OL | Organic Letters

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Isostearyl Mixed Anhydrides for the Preparation of *N*-Methylated Peptides Using *C*-Terminally Unprotected *N*-Methylamino Acids

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02984 Read Online

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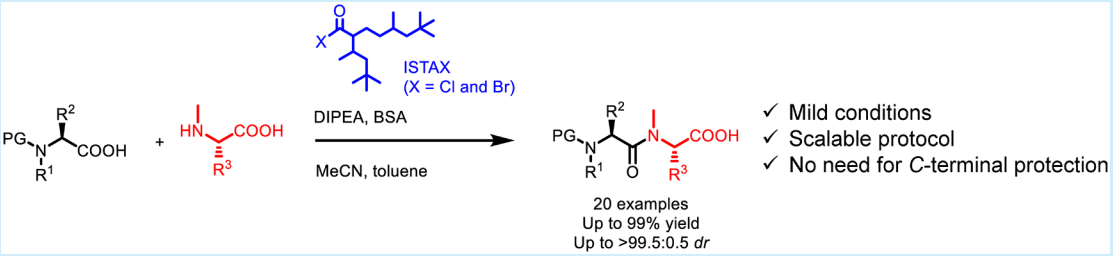


ABSTRACT: Sustainable and efficient manufacturing methods for *N*-methylated peptides remain underexplored despite growing interest in therapeutic *N*-methylated peptides within the pharmaceutical industry. A methodology for the coupling of *C*-terminally unprotected *N*-methylamino acids mediated by an isostearic acid halide (ISTAX) and silylating reagent has been developed. This approach allows for the coupling of a wide variety of amino acids and peptides in high yields under mild conditions without the need for a *C*-terminal deprotection step in the process of *C*-terminal elongation. These advantages make this a useful synthetic method for the production of peptide therapeutics and diagnostics containing *N*-methylamino acids.

Peptide therapeutics have been receiving increased attention in drug discovery and development due to their high efficacy and target selectivity, combined with their generally acceptable safety profiles.[1] Since the advent of solid-phase peptide synthesis techniques in the 1960s, various improvements have been made in both solid- and liquid-phase synthesis protocols.[2] Despite these advancements, peptide synthesis has not been able to move away from the requirement of repetitive deprotection steps between coupling reactions. These repetitive deprotection steps present difficulties in the manufacturing of complex peptide drugs. Accordingly, new synthetic methods are being actively pursued to reduce manufacturing steps to decrease synthesis time and cost as well as minimize negative environmental impact.[3]

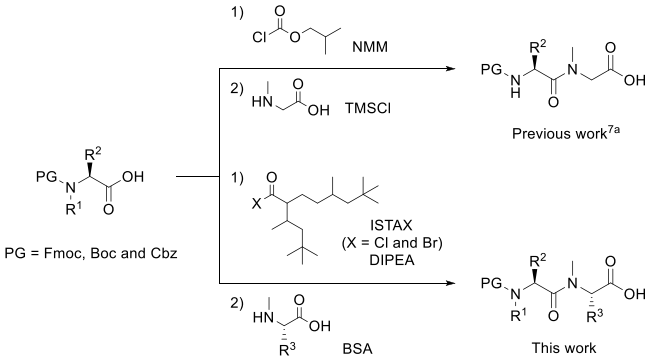
During the process of discovery and development of peptide therapeutics, the incorporation of *N*-methylamino acids is a well-established approach to improve permeability and/or proteolytic stability.[4] However, during synthesis, the formation of the amide bond between an *N*-methylamino acid and the adjacent activated carboxylic acid of an *N*-terminally protected amino acid can often result in lower yields than their non-*N*-methylated counterparts due to the low reactivity of the *N*-methylamine moiety.[5] In the context of *C*-terminal elongation of peptide chains, selective deprotection of the protected *C*-terminus that is to be reacted with the adjacent amino acid *N*-terminus necessitates iterative deprotection steps, increasing the required labor and reducing overall yield. Further complications can arise when selective deprotection is essential to differentiate between the *C*-terminal ester and other protective groups on the *N*-terminus or side chains of the peptide. Therefore, a new coupling method employing a *C*-terminally unprotected *N*-methylamino acid as the nucleophile, without the need for an intermediate deprotection reaction, could have great impact in overcoming the aforementioned drawbacks.[6] While peptide synthesis using *C*-terminally unprotected *N*-methylamino acids is an attractive synthetic approach, such methods have not been thoroughly examined to date (Scheme 1).[7] Tantry and Babu have reported the use of a mixed anhydride and TMSCl as silylating agent, but the substrate scope was limited, with sarcosine (H-MeGly-OH) the only *N*-methylamino acid examined, and the product formed in moderate yield.[7a]

To this end, we aimed to develop a more versatile amide coupling methodology using *C*-terminally unprotected *N*-methylamino acids that provides peptides in fewer steps and

Received: September 7, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02984
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. General Strategy for This Method

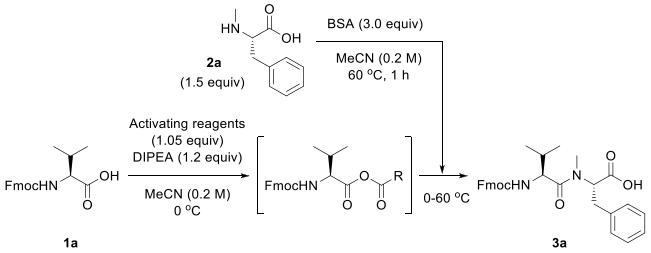


high yields. Here, we describe a practical synthetic methodology for the production of *N*-methylated peptides employing the reaction of a mixed acid anhydride formed by isostearic acid halide (ISTAX) activation with the putative silylated *N*-methylamino acids generated in situ (Scheme 1). As coupling via mixed anhydrides represents a cost-effective method that has historically been used for large-scale peptide manufacturing,[8] we expected that it would be amenable to use with *N*-methylamino acids. In addition, the utilization of isostearyl mixed anhydrides for amino acid coupling has not been reported to date. Furthermore, we expected that the generation of *O*-trimethylsilylated *N*-methylamino acids in situ, such as those demonstrated in these studies, would prevent overreaction, such as double incorporation of the nucleophilic *N*-methylated amino acid[6b] and increase the solubility of the resulting intermediates[9] to yield improved results.[10]

Our initial studies focused on sterically hindered Fmoc-Val-OH (**1a**) to compare the performance of various potential activating reagents. For the nucleophilic *N*-methylamino acid coupling partner, *N*-methylphenylalanine (H-MePhe-OH, **2a**) was selected after confirming that loss of enantiopurity of H-MePhe-OH is not observed under the silylating conditions employed using *N*,*O*-bis(trimethylsilyl)acetamide (BSA).[11] Usage of the common coupling reagent isobutyl chloroformate (IBCF,[8b] Table 1, entry 1) showed poor conversion due to insufficient regioselectivity in the subsequent reaction of the resulting mixed anhydride.[12] On the other hand, pivaloyl chloride (PivCl,[8c] entry 2) gave moderate conversion, but the corresponding pivaloylated derivative of **2a** and residual PivOH were formed as byproducts and could not be completely removed through any convenient workup process in our hands. These results indicated that the main challenge of the mixed anhydride method may be to maintain good conversion including regiochemical control and byproduct removal, which we sought to overcome by employing a new activating reagent with appropriate steric bulk[5a] that could also be readily removed by extraction with nonpolar solvents.[12]

On the basis of these initial results and hypotheses, we selected ISTAX as a sterically demanding acid halide, which can be easily prepared from the commercially available corresponding carboxylic acid (ISTAOH), while also anticipating that ISTAOH byproduct should be removable by extraction of the reaction mixture with nonpolar solvents. Moreover, unlike the use of chloroformate reagents, ISTAX does not generate CO_2, thus eliminating the safety hazards of reactor pressurization and CO_2 off-gassing in drummed waste streams. As expected, isostearic acid chloride (ISTACl) reacted with **1a** at 0 °C for 24 h followed by coupling with silylated **2a**

Table 1. Screening Activating Reagents with 1a and 2a



entry	activating reagents	scale (mmol)	activation time of **1a**[a] (h)	reaction with activated **1a** and silylated **2a**[b] time (h)	temp (°C)	yield (%)
1	IBCF	0.4	1	2	0	4[c]
2	PivCl	0.4	5	12	30	75[d]
3	ISTACl[e]	0.4	24	24	30	92[g]
4	ISTABr[e]	0.4	0.5	24	30	98[g]
5	ISTABr[e]	0.4	0.5	4	60	97[g]
6[f]	ISTABr[e]	4	0.5	4	60	94[g]

[a]Reaction time for **1a** and activating reagents. [b]Time and temperature after addition of silylated **2a** to activated **1a**. [c]Calculated based on ELSD area percentage of crude product. [d]Determined by quantitative ^{1}H NMR using internal standard. [e]Since ISTAX were insoluble in MeCN, a toluene solution of the ISTAX was added to a MeCN solution of **1a** (final volume ratio of toluene/MeCN was 1:4). [f]Concentration of combined final reaction mixture was 0.5 M. [g]Isolated yield without column chromatography.

at 30 °C afforded the target dipeptide **3a** with sufficient regioselectivity and no detectable epimerization (confirmed by comparison with authentic Fmoc-D-Val-L-MePhe-OH) in 92% isolated yield without column chromatography (entry 3). As for the workup process, after quenching the reaction with 1 M aq $KHSO_4$, the byproduct ISTAOH was easily removed by washing with heptane as well as a small amount of **2a** acylated with excess ISTACl. A wide variety of solvents, including toluene, THF, DMA, and NMP, gave comparable results to MeCN, and generally, the amide bond formation was completed in less than 24 h at room temperature (data not shown). Overall, MeCN was somewhat preferable due to the fast reaction rate and minimized anhydride formation of **1a**.[13] To further improve yield, we decided to identify minor impurities observed under these conditions. The main impurity observed was thought to be derived from anhydride formation of **1a**, generated from unreacted **1a** and activated **1a**. In order to minimize this impurity, the more reactive isostearic acid bromide (ISTABr) was tested to reduce the activation time. Reaction with ISTABr and **1a** smoothly completed at 0 °C within 30 min, and as expected, generation of the anhydride impurity was suppressed below the LC detection limit (entry 4).[14] To further reduce total reaction time, the reaction was conducted with activated **1a** and **2a** at 60 °C, resulting in not only shorter reaction time with the same yield, but it is also noteworthy that no epimerization was detected (entry 5). Moreover, conducting the reaction on larger scale and higher concentration gave 94% yield and satisfactory purity (96 area% HPLC), even without purification by column chromatography (Table 1, entry 6). With these favorable results in hand, we assessed the thermal stability of ISTACl and ISTABr by differential scanning calorimetry and confirmed that these

https://dx.doi.org/10.1021/acs.orglett.0c02984
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reagents are more stable than chloroformate reagents, and thus suitable for large-scale synthesis.[15]

With these new activating reagents and reaction conditions in hand, a survey of the scope of various *N*-methylamino acids amenable for use as the nucleophile was conducted. We first tested H-MeGly-OH (**2b**) to compare the reactivity of ISTABr to a previous report using IBCF.[7] The reaction produced the corresponding dipeptide **3b** in excellent yield (Figure 1. The

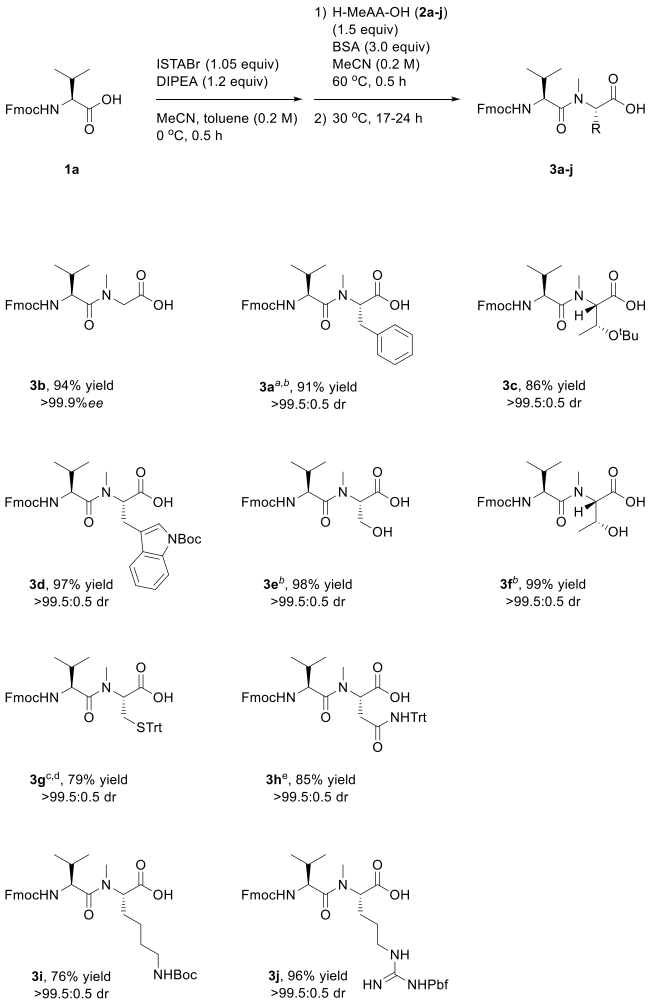

Figure 1. Exploration of substrate scope with Fmoc-Val-OH (**1a**). Isolated yields shown. [a]H-MePhe-OH hydrochloric acid salt was used. [b]BSA (4.5 equiv) was used. [c]THF was used as solvent for silylation. [d]The reaction was carried out at 60 °C. [e]NMP was used as solvent for silylation.

hydrochloride salt of H-MePhe-OH (**2a**) was tested and was also directly usable under these conditions without any neutralization needed when the hydrochloride salt was treated with 4.5 equiv of BSA. Turning our attention to the substrate scope of the nucleophile, *β*-branched *N*-methylamino acids such as H-MeThr(*t*Bu)-OH (**2c**) and the relatively sterically hindered H-MeTrp(Boc)-OH (**2d**) were also well tolerated to afford **3c** and **3d** in 86% and 94% yields, respectively. As expected, the unprotected hydroxyl groups in H-MeSer-OH (**2e**) and H-MeThr-OH (**2f**) were compatible with this method and the side chain unprotected peptides **3e** and **3f** were obtained in quantitative yields using a slight excess of BSA. Moreover, other functionalized *N*-methylamino acids with various side-chain protecting groups (**3g**−**3j**) could be isolated in good yield by using the corresponding H-MeCys(Trt)-OH (**2g**), H-MeAsn(Trt)-OH (**2h**), H-MeLys(Boc)-OH (**2i**), and H-MeArg(Pbf)-OH (**2j**). Notably, all dipeptides could be isolated in high yield and satisfactory purity without column chromatography.

Next, we tested the scope of various electrophile substrates reacted with H-MePhe-OH (**2a**). *N*-Boc- and *N*-Cbz-protected valines (**1b** and **1c**) both afforded the corresponding compounds **3k** and **3l** in good yields (Figure 2. Acyclic and

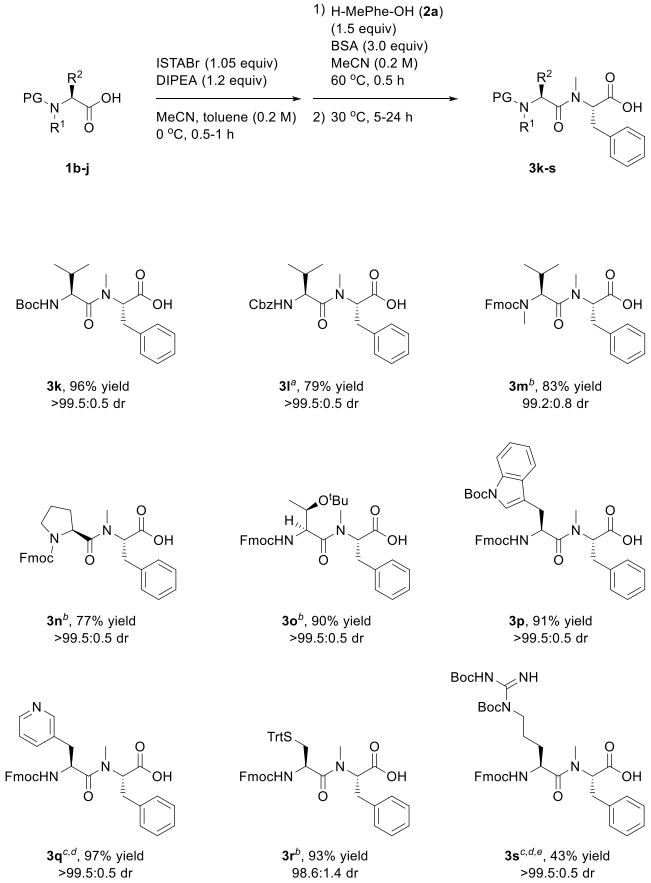

Figure 2. Exploration of substrate scope with H-MePhe-OH (**2a**). Isolated yields shown. [a]THF was used as solvent for silylation. [b]Coupling reaction was conducted at 60 °C. [c]Activation by ISTABr was conducted at −30 °C. [d]Coupling reactions were carried out at 0 °C. [e]Crude material was purified by reversed-phase column chromatography.

cyclic aliphatic amino acids, such as Fmoc-MeVal-OH (**1d**) and Fmoc-Pro-OH (**1e**), were also converted into the corresponding dipeptides **3m** and **3n** in good yields. The use of sterically hindered substrates such as Fmoc-Thr(*t*Bu)-OH (**1f**) and Fmoc-Trp(Boc)-OH (**1g**) was also tolerated under these reaction conditions to afford dipeptides **3o** and **3p** in 90% and 78% yields, respectively. An unnatural phenylalanine derivative, such as **3q** with a nucleophilic nitrogen atom in the phenyl ring, could also be prepared using ISTABr in high yield. Notably, functionalized amino acids such as Fmoc-Cys(Trt)-OH (**1i**) and Fmoc-Arg(Boc)$_2$-OH (**1j**), which are prone to epimerization, also afforded the desired products **3r** and **3s** without significant epimerization. Most dipeptides except for **3s** could be isolated in good yield and satisfactory purity without column chromatography.

https://dx.doi.org/10.1021/acs.orglett.0c02984
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To confirm the viability of this approach for peptide synthesis, we applied these conditions to the synthesis of tripeptides containing *N*-methylamino acids (Figure 3). Using

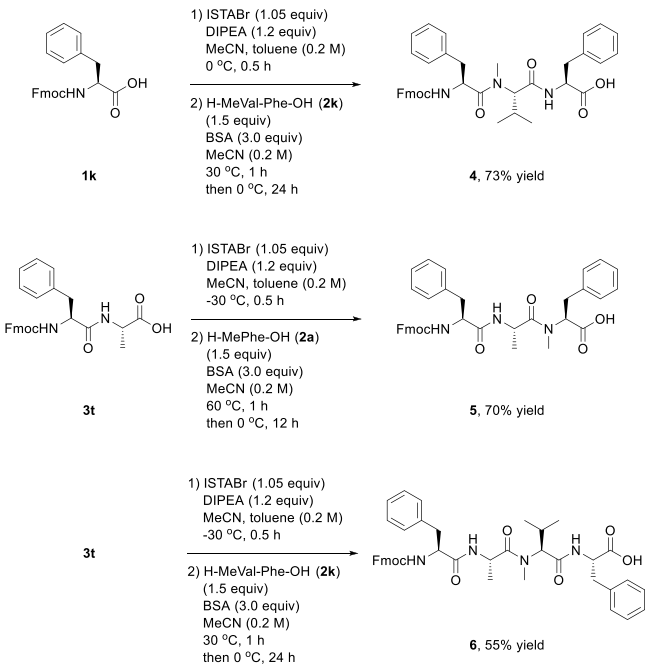

Figure 3. Peptide couplings with ISTABr. Isolated yields shown.

silylated H-MeVal-Phe-OH (**2k**) as the nucleophile, the reaction of **1k** activated with ISTABr afforded the tripeptide **4** in good yield. It is well established that dipeptides as electrophiles are more prone to epimerization than *N*-carbamate-protected monomers.[16] Therefore, we attempted the activation of a dipeptide to be coupled with an *N*-methylated amino acid as the nucleophile. The activation of Fmoc-Phe-Ala-OH (**3t**) with ISTABr proceeded at −30 °C, and the following reaction with silylated H-MePhe-OH (**2a**) was conducted at low temperature to prevent epimerization, affording tripeptide **5** in acceptable yield with an undetectable level of epimerization. With good results for both silylation and activation by ISTABr of dipeptides observed, reactions between the dipeptides was performed as a test of applying this method to the convergent synthesis of longer peptides. We were pleased to obtain tetrapeptide **6** in 55% yield from the reaction of dipeptides **3t** and **2k** without epimerization under the reaction. These results suggested the promising utility of this methodology in the synthesis of peptide compounds.

In summary, we have developed an efficient and general peptide synthetic methodology through the coupling of readily accessible mixed anhydrides of *N*-protected amino acids and peptides, using ISTAX as a new activation reagent, to in situ silylated *C*-terminally unprotected *N*-methylamino acids. We believe this represents the first systematic study demonstrating the practical synthesis of a variety of *N*-methylated peptides using *C*-terminally unprotected *N*-methylamino acids. We are confident that this new method will accelerate the further development of peptide therapeutics. Further studies on the utility of this new method for the development of constrained peptide therapeutics and diagnostics are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02984.

Detailed experimental procedures for all compounds and all spectral data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Takeru Ehara (PeptiDream, Inc.) for insightful discussions, Nasir K. Bashiruddin (PeptiDream, Inc.) for carefully proofreading the manuscript, and Tadamichi Nagashima (PeptiDream, Inc.) and Koji Yoshida (PeptiDream, Inc.) for experimental assistance.

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(11) Loss of enantiopurity under the silylating condition was not detected by chiral SFC analysis of Fmoc-MePhe-OH derived from silylated H-MePhe-OH. H-MeCys(Trt)-OH, which is prone to epimerization, also showed the same results; see the Supporting Information for chiral analysis data.

(12) See the Supporting Information for schematic representation of regiochemical control and byproduct removal using mixed anhydride method.

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