ONE-POT SELECTIVE ACYLATION OF AMINES USING 3,6-DIETHYL-2-HYDROXYPYRAZINE AS ACYL CARRIER

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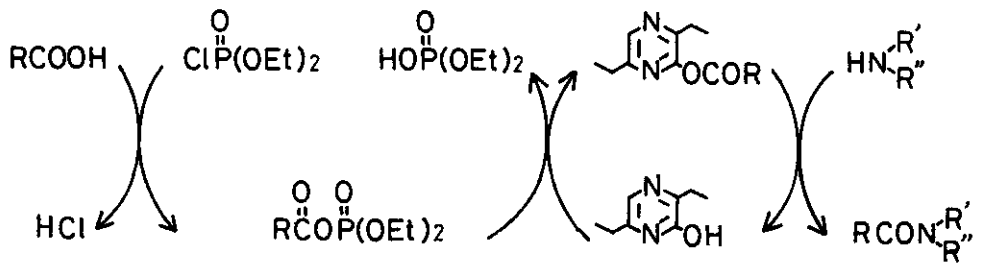
Abstract —— Introduction of 3,6-diethyl-2-hydroxypyrazine into a system of amide syntheses using acyl diethylphosphates resulted in the performance of selective acylation in satisfactory yields.

Activation of carboxyl groups under mild conditions is apparently of great value as a fundamental process in a wide scope of organic syntheses[1]. Recently, it has been noticed that the O-acyl products derived from 2-hydroxypyrazines are susceptible to aminolysis under mild conditions and the corresponding amides are prepared in high yields[2]. The present report is concerned with a further utilization of a 2-hydroxypyrazine for one-pot selective amide syntheses. As already known, the subsequent addition of an amine to a mixture of a carboxylic acid and diethyl chlorophosphate gives rise to prepare the corresponding amides[3]. In this reaction system, acyl diethylphosphates are thought to be formed as intermediates, which perform the acylation of amines. The addition of 3,6-diethyl-2-hydroxypyrazine[4] to this reaction



system led to the formation of 2-acyloxy-3,6-diethylpyrazines which exert the selective acylation of amines. The formation of 2-acyloxy-3,6-diethylpyrazines was confirmed with the isolation of 2-benzoyloxy-3,6-diethylpyrazine from a reaction system using benzoic acid.

The present efficient procedure for the one-pot amide syntheses may consist essentially of two reactions, the formation of the active esters, 2-acyloxy-3,6-diethylpyrazines, from acyl diethylphosphates and 3,6-diethyl-2-hydroxypyrazine, and the subsequent aminolysis of the active esters. This one-pot reaction proceeded smoothly at room temperature to give the corresponding amides in satisfactory yields as shown in Table 1. In all cases of the acylation, the starting 2-hydroxypyrazine was recovered in good yields.

Table 1. Acylation of Amines using 3,6-Diethyl-2-hydroxypyrazine as Acyl Carrier

Entry	Carboxylic Acid	Amine	Product	Yield (%)	mp (°C) or bp (°C/torr) found (reported)
1	benzoic	aniline	benzanilide	81	mp 164-165° (mp 163°)[5]
2	benzoic	benzylamine	N-benzoylbenzylamine	83	mp 102-104° (mp 105-106°)[5]
3	benzoic	N-methylaniline	N-methylbenzanilide	75	bp 155-156°/2 (bp 331-332°)[5]
4	benzoic	N-methyl-benzylamine	N-benzoyl-N-methyl-benzylamine	80	bp 160-165°/2 (bp 212-214°/10)[6]
5	benzoic	pyrrolidine	1-benzoyl-pyrrolidine	62	bp 133-136°/2 (bp 132°/2)[7]
6	crotonic	aniline	crotonanilide	71	mp 115-116° (mp 118°)[8]
7	crotonic	benzylamine	N-benzylcrotonamide	68	mp 114-116°
8	crotonic	piperidine	1-crotonoylpiperidine	56	bp 90°/1 (bp 160°/30)[9]
9	3-chloroacrylic	aniline	3-chloroacrylanilide	65	mp 152-153°
10	3-chloroacrylic	benzylamine	N-benzyl-3-chloro-acrylamide	62	mp 111-112°
11	3-chloroacrylic	pyrrolidine	1-(3-chloroacrylyl)-pyrrolidine	51	mp 44-45°
12	cinnamic	spermidine	maytenine	27	mp 158-159° (mp 158°)[10]

This one-pot system was shown to perform the selective acylation of amines. In the competition reactions on benzoylation, it was indicated that there is a difference of easiness of acylation between various amines as demonstrated in Table 2. Based on the data, one might conclude that the ease of acylation by this reaction system may eventually be in order as shown below.

aliphatic primary amines = aliphatic secondary amines > *aromatic primary amines* > *aromatic secondary amines*

The acylation without addition of 3,6-diethyl-2-hydroxypyrazine did not show such selectivity.

Consequently, it is worth to point out that this one-pot acylation system under mild conditions has a unique ability to cause a highly selective acylation of amines.

Table. 2. Competitive Acylation of Amines with Benzoic Acid

Entry	Amine	Product	Yield (%)
1	aniline, benzylamine	N-benzoylbenzylamine	95
2	aniline, N-methylaniline	benzanilide	89
3	benzylamine, N-methylbenzylamine	a 1:1 mixture of N-benzoyl-benzylamine and N-benzoyl-N-methylbenzylamine[b]	
4	aniline, N-methylbenzylamine	N-benzoyl-N-methylbenzylamine	92
5[a]	aniline, benzylamine	a 1:1 mixture of benzanilide and *N-benzoylbenzylamine*[b]	
6[a]	aniline, N-methylaniline	a 1:1 mixture of benzanilide and N-benzoyl-N-methylaniline[b]	

a: 3,6-Diethyl-2-hydroxypyrazine was not added.
b: The ratio was confirmed with the measurement of the ^{1}H-NMR spectra.

EXPERIMENTAL

All melting and boiling points are uncorrected. The following instruments were used for obtaining the spectral data. ^{1}H-NMR: Varian EM-360 and EM-390; IR spectra: Shimadzu IR-400; UV spectra: Hitachi Model557; MS: Hitachi M-80 spectrometer.

Isolation of 2-Benzoyloxy-3,6-diethylpyrazine --- To a mixture of benzoic acid (605 mg, 5 mmol) and triethylamine (606 mg, 6 mmol) in acetonitrile (25 ml), diethyl chlorophosphate (863 mg, 5 mmol) was added dropwise. After stirring for 3 h at room temperature, 3,6-diethyl-2-hydroxypyrazine (760 mg, 5 mmol) was added to the solution, which was allowed to be stirred overnight. The solvent was removed to dryness in vacuo, and the residue was dissolved in methylene chloride. The solution was then washed with cold 10% KOH (20 ml x 3), 10% HCl (20 ml x 3) and water (20 ml), successively, dried over Na_2SO_4 and concentrated to afford 2-benzoyloxy-3,6-diethylpyrazine (956 mg, 75%) as a colorless oil, which was identified by the comparison of the IR spectrum with that of the authentic specimen[2].

General Procedure for Acylation of Amines --- To a solution of a carboxylic acid (5 mmol) and triethylamine (606 mg, 6 mmol) in acetonitrile (25 ml) was added diethyl chlorophosphate (863 mg, 5 mmol) under stirring at room temperature in a few minutes. After stirring for 3 h, 3,6-diethyl-2-hydroxypyrazine (760 mg, 5 mmol) was added to the mixture, which was allowed to stand overnight. Then an amine (5 mmol) was added to the mixture, which was stirred for 2 h. After the solvent was removed in vacuo, the residue was dissolved in methylene chloride (25 ml). The solution was washed successively with 10% KOH (20 ml x 3), 10% HCl (20 ml x 3) and water (20 ml), and dried over Na_2SO_4. Evaporation of the solvent afforded the amides, which were purified by distillation or recrystallization. The starting pyrazinol was recovered from the 10% KOH layer in ca. 85% yields.

In the case of the preparation of maytenine, di-trans-cinnamoylspermidine, isolated from Maytenus chuchuhuasha[10], crystals appeared in the reaction mixture. The crystals were collected by suction filtration and washed successively with a small amount of chloroform and water, and then dried. The products were recrystallized from acetone to give colorless needles, mp 158-159°C.

N-Benzylcrotonamide: MS: m/e 175 (M^+), 160 (M^+-CH_3); IR (KBr): 1680 (C=O) cm^{-1}; UV: λ_{max}^{EtOH} 208.5 (log ε = 3.87) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.82 (dd, J = 2 and 7 Hz, 3H, CH_3), 4.48 (d, J = 6 Hz, 2H, CH_2), 5.87 (dq, J = 2 and 15 Hz, 1H, CH), 6.18 (br. s, 1H, NH), 6.92 (dq, J = 7 and 15 Hz, 1H, $CH_3\underline{CH}$), 7.03 (s, 5H, benzene H) ppm; Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.10; H, 7.48; N, 7.98.

3-Chloroacrylanilide: MS: m/e 181 (M^+), 146 (M^+-Cl); IR (KBr): 1660 (C=O) cm^{-1}; UV: λ_{max}^{EtOH} 215 (log ε = 4.01), 275 (3.85) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 6.45 (d, J = 14 Hz,

1H, CH), 7.52 (d, J = 14 Hz, 1H, CH), 7.52 (m, 5H, benzene H) ppm; Anal. Calcd. for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.58; H, 4.47; N, 7.50

N-Benzyl-3-chloroacrylamide: MS: m/e 195 (M^+), 160 (M^+-Cl); IR (KBr): 1650 (C=O) cm^{-1}; UV: λ_{max}^{EtOH} 212 (log ε = 4.12) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 4.45 (d, J = 6 Hz, 2H, CH_2), 6.29 (d, J = 13 Hz, 1H, CH), 7.31 (d, J = 13 Hz, 1H, CH), 7.37 (s, 5H, benzene H) ppm; Anal. Calcd. for $C_{10}H_{10}ClNO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.24; H, 5.28; N, 7.16.

1-(3-Chloroacrylyl)pyrrolidine: MS: m/e 159 (M^+), 124 (M^+-Cl); IR ($CHCl_3$): 1640 (C=O) cm^{-1}; UV: λ_{max}^{EtOH} 220 (log ε = 4.10), 250 (3.72, shoulder) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.73-2.13 (m, 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$), 3.37-3.73 (m, 4H, $\underline{CH_2}CH_2CH_2\underline{CH_2}$), 6.62 (d, J = 14 Hz, 1H, CH), 7.42 (d, J = 14 Hz, 1H, CH) ppm; Anal. Calcd. for $C_7H_{10}ClNO$: C, 52.67; H, 6.31; N, 8.78. Found: C, 52.46; H, 6.34; N, 8.68.

General Procedure for the Competitive Benzoylation of Amines --- Two amines (5 mmol each) were added at once to the mixture, prepared from benzoic acid, triethylamine, diethyl chlorophosphate, and 3,6-diethyl-2-hydroxypyrazine in acetonitrile as above, and stirred for 2 h. The reaction mixture was worked up as described above. The products were estimated by taking ^{1}H-NMR spectra.

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