Green Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2019, **21**, 5803

Received 20th August 2019,
Accepted 30th September 2019

DOI: 10.1039/c9gc02937k

rsc.li/greenchem

Rapid access to cinnamamides and piper amides *via* three component coupling of arylaldehydes, amines, and Meldrum's acid†

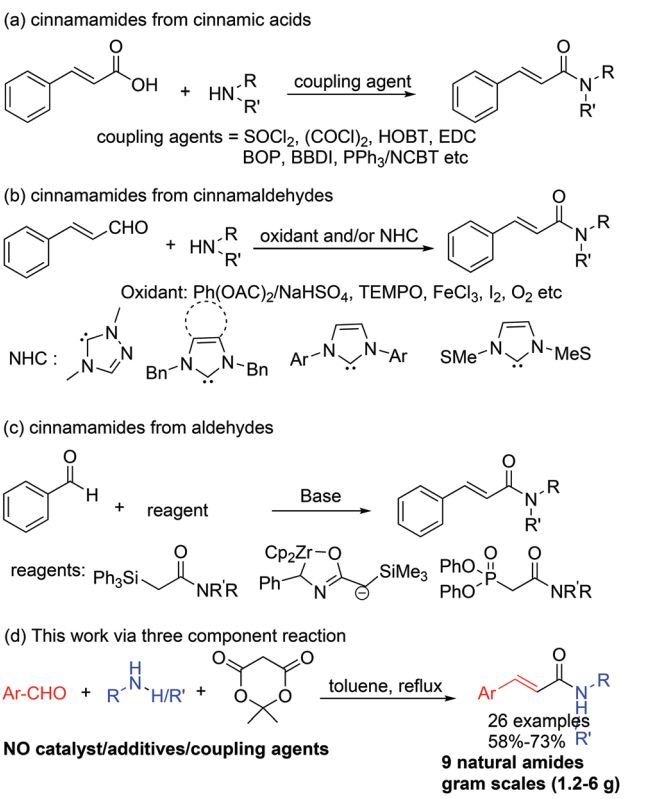
Santanu Ghosh and Chandan K. Jana *

A practical method for the synthesis of cinnamamides and piper amides *via* a conceptually novel three component reaction of aldehydes, amines and Meldrum's acid has been reported. The reaction proceeds under operationally simple conditions without the aid of coupling reagents, oxidants, or catalysts, which are essential for the preparation of cinnamamides/piper amides *via* known methods. The formation of undesired chemical wastes that generally originate from the use of coupling reagents, oxidants, or catalysts has been avoided to make this reaction more atom economical.

Cinnamamides are an important class of compounds having a wide spectrum of bioactivities, such as anticancer,[1] anti-malarial,[2] anti-trypanosomal,[3] anti-oxidant,[4] anti-diabetic,[5] anti-microbial activities,[6] *etc*.[7] In addition, cinnamamides are found to be the key structural unit of many natural products including piper amides.[8] A large number of cinnamamides with wide structural diversity have been synthesized to investigate the structure–activity relationship in the field of medicinal chemistry.[7] The syntheses of cinnamamides and piper amides mainly rely on the coupling reaction of cinnamic acid derivatives which are prepared from the Knoevenagel condensation of aromatic aldehydes and malonic acid (Scheme 1a).[9] Oxidative amidation of cinnamaldehydes is another approach for the synthesis of cinnamamides (Scheme 1b).[10] Wittig or Horner–Wadsworth–Emmons reactions were also used for the synthesis of cinnamamides starting from aromatic aldehydes (Scheme 1c).[11] However, most of the methods rely on multistep processes and involve the formation of unwanted by-products originating from coupling agents, oxidants, phosphine-based reagents, *etc*. Therefore, the development of an operationally simple method without using additional catalysts, reagents, or additives that produce hazardous chemical wastes is desirable.

Herein, we report a one-step process for the preparation of cinnamamides and piper amides *via* an unprecedented three component reaction without the aid of any additional catalysts, reagents or additives (Scheme 1d).

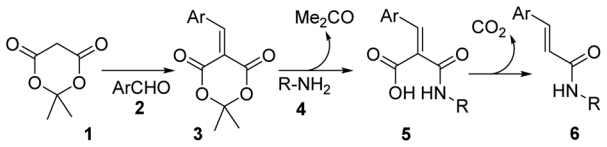
We anticipated that the Knoevenagel condensation of Meldrum's acid (**1**) with aldehyde **2** would provide enone **3** (Scheme 2).[12] The enone can react with amine **4** to produce the corresponding amide **5** which can undergo decarboxylation to give the desired cinnamamide **6**.



Scheme 1 Strategies for the synthesis of cinnamamides.

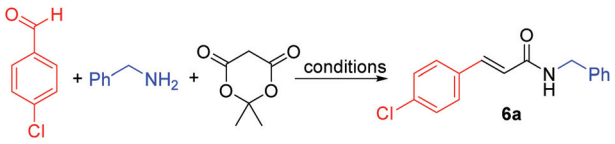
Department of Chemistry, Indian Institute of Technology Guwahati, 781039, India. E-mail: ckjana@iitg.ac.in

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c9gc02937k



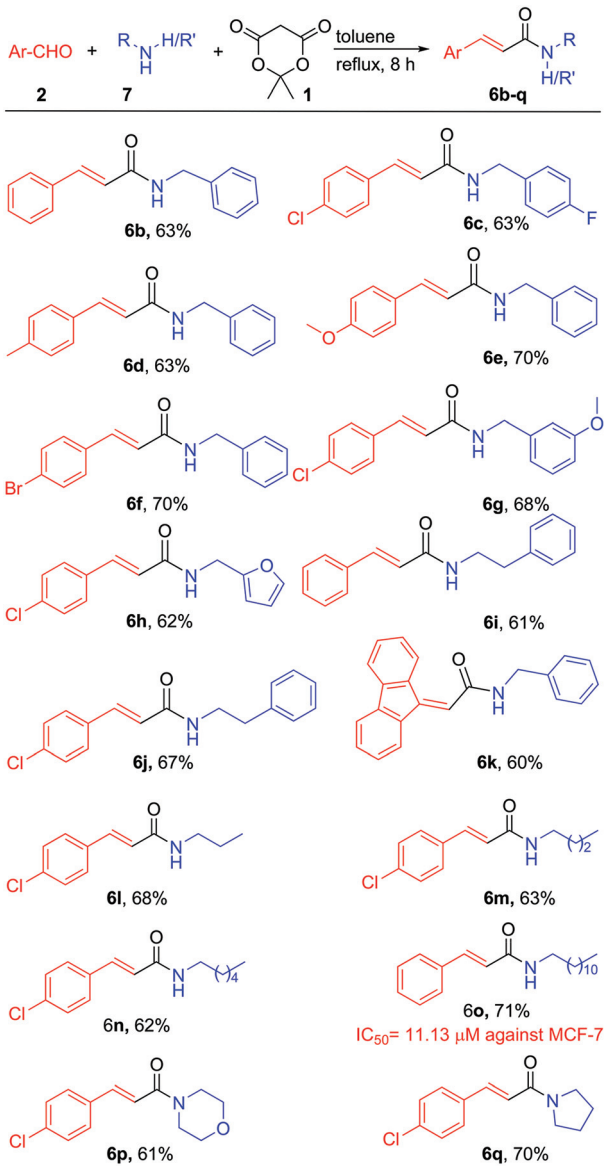
Scheme 2 Hypothesis for the one-step synthesis of cinnamamides.

Table 1 Optimization of reaction conditions[a]



Entry	Conditions	Yield[b] (%)
1	Toluene, rt, 12 h	0
2	Toluene, reflux, 12 h	67
3	Toluene, reflux, 24 h	64
4	**Toluene, 110 °C, 8 h**	**68**
5	Toluene, 110 °C, 2 h	56
6	DMF, 140 °C, 5 h	25
7	DCM, 40 °C, 5 h	5
8	*m*-Xylene, 140 °C, 5 h	66
9	Toluene, MW, 120 °C, 30 min	50
10	Methanol, 80 °C, 5 h	10
11	Neat, 120 °C, 12 h	60
12[c]	Toluene, 110 °C, 5 h	69
13[d]	Toluene, 110 °C, 5 h	67

[a] All reactions were carried out with 4-chlorobenzaldehyde (1.42 mmol), benzylamine (1 eq., 1.42 mmol), and Meldrum's acid (**1**) (1 eq., 1.42 mmol) in 3 mL of solvent. [b] Isolated yield. [c] Reaction was performed by using 1.2 eq. of benzylamine. [d] Reaction was performed by using 1.2 eq. of Meldrum's acid (**1**).

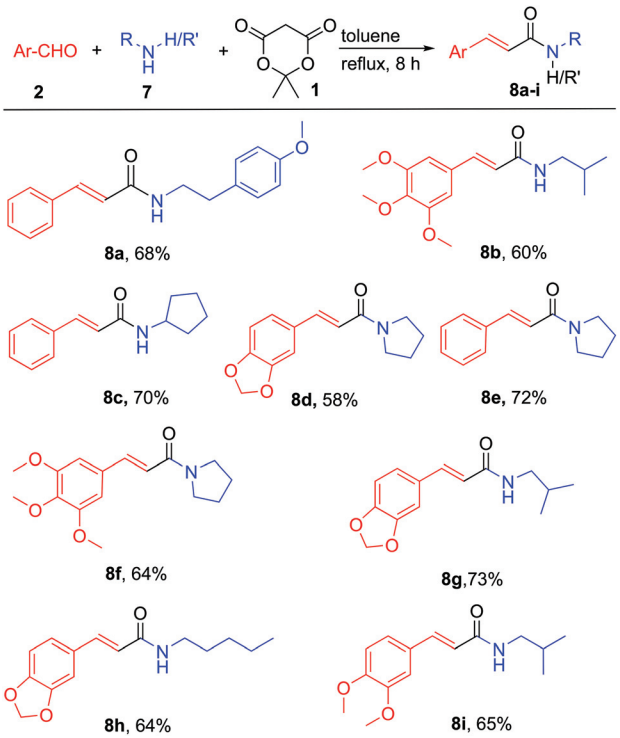


Scheme 3 Scope of the synthesis of cinnamamides.

According to our hypothesis, the investigation started with a reaction of benzylamine and 4-chlorobenzaldehyde in the presence of Meldrum's acid (**1**) at room temperature (Table 1, entry 1). However, the desired cinnamamide **6a** was not formed. Pleasingly, the desired cinnamamide **6a** was isolated with a 67% yield from the reaction which was carried out in refluxing toluene for 12 h (Table 1, entry 2). Different reaction conditions, such as solvents, temperatures, reactant stoichiometry, *etc*., were evaluated to maximize the yield of the desired product **6a** (Table 1). The best yield of **6a** (68%, Table 1, entry 4) was obtained from the reaction of a mixture of Meldrum's acid (**1**), 4-chlorobenzaldehyde and benzylamine in refluxing toluene without any other catalysts, reagents or additives.

Next, the optimized conditions were used to test the substrate scope of this three component reaction. A wide variety of aromatic aldehydes **2** and amines **7** were reacted with Meldrum's acid to obtain the corresponding cinnamamides **6b–q** with very good yields (Scheme 3). Substrates (aldehydes and amines) having both electron-donating (*e.g.* Me, OMe) and electron-withdrawing (*e.g.* F, Cl) groups were efficiently reacted to obtain the desired cinnamamides. Unsaturated amides **6h** containing heteroaromatic groups were also prepared in very good yields using this reaction. 9-Fluorenone also reacted with benzylamine and Meldrum's acid under the optimized reaction conditions to form the desired amide **6k** with a 60% yield. Acyclic primary and secondary amines reacted smoothly to produce the desired cinnamamides. Importantly, a potent molecule, *N*-dodecylcinnamamide **6o**, which was synthesized in two steps starting from cinnamic acid involving hazardous reagents like $SOCl_2$,[13] was prepared in a single step using our method. Aliphatic N-heterocycles and diheterocycles also participated in the reaction.

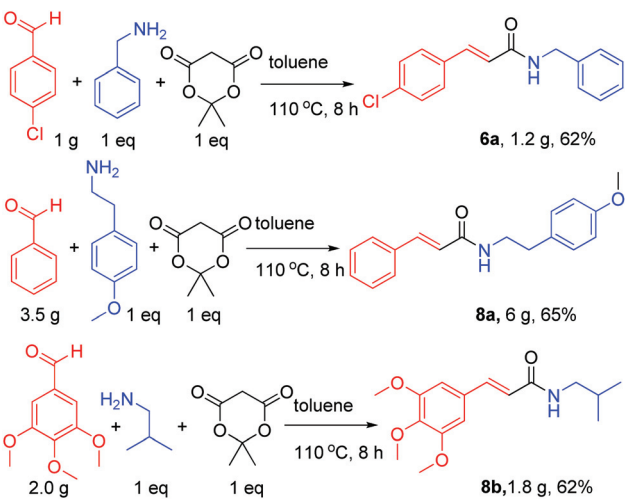
A large number of bioactive cinnamamides have been isolated from Piper species.[8] We were interested in applying our methods for the synthesis of natural cinnamamides (piper amides). Accordingly, the optimized reaction conditions were used to prepare structurally diverse piper amides **8a–i** with good to very good yields (Scheme 4).



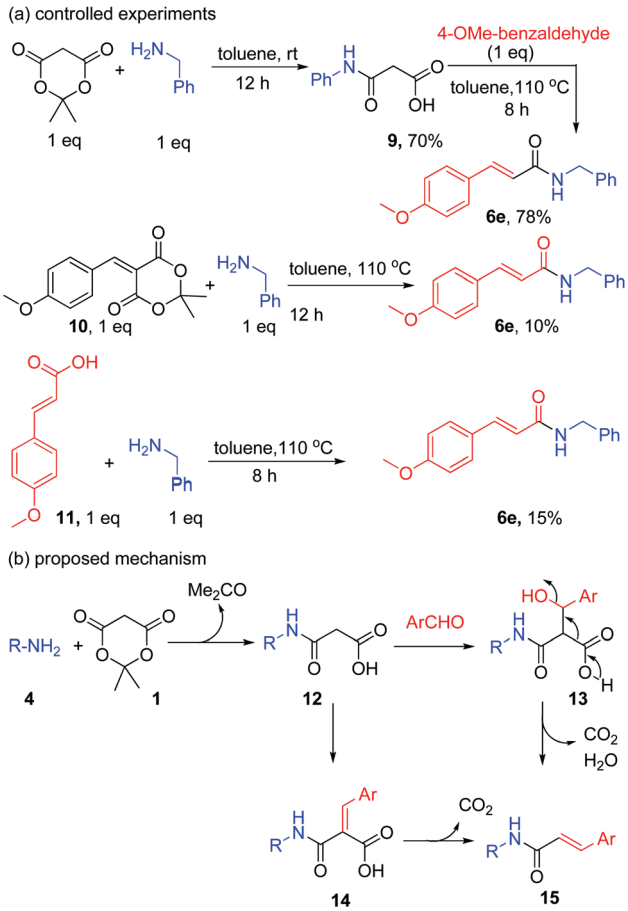
Scheme 4 Scope of the synthesis of piper amides.

The yield of this one-step reaction was observed to be higher than or comparable to those of the known methods. However, our method is superior to all the known methods in the context of atom economy, step economy and the reduction of undesired chemical waste (see Table S1 in the ESI†).

The reaction was found to be effective in gram-scale synthesis, which indicated its potential for practical application (Scheme 5). Natural cinnamamides **8a** and **8b** were synthesized in 1.8–6.0 grams using this methodology.



Scheme 5 Preparative scale synthesis of selected unnatural and natural cinnamamides.



Scheme 6 (a) Controlled experiments and (b) the proposed mechanism of the three component reaction.

Additional reactions were performed to understand the reaction mechanism of this three component coupling reaction (Scheme 6a). The reaction of benzylamine with Meldrum's acid (**1**) at room temperature gave monoamides of malonic acid **9** with good yields (70%). The desired cinnamamide **6e** was formed with a very good yield (78%) when acid **9** was reacted with 4-methoxybenzaldehyde under the standard conditions. This observation indicates that the reaction proceeds *via* the malonic acid derivative **9**. However, the reaction of benzylidene derivative **10** with benzylamine under the standard reaction conditions provided the desired product **6e** with a 10% yield. In addition, direct condensation of 4-OMe-cinnamic acid **11**, which can be formed *in situ*,[14] and benzylamine gave the corresponding cinnamamide **6e** with a poor yield (15%). These studies indicate that the reactions *via* benzylidene derivative **10** and cinnamic acid derivative **11** provide a minor contribution to the total yield of cinnamamides.

Based on the experimental evidence, a plausible mechanism for the three component coupling reaction is shown in Scheme 6b. The reaction of amine **4** with Meldrum's acid **1** provided monoamides of malonic acid **12** and acetone. The observed cinnamamide **15** can be formed *via* two possible pathways. The aldol reaction of **12** and an aromatic aldehyde

can provide beta-hydroxy acid **13**. In the second possibility, the Knoevenagel condensation of **12** and an aldehyde could occur to provide benzylidene derivative **14** *via* the corresponding alcohol **13**. Decarboxylation of **14** and/or decarboxylation assisted dehydration of alcohol **13** gave the thermodynamically more stable *trans*-cinnamamides **15**.

Conclusions

We have developed an original three component reaction of aldehydes, amines and Meldrum's acid to obtain a wide variety of cinnamamides and piper amides with very good yields which are superior to those obtained using most of the known methods. The reaction enables the synthesis of cinnamamides without using coupling reagents, oxidants or catalysts that produce undesired chemical wastes. The reaction is highly atom economical producing CO_2 and acetone as the by-products. We believe that this method will find wide applications for the rapid synthesis of a library of medicinally important cinnamamides/piper amides to facilitate the identification of the most potent molecule.

Conflicts of interest

A patent application has been filed on the synthesis of cinnamamides and piper amides.

Notes and references

1 (*a*) P. De, M. Baltas and F. Bedos-Belval, *Curr. Med. Chem.*, 2011, **18**, 1672; (*b*) R. S. Dothager, K. S. Putt, B. J. Allen, B. J. Leslie, V. Nesterenko and P. J. Hergenrother, *J. Am. Chem. Soc.*, 2005, **127**, 8686; (*c*) R. Romagnoli, P. G. Baraldi, M. K. Salvador, M. Chayah, M. E. Camacho, F. Prencipe, E. Hamel, F. Consolaro, G. Basso and G. Viola, *Eur. J. Med. Chem.*, 2014, **81**, 394.

2 B. C. Perez, C. Teixeira, I. S. Albuquerque, J. Gut, P. J. Rosenthal, J. R. B. Gomes, M. Prudencio and P. Gomes, *J. Med. Chem.*, 2013, **56**, 556.

3 F. Maiwald, D. Benítez, D. Charquero, M. A. Dar, H. Erdmann, L. Preu, O. Koch, C. Holscher, N. Loaec, L. Meijer, M. A. Comini and C. Kunick, *Eur. J. Med. Chem.*, 2014, **83**, 274.

4 M. Sova, *Med. Chem.*, 2012, **12**, 749.

5 P. Phuwapraisirisan, T. Puksasook, J. Jong-aramruang and U. Kokpol, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4956.

6 (*a*) B. Narasimhan, D. Belsare, D. Pharande, V. Mourya and A. Dhake, *Eur. J. Med. Chem.*, 2004, **39**, 827; (*b*) S. Michalet, G. Cartier, B. David, A.-M. Mariotte, M.-G. Dijoux-franca, G. W. Kaatz, M. Stavri and S. Gibbons, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1755.

7 (*a*) A. Gunia-Krzyzak, K. Panczyk, A. M. Waszkielewicz and H. Marona, *ChemMedChem*, 2015, **10**, 1302; (*b*) N. Gaikwad, S. Nanduri and Y. V. Madhavi, *Eur. J. Med. Chem.*, 2019, **181**, 111561.

8 E. Yankep, Z. T. Fomum and E. Dagne, *Phytochemisrry*, 1997, **46**, 591.

9 (*a*) Z.-H. Shi, N.-G. Li, Q.-P. Shi, H. Tang, Y.-P. Tang, W. Li, L. Yin, J.-P. Yang and J.-A. Duan, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1206; (*b*) T. Maki, K. Ishiharaa and H. Yamamoto, *Tetrahedron*, 2007, **63**, 8645; (*c*) Y. Saito, H. Ouchi and H. Takahata, *Tetrahedron*, 2008, **64**, 11129; (*d*) F. D. King and S. Caddick, *Tetrahedron*, 2013, **69**, 487; (*e*) G. Luo, L. Xu and G. S. Poindexter, *Tetrahedron Lett.*, 2002, **43**, 8909; (*f*) Z. Ruan, R. Michael Lawrence and C. B. Cooper, *Tetrahedron Lett.*, 2006, **47**, 7649; (*g*) S. M. Potadar, A. S. Mali, K. T. Waghmode and G. U. Chaturbhuj, *Tetrahedron Lett.*, 2018, **59**, 4582; (*h*) N. Li, L. Wang, L. Zhang, W. Zhao, J. Qiao, X. Xu and Z. Liang, *ChemCatChem*, 2018, **10**, 3532; (*i*) C. L. Allen, A. R. Chhatwal and J. M. J. Williams, *Chem. Commun.*, 2012, **48**, 666; (*j*) L. Gu, J. Lim, J. L. Cheong and S. S. Lee, *Chem. Commun.*, 2014, **50**, 7017; (*k*) E. Calcio Gaudino, D. Carnaroglio, M. A. G. Nunes, L. Schmidt, E. M. M. Flores, C. Deiana, Y. Sakhno, G. Martrac and G. Cravotto, *Catal. Sci. Technol.*, 2014, **4**, 1395; (*l*) X. Chen, B. Gao, Y. Su and H. Huanga, *Adv. Synth. Catal.*, 2017, **359**, 2535; (*m*) V. C. Agwada, *J. Chem. Eng. Data*, 1982, **27**, 479; (*n*) A. D. Kosal, E. E. Wilson and B. L. Ashfeld, *Angew. Chem., Int. Ed.*, 2012, **51**, 12036; (*o*) A. Ojeda-Porras, A. Hernandez-Santana and D. Gamba-Sanchez, *Green Chem.*, 2015, **17**, 3157; (*p*) T. Maki, K. Ishihara and H. Yamamoto, *Org. Lett.*, 2005, **7**, 5043; (*q*) N. D. Kokare, R. R. Nagawade, V. P. Rane and D. B. Shinde, *Synthesis*, 2007, 0766.

10 (*a*) S. S. Kulkarni, X. Hu and R. Manetsch, *Chem. Commun.*, 2013, **49**, 1193; (*b*) S. E. Kim, H. Hahm, S. Kim, W. Jang, B. Jeon, Y. Kim and M. Kim, *Asian J. Org. Chem.*, 2016, **5**, 222; (*c*) V. Prasad, R. R. Kale, B. B. Mishra, D. Kumar and V. K. Tiwari, *Org. Lett.*, 2012, **14**, 2936; (*d*) R. E. Rodriguez-Lugo, M. Trincado and H. Grutzmacher, *ChemCatChem*, 2013, **5**, 1079; (*e*) H. Yao, Y. Tang and K. Yamamoto, *Tetrahedron Lett.*, 2012, **53**, 5094; (*f*) B. Zhang, P. Feng, Y. Cuia and N. Jiao, *Chem. Commun.*, 2012, **48**, 7280; (*g*) M. Ji, S. Lima and H.-Y. Jang, *RSC Adv.*, 2014, **4**, 28225; (*h*) S. De Sarkar and A. Studer, *Org. Lett.*, 2010, **12**, 992; (*i*) N. Hazarika, G. Baishya and P. Phukan, *Synthesis*, 2015, **47**, 2851; (*j*) G. Singh, R. Dada and S. Yaragorla, *Tetrahedron Lett.*, 2016, **57**, 4424; (*k*) T. K. Achara and P. Mal, *Adv. Synth. Catal.*, 2015, **357**, 3977; (*l*) Y.-J. Wu, H. He, L.-Q. Sun, A. L'Heureux, J. Chen, P. Dextraze, J. E. Starrett Jr., C. G. Boissard, V. K. Gribkoff, J. Natale and S. I. Dworetzky, *J. Med. Chem.*, 2004, **47**, 2887.

11 (*a*) S. Kim, C. Lim, S. Lee, S. Lee, H. Cho, J.-Y. Lee, D. S. Shim, H. D. Park and S. Kim, *ACS Comb. Sci.*, 2013, **15**, 208; (*b*) V. Gandon, P. Bertus and J. Szymoniak, *Tetrahedron*, 2000, **56**, 4467; (*c*) E. Hernandez-Fernandez, M. Fernandez-Zertuche, O. Garcia-Barradas, O. Munoz-Muniz and M. Ordonez, *Synlett*, 2006, 440; (*d*) S. Ullah, D. Kang, S. Lee, M. Ikram, C. Park, Y. Park, S. Yoon, P. Chun and H. R. Moon, *Eur. J. Med. Chem.*, 2019, **161**, 78.

12 A. R. Mohite and R. G. Bhat, *Org. Lett.*, 2013, **15**, 4564.
13 M. Zhang, X. Lu, H.-J. Zhang, N. Li, Y. Xiao, H.-L. Zhu and Y.-H. Ye, *Med. Chem. Res.*, 2013, **22**, 986.
14 (*a*) S. Fiorito, V. A. Taddeo, S. Genovese and F. Epifano, *Tetrahedron Lett.*, 2016, **57**, 4795; (*b*) R. Maggi, F. Bigi, S. Carloni, A. Mazzacani and G. Sartori, *Green Chem.*, 2001, **3**, 173.