Preparation of 3-Acetamido-2,5-dihydrothiophenes

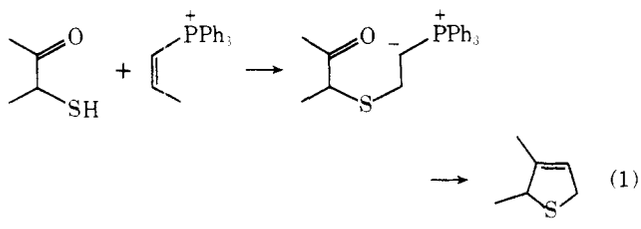
George F. Field

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110[1]

Received October 11, 1978

Heating of *N*-acetyl-*S*-(α-ketoalkyl)cysteines with acetic anhydride gives 3-acetamido-2,5-dihydrothiophenes. Under other conditions two types of undecarboxylated thiophene derivatives, **5** and **6**, have been obtained.

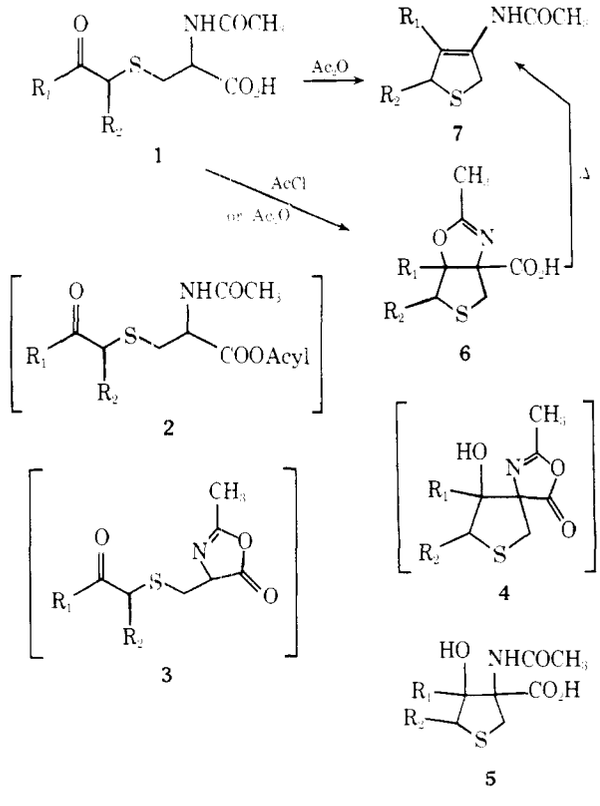
McIntosh and co-workers have developed a deft method for the preparation of 2,5-dihydrothiophenes.[2] This reaction involves the addition of an α-mercapto ketone or aldehyde to a vinylphosphonium salt and then ring closure of the intermediate with elimination of phosphine oxide as illustrated in eq 1.



(1)

We happened upon a similar reaction which gives 3-acetamido-2,5-dihydrothiophenes. This reaction is illustrated in Scheme I by the transformation of **1** to **7**. Since we had another objective in mind at the time, only two cases have been examined. The starting materials **1** are, of course, easily available by alkylation of *N*-acetylcysteine with an α-halo ketone. When **1a** was heated with acetic anhydride at 130 °C for 1 h, an 80% yield of **7a** was obtained. When **1b**[3] was treated in a similar manner, thiophene **7b** was obtained in 28% yield. The structures of the dihydrothiophenes **7** follow from their elemental composition and spectra. The NMR spectrum of **7b** contains a slight anomaly in that the methylene protons adjacent to sulfur appear as a triplet with a coupling constant of 5 Hz.[4]

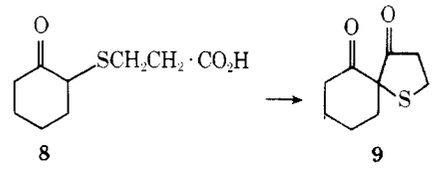
Scheme I



a, $R_1, R_2 = -(CH_2)_4-$; **b**, R_1 = Ph, R_2 = H

Change in reaction conditions led to the isolation of other products. When **1a** was heated for a brief period with acetic anhydride, the oxazoline **6a** was obtained. Also, when **1b** was heated with acetyl chloride in tetrahydrofuran, the hydrochloride of oxazoline **6b** precipitated. Heating of these products transformed them into **7a** and **7b**, respectively. When **1b** was treated with ethyl chloroformate and triethylamine at 35 °C, thiophene **5b** was obtained.

An alternative mode of cyclization, not encountered with the cysteine derivatives, was found with the deacetamido compound **8**. Heating of **8** with acetic anhydride and triethylamine led to a modest yield of the spiro diketone **9**. In this case the mixed anhydride intermediate is unable to form an oxazolone; therefore, reaction occurs at the α position of the ketone.



8 **9**

Discussion

While the mechanism of this reaction has not been investigated in detail, the isolation of compounds **5** and **6** suggests a sequence of intermediates as shown by **2**–**4** in Scheme I leading to **7**. The first step would be formation of a mixed anhydride **2** followed by ring closure to an oxazolone **3**. The susceptibility of the 4 position of an oxazolone ring to electrophilic attack is well known from studies of the Dakin–West reaction[5] and the Erlenmeyer azlactone synthesis.[6] Intramolecular attack at the 4 position by the ketone group would give **4** containing a hydroxyl group. The compound is analogous to an intermediate in the Erlenmeyer azlactone synthesis in which the presence of another hydrogen at the 4 position permits dehydration to the observed product, an unsaturated azlactone. In the present examples this hydrogen does not exist, and another path is followed. The existence of **4** is inferred from the isolation of **5** on aqueous workup. Rearrangement of **4**, either via **5** or directly to the oxazoline **6**, is feasible since the anhydride character of **4** is changed to the ester character of **6**. Transfer of a proton from the carboxyl group of **6** to the nitrogen would then lead to a structure which is beautifully arranged to undergo a fragmentation reaction with loss of carbon dioxide to give the final dihydrothiophene **7**.

This reaction can also be considered to be another example of the use of a currently popular concept, the acyl anion equivalent[7] or the Umpolung of a carbonyl group.[8] Good use has been made of cyanohydrin derivatives as acyl anion equivalents;[9] benzylidene amino acid esters have also been used in this fashion.[10] Here the amino acid, cysteine, becomes

0022-3263/79/1944-0825$01.00/0

the equivalent of the acyl anion of mercaptoacetaldehyde. These reactions suggest that other amino acids might be put to this use, especially if an enamide derivative is desired for a subsequent step.

Experimental Section[11]

***N*-Acetyl-3[(2-oxocyclohexyl)thio]alanine (1a).** To a solution of 98 g of *N*-acetylcysteine in 500 mL of ethanol cooled in an ice bath was added 250 mL of 3 N sodium hydroxide at such a rate that the temperature of the reaction mixture remained below 15 °C. Then a solution of 88 g of 2-chlorocyclohexanone in 150 mL of ethanol and more 3 N NaOH were added simultaneously during 15 min so that the pH remained about 8. After 40 mL total of sodium hydroxide solution had been added, the mixture remained alkaline to phenolphthalein. After 5 min, the reaction mixture was neutralized with 3 N hydrochloric acid and concentrated in vacuo to ~500 mL. It was acidified with 50 mL of concentrated hydrochloric acid. The oil which separated gradually solidified and was collected, washed with water and then hexane, and dried. Recrystallization from 200 mL of ethyl acetate gave 105.4 g (68%) of product, mp 117–125 °C. A sample was recrystallized from ethyl acetate for analysis: mp 124–128 °C; IR ($CHCl_3$) 1732, 1710, 1677, and 1523 cm^{-1}; NMR (Me_2SO) δ 8.29 (d, 1, J = 9 Hz, –NH), 4.37 (m, 1, NHC**H**CH_2), 3.55 (m, 1, COCHS), 2.75 (m, 2, $-SCH_2$), 1.85 (s, $-COCH_3$), and 1.73 (br m with δ 1.85 singlet, ~11, $(-CH_2-)_5$).

Anal. Calcd for $C_{11}H_{17}NO_4S$: C, 50.95; H, 6.61; N, 5.40. Found: C, 50.63; H, 6.62; N, 5.32.

***N*-(2,4,5,6,7,7a-Hexahydrobenzo[*b*]thiophen-3-yl)acetamide (7a). A.** A mixture of 7.8 g (30 mmol) of *N*-acetyl-3-[(2-oxocyclohexyl)thio]alanine (**1a**) and 3.5 mL (35 mmol) of acetic anhydride was stirred and heated in an oil bath at 130 °C for 1 h. It was then cooled and diluted with 25 mL of water. The solid was collected and washed with ether to give 4.9 g (82%) of product, mp 140–143 °C. An analytical sample was recrystallized from ethyl acetate: mp 139–144 °C; IR ($CHCl_3$) 3442 (NH), 1686 (–CONH), and 1490 (amide II) cm^{-1}; NMR ($CDCl_3$) δ 7.1 (s, 1, NH), 4.01 (br s, 3, $-CH_2S$, CHS), 2.05 (s, 3, $-CH_3$), and 1.85 (m, ~8, $(-CH_2-)_4$); mass spectrum, *m/e* 197.

Anal. Calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10; S, 16.25. Found: C, 60.99; H, 7.64; N, 6.98; S, 16.22.

B. From 6,7,8,9-Tetrahydro-2-methyl-5a*H*-[1]benzothieno[3,3a-*d*]oxazole-3a(4*H*)-carboxylic Acid (6a). A mixture of 0.5 g of **6a** and 10 mL of toluene was stirred and heated under reflux for 16 h. The solution so formed was concentrated in vacuo, and the residue crystallized from ether to give 0.3 g of product: melting point and mixture melting point with the sample described above, 141–144 °C. The IR spectrum was also identical.

***N*-(2,5-Dihydro-4-phenyl-3-thienyl)acetamide (7b). A.** A mixture of 28.4 g (0.1 mol) of *N*-acetyl-*S*-phenacylcysteine (**1b**),[3] 50 mL of glacial acetic acid, 15 mL of acetic anhydride, and 5 drops of pyridine was placed in an oil bath at 80 °C and stirred. The temperature was raised to 120 °C over 10 min and held there for 1 h. The reaction mixture was then concentrated in vacuo to ~30 g. The residue was triturated with 2 × 50 mL of water and then dried by adding ethanol and benzene and concentrating in vacuo. The residue was dissolved in methylene chloride and filtered through 150 g of alumina. Concentration of the first 250 mL gave 16.6 g of orange oil which was crystallized from ether to give 6.2 g (28%) of product, mp 127–135 °C (single spot with EtOAc, 10% MeOH/$CHCl_3$, or 2.5% MeOH/$CHCl_3$). A sample was recrystallized from aqueous ethanol: mp 124–129 °C; IR ($CHCl_3$) 3422 (NH), 1696 (–CONH), and 1488 (amide II) cm^{-1}; NMR ($CDCl_3$) δ 7.4 (m, 6, Ph and NH), 4.25 (t, 2, J = 5 Hz, $-CH_2S$), 3.95 (t, 2, J = 5 Hz, $-CH_2S-$), and 1.98 (s, 3, $-CH_3$); mass spectrum, *m/e* 219.

Anal. Calcd for $C_{12}H_{13}ONS$: C, 65.72; H, 5.97; N, 6.39. Found: C, 65.57; H, 5.93; N, 6.21.

B. From Dihydro-2-methyl-6a-phenylthieno[3,4-*d*]oxazole-3a(4*H*)-carboxylic Acid (6b). A solution of 1 g of **6b** in 25 mL of acetic acid was stirred and heated under reflux for 2.5 h. It was then concentrated in vacuo, and the residue crystallized from ether to give 0.6 g of product: melting point and mixture melting point with the sample described above, 127–132 °C. The IR spectrum was also identical with authentic material.

3-Acetamidotetrahydro-4-hydroxy-4-phenyl-3-thiophenecarboxylic Acid (5b). To a solution of 56 g (0.2 mol) of **1b** in 1 L of tetrahydrofuran at 35 °C was added 22 mL (0.23 mol) of ethyl chloroformate. Then 30 mL (0.21 mol) of triethylamine was added during 3 min. The temperature rose to 40 °C. The reaction mixture was cooled to 35 °C and kept there for 20 min until gas evolution stopped. Triethylamine hydrochloride was filtered off and washed with tetrahydrofuran. The filtrate was concentrated to a yellowish oil which was crystallized from a mixture of dilute hydrochloric acid and ether to give a sticky yellow solid. Recrystallization from acetonitrile gave 20.4 g (36%) of **5b**, mp 175–180 °C dec. An analytical sample was prepared by recrystallization from acetonitrile: mp 170–175 °C dec; IR (KBr) 3480 (OH), 3422 (NH), 3000 (Br–CO_2H), 1718 (–CO_2H), 1649 (–CONH), and 1538 (amide II) cm^{-1}; UV, no high intensity band above 210 nm; NMR (Me_2SO) δ 7.1–7.9 (m, 5, phenyl), 5.9 (br, ~2, NH exch.), 3.95 (d, 2, J = 11.3 Hz), 3.17 and 3.02 (overlapping d's, 2, J = 11.3 Hz), and 3.0 (s, 3, $-CH_3$).

Anal. Calcd for $C_{13}H_{15}NO_4S$: C, 55.50; H, 5.38; N, 4.98. Found: C, 55.45; H, 5.45; N, 4.88.

6,7,8,9-Tetrahydro-2-methyl-5a*H*-[1]benzothieno[3,3a-*d*]oxazole-3a(4*H*)-carboxylic Acid (6a). A mixture of 16.6 g of *N*-acetyl-3-[(2-oxocyclohexyl)thio]alanine (**1a**) and 25 mL of acetic anhydride was stirred and heated in an oil bath at 110–120 °C for 7 min. It was then seeded, cooled to room temperature, and diluted with 100 mL of ether. The solid was collected and washed with 100 mL of ether to give 7.7 g of product, mp 180–186 °C dec. A sample was recrystallized from ethanol: mp 178–187 °C dec; IR (KBr) 2480, 1721 (–CO_2H), and 1677 (C=N) cm^{-1}; NMR (Me_2SO) δ 12.0 (br, 1, –CO_2H), 3.80 (d, 1, J = 13 Hz, $-CH_AH_BS$), 3.23 (m, 1, –CHS), 2.75 (d, 1, J = 13 Hz, $-CH_AH_BS$), 2.00 (s, 3, $-CH_3$), and 1.7 (m, 8, $(-CH_2-)_4$).

Anal. Calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80. Found: C, 54.63; H, 6.30; N, 5.66.

Dihydro-2-methyl-6a-phenylthieno[3,4-*d*]oxazole-3a-(4*H*)-carboxylic Acid (6b) Hydrochloride. A mixture of 44.8 g (0.16 mol) of *N*-acetyl-*S*-phenacylcysteine (**1**), 200 mL of tetrahydrofuran, 20 mL of acetyl chloride, and 2 mL of pyridine was stirred and heated under reflux for 1 h. After 0.5 h, a precipitate formed. The reaction mixture was cooled, and the precipitate was collected and washed with tetrahydrofuran to give 27.2 g (56%) of product, mp 187–190 °C dec. A sample was recrystallized from tetrahydrofuran: mp 190–195 °C dec; IR (KBr) 2562 (N^+H, –CO_2H), 1743 (–CO_2H), and 1665 (C=N^+H) cm^{-1}.

Anal. Calcd for $C_{13}H_{13}NO_3S$·HCl: C, 52.09; H, 4.71; N, 4.67; Cl, 11.83; S, 10.69. Found: C, 52.33; H, 4.81; N, 4.54; Cl, 11.10; S, 10.88.

Dihydro-2-methyl-6a-phenylthieno[3,4-*d*]oxazole-3a-(4*H*)-carboxylic Acid (6b). To a suspension of 11.4 g of (38 mmol) of the hydrochloride in 20 mL of water was added 10 mL of 3 N sodium hydroxide. After being cooled, the precipitate was collected and washed with water to give 9 g (90%) of product, mp 166–168 °C dec. A sample was recrystallized from ethanol: mp 160–165 °C dec; IR (KBr) 2476 (–CO_2H), 1714 (CO_2H), and 1669 (C=N) cm^{-1}; NMR (Me_2SO) δ 12.4 (br s, 1, CO_2H), 7.35 (m, 5, Ph), 3.73 (d, 1, J = 12.3 Hz, $-CH_AH_BS$), 3.62 (d, 1, J = 12.3 Hz, $-CH_AH_BS$), 3.15 (d, 1, J = 12.5 Hz, $-CH_AH_BS$), 2.92 (d, 1, J = 12.5 Hz, $-CH_AH_BS$), and 2.12 (s, 3, $-CH_3$).

Anal. Calcd for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32. Found: C, 59.01; H, 4.83; N, 5.22.

1-Thiaspiro[4.5]decane-4,6-dione (9). A mixture of 40 g (0.2 mol) of 2-(carboxyethylthio)cyclohexanone,[12] 250 mL of benzene, 25 mL of triethylamine, and 50 mL of acetic anhydride was heated under reflux for 1 h, allowed to stand at room temperature overnight, stirred for 3 h with 25 mL of water, and diluted with 250 mL of ether. The solution was washed with 250 mL of 1.5 N hydrochloric acid, 3 × 125 mL of saturated sodium bicarbonate solution, and brine. It was then dried over sodium sulfate and concentrated to 41 g of oil. Distillation of this oil with a sausage tube gave 12.4 g (33%) of crude solid product, bp ~96 °C/0.4 mm. An analytical sample was prepared by recrystallization from hexane: mp 79–82 °C; IR ($CHCl_3$) 1744 and 1699 cm^{-1}; UV max 306 nm (ϵ 345), 296 (340), 255 sh (320), and 235 (680); NMR (Me_2SO), no band below δ 3.

Anal. Calcd for $C_9H_{12}O_2S$: C, 58.67; H, 6.56. Found: C, 58.75; H, 6.66.

Registry No.—**1a**, 68876-63-1; **1b**, 33869-67-9; **5b**, 68876-64-2; **6a**, 68876-65-3; **6b**, 68876-66-4; **6b**·HCl, 68876-67-5; **7a**, 68900-21-0; **7b**, 68876-68-6; **8**, 68876-69-7; **9**, 68876-70-0; *N*-acetylcysteine, 616-91-1; 2-chlorocyclohexanone, 822-87-7.

References and Notes

(1) Work done at F. Hoffmann-La Roche, Basel, Switzerland.
(2) (a) J. M. McIntosh, H. B. Goodbrand, and G. M. Masse, *J. Org. Chem.*, **39**, 202 (1974); (b) J. M. McIntosh and R. S. Steevensz, *Can. J. Chem.*, **52**, 1934 (1974); (c) J. M. McIntosh and G. M. Masse, *J. Org. Chem.*, **40**, 1294 (1975).
(3) J. B. Jones and D. W. Hysert, *Can. J. Chem.*, **49**, 3013 (1971).
(4) The complexity of the NMR spectra of reduced thiophenes has been commented on before; see J. M. McIntosh and H. Khalil, *J. Org. Chem.*, **42**, 2123 (1977), and ref 1b.
(5) S. I. Zavyalov, N. I. Aronova, and N. N. Makhova in "Organic Compounds:

Reactions and Methods", Vol. 22, B. A. Kazanskii et al., Eds., IFI/Plenum, New York, N.Y., 1973, p 1.
(6) H. E. Carter, *Org. React.*, **3**, 198 (1946).
(7) O. W. Lever, Jr., *Tetrahedron*, **32**, 1943 (1976).
(8) G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **96**, 5272 (1974).
(9) D. Seebach and M. Kolb, *Chem. Ind. (London)*, 687 (1974).
(10) G. Stork, A. Y. W. Leong, and A. M. Touzin, *J. Org. Chem.*, **41**, 3491 (1976).
(11) Elemental analyses were performed under the direction of Dr. A. Dirscherl. Spectra were determined in the Physical Chemistry Department. The author would like to thank Dr. P. Zeller for the hospitality of his laboratory and Mr. A. Senn for his skillful technical assistance.
(12) B. R. Baker, M. V. Querry, S. Bernstein, S. R. Safir, and Y. Subbarow, *J. Org. Chem.*, **12**, 167 (1947).

Chemistry of Diaminomaleonitrile. 4. Nitrile Hydration of the Schiff Bases[1]

Yozo Ohtsuka

Sagami Chemical Research Center, 4-4-1 Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan

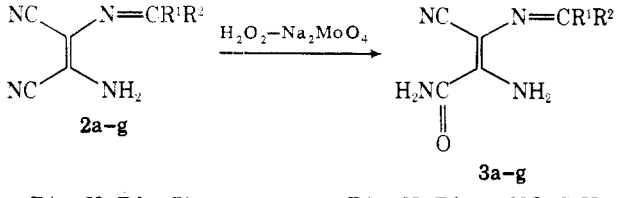
Received July 19, 1978

As a new transformation of diaminomaleonitrile (DAMN, **1**), nitrile hydration of DAMN Schiff base **2** was investigated. Open-chain amides **3a–g** were obtained by treatment of **2a–g** in ethanol with hydrogen peroxide and catalytic amounts of sodium molybdate. The structure **3** was determined on the basis of ^{13}C NMR spectrometry of a number of maleonitrile derivatives. The hydration of Schiff bases **4a,b** gave pyrazine derivatives **5a,b**. Amide **3a** was converted into imidazole **6** by oxidation and **3a–g** were cyclized with alkali into pyrrolones **7a–g**.

In contrast to the well-studied reactions of the amino groups in diaminomaleonitrile (DAMN, **1**), the reaction involving its nitrile groups has been little explored. Hydration of the nitrile group(s) has been carried out along with[1,2] or after[3] the conversion of the amino groups into heterocyclic derivatives. Direct hydration of **1** with acids or bases tends to result in degraded compounds by elimination of hydrogen cyanide or ammonia.[3b,4] Oxidation of **1** produces diiminosuccinonitrile (DISN), which decomposes rapidly in contact with polar substances.[5]

In the course of our study on DAMN derivatives, we have observed that DAMN Schiff bases **2** were more resistant than DAMN itself toward degradation reactions under several conditions. Oxidation of **2** with reagents, such as DISN and dichlorodicyanobenzoquinone (DDQ), is known to afford 2-substituted imidazole-4,5-dicarbonitrile.[6] The potential utility of nitrile reactions of the open-chain DAMN derivatives for synthesis of a wide variety of heterocyclic compounds has prompted us to study the nitrile hydration reaction of a series of Schiff bases **2a–g**.[3b,7]

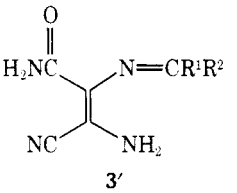
Reactions. Preliminary examination of **2** showed that they underwent preferential cleavages of the azomethine linkages upon heating with acid or base. In experiments to effect mild and almost neutral hydration of the nitrile function in **2**, they were treated in alcohol solution with hydrogen peroxide. Among the results, a 37% yield of an amide product (**3a**) was isolated from **2a**. Then, it was found that the yield of the



2a–g **3a–g**

a, R^1 = H; R^2 = Ph
b, R^1 = H; R^2 = 4-$CH_3C_6H_4$
c, R^1 = H; R^2 = 4-$CH_3OC_6H_4$
d, R^1 = H; R^2 = 9-anthranyl
e, R^1 = H; R^2 = 4-$NO_2C_6H_4$
f, R^1 = CH_3; R^2 = 4-$NO_2C_6H_4$
g, R^1 = R^2 = Ph

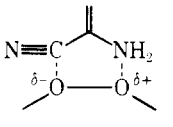
product could be increased when a catalytic amount of sodium molybdate[8] was added to the reaction mixture. The results of the reactions of a set of Schiff bases **2a–g** are summarized in Table I. Spectroscopic properties of the hydration products are shown in Tables II and III. The stereochemistry of the amide **3a–g** was assigned on the basis of ^{13}C NMR spectrometry, which is separately described in the next section. Meticulous examinations of the hydration product mixtures revealed no trace of the alternative stereoisomers **3′**. In most



3′

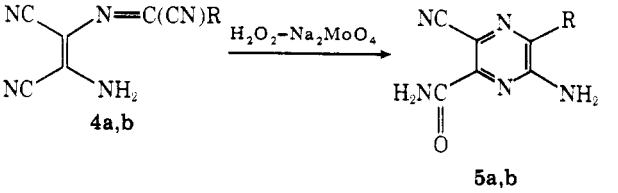
cases, the reaction was complete within 18 h at room temperature, and prolonged reaction times (more than 24 h) or a higher temperature (at 40 °C) tended to result in the formation of oxamide. *p*-Nitrobenzylidenediaminomaleonitrile (**2e**) was incompletely converted to the amide under the conditions and the product **3e** was isolated by partial crystallizations from acetonitrile.

The apparent regiospecificity of the hydration reaction may result from the interaction of the peroxy moiety with the NH_2 group in **2** illustrated as



Nitrile hydration by similar participation of NH_2 group has been observed previously by the reaction of carbonyl compounds with urea derivatives of **1**.[1]

Schiff bases **4a** and **4b**,[9] obtained from **1** with acetyl and benzoyl cyanide, respectively, were hydrated by the reagents under similar conditions and pyrazine derivatives **5a** and **5b**



4a,b **5a,b**

a, R = CH_3 b, R = Ph

0022-3263/79/1944-0827$01.00/0