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The intramolecular reaction of acetophenone *N*-tosylhydrazone and vinyl: Brønsted acid-promoted cationic cyclization toward polysubstituted indenes†

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In the presence of $TsNHNH_2$, a Brønsted acid-promoted intramolecular cyclization of *o*-(1-arylvinyl) acetophenone derivatives was developed, leading to polysubstituted indenes with complexity and diversity in moderate to excellent yields. In sharp contrast with either the radical or carbene involved cyclization of aldehydic *N*-tosylhydrazone with vinyl, a cationic cyclization pathway was involved, where *N*-tosylhydrazone served as an electrophile and alkylation reagent during this transformation.

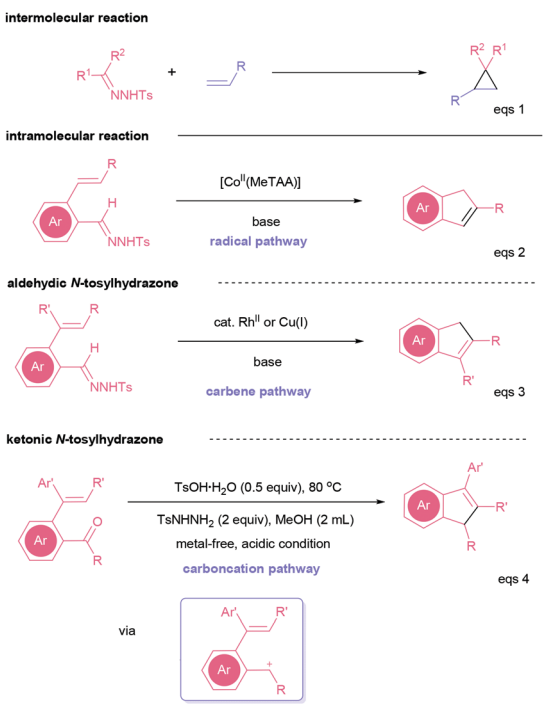
Recently, much attention has been paid to the development of *N*-tosylhydrazones in organic synthesis since they can serve as key building blocks in either transition-metal-catalyzed or metal-free organic reactions.[1] In some cases, *N*-tosylhydrazones proved to be ideal diazo or carbene precursors.[2] As expected, the intermolecular reaction of *N*-tosylhydrazone with vinyl resulted in the cyclopropanation products (eqn (1), Scheme 1).[3]

Alternatively, in the intramolecular type reaction, de Bruin reported the cobalt-catalyzed radical approach leading to indene, which involved the insertion of vinyl C–H into the *in situ* formed carbene intermediate (eqn (2), Scheme 1).[4] Afterward, Wang developed a rhodium(II)- or copper(I)-catalyzed formal intramolecular carbene insertion into vinylic C–H bonds to access indenes (eqn (3), Scheme 1).[5] The intramolecular reaction of ketonic *N*-tosylhydrazone with vinyl allowed the facile introduction of functional groups into the 1-position of indene with complexity and diversity. However, no example of this was reported or studied before, which was at least partly due to the less activation and more hindrance than the aldehydic analogues. To circumvent this, a mechanistically different pathway should be developed.

In the base-induced reaction of *N*-tosylhydrazones to afford alkenes, namely the Shapiro reaction, a carbocation mechanism may be involved under protic solvents.[6] Indeed, *N*-tosylhydrazones were also electrophiles, serving as carbocation equivalents and alkylation reagents in a series of transformations.[7]

This chemistry of *N*-tosylhydrazone spurred us to test the feasibility of intramolecular cationic cyclization of the ketonic analogues with vinyl toward indenes, which are ubiquious in pharmaceutical and biologically active compounds,[8] serving as antitumor,[9] antiallergic,[10] anti-inflammatory,[11] and antimicrobial[12] reagents.

Herein, we wish to report a metal-free intramolecular reaction of acetophenone *N*-tosylhydrazone derivatives and vinyl toward



Scheme 1 The reaction of *N*-tosylhydrazone with vinyl.

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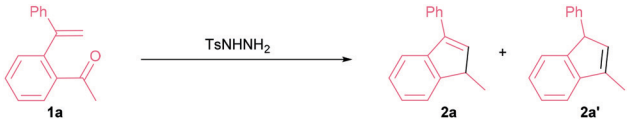
polysubstituted indenes in the presence of $TsNHNH_2$ promoted by a Brønsted acid (eqn (4), Scheme 1). In sharp contrast with the aforementioned examples on the annulation of aldehydic *N*-tosylhydrazone with vinyl, this procedure features: (1) less active substrates with more hindrance toward polysubstituted indenes with more complexity and diversity; (2) acidic reaction conditions rather than basic conditions; (3) a mechanistically different pathway involving a carbocation.

We began our investigation with the reaction of *o*-(1-arylvinyl) acetophenone **1a** (0.1 mmol), and $TsNHNH_2$ (0.2 mmol) in MeOH at 60 °C in the presence of base (2.0 equiv.) under a N_2 atmosphere. However, no reaction took place at all (entries 1 and 2). Replacing the base with HOAc (2.0 equiv.), PivOH (2.0 equiv.) and $TsOH{\cdot}H_2O$ (2.0 equiv.), trace indene was detected (entries 3–5). Fortunately, in the presence of $TsOH{\cdot}H_2O$ (2.0 equiv.), indene was isolated in 18% (4.4/1) yield (entry 6) and the yield was further increased to 47% (4.1/1) (0.1 equiv.), 75% (4.4/1) (0.3 equiv.) and 78% (4.4/1) (0.5 equiv.), respectively (entries 7–9). Under elevated reaction temperature (80 °C), the yield increased to 81% (**2a**/**2a′** = 5.6/1, entry 11). Under air atmosphere, the yield slightly decreased to 68% (5.6/1) (entry 9). Among the tested solvents, dioxane (70%, 0.5/1), THF (67%, 1.8/1), DCE (52%, 1.8/1), MeCN (45%, 0.5/1) and EtOH (69%, 4.4/1) were all inferior to MeOH (entries 12–16). Other Brønsted acids, such as MsOH (41%, 8.4/1), $HNTf_2$ (35%, 7.2/1), were tested, but all resulted in low yields (entries 17 and 18) (Table 1). The ratio of **2a** and **2a′** changed under increased temperature (3.4/1, 100 °C).

With the optimized catalytic system in hand, the scope of *o*-(1-phenylvinyl) acetophenone with substituents attaching in the carbonyl was studied, as shown in Fig. 1. As expected, the ethyl analogue produced **2b** in 87% yield (**2b**/**2b′** = 5.6/1). However, the iso-propyl (**2c**, 57%, 5.6/1), *tert*-butyl (**2d**, 52%, 2/1), and phenyl (**2e**, 48%) analogues delivered the cyclized products in relatively lower yields, which was at least partly due to the hindrance. *n*-Pentanyl and benzyl analogues ran smoothly under the standard procedure, and **2f** and **2g** were isolated in 74% (10/1) and 65% (5.6/1) yields, respectively. Notably, the 2-cyclohexanyl substituted substrate was also a suitable reaction partner, albeit in relatively low yield (**2h**, 35%, 4/1). Importantly, 2-(1-phenylvinyl) benzaldehyde worked under the procedure, providing **2i** in 38% yield (3.4/1).

Next, the scope of *o*-(1-phenylvinyl) acetophenone with substituents in both aryls was studied, as shown in Fig. 2. In the case of substrates with functional groups in the phenyl substituted by acyl, the reaction tolerated fluoro (**2k**, 75%, 3.4/1; **2n**, 69%, 5.6/1), methyl (**2p**, 78%, 6.7/1), and chloro (**2j**, 72%, 3.4/1; **2m**, 62%, 5/1), which provided facile handles for potential further functionalization. However, the *ortho*-fluoride substrate provided **2o** (42%, 3.4/1) in lower yields. For the substrates with groups in the phenyl attached in the vinyl, *o*-chloro substrate **1t** produced **2t** (37%, 5.6/1) in lower yield. However, the *p*-methyl (**2q**, 73%, 3.4/1), *p*-chloro (**2r**, 79%, 5.6/1), and *m*-chloro (**2s**, 56%, 5.6/1), analogues all ran smoothly under the standard procedure. As such, this procedure provided a facile pathway to access 1,3-difunctionalized indenes with complexity and diversity.

Table 1 Selected results for screening the optimized reaction conditions[a]



Entry	Additive (equiv.)	Solvent	Temperature	Yield[b] (%)
1	K_2CO_3 (2.0)	MeOH	60	N.R.
2	Cs_2CO_3 (2.0)	MeOH	60	N.R.
3	HOAc (2.0)	MeOH	60	Trace
4	PivOH (2.0)	MeOH	60	Trace
5	HOTf (2.0)	MeOH	60	Trace
6	$TsOH{\cdot}H_2O$ (2.0)	MeOH	60	18
7	$TsOH{\cdot}H_2O$ (0.1)	MeOH	60	47
8	$TsOH{\cdot}H_2O$ (0.3)	MeOH	60	75
9	$TsOH{\cdot}H_2O$ (0.5)	MeOH	60	78/68[b]/57[c]
10	$TsOH{\cdot}H_2O$ (0.5)	MeOH	r.t.	46
11	$TsOH{\cdot}H_2O$ (0.5)	MeOH	80	81
12	$TsOH{\cdot}H_2O$ (0.5)	Dioxane	80	70
13	$TsOH{\cdot}H_2O$ (0.5)	THF	80	67
14	$TsOH{\cdot}H_2O$ (0.5)	DCE	80	52
15	$TsOH{\cdot}H_2O$ (0.5)	MeCN	80	45
16	$TsOH{\cdot}H_2O$ (0.5)	EtOH	80	69
17	MsOH (0.5)	MeOH	80	41
18	$HNTf_2$ (0.5)	MeOH	80	35

[a] Reaction conditions: **1a** (0.1 mmol), $TsNHNH_2$ (0.2 mmol), solvent (2.0 mL), under N_2 for 6 h, isolated yields. [b] Under air. [c] $TsNHNH_2$ (0.12 mmol). The ratio of **2a** and **2a′** was determined by ^1H NMR.

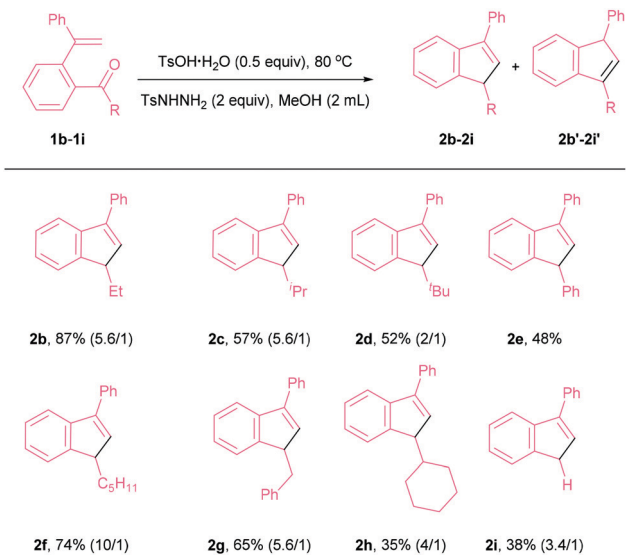


Fig. 1 The substrate scope of *o*-(1-phenylvinyl) acetophenone bearing substituents on the carbonyl. Reaction conditions: *o*-(1-phenylvinyl) acetophenone derivatives **1** (0.1 mmol), $TsNHNH_2$ (0.2 mmol), $TsOH{\cdot}H_2O$ (0.5 equiv.), MeOH (2.0 mL), under N_2 for 6 h, isolated yields. The ratio of **2** and **2′** was determined by ^1H NMR.

To get some insights into this reaction, more experiments were conducted. Under the standard procedure, **2a** was isolated in 73% yield in the presence of styrene (1.0 equiv.), and no cyclopropanation product **3** was detected at all (eqn (1), Scheme 2). This result ruled out the possibility of the involvement of a carbene pathway. Meanwhile, $TsOH{\cdot}H_2O$ could

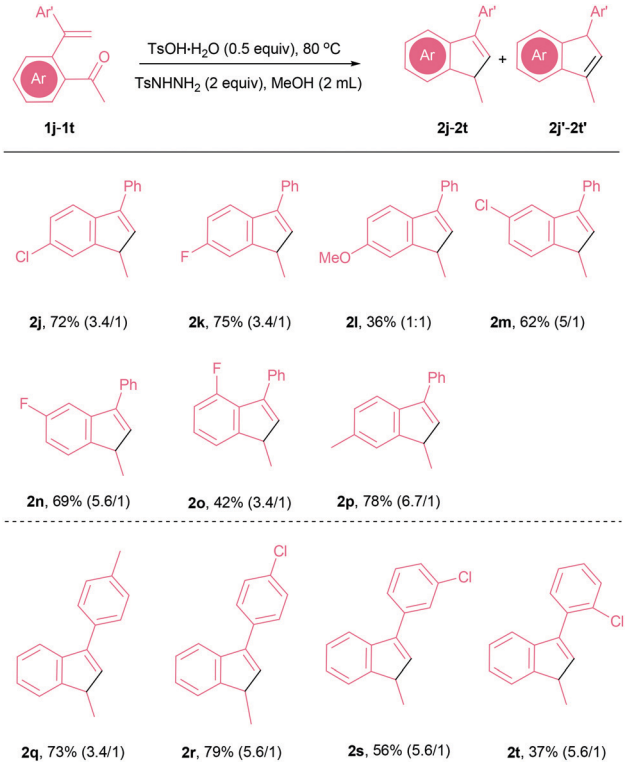
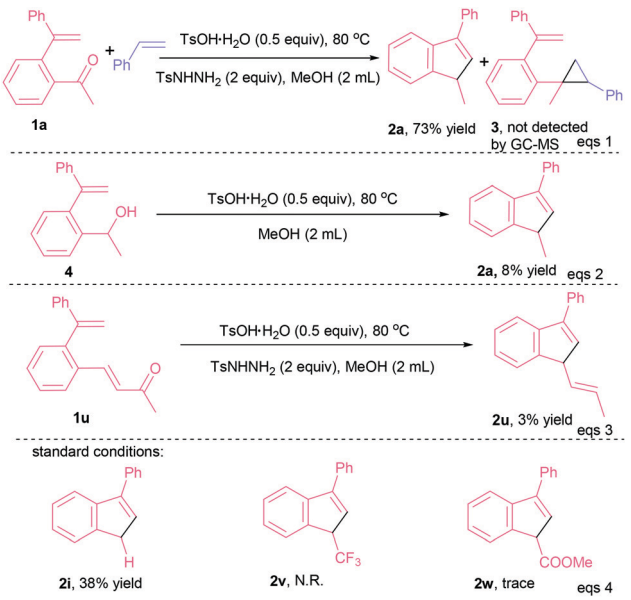
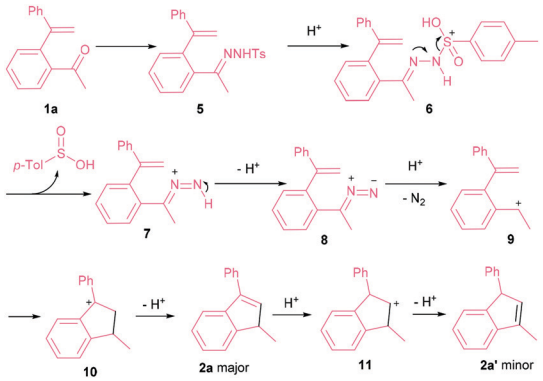


Fig. 2 The substrate scope of *o*-(1-phenylvinyl) acetophenone bearing groups on the phenyl. Reaction conditions: *o*-(1-arylvinyl) acetophenone derivatives **1** (0.1 mmol), $TsNHNH_2$ (0.2 mmol), $TsOH{\cdot}H_2O$ (0.5 equiv.), MeOH (2.0 mL), under N_2 for 6 h, isolated yields. The ratio of **2** and **2′** was determined by ^1H NMR.

promote the annulation of 1-(2-(1-phenylvinyl) phenyl)ethan-1-ol **4** leading to indene **2a** (8%, eqn (2), Scheme 2), indicating the participation of the produced carbocation in the subsequent cyclization. Moreover, (*E*)-4-(2-(1-phenylvinyl) phenyl)but-3-*en*-2-one **1u** was



Scheme 2 Mechanism study.



Scheme 3 A tentative mechanism.

subjected to the standard reaction conditions, and indene **2u** was isolated in 3% yield proceeding with a presumed carbocation migration (eqn (3), Scheme 2). These two results clearly confirmed the involvement of a carbocation pathway. However, 2-(1-phenylvinyl)benzaldehyde, which has no hyperconjugation in the corresponding cabocation, provided **2i** (38%) in relatively lower yield. Moreover, for substrates with an electron-withdrawing group attached in the carbonyl, neither **2v** nor **2w** was detected at all under the standard reaction (eqn (4), Scheme 2). These results were also consistent with the carbocation pathway.

Based on the aforementioned experimental results, a tentative mechanism was proposed (Scheme 3). First, in the presence of $TsNHNH_2$ and $TsOH{\cdot}H_2O$, *o*-(1-phenylvinyl) acetophenone **1a** converts into *N*-tosylhydrazone **5**. Afterward, intermediate **5** transforms into intermediate **6** under the acidic conditions. Second, intermediate **7** is formed whereby 4-methylbenzenesulfinic acid is released, which is detected by GC–MS (for details, see ESI†). Third, after the extrusion of a proton in intermediate **7**, the diazo intermediate **8** is generated, which produces the carbocation intermediate **9** in the presence of a proton. Fourth, the cation cyclization takes place leading to intermediate **10**. Finally, the product **2a** is formed after the releasing of one proton. Meanwhile, the isomer **2a′** is produced through the sequential addition of a proton to **2a** toward intermediate **11** and the extrusion of a proton.

In conclusion, we have developed a Brønsted acid-promoted intramolecular cyclization of *o*-(1-arylvinyl) acetophenone derivatives, leading to polysubstituted indenes with complexity and diversity in moderate to excellent yields. A carbocation pathway was involved during this procedure, which was different from either the radical or carbene involved cyclization of aldehydic *N*-tosylhydrazone with vinyl. In sharp contrast with the aforementioned examples on the annulation of aldehydic *N*-tosylhydrazone with vinyl, this procedure features: (1) less active substrates with more hindrance toward polysubstituted indenes with more complexity and diversity; (2) acidic reaction conditions rather than basic conditions; and (3) a mechanismly different pathway involved carbocation.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For reviews: (*a*) Y. Xia and J. Wang, *J. Am. Chem. Soc.*, 2020, **142**, 10592; (*b*) Y. Zhang and J. Wang, *Top. Curr. Chem.*, 2012, **327**, 239; (*c*) Z. Shao and H. Zhang, *Chem. Soc. Rev.*, 2012, **41**, 560; (*d*) D. Qiu, F. Mo, Y. Zhang and J. Wang, *Adv. Organomet. Chem.*, 2017, **67**, 151; (*e*) D. Arunprasath, B. D. Bala and G. Sekar, *Adv. Synth. Catal.*, 2019, **361**, 1172; (*f*) H. Wang, Y.-H. Deng and Z. Shao, *Synthesis*, 2018, 2281; (*g*) Y. Xia and J. Wang, *Chem. Soc. Rev.*, 2017, **46**, 2306; (*h*) A. P. Jadhav, D. Ray, V. U. B. Rao and R. P. Singh, *Eur. J. Org. Chem.*, 2016, 2369; (*i*) K. Xu, C. Shen and S. Shan, *Youji Huaxue*, 2015, **35**, 294; (*j*) Z. Liu and J. Wang, *J. Org. Chem.*, 2013, **78**, 10024; (*k*) Z. Liu, Y. Zhang and J. Wang, *Youji Huaxue*, 2013, **33**, 687; (*l*) Q. Xiao, Y. Zhang and J. Wang, *Acc. Chem. Res.*, 2013, **46**, 236; (*m*) J. Barluenga and C. Valdes, *Angew. Chem., Int. Ed.*, 2011, **50**, 7486; (*n*) J. R. Fulton, V. K. Aggarwal and J. de Vicente, *Eur. J. Org. Chem.*, 2005, 1479.

2 For selected examples: (*a*) H. Xiong, X. Wu, H. Wang, S. Sun, J.-T. Yu and J. Cheng, *Adv. Synth. Catal.*, 2019, **361**, 3538; (*b*) V. S. Ostrovskii, I. P. Beletskaya and I. D. Titanyuk, *Org. Lett.*, 2019, **21**, 9080; (*c*) K. Ishitobi, K. Muto and J. Yamaguchi, *ACS Catal.*, 2019, **9**, 11685; (*d*) L. Zhu, X. Ren, Y. Yu, P. Ou, Z.-X. Wang and X. Huang, *Org. Lett.*, 2020, **22**, 2087.

3 (*a*) D. F. Taber, P. Guo and N. Guo, *J. Am. Chem. Soc.*, 2010, **132**, 11179; (*b*) J. Barluenga, N. Quinones, M. Tomas-Gamasa and M.-P. Cabal, *Eur. J. Org. Chem.*, 2012, 2312; (*c*) J. S. Kapure, C. N. Reddy, P. R. Adiyala, R. Nayak, V. L. Nayak, J. B. Nanubolu, K. K. Singarapu and R. A. Maurya, *RSC Adv.*, 2014, **4**, 38425; (*d*) M. Lawson, J. Bignon, J.-D. Brion, A. Hamze and M. Alami, *Asian J. Org. Chem.*, 2015, **4**, 1144; (*e*) T. Iwai, F. Matsumoto, K. Hida, K. Moriwaki, Y. Takao, T. Ito, T. Mizuno and T. Ohno, *Synlett*, 2015, 960; (*f*) R. Barroso, A. Jimenez, M. C. Perez-Aguilar, M.-P. Cabal and C. Valdés, *Chem. Commun.*, 2016, **52**, 3677; (*g*) P. Cyr, A. Cote-Raiche and S. M. Bronner, *Org. Lett.*, 2016, **18**, 6448; (*h*) C. Zhu, J. Li, P. Chen, W. Wu, Y. Ren and H. Jiang, *Org. Lett.*, 2016, **18**, 1470; (*i*) W. Wu, Z. Lin, C. Zhu, P. Chen, J. Li and H. Jiang, *J. Org. Chem.*, 2017, **82**, 12746; (*j*) X. Nie, Y. Wang, L. Yang, Z. Yang and T. Kang, *Tetrahedron Lett.*, 2017, **58**, 3003.

4 B. G. Das, A. Chirila, M. Tromp, J. N. H. Reek and B. de Bruin, *J. Am. Chem. Soc.*, 2016, **138**, 8968.

5 Q. Zhou, S. Li, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2017, **56**, 16013.

6 For reviews, see: (*a*) W. Kirmse, *Eur. J. Org. Chem.*, 1998, 201; (*b*) R. M. Adlington and A. G. M. Barrett, *Acc. Chem. Res.*, 1983, **16**, 55; (*c*) J. P. Wolfe, *Name Reactions for Functional Group Transformations*, ed. J. J. Li and E. J. Corey, 2007, pp. 405–413; (*d*) J. J. Li, *Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications*, Spring Verlag, Berlin Heidelberg, 4th edn, 2011, pp 16–17.

7 (*a*) F. Ye, X. Ma, Q. Xiao, H. Li, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2012, **134**, 5742; (*b*) T. Wang, M. Wang, S. Fang and J. Y. Liu, *Organometallics*, 2014, **33**, 3941; (*c*) X. Zhao, G. Wu, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 3296; (*d*) T. Yao, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2012, **51**, 775; (*e*) Q. Xiao, L. Ling, F. Ye, R. Tan, L. Tian, Y. Zhang, Y. Li and J. Wang, *J. Org. Chem.*, 2013, **78**, 3879; (*f*) A. K. Jha and N. Jain, *Chem. Commun.*, 2016, **52**, 1831; (*g*) S. Xu, G. Wu, F. Ye, X. Wang, H. Li, X. Zhao, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2015, **54**, 4669.

8 For reviews, please see: (*a*) Q. He, Z. Yin, H. Chen, Z. Zhang, X. Wang and G. Yue, *Huaxue Jinzhan*, 2016, **28**, 801; (*b*) A. Rinaldi, D. Scarpi and E. G. Occhiato, *Eur. J. Org. Chem.*, 2019, 7401; (*c*) R. Pluskota and M. Koba, *Mini-Rev. Med. Chem.*, 2018, **18**, 1321; (*d*) B. An, Y.-M. Zhang, H.-B. Zhu, W. Teng and G.-J. Guo, *Guangzhou Huagong*, 2015, **43**, 34.

9 (*a*) S. Guzelj, M. Gobec, D. Urbancic, I. Mlinaric-Rascan, E. Corsini and Z. Jakopin, *Eur. J. Med. Chem.*, 2020, **190**, 112089; (*b*) D. Zhu, H. Huang, D. M. Pinkas, J. Luo, D. Ganguly, A. E. Fox, E. Arner, Q. Xiang, Z.-C. Tu and A. N. Bullock, *et al.*, *J. Med. Chem.*, 2019, **62**, 7431.

10 H. Lim, S. Y. Lee, K. R. Lee, Y. S. Kim and H. P. Kim, *Biomol. Ther.*, 2012, **20**, 477.

11 (*a*) S. Sanivarapu, N. Vaddiraju and L. Velide, *Med. Chem. Res.*, 2019, **28**, 1461; (*b*) S. S. Undare, N. J. Valekar, A. A. Patravale, D. K. Jamale, S. S. Vibhute, L. S. Walekar, G. B. Kolekar, M. B. Deshmukh and P. V. Anbhule, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 814.

12 (*a*) N. Akhter, C. Pan, Y. Liu, Y. Shi and B. Wu, *Nat. Prod. Res.*, 2019, **33**, 2939; (*b*) N. Sudhapriya, P. T. Perumal, C. Balachandran, S. Ignacimuthu, M. Sangeetha and M. Doble, *Eur. J. Med. Chem.*, 2014, **83**, 190.