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Dess–Martin periodinane oxidative rearrangement for preparation of α-keto thioesters†

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A Dess–Martin Periodinane (DMP) mediated oxidative rearrangement reaction was uncovered. The reaction proceeds *via* oxidation of a β-hydroxy thioester to a β-keto thioester, followed by an α-hydroxylation and then further oxidation to form a vicinal thioester tricarbonyl. This product then rearranges, extruding CO_2, to form an α-keto product. The mechanism of the rearrangement was elucidated using ^{13}C labelling and analysis of the intermediates as well as the products of the reaction. This efficient process allows for easy preparation of α-keto thioesters which are potential intermediates in the synthesis of pharmaceutically important heterocyclic scaffolds such as quinoxalinones.

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Introduction

Polyvalent iodine reagents emerged in the 1980s as selective oxidants in organic chemistry.[1–3] Most commonly used are 2-iodoxybenzoic acid (IBX)[4] and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one, known as Dess–Martin Periodinane (DMP).[5] DMP is one of the mildest reagents for oxidation of primary and secondary alcohols.[6] DMP also does α-oxidations of β-keto esters and amides to form vicinal tricarbonyl derivatives of pharmaceutical interest.[6,7] In addition it converts: allylic alcohols to α,β-unsaturated carbonyls;[8] aldoximes and ketoximes to aldehydes and ketones;[9] *N*-acyl hydroxylamines to acyl nitroso compounds;[10] 4-substituted anilides to *p*-quinones;[11] β-amino alcohols to α-amino aldehydes without epimerization;[12] and γ,δ-unsaturated aromatic amides to heterocycles.[13] However, there were no reports to show that DMP is involved in the rearrangement of β-hydroxy thioesters to α-keto thioesters, which we now describe.

DMP was first prepared by Dess and Martin in 1983 by reaction of 2-iodobenzoic acid with $KBrO_3$ in H_2SO_4 to give IBX, which was further treated with a mixture of acetic anhydride and acetic acid to yield the reagent in 87% overall yield.[5] As IBX is insoluble in many organic solvents, its applications were limited, and DMP offered considerable advantages. This preparation was further improved by Ireland and Liu in 1993, who addressed inconsistencies in the synthetic outcome by replacing acetic acid with catalytic *p*-toluenesulfonic acid in the second step.[14] This allowed reproducible formation of DMP with significantly higher yields.[14] Issues regarding the inconsistent behaviour of DMP were addressed when it was shown that exposure to the atmosphere or the addition of an equivalent of water vastly accelerated the rate of oxidations.[6] A rate increase also occurred when 2 equivalents of alcohol were added. The authors proposed that the water or alcohol replaces one of the acetoxy groups on DMP, and that this makes the remaining iodine–alkoxy bond more labile, thereby accelerating the reactions.[6]

Golec and coworkers showed that DMP may be used to transform β-diketones, β-ketoesters and β-ketoamides to produce the corresponding vicinal tricarbonyl compounds by α-oxidation in varying yields.[15] Subsequently, Meyer and Schreiber proposed that the α-methylene oxidation of β-keto esters is facilitated by the acetoxyiodinane oxide reacting with the enol form of the β-keto ester product, as depicted in Fig. 1.[6]

Interestingly there were no reports of analogous transformations with β-keto thioesters. Moreover, our group had oxidized β-hydroxy thioesters to β-keto thioesters with DMP in good yields (>75%) without detecting significant over-

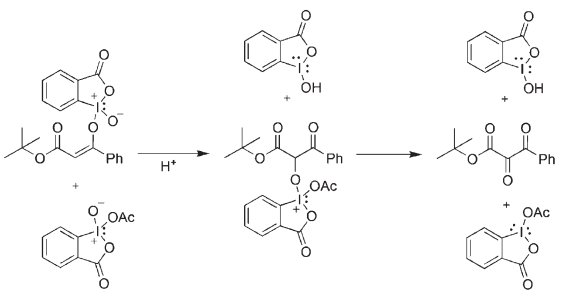

Fig. 1 The proposed mechanism for the oxidation of β-OH esters to vicinal tri-carbonyl compounds.[6]

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oxidation.[16–19] In the present work we show that excess DMP can form vicinal tricarbonyl thioesters, but under the conditions, these are susceptible to an unexpected rearrangement reaction to form α-keto thioesters. α-Keto carbonyl compounds are intermediates in the preparation of heterocyclic derivatives.[20] Although the use of α-keto acids to form heterocycles is quite common, the conditions required for transformation tend to be harsh.[21] However, as described below, reaction of α-keto thioesters with diamines proceeds under very mild conditions to give quinoxalinones. The quinoxalinone moiety is considered a privileged structure, and is often used as a core scaffold for a combinatorial library synthesis.[22]

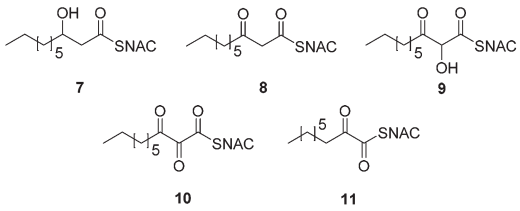
Results and discussion

Although oxidation of α-methyl β-hydroxy thioester **1** with excess DMP gives the expected product **2**,[16] identical conditions transform **3** to α-keto thioester **4** rather than the expected β-keto derivative. This compound contains one less carbon, and its formation was accompanied by the production of a gas (Scheme 1). We did not find literature precedent for this transformation. However, DMP oxidations of β-hydroxy thioesters to β-keto thioesters can sometimes result in low yields,[16–19] whereas the same reaction on β-hydroxy esters or amides have been reported with higher yields.[15] *N*-Acetylcysteamine (SNAC) thioesters were used in this work due to their utility for studies with polyketide synthases,[17,19] but the reaction works similarly with other thioesters as shown in Scheme 1. Since DMP is already known to convert β-hydroxy esters and amides to the vicinal tricarbonyl compounds,[15] it seemed likely that the β-keto thioester was further oxidized the vicinal tricarbonyl, which was then transformed to the α-keto thioester.

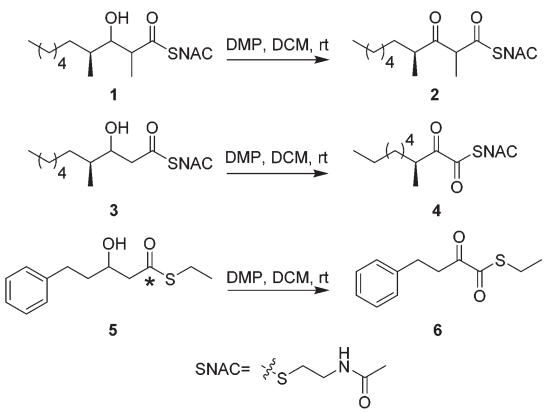
To test this, we investigated conversion of **7** to **11** by synthesis of proposed intermediates **8–10** and examination of the effect of varying equivalents of DMP (10% excess was used to account for the purity of the reagent supplied, 95% purity) on the product distribution (Table 1). The identities of the intermediates were confirmed by retention time and high resolution liquid chromatography coupled to mass spectrometry (LCMS) with matching to synthesized standards. Complete rearrangement starting from **7** requires 5 equivalents of DMP. Product ratios resulting from use of less DMP suggest that **9** and **10** are rapidly transformed to subsequent products if additional oxidizing agent is present. To confirm that the species observed in the reaction were true intermediates, each was reacted with the requisite equivalents of DMP. It was observed that all of the proposed intermediates were transformed to the α-keto thioester product as shown in Table 2. Under the same conditions, the vicinal tricarbonyl compound **10** was treated with 1-acetoxybenziodoxol-3-one, the by-product from the DMP reagent, but this did not give any rearrangement. Similarly, nucleophiles with heteroatom bonds such as hydrogen peroxide or *N*-hydroxyphthalimide did not rearrange the vicinal tricarbonyl compound **10**. With the intermediate species in the rearrangement established, the mechanism of transformation of the vicinal tricarbonyl to the α-keto thioester was examined.

Substrates labelled with ^{13}C at the β-carbon or at the thioester carbonyl (Scheme 2) were made to ascertain which

Table 1 The effect of DMP equivalents on the relative distribution of products (total equivalents of 7–11 set to 100%)

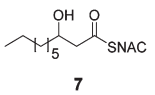
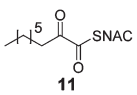
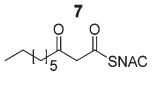
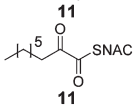
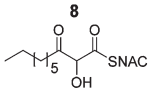
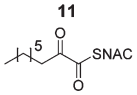
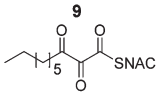
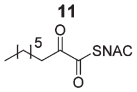


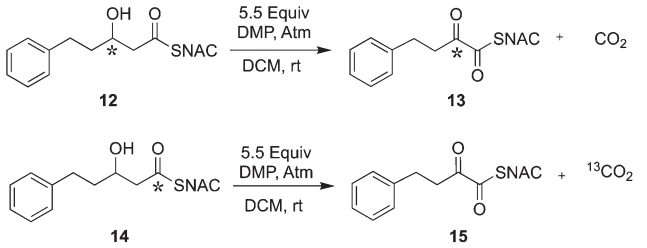
Equiv. of DMP	% 7	% 8	% 9	% 10	% 11
1.1	0	73	1	1	25
2.2	0	10	0	7	82
3.3	0	1	0	8	91
5.5	0	0	0	1	99



Scheme 1 Showing the transformation of β-hydroxy thioesters to different products under the same conditions.

Table 2 Showing the rearrangement of proposed intermediates to the α-keto thioester product using DMP

Substrate	Equiv. of DMP	Product
 7	5.5	 11
 8	4.4	 11
 9	2.2	 11
 10	1.1	 11



Scheme 2 Showing the products formed from the labelled substrates. * represents ^{13}C label.

carbon was being removed and to determine the identity of the species being extruded. Reaction of β-hydroxy thioester **12**, bearing the ^{13}C label at the β-carbon gave ^{13}C-labelled α-keto thioester **13** and *m*/*z* 44.1 was observed for unlabelled CO_2 in the headspace gas. This was confirmed by the gas phase IR spectra (Fig. 2). The reaction of β-hydroxy thioester **14** bearing the ^{13}C label at the thioester carbonyl produced unlabelled **15** and *m*/*z* 45.1 was observed for the $^{13}CO_2$. The corresponding shift in the IR spectra of the resulting $^{13}CO_2$ gas produced in the reaction vessel headspace is shown in Fig. 2. These results show that the thioester carbonyl carbon is extruded in the form of CO_2 gas.

A crossover experiment was used to determine whether the reaction was intermolecular or intramolecular. Equal amounts of unlabelled **17** and doubly ^{13}C-labelled **16** substrates were mixed and then oxidized. An intramolecular process would give α-keto thioester products that are either completely unlabelled or doubly labelled, whereas an intermolecular reaction would generate a mixture of unlabelled, singly labelled, and doubly labelled products. High resolution LCMS analysis showed only unlabelled **19** and doubly labelled **18** as products, thereby demonstrating intramolecular conversion (Scheme 3). The rearrangement mechanism of the vicinal tricarbonyl thioester to the corresponding α-keto thioester may occur as outlined in Fig. 3.

Overall the transformation proceeds by oxidation of the β-hydroxy thioester to a β-keto thioester, which then undergoes an α-hydroxylation followed by another oxidation to form the

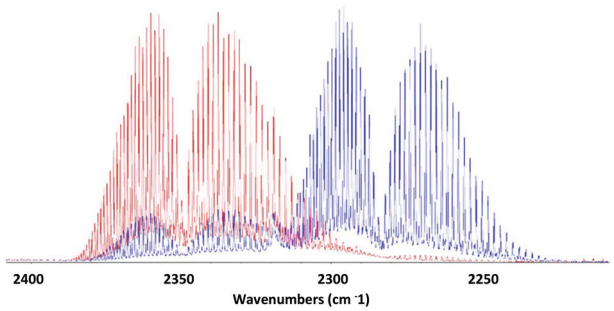
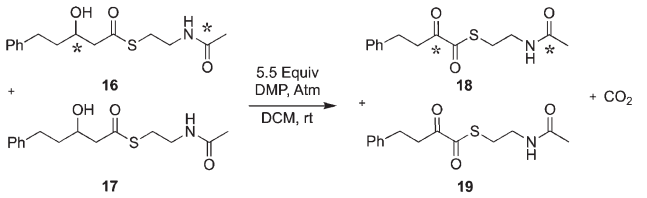


Fig. 2 Showing the overlaid results of the gas phase IR for $^{12}CO_2$ (red trace) *vs.* $^{13}CO_2$ (blue trace). Residual unlabelled CO_2 in the latter is background from air.



Scheme 3 Showing the results of the crossover experiment, between doubly labelled and unlabelled substrates (ratio of 14/15 = 1 : 1, and 16/17 = 1 : 1).

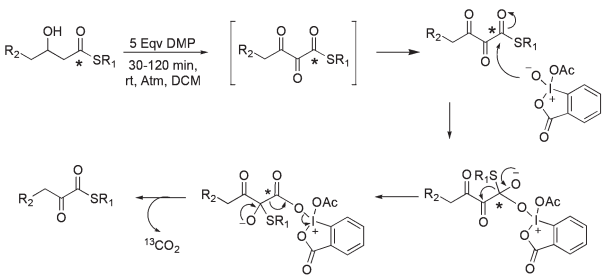
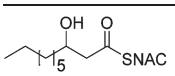
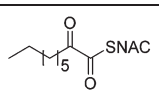
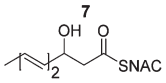
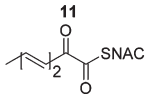
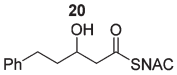
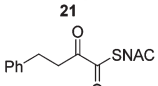
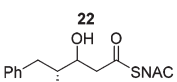
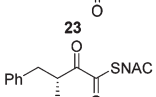
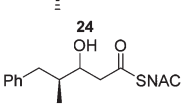
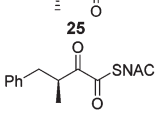


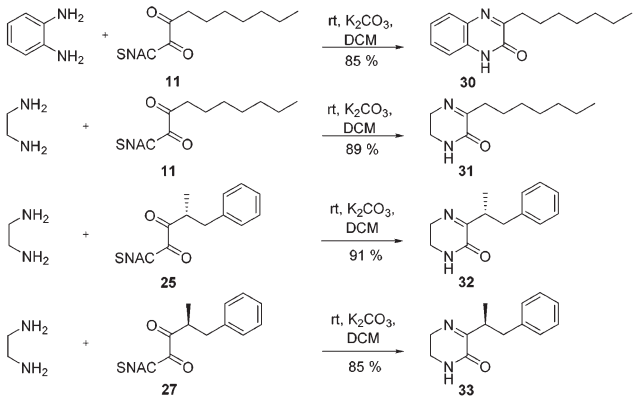
Fig. 3 Showing the proposed mechanism for the DMP oxidative rearrangement of β-hydroxy thioesters.

vicinal tricarbonyl thioester. This vicinal tricarbonyl then undergoes an intramolecular rearrangement using a molecule of acetoxyiodinane oxide to release CO_2 and the α-keto thioester product.

The substrate scope was briefly explored with variations at the γ–carbon of the thioesters. The reaction does not seem to be affected by steric bulk at the γ-position, but a methyl substituent at the α-position does prevent the rearrangement. It appears that very little racemization (if any) occurs at the γ-position relative to the thioester carbonyl during transformation of **24** and **26** to **25** and **27**, respectively (Table 3). This

Table 3 Showing a summary of the substrates tested and their corresponding products

Substrate	Yield %	Product
	74	
7 	66	**11** 
20 	63	**21** 
22 	60	**23** 
24 	62	**25** 
26		**27**



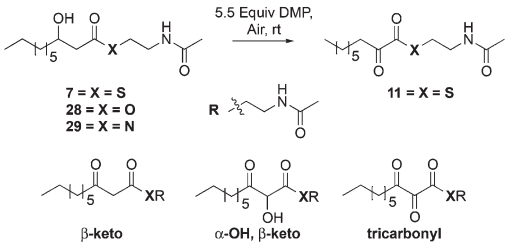
Scheme 4 Preparation of quinoxalinones from α-keto thioesters.

was determined by direct comparison of the optical rotations of enantiomeric compounds, both after rearrangement and also after transformatiuon to **32** and **33**, respectively (see below, Scheme 4). The rotation values were observed to be quite similar but in the opposite direction. While full conversion of the starting material is always observed, the average isolated yield is 65%. This is due to the polar nature of the products, making them harder to separate from the 2-iodobenzoic acid formed in the work-up of the reaction. We found that increasing the number of sodium bicarbonate washes aids in the removal of much of this impurity, but at the cost of a lower yield. However, if a stronger, more nucleophilic base is used, the targeted α-keto thioesters are destroyed. Other attempts were made to further improve the overall yield of the reaction. These included addition of a base (DBU, K_2CO_3, $CsCO_3$) to the reaction, and increasing of the reaction temperature (room temperature to 50 °C). However, these attempts provided no improvements to the yield. The elevated temperatures led to the decomposition of the product, and the addition of base resulted in lowered yields.

The reactivities of thioester, ester and amide functionalities for the rearrangement were compared. As expected, the thioester functionality is the most susceptible to the rearrangement of the three (Table 4). Under the conditions used, the rearrangement does not occur to a significant extent during oxidation of β-hydroxy amides. However, it does proceed with oxygen esters to some extent. These results may offer an explanation as to why this reaction was not previously observed, as there are reports of the use of DMP to oxidise β-hydroxy esters and amides to their corresponding β-keto and vicinal tricarbonyl compounds.[6,15]

The reactivity of α-keto thioesters with diamines was briefly examined. They react readily at room temperature to form the corresponding quinoxalinones in good yields (Scheme 4). One of the most common approaches to prepare quinoxalinones, is the treatment of α-keto acids with diamines under harsh conditions.[20] However, our results show that α-keto thioesters may be used effectively in place of α-keto acids, thereby reducing the reaction time and temperatures, while being compatible with thermo labile functionalities.

Table 4 Relative distribution of products (total equivalents of starting material-product set to 100%) for thioesters, esters and amides using LC-MS analysis



X	Starting material	β-Keto	α-OH-β-keto	Tri-carbonyl	Product
S	0.0	0.0	0.0	0.7	99
O	0.0	2.0	34	52	11
N	2.3	0.0	1.9	95	0.7

Conclusions

A new Dess–Martin Periodinane (DMP) mediated intramolecular rearrangement reaction was uncovered. Through a series of ^{13}C labelling studies and intermediate testing, it was found that the reaction converts β-hydroxy thioesters to α-keto thioesters, extruding the starting thioester carbon as CO_2 in the process. The attachment of the thiol functionality to the α-carbonyl was determined to be a 1,2 migration. This mild and efficient reaction allows for easy preparation of α-keto thioesters, which can be used to prepare valuable intermediates for the synthesis of pharmaceutically important heterocyclic compounds.

Experimental

General method for preparation of β-hydroxy thioesters

Step 1: Aldol condensation. In a flame dried round bottom flask 3-acetylthiazolidene-2-thione was dissolved in dry CH_2Cl_2 under an argon atmosphere and cooled to 0 °C. To this solution was added 1.1 equiv. of $TiCl_4$ and the mixture was stirred for 10 min before further cooling to −78 °C. Then 1.1 equiv. of diisopropylethylamine (DIPEA) were added and stirring was continued at −78 °C for 1 h. Next 1.2 equiv. of aldehyde was added, and the mixture stirred for 1.5 h at −78 °C. The mixture was warmed to 20 °C and the reaction was quenched by the addition of 10 mL saturated NH_4Cl. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL) then dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash column chromatography.

Step 2: Conversion of acyl thiazolidene-2-thiones to thioesters. To a flame dried round bottom flask containing dry acetonitrile was added the aldol product from Step 1. This was followed by 5.0 equiv. of K_2CO_3, then 1.3 equiv. of *N*-acetylcysteamine (HSNAC; this is a non-volatile thiol that

has no stench. However, other thiols may be used). The mixture was stirred at 20 °C until the colour disappeared (15–45 min). The solvent was removed under vacuum, and EtOAc (20 mL) and water (20 mL) were added. The phases were then separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), then dried over Na_2SO_4, and concentrated under vacuum. Purification of the resulting residue by flash column chromatography yielded the β-hydroxy thioester.

General method for DMP oxidative rearrangement of β-hydroxy thioesters

In a 100 ml round bottom flask, the β-hydroxy thioester was dissolved in CH_2Cl_2 and 5.5 equiv. of Dess–Martin periodinane (DMP) were added. The mixture was stirred (open to air) at 20 °C for 3 h. The reaction was quenched by slow addition of a 1 : 1 mixture of saturated $NaHCO_3$: $Na_2S_2O_3$ and the mixture was stirred for 15 min. The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (3 × 10 mL), then brine (2 × 10 mL), and then dried over Na_2SO_4. The solvent was removed under vacuum. The crude product was purified using flash column chromatography.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2002, **102**, 2523–2584.
2 R. L. Amey, *J. Am. Chem. Soc.*, 1978, **100**, 300–301.
3 R. L. Amey and J. C. Martin, *J. Am. Chem. Soc.*, 1979, **101**, 5294–5299.
4 T. Wirth, *Agnew. Chem., Int. Ed.*, 2001, **40**, 2812–2814.
5 D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155–4156.
6 S. D. Meyer and S. L. Schreiber, *J. Org. Chem.*, 1994, **59**, 7549–7552.
7 H. H. Wasserman and J. Parr, *Acc. Chem. Res.*, 2004, **37**, 687–701.
8 N. J. Lawrence, J. P. Crump, A. T. McGown and J. A. Hadfield, *Tetrahedron Lett.*, 2001, **42**, 3939–3941.
9 S. S. Chaudhari and K. G. Akamanchi, *Synthesis*, 1999, 760–764.
10 N. E. Jenkins, R. W. Ware, R. N. Atkinson and S. B. King, *Synth. Commun.*, 2000, **30**, 947–953.
11 K. C. Nicolaou, K. Sugita, P. S. Baran and Y. L. Zhong, *Agnew. Chem., Int. Ed.*, 2001, **40**, 207–210.
12 A. G. Myers, B. Zhong, M. Movassaghi, D. W. Kung, B. A. Lanman and S. Kwon, *Tetrahedron Lett.*, 2000, **41**, 1359–1362.
13 K. C. Nicolaou, P. S. Baran, Y. L. Zhong and K. Sugita, *J. Am. Chem. Soc.*, 2002, **124**, 2212–2220.
14 R. E. Ireland and L. Liu, *J. Org. Chem.*, 1993, **58**, 2899.
15 M. J. Batchelor, R. J. Gillespie, J. M. C. Golec and C. J. R. Hedgecock, *Tetrahedron Lett.*, 1993, **34**, 167–170.
16 R. A. Cacho, J. Thuss, W. Xu, R. Sanichar, Z. Gao, A. Nguyen, J. C. Vederas and Y. Tang, *J. Am. Chem. Soc.*, 2015, **137**, 15688–15691.
17 R. V. K. Cochrane, R. Sanichar, G. R. Lambkin, B. Reiz, W. Xu, Y. Tang and J. C. Vederas, *Angew. Chem., Int. Ed.*, 2016, **55**, 664–668.
18 H. Zhou, Z. Gao, K. Qiao, J. Wang, J. C. Vederas and Y. Tang, *Nat. Chem. Biol.*, 2012, **8**, 331–333.
19 Z. Gao, J. Wang, A. K. Norquay, K. Qiao, Y. Tang and J. C. Vederas, *J. Am. Chem. Soc.*, 2013, **135**, 1735–1738.
20 L. Shi, H. Zhou, J. Wu and X. Li, *Mini-Rev. Org. Chem.*, 2015, **12**, 96–112.
21 L. Shi, J. Zhou, J. Wu, J. Cao, Y. Shen, H. Zhou and X. Li, *Bioorg. Med. Chem.*, 2016, **24**, 1840–1852.
22 D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893–930.