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PAPER

Conversion of Esters to Thioesters under Mild Conditions

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We report conversion of esters to thioesters via selective C–O bond cleavage/weak C–S bond formation under transition-metal-free conditions. The method is notable for a general and practical transition-metal-free system, broad substrate scope and excellent functional group tolerance. The strategy was successfully deployed in late-stage thioesterification, site-selective cross-coupling/thioesterification/decarbonylation and easy-to-handle gram scale thioesterification. Selectivity and computational studies were performed to gain insight into the formation of weak C–S bond by C–O bond cleavage, which contrasts with the traditional trend of nucleophilic additions to carboxylic acid derivatives.

1. Introduction

The chemistry of carboxylic acid derivatives represents the cornerstone of organic synthesis.[1] While it is traditionally accepted that thioesters are more reactive than esters due to better leaving group aptitude (e.g. pKa = 15.2, MeOH vs. pKa = 10.3, MeSH) (Fig. 1A),[2] reversing the traditional reactivity trends represents a highly attractive approach in chemistry.

In this context, thioesters are fundamental building blocks in biochemistry and organic synthesis.[3] The versatile utility of thioesters includes their role in the synthesis of cellular components, such as fatty acids and terpenes.[3a] Furthermore, thioesters are key intermediates in various processes involving ATP.[3b] In chemistry, the key role of thioesters is as acylating reagents.[1] Moreover, thioesters contain the privileged sulfur moiety, which has gained prominence in sulfur therapeutics (Fig. 1B).[4] Among methods for the synthesis of thioesters, typical route involves the reaction of acyl chlorides with metal thiolates.[5] Other methods involve displacement of halides with thiocarboxylates, condensation of carboxylic acids with thiols,[6,7] Mitsunobu reaction of alcohols with thioacetic acids,[8] and carbonylation reactions in the presence of thiols.[9]

Recently, major progress has been made using carboxylic acid derivatives as electrophiles in metal-catalysis.[10,11] In particular, amides have emerged as powerful electrophiles by the selective N–C bond cleavage driven by amide bond destabilization and twist in order to decrease the $n_N \rightarrow \pi^*_{C=O}$ conjugation.[12-14] Aromatic esters have also been employed in cross-coupling reactions via O – C cleavage, wherein the high energy barrier is alleviated by electronic delocalization to lower the $n_O \rightarrow \pi^*_{C=O}$ conjugation and enable high chemoselectivity in the cross-coupling.[15] Furthermore, as the field has begun to mature, these processes have been expanded to carboxylic acids via O–C bond activation,[16-17] and thioesters via S–C bond activation, providing convenient methods for thioether synthesis.[18]

As such, recent studies spurred by electronic-activation[10,11] have shown that direct interconversion between carboxylic acid functional groups is possible, involving amide to amide,[19] amide to ester,[20] amide to thioester,[21] and ester to amide[22] interconversion using both transition-metal-catalysis and transition-metal-free conditions (Fig. 1C). While metal-catalyzed manifolds show promise for future developments, it should be noted that from environmental and practical standpoints transition-metal-free processes are vastly preferred.[23] In general, the acyl X–C functional group reactivity is in the following order: amides < esters < thioesters.[19-22] Therefore, the conversion from more reactive thioesters to less reactive esters is readily available.[24] In contrast, due to the high leaving group aptitude of thiolates,[1,2] there is no driving force for the conversion from esters to thioesters under typical conditions, and at present there are no general methods for the conversion of esters to thioesters available. While it should be noted that limited examples of ester to thioester conversion have been reported,[25] these methods are limited by the use of highly activated substrates (e.g. 4-NO_2-C_6H_4), polar solvents (e.g. DMF) that are impractical from the synthetic standpoint, and limited substrate scope.

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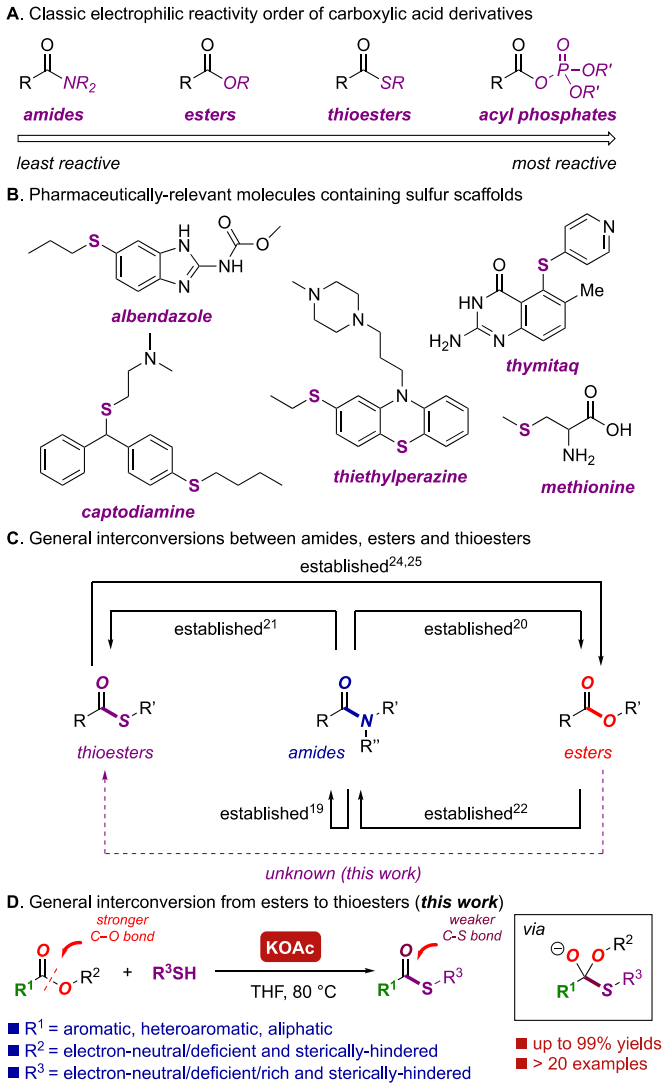

Fig. 1 (A) Reactivity order of carboxylic acid derivatives. (B) Pharmaceutically-relevant sulfur scaffolds. (C) Recently reported interconversions between amides, esters, and thioesters. (D) Thioesterification of esters (this work).

In particular, there are no general methods for the synthesis of *S*-aryl thioesters, which provide a pathway for decarbonylative thioether synthesis via decarbonylation.[18] As part of our program on the reactivity of carboxylic acid derivatives,[11–14,20,21] we report a general and practical method for the conversion of esters to thioesters via selective C–O bond cleavage/weak C–S bond formation under transition-metal-free conditions (Fig. 1D). The present method shows the following advantages: (1) mild conditions and significantly expanded substrate scope superseding previous methods; (2) practical and readily available KOAc as an activator in easily removable non-polar solvent, which are beneficial over previous protocols; (3) versatile synthetic applications in late-stage thioesterification of pharmaceuticals, including tandem protocols; (4) the conversion of esters to thioesters in a tandem C–Br/C–O/C–S bond activation for the synthesis of thioethers; (5) easy-to-handle gram scale synthesis of thioesters; (6) mechanistic and selectivity studies on the C–O/C–S bond cleavage. Overall, the method may open up new applications in engaging the versatile aryl ester bonds[22b,c] in a plethora of transformations.

2. Results and discussion

The proposed thioesterification was examined using phenyl benzoate (**1a**) and 4-methoxybenzenethiol (**2a**) as model substrates (see ESI). We were delighted to find that although no reaction was observed in the absence of base (Table ESI-1, entry 1, <2% conversion), promising results were obtained using Na_2CO_3, which delivered the desired product in 75% yield (Table ESI-1, entry 2). Examination of different bases (Table ESI-1, entries 1-9) resulted in identifying KOAc as the optimal base, which provided significantly improved yields of the desired product (Table ESI-1, entry 7). It is important to note that Cs_2CO_3 and NaOAc were ineffective (Table ESI-1, entries 4 and 6), while K_2CO_3 and K_3PO_4 delivered the product in modest yields (Table ESI-1, entries 3 and 5). Next, the effect of solvent was examined (Table ESI-1, entries 9-10), revealing that tetrahydrofuran is the optimal solvent for this transformation. Further examination of the reaction conditions revealed that the reaction proceeds at lower temperatures (Table ESI-1, entries 11-12), albeit with a decreased efficiency. Moreover, optimization of the reaction stoichiometry revealed that the reagent stoichiometry could be decreased to 1.5 equiv of thiol and 2.0 equiv of base with a minimal decrease in the reaction efficiency (Table ESI-1, entries 13-14). It is interesting to note that the sodium and potassium cations seem necessary, while the acetate counterion is more important in the current system. We believe that this effect is related to the stability of the thioester products under the reaction conditions.

With the optimal condition in hand, we next investigated the substrate scope of this KOAc-mediated conversion of aryl esters to thioesters via C–O bond cleavage/weak C–S bond formation (Fig. 2, top). As shown, we first selected 4-methoxybenzenethiol (**2a**) as a standard nucleophile. A wide range of unactivated esters bearing electron-neutral (**3a-b**) and electron-withdrawing substituents (**3c-k**) is well compatible with this transformation. Polycyclic aromatic substrates, such as naphthyl (**3b**) are also well tolerated, delivering the desired thioester product in 98% yield. Furthermore, halides, such as fluoro (**3d**), chloro (**3e**) and bromo (**3f**) are readily accommodated, delivering handles for further modification. Of note, halides are rarely compatible with transition-metal-mediated interconversion methods.[19–22] Moreover, cyano group (**3g**) is also compatible with this method. Importantly, the substrate containing two different ester groups (**3h**) underwent highly chemoselective thioesterification, delivering the product resulting from the nucleophilic addition to the aromatic ester bond (cf. aliphatic ester, vide infra). Furthermore, it is noteworthy that electrophilic functional groups, such as ketones (**3i**) can be readily employed under these mild conditions. Moreover, *ortho*-substitution as well as meta-substitution is well compatible as demonstrated by using the fluoro- (**3j**) and chloro-functionalized substrates (**3k**). Importantly, this method

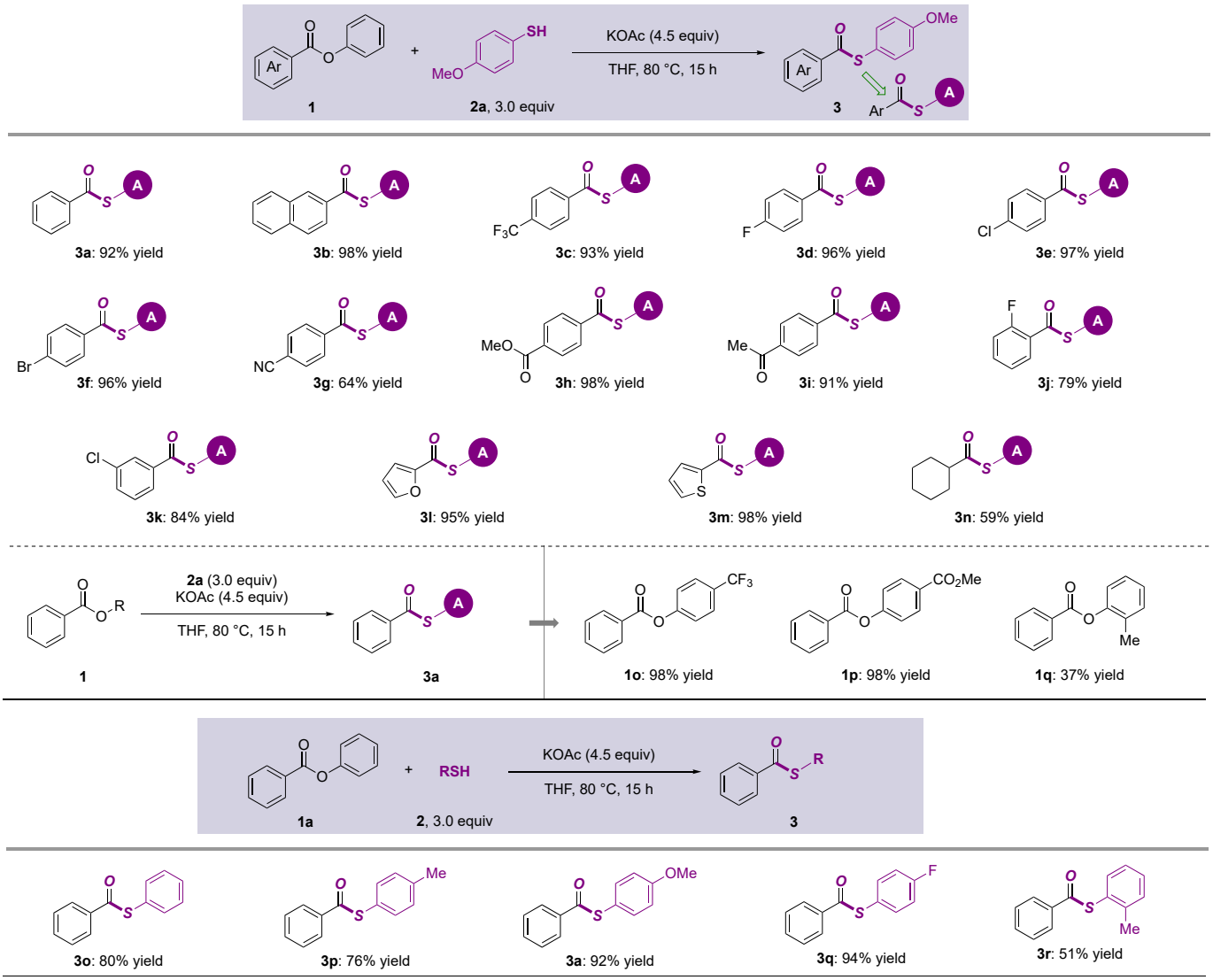

Fig. 2. Thioesterification of esters under transition-metal-free conditions. Conditions: ester (1.0 equiv), thiophenol (3.0 equiv), KOAc (4.5 equiv), THF, 80 °C, 15 h. Isolated yields. See SI for details.

can also be used to convert electron-rich heterocyclic substrates, such as 2-furyl and 2-thienyl to give the desired thioesters (**3l-m**) in excellent yields. Finally, we were delighted to find that α-alkyl ester (**3n**) is also compatible with this method, delivering the thioester product in 59% yield.

Next, we tested differently substituted esters on the aryl moiety (Fig. 2, middle). Notably, *para*-CF_3-functionalized ester (**1o**) delivered the desired thioester in excellent yield. Furthermore, the substrate containing two ester functional groups (**1p**) showed exquisite chemoselectivity in the reaction, delivering the product in 98% yield. Moreover, hindered *ortho*-substituted ester (**1q**) showed promising reactivity. Aliphatic esters are fully recovered from the reaction conditions, as expected from the excellent chemoselectivity observed in the intramolecular competition substrates (**3h**, **1p**).

Finally, we tested the generality of the method with respect to the thiol component (Fig. 2, bottom). It is noteworthy that the method tolerates fully unbiased electron-neutral (**3o-p**), electron-donating (**3a**) and electron-withdrawing (**3q**) substrates. Furthermore, steric hindrance is also tolerated (**3r**), delivering the product in 51% yield.

To demonstrate the synthetic utility of the method, we performed several studies (Fig. 3). First, in late-stage derivatization, we were delighted to find that this KOAc-mediated protocol could be applied to the direct thioesterification of an aryl ester of Probenecid, antihyperuricemic, (**1r**) to give the desired product in 98% yield in the presence of the sulfonamide bond (Fig. 3A). Second, to exemplify the potential of this method in sulfide synthesis, we demonstrated the site-selective Suzuki cross-coupling, thioesterification, decarbonylation sequence via C–Br/acyl C–O/acyl C–S bond cleavage (Fig. 3B). It is noteworthy that the direct Suzuki cross-coupling in the presence of thioester group was not feasible due to thioester degradation. This sequential approach highlights the strategic deployment of bench-stable carboxylic acid derivatives in aryl/acyl interconversion

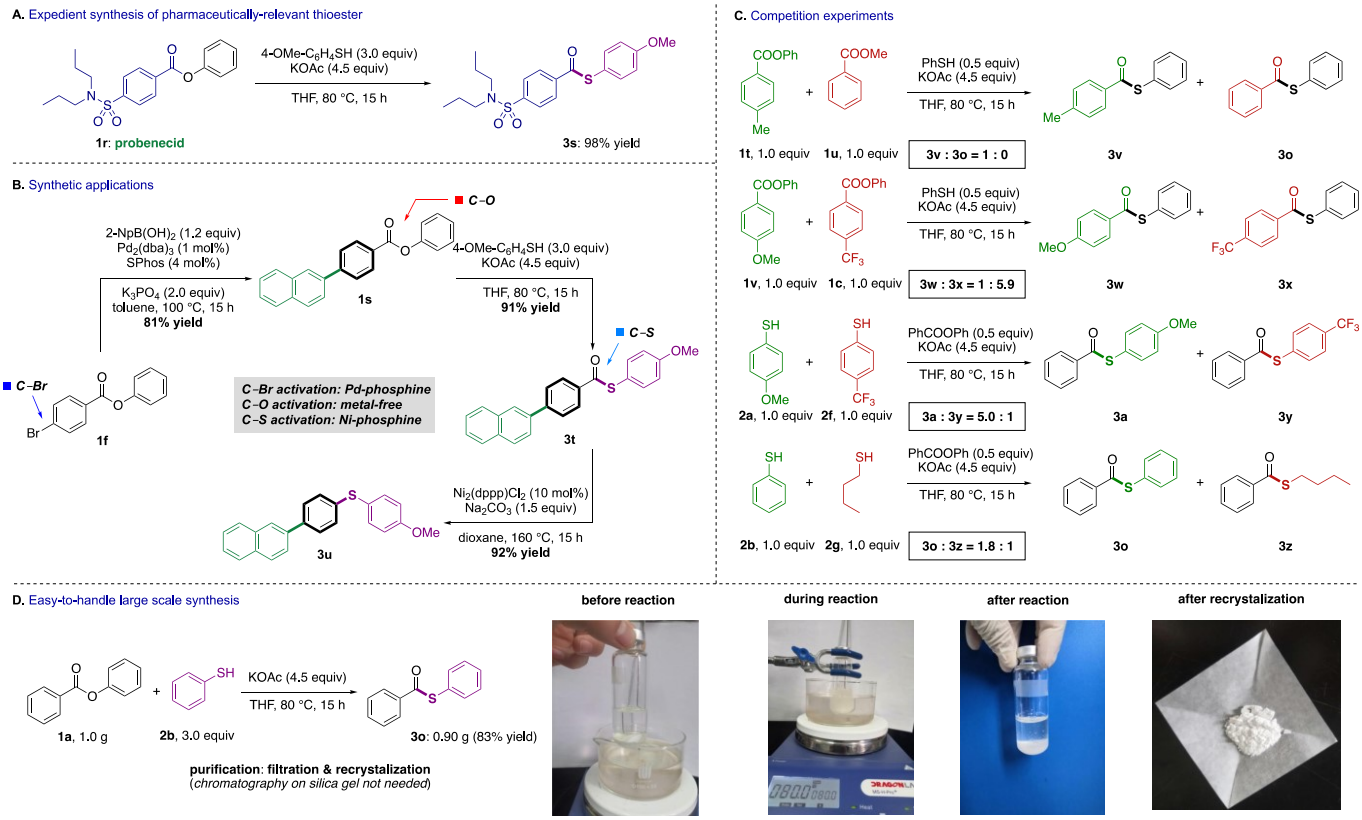

Fig. 3. (A) Synthesis of Probenecid thioester. (B) Sequential synthesis of sulfide. (C) Intermolecular competition experiments. (D) Gram scale synthesis via simple filtration. See SI for details.

reactions using Pd-, Ni- and transition-metal-free reactions.[10,11,19–22]

Preliminary mechanistic studies were conducted to gain insight into this intriguing process. We hypothesize that the observed reactivity is a balance of several contributing factors.

(1) First, intermolecular competition studies were conducted (Fig. 3C). Thus, aromatic esters are inherently more reactive than their alkyl counterparts (**3v**:**3o** > 20:1). Furthermore, electron-deficient esters are inherently more reactive than electron-rich esters (**3w**:**3x** = 15:85). In addition, electron-rich thiols are more reactive than their electron-deficient counterparts (**3a**:**3y** = 83:17). Finally, aromatic thiols are more reactive than *S*-alkyl thiols (**3o**:**3z** = 64:36). This experiment suggests that although the reaction is slightly slower with aliphatic thiols, *S*-alkyl thiols should be suitable for the reaction. Thus, we have investigated aliphatic thiols. For the synthesis of PhCOSEt, the desired product was obtained in 22% yield under standard conditions. Overall, these effects are consistent with nucleophilic addition to the ester bond.

(2) Next, resonance energies of the thioester bond in PhCOSPh and ester bond in $PhCO_2Ph$ were calculated using the COSNAR method.[26] Geometry optimization was performed at the B3LYP/6-311++G(d,p) level (see ESI). Extensive studies have shown that this level is accurate in predicting structural and energetic properties of carboxylic acid derivatives. Resonance energy of the S–C(O) bond in PhCOSPh is 7.6 kcal/mol, which is much lower than the resonance energy of the O–C(O) bond in $PhCO_2Ph$ of 16.1 kcal/mol. However, seminal studies by Liebman and Greenberg demonstrated that esters retain a large part of the resonance energy in the transition state.[27] Therefore, we obtained a detailed rotational profile of the thioester bond in PhCOSPh and ester bond in $PhCO_2Ph$ by systematic rotation along the O–C–X–C angle (see SI). The rotational barrier was determined to be 8.04 kcal/mol (90° O–C–S–C angle), and 8.07 kcal/mol (90° O–C–O–C angle).

(3) Furthermore, the thiolate is a better leaving group than alkoxide (pKa = 10.0, PhOH vs. pKa = 6.6, MeSH);[2] however, thiolates are significantly more nucleophilic than alkoxides (N = 22.6, RCH_2S^- vs. N = 16.0, RCH_2O^-).[28]

Overall, these preliminary studies are consistent with the relative facility of the nucleophilic addition to the acyl bond of aryl esters to give a weak S–C(O) acyl bond in thioesters via preferential collapse of the tetrahedral intermediate. An additional factor that could be involved is the relative solubility of the reaction components.

Finally, to demonstrate the practicality of the method, we conducted a gram scale reaction, which provided the desired thioester product in 83% yield after simple filtration (Fig. 3D), attesting to the practicality of the developed protocol.

3. Conclusions

In summary, we have developed a general and practical method for converting esters to thioesters via C–O bond cleavage/weak C–S bond formation. The method is notable for

operationally-simple and general reaction conditions, broad functional group tolerance and excellent chemoselectivity with respect to aryl esters and sensitive acyl groups. This approach tolerates a range of functional groups that are incompatible with previous methods. The utility has been demonstrated in late-stage thioesterification, sequential bond activation and large scale synthesis. We anticipate that studies on the reversal of the traditional reactivity trend of carboxylic acid derivatives will provide a powerful re-routing toolbox of the carboxylic acid reactivity in various aspects of synthetic chemistry. Future studies will focus on expanding the scope of the method to aliphatic thiols as well as investigation of transition-metal-catalyzed conditions to establish room temperature thioesterification including unactivated ester derivatives.

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Notes and references

1 (a) F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry: Part B: Reactions and Synthesis*; Springer: New York, 2001. (b) M. B. Smith, J. March, *Advanced Organic Chemistry*; Wiley: New York, 2007.
2 I. Ugur, A. Marion, S. Parant, J. H. Jensen, G. J. Monard, *Chem. Inf. Model.* 2014, **54**, 2200-2213.
3 A. L. Lehninger, D. L. Nelson, M. M. Cox, *Principles of Biochemistry*; Worth Publishing: New York, 2002. (b) C. de Duve, *Am. Sci.* 1995, **83**, 428-437.
4 For general reviews sulfur-containing drugs, see: (a) E. A. Ilardi, E. Vitaku, J. T. Njardarson, *J. Med. Chem.* 2014, **57**, 2832-2842. (b) B. R. Beno, K. S. Yeung, M. D. Bartberger, L. D. Pennington, N. A. Meanwell. *J. Med. Chem.* 2015, **58**, 4383-4438. (c) K. A. Scott, J. T. Njardarson. *Top Curr. Chem.* 2018, **376**, 1-34. (d) M. Feng, B. Tang, S. H. Liang, X. Jiang, *Curr. Top. Med. Chem.* 2016, **16**, 1200-1216. (e) N. Wang, P. Saidhareddy, X. Jiang, *Nat. Prod. Rep.* 2020, **37**, 246-275.
5 S. Patai, *Chemistry of Functional Groups: Carboxylic Acids and Esters*; Wiley: New York, 1969.
6 S. Fujiwara, N. Kambe, *Top. Curr. Chem.* 2005, **251**, 87-140.
7 Y. Mori, M. Seki, *Org. Synth.* 2007, **84**, 285.
8 R. Volante, *Tetrahedron Lett.* 1981, **22**, 3119-3122.
9 V. Hirschbeck, P. H. Gehrtz, I. Fleischer, *Chem. Eur. J.* 2018, **24**, 7092-7107.
10 (a) L. J. Goossen, N. Rodriguez, K. Goossen, *Angew. Chem. Int. Ed.* 2008, **47**, 3100-3120. (b) N. Rodriguez, L. J. Goossen, *Chem. Soc. Rev.* 2011, **40**, 5030-5048. (c) Y. Wei, P. Hu, M. Zhang, W. Su, *Chem. Rev.* 2017, **117**, 8864-8907.
11 G. Li, S. Ma, M. Szostak, *Trends Chem.* 2020, **2**, 914-928.
12 (a) G. Meng and M. Szostak, *Angew. Chem. Int. Ed.*, 2015, **54**, 14518-14522. (b) S. Shi, G. Meng and M. Szostak, *Angew. Chem. Int. Ed.*, 2016, **55**, 6959-6963.
13 C. Liu and M. Szostak, *Angew. Chem. Int. Ed.*, 2017, **56**, 12718-12722.
14 F. Bie, X. Liu, Y. Shi, H. Cao, Y. Han, M. Szostak, C. Liu, *J. Org. Chem.* 2020, **85**, 15676-15685.
15 (a) R. Takise, R. Isshiki, K. Muto, K. Itami, J. Yamaguchi, *J. Am. Chem. Soc.* 2017, **139**, 3340-3343. (b) C. A. Malapit, M. Borrell, M. W. Milbauer, C. E. Brigham, M. S. Sanford, *J. Am. Chem. Soc.* 2020, **142**, 5918-5923.
16 C. Liu, C. L. Ji, X. Hong, M. Szostak, *Angew. Chem. Int. Ed.* 2018, **57**, 16721-16726.
17 C. Liu, C. L. Ji, Z. X. Qin, X. Hong, M. Szostak, *iScience* 2019, **19**, 749-759.
18 C. Liu, M. Szostak, *Chem. Commun.* 2018, **54**, 2130-2133.
19 For interconversion from amides to amides (transamidation), see (a) G. Li, C. L. Ji, X. Hong, M. Szostak, *J. Am. Chem. Soc.* 2019, **141**, 11161-11172. (b) T. Ghosh, S. Jana, J. Dash, *Org. Lett.* 2019, **21**, 6690-6694.
20 For interconversion from amides to esters, see: (a) L. Hie, N. F. Fine Nathel, T. K. Shah, E. L. Baker, X. Hong, Y.-F. Yang, P. Liu, K. N. Houk, N. K. Garg, *Nature* 2015, **524**, 79-83. (b) G. Li, P. Lei, M. Szostak, *Org. Lett.* 2018, **20**, 5622-5625. (c) D. Ye, Z. Liu, H. Chen, J. L. Sessler, C. Lei, *Org. Lett.* 2019, **21**, 6888-6892. (d) N. Wu, C. Li, J. Mi, Y. Zheng, Z. Xu, *Org. Lett.* 2020, **22**, 7118-7122.
21 For interconversion from amides to thioesters, see: (a) M. M. Rahman, G. Li, M. Szostak, *Synthesis* 2020, **52**, 1060-1066. (b) Q. Wang, L. Liu, J. Dong, Z. Tian, T. Chen, *New J. Chem.* 2019, **43**, 9384-9388.
22 For interconversion from esters to amides (amidation), see: (a) L. Hie, N. F. Fine Nathel, X. Hong, Y.-F. Yang, K. N. Houk, N. K. Garg, *Angew. Chem. Int. Ed.* 2016, **55**, 2810-2814. (b) T. B. Halima, J. K. Vandavasi, M. Shkoor, S. G. Newman, *ACS Catal.* 2017, **7**, 2176-2180. (c) T. B. Halima, J. Masson-Makdissi, S. G. Newman, *Angew. Chem. Int. Ed.* 2018, **57**, 12925-12929. (d) See, ref. 19.
23 L. Summerton, H. F. Sneddon, L. C. Jones, J. H. Clark, *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*; RSC: Cambridge, 2016.
24 (a) W. K. Chan, S. Masamune, G. O. Spessard, *Org. Synth.* 1983, **61**, 48. (b) N. A. McGrath, R. T. Raines, *Acc. Chem. Res.* 2011, **44**, 752-761.
25 For most pertinent examples, see: (a) I. A. Oskina, V. M. Vlasov, *Russ. J. Org. Chem.* 2008, **44**, 561-569. (b) I. A. Oskina, V. M. Vlasov, *Russ. J. Org. Chem.* 2010, **46**, 326-330 (c) D. A. Watson, X. Fan, S. L. Buchwald, *J. Org. Chem.* 2008, **73**, 7096-7101. (d) A. K. Chakraborti, S. Rudrawar, G. Kaur, L. Sharma, *Synlett* 2004, **9**, 1533-1536. For specific examples of thiol-mediated deacylations, see: (e) M. Li, X. Han, B. J. Yu, *J. Org. Chem.* 2003, **68**, 6842-6845. (f) E. Iglesias, I. Brandariz, *RSC Adv.* 2015, **5**, 45740-45748.
26 A. Greenberg, C. A. Venanzi, *J. Am. Chem. Soc.* 1993, **115**, 6951-6957.
27 J. F. Liebman, A. Greenberg, *Biophys. Chem.* 1974, **1**, 222-226.
28 T. B. Phan, M. Breugst, H. Mayr, *Angew. Chem. Int. Ed.* 2006, **45**, 3869-3874.
29 T. Ben Halima, W. Zhang, I. Yalaoui, X. Hong, Y. F. Yang, K. N. Houk, S. G. Newman, *J. Am. Chem. Soc.* 2017, **3**, 1311-1318.
30 T. Fujihara, T. Hosoki, Y. Katafuchi, T. Iwai, J. Terao, Y. Tsuji, *Chem. Commun.* 2012, **64**, 8012-8014.
31 P. Arde, B. T. Ramanjaneyulu, V. Reddy, A. Saxena, R. V. Anand, *Org. Biomol. Chem.* 2012, **4**, 848-851.
32 N. Fattahi, M. Ayubi, A. Ramazani, *Tetrahedron* 2018, **32**, 4351-4356.

33 G. Li, P. Lei, M. Szostak, *Org. Lett.* 2018, **20**, 5622-5655.
34 R. Sun, Y. Qin, D. Nocera, *Angew. Chem. Int. Ed.* 2020, **24**, 9527-9533.
35 T. Okita, K. Muto, J. Yamaguchi, *Org. Lett.* 2018, **20**, 3132-3135.
36 X. Pu, J. Hu, Y. Zhao, Z. Shi, *ACS Catal.* 2016, **10**, 6692-6698.
37 G. Bogonda, D. Patil, H. Kim, K. Oh, *Org. Lett.* 2019, **21**, 3774-3779.
38 B. Kang, S. H. Hong, *Chem. Sci.* 2017, **8**, 6613-6618.
39 W. Ali, S. Guin, S. Rout, A. Gogoi, B. Pate, *Adv. Synth. Catal.* 2014, **356**, 3099-3105.
40 T. Hirai, H. Kuniyasu, N. Kambe, *Chem. Lett.* 2004, **33**, 1148-1149.
41 M. Kimura, S. Matsubara, Y. Yamamoto, Y. Sawaki, *Tetrahedron* 1991, **47**, 867-876.
42 N. Ichiishi, C. Malapit, L. Wozniak, M. Sanford, *Org. Lett.* 2018, **20**, 44-47.

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