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Amino Acids and Peptides. XLI.^{1, 2} Facile Synthesis of 5-Methyl-2(1*H*)pyrazinone Derivatives from Dipeptidyl Chloromethyl Ketones³

Hiroaki Taguchi, Toshio Yokoi, Masaki Tsukatani and Yoshio Okada*

Faculty of Pharmaceutical Sciences, Kobe-Gakuin University, Nishi-ku, Kobe 651-21, Japan

Abstract: 5-Methyl-2(1H)-pyrazinone derivatives were easily synthesized by short reflux of dipeptidyl enloromethyl ketone hydrochlorides in MeOH.

INTRODUCTION

Some naturally occurring 2(1H)-pyrazinone derivatives possess antibiotic and smooth muscle relaxation activities and its derivatives are key intermediates for preparing mold metabolites which exhibit antibiotic activities against gram-negative micro-organisms.⁴ It is also well known that 2(1H)-pyrazinones can be easily converted to the corresponding pyrazinethiols by 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent).⁵ Therefore, pyrazinone derivatives are useful intermediates of acyloxypyrazines⁶ and acylthiopyrazines,⁷ which are convenient acylating agents for amines, alcohols and phenols. Therefore, great efforts have been directed toward development of synthetic methods of 2(1H)-pyrazinone derivatives and various kinds of synthetic procedures were developed. Although 2(1H)-pyrazinone derivatives were prepared by condensation of 1,2-dicarbonyl compounds with amino acid amides⁸ or by hydrolysis of the corresponding methoxypyrazine derivatives, 6, 9 which were prepared from the corresponding chloride^{10, 11} and sodium methoxide, each method has some problems to be solved. For examples, cyclization reaction should be carried out under the milder condition with high yield, and the desired substituents should be introduced at position 3 and 6 easily. Therefore, the development of more convenient synthetic procedure of 2(1H)-pyrazinone derivatives has been required. Previously, we have reported that 5-methyl-2(1H)-pyrazinone derivatives were obtained from dipeptidyl chloromethyl ketones during acid hydrolysis (6N HCl, 110°C, 20h).¹² It was revealed that the above cyclized derivatives existed in pyrazinone derivatives rather than pyrazinol derivatives judging from data of NMR.¹² Therefore, we considered that this cyclization reacion might be applied to novel synthetic method of pyrazinone derivatives, and tried to optimize the reaction condition. This paper deals with a simple and convenient synthetic procedure of 5-methyl-2(1H)-pyrazinone derivatives.

RESULTS AND DISCUSSION

In order to assess the new synthetic procedure of 5-methyl-2(1*H*)-pyrazinone derivatives from dipeptidyl chloromethyl ketones, various kinds of Boc-NH-CH(R₁)-CONH-CH(R₂)-COCH₂Cl (1) were prepared by the coupling of Boc-NH-CH(R₁)-COOH and H₂N-CH(R₂)-COCH₂Cl¹³ by mixed anhydride method¹⁴ according

to Scheme 1. First of all, Boc-Phe-Ala-CH₂Cl was converted to the corresponding 3-benzyl-5, 6-dimethyl-2(1H)-pyrazinone (**3a**) under the condition of acid hydrolysis (6N HCl, 110°C, 20h).¹³ Although Boc-Phe-Ala-CH₂Cl was converted to **3a** with low yield of production of the corresponding amino acid residue (Phe) under



Scheme 1

the above condition, the yield of **3a** was very low presumably due to the degradation of **3a** formed. Therefore, the rate of the decomposition of **3a** during acid hydrolysis(6N HCl, 110°C) was examined by HPLC. As shown in Fig. 1, the peak corresponding to **3a** was disappeared after 48h. In order to avoid the decomposition of 5-methyl-2(1*H*)-pyrazinone derivative formed, water as solvent was substituted with MeOH, and we further studied the yield of **3a** from Boc-Phe-Ala-CH₂Cl under various conditions such as in 6N HCl, 1N HCl and 3N HCl/MeOH and HCl-H-Phe-Ala-CH₂Cl in MeOH. The results are summarized in Table 1. From the Table 1, it can be concluded that the condition (HCl-H-Phe-Ala-CH₂Cl in MeOH) is the most favorable to cyclize dipeptidyl chloromethyl ketone to **3a**.



Fig. 1 Decomposition of 3-Benzyl-5,6-dimethyl-2(1H)-pyrazinone(3a) in 6N HCl

Table 1. Formation of 3-Benzyl-5,6-dimethyl-2(1H)-pyrazinone under Various Conditions

Starting material	Condition*	(%)Yield **
Boc-Phe-Ala-CH ₂ Cl	6N HCl	29.3
	1N HCl	31.0
	3N HCl/MeOH	62.9
HCl•H-Phe-Ala-CH ₂ Cl	МеОН	65.3

reflux for 2h isolated yield **

Products		1 ₀ ^{R1}	(%)Yield *	M.p.(°C)
	R ₁	R ₂		
3a	Bzl	Ме	65.3	161-162
3b	Et	iBu	89.9	109-100
3c	iPr	iBu	88.0	166-167
3d	Pr	iBu	78.6	88-89
3e	iBu	iBu	74.2	132-134
3f	sec-Bu	iBu	58.5	111-112
3g	Bu	iBu	93.4	92-93
3h	Me	Bzl	75.4	154-155
3i	Et	Bzl	56.7	169-170
3ј	i Pr	Bzl	67.1	214-215
3k	Pr	Bzl	60.3	152-154
31	i Bu	Bzl	67.5	161-163
3m	sec-Bu	Bzl	72.0	177-178
3n	Bu	Bzl	93.0	145-146
30	н	iBu	90.6	128-130

Table 2. Formation of 5-Methyl-2(1H)-pyrazinone Derivatives from Dipeptidyl Chloromethyl Ketones.

* isolated yield

Next, in order to examine whether the distance between the amino group and carbonyl group of chloromethyl ketone moiety of dipeptidyl chloromethyl ketone affects the yield of 5-methyl-2(1*H*)-pyrazinone derivatives or not, stereoisomers of Boc-Phe-Leu-CH₂Cl (D-L, L-D, D-D) were prepared in the same manner as described for the synthesis of Boc-Phe-Leu-CH₂Cl.¹³ They were converted to the corresponding 2(1*H*)-pyrazinone derivative under the same condition. The yield of 2(1H)-pyrazinone derivative in each case was similar to that of L-L compound, ¹³ indicating that the distance between the amino group and carbonyl group of chloromethyl ketone moiety of dipeptidyl chloromethyl ketone was not related to reactivity of this cyclization reaction. These results show that racemic amino acid can be employed for preparing dipeptidyl chloromethyl ketone as starting material for 2(1*H*)-pyrazinone derivative. On the basis of the above studies, 2(1*H*)-pyrazinone derivatives (**3b-30**) were prepared by refluxing of the MeOH solution of the corresponding dipeptidyl chloromethyl ketone hydrochloride with fairly high yield. Yields and mps are summarized in Table 2.

Next, in order to examine the effect of chloride atom in dipeptidyl chloromethyl ketone on this cyclization reaction, we synthesized Boc-Phe-Leu-CH3 from Boc-Phe-Leu-CH2Cl by catalytic hydrogenation (Scheme 2).





It was treated with 6N HCl at 110°C for 20h to afford phenylalanine residue in an yield of 75% and pyrazinone derivative was not isolated. Then, H-Phe-Leu-CH₃·HCl in MeOH was refluxed for 2h to give the corresponding pyrazinone derivative in an yield of 65%, which was identified with 3-benzyl-5-methyl-6-isobutyl-2(1*H*)-pyrazinone¹² derived from H-Phe-Leu-CH₂Cl·HCl using NMR, MS and IR. The differences in reactivity between chloromethyl ketone derivative and methyl ketone derivative might be explained as follows: 1) Electrophilicity of carbonyl group of chloromethyl ketone is higher than that of methyl ketone. 2) The formation of stable pyrazinone derivative from dipeptidyl chloromethyl ketone derivative by leaving chloride anion is much easier than that from methyl ketone derivative, in which pyrazinone derivative might be formed oxidatively in the presence of oxygen more slowly than from the corresponding chloromethyl ketone derivative.

Finally it will be concluded that this novel method can afford 2(1H)-pyrazinone derivatives substituted at the position 3 and 6 (R₁ and R₂, Scheme 1) with the desired alkyl groups in high yield, so far examined, therefore, this simple and convenient synthetic procedure is a recommendable one.

EXPERIMENTAL SECTION

Mps were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were measured with an automatic polarimeter, model DIP-360 (Japan Spectroscopic Co.) and the [α]D values are given in 10⁻¹deg cm² g⁻¹. Amino acid compositions of hydrolysates (6N HCl, 110°C, 20h) were determined with an amino acid analyzer, K-202 SN (Kyowa Seimitu Co.). ¹H (400, 500MHz) and ¹³C (100, 125MHz) NMR spectra were recorded either on a Bruker AM400 or a ARX500 spectrometer. Chemical shift values are expressed as ppm down field from tetramethylsilane used as an internal standard (δ -value). J values are given in Hz. Attribution of ¹³C signals were made also with the aid of DEPT experiments, and multiplicities are indicated by *p* (primary), *s* (secondary), *t* (tetriary) or *q* (quaternary). Mass spectra were measured with a Hitachi M-2000 mass spectrometer using EI technique. On HPLC analysis, solvent gradient for analytical separation and coinjection was run at 1 ml/min as follows: cluent A, H₂O/0.05% TFA; cluent B, CH₃CN/0.05% TFA; isocratic 80% A for 5 min , 20 min linear gradient to 20% A, isocratic 20% A for 5min, 10 min linear gradient to initial conditions; column: Waters Nova-Pak C18 (3.9 x 150 mm); retention time was reported as *t*_R. TLC was conducted on precorted Kiesegel 60 F254 (Art. 5715; Merck) with the following solvent system: (A) CHCl₃-AcOEt-EtOH (30:19:1 v/v), (B) CHCl₃-MeOH (19:1 v/v), (C) AcOEt-hexane (1:2 v/v), (D) CHCl₃-MeOH-AcOH (90:8:2 v/v), (E) AcOEt-hexane (2:1 v/v) and the Rf values were reported as Rf(A), Rf(B), Rf(C), Rf(D) and Rf(E), respectively.

Optimization of cyclization reaction condition

1) Synthesis of Boc-Phe-Ala-CH₂Cl and H-Phe-Ala-CH₂Cl•HCl

Boc-Phe-Ala-CH₂Cl A mixed anhydride [prepared from Boc-Phe-OH (2.4 g, 9.0 mmol), Et₃N (1.4 ml, 9.9 mmol) and isobutyl chloroformate (1.2 ml, 9.0 mmol) as usual] in THF (100 ml) was added to an ice-cold solution of H-Ala-CH₂Cl•HCl [prepared from Boc-Ala-CH₂Cl¹⁵ (1.0 g, 3.4 mmol) and 5.1 N HCl/dioxane (7.4 ml, 54.0 mmol) as usual] in DMF (100 ml) containing Et₃N (1.4 ml, 9.9 mmol). The reaction mixture was stirred at 0°C for 1h and then at room temperature overnight. After removal of the solvent, the residue was extracted with AcOEt. The extract was washed with 10% citric acid, 5% NaHCO₃ and water, dried over Na₂SO₄ and evaporated down. Petroleum ether was added to the residue to afford crystals, which were collected by filtration and recrystallized from EtOH, yield 2.4 g (72.4%), mp 123-127°C, [α]D²⁵ -34.5° (c=1.0, MeOH), Rf(D) 0.71, Rf(B) 0.46. Anal. Calcd for C18H₂₅ClN₂O₄: C, 58.6; H, 6.83; N, 7.59. Found: C, 58.3; H, 6.85; N, 7.54.

H-Phe-Ala-CH₂Cl•*HCl* A solution of Boc-Phe-Ala-CH₂Cl(0.5 g, 1.4 mmol) in 5.1N HCl/dioxane(1.4 ml, 7.0 mmol) was kept at room temperature for 1h. Ether was added to the solution to form precipitate, which was collected by filtration and dried over KOH pellets *in vacuo*, yield 0.4 g (93.7%), mp 135-137°C, Rf(D) 0.1. *Anal.* Calcd for C₁₃H₁₇ClN₂O₂•HCl: C, 51.2; H, 5.94; N, 9.18. Found: C, 51.2; H, 5.91; N, 9.30.

2)Synthesis of 3-benzyl-5, 6-dimethyl-2(1H)-pyrazinone(3a) from Boc-Phe-Ala-CH₂Cl and H-Phe-Ala-CH₂Cl•HCl under various conditions.

i) From Boc-Phe-Ala-CH₂Cl under various acidic conditions A solution of Boc-Phe-Ala-CH₂Cl (0.6 g, 1.63 mmol) in acidic solvent (6N HCl , 3N HCl/MeOH or 1N HCl) (4 ml each) was refluxed for 2h. After removal of the solvent, the residue was extracted with CHCl₃. The extract was washed with water, dried over MgSO4 and evaporated down. Petroleum ether was added to the residue to afford crystals, which were collected by filtration and recrystallized from EtOH, mp 161-162°C, Rf(B) 0.46, MS m/z: 214 M⁺. ¹H NMR (CDCl₃ 400MHz) δ : ppm 13.5 (1H, brs, NH), 7.40-7.12 (5H, m, 3-CH₂-ph), 4.01 (2H, s, 3-CH₂-ph), 2.24 (3H, d, J=6.0, 6-CH₃), 2.18 (3H, s, 5-CH₃), ¹³C NMR (CDCl₃ 100MHz) δ : ppm 157.6 (q, C-2), 153.8 (q, C-3), 138.2 (q, C-1), 131.7 (q, C-6), 129.9 (q, C-5), 129.2 (t, C-3', 5'), 128.1 (t, C-2', 6'), 126.2 (t, C-4'), 39.3 (s, 6-CH₂-ph), 18.7 (p, 5-CH₃), 15.9 (p, 6-CH₃). Anal. Calcd for C₁₃H₁₄N₂O: C, 72.9 H, 6.59; N, 13.1. Found: C, 73.0; H, 6.59; N, 13.1. Yields are summarized in Table 1.

ii) From H-Phe-Ala-CH₂Cl in MeOH H-Phe-Ala-CH₂Cl•HCl (0.5 g, 1.64 mmol) was dissolved in MeOH (20ml). The reaction mixture was refluxed for 2 h. After removal of the solvent, the residue was extracted with CHCl₃. The extract was washed with water, dried over MgSO₄ and evaporated down. Petroleum ether was added to the residue to afford crystals, which were collected by filtration and recrystallized from EtOH, mp 161-162°C. Yield is shown in Table 1.

Studies on decomposition of **3a** during acid hydrolysis

3a (50 mg, 0.23 mmol) was dissolved in 6N HCl (2 ml). The reaction mixture was refluxed. An aliquot (0.05 ml) was taken periodically and diluted with MeOH (0.3 ml), and 0.01 ml of the diluted solution was analyzed with HPLC apparatus. The peak areas corresponding to 3-benzyl-5, 6-dimethyl-2(1H)-pyrazinone was plotted as a function of time (0.5, 1, 2, 6, 12, 24, 48h). The results is shown in Fig. 1.

Studies on the effect of diastereoisomer on cyclization reaction

Boc-D-Leu-CH2C1 Diazomethane [prepared from nitrosomethyl urea (14.2 g, 0.14 mol)] in ether (100 ml) was added to a mixed anhydride [prepared from Boc-D-Leu-OH (8.0 g, 34.6 mmol), Et3N (4.2 ml, 30 mmol) and isobutyl chloroformate (4.5 ml, 34.6 mmol) as usual] in THF (150 ml) at -15°C and the reaction mixture was stirred at 4°C overnight. Then 7.6N HCl/dioxane (18.4 ml, 0.14 mol) was added to the reaction mixture at 0°C, and the resultant solution was stirred at 0°C for 3h. After neutralization of the solution with Et3N and removal of the solvent, the residue was extracted with AcOEt. The extract was washed with 10% citric acid, 5% NaHCO3 and water, dried over Na2SO4 and evaporated down. Hexane was added to the residue to afford crystals, which were collected by filtration and recrystallized from EtOH, yield 5.97 g (63.3%), mp 49-50°C, [α]D²⁵ +50.9°(c=1.0, MeOH), Rf(B) 0.84. Anal. Calcd for C₁₂H₂₂ClNO₃: C, 54.6; H, 8.41; N, 5.31. Found: C, 54.3; H, 8.49; N, 5.33.

1) General procedure for the synthesis of diastereoisomers of Boc-Phe-Leu-CH₂Cl¹³

Boc-Phe-DLeu-CH₂Cl A mixed anhydride [prepared from Boc-Phe-OH (0.64 g, 2.5 mmol), NMM (0.33 ml, 3.0 mmol) and isobutyl chloroformate (0.33 ml, 2.5 mmol) as usual] in THF (30 ml) was added to an ice-cold solution of H-D-Leu-CH₂Cl•HCl [prepared from Boc-D-Leu-CH₂Cl (0.66 g, 2.5 mmol) and 5.1N HCl/dioxane (2.9 ml, 15.0 mmol) as usual] in DMF (30 ml) containing NMM (0.33 ml, 3.0 mmol). The reaction mixture was stirred at 0°C for 1h and then at room temperature overnight. After removal of the solvent, the residue was extracted with AcOEt. The extract was washed with 10% citric acid, 5% NaHCO3 and water, dried over Na₂SO4 and evaporated down. Petroleum ether was added to the residue to afford crystals, which were collected by filtration and recrystallized from EtOH, 0.72 g (69.6%), mp 131-134°C, $[\alpha]D^{25}$ 64.1° (c=1.0, MeOH), Rf(B) 0.97, Rf(D) 0.69. Anal. Calcd for C₂₁H₃₁ClN₂O4: C, 61.4; H, 7.60; N, 6.81. Found: C, 61.4; H, 7.73; N, 6.90.; D-1: Yield 0.7 g (67.2%), mp 126-128°C, $[\alpha]D^{25}$ -75.2° (c=1.0, MeOH), Rf(B) 0.97, Rf(D) 0.71. Anal. Calcd for C₂₁H₃₁ClN₂O4: C, 61.4; H, 7.60; N, 6.81. Found: C, 61.6; H, 7.61; N, 6.91.; D-D: Yield 0.64 g (65.2%), mp 153-155°C, $[\alpha]D^{25}$ 51.3° (c=1.0, MeOH), Rf(B) 0.9, Rf(D) 0.76. Anal. Calcd for C₂₁H₃₁ClN₂O4: C, 61.4; H, 7.46; N, 6.83.

2) Evaluation of yield of 3-benzyl-5-methyl-6-isobutyl-2(1H)-pyrazinone from diastereoisomeric dipeptidyl chloromethyl ketones

Each diastereoisomeric dipeptidyl chloromethyl ketone hydrochloride[prepared from 1.-L, ¹³ D-L, L-D or D-D, (0.82 g, 2.0 mmol) and 5.1N HCl/dioxane(1.96 ml, 10.0 mmol) as usual] was dissolved in MeOH(50 ml). The reaction mixture was refluxed for 2 h. After removal of the solvent, the residue was extracted with CHCl3. The extract was washed with water, dried over MgSO4 and evaporated down. Petroleum ether was added to the residue to afford 3-benzyl-5-methyl-6-isobutyl-2(1H)-pyrazinone¹² as crystals, which were collected by filtration and recrystallized from EtOH. Yields, from 1.-L: 65%; D-L: 70%; 1-D: 62% and D-D: 73%.

General procedure for the synthesis of dipeptidyl chloromethyl ketone derivatives

A mixed anhydride [prepared from Boc protected amino acid (5.0 mmol), NMM or Et3N (5.5 mmol) and isobutyl chloroformate (5.0 mmol) as usual] in THF (60 ml) was added to an ice-cold solution of H-Leu-CH₂Cl•HCl or H-Phe-CH₂Cl•HCl [prepared from Boc-Leu-CH₂Cl or Boc-Phe-CH₂Cl (5.0 mmol) and 5.1 N HCl/dioxane (30.0 mmol) as usual] in DMF (60 ml) containing NMM or Et3N (5.5 mmol). The reaction mixture was stirred at 0^oC for 1h and then at room temperature overnight. After removal of the solvent, the residue was extracted with AcOEt. The extract was washed with 10% citric acid, 5% NaHCO₃ and water, dried over Na₂SO₄ and evaporated down. The residue was purified by silica-gel column chromatography or recrystallization.

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Boc-Gly-Leu-CH₂Cl Recrystallized from EtOH, $[\alpha]D^{25}$ -60.0°(c=1.0, MeOH), Rf(D) 0.61, ¹H NMR (CDCl₃ 500MHz) & ppm 6.84 (1H, brs), 5.33 (1H, brs), 4.81 (1H, brs), 4.32 (1H, d, J=16.1), 4.26 (1H, d, J=16.1), 3.84 (1H, dd, J=5.4, 16.6), 3.77 (1H, dd, J=5.8, 16.6), 1.66 (2H, m), 1.53-1.46 (10H, m), 0.96 (3H, d, J=5.0), 0.95 (3H, d, J=6.1), ¹³C NMR (CDCl₃ 125MHz) & ppm 201.5 (q), 170.0 (q), 156.3 (q), 80.6 (q), 54.6 (t), 46.7 (s), 44.4 (s), 40.0 (s), 28.3 (p), 24.9 (s) 23.2 (p) 21.5 (p). Anal. Calcd for C_{14H25ClN2O4}: C, 52.4; H, 7.85; N, 8.73. Found: C, 52.3; H, 8.13; N, 8.64.

Boc-DL-Abu-Leu-CH₂Cl Work up followed by silica-gel column chromatography eluting with 1:2 v/v AcOEt-hexane, yield 0.42 g (62.5%), oil, Rf(C) 0.5.

Boc-Val-Leu-CH₂Cl Recrystallized from AcOEt, yield 0.75 g (45.8%), mp 139-141°C, $[\alpha]D^{25}$ -67.8°(*c*=1.0, MeOH), Rf(A) 0.83. *Anal.* Calcd for C₁₇H₃₁ClN₂O4: C, 56.3; H, 8.61; N, 7.72. Found: C, 56.2; H, 8.82; N, 7.65.

Boc-DL-Nva-Leu-CH₂Cl Recrystallized from EtOH, yield 1.2 g (73.7%), mp 79-81°C, Rf(A) 0.84. *Anal.* Calcd for C₁₇H₃₁ClN₂O4: C, 56.3; H, 8.61; N, 7.72. Found: C, 56.3; H, 8.75; N, 7.72.

Boc-Ile-Leu-CH2Cl Recrystallized from AcOEt, yield 0.61 g (46.4%), mp 142-143°C, $[\alpha]D^{25}$ -70.4°(c=1.0, MeOH), Rf(A) 0.84. Anal. Calcd for C₁₈H₃₃ClN₂O₄: C, 57.4; H, 8.82; N, 7.43. Found: C, 57.6; H, 8.92; N, 7.54.

Boc-Leu-CH2Cl Recrystallized from EtOH, yield 0.52 g (39.5%), mp 135-137°C, $[\alpha]D^{25}$ -79.1°(c=1.0, MeOH), Rf(A) 0.76. Anal. Calcd for C18H33ClN2O4: C, 57.4; H, 8.82; N, 7.43. Found: C, 57.1; H, 8.85; N, 7.31.

Boc-DL-Nle-Leu-CH₂Cl Recrystallized from EtOH, yield 0.54 g (58.6%), mp 86-88°C, Rf(A) 0.85. *Anal.* Calcd for C₁₈H₃₃ClN₂O4: C, 57.4; H, 8.82; N, 7.43. Found: C, 57.1; H, 8.66; N, 7.36.

Boc-Ala-Phe-CH2Cl Recrystallized from EtOH, yield 0.91 g (70.5%), mp 133-134°C, $[\alpha]D^{25}$ -101.1°(*c*=1.0, MeOH), Rf(B) 0.63, Rf(D) 0.81. *Anal.* Calcd for C₁₈H₂₅ClN₂O4: C, 58.6; H, 6.83; N, 7.59. Found: C, 58.7; H, 6.98; N, 7.58.

Boc-DL-Abu-Phe-CH₂Cl Recrystallized from EtOH, yield 0.71 g (65.4%), mp 158-159°C, Rf(D) 0.59. *Anal.* Calcd for C_{19H₂₇ClN₂O₄: C, 59.6; H, 7.14; N, 7.19. Found: C, 59.6; H, 7.11; N, 7.32.}

Boc-Val-Phe-CH2Cl Recrystallized from EtOH, yield 0.4 g (48.0%), mp 161-169°C, $[\alpha]D^{25}$ -90.4° (c=1.0, MeOH), Rf(C) 0.41. Anal. Calcd for C20H29CIN2O4: C, 60.5; H, 7.36; N, 7.06. Found: C, 60.4; H, 7.54; N, 7.04.

Boc-DL-Nva-Phe-CH₂Cl Recrystallized from EtOH, yield 0.55 g (61.2%), mp 138-140°C, Rf(D) 0.69. *Anal.* Calcd for C₂₀H₂₉ClN₂O₄: C, 60.5; H, 7.36; N, 7.06. Found: C, 60.3; H, 7.42; N, 6.79.

Boc-Ile-Phe-CH₂Cl Recrystallized from EtOH, yield 0.8 g (57.4%), mp 156-157°C, $[\alpha]D^{25}$ -87.8° (c=1.0, MeOH), Rf(A) 0.89. Anal. Calcd for C₂₁H₃₁ClN₂O4: C, 61.4; H, 7.60; N, 6.82. Found: C, 61.3; H, 7.68; N, 6.58.

Boc-Leu-Phe-CH₂Cl Recrystallized from EtOH, yield 0.83 g (66.7%), mp 138-139°C, $[\alpha]D^{25}$ -84.8°(*c*=1.0, MeOH), Rf(A) 0.85. *Anal.* Calcd for C₂₁H₃₁ClN₂O₄: C, 61.4; H, 7.60; N, 6.82. Found: C, 61.2; H, 7.73; N, 6.81.

Boc-DL-Nle-Phe-CH₂Cl Recrystallized from EtOH, yield 0.625 g (66.9%), mp 121-122°C, Rf(E) 0.85. *Anal.* Calcd for C₂₁H₃₁ClN₂O₄: C, 61.4; H, 7.60; N, 6.82. Found: C, 61.1; H, 7.58; N, 6.78. General procedure for the synthesis of 5-methyl-2(1H)-pyrazinone derivatives (**3b**-**3**o) Dipeptidyl chloromethyl ketone hydrochloride [prepared from Boc protected dipeptidyl chloromethyl ketone (0.5 mmol) and 5.4 N HCl/dioxane(3.0 mmol) as usual] was dissolved in MeOH (100 ml). The reaction mixture was refluxed for 2 h. After removal of the solvent, the residue was extracted with CHCl3. The extract was washed with water, dried over MgSO4 and evaporated down. Petroleum ether was added to the residue to afford crystals, which were collected by filtration. The crude product was purified by recrystallization from appropriate solvent as described below. Yields and mps are summarized in Table 2.

3-Ethyl-5-methyl-6-isobutyl-2(1H)-pyrazinone(3b) Recrystallized from acetone, Rf(A) 0.51, $t_{\rm R}$ 9.98 min, MS m/z: 194 M⁺. ¹H NMR (CDCl₃ 400MHz) δ : ppm 13.3 (1H, brs, NH), 2.80 (2H, q, J=7.5, 3-CH₂CH₃), 2.44 (2H, d, J=7.4, 6-CH₂CH(CH₃)₂), 2.29 (3H, s, 5-CH₃), 2.04 (1H, nonet, J=6.8, 6-CH₂CH(CH₃)₂), 1.26 (3H, t, J=7.5, 3-CH₂CH₃), 0.98 (6H, d, J=6.6, 6-CH₂CH(CH₃)₂), ¹³C NMR (CDCl₃ 100MHz) δ : ppm 157.5 (q, C-2), 157.0 (q, C-3), 134.0 (q, C-6), 129.6 (q, C-5), 38.9 (s, 6-CH₂CH(CH₃)₂), 28.9 (t, 6-CH₂CH(CH₃)₂), 26.2 (s, 3-CH₂CH₃), 22.3 (p, 6-CH₂CH(CH₃)₂), 18.8 (p, 5-CH₃), 11.2 (p, 3-CH₂CH₃). Anal. Calcd for C₁₁H₁₈N₂O•H₂O: C, 67.1; H, 9.42; N, 14.2.

3-Isopropyl-5-methyl-6-isobutyl-2(1H)-pyrazinone(3c) Recrystallized from acetone, Rf(A) 0.57, tR 18.83 min, MS m/z: 208 M⁺. ¹H NMR (CDCl3 400MHz) δ : ppm 13.4 (1H, brs, NH), 3.37 (1H, heptet, J=6.9, 3-CH(CH3)2), 2.41 (2H, d, J=7.4, 6-CH2CH(CH3)2), 2.28 (3H, s, 5-CH3), 2.05 (1H, nonet, J=6.8, 6-CH2CH(CH3)2), 1.25 (6H, d, J=6.9, 3-CH(CH3)2), 0.97 (6H, d, J=6.6, 6-CH2CH(CH3)2), ¹³C NMR (CDCl3 100MHz) δ : ppm 159.8 (q, C-2), 157.2 (q, C-3), 133.7 (q, C-6), 129.5 (q, C-5), 38.9 (s, 6-CH2CH(CH3)2), 30.6 (t, 3-CH(CH3)2), 28.8 (t, 6-CH2CH(CH3)2), 22.3 (p, 6-CH2CH(CH3)2), 20.0 (p, 3-CH(CH3)2), 18.9 (p, 5-CH3). Anal. Calcd for C12H20N2O: C, 69.2 H, 9.68; N, 13.5. Found: C, 68.9; H, 9.95; N, 13.4.

3-Propyl-5-methyl-6-isobutyl-2(1H)-pyrazinone(3d) Recrystallized from acetone, Rf(A) 0.5 , t_R 15.67 min, MS m/z: 208 M⁺. ¹H NMR (CDCl3 400MHz) δ : ppm 13.4 (1H, brs, NH), 2.74 (2H, t, J=7.7, 3-CH₂CH₂CH₃), 2.43 (2H, d, J=7.3, 6-CH₂CH(CH₃)₂), 2.29 (3H, s, 5-CH₃), 2.05 (1H, nonet, J=6.8, 6-CH₂CH(CH₃)₂), 1.74 (2H, hextet, J=7.7, 3-CH₂CH₂CH₃), 1.03-0.97 (9H, m, 3-CH₂CH₂CH₂CH₃, 6-CH₂CH(CH₃)₂), ¹³C NMR (CDCl₃ 100MHz) δ : ppm 157.7 (q, C-2), 156.1 (q, C-3), 134.1 (q, C-6), 129.6 (q, C-5), 38.9 (s, 6-CH₂CH(CH₃)₂), 35.0 (s, 3-CH₂CH₂CH₃), 28.8 (t, 6-CH₂CH(CH₃)₂), 22.2 (p, 6-CH₂CH(CH₃)₂), 20.6 (s, 3-CH₂CH₂CH₃), 18.8 (p, 5-CH₃), 14.1 (p, 3-CH₂CH₂CH₃). Anal. Calcd for C₁₂H₂₀N₂O: C, 69.2 H, 9.68; N, 13.5. Found: C, 68.9; H, 9.95; N, 13.4.

3,6-Diisobutyl-5-methyl-2(1H)-pyrazinone(3e) Recrystallized from acetone, Rf(A) 0.58, Rf(D) 0.72, tR 18.54 min, MS m/z: 222 M⁺. ¹H NMR (CDCl₃ 400MHz) δ : ppm 13.2 (1H, brs, NH), 2.65 (2H, d, J=7.2, 3-CH₂CH(CH₃)₂), 2.42 (2H, d, J=7.4, 6-CH₂CH(CH₃)₂), 2.29 (3H, s, 5-CH₃), 2.22 (1H, nonet, J=6.8, 3-CH₂CH(CH₃)₂), 2.06 (1H, nonet, J=6.7, 6-CH₂CH(CH₃)₂), 0.97 (6H, d, J=6.6, 6-CH₂CH(CH₃)₂), 0.96 (6H, d, J=6.7, 3-CH₂CH(CH₃)₂), ¹³C NMR (CDCl₃ 100MHz) δ : ppm 157.8 (q, C-2), 155.7 (q, C-3), 134.1 (q, C-6), 129.5 (q, C-5), 41.6 (s, 3-CH₂CH(CH₃)₂), 39.0 (s, 6-CH₂CH(CH₃)₂), 28.8 (t, 6-CH₂CH(CH₃)₂), 27.2 (t, 3-CH₂CH(CH₃)₂), 22.6 (p, 3-CH₂CH(CH₃)₂), 22.3 (p, 6-CH₂CH(CH₃)₂), 18.7 (p, 5-CH₃). Anal. Calcd for C₁₃H₂₂N₂O: C, 70.2; H, 9.97; N, 12.6. Found: C, 70.0; H, 10.0; N, 12.5.

3-sec-Butyl-5-methyl-6-isobutyl-2(1H)-pyrazinone(3f) Recrystallized from acetone, $[\alpha]D^{25}$ +7.2° (c=1.0, MeOH), Rf(A) 0.67, tR 23.70 min, MS m/z: 222 M⁺. ¹H NMR (CDCl3 400MHz) & pm 13.3 (1H, brs, NH), 3.17 (1H, hextet, J=6.9, 3-CH(CH3)CH2CH3), 2.42 (2H, d, J=7.4, 6-CH2CH(CH3)2), 2.28 (3H, s, 5-CH3), 2.06 (1H, nonet, J=6.7, 6-CH2CH(CH3)2), 1.85 (1H, pentet-like, J=7.3, 3-CH(CH3)CH2CH3) 1.55 (1H, pentet-like, J=7.3, 3-CH(CH3)CH2CH3), 1.23 (3H, d, J=6.7, 3-CH(CH3)CH2CH3), 0.98 (6H, d, J=6.6, 6-CH2CH(CH3)2), 0.90 (3H, t, J=7.4, 3-CH(CH3)CH2CH3), ¹³C NMR (CDCl3 100MHz) & ppm 159.3 (q, C-2), 157.3 (q, C-3), 133.6 (q, C-6), 129.6 (q, C-5), 38.9 (s, 6-CH2CH(CH3)2), 37.4 (t, 3-CH(CH3)CH2CH3), 28.8 (t, 6-CH2CH(CH3)2), 27.5 (s, 3-CH(CH3)CH2CH3), 22.3 (p, 6-CH2CH(CH3)2), 18.9 (p, 5-CH3), 15.3 (p, 3-CH(CH3)CH2CH), 12.2 (p, 3-CH(CH3)CH2CH3). Anal. Calcd for C13H22N2O: C, 70.2; H, 9.97; N, 12.6. Found: C, 70.1; H, 9.95; N, 12.4.

3-Butyl-5-methyl-6-isobutyl-2(1H)-pyrazinone(3g) Recrystallized from hexane, Rf(A) 0.64 , t_R 19.36 min, MS m/z: 222 M⁺. ¹H NMR (CDCl3 400MHz) &: ppm 13.3 (1H, brs, NH), 2.77 (2H, t-like, J=7.8, 3-CH₂CH₂CH₂CH₃), 2.43 (2H, d, J=7.4, 6-CH₂CH(CH₃)₂), 2.28 (3H, s, 5-CH₃), 2.05 (1H, nonet, J=6.7, 6-CH₂CH(CH₃)₂), 1.73-1.65 (2H, m, 3-CH₂CH₂CH₂CH₃), 1.43 (2H, hextet, J=7.5, 3-CH₂CH₂CH₂CH₃), 0.98 (6H, d, J=6.6, 6-CH₂CH(CH₃)₂), 0.94 (3H, t, J=7.4, 3-CH₂CH₂CH₂CH₂CH₃), ¹³C NMR (CDCl3 100MHz) &: ppm 157.6 (q, C-2), 156.4 (q, C-3), 134.0 (q, C-6), 129.5 (q, C-5), 39.0 (s, 6-CH₂CH(CH₃)₂), 32.8 (s, 3-CH₂CH₂CH₂CH₃), 29.4 (s, 3-CH₂CH₂CH₂CH₃), 28.8 (t, 6-CH₂CH(CH₃)₂), 22.8 (s, 3-CH₂CH₂CH₃), 22.3 (p, 6-CH₂CH(CH₃)₂), 18.8 (p, 5-CH₃), 13.9 (p, 3-CH₂CH₂CH₂CH₃). Anal. Calcd for C1₃H₂2N₂O: C, 70.2; H, 9.97; N, 12.6. Found: C, 70.0; H, 10.27; N, 12.5.

3, 5-Dimethyl-6-benzyl-2(1H)-pyrazinone(3h) MS m/z: 214 M⁺. ¹H NMR (CDCl₃ 500MHz) δ : ppm 11.3 (1H, brs, NH), 7.34-7.22 (5H, m, CH₂-ph), 3.89 (2H, s, 6-CH₂-ph), 2.41 (3H, s, 3-CH₃), 2.34 (3H, s, 5-CH₃), ¹³C NMR (CDCl₃ 125MHz) δ : ppm 157.0 (q, C-2), 154.4 (q, C-3), 135.8 (q, C-1'), 132.1 (q, C-6), 129.12 (q, C-5), 129.10 (t, C-3', 5'), 128.8 (t, C-2', 6'), 127.4 (t, C-4'), 36.2 (s, 6-CH₂-ph), 19.9 (p, 5-CH₃), 18.7 (p, 5-CH₃). Anal. Calcd for C₁₃H₁₄N₂O: C, 72.9 H, 6.59; N, 13.1. Found: C, 73.1; H, 6.62; N, 13.1.

3-Ethyl-5-methyl-6-benzyl-2(1H)-pyrazinone(3i) Recrystallized from EtOH, Rf(D) 0.77, tR 14.18 min, MS m/z: 228 M⁺. ¹H NMR (CDCl3 400MHz) δ : ppm 12.4 (1H, brs, NH), 7.31-7.23 (5H, m, CH2-ph), 3.89 (2H, s, 6-CH2-ph), 2.78 (2H, q, J=7.5, 3-CH2CH3), 2.35 (3H, s, 5-CH3), 1.24 (3H, t, J=7.5, 3-CH2CH3), 1³C NMR (CDCl3 100MHz) δ : ppm 158.0 (q, C-2), 157.1 (q, C-3), 136.4 (q, C-1⁻), 132.4 (q, C-6), 129.4 (q, C-5), 128.9 (t, C-3⁻, 5⁻), 128.7 (t, C-2⁻, 6⁻), 127.2 (t, C-4⁻), 36.2 (s, 6-CH2-ph), 26.2 (s, 3-CH2CH3), 18.8 (p, 5-CH3), 11.2 (p, 3-CH2CH3). Anal. Calcd for C14H16N2O: C, 73.7; H, 7.06; N, 12.3. Found: C, 73.4; H, 7.20; N, 12.0.

3-Isopropyl-5-methyl-6-benzyl-2(1H)-pyrazinone(3j) Recrystallized from EtOH, Rf 0.8, *t*R 19.30 min, MS m/z: 242 M⁺. *Anal.* Calcd for C15H18N2O: C, 74.4 H, 7.49; N, 11.6. Found: C, 74.4; H, 7.24; N, 11.6.

3-Propyl-5-methyl-6-benzyl-2(1H)-pyrazinone(3k) Recrystallized from acetone, Rf(D) 0.78, $t_{\rm R}$ 17.15 min, MS m/z: 242 M⁺. ¹H NMR (CDCl3 400MHz) δ : ppm 12.9 (1H, brs, NH), 7.29-7.21 (5H, m, CH₂-<u>ph</u>), 3.89 (2H, s, 6-CH₂-ph), 2.73 (2H, t-like, J=7.6, 3-CH₂CH₂CH₃), 2.35 (3H, s, 5-CH₃), 1.71 (2H, hexet, J=7.6, 3-CH₂CH₂CH₃), 0.99 (3H, t, J=7.4, 3-CH₂CH₂CH₃), ¹³C NMR (CDCl3 100MHz) δ : ppm 157.4 (q, C-2), 157.0 (q, C-3), 136.6 (q, C-1'), 132.6 (q, C-6), 129.5 (q, C-5), 128.8 (t, C-3', 5'), 128.7 (t, C-2', 6'), 127.1 (t, C-4'), 36.2 (s, 6-CH₂-ph), 24.9 (s, 3-CH₂CH₂CH₃), 20.5 (s, 3-CH₂CH₂CH₃), 18.9 (p, 5-CH₃), 14.1 (p, 3-CH₂CH₂CH₃). Anal. Calcd for C₁₅H₁₈N₂O: C, 74.4 H, 7.49; N, 11.6. Found: C, 74.2; H, 7.39; N, 11.6.

3-Isobutyl-5-methyl-6-benzyl-2(1H)-pyrazinone(3I) Recrystallized from EtOH, Rf(D) 0.82, t_R 20.03 min, MS m/z: 256 M⁺, ¹H NMR (CDCl₃ 400MHz) δ : ppm 13.2 (1H, brs, NH), 7.32-7.21 (5H, m, CH₂-ph), 3.90 (2H, s, 6-CH₂-ph), 2.65 (2H, d, J=7.2, 3-CH₂CH(CH₃)₂), 2.36 (3H, s, 5-CH₃), 2.20 (1H, nonet, J=6.9, 3-CH₂CH(CH₃)₂), 0.95 (3H, d, J=6.7, 3-CH₂CH(CH₃)₂), ¹³C NMR (CDCl₃ 100MHz) δ : ppm 157.7 (q, C-2), 156.5 (q, C-3), 136.6 (q, C-1'), 132.8 (q, C-6), 129.6 (q, C-5), 128.8 (t, C-3', 5'), 128.7 (t, C-2', 6'), 127.0 (t, C-4'), 41.6 (s, 3-CH₂CH(CH₃)₂), 36.2 (s, 6-CH₂-ph), 27.1 (t, 3-CH₂CH(CH₃)₂), 22.7 (p, 3-CH₂CH(CH₃)₂), 18.9 (p, 5-CH₃). Anal. Calcd for C₁₆H₂₀N₂O: C, 75.0; H, 7.86; N, 10.9. Found: C, 75.2; H, 8.03; N, 10.8.

3-sec-Butyl-5-methyl-6-benzyl-2(1H)-pyrazinone(3m) Recrystallized from EtOH, $[\alpha]D^{25}$ -13.7°(c=1.0, CHCl3), Rf(D) 0.82, tR 20.77 min, MS m/z: 256 M⁺, ¹H NMR (CDCl3 400MHz) δ : ppm 12.4 (1H, brs, NH), 7.30-7.22 (5H, m, CH2-ph), 3.88 (2H, s, 6-CH2-ph), 3.20 (1H, hexet, J=6.9, 3-CH(CH3)CH2CH3), 2.36 (3H, s, 5-CH3), 1.82 (1H, m, 3-CH(CH3)CH2CH3), 1.53 (1H, m, 3-CH(CH3)CH2CH3), 1.20 (3H, d, J=6.9, 3-CH(CH3)CH2CH3), 0.89 (3H, t, J=7.4, 3-CH(CH3)CH2CH3), 1³C NMR (CDCl3 100MHz) δ : ppm 160.4 (q, C-2), 157.0 (q, C-3), 136.5 (q, C-1'), 132.0 (q, C-6), 129.4 (q, C-5), 128.9 (t, C-3', 5'), 128.8 (t, C-2', 6'), 127.1 (t, C-4'), 37.0 (t, 3-CH(CH3)CH2CH3), 36.1 (s, 6-CH2-ph), 27.5 (s, 3-CH(CH3)CH2CH3),

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18.9 (p, 5-CH3), 17.7 (p, 3-CH(CH3)CH2CH3), 12.1 (p, 3-CH(CH3)CH2CH3). Anal. Calcd for C16H20N2O: C, 75.0; H, 7.86; N, 10.9. Found: C, 75.1; H, 7.85; N, 11.0.

Recrystallized from EtOH, Rf(D) 0.67, tR 22.03 min, 3-butyl-5-methyl-6-benzyl-2(1H)-pyrazinone(3n) MS m/z: 256 M⁺, ¹H NMR (CDCl₃ 400MHz) δ: ppm 13.1 (1H, brs, NH), 7.31-7.20 (5H, m, 6-CH₂-<u>ph</u>), CH2CH2CH2CH2CH3), ¹³C NMR (CDCl3 100MHz) & ppm 157.4 (q, C-2), 157.2 (q, C-3), 136.6 (q, C-1'), 132.6 (q, C-6), 129.5 (q, C-5), 128.8 (t, C-3', 5'), 128.7 (t, C-2', 6'), 127.1 (t, C-4'), 36.2 (s, 6-CH2-ph), 32.7 (s, 3-CH2CH2CH2CH3), 29.3 (s, 3-CH2CH2CH2CH3), 22.8 (s, 3-CH2CH2CH2CH3), 18.9 (p, 5-CH3), 14.0 (p, 3-CH2CH2CH2CH2CH3). Anal. Calcd for C16H20N2O: C, 75.0; H, 7.86; N, 10.9. Found: C, 75.1; H, 8.05; N, 10.8.

5-Methyl-6-isobutyl-2(1H)-pyrazinone(30) Recrystallized from EtOH, Rf(B) 0.17, tR 4.0 min, MS m/z: 166 M⁺. ¹H NMR (CDCl₃ 500MHz) δ: ppm 13.5(1H, brs, NH), 8.03(1H, s, 3-H), 2.48(2H, d, J=7.5, 6-CH2CH(CH3)2), 2.32(3H, s, 5-CH3), 2.05(1H, nonet, 6-CH2CH(CH3)2), 1.00(6H, d, J=7.0, 6-CH2CH(CH3)2), 1.00(6H, d, CH₂CH(CH₃)₂), ¹³C NMR (CDCl₃ 125MHz) & ppm 158.4 (q, C-2), 144.3 (q, C-3), 137.0 (q, C-6), 131.5 (q, C-5), 39.2 (s, 6-CH₂CH(CH₃)₂), 28.7 (t, 6-CH₂CH(CH₃)₂), 22.3 (p, 6-CH₂CH(CH₃)₂), 18.8 (p, 5-CH₃). Anal. Calcd for C9H₁₄N₂O: C, 65.0 H, 8.49; N, 16.9. Found: C, 65.0; H, 8.67; N, 16.7.

Boc-Phe-Leu-CH₃ The title compound was prepared from Boc-Phe-Leu-CH₂Cl (0.51 g, 1.24 mmol) by catalytic hydrogenation. After neutralization of the solution with Et3N and removal of Pd and the solvent, hexane was added to the residue to afford crystals, which were collected by filtration and recrystallized from EtOH, yield 456 mg (97.6%), mp 113-114°C, [α]D²⁵ -32.4°(c=0.1, MeOH), Rf(B) 0.46. Anal. Calcd for C₂₁H₃₂N₂O₄: C, 65.4; H, 8.63; N, 7.27. Found: C, 65.5; H, 8.50; N, 7.00, Amino acid analysis: Recovery of Phe was 79.4%.

Synthesis of 3-benzyl-5-methyl-6-isobutyl-2(1H)-pyrazinone ¹² from Boc-Phe-Leu-CH3 H-Val-Leu-CH2Cl+HCl [prepared from Boc-Phe-Leu-CH3 (0.12 g, 0.32 mmol) and 5.0 N HCl/dioxane (0.4 ml, 2.0 mmol) as usual] was dissolved in MeOH (5 ml). The reaction mixture was refluxed for 2 h. After removal of the solvent, the residue was extracted with CHCl3. The extract was washed with water, dried over MgSO4 and evaporated down. Petroleum ether was added to the residue to afford crystals, which were collected by filtration and recrystallized from EtOH, yield 60 mg (73.2%), mp 133-135°C.

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