A NEW ENTRY TO 5-UNSUBSTITUTED 3-ACYLTETRAMIC ACIDS FROM ALDEHYDES [1]

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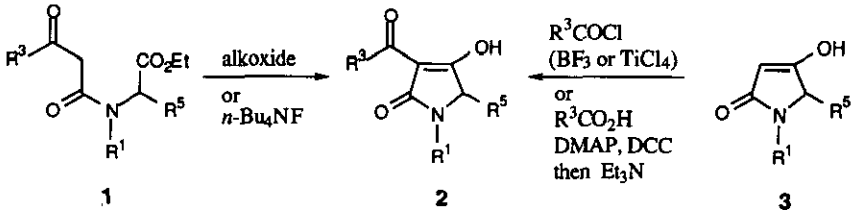
Abstract -- Reaction of aldehydes (*prim*-, *sec*-, and *tert*-) with diazoacetamide (**8**, **9**) of *N*-substituted glycinate in the presence of Zr(IV) chloride in CH_2Cl_2 affords β-keto amides (**11**, **12**) in good to high yields, which on treatment with *n*-Bu_4NF in THF are led to *N*-protected 3-acyltetramic acids (**13**, **14**).

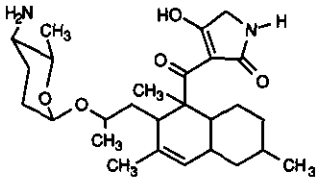
A standard synthetic route to 3-acyltetramic acid structure (**2**) involves as a key step the Dieckmann cyclization of β-keto amide (**1**) of α-amino acid ester (Scheme 1), and this technique has been extensively utilized in the synthesis of a variety of natural and unnatural bioactive tetramic acids.[2,3] However, there is a limitation in this methodology in which it is not feasible to prepare a wide range of R^3 groups in the β-keto amide (**1**). This problem has been partly solved by developement of direct or indirect 3-acylation method of tetramic acids (**3**): 1) BF_3 or $TiCl_4$ catalyzed acylation with acyl chlorides;[4] 2) Et_3N catalyzed O to C acyl migration of *O*-acylates[5] (Scheme 1); and 3) aldol reaction of *O*-methyl derivative and subsequent oxidation-deprotection sequence.[6] Even in these advanced acylation protocols there are serious limitations in introducing α-branched and/or acid-sensitive acyl groups to *5-unsubstituted* tetramic acid (**3**, R^5 = H). These drawbacks in the existing

Scheme 1

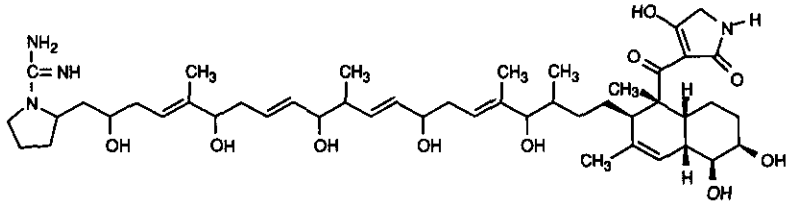


1 **2** **3**

methods should be overcome on planning the synthesis of recently discovered bioactive natural products, BU-4514N (neuritogenic) (**4**)[7] and lydicamycin (antibiotic) (**5**),[8] which are characterized by the presence of *tetramic acid subunit* bearing a sterically crowded acyl group at the 3-position.



BU-4514N (**4**)
(stereochemistry of the aglycone not determined)



Lydicamycin (**5**)
(relative stereochemistry for the hydronapthalene unit)

This paper reports a general synthetic method of *5-unsubstituted* 3-acyltetramic acids that features a new entry *to β-keto amide* (**11**) or (**12**) (Scheme 2) which involves a $ZrCl_4$ catalyzed C-H insertion reaction of aldehydes with diazoacetamide of *N*-protected glycinate.[9] This technique in combination with well-precedented Dieckmann cyclization and deprotection can be utilized in the synthesis of **4** and **5**.

Diazoacetamides (**8** and **9**) of *N*-benzyl glycine esters (**7**) were prepared by reaction of tosylhydrazone of glyoxylic acid chloride (**6**) with **7** in the presence of triethylamine (2 equiv) in dichloromethane (Scheme 2), according to the procedure of House for the preparation of diazoacetic esters.[10,11] We initially attempted the reaction of **8** with hexanal (**10a**) using 3 equiv of **8** and 1 equiv of $ZrCl_4$ as a catalyst in dichloromethane solvent at 0 °C for 0.5 h. From this reaction there was obtained β-keto amide (**11a**) in 79% yield after silica gel chromatography. Use of three-fold excess amount of the diazoamide (**8**) was required for obtaining the *high yield since there was a side reaction* producing $ClCH_2COCH_2CON(Bn)CH_2CO_2CH_3$. Likewise, 2-ethylhexanal (**10b**) and cyclohexanecarboxaldehyde (**10c**) afforded the corresponding keto amides (**11b**) and (**11c**), respectively, in good yields (Table 1). *On the other hand, α-tertiary aldehydes* (**10d,e**) *reacted rather sluggish* under the same conditions, resulting in poor yields of **11d,e** (*ca.* 35%). However, the yields could be greatly improved up to 60-70% by using 2 equiv of the $ZrCl_4$ catalyst . This protocol, which proved quite effective for sterically hindered aldehydes, was successfully employed in the preparation of keto amides (**12d,e**) of

Scheme 2

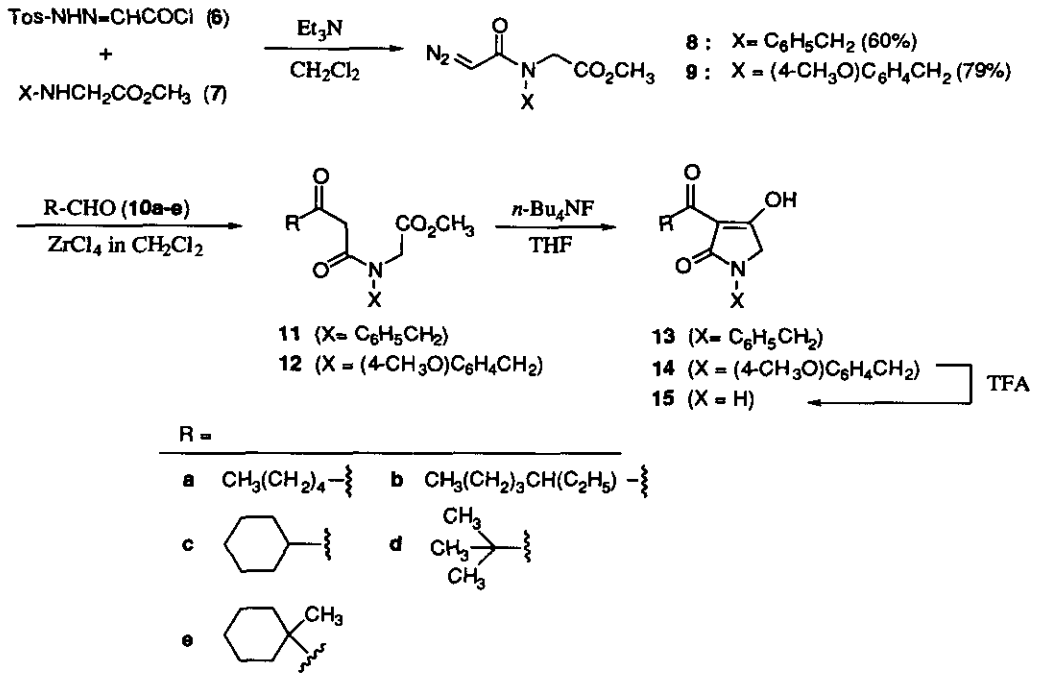


Table 1. Preparation of β-Keto Amides and γ-Unsubstituted α-Acyltetramic Acids

diazoamide[a]	β-keto amide (% yield)	tetramic acid (% yield),	mp or bp (Torr), °C
8	**11a** (79)[b]	**13a** (98)	55-56
8	**11b** (53)[b]	**13b** (97)	*d*
8	**11c** (78)[b]	**13c** (96)	110-112
8	**11d** (31)[b] (62)[c]	**13d** (98)	119 (0.02)
8	**11e** (36)[b] (64)[c]	**13e** (98)	*d*
9	**12d** (61)[c]	**14d** (97)	*d*
9	**12e** (78)[c]	**14e** (96)	*d*

a) All reactions with aldehydes were performed in dichloromethane at 0 °C for 0.5 - 1 h using 3 equiv of diazoacetamide, and all keto amide products were obtained as a pale yellow oil. *b*) 1 equiv of $ZrCl_4$ was used. *c*) 2 equiv of $ZrCl_4$ was used. *d*) This product was obtained as an oil.

methyl *N*-(4-methoxybenzyl)glycinate.

Dieckmann cyclization of the β-ketoamidoacetates was nicely effected by the method of Ley.[2a] Thus treatment of **11a-e** and **12d,e** with 2 equiv of *n*-Bu_4NF in THF at room temperature afforded the corresponding *N*-protected tetramic acids (**13a-e** and **14d,e**) in nearly quantitative yields. The *N*-4-methoxybenzyl protecting

group in **14e** was readily removed by treatment with trifluoroacetic acid under solvolytic conditions[2f] to give **15e** in quantitative yield.

EXPERIMENTAL SECTION[12]

Methyl *N*-(4-Methoxybenzyl)-*N*-diazoacetylglycinate (9). A solution of *p*-toluenesulfonyl hydrazone of glyoxylic acid chloride (**6**) (1.94 g, 9.27 mmol) in CH_2Cl_2 (10 ml) was cooled at 0 °C, and to this solution were successively added *N*-(4-methoxybenzyl)glycine methyl ester (2.41 g, 9.27 mmol) in CH_2Cl_2 (5 ml) and triethylamine (2.6 ml, 18.8 mmol) in CH_2Cl_2 (15 ml). The mixture was stirred at 0 °C for 30 min and then at room temperature for 30 min. The solvent was evaporated, and the residue was treated with benzene (40 ml) and filtered after addition of Florisil (10 g). The filtrate was concentrated, and the residue was subjected to a flash chromatography (silica gel 200 g, hexane/AcOEt = 1:1) to give **9** (2.02 g, 79%) as a pale yellow oil, which solidified on standing. An analytical sample was obtained by recrystallization from AcOEt-hexane as yellow plates, mp 87-88 °C, R_f = 0.23 (hexane/AcOEt = 1:1). FT-ir (neat): 2126, 1754, 1602 cm^{-1}. ^1H Nmr (500 MHz, $CDCl_3$) δ: 3.73 (3H, s, $COOCH_3$), 3.81 (3H, s, $ArOCH_3$), 4.11 (2H, br s, $C\underline{H}_2COOCH_3$), 4.38 (2H, br s, $ArC\underline{H}_2$), 5.05 (1H, br, N_2CH), 6.88 (2H, d, J = 8 Hz), 7.15 (2H, d, J = 8 Hz). ^{13}C Nmr (126 MHz, $CDCl_3$) δ: 47.09 ($N_2\underline{C}H$), 47.56 ($COO\underline{C}H_3$), 51.51 ($Ar\underline{C}H_2$), 52.22 ($COO\underline{C}H_3$), 55.33 ($ArO\underline{C}H_3$), 114.32, 128.28, 159.33 (Ar), 166.77, 169.88 (CO). EI-ms: *m/z* 278 (M^++1), 148 (base peak). *Anal.* Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.30; H, 5.39; N, 15.27.

By using the same procedure, there was obtained *N*-benzyl compound (**8**) in 63% yield as a pale yellow oil, R_f = 0.29 (hexane/AcOEt = 1:1). FT-ir (neat): 2109, 1749, 1610 cm^{-1}. ^1H Nmr (500 MHz, $CDCl_3$) δ: 3.73 (3H, s), 4.15 (2H, br s), 4.45 (2H, br s), 5.01 (1H, br), 7.22-7.38 (5H, m). ^{13}C Nmr (126 MHz, $CDCl_3$) δ: 46.96 (d), 47.65 (t), 51.37 (t), 52.07 (q), 126.72, 128.78, 135.93 (d), 166.77, 169.70 (s). EI-ms *m/z*:: 248 (M^++1), 219 (base peak).

Mthyl *N*-(4-Methoxybenzyl)-*N*-[3-(1-methylcyclohexyl)-3-oxopropanoyl]glycinate (12e) (General Procedure for the Preparation of β-Keto amides). To a stirred and cooled (-10 °C) suspension of $ZrCl_4$ (610 mg, 2.62 mmol) in dry CH_2Cl_2 (1.5 ml) under N_2 was added a solution of **9** (1.09 g, 3.93 mmol) in dry CH_2Cl_2 (1.5 ml). After addition of a solution of **11e** (165 mg, 1.31 mmol) in dry CH_2Cl_2 (1 ml) *via* a canula, the mixture was stirred at 0 °C (ice-water bath) for 1 h. The insoluble inorganic material was removed by filtration through a layer of Celite and washed with CH_2Cl_2 (30 ml). The combined filtrates were concentrated under reduced pressure, and the residue was dissolved in AcOEt (20 ml). The AcOEt solution

was successively washed with saturated $NaHCO_3$ (2 ml × 2) and brine (2 ml), dried ($MgSO_4$), and concentrated. The residue was subjected to flash chromatography (silica gel 50 g, hexane/ether = 1:1) to give **12e** (385 mg, 78%) as a colorless oil, Rf = 0.23 (hexane/AcOEt = 1:1). FT-ir (neat): 1751, 1653, 1613 cm^{-1}. ^1H Nmr (500 MHz, $CDCl_3$) δ (keto form, major/*minor* rotamers = 1.8)[13,14]: 1.13, *1.15* (C-CH_3), *3.68*, 3.78 ($COCH_2CO$), 3.70, *3.71* ($COOCH_3$), 3.81 ($ArOCH_3$), 4.02, *4.08* (CH_2COOCH_3), 4.53 ($ArCH_2$); δ (enol form, major/*minor* rotamers = 3.7)[14] 1.11 (C-CH_3), *3.73*, 3.74 ($COOCH_3$), 3.80, 3.81 (OCH_3), *3.89*, 3.92 (CH_2COOCH_3) 4.64, *4.65* ($ArCH_2$), *5.02*, 5.32 (C=CH). EI-ms *m/z*: 375 (M^+), 97 (base peak); HRms calcd for $C_{21}H_{29}NO_5$ 375.2044, found 375.2034.

***N*-(4-Methoxybenzyl)-3-(1-methylcyclohexanecarbonyl)tetramic Acid (14e)** To a solution of **13e** (127 mg, 0.34 mmol) in dry CH_2Cl_2 (0.9 ml) was added 1 M THF solution of *n*-Bu_4NF (0.68 ml), and the mixture was stirred at room temperature. After 2 h, the solvent was evaporated and the residue was dissolved in AcOEt (20 ml). The AcOEt solution was washed with a 1:1 mixture of 10% HCl and brine, dried on Na_2SO_4, and concentrated. The residual oil which showed single spot on tlc (1% KH_2PO_4 impregnated silica gel)[16] was purified by chromatography on KH_2PO_4-treated silica gel[17] (17 g, elution with benzene/AcOEt = 19:1) to give **14e** (112 mg, 96%) as a colorless oil, Rf = 0.34 (benzene/AcOEt = 19:1). ^1H Nmr (500 MHz, $CDCl_3$) δ (tautomer ratio = 6.5)[14,15]: 1.31 (s, C-CH_3), 3.55, *3.78* (s, H-5), *3.80*, 3.81 (s, OCH_3), *4.54*, 4.55 (s, $ArCH_2$), 6.86-6.90, 7.18-7.21 (m, ArH). ^{13}C Nmr (75.5 MHz, $CDCl_3$) δ (tautomer ratio = 6.5)[14,15]: 22.90 (C-$\underline{C}H_3$), 23.11, 25.83, 33.72 (cyclohexane), 43.68 ($\underline{C}$-CH_3), 45.33 ($Ar\underline{C}H_2$), *50.52*, 54.45 (C-5), 55.38 ($O\underline{C}H_3$), 99.57 (C-3), 114.43, 129.80 (d, Ar), 127.33, 159.56 (s, ArH), *166.40*, 176.28 (C-2), 188.88, *196.24* (3-CO), 199.32, *204.99* (C-4). HRms calcd for $C_{20}H_{25}NO_4$ 343.1783, found 343.1788.

3-(1-Methylcyclohexanecarbonyl)tetramic Acid (15e) A solution of **14e** (18 mg, 0.05 mmol) and trifluoroacetic acid (2 ml) was kept at 50 °C for 24 h, then concentrated under reduced pressure at room temperature. The residue was subjected to chromatography (KH_2PO_4-treated silica gel, benzene/AcOEt = 4:1) to give **15e** as a solid (11 mg, 100%), mp 145-146 °C (colorless plates after recrystallization from *i*-Pr_2O). EI-ms *m/z*: 223 (M^+), 126, 99. ^1H Nmr (500 MHz, $CDCl_3$) δ (tautomer ratio = 4)[14,15]: 1.34, *1.40* (s, C-$C\underline{H}_3$), 2.26 (2H, t, J = 8.4 Hz), 3.78, *4.02* (2H, s, H-5), *6.15*, 6.46 (1H, br s, H-1). ^{13}C Nmr (75.5 Hz, $CDCl_3$) δ[14,15]: *22.87*, 23.05 (CH_3), 23.14, 25.85, *25.95*, 33.72, *33.96* (cyclohexane CH_2), *43.98*, 51.17 (C-5), *45.65*, 47.23 ($\underline{C}$-CH_3), 99.16, *105.06* (C-3), 179.62 (C-2), 190.17, *197.71* (3-CO), 200.82, *206.09* (C-4). *Anal.* Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.46; H, 7.56; N, 6.08.

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1. *This paper is dedicated to Professor Yoshifumi Maki on the occasion of his retirement from Gifu* Pharmaceutical University in March, 1994.
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9. A similar $ZrCl_4$-catalyzed reaction of methyl (diazoacetoxy)acetate with aldehydes yielding (3-oxo-alkanoyloxy)acetates has been reported recently by us. K. Nomura, T. Iida, K. Hori, and E. Yoshii, *J. Org. Chem.*, **1994**, *59*, 488.
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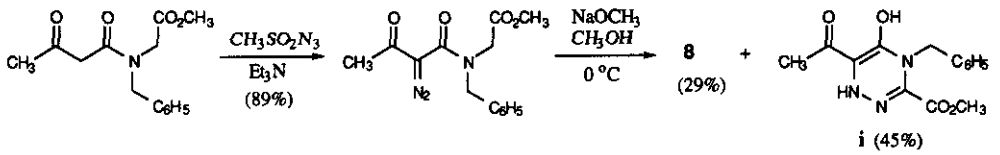
11. An alternative preparation of **8** by the route shown below resulted in a poor yield, producing 1,2,4-triazine (**i**) as the major product.



12. All new compounds were characterized by spectral data (^1H and ^{13}C Nmr, ir, and ms) and combustion analysis (CHN) and/or high-resolution ms).
13. Ratio of keto/enol forms = 2.
14. The signals due to minor rotamer or tautomer are indicated in italics.
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