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Tyrosine-Specific Modification via a Dearomatization–Rearomatization Strategy: Access to Azobenzene Functionalized Peptides

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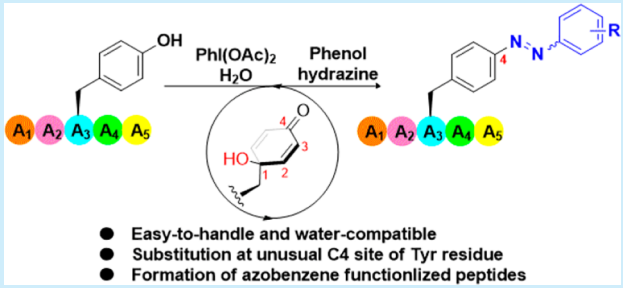
ABSTRACT: Azobenzene functionalized peptides are of great importance in photoresponsive biosystems and photopharmacology. Herein, we report an efficient approach to prepare azobenzene functionalized peptides through late-stage modification of tyrosine-containing peptides using a dearomatization–rearomatization strategy. This approach shows good chemoselectivity and site selectivity as well as sensitive group tolerance to various peptides. This method enriches the postsynthetic modification toolbox of peptides and has great potential to be applied in medicinal chemistry and chemical biology.



In recent years, peptides have emerged as powerful scaffolds in both pharmacology and chemical biology.[1] Along with the increasing interest in application of peptides as potential therapeutics, targeting ligands, and molecular probes, there has been a growing demand for direct functionalization of these structurally complex molecules. Late-stage chemical modification of a specific amino acid residue in peptides under mild, water-compatible, and easy-to-handle conditions has attracted much attention due to its convenience in achieving structural diversity, enabling rapid conjugation and labeling of peptides.[2] Although lysine and cysteine are the most commonly functionalized amino acids, chemoselective modification of alanine, phenylalanine, tryptophan, and histidine has been developed.[3] Presently, tyrosine (Tyr) is also considered to be an attractive residue for site-specific peptide functionalization due to its low natural abundance in bioactive peptides. Several elegant methods have emerged for Tyr modification, such as Pd-catalyzed cross-coupling reaction, *O*-functionalization, photochemical catalysis, electrochemistry, ene-type reactions, etc.[4] Despite the success achieved in C3 or *O*-modification of the Tyr side chain, little attention has been focused toward C1, C2, and C4 modification at the phenol motif.[5] Therefore, efficient methods that can modify these undeveloped sites of Tyr residue are required for the enrichment of peptide scaffolds.

Dearomatization of phenol derivatives is an important way for the synthesis of complex molecules from simple and cheap aromatic compounds.[6] Cyclohexadienones including quinonoidal spiro compounds formed by oxidation of the phenol group of tyrosine derivatives have been used as building blocks in organic synthesis.[7] As reported by John and co-workers, rearomatization of the quinonoidal spirolactone intermediates with arylhydrazines in the presence of a catalytic amount of ceric ammonium nitrate led to azobenzene–alanine amino acids.[8] Inspired by our works on developing asymmetric dearomatization of naphthols[9] and the previous works on tyrosine modifications, we are curious about whether the dearomatization–rearomatization method could be applied to the site-specific modification of complex peptides at the aromatic side chain of the Tyr residue. Taking advantage of the 4-hydroxylcyclohexadienone (**Int A**) intermediate obtained in the hypervalent iodine(III)-mediated oxidative dearomative step, we anticipate that modification at the C4 site could be realized by a subsequent rearomative step mediated by phenyl hydrazine *via* a hydrazone intermediate (**Int B**), affording the azobenzene functionalized peptides[10] (Scheme 1). Herein, we report such a novel dearomatization–rearomatization strategy to form azobenzene functionalized peptides and demonstrate the utility of it in the site-selective late-stage modification of peptides in mild conditions compatible with various amino acids *via* a two-step one-pot procedure.

It is particularly noteworthy that azobenzene functionalized peptides formed in this strategy are of great potential as photoswitches in biological systems.[11] As the most popular

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Scheme 1. Late-Stage Modification of Tyr-Containing Peptides through a Dearomatization–Rearomatization Sequence

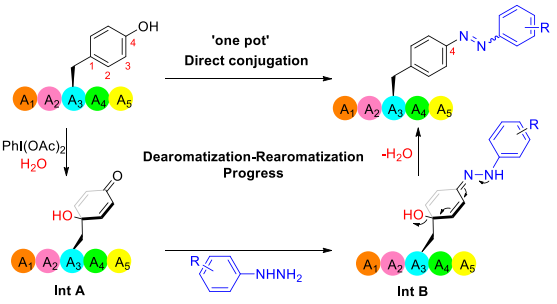
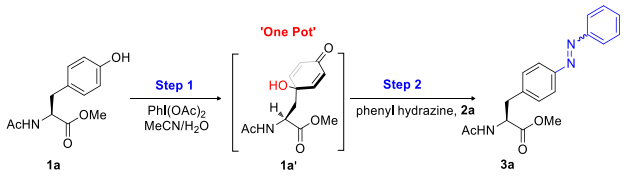


Table 1. Screening of Reaction Conditions

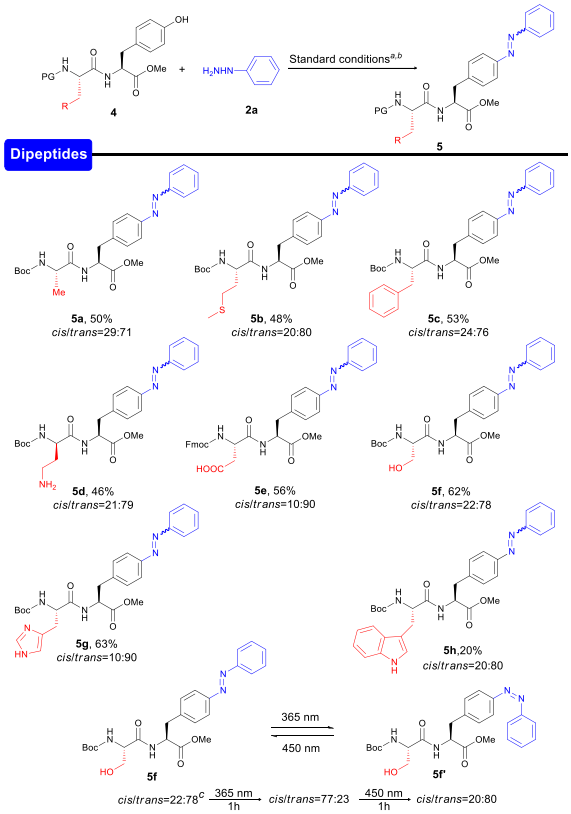


			Step 1		Step 2	
Entry[a]	Equiv of $PhI(OAc)_2$	Solvent (MeCN/H_2O)	Time	*T*	Time	Yield[b]
1	1.1	1/1	1.5 h	0 °C	12 h	52%
2	1.2	1/1	1.5 h	0 °C	12 h	52%
3	1.5	1/1	1.5 h	0 °C	12 h	33%
4	1.1	1/1	5 min	0 °C	12 h	54%
5	1.1	3/1	5 min	0 °C	12 h	38%
6	1.1	9/1	5 min	0 °C	12 h	17%
7	1.1	1/1	1 h	0 °C–rt	1.5 h	50%
8[c]	1.1	1/1	1 h	0 °C–rt	1.5 h	56%
9[c,d]	1.1	1/1	1 h	0 °C–rt	1.5 h	54%
10[c,e]	1.2	1/1	1 h	0 °C–rt	3.5 h	64%
11[c,e,f]	**1.2**	1/1	**0.5 h**	**0 °C–rt**	**3.5 h**	**66%**
12[c,e,f]	1.2	1/3	0.5 h	0 °C–rt	3.5 h	40%
13[c,e,f]	1.2	H_2O	0.5 h	0 °C–rt	3.5 h	44%

[a]To a solution of **1a** (0.10 mmol) in MeCN/H_2O (1/1, 1.0 mL) was added $PhI(OAc)_2$ (1.1 equiv) at 0 °C. After a specific period of time, phenyl hydrazine (**2a**, 1.2 equiv) and $Ce(NH_4)_2(NO_3)_6$ (10 mol %) were added to the mixture at 0 °C. [b]Isolated yield. [c]Without $Ce(NH_4)_2(NO_3)_6$. [d]Phenyl hydrazine (**2a**, 1.5 equiv). [e]Phenyl hydrazine (**2a**, 2.0 equiv). [f]To a mixture of step 1 was added a solution of phenyl hydrazine (**2a**, 2.0 equiv) in CH_3CN/H_2O (1/1, 1 mL) at 0 °C, and the reaction was stirred at rt for 3.5 h.

light-responsive ligands, azobenzene and its derivatives readily isomerize from *trans* to *cis* forms under irradiation at 300–380 nm, whereas the interconversion may be reversed at wavelengths >400 nm. The reversible *trans–cis* isomerization of azobenzene upon UV-blue light irradiation has opened the way to numerous applications in peptide engineering, which can induce the secondary structural changes of peptides and thus affect their binding affinity to the target.[12] To introduce an azobenzene moiety, chemical approaches mainly rely on incorporation of the azobenzene amino acids during peptide chain assembly or site-specific modification of peptides by the use of mono- or bifunctional azobenzene derivatives carrying residue-specific reacting groups. Different from the diazonium-mediated modification at the C3 site of the Tyr residue,[13] the dearomatization–rearomatization strategy developed in the

Scheme 2. Scope of Dipeptides



[a]To a solution of **4** (0.10 mmol) in MeCN/H_2O (1/1, 1.0 mL) was added $PhI(OAc)_2$ (1.2 equiv) at 0 °C. The mixture was stirred at rt for 0.5 h before a solution of phenyl hydrazine (**2a**, 2.0 equiv) in MeCN/H_2O (1/1, 1 mL) was added at 0 °C. Then the reaction was kept stirring at rt for 3.5 h. [b]The ratio of *cis*- and *trans*-isomers was determined by isolated yield. [c]The ratio of *cis*- and *trans*-isomers was determined by HPLC.

current work proved to be efficient to form an azobenzene linker at the C4 site of the Tyr residue *via* direct functionalization of the peptides.

We initiated our study by utilizing Ac-Tyr-OMe (**1a**) as the model substrate, $PhI(OAc)_2$ as the oxidant, phenyl hydrazine (**2a**) as the rearomative reagent, and a mixure of MeCN/H_2O as the solvent (Table 1). The reaction of Ac-Tyr-OMe (**1a**) with $PhI(OAc)_2$ (1.1 or 1.2 equiv) proceeded smoothly in MeCN/H_2O (v/v, 1:1) to form the hydroxyl substituted cyclohexadienone intermediate (**1a′**), which reacted with phenyl hydrazine (**2a**, 1.2 equiv) in the presence of $Ce(NH_4)_2(NO_3)_6$ (10 mol %) to reestablish the aromaticity,[14] affording azobenzene **3a** in 52% yield (entries 1 and 2). To be noted, azobenzene **3a** was obtained as a mixture of *cis*- and *trans*-isomers, in which the thermodynamically more stable *trans*-isomer is the major product.[8] When the amount of $PhI(OAc)_2$ was increased from 1.2 to 1.5 equiv, the total yield of **3a** significantly decreased from 52% to 33% (entry 3). The ratio of MeCN/H_2O also affected the reaction remarkably, as increasing the ratio of MeCN resulted in the decrease of the total yield (entries 4–6). Although the reaction could be performed with less MeCN or without MeCN, the yields were also lower due to the poor water solubility of **1a** (entries 11–13). Interestingly, a comparable yield was obtained when the reaction was carried out without the addition of $Ce(NH_4)_2(NO_3)_6$ (entries 7 and 8), indicating that Ce-

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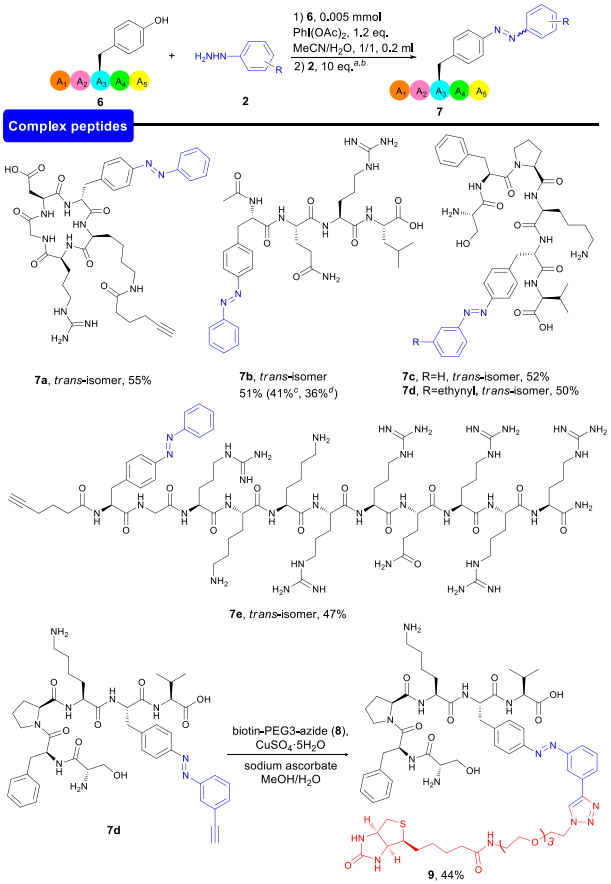
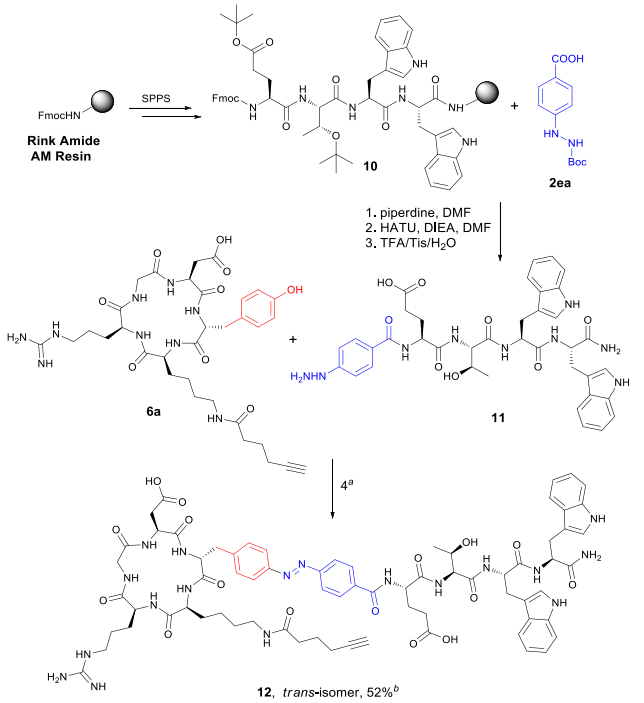
Scheme 3. Scope of Complex Bioactive Peptides



[a]To a solution of **6** (0.005 mmol) in MeCN/H_2O (1/1, 0.2 mL) was added $PhI(OAc)_2$ (1.2 equiv) at 0 °C. The mixture was stirred at rt for 0.5 h before phenyl hydrazine (**2**, 10.0 equiv) was added. Then the reaction was kept stirring at rt for 3.5 h. [b]Isolated yield. [c]Phenyl hydrazine (**2a**, 4.0 equiv). [d]Phenyl hydrazine (**2a**, 2.0 equiv).

Scheme 4. Direct Conjugation of Two Bioactive Peptides



[a]To a solution of **6a** (0.005 mmol) in MeCN/H_2O (1/1, 0.2 mL) was added $PhI(OAc)_2$ (1.2 equiv) at 0 °C. The mixture was stirred at rt for 45 min before a solution of **11** (2.0 equiv) and DIEA (3.0 equiv) in MeCN/H_2O (1:1, 20 μL) was added. Then the reaction was stirred at rt for 3 h. [b]Isolated yield.

$(NH_4)_2(NO_3)_6$ is not required for the rearomatization step. The effects of reaction time, reaction temperature, and the amount of phenyl hydrazine were further evaluated (entries 9–11). Although a small amount of the dimeric tyrosine **1a**[15] was detected as the byproduct, **3a** could be obtained in an overall yield of 66% through the two-step one-pot sequence under the optimized conditions (entry 11). The method proved to be compatible with various substituted phenyl hydrazines **2**, providing a mixture of *cis*- and *trans*-azobenzenes **3** in 58–70% yields (Scheme S1 in Supporting Information). In general, phenyl hydrazines bearing electron-donating groups generated the corresponding products in higher yields compared with electron-withdrawing groups.

Encouraged by this result, we next evaluated the compatibility of the reaction with a series of dipeptides **4a–h** (Scheme 2). Under the optimal conditions, a number of Boc- or Fmoc-protected dipeptides bearing various sensitive groups (**4a–4g**) were selectively modified with phenyl hydrazine (**2a**), indicating a broad functional group tolerance of the reaction. The corresponding products **5a–5g** were obtained in 46–63% isolated yields with a *cis*/*trans* ratio ranging between 1:9 and 1:3 depending on the second amino acid of the dipeptide. Dipeptide **4h** containing an indole group could be selectively functionalized at the phenol moiety to form **5h**, albeit with a low yield. As demonstrated in the photoisomerization of **5f** and **5f′**, the *cis*- and *trans*-isomers could exchange under UV/blue LED irradiation.

We further examined the compatibility of this protocol with unprotected and structurally more complex peptides (Scheme 3). To our delight, cyclopentapeptide (**6a**), containing an Arg-Gly-Asp (RGD) motif, which is an important peptide sequence commonly used in targeted therapy since it can specifically bind to integrin receptor on the cell surface,[16] could be well decorated with **2a** at the Tyr residue to give the major *trans*-isomer **7a** in 55% yield. Analysis of the crude reaction mixture indicated that a small amount of nonreacted tyrosine-containing peptide **6a**, the corresponding 4-hydroxylcyclohexadienone intermediate, as well as some unknown byproducts were present in the crude products. Tetrapeptide **6b**, a lysosome sorting peptide bearing the Tyr residue at the *N*-terminus,[17] could also be functionalized, affording **7b** (*trans*-isomer) in 51% yield. To further explore the scope of this strategy, hexapeptide **6c** was designed to contain different kinds of amino acid residues, while without any protection at both the *N*- and *C*-terminus. The reaction of hexapeptide **6c** with both phenyl hydrazine (**2a**) and *m*-ethynyl-phenyl hydrazine (**2c**) proceeded smoothly, furnishing **7c** and **7d** in moderate yields as the *trans*-isomers. Modification of Tat (**6e**), a cell penetrating peptide which contains 11 amino acid residues, was also accomplished *via* this method, providing *trans*-isomer **7e** in 47% isolated yield. To be noted, increasing the amount of phenyl hydrazine from 2 to 10 equiv led to better conversion of complex peptides. In all cases, the azobenzene functionalized peptides could be easily separated from the starting peptides by semipreparative RP-HPLC. Hexapeptide **7d**, tagged with *m*-ethynyl-substituted azoben-

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zene, could further react with biotin-PEG3-azide (**8**) *via* click chemistry to generate biotin labeled peptide **9**.

This protocol also proved to be efficient for direct conjugation of peptides with different bioactivities, offering unique azobenzene linked bifunctional peptides (Scheme 4). Using standard solid-phase peptide synthesis (SPPS), a free phenyl hydrazine group could be conveniently introduced to the *N*-terminus of ETWW (**10**), a major-groove-specific nuclear-localizing, cell-penetrating tetrapeptide,[18] generating phenyl hydrazine substituted ETWW (**11**). Since ETWW peptide **11** was obtained as the trifluoroacetate salt, pretreatment of it with 3 equiv of DIEA was carried out before it was used to react with cyclopeptide **6a** in the coupling reaction. As expected, azobenzene functionalized peptide **12** was isolated in good yield as the *trans*-isomer.

In summary, we have developed a dearomatization−rearomatization strategy for chemoselective and site-selective modification of Tyr-containing peptides under mild conditions, providing azobenzene functionalized peptides which are of great importance in photoresponsive biosystems and photopharmacology. As demonstrated by using a wide range of peptides, this approach shows good compatibility with various amino acid residues and different peptide lengths. This method enriches the postsynthetic modification toolbox of peptides and has great potential to be applied in medicinal chemistry and chemical biology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01013.

Experimental details and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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