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An Efficient and Practical N-Methylation of Amino Acid Derivatives

Mahavir Prashad,* Denis Har, Bin Hu, Hong-Yong Kim, Oljan Repic, and Thomas J. Blacklock

Process Research and Development, Chemical and Analytical Development, Novartis Institute for Biomedical Research, One Health Plaza, East Hanover, New Jersey 07936

mahavir.prashad@pharma.novartis.com

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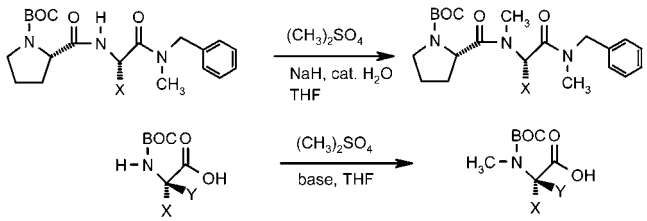
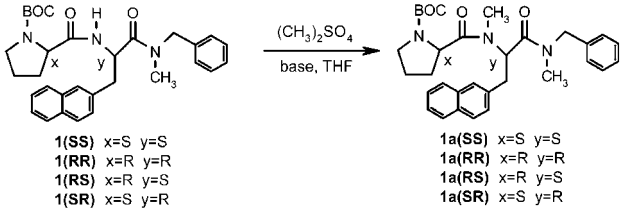
ABSTRACT



An efficient and practical N-methylation of amino acid derivatives with dimethyl sulfate in the presence of sodium hydride and a catalytic amount of water is described. Reaction of water with sodium hydride generated highly reactive dry sodium hydroxide, which led to much faster reaction rates than powdered sodium hydroxide itself.

Several methods are reported in the literature for the synthesis of *N*-methylamino acids and derivatives.[1] Commonly used methods involve N-methylation using methyl iodide as the methylating agent.[2] In a development program, we needed a practical method for the synthesis of **1a(*SS*)** (Scheme 1).

Scheme 1



Initially, we prepared **1a(*SS*)** by the N-methylation of **1-(*SS*)** with methyl iodide (8.0 equiv) in the presence of silver oxide (4.0 equiv) in DMF.[2j] Handling an excess of low-boiling methyl iodide during workup of the reaction mixture presented air-emission and health-safety problems for large-scale work. Additionally, silver oxide is an expensive reagent. We, therefore, studied the N-methylation of **1(*SS*)** with dimethyl carbonate,[3] which, however, under the attempted conditions led to significant epimerization. Dimethyl sulfate was selected because it is high boiling, and any excess reagent can be safely destroyed with ammonium hydroxide.

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Table 1. N-Methylation of Amino Acid Derivatives with Dimethyl Sulfate

			NaH, catalytic water, THF			powdered NaOH, THF		
entry	substrate	product	time[a]	conversion (%)	yield[b] (%)	time	conversion[a] (%)	yield[b] (%)
1	**1(*SS*)**	**1a(*SS*)**	1 min	84		1 min	36	
			30 min	99	94	30 min	63	
						2 h	76	
						4 h	80	
						24 h	88	NI
2	**1(*RR*)**	**1a(*RR*)**	30 min	>99	92			
3	**1(*RS*)**	**1a(*RS*)**	30 min	>99	94			
4	**1(*SR*)**	**1a(*SR*)**	30 min	>99	92			
5	**2**	**2a**	1 min	95		1 min	42	
			30 min	>99	93	30 min	75	
						2 h	89	
						4 h	94	
						24 h	>99	95
6	**3**	**3a**	1 min	98		1 min	46	
			30 min	>99	94	30 min	64	
						2 h	84	
						4 h	90	
						24 h	99	93
7	**4**	**4c**	1 min	>99	95	1 min	38	
						30 min	53	
						2 h	72	
						4 h	79	
						24 h	84	NI
8	**4a**	**4c**	1 min	99 (96)[c]		1 min	97 (15)[c]	
			30 min	>99 (98)[c]	92	30 min	97 (33)[c]	
						2 h	97 (56)[c]	
						4 h	97 (64%)[c]	
						24 h	97 (79)[c]	NI
9	**5**	**5c**	1 min	99		1 min	26	
			30 min	>99	98	30 min	35	
						2 h	54	
						4 h	65	
						24 h	94	NI
10	**5a**	**5c**	1 min	99 (99)[c]		1 min	65 (12)[c]	
			30 min	>99 (99)[c]	97	30 min	80 (23)[c]	
						2 h	96 (49)[c]	
						4 h	99 (66)[c]	
						24 h	>99 (90)[c]	NI
11	**6**	**6c**	1 min	99		1 min	20	
			30 min	>99	97	30 min	35	
						2 h	60	
						4 h	75	
						24 h	94	NI
12	**6a**	**6c**	1 min	99 (90)[c]		1 min	70 (10)[c]	
			30 min	>99 (95)[c]	90	30 min	81 (20)[c]	
						2 h	92 (35)[c]	
						4 h	96 (54)[c]	
						24 h	96 (70)[c]	NI

[a] Time after the addition of dimethyl sulfate is finished. [b] Isolated yield. [c] Conversion to dimethylated product.

Herein, we report the development of an efficient and practical method for the N-methylation of amino acid derivatives in the presence of sodium hydride and a catalytic amount of water. Water-assisted reactions have been reviewed recently, but such a reaction is not reported therein.[4]

Initially, reaction of **1(*SS*)** with dimethyl sulfate in the presence of sodium hydride (2.0 equiv) in tetrahydrofuran did not lead to any N-methylation. However, when the reaction was allowed to proceed for an extended period of time, the desired N-methylated product **1a(*SS*)** was obtained as the only product. We postulated that, with time, absorbed moisture from nitrogen reacted with sodium hydride to generate in situ highly reactive, dry sodium hydroxide, which was the actual base.[5] The amount of water was subsequently optimized to be 0.2 equiv of the substrate. Use of methanol

(4) Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299−307.

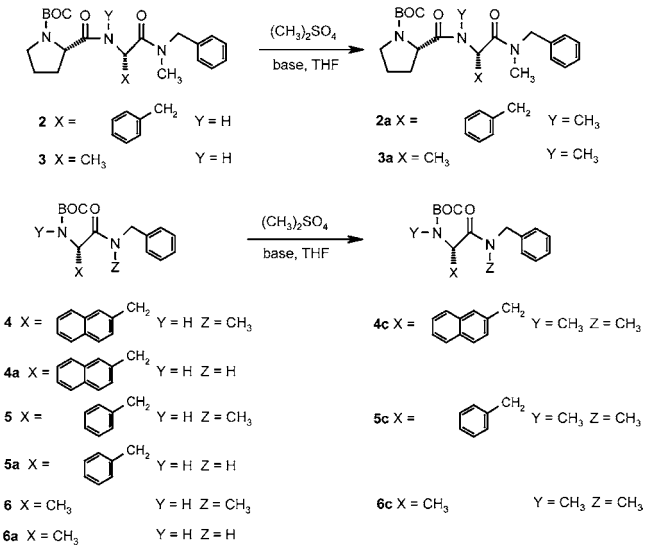
instead of water also facilitated this reaction. However, water was preferred over methanol because methanol could lead to the formation of dimethyl ether as the byproduct.

Thus, treatment of a solution of **1(*SS*)** in tetrahydrofuran with dimethyl sulfate (1.8 equiv) in the presence of sodium hydride (2.0 equiv) and water (0.2 equiv) at 17−20 °C afforded **1a(*SS*)** in 94% yield (entry 1, Table 1).[6] To ensure that there was no epimerization under these newly developed conditions, the three other diastereomers **1a(*RR*)**, **1a(*RS*)**, and **1a(*SR*)** (Scheme 1) were also synthesized using this method. A chiral HPLC method[7] revealed that there was no epimerization. Temperature was critical for this reaction as ∼10% epimerization was observed at 30 °C.

The N-methylation of **1(*SS*)** in the presence of powdered commercially available sodium hydroxide was also studied and was found to be much slower (24 h, entry 1, Table 1) compared to sodium hydride and water conditions (30 min).

To test the general synthetic utility of this method, we studied the N-methylation of several substrates (**2**−**6**; Scheme 2), and the results are listed in Table 1.[8] In all cases, the

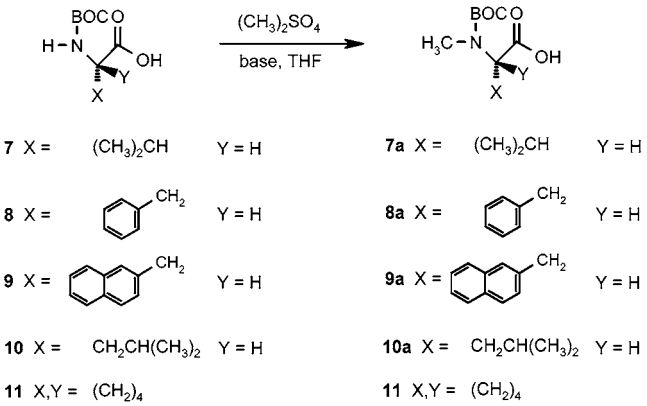
Scheme 2



reaction was faster in the presence of sodium hydride and water compared to powdered sodium hydroxide, yielding the N-methylated products in >90% yield. Di-N-methylation of **4a**−**6a** (Scheme 2) was also achieved in >90% yield (entries 8,10, and 12) using 4.0 equiv of sodium hydride, 0.4 equiv of water, and 3.6 equiv of dimethyl sulfate.

N-Methylation of BOC-L-valine (**7**), BOC-L-phenylalanine (**8**), BOC-L-3-(2-naphthyl)alanine (**9**), BOC-L-leucine(**10**), and 1-(BOC-amino)cyclopentanecarboxylic acid (**11**) with dimethyl sulfate (3.1 equiv) in the presence of sodium hydride (4.6 equiv) and water (0.2 equiv) at 17−20 °C also afforded N-methylated amino acids (**7a**−**11a**, Scheme 3) in

Scheme 3



excellent yield (Table 2). A chiral HPLC method[9] indicated that there was ∼1% racemization in the case of **8** and **9** under these conditions. Again, at higher temperature (26 °C), ∼5% racemization was observed; however, a recrystallization of crude products from a mixture ethyl acetate and heptane afforded **8a** and **9a** with undetectable amounts of the undesired enantiomer.[10] As before, powdered sodium hydroxide led to much slower reaction in all three cases (after

Table 2. N-Methylation of Amino Acids

entry	substrate	product	time (h)	yield (%)
1	**7**	**7a**	2	91
2	**8**	**8a**	2	90
3	**9**	**9a**	2	80
4	**10**	**10a**	1	92
5	**11**	**11a**	1	85

(5) Pure sodium hydride is not as reactive as sodium hydroxide, perhaps due to lower solubility in tetrahydrofuran.

(6) **Typical Procedure.** To a suspension of sodium hydride (60% dispersion in mineral oil; 10.0 mmol) in tetrahydrofuran (12 mL) was added a solution of the substrate (5.0 mmol) and water (1.0 mmol) in tetrahydrofuran (10 mL) dropwise over a period of 20 min while maintaining an internal temperature of 17−20 °C. The mixture was stirred at the same temperature for 10 min, and dimethyl sulfate (9.0 mmol) was added over a period of 20 min while maintaining an internal temperature of 17−20 °C. The stirring was continued at the same temperature for the specified time in Table 1, and the reaction was monitored by HPLC. The reaction mixture was quenched with 30% ammonium hydroxide (6 mL) over a period of 10 min while maintaining an internal temperature of 17−20 °C, and the stirring was continued for an additional 1 h (to ensure complete destruction of dimethyl sulfate as monitored by GC). The mixture was diluted with toluene (20 mL) and water (10 mL). The organic layer was separated, washed with water (10 mL), and concentrated under reduced pressure, and the crude product was purified by silica gel chromatography. (The procedure with powdered sodium hydroxide was similar except no water was used.)

(7) Chiral purity was determined on a Waters HPLC system using a Chiralcel OD column (4.6 × 250 mm) and a mixture of hexane/ethanol/TFA (100:2:0.2 v/v/v) as the mobile phase (isocratic at a flow rate of 1 mL/min and UV detector at 210 nm) at 40 °C. The retention times for **1a(*RS*)**, **1a(*RR*)**, **1a(*SS*)**, and **1a(*SR*)** were 19.3, 23.0, 25.4, and 36.4 min, respectively.

(8) All the compounds gave satisfactory spectral data.

(9) Determined by derivatizing the amino acid (obtained from deprotecting the BOC group) with 2,3,4,6-tetra-*o*-acetyl-*β*-D-glucopyranosyl isothiocyanate (GITC), using a Waters Symmetry C-18 column (4.6 × 150 mm) and a mixture of acetonitrile (40%) and water (60%, contaning 0.1% TFA) as the mobile phase (isocratic at a flow rate of 1.5 mL/min and UV detector at 254 nm).

20 h: 47% conversion for **7**, 8% conversion for **8**, and 10% conversion for **9**).

In summary, an efficient and practical N-methylation of amino acid derivatives with dimethyl sulfate in the presence of sodium hydride and catalytic amounts of water is described. Reaction of water with sodium hydride generated a highly reactive dry sodium hydroxide, which led to much faster reaction rates than powdered commercially available sodium hydroxide itself. This new water-catalyzed N-methylation of amino acid derivatives promises to be an important addition to the area of water-assisted reactions.[4]

Acknowledgment. We thank Prof. R. K. Boeckman, Jr., of the University of Rochester for helpful discussions, Dr. D. Munch and Ms. Jiayu Li for the chiral HPLC method, and Dr. Wen Shieh for an N-methylation experiment with dimethyl carbonate.

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(10) Enantiomeric enrichment by recrystallizations is known. For example: (a) Jacques, J. Collet, A.; Wilen, S. H. *In Enantiomers, Racemates, and Resolution*; Wiley-Interscience Publication: New York, 1981; pp 369−377. (b) Shieh, W.; Carlson, J. A. *J. Org. Chem.* **1994**, *59*, 5463−5465. (c) Prashad, M.; Har, D.; Chen, L.; Kim, H. Y.; Repic, O.; Blacklock, T. J. *J. Org. Chem.* **2002**, *67*, 6612−6617.