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Intermolecular sulfur atom transfer cascade enabled late-stage introduction of sulfilimines into peptides†

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Sulfilimines, a privileged class of $-S(IV)=N-$ functional groups found in nature, have been exploited as valuable building blocks in organic synthesis and as pharmacophores in drug discovery, and have aroused significant interest in the chemical community. Nevertheless, strategies for late-stage introduction of sulfilimines into peptides and proteins have still met with limited success. Herein, we have developed a method of introducing biological sulfilimine fragments into peptides by an intermolecular sulfur atom transfer cascade reaction, utilizing hydroxylamine condensed with the acid moieties of peptides and varied diaryl disulfides. It provides a convenient, efficient, metal-free and widely applicable method for late-stage modification and functionalization of peptides at their acid sites both in the homogeneous phase and on-resins in SPPS. Moreover, the modified peptides with sulfilimines have been demonstrated as cleavable linkers for peptide conjugates under reducible conditions, providing unique opportunities in peptide therapeutics development and drug discovery.

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Introduction

Thanks to the significance of peptides as therapeutics,¹ a platform for targeted therapeutics,² and chemical biology probes,³ conjugations of peptides with functional molecules and conventional drugs have drawn tremendous interest during the past two decades, leading to an arsenal of peptide bioconjugations and modifications.⁴ Despite the fruitful advances, the development of novel peptide bioconjugation and modification is still urgently needed. Sulfilimines, a privileged class of $-S(IV)=N-$ functional groups, that were initially discovered approximately a century ago, have been exploited as valuable building blocks in organic synthesis,⁵ and as pharmacophores in drug discovery.⁶ More interestingly and significantly, they were identified by Hudson *et al.* in 2009 as unique crosslinks that covalently bind hydroxylysine-211 and methionine-93 in the collagen IV network, which is a highly conserved major component of basement membranes and associated with the occurrence of several biofunctions and diseases.⁷ Later, the same group disclosed the Br-dependent peroxidase catalyzed

biochemical formation of sulfilimines between methionine-93 and hydroxylysine-211 within collagen IV, an event critical for basement membrane assembly and tissue development in

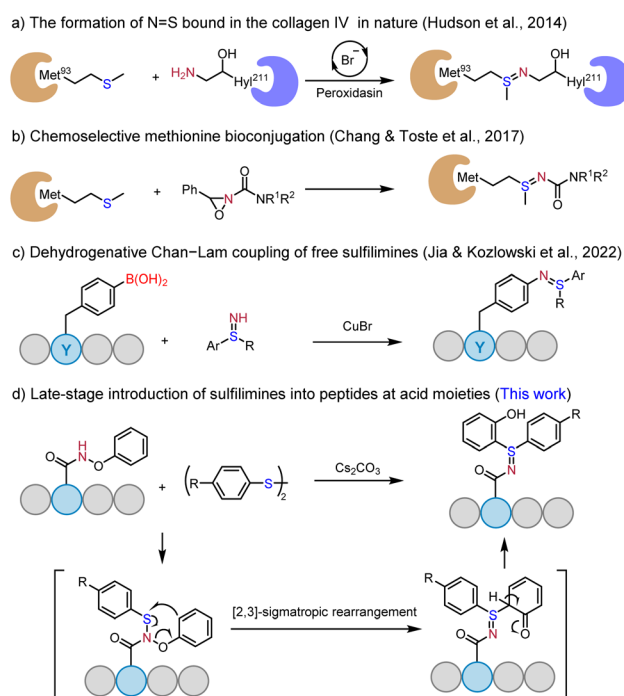


Fig. 1 Strategies for the introduction of sulfilimines into peptides and proteins.

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animals (Fig. 1a).⁸ Inspired by this discovery, Tang *et al.* developed sulfilimine-based molecular probes for imaging native HOBr in live cells and Zebrafish.⁹

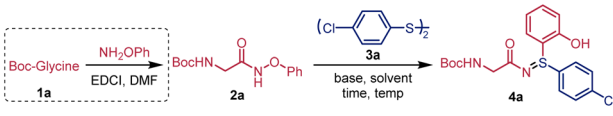
These elegant seminal studies have aroused scientists to artificially build sulfilimines between biomolecules, particularly peptides and proteins, and small functional molecules. Chang, Toste, and co-workers developed a methionine selective bioconjugation by oxidizing methionines to corresponding sulfilimines with oxaziridines,¹⁰ which was demonstrated successful in cyclization of peptides, protein functionalization, antibody–drug conjugates (ADCs), and chemoproteomic identification of functional methionines in cells (Fig. 1b).^{10,11} These studies indicate that N=S bonds have significant potential in drug conjugates. More recently, Kozłowski, Jia, and co-workers have developed a biocompatible Chan–Lam coupling reaction, which can introduce *N*-Ar diaryl sulfilimines into peptides and proteins at the site of an exogenous inserted arylboronic acid (Fig. 1c).¹² Nevertheless, a novel and mild alternative that is beyond the above methods to construct sulfilimines between peptides and functional small molecules, which could be of great potential for peptide–drug conjugates (PDCs) construction, is still appealing to the chemical community.

Very recently, we disclosed the late-stage introduction of oxime ethers into peptides using *N*-alkoxylpeptidylamides that were prepared *in situ* from amino acids¹³ and C–S bond formation between tryptophan and thiophenol enabled site-selective functionalization of peptides.¹⁴ As a continuation of our ongoing interests in peptide bioconjugation and medicinal chemistry,^{13–15} and inspired by the intermolecular sulfur atom transfer cascade reaction between aryloxyamides and thiols that was reported by Xiong *et al.*,¹⁶ we sought to explore the reaction between thiols and *N*-phenoxypeptidylamides that could be prepared *in situ* from the acid moiety of peptides to furnish late-stage incorporation of sulfilimines with diverse functional groups into peptides at the position of interest *via* an intermolecular sulfur atom transfer cascade reaction, and thereby provide a novel alternative for peptide modification and PDC construction (Fig. 1d).

Results and discussion

Our investigation was initiated by using *N*-phenoxyglycinamide **2a** that was prepared by condensation of *N*-Boc-glycine **1a** and *O*-phenylhydroxylamine, and 4,4'-dichlorodiphenyl disulfide **3a** as a model substrate in the presence of CsOAc in DMSO at room temperature for 10 h. To our delight, glycyll sulfilimine **4a** was obtained smoothly, albeit with moderate yield (Table 1, entry 1). Encouraged by this result, a series of reaction conditions including reaction media, base, temperature, and other parameters (for a complete list of the conditions screened, see the section 'Optimization studies' in the ESI†) were screened to verify optimal reaction conditions. It revealed that base was crucial for the reaction (Table 1, entries 1–4 and Tables S1–S3†) and 0.5 equiv. Cs₂CO₃ gave the optimal results (Table 1, entry 3). The reaction could be promoted at 37 °C with a significantly shortened reaction time in high isolated yield (Table 1, entry 5, defined as method A). Interestingly, when simple 4-

Table 1 Optimization of the reaction conditions



Entry	Solvent	Base	Time (h)	Temp. (°C)	Yield ^e (%)
1 ^a	DMSO	CsOAc (1 eq.)	10	rt	61
2 ^a	DMSO	Cs ₂ CO ₃ (1 eq.)	10	rt	83
3 ^a	DMSO	Cs ₂ CO ₃ (0.5 eq.)	10	rt	90
4 ^a	DMSO	—	10	rt	0
5 ^a	DMSO	Cs ₂ CO ₃ (0.5 eq.)	6	37	90 (85)
6 ^{a,d}	DMSO	Cs ₂ CO ₃ (0.5 eq.)	6	37	90
7 ^a	DMF	Cs ₂ CO ₃ (0.5 eq.)	6	37	89
8 ^b	DMF	Cs ₂ CO ₃ (1.7 eq.)	6	37	53
9 ^c	DMF	Cs ₂ CO ₃ (1.7 eq.)	6	37	0

^a **2a** (0.05 mmol), **3a** (0.05 mmol) and base in 1 mL solvent. ^b **1a** (0.1 mmol), NH₂OPh (0.1 mmol), EDCI (0.12 mmol) and HOBT (0.12 mmol) in 2 mL DMF at 37 °C for 6 h, then **3a** (0.1 mmol) and Cs₂CO₃ (0.17 mmol) were added and stirred for an additional 6 h. ^c **1a** (0.1 mmol), NH₂OPh (0.1 mmol), EDCI (0.12 mmol), HOBT (0.12 mmol), **3a** (0.1 mmol) and Cs₂CO₃ (0.17 mmol) in 2 mL DMF at 37 °C for 6 h. ^d 0.1 mmol 4-chlorothiophenol **3a'** was used instead of **3a**. ^e Yield was determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield after column chromatography was given in parentheses.

chlorothiophenol monomer **3a'** was used instead of 4,4'-dichlorodiphenyl disulfide **3a**, the reaction could proceed smoothly as well, providing glycyll sulfilimine **4a** in equivalent yield (Table 1, entry 5 *vs.* 6), probably because simple thiophenols were easily oxidized to disulfides under air.^{16b} Meanwhile, DMF, the most commonly used solvent in solid-phase peptide synthesis (SPPS), was also well compatible with this reaction (Table 1, entry 5 *vs.* 7). To further simplify the reaction protocol, a two-step-one-pot procedure was investigated. The reaction proceeded smoothly when **1a**, *O*-phenylhydroxylamine, EDCI and HOBT were stirred for 6 hours in DMF before addition of **3a** and Cs₂CO₃ (Table 1, entry 8, two-step-one-pot procedure defined as method B). The condensation reaction between the carboxyl group and *O*-phenylhydroxylamine could generate some by-products, which may explain why the yields of the two-step-one-pot procedure are lower than those of the one-step reaction. Unluckily, it failed when **1a**, **3a**, *O*-phenylhydroxylamine, EDCI, HOBT and Cs₂CO₃ were all added together in solution (Table 1, entry 9, one-pot procedure).

With the optimum conditions in hand, we explored the scope of the reaction (Fig. 2). We first test the universality of the reaction by changing the *N*-phenoxypeptidylamide substrate scope. To our delight, all the substrates that started from different *N*-protected amino acids could be involved in the reaction through method A or method B. A wide variety of functional residues, including aromatic amino acid residues, aliphatic amino acid residues, and polar amino acid residues (**4a–4h**), were tolerated, albeit the presence of reactive side chains like hydroxyl and indole results in lower yield. Large scale (10 mmol) reactions can be carried out using method A or



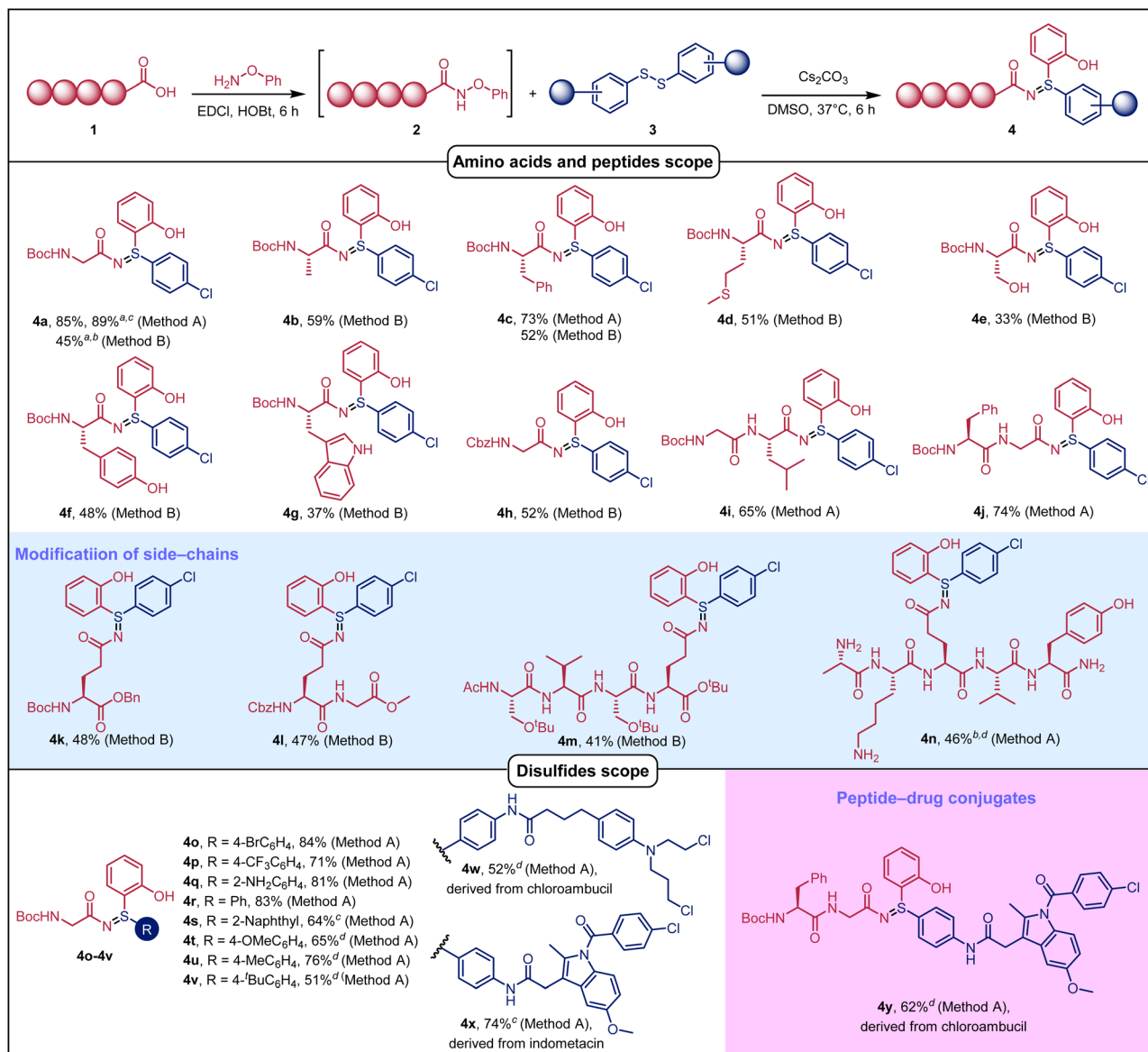


Fig. 2 Substrate scope. Method A: **2** (0.05 mmol), **3** (0.05 mmol), and Cs₂CO₃ (0.025 mmol) in DMSO (1.0 mL) at 37 °C for 6 h. Method B: corresponding amino acids or peptides **1** (0.1 mmol), NH₂O^tPh (0.1 mmol), EDCI (0.12 mmol) and HOBT (0.12 mmol) in 2 mL DMF at 37 °C for 6 h, then **3a** (0.1 mmol) and Cs₂CO₃ (0.17 mmol) were added and stirred for an additional 6 h. Yields of isolated products are given. ^a 10 mmol scale. ^b 0.025 mmol scale. ^c 12 h. ^d 24 h.

method B to obtain corresponding high and moderate yields (**4a**). In addition, the reaction can implement late-stage modification of oligopeptides, incorporating special sulfilimines into oligopeptides at their C-terminal with good yields (**4i**, **4j**). Meanwhile, the late-stage introduction of sulfilimines into the side chain of amino acid or oligopeptide was demonstrated by a one-pot reaction using Glu-containing oligopeptides (**4k–4n**). Significantly, fully deprotected peptides worked well in reaction solution (**4n**), indicating that *O*-aryl hydroxamic acid derivatives have the potential to be biorthogonal precursors for incorporation of a disulfide reagent.

Unfortunately, however, unprotected cysteine is incompatible with this reaction, which may be due to the high reactivity of thiol groups. Subsequently, we explored the substrate scope

of diaryl disulfides. Various alkyl-, amino-, Cl-, Br- and CF₃-substituted phenyl or dinaphthyl disulfides could participate in the reaction smoothly to give the desired products in moderate to good yields (**4o–4v**). Compared with electron withdrawing group substitutions such as 4-Cl, 4-Br and 4-CF₃ (71–89%), diaryl disulfides possessing electron donating substitutions such as 4-OMe, 4-Me, 4-^tBu or 2-naphthyl provided lower yield (51–65%) and needed a longer reaction time. It is particularly noticeable that drugs such as chlorambucil and indomethacin could be introduced as payloads into amino acids (**4w**, **4x**) and oligopeptides (**4y**) with good yields.

We then turned our attention to examine the practicality of the reaction on-resin (Fig. 3). Allyl protected Glu(Oallyl)-OH or Asp(Oallyl)-OH was inserted at the position of interest during



the routine Fmoc SPSS on-resin and thereby site-specific modification could be achieved with orthogonal protection of *tert* butyl ester and allyl ester. After the routine Fmoc-SPSS on-resin, the *N*-phenoxypeptidylamide substrate was obtained by

coupling with *O*-phenylhydroxylamine after deallylation of Allyl. The substrate on-resin was reacted with diaryl disulfide substrate **3** in DMF or DMSO for 24–48 hours, followed by

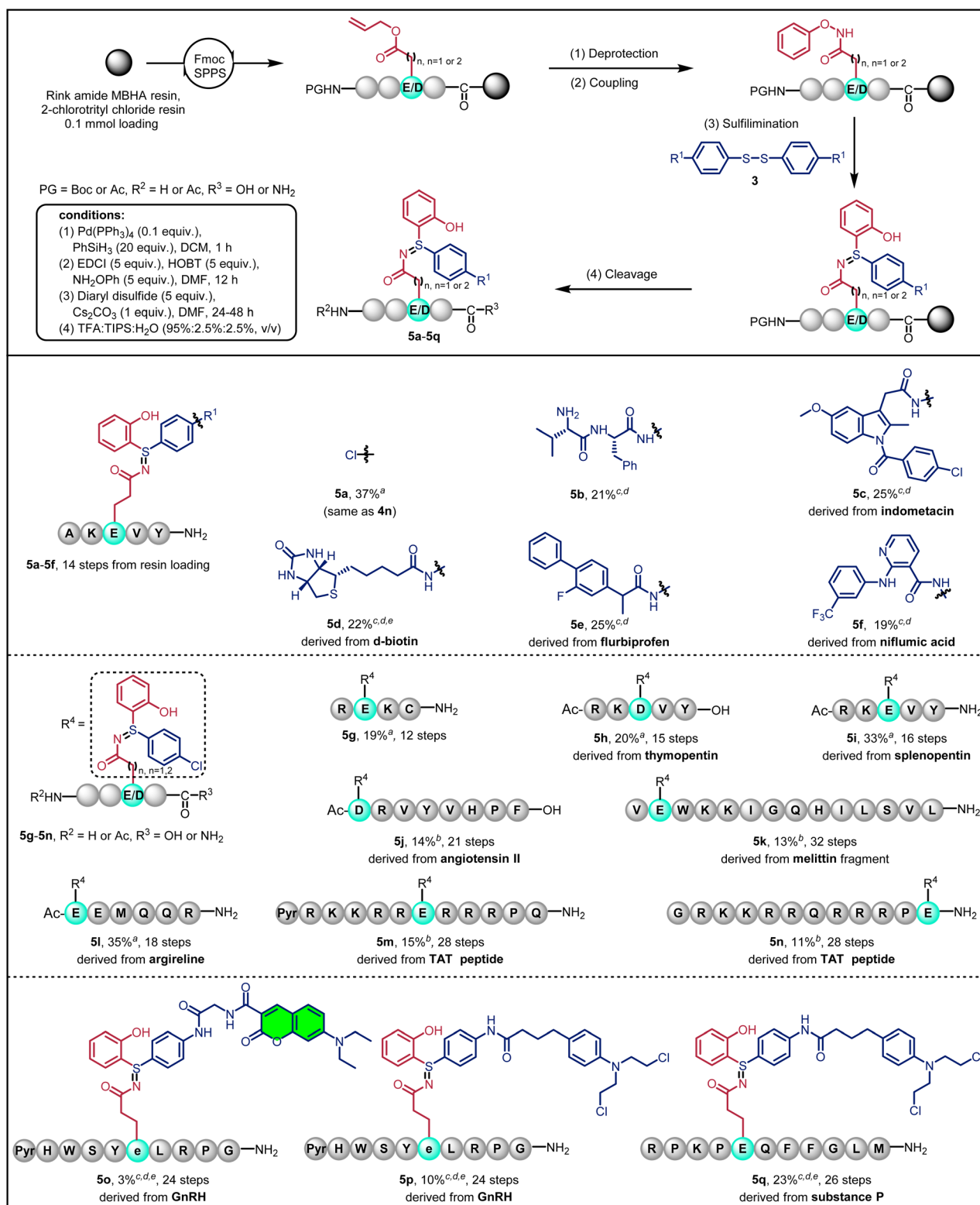


Fig. 3 Late-stage sulfilimination of glutamate/aspartate-containing peptides on resin. Pyr, pyroglutamic acid; e, *D*-Glu. Isolated yield after semi-preparative HPLC was given. ^a 24 h in step (3). ^b 36 h in step (3). ^c 48 h in step (3). ^d 5 equiv. Cs₂CO₃ was added. ^e DMSO instead of DMF in step (3).



cleavage from the resin and purification by semi-preparative HPLC.

To our delight, this protocol worked well with some bioactive molecule analogues and bioactive peptide analogues. **5a** was obtained in 37% isolated yield after 14 steps from resin loading compared to the 46% isolated yield of the one-step reaction in solution (**4n** in Fig. 2). Peptide-peptide conjugates (**5b**), peptide-indomethacin conjugates (**5c**), peptide-D-biotin conjugates (**5d**), peptide-flurbiprofen conjugates (**5e**) and peptide-niflumic acid conjugates (**5f**) were successfully obtained through this strategy after 14 steps. More importantly, product **5g** containing cysteine can be synthesized through this solid-phase synthesis using a Trt-protected cysteine. Conjugate **5g** was slowly degraded in solution due to the unprotected thiol

group, which is consistent with the subsequent experimental results. Bioactive peptides such as thymopentin (**5h**), splenopentin (**5i**), angiotensin II (**5j**), melittin fragment (**5k**), argireline (**5l**) and TAT cell penetrating peptides (**5m**, **5n**) were all applicable to this protocol. Conjugate **5o** only achieved 3% yield, possibly due to the poor solubility of substrate coumarin (**3o**). Furthermore, the success of gonadotropin-releasing hormone (GnRH) derivatives and substance P conjugated with chlorambucil (**5p**, **5q**) further demonstrated the potential application of this reaction to construct PDCs for cancer therapy.

As the connecting bridge between drugs and peptides in PDCs, linkers determine the circulation time and stability of PDCs *in vivo*.¹⁷ To explore the possibility of these sulfilimines as releasable PDC linkers under reducible conditions,^{5b,10a,10b} a series of experiments were then carried out. It was found that sulfilimines could be decomposed into corresponding peptidyl amides and diaryl thioethers under reducible conditions (Fig. 4). Particularly interesting, for example, is that the product peptide conjugate **5i** could be deconjugated in a GSH concentration-dependent manner. Specifically, **5i** was decomposed slowly ($t_{1/2} \sim 12$ h) in 1 mM GSH of PBS buffer (pH 7.4) solution and decomposed rapidly ($t_{1/2} < 1$ h) in 10 mM GSH of PBS buffer (pH 7.4) solution, with complete decomposition within 6 hours (Fig. 4b). In addition, **5i** was stable in PBS solution and relatively stable in FBS (Fetal Bovine Serum) solution, with more than 79% existing in its original form after 24 hours (Fig. 4c and S19–S22†). These features provide us with an opportunity to design GSH-sensitive PDCs and prodrugs for therapy.¹⁸

Conclusions

In summary, a late-stage introduction of sulfilimines into peptides at a carboxylic acid site has been achieved. This method enabled the introduction of sulfilimines with diverse functional groups, such as drugs, natural products, bioactive handles, and fluorescent tags into peptides both in the homogeneous phase and on-resins in SPPS under mild conditions. Moreover, sulfilimines were demonstrated as cleavable linkers for peptide conjugates under reducible conditions, enabling on-demand control of peptide functions. It might provide a novel tool kit for peptide chemical biology and prodrug discovery. Further applications of this strategy in these areas are currently under investigation in our laboratory.

Data availability

All data associated with this study are available in the article and ESI.†

Author contributions

W. S. and R. W. conceptualized the project, supervised the work, designed the experiments, and assisted in data analysis. Z. H., Y. L., G. B., Y. L., X. Z., Q. Z. and K. L. performed the experiments and analyzed the data. All authors discussed the results and commented on the manuscript. W. S. and Z. H. wrote the manuscript.

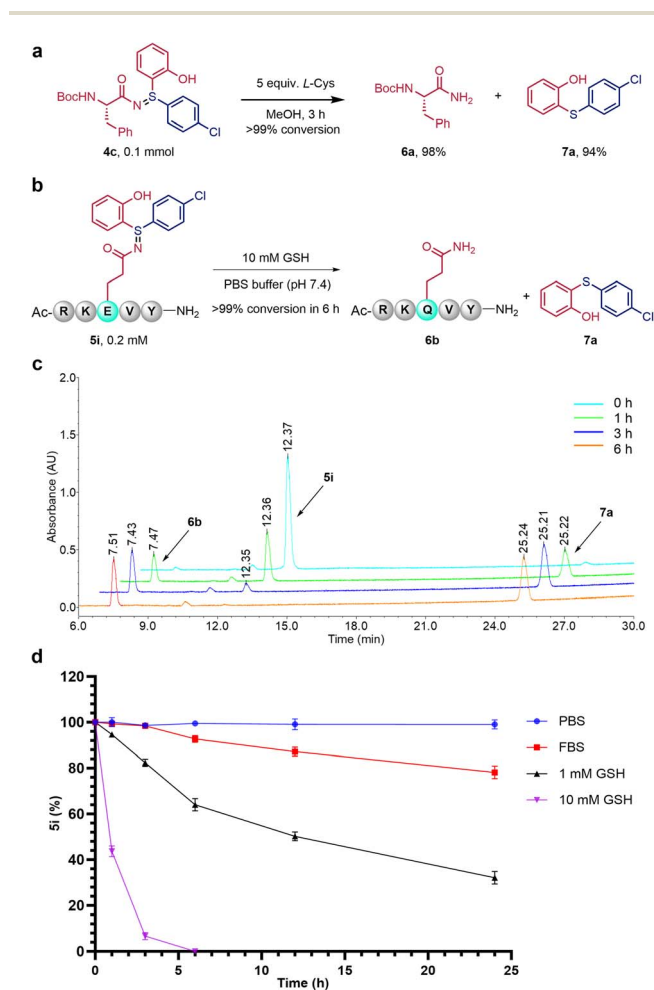


Fig. 4 Deconjugation and stability of modified products. (a) Deconjugation of products **4c**. The reaction was carried out with 0.1 mmol **4c**, 0.5 mmol L-Cys in 1 mL MeOH at room temperature for 3 h, isolated yield of **6a** (98%) and **7a** (94%) were given. (b) Deconjugation of product **5i**. **5i** (0.2 mM) could be decomposed into corresponding peptidyl amides (**6c**) and diaryl thioether (**7a**) by 10 mM GSH in PBS buffer (pH 7.4) solution. (c) Schematic diagram of the HPLC chromatogram indicates the conversion of peptide **5i** in 10 mM GSH solution at different times. (d) Stability of **5i**. **5i** (0.2 mM) was incubated at 37 °C with PBS buffer (pH 7.4) solution, 95% FBS in PBS buffer solution (pH 7.4), 1 mM GSH in PBS buffer (pH 7.4) solution and 10 mM GSH in PBS buffer (pH 7.4) solution respectively.



Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

- (a) I. W. Hamley, *Chem. Rev.*, 2017, **117**, 14015–14041; (b) M. Muttenthaler, G. F. King, D. J. Adams and P. F. Alewood, *Nat. Rev. Drug Discovery*, 2021, **20**, 309–325; (c) L. Wang, N. Wang, W. Zhang, X. Cheng, Z. Yan, G. Shao, X. Wang, R. Wang and C. Fu, *Signal Transduction Targeted Ther.*, 2022, **7**, 48–74.
- (a) B. M. Cooper, J. Iegre, D. H. O' Donovan, M. Ö. Halvarsson and D. R. Spring, *Chem. Soc. Rev.*, 2021, **50**, 1480–1494; (b) M. Alas, A. Saghaeidehkordi and K. Kaur, *J. Med. Chem.*, 2021, **64**, 216–232; (c) L. Gong, H. Zhao, Y. Liu, H. Wu, C. Liu, S. Chang, L. Chen, M. Jin, Q. Wang, Z. Gao and W. Huang, *Acta Pharm. Sin. B*, 2023, **13**, 3659–3677.
- (a) C. L. Charron, J. L. Hickey, T. K. Nsiamia, D. R. Cruickshank, W. L. Turnbull and L. G. Luyt, *Nat. Prod. Rep.*, 2016, **33**, 761–800; (b) S. J. de Veer, J. Weidmann and D. J. Craik, *Acc. Chem. Res.*, 2017, **50**, 1557–1565.
- (a) J. N. deGruyter, L. R. Malins and P. S. Baran, *Biochemistry*, 2017, **56**, 3863–3873; (b) A. S. Mackay, R. J. Payne and L. R. Malins, *J. Am. Chem. Soc.*, 2022, **144**, 23–41; (c) V. M. Lechner, M. Nappi, P. J. Deneny, S. Folliet, J. C. K. Chu and M. J. Gaunt, *Chem. Rev.*, 2022, **122**, 1752–1829; (d) C. Wang, R. Qi, R. Wang and Z. Xu, *Acc. Chem. Res.*, 2023, **56**, 2110–2125.
- (a) T. L. Gilchrist and C. J. Moody, *Chem. Rev.*, 1977, **77**, 409–435; (b) S. Yoshida, T. Yano, Y. Misawa, Y. Sugimura, K. Igawa, S. Shimizu, K. Tomooka and T. Hosoya, *J. Am. Chem. Soc.*, 2015, **137**, 14071–14074; (c) X. Tian, L. Song, M. Rudolph, F. Rominger, T. Oeser and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2019, **58**, 3589–3593; (d) X. Tian, L. Song and A. S. K. Hashmi, *Chem.–Eur. J.*, 2020, **26**, 3197–3204; (e) X. Tian, L. Song and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2020, **59**, 12342–12346; (f) L. Song, X. Tian, C. Han, M. Amanpur, F. Rominger and A. S. K. Hashmi, *Org. Chem. Front.*, 2021, **8**, 3314–3319; (g) X. Xie and J. Sun, *Org. Lett.*, 2021, **23**, 8921–8925; (h) U. Lücking, *Angew. Chem., Int. Ed.*, 2013, **52**, 9399–9408.
- (a) S. Zhou, T. Yan, Y. Li, Z. Jia, B. Wang, Y. Zhao, Y. Qiao, L. Xiong, Y. Li and Z. Li, *Org. Biomol. Chem.*, 2014, **12**, 6643–6652; (b) X. Yu, Y. Zhang, Y. Liu, Y. Li and Q. Wang, *J. Agric. Food Chem.*, 2019, **67**, 4224–4231.
- (a) R. Vanacore, A. J. L. Ham, M. Voehler, C. R. Sanders, T. P. Conrads, T. D. Veenstra, K. B. Sharpless, P. E. Dawson and B. G. Hudson, *Science*, 2009, **325**, 1230–1234; (b) V. Pedchenko, O. Bondar, A. B. Fogo, R. Vanacore, P. Voziyan, A. R. Kitching, J. Wieslander, C. Kashtan, D.-B. Borza, E. G. Neilson, C. B. Wilson and B. G. Hudson, *N. Engl. J. Med.*, 2010, **363**, 343–354; (c) A. L. Fidler, R. M. Vanacore, S. V. Chetyrkin, V. K. Pedchenko, G. Bhave, V. P. Yin, C. L. Stothers, K. L. Rose, W. H. McDonald, T. A. Clark, D. B. Borza, R. E. Steele and M. T. Ivy, *Proc. Natl. Acad. Sci. U. S. A.*, 2014, **111**, 331–336.
- A. S. McCall, C. F. Cummings, G. Bhave, R. Vanacore, A. Page-McCaw and B. G. Hudson, *Cell*, 2014, **157**, 1380–1392.
- K. Xu, D. Luan, X. Wang, B. Hu, X. Liu, F. Kong and B. Tang, *Angew. Chem., Int. Ed.*, 2016, **55**, 12751–12754.
- (a) S. Lin, X. Yang, S. Jia, A. M. Weeks, M. Hornsby, P. S. Lee, R. V. Nichiporuk, A. T. Iavarone, J. A. Wells, F. D. Toste and C. J. Chang, *Science*, 2017, **355**, 597–602; (b) A. H. Christian, S. Jia, W. Cao, P. Zhang, A. T. Meza, M. S. Sigman, C. J. Chang and F. D. Toste, *J. Am. Chem. Soc.*, 2019, **141**, 12657–12662; (c) J. Ohata, L. Krishnamoorthy, M. A. Gonzalez, T. Xiao, D. A. Iovan, F. D. Toste, E. W. Miller and C. J. Chang, *ACS Cent. Sci.*, 2020, **6**, 32–40.
- (a) D. Lin, M. Wallace, A. J. Allentoff, D. J. Donnelly, E. Gomes, K. Voronin, S. Gong, R. Y. C. Huang, H. Kim, J. Caceres-Cortes and S. Bonacorsi Jr, *Bioconjugate Chem.*, 2020, **31**, 1908–1916; (b) T. T. C. Yue, Y. Ge, F. A. Aprile, M. T. Ma, T. T. Pham and N. J. Long, *Bioconjugate Chem.*, 2023, **34**, 1802–1810.
- T. Meng, L. A. Wells, T. Wang, J. Wang, S. Zhang, J. Wang, M. C. Kozlowski and T. Jia, *J. Am. Chem. Soc.*, 2022, **144**, 12476–12487.
- Y. Liu, Z. He, W. Ma, G. Bao, Y. Li, C. Yu, J. Li, R. E. Z. Xu, R. Wang and W. Sun, *Org. Lett.*, 2022, **24**, 9248–9253.
- G. Bao, P. Wang, J. Li, X. Song, T. Yu, J. Zhang, Y. Li, Z. He, R. E. X. Miao, J. Xie, J. Ni, R. Wang and W. Sun, *CCS Chem.*, 2024, **6**, 1547–1556.
- (a) G. Bao, X. Song, Y. Li, Z. He, Q. Zuo, R. E. T. Yu, K. Li, J. Xie, W. Sun and R. Wang, *Nat. Commun.*, 2024, **15**, 6909; (b) Q. Zuo, Y. Li, X. Lai, G. Bao, L. Chen, Z. He, X. Song, R. E. Wang, Y. Shi, H. Luo, W. Sun and R. Wang, *Adv. Sci.*, 2024, **11**, 2308491; (c) Y. Liu, G. Li, W. Ma, G. Bao, Y. Li, Z. He, Z. Xu, R. Wang and W. Sun, *Chem. Sci.*, 2024, **15**, 11099–11107; (d) G. Bao, P. Wang, X. Guo, Y. Li, Z. He, X. Song, R. E. T. Yu, J. Xie and W. Sun, *Org. Lett.*, 2023, **25**, 8338–8343; (e) G. Bao, P. Wang, G. Li, C. Yu, Y. Li, Y. Liu, Z. He, T. Zhao, J. Rao, J. Xie, L. Hong, W. Sun and R. Wang, *Angew. Chem., Int. Ed.*, 2021, **60**, 5331–5338; (f) Y. Li, J. Li, G. Bao, C. Yu, Y. Liu, Z. He, P. Wang, W. Ma, J. Xie, W. Sun and R. Wang, *Org. Lett.*, 2022, **24**, 1169–1174.
- (a) F. Xiong, L. Lu, T.-Y. Sun, Q. Wu, D. Yan, Y. Chen, X. Zhang, W. Wei, Y. Lu, W. Sun, J. J. Li and J. Zhao, *Nat. Commun.*, 2017, **8**, 15912; (b) F. Xiong, Y. Zuo, Y. Song, L. Zhang, X. Zhang, S. Xu and Y. Ren, *Org. Lett.*, 2020, **22**, 3799–3803.
- (a) M. Alas, A. Saghaeidehkordi and K. Kaur, *J. Med. Chem.*, 2020, **64**, 216–232; (b) B. M. Cooper, J. Iegre, D. H. O' Donovan, M. Ö. Halvarsson and D. R. Spring, *Chem. Soc. Rev.*, 2021, **50**, 1480–1494.
- (a) Y. Xiong, C. Xiao, Z. Li and X. Yang, *Chem. Soc. Rev.*, 2021, **50**, 6013–6041; (b) J. Zhao, X. Li, T. Ma, B. Chang, B. Zhang and J. Fang, *Med. Res. Rev.*, 2024, **44**, 1013–1054.

