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Cesium carbonate-promoted synthesis of aryl methyl sulfides using *S*-methylisothiourea sulfate under transition-metal-free conditions

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In the presence of cesium carbonate, an efficient synthesis of aryl methyl sulfides by the reactions of aryl halides with commercially available S-methylisothiourea sulfate is developed. This odourless and highly crystalline solid can be used as the surrogate for malodorous methanethiol. The gram-scale reaction also proceeds smoothly without the use of column chromatography separation. Similarly, 2-(dimethylamino)ethylthio and cyclopropylmethylthio groups can be easily introduced into the aromatic rings from the corresponding *S*-[2-(dimethylamino)ethyl]isothiourea dihydrochloride and *S*-cyclopropylmethylisothiourea hydrobromide. The possible reaction mechanism is proposed. It is believed that this route to aryl alkyl sulfides is well competitive in currently known methods due to the wide substrate scope, excellent yields, easy operation and transition-metal-free conditions.

Introduction

Aryl methyl sulfide is an ubiquitous structural motif that occurs in a variety of natural products, such as Roseochelin B,[1] Macrophilone A[2] and Collismycin A.[3] Thioridazine as an antipsychotic drug also contains this fragment.[4] Meanwhile, methyl sulfides can be efficiently oxidized to methyl sulfoxides or methyl sulfones with high selectivity,[5] which are usually the key steps for the synthesis of the nonsteroidal anti-inflammatory drug sulindac[6] and pesticide isoxaflutole.[7] Many thiomethyl-containing aromatics are also attractive candidates for organic semiconductors.[8] In addition, thiomethyl group has been widely used as the leaving group for the formation of carbon-carbon bond by Liebeskind-Srogl cross-coupling reaction[9] and other transformations.[10, 11] Accordingly, the introduction of thiomethyl group into the aromatic molecules is particularly significant.[12] Generally, the synthesis of aryl methyl sulfides can be performed through the methylation of malodorous aryl thiols with methyl iodide[13, 14] or dimethylcarbonate catalyzed by ionic liquids under continuous flow conditions.[15] The transition metal-catalyzed direct C–H methylthiolation of heteroarenes using dimethyl disulfide or DMSO as the thiomethyl source is one of the feasible approaches,[16] whereas these reactions often afforded the desired aryl methyl sulfides in moderate yields with the requirement of more than a stoichiometric amount of metal catalysts.[17] Recently, Cai established a practical palladium-catalyzed decarboxylative methylthiolation of 2-nitrobenzoic acids by using DMSO as the sulfurizing reagent in the presence of 2.0 equiv of copper(I) iodine (Scheme 1a).[18] Tan found that this transformation could be achieved using the arenecarboxylate salts as the substrates by the combination of copper(I) bromide with zinc(II) trifluoromethanesulfonate.[19] Wangelin demonstrated that aryl methyl sulfides can be prepared by the reaction of arene-diazonium salts with dimethyl disulfide in the presence of organic photoredox catalyst or base (Scheme 1b).[20] Wu and coworkers reported an efficient di-*tert*-butyl peroxide (DTBP)-mediated methylthiolation of arylboronic acids with dimethyl disulfide under metal-free conditions (Scheme 1c).[21] Although so many routes have been reported for the preparation of aryl methyl sulfides, aryl halide is still the most frequently used starting material due to its easily availability and diversity. The reaction of aryl halides with a malodorous CH_3SNa solution often gives the thiomethylated products in good yields,[22] but the substrates are often limited by the strong base conditions. Recently, Cheng and coworkers also found a cooper-mediated methylthiolation of aryl halides with dimethylsulfoxide in the presence of ZnF_2 (2.0 equiv) at 150 °C (Scheme 1d).[23, 24] Apparently, the development of more green and mild synthetic routes to aryl methyl sulfides, with improved availability of starting material is still highly desired.

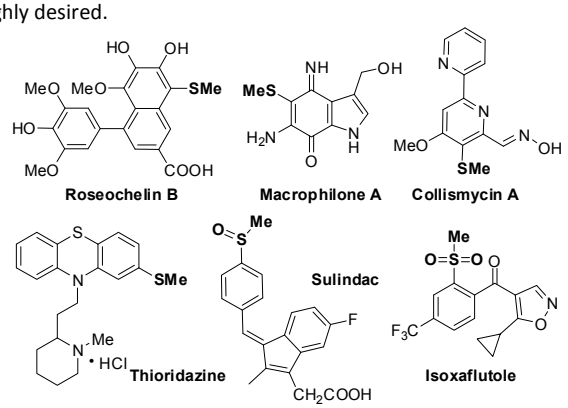

Fig. 1 Natural products and pharmacological molecules containing methyl sulfides, methyl sulfoxides and methyl sulfones.

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†Electronic Supplementary Information (ESI) available: Spectral data, copies of ^{1}H NMR and ^{13}C NMR spectra of synthesized compounds. See DOI: 10.1039/x0xx00000x

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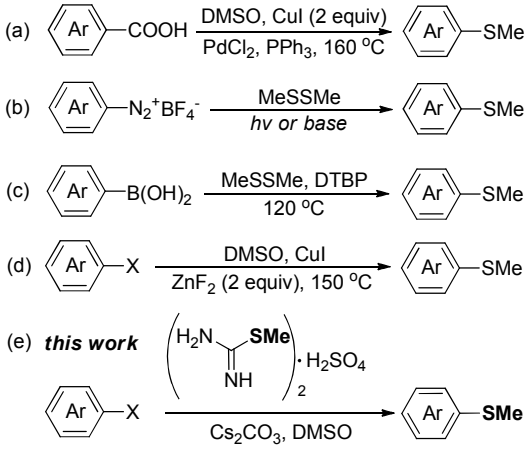
Commercially available *S*-methylisothiourea sulfate (SMT) as an odourless and highly crystalline solid is easily prepared from cheap thiourea and dimethyl sulfate.[25] Although it has been widely employed in organic synthesis for the formation of functionalized heterocycles,[26] few reports focus on it as the thiomethyl group source.[27] Herein, we report an efficient cesium carbonate-promoted synthesis of aryl methyl sulfides by the reactions of aryl halides with *S*-methylisothiourea sulfate under metal-free conditions, and two representative *S*-alkylisothiourea salts also deliver the corresponding aryl alkyl sulfides with excellent yields (Scheme 1e).



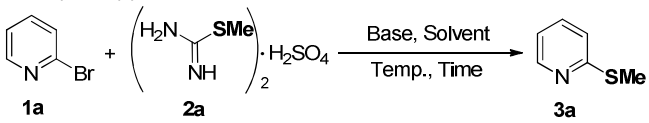
Scheme 1 General routes for aryl methyl sulfides.

Results and discussion

At the start of our study, the reaction of 2-bromopyridine (**1a**, 0.5 mmol) and *S*-methylisothiourea sulfate (**2a**, 0.5 mmol) was carried out in DMSO at 80 °C in the presence of K_2CO_3, and the reaction gave 2-(methylthio)pyridine (**3a**) in 40% yield (Table 1, entry 1). Na_2CO_3, $NaHCO_3$ and Et_3N were ineffective for the reactions (Table 1, entries 2–4). No reaction occurred in the absence of the base (Table 1, entry 5). Satisfyingly, **3a** was obtained in nearly quantitative yield when Cs_2CO_3 was used (Table 1, entry 6). Reducing the amount of base or **2a** led to a slightly lower yield (Table 1, entries 7–11). The yield was obviously influenced by the reaction temperature, and the reaction time can be shortened at the temperature of 100 °C (Table 1, entries 12–15). This transformation was also attempted in other different solvents, such as DMF, EtOH, 1,4-dioxane, H_2O and the mixture of DMSO/H_2O (v:v, 1:1), and it was found that DMF was also efficient (Table 1, entries 16–20).

With the aforementioned optimized reaction conditions in hand (Table 1, entry 6), the scope of aryl halides was investigated (Table 2). The reaction of 2-chloropyridine with **2a** also furnished the desired product **3a** in 95% yield. It was found that 3-, 4-, 5- and 6-position methyl substituted 2-bromopyridines were tolerated in this transformation to deliver the corresponding **3b–e** in good yields. 2-Bromo-5-chloropyridine and 2,5-dibromopyridine gave 2-(methylthio)pyridine derivatives **3f** and **3g** in 86% and 84% yields respectively under the standard reaction conditions, and the 5-position halogen atom was not replaced by methylthio group due to its lower reaction activity than 2-position bromo atom. When the reaction temperature was increased to 110 °C, 2,5-bis(methylthio)pyridine (**3h**) was obtained in 80% yield from 2,5-dibromopyridine. In addition, the substrates bearing strong electron-donating (OMe) and electron-withdrawing (CN, CF_3) groups at the 5-position for 2-bromopyridines also delivered the target products **3i–k** in excellent yields. Notably, the reaction proceeded smoothly to afford **3l** at room temperature. 3-Bromopyridine, and 4-bromopyridine hydrochloride also gave **3m** and **3n** in good yields. Other mono- and dibromo-substituted heterocyclic substrates, such as thiazole, benzo[*d*]thiazole, pyridazine, pyrimidine, quinolone and isoquinoline were also suitable for this transformation, affording the corresponding products **3o–w** in 88–99% yields.

Table 1 Optimization of reaction conditions for the synthesis of 2-(methylthio)pyridine (**3a**)[a]



Entry	Base (mmol)	Solvent	Temp (°C)	T (h)	**3a** Yield[b] (%)
1	K_2CO_3 (2.0)	DMSO	80	8	40
2	Na_2CO_3 (2.0)	DMSO	80	8	< 5
3	$NaHCO_3$ (2.0)	DMSO	80	8	< 5
4	Et_3N (2.0)	DMSO	80	8	0
5	None	DMSO	80	8	0
6	Cs_2CO_3 (2.0)	DMSO	80	4	99
7	Cs_2CO_3 (1.5)	DMSO	80	8	94
8	Cs_2CO_3 (1.0)	DMSO	80	8	89
9[c]	Cs_2CO_3 (2.0)	DMSO	80	6	92
10[d]	Cs_2CO_3 (2.0)	DMSO	80	6	85
11[e]	Cs_2CO_3 (2.0)	DMSO	80	6	80
12	Cs_2CO_3 (2.0)	DMSO	60	12	90
13	Cs_2CO_3 (2.0)	DMSO	40	12	75
14	Cs_2CO_3 (2.0)	DMSO	25	24	60
15	Cs_2CO_3 (2.0)	DMSO	100	2	99
16	Cs_2CO_3 (2.0)	DMF	80	8	95
17	Cs_2CO_3 (2.0)	EtOH	80	4	58
18	Cs_2CO_3 (2.0)	1,4-dioxane	80	4	25
19	Cs_2CO_3 (2.0)	H_2O	80	4	0
20	Cs_2CO_3 (2.0)	DMSO:H_2O (1:1)[f]	80	4	0

[a] Unless otherwise specified, the reactions were carried out on a 0.5 mmol scale and conducted at **1a**/**2a** = 0.5/0.5 in 3 mL solvent.
[b] Isolated yield.
[c] **1a**/**2a** = 0.5/0.4.
[d] **1a**/**2a** = 0.5/0.3.
[e] **1a**/**2a** = 0.5/0.25.
[f] The volume ratio.

Next, it is our desire to effectively obtain the non-heteroaryl methyl sulfides by using the present strategy. To our delight, it was found that bromobenzene and iodobenzene could give the methyl(phenyl)sulfane (**4a**) in 82% and 85% yields, respectively. The substrates bearing electron-withdrawing substituents (COOMe, SO_2Me, COMe, NO_2, CN, CF_3) on phenyl rings also afforded the expected product **4b–g** in excellent results. Nevertheless, a higher reaction temperature (110 °C) and longer reaction time were required for electron-donating (Me, OMe) substituted substrates. Notably, (4-methoxyphenyl)(methyl)sulfane (**4i**) was only obtained in 20% yield and 4-(methylthio)phenol (**4i'**) was isolated as the main product in 70% yield involving the C-O bond cleavage reaction. We also found that methyl(naphthalen-1-yl)sulfane (**4j**) and anthracen-

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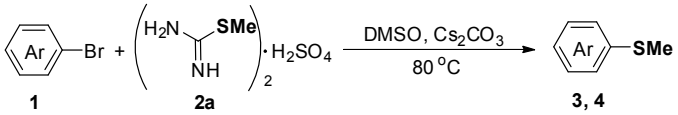
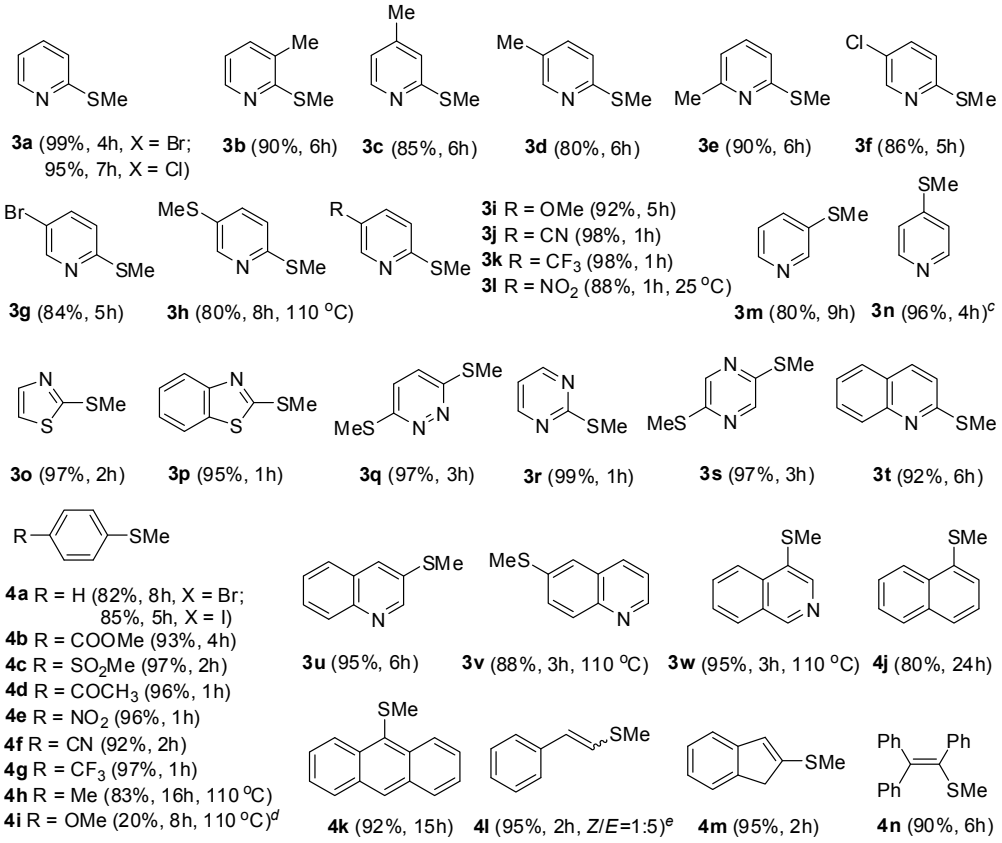
Table 2 The scope of (hetero)aryl halides[a,b]



1 2a 3, 4



[a]Unless otherwise specified, all of the reactions were carried out using (hetero)aryl bromides **1** (0.5 mmol), **2a** (0.5 mmol) and Cs_2CO_3 (2.0 mmol) in DMSO (3 mL) at 80 °C.
[b]Isolated yield.
[c]4-Bromopyridine hydrochloride was employed as the substrate.
[d]4-(Methylthio)phenol (**4i'**) was obtained in 70% yield.
[e]The *Z/E* ratio of starting material (2-bromovinyl)benzene was 1:5.

9-yl(methyl)sulfane (**4k**) were also obtained in 80% and 92% yields, respectively. Recently, Suárez-Pantiga and coworkers reported a cross-coupling reaction of alkenyl sulfides by palladium-catalyst thioetherification of alkenyl halides with thiols.[28] Satisfyingly, in the absence of transition metal catalyst, the reaction of mono-, di-, and trisubstituted vinyl bromides with **2a** also gave the corresponding methyl(styryl)sulfane (**4l**, *Z/E* = 1:5), (1*H*-inden-2-yl)(methyl)sulfane (**4m**) and methyl(1,2,2-triphenylvinyl)sulfane (**4n**) in satisfying result.

Furthermore, we are expected to prepare the aryl non-methyl sulfides. It is considered that one-pot reaction[29] of aryl halides, thiourea and alkyl bromides is a more attractive protocol. It has been reported that the transition-metal catalysis (Cu or Pd) was indispensable for this kind of three-component reaction.[30,31] In addition, it is hard to avoid the formation of the by-products diaryl disulfides and alkyl disulfides.[32] recently, Lu reported an efficient synthesis of nitroaryl thioethers by S_NAr reaction in aqueous Triton X-100 using thiourea as the sulfur source. Nevertheless, the reported substrates are limited to

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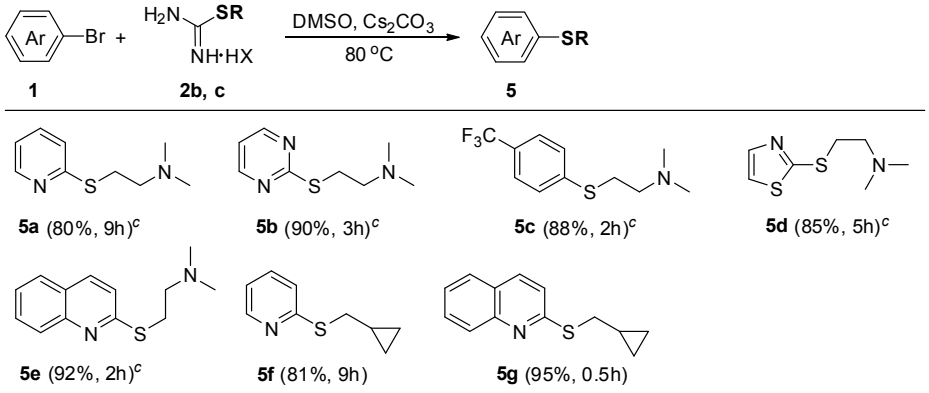
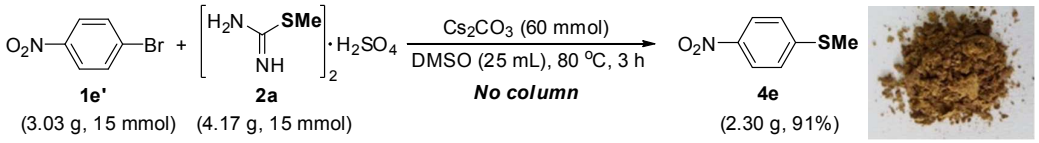
Table 3 The extension of *S*-alkylisothiourea salts[a,b]



[a]Unless otherwise specified, all of the reactions were carried out using (hetero)aryl bromides **1** (0.5 mmol), **2b**/**2c** (1.0 mmol) and Cs_2CO_3 (2.0 mmol) in DMSO (3 mL) at 80 °C.
[b]Isolated yield.
[c]*S*-[2-(dimethylamino)ethyl]isothiourea dihydrochloride (**2b**) was employed.

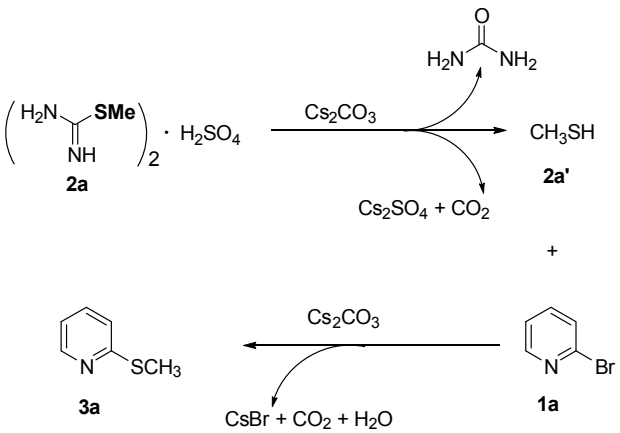


Scheme 2 Gram-scale experiment for the synthesis of **4e**.

particular examples for 2- and 4-nitrobenzene fluorides. No expected products were obtained from 3-nitrobenzene fluorides and fluoro-substituted heterocycles.[33] Therefore, we believe that the use of *S*-alkylisothiourea salts as the starting materials is more convenient due to their easily availability[34] and it would avoid the generation of inseparable by-products.

The structural fragment of 2-(dimethylamino)ethylthio substituted aromatics exists widely in a number of biologically active molecules and drug candidates. For example, *N*,*N*-dimethyl-2-(3-phenylquinolin-2-yl)sulfanylethanamine is an important 5-HT_2 antagonist,[35] which is prepared from chlorinated quinoline with the expensive starting material 2-(dimethylamino)ethanethiol hydrochloride. As shown in Table 3, by using our present method, available *S*-[2-(dimethylamino)ethyl]isothiourea dihydrochloride (**2b**)
and several representative products **5a–e** were obtained in 80–92% yields. Similarly, the reactions gave the corresponding **5f** and **5g** in excellent yields from *S*-cyclopropylmethylisothiourea hydrobromide (**2c**). Apparently, some functionalized alkylthio groups can be easily introduced into the aromatic rings compared with the commonly used methods, especially for the reactions involving the use of not easily available thiols as the starting materials.

In order to further demonstrate the synthetic utility of this strategy, a representative example for the gram-scale reaction of 1-bromo-4-nitrobenzene (**1e'**) and **2a** was explored. It was found that the expected yellow solid **4e** was expediently isolated in 91% yield without the use of column chromatography, as shown in Scheme 2.



Scheme 3 Possible reaction mechanism.

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On the basis of these experimental results and previous reported work, a possible reaction mechanism was proposed using the synthesis of **3a** as an example, as shown in Scheme 3. In the presence of cesium carbonate, *S*-methylisothiourea sulfate (**2a**) can be easily converted into **2a'**, simultaneously releasing urea, cesium sulfate and carbon dioxide. Then, the reaction of **1a** with **2a'** furnished the desired product **3a** under the basic condition.

Conclusions

In summary, we have developed an efficient method for the synthesis of aryl methyl sulfides from easily available aryl halides and with commercially available *S*-methylisothiourea sulfate in the presence of cesium carbonate. Cheap, stable and odourless crystalline solid *S*-methylisothiourea sulfate can be used as the surrogate for malodorous methanethiol. Similarly, some functionalized alkylthio groups, such as 2-(dimethylamino)ethylthio and cyclopropylmethylthio group can be conveniently introduced into the molecules by using this strategy, while other reported methods usually require not easily available or non-commercial thiols as the starting materials. This reaction shows wide substrate scope, excellent yields, the tolerance of functional groups and easy operation. The gram-scale reaction also proceeds smoothly and the product can be easily purified without the use of column chromatography. Accordingly, it is believed that this route to aryl alkyl sulfides is well competitive in currently known methods. The application of *S*-alkylisothiourea salts in other organic reactions is underway in our laboratory.

Experimental

General Information: All the chemicals were commercially available and used without further purification. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ using Bruker Avance II 300 MHz spectrometer at 300 MHz and 75 MHz, respectively. Chemical shifts are reported relative to internal standard tetramethylsilane (TMS). Mass spectra were measured on LCQ Advantage MAX or Solanx70 FT-MS. Infrared spectra (IR) were obtained as KBr pellet samples using a Nicolet 5700 FTIR spectrometer. Melting points were determined using an uncorrected X-4 apparatus. Flash column chromatography was performed on 200–300 mesh silica gel.

General procedure for aryl alkyl sulfides 3–5

A mixture of (hetero)aryl halides (**1**, 0.5 mmol), *S*-alkylisothiourea salts (**2a**, 0.5 mmol; **2b**/**2c**, 1.0 mmol), cesium carbonate (652 mg, 2.0 mmol) and DMSO (3 mL) was reacted in the range of room temperature to 110 ^{o}C for 0.5**–**24 h. After completion of the reaction, the mixture was poured into the water and extracted with dichloromethane (3×15 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtered. After removal of the solvent, the residue was directly used for structural analysis or purified by flash column chromatography on silica gel using petroleum ether or petroleum ether/ethyl acetate (v:v, 50:1 to 3:1) as the eluent to afford the target products.

Gram-scale reaction for the synthesis of 4e

A mixture of 1-bromo-4-nitrobenzene (3.03 g, 15 mmol), *S*-methylisothiourea sulfate (4.17 g, 15 mmol), cesium carbonate (19.55 g, 60 mmol) and DMSO (25 mL) was heated at 80 ^{o}C for 3 h. After completion of the reaction, the mixture was poured into the water and extracted with dichloromethane (3×40 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtered. After removal of the solvent, the residue was drying in vacuum oven to give yellow solid (2.30 g), which was pure enough for structural analysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 R. Wang and M. R. Seyedsayamdost, *Org. Lett.*, 2017, **19**, 5138.
2 K. Zlotkowski, W. M. Hewitt, P. Yan, H. R. Bokesch, M. L. Peach, M. C. Nicklaus, B. R. O'Keefe, J. B. McMahon, K. R. Gustafson and J. S. Schneekloth Jr, *Org. Lett.*, 2017, **19**, 1726.
3 (a)J. López-Ogalla, G. Saiz and F. E. Palomo, *Org. Process Res. Dev.*, 2013, **17**, 120; (b) S. Gomi, S. Amano, E. Sato, S. Miyadoh and Y. Kodama, *J. Antibiot.*, 1994, **47**, 1385.
4 X.-Y. Ke, V. W. L. Ng, S.-J. Gao, Y. W. Tong, J. L. Hedrick and Y.-Y. Yang, *Biomaterials*, 2014, **35**, 1096.
5 J. Legros, J. R. Dehli and C. Bolm, *Adv. Synth. Catal.*, 2005, **347**, 19.
6 E. Prade, C. Barucker, R. Sarkar, G. Althoff-Ospelt, J. M. L. del Amo, S. Hossain, Y. Zhong, G. Multhaup and B. Reif, *Biochemistry*, 2016, **55**, 1839.
7 K. E. Pallett, S. M. Cramp, J. P. Little, P. Veerasekaran, A. J. Crudace and A. E. Slater, *Pest Manag. Sci.*, 2001, **57**, 133.
8 T. Kimoto, K. Tanaka, M. Kawahata, K. Yamaguchi, S. Otsubo, Y. Sakai, Y. Ono, A. Ohno and K. Kobayashi, *J. Org. Chem.*, 2011, **76**, 5018.
9 (a) H. Prokopcová and C. O. Kappe, *Angew. Chem. Int. Ed.*, 2009, **48**, 2276; (b) L. Betancourt-Mendiola, I. Valois-Escamilla, T. Arbeloa, J. Bañuelos, I. L. Arbeloa, J. O. Flores-Rizo, R. Hu, E. Lager, C. F. A. Gómez-Durán, J. L. Belmonte-Vázquez, M. R. Martínez-González, I. J. Arroyo, C. A. Osorio-Martínez, E. Alvarado-Martínez, A. Urías-Benavides, B. D. Gutiérrez-Ramos and B. Z. Tang, E. Peña-Cabrera, *J. Org. Chem.*, 2015, **80**, 5771.
10 (a) S. G. Modha, V. P. Mehta and E. V. Van der Eycken, *Chem. Soc. Rev.*, 2013, **42**, 5042; (b) L. Wang, W. He and Z Yu, *Chem. Soc. Rev.*, 2013, **42**, 599; (c) F. Zhu and Z.-X. Wang, *Org. Lett.*, 2015, **17**, 1601; (d) Z.-J. Quan, Y. Lv, F.-Q. Jing, X.-D. Jia, C. D. Huo and X. C. Wang, *Adv. Synth. Catal.*, 2014, **356**, 325.
11 (a) N. Barbero and R. Martin, *Org. Lett.*, 2012, **14**, 796; (b) Y. Uetake, T. Niwa and T. Hosoya, *Org. Lett.*, 2016, **18**, 2758. (c) D. Wang, K. Zhao, C. Xu, H. Miao and Y. Ding, *ACS Catal.*, 2014, **4**, 3910. (d) C. Ge, X. Sang, W. Yao, L. Zhang and D. Wang, *Green Chem.*, 2018, **20**, 1805. (e) Z. Xu, X. Yu, X. Sang and D. Wang, *Green Chem.*, 2018, **20**, 2571.
12 (a) X.-F. Wu and K. Natte, *Adv. Synth. Catal.*, 2016, **358**, 336; (b)Q. Gao, X. Wu, Y. Li, S. Liu, X. Meng and A. Wu, *Adv. Synth. Catal.*, 2014, **356**, 2924; (c) E. Jones-Mensah, M. Karki and J.Magolan, *Synthesis*, 2016, **48**, 1421; (d) S. Liu, H. Xi, J. Zhang, X. Wu, Q. Gao and A. Wu, *Org. Biomol. Chem.*, 2015, **13**, 8807; (e) G. Yin, Z. Wang, A. Chen, M. Gao, A. Wu and Y. Pan, *J. Org. Chem.*, 2008, **73**, 3377.
13 (a) Y. Uetake, T. Niwa and T. Hosoya, *Org. Lett.*, 2016, **18**, 2758; (b) J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu and J. Hu, *Angew. Chem. Int. Ed.*, 2016, **55**, 2743.

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DOI: 10.1039/C8OB01758A

14 Y. Jiang, Y. Qin, S. Xie, X. Zhang, J. Dong and D. Ma, *Org. Lett.*, 2009, **11**, 5250.
15 T. N. Glasnov, J. D. Holbrey, C. O. Kappe, K. R. Seddon and T. Yan, *Green Chem.*, 2012, **14**, 3071.
16 C. Shen, P. Zhang, Q Sun, S. Bai, T. S. A. Hor and X. Liu, *Chem. Soc. Rev.*, 2015, **44**, 291.
17 X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790; (b) M. Klečka, R. Pohl, J. Čejka and M. Hocek, *Org. Biomol. Chem.*, 2013, **11**, 5189; (c) C. Dai, Z. Xu, F. Huang, Z. Yu and Y. F. Gao, *J. Org. Chem.*, 2012, **77**, 4414; (d) L. Chu, X. Yue and F.-L. Qing, *Org. Lett.*, 2010, **12**, 1644.
18 (a) Z. Fu, Z. Li, Q. Xiong and H. Cai, *Eur. J. Org. Chem.*, 2014, **2014**, 7798; (b) M. Li and J. M. Hoover, *Chem. Commun.*, 2016, **52**, 8733. (c) D. Wang, X. Yu, W. Yao, W. Hu, C. Ge and X. Shi, *Chem. Eur. J.*, 2016, **22**, 5543. (d) Z. Xu, D.-S. Wang, X. Yu, Y. Yang and D. Wang, *Adv. Synth. Catal.*, 2017, **359**, 3332. (e) R. Huang, Y. Yang, D.-S. Wang, L. Zhang and D. Wang, *Org. Chem. Front.*, 2018, **5**, 203.
19 L. Hu, D. Wang, X. Chen, L. Yu, Y. Yu, Z. Tan and G. Zhu, *Org. Biomol. Chem.*, 2017, **15**, 5674.
20 (a) M. Majek and A. J. von Wangelin, *Chem. Commun.*, 2013, **49**, 5507; (b) D. Koziakov, M. Majek and A. J. von Wangelin, *Org. Biomol. Chem.*, 2016, **14**, 11347.
21 X. Wu, J. Lou and G. Yan, *Synlett*, 2016, **27**, 2269.
22 L. Testaferri, M. Tiecco, M. Tingoli, D. Bartoli and A. Massoli, *Tetrahedron*, 1985, **41**, 1373.
23 F. Luo, C. Pan, L. Li, F. Chen and J. Cheng, *Chem. Commun.*, 2011, **47**, 5304.
24 P. J. A. Joseph, S. Priyadarshini, M. L. Kantam and B. Sreedhar, *Tetrahedron*, 2013, **69**, 8276.
25 C. A. Barker, S. E. Allison, S. Zlitni, N. D. Nguyen, R. Das, G. Melacini, A. A. Capretta and E. D. Brown, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 2426.
26 (a) E. da C. Aquino, M. M. Lobo, G. Leonel, M. A. P. Martins, H. G. Bonacorso and N. Zanatta, *Eur. J. Org. Chem.*, 2017, **2017**, 306; (b) Z. Yang, L. Li, J. Zheng, H. Ma, S. Tian, J. Li, H. Zhang, X. Zhen and X. Zhang, *ACS Chem. Neurosci.*, 2016, **7**, 1575; (c) S. Salerno, A. M. Marini, G. Fornaciari, F. Simorini, C. L. Motta, S. Taliani, S. Sartini, F. D. Settimo, A. N. García-Argáez, O. Gia, S. Cosconati, E. Novellino, P. D'Ocon, A. Fioravanti, P. Orlandi, G. Bocci and L. D. Via, *Eur. J. Med. Chem.*, 2015, **103**, 29.
27 (a) P. Fruhmann, T. Weigl-Pollack, H. Mikula, G. Wiesenberger, G. Adam, E. Varga, F. Berthiller, R. Krska, C. Hametnera and J. Fröhlich, *Org. Biomol. Chem.*, 2014, **12**, 5144; (b) D. T. Hurst, *J. Heterocycl. Chem.*, 1995, **32**, 697. (c) K. Marciniec, A. Maślankiewicz and M. J. Maślankiewicz, *J. Heterocycl. Chem.*, 2015, **52**, 1019.
28 N. Velasco, C. Virumbrales, R. Sanz, S. Suárez-Pantiga, M. A. and Fernández-Rodríguez, *Org. Lett.*, 2018, **20**, 2848.
29 (a) T. Ding, L. Jiang and W. Yi, *Org. Lett.*, 2018, **20**, 170; (b) Y. Li, J. Pu and X. Jiang, *Org. Lett.*, 2014, **16**, 2692; (c) B. B. Liu, X.-Q. Chu, H. Liu, L. Yin, S.-Y. Wang and S.-J. Ji, *J. Org. Chem.*, 2017, **82**, 10174.
30 (a) H. Firouzabadi, N. Iranpoor and M. Gholinejad, *Adv. Synth. Catal.*, 2010, **352**, 119; (b) J. Mondal, A. Modak, A. Dutta, S. Basu, S. N. Jha, D. Bhattacharyya and A. Bhaumik, *Chem. Commun.*, 2012, **48**, 8000.
31 (a) Z. Qiao, J. Wei and X. Jiang, *Org. Lett.*, 2014, **16**, 1212; (b) J. T. Reeves, K. Camara, Z. S. Han, Y. Xu, H. Lee, C. A. Busacca and C. H. Senanayake, *Org. Lett.*, 2014, **16**, 1196; (c) D. J. C. Prasad and G. Sekar, *Org. Lett.*, 2011, **13**, 1008; (d) K. M. Wager and M. H. Daniels, *Org. Lett.*, 2011, **13**, 4052; (e) V. K. Akkilagunta and R. R. Kakulapati, *J. Org. Chem.*, 2011, **76**, 6819.
32 (a) X. Ma, L. Yu, C. Su, Y. Yang, H. Li and Q. Xu, *Adv. Synth. Catal.*, 2017, **359**, 1649; (b) J. E. Argüello, L. C. Schmidt and A. B. Peñéñory, *Org. Lett.*, 2003, **5**, 4133.
33 G. Lu and C. Cai, *RSC Adv.*, 2014, **4**, 59990.
34 A. Jamaleddini and M. R. Mohammadizadeh, *Tetrahedron Lett.*, 2017, **58**, 78.
35 T. P. Blackburn, B. Cox, A. J. Guildford, D. J. L. Count, D. N. Middlemiss, R. J. Pearce and C. W. Thornber, *J. Med. Chem.*, 1987, **30**, 2252.