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

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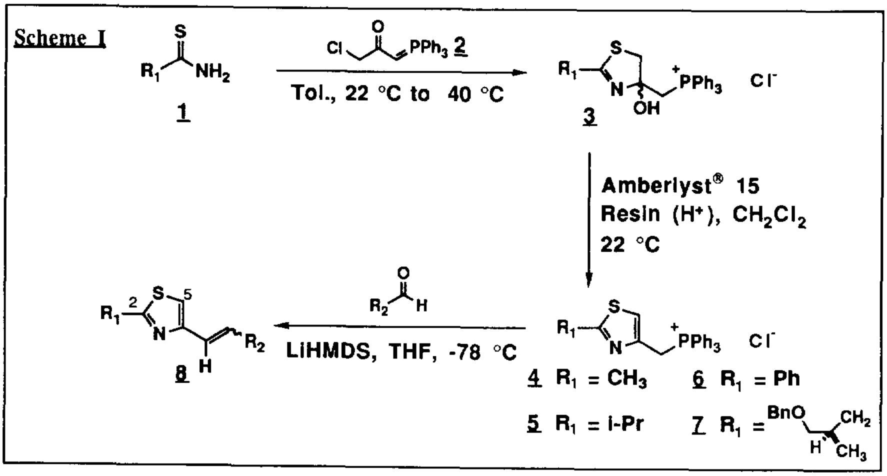
Abstract: *A modification of the Hantzsch thiazole synthesis is described which produces C_4 thiazolylmethyl phosphonium salts. Ylides are condensed with a variety of aldehydes to produce a series of 2,4-disubstituted thiazoles.*

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 synthesis[4] 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 thiazolylmethyl 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.

Scheme I



Our preparation of the 4-thiazolylmethyl phosphonium salts **4** - **7** was initiated by the *S*-alkylation of thioamides **1**[7] with α-chloroacetonyltriphenylphosphorane **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 ^{13}C-NMR for the quaternary hemiaminal carbon (δ 106.0), and two sets of diastereotopic protons in the ^{1}H-NMR spectra for the C_5 methylene and the methylene adjacent to phosphorous (for R_1 = iPr example: $\delta = 3.69$ (m, 2H) and $\delta = 3.52$ (dd, $J_{AB} = 15.1$ Hz; $J_{A\text{-}P} = 12.1$ Hz, $1H_A$), and $\delta = 5.58$ (dd, $J_{AB} = 15.1$ Hz; $J_{B\text{-}P} = 11.4$ Hz, $1H_B$) respectively). The absence of a carbonyl stretch in the infrared spectra, taken together with the confirming ^{13}C-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 ($J_{H\text{-}P} = 14$ Hz) for the methylene at C_4. The thiazole C_5 ring hydrogen appeared as a doublet at 7.8 ppm ($J_{H\text{-}P} = 3$ Hz). Carbon spectra displayed the methylene (C_4) 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 C_2 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 C_5 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.

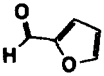
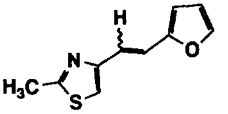
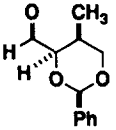
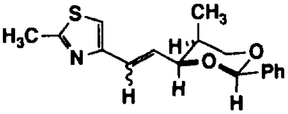
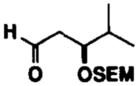
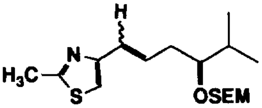
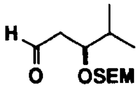
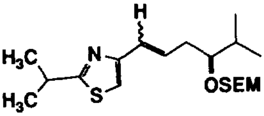
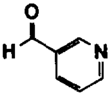
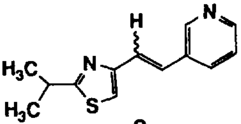
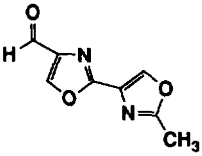
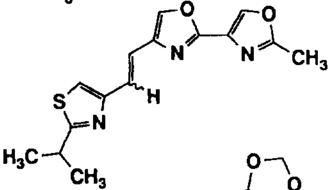
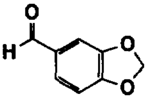
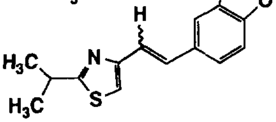
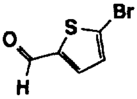
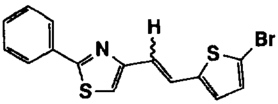
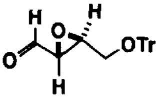
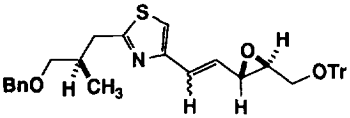
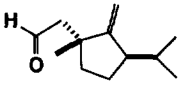
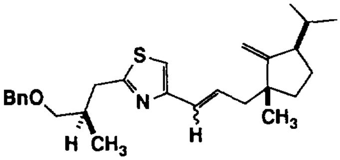
An efficient approach for preparation of 4-thiazolylmethyl phosphonium salts has been described. Further advancements are in progress.

Acknowledgements: The authors thank Abbott Laboratories and the National Institutes of Health (GM-41560) (D.R.W.) for their generous financial support.

References:

1. Some examples include: a) *Patellazoles*: Zabriskie, T.M.; Mayne, C.L.; Ireland, C.M. *J. Am. Chem. Soc.* **1988**, *110*, 7919. b) *Leinamycin*: Hara, M.; Asano, K.; Kawamoto, I.; Takiguchi, I.; Katsumata, S.; Takahashi, K.; Nakano, H. *J. Antibiot.* **1989**, *42*, 1768. c) *Cyclothiazomycin*: Aoki, M.; Ohtsuka, T.; Itezono, Y.; Yokose, K.; Furihata, K.; Seto, H. *Tetrahedron Lett.* **1991**, *32*, 221. d) *Mycothiazole*: Crews, P.; Kakou, Y.; Quinoa, E. *J. Am. Chem. Soc.* **1988**, *110*, 4365.

Table: Examples of 2,4-Disubstituted Thiazoles

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

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6. Halogen displacements by triphenylphosphine have been used for preparation of C-2 and C-4 thiazolylmethyl phosphonium salts as a prelude to Wittig condensations. a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron* **1988**, *44*, 2021. b) Dondoni, A.; Perrone, D. *J. Org. Chem.* **1995**, *60*, 4749. c) Martin, B.; Clough, J. Pattenden, G.; Waldron, I. *Tetrahedron Lett.* **1993**, *34*, 5151.
7. 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.
8. 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.
9. Precursor alcohol **3**, leading to **7**, was obtained as a hygroscopic foam.
10. Our phosphonium salts **4** - **7** were fully characterized by proton and carbon NMR, infrared, and high-resolution mass spectrometry (CI).
11. For all entries, isolated yields are reported for purified (>97%) and fully characterized products following silica gel flash chromatography. The C_5 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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