

Nobuhiro Sato,\* Naoko Miwa, Hiroko Suzuki and Tohru Sakakibara

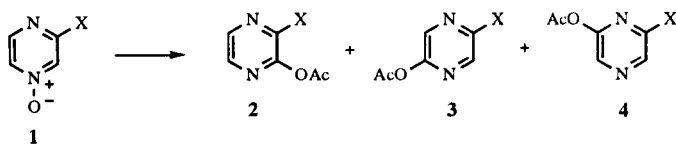
Department of Chemistry,  
Yokohama City University,  
Yokohama 236, Japan  
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Deoxydative acetoxylation of 3-methoxy-, 3-phenyl-, 3-methyl-, 3-chloro-, and 3-methoxycarbonylpyrazine 1-oxides furnished predominantly 2-acetoxy-6-substituted pyrazines, some of which were more selectively prepared by addition of zinc bromide and triethylamine to the reaction. Regioselectivity of the acetoxylation is discussed based upon heat of formation by AM1 and AM1-COSMO for all possible isomers of each set.

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Reaction of heterocyclic *N*-oxides with acetic anhydride permits introduction of an acetoxy group onto the electron-deficient ring system with loss of the *N*-oxide oxygen [2,3]. A variety of 2-acetoxypyridine and quinoline compounds were prepared in this fashion. However, the acetoxylation in pyrazine series was limited to fewer *N*-oxides, *i.e.*, the parent and 3-methylpyrazine 1-oxides could not be acetoxyated [4,5] while diphenylpyrazine *N*-oxides were affected under relatively mild conditions to provide high yields of the acetoxypyrazines [6]. We are currently engaged in a program aimed at deoxydative acetoxylation of 3-methoxy-, 3-phenyl-, 3-methyl-, 3-chloro-, and 3-methoxycarbonylpyrazine 1-oxides **1**, to clarify the scope of reaction, the substituent effect on the regiochemistry and the mechanism.

Scheme 1



**1, 2, 3, 4** a X = OMe, b X = Ph, c X = Me, d X = Cl, e X = CO<sub>2</sub>Me

Acetoxylation of the pyrazine *N*-oxides was performed by treatment in refluxing acetic anhydride. Each component in the reaction mixture was separated by column chromatography or high performance liquid chromatography on silica gel. These acyloxy compounds are relatively unstable, *e.g.*, 2-acetoxy-6-substituted pyrazines **4d** and **4e** were occasionally hydrolyzed in part during the chromatographic workup to form the 2(*1H*)-pyrazinones so that the products should be isolated by distillation from the reaction residue. After standing for a week or two such a hydrolysis also occurred probably by moisture in the air. The 2-acetoxy-3-methoxypyrazine **2a** was completely decomposed into the 3-methoxy-2(*1H*)-pyrazinone by recrystallization procedure. The identities of the acetoxylation products were confirmed by the <sup>1</sup>H nmr spectrum [7], analogous to structure determination in our earlier works on the substitution reactions [8,9] of pyrazine *N*-oxides.

Table 1 summarizes our outcomes on the acetoxylation of pyrazine *N*-oxides **1a-e**, in which the ease of reaction is certainly dependent on the type of substituent. Thus an electron-donating methoxy group enhances the reaction whereas the electron-withdrawing chloro and methoxycarbonyl groups demand a longer period to consume the *N*-oxide. The order of reactivity is in agreement with that of aromatic electrophilic substitution. In other words, the deoxydative acetoxylation is remarkably influenced by nucleophilicity of the *N*-oxide oxygen in a similar manner as the thiation reaction established earlier [9]. Meanwhile, the displacement on **1a** and **1d** took place primarily at the C-6 carbon β to the *N*-oxide function yielding 6-acetoxy-2-substituted pyrazines **4**, which were hydrolyzed to the known 6-substituted 2(*1H*)-pyrazinones [10] for establishing the structure of **4**. The observed regioselectivity is in contrast to that of cyanation [8] or thiation [9] where the 2,3-disubstituted pyrazine is major product and the 2,6-isomer is the minority. Conversely, the products in the acetoxylation of 3-methoxycarbonylpyrazine 1-oxide **1e** was non-regioselective unlike previous reports [11,12] to claim the exclusive formation of 2-acetoxy-6-methoxycarbonylpyrazine **4e**.

Although the 3-methylpyrazine 1-oxide **1c** is inert to acetic anhydride under mild conditions [5], prolonged heating for 24 hours caused the starting *N*-oxide to be completely consumed. The only isolated material was an 18% yield of 2-acetoxymethylpyrazine, and the other substitution products were contaminated with several unidentified materials in an inseparable mixture. Reaction of 3-phenylpyrazine 1-oxide **1b** similarly afforded non-regioselective products. When the acid anhydride was used without purification, the contaminated products were more complex. Consequently, it is conceivable that the substitution products

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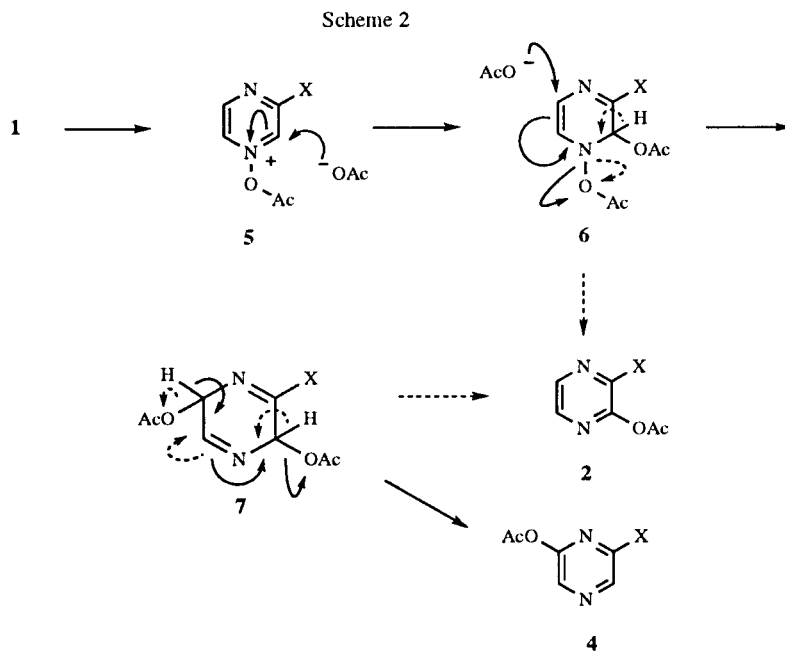
**2**, **3** and **4** formed at an initial stage are hydrolyzed by acetic acid generated in the process leading to 2(1*H*)-pyrazinones that are reacylated to give a mixture of acetoxypyrazines and 1-acetyl-2(1*H*)-pyrazinones as the unidentified materials. Added triethylamine to the reaction scavenges the acid to simplify the acetoxylation of **1b** and **1c** as shown in Table 1. The most noteworthy feature is the reversal of regioselectivity in deoxydative acetoxylation of 3-methoxypyrazine 1-oxide **1a** to furnish the 2,3-isomer **2a**.

Since the presence of a Lewis acid in the reaction enhances the substitution [8,9], we attempted the acetoxylation of *N*-oxides **1** with zinc bromide. The use of Lewis acid alone led to the formation of tarry material, but the addition of triethylamine to the reaction mixture accomplished the substitution with higher regioselectivity for 2,6-isomers **4**, particularly 2-acetoxy-6-methylpyrazine **4c**. The parent pyrazine 1-oxide decomposed completely under identical conditions. Zinc acetate and magnesium

Table 1  
Reaction of 3-Substituted Pyrazine 1-Oxides **1** with Refluxing Acetic Anhydride

Substrate	Reagent system [a] /time (hours)	Separation method [b]	Product and yield (%)			Total yield (%)	Starting material [c]
			<b>2</b>	<b>3</b>	<b>4</b>		
<b>1a</b>	A/2	C	9	0	60	69	0%
	A + B/2	C	63	0	9	72	0%
	A + B + Z/2	D	50	0	9	59	-
		C	7	0	72	79	0%
<b>1b</b>	A + B/6	D	5	0	59	64	-
	A + B + Z/6	D	11	8	68 [d]	87	+
<b>1c</b>	A + B/24	D	6	3	62 [d]	71	-
	A + B/24	C	18	0	18 [d]	36	0%
	A + B + Z/24	C	0	0	32	32 [e]	0%
		D	0	0	16	16	-
<b>1d</b>	A + B + Z/42	D	0	0	21	21	-
	A/30	C	0	0	54	54	24%
	A/42	D	0	0	44	44	+
<b>1e</b>	A/30	D	0	0	52	52	-
	A/72	D	28	7	21 [d]	56	+
			26	9	38 [d]	73	-

[a] A: Acetic anhydride. B: Triethylamine (3.5 molar equivalents). Z: Zinc bromide (1.5 molar equivalents). [b] C: By column chromatography on silica gel. D: By direct distillation. [c] Recovered. [d] Product ratio was determined by <sup>1</sup>H nmr spectroscopy. [e] Additional product: 2-acetoxymethylpyrazine (4%).

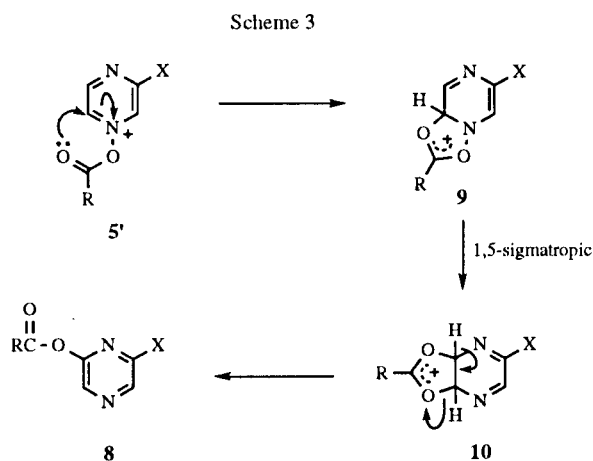


acetate were also effective for the acetoxylation of **1a** but the yields were lower than that produced by zinc bromide. On the other hand, acetoxylation of **1d** and **1e** was nearly suppressed by the addition of triethylamine or zinc bromide. When higher-boiling *N,N*-dimethylaniline was used instead of triethylamine, the reaction was rapidly completed but the base incorporated into the substitution products to form a complex mixture.

On the basis of work previously reported from this laboratory, a mechanism for acetoxylation on the carbon  $\beta$  to the *N*-oxides function is outlined in Scheme 2. The crucial step is the second attack of nucleophile on the Meisenheimer complex **6**, producing a further intermediate **7** or the 2,3-diacetoxy isomer to ensue the competitive formation of  $\alpha$ - and  $\beta$ -acetoxy pyrazines. In rare cases, such a common intermediate can be isolated, *e.g.*, 2,3-diacetoxy-5,6-diphenyl-2,3-dihydropyrazine was formed from the reaction of 2,3-diphenylpyrazine 1-oxide with acetic anhydride at 130°, which decomposed with elimination of acetic acid by pyrolysis at 230° to yield 2-acetoxy-5,6-diphenylpyrazine [6b]. Proceeding to the diacetoxy intermediate **7** is facilitated by sufficient life-time in **6** since the abstraction of hydrogen to **2** is suppressed for lack of its acidity. This phenomenon is presumably rationalized by a deficiency of the electron-withdrawing effect of the acetoxy group on the C-2 carbon. Owing to the same reason, the diacetoxy **7** could not aromatize to the acetoxy pyrazines in most cases, resulting in decomposition. Also added amine to the reaction had an effect on the dehydrogenation to improve the yields of the acetoxy pyrazines. It is worthy to note that it reversed the course of substitution as can be seen in the reaction of **1a** to give mainly 2-acetoxy-3-methoxy pyrazine **2a** of the  $\alpha$ -substituted product. In contrast, an electron-withdrawing chloro or methoxycarbonyl substituent enables the final process to form the acetoxy pyrazines though a totally slow progression without the base.

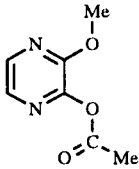
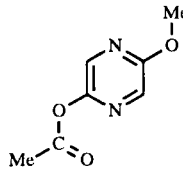
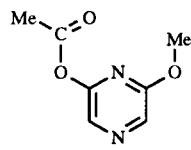
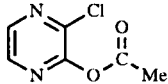
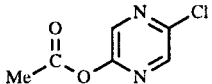
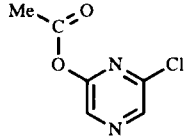
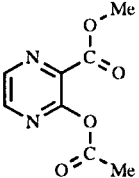
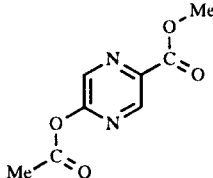
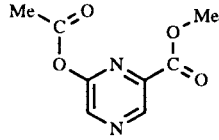
Unlike the above intermolecular reaction, another pathway to the dihydropyrazine intermediate is suggested from our earlier finding [1] about the novel formation of 2-diethylcarbamoyloxy-6-methoxy pyrazine **8** as a by-product in the synthesis of 2-azido-3-methoxy pyrazine through the reaction of **1a** with trimethylsilyl azide and diethylcarbamoyl chloride. Despite the presence of the azido ion which is a stronger nucleophile than the acyloxy anion, the competitive formation of acyloxy pyrazine **8** is predicted due to intramolecular rearrangement of the faster process as illustrated in Scheme 3. This compound **8** is alternatively prepared by treatment of **1a** with diethylcarbamoyl chloride in refluxing acetonitrile, whose yield was increased from 18% to 32% by the added diethylamine to the reaction for the same period of 18 hours. The fact indicates that its formation has no connec-

tion with trimethylsilyl azide. Transformation from the intermediate **9** to **10** should ensue *via* a 1,5-sigmatropic shift, and the succeeding dehydration results in the formation of the acyloxy product **8**. That sigmatropic rearrangement is not so rare as many examples were observed in adducts of pyridine *N*-oxides with aryl isocyanates, imidoyl chlorides, nitrilium salts, activated acetylenes and benzyne [13]. Accordingly, the intramolecular process is a highly possible pathway to the  $\beta$ -acetoxy products **4**.



A feasible factor in controlling the direction of aromatization in the final step is the thermodynamical stability of the isomeric acetoxy pyrazines. Hence, heats of formation for all possible isomers of methoxy, chloro and methoxycarbonyl substituted acetoxy pyrazines were calculated by the semi-empirical AM1 level of molecular orbital calculations. The MOPAC-6 or MOPAC-93 [14] programs were used and all geometries were fully optimized. The AM1-COSMO [15] continuum model was used for acetic anhydride modelling, selecting default values except EPS = 20.7, to the optimum conformation for each set of isomers. Table 2 shows the results, in which the heat of formation order is 2,3- > 2,6-  $\approx$  2,5-disubstituted pyrazines regardless of the original substituent. A difference of 1.0-1.4 Kcal·mol<sup>-1</sup> by AM1-COSMO in the heat of formation between 2-acetoxy-6-substituted pyrazines **4** and the 2,3-isomer **2** is sufficient evidence for the preferable formation of the former compound **4** from the intermediate **7**. Consequently, if the Meisenheimer complex **6** forms preferentially to the one leading to 2-acetoxy-5-substituted pyrazine **3**, one may be convinced of the observed regioselectivity. However, a lower heat of formation in the 2,5-isomers than in the 2,6-isomers is indeed in opposition to the proposed mechanism for the exclusive formation of 2-acyloxy-6-methoxy pyrazine **8**. Another driving force needs to be devised, one of which is an acidity of the sp<sup>3</sup> hydrogen atoms in intermediate **10**, and it will be undertaken in a future paper.

Table 2  
AM1(SCF) and AM1(COSMO) Calculated Heat of Formation for Optimized Conformers

			
	<b>2a</b>	<b>3a</b>	<b>4a</b>
$\Delta H(\text{SCF})/\text{Kcal}\cdot\text{mol}^{-1}$	-65.4	-67.2	-67.7
$\Delta H(\text{COSMO})/\text{Kcal}\cdot\text{mol}^{-1}$	-83.6	-84.9	-84.6
			
	<b>2d</b>	<b>3d</b>	<b>4d</b>
$\Delta H(\text{SCF})/\text{Kcal}\cdot\text{mol}^{-1}$	-33.2	-35.1	-35.0
$\Delta H(\text{COSMO})/\text{Kcal}\cdot\text{mol}^{-1}$	-49.8	-51.4	-51.3
			
	<b>2e</b>	<b>3e</b>	<b>4e</b>
$\Delta H(\text{SCF})/\text{Kcal}\cdot\text{mol}^{-1}$	-106.3	-108.4	-107.6
$\Delta H(\text{COSMO})/\text{Kcal}\cdot\text{mol}^{-1}$	-129.1	-131.1	-130.5

## EXPERIMENTAL

All melting points were determined using a Büchi 535 apparatus and are uncorrected. Boiling points were oven temperatures at Kugelrohr-distillation and are uncorrected. The IR spectra were recorded on a JASCO IR-810 spectrometer. The NMR spectra were obtained with JEOL JNM EX270 instrument with solutions in deuteriochloroform containing tetramethylsilane as the internal standard.

General Procedure of Deoxydiacetylation of Pyrazine *N*-Oxides **1**.

A solution of **1** (1 mmole) or the mixture with triethylamine (0.49 ml, 3.5 mmoles) and zinc bromide (338 mg, 1.5 mmoles) when using it, in freshly distilled acetic anhydride (5 ml) was refluxed with stirring under argon. After cooling to room tem-

perature, the mixture was evaporated *in vacuo*, and the residue was subjected to chromatography on silica gel (20 g) eluted with hexane-ethyl acetate (10:1 to 3:1), or to Kugelrohr distillation (2 mm Hg). The mixture of substitution products was separated by high performance liquid chromatography equipped with the pre-packed column (2.2 x 30 cm, 10  $\mu\text{m}$  silica gel) eluted with the same solvent.

The following compounds were obtained by the above procedure.

2-Acetoxy-3-methoxypyrazine (**2a**).

This compound was obtained as a colorless solid, bp 90° (2 mm Hg), mp 40°; IR (potassium bromide): 1765  $\text{cm}^{-1}$  (CO);  $^1\text{H}$  NMR: 2.37 (3H, s), 4.01 (3H, s), 7.89 (1H, d,  $J = 2.6$  Hz), 8.03 (1H, d).

Anal. Calcd. for  $\text{C}_7\text{H}_8\text{N}_2\text{O}_3$ : C, 50.00; H, 4.80; N, 16.66. Found: C, 49.51; H, 4.70; N, 16.27.

2-Acetoxy-6-methoxypyrazine (**4a**).

This compound was obtained as a colorless solid, bp 90° (2 mm Hg), mp 33-35°; ir (potassium bromide): 1770 cm<sup>-1</sup> (CO); <sup>1</sup>H nmr: 2.36 (3H, s), 3.94 (3H, s), 8.03 (1H, s), 8.16 (1H, s).

*Anal.* Calcd. for C<sub>7</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.59; H, 4.75; N, 16.63.

#### 2-Acetoxy-6-phenylpyrazine (4b).

This compound was obtained as a pale yellow oil, bp 135° (2 mm Hg); ir (neat): 1770 cm<sup>-1</sup> (CO); <sup>1</sup>H nmr: 2.40 (3H, s), 7.47-7.49 (3H, m), 7.98-8.01 (3H, m), 8.42 (1H, s), 8.93 (1H, s).

*Anal.* Calcd. for C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.20; H, 4.71; N, 13.11.

#### 2-Acetoxy-6-methylpyrazine (4c).

This compound was obtained as a colorless oil, bp 80° (2 mm Hg); ir (neat): 1770 cm<sup>-1</sup> (CO); <sup>1</sup>H nmr: 2.38 (3H, s), 2.56 (3H, s), 8.32 (1H, s), 8.40 (1H, s).

*Anal.* Calcd. for C<sub>7</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.67; H, 5.36; N, 17.93.

#### 2-Acetoxy-6-chloropyrazine (4d).

This compound was obtained as a pale yellow oil, bp 90° (2 mm Hg); ir (neat): 1775 cm<sup>-1</sup> (CO); <sup>1</sup>H nmr: 2.39 (3H, s), 8.44 (1H, s), 8.54 (1H, s).

*Anal.* Calcd. for C<sub>6</sub>H<sub>5</sub>N<sub>2</sub>O<sub>2</sub>Cl: C, 41.76; H, 2.92; N, 16.23. Found: C, 41.87; H, 2.94; N, 16.28.

The following materials could not be isolated or obtained in sufficient quantity for analysis so that only their nmr spectral data are given.

#### 2-Acetoxy-3-phenylpyrazine (2b).

The spectrum of this compound was observed as follows; <sup>1</sup>H nmr: 2.23 (3H, s), 7.47-7.49 (3H, m), 7.44-7.84 (2H, m), 8.31 (1H, d, J = 2.7 Hz), 8.59 (1H, d).

#### 2-Acetoxy-5-phenylpyrazine (3b).

The spectrum of this compound was observed as follows; <sup>1</sup>H nmr: 2.32 (3H, s), 7.47-7.49 (3H, m), 8.0-8.1 (2H, m), 8.52 (1H, d, J = 1.3 Hz), 8.76 (1H, d).

#### 2-Acetoxy-3-methylpyrazine (2c).

The spectrum of this compound was observed as follows; <sup>1</sup>H nmr: 2.39 (3H, s), 2.50 (3H, s), 8.22 (1H, d, J = 2.4 Hz), 8.42 (1H, d).

#### Methyl 2-Acetoxy-3-pyrazinecarboxylate (2e).

The spectrum of this compound was observed as follows; <sup>1</sup>H nmr: 2.37 (3H, s), 3.94 (3H, s), 8.55 (1H, d, J = 2.6 Hz), 8.61 (1H, d).

#### Methyl 2-Acetoxy-5-pyrazinecarboxylate (3e).

The spectrum of this compound was observed as follows; <sup>1</sup>H nmr: 2.35 (3H, s), 3.98 (3H, s), 9.05 (1H, d, J = 1.3 Hz), 8.61 (1H, d).

#### Methyl 2-Acetoxy-6-pyrazinecarboxylate (4e).

The spectrum of this compound was observed as follows; <sup>1</sup>H nmr: 2.34 (3H, s), 3.97 (3H, s), 8.64 (1H, s), 9.17 (1H, s).

#### 3-Methoxy-2(1H)-pyrazinone.

This compound was obtained by recrystallization of **2a** from hexane-ethyl acetate (1:1) as colorless tiny needles, mp 205°; ir (potassium bromide): 3220 cm<sup>-1</sup> (OH); <sup>1</sup>H nmr: 4.01 (3H, s), 6.90 (1H, d, J = 4.3 Hz), 6.99 (1H, d), 12.77 (1H, br s).

*Anal.* Calcd. for C<sub>5</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.51; H, 4.79; N, 21.80.

#### Acknowledgements.

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#### REFERENCES AND NOTES

- [1] Part 28: N. Sato, N. Miwa and N. Hirokawa, *J. Chem. Soc., Perkin Trans. I*, 885 (1994).
- [2] E. Ochiai, *Aromatic Amine Oxides*, Elsevier, Amsterdam, 1967, p 290.
- [3] A. R. Katritzky and J. M. Lagowski, *Chemistry of the Heterocyclic N-Oxides*, Academic Press, London, 1971, p 281.
- [4] M. Asai, *Yakugaku Zasshi*, **79**, 1273 (1959).
- [5] B. Klein, J. Berkowitz and N. E. Hetmann, *J. Org. Chem.*, **26**, 126 (1961).
- [6] [a] A. Ohta, Y. Akita and Y. Nakane, *Chem. Pharm. Bull.*, **27**, 2980 (1978); [b] A. Ohta, S. Masano, S. Iwakura, A. Tamura, H. Watahiki, M. Tsutsui, Y. Akita and T. Watanabe, *J. Heterocyclic Chem.*, **19**, 465 (1982); [c] A. Ohta, A. Imazeki, Y. Itoigawa, H. Yamada, C. Suga, C. Takagi, H. Sano and T. Watanabe, *J. Heterocyclic Chem.*, **20**, 311 (1983).
- [7] R. H. Cox and A. A. Bothner-By, *J. Phys. Chem.*, **72**, 1642 (1968); T. J. Batterham, *NMR Spectra of Simple Heterocycles in General Heterocyclic Chemistry Series*, E. C. Taylor and A. Weissberger, eds, John Wiley and Sons, New York, 1973, p 120.
- [8] N. Sato, Y. Shimomura, Y. Ohwaki and R. Takeuchi, *J. Chem. Soc., Perkin Trans. I*, 2877 (1991).
- [9] N. Sato, K. Kawahara and N. Morii, *J. Chem. Soc., Perkin Trans. I*, 15 (1993).
- [10] G. W. H. Cheeseman and E. S. G. Trörz, *J. Chem. Soc.*, 6681 (1965).
- [11] H. Foks and J. Sawlewicz, *Acta Pol. Pharm.*, **33**, 153 (1976).
- [12] S. Okada, A. Kosasayama, T. Konno and F. Uchimar, *Chem. Pharm. Bull.*, **19**, 1344 (1971).
- [13] R. A. Abramovitch and I. Shinkai, *Acc. Chem. Res.*, **9**, 192 (1976).
- [14] J. J. P. Stewart, *J. Comput. Chem.*, **10**, 209 and 221 (1989) implemented in MOPAC-93 from Fujitsu, Tokyo, Japan, and available from Quantum Chemistry Program Exchange, University of Indiana, Bloomington, IN.
- [15] A. Klamt and G. Schüürmann, *J. Chem. Soc., Perkin Trans. 2*, 799 (1993).