Communications to the Editor

[Chem. Pharm. Bull.]
35(10)4368—4371(1987)

AN EFFICIENT 3(C)-ACYLATION OF TETRAMIC ACIDS
INVOLVING ACYL MIGRATION OF 4(O)-ACYLATES

Kozo Hori, Mikio Arai, Keiichi Nomura, and Eiichi Yoshii*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical
University, Sugitani 2630, Toyama 930-1, Japan

3(C)-Acylation of 3-unsubstituted tetramic acids with carboxylic acid has been achieved by two sequential reactions in one flask: (1) 4(O)-acylation in the presence of DCC and a catalytic amount of DMAP, and (2) 4(O)→3(C) acyl-migration promoted by adding Et_3N .

KEYWORDS — tetramic acid; acylation; carboxylic acid; phosphonoacetic acid; acyl-migration

In connection with the total syntheses of triandamycin A (1), ikarugamycin (2), and their congeners,¹⁾ there have been reported various methods for synthesizing the 3-acyltetramic acid structure. Tetramic acids (pyrrolidine-2,4-diones) can be directly 3(C)-acylated in moderate to good yields with carboxylic chloride in the presence of Lewis acid ($\text{BF}_3\text{-Et}_2\text{O}$ or TiCl_4 , heating)²⁾. But this method is apparently not suitable for those carboxylic acid which are sensitive to harsh reaction conditions. Base-induced acylation, on the other hand, has been reported to result in predominant formation of 4-O-acyltetramic acid.³⁾ For the construction of the tetramic acid units in 1 and 2, it has been introduced in a novel method⁴⁾ that employs Emmons-Horner reaction of the (phosphonoacetyl)tetramic acid 3.⁵⁾ We report herein a new and efficient method for the direct 3(C)-acylation of 5 which involves an acyl migration of the kinetic O-acylate induced by 4-N,N-dimethylaminopyridine (DMAP).

We recently demonstrated⁶⁾ that tetronic acid (**4**) can be nicely acylated with carboxylic acid at the 3-position in the presence of dicyclohexylcarbodiimide (DCC), DMAP (0.3 eq) and triethylamine (1.1 eq) in CH_2Cl_2 . The reaction proceeds via kinetic *O*-acyl intermediate. This prompted us to investigate whether the same experimental protocol can be utilized for 3(C)-acylation of tetramic acids which are less acidic (pK_a 6.4-7.1).⁷⁾ A preliminary experiment using 5-benzyltetramic acid (**5a**) and hexanoic acid resulted in formation of a complex mixture of products, from which the desired 5-benzyl-3-hexanoyltetramic acid (**7a**) ($\text{R} = n\text{-C}_5\text{H}_{11}$) was isolated in low yield (15-20%) after chromatography. A serious side reaction observed here was *N*-acylation and a double-bond migration in the *O*-acylate **6a** to the 5(exo) position.⁸⁾ Fortunately, however, the yield of the acyltetramic acid could be greatly improved up to 95% by conducting the reaction in a stepwise manner in one flask: (1) formation of kinetic *O*-acylate mediated with 1.1 eq DCC and ca. 0.1 eq DMAP and (2) subsequent slow *O*(4)→*C*(3) acyl migration induced by addition of 1.1 eq triethylamine. This technique, which can be easily controlled by thin layer chromatography, was equally effective for 3-alkanoylation of both *N*-substituted and unsubstituted tetramic acids (**5a-d**)⁹⁾ (Table I).¹⁰⁾ 2-Butenoylation and 2,4-hexadienoylation should be carried out at low temperatures (0° to 8°C) to minimize side reactions,¹¹⁾ giving modest yields (37 - 50%) of the corresponding 3-acyltetramic acids.

Table I. 3-Acyltetramic Acids¹⁷⁾

R_3	% yield ^{a)}	mp/bp($^\circ\text{C}$)	R_3	% yield ^{a)}	mp/bp($^\circ\text{C}$)
7a $n\text{-C}_5\text{H}_{11}$	95	126-8	7c $n\text{-C}_5\text{H}_{11}$	89	oil
$\text{C}_6\text{H}_5\text{CH}_2$	83	143-6	$(\text{EtO})_2\text{P}(\text{O})\text{CH}_2$	(<u>ca.</u> 80)	oil
$(\text{CH}_3)_2\text{CH}$	58	125-8	-----		
$\text{CH}_3\text{CH}=\text{CH}$	50	198-203	7d $n\text{-C}_5\text{H}_{11}$	72	57
$\text{CH}_3\text{CH}=\text{CH}-\text{CH}=\text{CH}$	50	201-3	$\text{CH}_3\text{CH}=\text{CH}$	37	81-3
$(\text{EtO})_2\text{P}(\text{O})\text{CH}_2$	84	oil	$\text{CH}_3\text{CH}=\text{CH}-\text{CH}=\text{CH}$	49	100-2
-----			$(\text{EtO})_2\text{P}(\text{O})\text{CH}_2$	84(96)	oil
7b $n\text{-C}_5\text{H}_{11}$	88	85-95/0.04	-----		
cyclo- C_3H_5	87	129-131	a) Isolated yield by distillation or silica gel chromatography. Yield determined by proton NMR (270 MHz) spectral analysis of the crude product is indicated in parenthesis.		
$\text{C}_6\text{H}_5\text{CH}_2$	86	68-73			
$\text{CH}_3\text{CH}=\text{CH}-\text{CH}=\text{CH}$	50	153-7			
$(\text{EtO})_2\text{P}(\text{O})\text{CH}_2$	73(97)	105-8			

Since acylation with the conjugated acids was less efficient than alkanoylation, we turned our attention to (diethoxyphosphinyl)acetylation in the light of the literature precedent that the compound 3 can serve as an excellent precursor of enoyl and dienoyl tetramic acids.⁴⁾ The reaction of $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOH}$ ^{12,13)} with *N*-benzyltetramic acid (5d) occurred smoothly to give 7d [$\text{R}_3 = (\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}$] in 96% yield after an acid-base extraction (0.15 M $\text{Na}_3\text{PO}_4/\text{HCl}$) of the reaction mixture. The (phosphinyl)acetylation of 5a-c was also achieved in high yields (Table I).

In conclusion, we could have introduced an efficient method for 3(C)-acylation of tetramic acids that can be performed under weakly basic conditions. It is also significant that the present method provides a ready access to 3-(diethoxyphosphinyl)acetyl tetramic acids which are useful intermediates in the synthesis of a variety of 3-alkenoyl derivatives.

A typical experimental procedure: A stirred mixture of 5a (80 mg, 0.42 mmol) and DMAP (10 mg, 0.082 mmol) in dry dichloromethane (3 ml) at 0°C (an ice-water bath) was treated sequentially with hexanoic acid (58 μl , 0.46 mmol) and DCC (105 mg, 0.50 mmol). The cooling bath was removed after 10 min, and stirring of the mixture at room temperature was continued for 1.5 h to complete formation of *O*-acylate 6a ($\text{R}_3 = \text{C}_5\text{H}_{11}$) [essentially one spot on a silica gel plate, $R_f = 0.58$ ($\text{CHCl}_3/\text{MeOH} = 19:1$)]. The resulting suspension (dicyclohexylurea) was cooled to 0°C again before adding triethylamine (71 μl , 0.50 mmol) and, after 10 min, it was stirred at room temperature for 4.5 h. The reaction mixture was filtered with suction, and the filtrate was washed with 10% HCl and brine. The organic layer was dried over anhydrous MgSO_4 and concentrated with a rotary evaporator. The solid residue was subjected to column chromatography (KH_2PO_4 -treated silica gel,¹⁵⁾ 8 g; solvent, benzene/AcOEt = 4:1) to give 7a ($\text{R}_3 = \text{C}_5\text{H}_{11}$) (115 mg, 95%) as a white solid, which was homogeneous on KH_2PO_4 -impregnated silica gel thin-layer,¹⁶⁾ $R_f = 0.42$ (benzene/AcOEt = 4:1). An analytical sample was obtained by recrystallization from diisopropyl ether, mp 126–128°C.

REFERENCES AND NOTES

- 1) Synthetic study on 3-acyltetramic acid antibiotics: a) R. E. Ireland and R. B. Wardle, *J. Org. Chem.*, **52**, 1780(1987); b) R. K. Boeckman, Jr., J. C. Potenza, and E. J. Enholm, *ibid.*, **52**, 469(1987); c) C. Neukom, D. P. Richardson, J. H. Myerson, and P. A. Bartlett, *J. Am. Chem. Soc.*, **108**, 5559(1986); d) R. K. Boeckman, Jr., J. E. Starrett, Jr., D. G. Nickell, and P.-E. Sum, *J. Am. Chem. Soc.*, **108**, 5549(1986); e) R. K. Boeckman, Jr. and R. B. Perni, *J. Org. Chem.*, **51**, 5486(1986); f) P. DeShong, S. Ramesh, V. Elango, and J. J. Perez, *J. Am. Chem. Soc.*, **107**, 5219(1985); g) R. H. Schlessinger, G. R. Bebernitz, and P. Lin, *J. Am. Chem. Soc.*, **107**, 1777(1985).
- 2) R. C. F. Jones and G. E. Peterson, *Tetrahedron Lett.*, **24**, 4757(1983); R. C. F. Jones and S. Sumaria, *ibid.*, 3173(1978).
- 3) S. Toda, S. Nakagawa, T. Naito, and H. Kawaguchi, *J. Antibiot.*, **33**, 173(1980); V. J. Lee, A. R. Branfman, T. R. Herrin, and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **100**, 4225(1978); J. L. van der Baan, J. W. F. K. Barnick, and F. Bickelhaupt, *Tetrahedron*, **34**, 223(1978).

- 4) R. H. Schlessinger and G. R. Bebernitz, J. Org. Chem., **50**, 1344(1985); R. K. Boeckman, Jr. and A. J. Thomas, ibid., **47**, 2823(1982).
- 5) Other synthetic methods of 3-acyltetramic acid structure: R. C. F. Jones and A. D. Bates, Tetrahedron Lett., **28**, 1565(1987); R. C. F. Jones and G. E. Peterson, ibid., **24**, 4751(1983); P. DeShong, N. E. Lowmaster, and O. Bavalt, J. Org. Chem., **48**, 1149(1983).
- 6) K. Nomura, K. Hori, M. Arai, and E. Yoshii, Chem. Pharm. Bull., **34**, 5188(1986).
- 7) T. P. C. Mulholland, R. Foster, and D. B. Haydock, J. Chem. Soc. Perkin Trans. 1, 2121(1972).
- 8) R. C. F. Jones and G. E. Peterson, Tetrahedron Lett., **24**, 4755(1983).
- 9) Compounds **5a-c** are racemic.
- 10) O-Acylate intermediates (**6**) can be isolated in excellent yields.
- 11) In the 2-butenoylation of **5a**, a bicyclic compound **8** was isolated, presumably formed by an internal Michael reaction of **6a**.
- 12) We prepared this compound by the following sequence.

- 13) M. P. Cooke, Jr. and K. P. Biciunas, Synthesis, 283(1981); J. P. Clayton, K. Luk, and N. H. Rogers, J. Chem. Soc. Perkin Trans. 1, 308(1979).
- 14) E. Yoshii and K. Takeda, Chem. Pharm. Bull., **31**, 4586(1983).
- 15) W. W. Lee, A. P. Martinez, T. H. Smith, and D. W. Henry, J. Org. Chem., **41**, 2296(1976).
- 16) J. St. Pyrek, O. Achmatowicz, Jr., and A. Zamojski, Tetrahedron, **33**, 673(1977).
- 17) All compounds were characterized by ^1H -NMR and mass spectroscopy, and crystalline compounds gave satisfactory combustion analyses (C, H).

(Received September 1, 1987)