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Direct Mono-*N*-methylation of Solid-Supported Amino Acids: A Useful Application of the Matteson Rearrangement of α-Aminoalkylboronic Esters

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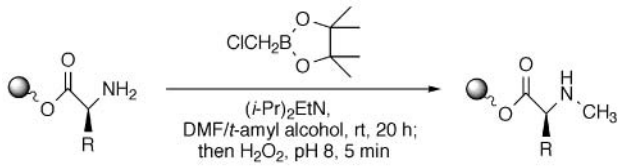
ABSTRACT



A novel solid-phase method for the mono-*N*-methylation of resin-supported amino acids was developed on the basis of Matteson's 1,2-carbon-to-nitrogen migration of boron in α-aminoalkylboronic esters. Amino acids supported on either Wang resin or the highly acid-sensitive SASRIN resin can be methylated by reaction with pinacol chloromethylboronic ester, followed by rearrangement of the resulting aminomethylboronate and subsequent cleavage of the boronate group. This direct method requires only a simple and expedient oxidative resin wash to repair overalkylated sites.

The selective mono-*N*-alkylation of primary amines with alkyl halides is a synthetic transformation of highly deceptive simplicity. Since Hofmann's original investigations of this chemistry in the mid-19th century, there has been no simple and direct solution to control overalkylation when the amine is employed as the limiting substrate.[1] Indeed, isolation of tertiary and even quaternized amines is hard to overcome because the desired secondary amine product is usually more nucleophilic than the starting primary amine. Interest in developing efficient solutions to this problem is prompted largely by the promising biological properties of *N*-alkylated peptides.[2] The integration of *N*-methyl tertiary amide linkages is a recognized strategy to affect peptide conformational rigidity and secondary structure,[3] while also conferring increased bioavailability.[4] Several cyclopeptide natural products embody *N*-methylated residues.[5] Unfortunately, only a small number of protected *N*-methyl amino acids, most with simple side chains, are commercially available. There is a need for developing general solid-phase methodologies for the *N*-methylation of amino acids containing sensitive and/or unnatural residues. Most existing solution-phase methodologies,[6] however, are not applicable in solid-phase chemistry. The most straightforward solid-phase approaches currently available involve the reduction of *N*-formyl derivatives[7] or a three-step sequence[8] composed of terminal amine

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(2) For a recent example, see: Schmidt, R.; Kalman, A.; Chung, N. N.; Lemieux, C.; Horvath, C.; Schiller, P. W. *Int. J. Pept. Protein Res.* **1995**, *46*, 47−55.
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functionalization as an *o*-nitrobenzenesulfonamide, followed by alkylation[8a] or Mitsunobu reaction[8b] on the activated nitrogen and then removal of the sulfonamide group. Although these methods are relatively efficient and can be generalized to other *N*-alkyl substituents, they require multiple operations involving harsh reagents. We realized that the 1,2-carbon-to-nitrogen rearrangement of boron in α-aminoalkylboronic esters, first reported by Matteson et al.,[9] could potentially provide a straightforward one-step access to *N*-methylated secondary amines. This unique, rather obscure rearrangement was discovered as a side reaction in the course of an attempted synthesis of α-aminoboronic acids.[9,10] Its synthetic potential has remained unexploited to this day. Herein, we report our successful efforts to turn it into a simple and efficient method for the direct *N*-methylation of solid-supported amino acids.

In principle, reaction of a terminal amino acid with a halomethylboronic ester[11] first leads to a putative boronoaziridine intermediate of type A (Figure 1). We anticipated that internal coordination in A could help suppress double alkylation by reducing the nucleophilicity of the secondary amine, thereby allowing full consumption of the primary amine (**1**). Intermediate A, however, is expected to rearrange by migration of the boronate group from carbon to nitrogen, affording aminoboronate intermediate B. According to Matteson's original observations, hydroxylic solvents accelerate this rearrrangement.[9b] The addition of an alcohol or water as cosolvent will not only favor the migration step, it will also lead to aminoboronate cleavage in B to give the final resin-bound product C. The use of a hydroxylic solvent therefore may still allow the undesired doubly alkylated product to form. Nonetheless, we set out to examine the feasibility of this one-stage approach (Scheme 1). To this end, a mixture of methanol and DMF (for resin swelling) was chosen as solvent. At the onset, Wang resin supported valine (**1a**) was chosen as a model amino acid because it provides steric challenge to optimize the alkylation step.

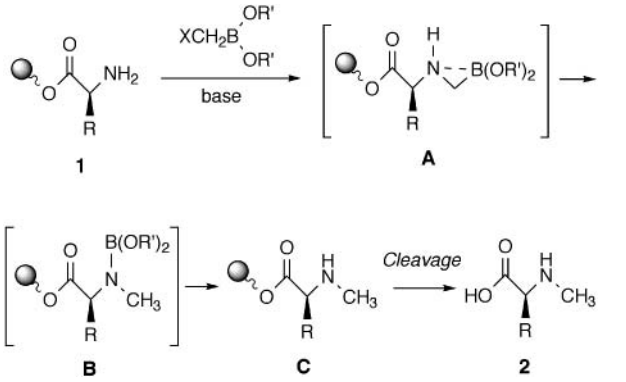
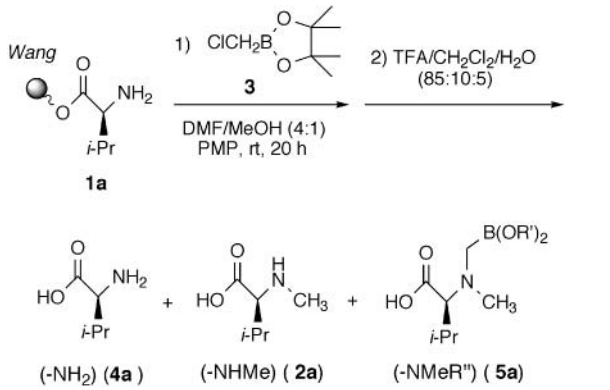


Figure 1. Proposed mechanistic steps in the *N*-methylation of resin-bound amino acids with halomethylboronic esters.

Scheme 1. Optimization of a One-Step Process: Possible Products from **1a** after Cleavage from the Resin



Initial tuning of reaction conditions for this process revealed that pinacol iodomethylboronic ester undergoes substantial degradation in the presence of methanol. Moreover, both the iodo and bromo analogues were too reactive for our purpose, as evidenced by the observation of unrearranged doubly alkylated product of type $HO_2CCH(i\text{-}Pr)N[CH_2B(OR')_2]_2$ in the mass spectral analysis of cleaved product from the resin. The presence of this species implies that the rearrangement of A (Figure 1) occurred with a rate slower than or comparable to that of the second alkylation by the electrophile. It is not surprising that this unrearranged doubly boronomethylated side product can be isolated, since it is known that α-aminoalkylboronic esters lacking a hydrogen on the nitrogen, i.e., tertiary amines, do not rearrange.[9] An electrophile of mitigated reactivity, the chloro analogue **3**,[12] was thus selected along with 1,2,2,6,6-pentamethylpiperidine (PMP), a nonquaternizing base[13] that seemed relatively inert toward this electrophile. Unfortu-

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Table 1. One-Step Process: Effect of Reagent Stoichiometry on the Relative Proportion of Products from **1a**

entry	**3** (equiv)	base (equiv)	$-NH_2$ (**4a**) (%)	$-NHMe$ (**2a**) (%)	$-NMeR''$ (**5a**) (%)
1	3.5	2	<5	60	35
2	3	3	<5	60	35
3	3	2	<5	65	30
4	2.5	2	<5	75	25
5	2	1.2	25	70	5

[a] Typical trials were conducted by shaking the resin-bound amino acid (ca. 100 mg, 0.64 mmol/g) with pentamethylpiperidine and pinacol chloromethylboronic ester in 4:1 DMF/methanol (2 mL) at room temperature for 12−24 h in a polypropylene fritted vessel. [b] Ratio of crude product mixture obtained after cleavage from the resin ($TFA/CH_2Cl_2/H_2O$ 85:10:5).

nately, as summarized in Table 1, all attempts to optimize reagent equivalence and reaction time amounted to a typical futile case of uncontrolled alkylation. As observed after cleavage of the resin with concentrated TFA and ^1H NMR analysis of the crude product mixture (Scheme 1), there was no possibility, even with a minimal excess of electrophile, to consume **1a** entirely and isolate **2a** without leading to overalkylated unrearranged product **5a**.

Our second approach was aimed at conducting the reaction in a two-stage fashion. In this approach, the reaction was performed in DMF alone, without a hydroxylic cosolvent. In principle, in the absence of protic/nucleophilic species, the process should stop at the stage of intermediates A and/or B and thus should not lead to C (Figure 1). Excess electrophile could be rinsed away, and in the second stage of the procedure a hydroxylic solvent could be added to promote formation of C with no danger of overalkylation. This two-stage approach failed as well, providing proportions of cleaved products **4a**/**2a**/**5a** very similar to the former approach.[14]

In light of these disappointing results, we then decided to employ conditions found earlier that ensure full consumption of the primary amine (5 equiv each of **3** and PMP for >20 h) and to seek a simple resin wash operation to repair overalkylated sites. We envisioned that oxidation[10] of the C−B bond in **6** would lead to a boroaminal intermediate (**7**) that should hydrolyze to give a *N*-methylol derivative (**8**) (Figure 2). The latter could break down to form either an iminium intermediate (**9**) or the desired *N*-methylamine **10** accompanied by evolution of formaldehyde. Should it be favored, the former pathway is nonetheless expected to eventually afford the latter in the presence of excess water.

To our delight, a sample of Wang resin supported valine (**1a**) containing a large proportion of overalkylated sites was completely repaired after treatment with excess hydrogen peroxide in a buffered (pH 8) aqueous THF solution for a few minutes. The comparison of ^1H NMR spectra of crude product cleaved from the resin with and without a repair

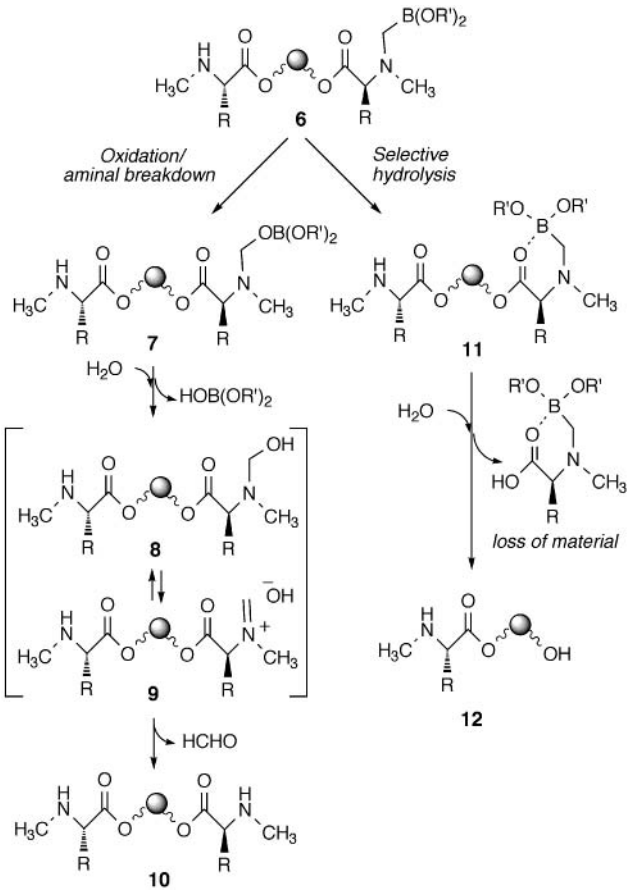

Figure 2. Possible mechanisms for the repair of overalkylated amino acid sites under aqueous hydrogen peroxide treatment.

wash was striking (Figure 3). All peaks exhibited by the boronomethyl group (spectrum A), the overalkylated branch in **5a**, disappeared after cleavage of a resin sample that underwent a 3-min wash with a 5-equiv excess of H_2O_2 prior to the usual rinses. A clean *N*-methylated valine product (**2a**) was obtained (spectrum B). No traces of *N*-oxide products were detected under these conditions.[15]

Initially, we were worried that another repair mechanism, selective hydrolysis, could occur (Figure 2). It seemed plausible that the pending boronic ester in **11** could coordinate the Wang ester linker carbonyl, thereby activating the overalkylated sites for hydrolysis. This unwanted mechanism would lead to a loss of material from resin **12**, thereby reducing the yield of product after cleavage. However, control experiments without hydrogen peroxide helped verify that the oxidant, and not the basic buffer alone, was responsible for the actual repair.[16]

Reaction conditions were further improved prior to a study of the generality of this new *N*-methylation method. First,

(14) It may be possible that an adventitious nucleophile such as traces of water, or perhaps the chloride counteranion, could cleave the aminoboronate B and lead to C prior to rinsing away excess electrophile (Figure 1).

(15) *N*-Oxide formation was observed only in trials involving larger amounts of hydrogen peroxide for longer reaction times.

(16) It also appears unlikely that hydrolysis of the ester linker by peroxide anion could play a role. The high yields of *N*-methylated amino acids from highly overalkylated resins did not correlate with the possibility of a repair mechanism involving selective hydrolysis.

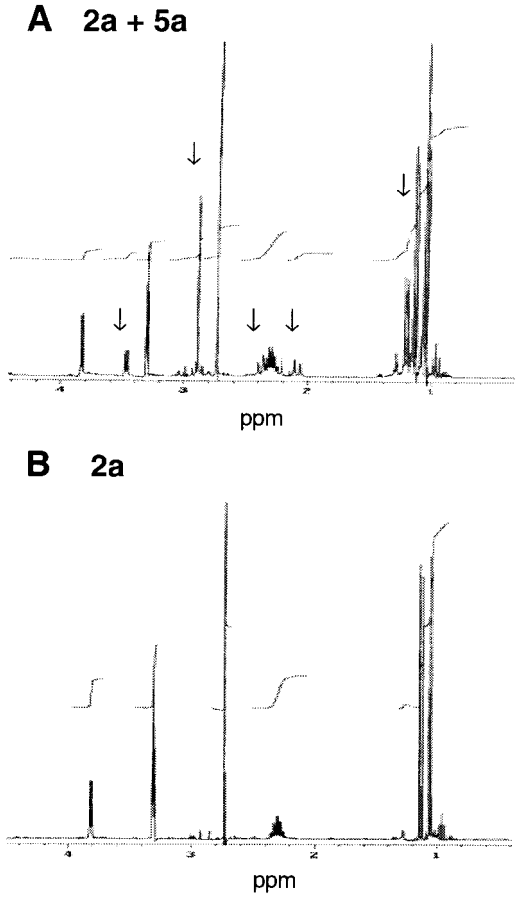

Figure 3. Proton NMR comparison (300 MHz, CD_3OD) of crude samples from the reaction of Wang resin supported valine (**1a**) to give *N*-methylvaline (**2a**) after cleavage from the resin: (A) without and (B) with the oxidative repair wash. Signals exhibited by **5a** are indicated by a small arrow. Solvent peak appears at 3.30 ppm.

we realized that DIPEA could replace PMP as the base and provide even faster rates of alkylation.[17] Moreover, the addition of *tert*-amyl alcohol as a protic cosolvent, a precautionary measure to ensure that the 1,2-migration of boron is rapid and complete, was found not to be detrimental to product yields and purity. We have also ascertained that the optimized general procedure leads to little or no racemization. A large scale *N*-methylation of resin-bound valine followed by protection and cleavage from the resin afforded Fmoc-*N*-methylvaline with optical purity similar to that of a commercial sample.[18] The optimized procedure was then applied to a set of model amino acids supported on different linkers and supports (Table 2). Crude *N*-methylated amino acids **2** were isolated in good to high purity according to ^{1}H NMR and MS analysis.[19]

In addition to the popular PHB[20] (Wang) linker (entries 1−3), we have tested the applicability of this method to a highly acid-sensitive resin. This application would allow the synthesis and release of free or even Fmoc-protected amino acids with intact Boc- and *tert*-butyl-protected side chains.[8b] To this end, whereas amino acids immobilized to the bulky trityl resin failed to undergo reaction completion, residues attached to HMPB-BHA resin[20] provided *N*-methyl amino acids such as *tert*-butyl-protected MeAsp (**2e**) in excellent purity (entries 4−6).[21]

Table 2. Monomethylation of Resin-Bound Amino Acids[a]

entry	resin	residue	product	yield[b] (%)	purity[c] (%)
1	PHB (Wang)	Val	**2a**	92	95
2	PHB (Wang)	Phe	**2b**	95	>90
3	PHB (Wang)	Leu	**2c**	83	>90
4	HMPB−BHA (SASRIN)	Val	**2a**	90	>95
5	HMPB−BHA (SASRIN)	Tyr(*t*-Bu)	**2d**	81	90[d]
6	HMPB−BHA (SASRIN)	Asp(*t*-Bu)	**2e**	74	>90[d]

[a] Reactions were conducted by shaking the resin-bound amino acid (typical scale 0.1−0.5 g) with diisopropylethylamine (5 equiv) and pinacol chloromethylboronic ester (5 equiv) suspended in 9:1 DMF/*tert*-amyl alcohol at room temperature for 20 h in a polypropylene fritted vessel. The oxidative repair wash (5 equiv of H_2O_2 in aqueous pH 8 buffer/THF (1:4) for 3−5 min) is integrated to the usual rinsing operations (see Supporting Information). [b] Non-optimized yields of crude products obtained as trifluoroacetate salts after cleavage from the resin (entries 1−3, TFA/CH_2Cl_2/H_2O 85:10:5; entries 4−6, 1% TFA/CH_2Cl_2). [c] Estimated from inspection of the ^{1}H NMR spectra. [d] Products contain minor amounts of side-chain deprotected residues. Neutralization of the mixture with pyridine immediately after cleavage provided products of higher quality but containing a large amount of pyridinium triflate.

In summary, a novel solid-phase method for the mono-*N*-methylation of amino acids was developed on the basis of Matteson's 1,2-carbon-to-nitrogen migration of boron in α-aminoalkylboronic esters. It was shown that amino acids supported on either Wang resin or the highly acid-sensitive SASRIN resin can be methylated by reaction with pinacol chloromethylboronic ester, followed by rearrangement of the resulting aminomethylboronate and subsequent cleavage of the boronate group. This direct method requires only a simple and expedient oxidative resin wash to repair overalkylated sites. It constitutes the first useful application of the Matteson rearrangement, which could be employed for the preparation of *N*-methyl amino acids of unusual structure such as those frequently encountered in cyclopeptide natural products.

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Supporting Information Available: A typical experimental procedure for the mono-*N*-methylation of resin-supported amino acids, along with ^{1}H NMR and ES-MS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Presumably, proton transfer from the hydrochloride salt of initial intermediate A by the base may be rate-limiting.

(18) Ascertained by optical rotation measurements of a purified synthetic sample and an authentic sample (Novabiochem). For the synthetic one, resin-bound *N*-methylvaline was protected on support (4 equiv of FmocCl, 6 equiv of DIPEA, CH_2Cl_2, 6 h) and then cleaved off with TFA/CH_2Cl_2/H_2O (85:10:5).

(19) Common minor impurities often originate from the starting resin (e.g., benzoic acid from capping of unfunctionalized sites, concomitant cleavage of small amounts of the PHB or HMPB-BHA linkers).

(20) PHB: *p*-hydroxybenzyl. HMPB-BHA: 4-hydroxymethyl-3-methoxyphenoxybutyric acid benzhydrylamide, or SASRIN.

(21) Highly functionalized amino acids with nucleophilic or oxidazable centers may not be suitable as substrates. For instance, methionine was found not to be tolerant of these *N*-methylation conditions.