Heterocycles from Phosphonium Salts: A Facile Method for Modification of the 4(5)-Methyl Group of Thiazoles

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Thiazolyl phosphonium salts, formed from the condensation of acyl vinyl phosphonium salts with thioamides and thiourea, are readily functionalized in high yield. The sequence represents a useful general synthesis of multifunctional thiazoles.

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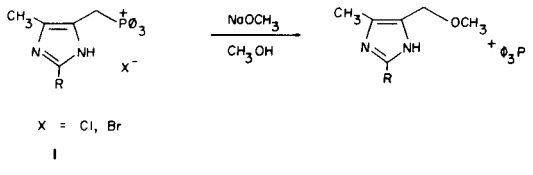
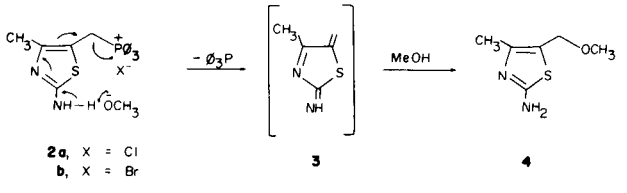
In an earlier paper (1), we described a novel synthesis of the histamine receptor antagonist cimetidine, employing a unique method for functionalizing the 4(5) methyl group of imidazoles. This approach has now been extended to analogous ether formation in the thiazole series.

Figure 1



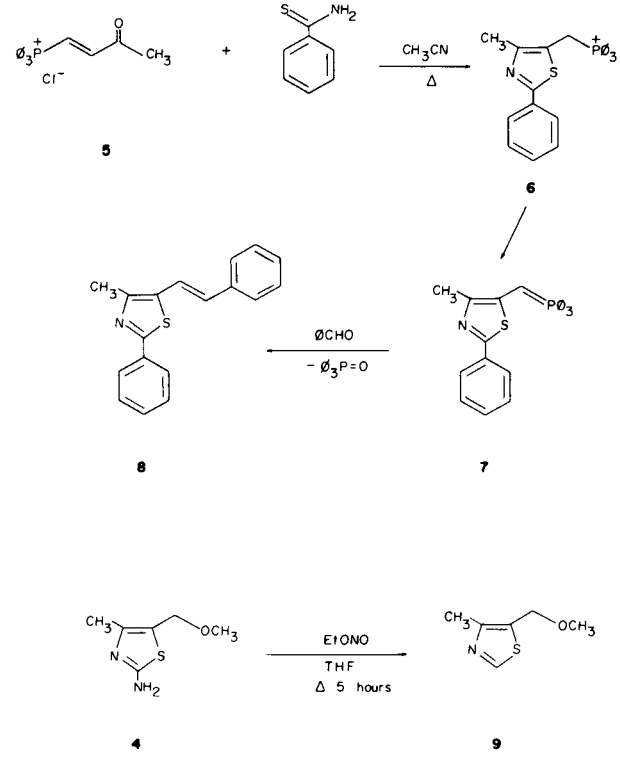


The formation of thiazolyl phosphonium salts such as **2** from acyl vinyl phosphonium salts has been described by Zbiral (2). Only a single isomer is produced in the condensation due to attack by the nucleophilic sulphur on the carbon atom α to the carbonyl group of the acyl vinyl synthon. We have prepared a variety of these thiazolyl phosphonium salts and used them as intermediates in the synthesis of multifunctional thiazoles.

Thus, when the thiazolyl phosphonium salt **2** (2,3) is treated with a commercial solution of sodium methoxide in methanol, the thiazolyl ether **4** is formed in high yield. Triphenylphosphine of excellent purity is recovered in near quantitative yield. The mechanism of this reaction, by analogy with the imidazole case, (1,4) could proceed *via* the reactive intermediate **3** (formed by removal of the N-H proton exocyclic to the ring). The elimination-addition sequence, rather than ylide formation, has been reported previously (4) for the imidazole system in which the proton abstracted is bound to the ring nitrogen. To our knowledge, the reaction of the amino thiazole **2** is the first report in which such a reaction sequence takes place *via* removal of the proton bonded to an exocyclic nitrogen atom. The implications are that similar reactions could take place in other appropriately substituted systems, and relevant studies are under investigation. The phenylthiazole **6** was prepared in good yield by condensing the phosphonium salt **5** with thiobenzamide. After refluxing the phosphonium salt **6** with sodium methoxide in methanol for 12 hours, only starting material could be recovered. The normal ylide **7** was formed by treating **6** with butyllithium in tetrahydrofuran. Reacting **7** with benzaldehyde gave on work up the olefin **8**.

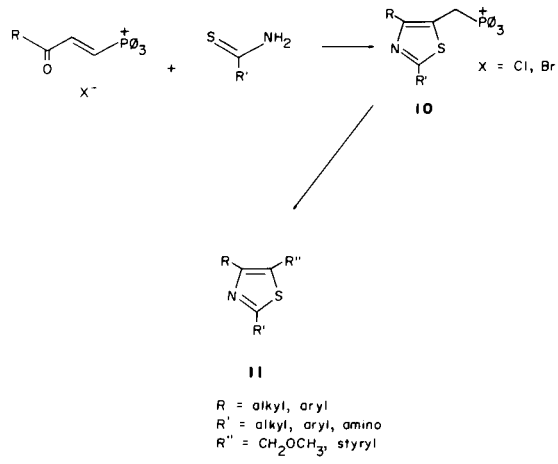
To extend the method of synthesis to thiazoles unsubstituted in the 2 position, compound **4** converted to **9** by treatment with ethyl nitrite in tetrahydrofuran.

Figure 2



Since thiazoles such as **10** may be readily prepared (5) by the appropriate choice of acyl vinyl phosphonium salts and thioamides, modification of the 4(5)-methyl group by the methods described above offers a useful synthetic method for obtaining the functionalized thiazoles **11**.

Figure 3



EXPERIMENTAL

Melting points were determined with Hoover capillary apparatus and are uncorrected. The ir and nmr spectra were recorded on Perkin Elmer 137 and R-24 spectrometers. Mass spectra were obtained using Hitachi Perkin Elmer RMV-GE (ei) and Finnigan 330 (ci) spectrometers.

The thiazolyl phosphonium salts **2a** and **2b** were prepared as outlined in reference (2) as was the acyl vinyl synthon **5**.

2-Amino-5-methoxymethyl-4-methylthiazole (**4**).

The thiazolyl phosphonium salt **2a**, (60 g, 0.14 mole) was dissolved in 500 ml of dry methanol. Sodium methoxide solution (33 g of 25% w/v solution in methanol) was added with stirring and the mixture heated to 55-65° for 30 minutes. On cooling the mixture was concentrated to one third of the original volume, 150 ml of water added and the resultant suspension was acidified tp *p*H 2 with hydrochloric acid. The mixture was filtered and the filtrate extracted once with 100 ml benzene. The aqueous phase was neutralized with 10 *M* sodium hydroxide and extracted with 2 × 150 ml protions of chloroform. The chloroform extracts were combined, dried with magnesium sulfate and evaporated to yield 10.01 g (45%) of **4** mp 132-135°; nmr (deuteriochloroform): δ 2.15 (s, CH_3, 3H), 3.30 (s, OCH_3, 3H), 4.35 (s, CH_2, 2H), 5.15 (broad s, NH_2, 2H); ms: 158 (M^+, 100).

Anal. Calcd. for $C_6H_{10}N_2OS$: C, 45.6; H, 6.4; N, 17.7; S, 20.3. Found: C, 45.3; H, 6.2; N, 17.9; S, 20.3.

[(2-Phenyl-4-methylthiazolyl)-5-methyl]triphenylphosphonium Chloride (**6**).

Triphenyl-β-acetylvinyl phosphonium chloride (**5**) 36.7 g (0.1 mole) and 17.7 g (0.1 mole) of thiobenzamide were dissolved in 250 ml of acetonitrile and the solution refluxed for 1½ hours. On cooling, the precipitate of **6** was filtered and washed with a little cold acetonitrile, yield 31.5 g (65%), mp 261-263° dec; nmr deuteriochloroform): δ 2.30 (d, CH_3, JP-H 3Hx, 3H), δ 5.10 (d, CH_2, JP-H 14 Hz, 2H) δ 8.2 (m, aromatics, 15H).

Anal. Calcd. for $C_{29}H_{25}ClNPS$: C, 71.7; H, 5.2; N, 2.9; P, 6.4; S, 6.6. Found: C, 71.5; H, 5.0; N, 3.0; P, 6.5; S, 6.3.

trans-2-Phenyl-4-methyl-5-styrylthiazole (**8**).

To a stirred suspension of 5.3 g (0.011 mole) of **6** in 100 ml of tetrahydrofuran under nitrogen was added 6.9 ml of a 1.6*M* solution of butyl lithium in hexane *via* syringe. The deep red solution was stirred for 5 minutes followed by the addition of 1.2 g (0.011 mole) of benzaldehyde in 5 ml of tetrahydrofuran. The mixture was refluxed for 1 hour, concentrated and chromatographed on silica gel using methylene chloride as eluent. Recrystallization of the yellow residue from ethyl acetate/ethanol afforded 1.75 g of **8** (57%) mp 116-117°; nmr (deuteriochloroform): δ 2.50 (s, CH_3, 3H), δ 6.70 (d, olefinic, 1H, J = 18 Hz); δ 7.10 (d, olefinic, 1H, J = 18 Hz), δ 7.1-8.0 (m, aromatics, 10H); ms: 277 (M^+, 100).

Anal. Calcd. for $C_{18}H_{15}NS$: C, 77.9; H, 5.5; N, 5.1; S, 11.6. Found: C, 77.9; H, 5.7; N, 5.4; S, 11.3.

4-Methyl-5-methoxymethylthiazole (**9**).

To a refluxing solution of 3.2 g (0.0203 mole) of **4** in 100 ml of dry tetrahydrofuran was added dropwise 6 g of ethyl nitrite dissolved in 75 ml of tetrahydrofuran. After refluxing an additional 5 hours. The mixture was cooled, evaporated and the residue taken up in hexane. Evaporation of the hexane extracts afforded 2.4 g (82%) of **9** as an oil; nmr (deuteriochlorofrom): δ 2.68 (s, CH_3, 3H); δ 3.49 (s, OCH_3, 3H); δ 4.62 (s, $-CH_2O$, 2H); δ 9.91 (s, aromatic, 1H). Treatment of **9** with propanol saturated with hydrogen chloride followed by recrystallization afforded the hydrochloride salt mp 150-152°.

Anal. Calcd. for $C_6H_{10}ClNOS$: C, 40.1; H, 5.6; N, 7.8; S, 17.9; Cl, 19.8. Found: C, 39.9; H, 5.6; N, 8.0; S, 17.8; Cl, 19.7.

Acknowledgment.

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REFERENCES AND NOTES

(1) R. L. Webb and J. J. Lewis, *J. Heterocyclic Chem.*, **18**, 1301 (1981).

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(3) Satisfactory elemental and mass spectral data were obtained for all compounds.

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