Tetrahedron Letters,Vol.30,No.19,pp 2553-2554,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

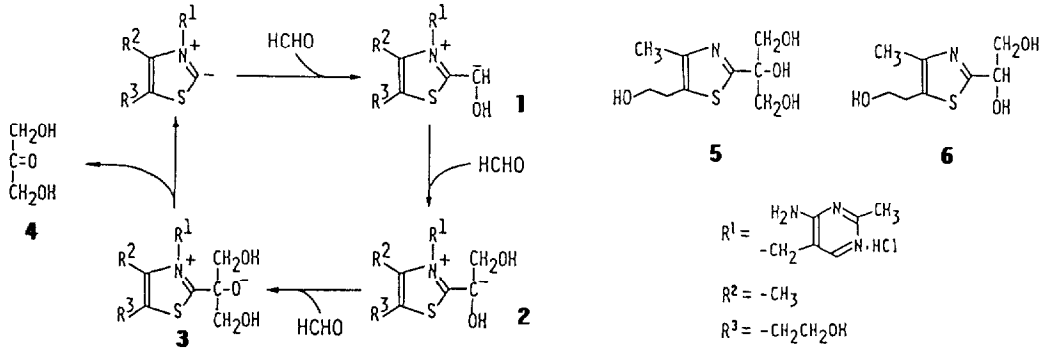
ISOLATION OF AN INTERMEDIATE OF FORMOSE REACTION CATALYZED BY THIAMIN·HCl

Hiroyuki Saimoto, Kazuya Kotani, Yoshihiro Shigemasa,*
Makoto Suzuki,† Ken-ichi Harada†
Department of Industrial Chemistry, Faculty of Engineering,
Tottori University, Tottori 680, Japan
†Faculty of Pharmacy, Meijo University, Nagoya 468, Japan

2-[1,2-Dihydroxy-1-(hydroxymethyl)ethyl]-5-(2-hydroxyethyl)-4-methylthiazole (**5**) was isolated in the formose reaction catalyzed by thiamin·HCl, giving an insight into the reaction mechanism of benzoin type HCHO condensation to form dihydroxyacetone.

Reaction intermediates derived from thiazolium salt catalysts have recently been of interest from a synthetic viewpoint.[1] Particularly, in the formose reaction mediated by thiazolium salts such as thiamin(vitamin B_1)·HCl, mechanistic studies have been important to achieve selective carbohydrate formation. In the highly selective synthesis of dihydroxyacetone (**4**), thiazolium derivatives **1**-**3** were proposed[2] as reaction intermediates of benzoin type HCHO condensation (Scheme 1).[3] In the course of the studies for the synthesis of tetrulose and pentulose derivatives,[4] we were able to isolate 2-[1,2-dihydroxy-1-(hydroxymethyl)ethyl]-5-(2-hydroxyethyl)-4-methylthiazole (**5**), which suggests the presence of the intermediate **3**. A typical procedure was as follows.

A mixture of paraformaldehyde (9.0 g, 0.30 mol as HCHO), 2-(dimethylamino)ethanol (1.3 g, 15 mmol), boric acid (0.93 g, 15 mmol), and thiamin·HCl (2.5 g, 7.5 mmol) in N,N-dimethylformamide (100 ml) was stirred at 100°C. After 10 min, 24% of HCHO was consumed and the following compounds were produced: **4**, 30 glc%; DL-glycero-tetrulose, 7 glc%; **5**, 25 glc%; 2-(1,2-dihydroxyethyl)-5-(2-hydroxyethyl)-4-methylthiazole (**6**),[2a] 13 glc%.[5] In order to isolate **5**, the formose reaction was carried out under the same reaction conditions except that thiamin·HCl (3.4 g, 10 mmol) was employed and the



Scheme 1.

reaction mixture was stirred for 2 h (HCHO consumption, 48%). After acidification with 9 mol dm^{-3} HCl, the reaction mixture was filtered and concentrated to give a syrup (9.4 g), which was fractionated by column chromatography (active carbon, first with water and then with methanol). Concentration of the latter fraction gave a brown syrup (4.41 g) containing **5** (67 glc%) and **6** (27 glc%). Finally the brown syrup (88 mg) was subjected to purification by preparative TLC (silica gel, water saturated butanol/hexane = 4/1) to give **5**[6] (R_f 0.44, eluted with dichloromethane/methanol = 10/1, 15 mg, 33% yield from thiamin·HCl) as a colorless syrup along with **6** (R_f 0.53, 8 mg, 18% yield from thiamin·HCl).

The isolation of **5** corresponds to the formation of **4** catalyzed by thiamin·HCl in the formose reaction. The intermediacy of **2** in Scheme 1 is also supported by the isolation of **6**.[2a] It is, however, particularly interesting that glycolaldehyde has not been detected nor isolated even in the initial stage of the reaction.[2] Further studies are in progress on the formation and reaction of these C_2 and C_3 building blocks in the formose reaction.[7]

We are indebted to Dr. Koji Kimura, Faculty of Medicine, Tottori University, for recording mass spectra.

References and Notes

1. H. Inoue and S. Tamura, J. Chem. Soc., Chem. Commun., **1986**, 858; F. Jordan, Z. H. Kudzin, and C. B. Rios, J. Am. Chem. Soc., **109**, 4415 (1987); R. Kluger, K. Karimian, and K. Kitamura, ibid., **109**, 6368 (1987); R. Breslow, and E. Kool, Tetrahedron Lett., **29**, 1635 (1988); H. Stetter, H. Kuhlmann, and W. Haese, Org. Synth., **65**, 26 (1987) and references cited therein.
2. a) Y. Shigemasa, Y. Sasaki, N. Ueda, and R. Nakashima, Bull. Chem. Soc. Jpn., **57**, 2761 (1984); b) T. Matumoto, H. Yamamoto, and S. Inoue, J. Am. Chem. Soc., **106**, 4829 (1984).
3. Selective synthesis of **4**: T. Matsumoto and S. Inoue, J. Chem. Soc., Chem. Commun., **1983**, 171; formose reaction with a thiazolium salt: J. Castells, F. Geijo, and F. Lopez-Calahorra, Tetrahedron Lett., **21**, 4517 (1980).
4. Y. Shigemasa, A. Okano, H. Saimoto, and R. Nakashima, Carbohydr. Res., **162**, C1 (1987); Y. Shigemasa, T. Ueda, and H. Saimoto, J. Carbohydr. Chem., in print.
5. Measurement of HCHO consumption and glc analysis of the products were performed by the reported procedures.[2a]
6. IR (KBr) 3200, 1550 cm^{-1}; ^1H NMR (CD_3OD) δ = 2.32 (s, 3H), 2.93 and 3.71 (2t, J = 6.5 Hz, 2H), 3.82 (4H, s); ^{13}C NMR (CD_3OD) δ = 14.8 (q), 30.7 and 63.4 (2t), 67.3 (t, $C(\mathbf{C}H_2OH)_2$), 79.2, 130.1, 149.5 and 173.4 (4s); tetrakis(trimethylsilyl) derivative of **5**: MS m/z (rel intensity) 521 (M^+, 16), 506 (100). Tetraacetate of **5**: ^1H NMR ($CDCl_3$) δ = 2.04 (s, 6H), 2.06, 2.11, and 2.33 (3s, 3H), 3.05 and 4.22 (2t, J = 6.8 Hz, 2H), 4.74 and 4.81 (2d, J = 11.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ = 15.0 (q), 20.7 (q, two of $\mathbf{C}H_3CO$), 20.9 and 21.7 (2q), 25.9 (t, two of $\mathbf{C}H_2$-OAc), 63.8 and 64.1 (2t), 81.2, 128.0, 149.1, 163.2, and 169.2 (5s), 170.0 (s, two of $CH_3\mathbf{C}O$), 170.8 (s); CIMS (isobutane), found: m/z 402.1205. Calcd for $C_{17}H_{24}NO_8S$: MH^+, 402.1220.
7. Financial support by the Ministry of Education, Science, and Culture of Japan (Grant-in-Aid for Scientific Research No. 61303011) is acknowledged.

(Received in Japan 9 March 1989)