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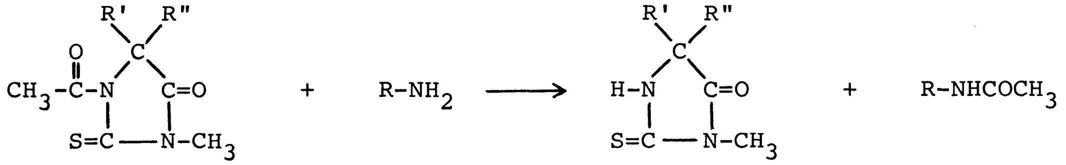
1-ACETYL-2-THIOXO-4-IMIDAZOLIDINONES AS REACTIVE ACETYLATING AGENT

Minoru SASHIO, Shozo IMONO, and Makoto TANAKA
Department of Applied Chemistry, College of Engineering,
University of Osaka Prefecture, Sakai, Osaka 591

Trans-acetylation of 1-acetyl-2-thioxo-4-imidazolidinones was investigated under mild and neutral conditions. It was found that the reagents were active toward amino group, but inactive toward hydroxy group.

Many studies have been carried out on the trans-acylation of N-acyl compounds,[1-3] but only few papers have been published on the reaction of N-acetyl-2,4-imidazolidinediones as N-acyl compound. Sekiguchi and Froyer[4] reported that 1-acetyl-3-methyl-2,4-imidazolidinedione was effective as an activator of the anionic polymerization of N-carboxy-α-amino acid anhydrides. Orazi and Corral[5] found that 3-acetyl-1,5,5-trimethyl-2,4-imidazolidinedione was useful for the selective acetylation of phenolic hydroxy group in the presence of alcoholic hydroxy group.

We wish to report here that 1-acetyl-3,5,5-trimethyl-2,4-imidazolidinedione is inactive for the acetylation of either of hydroxy and amino compounds, differing from the corresponding 3-acetyl compound, but 1-acetyl-2-thioxo-4-imidazolidinone are effective for the acetylation of amino group but not hydroxy group.



3-Acetyl-1,5,5-trimethyl-2,4-imidazolidinedione (I) and 1-acetyl-3,5,5-trimethyl-2,4-imidazolidinedione (II) were prepared by the methods described in the references cited. (I): mp 124-126°C. (lit,[5] mp 126-127°C). IR ($CHCl_3$) C=O: 1800, 1750, 1705 cm^{-1}, NMR (C_6H_5CN,δ): 2.58 (s,3H,$COCH_3$), 2.84 (s,3H,N-CH_3). Found: C, 52.10; H, 6.59; N, 15.19%. Calcd for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21%. (II): mp 97-99°C. (lit,[6] mp 99-100°C). IR (CCl_4) C=O: 1790, 1720, 1710 cm^{-1}, NMR (C_6H_5CN,δ): 2.53 (s,3H,$COCH_3$), 3.03 (s,3H,N-CH_3). Found: C, 51.41; H, 6.46; N, 15.07%. Calcd for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21%.

1-Acetyl-3-methyl-2-thioxo-4-imidazolidinone (III) was prepared by acetylation of 3-methyl-2-thioxo-4-imidazolidinone which was prepared by the method of Stepanov and Krivtsov[7] with acetic anhydride. mp 143-145°C. IR ($CHCl_3$) C=O: 1755, 1700 cm^{-1}, C=S: 1350 cm^{-1}, NMR (C_6H_5CN,δ): 2.75 (s,3H,$COCH_3$), 3.17 (s,3H,N-CH_3). Found: C, 41.78; H, 4.63; N, 16.30%. Calcd for $C_6H_8N_2O_2S$: C, 41.82; H, 4.68; N, 16.28%.

1-Acetyl-3,5-dimethyl-2-thioxo-4-imidazolidinone (IV) and 1-acetyl-3,5,5-trimethyl-2-thioxo-4-imidazolidinone (V) were prepared by treating the adducts of amino acids [alanine for (IV), 2-amino-2-methyl-propionic acid for (V)] and isothiocyanatomethane with acetic anhydride. (IV): mp 52-54°C, bp 112-113°C/4 mmHg. IR ($CHCl_3$) C=O: 1750, 1700 cm^{-1}, C=S: 1350 cm^{-1}, NMR (C_6H_5CN,δ): 2.78 (s,3H,$COCH_3$), 3.23 (s,3H,N-CH_3). Found: C, 44.91; H, 5.43; N, 15.10%. Calcd for $C_7H_{10}N_2O_2S$: C, 45.14; H, 5.41; N, 15.03%. (V): mp 79-81°C, bp 127°C/11 mmHg. IR (CCl_4) C=O: 1750, 1700 cm^{-1}, C=S: 1340 cm^{-1}, NMR (C_6H_5CN,δ): 2.80 (s,3H,$COCH_3$), 3.26 (s,3H,N-CH_3). Found: C, 47.98; H, 6.10; N, 13.98%. Calcd for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99%.

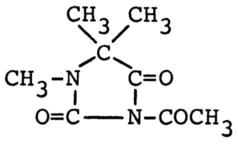
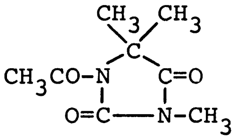
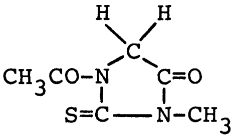
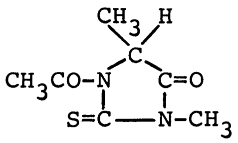
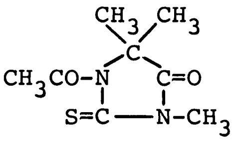
In the acetylation of the adducts, formation of the two tautomeric compounds, N-acetyl and S-acetyl compounds, is conceivable. The IR spectra of the products, however, showed a band at about 1350 cm^{-1} due to C=S, but not a band due to C=N at about 1560 cm^{-1}, supporting the formation of N-acetyl compounds.

Experiments were carried out by heating an equimolar mixture of acetylating agent and substrate in benzonitrile or DMSO-d_6 at given temperatures. After a certain time, an aliquot of the solution was subjected to NMR analysis.

The peak of the N-methyl protons of deacetylated acetylating agent slightly shifted from the position of that of the original compound. The summarized intensities of the N-methyl protons deacetylated and unreacted acetylating agents, however, agreed with the sum of the intensities of the methyl protons of acetyl groups of unreacted acetylating agent and acetylated substrate. This result suggests the usefulness of the N-methyl protons as internal standard for NMR analysis and the absence of intermediate, such as the ring-open adduct which was found in the reaction of 2-benzoyl-1,2-benzisothiazol-3(2H)-one-1,1-dioxide with amine.[8]

The degree of acetylation was estimated from the ratio of the integrated intensity of the methyl protons of acetyl group of acetylated substrate to that of the N-methyl protons of the internal standard. The results are shown in Table I.

Table I. Trans-acetylation with acetylating agents

Acetylating agent	Substrate	Reaction temp. (°C)	Reaction time (h)	Degree of acetylation (%)	
(I): 	Phenol	80	3	13.5	
	2-Naphthalenol	80	3	15.5	
	4-Hydroxy benzene-methanol	80	40	100	phenolic 87% alcoholic 13%
	Benzenamine	80	3	74	
	2-Aminophenol*	80	15	100	only N-acetylation
	2-Aminoethanol	40	0.5	100	"
	L-Tyrosine methyl ester**	40	1	100	"
(II): 	Phenol	80	40	0	
	2-Naphthalenol	80	40	0	
	Benzenamine	80	12	0	
	L-Tyrosine methyl ester**	40	12	0	
(III): 	Phenol	80	40	0	
	2-Naphthalenol	80	40	0	
	4-Hydroxy benzene-methanol	80	40	0	
	Benzenamine	80	6	6	
	DL-Alanine methyl ester	40	3	58	
(IV): 	Phenol	80	40	0	
	2-Naphthalenol	80	40	0	
	4-Hydroxy benzene-methanol	80	40	0	
	Benzenamine	80	3	88	
	2-Aminoethanol	40	0.5	100	only N-acetylation
	DL-Alanine methyl ester	40	3	90.5	
	L-Tyrosine methyl ester**	40	1	100	only N-acetylation
(V): 	Phenol	80	40	0	
	2-Naphthalenol	80	40	0	
	4-Hydroxy benzen-methanol	80	40	0	
	Benzenamine	80	3	37.5	
	DL-Alanine methyl ester	40	3	83	
	L-Tyrosine methyl ester**	40	1	100	only N-acetylation

Solvent: Benzonitrile Acetylating agent: 500 mmol/l Substrate: 500 mmol/l

*) Substrate: 250 mmol/l **) Solvent: DMSO-d_6

(I) showed not only the selectivity toward phenolic hydroxy group in O-acetylation, as reported by Orazi and Corral,[5)] but exhibited the higher reactivity toward amino group in amino alcohols and amino phenols. On the other hand, (II) was unreactive even for amino group.

Compounds (III), (IV) and (V), were inactive for the acetylation of hydroxy group but reactive for the acetylation of amino group. In particular, the activity of (IV) for the acetylation of amino group was nearly equal to that of (I).

The inactivity of (II), differing from (I), may be attributed to the smaller acidity of the imino group of 1-position than that of 3-position.

The fact that (III), (IV) and (V) show the high activity toward amino group but (II) is inactive, is of quite interest.

Okawara *et al.*[9)] found that 4-acetyl-2-phenyl-1,3,4-oxadiazoline-5-thione and 4-acetyl-2-phenyl-1,3,4-thiadiazoline-5-thione are reactive about 1000 times more than the corresponding 5-one derivatives in the acetylation of cyclohexanamine.

The reason why the thiocarbonyl derivatives are more active compared with the carbonyl derivatives is not clear but it might be attributed to the greater acidity of the imino group in the thiocarbonyl derivatives compared with that in the carbonyl derivatives.

The difference in the activity among (III), (IV) and (V) should be ascribed to the difference in the substituents in 5-position but the exact nature of the substituent effect is obscure.

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