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Iodine-triphenylphosphine mediated sulfenylation of imidazoheterocycles with sodium sulfinates

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An efficient approach to sulfenyl imidazoheterocycles has been developed via iodine-triphenylphosphine mediated direct sulfenylation of imidazoheterocycles with sodium sulfinates. The reactions proceed smoothly under transition-metal-free conditions with a broad range of substrate scope, giving the desired products in moderate to excellent yields.

Imidazoheterocycle is a ubiquitous core found in many natural products and biologically active compounds.[1] In particular, imidazo-pyridine derivatives show an extensive range of biological activities, such as antiviral, antitumor, antiparasitic, antimicrobial, fungicidal, anti-inflammatory, hypnotic, etc.[2] Several compounds with imidazo[1,2-*a*]pyridine scaffold have been successfully developed into commercially available drugs, including alpidem,[3] zolpidem,[4] necopidem,[5] saripidem,[6] zolimidine,[7] minodronic acid[8] and olprin-one.[9] Therefore, the development of straightforward and diversity-oriented reactions for the synthesis of imidazopyridine derivatives has attracted great attention for pharmaceutical chemists.[10]

Generally, the biological profile is mainly dependent on the nature of the substitutional groups. Introduction of sulfenyl groups on the aza-aromatic rings could impart marked biological properties.[11] Therefore, a number of sulfenylating agents, such as thiols,[12] disulfides,[13] quinonemono-O,S-acetals,[14] sulfenyl halides,[15] N-thioarylphthalimides,[16] arylsulfonyl cyanides[17] and sulfonyl hydrazide[18] were used to couple with electron-rich(hetero)-arenes. However, there are few reports available for the synthesis of sulfenated imidazoheterocycles.[19] Zhou and co-workers reported an efficient CuI-catalyzed sulfenylation of imidazopyridines with disulfides.[19a] Wei and co-workers developed an aerobic $CeCl_3.7H_2O$/NaI catalyzed three-component tandem reaction from ketones, 2-amino-pyridines, and disulfides for the synthesis of 3-sulfenylimidazopyridines.[19b] Abhijit and co-workers also developed a practical method for methylthiolation of imidazoheterocycles using DMSO-$POCl_3$ as a reagent at room temperature.[19c] Very recently, Adimurthy and co-workers described an efficient N-chlorosuccinimide promoted regioselective sulfenylation of imidazoheterocycles using thiols as sulfenylating reagent.[19d] Nevertheless, many of these sulfenylating agents are unstable to air and moisture, are expensive, or possess unpleasant odors. In addition, previously reported methods suffer from harsh reaction conditions, uncommon solvents, the use of transition metal catalysts and narrow substrate scope. Thus, it is still desirable to develop more efficient methods for the sulfenylation of imidazoheterocyclic derivatives. As we known, sodium sulfinates are relatively stable, easy to handle, and conveniently prepared from the corresponding inexpensive

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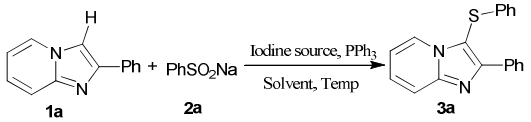
sulfonyl chlorides. They have been widely used as sulfenylating agents.[20] However, there are only few examples on the direct sulfenylation of heteroarene C-H bonds using sodium sulfinates as sulfenylating reagent.[21] As continuation of our research to develop odorless thiol equivalents,[22] we report herein an efficient iodine-triphenylphosphine mediated sulfenylation of imidazoheterocycles using sodium sulfinates as sulfenylating reagent under transition-metal-free conditions.

Initially, the sulfenylation of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) with sodium benzenesulfinate (**2a**) was chosen as the model reaction to optimize the reaction conditions, and the results were summarized in Table 1. When 2-phenylimidazo[1,2-*a*]pyridine (**1a,** 1 equiv.) was treated with sodium benzenesulfinate (**2a**, 2 equiv.), iodine (1 equiv.) and triphenylphosphine (2 equiv.) in dichloromethane at room temperature for 12h, the expected product 2-phenyl-3-(phenylthio)imidazo[1,2-*a*]pyridine (**3a**) was obtained in 30% yield (Table 1, entry 1). Replacing the solvent DCM with DMF, a 52% yield of **3a** was achieved (Table 1, entry 2). Surprisingly, when the reaction temperature was raised to 80 °C, the yield of **3a** was dramatically increased to 95% (Table 1, entry 3). However, when the reaction was carried out at 60 °C or 100 °C, the yield of **3a** was slightly reduced (Table 1, entries 4–5). Reducing the amount of sodium benzenesulfinate (**2a**) and triphenylphosphine from 2 equiv. to 1.5 equiv.， the yield of **3a** was decreased from 95% to 77% (Table 1, entry 6). Other organic solvents, such as DCE, DMSO, EA, EtOH, ACN and toluene, were also examined and DMF remained the best one (Table 1, entries 7–12). Moreover, when the reaction were carried out in the absence of iodine or triphenylphosphine, no product **3a** or only 44% yield of **3a** was obtained (Table 1, entries 13–14), indicating that iodine and triphenylphosphine play an important role in the reaction. Instead of iodine with other iodine sources, such as TBAI, KI and NIS, the product **3a** was trace or not detected (Table 1, entries 15–17). Thus, the optimum reaction conditions are as follows: imidazo[1,2-*a*]pyridines (**1**, 1 equiv.), sodium sulfinate (**2**, 2 equiv.), iodine (1 equiv.) and triphenylphosphine (2 equiv.) in DMF at 80°C for 12 h.

Table 1. Optimization of the reaction conditions [a]



Entry	Iodine source	Solvent	Temp	Yield[b]
1	I_2	DCM	r.t.	30%
2	I_2	DMF	r.t.	52%
3	**I_2**	**DMF**	**80**	**95%**
4	I_2	DMF	60	85%
5	I_2	DMF	100	92%
6[c]	I_2	DMF	80	77%
7	I_2	DCE	80	81%
8	I_2	EA	80	69%
9	I_2	DMSO	80	90%
10	I_2	ACN	80	54%
11	I_2	EtOH	80	43%
12	I_2	Toluene	80	82%
13[d]	-	DMF	80	n.r
14[e]	I_2	DMF	80	44%
15	TBAI	DMF	80	n.r
16	KI	DMF	80	n.r
17	NIS	DMF	80	trace

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), iodine source (0.3 mmol), PPh_3(0.6 mmol), solvent (3 mL), 12 h. [b] Isolated yield after column chromatography. [c] **2a** (0.45mmol), PPh_3 (0.45 mmol) were used. [d] In the absence of I_2. [e] In the absence of PPh_3.

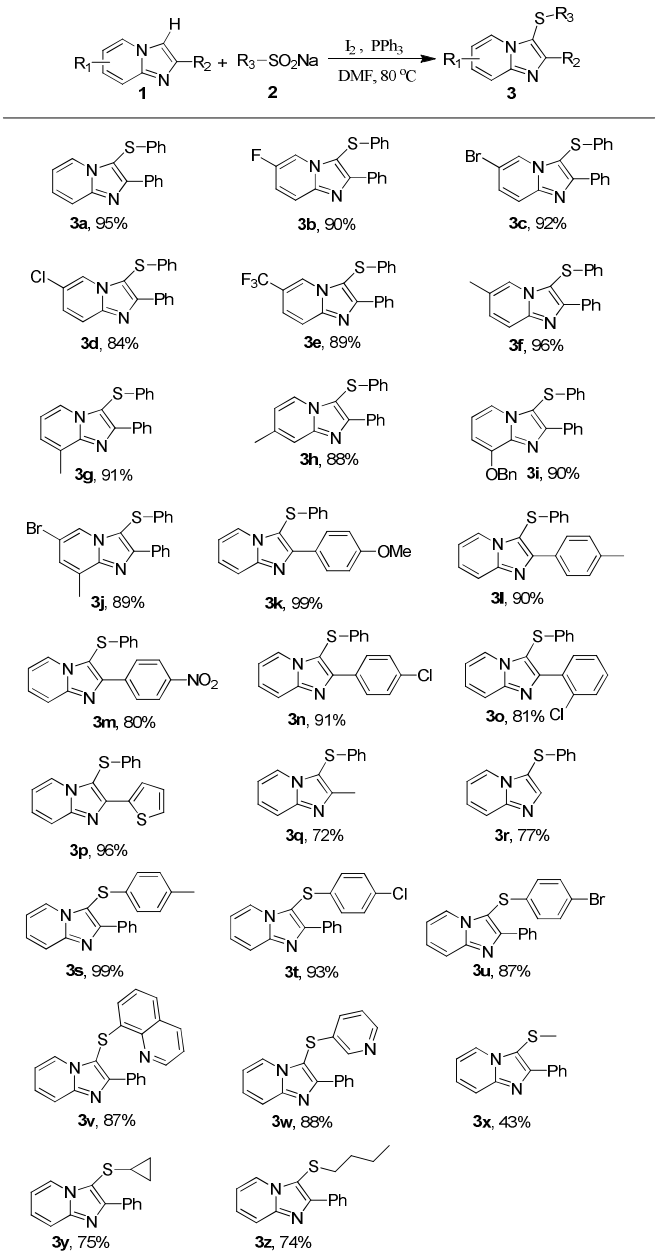
Having obtained the optimum reaction conditions, we next explored the scope and limitation of this process. First, a variety of substituted 2-phenylimidazo[1,2-*a*]pyridines (**1b-1j)** were allowed to react with sodium benzenesulfinate (**2a**) under the optimized reaction conditions to examine the impact of substituent at pyridine moiety (Scheme 1, entries **3b-3j**). It was found that the property and the position of substituents did not obviously effect on the reaction. All the reactions proceeded smoothly and led to the desired products in excellent yields (84-96%). Such as, **1e** with electron-withdrawing group (R^1 = 6-CF_3) and **1f** with electron-donating group (R^1 = 6-Me) gave the corresponding products **3e** and **3f** in 89% and 96% yields, respectively. The substrates with methyl group at C-6 (**1f**), C-7 (**1g**) and C-8 (**1h**) gave the desired products (**3f-3h)** in 88%-96% yields. Even 6-bromo-8-methyl-2-phenylimidazo[1,2-*a*]pyridine (**1j**) still formed the product **(3j**) in 89% yield.

Subsequently, a number of 2-substituted imidazo[1,2-*a*]pyridines were selected to react with sulfenylating agent (**2a**) under optimized

reaction conditions. As shown in Scheme 1, all the substrates (**1k-1r**) were easily converted to the desired products (**3k-3r**) in good to excellent yields. In particular, the products (**3p**, 2-thiophen) and (**3q,** 2-Me) were obtained in 96% and 72% yields, respectively. For the 2-arylsubstituted imidazo[1,2-*a*]pyridines, both the electron-donating and the electron-withdrawing groups on the benzene ring of imidazo[1,2-a]pyridines, could be also easily transformed to the desired products (**3k-3o**) in high yields. Comparing with the *para*-substitutent (**3n**, *p*-Cl, 91% yield), the *ortho*-substitutent on the benzene ring of 2-arylsubstituted imidazo[1,2-*a*]pyridine (**3o**, *o*-Cl, 81% yield) led to the slightly decrease of yield owing to the *ortho* effect.[19e] Interestingly, when unsubstituted imidazo[1,2-a]pyridine was subjected to the same reaction conditions, the regioselective C-3 sulfenated product **3r** was obtained in 77% yield, and no C-2 sulfenated product formation was observed.

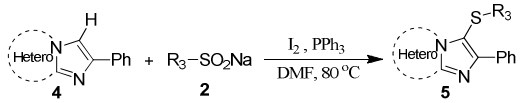
Furthermore, **1a** was fixed as substrate to test various sodium sulfinates under the optimized reaction conditions. Various aryl and heteroaryl sodium sulfinates reacted well with **1a** and gave the desired products **3s-3w** in good to excellent yields. It is worth noting that this method could be extended to aliphatic sulfinates, including sodium methanesulfinate, sodium cyclopropanesulfinate and sodium n-butanesulfinate, to afford the corresponding sulfenylated products (**3x-3z)** in 43%-75% yields.

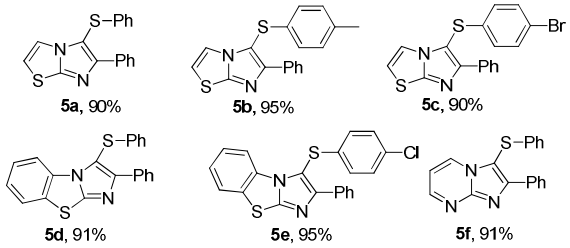
Scheme 1. Substrate scope of sulfenylation reactions[a,b]



[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), I_2 (0.3 mmol), PPh_3 (0.6 mmol), DMF (3 mL), 80°C, 12 h. [b] Isolated yield after column chromatography.

Scheme 2. Sulfenylation of imidazoheterocyclic compounds[a,b]





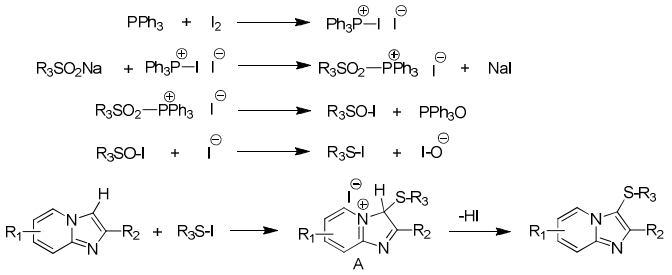
[a] Reaction conditions: **4** (0.3 mmol), **2** (0.6 mmol), I_2 (0.3 mmol), PPh_3 (0.6 mmol), DMF (3 mL), 80°C, 12 h. [b] Isolated yield after column chromatography.

To further expand the scope of this novel methodology, other kinds of imidazoheterocyclic substrates, including 6-phenyl imidazo[2,1-*b*]thiazole, 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole and 2-phenyl imidazo[1,2-*a*]pyrimidine, were also subjected to optimized reaction conditions (Scheme 2). As expected, all the tested imidazoheterocyclic substrates could be also converted to the desired products (**5a-5f**) in high yields.

Based on relevant reports in the literature[19d, 21b] and our observation in the present work, a plausible reaction mechanism for this sulfenylation of imidazopyridines has been proposed in Scheme 3. Initially, iodine reacts with triphenylphosphine to form iodotriphenylphosphonium iodide, which then reacts with sodium sulfinate generating sulfenyl iodide. Subsequently, the imidazolenium intermediate A is formed by regioselective electrophilic attack of sulfenyl iodide on the C-3 position of

imidazo[1,2-*a*]pyridines. Finally, elimination of HI from the intermediate A afforded the desired product.

Scheme 3. Plausible Mechanism



Conclusions

In conclusion, we have developed an efficient iodine-triphenylphosphine mediated synthesis of sulfenated imidazoheterocycles using sodium sulfinates as sulfenylating reagents under transition-metal-free conditions. The methodology features broad substrate scope, convenient sulfenylating reagents and high yields. Since imidazoheterocycles are important core structures for pharmaceuticals, we expected that an efficient synthesis for this kind of compounds could find application in medicinal chemistry.

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Notes and references

1 (a) A. R. Katritzky, C. A Ramsden, E. F. V. Scriven and R. J. K. Taylor, *Comprehensive Heterocyclic Chemistry III*, Elsevier: Oxford, 2008; (b) A. R. Katritzky, Y. J. Xu and H. Tu, *J. Org. Chem*., 2003, **68**, 4935 and references cited therein.

2 (a) M. Lhassani, O. Chavignon, J. M. Chezal, J. C. Teulade, J. P. Chapat, R. Snoeck, G. Andrei, J. Balzarini, E. D. Clercq and A. Gueiffier, *Eur. J. Med. Chem.*, 1999, **34**, 271, and the references cited therein; (b) C. Enguehard-Gueiffier, A. Gueiffier, *Mini-Rev. Med. Chem.*, 2007, **7**, 888, and references cited therein.

3 (a) T. Okubo, R. Yoshikawa, S. Chaki, S. Okuyama and A. Nakazato, *Bioorg. Med. Chem.,* 2004, **12**, 423; (b) P. G. George, G. Rossey, M. Sevrin, S. Arbilla, H. Depoortere and A. E. Wick, *L. E. R. S. Monograph. Ser.*, 1993, **8**, 49.

4 S. Z. Langer, S. Arbilla, J. Benavides and B. Scatton, *Adv. Biochem. Psychopharmacol.*, 1990, **46**, 61.

5 H. Depoortere and P. George, US 5064836, 1991.

6 D. J. Sanger, *Behav. Pharmacol.*, 1995, **6**, 116.

7 (a) D. Belohlavek, P. Malfertheiner and J. Scand, *Gastroenterol Suppl*., 1979, **54**, 44; (b) L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba and W. Murmann, *J. Med. Chem.*, 1965, **8**, 305.

8 L. A. Sorbera, J. Castaner and P. A. Leeson, *Drugs Future*, 2002, **27**, 935.

9 (a) T. Ueda, K. Mizusgige, K. Yukiiri and T. Takahashi, *Cerebrovasc. Dis.*, 2003, **16**, 396; (b) Y. Uemura, S. Tanaka, S. Ida and T. J. Yuzuriha, *Pharm.Pharmacol*., 1993, **45**, 1077.

10 (a) N. Chernyak, and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2010, **49**, 2743; (b) H. Wang, Y. Wang, C. Peng, J. Zhang and Q. Zhu, *J. Am. Chem. Soc.*, 2010, **132**, 13217; (c) M. Adib, E. Sheikhi and N. Rezaei, *Tetrahedron Lett.*, 2011, **52**, 3191; (d) E. F. Dimauro and J. M. Kennedy, *J. Org. Chem.*, 2007, **72**, 1013; (e) H. Wang, Y. Wang, D. Liang, L. Liu, J. Zhang and Q. Zhu, *Angew. Chem., Int. Ed.*, 2011, **50**, 5678; (f) S. K. Guchhait, A. L. Chandgude and G. Priyadarshani, *J. Org. Chem.*, 2012, **77**, 4438; (g) L. Ma, X. Wang, W. Yu and B. Han, *Chem. Commun.*, 2011, **47**, 11333; (h) K. S. Masters, T. R. M. Rauws, A. K. Yasav, W. A. Herrebout, B. V. Veken and B. U. W. Mases, *Chem. Eur. J.*, 2011, **17**, 6315; (i) C. He, J. Hao, H. Xu, Y. Mo, H. Liu, J. Han and A. Lei, *Chem. Commun.*, 2012, **48**, 11073; (j) J. Zeng, Y. J. Tan, M. L. Leow and X. W. Liu, *Org. Lett.*, 2012, **14**, 4386; (l) S. Santra, A. K. Bagdi, A. Majee and A. Hajra, *Adv. Synth. Catal.*, 2013, **355**, 1065; (m) H. Yan, Y. L. Wang and C. M. Pan, *Eur. J. Org. Chem.*, 2014, **13**, 2754; (n) Y. X. Wang, B. Frett and H. Y. Li. *Org. Lett.*, 2014, **16**, 3016; (o) H. Cao, X. H Liu and L. M. Zhao, *Org. Lett.*, 2014, **16**, 146; (p) K. L. Monir, A. K. Bagdi, M. Ghosh and A. Hajra, *Org. Lett*., 2014, **16**, 146.

11 (a) D. Huang, J. Chen, W. Dan, J. Ding, M. Liu and H. Wu, *Adv.Synth. Catal.*, 2012, **354**, 2123; (b) O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Köhn, M. K. Whittlesey and C. G. Frost, *J. Am. Chem. Soc.*, 2011, **133**, 19298; (c) K. M. Schlosser, A. P. Krasutsky, H. W. Hamilton, J. E. Reed and K. Sexton, *Org. Lett.*, 2004, **6**, 819; (d) M. Tudge, M. Tamiya, C. Savarin and G. R. Humphrey, *Org. Lett.*, 2006, **8**, 565； (e) E. Kianmehr, M. Ghanbari, M. N. Niri and R. Faramarzi, *J. Comb. Chem*., 2010, **12**, 41 and references cited therein.

12 (a) K. M. Schlosser, A. P. Krasutsky, H. W. Hamilton, J. E. Reed and K. Sexton, *Org. Lett.*, 2004, **6**, 819; (b) J. S. Yadav, B. V. S. Reddy and Y. J. Reddy, *Tetrahedron Lett.*, 2007, **48**, 7034; (c) C. Dai, Z. Q. Xu, F. Huang, Z. K. Yu and Y. F. Gao*, J. Org. Chem.*, 2012, **77**, 4414; (d) S. Ranjit, R. Lee, D. Heryadi, C. Shen, J. Wu, P. F. Zhang, K. W. Huang and X. G. Liu, *J. Org. Chem.*, 2011, **76**, 8999; (e) Y. Maeda, M. Koyabu, T. Nishimura and S. Uemura, *J. Org. Chem.*, 2004, **69**, 7688; (f) G. Wu, J. Wu and L. Wu, *Synth. Commun.*, 2008, **38**, 1036.

13 (a) S. Zhang, P. Qian, M. Zhang, M. Hu and J. Cheng, *J. Org. Chem.*, 2010, **75**, 6732; (b) S. Fukuzawa, E. Shimizu, Y. Atsuumi, M. Haga and K. Ogata, *Tetrahedron Lett.*, 2009, **50**, 2374; (c) C. D. Prasad, S. J. Balkrishna, A. Kumar, B. S. Bhakuni, K. Shrimali, S. Biswas and S. Kumar, *J. Org. Chem.*, 2013, **78**, 1434; (d) W. Ge and Y. Wei, *Green Chem*., 2012, **14**, 2066; (e) L. H. Zou, J. Reball, J. Mottweiler and C. Bolm, *Chem. Commun*., 2012, **48**, 11307; (f) P. Sang, Z. Chen, J. Zou and Y. Zhang, *Green Chem*., 2013, **15**, 2096; (h) P. Gogoi, M. Kalita, P. Barman and S. R. Gogoi, *Synlett*, 2013, **24**, 873; (i) M. Klecka, R. Pohl, J. Cejka and M. Hocek, *Org. Biomol. Chem*., 2013, **11**, 5189; (j) C. D. Prasad, S. Kumar, M. Sattar, A. Adhikary and S. Kumar, *Org. Biomol. Chem*., 2013, **11**, 8036.

14 M. Matsugi, K. Murata, K. Gotanda, H. Nambu, G. Anikumar, K. Matsumoto and Y. Kita, *J. Org. Chem*., 2001, **66**, 2434.

15 (a) M. Raban and L. J. Chern, *J. Org. Chem*., 1980, **45**, 1688; (b) F. Bottino, R. Fradullo and S. Pappalardo, *J. Org. Chem.*, 1981, **46**, 2793; (c) I. V. Koval', *Russ. J. Gen. Chem.*, 1995, **64**, 731; (d) P. Hamel, *J. Org.*

Chem., 2002, **67**, 2854; (e) Y. Chen, C. H. Cho and R. C. Larock, *Org. Lett*., 2009, **11**, 173.

16 (a) Y. Cai, J. Li, W. Chen, M. Xie, X. Liu, L. Lin, X. M. Feng, *Org. Lett*., 2012, **14**, 2726; (b) C. C. Silveira, S. R. Mendes, L. Wolf and G. M. Martins, *Tetrahedron Lett*., 2010, **51**, 2014; (c) M. Tudge, M. Tamiya, C. Savarin and G. R. Humphrey, *Org. Lett*., 2006, **8**, 565.

17 P. Anbarasan, H. Neumann and M. Beller, *Chem. Commun*., 2011, **47**, 3233.

18 F. L. Yang and S. K. Tian, *Angew. Chem., Int. Ed.*, 2013, **52**, 4929.

19 (a) Z. Li, J. Hong and X. Zhou, *Tetrahedron*, 2011, **67**, 3690; (b) W. L. Ge, X. Zhu and Y. Y. Wei, *Eur. J. Org. Chem*., 2013, **27**, 6015; (c) S. M. Patil, S. Kulkarni, M. Mascarenhas, R. Sharma, S. M. Roopan and A. Roychowdhurya, *Tetrahedron*, 2013, **69**, 8255; (d) C. Ravi, D. C. Mohan, and S. Adimurthy， *Org. Lett*.， 2014, **16**, 2978; (e) Z. C. Gao, X. Zhu and R. H Zhang， *RSC Adv*., 2014, **4**, 19891; (f) D. C. Mohan, S. N. Rao, C. Ravi and S. Adimurthy, *Asian J. Org. Chem.*, 2014, **3**, 609; (g) C. Hamduchi, J. D. Blas and J. Ezquerra, *Tetrahedron*, 1999, **55**, 541； (h) C. Hamdouchi, C. Sanchez and J. Ezquerra, *Synthesis*, 1998, **6**, 867; (i) R. J. Bochis, L. E. Olen, M. H. Fisher, R. A. Reamer, G. Wilks, J. E. Taylor and G. Olson, *J. Med. Chem*., 1981, **24**,1483.

20 (a) P. Page, *Organosulfur Chemistry: Stereochemical Aspects*, AcademicPress, Inc., San Diego, 1998; (b) S. Dubbaka and P. Vogel, *Angew. Chem., Int. Ed.* 2005, **44**, 7674; (c) G. G. Liang, M. C. Liu, J. X. Chen, J. C. Ding, W. X. Gao and H. Y. Wu, *Chin. J. Chem.,* 2012, **30** ,1611 (d) G. G. Liang, J. Chen, J. L Chen, W. M. Li, J. X. Chen and H. Y. Wu, *Tetrahedron Lett*., 2012, **53**, 6768.

21 (a) F. H. Xiao, H. Xie, S. W. Liu and G. J. Deng, *Adv. Synth. Catal.*, 2014, **356**, 364; (b) P. Katrun, S. Hongthong, S. Hlekhlai, M. Pohmakotr, V. Reutrakul, T. Jaipetch and C. Kuhakarn, *RSC Adv.*, 2014, **4**, 18933; (c) H. H. Rao, P. Wang, J. C. Wang, Z. F. Li, X. Z. Sun and S. L. Cao, *RSC Adv.*, 2014, **4**, 49165.

22 (a) Y. Zhao, Z. M. Ge, T. M. Cheng and R. T. Li, *Synlett*, 2007, **10**, 1529; (b) P. C. Gao, P. L. Leng, Q. Sun, X. Wang, Z. M. Ge and R. T. Li. *RSC Adv.*, 2013, **3**, 17150.