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GENERATION OF AN ACTIVE ACYL SPECIES FROM STABLE 1-METHYL-2-ACYL-1H-IMIDAZOLES

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Abstract: 1-Methyl-2-(1'-cyano-1'-trimethylsilyloxy)alkyl-1H-imidazoles (2) were easily prepared from the corresponding stable carbonyl compounds, 1-methyl-2-acyl-1H-imidazoles (1). When the quarternary salts of 2 were treated with various nucleophiles, reactive acyl species, which was presumed to be acylcyanide (12), was generated *in situ* under C-C bond fission to result in producing the corresponding acylated compounds (5 - 10) in good yields.

Recently many useful activation methods for carboxyl group have been reported and generally speaking the acyl group in their activated forms are usually linked to a heteroatom such as O, N, S or halogen[1]. In the previous paper[2], the authors reported a useful methodology for masking of carbonyl groups by using 1-methyl-1H-imidazol-2-yl moiety[3]. In this communication, the authors would like to report a new type of active acyl source, in which 1-methyl-2-acyl-1H-imidazole system was concerned and reaction of which with nucleophiles included a unique C-C bond fission[4].

2-Acyl-1H-imidazole derivatives have been well known as stable compounds while 1-acyl-1H-imidazole derivatives have been well applied in organic syntheses as one of the important active acyl species[5,6]. In our experiments, 1-methyl-2-benzoyl-1H-imidazole (1a) was almost inactive toward the following conditions: n-propylamine (as a solvent)/80°/10 hr; 10% K_2CO_3 aq./EtOH/80°/10 hr; 20% H_2SO_4/80°/10 hr; CF_3COOH (as a solvent)/r.t./17 hr[7]. The authors considered that the acyl group of 1 might be activated by quarternization of 1 with appropriate alkylating agent sufficiently to permit attacks of various nucleophiles[8]. However prolonged reaction time (>10 hr) or higher reaction temperature (>100° in a sealed tube) was required for quantitative conversions of 1 to their quarternary salts (4) by treating with CH_3I, $C_6H_5CH_2Br$ or $(CH_3)_2SO_4$ in refluxed THF or ethyl acetate[9]. Therefore, conversion of 1 to cyanhydrin was attempted in order to increase the basicity of the imidazole ring prior to the quarternization step. Although treatment of the imidazoles (1) with acetone cyanhydrin[10] did not afford the corresponding cyanhydrin except in case of 1-methyl-2-formyl-1H-imidazole[11], treatment of the imidazoles (1) with trimethylsilylcyanide[12] in the presence of a catalytic amount of n-BuLi easily afforded the corresponding O-silylated cyanhydrins (2)[13]. It was found that the O-silylated cyanhydrins (2) were easily

Scheme 1

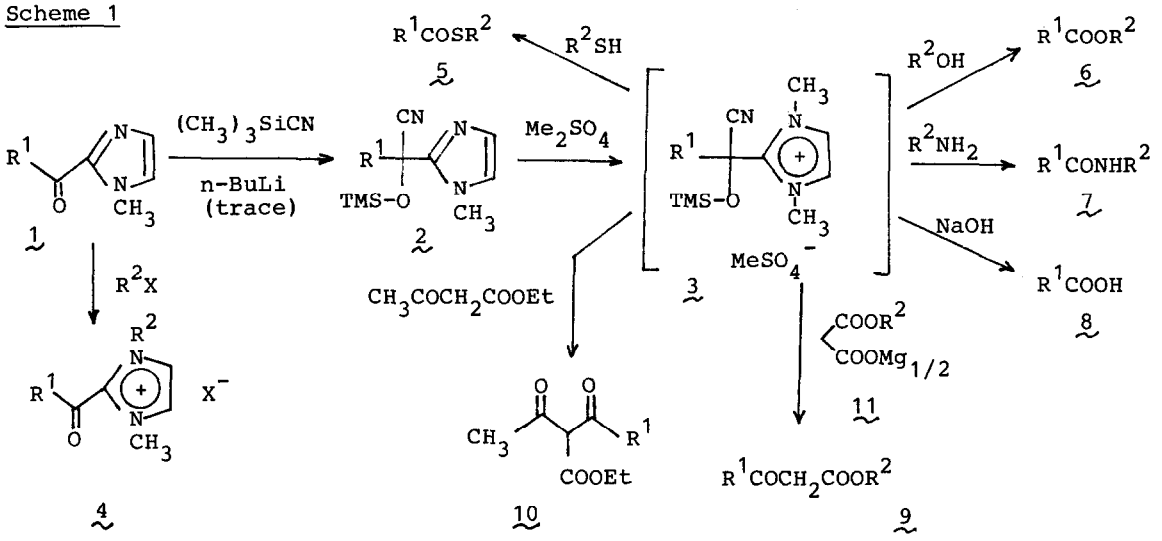
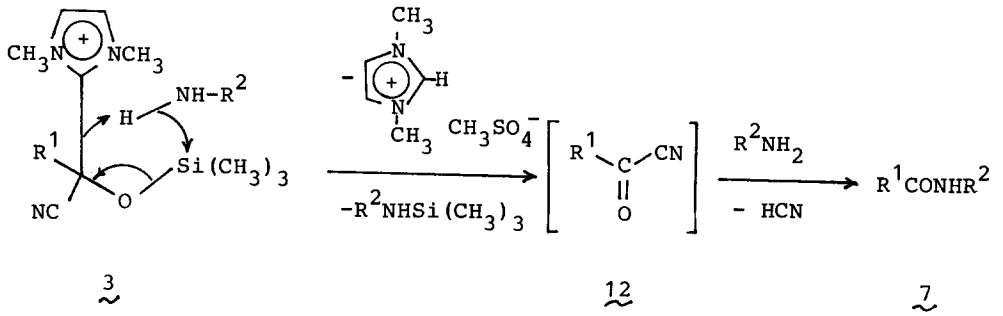


TABLE 1. REACTION OF THE O-SILYLATED CYANHYDRIN QUARTERNARY SALT (3) WITH VARIOUS NUCLEOPHILES

Starting Material (1)	R^1 of 1	Nucleophile	Condition (3 to 5 - 10)	Product	Isolated Yield (%)
1a	C_6H_5	$H_2N(CH_2)_5COONa$	a	7a ($C_6H_5CONH(CH_2)_5COOH$)	93.3
1a	C_6H_5	11 (R^2= CH_3)	b	9a (R^1= Ph;R^2= CH_3)	92.4
1a	C_6H_5	CH_3OH	c	6a (R^1= Ph;R^2= CH_3)	87.1
1b	c-C_6H_{11}	n-$PrNH_2$	d	7b (R^1= c-C_6H_{11};R^2= n-Pr)	73.0
1b	c-C_6H_{11}	C_2H_5SH	e	5b (R^1= c-C_6H_{11};R^2= Et)	96.3
1c	piperonyl	i-PrOH	c	6c (R^1=piperonyl;R^2= i-Pr)	76.1
1c	piperonyl	NaOH	f	8c (piperonylic acid)	74.7
1c	piperonyl	CH_3COCH_2COOEt	g	10c (R^1= piperonyl)	66.3
1d	n-hexyl	NaOH	f	8d (n-heptanoic acid)	65.4
1d	n-hexyl	11 (R^2= benzyl)	b	9d (R^1= n-hexyl;R^2= benzyl)	89.9
1f	$Me_2C{=}C^{H}(CH_2)_2C^{Me}HCH_2$	CH_3OH	c	6f ($Me_2C{=}C^{H}(CH_2)_2C^{Me}HCH_2COOMe$)	80.3
1g	TMSO-$(CH_2)_3$	$C_6H_5(CH_2)_3NH_2$	d,h	7g ($HO(CH_2)_3CONH(CH_2)_3C_6H_5$)	71.0

a: four equiv. of 1.6M solution of the nucleophile/r.t./3hr.
b: 5 mmol of 1/2.5 equiv. of the nucleophile/DMF 5ml/r.t./17hr.
c: 5 mmol of 1/3ml of the nucleophile/triethylamine 1ml/r.t./3hr.
d: 5 mmol of 1/the nucleophile (12.5 mmol)/r.t./3hr.
e: 5 mmol of 1/2.5 equiv. of the nucleophile/triethylamine 1ml/r.t./3hr.
f: 5 mmol of 1/2N-NaOH aq. (5ml)/r.t./3hr.
g: equimolar amount of the nucleophile/1.5 equiv. of triethylamine/r.t./2hr.
h: The trimethylsilylether protection of the initial product was removed by treating with trifluoroacetic acid.

converted to the quarternary salts (3) by treating with $(CH_3)_2SO_4$ at 70° for several hours. Furthermore, sufficient electrophilicities of the salts (3) were observed in the reactions with more than two equivalents of various nucleophiles such as alcohol[14], amine, mercaptane[14], NaOH, Masamune's reagent (11)[15] or ethyl acetoacetate[14] producing their respective acylated compounds (5 - 10). The authors postulated the acylcyanide (12)[16] as a possible intermediate in the present acylation reaction as well as the acylated quarternary salt (4). Thus the following experiments were practiced for presuming the reaction path. The quarternary salt (4a, R^1=Ph, R^2=CH_3, X=I, mp 220° decomp.), which was prepared by refluxing a solution of 1a in AcOEt-CH_3I at 100° in a sealed tube, reacted with methanol[14], n-propylamine and NaOH to give the respective acylated products (6a, 7a and 8a). So the authors believed initially that the salt (4) might be an intermediate in the reaction of 1 with nucleophiles. However the salt (4a) reacted in only slight extent (<10% yield) with Masamune's reagent (11, R^2=CH_3) under the similar reaction condition as in the case of 3a. Therefore, the authors now tentatively speculate that the acylcyanide (12) might be produced as an active acyl intermediate as illustrated in the scheme 2, in which reaction with primary amine is shown as an example.



3 12 7

Scheme 2

TYPICAL PROCEDURE (Conversion of 1b to n-Propyl Cyclohexanecarboxamide, 7b, R^1=c-C_6H_{11}, R^2=n-propyl): Five drops of 1.6M-n-BuLi in n-hexane were added to a solution consisting of 1-methyl-2-cyclohexylcarbonyl-1H-imidazole (1b, 5 mmol), trimethylsilylcyanide (5.5 mmol) and THF (10 ml) under N_2, and the mixture was stirred at r.t. for 2 hr. Dimethyl sulphate (6 mmol) was added to it and the mixture was stirred at 70° for 2 hr[17]. n-Propylamine (12.5 mmol) was added to it under ice-cooling followed by stirring at r.t. for 3 hr. EtOAc and d-HCl were added, and the organic phase was washed with H_2O, 5% $NaHCO_3$, then dried. Crystalline residue after evaporation of the solvent was distilled under vacuum, bp 140 - 145° (bath temp. of Kugel-Rohr dist.) at 2 mmHg (mp 68 - 70°), yield: 617 mg (73.0%). The product was identical in all respects with the sample obtained by treating 1-cyclohexylcarbonyl-1H-imidazole with n-propyl-

amine[5]. Variations of the procedure for other nucleophiles are listed in the Table 1.

Characteristic features of the compound 1 are being basic, being stable under various severe conditions and having strong UV absorptions, and these properties may add some practically useful value to the present acyl activation reaction. Recently uses of stable molecular system as "latent synthon" or "built-in block" have become important for syntheses of complex molecules[18]. 2-Acyl-1H-imidazole (1) can be regarded as a new latent synthon as well as 2-(1'-hydroxyalkyl)-1H-imidazole which was introduced in the previous paper[2,19].

REFERENCES AND FOOTNOTES

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2) S.Ohta, S.Hayakawa, K.Nishimura, M.Okamoto, Tetrahedron Lett., 25, 3251 (1984).
3) It should be added to the previous paper (ref. 2) that production of aldehyde by basic treatment of 2-(1'-hydroxyalkyl)thiazolinium salt was reported in ref. 4 below in connection with study on mechanism of thiamine pyrrophosphate-catalysed reactions. But the reaction was not treated with preparative sense.
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7) When heated 1a at 80° for 10 hr in 2N-NaOH-EtOH, about fourty percent of 1a was consumed (GLC analysis).
8) Kamijo reported that the quarternary salt of 1-acyl-1H-imidazole derivatives were efficient acylating agents (T.Kamijo, R.Yamamoto, H.Harada, and K.Iizuka, Chem. Pharm. Bull. (Tokyo), 30, 4242 (1982)).
9) Among these reagents, Me_2SO_4 was most powerful. Conversion of 1a to 4a was relatively easy (>95% conversion: 1.2 equiv. Me_2SO_4/THF/reflux/2hr), but sixty % of 1b was recovered under the same condition (25% was recovered after 10hr).
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11) mp ca. 240° decomp.
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13) They were too unstable to isolate probably because of high instability toward moisture, but the conversion of 1 to 2 could be checked by GLC.
14) Cooperation with triethylamine was required.
15) D.W.Brooks, L.-D.Lu, and S.Masamune, Angew. Chem. Int. Ed., 18, 72 (1979).
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17) Deposit of the quarternary salt (3) was sometimes formed at this stage.
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19) All isolated products, appeared in this paper, have been fully characterized.

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