A NEW SYNTHESIS OF 1,3-THIAZIN-4-ONES VIA 1,3-OXAZINIUM SALTS FROM N-ACETOACETYLCARBOXAMIDES.

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Abstract —— In the formation of 1,3-oxazinium salts from N-acetoacetylcarboxamides (1), the effect of acids such as 70% perchloric acid (3a), 98% sulfuric acid (3b), 36% hydrochloric acid (3c), saturated hydrogen chloride-ethanol solution (3d), trifluoroacetic acid (3e), and acetic acid (3f) was examined by the established method leading to the pyrazole (5) via 1,3-oxazinium salt (2), and the order was as follows; 3a > 3b > 3e ≧ 3d > 3c (3f was uneffective). The result was applied to synthesize 2-substituted 1,3-thiazine derivatives (7a-e, 8a,b) via 1,3-oxazinium salts from 1a-f and hydrogen sulfide in the presence of acetic anhydride in satisfactory yields.

We have previously reported that 1,3-oxazinium salts are formed as intermediate during the ring transformation reaction of 1,3-oxazin-4-ones with salts of hydrazines and hydroxylamine into pyrazoles[1] and isoxazoles[2], respectively. A direct simple method for preparation of the 1,3-oxazinium salt starting from any other readily available compounds than the 1,3-oxazin-4-one would offer a considerable advantage in an extension of the ring transformation reaction. In the present paper, we wish to report the synthesis of 1,3-oxazinium salts from N-acetoacetylcarboxamides (1)[3] and various acids (3), and further ring transformation of the 1,3-oxazinium salt into 1,3-thiazin-4-one derivatives.

Synthesis of 1,3-oxazinium salts (2) from N-acetoacetylcarboxamides (1):
Reaction of N-acetoacetylcarboxamides (1) with various organic and inorganic acids such as 70% perchloric acid (3a), 98% sulfuric acid (3b), 36% hydrochloric acid (3c), saturated hydrogen chloride-ethanol (3d), trifluoroacetic acid (3e), and acetic acid (3f) was carried out.

Reaction of N-acetoacetylbenzamide (1a) with 3a is representatively described; to an ice-cooled solution of 1a (3 g) and acetic anhydride (14 g) in chloroform (30 ml) was added dropwise 3a (1.2 ml) with stirring. In a few minutes, 4-hydroxy-6-methyl-2-phenyl-1,3-oxazinium perchlorate (2a, 3.5 g) was separated out as colorless powder. The perchlorate 2a was also obtained by similar treatment of 6-methyl-2-phenyl-4H-1,3-oxazin-4-one (4) with 3a. Attempt for purification of 2a was unsuccessful, since 2a was highly sensitive to moisture and underwent hydrolysis to give the starting 1a. The NMR spectrum (DMSO-d_6) of the crude 2a showed a three-proton singlet at δ 2.35 (methyl protons), a one-proton singlet at δ 6.21 (olefinic proton), and a five-proton multiplet at δ 7.3-8.5 (ring protons of phenyl group) together with signals of the contaminated 1a in a ratio of 2a : 1a = 5 : 2. These chemical shifts are unexpectedly very close to those of 4. In order to gain chemical support for the structure and further evidence for the practical yield of 2a, the particular ring transformation of 1,3-oxazinium salts, which was previously reported, was accomplished (Chart 1). Thus, 2a was treated with methylhydrazine to afford 5 in 66% yield. By this means, the other acids 3b-f were examined for diversifying the selectivity of the acid in preparation of the 1,3-oxazinium salt. 3b-e except 3f were finally determined to be effective in the formation of 2a. The results obtained were shown in Table 1.

Table 1. Overall Yields of 5 from 1a.

The employed acids 3		Yields (%) of 5
70% $HClO_4$	3a	56
98% H_2SO_4	3b	40
36% HCl	3c	15.4
HCl-EtOH	3d	34.5
CF_3COOH	3e	36.5
CH_3COOH	3f	0

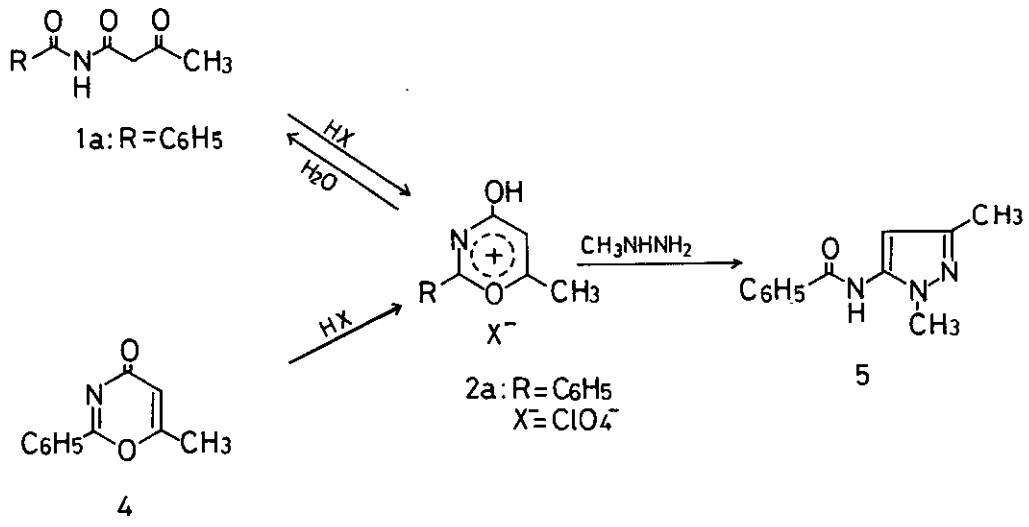

Chart 1

Synthesis of 2-substituted 1,3-thiazin-4-ones (7a-e, 8a,b):

The evidence described above seems to provide a useful route for the ring transformation. As an application, synthesis of 2-substituted 1,3-thiazin-4-ones (7a-e) from a variety of N-acetoacetylcarboxamides (1a-f) was investigated.

A typical procedure is described for the preparation of 6-methyl-2-phenyl-4H-1,3-thiazin-4-one (7a) from 1a and hydrogen sulfide in the presence of 3a; to an ice-cooled solution of 1a (2 g) and acetic anhydride (5 g) in chloroform (20 ml) was added dropwise 3a (1 ml) with stirring. Subsequently hydrogen sulfide was passed into the reaction mixture for 2 hr at room temperature. The 1,3-thiazinium salt[4] (6a) precipitated was taken by filtration and suspended in chloroform. Treatment of the suspension with saturated sodium carbonate solution, followed by recrystallization from acetone afforded 7a as pale yellow prisms, mp 125-126°, in 72% yield.

N-Acetoacetyl derivatives 1b-e of isobutyramide, pivalamide, p-chlorobenzamide, and p-nitrobenzamide analogously converted into the corresponding 1,3-thiazin-4-one derivatives (7b-e), respectively (Table 2).

On the other hand, similar treatment of N-acetoacetylphenylacetamide (1f) gave rise to 2,3-dihydro-1,3-thiazin-4-one 8b, an isomer of 7, exclusively. Furthermore, it was found that 7b obtained was also isomerized to 8a on standing at room temperature. The structural determination of 7 and 8 was based on their NMR, IR, and MS spectra together with elemental analysis. The spectral data were summarized in Table 2.

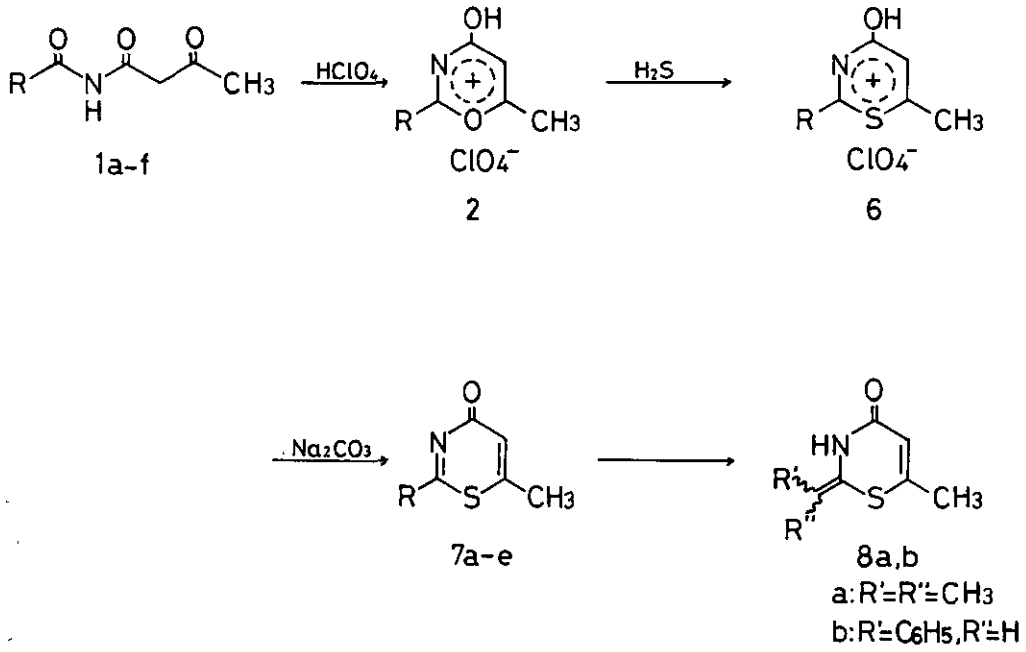

Chart 2

Table 2. Preparation of 2-Substituted 6-Methyl-1,3-thiazin-4-ones (7a-e, 8a,b)

Starting Material	Product	R or $R'_{R'}$C=	Yield (%)	mp (°C) or bp (Torr)	Formula	IR (KBr) [cm^{-1}]	NMR[a] δ (ppm)
1a	7a	C_6H_5	72	125-126	$C_{11}H_9NOS$	1640	2.37 (3H,s,C<u>H</u>$_3$) 6.53 (1H,s,C<u>H</u>=C) 7.36-8.10 (5H,m,ring protons)
1b	7b	$(CH_3)_2CH$	52	51-52[b]	$C_8H_{11}NOS$	1640	1.35 (6H,d,J=7Hz,(C<u>H</u>$_3$)$_2$CH) 2.30 (3H,s,C<u>H</u>$_3$) 2.70-3.16 (1H,m,(CH$_3$)$_2$C<u>H</u>) 6.47 (1H,s,C<u>H</u>=C)
1b	8a	CH_3 , CH_3	63	153-155[c]	$C_8H_{11}NOS$	1650	1.73 (6H,s,(C<u>H</u>$_3$)$_2$=C) 2.07 (3H,s,C<u>H</u>$_3$) 5.80 (1H,s,C<u>H</u>=C) 8.00 (1H,b,N<u>H</u>)
1c	7c	$(CH_3)_3C$	58	70 (0.04)	$C_9H_{13}NOS$	1650	1.43 (9H,s,(C<u>H</u>$_3$)$_3$C) 2.33 (3H,s,C<u>H</u>$_3$) 6.40 (1H,s,C<u>H</u>=C)
1d	7d	p-ClC_6H_4	68	172.5-174	$C_{11}H_8ClNOS$	1640	2.33 (3H,s,C<u>H</u>$_3$) 6.53 (1H,s,C<u>H</u>=C) 7.28-8.13 (4H,m,ring protons)
1e	7e	p-$NO_2C_6H_4$	59	218-220	$C_{11}H_8N_2O_3S$	1660	2.47 (3H,s,C<u>H</u>$_3$) 6.67 (1H,s,C<u>H</u>=C) 8.33 (4H,s,ring protons)
1f	8b	C_6H_5 , H	73	160-161	$C_{12}H_{11}NOS$	1660	2.07 (3H,s,C<u>H</u>$_3$) 5.80 (1H,s,C<u>H</u>=C) 6.06 (1H,s,C$_6$H$_5$C<u>H</u>$_2$) 7.10-7.33 (5H,m,ring protons) 9.83 (1H,b,N<u>H</u>)

*a Spectra were recorded on a Hitachi R-24B instrument with TMS internal standard; $CDCl_3$ (7a-d, 8a) or $CDCl_3$-DMSO-d_6 (10:1) (7e, 8b).

*b 7b was obtained by recrystallization from ether in refrigerator.

*c 8a was obtained by recrystallization from benzene.

A feasible pathway for the transformation into 1,3-thiazin-4-ones 7 could be explained to involve the following sequential steps as depicted in Chart 3.

In addition, it was found that the reactions of N-acetoacetyl derivatives of acetamide, propionamide, and n-butyramide resulted in the formation of dimers of the expected 7, respectively.

Further investigation involving the structure elucidation of dimers is under way.

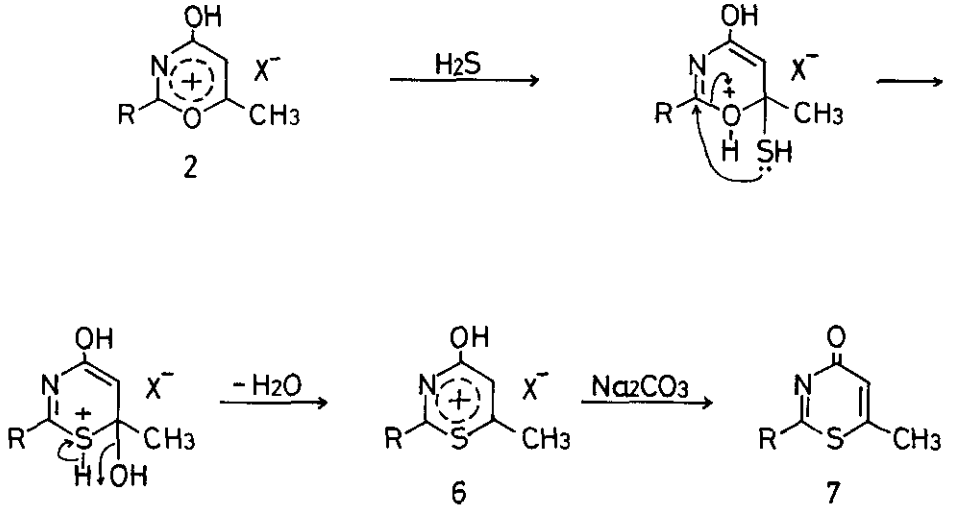

Chart 3

REFERENCES AND NOTE

1. Y. Yamamoto, Y. Azuma, and K. Miyakawa, Chem. Pharm. Bull., 1978, 26, 1825-1831.
2. Y. Yamamoto and Y. Azuma, Heterocycles, 1978, 9, 185-192.
3. The 18th Annual Meeting of Tohoku Branch, Pharmaceutical Society of Japan, Sendai, October 1979, Abstracts of Papers, p. 14.
4. The spectral data of crude 6a; NMR (DMSO-d_6) δ: 2.43(3H, t, J=1.2 Hz, -C<u>H</u>$_3$), 6.63(1H, q, J=1.2 Hz, >C=C<u>H</u>-), 7.43-8.13(5H, m, -C_6<u>H</u>$_5$); IR (KBr) cm^{-1}: 3400(br), 1590(m), 1575(m).

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