

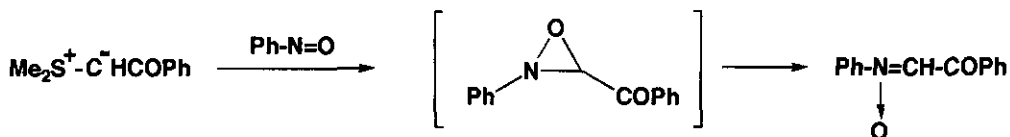
SYNTHESIS OF PYRAZOLO[3,4-*b*]PYRAZINES FROM 5-AMINO-4-NITROSOPYRAZOLES AND DIMETHYLPHENACYSULFONIUM BROMIDES

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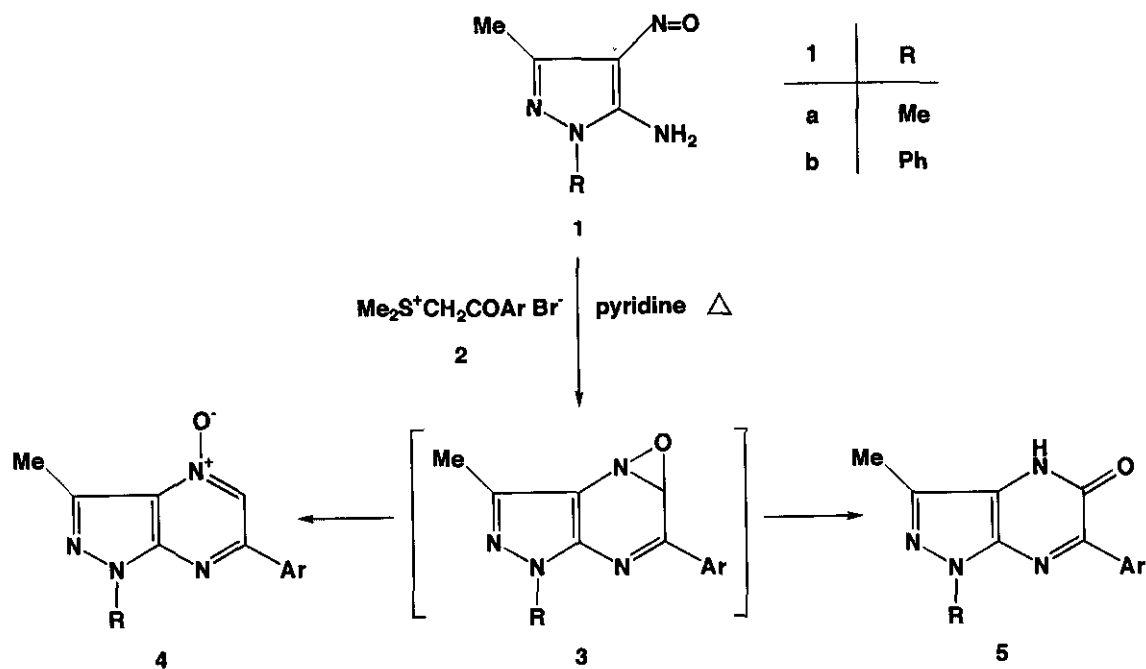
Abstract- Reaction of 1,3-disubstituted 5-amino-4-nitrosopyrazoles (1) with dimethylphenacysulfonium bromides (2) in boiling pyridine gave 1,3,6-trisubstituted pyrazolo[3,4-*b*]pyrazine 4-oxides (4) and / or 1,3,6-trisubstituted pyrazolo[3,4-*b*]pyrazin-5(4*H*)-ones (5).

Phenacysulfonium ylides and their precursors, phenacysulfonium halides have been used as useful reagents for introduction of C₁ or C₂ unit into heterocycles. Thus, the following heterocycles have been synthesized by the use of the reagents; 2-acyloxiranes from carbonyl compounds,¹ 2-pyrones from diphenylcyclopropanone,² 2-phenylindoles from aromatic amines,³ isoxazoline *N*-oxides from nitro sugars,⁴ 2,4,6-triarylpyridines from α,β -unsaturated ketones,⁵ 2-phenylquinoxalines from *o*-phenylenediamines,⁶ dihydrotetrazine from benzenediazonium chloride,⁷ and 1,2,5-oxadiazole 2-oxides by nitrosation.⁸ The reaction of sulfonium ylides with nitroso compounds was known to give nitrones *via* oxaziridine intermediates^{1,9} while 2-bromophenylglyoxal 2-arylhyazones were formed from *N*-nitrosoacetanilides.⁷ However, utilization of the



reaction of sulfonium ylides or halides with nitroso compounds for the synthesis of heterocycles has not been reported. It seemed interesting to investigate the reactivity of acylsulfonium ylides towards β -nitrosoamines because of the possibility of forming pyrazine *N*-oxide by condensation in one step.¹⁰ We chose 5-amino-4-nitrosopyrazoles¹¹ as β -nitrosoamine and found a new synthetic route to pyrazolo[3,4-*b*]pyrazines.

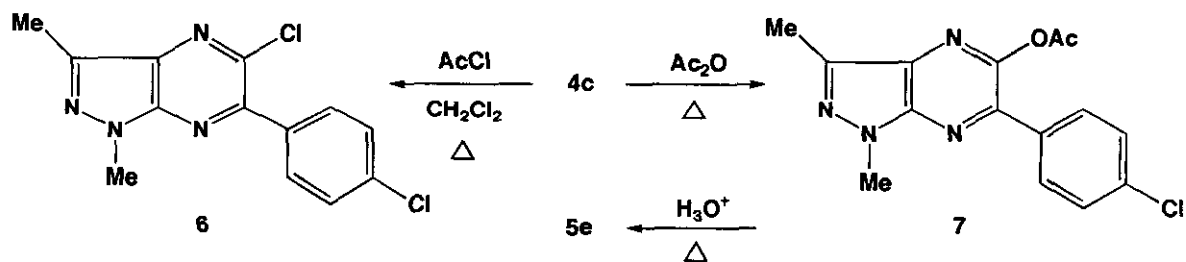
A mixture of 1,3-disubstituted 5-amino-4-nitrosopyrazole (**1**) and acylsulfonium bromide (**2**) in pyridine was heated under reflux and removal of the solvent followed by recrystallization gave yellow solids. The structures



4	R	Ar	Yield (%)
a	Me	Ph	20
b	Me	4-BrC ₆ H ₄	45
c	Me	4-ClC ₆ H ₄	38
d	Ph	Ph	30
e	Ph	4-BrC ₆ H ₄	47
f	Ph	4-ClC ₆ H ₄	46
g	Ph	4-MeC ₆ H ₄	—
h	Ph	4-MeOC ₆ H ₄	—

5	R	Ar	Yield (%)
a	Me	4-MeC ₆ H ₄	28
b	Me	4-MeOC ₆ H ₄	20
c	Ph	4-MeC ₆ H ₄	—
d	Ph	4-MeOC ₆ H ₄	—
e	Me	4-ClC ₆ H ₄	—

of the products were classified into two groups; 1-substituted 6-aryl-3-methylpyrazolo[3,4-*b*]pyrazine 4-oxides (**4**) and 1-substituted 6-aryl-3-methylpyrazolo[3,4-*b*]pyrazin-5(4*H*)-ones (**5**) on the basis of the spectral and analytical data. In the $^1\text{H-nmr}$ spectra the products (**4a-f**) showed the resonances of the C-5 proton around δ 9.1, while the corresponding proton resonances were not observed in those of **5a** and **b**. On the other hand, the carbonyl and the amine absorptions were shown at $1635\text{-}1640\text{ cm}^{-1}$ and $2925\text{-}2750\text{ cm}^{-1}$, respectively, in the IR spectra of **5a** and **b**, and the *N*-oxide absorptions were observed at $1225\text{-}1240\text{ cm}^{-1}$ in those of **4a-f**. Moreover, in the mass spectra of **4a-f**, M^+-17 peaks corresponding to loss of hydroxyl radical were observed as the base peaks, which would be explained as the results of abstraction of one proton of the methyl group at the C-3 position by the oxygen of *N*-oxide. In contrast, pyrazin-5-ones (**5a** and **b**) showed M^+-CO peaks instead of M^+-OH in the mass spectra. In order to confirm the *N*-oxide structure¹² the compound (**4c**) was treated with acetyl chloride at reflux in dichloromethane, giving the expected 5-chloro derivative (**6**) in 65% yield. Furthermore, 5-acetoxy derivative (**7**) was produced in 66% yield on treatment of **4c** in acetic anhydride at reflux. In the $^1\text{H-nmr}$ spectra of **6** and **7** the resonance of the C-5 proton observed in **4c** at δ 9.09 disappeared, showing that the substitution reaction by chloride or acetate anion took place at this position. In fact, hydrolysis of the 5-acetoxy group of **7** in boiling hydrochloric acid gave pyrazin-5-one (**5e**) in 73% yield.



In most cases the reactions proceeded selectively to give either 4-oxides (**4a-f**) in 20-47% yields or pyrazin-5-ones (**5a,b**) in 20-28% yields as the isolated products. However, the reactions of **1b** with **2** bearing 4-methylphenyl or 4-methoxyphenyl substituent gave the unseparable mixtures of **4g** and **5c** (ratio 1/0.8) in 28% yield, and **4h** and **5d** (ratio 1/3) in 29% yields, respectively.

The formation of 4-oxides (**4**) may be interpreted by the rearrangement of the initially formed oxaziridine intermediate (**3**) in the same way as nitrene formation from a simple nitroso compound and sulfonium ylides.¹

On the other hand, the thermal rearrangement of oxaziridine to amide is a well known process,¹³ explaining the formation of pyrazin-5-ones (**5**). There was a tendency that the electron-withdrawing substituents on **3** preferred the formation of **4** to that of **5**.

EXPERIMENTAL

All melting points were determined with a MRK MEL-TEMP II and uncorrected. Ir spectra were recorded on a JASCO A-102 spectrophotometer. Nmr and mass spectra were taken with a JEOL GSX-400 and a JEOL JMS-DX300 spectrometers, respectively. Microanalyses were performed with a YANACO CHN-Corder MT-5.

A general procedure for the synthesis of **4** and **5**

A mixture of **1** (1.0 mmol) and **2**¹⁴ (1.2 mmol) in pyridine (5 ml) was heated under reflux for 3 h. After evaporation the solvent the residue was washed with MeOH and then recrystallized to give the products **4** and / or **5**.

1,3-Dimethyl-6-phenylpyrazolo[3,4-*b*]pyrazine 4-oxide (**4a**)

mp 184-185°C (pyridine); ir (KBr) cm^{-1} : 3070, 1545, 1420, 1350, 1225; ms m/z (%): 240 (M^+ , 41), 224 (29), 223 (M^+ -OH, 100), 182 (7); ¹H-nmr (CF_3COOD) δ : 3.00 (s, 3H), 4.36 (s, 3H), 7.60-8.18 (m, 5H), 9.10 (s, 1H). *Anal.* Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}$: C, 64.98; H, 5.03; N, 23.31. Found: C, 65.16; H, 5.10; N, 23.28.

6-(4-Bromophenyl)-1,3-dimethylpyrazolo[3,4-*b*]pyrazine 4-oxide (**4b**)

mp 218-219°C (pyridine); ir (KBr) cm^{-1} : 3070, 1580, 1550, 1440, 1350, 1240; ms m/z (%): 320 (M^{++2} , 32), 318 (M^+ , 32), 303 (98), 301 (M^+ -OH, 100), 262 (7), 220 (7); ¹H-nmr (CF_3COOD) δ : 2.93 (s, 3H), 4.35 (s, 3H), 7.77 (d, $J=9.0$ Hz, 2H), 8.07 (d, $J=9.0$ Hz, 2H), 9.11 (s, 1H). *Anal.* Calcd for $\text{C}_{13}\text{H}_{11}\text{N}_4\text{OBr}$: C, 48.92; H, 3.47; N, 17.55. Found: C, 48.86; H, 3.54; N, 17.42.

6-(4-Chlorophenyl)-1,3-dimethylpyrazolo[3,4-*b*]pyrazine 4-oxide (**4c**)

mp 222-224°C (pyridine); ir (KBr) cm^{-1} : 3070, 1580, 1550, 1440, 1345, 1240; ms m/z (%): 276 (M^{++2} , 11), 274 (M^+ , 34), 259 (34), 257 (M^+ -OH, 100); ¹H-nmr (CF_3COOD) δ : 2.97 (s, 3H), 4.35 (s, 3H), 7.57 (d, $J=10.2$ Hz, 2H), 8.15 (d, $J=10.2$ Hz, 2H), 9.09 (s, 1H). *Anal.* Calcd for $\text{C}_{13}\text{H}_{11}\text{N}_4\text{OCl}$: C, 56.83; H, 4.03; N, 20.39. Found: C, 56.60; H, 4.06; N, 20.26.

3-Methyl-1,6-diphenylpyrazolo[3,4-*b*]pyrazine 4-oxide (**4d**)

mp 239-242°C (pyridine); ir (KBr) cm^{-1} : 3050, 1555, 1485, 1420, 1350, 1240; ms m/z (%): 302 (M^+ , 56), 285 (M^+ -OH, 100), 258 (7); $^1\text{H-nmr}$ (CF_3COOD) δ : 3.06 (s, 3H), 7.58-8.10 (m, 10H), 9.11 (s, 1H). *Anal.* Calcd for $\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}$: C, 71.50; H, 4.66; N, 18.53. Found: C, 71.59; H, 4.78; N, 18.37.

6-(4-Bromophenyl)-3-methyl-1-phenylpyrazolo[3,4-*b*]pyrazine 4-oxide (4e)

mp 290-292°C (MeOH-pyridine); ir (KBr) cm^{-1} : 3070, 1580, 1550, 1500, 1455, 1430, 1350, 1240; ms m/z (%): 382 (M^+ +2, 49), 380 (M^+ , 49), 365 (100), 363 (M^+ -OH, 93), 284 (8); $^1\text{H-nmr}$ (CF_3COOD) δ : 3.06 (s, 3H), 7.60-7.75 (m, 5H), 7.89 (d, $J=7.7$ Hz, 2H), 7.98 (d, $J=7.7$ Hz, 2H), 9.11 (s, 1H). *Anal.* Calcd for $\text{C}_{18}\text{H}_{13}\text{N}_4\text{OBr}$: C, 56.71; H, 3.43; N, 14.69. Found: C, 56.93; H, 3.64; N, 14.67.

6-(4-Chlorophenyl)-3-methyl-1-phenylpyrazolo[3,4-*b*]pyrazine 4-oxide (4f)

mp 280-282°C (MeOH-pyridine); ir (KBr) cm^{-1} : 3060, 1580, 1550, 1450, 1430, 1345, 1240; ms m/z (%): 338 (M^+ +2, 17), 336 (M^+ , 49), 321 (41), 320 (54), 319 (M^+ -OH, 100); $^1\text{H-nmr}$ (CF_3COOD) δ : 3.05 (s, 3H), 7.56-7.68 (m, 5H), 7.89 (d, $J=10.3$ Hz, 2H), 8.07 (d, $J=10.3$ Hz, 2H), 9.12 (s, 1H). *Anal.* Calcd for $\text{C}_{18}\text{H}_{13}\text{N}_4\text{OCl}$: C, 64.20; H, 3.89; N, 16.64. Found: C, 64.23; H, 4.07; N, 16.65.

1,3-Dimethyl-6-(4-methylphenyl)pyrazolo[3,4-*b*]pyrazin-5(4H)-one (5a)

mp 280-283°C (pyridine); ir (KBr) cm^{-1} : 2925, 2750, 1635, 1570, 1245, 1170; ms m/z (%): 254 (M^+ , 100), 226 (M^+ -CO, 34), 118 (49); $^1\text{H-nmr}$ (CF_3COOD) δ : 2.50 (s, 3H), 2.76 (s, 3H), 4.35 (s, 3H), 7.43 (d, $J=7.5$ Hz, 2H), 8.35 (d, $J=7.5$ Hz, 2H). *Anal.* Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}$: C, 66.12; H, 5.54; N, 22.03. Found: C, 66.07; H, 5.52; N, 21.73.

6-(4-Methoxyphenyl)-1,3-dimethylpyrazolo[3,4-*b*]pyrazin-5(4H)-one (5b)

mp 265-267°C (pyridine); ir (KBr) cm^{-1} : 2925, 2775, 1640, 1570, 1245, 1170; ms m/z (%): 270 (M^+ , 100), 242 (M^+ -CO, 22), 227 (26), 134 (45); $^1\text{H-nmr}$ (CF_3COOD) δ : 2.72 (s, 3H), 4.07 (s, 3H), 4.37 (s, 3H), 7.17 (d, $J=11.3$ Hz, 2H), 8.59 (d, $J=11.3$ Hz, 2H). *Anal.* Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_2$: C, 62.21, H, 5.22, N, 20.72. Found: C, 62.12; H, 5.21, N, 20.79.

6-(4-chlorophenyl)-1,3-dimethylpyrazolo[3,4-*b*]pyrazin-5(4H)-one (5e)

A mixture of **7** (50 mg, 0.15 mmol) in 2N hydrochloric acid (10 ml) was heated under reflux for 1h. The precipitates were collected by filtration and recrystallized from isopropanol to give **5e** (30 mg, 73%), mp 329-330°C. ir (KBr) cm^{-1} : 2920, 2775, 1640, 1570, 1420, 1390, 1280; ms m/z (%): 276 (M^+ +2, 35), 274 (M^+ , 100), 246 (M^+ -CO, 25), 138 (14); $^1\text{H-nmr}$ (CF_3COOD) δ : 2.75 (s, 3H), 4.37 (s, 3H), 7.56 (d, $J=8.5$ Hz, 2H),

8.44 (d, $J=8.5$ Hz, 2H). *Anal.* Calcd for $C_{13}H_{11}N_4OCl$: C, 56.83; H, 4.03; N, 20.39. Found: C, 56.68; H, 4.25; N, 20.66.

5-Chloro-6-(4-chlorophenyl)-1,3-dimethylpyrazolo[3,4-*b*]pyrazine (6)

A mixture of **4c** (274 mg, 1.0 mmol) and acetyl chloride (2.0 ml, 21 mmol) in dichloromethane (20 ml) was heated under reflux for 30 h under nitrogen atmosphere. Evaporation of the solvent left solids, which were recrystallized from isopropanol to give **6** as pale yellow crystals (190 mg, 65%), mp 171-173°C. *ir* (KBr) cm^{-1} : 1490, 1335, 1185, 1130, 1095; *ms m/z* (%): 294 ($M^{+}+2$, 63), 292 (M^{+} , 100), 259 (17), 257 ($M^{+}-Cl$, 51), 111 (12); 1H -nmr ($CDCl_3$) δ : 2.66 (s, 3H), 4.10 (s, 3H), 7.50 (d, $J=8.5$ Hz, 2H), 7.76 (d, $J=8.5$ Hz, 2H).

Anal. Calcd for $C_{13}H_{10}Cl_2N_4$: C, 53.26; H, 3.44; N, 19.11. Found: C, 52.91; H, 3.51; N, 19.22.

5-Acetoxy-6-(4-chlorophenyl)-1,3-dimethylpyrazolo[3,4-*b*]pyrazine (7)

A mixture of **4c** (137 mg, 0.50 mmol) in acetic anhydride (15 ml, 136 mmol) was heated under reflux for 7 h. Removal of acetic anhydride left solids, which were recrystallized from isopropanol to give **7** (105 mg, 66% yield), mp 138-139°C. *ir* (KBr) cm^{-1} : 2900, 1745, 1330, 1165; *ms m/z* (%): 318 ($M^{+}+2$, 1), 316 (M^{+} , 5), 276 (34), 274 ($M^{+}-MeCO$, 100), 246 (24), 138 (11); 1H -nmr ($CDCl_3$) δ : 2.22 (s, 3H), 2.61 (s, 3H), 4.13 (s, 3H), 7.48 (d, $J=7.6$ Hz, 2H), 7.82 (d, $J=7.6$ Hz, 2H). *Anal.* Calcd for $C_{15}H_{13}N_4O_2Cl$: C, 56.87; H, 4.13; N, 17.68. Found: C, 56.76; H, 4.25; N, 17.76.

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Received, 18th January, 1995