CHEMISTRY LETTERS, pp. 1621-1624, 1982. © The Chemical Society of Japan 1982

DESULFURIZATION OF 2-THIOURIDINES BY DIPOTASSIUM DIAZENEDICARBOXYLATE

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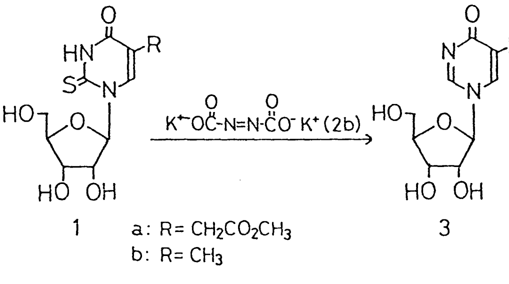
The reaction of 5-methoxycarbonylmethyl-2-thiouridine (1a) with dipotassium diazenedicarboxylate and with N_2H_4-H_2O_2 afforded 1-(β-D-ribofuranosyl)-5-methoxycarbonylmethyl-4-(1H)-pyrimidinone (3a) in good yields, suggesting that the reaction involves diimide. On treatment with H_2O_2, 1a also gave 3a.

The preceding paper describes that the reaction of 2-thiouridines (1) with dibenzoyldiazene (2a) gave the corresponding desulfurized products (3) along with a trace of uridine derivatives.[1)] Since diimide (4) is suggested as a product of decomposition of 2a,[2)] we postulated that 4 might be responsible for desulfurization of 1. We wish to report herein the reaction of 1 with dipotassium diazene dicarboxylate (2b) and with N_2H_4-H_2O_2 which are known as precursors of 4.[3)]

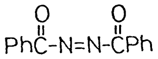
5-Methoxycarbonylmethyl-2-thiouridine (1a) reacted smoothly with 2b in dioxane-H_2O (buffered at pH 7 or 8) giving 1-(β-D-ribofuranosyl)-5-methoxycarbonylmethyl-4(1H)-pyrimidinone (3a) in good yield (Table 1, entry 2-5 and 7). Dioxane could be replaced by tetrahydrofuran, but the rate of the reaction decreased (Table 1, entry 8). On the other hand, no reaction took place when methanol-H_2O (pH 7) or H_2O (pH 7) was used as a solvent (Table 1, entry 9, 10). The role of the solvent for the success of the desulfurization has not yet been elucidated.

5-Methyl-2-thiouridine (1b) also afforded the corresponding desulfurized product (3b) in 79% yield under the same conditions of entry 2 (Table 1) with 13% recovery of 1b.



1 a: R= $CH_2CO_2CH_3$
b: R= CH_3

3



$PhC(=O)-N=N-C(=O)Ph$

2a

It would be reasonable to assume that the desulfurization of 1 by 2b proceeds by the initial formation of 4, which reduces the >C=S bond of 1, followed by elimination of H_2S.[4)] The generation of 4 was supported by the reaction of 3-phenyl-2-propen-1-ol (5) with 2b under the similar conditions to entry 2 (Table 1), where 3-phenylpropanol (6) was formed in 67% yield (Table 2, entry 1). Treatment of 5 with

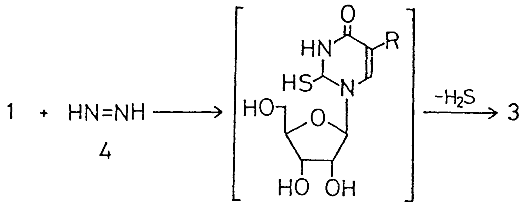
Table 1. Desulfurization of 1a (0.025 mmol) at Room Temperature

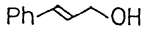
Entry	Molar ratio 2b/1a	pH of buffer	Org. solv.^{a}	H_2O/Org. solv. v/v, total 10 ml	Time (day)	Yield of 3a (%)^b	Recovery of 1a (%)^b
1	5	7	D	9 : 1	1	24	75
					3	45	55
					5	49	47
2	10	7	D	9 : 1	1	70	16
					2	91	-
					3	96	-
3	20	7	D	9 : 1	1	85	13
					2	97	-
					3	98	-
4	10	7	D	3 : 1	1	63	33
					3	85	9
					5	93	-
5	10	7	D	19 : 1	1	72	17
					3	89	8
					5	94	-
6	10	6	D	9 : 1	1	0	100
					5	19	81
7	10	8	D	9 : 1	1	49	44
					2	85	-
					6	83	-
8	10	7	T	9 : 1	1	35	65
					2	56	43
					5	61	38
9	10	7	M	9 : 1	1	0	99
					2	0	99
					6	0	94
10	10	7	None		1	0	74
					3	0	58
					5	0	53

a) D = dioxane, T = tetrahydrofuran, M = methanol.
b) Determined by paper chromatography (solvent system; butanol-AcOH-H_2O = 5 : 2 : 3).

2b in MeOH-H_2O (pH 7) hardly afforded 6. Thus, the ratio of 5/6 was determined by glc to be 89/11 after 2 days and 73/27 after 4 days. This result is consistent with the view that no desulfurization of 1a took place in the same solvent system. Contrary to our expectation, however, no 6 was detected by glc when 5 was treated with 2a for 4 days under the conditions used for the desulfurization of 1 [dioxane-H_2O (pH 8 and 7)]. These results suggest that the reaction of 1 with 2b involves diimide, while that with 2a proceeds through a different intermediate which has not yet been elucidated.

In order to obtain further evidence for the intermediacy of 4, 1a and 5 were allowed to react with N_2H_4-H_2O_2 in the presence of catalytic amount of $CuSO_4$,3) 3a and 6 being formed in 89% and 70% yields, respectively (Table 2, entry 2). Desulfurization of 1a and reduction of 5 were also took place when the substrates were treated with N_2H_4 in the absence of H_2O_2 under an atmosphere of air, while virtually no reaction occurred under nitrogen atmosphere (Table 2, entry 3 and 4).





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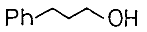

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Table 2. Reduction of **1a** and **5** at Room Temperature

Entry	Method (reagent)[a]	Time (day)	Reaction and yield of product, **3a** or **6** (%)[b]	
			1a → **3a**	**5** → **6**
1	A (**2b**)	1	70	-
		2	91	21
		3	96	40
		4	96	49
		6		67
2	B (N_2H_4-H_2O_2)	1	78	44
		2		50
		3	87	54
		5		66
		6	89	70
3	C (N_2H_4 under air)	1	10	2
		2	22	4
		3	41	5
		4	60	8
		6	75	12
4	D (N_2H_4 under N_2)	3	<7	1
		5	c	3
5	E (H_2O_2)	1	45	
		3	58	
		5	64	

a) Compound **1a** (0.025 mmol) or **5** (0.25 mmol) was dissolved in 10 ml of H_2O (buffered at pH 7)-dioxane (9 : 1, v/v) followed by addition of reagent indicated. Method A; Ten molar amounts of **2b** were added. Method B; To a solution of **1a** were added 1% $CuSO_4 6H_2O$ (2 μl), 80% $N_2H_4H_2O$ (16 μl), and 30% H_2O_2(5 μl). In the reaction of **5**, 1% $CuSO_4 6H_2O$ (2 μl), 80% $N_2H_4 \cdot H_2O$ (150 μl), and 30% H_2O_2 (50 μl) were used. Method C; The reactions were carried out under the similar conditions to the method B except for omitting $CuSO_4 6H_2O$ and H_2O_2. Method D; The reactions were carried out as method C under N_2. Method E; Five μl of 30% H_2O_2 was used.

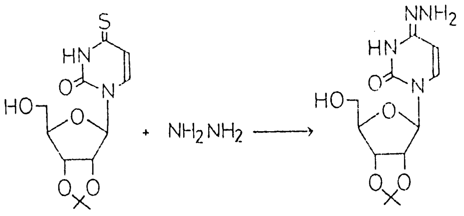
b) The yields of **3a** and **6** were determined by paper chromatography and glc, respectively.

c) A 94% of **1a** was recovered.

It is noteworthy that, on treatment with 30% H_2O_2, **1a** afforded **3a** in 64% yield (Table 2, entry 5).[5)] In this case, the reaction would proceed through sulfur oxy-acids, which converted into **3a** by the elimination of hydrogen sulfate and/or -sulfite. Under a separate experiment, $Ba(OH)_2$ solution was added to the resulting reaction mixture to precipitate $BaSO_4$, which was confirmed by X-ray analysis.

Similarly to the case of 2a, adenosine, guanosine, cytidine, uridine, and dihydrouridine were not affected by 2b under the conditions described above. However, 2',3'-O-isopropylidene-4-thiouridine (7) reacted with 2b to give uridine-4-hydrazone (8) in 94% isolated yield. Compound 8 would be formed by the reaction of 7 with hydrazine arised from disproportionation of 4.[6]

$$2\,HN{=}NH \longrightarrow NH_2NH_2 + N_2$$



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The authors express their thanks to Prof. Osamu Matsumoto for X-ray analysis, and Otsuka Chemical Co. Ltd., for generous gift of diazenedicarboxamide, precursor of 2b. This work was supported in part by a Grant-in Aid for Scientific Research from Ministry of Education, Science, and Culture.

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3) For reviews of diimide, see for example, S. Hünig, H. R. Müller, and W. Thier, Angew. Chem., 77, 368 (1965); H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc., Menlo Park, Carifornia (1972), pp. 248-256; J. Hayami, in "Shin Jikken Kagaku Koza" Vol. 15-II, Chemical Society of Jpn., Ed., Maruzen Co., Tokyo (1977), pp. 260-272. For the conversion of thymine to 5,6-dihydrothymine by the use of diimide, see D. M. Brown, in "Methods in Enzymology", Vol. XII, Part A, L. Grossman and K. Moldave, Eds., Academic Press, New York (1967) pp. 31-34.
4) When 2',3'-O-isopropylidene-S-methyl-2-thiouridine (9; mp 176°-177 °C, UV_{max}(MeOH) 235.5 (ε 25600), 265 sh (ε 8000))[7] was used in the place of 1a, no reaction took place, suggesting >C=S bond rather than $-N{=}\overset{|}{C}-SH$ bond is amiable to be reduced.
5) There are some precedents for the oxidation and desulfurization of thioxoheterocycles by H_2O_2. See for example, F. Asinger, A. Saus, H. Offermenns, P. Krings, and H. Andree, Ann., 744, 51 (1971); M. Ikehara and Y. Ogiso, Tetrahedron, 28, 3695 (1972).
6) For 8; mp 175°-176 °C, UV_{max}(MeOH) 277 (ε 11900), UV_{min} 243 (ε 7800), M^+ 298. For the reaction of 4-thiopyrimidine nucleoside derivatives with NH_2NH_2, see for example, I. Wempen, N. Miller, E. A. Falco, and J. J. Fox, J. Med. Chem., 11, 144 (1968); D. Cech and A. Holy, Coll. Czech. Chem. Comm., 42, 2246 (1977).
7) Compound 9 was prepared by Ueda's procedure used in the synthesis of unprotected 2-methyl-2-thiouridine. T. Ueda and H. Nishino, Chem. Pharm. Bull., 17, 920 (1969).

(Received July 29, 1982)