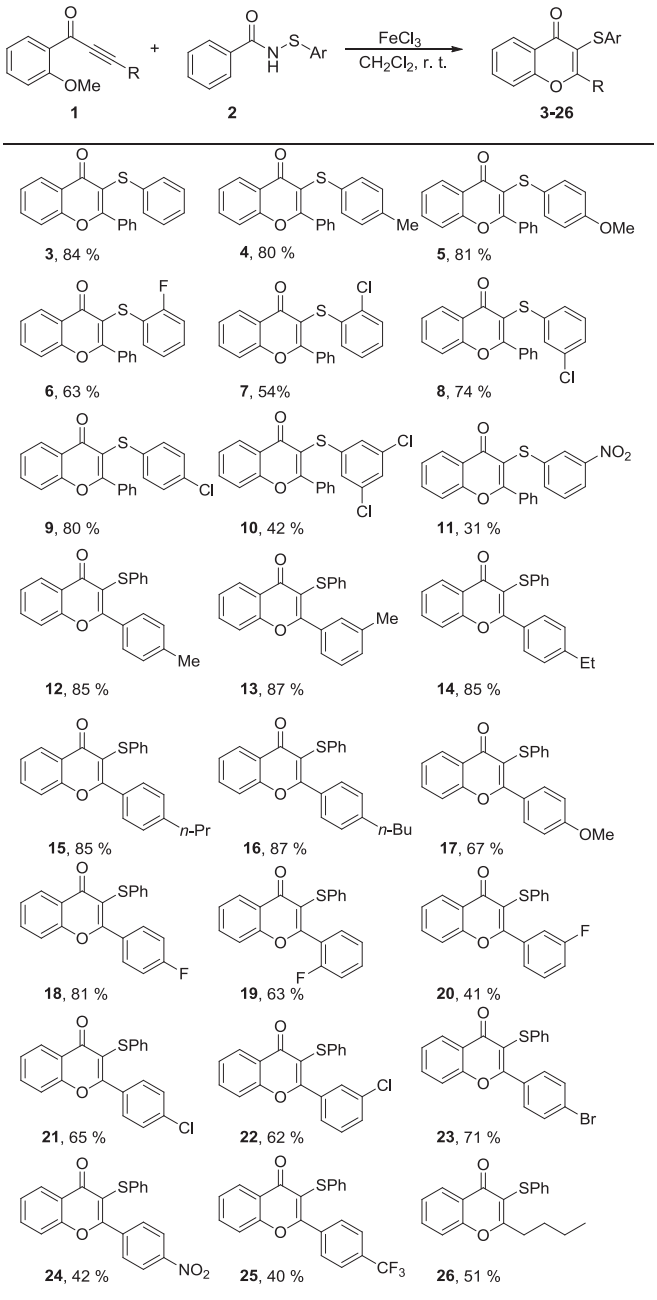
[a] Reaction conditions: **1a** (0.2 mmol), **2a**, $FeCl_3$ in solvent (2 mL) at room temperature for 20 h.
[b] Isolated yields.
[c] At 50 °C.
[d] 15 h.
[e] 0.24 mmol PhSSPh.
[f] 0.24 mmol PhSSPh with 0.24 mmol I_2.
[g] 0.24 mmol *N*-phenylthiosuccimimide.



Scheme 2. Regioselective Cyclization.

Please cite this article in press as: Shi L-F, et al., The synthesis of 3-sulfenylflavones *via* $FeCl_3$-promoted regioselective cyclization of alkynyl aryl ketones with *N*-arylthiobenzamides, Tetrahedron (2016), http://dx.doi.org/10.1016/j.tet.2016.11.034

Table 2
Scope of the cyclization reaction.[a,b]



[a] Reaction conditions: 1 (0.2 mmol), 2 (0.24 mmol), $FeCl_3$ (2.0 equiv) in CH_2Cl_2 (2 mL) at room temperature for 20 h.
[b] Isolated yields.

To understand the mechanism of this reaction, the substrate **1a** with *N*-(phenylthio) benzamide **2a** was performed in $FeCl_3$/DMF using 0.3 equiv HCl and 34% yield of product **3** was isolated (eq. (4), Scheme 3), whereas no reaction can be observed when using 1.0 equiv HCl in the absence of $FeCl_3$ or in the presence of $Cu(OAc)_2$ (eqs. (5) and (6), Scheme 3). The results demonstrated that $FeCl_3$ or Cl^- played an important role in the electrophilic cyclization reaction. Moreover, the reaction of substrate **1c** and *N*-(phenylthio) benzamide **2a** was selected to show the role of $FeCl_3$/solvent and the left of alkoxy group under the optimal reaction conditions. It was found that the by-product $PhCH_2Cl$ was observed by GC-MS accompanied with a small amount of $PhCH_2SPh$, which generated from the reaction of $PhCH_2Cl$ with *N*-(phenylthio) benzamide **2a** (see supporting information). Based on the experimental results and previous reports,[18] a possible mechanism for the cyclization was proposed as outlined in Scheme 4. Initially, the N—S bond cleavage of *N*-(phenylthio) benzamide with $FeCl_3$ generated the PhS^+ cation and the anion $[FeCl_3(NHCOPh)]^-$, which undergoes protonation to release benzamide detected by GC-MS. Subsequently, the selectively electrophilic addition of PhS^+ cation to the triple bond of substrate **1c** afforded intermediate **A**. Then the oxygen atom attacked the cyclo-sulfur cation to provide the targeted product **3** associated with the left of benzyl group by Cl^- yielded from the interaction of $FeCl_3$ and solvent CH_2Cl_2.[19]

Please cite this article in press as: Shi L-F, et al., The synthesis of 3-sulfenylflavones *via* $FeCl_3$-promoted regioselective cyclization of alkynyl aryl ketones with *N*-arylthiobenzamides, Tetrahedron (2016), http://dx.doi.org/10.1016/j.tet.2016.11.034

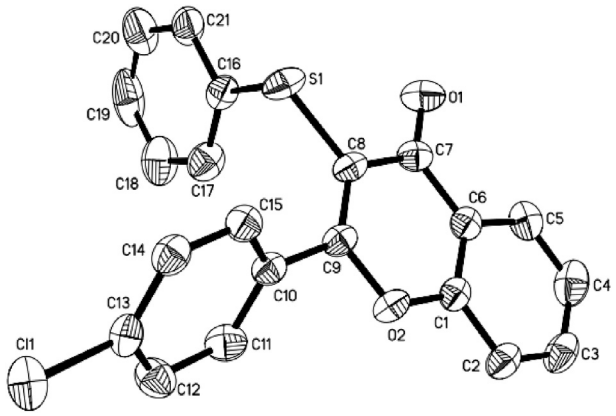
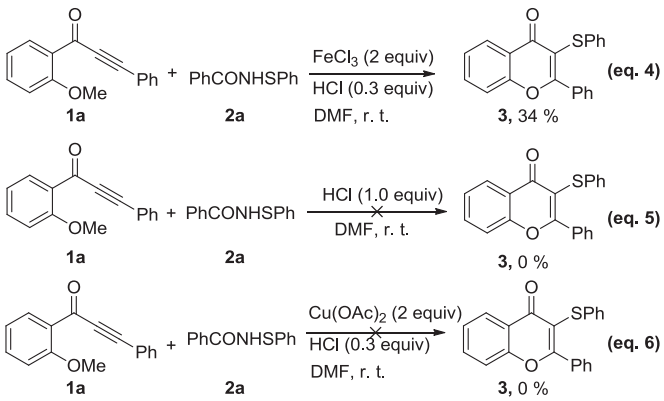
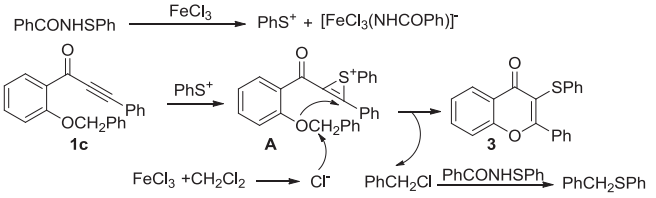


Fig. 1. X-ray structure of compound **21**.



Scheme 3. Control Experiments.



Scheme 4. Possible Mechanism.

3. Conclusions

In conclusion, we have developed an effective protocol for the synthesis of 3-sulfenylflavones *via* $FeCl_3$-promoted regioselective cyclization. A variety of alkynyl aryl ketones bearing 2-methoxy groups and *N*-arylthiobenzamides underwent the reaction successfully to give the corresponding 3-sulfenylflavones in moderate to good yields. The present method would serve as a good route for the synthesis of 3-sulfenylflavone derivatives. Moreover, the mechanism was described in detail.

4. Experimental section

4.1. General

Chemicals were either purchased or purified by standard techniques. ^1H NMR and ^{13}C NMR spectra were measured on a 500 MHz spectrometer (^1H at 500 MHz, ^{13}C at 125 MHz), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in hertz. High-resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometer. Melting point data are uncorrected. Column chromatography was performed using EM silica gel 60 (300–400 mesh).

4.2. General procedure for the synthesis of 3-sulfenylflavones derivative 3-26

To a flame-dried Schlenk tube with a magnetic stirring bar was charged with **1a** (0.2 mmol), **2a** (0.24 mmol), $FeCl_3$ (66 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) under air atmosphere. The reaction mixture was stirred at room temperature until complete consumption of starting material as detected by TLC or GC-MS analysis. After the reaction was finished, brine and ethyl acetate were added to the reaction mixture. The mixture was extracted with ethyl acetate three times, and the combined organic layer was dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography to give the products **3**–**26**.

4.3. Characterization data

4.3.1. 2-phenyl-3-(phenylthio)-4H-chromen-4-one (*3*)

Yellow solid (55.4 mg, 84% yield), m.p. 129–131 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 7.0 Hz, 1H), 7.78 (d, J = 7.5 Hz, 2H), 7.73 (t, J = 7.0 Hz, 1H), 7.54–7.51 (m, 2H), 7.49–7.44 (m, 3H), 7.21 (d, J = 4.5 Hz, 4H), 7.14–7.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 168.8, 156.0, 136.3, 134.3, 133.2, 131.2, 129.3, 129.1, 128.3, 127.3, 126.8, 126.0, 125.9, 122.9, 118.1, 115.3; HRMS (ESI) Calcd for $C_{21}H_{15}O_2S^+$ ($[M+H]^+$) 331.0787, Found: 331.0779.

4.3.2. 2-phenyl-3-(p-tolylthio)-4H-chromen-4-one (*4*)

Yellow solid (55.1 mg, 80% yield), m.p. 104–106 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 7.81–7.79 (m, 2H), 7.70 (t, J = 8.5 Hz, 1H), 7.54–7.51 (m, 2H), 7.49–7.46 (m, 2H), 7.43 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 168.4, 155.9, 135.9, 134.1, 133.1, 132.5, 131.0, 129.8, 129.3, 128.1, 127.8, 126.6, 125.7, 122.9, 118.0, 115.8, 21.0; HRMS (ESI) Calcd for $C_{21}H_{17}O_2S^+$ ($[M+H]^+$) 345.0944, Found: 345.0944.

4.3.3. 3-((4-methoxyphenyl)thio)-2-phenyl-4H-chromen-4-one (*5*)

Yellow soild (58.3 mg, 81% yield), m.p. 117–119 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 7.5 Hz, 2H), 7.69 (t, J = 7.5 Hz, 1H), 7.55–7.48 (m, 4H), 7.42 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 168.1, 158.8, 156.0, 134.1, 133.4, 131.1, 131.0, 129.5, 128.2, 126.7, 126.6, 125.7, 123.1, 118.1, 117.2, 114.7, 55.4; HRMS (ESI) Calcd for $C_{22}H_{16}O_3S^+$ ($[M+Na]^+$) 383.0712, Found: 383.0725.

4.3.4. 3-((2-fluorophenyl)thio)-2-phenyl-4H-chromen-4-one (*6*)

Yellow soild (43.9 mg, 63% yield), m.p. 120–121 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 7.5 Hz, 2H), 7.73–7.69 (m, 1H), 7.54–7.51 (m, 2H), 7.49–7.42 (m, 3H), 7.17 (t, J = 7.5 Hz, 1H), 7.13–7.09 (m, 1H), 7.02–6.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 168.3, 160.6 (d, $J_{C\text{-}F}$ = 243.8 Hz), 155.9, 134.3, 133.0, 131.2, 129.8, 129.3, 128.2, 127.8 (d, $J_{C\text{-}F}$ = 7.5 Hz), 126.6, 125.8, 124.5 (d, $J_{C\text{-}F}$ = 3.8 Hz), 123.0 (d, $J_{C\text{-}F}$ = 16.3 Hz), 122.7, 118.1, 115.7 (d, $J_{C\text{-}F}$ = 21.3 Hz), 114.1; HRMS (ESI) Calcd for $C_{21}H_{13}FO_2S^+$ ($[M+Na]^+$) 371.0512, Found: 371.0525.

4.3.5. 3-((2-chlorophenyl)thio)-2-phenyl-4H-chromen-4-one (*7*)

Yellow soild (39.2 mg, 54% yield), m.p. 163–164 °C; ^1H NMR

Please cite this article in press as: Shi L-F, et al., The synthesis of 3-sulfenylflavones *via* $FeCl_3$-promoted regioselective cyclization of alkynyl aryl ketones with *N*-arylthiobenzamides, Tetrahedron (2016), http://dx.doi.org/10.1016/j.tet.2016.11.034

(500 MHz, $CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 7.76–7.73 (m, 3H), 7.56–7.51 (m, 2H), 7.49–7.45 (m, 3H), 7.32 (d, J = 8.0 Hz, 1H), 7.11–7.02 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 169.2, 156.0, 135.5, 134.4, 132.9, 131.9, 131.4, 129.8, 129.2, 128.3, 127.3, 127.1, 126.8, 126.5, 126.0, 122.7, 118.2, 113.9; HRMS (ESI) Calcd for $C_{21}H_{13}ClO_2S^+$ ($[M+Na]^+$) 387.0217, Found: 387.0232.

*4.3.6. 3-((3-chlorophenyl)thio)-2-phenyl-4H-chromen-4-one (**8**)*

Yellow soild (54.0 mg, 74% yield), m.p. 143–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (dd, J = 8.0, 1.5 Hz, 1H), 7.76–7.73 (m, 3H), 7.56–7.53 (m, 2H), 7.50–7.46 (m, 3H), 7.16–7.13 (m, 2H), 7.10–7.08 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 169.1, 156.0, 138.4, 134.9, 134.4, 132.9, 131.4, 130.1, 129.3, 128.4, 126.8, 126.2, 126.0, 125.3, 122.9, 118.2, 114.5; HRMS (ESI) Calcd for $C_{21}H_{13}ClO_2S^+$ ($[M+Na]^+$) 387.0217, Found: 387.0235.

*4.3.7. 3-((4-chlorophenyl)thio)-2-phenyl-4H-chromen-4-one (**9**)*

Yellow soild (58.2 mg, 80% yield), m.p. 161–162 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 7.0 Hz, 1H), 7.76–7.71 (m, 3H), 7.54–7.52 (m, 2H), 7.50–7.46 (m, 3H), 7.19–7.12 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 168.9, 156.0, 134.8, 134.4, 133.0, 132.0, 131.3, 129.3, 129.2, 128.9, 128.3, 126.7, 126.0, 122.9, 118.2, 115.1; HRMS (ESI) Calcd for $C_{21}H_{13}ClO_2S^+$ ($[M+Na]^+$) 387.0217, Found: 387.0236.

*4.3.8. 3-((3,5-dichlorophenyl)thio)-2-phenyl-4H-chromen-4-one (**10**)*

Yellow soild (33.4 mg, 42% yield), m.p. 116–117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (dd, J = 8.0, 1.5 Hz, 1H), 7.78–7.73 (m, 3H), 7.57–7.54 (m, 2H), 7.51–7.47 (m, 3H), 7.10 (t, J = 1.8 Hz, 1H), 7.04 (d, J = 1.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 169.4, 156.0, 140.1, 135.4, 134.6, 132.7, 131.6, 129.2, 128.4, 126.8, 126.2, 124.9, 122.8, 118.3, 113.6; HRMS (ESI) Calcd for $C_{21}H_{12}Cl_2O_2S^+$ ($[M+Na]^+$) 420.9827, Found: 420.9834.

*4.3.9. 3-((3-nitrophenyl)thio)-2-phenyl-4H-chromen-4-one (**11**)*

Yellow soild (23.3 mg, 31% yield), m.p. 114–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 8.0 Hz, 1H), 8.00–7.94 (m, 2H), 7.78–7.75 (m, 3H), 7.58–7.54 (m, 3H), 7.52–7.47 (m, 3H), 7.38 (t, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 169.4, 156.0, 148.7, 139.1, 134.7, 132.8, 132.7, 131.6, 129.8, 129.2, 128.5, 126.7, 126.2, 122.7, 121.5, 120.8, 118.3, 113.7; HRMS (ESI) Calcd for $C_{21}H_{13}NO_4S^+$ ($[M+Na]^+$) 398.0457, Found: 398.0455.

*4.3.10. 3-(phenylthio)-2-(p-tolyl)-4H-chromen-4-one (**12**)*

Yellow soild (58.5 mg, 85% yield), m.p. 118–119 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 7.72–7.70 (m, 3H), 7.52 (d, J = 7.5 Hz, 1H), 7.44 (t, J = 7.0 Hz, 1H), 7.28 (d, J = 7.0 Hz, 2H), 7.24–7.20 (m, 4H), 7.14–7.10 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 169.0, 156.0, 141.7, 136.4, 134.1, 130.3, 129.3, 129.0, 128.9, 127.2, 126.7, 125.9, 125.7, 122.9, 118.1, 114.7, 21.7; HRMS (ESI) Calcd for $C_{21}H_{17}O_2S^+$ ($[M+H]^+$) 345.0944, Found: 345.0947.

*4.3.11. 3-(phenylthio)-2-(m-tolyl)-4H-chromen-4-one (**13**)*

Yellow soild (59.9 mg, 87% yield), m.p. 126–127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.0 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.25–7.18 (m, 2H), 7.14–7.06 (m, 4H), 7.01–6.98 (m, 1H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 169.0, 155.9, 137.9, 136.4, 134.1, 133.0, 131.8, 129.7, 128.9, 128.0, 127.4, 126.6, 126.4, 125.8, 125.7, 122.8, 118.0, 115.2, 21.4; HRMS (ESI) Calcd for $C_{21}H_{17}O_2S^+$ ($[M+H]^+$) 345.0944, Found: 345.0949.

*4.3.12. 2-(4-ethylphenyl)-3-(phenylthio)-4H-chromen-4-one (**14**)*

Yellow oil (60.9 mg, 85% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 8.0 Hz, 1H), 7.74–7.70 (m, 3H), 7.52 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.22–7.20 (m, 4H), 7.14–7.10 (m, 1H), 2.73 (q, J = 7.5 Hz, 2H), 1.28 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 169.0, 156.0, 147.9, 136.4, 134.2, 130.5, 129.4, 129.1, 127.8, 127.2, 126.8, 125.8, 125.7, 122.9, 118.1, 114.7, 29.0, 15.3; HRMS (ESI) Calcd for $C_{23}H_{19}O_2S^+$ ($[M+H]^+$) 359.1100, Found: 359.1107.

*4.3.13. 3-(phenylthio)-2-(4-propylphenyl)-4H-chromen-4-one (**15**)*

Yellow oil (63.2 mg, 85% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.70 (t, J = 7.0 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.25–7.20 (m, 4H), 7.12 (m, 1H), 2.66 (t, J = 7.5 Hz, 2H), 1.75–1.65 (m, 2H), 0.98 (t, J = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 168.8, 155.9, 146.3, 136.4, 134.1, 130.4, 129.3, 129.0, 128.2, 127.2, 126.6, 125.8, 125.6, 122.8, 118.0, 114.7, 38.0, 24.2, 13.9; HRMS (ESI) Calcd for $C_{24}H_{21}O_2S^+$ ($[M+H]^+$) 373.1257, Found: 373.1265.

*4.3.14. 2-(4-butylphenyl)-3-(phenylthio)-4H-chromen-4-one (**16**)*

Yellow soild (67.2 mg, 87% yield), m.p. 84–85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 7.76–7.67 (m, 3H), 7.52 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.25–7.19 (m, 4H), 7.14–7.10 (m, 1H), 2.68 (t, J = 7.5 Hz, 2H), 1.68–1.62 (m, 2H), 1.44–1.33 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 168.9, 155.9, 146.6, 136.4, 134.1, 130.4, 129.3, 129.0, 128.2, 127.2, 126.7, 125.8, 125.7, 122.8, 118.0, 114.7, 35.7, 33.3, 22.4, 14.0; HRMS (ESI) Calcd for $C_{25}H_{23}O_2S^+$ ($[M+H]^+$) 387.1413, Found: 387.1421.

*4.3.15. 2-(4-methoxyphenyl)-3-(phenylthio)-4H-chromen-4-one (**17**)*

Yellow soild (48.3 mg, 67% yield), m.p. 99–100 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 7.5 Hz, 1H), 7.80 (d, J = 7.5 Hz, 2H), 7.71 (t, J = 7.5 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 4.5 Hz, 4H), 7.13–7.10 (m, 1H), 6.97 (d, J = 8.5 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 168.6, 162.0, 155.9, 136.5, 134.1, 131.3, 129.1, 127.0, 126.8, 125.8, 125.7, 125.3, 122.9, 118.0, 114.0, 113.6, 55.6; HRMS (ESI) Calcd for $C_{22}H_{16}O_3S^+$ ($[M+Na]^+$) 383.0712, Found: 383.0726.

*4.3.16. 2-(4-fluorophenyl)-3-(phenylthio)-4H-chromen-4-one (**18**)*

Yellow soild (56.5 mg, 81% yield), m.p. 123–124 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 7.84–7.77 (m, 2H), 7.73 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.24–7.18 (m, 4H), 7.18–7.09 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 167.7, 164.3 (d, $J_{C\text{-}F}$ = 251.2 Hz), 155.9, 136.1, 134.3, 131.8 (d, $J_{C\text{-}F}$ = 8.8 Hz), 129.24 (d, $J_{C\text{-}F}$ = 2.5 Hz), 129.20, 127.3, 126.8, 126.1, 125.9, 122.9, 118.1, 115.5 (d, $J_{C\text{-}F}$ = 22.5 Hz), 115.3; HRMS (ESI) Calcd for $C_{21}H_{13}FO_2S^+$ ($[M+Na]^+$) 371.0512, Found: 371.0528.

*4.3.17. 2-(2-fluorophenyl)-3-(phenylthio)-4H-chromen-4-one (**19**)*

Yellow soild (43.8 mg, 63% yield), m.p. 107–108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, J = 8.0 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.56–7.51 (m, 3H), 7.48 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.25–7.20 (m, 5H), 7.14 (t, J = 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 164.3, 159.7 (d, $J_{C\text{-}F}$ = 250.0 Hz), 156.2, 135.4, 134.3, 132.7 (d, $J_{C\text{-}F}$ = 8.8 Hz), 130.7, 128.9, 128.3, 126.7, 126.3, 125.9, 124.1 (d, $J_{C\text{-}F}$ = 3.75 Hz), 123.1, 121.6 (d, $J_{C\text{-}F}$ = 15.0 Hz), 118.6, 118.2, 116.2 (d, $J_{C\text{-}F}$ = 20.0 Hz); HRMS (ESI) Calcd for $C_{21}H_{13}FO_2S^+$ ($[M+Na]^+$) 371.0512, Found: 371.0527.

*4.3.18. 2-(3-fluorophenyl)-3-(phenylthio)-4H-chromen-4-one (**20**)*

Yellow soild (28.5 mg, 41% yield), m.p. 129–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 7.0 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.50–7.41 (m, 3H),

Please cite this article in press as: Shi L-F, et al., The synthesis of 3-sulfenylflavones *via* $FeCl_3$-promoted regioselective cyclization of alkynyl aryl ketones with *N*-arylthiobenzamides, Tetrahedron (2016), http://dx.doi.org/10.1016/j.tet.2016.11.034

7.24–7.21 (m, 5H), 7.16–7.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 167.0 (d, J_{C-F} = 2.5 Hz), 162.2 (d, J_{C-F} = 246.3 Hz), 155.9, 135.9, 134.9 (d, J_{C-F} = 7.5 Hz), 134.4, 130.0 (d, J_{C-F} = 7.5 Hz), 129.2, 127.6, 126.8, 126.2, 126.0, 125.3 (d, J_{C-F} = 3.8 Hz), 122.8, 118.13 (d, J_{C-F} = 21.0 Hz), 118.12, 116.5 (d, J_{C-F} = 23.8 Hz), 116.0; HRMS (ESI) Calcd for $C_{21}H_{13}FO_2S^+$ ([M+Na]$^+$) 371.0512, Found: 371.0526.

*4.3.19. 2-(4-chlorophenyl)-3-(phenylthio)-4H-chromen-4-one (**21**)*

Yellow soild (47.2 mg, 65% yield), m.p. 136–137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 8.5 Hz, 3H), 7.52 (d, J = 8.5 Hz, 1H), 7.45 (t, J = 8.5 Hz, 3H), 7.23–7.19 (m, 4H), 7.14–7.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 167.5, 155.9, 137.4, 136.0, 134.4, 131.5, 130.8, 129.2, 128.6, 127.4, 126.8, 126.2, 126.0, 122.9, 118.1, 115.5; HRMS (ESI) Calcd for $C_{21}H_{13}ClO_2S^+$ ([M+Na]$^+$) 387.0217, Found: 387.0234.

*4.3.20. 2-(3-chlorophenyl)-3-(phenylthio)-4H-chromen-4-one (**22**)*

Yellow soild (45.1 mg, 62% yield), m.p. 119–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 8.0 Hz, 1H), 7.78–7.69 (m, 2H), 7.66 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.49–7.44 (m, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.22–7.19 (m, 4H), 7.15–7.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 166.9, 155.9, 135.9, 134.7, 134.4, 134.3, 131.1, 129.5, 129.2, 129.1, 127.7, 127.6, 126.8, 126.2, 126.0, 122.8, 118.1, 116.1; HRMS (ESI) Calcd for $C_{21}H_{13}ClO_2S^+$ ([M+Na]$^+$) 387.0217, Found: 387.0237.

*4.3.21. 2-(4-bromophenyl)-3-(phenylthio)-4H-chromen-4-one (**23**)*

Yellow soild (57.9 mg, 71% yield), m.p. 154–155 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.23–7.19 (m, 4H), 7.15–7.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 167.6, 155.9, 136.0, 134.4, 131.9, 131.6, 130.9, 129.2, 127.3, 126.8, 126.1, 126.0, 125.9, 122.9, 118.1, 115.5; HRMS (ESI) Calcd for $C_{21}H_{13}BrO_2S^+$ ([M+Na]$^+$) 430.9712, Found: 430.9710.

*4.3.22. 2-(4-nitrophenyl)-3-(phenylthio)-4H-chromen-4-one (**24**)*

Yellow soild (31.5 mg, 42% yield), m.p. 155–156 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, J = 8.5 Hz, 2H), 8.27 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 9.0 Hz, 2H), 7.76 (t, J = 8.5 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.24–7.20 (m, 4H), 7.15 (t, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 165.9, 155.9, 149.1, 138.9, 135.4, 134.7, 130.5, 129.3, 127.6, 126.9, 126.5, 126.3, 123.5, 122.9, 118.2, 116.9; HRMS (ESI) Calcd for $C_{21}H_{13}NO_4S^+$ ([M+Na]$^+$) 398.0457, Found: 398.0460.

*4.3.23. 3-(phenylthio)-2-(4-(trifluoromethyl)phenyl)-4H-chromen-4-one (**25**)*

Yellow soild (31.8 mg, 40% yield), m.p. 149–150 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.76–7.72 (m, 3H), 7.53 (d, J = 8.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.23–7.19 (m, 4H), 7.15–7.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 167.0, 156.0, 136.5, 135.8, 134.5, 132.8 (q, J = 32.5 Hz), 129.8, 129.2, 127.6, 126.8, 126.3, 126.1, 125.3 (q, J = 3.7 Hz), 123.8 (q, J = 270.0 Hz), 122.9, 118.1, 116.3; HRMS (ESI) Calcd for $C_{22}H_{14}F_3O_2S^+$ ([M + H]$^+$) 399.0661, Found: 399.0661.

*4.3.24. 2-butyl-3-(phenylthio)-4H-chromen-4-one (**26**)*

Yellow oil (31.7 mg, 51% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.26–7.19 (m, 4H), 7.13–7.10 (t, J = 6.6 Hz, 1H), 3.10 (t, J = 7.5 Hz, 2H), 1.77–1.71 (m, 2H), 1.46–1.39 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 174.9, 155.8, 136.2, 133.9, 129.0, 127.5, 126.8, 126.0, 125.6, 123.1, 117.8, 115.1, 33.9, 29.8, 22.6, 13.8; HRMS (ESI) Calcd for $C_{19}H_{19}O_2S^+$ ([M + H]$^+$) 311.1100, Found: 311.1111.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 21302144 and 21272177) for financial support.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2016.11.034.

References

1. (a) Sritularak B, Likhitwitayawuid K, Conrad J, et al. *J Nat Prod*. 2002;65:589;
   (b) Wang Y-H, Hou A-J, Chen L, et al. *J Nat Prod*. 2004;67:757;
   (c) Lin C-N, Kuo S-H, Chung M-I. *J Nat Prod*. 1997;60:851;
   (d) Hakim EH, Fahriyati A, Kau MS, et al. *J Nat Prod*. 1999;62:613;
   (e) Jones JR, Lebar MD, Jinwal UK, et al. *J Nat Prod*. 2011;74:38.
2. (a) Losiewicz MD, Carlson BA, Kaur G, Sausville EA, Worland PJ. *Biochem Biophys Res Commun*. 1994;201:589;
   (b) Minagawa A, Otani Y, Kubota T, et al. *M Jpn J Cancer Res*. 2001;92:1322.
3. (a) Narwal M, Haikarainen T, Fallarero A, Vuorela PM, Lehtio L. *J Med Chem*. 2013;56:3507;
   (b) Narwal M, Koivunen J, Haikarainen T, et al. *J Med Chem*. 2013;56:7880.
4. (a) Imran S, Taha M, Ismail NH, et al. *Eur J Med Chem*. 2015;105:156;
   (b) Lebovitz HE. *Endocrinol Metab Clin N Am*. 1997;26:539;
   (c) Lebovitz HE. *Drugs*. 1992;44:21;
   (d) Inui Y, Kawata S, Matsuzawa Y, et al. *J Hepatol*. 1990;10:62;
   (e) Giorgino R, Damato A. *Ann Ital Med Int*. 1995;10:61.
5. Ares JJ, Outt PE, Randall JL, et al. *J Med Chem*. 1995;38:4937.
6. Wu ESC, Cole TE, Davidson TA, et al. *J Med Chem*. 1989;32:183.
7. (a) Freitas M, Ribeiro D, Tome SM, Silva AMS, Fernandes E. *Eur J Med Chem*. 2014;86:153;
   (b) Ballesteros JF, Sanz MJ, Ubeda A, et al. *J Med Chem*. 1995;38:2794.
8. (a) Shobeiri N, Rashedi M, Mosaffa F, et al. *Eur J Med Chem*. 2016;114:14;
   (b) Zemanova L, Hofman J, Novotna E, et al. *J Nat Prod*. 2015;78:2666.
9. (a) Klier L, Bresser T, Nigst TA, Karaghiosoff K, Knochel P. *J Am Chem Soc*. 2012;134:13584;
   (b) Banerjee D, Kayal U, Maiti G. *Tetrahedron Lett*. 2016;57:1667;
   (c) Liu J, Song W, Yue Y, et al. *Chem Commun*. 2015;51:17576.
10. Garcia H, Iborra S, Primo J, Miranda MA. *J Org Chem*. 1986;51:4432.
11. (a) Huang X, Tang E, Xu W-M, Cao J. *J Comb Chem*. 2005;7:802;
   (b) Perez M, Ruiz D, Autino J, Sathicq A, Romanelli G. *Chimie*. 2016;19:551;
   (c) Sashidhara KV, Kumar M, Kumar A. *Tetrahedron Lett*. 2012;53:2355;
   (d) Wen S-S, Wang J, Luo Y-M, Yang H. *Tetrahedron*. 2014;70:9314.
12. Zhang S, Wan C, Wang Q, et al. *Eur J Org Chem*. 2013:2080.
13. Lahyani A, Trabelsi M. *Ultrason Sonochem*. 2016;31:626.
14. (a) Zhou C, Dubrovsky AV, Larock RC. *J Org Chem*. 2006;71:1626;
   (b) Zhao J, Zhao Y, Fu H. *Org Lett*. 2012;14:2710.
15. Godoi B, SperanÅa A, Bruning CA, et al. *Adv Synth Catal*. 2011;353:2042.
16. (a) Liu J, Liu M, Yue Y, Zhang N, Zhang Y, Zhuo K. *Tetrahedron Lett*. 2013;54:1802;
   (b) Liang B, Huang M, You Z, et al. *J Org Chem*. 2005;70:6097;
   (c) Yang Q, Alper H. *J Org Chem*. 2010;75:948;
   (d) Xue L, Shi L, Han Y, Xia C, Huynh HV, Li F. *Dalton Trans*. 2011;40:7632;
   (e) Miao H, Yang Z. *Org Lett*. 2000;2:1765;
   (f) Wu X-F, Neumann H, Beller M. *Chem Eur J*. 2012;18:12595.
17. (a) Zhang X-S, Li G, Zhang X-G, Zhang X-H. *Tetrahedron*. 2015;71:5458;
   (b) Zhang X-S, Jiao J-Y, Zhang X-H, Hu B-L, Zhang X-G. *J Org Chem*. 2016;81:5710.
18. Yang Z-J, Hu B-L, Deng C-L, Zhang X-G. *Adv Synth Catal*. 2014;356:1962.
19. Chen X, Hao X-S, Goodhue CE, Yu J-Q. *J Am Chem Soc*. 2006;128:6790.