Advanced Synthesis & Catalysis

Accepted Article

Title: Iodine-Promoted Tunable Synthesis of 2-Naphthyl Thioethers and 1-Naphthyl Thioethers

Authors: Yishu Bao, Xiuqin Yang, Zonghao Dai, Suyu Ji, Qing-Fa Zhou, and Fulai Yang

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201801562

Link to VoR: http://dx.doi.org/10.1002/adsc.201801562

10.1002/adsc.201801562

UPDATE

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Iodine-Promoted Tunable Synthesis of 2-Naphthyl Thioethers and 1-Naphthyl Thioethers

Yishu Bao,[a] Xiuqin Yang,[a] Zonghao Dai,[a] Suyu Ji,[a] Qingfa Zhou [a]* and Fulai Yang[a]*

[a] State Key Laboratory of Natural Medicines, Department of Organic Chemistry, China Pharmaceutical University, Nanjing, 210009, P. R. China.
Fax: (+86)-025-8628-5179; Phone: (+86)-025-8618-5160; Email: zhouqingfa@cpu.edu.cn; fly1986@ustc.edu.cn

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

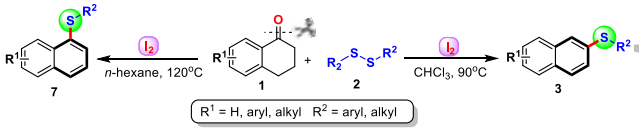
Abstract. An iodine-promoted regioselective sulfenylation/deoxygenation/aromatization reaction of 1-tetralones with disulfides has been developed. This process could be modified to synthesize 2-naphthyl thioethers and 1-naphthyl thioethers in moderate to excellent yields, respectively. Furthermore, when the reaction was extended to 2-tetralones, 2-naphthyl thioethers were obtained as the sole products. The current study bridges the deoxygenation and sulfenylation/aromatization of ketones, thus providing a new tool in organic synthesis.

Keywords: Tetralones; Disulfides; Iodine; Deoxygenation; Synthetic methods

The selective formation of C(sp^2)-S bonds is a fundamental transformation in organic synthesis.[1] Recent years have witnessed a growing interest in transition-metal-catalyzed cross-coupling reactions of carbon-halides[2] or carbon-boronic acids/esters[3] with sulfenylating agents to form C(sp^2)-S bonds. Despite considerable advances, in view of sustainable and green chemistry, these reactions have several limitations. Therefore, developing alternative methodologies that could be advantageous in terms of catalyst, availability of starting materials, convenience of manipulation, substrate scope, and environmental friendliness is one of the research hotspots in organic synthesis.

The carbonyl group, which is a reactive center for a wide range of functional group transformations, is among the most fundamental functionalities in organic chemistry.[4] Among them, both deoxygenation[5] and α-sulfenylation[6] have long been important pursuits in the synthetic community. Many impressive accomplishments have been achieved in these fields; for example, well-known milestones in the deoxygenation of ketones include the Wolff-Kishner-Huang reaction,[7] the Bamford-Stevens-Shapiro Olefination[8] and the Clemmensen Reduction.[9] Sulfenylation of ketones has also made great progress. Recently, Wei[10] reported excellent studies on the sulfenylation/aromatization of unactivated cyclohexanones to give 2-sulfanylphenols with retention of an oxygen atom. Nevertheless, to the best of our knowledge, tandem deoxygenation and sulfenylation/aromatization of ketones with sulfenylating agents have never been documented.

Very recently, we have developed a new iodine-promoted protocol for the synthesis of β-iodoalkenyl sulfides via tandem deoxygenated iodization/olefination/sulfenylation of ketones with sulfonyl hydrazides.[11] Intriguingly, we found that ketones could react with disulfides to give a trace amount of vinyl sulfides. Encouraged by this result, we investigated whether this reaction could be optimized into a synthetically useful transformation. To our surprise, this process afforded not only 2-naphthyl thioethers but also 1-naphthyl thioethers (Scheme 1).



Scheme 1. Iodine-Promoted Tunable Synthesis of 2-Naphthyl Thioethers and 1-Naphthyl Thioethers.

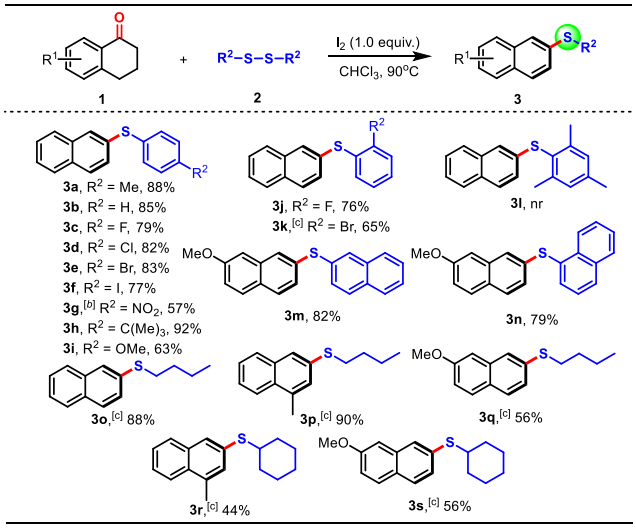
The reaction of 1-tetralones (**1a**) with disulfides (**2a**) was selected as a model reaction. Initially, various solvents were screened, and satisfactory regioselectivity and yield of 2-naphthyl thioether **3a** (83%, **3a**:**7a** 14:1) were achieved when using $CHCl_3$ as the solvent, while *n*-hexane afforded a moderate yield with poor regioselectivity. Running the reaction in $CHCl_3$ (1.5 mL) yielded a better result (88%, **3a**:**7a** 20:1). Heating the mixture at 110 °C led to a higher yield but poorer regioselectivity (94%, **3a**:**7a** 12:1). It is worth noting that the ratio of starting materials is crucial for the regioselectivity. Raising the ratio of **1a** and **2a** gave poorer regioselectivity. Thus, the optimal reaction conditions for 2-naphthyl thioether **3a** synthesis were 2.0 equiv. of **1a**, 1.0 equiv. of **2a** and

10.1002/adsc.201801562

1.0 equiv. of I_2 in $CHCl_3$ at 90 °C. The optimization of the above reaction conditions suggests that using *n*-hexane as a solvent, raising the temperature and increasing the loading of **1a** favored the formation of 1-naphthyl thioether **7a**. In addition, replacing iodine with NIS, TBAI and NBS led to much lower yield. Decreasing the amount of I_2 with adding TBHP or H_2O_2 failed to give higher yields. Interestingly, a change in regioselectivity was observed when the temperature was raised to 120 °C, and the ratio of **1a** and **2a** was adjusted to 4:1. Further examination showed that the optimal reaction conditions for the synthesis of 1-naphthyl thioether **7a** were 4.0 equiv. of **1a**, 1.0 equiv. of **2a** and 1.5 equiv. of iodine in *n*-hexane at 120 °C (*Table S1 in the Supporting Information*).

With the optimized reaction conditions identified, we then investigated the substrate scope of this novel reaction. The scope of the disulfides was first examined, and the results are summarized in Table 1. A range of substituted aryl disulfides **2** could react with 1-tetralones **1** to give structurally diverse 2-naphthyl thioethers **3** in moderate to excellent yields. Halogen substitution in the aromatic rings was tolerated in this protocol (**3c**-**3f**, **3j**, **3k**), enabling further derivatization through cross-coupling reactions. In addition, acceptable yields were obtained when strong electron-rich and strong electron-deficient substituents on the benzene ring were applied in this transformation (**3g**, **3i**). However, no product was detected from the reaction between dimesityldisulfane and 1-tetralone (**3l**), most likely owing to the steric repulsion in the sulfenylation step. As we hoped, this optimized protocol can also be applied to aliphatic disulfides (**3o**-**3s**).

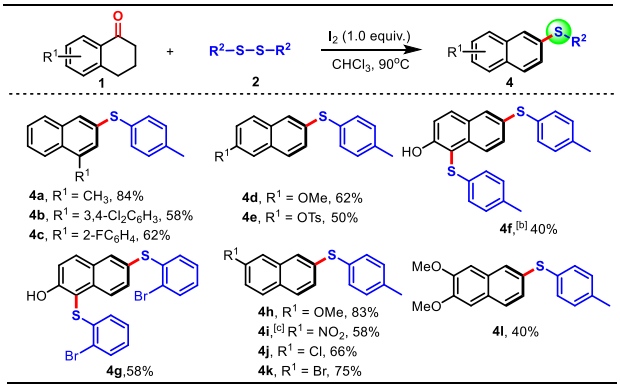
Table 1. The Scope of ~~the~~ Disulfides **2** for Synthesis of 2-Naphthyl Thioethers **3**.[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), I_2 (0.1 mmol), $CHCl_3$ (1.5 mL), under air in a sealed tube at 90 °C (oil bath) for 12 h.
[b] **2** (0.2 mmol), at 130 °C, for 24 h.
[c] **1** (0.4 mmol), at 110 °C.

Subsequently, the reaction was successfully extended to 1-tetralones (Table 2). [12] The desired reaction worked well when 4-methyl 1-tetralone was applied under standard conditions (**4a**), while replacing the methyl group with aryl groups resulted in moderate yields (**4b**, **4c**). 1-Tetralones with both electron-rich and electron-deficient functional groups on the phenyl ring gave the desired products in good yields (**4d**, **4e**, **4h**-**4k**, **4l**). Notably, when the C-6 position of 1-tetralone was occupied by an OH group, a strong electron-donating group, desired products underwent further sulfenylation to give disulfenylation compounds (**4f**, **4g**) as the only products with high regioselectivity.[13]

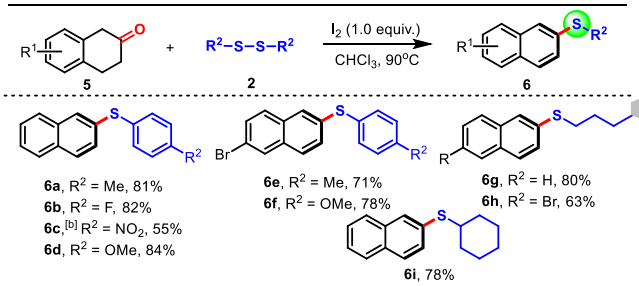
Table 2. The Scope of 1-Tetralones **1** for Synthesis of 2-Naphthyl Thioethers **4**.[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), I_2 (0.1 mmol), $CHCl_3$ (1.5 mL), under air in a sealed tube at 90 °C (oil bath) for 12 h.
[b] **2** (0.2 mmol), at 130 °C, for 24 h.
[c] **1** (0.4 mmol), at 110 °C.

Furthermore, when 2-tetralones (**5**) were investigated under standard conditions, 2-naphthyl thioethers were observed as the sole products, which is different from the iodine-promoted reaction of 1-tetralones with disulfides. This reaction showed a wide scope and functional-group tolerance with good yields, and selected examples are presented in Table 3.

Table 3. The Scope of 1-Tetralones **5** with Disulfides **2** for Synthesis of 2-Naphthyl Thioethers **6**. [a]

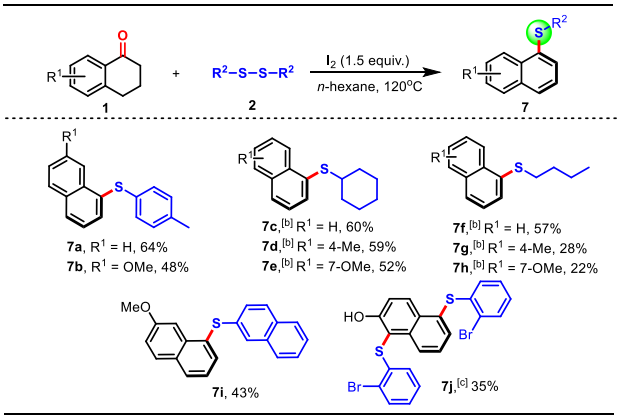


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), I_2 (0.1 mmol), $CHCl_3$ (1.5 mL), under air in a sealed tube at 90 °C (oil bath) for 12 h.
[b] **1** (0.4 mmol) at 120 °C.

10.1002/adsc.201801562

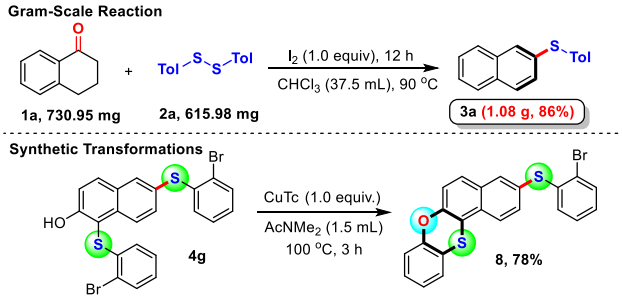
Lastly, the scope of 1-tetralones and disulfides was examined for the synthesis of 1-naphthyl thioethers **7**. As shown in Table 4, a range of aryl- and alkyldisulfides smoothly underwent the sulfenylation/deoxygenation/aromatization reaction with 1-tetralone in *n*-hexane to give structurally diverse thioethers in moderate to good yields.

Table 4. The Scope of ~~the~~ 1-Tetralones **1** with Disulfides **2** for Synthesis of 1-Naphthyl Thioethers **7**.[a]



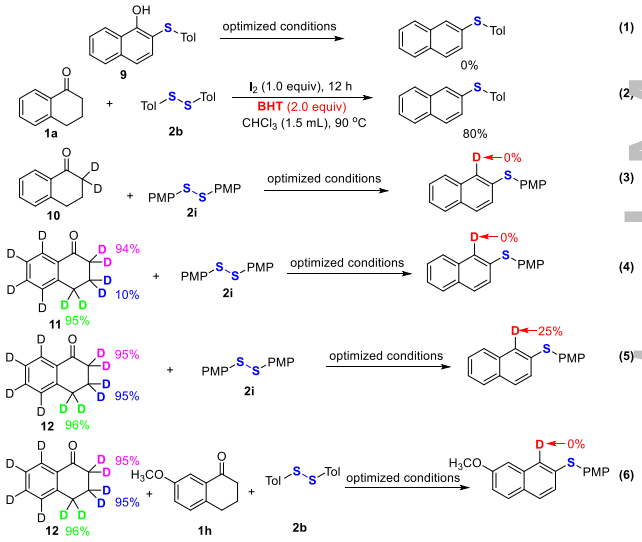
[a] Reaction conditions: **1** (0.4 mmol), **2** (0.1 mmol), I_2 (0.3 mmol), *n*-hexane (1.5 mL), under air in a sealed tube at 120 °C (oil bath) for 12 h.
[b] **1** (0.4 mmol), in $CHCl_3$ (1.5 mL), at 110 °C.
[c] **2** (0.25 mmol), at 130 °C, for 24 h.

To further show the synthetic potential of our new reaction, a gram-scale reaction was performed using 5 mmol (731.0 mg) of 1-tetralone **1a**, giving 2-naphthyl thioether **3a** in 86% yield (1.08 g) (Scheme 2). Treatment of **4g** with CuTc in $AcNMe_2$ afforded ~~the~~ compound **8** in 78% yield.



Scheme 2. Gram-Scale Synthesis and Synthetic Transformations.

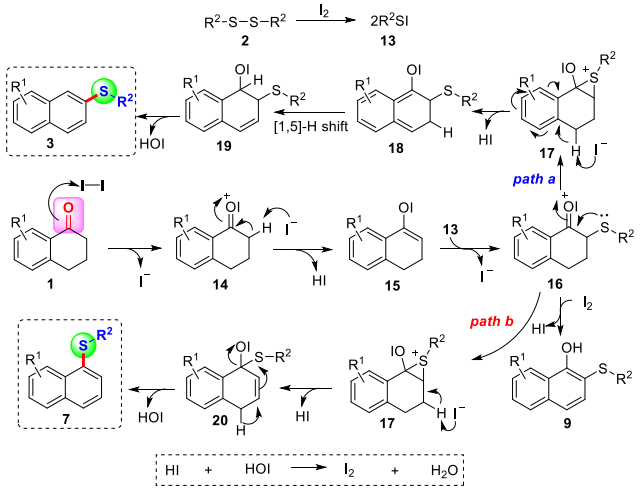
To gain insight into the reaction mechanism, several control experiments were performed (Scheme 3). Initially, treatment of byproduct 2-(*p*-tolylthio)naphthalene-1-ol **9** with disulfides and iodine did not afford the desired product **3a** (eq (1)), which implied that sulfenylation/aromatization of tetralone with disulfides is easy and the deoxygenation process proceeds prior to aromatization. Subsequently, the commonly used free radical inhibitor, 2,6-di-tert-butyl-4-methylphenol (BHT), was tested to elucidate the nature of the reaction. Addition of ~~the~~ 2.0 equiv. of BHT to the reaction mixture under standard conditions had a minor effect on the yield (eq (2)), suggesting this reaction might not involve a radical intermediate. Furthermore, to clarify the hydrogen source that previously placed the carbonyl group, several deuterium-labeling experiments were conducted. No deuterium incorporation at the C-1 position was observed for the reaction of deuterated 1-tetralones (**10** and **11**) with disulfides (eqs (3) and (4)); however, when polydeuterated 1-tetralone (**12**) was subjected to standard conditions, 2-naphthyl thioether with 25% deuterium incorporation at the C-1 position was observed (eq (5)). Moreover, a crossover experiment was performed using a 1:1 mixture of polydeuterated 1-tetralone **12** and undeuterated 6-methoxy-1-tetralone, giving no deuterium incorporation product **3i** (eq (6)), which implies that the hydrogen transfer might undergo an intramolecular process. These reaction outcomes demonstrate that a hydrogen/deuterium shift occurred from C-3 to C-1, consistent with our previous reports on byproduct-catalyzed tandem sulfenylation/deiodination/aromatization of cyclic alkenyl iodides with sulfonyl hydrazides.[14] However, no cyclic alkenyl iodide was detected in the reaction mixture of **1a** and **2a**. Therefore, we speculate that this new protocol might undergo an intermediate similar to the cyclic alkenyl iodide.



Scheme 3. Control Experiments.

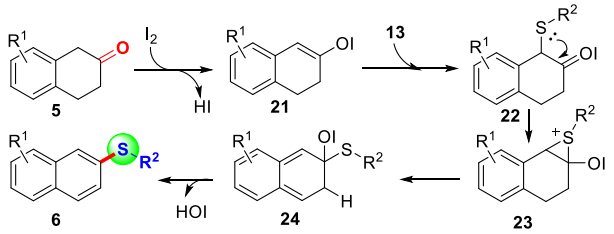
According to the above experimental results and previous reports,[10], [14] we propose the following reaction pathways as depicted in Scheme 4 for the iodine-promoted sulfenylation/deiodination/aromatization of 1-tetralone with disulfides. First, 1-tetralone **1** reacts with iodine to yield intermediate **14**, followed by the sulfenylation of this compound with disulfides to afford intermediate **15**. With iodine, disulfide **2** easily transforms into **13** [15] which reacts with **15** to give **16**. Oxidation of intermediate **16** gives the byproduct 2-sulfanylnaphthol **9** in the presence of iodine.[10] Alternatively, intermediate **16** undergoes intramolecular nucleophilic addition to give sulfonium salt **17**. Deprotonation of **17** affords

dihydronaphthalene **18** or **20**. Then, a [1,5]-sigmatropic hydrogen shift of **18** leads to the production of alkene **19**.[14] Elimination of HOI from **19** gives 2-naphthyl thioethers via *path a*. Meanwhile, alkene **20** could also undergo elimination to generate 1-naphthyl thioethers via *path b* with extrusion of HOI.



Scheme 4. Possible Reaction Pathway for the Synthesis of **3** and **7**.

Possible reaction pathways have also been proposed for the iodine-promoted reaction of 2-naphthyl thioether from 2-tetralone with disulfides (Scheme 5). 2-Tetralone is activated in the presence of iodine, thus forming intermediate **21**, which undergoes a regioselective sulfenylation reaction with disulfide **13** to give intermediate **22**. Subsequently, intermediate **22** undergoes an intramolecular nucleophilic addition, deprotonation, and elimination of HOI to give 2-naphthyl thioether **6** as the exclusive product.



Scheme 5. Possible Reaction Pathway for the Synthesis of **6** from 2-Tetralone with Disulfides.

In summary, we have developed an iodine-promoted sulfenylation/deoxygenation/aromatization reaction of 1-tetralones with disulfides to give structurally diverse naphthyl thioethers in moderate to excellent yields. The different reaction conditions lead to a switched regioselectivity, and therefore, 2-naphthyl thioethers and 1-naphthyl thioethers could be obtained. Furthermore, when the reaction was extended to 2-tetralones, 2-naphthyl thioethers were obtained as sole products. All of these reactions show a wide substrate scope and functional-group tolerance. A gram-scale reaction proceeded smoothly without apparent yield loss. The current study bridges the deoxygenation and sulfenylation/aromatization of ketones, thus providing a new tool in organic synthesis.

Experimental Section

To a solution of disulfides **2** (0.10 mmol) in $CHCl_3$ (1.5 mL) was added tetralones **1** (0.20 mmol) and I_2 (50.76 mg, 0.20 mmol). The resulting mixture was stirred at 90 °C (oil bath) under air for 12 h, cooled to room temperature, and purified by silica gel chromatography, eluting with petroleum ether to give mainly desired product **3** or **4**.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (21502182, 21102179 and 21572271), Qing Lan Project of Jiangsu Province, National Found for Fostering Talents of Basic Science (J1030830), the Fundamental Research Funds for the Central Universities (3010050077), Young Teachers' Research Funding from the College of Science, China Pharmaceutical University (2018CSYT008) and Double First-Class University project (CPU2018GY35).

References

[1] For reviews, see: a) Organic Sulfur Chemistry. *Theoretical and Experimental Advances*, *Vol. 19* (Eds.: F. Bernardi, I. G. Csizmadia, A. Mangini), Elsevier, Amsterdam, **1985**; b) N. V. Zyk, E. K. Beloglazkina, M A. Belova, N. S. Dubinina, *Russ. Chem. Rev.* **2003**, *72*, 769; c) E. M. Beccalli, G. Broggini, M. Martinelli, S Sottocornola, *Chem. Rev.* **2007**, *107*, 5318; d) I. P. Beletskaya, V. P. Ananikov, *Chem. Rev.* **2011**, *111*, 1596.

[2] For selected examples, see: a) K. Ghosha, S. Ranjita, D. Mala, *Tetrahedron Lett.* **2015**, *56*, 5199; b) F. Luo, C. Pan, L. Li, F. Chen, J. Cheng, *Chem. Commun.* **2011**, *47*, 5304; c) C. C. Eichman, J. P. Stambuli, *J. Org. Chem.* **2009**, *74*, 4005; d) J. R. Schmink, S. A. B. Dockrey, T. Zhang, N. Chebet, A. van Venrooy, M. Sexton, S. I. Lew, S. Chou, A. Okazaki, *Org. Lett.* **2016**, *18*, 6360; e) K. D. Jones, D. J. Power, D. Bierer, K. M. Gericke, S. G. Stewart, *Org. Lett.* **2018**, *20*, 208; f) C.-W. Chen, Y.-L. Chen, D. M. Reddy, K. Du, C.-E. Li, B.-H. Shih, Y.-J. Xue, C.-F. Lee, *Chem. Eur. J.* **2017**, *23*, 10087; g) E. Guzmán-Percástegui, D. J. Hernández, I. Castillo, *Chem. Commun.* **2016**, *52*, 3111; h) M. A. Fernandez-Rodriguez, Q. Shen, J. F. Hartwig, *Chem Eur. J.* **2006**, *12*, 7782; i) S. D. Timpa, C. J. Pell, O. V. Ozerov, *J. Am. Chem. Soc.* **2014**, *136*, 14772; j) M. Jiang, H. Li, H. Yang, H. Fu, *Angew. Chem. Int. Ed.* **2017**, *56*, 874.

[3] For selected examples, see: a) N. *J.* Taniguchi, *Org. Chem.* **2007**, *72*, 1241; b) R. Peng, Y. Si, T. Deng, J. Zheng, J. Li, R. Yang, W. Tan, *Chem. Commun.* **2016**, *52*, 8553; c) X.-M. Wu, J.-M. Lou, G.-B. Yan, *Synlett* **2016,** *27*, 2269; d) K. Kanemoto, S. Yoshida, T. Hosoya, *Chem. Lett.* **2018**, *47*, 85; e) H.-J. Xu, Y.-Q. Zhao, T. Feng, Y.-S. Feng, *J. Org. Chem.* **2012**, *77*, 2878; f) C. Savarin, J. Srogl, L. S. Liebeskind, *Org.*

Lett. **2002**, *4*, 4309; g) Z. Qiao, N. Ge, X. Jiang, *Chem. Commun.* **2015**, *51*, 10295; h) S. Yoshida, Y. Sugimura, Y. Hazama, Y. Nishiyama, T. Yano, S. Shimizu, T. Hosoya, *Chem. Commun.* **2015**, *51*, 16613.

[4] For reviews, see: a) *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, *6th* (Eds.: M. B. Smith, J. March) John Wiley & Sons, Inc., Cananda, **2007**; b) *Modern Carbonyl Chemistry*, (Ed.: J. Otera), Wiley-VCH: Weinheim, Germany, **2000**.

[5] For reviews, see: a) R. O. Hutchins, M. K. Hutchins, *in Comp. Org. Synth. Vol. 8*, (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, 327; b) R. M. Adlington, A. G. M. Barrett, *Acc. Chem. Res.* **1983**, *16*, 55; c) J. G. S. C. Buchanan, P. D. Woodgate, *Quart. Rev.* **1969**, *23*, 522; d) E. Vedejs, *Org. React.* **1975**, *22*, 401-422; e) R. H. Shapiro, *Org. React.* **1976**, *23*, 405; f) A. R. Chamberlin, S. H. Bloom, *Org. React.* **1990**, *39*, 1-83; g) D. Todd, *Org. React.* **1948**, *4*, 378.

[6] a) J. S. Yadav, B. V. S. Reddy, R. Jain, G. Baishya, *Tetrahedron Lett.* **2008**, *49*, 3015; b) S. E. Denmark, S. Rossi, M. P. Webster, H. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 13016; c) M. Arisawaa, F. Toriyamab, M. Yamaguchia, *Tetrahedron* **2011**, *67*, 2305.

[7] a) N. J. Kishner, *Russ. Phys. Chem. Soc.* **1911**, *43*, 582; b) L. Wolff, *Ann. Chem.* **1912**, *394*, 23; c) M. Huang, *J. Am. Chem. Soc.* **1946**, *68*, 2487; d) M. Huang, *J. Am. Chem. Soc.* **1949**, *71*, 3301.

[8] a) W. R. Bamford, T. S. Stevens, *J. Chem. Soc.* **1952**, 4735; b) R. H. Shapiro, M. J. Heath, *J. Am. Chem. Soc.* **1967**, *89*, 5734.

[9] a) E. Clemmensen, *Chem. Ber.* **1913**, *46*, 1837; b) E. Clemmensen, *III. Ber.* **1914**, *47*, 681; c) E. Clemmensen, *II. Ber.* **1914**, *47*, 51.

[10] W. Ge, X. Zhu, Y. Wei, *Adv. Synth. Catal.* **2013**, *355*, 3014.

[11] Y. Bao, X. Yang, Q. Zhou, F. Yang, *Org. Lett.* **2018**, *20*, 1966.

[12] Under the same reaction conditions, no desired reaction was observed with cyclohenanone.

[13] a) D. Wang, R. Zhang, S. Lin, Z. Yan, S. Guo, *RSC Adv.* **2015**, *5*, 108030; b) C. Anjaiah, M. Nagamani, C. A. Lincoln, D. Ashok, *Russ. J. Gen. Chem.* **2017**, *87*, 2930; c) P. Gogoi, S. R. Gogoi, M. Kalita, P. Barman, *Synlett*, **2013**, *24*, 873.

[14] F.-L. Yang, Y. Gui, B.-K. Yu, Y.-X. Jin, S.-K. Tian, *Adv. Synth. Catal.* **2016**, *358*, 3368.

[15] T.-a. Okamura, T. Kaga, S. Yamashita, R. Furuya, K. Onitsuka, *J. Org. Chem.* **2017**, *82*, 2187.

10.1002/adsc.201801562

UPDATE

Iodine-Promoted Tunable Synthesis of 2-Naphthyl Thioethers and 1-Naphthyl Thioethers

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Yishu Bao,[a] Xiuqin Yang,[a] Zonghao Dai,[a] Suyu Ji,[a] Qingfa Zhou [a]* and Fulai Yang[a]*