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Authors: Jiawei Hua, Jiaqi Xu, Jia Xu, Bochao Zhou, Dong Zhang, Zhao Yang, Zheng Fang, and Kai Guo

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FULL PAPER

1,3-Dibromo-5,5-dimethylhydantoin (DBH)/DMSO mediated oxidative thioesterification of alkenes for the synthesis of α-ketothioesters

Jiawei Hua, [a] Jiaqi Xu, [a] Jia Xu, [a] Bochao Zhou, [a] Dong Zhang, [a] Zhao Yang, [b] Zheng Fang, * [a] Kai Guo*[a][c]

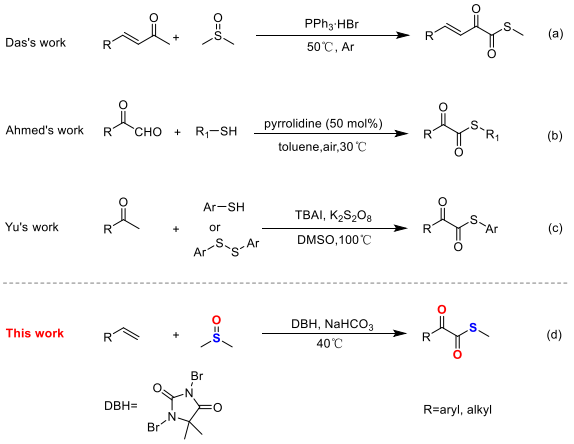
Abstract: A simple and mild approach for the synthesis of α-ketothioesters via 1,3-Dibromo-5,5-dimethylhydantoin (DBH)/DMSO mediated oxidative thioesterification of alkenes has been developed. Various of α-ketothioesters products were produced in moderate to good yields under metal-free conditions. And this method features readily available starting materials and broad substrate scope. Moreover, a plausible mechanism was proposed based on the methyl bromide captured experiment.

Introduction

α-ketothioesters, one of the unique C-S bond structures units, play an important role in constructing various natural products.[1] And α-ketothioesters have been applied for the synthesis of the promising cephalosporin, anticonvulsant, analgesic and antitumor versatile drug precursors,[2] which possess a great advantage in transforming to useful pharmaceutical intermediates. Consequently, these compounds have gradually attracted chemistry researchers around the world.[3]

Traditionally, α-ketothioesters were obtained by means of the hydrolysis of trimethyl α-oxo trithioorthoesters, the aerobic oxidation of α-hydroxythioesters, and the hydrolysis of β-keto α, α-dichloro sulfides.[2a,4] These classic procedures mentioned above still suffer from some apparent drawbacks, such as the use of the flammable reagent (*tert*-Butyllithium) and the demand of expensive metal. The reactions involving metal reagents usually are heterogeneous and have large amount of residue, which may restrict their application in industry. Recently, several synthetic methodologies for the oxidative thioesterification reactions under metal-free conditions have been successfully presented. In 2014, Das's group reported a novel method for preparing γ-substituted β, γ-unsaturated a-ketomethylthioesters via a PPh_3·HBr-DMSO mediated oxidative bromination system (Scheme 1a).[5] Ahmed's group developed an amino catalytic oxidative thioesterification of 2-oxoaldehydes with aliphatic thiols for the synthesis of α-ketothioesters (Scheme 1b).[6] In 2018, Yu and co-workers discovered a TBAI/$K_2S_2O_8$ promoted oxidative thioesterification strategy for synthesizing α-ketothioesters under metal-free conditions (Scheme 1c).[7] However, there are also some drawbacks including the uneasy available starting materials and failing to afford alkyl ketone thioester, which have great limitations for practical applications. Therefore, it is highly necessary to develop simple and mild methods for the preparation of α-ketothioesters.

With the X_2/HX-DMSO system, various conventional oxidative transformations by means of oxidative halogenations followed by DMSO oxidation have been reported.[8] Classic process about the usage and release of X_2 (Cl_2, Br_2 and I_2) would result in lots of environmental pollution. Consequently, looking for a green and efficient reagent alternative will make these methods more environmental-friendly. DBH not only performs as a bleaching and sterilizing agent in handling industrial and domestic water pollution,[9] but also is widely used for various transformations in chemical synthesis, which is competent for the bromination of alkenes, alkynes and aromatic C–H bonds.[10] Furthermore, as the simple, commercially available and cheap starting materials, alkenes provide the C-C double bonds to build valuable and useful molecules, that possess extensive application in chemical synthesis.[11] For all we know, oxidative thioesterification of alkenes for the synthesis of α-ketothioesters has never been reported yet. DBH-DMSO combination might be an interesting attempt to generate α-ketothioesters from alkenes. Herein, we develop a mild DBH/DMSO mediated oxidative thioesterification of alkenes to α-ketothioesters (Scheme 1d).



[a] J. Hua, J. Xu, J. Xu, B. Zhou, D. Zhang, Z. Yang, Prof. Z. Fang, and Prof. K. Guo
Department: College of Biotechnology and Pharmaceutical Engineering
Institution: Nanjing Tech University
Address 1: 30 Puzhu Rd S., Nanjing 211816, China
E-mail: guok@njtech.edu.cn; fzcpu@163.com
[b] Z. Yang
Department; *College of Engineering*
Institution: China Pharmaceutical University
Address 2: 24 Tongjiaxiang, Nanjing, 210003, China
[c] K. Guo
Department; State Key Laboratory of Materials-Oriented Chemical Engineering
Institution: Nanjing Tech University
Address 3: 30 Puzhu Rd S., Nanjing 211816, China
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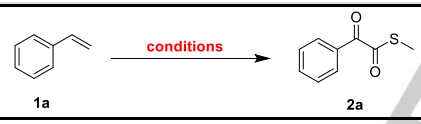
Scheme 1. DBH/DMSO mediated oxidative thioesterification of alkenes for the synthesis of α-ketothioesters.

Results and Discussion

Initially, the oxidative thioesterification of styrene **1a** to form α-ketothioesters **2a** was chosen as the model reaction. And the results of the reaction optimization were summarized in Table 1. First, styrene **1a** was treated with DBH (2equiv.) and Na_2CO_3 (1equiv.) at room temperature in anhydrous DMSO for 10h, the desired product **2a** merely obtained in 48% yield (Table1, entry 1). Several bases were screened to improve the yield of **2a** (Table1, entries 2-7). The results indicated that $NaHCO_3$ was the favorable choice, compared to a series of bases such as Na_2CO_3, Cs_2CO_3, Et_3N, DBU, Pyridine and Piperidine. With the further investigation of the reaction conditions, we were pleased to discover that DBH (1.5equiv.) exhibited the better effect with 63% yield of α-ketothioesters **2a** (Table1, entry 10). Raising the reaction temperature to 40℃ successfully improved the yield of product **2a** to 70% (Table1, entry 12). Finally, either increasing or decreasing the amount of $NaHCO_3$ failed to afford higher yields of **2a** (Table1, entries 14 and 15). To verify the practical application of this strategy, a scale-up reaction was conducted by using 10mmol **1a** and 30mL DMSO under the optimized reaction conditions (Table1, entry 16). We were pleased that the product **2a** was obtained in 62% yield, suggesting that the oxidative thioesterification method is suitable for large scale preparation.

Table 1. Optimization of reaction conditions [a]

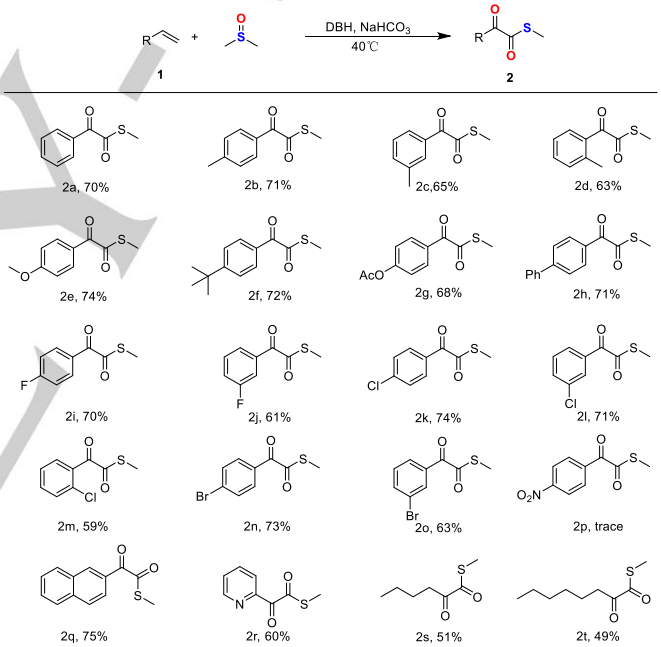


Entry	DBH (eq)	base	T (℃)	Yield [b] (%)
1	2	Na_2CO_3	rt	48
2	2	Cs_2CO_3	rt	40
3	2	$NaHCO_3$	rt	58
4	2	Et_3N	rt	25
5	2	DBU	rt	19
6	2	Pyridine	rt	17
7	2	Piperidine	rt	20
8	0.5	$NaHCO_3$	rt	trace
9	1	$NaHCO_3$	rt	20
10	1.5	$NaHCO_3$	rt	63
11	2.5	$NaHCO_3$	rt	35
12	1.5	$NaHCO_3$	40	70
13	1,5	$NaHCO_3$	60	53
14	1.5	$NaHCO_3$	40	20[c]
15	1.5	$NaHCO_3$	40	65[d]
16	1.5	$NaHCO_3$	40	62[e]

[a] Reaction conditions: **1a** (1mmol, 1equiv.) DBH, base (1equiv.), (**1a** was added into a sealed tube in the end, otherwise fail to react), solved in 4mL anhydrous DMSO and stirred for 10 h. [b] Isolated yields. [c] 0.5equiv. of $NaHCO_3$, [d] 1.5 equiv. of $NaHCO_3$. [e] 10mmol of 1a.

Under the optimized reaction conditions, a variety of alkenes **1** were chosen to expand the scope of the oxidative thioesterification. As shown in Table 2, styrene derivatives bearing both electron-donating groups (Me, MeO, t-Bu, AcO, Ph), and halogenated groups (F, Cl, Br), proceeded smoothly to afford the corresponding products in moderate to good yields (Table 2, **2b-2o**). Generally, the positions of substitution patterns (*para*-, *meta*-, and *ortho*-) have no great influence on the reaction activity (Table 2, **2b-2d**, **2i-2o**). However, the strong electron-withdrawing groups (NO_2) substituted styrene failed to generate the desired product, which might be caused by the decreased electron density (Table 2, **2p**). Fused rings and heterocycle alkenes including 2-Vinylnaphthalene and 2-Vinylpyridine tolerated well to provide the corresponding α-ketothioesters in 75% and 60% yields under the optimal reaction conditions (Table 2, **2q** and **2r**). Gratifyingly, simple aliphatic alkenes were successfully suitable for the approach to transform to **2s** and **2t** in 51% and 49% yields, respectively.

Table 2. Substrate scope of alkenes for the synthesis of 2a [a,b]



[a] Reaction conditions: **1** (1mmol, 1equiv.), DBH (1.5equiv.), $NaHCO_3$ (1equiv.), (**1** was added into a sealed tube in the end, otherwise fail to react), solved in 4mL anhydrous DMSO and stirred for 10h at 40℃. [b] Isolated yields.

Next, several control experiments were performed to gain an insight into the mechanism of this strategy (Scheme 2). The different gas atmosphere (N_2, air, O_2) was tested smoothly under the standard reaction conditions, and all gave the product **2a** in excellent yield (Scheme 2a). And the results demonstrated that O_2 was the unnecessary part of the oxidative thioesterification reaction. The addition of 5 equiv. of H_2O into the standard conditions failed to afford the desired product (Scheme 2b). When styrene **1a** reacted with 2mmol DMSO in 4mL DMF, the product 2a was obtained in 28% yield. Meanwhile, the reaction was carried out in 4mL DMF without DMSO, no product was generated (Scheme 2c). Combined with the above results, the oxygen atom of the newly formed carbonyl could come from DMSO. It was

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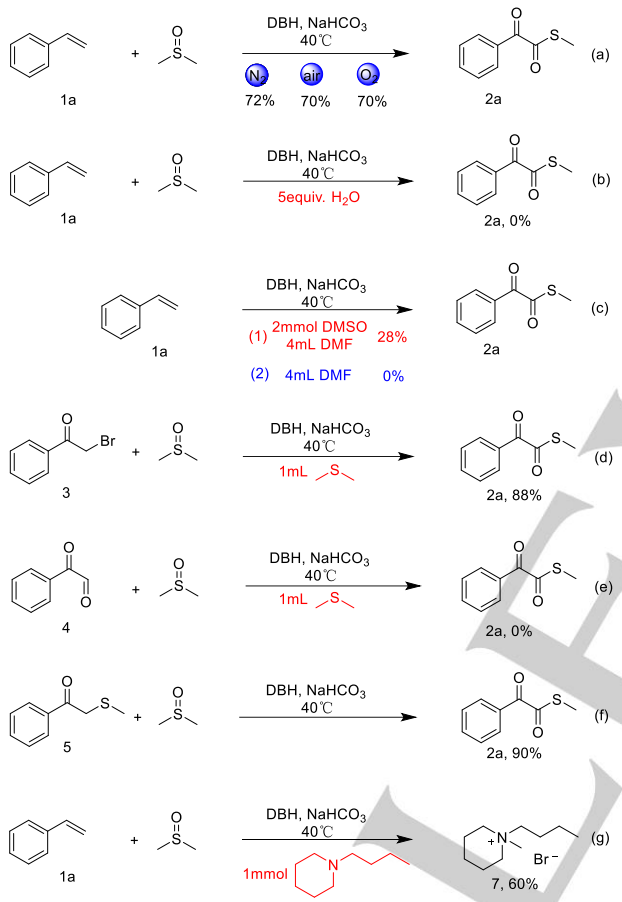
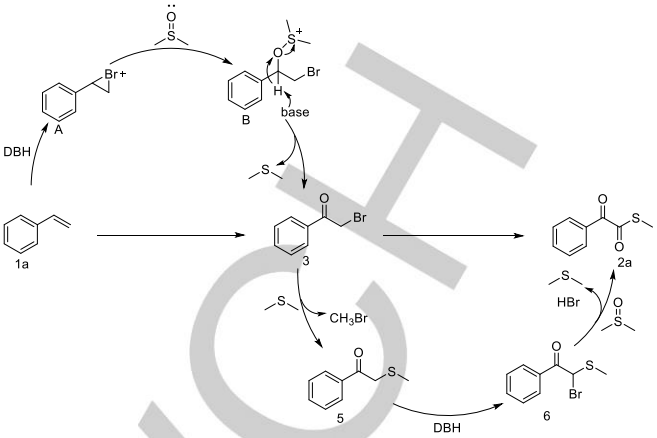
noteworthy that 2-bromoacetophenone **3** and 2-(methylthio)-1-phenylethan-1-one **5** were the key intermediates of this method, which was proven by the control experiments (Scheme 2d, 2f). Besides, adding 1mL dimethyl sulphide into the reaction ensured the possibility of generating **2a**. However, styrene was replaced by phenyl glyoxal **4** to react under the optimized reaction conditions with 1mL dimethyl sulfide, no desired product **2a** detected (Scheme 2e). Additionally, methyl bromide was successfully captured by adding 1mmol 1-butyl-piperidine into the reaction conditions, and the product **7** was isolated in 60% yield (Scheme 2g).



Scheme 2. Control experiments



Scheme 3. Proposed mechanism

Based on the above results and previous literatures,[12] a possible mechanism is depicted as shown in Scheme 3. First, styrene **1a** reacts with DBH to generate the bromonium ion **A**, which undergoes regioselective ring opening and eliminates Me_2S to afford 2-bromoacetophenone **3** in the presence of DMSO. The intermediate **5** is generated through nucleophilic substitution of 2-bromoacetophenone **3** and dimethyl sulfide with the release of methyl bromide. Further bromination of **5** would provide intermediate **6**, followed by Kornblum oxidation to produce the α-ketothioesters product **2a**, which continues to provide the enough amount of dimethyl sulfide.

Conclusions

In summary, we have developed a simple and novel (DBH)/DMSO mediated oxidative thioesterification method for the synthesis of α-ketothioesters from alkenes under metal-free conditions. Various of readily available alkenes were consistent with the standard conditions to afford the corresponding α-ketothioesters in moderate to good yields. A scale-up reaction to α-ketothioesters was successfully conducted. Moreover, a series of control experiments were carried out to investigate the reaction mechanism and a possible reaction mechanism was proposed. Further research on the reaction mechanism and the synthetic applications of this strategy are keeping going in our laboratory.

Experimental Section

General methods: To a 35 mL sealed tube (with a Teflon cap) equipped with a magnetic stir bar were sequentially added DBH (1.5mmol, 1.5equiv.), $NaHCO_3$ (1mmol, 1equiv.), alkenes (1mmol, 1equiv.), (alkenes were added into a sealed tube in the end, otherwise fail to react) and 4mL anhydrous DMSO. The tube was capped and submerged into a preheated 40℃ oil bath. The reaction was stirred for 10 h and cooled down to room temperature. Then the reaction mixture was washed with saturated NaCl solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and solvent was removed under vacuum. And the crude product was

purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum, affording the desired product **2** in good yields.

General procedure for the methyl bromide captured experiment: To a 35 mL sealed tube (with a Teflon cap) equipped with a magnetic stir bar were sequentially added DBH (1.5mmol, 1.5equiv.), 1-butyl-piperidine (1mmol, 1equiv.), $NaHCO_3$ (1mmol, 1equiv.), alkenes (1mmol, 1equiv.), (alkenes were added into a sealed tube in the end, otherwise fail to react) and 4mL anhydrous DMSO. The tube was capped and submerged into a preheated 40℃ oil bath. The reaction was stirred for 10 h and cooled down to room temperature. Diethyl ether (20 mL) was added to the resulting suspension. The resulting solid was collected by filtration. The solid was solved in 2-propanol. The liquid was collected by filtration and dried under a high vacuum. Then the raw product was purified by recrystallization twice from 2-propanol by addition of tetrahydrofuran to afford a white solid (product **7**).

Acknowledgments

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Keywords: oxidative thioesterification • alkenes • α-ketothioesters • metal-free

[1] a) R. Maity, S. Naskar, K. Mal, S. Biswas, I. Das, *Adv. Synth. Catal.* **2017**, *359*, 4405-4410; b) K. Mal, I. Das, *Adv. Synth. Catal.* **2017**, *359*, 2692-2698; c) K. Mal, S. Das, N. C. Maiti, R. Natarajan, I. Das, *J. Org. Chem.* **2015**, *80*, 2972-2988; d) K. Mal, S. Naskar, S. K. Sen, R. Natarajan, I. Das, *Adv. Synth. Catal.* **2016**, *358*, 3212-3230; e) S. Naskar, S. R. Chowdhury, S. Mondal, D. K. Maiti, S. Mishra, I. Das, *Org. Lett.* **2019**, *21*, 1578-1582; f) S. Y. Park, I.-S. Hwang, H.-J. Lee, C. E. Song, *Nat. Commun.* **2017**, *8*, 14877; g) B. ter Horst, B. L. Feringa, A. J. Minnaard, *Chem. Commun.* **2007**, 489-491; h) J. A. Turpin, Y. S. Song, J. K. Inman, M. J. Huang, A. Wallqvist, A. Maynard, D. G. Covell, W. G. Rice, E. Appella, *J. Med. Chem.* **1999**, *42*, 67-86; i) N. Utsumi, S. Kitagaki, C. F. Barbas, III, *Org. Lett.* **2008**, *10*, 3405-3408; j) Z.-J. Zheng, C. Jiang, P.-C. Shao, W.-F. Liu, T.-T. Zhao, P.-F. Xu, H. Wei, *Chem. Commun.* **2019**, *55*, 1907-1910.

[2] a) I. Degani, S. Dughera, R. Fochi, A. Gatti, *Synthesis-Stuttgart* **1996**, 467-+; b) R. Maity, S. Naskar, I. Das, *J. Org. Chem*. **2018**, *83*, 2114-2124.

[3] a) R. Sanichar, C. Carroll, R. Kimmis, B. Reiz, J. C. Vederas, *Org. Biomol. Chem.* **2018**, *16*, 593-597; b) H. Tokuyama, S. Yokoshima, S. C. Lin, L. P. Li, T. Fukuyama, *Synthesis-Stuttgart* **2002**, 1121-1123; c) C.-L. Yi, Y.-T. Huang, C.-F. Lee, *Green Chem.* **2013**, *15*, 2476-2484.

[4] a) C.-T. Chen, S. Bettigeri, S.-S. Weng, V. D. Pawar, Y.-H. Lin, C.-Y. Liu, W.-Z. Lee, *J. Org. Chem.* **2007**, *72*, 8175-8185; b) C. C. Fortes, C. R. O. Souto, E. A. Okino, *Synthetic Commun.* **1991**, *21*, 2045-2052.

[5] K. Mal, A. Sharma, P. R. Maulik, I. Das, *Chem. - Eur. J.* **2014**, *20*, 662-667.

[6] N. Mupparapu, M. Khushwaha, A. P. Gupta, P. P. Singh, Q. N. Ahmed, *J. Org. Chem.* **2015**, *80*, 11588-11592.

[7] B. Hu, P. Zhou, Q. Zhang, Y. Wang, S. Zhao, L. Lu, S. Yan, F. Yu, *J. Org. Chem.* **2018**, *83*, 14978-14986.

[8] a) Q. Gao, J. Zhang, X. Wu, S. Liu, A. Wu, *Org. Lett.* **2015**, *17*, 134-137; b) S. Guo, Z. Dai, J. Hua, Z. Yang, Z. Fang, K. Guo, *React. Chem. Eng.* **2017**, *2*, 650-655; c) Y. Siddaraju, K. R. Prabhu, *Org. Lett.* **2016**, *18*, 6090-6093; d) X.-F. Wu, K. Natte, *Adv. Synth. Catal.* **2016**, *358*, 336-352; e) S. A. Rather, A. Kumar, Q. N. Ahmed, *Chem. Commun.* **2019**, *55*, 4511-4514.

[9] a) T. Mitchenko, P. Stender, N. Makarova, *Solvent Extr. Ion Exch.* **1998**, *16*, 75-149; b) N. Fan and W. Wang, *HuaxueShijie*, **1998**, *39*, 297. c) L.-J. Xu, Y.-M. Lu and Z.-G. Cui, Chin. *J. Spectrosc. Lab.*, **2008**, *25*, 1044. d) B. R. Kim, J. E. Anderson, S. A. Mueller, W. A. Gaines and A. M. Kendall, *Water Res.*, **2002**, *36*, 4433.

[10] a) A. Alam, *Synlett* **2005**, 2403-2404; b) S. Xu, P. Wu, W. Zhang, *Org. Biomol. Chem.* **2016**, *14*, 11389-11395; c) Q. Yin, S.-L. You, *Org. Lett.* **2012,** *14*, 3526-3529.

[11] a) Y. Duan, W. Li, P. Xu, M. Zhang, Y. Cheng, C. Zhu, *Org. Chem. Front.* **2016**, *3*, 1443-1446; b) S. N. Gockel, T. L. Buchanan, K. L. Hull, *J. Am. Chem. Soc.* **2018**, *140*, 58-61; c) Y.-Y. Liu, X.-H. Yang, R.-J. Song, S. Luo, J.-H. Li, *Nat. Commun.* **2017**, *8*; d) X.-H. Ouyang, M. Hu, R.-J. Song, J.-H. Li, *Chem. Commun.* **2018**, *54*, 12345-12348; e) C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464-3484; f) K. B. Urkalan, M. S. Sigman, *Angew. Chem., Int. Ed.* **2009**, *48*, 3146-3149; g) F. Wang, D. Wang, X. Mu, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2014**, *136*, 10202-10205.

[12] a) S. Liu, H. Xi, J. Zhang, X. Wu, Q. Gao, A. Wu, *Org. Biomol. Chem.* **2015**, *13*, 8807-8811; b) P. K. Prasad, R. N. Reddi, A. Sudalai, *Org. Lett.* **2016**, *18*, 500-503; c) R. N. Reddi, P. K. Prasad, A. Sudalai, *Angew. Chem., Int. Ed.* **2015**, *54*, 14150-14153; d) M. H. Shinde, U. A. Kshirsagar, *Org. Biomol. Chem.* **2016**, *14*, 858-861.

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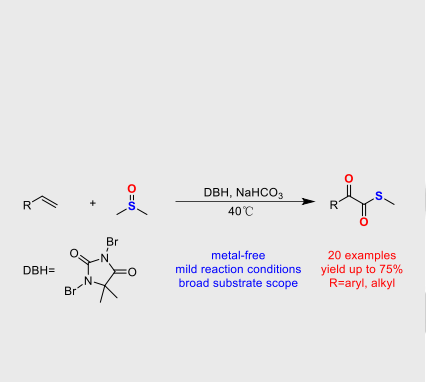

synthetic methods *

Jiawei Hua, Jiaqi Xu, Jia Xu, Bochao Zhou, Dong Zhang, Zhao Yang, Zheng Fang, Kai Guo**

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