

View Article Online View Journal

ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: G. Deng, Y. Liao, Y. Peng, H. Qi, H. Gong and C. Li, *Chem. Commun.*, 2014, DOI: 10.1039/C4CC08370A.



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard <u>Terms & Conditions</u> and the <u>Ethical guidelines</u> still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



www.rsc.org/chemcomm

View Article Online

www.rsc.org/xxxxx

Published on 26 November 2014. Downloaded by Northern Illinois University on 26/11/2014 13:32:48

Palladium-Catalyzed Benzothieno[2,3-b]indole Formation via **Dehydrative-Dehydrogenative Double C-H Sulfuration with Sulfur Powder, Indoles and Cyclohexanones**

Yunfeng Liao,^[a,c] Yi Peng,^[a] Hongrui Qi,^[a] Guo-Jun Deng,^{*[a]} Hang Gong,^[a,b] Chao-Jun Li^{*[b]}

s Received (in XXX, XXX) Xth XXXXXXXX 20XX, Accepted Xth XXXXXXXX 20XX DOI: 10.1039/b000000x

A palladium-catalyzed C-S bond formation via dehydrativedehydrogenative double C-H sulfuration with sulfur powder described. The dehydrogenated intermediates of 10 cyclohexanones were trapped to act as efficient aryl source under oxygen atmosphere. This procedure provided a novel approach for the preparation of benzothieno[2,3-b]indoles.

Sulfur-containing organic compounds play important roles in organic synthesis, pharmaceutical drugs and materials science. 15 In recent years, organosulfur compounds have received considerable attention and numerous methods for the construction of C-S bonds have been developed.² Among them, transition metal-catalyzed cross-coupling reaction has become one of the most important methods for the construction of C-S bonds.³ On 20 the basis of sulfur source, there are two general approaches for the construction of C-S bonds via cross-coupling reactions. One is the transition metal-catalyzed cross-coupling reaction of organic halides with organosulfur substrates; among which thiols have been the most popular reagents in these reactions.⁴ However,

- 25 most thiols have unpleasant odors, which impedes their applications by these processes. The second general crosscoupling approach is based on inorganic sulfur reagents; sulfurcontaining inorganic compounds such as Na₂S,⁵ K₂S⁶, Na₂S₄⁷ Na₂S₂O₃⁸ and K₂CS₃⁹ are used as cleaner and more sustainable
- 30 inorganic sulfur sources. Recently, the cheap and abundant sulfur powder (S₈) has also been successfully applied for the construction of C-S bonds.¹⁰ In most cases, active substrates R-X $(X = Cl, Br, I, OTf, and B(OH)_2)$ with leaving groups were coupled with inorganic sulfides or sulfur power in the presence of
- 35 transition metals. In recent years, the direct sulfuration of C-H bonds has attracted considerable interest since this strategy can provide a more atom-economic route for C-S bond formation by omitting substrate pre-activation.¹¹ However, C-S bond formation via a double C-H sulfuration using inorganic sulfur sources is
- 40 very challenging due to the low activity of both C-H bond and inorganic sulfur sources, and there are only a few reports on this kind of transformation.¹²

Condensed indole derivatives are valued for their biological activities and electronic properties.¹³ Thieno[2,3-*b*]indole (A) 45 shows potent applications in treating diseases of the human

central nervous system (Scheme 1).¹⁴ Thienodolin (**B**) has

50 Scheme 1 Examples of thieno-fused indole derivatives



55 been isolated from Streptomyces albogriseolus and exhibits plant-growth regulatory properties.¹⁵ Benzothieno[2,3-*b*]indole (**C**) shows great potential applications in organic electroluminescent devices.¹⁶ However, efficient methods for the preparation of these indole-containing heterocycles in one-pot are 60 rare. Unsubstituted benzothieno[2,3-b]indole (C) can be synthesized from indoline-2,3-diones, cyclohexanones and P₄S₁₀ via a five-step procedure.¹⁷ Very recently, Hotta et al. reported that the reaction of 3-bromobenzo[b]thiophene with 1-iodo-2nitrobenzene could provide benzothieno[2,3-b]indole C by a 65 sequential reaction of replacement, coupling and cyclization operations.^{16b, 16c} Similarly, N-substituted benzothieno[2,3- b]indoles can also be synthesized from 3-bromobenzo[b]thiophene via a six-step procedure.¹⁸ Flynn and co-workers reported a five-step procedure to convert 2-iodoaniline to 3-iodothienoindole using 70 iodine as a key promoter.¹⁹ These methods all require highly prefunctionalized substrates and multi-step operations, which severely limited the substrate scope and their further applications.



It is highly desirable to develop efficient methods for the synthesis of benzothieno[2,3-b]indoles in one pot using readily available raw materials. Recently, the Stahl group developed a strategy to convert cyclohexanones into phenols

mcomm Accepted Manuscrip

This journal is © The Royal Society of Chemistry [year]

cyclohexenones via a dehydrogenation-tautomerization process.²⁰ We and others successfully trapped the dehydrogenated intermediates of cyclohexanones for C-C²¹ and C-hetero²² bonds formation. Herein, we report a novel strategy for one-pot ⁵ benzothieno[2,3-*b*]indole formation from readily available and simple starting materials via dehydrative-dehydrogenative double C-H sulfuration under oxygen atmosphere (Scheme 2).

Our study was initiated by using 1-methyl-1H-indole (1a), cyclohexanone (2a) and sulfur powder (S_8) as the starting 10 materials to determine the optimized reaction conditions (Table 1). No desired product was observed when the reaction was carried out in the absence of any catalyst under an oxygen atmosphere at 125 °C (Table S1 in SI, entry 1). To our delight, the desired product 6-methyl-6H-benzo[4,5]thieno[2,3-b]indole 15 (3a) was observed in 35% yield when 5 mol % iodine was used as the catalyst (entry 2). Inspired by this observation, several iodide-containing catalysts were examined, and among them PdI₂ showed the best efficiency to give 3a in 42% yield (entry 6). Several nitrogen containing ligands were investigated, and among 5*H*-cyclopenta[1,2-*b*:5,4-*b*']dipyridin-5-one 20 them (CPDO) showed the best efficiency (entries 7-9). The yield of 3a could be improved to 80% when 2.0 equiv of cyclohexanone was used (entry 13). Other palladium salts showed lower catalytic

Table 1 Reaction of cyclohexanones (2) with 1-methyl-1*H*-indole (1a)^a

2a

2h

2c

2d

2e

2f

2g

2h

2i

2j

Me

5 mol% Pdl₂

10 mol% CPDO

O₂, 125 °C, 16 h

o-dichlorobenzene

Product

3a

3b

3c

3d

3e

3f

3g

3h

3

 $-R^1$

Yield (%)^b

70 (68)^c

85

80

73

87

85

81

74

60

trace

^a Conditions: **1a** (0.5 mmol), **2** (1.0 mmol), Pdl₂ (0.025 mmol), CPDO (0.05 mmol), sulfur (1.0 mmol), *o*-dichlorobenzene (2.0 mL), 125 °C, 16 h, under oxygen. ^b Isolated yield based on **1a**. ^c Reaction was performed on a 5.0 mmol scale. ^d 24 h.

²⁵ efficiency than PdI_2 under similar reaction conditions (entries 14-16). However, a combined use of $Pd(OAc)_2$ and iodine could



 Table 2 Reaction of indoles with cyclohexanone (2a)
 11.1039/C4CC08370A



^{*a*} Conditions: **1** (0.5 mmol), **2a** (1.0 mmol), PdI₂ (0.025 mmol), CPDO (0.05 mmol), sulfur (1.0 mmol), o-dichlorobenzene (2.0 mL), 125 °C, 16 h, under oxygen. ^{*b*} Isolated yield based on **1**. ^{*c*} 24 h. ^{*d*} PdI₂ (0.05 mmol), CPDO (0.1 mmol). ^{*e*} 150 °C.

With the optimized reaction conditions established, the substrate scope with respect to cyclohexanones was explored (Table 1). When the reaction scale was enlarged to 5.0 mmol, the desired product 3a was obtained in 68% yield (entry 1). Cyclohexanones bearing an alkyl substituent at the 4-position ³⁵ were able to smoothly couple with **1a** and sulfur powder to give the corresponding product in good to high yields (entries 2-6). When 4-pentylcyclohexanone (2e) was employed, the desired product 3e was obtained in 87% yield (entry 6). The presence of a phenyl substituent at the 4-position did not significantly decrease 40 the reaction yield (entry 7). The ester functional group was well tolerated to give the product 3h in 74% yields (entry 8). The position of the methyl substituent on the cyclohexanone ring affected the reaction yield; profoundly when 3methylcyclohexanone (2i) was used, the desired product 3i was 45 obtained in 60% yield (entry 9); however, no desired product 3j was observed when 2-methylcyclohexanone (2j) was used (entry 10). The structure of 3b was further confirmed by X-ray crystallography (scheme 3).

Scheme 3 X-ray structure of 3b

This journal is © The Royal Society of Chemistry [year]

ChemComm Accepted Manuscript

1a

R¹

 $R^1 = H$

 $R^1 = Me$

 $R^1 = Et$

 $R^1 = Ph$

Me

 $R^1 = CO_2Et$

R¹ = isopropyl

 $R^1 = n$ -pentyl

 $R^1 = tert$ -pentvl

Entry

1

2

3

4

5

6

7^d

8

9d

10

2

Cyclohexanone



To further examine the scope and limitation of the reaction, we tested various indoles for this kind of reaction (Table 2). Firstly, 5 the influence of various substituents at C-5 position was evaluated (entries 1-7). In all cases, the reaction proceeded smoothly to give the corresponding products in moderate to good yields. Functional groups such as cyano, fluoro, bromo and even iodo were all compatible under the optimized reaction conditions. 10 Similar results were observed when the substituents were located at the C-6 position of 1-methyl-1H-indole (entries 8-12). When an ester group was present, the desired product 3s was obtained in 65% yield (entry 9). However, 3x was achieved in only 38% yield when the same group was located at C-7 position (entry 14). 15 Only a trace amount of 3y was observed when the methyl substituent was located at C-4 position (entry 15). In addition, 1benzyl-1H-indole (1q) could also react with 2a and sulfur powder to give the corresponding product 3z in 73% yield (entry 16).

To have a better understanding of the reaction, some control 20 experiments were performed under various conditions. The reaction of 1-methyl-1H-indole (1a) with 4-methylcyclohexanone (2b) and sulfur powder gave 1-methyl-3-(4-methylcyclohex-1-en-1-yl)-1H-indole (5a) in 27% yield in 1 h. Meanwhile, 3,6dimethyl-2,3,4,6-tetrahydro-1H-benzo[4,5]thieno[2,3-b]indole

25 (4a) and the desired product 3b were observed in 43% and 5% yields, respectively (Table 3, entry 1). When the reaction time was extended to 4 h, the yield of 3b increased to 50% while the yields of 5a and 4a both decreased (entry 2). No desired product could be obtained when the reaction was carried out under argon ³⁰ atmosphere (entry 3). Interestingly, **5a** could be observed even in the absence of palladium catalyst and ligand by GC-MS (entries 4-5). Treating 5a with sulfur powder afforded 4a and 3b with 70% and 25% yields (Scheme 4, a). 4a could be further converted into **3b** in 94% yield under the catalytic conditions (Scheme 4, b).

Table 3 Control experiments I⁶

1a +	2b — S ₈	- , N_	5a	N	4a	 + 3b
Entry	Catalyst	Licand	Time		Yield (%)	
	Catalyst	Eigana	nine	5a	4a	3b
1	Pdl ₂	CPDO	1 h	27	43	5
2	Pdl ₂	CPDO	4 h	6	20	50
3 ^b	Pdl ₂	CPDO	16 h	0	90	trace
4			16 h	15	0	0
5 ^b			16 h	30	0	0

^a condition: **1a** (0.2 mmol), **2b** (0.4 mmol), S₈ (0.4 mmol), Pdl₂ (0.01 mmol), CPDO (0.02 mmol), o-dichlorobenzene (1.0 mL) under oxygen unless otherwise noted, 125 °C, GC yield based on 1a. b under argon.

Scheme 4 Control experiments II

This journal is © The Royal Society of Chemistry [year]



Based on these observations, a plausible mechanism to 45 rationalize this transformation is illustrated in Scheme 5. 1-methyl-1H-indole (1a) with Treatment of 4methylcyclohexanone (2b) in the presence of sulfur powder affords intermediate 1-methyl-3-(4-methylcvclohex-1-en-1-yl)-1H-indole (5a).²¹ C-H activation of 5a with Pd(0) generates a 50 Pd(II) complex 6a. A subsequent insertion reaction and reductive elimination afford the cyclized intermediate 4a. In the meanwhile, Pd(II) can be transformed into Pd(0) in the presence of S_8 and CPDO, closing the first catalytic cycle. Another Pd(II) complex 7a can be formed by palladation of intermediate 4a. Subsequent 55 β -hydride-elimination will liberate intermediate 8a, which can be converted into the final product 3b via a further oxidative dehydrogenation-tautomerization process. A metal-hydride species 9a can be regenerated into the initial catalyst 10a in the presence of oxygen, thus closing the second catalytic cycle.^{20a}

60 Scheme 5 Proposed mechanism



Conclusions

65 In conclusion, we have developed an efficient approach for the construction of C-S bonds via double C-H sulfuration using sulfur powder as the sulfur source. Cyclohexanones acted as the novel aryl source via dehydrogenation-tautomerization process

Published on 26 November 2014. Downloaded by Northern Illinois University on 26/11/2014 13:32:48.

65

under oxygen atmosphere. The three-component reaction was realized in one pot to selectively give the corresponding benzothieno[2,3-*b*]indoles in good yields. This method affords an efficient approach for the synthesis of thieno-fused indole s derivatives using readily available starting materials under mild

reaction conditions. Further studies of the reaction mechanism are in progress in our laboratory.

Acknowledgements

This work was supported by the National Natural Science ¹⁰ Foundation of China (21172185, 21372187), the New Century Excellent Talents in University from Ministry of Education of China (NCET-11-0974) and the Research Fund for the Education Department of Hunan Province of China (13C192).

Notes and references

- ¹⁵ ^a Key Laboratory of Environmentally Friendly Chemistry and Application of Ministry of Education, College of Chemistry, Xiangtan University, Xiangtan 411105, China; E-mail: gjdeng@xtu.edu.cn.
- ^b Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, QC H3A 0B8, Canada; E-mail: E-mail: cj.li@mcgill.ca
- ²⁰ School of Chemistry & Chemical Engineering, Hunan Institute of Engineering Xiangtan 411104, China.
 † Electronic Supplementary Information (ESI) available: [details of any
- supplementary information available should be included here]. See DOI: 10.1039/b000000x/
 25 1 a) F. Bernardi, I. G. Csizmadia, A. Mangini, *Organic Sulfur*
- a) F. Bernardi, I. G. Csizmadia, A. Mangini, Organic Sulfur Chemistry. Theoretical and Experimental Advances, Vol. 19 Elsevier, Amsterdam, 1985; b) P. Kielbasinski, Phosphorus Sulfur Silicon Relat. Elem. 2011, 186, 1104; c) A. Q. Acton, Ed. Sulfur Compounds: Advances in Research and Application, Scholarly Editions: Atlanta, GA, 2012.
- a) H. Liu, X. F. Jiang, *Chem. Asian J.* 2013, **8**, 2546; b) T. Kondo, T. A. Mitsudo, *Chem. Rev.* 2000, **100**, 3205; c) M. D. McReynolds, J. M. Dougherty, P. R. Hanson, *Chem. Rev.* 2004, **104**, 2239.
- 3 I. P. Beletskaya, V. P. Anikov, *Chem. Rev.* 2011, **111**, 1596
- ³⁵ 4 For recent selected examples, see: a) E. Alvaro, J. F. Hartwig, J. Am. Chem. Soc. 2009, **131**, 7858; b) D. Ma, Q. Geng, H. Zhang, Y. Jiang, Angew. Chem. 2010,**122**, 1313; Angew. Chem. Int. Ed. 2010, **49**, 1291; c) T. Dahl, C. W. Tornøe, B. Bang-Anderson, P. Nielsen, M. Jøegensen, Angew. Chem. 2008, **120**, 1750; Angew. Chem. Int.
- Ed. 2008, 47, 1726; d) A. Correa, M. Carril, C. Bolm, Angew. Chem. 2008, 120, 2922; Angew. Chem. Int. Ed. 2008, 47, 2880; e)
 J. R. Wu, C. H. Lin, C. F. Lee, Chem. Commun. 2009, 4450; f) M.
 A. Fernandez-Rodriguez, Q. Shen, J. F. Hartwig, J. Am. Chem. Soc.
 2006, 128, 2180; g) X. B.Xu, J. Liu, J. J. Zhang, Y. W. Wang, Y.
- ⁴⁵ Peng, Org. Lett. 2013, **15**, 550; h) C. Dai, X. Sun, X. Tu, L. Wu, D. Zhan, Q. Zeng, Chem. Commun. 2012, **48**, 5367; i) K.Inamoto, Y. Arai, K.Hiroya, T. Doi, Chem. Commun. 2008, 5529.
- 5 a) Ma, D.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. Angew. Chem. 2009, 121, 4286; Angew. Chem. Int. Ed. 2009, 48, 4222; b)
- 50 Kashiki, T.; Shinamura, S.; Kohara, M.; Takimiya, K.; Ikeda, M.; Kuwabara, H. *Org. Lett.* 2009, **11**, 2473; c) Sun, L. L.; Deng, C. L.; Tang, R. Y.; Zhang, X. G. *J. Org. Chem.* 2011, **76**, 7546; d) Li, C. L.; Zhang, X. G.; Tang, R. Y.; Zhong, P.; Li, J.; H. *J. Org. Chem.* 2010, **75**, 7037.
- 55 6 W. You, X. Yan, Q. Liao, C. Xi, Org. Lett. 2010, 12, 3930.
- D. J. Jansen, R. A. Shenvi, J. Am. Chem. Soc. 2013, 135, 1209.
 a) Z. Qian, H. Liu, X. Xiao, Y. Fu, J. Wei, Y. Li, X. Jiang, Org. Lett. 2013, 15, 2594; b) Y. M. Li, J. H. Pu, X. F. Jiang, Org. Lett. 2014, 16, 2692; c) J. T. Reeves, K. Camara, Z. S. Han, Y. Xu, H. Lee, C.
 A. Busacca, C. H. Senanayake, Org. Lett. 2014, 16, 1196; d) Z. J.
- Qiao, J. P. Wei, X. F. Jiang, *Org. Lett.* 2014, 16, 1212.
 J. Kim, J. Ashenhurst, A. M. Movassaghi, *Science* 2009, 324, 238.
- 10 a) Y. Jiang, Y. Qin, S. Xie, X. Zhang, J. Dong, D. Ma, Org. Lett. 2009, 11, 5250; b) C. Chen, Y. Xie, L. Chu, R. W. Wang, X. Zhang,

4 | *Journal Name*, [year], [vol], 00–00

- F. L. Qing, Angew. Chem. 2012, **124**. 2542; Angew. Chem. Int. Ed. 2012, **51**, 2492; c) H. Deng, Z. Li, F. Ke, X. Zhou, Chem. Eur. J. 2012, **18**, 4840; d) M. Arisawa, T. Ichkawa, M. Yamaguchik, Organine Lett. 2012, **14**, 5318; e) J. T. Yu, H. Guo, WOW, OHOFEL, WCGARG, OA Adv. Synth. Catal. 2014, **356**, 749.
- 70 11 For selected examples on single C-H sulfuration using inorganic sulfur source, see: a) C. Chen, L. Chu, F. L. Qing, *J. Am. Chem. Soc.* 2012, **134**, 12454; b) T. B. Nguyen, L. Ermolenko, A. Al-Mourabit, *Org. Lett.* 2013, **15**, 4218; c) X. Zhang, W. Zeng, Y. Yang, H. Huang, Y. Liang, *Org. Lett.* 2014, **16**, 876.
- 75 12 a) S. P. Massie, P. K. Kadaba, J. Org. Chem. 1955, 21, 347; b) W. Carpenter, M. S. Grant, H. R. Snyder, J. Am. Chem. Soc. 1960, 82, 2739; c) K. S. Rao, T. S. Wu, Tetrahedron 2012, 68, 7735; d) F. Shibahara, T. Kanai, E. Yamaguchi, A. Kamei, T. Yamauchi, T. Murai, Chem. Asian J. 2014, 9, 237.
- 80 13 For reviews see: (a) J. Casado, R. O. Ponce, J. T. López Navarrete, *Chem. Soc. Rev.* 2012, 41, 5672; b) I. F. Perepichka, D. F. Perepichka, *Handbook of Thiophene-Based Material: Applications in Organic Electronics and Photonic*, John Wiley & Sons, Chichester, U. K., 2009.
- 85 14 M. Pedras, C. Soledade, M. Suchy, *Bioorg. Med. Chem.* 2006, 14, 714.
 - 15 K. Kanbe, H. Naganawa, K. T. Nakamura, Y. Okami, T. Takeuchi, *Biosci. Biotechnol. Biochem.* 1993, 57, 632.
 - a) I. M. Griesheim, A. W. F. Kelkheim, C. P. Darmstadt, et al. US
 20130126792, 2013; b) H. Masanori, S. Yuichi, K. Atsushi, et al.
 EP2617724, 2013; c) S. Yuichi, H. Masanori, M. Megumi,
 EP2628743, 2013.
 - 17 L. Jean, R. Daniel, G. Jean, C. Michele, P. Claudine, *Bull. Soc. Chim. Fr.* 1987, **1**, 193.
- 95 18 M. Kienle, A. J. Wagner, C. Dunst, P. Knochel, *Chem. Asian J.* 2011, 2, 517.
- 19 L. Aurelio, R. Volpe, R. Halim, P. J. Scammells, B. L. Flynn, Adv. Synth. Catal. 2014, 356, 1974.
- a) Y. Izawa, D. Pun, S. S. Stahl, *Science* 2011, 333, 209; b) T. N.
 Diao, S. S. Stahl, *J. Am. Chem. Soc.* 2011, 133, 14566; c) Y. Izawa,
 C. W. Zheng, S. S. Stahl, *Angew. Chem.* 2013, 125, 3760; *Angew. Chem. Int. Ed.* 2013, 52, 3672.
 - 21 S. P. Chen, Y. F. Liao, F. Zhao, H. R. Qi, S. W. Liu, G. J. Deng, Org. Lett. 2014, 16, 1618.
- a) Y. Xie, S. Liu, Y. Liu, W. Chen, G. J. Deng, Org. Lett. 2012, 14, 1692; b) F. H. Xiao, Y. F. Liao, M. Y. Wu, G. J. Deng, Green Chem. 2012, 14, 3277; c) M. Simon, S. A. Girard, C. J. Li, Angew. Chem. 2012, 124, 7655; Angew. Chem. Int. Ed. 2012, 51, 7537; d) S. Girard, X. Hu, T. Knauber, F. Zhou, M. Simon, G. J. Deng, C. J.
 - Li, Org. Lett. 2012, 14, 5606; e) A. Hajra, Y. Wei, N. Yoshika, Org. Lett. 2012, 14, 5488; f) M. Barros, S. Dey, C. Maycock, P. Rodrigues, Chem. Commun. 2012, 48, 10901; g) J. Zhao, H. W. Huang, W. Q. Wu, H. J. Chen, H. F. Jiang, Org. Lett. 2013, 15, 2604; h) Y. F. Liao, P. C. Jiang, S. P. Chen, H. R. Qi, G. J. Deng, Green Chem. 2013, 15, 3302; i) W. L. Ge, X. Zhu, Y. Y. Wei, Adv. Synth. Catal. 2013, 355, 3014; j) Y. F. Liao, P. C. Jiang, S. P. Chen, F. H. Xiao, G. J. Deng, RSC Adv. 2013, 3, 18605.

This journal is © The Royal Society of Chemistry [year]

v. 110

115