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Practical Peptide Synthesis Mediated by a Recyclable Hypervalent Iodine Reagent and Tris(4-methoxyphenyl)phosphine

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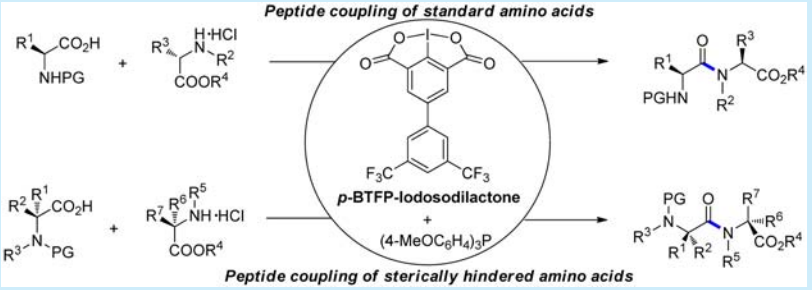
Supporting Information



ABSTRACT: 6-(3,5-Bis(trifluoromethyl)phenyl)-1*H*,4*H*-2aλ^3-ioda-2,3-dioxacyclopenta[*hi*]indene-1,4-dione (*p*-BTFP-iodosodilactone, **1a**) was synthesized and demonstrated to be an efficient hypervalent iodine(III) reagent for the synthesis of dipeptides from various standard amino acids, including sterically hindered amino acids, in good to high yields within 30 min in the presence of tris(4-methoxyphenyl)phosphine. In addition, the combined system of **1a**/(4-MeOC$_6$H$_4$)$_3$P was used to synthesize the pentapeptide leu-enkephalin in protected form. It is worth noting that **1a** can be regenerated readily after reaction.

Peptide linkages are present not only in proteins but also in many natural products and pharmaceuticals, such as the opioid pentapeptide enkephalins (Tyr-Gly-Gly-Phe-Leu and Tyr-Gly-Gly-Phe-Met),[1a,b] which were first isolated from pig brains, and the antihypertension drug lisinopril[1c] (Figure 1).

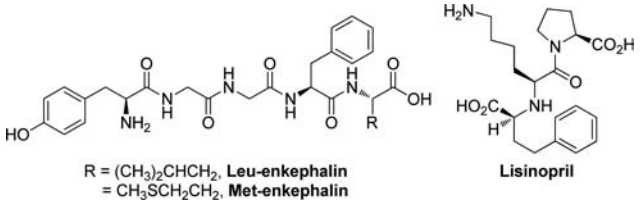
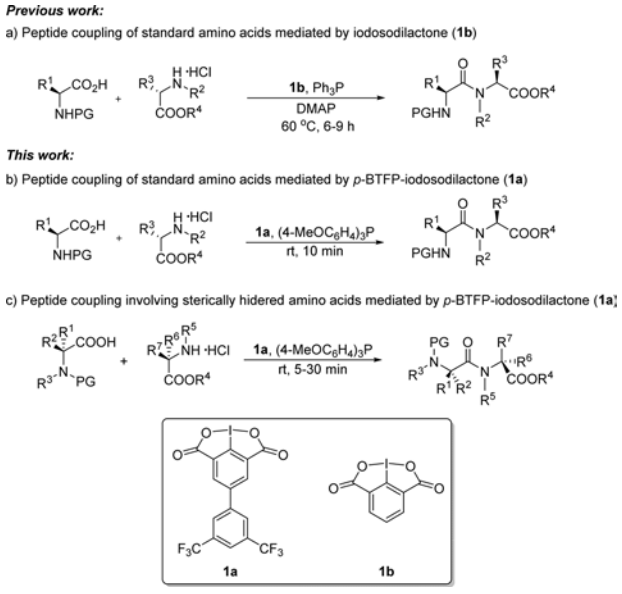


Figure 1. Peptide natural products and a dipeptide drug.

Peptides play crucial roles in various physiological processes including neuronal signaling (neuropeptides),[2a] blood calcium homeostasis (calcitonin peptides),[2b] and immunomodulation.[2c] Therefore, peptide-coupling reactions are among the most important reactions in organic synthesis and medicinal and biological chemistry. Recent decades have witnessed substantial progress in the development of peptide coupling reactions and reagents, such as carbodiimides, phosphonium salts, and aminium and uronium salts.[3] In coupling reactions mediated by these reagents, a compromise must be made to maximize efficiency while minimizing racemization and side reactions.[4]

We recently reported that iodosodilactone **1b** (1*H*,4*H*-2aλ^3-ioda-2,3-dioxacyclopenta[*hi*]indene-1,4-dione), an organic hypervalent iodine(III) reagent, efficiently promotes amidation and peptide coupling reactions (Scheme 1a).[5] Although this highly efficient peptide coupling reaction proceeds without racemization (even in the absence of a racemization

Scheme 1. Peptide Synthesis Mediated by 1a and 1b



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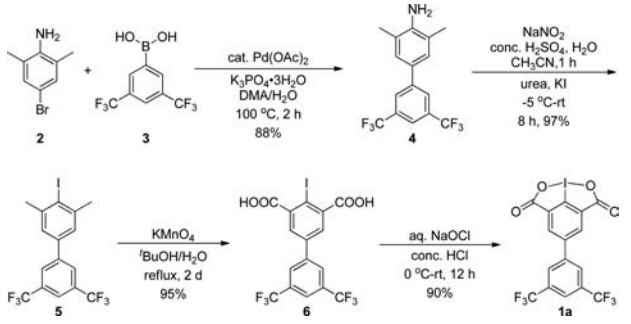
suppressant) and the iodosodilactone is readily recyclable, several issues needed to be addressed to make the reaction more practical. Specifically, the reaction usually requires a high temperature (60 °C) and a long reaction time (6–9 h), and 4-(dimethylamino)pyridine, which is toxic, is indispensable. As part of our ongoing interest in oxidation reactions induced by hypervalent iodine reagents[6] and in peptide coupling reactions mediated by such reagents,[5] we have now developed a more powerful iodosodilactone type reagent by introducing a 3,5-bis(trifluoromethyl)phenyl group at the position *para* to the iodine center. We designed the reagent on the basis of the following rationales: we expected (a) that the strongly electron-withdrawing trifluoromethyl groups would enhance the electrophilicity of the iodine(III) center, thus resulting in increased reactivity, and (b) that the high liposolubility of the trifluoromethyl-substituted phenyl group would make the coupling reagent more soluble in organic solvents than the parent reagent. In this study, we synthesized and determined the structure of a new iodosodilactone derivative, 6-(3,5-bis(trifluoromethyl)phenyl)-1*H*,4*H*-2aλ^3-ioda-2,3-dioxacyclopenta[*hi*]indene-1,4-dione (*p*-BTFP-iodosodilactone, **1a**), which mediated peptide-coupling reactions rapidly under mild conditions when used in combination with tris(4-methoxyphenyl)phosphine (4-MeOC$_6$H$_4$)$_3$P (Scheme 1b). Even reactions involving sterically hindered amino acids worked well, providing the corresponding dipeptides in good to high yields (Scheme 1c).

p-BTFP-Iodosodilactone (**1a**) was readily synthesized in 73% overall yield by means of the route shown in Scheme 2.

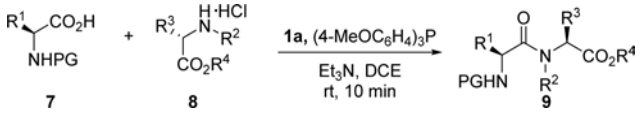
Scheme 2. Synthesis of 1a



Specifically, Suzuki coupling of commercially available 4-bromo-2,6-dimethylaniline (**2**) and 3,5-bis(trifluoromethyl)-phenyl boronic acid (**3**) provided the coupling product **4** (88%),[7] which was subjected to diazotization followed by iodination to afford iodinated compound **5** (97%). Compound **6** was produced in excellent yield by oxidation of the two methyl groups of **5** with potassium permanganate. Finally, oxidation of **6** with aqueous sodium hypochlorite[6a] furnished **1a** in 90% yield. The structure of **1a** was determined by means of NMR and IR spectroscopy and high-resolution electrospray ionization mass spectrometry. In the ^{13}C NMR spectrum of **1a**, the signal of the carbon atom connected to the iodine(III) center was found at a chemical shift of 126.5 ppm, which is similar to that for the corresponding carbon of **1b** (125.7 ppm). Reagent **1a** is neither air nor moisture sensitive and can be stored for a year at room temperature without detectable decomposition.

Investigation of reaction conditions for the peptide coupling revealed that a system consisting of 1.2 equiv of **1a**, 1.0 equiv of (4-MeOC$_6$H$_4$)$_3$P, and 3.0 equiv of Et$_3$N in 1,2-dichloroethane (DCE) at room temperature was optimal (for details, see the Supporting Information). Using the optimized conditions, we evaluated the scope of the reaction and synthesized a variety of dipeptides (Table 1). All of the reactions conducted with

Table 1. 1a-Mediated Synthesis of Peptides from Standard Amino Acids[a]



entry	dipeptide (**9**)	yield[b] (%) **1a**	yield[b] (%) **1b**	D/DL[c] (%)
1	Cbz-L-Phe-L-Ile-OMe, **9aa**	91	82 (3 h)	0
2	Cbz-L-Phe-L-Tyr-OEt, **9ab**	86	80 (4 h)	0
3	Cbz-L-Phe-L-Ser-OMe, **9ac**	83[d]	80 (3 h)[d]	0
4	Cbz-L-Phe-L-Thr-OMe, **9ad**	79	78 (4 h)[d]	0
5	Cbz-L-Ala-L-His(Trt)-OMe, **9be**	90	73 (4 h)[d]	0.024
6	Cbz-L-Ala-L-Cys(Trt)-OMe, **9bf**	88	85 (3 h)	0
7	Cbz-L-Leu-L-Ala-OMe, **9cg**	86		0.017
8	Cbz-L-Leu-L-Lys(Z)-OMe, **9ch**	80		0
9	Cbz-L-Met-Gly-OMe, **9di**	78		0
10	Cbz-L-Asn(Trt)-L-Leu-OMe, **9ej**	81		0
11	Cbz-L-Val-L-Glu(OEt)-OEt, **9fk**	82		0
12	Boc-Gly-Gly-OMe, **9gi**	80		
13	Boc-L-Leu-L-Lys(Z)-OMe, **9hh**	81[d]		0
14	Boc-L-Leu-L-Ala-OMe, **9hg**	82		0.016
15	Boc-L-Val-L-Pro-OMe, **9il**	75		0
16	Boc-L-Val-L-Asp(OMe)-OMe, **9im**	77		0.016
17	Boc-L-Phe-L-Leu-OMe, **9jj**	84		0

[a]Performed with **7** (1.0 equiv), **8** (1.0 equiv), **1a** (1.2 equiv), (4-MeOC$_6$H$_4$)$_3$P (1.0 equiv), and Et$_3$N (3.0 equiv) in DCE (0.03 M) at room temperature. [b]Isolated yield. [c]Product optical purity was determined by HPLC. [d]1.2 equiv of (4-MeOC$_6$H$_4$)$_3$P was used.

standard amino acids proceeded swiftly within 10 min to afford the desired dipeptides in good to high yields with no racemization. Comparison of results obtained with **1a** and **1b** under otherwise identical conditions showed that **1b** was less effective, yielding the dipeptides in lower yields and requiring longer reaction times (3–4 h, entries 1–6). With **1a** as the coupling reagent, the reaction proved to be fully compatible with common amine protecting groups, including Cbz and Boc, making the method applicable for routine peptide synthesis. Notably, the coupling efficiency was not obviously affected by the presence of the unprotected hydroxyl group of tyrosine (entry 2), serine (entry 3), or threonine (entry 4). Furthermore, reactions of sterically hindered amino acids such as valine (entries 11, 15, and 16) and proline (entry 15) also worked well, affording the corresponding dipeptides in yields ranging from 75% to 82%.

Sterically hindered amino acids, such as α,α-disubstituted amino acids and *N*-methylamino acids, are important constituents of diverse naturally occurring peptides.[8] However, the synthesis of peptides containing such amino acids with the usual coupling reagents is difficult, and the existing methods usually require preparation of activated amino acid derivatives to obtain ideal results.[9] Therefore, we evaluated the protocol reported herein with several sterically hindered amino acids (Table 2). Coupling reactions between *N*-methyl amino acid

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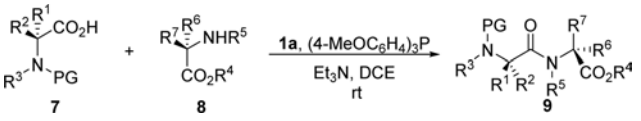
Table 2. 1a-Mediated Peptide Synthesis from Sterically Hindered Amino Acids[a]



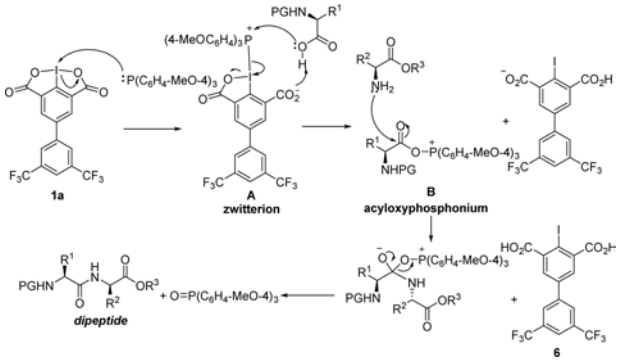
entry	dipeptide (**9**)	time (min)	yield[b] (%)	D/DL[c] (%)
1	Cbz-L-*N*MePhe-Gly-OMe, **9ki**	30	90 (72, 4 h)[d]	0
2	Cbz-L-*N*MePhe-L-Ile-OMe, **9ka**	10	86	0.08
3	Cbz-L-*N*MePhe-L-His(Trt)-OMe, **9ke**	5	86	0
4	Cbz-L-*N*MePhe-L-Ser-OMe, **9kc**	10	76	0
5	Cbz-L-*N*MePhe-Sar-OMe, **9kn**	10	70	0
6	Cbz-L-*N*MePhe-Aib-OMe, **9ko**	30	85 (60, 4 h)[d]	0.03
7	Cbz-L-Phe-Sar-OMe, **9an**	25	62 (61, 4 h)[d]	0
8	Cbz-L-Met-Sar-OMe, **9dn**	10	57	0
9	Cbz-L-Ala-Sar-OMe, **9bn**	10	64	0.11
10	Cbz-Aib-Gly-OMe, **9li**	30	71 (59, 4 h)[d]	
11	Cbz-Aib-L-Leu-OMe, **9lj**	10	59	
12	Cbz-L-Val-Aib-OMe, **9fo**	25	64	0
13	Cbz-L-Phe-Aib-OMe, **9ao**	25	90 (64, 4 h)[d]	0
14	Cbz-L-Ala-Aib-OMe, **9bo**	10	91	0.22
15	Cbz-L-Met-Aib-OMe, **9do**	10	90	0.03
16	Cbz-L-Asn(Trt)-Aib-OMe, **9eo**	10	63	0.14
17	Boc-L-Tyr-Aib-OMe, **9mo**	5	63	0.12
18	Boc-Gly-Aib-OMe, **9go**	10	88	
19	Fmoc-Aib-Gly-OMe, **9ni**	30	73	

[a]Performed with **7** (1.0 equiv), **8** (1.0 equiv), **1a** (1.2 equiv), (4-$MeOC_6H_4)_3P$ (1.0 equiv), and Et_3N (3.0 equiv) in DCE (0.03 M) at room temperature. [b]Isolated yield. [c]Product optical purity was determined by HPLC. [d]Iodosodilactone **1b** was used as the coupling reagent.

Cbz-L-*N*(Me)-Phe-OH and a series of standard amino acids provided the corresponding dipeptides in good to high yields (76−90%, entries 1−4). Notably, even when both amino acids were sterically hindered, the coupling reactions also proceeded smoothly, affording the corresponding dipeptides in good yields (entries 5 and 6). Similarly, reaction of *N*-methylamino acid ester H-Sar-OMe with standard amino acids proved to be feasible under the present conditions, affording dipeptides in 57−64% yields (entries 7−9). Coupling of α,α-disubstituted amino acids such as Cbz-Aib-OH and H-Aib-OMe with various standard amino acids produced the corresponding dipeptides in 59−91% yields (entries 10−18). Comparison of the coupling efficiencies achieved with **1a** and **1b** under otherwise identical reaction conditions (entries 1, 6, 7, 10, and 13) indicated that **1a** was more effective, affording the corresponding dipeptides in high yields within 30 min. It is worth noting that common amine protecting groups including Cbz, Boc, and Fmoc are compatible in the present reaction system.

We propose the mechanism outlined in Scheme 3 for the peptide-coupling reaction mediated by **1a** and (4-$MeOC_6H_4)_3P$. The (4-$MeOC_6H_4)_3P$ nucleophile reacts with **1a** to form zwitterion intermediate **A**, which reacts with the carboxylic acid component to form acyloxyphosphonium intermediate **B**. Intermediate **B** is attacked by the amino

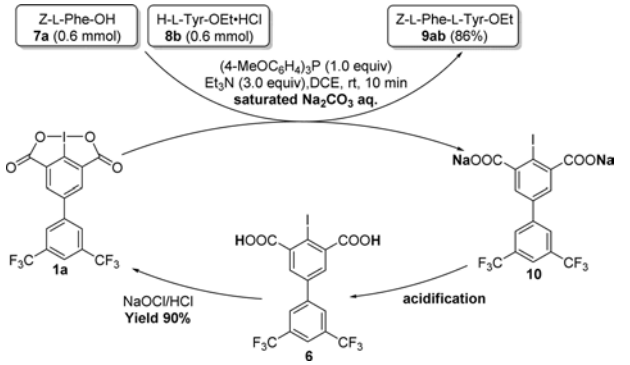
Scheme 3. Proposed Mechanism for 1a/(4-$MeOC_6H_4)_3P$-Mediated Peptide-Coupling Reaction



group of an amino acid to afford a dipeptide and tris(4-methoxyphenyl)phosphine oxide.

Note that **1a** could be regenerated easily (Scheme 4).[10] After completion of the reaction listed as entry 2 in Table 1, the

Scheme 4. Recycling of 1a



reaction mixture was diluted with ethyl acetate and washed with saturated Na_2CO_3. The aqueous phase was then acidified with 5 N HCl (pH < 7), and precipitated precursor **6** was filtered off and subsequently oxidized with NaOCl/HCl to give **1a** in 90% yield.

The versatility of our peptide coupling methodology is illustrated by its use for the synthesis of protected leu-enkephalin (Scheme 5). Hydrolysis of Boc-Gly-Gly-OMe (**9gi**; Table 1, entry 12) and deprotection of Boc-L-Phe-L-Leu-OMe (**9jj**; Table 1, entry 17) gave corresponding dipeptide segments Boc-Gly-Gly-OH (**11**) and H-L-Phe-L-Leu-OMe·TFA (**12**), respectively, in excellent yields. Dipeptides **11** and **12** were then subjected to the standard coupling reaction conditions, which afforded tetrapeptide **13** in high yield (85%) within 15 min. Removal of the *N*-Boc protecting group of **13** followed by coupling with Boc-L-Tyr-OH under the standard coupling reaction conditions afforded protected leu-enkephalin (**15**) in 75% yield over two steps. This successful synthesis of *N*-,*C*-protected leu-enkephalin demonstrates that the coupling protocol is suitable for the synthesis of not only dipeptides but also a heterotetrapeptide and a heteropentapeptide.

In summary, we synthesized a powerful, bench-stable hypervalent iodine(III) reagent with a 3,5-bis(trifluoromethyl)-phenyl substituent on the phenyl ring of an iodosodilactone. In combination with tris(4-methoxyphenyl)phosphine, the reagent efficiently mediated peptide-coupling reactions of standard amino acids to provide the corresponding dipeptides in

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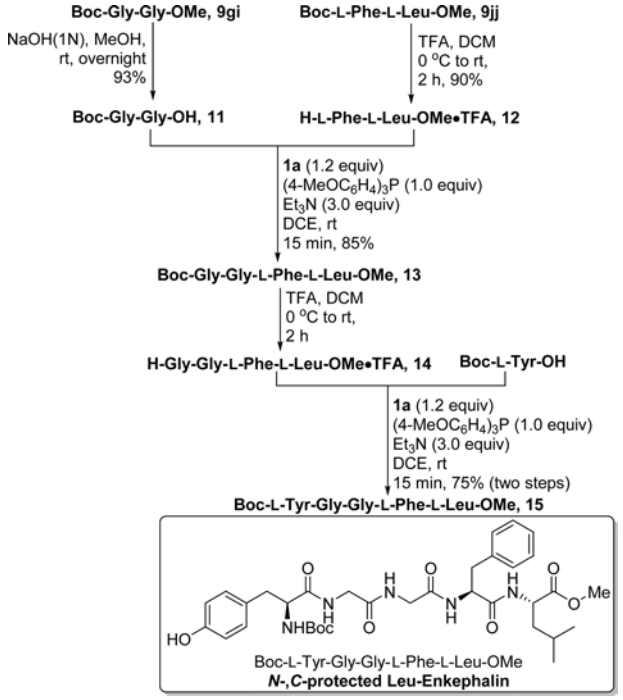
Scheme 5. Synthesis of Protected Leu-enkephalin



excellent yields. Of particular importance is the fact that this reagent system was suitable for the synthesis of dipeptides from sterically hindered amino acids. The reactions proceeded without racemization, and **1a** could be regenerated conveniently, making this method an attractive alternative to traditional methods for peptide coupling.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02045.

Experimental details, characterization data for new compounds, ^{1}H, ^{13}C, and ^{19}F NMR spectra, and HRMS and IR data (PDF)

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Notes

The authors declare no competing financial interest.

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