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Ozonation of Substituted 2-Thiouracils And Pyrimidine-2-Thione.

Claudia Crestini, Raffaele Saladino* and Rosario Nicoletti*

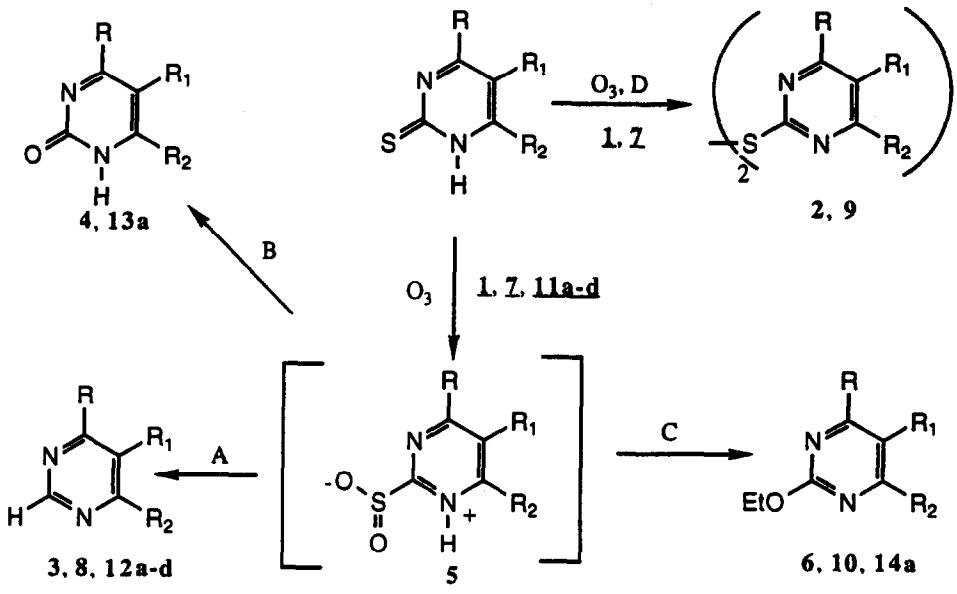
Dipartimento di Chimica Università degli Studi di Roma "La Sapienza", p.le Aldo Moro 5, 00100, Italy.

Abstract: The ozonation of substituted 2-thiouracils and pyrimidine-2-thione is reported; this provides a new method for the synthesis of several pyrimidine derivatives.

Although it seems clear from literature data[1] that 5,6-substituted uracils react with ozone to give the corresponding 5-hydroxyhydantoins, the ozonation of 2-thiouracils as far as we know has never been investigated. Ozone might be expected to react with 2-thiouracils at either of two reactive centers, the 5,6-double bond and the thioamide group. It has been reported[2] that tri-n-butylthiourea reacts with ozone to give a mixture of tri-n-butylurea and n-butylisocyanate but to our knowledge no further data are available. In order to study thoroughly the ozonation of thioamide moiety in the 2-thiouracils we have chosen as model 2-mercapto-4(3H)quinazolinone **1** which lacks a reactive 5,6-double bond. Different products were obtained depending on reaction conditions. Using an excess of ozone at 25°C for 0.5 h. in dry CH_2Cl_2 the disulfide **2** was isolated in 69% yield[3]. The compound **2** was stable when submitted to further ozonation. When the reaction was carried out in glacial acetic acid at 25°C for 0.5 hours, 4(3H)quinazolinone **3** was selectively obtained in 82% yield[4]. Moreover, the same reaction carried out in acetic acid-water (1:1 v/v) gave a separable mixture of 2,4(1H,3H)quinazolindione **4** (75%)[4] and a small amount of **3** (13%). Scheme 1 shows a reasonable reaction path for the ozonation of **1**. Probably, the ozonation in protic solvents proceeds through a reactive sulfinic acid intermediate[5] **5** formed by exhaustive oxidation of the thioamide group. This intermediate, depending on the reaction conditions, can lose sulphur dioxide to give compound **3**, whereas in presence of water it may be hydrolyzed to yield the corresponding pyrimidinone **4** as the main product. To test our hypothesis on the pathway of the reaction we have performed the ozonation of **1** in CH_2Cl_2 in presence of EtOH as nucleophile: only compound **6** was

obtained in good (91%) yield (Scheme 1, Table 1, entry 1).
In a similar manner, ozonation of pyrimidine-2-thione **7** gave, in the previous experimental conditions, pyrimidine **8**[4] in glacial acetic acid, pyrimidine-2-disulfide **9**[4] in dry CH_2Cl_2 and 2-ethoxypyrimidine **10**[4] in CH_2Cl_2 / EtOH (Scheme 1, Table 1, entry 2).

SCHEME 1



1, 2, 3, 4, 6: R=OH, R_1=R_2= -CH=CH-CH=CH-
7, 8, 9, 10: R=R_1=R_2=H.
11, 12, 13, 14: **a** R=OH, R_1=n-C_8H_{17}, R_2=CH_3; **b** R=OH, R_1=i-C_4H_9, R_2=CH_3
c R=OH, R_1=R_2= -$CH_2CH_2CH_2CH_2$-; **d** R=OH, R_1=H, R_2=CH_3.
A, B, C, D: see Table 1, note b.

Mercapto groups on thiouracils may be removed in favour of hydrogen by reductive[6] or oxidative[5] desulfurization. The oxidative process is much less reliable than the reductive one but it may be necessary when a reduction sensitive group is present or when the desulfurization has to be done on a large scale. However, the different reagents used for this conversion have varying degree of success as well as limitations due to side reactions. If the ozonation of 2-thiouracils to afford desulfurized products was a general reaction, it might be a mild and efficient synthetic alternative to the known methods: in order to evaluate this point we studied the ozonation of several 5,6-disubstituted-2-thiouracils (**11a-d**). For example, ozonation of 6-methyl-

5-n-octyl-4(3H)-2-thiopyrimidinone **11a** gave 6-methyl-5-n-octyl-4(3H)pyrimidinone **12a**[7] in glacial acetic acid, 6-methyl-5-n-octyl-2,4(1H,3H)pyrimidindione **13a**[4] in aqueous acetic acid and 6-methyl-5-n-octyl-2-ethoxy-4(3H)pyrimidinone **14a**[8] in dry CH_2Cl_2:EtOH (1:1 v/v) [Scheme 1, Table 1, entry 3]. Studies on ozonation of substituted uracils have shown that C-5 substituents influence the rate of oxidation of the 5,6-double bond while the C-6 substituents do not influence the course of the reaction[1]. We have found that in the case of substituted 2-thiouracils **11a-d** the properties of the C-5 substituent are able to influence the fate of the ozonation performed in glacial acetic acid. In fact, when the hydrophobicity of the substrate decreases, appreciable amounts of uracil derivatives are formed (see Table 1, entries 4, 5 and 6); the formation of uracils, which requires water, can be due to the presence of moisture, even if a different route, the cycloaddition of ozone to the thiocarbonyl group[9], can not be ruled out.

Table 1. Ozonation of substituted 2-thiouracils and pyrimidine-2-thione[a]

Entry	Substrate	Method[b]	Product(s)	Yield(%)
1	1	D	2	69
		A	3	82
		B	4	75
		C	6	91
2	7	A	8	64
		D	9	82
		C	10	72
3	11a	A	12a	92
		B	13a	73
		C	14a	81
4	11b	A	12b	53
			13b	16
5	11c	A	12c	35
			13c	30
6	11d	A	12d	10
			13d	28
			15	33

a All ozonations were carried out using 1 mmole of substrate and an O_2/O_3 flow of 10 mL/min.
b Method A: glacial acetic acid, 25 °C, 0.5 h. Method B: acetic acid-water (1:1 v/v), 25 °C, 1h. Method C: CH_2Cl_2-EtOH (1:1 v/v), 25 °C, 1h. Method D: dry CH_2Cl_2, 25 °C, 0.5 h.

When the C-5 substituent is hydrogen, the ozonolysis of 5,6-double bond becomes fast, and the hydantoin derivative **15** (not shown) appears among the reaction products. Ozonation of **11a-d** in dry CH_2Cl_2 did not give the disulfides, probably due to the minor amount of the thiol tautomer, according to a less favourable prototropic equilibrium as compared to that of compounds **1,7**. The results reported above show that the ozonation of 2-thiouracils and pyrimidine-2-thione provides a new method for the synthesis of numerous and interesting pyrimidine derivatives.

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References and notes

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3. **2**, m.p. 203-204 °C, Mass spectrum m/e=177 (M^+/2, 11%), Anal. Calcd. for $C_{16}H_{10}N_4O_2S_2$: C, 54.22 ; H, 2.84; N, 15.80. Found. C, 54.18 ; H, 2.85 ; N, 15.77. ^{1}H-NMR (DMSO-d_6) δ ppm: 12.15 (2H, broad singlet, NH) 7.61(8H, m, Ph); ^{13}C-NMR (DMSO-d_6) δ ppm: 163.05 (C),154.4 (C), 148.87 (C),134.74 (CH), 126.45 (CH), 125.84 (CH), 124.51 (CH), 119.47 (C).
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7. **12a**, m.p. 77-79 °C, Mass spectrum m/e=222 (M^+, 8%) Anal.Calcd. for $C_{13}H_{22}N_2O$: C, 70.23 ; H, 9.97 ; N 12.60. Found. C, 70.25; H, 10.00; N, 12.58. ^{1}H-NMR ($CDCl_3$) δ ppm: 8.00 (1H, s, CH), 2.25 (2H, m, CH_2), 2.13 (3H, s, CH_3), 1.19 (12H, m, CH_2), 0.95 (3H, m, CH_3). ^{13}C-NMR ($CDCl_3$) δ ppm: 164.36 (C), 161.24 (C), 145.10 (CH), 125.90 (C), 31.60 (CH_2), 29.52 (CH_2), 29.21(CH_2), 29.00 (CH_2), 27.86 (CH_2), 25.42 (CH_2), 22.36 (CH_2), 21.07 (CH_3), 13.77 (CH_3).
8. **14a**, oil, Mass spectrum m/e=266 (M^+, 21%), ^{1}H-NMR ($CDCl_3$) δ ppm: 4.38 (2H,d, J= 7 Hz, CH_2), 2.40 (2H, m, CH_2), 2.22 (3H, s, CH_3), 1.43 (3H, t, J= 7 Hz, CH_3), 1.28 (12H, m, CH_2), 0.85(3H, m, CH_3); ^{13}C- NMR ($CDCl_3$) δ ppm: 165.66 (C), 161.20 (C), 153.83 (C), 117.83 (C), 60.47 (CH_2), 31.70 (CH_2), 29.50 (CH_2), 29.47 (CH_2), 29.31 (CH_2), 29.12 (CH_2), 28.48 (CH_2),25.06(CH_2), 21.42 (CH_3), 13.97 (CH_3), 13.85 (CH_3).
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