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ARTICLE TYPE

Syntheses of thiol and selenol esters by oxidative coupling reaction of aldehydes with RYYR (Y = S, Se) under metal-free conditions

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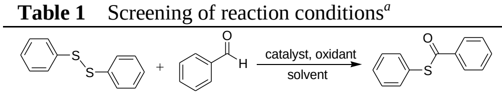
Thiol and selenol esters were synthesized by a direct oxidative coupling reaction of aldehydes with disulfides or diselenides in ethyl acetate under metal-free conditions. Among the oxidants examined, *tert*-butyl peroxide (TBP) was shown to give the best results. For the substrates with both electron-donating and electron-withdrawing substituents, the reaction proceeded smoothly and gave moderate to good yields. Compared with the previous method, the present route was very simple, atom-economic and environmentally friendly.

Chalcogenoesters, especially thiol and selenol esters are not only biologically active building blocks playing central roles in living cells[1] but also important organic precursors used in synthetic chemistry.[2] There is a growing interest to develop effective organic transformations for the preparation of this class of compounds in this context, but available preparative methods are still limited. The vast majority of reported approaches have employed acyl chlorides or aldehydes with nucleophilic organic sulfide or organic selenide species, e.g., organometallic reagents.[3] Metal-catalyzed transformations have been widely studied for this purpose in recent years, by this means metals such as Pd,[4] Rh,[5] Cu,[6] Zn,[7] In[8] *etc* have been used as the catalyst. Nevertheless, the reactions under metal-free conditions are desired particularly in the pharmaceutical synthesis. Several oxidative coupling from aldehydes in the absence of metal for the preparation of thioesters were reported in the last decade. Kita *et al*[9] reported a synthesis of thioesters from aldehydes and disulfides by a radical-mediated coupling in the presence of an azo-type initiator under the metal-free conditions, in which disulfides were used as the sulfur source. Unfortunately, only the reaction of pentafluorophenyl disulfide gave moderate to good yields, while other disulfides showed poor reactivity. A hypervalent iodine reagent (DMP) was employed as the oxidant to synthesize thioesters from aldehydes and thiophenol,[10] but excess explosive sodium azide had to be used as the activator. Recently, the NHC or TEAB-catalyzed thioesterifications of aldehydes with thiols were also developed, in which phenazine, $Na_2S_2O_8$, or electrochemical oxidation were employed.[11] Our research interest continuously focuses on developing the efficient and environmentally benign routes for the construction of carbon–carbon and carbon–heteroatom bonds, especially, the direct oxidative coupling reactions under the metal-free conditions.[12] We now wish to report the effective route to synthesize thiol and selenol esters by a direct oxidative coupling reaction of aldehydes with disulfides or diselenides using a simple oxidant.

Initially the optimization of the reaction conditions for the thioesterification of aldehydes was carried out using the simple compounds diphenyl disulfide (**1a**) and benzaldehyde (**2a**) as the substrates (Table 1). Previous reports revealed that peroxide is an effective radical initiator (oxidant) for aldehyde to generate acyl radical.[13] Thus 2 equiv. *tert*-butyl peroxide (TBP) was first selected as the oxidant. To our delight, in ethyl acetate (EA) and at 120 ℃, the reaction gave a desired oxidative coupling product phenyl benzothioate (**3aa**) in 79% yield (entry 1). For improving the yield, several Cu compounds such as $Cu(OAc)_2$, CuBr and CuI were tested as the catalyst. The results showed that the presence of such compounds was not helpful in affording the product (entries 2−4). But when the amount of TBP was increased to 4 equiv., a yield of 90% could be achieved in the absence of any metal catalyst (entry 5). The oxidant was proved to have considerable effect on the reaction. Among the set of oxidants examined, TBP gave the highest yield, while H_2O_2, dicumyl peroxide (DCP) and benzoyl peroxide (BPO) gave inferior results (entries 6−8), whereas *tert*-butyl hydroperoxide (TBHP), $K_2S_2O_8$ and O_2 failed to produce the target product (entries 9−11). In case of the solvents, ethyl acetate was found to be superior to CH_3CN and 1,2-dichloroethane (DCE) (entries 12, 13). In water, the reaction could not take place at all (entry 14). Reaction temperature was also investigated. The most suitable temperature was proved to be 120 ℃. Lowering the temperature to 100 ℃ brought a decrease in the yield (entry 16), yet increasing it to 140 ℃ did not exhibit obvious promotion with the reaction (entry 17). It is noteworthy that an inert atmosphere was helpful for the present transformation. When the reaction took place in air, a lower yield of 71% was obtained (entry 15).

Table 1 Screening of reaction conditions[a]



1a 2a 3aa

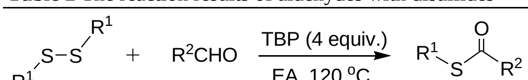
Entry	Catalyst (mol %)	Oxidant (equiv.)	Solvent	Yield (%)[b]
1		TBP (2)	EA	79
2	$Cu(OAc)_2$ (10)	TBP (2)	EA	70
3	CuBr (10)	TBP (2)	EA	42
4	CuI (10)	TBP (2)	EA	61
5		TBP (4)	EA	90

6	H_2O_2 (4)	EA	62
7	DCP (4)	EA	24
8	BPO (4)	EA	33
9	TBHP (4)	EA	trace
10	$K_2S_2O_8$ (4)	EA	trace
11	O_2 (1 atm)	EA	trace
12	TBP (4)	CH_3CN	85
13	TBP (4)	DCE	43
14	TBP (4)	H_2O	0
15[c]	TBP (4)	EA	71
16[d]	TBP (4)	EA	70
17[e]	TBP (4)	EA	92

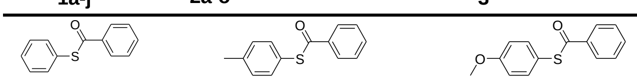
[a] Unless otherwise specified, the reaction was carried out in a sealed tube in the presence of **1a** (0.5 mmol), **2a** (1.2 mmol), solvent (1 mL), catalyst (10 mol %), and oxidant at 120 ℃ under Ar atmosphere for 12 h. [b] Isolated yield. [c] Under air. [d] At 100 ℃. [e] At 140 ℃.

With the optimal conditions in hand, we next explored the oxidative thioesterification of various aldehydes with disulfides (Table 2). For the thioesterification of benzaldehyde, a series of aryl disulfides and alkyl disulfides were employed as the coupling partners. Delightedly, aryl disulfides substituted with both electron-donating groups (Me, OMe) (**3ba**, **3ca**) and electron-withdrawing groups (Br, Cl) (**3da**−**ga**) on the aromatic ring reacted with benzaldehyde to give the desired thiol esters in moderate to good yields (**3ba**−**ga**), and the connection position of substituents had no obvious effect on this coupling reaction (**3da**−**fa**). When a heterocyclic compound 2-(2-(benzo[d]thiazol-2-yl)disulfanyl)benzo[d]thiazole (**1i**) was used as the thioaryl reagent, it gave a moderate yield of 58% (**3ia**). Similar to aryl disulfides, the reaction of aliphatic disulfides also gave good yields (**3ha**, **3ja**). The reactions of various aldehydes were further investigated. As that was revealed in disulfides, the reaction could proceed smoothly whether electron-donating or electron-withdrawing groups substituted on the benzene ring of the aldehydes, even though the yields were somewhat lower when the electron-donating groups existed. When heterocyclic aromatic aldehydes were used, the reaction gave moderate yields (**3al**, **3am**). Compared with the aromatic aldehydes, the aliphatic aldehydes propylaldehyde (**2n**) and isobutylaldehyde (**2o**) gave the corresponding products in lower yields (**3an**, **3ao**).

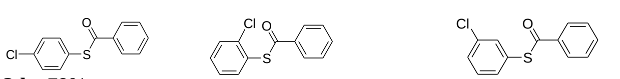
Table 2 The reaction results of aldehydes with disulfides[a, b]



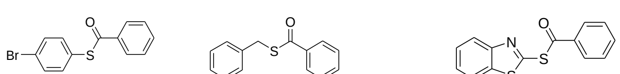
1a-j **2a-o** **3**



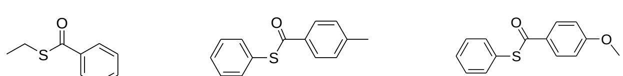
3aa, 90% **3ba**, 69% **3ca**, 65%



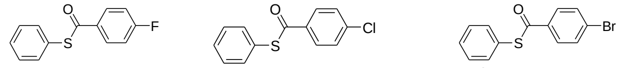
3da, 79% **3ea**, 73% **3fa**, 72%



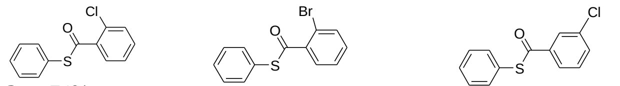
3ga, 84% **3ha**, 71% **3ia**, 58%



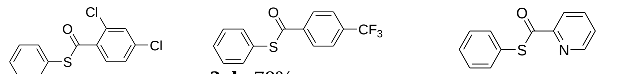
3ja, 87% **3ab**, 73% **3ac**, 70%



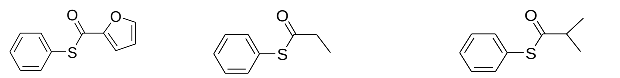
3ad, 84% **3ae**, 82% **3af**, 81%



3ag, 74% **3ah**, 76% **3ai**, 73%



3aj, 75% **3ak**, 78% **3al**, 61%

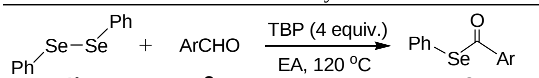


3am, 63% **3an**, 35% **3ao**, 30%

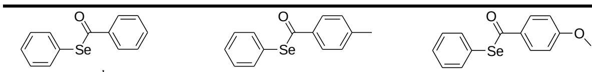
[a] Reaction conditions: **1** (0.5 mmol), **2** (1.2 mmol) and TBP (4.0 equiv.), in EA (1 mL) in a sealed tube under Ar at 120 °C for 12 h. [b] The yields are isolated one.

As the congeneric elemento-organic compounds, diselenides have the similar reactivity with disulfides for some transformations.[12b] In the subsequent work, we applied this direct oxidative coupling protocol for the synthesis of selenol esters. Using diphenyl diselenide as the reaction partner, for the different substituted aldehydes, the reaction gave moderate to good yields under the same reactions as above (Table 3).

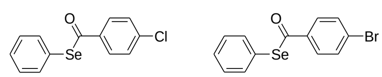
Table 3 The reaction results of aldehydes with diselenides[a]



1k **2** **3**



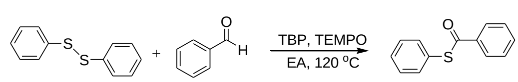
3ka, 88%[b] **3kb**, 71% **3kc**, 68%



3ke, 77% **3kf**, 79%

[a] Reaction conditions: **1k** (0.5 mmol), **2** (1.2 mmol) and TBP (4.0 equiv.), in EA (1 mL) in a sealed tube under Ar at 120 °C for 12 h. [b] Isolated yield.

In order to study the possible pathway of this reaction, a radical-trapping reagent 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added under the standard reaction conditions. The results showed that in the presence of 2 equiv. TEMPO, the yield of **3aa** was reduced to 33%, while the amount of TEMPO was increased to 4 equiv., no target product was found (Scheme 1). The inhibitory effect of TEMPO to the reaction indicated that the radicals existed in this transformation.

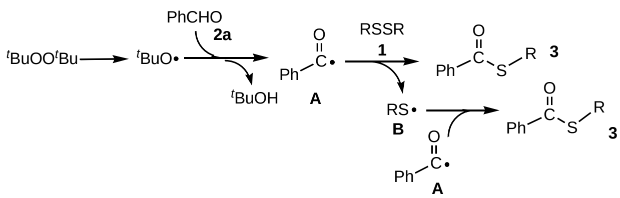


1a **2a** **3aa**

TEMPO: 2 equiv yield 33%
4 equiv 0%

Scheme 1 The effect of TEMPO to reaction.

In the presence of a peroxide, the acyl radical would be produced from aldehyde, which was proved by a series of reports.[9,13] The high yield based on disulfide or diselenide showed a homolytic cleavage of S–S (or Se–Se) bond might exist in this process. On the basis of the present experimental results and previous related reports,[9,12b,13] a plausible mechanism is depicted in Scheme 2. First, the homolytic cleavage of TBP produced a *tert*-butoxyl radical. The *tert*-butoxyl radical then abstracted hydrogen from the C(sp^2)–H bond of aldehyde to afford a acyl radical (**A**). (**A**) finally reacted with RSSR (or RSeSeR) (**1**) to generate the product **3**.



Scheme 2 Proposed reaction mechanism.

Conclusions

In summary, a convenient C−S and C−Se bond formation based on the direct oxidative cross-couplings of aldehydes with disulfides or diselenides under metal-free conditions was developed. This method provides a very simple, atom-economic and environmentally friendly route for the syntheses of thiol and selenol esters.

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Notes and references

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1 (a) N. A. McGrath and R. T. Raines, *Acc. Chem. Res.*, 2011, **44**, 752; (b) P. E. Dawson and S. B. H. Kent, *Annu. Rev. Biochem.*, 2000, **69**, 923; (c) J. P. Tam and C. T. T. Wong, *J. Biol. Chem.*, 2012, **287**, 27020; (d) L. Longobardo, N. Cecere, M. DellaGreca and I. de Paola, *Amino Acids*, 2013, **44**, 443; (e) J. Oh, E. Goo, I. Hwang and S. Rhee, *J. Biol. Chem.*, 2014, **289**, 11465; (f) A. Ghassemian, X. Vila-Farres, P. F. Alewood and T. Durek, *Bioorgan. Med. Chem.*, 2013, **21**, 3473.

2 (a) G. Perin, E. J. Lenardao, R. G. Jacob and R. B. Panatieri, *Chem. Rev.*, 2009, **109**, 1277; (b) G. P. Howell, S. P. Fletcher, K. Geurts, B. Horst and B. L. Feringa, *J. Am. Chem. Soc.*, 2006, **128**, 14977; (c) M. Toyofuku, E. Murase, S. Fujiwara, T. Shin-ike, H. Kuniyasu and N. Kambe, *Org. Lett.*, 2008, **10**, 3957; (d) K. Kunchithapatham, C. C. Eichman and J. P. Stambuli, *Chem. Commun.*, 2011, **47**, 12679; (e) N. Hara, S. Nakamura, Y. Funahashi and N. Shibata, *Adv. Synth. Catal.*, 2011, **353**, 2976; (f) S. Ozaki, M. Adachi, S. Sekiya and R. Kamikawa, *J. Org. Chem.*, 2003, **68**, 4586.

3 (a) T. Inoue, T. Takeda, N. Kambe, A. Ogawa, I. Ryu and N. Sonoda, *J. Org. Chem.*, 1994, **59**, 5824; (b) C. C. Silveira, A. L. Braga and E. L. Larghi, *Organometallics*, 1999, **18**, 5183; (c) Y. Nishiyama, H. Kawamatsu, S. Funato, K. Tokunaga and N. Sonoda, *J. Org. Chem.*, 2003, **68**, 3599.

4 (a) H. Cao, L. McNamee and H. Alper, *J. Org. Chem.*, 2008, **73**, 3530; (b) M. N. Burhardt, R. H. Taaning and T. Skrydstrup, *Org. Lett.*, 2013, **15**, 948.

5 (a) M. Arisawa, T. Yamada and M. Yamaguchi, *Tetrahedron Lett.*, 2010, **51**, 6090; (b) K. Ajiki, M. Hirano and K. Tanaka, *Org. Lett.*, 2005, **7**, 4193.

6 (a) J. B. Azeredo, M. Godoi, R. S. Schwab, G. V. Botteselle and A. L. Braga, *Eur. J. Org. Chem.*, 2013, 5188; (b) N. Sawada, T. Itoha and N. Yasuda, *Tetrahedron Lett.*, 2006, **47**, 6595.

7 (a) M. Godoi, E. W. Ricardo, G. V. Botteselle, F. Z. Galetto, J. B. Azeredo and A. L. Braga, *Green Chem.*, 2012, **14**, 456; (b) S. Narayanaperumal, E. E. Alberto, K. Gul, C. Y. Kawasoko, L. Dornelles, O. E.D. Rodrigues and A. L. Braga, *Tetrahedron*, 2011, **67**, 4723.

8 G. Marin, A. L. Braga, A. S. Rosa, F. Z. Galetto, R. A. Burrowa, H. Gallardo and M. W. Paixao, *Tetrahedron*, 2009, **65**, 4614.

9 (a) H. Nambu, K. Hata, M. Matsugi and Y. Kita, *Chem. Eur. J.*, 2005, **11**, 719; (b) H. Nambu, K. Hata, M. Matsugi and Y. Kita, *Chem. Commun.*, 2002, 1082.

10 S. B. Bandgar, B. P. Bandgar, B. L. Korbad and S. S. Sawant, *Tetrahedron Lett.*, 2007, **48**, 1287.

11 (a) T. Uno, T. Inokuma and Y. Takemoto, *Chem. Commun.*, 2012, **48**, 1901; (b) K. A. Ogawa and A. J. Boydston, *Org. Lett.*, 2014, **16**, 1928; (c) X. B. Zhu, Y. Shi, H. B. Mao, Y. X. Cheng and C. J. Zhu, *Adv. Synth. Catal.*, 2013, **355**, 3558.

12 (a) B. N. Du, B. Jin and P. P. Sun, *Org. Bimol. Chem.*, 2014, **12**, 4586; (b) B. N. Du, B. Jin and P. P. Sun, *Org. Lett.*, 2014, **16**, 3032.

13 (a) Z. J. Liu, J. Zhang, S. L. Chen, E. B. Shi, Y. Xu and X. B. Wan, *Angew. Chem. Int. Ed.*, 2012, **51**, 3231; (b) W. Wei, C. Zhang, Y. Xu and X. B. Wan, *Chem. Commun.*, 2011, **47**, 10827; (c) J. Y. Luo, H. L. Hua, Z. S. Chen, Z. Z. Zhou, Y. F. Yang, P. X. Zhou, Y. T. He, X. Y. Liu and Y. M. Liang. *Chem. Commun.*, 2014, **50**, 1564.