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The Preparation and Wittig Condensations of C-4 Thiazole Phosphonium Methylides

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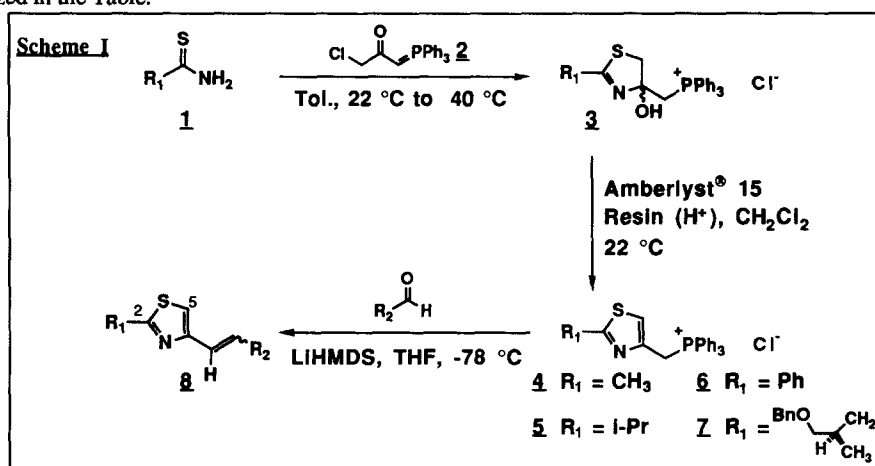
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Abstract: A modification of the Hantzsch thiazole synthesis is described which produces C₄ thiazolymethyl phosphonium salts. Ylides are condensed with a variety of aldehydes to produce a series of 2,4-disubstituted thiazoles.

Recently, the thiazole ring has been identified as a central feature of a number of biologically active natural products.¹ Predominantly these substances are characterized as 2,4-disubstituted thiazoles, many of which are isolated from marine sources. Several examples of this family have stimulated interesting efforts for organic synthesis.² Of course, medicinal chemists have routinely sought opportunities for the incorporation of the thiazole heterocycle for drug development and structure-activity studies.³

Thiazoles are commonly prepared by the Hantzsch synthesis⁴ or via thiazolines by condensation of an aldehyde with a cysteine derivative followed by oxidation.⁵ Herein, an interesting modification of the Hantzsch procedure is communicated to directly produce the C-4 substituted thiazolymethyl phosphonium salts (4 - 7).⁶ As illustrated in Scheme I, generation of the corresponding triphenylphosphoranes affords utility for Wittig olefinations and the production of 2,4-disubstituted thiazoles. A survey of reactions with various aldehydes is summarized in the Table.



Our preparation of the 4-thiazolymethyl phosphonium salts 4 - 7 was initiated by the S-alkylation of thioamides 1⁷ with α-chloroacetyltriphenylphosphorane 2, which was readily available from 1,3-

dichloroacetone.⁸ The reactants were dissolved in dry toluene by warming briefly to 40 °C (approximately 20 min). Subsequent stirring at room temperature for 24 hours led to the accumulation of a white precipitate. Solvent was decanted under nitrogen using a syringe, and the resulting white powder was dried *in vacuo*.⁹ The 4-hydroxy-2-thiazolines **3** were characteristically identified by a singlet in the ¹³C-NMR for the quaternary hemiaminal carbon (δ 106.0), and two sets of diastereotopic protons in the ¹H-NMR spectra for the C₅ methylene and the methylene adjacent to phosphorous (for R₁ = *i*Pr example: δ = 3.69 (m, 2H) and δ = 3.52 (dd, J_{AB} = 15.1 Hz; J_{A-P} = 12.1 Hz, 1H_A), and δ = 5.58 (dd, J_{AB} = 15.1 Hz; J_{B-P} = 11.4 Hz, 1H_B) respectively). The absence of a carbonyl stretch in the infrared spectra, taken together with the confirming ¹³C-NMR evidence, would suggest little contribution of the corresponding keto tautomers of **3**. Yields of the phosphonium salts ranged from 70-85%.

Dehydrations of the tertiary alcohols were accomplished upon stirring a methylene chloride solution of **3** overnight (16 hours) at 22 °C with anhydrous Amberlyst®-15 resin. Filtration through dry sodium sulfate and solvent evaporation *in vacuo* provided the 4-thiazolylmethyl phosphonium salts **4** - **7** as hygroscopic foams. These materials were stored in a drying pistol under vacuum at 70 °C (16 hours) prior to characterization and utilization in Wittig condensations. Our phosphonium salts **4** - **7** exhibited a broadened doublet in proton NMR spectra centered at 5.5 ppm (J_{H-P} = 14 Hz) for the methylene at C₄. The thiazole C₅ ring hydrogen appeared as a doublet at 7.8 ppm (J_{H-P} = 3 Hz). Carbon spectra displayed the methylene (C₄) carbon strongly coupled to phosphorous (J_{CP} = 50.8 Hz) at 26.0 ppm.¹⁰

Wittig reactions of ylides derived from **4** - **7** were undertaken to demonstrate general utility. Our survey, shown in the Table, has documented an efficient route to 2,4-disubstituted thiazoles **8** with isolated yields ranging from 52 to 88%. Ylides were generated by deprotonation with LiHMDS in THF at -78 °C. No evidence of competing deprotonations involving the C₂ alkyl substituents of **4**, **5**, and **7** was observed. Aldehydes reacted upon addition at -78 °C (stirring 30 min), and reaction were quenched upon warming to 20 °C leading to isolation of our thiazole products. No attempts to optimize yields or to improve alkene stereoselectivity were made. The ratios of *E/Z*-alkenes were determined by integration of C₅ thiazole proton signals in the NMR spectra of crude product mixtures. Thereafter, individual *E*- and *Z*-olefins for entries 2, 3, and 4 were separated by flash chromatography for full characterizations.¹¹ Overall, our thiazole-substituted methylides generally behaved as reactive, albeit stabilized, phosphoranes delivering predominantly *E*-olefin product mixtures. However, highly reactive aldehydes (entries 2 and 9) afforded results (*E/Z* ratios) typically associated with unstabilized ylides under these conditions.

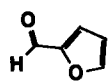
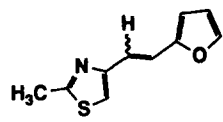
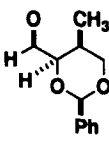
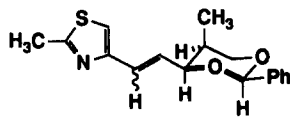
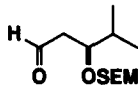
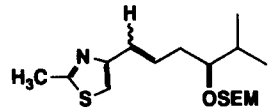
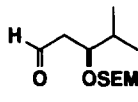
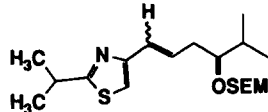
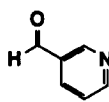
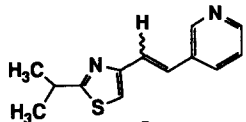
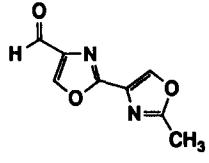
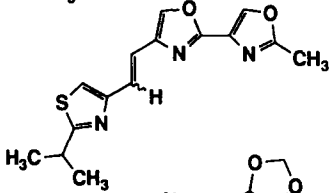
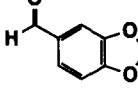
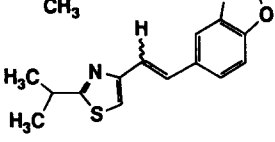
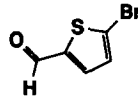
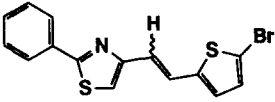
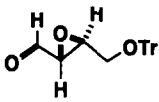
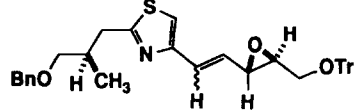
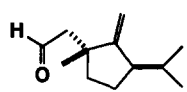
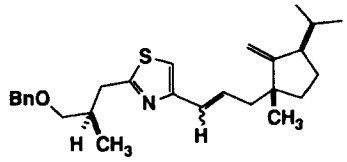
An efficient approach for preparation of 4-thiazolylmethyl phosphonium salts has been described. Further advancements are in progress.

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Table: Examples of 2,4-Disubstituted Thiazoles

ENTRY	ALDEHYDE	PHOSPHONIUM SALT	PRODUCT	ALKENE (E : Z) RATIO	YIELD
1		<u>4</u>		84 : 16	61%
2		<u>4</u>		26 : 74	62%
3		<u>4</u>		77 : 23	61%
4		<u>5</u>		73 : 27	62%
5		<u>5</u>		81 : 19	74%
6		<u>5</u>		63 : 37	54%
7		<u>5</u>		78 : 22	72%
8		<u>6</u>		82 : 18	88%
9		<u>Z</u>		52 : 48	52%
10		<u>Z</u>		83 : 17	54%

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 - Starting thioamides are commercially available for production of **4** and **6**. Thioamides used in synthesis of **6** and **7** were obtained from the corresponding amides upon treatment with Lawesson's reagent.
 - a) For preparation of **2**: Hudson, R.F.; Chopard, P.A. *J. Org. Chem.* **1963**, *28*, 2446. b) The synthesis of 4-chloromethylthiazoles has been reported from 1,3-dichloroacetone. Marzoni, G. *J. Heterocyclic Chem.* **1986**, *23*, 577.
 - Precursor alcohol **3**, leading to **7**, was obtained as a hygroscopic foam.
 - Our phosphonium salts **4** - **7** were fully characterized by proton and carbon NMR, infrared, and high-resolution mass spectrometry (CI).
 - For all entries, isolated yields are reported for purified (>97%) and fully characterized products following silica gel flash chromatography. The C₅ thiazole ring hydrogens were individually distinguished in proton NMR spectra for each *E/Z* pair (located in the range $\delta = 6.8$ to 7.3). *E*-olefins showed the expected large vicinal coupling ($J = 16$ Hz).

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