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On the Selective *N*-Methylation of BOC-Protected Amino Acids

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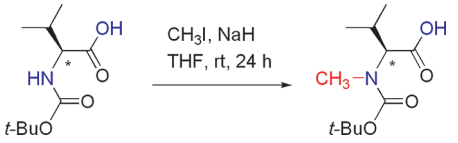
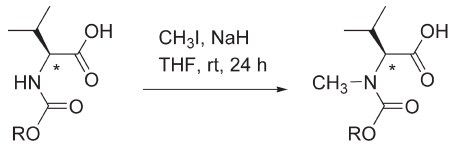


The selective *N*-methylation of BOC-protected valine **1a** with MeI and NaH in THF (i.e., in the presence of a free carboxyl group) has been attributed to the protection of the carboxylate by chelation to Na^+. An alternative mechanism, involving the formation of the carbene intermediate generated from MeI and its insertion into the N−H bond, has been ruled out by isotopic labeling.

N-Methylamino acids are valuable building blocks in medicinal chemistry and as substitutes for "natural" amino acids.[1−5] Their popularity stems, in particular, from various effects they introduce to peptides, such as the restriction of conformational mobility, conformational change, and an increased stability to proteolytic enzymes.[1−5] The *N*-methylamino acids have also been frequently employed in the construction of various catalysts[6] and ligands for transition metals.[7] Thus, we have extensively used formamides derived from *N*-methylvaline and other *N*-methylamino acids as a scaffold in designing novel organocatalysts for asymmetric reduction of imines with trichlorosilane.[8]

SCHEME 1. *N*-Methylation of Carbamate Derivatives of Valine



1a, R = *t*-Bu
1b, R = $PhCH_2$
2a, R = *t*-Bu
2b, R = $PhCH_2$

Selective *N*-alkylation of amino acids is a challenging problem that generally requires selective protection and the use of procedures that minimize racemization. From a number of existing methods, the *N*-methylation of carbamate derivatives of amino acids, such as *N*-BOC or *N*-Cbz (**1a,b**), with CH_3I and NaH, stands as one that is potentially most simple (Scheme 1). This methodology was first developed by Benoiton[3] and later further improved or modified.[2,4,5] Other approaches, relying, e.g., on double-reductive amination of the free amino group (first with PhCHO and then with CH_2O), have been developed for polyfunctional amino acids, such as histidine, where *N*-methylation of the imidazole moiety must be avoided.[9]

The original Benoiton protocol,[3a] employing CH_3I and NaH, followed the traditional wisdom, i.e., initial double deprotonation of **1** by ≥2 equiv of NaH to generate the corresponding dianion, followed by treatment with MeI, which provided the product of *N*,*O*-bismethylation. Subsequent hydrolysis of the ester group, which may be accompanied by a certain degree of racemization, then gave the free acid **2**. In fact, the double methylation required elevated temperature and/or addition of DMF to improve the solubility of the dianion.[3a] A modification of this protocol in the way that **1a** was first mixed with MeI prior to the addition of NaH resulted in a dramatic change: thus, at room temperature, with just THF as a solvent, Benoiton was able to obtain the enantiopure *N*-methylated product **2a** in an excellent yield, with only trace amounts of the unreacted starting material and the bismethylated product.[3c]

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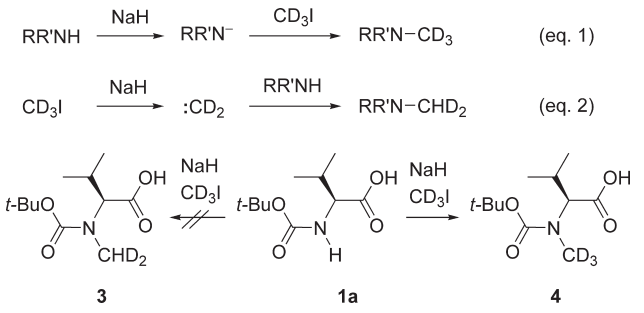
SCHEME 2. Possible Pathways for the *N*-Methylation of BOC-valine



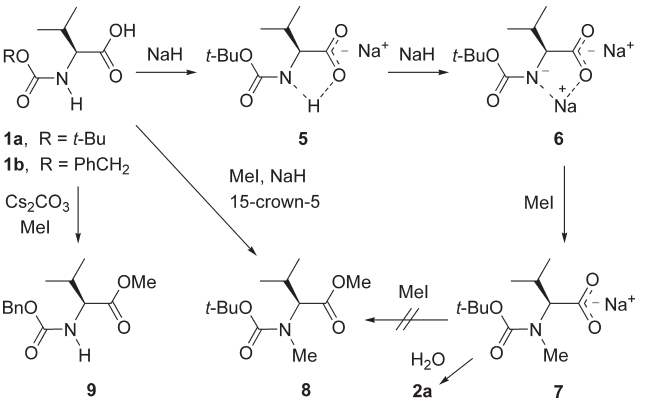
According to our experience,[8b] when **1a** was first deprotonated by NaH in THF before methyl iodide was added, this procedure resulted in an incomplete conversion of the BOC derivative **1a**, affording a ~1:1 mixture of the unreacted **1a** and the *N*-methylated product **2a**, even when 10 equiv of NaH and long reaction time were used (at room temperature). This behavior is in line with the previous and parallel observations reported by other groups for the analogous Cbz derivatives.[2−5] On the other hand, when **1a** was first mixed with MeI and NaH was added after that in several portions, the yield of the desired *N*-methyl derivative **2a** was practically quantitative in accord with Benoiton's[3c] second protocol; notably, the carboxyl was not methylated under these conditions, and the product obtained was enantiomerically pure.[3c,4b,5,8b] The former experiment clearly suffers from the poor solubility of the corresponding dianion salt which, being in fact a precipitate, is not readily available for methylation.[10] On the other hand, if the deprotonation occurs in the presence of MeI, as in the latter experiment, concentration of the dianion is kept relatively low at any time as it gradually reacts with MeI, which apparently prevents the precipitation.

The methylation can be expected to proceed via an S_N2 mechanism (Scheme 2, eq 1). However, in view of the high *N*-selectivity, another mechanism can be conjectured, according to which NaH would react with MeI to generate the corresponding carbene via a 1,1-elimination (eq 2). Insertion of the carbene into the N−H bond would then afford the same *N*-methylated product. To address this mechanistic issue, deuterated methyl iodide was employed. If the methylation occurred via the S_N2 mechanism, the product should contain the N-CD_3 group (eq 1). On the other hand, the carbene insertion would give the product with the N-CHD_2 group instead (eq 2). Methylation of **1a** was therefore carried out with CD_3I under the same conditions as those employed for CH_3I. The ^1H NMR spectrum of the product thus obtained revealed no trace of a signal corresponding to the N-CHD_2 group (**3**), demonstrating that the product must contain the N-CD_3 group (**4**), which rules out the carbene mechanism (eq 2).

It can be assumed that the deprotonation of **1a** first generates the carboxylate salt **5**, where the remaining *N*-proton may be bonded between the nitrogen and the carboxylate (Scheme 3). Deprotonation with the second equivalent of NaH would then give rise to dianion **6** with the second Na^+ presumably chelated between the oxygen

(10) The solubility can be improved by heating the mixture at 60 °C.[5]

SCHEME 3. Methylation of BOC- and Cbz-valine



and nitrogen atoms. This species can be expected to be preferentially methylated on the nitrogen to produce **7**. However, the reaction requires an excess of MeI to reach completion, which raises the question as to the possible subsequent methylation of the carboxyl in **7** to produce the corresponding methyl ester **8**. In fact, methylation of the Cbz derivative **1b**, carried out in the presence of Cs_2CO_3 instead of NaH, is known to produce the corresponding methyl ester **9**.[5,11] The lack of *N*-methylation in this case is understandable, as Cs_2CO_3 is too weak a base to deprotonate the NH group. However, the observed clean methylation of the carboxyl (**1b** → **9**) stays in stark contrast to the lack of *O*-methylation of the sodium salt **6**/**7**, suggesting that Na^+ protects the carboxyl, presumably by coordination, as in **6**/**7** or rather in an analogous higher order complex. To shed light on this issue, another experiment was performed in the presence of 15-crown-5-ether that should sequester the Na^+ ions. Here, the crown ether was added to a mixture of **1a** and MeI, followed by a slow addition of NaH. Under these conditions, clean formation of the *N*,*O*-bismethylated product **8** was observed at room temperature (in THF), clearly demonstrating the protecting role of Na^+ in the previous experiments.[12] It is pertinent to note that no racemization has occurred during this double methylation, as revealed by the optical rotation of the product.

In conclusion, the selective *N*-methylation of BOC-protected amino acids, such as **1a**, by CH_3I and NaH in THF at room temperature appears to originate from the chelation of the carboxylate group by the sodium cation, which dramatically decelerates its methylation at room temperature; the carbamate nitrogen is thus methylated preferentially to produce **2a**. In the presence of 15-crown-5 ether, the chelate is disrupted, which results in the clean *N*,*O*-bis-methylation to afford **8**.[13] An alternative mechanism, involving a carbene insertion into the N−H bond, has been ruled out by isotopic labeling.

(11) *N*,*O*-Bis-methylation with the NaH/MeI system was observed at 80 °C (in THF/DMF) for the corresponding Cbz-protected valine **1b** and other amino acids.[3a,5]

(12) Note that in the methylation carried in with Cs_2CO_3 (**1b** → **9**),[3a,5] the Cs^+ ion is not capable of coordinating the carboxylate ion and the *O*-methylation occurs readily. Furthermore, elevated temperature and/or the presence of DMF as an additive solvent are also likely to disrupt the Na^+-chelate, which is in agreement of the experimental observation of the *N*,*O*-bis-methylation when DMF is used as solvent.[3a,5,11]

(13) A similar behavior was observed by Berkessel on the attempted bis methylation (with MeI) of the dianions generated from β-keto esters and NaH in THF (A. Berkessel, personal communication).

Experimental Section

General Procedure for *N*-Methylation of *N*-BOC-valine. Method A. Neat sodium hydride (160 mg, 6.67 mmol, 10 equiv) was added slowly in portions over a period of 2 h to a cooled (0 °C) solution of *N*-BOC-valine (**1a**) (145 mg, 0.67 mmol, 1 equiv) and iodomethane (0.42 mL, 947 mg, 6.67 mmol, 10 equiv) or iodomethane-d_3 (0.42 mL, 967 mg, 6.67 mmol, 10 equiv) in anhydrous THF (2 mL) under a stream of argon. The reaction mixture was stirred at room temperature for 24 h under an argon atmosphere and then diluted with ether (20 mL) and quenched with water (30 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 15 mL), acidified to pH 3 with a 20% aqueous solution of citric acid, and extracted with AcOEt (3 × 20 mL). The combined organic phase was dried over $MgSO_4$ and evaporated to afford the corresponding *N*-methylated product **2a** (152 mg, 0.653 mmol, 98%) as a thick colorless oil that solidified upon standing in a refrigerator: mp 69−71 °C (by evaporation from AcOEt) [lit.[3c] mp 58−59 °C or lit.[14] mp 86 °C];[15] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (d, J = 10.4 Hz, 1H), 2.87 (s, 3H), 2.20−2.36 (m, 1H), 1.47 (s, 9H), 1.03 (t, J = 6.6 Hz, 3H), 0.92 (t, J = 6.7 Hz, 3H) in accordance with the literature and with an authentic sample.[4b,8b] **4**: thick colorless oil (151 mg, 0.640 mmol, 96%); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of rotamers) δ 4.14 (d, J = 10.9 Hz) and 4.09 (d, J = 9.8 Hz) (together 1H), 2.16−2.33 (m, 1H), 1.45 (s) and 1.47 (s) (together 9H), 1.02 (t, J = 6.6 Hz, 3H), 0.91 (t, J = 6.7 Hz, 3H); ^{13}C NMR δ 176.3 and 175.3 (C), 157.0 and 155.7 (C), 80.9 and 80.7 (C), 65.4 and 65.1 (CH), 28.4 (3 × CH_3), 27.8 and 27.5 (CH), 20.1 and 19.8 (CH_2), 19.1 and 19.0 (CH_3); MS (CI, isobutane) m/z 235 ($[M + H]^+$, 10), 179 (100), 135 (15), 133 (10); MS (EI) m/z 133 ($[(M^{+\bullet}) - BOC]$, 100), 91 (45), 89 (60), 84 (28), 57 (93); HRMS (EI) 133.1059 ($C_6H_9D_3NO_2$ requires 133.1055).

Method B. A solution of *N*-BOC-valine (**1a**) (217 mg, 1.0 mmol, 1 equiv) in anhydrous THF (2 mL) was added dropwise to a cooled (0 °C) suspension of neat sodium hydride (240 mg, 10 mmol, 10 equiv) in THF (1 mL) under an argon atmosphere. The mixture was allowed to warm to room temperature, and then neat iodomethane (0.62 mL, 1.42 g, 10 mmol, 10 equiv) was added dropwise with stirring. The reaction mixture was stirred at room temperature for 24 h and then worked up as in method A. The crude material was composed of ca. 1:1 mixture of the starting material **1a** and product **2a**.

Method C. Neat sodium hydride (240 mg, 10 mmol, 10 equiv) was added slowly in portions over a period of 2 h to a cooled (0 °C) solution of *N*-BOC-valine (**1a**) (217 mg, 1.0 mmol, 1 equiv), 15-crown-5-ether (1.98 mL, 2.20 g, 10 mmol, 10 equiv), and iodomethane (0.62 mL, 1.42 g, 10 mmol, 10 equiv) in anhydrous THF (3 mL) under a stream of argon. The reaction mixture was stirred at room temperature for 24 h under an argon atmosphere and then diluted with ether (20 mL) and quenched with water (30 mL). The layers were separated, the aqueous layer (basic) was extracted with ether (2 × 15 mL), acidified to pH 3 with a 20% aqueous solution of citric acid, and extracted with AcOEt (3 × 20 mL). The original organic phase was combined with the extract of the basic aqueous layer, dried over $MgSO_4$, and evaporated to afford the *N*,*O*-bismethylated product **8** (252 mg, 0.943 mmol, 94%) as a colorless oil: $[\alpha]^{25}_D$ −89.2 (c 0.1, $CHCl_3$) [lit.[4b] $[\alpha]^{25}_D$ −87.3 (c 0.1, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of rotamers) δ 4.44 (d, J = 10.5 Hz, 0.55H) and 4.08 (d, J = 10.6 Hz, 0.45H), 3.69 (s, 3H), 2.83 (s) and 2.80 (s) (together 3H), 2.11−2.22 (m, 1H), 1.45 (s, 9H), 0.95 (t, J = 6.5 Hz, 3H), 0.88 (t, J = 6.3 Hz, 3H) in accordance with the literature.[3,5] The extract of the acidified aqueous layer only afforded ethylene glycol (a degradation product of the crown ether), while no trace of the *N*-monomethylated **2a** was detected.

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Supporting Information Available: General experimental methods and ^{1}H and ^{13}C NMR spectra for **2a**, **4**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) In fact, Benoiton attained the crystalline material after 2 years,[3c] showing the difficulties associated with the crystallization of **2a**, which is apparently reflected in the variation of the melting point.