3,6-Dialkyl-2-hydroxypyrazine 1-Oxides as Acyl Carriers

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3,6-Dialkyl-2-hydroxypyrazine 1-oxides were found to be useful as acyl carriers. Benzoyl derivatives were convenient reagents for benzoylation of amines and hydroxy compounds.

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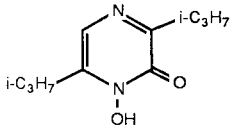
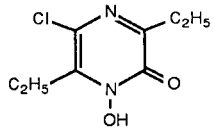
In the previous papers [1], we described that the respective *O*- and *S*-acyl derivatives of 2-hydroxypyrazines and 2-pyrazinethiols are potent acylating agents for amino groups. In other words, 2-hydroxypyrazines and 2-pyrazinethiols are good carriers of acyl groups, such as acetyl, benzoyl, *t*-butoxycarbonyl and benzyloxycarbonyl groups. In continuation of the research on 2-hydroxypyrazines, the present paper describes that 3,6-dialkyl-2-hydroxypyrazine 1-oxides also fulfil the function as acyl carriers, though the function is inferior to that of 2-hydroxypyrazines.

Scheme I

Pyrazinols **1-2** used as Carriers



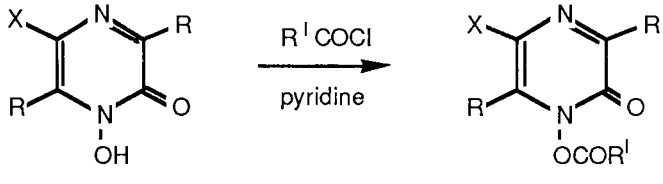
1 [2]



2 [2]

Table I

Preparation of 1-Benzoyloxy-1,2-dihydro-2-oxopyrazines **3-8**



1 - 2 **3 - 8**

Compounds	R	X	R'	Yield (%)
3	i-C_3H_7	H	C_6H_5	64
4	i-C_3H_7	H	p-$CH_3C_6H_4$	79
5	i-C_3H_7	H	p-ClC_6H_4	91
6	C_2H_5	Cl	C_6H_5	99
7	C_2H_5	Cl	p-$CH_3C_6H_4$	79
8	C2H5	Cl	p-ClC6H4	91

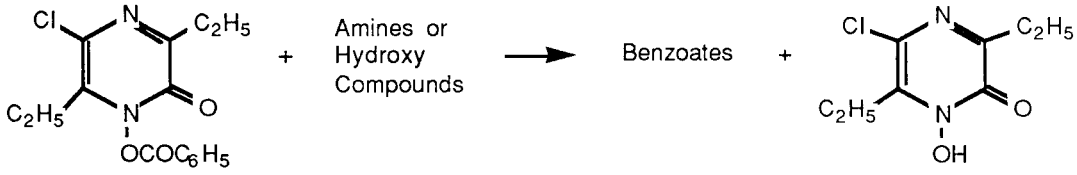
First, the acylation of 3,6-diisopropyl-2-hydroxypyrazine 1-oxide (**1**) [2] and 5-chloro-3,6-diethylpyrazine 1-oxide (**2**) [2] was studied. These compounds were treated with acyl chlorides in pyridine. Among the acylated products, the ones derived from aromatic acid chlorides like benzoyl chloride, *p*-methylbenzoyl chloride and *p*-chlorobenzoyl chloride were stable enough to be recrystallized from the appropriate solvents. As the infrared spectra of the products showed two strong bands of the carbonyl group, the structure of these compounds may be consistent with 1-acyloxy-1,2-dihydro-2-oxopyrazine. On the other hand, the fatty acid esters derived from acetyl chloride, propionyl chloride and butyryl chloride were unstable, and could not be purified by distillation and recrystallization.

The esters thus prepared were submitted to the reaction with some amines and hydroxy compounds, under the conditions in Table II. When **6** was allowed to stand for 30 minutes at room temperature with benzylamine, *N*-methylbenzylamine and aniline, respectively, the corresponding benzoates were obtained in almost quantitative yields. However, the benzoate of *N*-methylaniline was barely prepared in satisfactory yields, by extending the reaction time. Benzyl alcohol and cyclohexanol gave the respective benzoates only in poor yields in the reaction at room temperature, and in satisfactory yields under reflux in benzene. The yield of the benzoate of β-naphthol was unsatisfactory, even under reflux in benzene in the presence of triethylamine.

The reaction of **3** with amines and hydroxy compounds was also studied. The results were much the same as those in the reaction of **6**.

Because the acetates of compounds **3-8** were unstable, the acetylation in a one-pot reaction system using **2** as the carrier of the acetyl group was studied under similar conditions reported [3]. To a solution of **2** in 1,2-dimethoxyethane, sodium hydride, acetyl chloride, and then an amine or hydroxy compound were successively added. The results, shown in Table III, indicate that the acetates of 2-hydroxypyrazine 1-oxides have the ability to acetylate amines and hydroxy compounds.

Table II
Benzoylation of Amines and Hydroxy Compounds with Benzoate 6

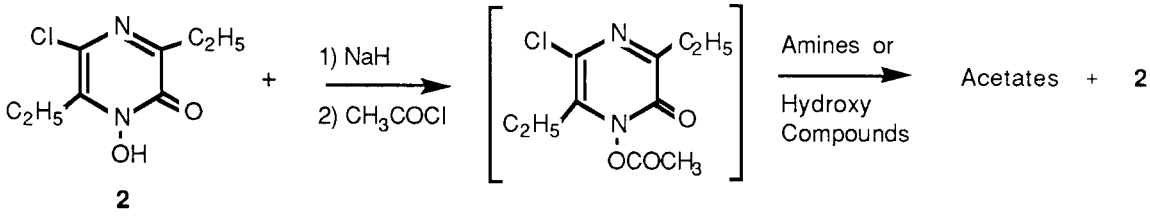


6 2

Substrates	Solvent	Reaction Temperature	Reaction Time (hour)	Yield (%)
Benzylamine	ether	rt	0.5	99
N-Methylbenzylamine	ether	rt	0.5	96
Aniline	ether	rt	0.5	98
N-Methylaniline	ether	rt	0.5	33
N-Methylaniline	ether	rt	4	91
Benzylalcohol	benzene	reflux	3	90
Cyclohexanol	benzene	reflux	3	87
β–Naphthol	benzene	reflux	3	4
β–Naphthol	benzene	reflux	3	38 [a]

[a] Triethylamine was added.

Table III
Acetylation of Amines and Hydroxy Compounds using **2** as the Carrier

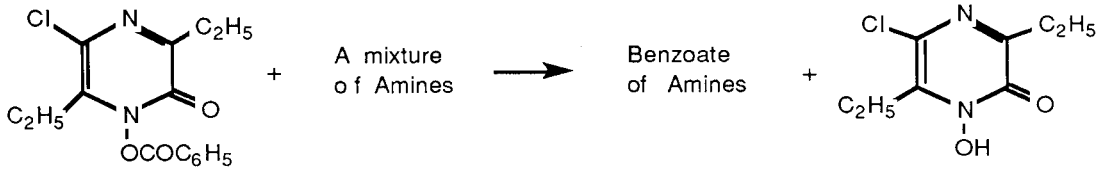


2

Substrates	Reaction Temperature	Reaction Time (minutes)	Yield (%)
Benzylamine	rt	10	82
N-Methylbenzylamine	rt	10	84
Aniline	rt	10	79
N-Methylaniline	rt	10	74
Benzylalcohol	reflux	60	85
β-Naphthol	reflux	60	4
β–Naphthol	reflux	60	3[a]

[a] Triethylamine was added.

Table IV
Concurrent Benzoylation of Amines



6 2

Substrates	Product (ratio)
Bezylamine/ Aniline	N-Acetylbenzylamine/ Acetanilide (28:1)
Benzylamine/ N-Methylbenzylamine	N-Acetylbenzylamine/ N-Acetyl-N-methylbenzylamine (1:1)
Benzylamine/ N-Methylaniline	N-Acetylbenzylamine
Aniline/ N-Methylaniline	Acetanilide
Aniline/ N-Methylbenzylamine	Accetanilide/ N-Acetyl-N-methylbenzylamine (1:18)

The concurrent reaction on benzoylation of benzylamine, *N*-methylbenzylamine, aniline and *N*-methylaniline was next studied. Various mixtures composed of the two amines (2 mmoles of each) in ether were allowed to stand with **6** (2 mmoles) for 3 hours at room temperature. The products were purified by hplc and identified by comparison of the ir spectra with those of authentic specimens, and the results are given in Table IV. On the basis of these results, one might conclude that this reagent may discriminate between amines, namely, ease of benzoylation by this reagent may eventually be in order as follows; aliphatic primary amines = aliphatic secondary amines > aromatic primary amines > aromatic secondary amines.

Conclusively, the acyl derivatives of 3,6-dialkyl-2-hydroxypyrazine 1-oxides have the ability to acylate amines and hydroxy compounds. However, the ability of the acyl derivatives of 3,6-dialkyl-2-hydroxypyrazines and 3,6-dialkyl-2-pyrazinethiols is slightly superior to those of the acyl derivatives of 3,6-dialkyl-2-hydroxypyrazine 1-oxides in regard to selective acylation of amines.

EXPERIMENTAL

Melting points were recorded on a Yanagimoto micro-melting point apparatus and are uncorrected. The uv spectra were recorded in 95% ethanol using a Hitachi 557 spectrophotometer, ir spectra on a Shimadzu IR-400 spectrometer and pmr spectra in deuteriochloroform using a Varian EM-360 instrument with tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi M-80 spectrometer. For silica gel column chromatography, Wakogel C-200 (Wako Pure Chemical Industries, Ltd., Tokyo) was used. The hplc were carried out with a UVILOG ALPC-100 (Oyo-Bunko Kiki Co., Ltd., Tokyo) as a pump, a UVLILOG 5 IIIa as a detector and Kieselgel 60 (Merck AG, Darmstadt) as a packing material.

General Procedure for Preparation of 1-Benzoyloxy-3,6-dialkyl-1,2-dihydro-2-oxopyrazines **3-8**.

An acyl chloride (30 mmoles) was added dropwise to a solution of a 3,6-dialkyl-2-hydroxypyrazine 1-oxide (20 mmoles) and pyridine (10 ml) in dichloromethane (100 ml) in 10 minutes under ice-cooling, and the reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was washed successively with 1% hydrochloric acid, 1% potassium hydroxide, and water, and then dried over sodium sulfate. After removing the solvent by distillation, the resulting solid was recrystallized from hexane. According to the circumstances the product was purified by column chromatography on silica gel eluting with hexane containing increasing amounts of ethyl acetate.

1-Benzoyloxy-1,2-dihydro-3,6-diisopropyl-2-oxopyrazine (**3**).

This compound had the following physical properties: colorless prisms (from hexane), mp 66-68°; uv: λ max 233 (log ε = 4.44), 320-324 (4.03) nm; ir (potassium bromide): 1670, 1780 (C=O) cm^{-1}; pmr: δ 1.27 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 1.30 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 2.90 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 3.47 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 7.22 (1H, s, pyrazine H), 7.43-7.77 (3H, m, benzene H), 8.13-8.30 (2H, m, benzene H) ppm; ms: m/e 300 (M^+), 105 ($C_6H_5CO^+$).

Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.30. Found: C, 68.07; H, 6.53; N, 9.23.

1-*p*-Methoxybenzoyloxy-1,2-dihydro-3,6-diisopropyl-2-oxopyrazine (**4**).

This compound had the following physical properties: colorless needles (from hexane), mp 85-87°; uv: λ max 237 (log ε = 4.20), 317-322 (3.82) nm: ir (potassium bromide): 1670, 1780 (C=O) cm^{-1}; pmr: δ 1.25 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 1.29 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 2.44 (3H, s, CH_3), 2.88 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 3.45 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 7.15 (1H, s, pyrazine H), 7.30 (2H, d, J = 8 Hz, benzene H), 8.03 (2H, d, J = 8 Hz, benzene H) ppm; ms: m/e 314 (M^+), 119 ($CH_3C_6H_4CO^+$).

Anal. Calcd. for $C_{16}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.91; H, 7.08; N, 9.13.

1-*p*-Chlorobenzoyloxy-1,2-dihydro-3,6-diisopropyl-2-oxopyrazine (**5**).

This compound had the following physical properties: colorless prisms (from hexane), mp 77-80°; uv: λ max 231 (log ε = 4.22), 323-328 (3.72) nm; ir (potassium bromide): 1660, 1770 (C=O) cm^{-1}; pmr: δ 1.24 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 1.29 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 2.89 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 3.46 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 7.21 (1H, s, pyrazine H), 7.55 (2H, d, J = 8 Hz, benzene H), 8.17 (2H, d, J = 8 Hz, benzene H) ppm; ms: m/e 334 (M^+), 139 ($ClC_6H_4CO^+$).

Anal. Calcd. for $C_{17}H_{19}ClN_2O_3$: C, 60.99; H, 5.72; N, 8.37. Found: C, 60.80; H, 5.71; N, 8.24.

1-Benzoyloxy-5-chloro-3,6-diethyl-1,2-dihydro-2-oxopyrazine (**6**).

This compound had the following physical properties: colorless prisms (from hexane), mp 84-85°; uv: λ max 236 (log ε = 4.54), 332-334 (4.02) nm; ir (potassium bromide): 1680, 1780 (C=O) cm^{-1}; pmr: δ 1.23 (3H, t, J = 6 Hz, CH_2CH_3), 1.27 (3H, t, J = 6 Hz, CH_2CH_3), 2.85 (4H, q, J = 6 Hz, 2 x CH_2CH_3), 7.37-7.73 (3H, m, benzene H), 8.07-8.23 (2H, m, benzene H) ppm; ms: m/e 306 (M^+), 105 ($C_6H_5CO^+$).

Anal. Calcd. for $C_{15}H_{15}ClN_2O_3$: C, 58.73; H, 4.93; N, 9.13. Found: C, 58.73; H, 4.91; N, 9.13.

1-*p*-Methylbenzoyloxy-5-chloro-3,6-diethyl-1,2-dihydro-2-oxopyrazine (**7**).

This compound had the following physical properties: colorless prisms (from hexane), mp 126-127°; uv: λ max 241 (log ε = 4.32), 333-337 (3.80) ppm; ir (potassium bromide): 1670, 1780 (C=O) cm^{-1}; pmr: δ 1.23 (3H, t, J = 7.5 Hz, CH_2CH_3), 1.26 (3H, t, J = 7.5 Hz, CH_2CH_3), 2.43 (3H, s, CH_3), 2.49-3.03 (4H, m, J = 7.5 Hz, 2 x CH_2CH_3), 7.29 (2H, d, J = 8 Hz, benzene H), 8.01 (2H, d, J = 8 Hz, benzene H) ppm; ms: m/e 320 (M^+), 119 ($CH_3C_6H_4CO^+$).

Anal. Calcd. for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; N, 8.73. Found: C, 60.04; H, 5.41; N, 8.71.

1-*p*-Chlorobenzoyloxy-5-chloro-3,6-diethyl-1,2-dihydro-2-oxopyrazine (**8**).

This compound had the following physical properties: colorless prisms (from hexane), mp 88-89°; uv: λ max 241 (log ε = 4.49), 342-346 (4.03) nm; ir (potassium bromide): 1690, 1790 (C=O) cm^{-1}; pmr: δ 1.19 (3H, t, J = 7.5 Hz, CH_2CH_3), 1.23 (3H, t, J = 7.5 Hz, CH_2CH_3), 2.50-3.03 (4H, m, J = 7.5 Hz, 2 x CH_2CH_3), 7.54 (2H, d, J = 8 Hz, benzene H), 8.11 (2H, d, J = 8 Hz, benzene H) ppm; ms: m/e 341 (M^+), 139 ($ClC_6H_4CO^+$).

Anal. Calcd. for $C_{15}H_{14}Cl_2N_2O_2$: C, 52.80; H, 4.14; N, 8.21. Found: C, 52.83; H, 4.05; N, 7.95.

General Procedure for Benzoylation of Amines and Hydroxy Compounds.

After a solution of **6** (1 mmole) and an amine (1 mmole) in ether (30 ml) was allowed to stand 30 minutes under stirring, the solution was washed with 10% potassium hydroxide, 10% hydrochloric acid and water, successively. After being dried with sodium sulfate, the solvent was evaporated to leave the product. In the case of hydroxy compounds, benzene (10 ml) was employed as solvent and the reaction mixtures were worked up the same as before. For the reaction of β-naphthol, 1.5 mmoles of triethylamine was added.

General Procedure for One-pot Acetylation of Amines and Hydroxy Compounds.

Sodium hydride (2 mmoles) was dissolved in a 1,2-dimethoxyethane solution (20 ml) of **2** (2 mmoles) under stirring, and then acetyl chloride (2 mmoles) was added at once to the mixture. After being stirred for 1 minute, an amine or hydroxy compound (2 mmoles) was added to the mixture, which was treated under the conditions as stated in Table III, and worked up as before.

Concurrent Benzoylation of Amines.

A solution of two amines (2 mmoles of each) in ether (2 ml) was added at once to a solution of **6** (2 mmoles) in ether (30 ml) under stirring at room temperature. After being stirred further for 3 hours, the reaction mixture was washed with 10% potassium hydroxide, 10% hydrochloric acid and water, successively. After the solution was dried with sodium sulfate, the ether was removed by distillation. According to circumstances, the products were submitted to preparative hplc (column; 20 cm x 20 mm, pressure; 2 kg/cm^2, solvent; hexane-ethyl acetate (2:1 or 3:1)).

REFERENCES AND NOTES

[1] A. Ohta, Y. Inagawa and C. Mitsugi, *J. Heterocyclic Chem.*, **22**, 1643 (1985) and references cited therein.

[2] A. Ohta, S. Masano, M. Tsutsui, F. Yamamoto, S. Suzuki, H. Makita, H. Tamamura and Y. Akita, *J. Heterocyclic Chem.*, **18**, 555 (1981).

[3] A. Ohta, M. Shimazaki, N. Tanekura and S. Hayashi, *Heterocycles*, **20** 797 (1983).