*ythro*-**24**, 109307-95-1; *threo*-**24**, 109307-96-2; *erythro*-**26**, 109307-99-5; *threo*-**26**, 109308-00-1; *erythro*-**27**, 109308-01-2; *threo*-**27**, 109308-02-3; (*Z*)-**29a**, 109308-03-4; (*E*)-**29a**, 109308-04-5; (*E*)-**29b**, 109308-05-6; (*Z*)-**29b**, 109308-06-7; (*Z*)-**29c**, 109308-07-8; (*E*)-**29c**, 109308-08-9; **30a**, 109308-09-0; **30b**, 109308-10-3; **30c**, 109308-11-4; **31a**, 109308-12-5; **31b**, 109308-13-6; **31c**, 109308-14-7; **32a**, 109308-23-8; **32b**, 109308-25-0; **32c**, 109308-27-2; **32d**, 109308-29-4; **33a**, 109308-24-9; **33b**, 109308-26-1; **33c**, 109308-28-3; **33d**, 109308-30-7; **34a**, 109308-17-0; **34b**, 109308-19-2; **34c**, 109308-21-6; **35a**, 109308-18-1; **35b**, 109308-20-5; **35c**, 109308-22-7; *erythro*-**48**, 109307-97-3; *threo*-**48**, 109307-98-4; (α-bromocarbethoxy)methylenetriphenylphosphorane, 109307-65-5; ethyl phosphonoacrylate, 109307-78-0; heptaldehyde, 111-71-7; methyltriphenylphosphonium bromide, 1779-49-3; methyltriphenylphosphonium iodide, 2065-66-9; triethyl 2-phosphonopropionate, 3699-66-9; vitamin D, 1406-16-2.

# *Notes*

## Methanesulfonanilides and the Mannich Reaction

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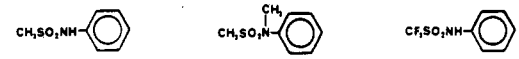
Numerous reviews on the Mannich reaction have appeared.[1] The reaction of phenols under typical Mannich conditions (i.e., amine and aqueous formaldehyde in alcoholic solvents) affords preponderantly ortho aminomethylation products,[2] which is consistent with a quasi six-membered transition-state mechanism.[3] The use of methanesulfonanilide (**1**) ($pK_a$ = 9.9)[4] in the Mannich reaction has not previously been reported although the acidity is similar to that of phenol ($pK_a$ = 11.0). We now report our investigations on the reaction of various methanesulfonanilides under typical Mannich conditions.

Methanesulfonanilides **1–10** (Table I) were prepared in good to excellent yields by using a modification of the procedure of Marvel et al.[5] (see Experimental Section). Reaction of methanesulfonanilide **1** with pyrrolidine ($pK_a$ = 11.27)[6] and aqueous formaldehyde in hot ethanol (reaction mixture pH 8.0) affords only the para-substituted aminomethylation product **11** (Table II). This is evident from the 300-MHz NMR spectrum of **11**, which displays the aromatic protons as an AB quartet centred at δ 7.40 with $J_{AB}$ = 8.0 Hz and $\Delta\nu_{AB}$ = 26.8 Hz. Similar results were obtained by using diethylamine ($pK_a$ = 10.49)[6] and piperidine ($pK_a$ = 11.12)[6] as the secondary amines (Table II, **12** and **13**). In each case the product can be obtained by filtering the concentrated reaction mixture through a short column of alumina.[7] This reaction does not appear to be reversible since submitting pure **13** to the reaction conditions does not lead to production of **1** (TLC analysis) and **13** was isolated unchanged. Addition of a catalytic amount of HCl to the reaction mixture or limiting the amounts of formaldehyde used to 1.1 equiv did not improve the chemical yield, although these conditions are sometimes the method of choice for the Mannich reaction.[1] *N*-Methylmethanesulfonanilide (**21**)[8] does not react with the pyrrolidine/formaldehyde mixture, demonstrating that the NH group is essential for reactivity. Similarly, trifluoromethanesulfonanilide (**22**) ($pK_a$ = 4.45)[9] was recovered unchanged from the reaction mixture, indicating that $pK_a$ is also an important aspect of this transformation.




**1** **21** **22**

No aminomethylation products were observed when methanesulfonanilide (**1**) was treated with either ethylbenzylamine ($pK_a$ = 9.64)[10] or benzylamine ($pK_a$ = 9.33)[6] under the usual reaction conditions. This is attributed to the lower basicity of these amines.

Methanesulfonanilides **3** and **9** failed to react with the pyrrolidine/formaldehyde mixture. Deactivated systems do react, albeit in poor yield, with mostly starting material being recovered (Table II, **14**, **17**, and **19**).

The position of the pyrrolidinylmethyl group in adducts **14** and **17** was determined by proton NOE difference NMR. Selective irradiation of the benzylic methylene protons (δ 3.57) of **14**, which were well-resolved in the spectrum, resulted in enhancement of two aromatic protons (δ 7.24 and 7.44). This is consistent only with two aromatic ortho protons as in structure **14**. Similarly, irradiation of the methoxy protons (δ 3.79) of **17** resulted in enhancement of two aromatic protons (δ 6.69 and 6.82). This allows for the assignment of the pyrrolidinylmethyl group to the 2-position of the aromatic ring as in **17**.

Aminomethylation takes place only on the acetyl methyl group of compound **7**. Similar results were reported by Gallo and Comer[11] for this substrate using acidic condi-

(1) Tramontini, M. *Synthesis* **1973**, 703. Thompson, B. B. *J. Pharm. Sci.* **1968**, *57*, 715. Blicke, F. F. *Org. React.* (*N.Y.*) **1942**, *1*, 303 and references cited therein.

(2) Magarian, R. A.; Nobles, W. L. *J. Pharm. Sci.* **1967**, *56*, 987. Mehta, R. H. *Indian J. Chem.* **1964**, *2*, 336; *Chem. Abstr.* **1964**, *61*, 14630. Desai, R. B. *J. Org. Chem.* **1961**, *26*, 5251. Hideg, K.; Hamkovszky, O. H. *Acta Chim. Acad. Sci. Hung.* **1967**, *53*, 271.

(3) Burckhalter, J. H.; Leib, R. I. *J. Org. Chem.* **1961**, *26*, 4078. Burckhalter, J. H.; Wells, J. N.; Mayer, W. J. *Tetrahedron Lett.* **1964**, 1353.

(4) Uloth, R. H.; Kirk, J. R.; Gould, W. A.; Larsen, A. A. *J. Med. Chem* **1966**, *9*, 88.

(5) Marvel, C. S.; Helfrick, M. D.; Belsley, J. P. *J. Am. Chem. Soc.* **1929**, *51*, 1272.

(6) Weast, R. C. *CRC Handbook of Chemistry and Physics*, 55th ed.; CRC Press: Cleveland, OH, 1974; pp D126–128.

(7) The aminomethylation products are quite water-soluble. For example, the methylene chloride/aqueous phosphate buffer partition coefficients for compound **11** are as follows: pH 6.0, 0.02; pH 8.0, 0.77; pH 10.0, 1.42.

(8) Closson, W. D.; Ji, S.; Schulenberg, S. *J. Am. Chem. Soc.* **1970**, *92*, 650.

(9) Trepka, R. D.; Harrington, J. K.; Belisle, J. W. *J. Org. Chem.* **1974**, *39*, 1094.

(10) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1965; p 118.

(11) Gallo, D. G.; Comer, W. T. U.S. Pat. 3968242, 1976.

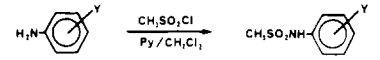
(12) Varro, A.; Toldy, L.; Zubovics, Z.; Elek, S.; Rabioczky, G.; Andrasi, F.; Elekes, I. Brit. Pat. 2098599, 1982.

(13) Inada, S.; Hirabayashi, S.; Taguchi, K.; Okazaki, M. *Nippon Kagaku Kaishi* **1978**, 86; *Chem. Abstr.* **1978**, *88*, 151779d.

(14) Abramovitch, R. A.; Uma, A. *Can. J. Chem.* **1965**, *43*, 3407.

0022-3263/87/1952-4377$01.50/0 

**Table I. Preparation of Methanesulfonamides 1–10**

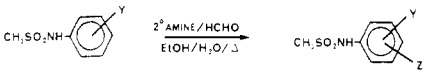



1–10

| no. | Y | mp (solv),[a] °C | yield,[b] % | NMR |
|---|---|---|---|---|
| 1 | H | 99–101[c] | 94 | [d] 2.97 (s, 3 H), 7.10 (t, 1 H), 7.20 (d, 2 H), 7.33 (t, 2 H), 9.72 (br s, 1 H) |
| 2 | 2-chloro | 89–90[e] | 82 | [d] 3.07 (s, 3 H), 7.29 (m, 1 H), 7.39 (m, 1 H), 7.49 (m, 1 H), 7.55 (m, 1 H), 9.48 (s, 1 H) |
| 3 | 2,6-dimethyl | 124–126[f] (A) | 86 | [g] 2.43 (s, 6 H), 3.10 (s, 3 H), 5.89 (br s, 1 H), 7.12 (m, 3 H) |
| 4 | 3,5-dimethyl | 103–104[h] (A) | 88 | [g] 2.31 (s, 6 H), 3.01 (s, 3 H), 6.38 (br s, 1 H), 6.83 (s, 3 H) |
| 5 | 3-methoxy | 66–68[i] | 89 | [g] 3.03 (s, 3 H), 3.80 (s, 3 H), 6.74 (dd, 1 H), 6.81 (m, 2 H), 7.00 (br s, 1 H), 7.25 (t, 1 H) |
| 6 | 4-methoxy | 108–110[j] (B) | 93 | [d] 2.83 (s, 3 H), 3.68 (s, 3 H), 6.96 (AB quartet, $J_{AB}$ = 9.5 Hz, $\Delta\nu_{AB}$ = 17.6 Hz, 4 H), 9.25 (s, 1 H) |
| 7 | 4-acetyl | 157–159.5[k] | 92 | [d] 2.57 (s, 3 H), 3.17 (s, 3 H), 3.70 (br s, 1 H), 7.75 (AB quartet, $J_{AB}$ = 9.0 Hz, $\Delta\nu_{AB}$ = 37.9 Hz, 4 H) |
| 8 | 4-methyl | 97–98[l] (A) | 86 | [d] 2.23 (s, 3 H), 2.88 (s, 3 H), 7.05 (s, 4 H), 9.15 (s, 1 H) |
| 9 | 4-carbomethoxy | 145–147 (B) | 99 | [g] 3.10 (s, 3 H), 3.82 (s, 3 H), 7.62 (AB quartet, $J_{AB}$ = 8.5 Hz, $\Delta\nu_{AB}$ = 35.0 Hz, 4 H), 10.30 (s, 1 H) |
| 10 | 3-(methylsulfonyl)amino | 215–217 (B) | 97 | [d] 3.00 (s, 6 H), 6.92 (dd, 2 H), 7.13 (t, 1 H), 7.27 (t, 1 H), 9.82 (s, 2 H) |

[a] Recrystallization solvent: A = $H_2O$, B = EtOH. [b] Isolated yield. All compounds gave satisfactory elemental analyses (±0.4% C, H, N). [c] Lit.[5] mp 100.5 °C. [d] $Me_2SO$-$d_6$ ($\delta$). [e] Lit.[5] mp 90.5 °C. [f] Lit.[12] mp 128–129 °C. [g] $CDCl_3$ ($\delta$). [h] Lit.[13] mp 105.5–106 °C. [i] Lit.[14] mp 67.5 °C. [j] Lit.[5] mp 116 °C. [k] Lit.[4] mp 156.5–158.5 °C. [l] Lit.[5] mp 102.5 °C.

**Table II. Preparation of [(Aminomethyl)phenyl]methanesulfonamides 1–20**




1–10 11–20

| no. | Y | Z | amine | mp (solv),[a] °C | yield,[b] % | time, h | temp, °C | mol form | anal.[c] |
|---|---|---|---|---|---|---|---|---|---|
| 11 | H | 4-(1-pyrrolidinylmethyl) | pyrrolidine | 189–191 (A) | 31 | 28 | 90 | $C_{12}H_{18}N_2O_2S$·HCl | CHN |
| 12 | H | 4-[(diethylamino)methyl] | diethylamine | 181–183 (B) | 13[d] | 23 | 90 | $C_{12}H_{20}N_2O_2S$·HCl | CHN |
| 13 | H | 4-(1-piperidinylmethyl) | piperidine | 132–135 | 31 | 50 | 100 | $C_{13}H_{20}N_2O_2S$ | CHNS[e] |
| 14 | 2-chloro | 4-(1-pyrrolidinylmethyl) | pyrrolidine | 103–104 | 7[f] | 50 | 100 | $C_{12}H_{17}ClN_2O_2S$ | CHN |
| 15 | 3,5-dimethyl | 2-(1-pyrrolidinylmethyl) | pyrrolidine | 80–82 | 44 | 50 | 100 | $C_{14}H_{22}N_2O_2S$ | CHNS[g] |
| 16 | 5-methoxy | 2,4-bis(1-pyrrolidinylmethyl) | pyrrolidine | *h* | 75 | 50 | 100 | $C_{18}H_{29}N_3O_3S$ | CHN |
| 17 | 4-methoxy | 2-(1-pyrrolidinylmethyl) | pyrrolidine | 87–88 (C) | 7[i] | 50 | 100 | $C_{13}H_{20}N_2O_3S$ | CHN |
| 18 | 4-acetyl | 4-[1-oxo-3-(1-pyrrolidinyl)propyl] | pyrrolidine | 91–94 | 17[j] | 50 | 100 | $C_{14}H_{20}N_2O_3S$·0.9$H_2O$ | CHNS |
| 19 | 4-methyl | 2-(1-pyrrolidinylmethyl) | pyrrolidine | 108–110 | 9[k] | 50 | 100 | $C_{13}H_{20}N_2O_2S$ | CHN |
| 20 | 5-(methylsulfonyl)amino | 2,4-bis(1-pyrrolidinyl)methyl | pyrrolidine | 240–242 (B) | 53 | 50 | 100 | $C_{18}H_{30}N_4O_4S_2$·2HCl | CHN |

[a] Recrystallization solvent: A = EtOAc/EtOH (6:1); B = EtOH; C = hexane/EtOAc (9:1). [b] Yield not optimized. [c] Elemental analyses are within ±0.4% of the calculated values except where indicated. [d] Free base obtained in 27% yield. [e] Calcd for $C_{13}H_{20}N_2O_2S$: C, 58.18; H, 7.51; N, 10.44; S, 11.95. Found: C, 57.73; H, 7.49; N, 10.47; S, 11.37. [f] Starting material (2) recovered in 77% yield. [g] Calcd for $C_{14}H_{22}N_2O_2S$: C, 59.54; H, 7.85, N, 9.92, S. 11.35. Found: C, 59.08; H, 7.85; N, 9.64; S, 11.48. [h] Obtained as a yellow oil. [i] Starting material (6) recovered in 73% yield. [j] Starting material (7) recovered in 22% yield. [k] Starting material (8) recovered in 50% yield.

tions. The highly activated substrates **5** and **10** afforded the bis(1-pyrrolidinylmethyl) products **16** and **20** in 75% and 53% yields, respectively. No attempt was made to try to produce only the mono aminomethylation products in the above reactions. Aminomethylation takes place ortho to the methanesulfonamide moiety in compound **4**, giving rise to a 44% yield of product **15**. Steric hindrance at the 4-position of **4** explains the ortho attack.

We have demonstrated that methanesulfonanilide (**1**) reacts with various secondary amines and aqueous formaldehyde under typical Mannich conditions. In contrast to phenols, which give preponderantly ortho aminomethylation products,[2] methanesulfonanilide (**1**) gives exclusively para adducts. Activated and deactivated methanesulfonanilides were prepared and used as substrates in these aminomethylations with yields ranging from 7% to 75%.

## Experimental Section

Proton nuclear magnetic resonance ($^1$H NMR) spectra were taken at 300 MHz (Varian XL-300) with chemical shifts relative to tetramethylsilane. Infrared (IR) spectra were taken on a Sargent-Welch 3-300 or a Beckman Acculab 2 spectrophotometer as a KBr pellet, Nujol mull, or in $CHCl_3$ solution as indicated. Elemental analyses were performed by the analytical department of Berlex Laboratories, Inc. Melting points were obtained on a Fisher-Johns hot-stage or a Thomas-Hoover capillary melting point apparatus and are uncorrected.

**General Procedure for Preparation of Methanesulfonamides 1–8.** To a 0 °C solution of the corresponding aniline (0.20 mol) in pyridine (0.22 mol) and methylene chloride (500 mL) under a nitrogen atmosphere was added methanesulfonyl chloride (0.22 mol) at such a rate as to prevent the temperature from rising above 10 °C. After addition the mixture was warmed to room temperature and stirred overnight. The reaction was quenched with 6 N NaOH (100 mL) and enough water added to dissolve the resultant anion. The layers were separated and the aqueous layer washed with methylene chloride (200 mL). The aqueous layer was cooled (0 °C) and acidified to pH 2.0 by using 18% aqueous HCl. The product precipitates and was collected on a sintered glass funnel and air-dried to constant weight.

**Methyl [(4-Methylsulfonyl)amino]benzoate (9).** The general procedure was followed except that the reaction was quenched by being poured into water (500 mL). The product

precipitated from the heterogeneous mixture.

***N,N'*-1,3-Phenylenebis(methanesulfonamide) (10).** The general procedure was followed except that the amounts of pyridine and methanesulfonyl chloride were increased (0.46 mol) as well as the amount of 6 N NaOH used in the workup (200 mL).

**General Procedure for the Preparation of [(Aminomethyl)phenyl]methanesulfonamides 11–20.** The amine (0.234 mol) was added to a room temperature solution of the methanesulfonamide (0.058 mol), 37% aqueous formaldehyde (0.299 mol), and ethanol (50 mL) in a pressure bottle. In some cases an exotherm was observed. The mixture was then stirred and heated at the temperature and time shown in Table II. The reaction mixture was concentrated in vacuo and the residue chromatographed on alumina (Fisher, neutral, activity II, 600 g).

Elution with hexane/EtOAc (3:2) afforded **11** as the free base. Treatment with ethanolic HCl gave the hydrochloride salt, which was recrystallized from EtOAc/EtOH (6:1): $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.87–1.99 (m, 4 H), 3.03 (s, 3 H), 3.33 (br s, 4 H), 4.27 (s, 2 H), 7.40 AB quartet, $J_{AB}$ = 8.0 Hz, $\Delta\nu_{AB}$ = 26.8 Hz, 4 H), 11.00 (br s, 1 H).

Elution with $CH_2Cl_2$/MeOH (97:3) afforded **12** as the free base. Treatment with ethanolic HCl gave the hydrochloride salt, which was recrystallized from EtOH: $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.24 (t, 6 H), 2.92–3.10 (m, 4 H), 3.04 (s, 3 H), 4.20 (s, 2 H), 7.42 (AB quartet, $J_{AB}$ = 8.6 Hz, $\Delta\nu_{AB}$ = 99.6 Hz, 4 H), 10.06 (s, 1 H), 10.68 (br s, 1 H).

Elution with $CH_2Cl_2$ afforded **13**. $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.39–1.50 (m, 6), 2.30 (m, 4), 2.96 (s, 3), 3.37 (s, 2), 7.19 (AB quartet, $J_{AB}$ = 8.0 Hz, $\Delta\nu_{AB}$ = 25.9 Hz, 4 H), 9.63 (br s, 1).

Elution with $CH_2Cl_2$ afforded recovered starting material **2** (77%) followed by **14**: $^1$H NMR ($CDCl_3$) $\delta$ 1.79 (m, 4 H), 2.50 (m, 4 H), 3.00 (s, 3 H), 3.57 (s, 2 H), 6.40 (br s, 1 H), 7.24 (dd, 1 H), 7.44 (d, 1 H), 7.57 (d, 1 H).

Elution with $CH_2Cl_2$/MeOH (19:1) afforded **15**: $^1$H NMR ($CDCl_3$) $\delta$ 1.82 (m, 4 H), 2.27 (s, 3 H), 2.29 (s, 3 H), 2.53 (m, 4 H), 3.01 (s, 3 H), 3.72 (s, 2 H), 6.72 (s, 1 H), 7.19 (s, 1 H).

Elution with $CH_2Cl_2$ afforded **16** as a yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 1.79–1.83 (m, 8 H), 2.53–2.58 (m, 8 H), 2.98 (s, 3 H), 3.61 (s, 2 H), 3.69 (s, 2 H), 3.82 (s, 3 H), 5.10 (br s, 1 H), 7.09 (s, 1 H), 7.11 (s, 1 H).

Elution with $CH_2Cl_2$ afforded recovered starting material **6** (73%) followed by **17**, which was recrystallized from hexane/EtOAc (9:1): $^1$H NMR ($CDCl_3$) $\delta$ 1.81–1.86 (m, 4 H), 2.52–2.56 (m, 4 H), 2.96 (s, 3 H), 3.71 (s, 2 H), 3.79 (s, 3 H), 6.69 (d, 1 H), 6.82 (dd, 1 H), 7.27 (s, 1 H), 7.44 (d, 1 H).

Elution with $CH_2Cl_2$/MeOH (24:1) afforded recovered starting material **7** (22%) followed by **18**: $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.71 (m, 4 H), 2.54 (m, 4 H), 2.82 (t, 2 H), 3.10 (s, 3 H), 3.16 (t, 2 H), 7.62 (AB quartet, $J_{AB}$ = 8.9 Hz, $\Delta\nu_{AB}$ = 205.8 Hz, 4 H).

Elution with $CH_2Cl_2$ afforded recovered starting material **8** (50%) followed by **19**: $^1$H NMR ($CDCl_3$) $\delta$ 1.83 (m, 4 H), 2.29 (s, 3 H), 2.54 (m, 4 H), 2.99 (s, 3 H), 3.70 (s, 2 H), 6.93 (br s, 1 H), 7.08 (d, 1 H), 7.40 (d, 1 H), 10.20 (br s, 1 H).

Elution with $CH_2Cl_2$/MeOH (19:1) afforded **20** as the free base. Treatment with ethanolic HCl gave the dihydrochloride salt, which was recrystallized from EtOH: $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.99 (m, 4 H), 2.03 (m, 4 H), 3.13 (s, 6 H), 3.38 (m, 4 H), 3.46 (m, 4 H), 4.45 (s, 4 H), 7.58 (s, 1 H), 8.25 (s, 1 H), 9.94 (s, 2 H), 10.96 (br s, 2 H).

**Acknowledgment.** We thank Dr. C. Anderson Evans and Mr. Joseph A. Traina for the proton NOE difference NMR spectra for adducts **14** and **17**.

**Registry No.** **1**, 1197-22-4; **2**, 7022-20-0; **3**, 66236-09-7; **4**, 66236-08-6; **5**, 7022-24-4; **6**, 4284-48-4; **7**, 5317-89-5; **8**, 4284-47-3; **9**, 50790-28-8; **10**, 6966-38-7; **11**, 108297-23-0; **11**·HCl, 108297-31-0; **12**, 100632-99-3; **12**·HCl, 108297-32-1; **13**, 108297-24-1; **14**, 108297-25-2; **15**, 108297-26-3; **16**, 108297-27-4; **17**, 108297-28-5; **18**, 76467-72-6; **19**, 108297-29-6; **20**, 108297-30-9; **20**·2HCl, 108297-33-2; $C_6H_5NH_2$, 62-53-3; 2-$ClC_6H_4NH_2$, 95-51-2; 2,6-$(CH_3)_2C_6H_3NH_2$, 87-62-7; 3,5-$(CH_3)_2C_6H_3NH_2$, 108-69-0; 3-$CH_3C_6H_4NH_2$, 536-90-3; 4-$CH_3OC_6H_4NH_2$, 104-94-9; 4-$CH_3COC_6H_4NH_2$, 99-92-3; 4-$CH_3C_6H_4NH_2$, 106-49-0; 4-$CH_3O_2CC_6H_4NH_2$, 619-45-4; 1,3-$C_6H_4(NH_2)_2$, 108-45-2; $(C_2H_5)_2NH$, 109-89-7; pyrrolidine, 123-75-1; piperidine, 110-89-4.

# Synthesis of 6-Phenylimidazo[1,2-*a*]pyrazin-8-one and 1-Methyl-6-phenylimidazo[1,5-*a*]pyrazin-8-one via Quaternary Intermediates

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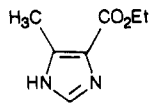
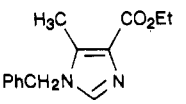
We were interested in 6-aryl-substituted imidazo[1,2-*a*]pyrazin-8-ones and imidazo[1,5-*a*]pyrazin-8-ones for evaluation as potential cardiovascular drugs.[1] While the most direct synthetic approach to these systems appeared to be reaction of an imidazole carboxamide with a 2-haloacetophenone, an important consideration for preparing the 1,5-*a* ring system is the site of alkylation, since only attack at the 3-position will lead to the desired target.

In this regard, we have previously prepared **2** from **1** in 71% isolated yield by a modification of a published procedure[2] in which an inseparable mixture of the 1- and 3-isomers was reported. Thus, we had an efficient means of protecting the 1-position with a group that could be removed by hydrogenolysis.




1




2

Reaction of **2** with concentrated ammonium hydroxide in a pressure reactor at 100 °C gave carboxamide **3** in 69% yield. Treatment of **3** with 2-bromoacetophenone in a mixture of DMF/acetonitrile at 90–100 °C afforded **4** in 87% yield. Several attempts to remove the benzyl group by hydrogenolysis resulted in the formation of **5** as the major product. Complete conversion to **5** could be accomplished by prolonging the reaction time.

Since reduction of the 5,6-double bond was occurring simultaneously with hydrogenolysis of the benzyl group, a different approach was sought. However, a major obstacle toward employing other known methods for debenzylation, i.e., nucleophilic displacement, was the poor solubility of **4** in both aqueous and organic media. From previous work,[3] we have demonstrated that neat imidazole at high temperature is an effective reagent for the demethylation of methoxyphenyl ketones. This method also has the benefict of dissolving the quaternary compounds. When **4** was treated with excess imidazole at 175 °C, debenzylation proceeded smoothly to afford **6** in 98% yield (Scheme I).

Compound **10** was prepared in an analogous manner. Treatment of 1-methylimidazole with ethyl chloroformate,[4] followed by reaction with aqueous ammonia, afforded carboxamide **7** in 65% overall yield. Treatment of **7** with 2-bromoacetophenone in acetonitrile resulted in a mixture of the desired imidazopyrazinium salt **8** and the uncyclized imidazolium salt **9**. Since these compounds could not be readily separated, the mixture was combined with excess imidazole and heated at 175 °C for 20 h. Workup afforded **10** in 89% yield (Scheme II).

During the course of this work a patent was issued to USV Corp.,[5] which described a series of substituted imi-

(1) Erhardt, P. W. *J. Med. Chem.* **1987**, *30*, 231.
(2) Bolhofer, W. A.; Cragoe, E. J.; Hoffman, J. M. U.S. Pat. 4 220 654, 1980.
(3) Davey, D. D. *J. Org. Chem.* **1987**, *52*, 1863–1867.
(4) Prepared by the method of Regel and Büchel: Regel, E.; Büchel, K. *Liebigs Ann. Chem.* **1977**, 145–158.
(5) Lee, T. D. U.S. Pat. 4 578 386, 1986.

0022-3263/87/1952-4379$01.50/0 