ONE-POT ACYLATION SYSTEM USING PYRAZINETHIOLS

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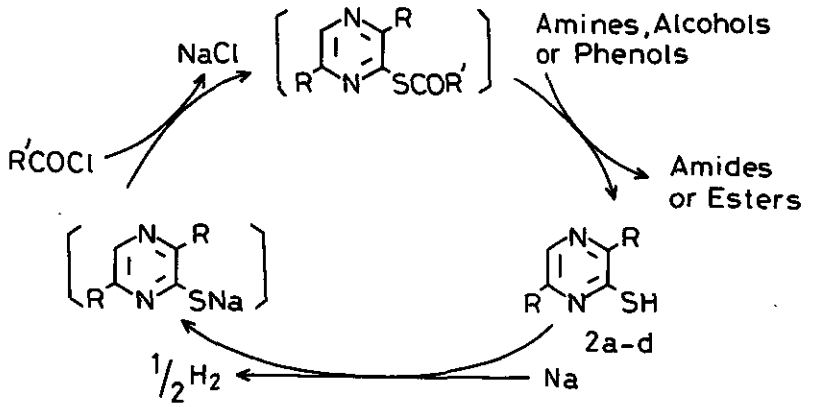
Abstract --- 3,6-Dialkyl-2-pyrazinethiolcarboxylic esters, prepared from 3,6-dialkyl-2-pyrazinethiols, sodium and acyl chlorides in DME, were found to be convenient acylating reagents for amines and hydroxy compounds. Preparation of 3,6-dialkyl-2-pyrazinethiolcarboxylic esters and the following acylation were achieved in a one-pot system. The competition reaction on benzoylation showed that this one-pot system gave rise to the selectivity between acylations of amines, alcohols, and phenols.

Active amides have attracted much attention in recent years because of their ability to acylate amines, alcohols, and phenols.[1-4] In the course of our investigation on pyrazines, we already reported that 2-acyloxy-3,6-dialkylpyrazines, although only applicable to acylation of amines, belong to this class of compounds.[5]



Scheme I

In the present work, pyrazinethiol esters have been adopted in expectation of bigger acylation ability, and we now found that pyrazinethiol esters may be convenient acylating reagents for amines and also for alcohols and phenols. Pyrazinethiol esters were so unstable that they could not be obtained in pure forms. Accordingly, a convenient acylation method as shown in Scheme I was invented, in which the preparation of pyrazinethiol esters and the acylation were carried out continuously in one pot.

The preparation of 3,6-dialkylpyrazinethiols (2a-d) was achieved by heating the corresponding pyrazinols[5,6] with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent),[7] in excellent yields (Table I).

Table I. Physical Properties of Pyrazinethiols

1a-d 2a-d

3,6-Diethyl-2-pyrazinethiol (2a): mp 133-135°C; yield 97%; MS: m/e 168 (M^+); UV: λ_{max}^{EtOH} 242 (log ε = 3.41), 281 (3.86) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.32 (t, J = 7 Hz, 3H, CH_2CH_3), 1.37 (t, J = 7 Hz, 3H, CH_2CH_3), 2.80 (q, J = 7 Hz, 2H, CH_2CH_3), 3.20 (q, J = 7 Hz, 2H, CH_2CH_3), 7.76 (s, 1H, pyrazine H), 13.10-15.00 (bs, 1H, SH or NH) ppm; Anal. Calcd. for $C_8H_{12}N_2S$: C, 57.10; H, 7.19; N, 16.65. Found: C, 57.02; H, 7.07; N, 16.59.

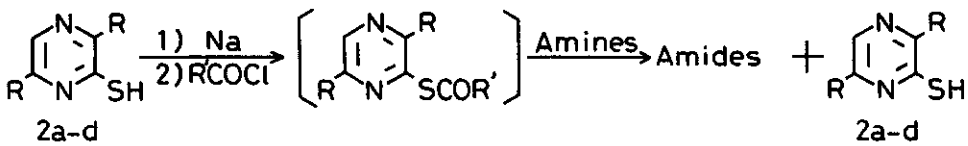
3,6-Dipropyl-2-pyrazinethiol (2b): mp 145-146°C; yield 94%; MS: m/e 196 (M^+); UV: λ_{max}^{EtOH} 248 (log ε = 2.63), 283 (3.09) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 0.94 (t, J = 7 Hz, 6H, $CH_2CH_2CH_3$), 1.62 (m, 2H, $CH_2CH_2CH_3$), 1.73 (m, 2H, $CH_2CH_2CH_3$), 2.53 (t, J = 7 Hz, 2H, $CH_2CH_2CH_3$), 2.89 (t, J = 7 Hz, 2H, $CH_2CH_2CH_3$), 7.52 (s, 1H, pyrazine H), 13.56-14.56 (bs, 1H, SH or NH) ppm; Anal. Calcd. for $C_{10}H_{16}N_2S$: C, 61.18; H, 8.22; N, 14.27. Found: C, 61.09; H, 8.23; N, 14.16.

3,6-Diisopropyl-2-pyrazinethiol (2c): mp 144-146°C; yield 98%; MS: m/e 196 (M^+); UV: λ_{max}^{EtOH} 247 (log ε = 2.74), 283 (3.21) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.33 (d, J = 7 Hz, 6H, $CH(CH_3)_2$), 1.46 (d, J = 7 Hz, 6H, $CH(CH_3)_2$), 3.33 (m, J = 7 Hz, 1H, $CH(CH_3)_2$), 4.26 (m, J = 7 Hz, 1H, $CH(CH_3)_2$), 8.23 (s, 1H, pyrazine H), 12.83-14.00 (bs, 1H, SH or NH) ppm; Anal. Calcd. for $C_{10}H_{16}N_2S$: C, 61.18; H, 8.22; N, 14.27. Found: C, 61.16; H, 8.19; N, 14.35.

3,6-Diisobutyl-2-pyrazinethiol (2d): mp 176-177°C; yield 96%; MS: m/e 224 (M^+); UV: λ_{max}^{EtOH} 246 (log ε = 3.38), 283 (3.78) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 0.95 (d, J = 6 Hz, 12H, $CH_2CH(CH_3)_2$), 2.08 (m, 2H, $CH_2CH(CH_3)_2$), 2.48 (d, J = 7 Hz, 2H, $CH_2CH(CH_3)_2$), 2.88 (d, J = 7 Hz, 2H, $CH_2CH(CH_3)_2$), 7.63 (s, 1H, pyrazine H), 13.70-14.33 (bs, 1H, SH or NH) ppm; Anal. Calcd. for $C_{12}H_{20}N_2S$: C, 64.24; H, 8.99; N, 12.49. Found: C, 64.03; H, 8.97; N, 12.39.

Amines or hydroxy compounds were added to the pyrazinethiol esters, prepared by the continuous reactions of pyrazinethiols with metallic sodium and acyl chlorides in 1,2-dimethoxyethane (DME), and the reaction mixtures were worked up, after being stirred for 10 min to 24 h, to give the corresponding amides or esters in satisfactory yields (Table II and III). The products were identified by the comparison of IR and ^{1}H-NMR spectra with those of the authentic specimens. The benzoylation of benzylamine indicated that all thiols (2a-d) had almost the same ability as reagents (Table II), and 3,6-diisobutyl-2-pyrazinethiol (2d) was, therefore, adopted for acylation in other cases. As shown in Table III, addition of triethylamine remarkably increased the yields of esters in most cases. In all cases of acylation, the starting pyrazinethiols were recovered in good yields.

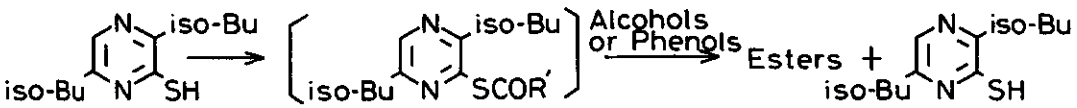
Table II. Acylation of Amines



Entry	Amines	Pyrazinethiols	R'	Products	Yields (%)*
1	benzylamine	2a	C_6H_5	N-benzoylbenzylamine[8]	99
2	''	2b	''	''	91
3	''	2c	''	''	80
4	''	2d	''	''	94
5	''	''	CH_3	N-acetylbenzylamine[8]	94
6	aniline	''	''	acetanilide[8]	89
7	''	''	C_6H_5	benzanilide[8]	92
8	cyclohexylamine	''	''	N-benzoylcyclohexylamine[8]	80
9	''	''	CH_3	N-acetylcyclohexylamine[8]	96
10	pyrrolidine	''	C_6H_5	N-benzoylpyrrolidine[9]	72

* Reaction time was 10 minutes.

Table III. Acylation of Hydroxy Compounds

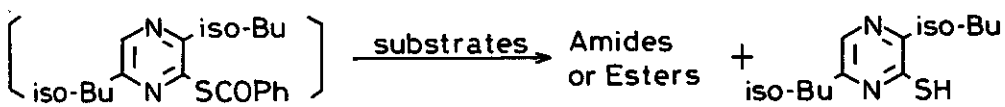


Entry	Substrates	R'	Products	Reaction Time(hr)	Yields (%)
1	methanol	C_6H_5	methylbenzoate[10]	0.5	77
2	β-naphthol	CH_3	β-naphthylacetate[9]	1	80*
3	''	C_6H_5	β-naphthylbenzoate[9]	2	35
4	''	''	''	0.5	77*
5	benzyl alcohol	CH_3	benzylacetate[10]	24	34
6	''	''	''	''	67*
7	geraniol	C_6H_5	geranylbenzoate[10]	''	52
8	''	''	''	1	76*

* Triethylamine was added.

The competition reactions on benzoylation indicated that this one-pot reaction gave rise to selectivity between acylations of amines, alcohols, and phenols.

Table IV. Selective Benzoylation



Entry	Substrates	Products	Yields* (%)
1	aniline/benzylamine	N-benzoylbenzylamine[8]	96
2	aniline/N-methylaniline	benzanilide[8]	90
3	aniline/β-naphthol	''	90
4	benzylamine/benzylalcohol	N-benzoylbenzylamine[8]	89
5	methanol/β-naphthol	β-naphthylbenzoate[8]	82
6	β-naphthol/N-methylaniline	''	79
7	pyrrolidine/N-methylaniline	N-benzoylpyrrolidine[9]	69
8	methanol/cyclohexanol	methylbenzoate[10]	81

* Reaction time was 30 minutes.

On the basis of these reagents, one might conclude that ease of acylation by this reaction system may eventually be in order as shown below.

aliphatic primary amines > aromatic primary amines > phenols and aliphatic secondary amines > primary alcohols and aromatic secondary amines > secondary alcohols

The present one-pot reaction will, therefore, be a mild and convenient method for acylation of amines and hydroxy compounds.[11] It is worth also to point out that this system has unique ability to cause a highly selective acylation between amines and hydroxy compounds.

EXPERIMENTAL

All melting 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 Model 557; MS: Hitachi M-80 spectrometer.

General Procedure for Preparation of 3,6-Dialkyl-2-pyrazinethiols (2a-d)--- After a solution of 3,6-dialkyl-2-hydroxypyrazine (1a-d; 10 mmol) and the Lawesson's reagent (2.02 g, 5 mmol) in toluene (100 ml) was refluxed for 2 h, the reaction mixture was extracted with 10% KOH (50 ml x 4). The aqueous layer was acidified with 10% HCl and extracted with methylene chloride (50 ml x 4). The organic layer was dried with Na_2SO_4 and the solvent was evaporated to give the corresponding thiols, which were recrystallized from ethanol to furnish yellow needles.

General Procedure for Acylation of Amines and Hydroxy Compounds --- Sodium (0.23 g, 10 mgatoms) was dissolved in a DME solution (60 ml) of 3,6-dialkyl-2-pyrazinethiol (10 mmol) under stirring, and an acyl chloride (10 mmol) was then added at once to the mixture. After being stirred for 1 min, an amine or hydroxy compound (10 mmol) was added to the mixture, which was stirred further for 10 min to 24 h. The solvent was removed in vacuo, and the residue was triturated with water (20 ml) and extracted with ether (30 ml x 2). In the case of acylation of amines, the ethereal layer was washed successively with 10% KOH (30 ml x 3) and 10% HCl (30 ml x 3) and dried with Na_2SO_4, and the solvent was evaporated to give the corresponding amides. In the case of esterification, the ethereal layer was washed with 10% KOH (30 ml x 3), and worked up as before to afford the corresponding esters. In both cases, the starting thiols were recovered from the 10% KOH layer in ca 90% yields.

Competitive Benzoylation --- A DME solution (20 ml) of two substrates (10 mmol : 10 mmol) was added at once to a DME solution of 3,6-dialkyl-2-pyrazinethiol benzoate (sodium: 10 mgatoms; 3,6-dialkyl-2-pyrazinethiol: 10 mmol; DME: 60 ml) under stirring at room temperature and the reaction mixture was stirred further for 30 min. The solvent was removed in vacuo, and the residue was triturated with water (20 ml) and extracted with ether (30 ml x 2). The ethereal layer was worked up as before and the purity of the products was estimated by GLC (1.5% SE-30 on Chromosorb W, 3 mm x 1.5 m column, Shimadzu GC-4B instrument).

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11 The pyrazinethiols (2a-d) used have some advantages in comparison with the acyl carriers reported.[1-3] Because of high solubility in water, 2-mercaptothiazoline[2] and 2-oxazolone[3] are not recovered after acylation. Although 6-pyridyl-2-pyridone[1] is less soluble in water, the preparation of this compound makes much work. On the other hand, 2a-d can be easily prepared from commercial amino acids. What is more, 2a-d can be recovered without difficulty after acylation, since these compounds are hardly soluble in water. 2-Mercaptobenzoxazole[4] is on the market and an excellent acyl carrier. One might conclude that 2a-d are not inferior to 2-mercaptobenzoxazole.

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