



Cite this: *RSC Adv.*, 2019, 9, 26768

Received 17th June 2019
Accepted 17th August 2019

DOI: 10.1039/c9ra04540f

rsc.li/rsc-advances

One-step construction of unsymmetrical thioureas and oxazolidinethiones from amines and carbon disulfide *via* a cascade reaction sequence†

Chaochao Ding, Shaoli Wang, Yaoguang Sheng, Qian Dai, Yunjie Zhao,* Guang Liang* and Zengqiang Song *

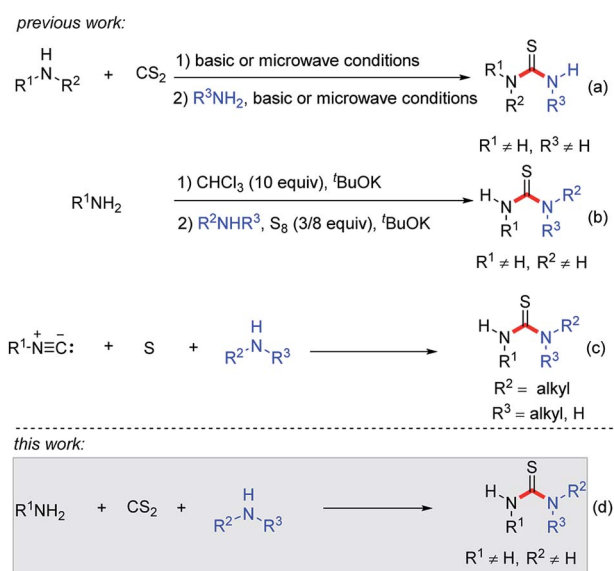
A concise and versatile method for the construction of unsymmetrical thioureas and oxazolidinethiones from amines and carbon disulfide has been achieved in DMSO without addition of extra reagents. The present protocol is compatible with various secondary amines and primary amines, and suitable for intermolecular and intramolecular reactions. Diverse unsymmetrical thioureas and oxazolidinethiones were efficiently obtained in good to excellent yields *via* a cascade reaction sequence.

Introduction

Thioureas have attracted significant interest in medicinal chemistry due to their broad spectrum of biological activities. Their derivatives and metal complexes have been demonstrated to have antimicrobial, analgesic, anticancer and anti-inflammatory activities.¹ Some of them have been developed as drugs, such as hyperthyroidism drugs,^{1c} sedative hypnotics drugs,^{1d} to treat diseases in clinics. Thioureas are also important in pesticide chemistry, a variety of thiourea derivatives have been used as insecticides, herbicides, rodenticides and fungicides.² In synthetic chemistry, thioureas are useful blocking buildings for the construction of many valuable compounds, such as guanidines, amides and sulfur-containing heterocycles.³ Additionally, they also play an important role in organocatalysis as auxiliaries or catalysts.⁴

On account of the usefulness of thioureas in different fields, methods for synthesizing this type of compounds have been widely explored.^{5–8} Generally, three synthetic strategies are commonly used for the preparation of substituted thioureas. One way is transforming carbonyl to thiocarbonyl employing Lawesson reagents or P₂S₅.⁶ The second way is condensation or substitution of amines with prepared isothiocyanate, 1-(methyldithiocarbonyl)imidazole, thiocarbamoylbenzotriazoles, or derivatives thereof.⁷ Based on these two synthetic strategies, many methods were developed for the synthesis of symmetrical and unsymmetrical thioureas. However, these protocols require extra synthetic steps for the preparation of starting materials, leading to low synthetic efficiency and a poor substrate scope.

The third alternative way is the direct reaction of amines and carbon disulfide.⁸ In this transformation, starting materials are easy to be gained and no extra synthetic steps are required. Therefore, it is considered as a straightforward route for the preparation of substituted thioureas. In this regard, several methods have been developed on the basis of this strategy for the preparation of symmetrical and unsymmetrical thioureas. Nevertheless, the reported methods for the synthesis of unsymmetrical thioureas contain two steps, two kinds of amines need to be separately added to the reaction system under basic or microwave conditions (Scheme 1a).^{8e,8f} In 2017, the Jiang's group reported a novel method for the preparation of unsymmetrical thioureas with amines, sulfur and chloroform in



Scheme 1 Straightforward methods for the synthesis of unsymmetric thioureas.

Chemical Biology Research Center at School of Pharmaceutical Sciences, Wenzhou Medical University, Wenzhou, Zhejiang 325035, China. E-mail: songzengqiang09@163.com; Fax: +86-577-86699396; Tel: +86-577-86699396

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9ra04540f



the presence of potassium *tert*-butoxide in mixture solvents (Scheme 1b).⁹ This transformation also contains two steps. A one-step reaction for the synthesis of unsymmetrical thioureas was achieved by Nguyen's group with isocyanides, amines and elemental sulfur (Scheme 1c).¹⁰ However, this protocol is only suitable for aliphatic amines. Obviously, the development of convenient and versatile methods for one-step construction of unsymmetrical thioureas is in high demand.

Cascade reactions,¹¹ which involve multistep transformations in a one-pot fashion, are attractive in modern synthetic chemistry due to their simplicity and atom-economy. In continuation of our study on the development of efficient routes for the preparation or modification of heteroatom-containing compounds,¹² we are of great interest in the exploration of new routes for the preparation of unsymmetrical thioureas. Herein, we wish to disclose a novel protocol for the synthesis of unsymmetrical thioureas *via* a cascade reaction sequence (Scheme 1c).

Results and discussion

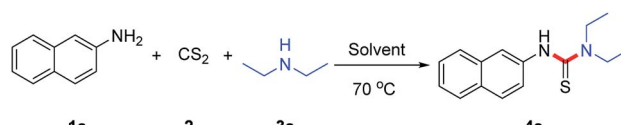
Methods for the preparation of unsymmetrical thioureas using naphthylamines as substrates are rare.^{1f,7g,9} Our exploration started with using 2-naphthylamine (**1a**), carbon disulfide (**2**) and diethylamine (**3a**) as model substrates, all substrates were added into the reaction system in one step. Initially, the reaction was performed in DCE at 70 °C. Unfortunately, only a trace amount of the desired product was observed after 12 h (Table 1, entry 1). Changing DCE to toluene, the desired product was obtained in 58% isolated yield (entry 2).

Encouraged by this result, the reaction was examined with different solvents to improve the yield of **4a**. It was found that

DMSO was the best solvent for this transformation compared to THF, MeOH, MeCN, HFIP and chlorobenzene (entries 3–9); the reaction provided the expected product in 89% yield in 1.5 h (entry 5). This is probably because the solvent increased the basicity of the amines. Dropping the temperature to 40 °C, the reaction time was prolonged and the yield of the product was lowered (entry 10). To our delight, the product was obtained in 95% yield when the amounts of carbon disulfide and diethylamine were changed to 1.2 equiv. (entry 12). Therefore, the optimal conditions for the synthesis of unsymmetrical thioureas *via* a cascade reaction sequence were gained: carbon disulfide (1.2 equiv.), diethylamine (1.2 equiv.), in DMSO (2 mL) at 70 °C for 1 h (entry 12). Moreover, a 10 mmol scale reaction was carried out under optimal reaction conditions, affording the desired product in 89% yield (entry 14). This result demonstrated the easy scalability of this transformation.

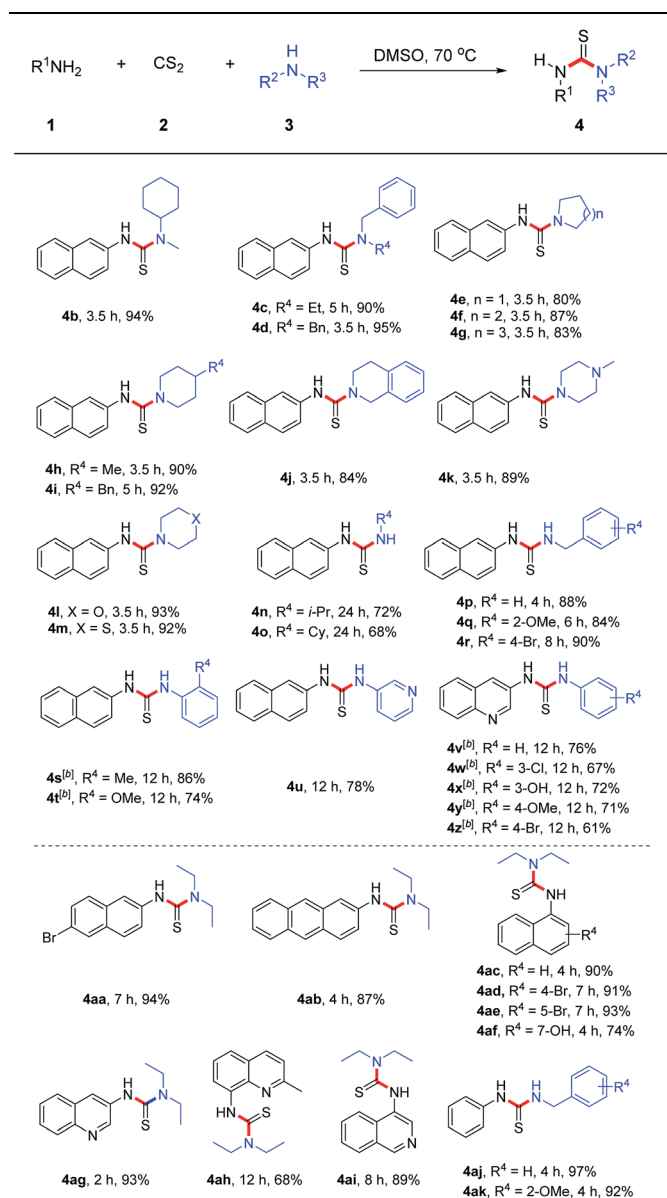
Having identified the optimal parameters of the model reaction, the substrate scope and generality of this transformation were evaluated. First of all, various secondary amines were tested with 2-naphthylamine under standard reaction conditions (Table 2, **4b–4m**). Application of *N*-methylcyclohexylamine was successful, providing the desired product in 94% yield (**4b**). Changing dialkylamines to *N*-benzylethanamine or dibenzylamine, the corresponding products were afforded with 90% and 95% yields, respectively (**4c**, **4d**). Reactions of 2-naphthylamine with cyclic amines containing different ring numbers, substituents or heteroatoms proceeded well, giving the related products in good to excellent yields (**4e–4m**). Subsequently, we turned our attention to explore the reaction of 2-naphthylamines with primary amines under the optimal conditions. To our delight, non-cyclic and cyclic alkylamines were suitable for this transformation, the desired products were obtained in good yields in 24 h (**4n**, **4o**). This protocol was also applicable for benzylamines. Reactions of benzylamines with various substituents at different positions of benzene ring worked well, affording the desired products in good to excellent yields (**4p–4r**). Aniline and its derivatives were also examined in this transformation. Gratifyingly, when methyl or methoxyanilines were used as substrates, the expected products were obtained in good yields in 12 h (**4s**, **4t**). However, reactions of aniline or anilines with electron-withdrawing substituents provided not only unsymmetrical thioureas but also symmetrical thioureas from the reactions of anilines with carbon disulfide, and the formed two products were inseparable due to their similar polarity. This is probably because of weak nucleophilicity of these anilines. Application of 3-aminopyridine in this transformation was successful, the desired product was obtained in 78% yield in 12 h (**4u**). Intriguingly, this protocol was also suitable for the reactions of 3-aminoquinoline and anilines, the desired products were gained in good yields (**4v–4z**).¹³ Symmetrical thioureas were obtained from the reactions of anilines with weak nucleophilicity, which were consistent with the results of the reactions of 2-naphthylamine and anilines. This transformation allows the preparation of unsymmetrical thioureas using diverse naphthylamines, aminoquinolines and aminoisoquinolines (**4aa–4ai**). Moreover, the reactions of anilines with benzyl amines were successful, the

Table 1 Optimization of the reaction conditions^a



Entry	Solvent	Time (h)	Yield ^b (%)
1	DCE	12	Trace
2	Toluene	12	58
3	THF	12	72
4	MeOH	12	78
5	DMSO	1.5	89
6	MeCN	12	81
7	DMF	4	85
8	HFIP	12	Trace
9	Chlorobenzene	12	69
10 ^c	DMSO	12	62
12 ^d	DMSO	1	95
14 ^e	DMSO	12	89

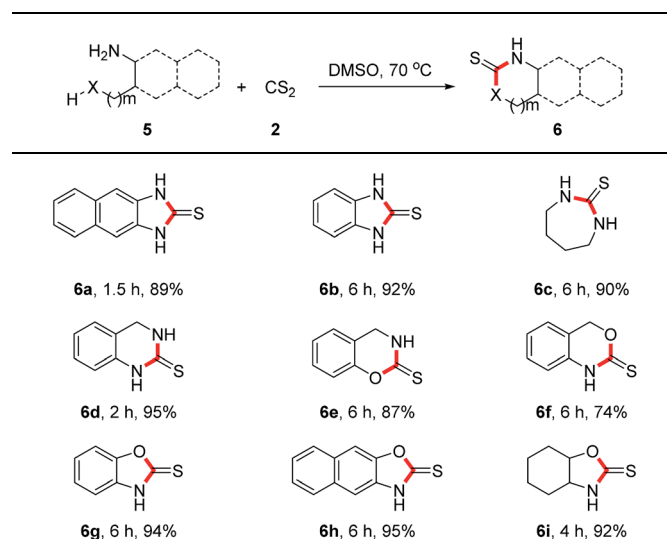
^a Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), **3a** (0.4 mmol) in solvent (2 mL) at 70 °C. ^b Yield refers to isolated products after column chromatography. ^c Reaction was performed at 40 °C. ^d 1.2 equiv. of **2** and **3a** were used. ^e 10 mmol of **1a** were used. HFIP = hexafluoroisopropanol.

Table 2 Exploration of substrate scope of amines^a

^a Reaction conditions: 1 (0.2 mmol), 2 (0.24 mmol), 3 (0.24 mmol) in DMSO (2 mL) at 70 °C. ^b 0.24 mmol of 1 were used, 0.2 mmol of 3 were used.

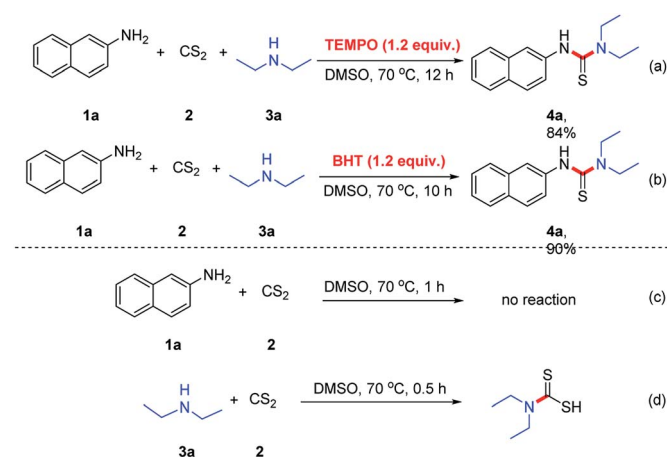
corresponding products were obtained in excellent yields (4aj, 4ak).

After successful application of this novel transformation for the preparation of unsymmetrical thioureas by intermolecular reactions of different amines with carbon disulfide, we wondered if this protocol is suitable for the intramolecular reactions.^{7c,8c,8d,8g,9} Reactions of naphthylamine, aniline, alkylamine and benzylamine were tested under standard reaction conditions, all of them gave the desired products in excellent yields (Table 3, 6a–6d). To our delight, this approach was also applicable for the construction of oxazolidinethiones (6e–6i), which are great of importance in organic chemistry and medicinal chemistry.^{9,14}

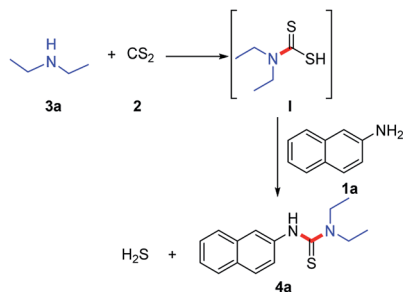
Table 3 Exploration of intramolecular reactions^a

^a Reaction conditions: 5 (0.2 mmol), 2 (0.24 mmol) in DMSO (2 mL) at 70 °C.

We also investigated the mechanism of this protocol. Radical trapping experiments were examined in the presence of 1.2 equiv. of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (butylhydroxytoluene) under the standard reaction conditions (Scheme 2(a) and (b)). Almost no inhibition of the generation of the desired product 4a was observed. These results indicated that this process did not involve radicals. In order to understand the sequence of this three components reaction, the reaction of 2-naphthylamine and carbon disulfide was carried out under the standard reaction conditions. After 1 h, almost no reactions occurred (Scheme 2(c)). A new spot was observed from the reaction of diethylamine and carbon disulfide under the standard reaction conditions, it was confirmed as diethylcarbamide dithioic acid (Scheme 2(d)).^{8d-f} Subsequently, adding 2-naphthylamine to the reaction system, the desired product was obtained in 95% yield. These experiments suggested that this transformation was initiated by the reaction of diethylamine and carbon disulfide.



Scheme 2 Mechanistic investigation.



Scheme 3 Proposed mechanism.

On the basis of relevant reports in literatures^{8d-f} and our experimental results, a tentative mechanism for this transformation was proposed by taking 2-naphthylamine **1a** and diethylamine **3a** as examples (Scheme 3).¹⁵ Initially, intermediate **I** is formed by nucleophilic attack of diethylamine **3a** to carbon disulfide. Subsequently, 2-naphthylamine **1a** attacks the intermediate **I**, affording the desired products **4a** with concomitant release of H₂S.

Conclusions

In conclusion, we have developed an efficient and versatile protocol for the preparation of thioureas and oxazolidinethiones from amines and carbon disulfide *via* a cascade reaction sequence. This approach features mild reaction conditions, good compatibility with different amines as well as broad substrate scopes. Further investigations on biological activity of the synthesized thioureas and oxazolidinethiones are ongoing in our laboratory.

Experimental

A mixture of amine **1** (0.2 mmol), carbon disulfide **2** (0.24 mmol), amine **3** (0.24 mmol) or amine **5** (0.2 mmol), carbon disulfide **2** (0.24 mmol) in DMSO (2 mL) was added in a 5 mL glass tube, which was stirred at 70 °C for 1–12 h. When the reaction was completed, it was mixed with water and ethyl acetate. The reaction mixture was extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was evaporated under vacuum and the residue was purified by flash column chromatography on silica gel (eluting with petroleum ether-ethyl acetate) to provide the desired products **4** or **6**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This study was supported by the National Key Research Project (2017YFA0506000), National Natural Science Foundation of China (21807080, 21572166), Natural Science Foundation of Zhejiang Province (LQ18B020004).

Notes and references

- (a) M. Weiss, R. Buhl, M. Medve and E. M. Schneider, *Crit. Care Med.*, 1997, **25**, 128; (b) J. Lee, J. Lee, M. Kang, M. Shin, J. M. Kim, S. U. Kang, J. O. Lim, H. K. Choi, Y. G. Suh, H. G. Park, U. Oh, H. D. Kim, Y. H. Park, H. J. Ha, Y. H. Kim, A. Toth, Y. Wang, R. Tran, L. V. Pearce, D. J. Lundberg and P. M. Blumberg, *J. Med. Chem.*, 2003, **46**, 3116; (c) E. Rodríguez-Fernández, J. L. Manzano, J. J. Benito, R. Hermosa, E. Monte and J. J. Criado, *J. Inorg. Biochem.*, 2005, **99**, 1558; (d) O. J. D'Cruz and F. M. Uckun, *Curr. HIV Res.*, 2006, **4**, 329; (e) I. V. Daele, H. Munier-Lehmann, M. Froeyen, J. Balzarini and S. V. Calenbergh, *J. Med. Chem.*, 2007, **50**, 5281; (f) M. I. C. Begum and K. M. Khan, *Nat. Prod. Res.*, 2009, **23**, 1719; (g) Y. Touati-Jallabe, E. Bojnik, B. Legrand, E. Mauchauffée, N. N. Chung, P. W. Schiller, S. Benyhe, M. C. Averlant-Petit, J. Martinez and J. F. Hernandez, *J. Med. Chem.*, 2013, **56**, 5964; (h) L. Y. Ma, Y. C. Zheng, S. Q. Wang, B. Wang, Z. R. Wang, L. P. Pang, M. Zhang, J. W. Wang, L. Ding, J. Li, C. Wang, B. Hu, Y. Liu, X. D. Zhang, J. J. Wang, Z. J. Wang, W. Zhao and H. M. Liu, *J. Med. Chem.*, 2015, **58**, 1705.
- (a) N. G. Gratz, *Bull. W. H. O.*, 1973, **48**, 469; (b) G. Y. Sarkis and E. D. Faisal, *J. Heterocycl. Chem.*, 1985, **22**, 137; (c) C. Walpole, S. Y. Ko, M. Brown, D. Beattie, E. Campbell, F. Dickenson, S. Ewan, G. A. Hughes, M. Lemaira, J. Lerpiniere, S. Patel and L. Urban, *J. Med. Chem.*, 1998, **41**, 3159; (d) H. Kayser and P. Eilinger, *Pest Manage. Sci.*, 2001, **57**, 975; (e) B. L. Wang, H. W. Zhu, Y. Ma, L. X. Xiong, Y. Q. Li, Y. Zhao, J. F. Zhang, Y. W. Chen, S. Zhou and Z. M. Li, *J. Agric. Food Chem.*, 2013, **61**, 5483.
- (a) D. G. Patil and M. R. Chedekel, *J. Org. Chem.*, 1984, **49**, 997; (b) P. C. Kearney, M. Fernandez and J. A. Flygare, *J. Org. Chem.*, 1998, **63**, 196; (c) M. Kidwai, R. Venkataramanan and B. Dave, *Green Chem.*, 2001, **3**, 278; (d) D. Anshu, A. Kapil and S. Meha, *Synth. Commun.*, 2004, **34**, 1141; (e) R. Yella, H. Ghosh and B. K. Patel, *Green Chem.*, 2008, **10**, 1307; (f) I. Cano, E. Gómez-Bengoia, A. Landa, M. Maestro, A. Mielgo, I. Olaizola, M. Oiarbide and C. Palomo, *Angew. Chem., Int. Ed.*, 2012, **51**, 10856; (g) J. Zhao, H. Huang, W. Wu, H. Chen and H. Jiang, *Org. Lett.*, 2013, **15**, 2604.
- (a) D. J. Ager, I. Prakash and D. R. Schaad, *Chem. Rev.*, 1996, **96**, 835; (b) P. R. Schreiner, *Chem. Soc. Rev.*, 2003, **32**, 289; (c) P. M. Pihko, *Angew. Chem., Int. Ed.*, 2004, **43**, 2062; (d) Y. Hoashi, T. Okino and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2005, **44**, 4032; (e) T. Inokuma, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2006, **128**, 9413; (f) Y. Zhang, Y. K. Liu, T. R. Kang, Z. K. Hu and Y. C. Chen, *J. Am. Chem. Soc.*, 2008, **130**, 2456; (g) Á. Madarász, Z. Dósa, S. Varga, T. Soós, A. Csámpai and I. Pápai, *ACS Catal.*, 2016, **6**, 4379.
- (a) F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, 1967, **67**, 107; (b) B. Love, P. E. Bender, H. Bowman, A. Helt, R. Mclean and T. Jen, *J. Med. Chem.*, 1972, **15**, 1024; (c)

- C. Larsen, K. Steliou and D. N. Harpp, *J. Org. Chem.*, 1978, **43**, 337; (d) C. R. Rasmussen, F. J. Villani Jr, L. E. Weaner, B. E. Reynolds, A. R. Hood, L. R. Hecker, S. O. Nortey, A. Hanslin, M. J. Costanzo, E. T. Powell and A. J. Molinari, *Synthesis*, 1988, 456; (e) H. Sugimoto, I. Makino and K. Hirai, *J. Org. Chem.*, 1988, **53**, 2263; (f) K. Ramadas and N. Srinivasan, *Synth. Commun.*, 1995, **25**, 3381; (g) M. Xian, X. Zhu, Q. Li and J. P. Cheng, *Tetrahedron Lett.*, 1999, **40**, 1957; (h) B. Yin, Z. Liu, M. Yi and J. Zhang, *Tetrahedron Lett.*, 2008, **49**, 3687.
- 6 (a) T. Ozturk, E. Ertas and O. Mert, *Chem. Rev.*, 2007, **107**, 5210; (b) T. Ozturk, E. Ertas and O. Mert, *Chem. Rev.*, 2010, **110**, 3419.
- 7 (a) H. A. Staab, *Angew. Chem., Int. Ed.*, 1962, **1**, 351; (b) G. L'abbe and S. Leurs, *Tetrahedron*, 1992, **48**, 7505; (c) P. K. Mohanta, S. Dhar, S. K. Samal, H. Ila and H. Junjappa, *Tetrahedron*, 2000, **56**, 629; (d) A. R. Katritzky, S. Ledoux, R. M. Witek and S. K. Nair, *J. Org. Chem.*, 2004, **69**, 2976; (e) A. Ortiz and E. Sansinenea, *J. Sulfur Chem.*, 2007, **28**, 109; (f) J. Li, Z. Tan, S. Tang, I. Hewlett, R. Pang, M. He, S. He, B. Tian, K. Chen and M. Yang, *Bioorg. Med. Chem.*, 2009, **17**, 3177; (g) M. I. C. Begum and K. M. Khan, *Nat. Prod. Res.*, 2009, **23**, 1719; (h) M. Đud, O. V. Magdysyuk, D. Margetića and V. Štrukil, *Green Chem.*, 2016, **18**, 2666.
- 8 (a) J. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martins and W. A. Lott, *J. Am. Chem. Soc.*, 1951, **73**, 906; (b) J. Erickson, *J. Org. Chem.*, 1956, **21**, 483; (c) M. Ballabeni, R. Ballini, F. Bigi, R. Maggi, M. Parrini, G. Predieri and G. Sartori, *J. Org. Chem.*, 1999, **64**, 1029; (d) M. R. Maddani and K. R. Prabhu, *J. Org. Chem.*, 2010, **75**, 2327; (e) Z. Zhang, H. H. Wu and Y. J. Tan, *RSC Adv.*, 2013, **3**, 16940; (f) C. M. Chau, T. J. Chuan and K. M. Liu, *RSC Adv.*, 2014, **4**, 1276; (g) T. Haywood, S. Kealey, S. Sánchez-Cabezas, J. J. Hall, L. Allott, G. Smith, C. Plisson and P. W. Miller, *Chem.–Eur. J.*, 2015, **21**, 9034.
- 9 W. Tan, J. Wei and X. Jiang, *Org. Lett.*, 2017, **19**, 2166.
- 10 T. B. Nguyen, L. Ermolenko and A. Al-Mourabit, *Synthesis*, 2014, **46**, 3172.
- 11 (a) B. M. Trost, *Science*, 1991, **254**, 1471; (b) M. Malacria, *Chem. Rev.*, 1996, **96**, 289; (c) K. C. Nicolaou, T. Montagnon and S. A. Snyder, *Chem. Commun.*, 2003, **34**, 551; (d) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134; (e) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167; (f) J. Xie, H. Jiang, Y. Cheng and C. Zhu, *Chem. Commun.*, 2012, **48**, 979; (g) H. G. Cheng, L. Q. Lu, T. Wang, Q. Q. Yang, X. P. Liu, Y. Li, Q. H. Deng, J. R. Chen and W. J. Xiao, *Angew. Chem., Int. Ed.*, 2013, **52**, 3250; (h) H. Pellissier, *Chem. Rev.*, 2013, **113**, 442; (i) C. M. R. Volla, I. Atodiresei and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390.
- 12 (a) Z. Song, Y. M. Zhao and H. Zhai, *Org. Lett.*, 2011, **13**, 6331; (b) Y. Yu, Y. Zhou, Z. Song and G. Liang, *Org. Biomol. Chem.*, 2018, **16**, 4958; (c) C. Ding, Y. Yu, Q. Yu, Z. Xie, Y. Zhou, J. Zhou, G. Liang and Z. Song, *ChemCatChem*, 2018, **10**, 5397.
- 13 For aniline, 3-chloroaniline and 4-bromoaniline, the symmetrical thioureas from the reactions of these anilines and carbon disulfide were isolated in 21%, 14% and 17% yields, respectively.
- 14 (a) B. Krebs and G. Henkel, *Angew. Chem., Int. Ed.*, 1991, **30**, 769; (b) F. Velazquez and H. F. Olivo, *Curr. Org. Chem.*, 2002, **6**, 303; (c) A. Ortiz and E. Sansinenea, *J. Sulfur Chem.*, 2007, **28**, 109; (d) S. Sahu, P. R. Sahoo, S. Patel and B. K. Mishra, *J. Sulfur Chem.*, 2011, **32**, 171.
- 15 For the reactions of naphthylamines, primary amines (alkylamines, benzyl amines, anilines) and carbon disulfide: dithiocarbamates were initially formed by the reactions of primary amines with carbon disulfide, subsequently they were converted to isothiocyanates (for example, *J. Org. Chem.*, 2010, **75**, 2327; *RSC Adv.*, 2013, **3**, 16940). These reactions not only generated unsymmetrical thioureas by the reactions of the formed isothiocyanates with naphthylamines, but also produced symmetrical thioureas by the reactions of the formed isothiocyanates with primary amines (like anilines) which have similar nucleophilicity with naphthylamines.