Functionalization of the 4(5)Methyl Group of Imidazoles: A Novel Synthesis of Substituted Imidazoles

R. Lee Webb and Joseph J. Lewis*

Organic Chemistry Department, Smith Kline and French Laboratories 1500 Spring Garden Street, Philadelphia, Pennsylvania 19101

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Acyl vinyl phosphonium salts react with amidines to form imidazolyl phosphonium salts. These imidazolyl salts can be readily converted to multifunctional imidazoles with quantitative recovery of triphenyl phosphine.

J. Heterocyclic Chem., **18**, 1301 (1981).

The use of acyl vinyl phosphonium salts in the synthesis of 2-substituted imidazolyl phosphonium salts has been reported recently by Zbiral and co-workers (1,2,3). We have utilized these imidazolyl phosphonium salts to synthesize a variety of substituted imidazoles, including the H_2-antagonist cimetidine **1**.

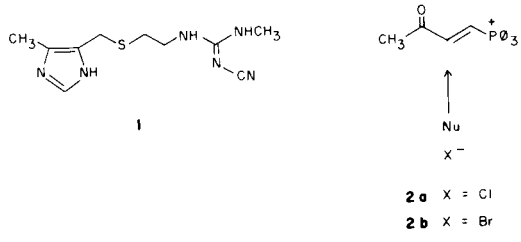

Figure 1

The acyl vinyl phosphonium salt **2** represents a masked α-dicarbonyl system in which attack by a nucleophile takes place at the C atom adjacent to the carbonyl group in the reverse of a normal Michael addition (2). Thus, the reaction of *S*-methylisothiourea with **2a** or **2b** affords the crystalline imidazolyl phosphonium salt **3** in 75% yield (3). Reaction of **3a** or **3b** with sodium methoxide in methanol gave an excellent yield of the ether **4** as a viscous yellow oil. This simple, high yield formation of a C-O bond represents a new and useful method for funtionalizing the 4(5)methyl group of imidazoles.

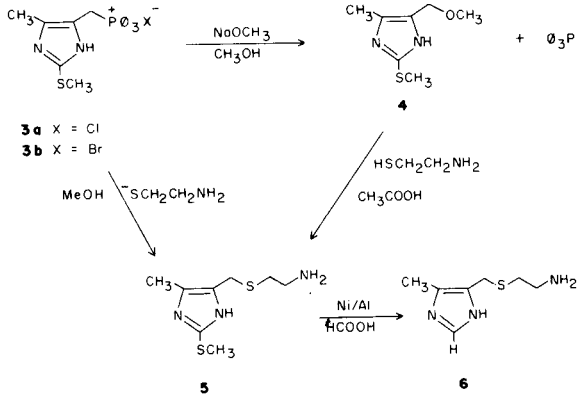

Figure 2

Refluxing **4** with cysteamine in acetic acid produced on work up the thioamine **5**. Reaction of the phosphonium salt **3a** or **3b** with the sodium salt of cysteamine in methanol also yields **5** in good yield. Refluxing **5** with nickel aluminum alloy in formic acid gives **6**.

In order to obtain imidazoles unsubstituted in the 2 position, a direct condensation of **2a** or **2b** with formamidine in a variety of solvents was tried but they gave only low yields of imidazole. When the condensation of **2a** or **2b** with formamidine sulfinic acid **7** was run in dimethyl sulfoxide with a variety of bases (sodium hydride, "proton sponge," 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)) the imidazolyl phosponium salt **8** was obtained in high yield. The reaction must presumably proceed through the sulfinic acid **9** which rapidly loses sulphur dioxide under the reaction

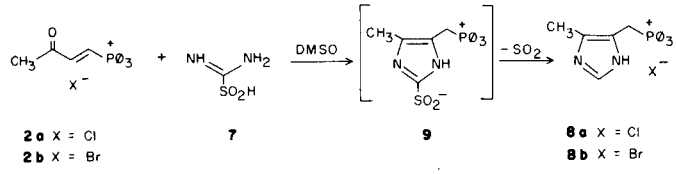

Figure 3

conditions. **8a** or **8b** could be smoothly converted to the ether **10** in 80% yield on treatment with sodium methoxide in methanol. On work up, **10** was isolated as a white solid.

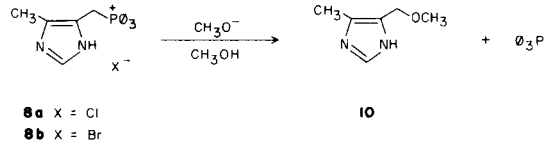

Figure 4

Treatment of **10** with cysteamine hydrochloride in acetic acid afforded **6** in high yield. The key thioamine **6** was converted to cimetidine by standard procedures (4).

The mechanism by which the imidazolyl salts **3** and **8** are functionalized in the 4(5)-position probably involves the intermediate **11** (3,5). Direct functionalization of **3** with the sodium salt of cysteamine in methanol gives only

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5. This is presumably a reflection of the much greater

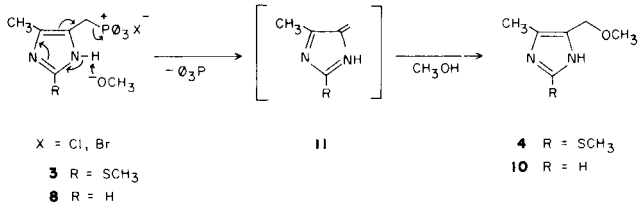
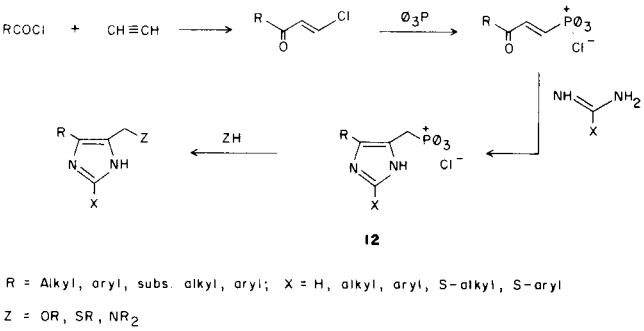


Figure 5

nucleophilicity of the thiol compared to the hydroxyl group. The thioamine **6** may be prepared from **8** in an analogous fashion.

Sequence 1 shows the potential of this route to produce a wide variety of substituted imidazoles. Substitution patterns can be varied with the substituents in the phosphonium salt and the amidine. In addition, the intermediate **11** could possibly be trapped by a variety of nucleophiles. An additional attraction is the high yield recovery of the triphenyl phosphine which can be re-used.



Sequence 1

Other extensions could include fusion of an additional ring with the imidazoles *via* the functionalized 4(5) methyl group and the use of *N*-substituted derivatives of **12** in a Wittig reaction.

We are currently investigating the scope and limitation of Sequence 1 as a general method of synthesis of imidazole derivatives.

EXPERIMENTAL

Melting points were determined with a Hoover capillary apparatus and are uncorrected. Ir and nmr spectra were recorded on Perkin Elmer 137 and R-24 spectrophotometers. Mass spectra were obtained using Hitachi-Perkin Elmer RMV-GE (ei) and Finnigan 3300 (ci) spectrometers.

The triphenyl β-acetylvinylphosphonium halides **2a** and **2b** were prepared by the method of Zbiral and Werner (6). In most cases the bromide salt **2b** is preferred for the synthesis of the imidazolyl phosphonium halides **3a** and **8** since they crystallize more readily than their chloride counterparts. [(2-Methylthio-5-methylimidazolyl)-4-methyl]triphenyl phosphonium halides **3a** and **3b** were synthesized using the procedure of Zbiral and Hugl (3).

4-Methoxymethyl-5-methyl-2-methylthioimidazole (**4**).

To a stirred solution of 48.3 g (0.1 mole) of **3b** in 250 ml of methanol at room temperature was added a solution of 35 ml of 25% sodium methoxide (Aldrich). The mixture was refluxed for 20 minutes and then concentrated to half the volume. After dilution with 500 ml of water the triphenyl phosphine was removed by filtration and dried, yeild 25.8 g (98%). The aqueous solution was extracted twice with 150 ml portions of benzene and three times with 250 ml portions of chloroform. The chloroform extracts were dried (magnesium sulfate) and evaporated to dryness to yield 13.0 g (75%) of **4** as a yellow oil; nmr (deuteriochloroform): δ 2.20 (s, CH_3, 3H), 2.46 (s, SCH_3, 3H), 3.31 (s, OCH_3, 3H), 4.36 (s, CH_2O, 2H), 9.1 (broad, NH, 1H); ms 172 (M^+ 21), 171 (M-1, 100).

Anal. Calcd. for $C_7H_{12}N_2OS$: C, 48.8; H, 7.0; N, 16.3; S, 18.6. Found C, 48.8; H, 7.1; N, 16.0; S, 18.4.

The picrate had mp 110-111°.

2-(2-Thiomethyl-4-methyl-5-imidazolyl)methylmercaptoethylamine (**5**).

Cysteamine (12.23 g, 0.13 mole) was dissolved in 100 ml methanol and 46.5 ml of 25% sodium methoxide in methanol added. This mixture was stirred at ambient temperature for 10 minutes when **3b** (52.0 g, 0.11 moles) was added and the resultant suspension was refluxed for 20 minutes. The solution was diluted to twice its volume with ice water and stirred. The resultant precipitate of triphenyl phosphine was removed by filtration. The filtrate was extracted with three 100 ml portions of chloroform and dried over anhydrous magnesium sulfate. Evaporation of the chloroform extract affored **5** 19.0 g (86%) as a vicous oil; nmr (deuteriochloroform): δ 2.17 (s, CH_3, 3H), 2.45 (s, SCH_3, 3H), 2.4-3.0 (m, CH_2CH_2, 4H, 3.68 (s, CH_2S, 2H), 5.6 (broad S, NH's, 4H, exchanges with deuterium oxide); ms: 217 (m^+ 100).

The dihydrochloride salt is prepared by suspending **5** in ethyl acetate and adding an excess of ethanolic hydrogen chloride. The resultant precipitate is recrystallized from ethanol/ethyl acetate as white crystals mp 165°; nmr (deuterium oxide): δ 2.33 (s, CH_3, 3H), 2.72 (s, SCH_3, 3H), 2.7-3.5 (m, CH_2CH_2, 4H), 3.91 (s, CH_2S, 2H).

Anal. Calcd. for $C_8H_{17}Cl_2N_3S_2$: C, 33.1; H, 5.9; N, 14.5; S, 22.1. Found:C, 32.9; H, 5.7; N, 14.2; S, 21.9.

Compound **5** was also prepared from **4** and cysteamine in 80% yield using the procedure outlined in reference (4).

2-(4-Methyl-5-imidazolyl)methylmercaptoethylamine (**6**).

To a solution of **5** (6.6 g 0.03 mole) in 50 ml of formic acid was added powdered nickel aluminum alloy (50:50 mixture, 6.6 g) and the suspension stirred and refluxed until methyl mercaptan evolution slowed and tlc showed no remaining starting material (approximately 8 hours). The metal was filtered and the filtrate evapprated to dryness and taken up in ethanol. The ethanol solution of **6** was treated with hydrogen sulfide gas and filtered to remove traces of nickel salts. Treatment of the ethanol filtrate with hydrogen chloride yielded **6** as the di-hydrochloride, yield 5.5 g (75%) mp 190-192.5° (7). The dihydrobromide prepared in a similar manner has mp 177-179° (lit mp 178-179 (4)).

[4-Methyl-(5-methylimidazolyl)]triphenyphosphonium Chloride (**8a**).

To a stirred solution of **2a** (3.65 g, 0.01 mole) and formamidine sulfinic acid **7** (1.1 g, 0.01 mole) in 50 ml of dimethyl sulfoxide was added 1,8-bis-(dimethylaminonapthalene ("Proton sponge"; 2.14 g, 0.01 mole) and the mixture heated to 80°. The solution was allowed to cool and the solvent evaporated. Treatment of the residue with chloroform followed by filtration removed inorganic salt. Evaporated of the chloroform and recrystallization from acetone afforded 3.5 g (89%) of **8a** as white prisms mp 227-229°; nmr (triflouroacetic acid: δ 2.01 (d, CH_3, 3H, J_{H-P} = 3 Hz), 4.92 (d, CH_2P, 2H, J_{HP} = 12 Hz), 7.4-8.1 (m, aromatics, 15H), 8.62 (S, imidazole-2H, 1H); ms: 357 (M^+).

Anal. Calcd. for $C_{23}H_{22}CLN_2P$: C, 70.32; H, 5.64; N, 7.13; P, 7.88; Cl, 9.02. Found: C, 70.53; H, 5.59; N, 7.44; P, 7.60; Cl, 8.85.

1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) or 1,8-Diazabicyclo [5.4.0]undec-7-ene (DBU) can also be used in place of "proton sponge".

In a similar manner **8b** was prepared mp 238-239° dec.

Anal. Calcd. for $C_{23}H_{22}BrN_2P$: C, 63.17; H, 5.07 N, 6.41; P, 7.08; Br, 18.27. Found: C, 62.93; H, 4.93; N, 6.71; P, 6,98; Br, 18.01.

5-Methyl-4-methoxymethylimidazole (**10**).

To a stirred solution of 4.83 g (0.01 mole) of **8b** in 50 ml of methanol at ambient temperature was added 35 ml of 25% sodium methoxide in methanol and the mixture heated to reflux for twenty minutes. On cooling the solution was concentrated to half the volume and 90 ml of water added. The triphenyl phosphine was removed by filtration and the aqueous solution extracted twice with 20 ml portion of benzene and three times with 30 ml of chloroform. The chloroform extracts were combined, dried (magnesium sulfate) and evaporated to dryness to yield **10** as a white solid mp 69-70°, yield 1.0 g (80%). The hydrochloride salt was formed by treatment of **10** with hydrogen chloride in 50:50 ethanol ethyl acetate, mp 149-151°; nmr (deuteriochloroform): δ 2.39 (s, CH_3, 3H), 3.35 (s, OCH_3, 3H), 4.45 (s, CH_20, 2H), 6.2-7.1 (broad S, NH, 1H), 8.25 (s, imidazole 2H, 1H).

Anal. Calcd. for $C_6H_{11}ClN_20$: C, 44.32; H, 6.82; N, 17.23; Cl, 21.80. Found: C, 44.41; H, 6.92; N, 17.34; Cl, 21.51.

Conversion of **10** to **6**.

The hydrochloride of **10** described above (4.5 g 0.03 mole) and 3.4 g (0.03 mole) of cysteamine hydrochloride were dissolved in 35 ml of glacial acetic acid and refluxed 18 hours. After cooling in an ice bath, filtration and drying, 5.8 g (80%) of **6** was obtained mp 190-193°.

Compound **6** was also prepared by the following procedure: cysteamine (1.22 g 0.013 mole) was dissolved in 10 ml of methanol and 4.7 ml of 25% wt/v sodium methoxide in methanol added. After stirring at ambient temperature for 10 minutes 5.1 g (0.013 mole of **8a** was added and the mixture refluxed for 20 minutes. The solution was diluted to twice its volume with ice water and the precipitated triphenyl phosphine removed by filtration. The filtrate was extracted with 3 × 50 ml chloroform, dried (magnesium sulfate) and evaporated. The residue was taken up in ethyl acetate and treated with hydrogen chloride to yield **6** as the dihydrochloride mp 190-193°, yield 1.5 g (70%).

REFERENCES AND NOTES

(1) E. Zbiral and E. Hugl, *Tetrahedron Letters*, 439 (1972).

(2) E. Zbiral , *Synthesis*, **2**, 974 (1974).

(3) E. Zbiral, and E. Hugl, *Phosphorus*, **2**, 29 (1972).Satisfactory elemental and mass spectral data were obtained for all compounds reported.

(4) G. J. Durant, J. C. Emmett, C. R. Ganellin, P. D. Miles, M. E.Parsons, H. D. Prain and G. R. White, *J. Med. Chem.*, **20**, 901 (1977).

(5) T. C. Bruice and J. L. Herz, *J. Am. Chem Soc.*, **86**, 4109 (1964).

(6) E. Zbiral and E. Werner, *Ann. Chem.*, **707**, 130 (1967).

(7) Compound **6** is a commercial intermediate in the production of cimetidine. The reference material (SK&F 92087-A_2) has mp 191.5-193°.