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AN EFFICIENT ONE-STEP REDUCTIVE N-MONOALKYLATION OF α-AMINO ACIDS

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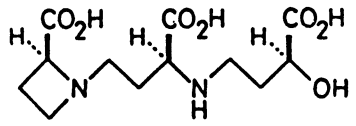
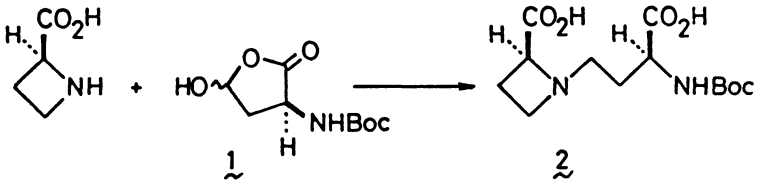
Reactions of protection-free α-amino acids with aldehydes or ketones in the presence of sodium cyanoborohydride afforded the N-monoalkylated amino acids in inorganic salt-free form. Application of this method to the synthesis of N-alkyl derivatives of biologically important amino acids is also described.

Reductive amination employing sodium cyanoborohydride($NaBH_3CN$) played an important role in connecting α-amino acid moieties in the total synthesis of metal chelating novel amino acid, "2'-deoxymugineic acid".[1] However, the N-C bond formation in this synthesis required protection and deprotection of amino, carboxyl, and hydroxyl functions. In the following, we describe an efficient one-step N-alkylation process which requires no blocking.

A trial reaction using L-azetidine-2-carboxylic acid, the aldehyde equivalent 1,[2] and $NaBH_3CN$/MeOH remarkably gave the desired diamino acid 2[3] in almost quantitative yield with no racemization. The possibility of developing this preliminary findings into a general synthesis of N-alkylamino acids was explored. Despite their wide utilities in organic synthesis only a few methods are known for the preparation of such compounds.[1,4,5]



2'-Deoxymugineic acid



1 2

L-Methionine and acetone were employed to optimize the reaction conditions as summarized in Table 1. These results suggested that the reaction proceeded smoothly in methanol probably due to its weakly acidic nature and required theoretically 2/3 equiv. $NaBH_3CN$ (Table 1, entry 2; Eq.1).[6] It should be noted that the N-isopropyl-L-methionine (7) thus produced is inorganic salt-free.[7]

In general, N-alkylation products produced from neutral amino acids (Table 2, entry 7-9) formed a white precipitate during the reaction, which after completion of the reaction was filtered and washed with methanol to afford the pure material. If the product was soluble in the solvent, it was purified by silica gel column chromatography with $CHCl_3$/MeOH. In the case of acidic amino acids (Table 2, entry 11)

Table 1. Reactions of L-methione with acetone[a] in various solvent systems[b]

	Solvent	$NaBH_3CN$(equiv.)	N-Isopropyl-L-methionine(7)[c]
Entry 1	MeOH	0.5	70% yield
2	MeOH	0.7	89%
3	MeOH	1.1	90%
4	H_2O	0.8	49%
5	EtOH	0.8	41%
6	DMF	0.8	0%

[a] 1.1 equiv. of acetone was used. [b] All reactions were carried out under N_2 at room temperature for 16 h. [c] Mp 235-238 °C(decomp); $[\alpha]_D$ +43.2°(c 1.0, 2M HCl); MS (CI method), m/z 192$(M+H)^+$. Found: C, 50.10; H, 8.95; N, 7.33%. Calcd for $C_8H_{17}SO_2$: C,50.25; H, 8.96; N, 7.33%.

$$3L\text{-Met} + 3(CH_3)_2CO + 2NaBH_3CN \xrightarrow{6MeOH} 3N\text{-isopropyl-}L\text{-Met} + 2NaCN + 3H_2O + 2B(OMe)_3 + 3H_2 \quad (1)$$

the reaction required 1.5 equiv. of $NaBH_3CN$, probably to controll the pH; otherwise the reaction was very sluggish and yields were poor.[8]

The typical experimental procedure is as follows. To a suspension of L-methionine(1.49 g, 10 mmol) and $NaBH_3CN$(440 mg, 7 mmol) in MeOH(15 ml) was added isovaleraldehyde(1.18 ml, 11 mmol) at room temperature and the reaction mixture was stirred for 18 h. The white precipitate formed was collected and washed with MeOH to give pure N-isopentyl-L-methionine(5) (1.12 g, 51% yield). The filtrate and washings were combined and concentrated in vacuo to give a crude mixture of mono-alkylated product and starting material, which upon chromatography on SiO_2($CHCl_3$/MeOH) afforded additional 570 mg(25%) of 5.

Attempts to shorten the known multi-step N-monomethylation process[4] using aqueous formaldehyde or paraformaldehyde were not successful and gave an inseparable mixture of N,N-dimethyl, N-methyl derivatives, and the starting amino acid. On the other hand, treatment of L-serine and 2 equiv. of $NaBH_3CN$ with excess

Table 2. Yields for reactions of α-amino acids with aldehydes or ketones

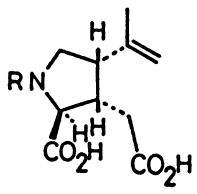
	CH_3CHO[a]	CH_3CH_2CHO[a]	$(CH_3)_2CHCH_2CHO$	PhCHO	$(CH_3)_2CO$	
Entry 7	L-Met. 75% (3)[b,c]	84% (4)	77% (5)	96% (6)	89% (7)	87% (8)
8	L-Phe. 80% (9)[c]	80%(10)	82%(11)	83%(12)	87%(13)	84%(14)
9	L-Val. 67%(15)	69%(16)	79%(17)	82%(18)	81%(19)	85%(20)
10	L-Ser. 51%(21)[c]	60%(22)	66%(23)	73%(24)	96%(25)	64%(26)
11	L-Glu.[d] ——	75%(27)	77%(28)[9]	55%(29)	66%(30)	58%(31)

Unless otherwise stated, reactions were conducted at room temperature under N_2 for 16-20 h with 0.8 equiv. of $NaBH_3CN$. [a] Acetaldehyde or propionaldehyde was added at 0 °C. [b] Compound number of the corresponding N-alkylated amino acid. Physical properties and spectroscopic data were indicated in Table 3.[10] [c] A small amount of N,N-diethyl compound was by-produced and was separated by column chromatography(SiO_2) or recrystallization. [d] 1.5 equiv. of $NaBH_3CN$ was used for the N-alkylation of L-glutamic acid.

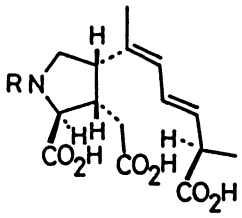
paraformaldehyde afforded N,N-dimethyl-L-serine[11] in excellent yield.

Finally, we have investigated the derivatization by several alkyl groups of the neurotransmitting active amino acids, "kainic acid" and "domoic acid",[12] using this process. The reaction proceeded smoothly without any protection and afforded corresponding N-alkyl derivatives in their salt-free form.[13]

Application of this method to the synthesis of biologically important nitrogen containing natural products and their derivatives is in progress.



R=H, kainic acid
R=CH_3, 32
R=$CH_2CH_2CH_3$, 33



R=H, domoic acid
R=$CH(CH_3)_2$, 34

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References

1) Y. Ohfune, M. Tomita, and K. Nomoto, J. Am. Chem. Soc., 103, 2409 (1981) and references for forming N-alkyl bond in α-amino acid cited therein.
2) Prepared from N-t-butoxycarbonyl-L-allylglycine by ozonolysis.
3) Mp 178-180 °C; $[\alpha]_D$ -31.1°(c 1.0, 2M HCl); ^{1}H NMR(D_2O) δ1.37(9H, s, t-Bu), 4.60(1H, t, J=9 Hz, 2-H); MS(CI method), m/z 229$(M+H-CH_2CH_2CO_2H)^+$.
4) P. Quitt, J. Hellerbach, and K. Vogler, Helv. Chim. Acta, 46, 327 (1963).
5) A similar procedure without description of stoichiometry of reactions, etc., was briefly reported; J. Bastide, C. Coste, and J-L. Marty, C. R. Acad. Sci., Ser. C, 287, 471 (1978); R. E. Jensen, W. T. Zdybak, K. Yasuda, and W. S. Chilton, Biochem. Biophys. Res. Commun., 75, 1066 (1977).
6) J. R. Berschied Jr. and K. F. Purcell, Inorg. Chem., 9, 624 (1970); R. F. Borch, M. D. Bernstein, and H. D. Durst, J. Am. Chem. Soc., 93, 2897 (1971); In general, reductive amination with $NaBH_3CN$ was employed for N-alkylation of sec-amines to t-amines, or prim-amines to t-amines(the sec-amine having a stronger basicity than prim-amine results in further alkylation to give t-amine). In the present case, it is considered that the free carboxyl group of the amino acid plays an important role for N-monoalkylation due to stronger zwitter ion formation in this product compared with the starting amino acid. However, the steric factors involved in this reaction may also be important.
7) This was indicated by TLC behaviour and elementary analytical data.
8) Treatment of the basic amino acid, L-lysine, by this method gave a mixture of N^{α}- and/or N^{ε}-alkylated products.
9) Some plant growth regulatory activity was observed; to be published.
10) Melting point, $[\alpha]_D$, mass spectral data for compounds in Table 2 are listed in Table 3.
11) Mp 183-184 °C(decomp); $[\alpha]_D$ +13.6°(c 1.0, 2M HCl); MS(CI method), m/z 134 $(M+H)^+$. For N,N-dimethylamino acid; W. Kwapiszewski and P. Koziej, Chem. Abstr., 92, 111292r (1980).

Table 3. Analytical data of N-alkylamino acids

N-Alkylamino acid[a]		Mp/°C	$[\alpha]_D$ (2M HCl)	MS(CI method), m/z
N-Ethyl-L-Met	(3)	215-218(decomp)	+45.7°(c 1.0)	178$(M+H)^+$
N-Propyl-L-Met	(4)	233-236(decomp)	+40.7°(c 1.0)	192$(M+H)^+$
N-Isopentyl-L-Met	(5)	220-222(decomp)	+32.5°(c 1.0)	220$(M+H)^+$
N-Benzyl-L-Met	(6)	228-230(decomp)	+24.7°(c 1.0)	240$(M+H)^+$
N-Cyclopentyl-L-Met	(8)	143-146(decomp)	+38.1°(c 1.0)	218$(M+H)^+$
N-Ethyl-L-Phe	(9)	263-268(subl)	+33.3°(c 1.0)	194$(M+H)^+$
N-Propyl-L-Phe	(10)	>270	+31.2°(c 1.0)	208$(M+H)^+$
N-Isopentyl-L-Phe	(11)	239	+31.3°(c 1.0)	236$(M+H)^+$
N-Benzyl-L-Phe	(12)	243	+23.6°(c 1.0)	256$(M+H)^+$
N-Isopropyl-L-Phe	(13)	260-263(subl)	+34.2°(c 1.0)	208$(M+H)^+$
N-Cyclopentyl-L-Phe	(14)	245-248(decomp)	+37.9°(c 1.0)	234$(M+H)^+$
N-Ethyl-L-Val	(15)	235-238(subl)	+28.8°(c 1.0)	146$(M+H)^+$
N-Propyl-L-Val	(16)	235-238(subl)	+24.0°(c 1.0)	160$(M+H)^+$
N-Isopentyl-L-Val	(17)	237-239(subl)	+21.0°(c 1.0)	188$(M+H)^+$
N-Benzyl-L-Val	(18)	252-255(subl)	+14.1°(c 1.0)	208$(M+H)^+$
N-Isopropyl-L-Val	(19)	218-220(subl)	+33.2°(c 1.0)	160$(M+H)^+$
N-Cyclopentyl-L-Val	(20)	217-222(subl)	+21.7°(c 1.0)	186$(M+H)^+$
N-Ethyl-L-Ser	(21)	172-175(decomp)	+13.6°(c 1.0)	134$(M+H)^+$
N-Propyl-L-Ser	(22)	229-231(decomp)	+13.7°(c 1.0)	148$(M+H)^+$
N-Isopentyl-L-Ser	(23)	216-218(decomp)	+10.8°(c 1.0)	176$(M+H)^+$
N-Benzyl-L-Ser	(24)	220-222(decomp)	+6.8°(c 1.0)	196$(M+H)^+$
N-Isopropyl-L-Ser	(25)	251-253(decomp)	+20.5°(c 1.0)	148$(M+H)^+$
N-Cyclopentyl-L-Ser	(26)	258-260(decomp)	+22.9°(c 1.0)	174$(M+H)^+$
N-Propyl-L-Glu	(27)	172-173(decomp)	+22.0°(c 1.1)	172$(M+H-H_2O)^+$
N-Isopentyl-L-Glu	(28)	185-186(decomp)	+15.6°(c 1.1)	200$(M+H-H_2O)^+$
N-Benzyl-L-Glu	(29)	156-157(decomp)	+17.5°(c 1.0)	220$(M+H-H_2O)^+$
N-Isopropyl-L-Glu	(30)	———	+24.3°(c 1.0)	172$(M+H-H_2O)^+$
N-Cyclopentyl-L-Glu	(31)	182-183(decomp)	+20.9°(c 1.1)	198$(M+H-H_2O)^+$

[a] Satisfactory ^1H NMR and IR spectroscopic data as well as elementary analytical data were obtained.

12) Y. Ohfune and M. Tomita, J. Am. Chem. Soc., 104, 3511 (1982).

13) 32: 86% yield; Mp 182-184 °C(decomp); $[\alpha]_D$ +13.6°(c 1.0, 2M HCl); MS(CI method), m/z 228$(M+H)^+$. 33: 82% yield; Mp 214-216 °C(decomp); $[\alpha]_D$ -25.4°(c 1.0, 2M HCl); MS(CI method), m/z 256$(M+H)^+$. 34: Amorphous solid; MS(CI method), m/z 354$(M+H)^+$. Satisfactory ^1H NMR and IR spectroscopic data for 32-34 were obtained.

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