J = 18.1, 12.6) (1 H, $H_bC(1')$), 2.61–2.51 (m) and 2.45–2.33 (m) (1 H, $H_bC(4')$), 2.15 (quint, J = 7.4, 1 H, HC(3')), 1.80 (s, 3 H) and 1.37 (s, 3 H) ($CH_3C(7)$, $CH_3C(8)$), 1.18 (d, J = 6.8) and 1.13 (d, J = 7.1) (3 H, $CH_3C(3')$); ^{13}C NMR (75.5 MHz) 207.78 (J_{CP} = 4.9), 207.46 (J_{CP} = 4.7, C(2')), 140.39, 139.68, 137.94, 137.37, 137.23, 137.14, 136.59, 135.81, 135.15, 128.35, 128.19, 128.03, 127.81, 127.60, 127.52, 127.02, 126.77, 126.53, 123.81, 122.60 (C(Ar), C(5')), 117.18, 116.80 (C(6')), 52.55, 52.50, 51.13, 51.05 (NCH_2Ph), 47.20 (C(3')), 40.23 (J_{CP} = 99.9), 39.36 (J_{CP} = 100.3, C(1')), 37.33, 36.19 (C(4')), 19.63, 19.58, 19.25, 19.19 ($CH_3C(1')$, $CH_3C(1'')$), 16.05, 15.25 ($CH_3C(3')$); IR (CCl_4) 3065 m, 3030 m, 2978 m, 2928 m, 2874 w, 1707 s, 1595 w, 1495 m, 1454 s, 1360 m, 1317 m, 1223 s, 1170 m, 1101 s, 1076 m, 1028 s, 993 m, 929 s, 868 m, 829 m; MS (70 eV) 549 (M^+ + 1, 19), 548 (M^+, 43), 438 (37), 437 (100), 392 (11), 391 (36), 390 (13), 389 (42), 105 (11); high-resolution MS calcd for $C_{35}H_{37}N_2O_2P$ 548.2593, found 548.2589; TLC R_f 0.48 (hexane/acetone (7:3)).

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The Reaction of Thioimides with Phosphorus Ylides

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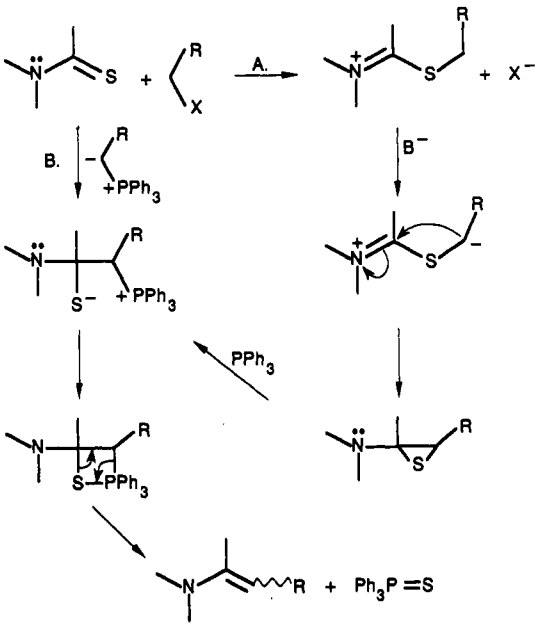
The reaction of a series of thioimides with phosphorus ylides, in a manner analogous to the Wittig reaction, has been examined. The resulting reaction products represent potentially valuable intermediates in tetrapyrrole pigment synthesis. In addition to the desired thio-Wittig-type coupling reaction, the presence of two competing reaction pathways, S-alkylation and oxidation/reduction, has been observed with certain substrates. These empirical observations have been correlated to theoretical data, derived from MNDO and ab initio calculations, which delineate the structure–reactivity relationships governing product distribution from the various reaction pathways. A detailed analysis is presented of the mechanisms of the thio-Wittig coupling reaction and the competitive S-alkylation reaction.

Introduction

The Wittig reaction has a place of obvious importance in synthetic organic chemistry. A wide array of carbonyl and phosphorus ylide components react under relatively mild conditions to form carbon–carbon double bonds, often as a crucial step in convergent syntheses. A limitation of the reaction is the low degree of reactivity of carboxylic acid derivatives, e.g., amides, with ylides.[1] From the standpoint of electrostatic interactions, this can be ascribed to the decreased carbon electrophilicity of these carbonyl groups when compared with ketones and aldehydes. If this decreased reactivity could be overcome, such an extension of the Wittig reaction would often be convenient for carbon–carbon bond formation at an amide functionality, under conditions compatible with the presence of other functional groups, while leaving the carbon–nitrogen bond intact.

Two methods involving the activation of amides as thioamides have been devised to achieve this type of transformation. The first method involves successive S-alkylation and sulfide contraction and has been well documented.[2-4] The second involves reaction of a phosphorus ylide with a thioamide. This sulfur analogue of the Wittig reaction, also called a thio-Wittig reaction, has received less attention.[5-13]

Scheme I. Postulated Sulfur Contraction and Thio-Wittig Mechanisms



A. S-alkylation/sulfur contraction path.
B. Thio-Wittig path

Although the mechanistic details of these reactions are not entirely clear, both routes are thought to proceed through betaine and/or thiaphosphetane intermediates, leading to the observed enamine-type products and tri-

(1) Flitsch, W.; Schindler, S. R. *Synthesis* **1975**, 685.
(2) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.
(3) Gossauer, A.; Hirsch, W. *Liebigs Ann. Chem.* **1974**, 1496.
(4) Shiosaki, K.; Fels, G.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 3230.
(5) Gossauer, A.; Hinze, R.-P.; Zilch, H. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 418.
(6) Gossauer, A.; Hinze, R.-P. *J. Org. Chem.* **1978**, *43*, 283.
(7) Gossauer, A.; Roessler, F.; Zilch, H. *Liebigs Ann. Chem.* **1979**, 1309.
(8) Slopianka, M.; Gossauer, A. *Synth. Commun.* **1981**, *11*, 95.
(9) Slopianka, M.; Gossauer, A. *Liebigs Ann. Chem.* **1981**, 2258.
(10) Tewari, R. S.; Suri, S. K.; Mishra, G. K.; Gupta, K. C. *Ind. J. Chem.* **1978**, *16B*, 431.
(11) Tewari, R. S.; Suri, S. K.; Gupta, K. C. *Z. Naturforsch.* **1979**, *34b*, 606.
(12) Arnott, D. M.; Battersby, A. R.; Harrison, P. J.; Henderson, G. B.; Sheng, Z.-C. *J. Chem. Soc., Chem. Commun.* **1984**, 525.
(13) Block, M. H.; Zimmerman, S. C.; Henderson, G. B.; Turner, S. P. D.; Westwood, S. W.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Chem. Commun.* **1985**, 1061.

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Scheme II. Thio-Wittig Reaction Applied to the Synthesis of PCB Dimethyl Ester

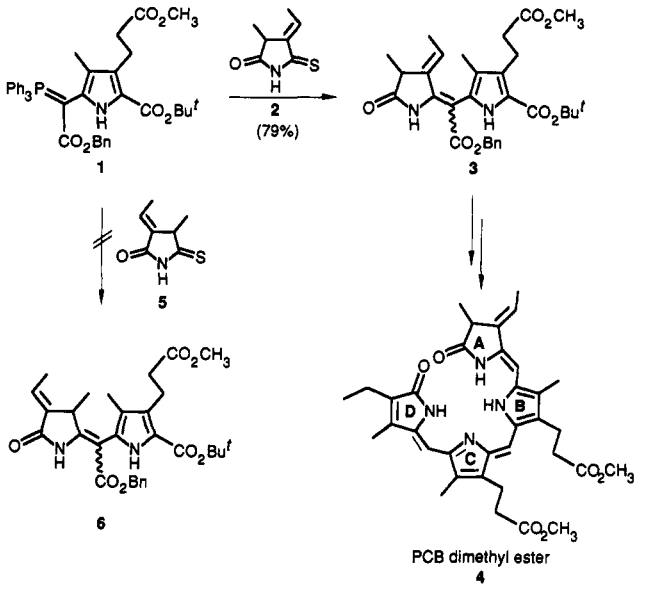
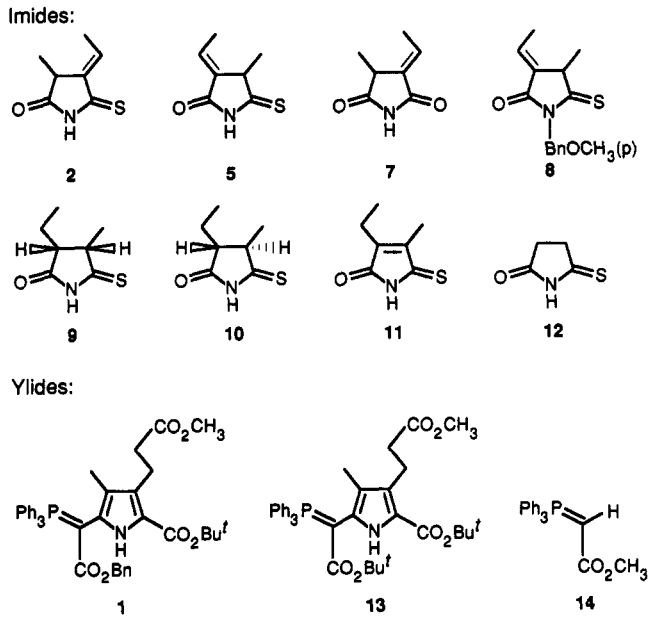


Chart I. Substrates for Study of Thio-Wittig Reaction



phenylphosphine sulfide as shown in Scheme I. In the sulfur contraction pathway, this betaine is formed by the nucleophilic ring opening of a postulated episulfide intermediate by a phosphine thiophile. Although the regioselectivity of ring opening is not known, both possible betaines would be expected to furnish the same enamine product after sulfur extrusion. This episulfide is, in turn, formed on treatment of an S-alkylated thioamide with base. In the case of the thio-Wittig reaction, the betaine is presumably directly accessed by nucleophilic attack of the ylide onto the thiocarbonyl group.

Each reaction has its advantages and disadvantages, depending on the substitution pattern of the reactants. In general, the sulfur contraction route is favored by having a trisubstituted nitrogen atom. S-Alkylation leads to a thioiminium ion, thereby facilitating ring closure to the episulfide intermediate. In such cases, the S-alkylation step may be troublesome and frequently benefits from the use of very reactive alkylating species, like triflates. The thio-Wittig route, at least conceptually, has the advantage that both nucleophilic and thiophilic properties are built into one of the reactants; the phosphorus ylide is capable both of forming a carbon–carbon bond and abstracting sulfur from the thioamide.

In the course of synthetic work on plant bile pigments, we were attracted to the potential of the thio-Wittig reaction which had been successfully applied in the synthesis of racemic phycocyanobilin (PCB) dimethyl ester **4** (Scheme II), a plant bile pigment degradation product.[6] In an earlier approach, PCB had been constructed using the less convenient and lower yielding S-alkylation/sulfide contraction procedure.[3] In the crucial thio-Wittig coupling step, ylide **1** and monothiosuccinimide **2** afforded a 79% yield of the A/B ring system, pyrromethenone **3**. The improved ability to generate thioimides as well as pyrrole ylides, described below, provided stimulus for further exploration of this thio-Wittig methodology.

Our initial synthetic goal was to incorporate one modification of the existing procedure: a transposition of ethylidene and methyl groups in the succinimide component **2** to that of **5** (Scheme II). It was planned that thioimide **5** would serve as a precursor to pyrromethenone **6**. Eventually **6** would be incorporated as the C/D ring system of dilinked bilipeptides, with thioether linkages at the α-carbon of both ethyl groups on the tetrapyrrole framework, identical with the substitution pattern found in several recently characterized plant bile pigments.[14] Surprisingly, the thio-Wittig coupling reaction with thiosuccinimide **5** failed. Equally unsuccessful was the S-alkylation/sulfide contraction route to **6**.

This disparity in behavior prompted a study of the reaction which diverged in two directions. We first synthesized a number of structurally distinct thioimides and analyzed the products obtained from reaction with ylides. Such reactions were found to afford a variety of products resulting from multiple reaction pathways. Secondly, a theoretical analysis of the substrates was undertaken. MNDO and ab initio calculations were found to correlate well with the experimental data, allowing delineation of the competing reaction mechanisms and structure–reactivity principles.

The substrates used in this study are shown in Chart I. Rationale for inclusion of the various succinimide-type compounds has been previously described, as have their syntheses.[15] Ylide **13**, the di-*tert*-butyl ester analogue of **1**, was the major reagent due to its adaptability to further synthetic transformations. Compounds **1**, **12**, and **14** were included mainly to correlate our results with those previously described.[5,6]

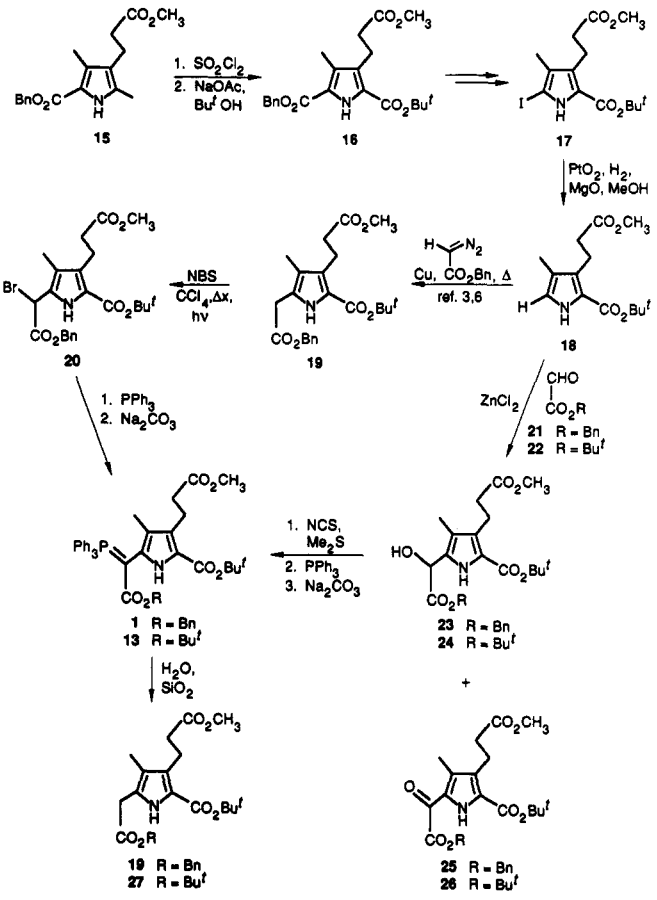
Synthesis of Ylides

The methodology developed for generation of the pyrrole ylides (Scheme III) represents significant improvements over reported procedures.[3,6] The reported diazo coupling of α-unsubstituted pyrrole **18** in the melt to afford **19** in 54% yield could not be reproduced in our hands; yields of **19** and the recovery of starting material were both very low. Functionalization of the methylene group of **19** was also problematic. Bromopyrrole **20**, an intermediate also used in the S-alkylation/sulfide contraction synthesis of PCB,[3] was very unstable. Our present process involves an acid-mediated condensation of pyrrole **18** with a glyoxylate ester. This affords pyrrolyl carbinols **23** and **24**, having the desired methylene group already functionalized. These

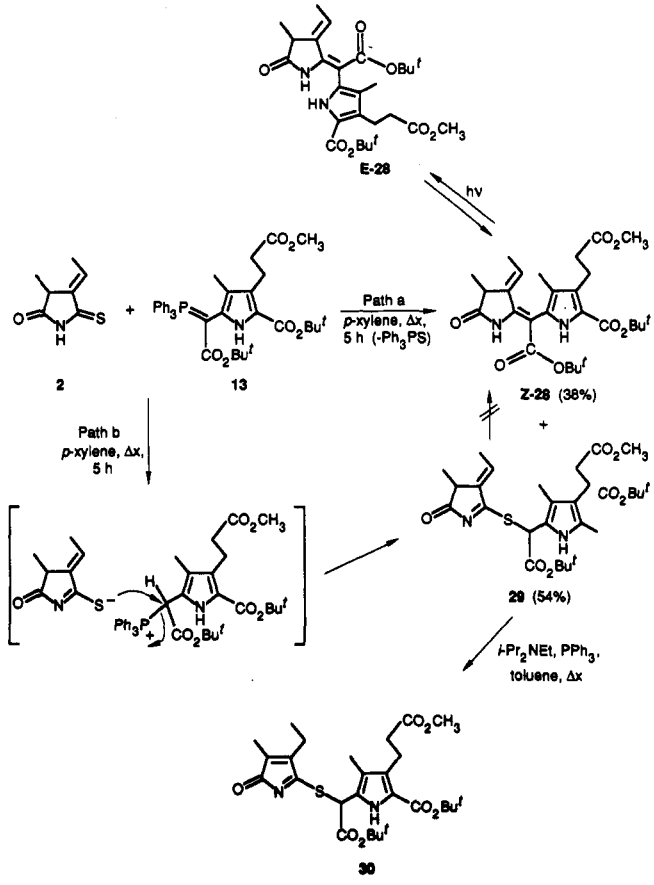
(14) (a) Schoenleber, R. W.; Lundell, D. J.; Glazer, A. N.; Rapoport, H. *J. Biol. Chem.* **1984**, *259*, 5481. (b) Nagy, J. O.; Bishop, J. E.; Klotz, A. V.; Glazer, A. N.; Rapoport, H. *J. Biol. Chem.* **1985**, *260*, 4864.

(15) Bishop, J. E.; Dagam, S. A.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1876.

Scheme III. Procedures for Synthesis of Pyrrole Ylides



Scheme IV. Possible Reaction Paths between Thioimide 2 and Pyrrole Ylide 13



alcohol intermediates, as well as ylides **1** and **13**, are stable, readily purifiable, and can be produced in large quantities.

The synthesis of α-unsubstituted pyrrole **18** utilized several modifications of literature precedent. The Knorr condensation of methyl 4-acetyl-5-oxohexanoate and benzyl acetoacetate was performed as described,[16] affording dimethylpyrrole **15**. Conversion of the α-methyl group of **15** to the *tert*-butyl ester **16** had previously been accomplished by regiospecific trichloromethylation with sulfuryl chloride,[17] hydrolysis to the carboxylic acid,[17] formation of the acid chloride by treatment with thionyl chloride,[18] and ester formation with *tert*-butyl alcohol.[18] This process could be simplified by direct treatment of the trichloromethyl intermediate with *tert*-butyl alcohol and sodium acetate to afford the desired *tert*-butyl ester pyrrole **16**. Conversion of **16** to iodopyrrole **17** was accomplished by hydrogenolysis of the benzyl ester and decarboxylation, as previously described.[18] Dehalogenation of **17** proceeded by hydrogenolysis with platinum oxide in the presence of magnesium oxide as an acid scavenger. Although this dehalogenation step had been noted in the literature using sodium acetate as acid scavenger, a detailed experimental protocol and characterization of product **18** were not presented.[18]

Pyrrole **18** was then condensed with benzyl glyoxylate (**21**)[19] and *tert*-butyl glyoxylate (**22**)[20] in the presence of zinc chloride. Aqueous sodium bisulfite in the isolation procedure removed the excess glyoxylate, and pyrrolyl carbinols **23** and **24** were obtained in 86% and 81% yields, respectively. Accompanying these products were small amounts of the corresponding higher R_f (TLC) keto pyrroles **25** and **26**, formed in larger quantities if care was not taken to conduct the reaction under an inert atmosphere in the dark. Minimizing the formation of these keto pyrroles was necessary as it proved difficult to selectively reduce the ketone to the desired alcohol.

Extensive efforts were made to convert the hydroxy group of **23** and **24** to a leaving group suitable for displacement with triphenylphosphine. Attempts at converting the alcohol to various sulfonate esters were futile. However, treatment of the pyrrolylcarbinols with a preformed complex of *N*-chlorosuccinimide and dimethyl sulfide[21] afforded an intermediate chloropyrrole that was unstable to isolation. Addition of triphenylphosphine resulted in the formation of the phosphonium chloride, which, when treated with aqueous sodium carbonate, produced multigram quantities of ylides **1** (53%) and **13** (56%). Upon chromatography, varying amounts of methylenepyrroles **19** and **27** were formed by hydrolysis of the ylides on silica gel, making it difficult to free the ylides entirely of this side product. The inhomogeneity (<5%) did not interfere with the subsequent thio-Wittig reactions because an excess of the ylide was routinely used.

Reactions of Ylides and Thioimides

To establish a positive experimental control, the prototype thio-Wittig reaction was repeated as described.[6] It

(16) Johnston, A. W.; Markham, E.; Price, R.; Shaw, K. B. *J. Chem. Soc.* **1958**, 4254.
(17) Jackson, A. H.; Kenner, G. W.; Warburton, D. *J. Chem. Soc.* **1965**, 1328.
(18) Jackson, A. H.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc. C* **1971**, 502.
(19) Jung, M. E.; Shishido, K.; Davis, L. H. *J. Org. Chem.* **1982**, *47*, 891.
(20) Blake, J.; Tretter, J. R.; Juhasz, G. J.; Bonthrone, W.; Rapoport, H. *J. Am. Chem. Soc.* **1966**, *88*, 4061.
(21) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339.

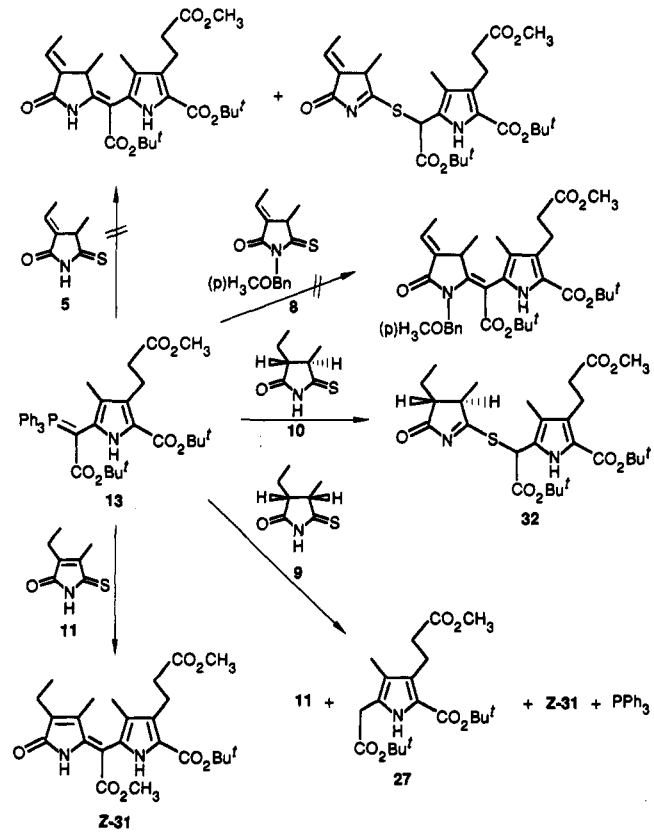
was found that the addition of ylide 1 to monothiosuccinimide 2 (Scheme II) proceeded smoothly in refluxing toluene (18 h)[6] or refluxing *p*-xylene (5 h) using the more readily accessible ylide in excess. Optimized conditions therefore called for a 1.5/1 molar ratio of 1 and 2 in a 35 mM solution (based on 2) in refluxing *p*-xylene for 5 h. Two products were observed: triphenylphosphine sulfide and adduct 3, which was obtained in 61% yield after chromatography and recrystallization.

Extending this reaction to prepare the more synthetically useful di-*tert*-butyl ester of dihydropyrromethenone 28 (Scheme IV) entailed an analogous reaction between 2 and the di-*tert*-butyl ylide 13. Quite surprisingly, under the optimized reaction conditions, four products were observed by TLC. Chromatography led to the isolation of triphenylphosphine sulfide and thio-Wittig product (*Z*)-28, both in 38% yield, as well as the S-alkylated material 29 in 54% yield and triphenylphosphine in 67% yield.

The reaction pathways illustrated in Scheme IV are proposed to account for these findings. Reaction between 2 and 13 can proceed by two different paths. The first (path a) involves nucleophilic attack of the ylide on the thiocarbonyl group leading to the observed thio-Wittig coupling products, (*Z*)-28 and triphenylphosphine sulfide. In the second pathway (path b), the ylide acts as a base, abstracting the acidic imide proton. The thioamide is then S-alkylated by the phosphonium intermediate producing thioimidate ester 29 and liberating triphenylphosphine. The preference for S- versus O- or N-alkylation has been well-documented.[22] The only structural question centered around distinguishing between an S-alkylated material (i.e., 29) and its tautomeric episulfide (see Scheme I). By ^{1}H NMR spectroscopy, two diastereomeric products were observed, each diastereomer exhibiting a resonance corresponding to the tautomeric hydrogen atom at 6.62 and 6.79 ppm, respectively. The narrow line widths of these resonances, approximately 1 Hz at the half-height, strongly support the presence of a C–H rather than N–H bond and allows assignment of the product to the thioimidate form 29. Attempts to verify this conclusion using ^{13}C NMR spectroscopy were complicated by the mixture of diastereomers present. A number of conditions involving different solvents and various temperatures were tried in an attempt to suppress the undesired acid–base reaction. Addition of a large excess of triphenylphosphine also failed to alter the product ratio; this suggested that the postulated displacement step did not govern the distribution of products.

Since repression of the side reaction could not be achieved, extensive efforts aimed at converting 29 to the desired material 28 were also made. Such a conversion has close precedence since a postulated thioimidate intermediate from S-alkylation of monothiosuccinimide 2 with bromopyrrole benzyl ester 20 (Scheme III) furnished the meso benzyl ester analogue of 28, albeit in low yields.[3] The sulfur contraction conditions called for treatment of the postulated thioimidate with an excess of triphenylphosphine and diisopropylethylamine in refluxing benzene. Under these conditions, thioimidate 29 gave a quantitative recovery of starting materials. Using refluxing toluene, only a slow conversion to the endo double bond isomer 30 was observed. Reaction conditions involving different combinations of bases, thiophiles, and solvents were used, but all led to recovery of starting materials, decomposition materials, or internalization of the double bond. In no case was sulfur contraction to 28 observed.

Scheme V. Reaction of Pyrrole Ylide 13 and Various Thioimides



To explore the mechanism for formation of thio-Wittig adduct 28, the purified S-alkylation product 29 was resubjected to the experimental conditions. Treating 29 in *p*-xylene at reflux with 150 mol % of triphenylphosphine and 150 mol % of ylide 13 led to the quantitative recovery of starting materials after 19 h. No sulfide contraction (29 → 28) was observed, convincingly demonstrating that thio-Wittig product 28 is not formed by an S-alkylation/sulfur contraction sequence, and adding credence to the postulate of two independent pathways in the reaction of substrates 2 and 13.

The next pair of compounds investigated was regioisomer 5 and the di-*tert*-butyl ylide 13 (Scheme V). In sharp contrast to the two preceding reactions, no identifiable products were observed. After several hours in refluxing *p*-xylene, the starting materials had been replaced by a multitude of closely spaced product bands by TLC. The products were purified by chromatography and then analyzed by ^{1}H NMR and FAB mass spectrometry. In the reaction of regioisomer 2 and 13, ratios of the mass spectral peaks of the crude reaction mixture were found to closely reflect the product composition based on isolated yields. In the case of 5, the only identifiable peak was triphenylphosphine oxide, which may suggest polymerization of the ylide. No ylide–succinimide adduct of any kind was observed.

The fact that triphenylphosphine oxide was present in the reaction mixture prompted an investigation of the reaction of ylide 13 with a normal, oxygen-containing amide 7 (Chart I). When subjected to the standardized reaction conditions for 8 h, about 50% of both starting materials were recovered. The remaining material consisted of several spots by TLC and with the exception of triphenylphosphine and a trace amount of triphenylphosphine oxide, these products were unidentifiable.

(22) Walter, W.; Voss, J. *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley-Interscience: New York, 1970.

Again, no coupling product was detected by ^1H NMR or FAB mass spectroscopy.

Because acid–base chemistry, manifested by S-alkylation (path b) in the reaction of **2** and **13**, may be competing with the thio-Wittig coupling of regioisomer **5** with **13**, N-substitution of the succinimide should eliminate the acidic imide proton and suppress formation of any readily alkylated thioimidate species. Tertiary thioamides are more difficult to alkylate because of the formation of charged species. Thus, *N*-(*p*-methoxybenzyl)monothiosuccinimide **8** was refluxed with ylide **13** in a number of different solvents. Again, no coupling reaction was observed. Interestingly, however, the starting material decomposition, so dramatic with the unprotected imide **5**, was not observed with **8**. The starting materials were recovered essentially quantitatively under the standardized conditions.

The next set of thio-Wittig educts made use of the saturated cis succinimide **9**. Reaction with ylide **13** produced a purple oxidation product, monothiomaleimide **11**, in 34% yield (Scheme V). Methylenepyrrole **27** was also isolated in 32% yield and apparently results from accompanying reduction of the ylide. A highly yellow-colored product, pyrromethenone (*Z*)-**31**, which was synthesized and fully characterized by a different route, was also recovered.

In contrast to its cis isomer, *trans*-monothiosuccinimide **10** reacted with ylide **13** to give a 73% yield of S-alkylated product **32** as a 1/1 mixture of diastereomers. Both diastereomers retained the trans dihydro stereochemistry as indicated by the 4.5-Hz coupling constant of the ring protons in the ^1H NMR spectrum.[15] The absence of sulfur contraction with the ethylidene analogue **29** was also the case with thioimidate **32**. Indeed, treatment of **32** with triphenylphosphine and diisopropylethylamine in refluxing benzene or toluene provided only recovered starting materials. Use of stronger, less sterically hindered bases, for example sodium methoxide, with triphenylphosphine, resulted in decomposition of the starting material.

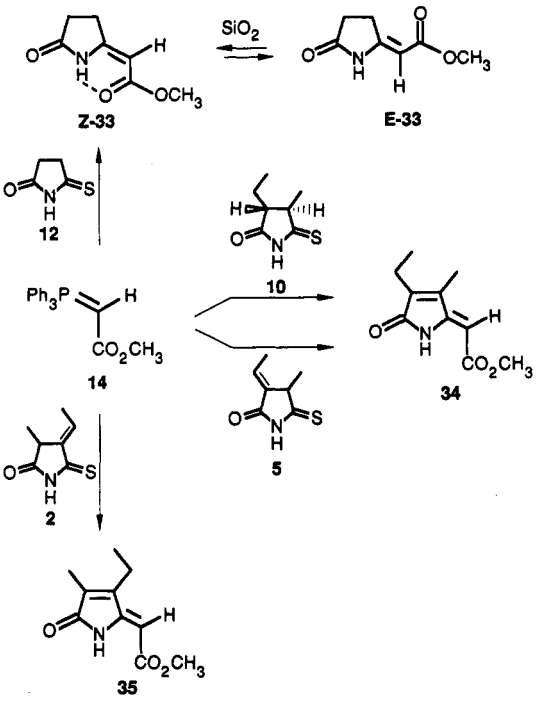
Freshly generated monothiomaleimide **11**, when reacted with ylide **13**, furnished a 97% yield of one thio-Wittig adduct, (*Z*)-**31**, which isomerized to a mixture of geometric isomers upon exposure to silica gel or upon sitting in solution.

The parent compound, monothiosuccinimide **12**, is reported to react with the nonpyrrolic ylide **14**, affording a 58% yield of a thio-Wittig condensation product.[5] This ylide is considerably more reactive than the pyrrole ylides because of less steric hindrance as well as the absence of an adjacent stabilizing aromatic group. Although a detailed experimental description was not presented, we attempted to duplicate this result. Refluxing **12** and **14** in a 1/1 ratio in *p*-xylene generated the vinylogous carbamate **33** in a reproducible 17% yield (Scheme VI). The product was accompanied by a small amount of starting materials and a large quantity of polymeric material.

Although this result was not very promising for the synthesis of more complex analogues, we also used monothiosuccinimides **2** and **5** in reactions with the more reactive ylide **14**. In both cases, only low yields of adducts containing an endo double bond were obtained. The ylide was apparently basic enough to promote the double bond isomerization; however, it is not known whether this occurred before or after the coupling reaction took place.

An experiment was also performed in which ylide **14** was reacted with the trans-substituted monothiosuccinimide **10** (Scheme VI). After 4 h in refluxing *p*-xylene, a large quantity of starting materials was recovered accompanied by a 9% yield of oxidized thio-Wittig coupling product **34**.

Scheme VI. Reaction of (Methoxycarbonyl)methyl Ylide with Various Thioimides



This type of product is similar to that formed in the reaction of the more oxidatively labile cis isomer **9** with the less reactive ylide **13**. Given the previously observed patterns of reactivity as well as the lack of any unoxidized coupling product, it is probable that oxidation of the succinimide preceded thio-Wittig coupling.

The remaining structure-related question with the thio-Wittig adducts centers around identification of the geometry of the resulting double bond. In the simplest case, the reaction of monothiosuccinimide **12** with ylide **14** (Scheme VI), the assignment of *Z* geometry had been made on the basis of the N–H stretching frequency in the infrared spectrum.[5] In our hands, this result was confirmed by ^1H NMR spectroscopy. It was found that chromatography with silica gel slowly isomerized the reaction mixture to the more polar *E* isomer, which lacks intramolecular hydrogen bonding. The two forms were distinguishable by their allylic coupling constants in the ^1H NMR spectra, that for the *Z* form being 1.1 Hz, while the *E* isomer showed 2.0 Hz, indicative of a trans-allylic geometry.[23,24] The assignments are also in accord with the distinctive chemical shifts of the allylic protons. The *E* isomer shows this resonance at 2.55 ppm, whereas the *Z* form, with the allylic protons in the deshielding region of the carbonyl group, shows this resonance at 3.30 ppm.[25] That (*Z*)-**33** was the sole isomer observed before chromatography can be explained by a lower activation energy in the thio-Wittig transition state resulting from a hydrogen bonding effect between the hydrogen of the NH group and the ester carbonyl.

Assigning the double-bond stereochemistry of thio-Wittig adduct **28** (Scheme IV) was more difficult. The ^1H NMR spectrum of this product suggested the presence of two geometric isomers in a 1/1 ratio, as all signals were doubled. In an attempt to lessen the pronounced line broadening, the spectrum was recorded at higher tem-

(23) Brockman, H., Jr.; Knobloch, G. *Chem. Ber.* **1973**, *106*, 803.
(24) Newsoroff, G. P.; Sternhell, S. *Tetrahedron Lett.* **1968**, 6117.
(25) ApSimon, J. W.; Demarco, P. V.; Mathieson, D. W.; Craig, W. G.; Karim, A.; Saunders, L.; Whalley, W. B. *Tetrahedron* **1970**, *26*, 119.

peratures. Coalescence of the signals was observed at approximately 50 °C; the 1/1 mixture was restored upon cooling to room temperature. This coalescence temperature corresponds roughly to a 17 kcal/mol energy barrier,[26] indicating the interconversion of conformational, not configurational, isomers. The axis of rotation in this case would be the single bond separating the two rings.

We have previously used two-dimensional NOE techniques to solve more complex structural problems in tetrapyrrole natural products,[27] and similar experiments were used to examine the double-bond geometry of **28**. After measuring the spin–lattice (T_1) relaxation times of all protons, a series of NOESY experiments was performed with varying mixing times. All of these experiments showed strong chemical exchange cross-peaks; however, in no case was dipole–dipole exchange between substituents on the two rings observed, making assignment of the double-bond geometry impossible by this method.

It was additionally observed that thio-Wittig product **28** slowly isomerized in ambient light to a more polar material, a process that could be hastened to a photostationary state by irradiation in methanol. After isolation of the irradiation product by chromatography, subsequent treatment with catalytic base (1,8-diazabicyclo[5.4.0]undec-7-ene; DBU) or acid (trifluoroacetic acid; TFA) rapidly regenerated the higher R_f isomer. This photochemical behavior has precedence[28] and strongly suggests isomerization at the meso rather than ethylidene double bond.

Although NOESY experiments were unsuccessful in directly assigning double-bond geometries of the isomers, indirect evidence strongly supports a (*Z*)-**28** → (*E*)-**28** rather than *E* → *Z* photoisomerization. The *Z* form, with its potential for forming intramolecular hydrogen bonds between the meso carbonyl substituent and the two NH groups, would be expected to have decreased polarity and a correspondingly higher R_f on TLC, relative to the *E* form. This chromatographic behavior is qualitatively consistent with model compounds (*Z*)-**33** and (*E*)-**33** (Scheme VI), for which definitive assignments of double-bond geometry were made. It is postulated that the proposed hydrogen bonding interactions that appear to exclusively produce (*Z*)-**33** also produce (*Z*)-**28** upon thio-Wittig condensation. Similar lines of reasoning also lead to assignment of (*Z*)-**31** as the sole product from reaction of monothiomaleimide **11** with ylide **13** (Scheme V).

Reaction Mechanisms

A theoretical analysis of the reaction of thioamides with phosphorus ylides was undertaken in an attempt to rationalize the variations exhibited by the model monothiosuccinimides. Of particular interest was the effect of substrate structure on thio-Wittig coupling. Why does monothiosuccinimide **2** undergo thio-Wittig coupling with the stabilized ylides **1** and **13** in reasonable yields, while regioisomer **5** is totally resistant? Additionally, the substrate factors that determine whether the reaction proceeds via the thio-Wittig or S-alkylation pathway were of interest. Why does monothiomaleimide **11** afford all thio-Wittig product in near quantitative yield, whereas the saturated trans monothiosuccinimide **10** affords only S-alkylated product? Since the reaction conditions and ylide substrates remained constant the answer must lie in the electronic differences among the monothiosuccinimides. To rationalize these dramatic differences, the substrates and reaction mechanisms were investigated computationally by a series of calculations at both semiempirical (MNDO)[29] and ab initio[30] levels.

Initially, prototype substrates were investigated at the semiempirical level to elucidate the pertinent electronic factors affecting the different reaction pathways. Since the treatment of the substrates of interest is more feasible at semiempirical levels due to their size, correlations could then be made between the prototype and the actual substrates. The prototype substrates to be considered were formaldehyde, thioformaldehyde, formamide, and thioformamide in their reaction with phosphonium methylide. Presumably the S-alkylated product would proceed from initial acid/base reaction with the ylide, followed by displacement of phosphine from the protonated ylide. As discussed previously, the Wittig product would probably arise from a Wittig-type mechanism rather than through an initial episulfide. Since the thio-Wittig and S-alkylation pathways were experimentally independent, the initial transition states of both reaction pathways had to direct the product distribution.[31]

The Wittig reaction mechanism has received several theoretical treatments. A previous MNDO treatment emphasized the stereochemical aspects.[32] Also, ab initio treatments at the STO-3G and double-ζ basis set levels on the mechanism of the prototype Wittig reaction between phosphonium methylide ($H_3P{=}CH_2$) and formaldehyde have been reported.[33] A similar treatment at the 4-31G* basis set level for geometry optimization using the 4-31+G* basis set for single point energy calculations has also been reported.[34] For the reaction of phosphonium methylide with formaldehyde, the initial transition-state energy was computed at +5.2 kcal/mol with a C–C bond length of 2.079 Å at the 4-31G* level.[34] Of course, gas-phase theoretical treatments are inherently biased toward concerted [2 + 2]-cycloaddition type Wittig mechanisms since the significant charge separation in both extended and tight-ion-pair betaines would be much higher in energy. Multiconfigurational treatments would not be expected to recover much of this energy. Nevertheless, given the relatively nonpolar, hydrocarbon solvents employed experimentally, theoretical methods should still provide significant insights.

The initial Wittig transition-state energies of the prototype substrates were determined by saddle point calculations after initial MNDO reaction path calculations along the carbon–carbon bond formation pathway. The two transition states (TS-I and TS-II) were confirmed by a numeric force constant calculation, which afforded in each case a single imaginary frequency. Table I shows calculated energies for the prototype substrates while Table II gives calculated LUMO energies, transition-state energies (ΔH^*), and reaction enthalpies. For formaldehyde, the

(26) Günther, H. *NMR Spektroskopie*; Georg Thieme Verlag: Stuttgart, 1973; pp 243–250.

(27) Lagarias, J. C.; Klotz, A. V.; Dallas, J. L.; Glazer, A. N.; Bishop, J. E.; O'Connell, J. F.; Rapoport, H. *J. Biol. Chem.* **1988**, *263*, 12977.

(28) Pyrromethenone isomerizations are discussed in Bonnett, R.; Hamzetash, D.; Vallés, M. A. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1383 and references cited therein. Note that in the absence of a meso ester substituent, the *E*/*Z* assignments change based on substituent priority rules.

(29) (a) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899. (b) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4907. (c) Dewar, M. J. S.; McKee, M. L.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 3607.

(30) Frisch, M. J.; Binkley, J. S.; Schlegel, H. B.; Raghavachari, K.; Melius, C. F.; Martin, R. L.; Stewart, J. J. P.; Bobrowicz, F. W.; Rohlfing, C. M.; Kahn, L. R.; Defrees, D. J.; Seeger, R. A.; Whiteside, R. A.; Fox, D. J.; Fleuder, E. M.; Pople, J. A. *Gaussian 86*; Carnegie-Mellon Quantum Chemistry Publishing Unit: Pittsburgh, PA, 1984.

(31) Isaacs, N. S. *Physical Organic Chemistry*; John Wiley and Sons: New York, 1987; pp 317–318 and references therein.

(32) Bestman, H. J. *Pure Appl. Chem.* **1980**, *52*, 771.

(33) Höller, R.; Lischka, H. *J. Am. Chem. Soc.* **1980**, *102*, 4632.

(34) Volatron, F.; Eisenstein, O. *J. Am. Chem. Soc.* **1987**, *109*, 1.

Table I. Energies of Prototype Structures[a]

structure	ΔH_f, MNDO	electronic energy HF/3-21G(*)	HF/6-31G*	MP2/6-31G*
$H_2C{=}O$	-32.9	-113.22182	-113.8652854	-114.1668186
$H_2C{=}S$	27.8	-434.4463947	-436.5064403	-436.7543656
$H_3P{=}O$	9.9	-415.2660419	-417.3066843	-417.5942412
$H_3P{=}S$	37.7	-736.4486223	-739.9633773	-740.1850432
$H_3P{=}CH_2$	77.5	-379.5462704	-381.3881227	-381.6251636
$H_2C{=}CH_2$	15.5	-77.6009881	-78.0316975	-78.2841229
$HC(O)NH_2$	-39.9	-167.9849003	-168.9299367	-169.3934748
$HC(S)NH_2$	12.3	-489.20420701	-491.5666002	-491.9754368
$HC(=CH_2)NH_2$	16.2	-132.32644361	-133.0591169	-133.4741724
PH_3	3.9	-340.8139895	-342.4479477	-342.5515154
$HC(=NH)OCH_3$	-27.5	-206.769092	-207.9309964	-208.5232772
$HC(=NH)SCH_3$	8.9	-527.9902535	-530.5823807	-531.1228878
Wittig (H_2CO) TS-I	52.4 (2.18 Å)[b]	-	-	-
thio-Wittig (H_2CS) TS-I	111.6 (2.48 Å)[b]	-	-	-
Wittig ($HCONH_2$) TS-I	51.1 (2.04 Å)[b]	-	-	-
thio-Wittig ($HCSNH_2$) TS-I	107.5 (2.24 Å)[b]	-	-	-

[a] Energies in Hartrees except for MNDO (kcal/mol); geometry optimization was done at HF/3-21G(*) level; HF/6-31G* and MP2/6-31G* are single-point calculations. [b] C–C bond length in the transition state.

Table II. Prototype Substrate Energies[a]

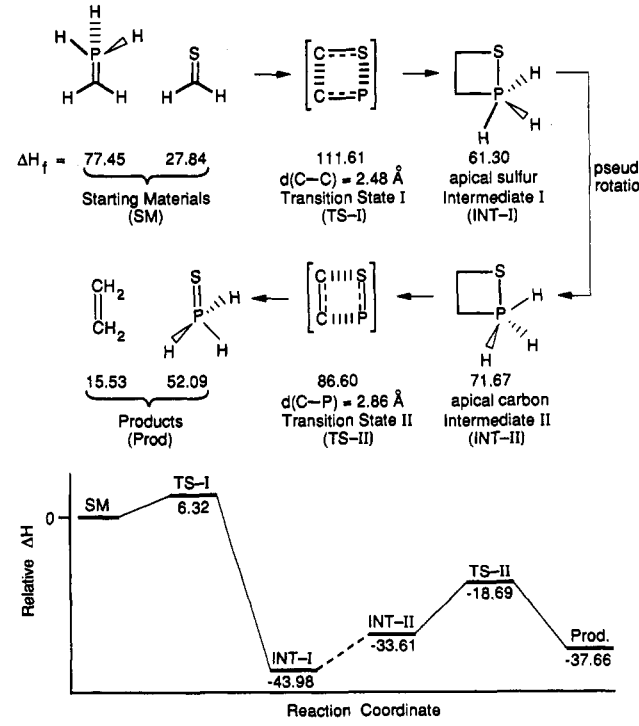
reaction	carbonyl MNDO LUMO (eV)	MNDO ΔH^*	MNDO ΔH_{rxn}	HF/3-21G* ΔE_{rxn}	HF/6-31G*//HF/3-21G(*) ΔE_{rxn}	MP2/6-31G*//HF/3-21G(*) ΔE_{rxn}
$H_2C{=}O + H_2C{=}PH_3 \rightarrow CH_2{=}CH_2 + H_3P{=}O$	0.86	+7.9 (+5.2)[b]	-19.1	-62.1 (-50.8)[b]	-53.3	-54.2 (-53.1)[d]
$H_2C{=}S + H_2C{=}PH_3 \rightarrow CH_2{=}CH_2 + H_3P{=}S$	-0.83	+6.3	-37.7	-35.7	-63.1	-56.2 (-55.7)[d]
$HC(=O)NH_2 + H_2C{=}PH_3 \rightarrow HC(=CH_2)NH_2 + H_3P{=}O$	1.52	+13.5	014.0	-38.5	-30.0	-31.2
$HC(=S)NH_2 + H_2C{=}PH_3 \rightarrow HC(=CH_2)NH_2 + H_3P{=}S$	0.05	+9.4	-31.7	-15.4	-42.5	-36.8
$HC(=O)NH_2 + H_2C{=}PH_3 \rightarrow HC(=NH)OCH_3 + PH_3$	1.52	-	-62.2	-32.6	-38.2	-35.2
$HC(=S)NH_2 + H_2C{=}PH_3 \rightarrow HC(=NH)SCH_3 + PH_3$	0.05	+5.2[c]	-85.3	-33.8	-47.4	-46.3

[a] Energies in kcal/mol unless otherwise indicated. [b] Reference 34: HF/4-31G*+//HF/4-31G*. [c] From reaction coordinate. [d] MP4 (SDTQ)/6-31G*//HF/3-21G(*).

initial relative transition-state energy was found to be +7.9 kcal/mol with a C–C bond length of 2.177 Å by MNDO, agreeing fairly well with the reported[34] ab initio energies and geometries. In general, amides are experimentally inert to Wittig couplings. As expected the transition state for formamide was found to be higher, +13.5 kcal/mol. In both cases, after the initial transition state, an intermediate oxaphosphetane with an apical oxygen was located. After pseudorotation affording an apical carbon substituent[35] the reaction proceeded through a second transition state in which products were then formed. As noted previously,[34] the latter oxaphosphetane requires a relatively large activation energy to go to final products. Because the energy of the second transition state is below that of the reactants, the system preferentially proceeds to completion, rather than returning to starting materials. Though the MNDO energies do not agree extremely well with the reported 4-31G* ab initio data, it should be stressed that the calculated MNDO energy profile shows a reasonable correlation with the 4-31G* data. Thus, MNDO calculations appear to provide qualitatively reliable results for the relative energies and geometries.

It was expected that the thiocarbonyls should proceed in a similar fashion in a Wittig-type mechanism since control experiments showed convincingly the alternative mechanism, S-alkylation followed by sulfur contraction, was not operative. The energy profile was studied carefully, however, to ascertain whether deviations exist. Thioformaldehyde with phosphonium methylide proceeded through an initial transition state (TS-I) at a C–C bond distance of 2.48 Å with an activation energy of ΔH^* = 6.3 kcal/mol (Scheme VII). This was followed by an

Scheme VII. Mechanism and Energy Profile (kcal/mol) Derived from MNDO for Reaction of $H_3P{=}CH_2$ with $H_2C{=}S$



(35) McDowell, R. S.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 5849.

intermediate (Int-I) thiaphosphetane at a much lower energy with an apical sulfur ligand on the trigonal bipyrimidal phosphorus. The phosphorus then undergoes a pseudorotation, placing the carbon atom in an apical position, affording a second thiaphosphetane (Int-II) at slightly higher energy. This follows the rules for ligand apicophilicity.[35] Pseudorotation is required since ligand departure is much less energetically costly from the apical position.[34,35] A second transition state was then located with a C–P bond distance of 2.86 Å and activation energy of $\Delta H^{\ddagger}$ = 14.9 kcal/mole relative to Int-2. Collapse to products ethylene and trihydridophosphine sulfide was then observed.

The thio-Wittig reaction mechanism appears to be totally analogous to the Wittig reaction. This is not surprising, but none the less an important point. The initial transition state is low lying and therefore determines the partitioning of products. It is interesting to note that the products were found to be slightly less stable than the apical sulfur intermediate (Int-I). This may be an artifact of MNDO's difficulties with sulfur and pentavalent phosphorus and its tendency to overestimate the stability of 4-membered rings.[36] An increase in entropy will also favor formation of products from Int-I.

Thioformamide exhibited a similar reaction profile to thioformaldehyde with an initial transition state at $\Delta H^{\ddagger}$ = +9.4 kcal/mol relative to the educts. As is experimentally observed with certain model monothiosuccinimides, the thiocarbonyl significantly activates the amide substrate for Wittig couplings. This trend is reproduced at the MNDO level, although for these particular substrates, the barrier is only lowered by 4.1 kcal/mol.

Employing frontier molecular orbital (FMO) analysis, one notes that the thioimide represents the electron-deficient component and the major participating orbital in the cycloaddition is the lowest unoccupied molecular orbital (LUMO), whereas the most important orbital of the electron-rich ylide is the highest occupied molecular orbital (HOMO). Thus, it would be expected that the lower LUMO energy of the thioamide relative to the oxoamide would facilitate the thio-Wittig coupling reaction by lowering the initial transition-state energy via an increase in the energetically favorable mixing of the reacting orbitals.[37] Empirically, the lower energy LUMO of thiocarbonyls relative to isosteric carbonyl groups manifests itself spectroscopically as a longer wavelength $\pi \rightarrow \pi^*$ transition, and chemically, as a greater tendency toward spontaneous enolization or oligomerization.[38]

While the prototype substrates have similar minimum energy profiles with phosphonium methylide along the carbon–carbon bond formation pathway, thioformaldehyde would be expected to react more readily than formaldehyde due to its low-lying LUMO (–0.83 eV) and indeed has a lower Wittig activation: $\Delta H^{\ddagger}$ = +6.3 kcal/mol relative to educts. On the other hand, thioformamide has a lower energy LUMO than formamide (0.05 eV versus 1.52 eV), with an accompanying lower activation barrier.

To further corroborate that Wittig and S-alkylation reactions are directed by initial transition-state energy rather than by thermodynamics and to further gauge the accuracy of the MNDO data, ab initio calculations were made on the prototype systems. The geometries of reactants and products were optimized at the HF/3-21G(*) level. Single-point energy calculations were then performed at the MP2/6-31G* level. Not surprisingly, there is a large effect of basis set on the reaction enthalpies, especially in the case of the sulfur analogues (Tables I and II). Treatment of correlation at the MP2 level affords significant energy corrections as well. Single points at the MP4(SDTQ) level gave only a very slight correction over the MP2 values with formaldehyde and thioformaldehyde. At the highest level of theory, there is surprisingly little difference between oxo/thio for Wittig type couplings in terms of reaction energies. As expected, aldehyde Wittig couplings are more exothermic than those of amide. Wittig and alkylation reactions have similar energies, oxo and thio both favoring alkylation. These results add greater credence to the importance of the relative initial transition states directing between Wittig and alkylation pathways. While it is not possible to accurately model solution phase acid–base chemistry via MNDO or ab initio methodology, one may infer from experiment that the overall activation barriers to S- or O-alkylation for these model substrates must be considerably higher than those for cycloaddition, based on the observed products.

Table III. Selected Bond Length and Bond Angle Values for Monothiomaleimide 11 Derived from X-ray Crystallography[15] and from MNDO Calculations (Arbitrary Numbering Scheme; See Table IV)

bond lengths (Å)	X-ray	MNDO
C4–S5	1.62	1.56
C4–N3	1.37	1.39
C4–C6	1.48	1.51
C2–O1	1.22	1.22
C2–N3	1.39	1.43
C2–C7	1.48	1.52
C6–C7	1.33	1.37
bond angles (deg)	**X-ray**	**MNDO**
S5–C4–N3	125.66	124.30
S5–C4–C6	128.09	129.96
N3–C4–C6	106.25	105.74
O1–C2–N3	124.72	121.75
O1–C2–C7	128.72	132.83
N3–C2–C7	106.56	105.42
C2–N3–C4	110.46	111.61
C2–C7–C6	107.74	108.13
C4–C6–C7	108.99	109.10

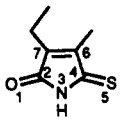
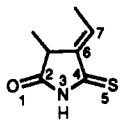
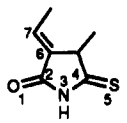
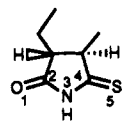
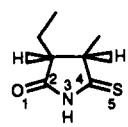
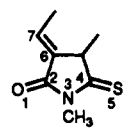
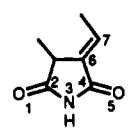
Substrate Calculations

MNDO calculations were then carried out to evaluate the electronic differences of the model succinimides. This semiempirical method was chosen because of the reasonably good energies obtainable and the prohibitive cost of ab initio calculations for these large molecules. Data set parameterizations were judged to be sufficiently accurate, as observed in the close correspondence between bond length and bond angle values obtained from the MNDO calculation for monothiomaleimide **12** and values obtained from X-ray crystallography[15] (Table III). Frontier orbital energies and formation enthalpies for the model substrates are shown in Table IV in the order of increasing LUMO energy. While the absolute orbital energies are unlikely to be accurate, their relative ordering should be. For computational ease, *N*-methylmonothiosuccinimide **36** was substituted for its *N*-*p*-methoxybenzyl analogue **8**, since differing *N*-alkyl substituents should not significantly alter the important orbital relationships.

The effect of the double bond is of considerable interest. Note that the saturated monothiosuccinimides **9** and **10** have significantly higher LUMO energies than the unsaturated species, suggesting lower thio-Wittig reactivity. This is indeed observed experimentally as thio-Wittig coupling products are not observed with the educts lacking

(36) Clark, T. *A Handbook of Computational Chemistry*; John Wiley and Sons: New York, 1985; p 151.
(37) Salem, L. *Electrons in Chemical Reactions*; John Wiley and Sons: New York, 1982.
(38) Lightner, D. A.; Bouman, T. D.; Wijekoon, W. M. D.; Hansen, A. E. *J. Am. Chem. Soc.* **1984**, *106*, 934.

Table IV. MNDO Heats of Formation and LUMO Energies

substrate	MNDO heats of formation and LUMO energies		
	ΔH_f (kcal/mol)	HOMO (eV)	LUMO (eV)
 11	-22.93	-9.97	-1.80
 2	-24.94	-9.78	-1.16
 5	-23.91	-9.78	-0.91
 10	-43.58	-9.85	-0.85
 9	-40.15	-9.85	-0.85
 36	-21.70	-9.71	-0.84
 7	-77.22	-10.70	-0.46

a double bond. The position of the double bond also appears to have a profound effect on reactivity. This can be understood by examining theoretical data from the isomeric monothioimides **11**, **2**, and **5**. Taking the double bond out of conjugation with the thiocarbonyl group as with **5** has the effect of increasing LUMO energy by 0.25 eV (5.8 kcal/mol) relative to **2** and, as a result, no thio-Wittig coupling is observed in the reaction of **5** with ylide **13**. In marked contrast, monothiomaleimide **11**, with the lowest lying LUMO energy of all the model substrates, -1.8 eV, undergoes thio-Wittig coupling with ylide **13** in 97% yield.

In correlating the theoretical and experimental data it becomes apparent that the LUMO energy, as anticipated, exerts a dominant role in determining if thio-Wittig condensation takes place. It can also be seen, both in experiment and in theory, that nitrogen protection offers no advantages in enhancing thio-Wittig reactivity; in fact the LUMO of **38** is calculated to be even higher in energy, and consequently less reactive, then unprotected **5**.

Alternative Reaction Pathways

Results from the thioimide compounds indicate that there is a threshold LUMO energy that governs thio-Wittig coupling. This threshold appears to lie between regioisomers **2** (-1.16 eV) and **5** (-0.91 eV). This MNDO energy difference of 0.25 eV is apparently sufficient to raise the activation energy to the point of completely suppressing thio-Wittig coupling of **5** with ylide **13** (Scheme V). These higher transition-state energies then presumably allow alternate reactions to occur. The two observed alternatives are S-alkylation and oxidation/reduction.

Nowhere are the competing reaction pathways better illustrated than in the reaction of **2** with pyrrole ylide **13** (Scheme IV), where a 38% yield of thio-Wittig condensation product was accompanied by a 54% yield of S-alkylated material. As discussed previously, control experiments verified the independent nature of the two pathways, that is, formation of thio-Wittig adduct (*Z*)-**28** did not proceed through S-alkylated intermediate **29**. Interestingly, a higher yield of thio-Wittig product (61%) was obtained, and no S-alkylation products were observed, when benzyl ester ylide **1** (Chart I), rather than *tert*-butyl ester analogue **13**, was condensed with thioimide **2**. These differences are attributed to presence of the more sterically demanding *tert*-butyl group, which could raise the thio-Wittig transition-state energy and allow the alternate S-alkylation pathway to predominate. It appears that the numerous, unidentifiable products from the reaction of regioisomer **2** with ylide **13** originate from a similar type of reaction pathway. While removal of the acidic imidic hydrogen atom by the basic ylide led to S-alkylation for **2**, oligomerization, possibly by a very favorable 1,4-Michael addition, or decomposition was observed for **5**. Removal of the imide proton by N-protection, in contrast, led to recovery of starting materials. It is not clear why the anions of **2** and **5** would differ so dramatically in reactivity. Attempts were made to study the anions derived from NH and α-CH deprotonation by MNDO methods; however, results were ambiguous, as might be expected for a gas-phase model.

A startlingly different reaction pathway predominated when cis saturated monothiosuccinimide **9** was reacted with ylide **13** (Scheme V). Whereas trans diastereomer **10** furnished S-alkylated **32** in 73% yield, products from **9** were derived from an oxidation/reduction pathway. Empirical data showed an energetically unfavorable two-electron oxidation of **9** to monothiomaleimide **11**, the difference in heats of formation (MNDO) being approximately 17 kcal/mol. The monothiomaleimide then partially reacted with excess ylide in a very electronically favorable reaction, to form adduct **31**. This oxidation was accompanied by two-electron reduction of phosphorus from P(V) to P(III), resulting in triphenylphosphine and methylenepyrrole **27**. Although the cis diastereomer would be expected to be more oxidatively labile than the trans, this type of oxidation/reduction behavior was not confined solely to the cis form. When reacted with the more reactive ylide **14**, the trans isomer similarly furnished an oxidation product **34** (Scheme VI). Although there is precedence for the reduction of phosphonium ylides under strong reducing conditions, i.e. Raney nickel or Zn/HCl,[39] we were unable to find examples of reduction by a potential Wittig reaction substrate in the literature. A convincing mechanistic explanation for this type of conversion cannot be made at this time.

Reactivity of Ylides

Increasing the reactivity of an ylide can be accomplished in two ways. One method, as demonstrated by the re-

(39) Johnson, A. W. *Ylid Chemistry*; Academic Press: New York, 1966; pp 92-94.

activity difference between benzyl and *tert*-butyl ester ylides **1** and **13**, is to incorporate less sterically demanding substituents on the ylide. The other is to minimize the presence of stabilizing groups connected to the anionic center. The effect of this latter method is to raise HOMO energy, thereby making bond formation a more favorable process.

Extensive efforts were made to increase the reactivity of ylide **13** to allow condensation with thioimide **5**. Variations in ylide structure could occur in three possible places: either of the two substituents attached to the anionic center could be altered or different groups on phosphorus could be used. The first option, that of changing the pyrrole group, was not attractive because of the nature of our synthetic targets. The second option, that of changing the adjacent *tert*-butyl ester, was considered.

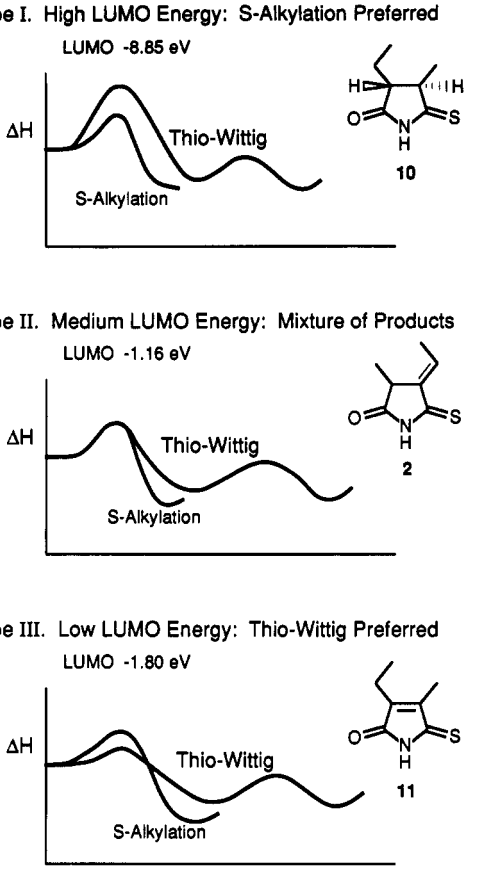
Two recent communications report the successful condensation of a nitrile-substituted pyrrole ylide with a completely saturated monothiosuccinimide.[12,13] Substitution of a nitrile for an ester group serves the dual purpose of reducing steric constraints and increasing HOMO energy. Unfortunately, the vigorous conditions necessary for subsequent removal of the nitrile group were not compatible with our anticipated synthetic intermediate; an acid labile ester group at this position was absolutely necessary for further manipulations. The last option, that of changing the phosphorus ligands, was considered the most attractive possibility, primarily because such changes would not be incorporated in the ensuing thio-Wittig adduct. Efforts at producing a tri-*n*-butylphosphine-substituted ylide were unsuccessful, apparently due to instability during chromatography. However, derivatives containing electron-donating groups on the phenyl rings were accessible. It was reasoned that the presence of electron-donating substituents would destabilize the ylide by raising the HOMO energy, thereby increasing nucleophilicity. This concept was unsuccessfully tested in a Wittig reaction model study using various 2,6-dimethoxyphenyl-substituted phosphines.[40]

Even though it was not of relevance to the generation of desired products, reaction of monothiosuccinimide **2** with ylide **14** provided an interesting test to the hypothesis of thio-Wittig reactivity as a function of ylide HOMO energy. Ylide **14**, without the adjacent stabilizing and sterically bulky pyrrole group, would be expected to afford higher yields of thio-Wittig product than the pyrrole ylide **13**. As mentioned previously, it was found that the only coupled product had experienced double bond migration as a result of the more reactive ylide (Scheme VI), indicating that certain sensitive functional groups are not always compatible with these reaction conditions.

Conclusions

Since S-alkylation and thio-Wittig alkenylation pathways are discriminated by the initial transition-state energies, it is of importance to examine what relevant factors effect this energy. What appears to be most important are (1) thioamide NH acidity and (2) LUMO energy of the thioamide substrate. Since the transition-state energy for NH proton abstraction is related to the basicity of the ylide, this should be relatively constant for our thioamides, which are all of similar acidity. However, the electron-accepting character of the thioamide substrate is directly dependent on substitution, and this is reflected in the LUMO energy of the thioamide. Thus, the LUMO energy should correlate directly with the transition-state energy. It is proposed that the S-alkylation/thio-Wittig product distribution is governed by the energy of the Wittig-type C–C bond formation transition state, which depends directly on the LUMO energy of the thioamide educt, relative to the activation barrier for S-alkylation, which is effectively the same for a given ylide, as diagrammed in Scheme VIII.

Scheme VIII. Thermodynamic Parameters Comparing S-Alkylation and Thio-Wittig Pathways (kcal/mol)



The substituent perturbation on transition-state energy was dramatically illustrated with the experimental thiosuccinimides **2**, **10**, and **11**. If the electronic effects of the substituents affected the NH proton abstraction transition state, then one would expect similar product distributions. However, since the thioamide NH proton is already intrinsically quite acidic, the S-alkylation transition state is relatively independent of electron-withdrawing substituents, at least over the range of basicities displayed by the stabilized ylides used in this model study. Meanwhile, the thio-Wittig transition state is strongly perturbed by such substituent effects and the spectrum of substitution-dependent product distributions is observed (Scheme VIII): compound **10** shows type I behavior, **2** shows type II behavior, and **11** shows type III behavior. Compound **8**, with N-protection, failed to react by any of these pathways, demonstrating that suppression of the S-alkylation pathway does not necessarily enhance the alternate pathway, if the substrate is not well-suited in terms of LUMO energy, for thio-Wittig coupling.

Attempts have been made to carefully examine the structure–reactivity relationships of a series of thioimides in their reaction with stabilized pyrrole ylides. Additionally, attempts have been made to correlate these results with the few examples of the thio-Wittig reaction that appear in the literature. Several of the model reactions displayed yet another type of apparently unprecedented

(40) Wada, M.; Higashizaki, S. *J. Chem. Soc., Chem. Commun.* **1984**, 482.

reactivity, oxidation/reduction, and no attempts were made to study this type of reaction computationally, because no fully suitable mechanistic model could be advanced.

The thio-Wittig reaction appears to be of limited synthetic applicability, success depending heavily on the structure of the thioamide substrate. If certain substituents are present, for example a double bond in conjugation with the thiocarbonyl group, then the thio-Wittig pathway is greatly enhanced. Having established a series of structure–reactivity relationships, it is felt that accurate prediction of the potential of success for a thio-Wittig reaction could be made, at least with compounds similar to those contained in the model study. In fact, prediction of success for condensation of monothiomaleimide **11** with ylide **13** (Scheme V) actually preceded the laboratory results. These predictions must, however, be viewed with some apprehension, especially when examining highly functionalized substrates that may undergo alternate types of reactions. Nonetheless, we hope to have demonstrated the potential of using modern computational methods, in combination with well-established empirical data, for the understanding of reaction mechanisms and reactivities, which may ultimately aid in the design of synthetic strategy.

Experimental Procedures[41]

Computational Details. Ab initio calculations were performed using the GAUSSIAN 86 series of programs.[30] Geometries were fully optimized with the 3-21G(*)[42-44] basis set at the Hartree–Fock (HF) level of theory. Single-point calculations were carried out at the MP2 level[45] using the 6-31G* basis set[46] on the HF/3-21G(*) geometries. Single-point calculations on the HF/3-21G(*) geometries for the prototype Wittig and thio-Wittig reactants and products were also done at the MP4(SDTQ)/6-31G* level (frozen core). Semiempirical MNDO calculations[29] were performed using the MOPAC package[47] with revised sulfur parameters.[48]

***tert*-Butyl 5-(Benzyloxycarbonyl)-3-(2′-(methoxycarbonyl)ethyl)-4-methylpyrrole-2-carboxylate (16).** To 5.00 g (15.9 mmol) of pyrrole **15**[16] and 200 mL of diethyl ether at 0 °C was added 5.1 mL (400 mol %) of sulfuryl chloride at a rate of 4.3 mL/h. After stirring under N_2 in the dark at 5 °C for 21 h, the solution was concentrated (bath temperature <35 °C) and 100 mL of *tert*-butyl alcohol followed by 7.50 g (557 mol %) of anhydrous sodium acetate was added. The heterogeneous mixture was refluxed (bath temperature = 98 °C) under N_2 for 18 h. After cooling to rt, excess *tert*-butyl alcohol was removed by rotary evaporation, 100 mL of H_2O and 120 mL of CH_2Cl_2 were added, the layers were separated, and the aqueous layer was washed with CH_2Cl_2 (4 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by LPC (5 × 38 cm column; hexanes/EtOAc, 6/1) and recrystallized (hexanes/EtOAc), yielding 3.94 g (62%) of **16** as a white powder: mp 90–90.5 °C (lit.[18] mp 91–92 °C); ^1H NMR δ 9.38 (br s, 1 H), 7.36–7.42 (m, 5 H), 5.32 (s, 2 H), 3.67 (s, 3 H), 3.01 (t, 2 H, J = 7.4), 2.50 (t, 2 H, J = 7.4), 2.29 (s, 3 H), 1.57 (s, 9 H).

***tert*-Butyl 3-(2′-(Methoxycarbonyl)ethyl)-4-methylpyrrole-2-carboxylate (18).** Iodopyrrole **17** (34.40 g, 87.5 mmol), obtained by hydrogenolysis and iodinative decarboxylation of **16**,[18] was dissolved in 200 mL of methanol, and 17.6 g (500 mol %) of MgO followed by 1.7 g of PtO_2 was added. The mixture was hydrogenated at 50 psi until starting material was no longer detected by TLC (hexanes/EtOAc, 2/1). It was then filtered through Celite and evaporated, and the residue was purified by LPC (hexanes/EtOAc, 2/1), affording 22.59 g (97%) of a viscous yellow oil, which slowly solidified: mp 61.5–63 °C; ^1H NMR δ 8.85 (br s, 1 H), 6.63 (d, 1 H, J = 2.6), 3.67 (s, 3 H), 3.01 (t, 2 H, J = 7.5), 3.52 (t, 2 H, J = 7.5), 2.03 (d, 3 H, J = 0.5), 1.56 (s, 9 H). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.9; H, 7.9; N, 5.2. Found: C, 62.8; H, 7.7; N, 5.2.

A preparation of **18** has been reported;[18] however, experimental details and full characterization were not provided.

Dibenzyl Tartrate. To a 500-mL round-bottomed flask equipped with a Dean–Stark trap, a reflux condensor, a N_2 bubbler, and a stir bar were added 37.75 g (0.25 mol) of *d*-tartaric acid, 46.5 g (195 mol %) of benzyl alcohol, 2.37 g (5 mol%) of *p*-toluenesulfonic acid monohydrate, and 110 mL of benzene. The solution was refluxed until evolution of H_2O had ceased (20 h) and was then brought to rt. Isooctane (100 mL) was added, and the precipitate was filtered off and then redissolved in 300 mL of EtOAc. After being washed with saturated $NaHCO_3$ (2 × 75 mL) and saturated NaCl (2 × 50 mL), the organic solution was dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in 200 mL of toluene, and the product was precipitated out by addition of 200 mL of isooctane. After filtration and drying under high vacuum (0.05 mm), 46.02 g (56%) of a white solid was obtained: mp 50–50.5 °C; ^1H NMR δ 7.35 (s, 5 H), 5.26 (d, 2 H, J = 2.8), 4.61 (s, 1 H). Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.4; H, 5.5. Found: C, 65.3; H, 5.4.

Dibenzyl tartrate has previously been characterized only as white flakes.[50]

Benzyl Glyoxylate (21). To a solution of dibenzyl tartrate (4.13 g, 12.5 mmol) in 30 mL of diethyl ether was added 2.85 g (100 mol %) of periodic acid dihydrate, and the solution was stirred at rt for 15 min. After filtration, the filtrate was washed with saturated $NaHCO_3$ (15 mL) and saturated NaCl (15 mL), dried ($MgSO_4$), filtered, and evaporated (bath temperature < 35 °C). The residue was Kugelrohr distilled at 90 °C (0.1 mm), and the viscous, clear liquid (2.94 g, 72%) that condensed in the dry ice/acetone-cooled receiver bulb was used directly in the next reaction: ^1H NMR δ 9.40 (s, 1 H), 7.33–7.43 (m, 5 H), 5.33 (s, 2 H).

Treatment of a dibenzyl fumarate/maleate mixture with ozone followed by dimethyl sulfide gives a 36% yield of benzyl glyoxalate.[19]

Benzyl α-Hydroxy-α-(5-(*tert*-butoxycarbonyl)-4-(2′-(methoxycarbonyl)ethyl)-3-methylpyrrol-2-yl)acetate (23). To 150 mL of CH_2Cl_2 was added 12.31 g (46.1 mmol) of α-unsubstituted pyrrole **18** followed by 11.34 g (150 mol %) of benzyl glyoxylate (**21**) dissolved in 50 mL of CH_2Cl_2. After addition of 0.15 g (2 mol %) of $ZnCl_2$, the mixture was stirred at rt under N_2 until the reaction appeared complete by TLC (8 h; $CHCl_3$/Et_2O, 9/1). The solution was washed with saturated $NaHCO_3$ (100 mL), 10% (wt/wt) aqueous $NaHSO_3$ (2 × 75 mL), and H_2O (100 mL). After drying ($MgSO_4$), filtration, and evaporation of the solution, the residue was purified by LPC ($CHCl_3$/Et_2O, 9/1), yielding 17.09 g (86%) of a viscous orange oil: ^1H NMR δ 8.97 (br s, 1 H), 7.22–7.37 (m, 5 H), 5.17–5.28 (m, 3 H), 3.66 (s, 3 H), 3.49 (br s, 1 H), 2.98 (t, 2 H, J = 7.8), 2.50 (t, 2 H, J = 7.7), 1.98 (s, 3 H), 1.55 (s, 9 H); high-resolution EI MS m/z calcd for $C_{23}H_{29}NO_7$ (M^+) 431.1944, found 431.1953.

In some runs, the desired alcohol pyrrole **23** was accompanied by varying amounts of a less polar side product, identified as keto pyrrole **25**: yellowish solid; mp 103–104 °C; ^1H NMR δ 7.36–7.44 (m, 5 H), 5.37 (s, 2 H), 3.66 (s, 3 H), 3.02 (t, 2 H, J = 7.5), 2.50

(41) General methods correspond to those previously described (see ref 15). In addition, CH_2Cl_2, *p*-xylene, diisopropylethylamine, and glyme were distilled from CaH_2. Dimethyl sulfide was distilled from sodium and chloroform was distilled from P_2O_5. *N*-Chlorosuccinimide was recrystallized from benzene while triphenylphosphine was recrystallized from absolute ethanol. Low-pressure chromatography (LPC) was carried out on EM Reagents silica gel 60, 230–400 mesh. All NMR spectra were recorded at 500 MHz in $CDCl_3$ unless otherwise noted.

(42) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.
(43) Gordon, M. S.; Binkley, J. S.; Pople, J. A.; Pietro, W. J.; Hehre, W. J. *J. Am. Chem. Soc.* **1982**, *104*, 2797.
(44) Pietro, W. J.; Francl, M. M.; Hehre, W. J.; DeFrees, D. J.; Pople, J. A.; Binkley, J. S. *J. Am. Chem. Soc.* **1982**, *104*, 5039.
(45) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.
(46) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654.
(47) MOPAC was developed by J. J. P. Stewart at the Frank J. Seiler Research Laboratory of the U.S. Air Force Academy and obtained through the Quantum Chemistry Program Exchange QCPE 455.
(48) Dewar, M. J. S.; Reynolds, C. H. *J. Comput. Chem.* **1986**, *7*, 140.
(49) Isler, O.; Gutmann, H.; Montavon, M.; Rüegg, R.; Ryser, G.; Zeller, P. *Helv. Chim. Acta* **1957**, *40*, 1242.
(50) Medinger, R. *J. Prakt. Chem.* **1912**, *86*, 345.

(t, 2 H, J = 7.5), 2.31 (s, 3 H), 1.59 (s, 9 H). Anal. Calcd for $C_{23}H_{27}NO_7$: C, 64.3; H, 6.3; N, 3.3. Found: C, 64.1; H, 6.3; N, 3.2.

Benzyl α-(Triphenylphosphoranylidene)-α-(5-(*tert*-butoxycarbonyl)-4-(2'-(methoxycarbonyl)ethyl)-3-methylpyrrol-2-yl)acetate (1). To 300 mL of CH_2Cl_2 were added 13.15 g (250 mol %) of *N*-chlorosuccinimide and 8.0 mL (275 mol %) of dimethyl sulfide. The solution was brought to 5 °C, and pyrrolyl carbinol **23** (17.01 g, 39.4 mmol) dissolved in 200 mL of CH_2Cl_2 was added dropwise over 30 min. The solution was stirred under N_2 in the dark for 12 h at 5 °C, and then triphenylphosphine (72.58 g, 700 mol %), dissolved in 300 mL of CH_2Cl_2, was added in one portion, and the solution was stirred at rt for 24 h. The ylide was generated by washing with saturated Na_2CO_3 (2 × 200 mL). The organic phase was washed with 100 mL of H_2O and 100 mL saturated NaCl, dried ($MgSO_4$), filtered, and evaporated. Purification by LPC (hexanes/EtOAc, 6/1, gradient to 2/1) yielded 14.18 g (53%) of ylide **1** as an amorphous, light yellow foam, mp 60 °C (lit.[6] mp 65 °C). Additionally 2.16 g (12%) of **23** was recovered, suitable for recycle: ^{1}H NMR δ 8.14 (br s, 1 H), 7.31–7.67 (m, 20 H), 4.95 (br s, 2 H), 3.61 (s, 3 H), 2.82 (br s, 2 H), 2.29 (br s, 2 H), 1.59 (s, 3 H), 1.44 (s, 9 H); high-resolution FAB MS m/z calcd for $C_{41}H_{43}NO_6P$ (MH^+) 676.2828, found 676.2858.

***tert*-Butyl Glyoxylate (22).** Ozone was passed through a solution of di-*tert*-butyl fumarate[20] (10.00 g, 43.8 mmol) in 50 mL of CH_2Cl_2 and cooled to −78 °C until the solution turned blue. Excess ozone was swept out by a stream of N_2 until the solution became clear. Dimethyl sulfide (8.4 mL, 300 mol %) was added, and the solution was brought to rt, stirred over Na_2SO_4 for 30 min, filtered, and concentrated by rotary evaporation (bath temperature <40 °C). The crude material (14.5 g) contained approximately 68% of glyoxylate ester **22** and 32% of DMSO, as measured by integration of the ^{1}H NMR spectrum and was used directly in the next reaction: ^{1}H NMR δ 9.31 (s, 1 H), 1.57 (s, 9 H). A previously described procedure[20] for the conversion of di-*tert*-butyl fumarate to **22** necessitates a two-step procedure, is less convenient, and affords only a 14% yield.

***tert*-Butyl α-Hydroxy-α-(5-(*tert*-butoxycarbonyl)-4-(2'-(methoxycarbonyl)ethyl)-3-methylpyrrol-2-yl)acetate (24).** To 90 mL of CH_2Cl_2 were added 10.00 g (37.41 mmol) of pyrrole **18**, freshly generated crude *tert*-butyl glyoxylate (**22**, 87.6 mmol, 234 mol %, based on di-*tert*-butyl fumarate), and 0.50 g (10 mol %) of $ZnCl_2$. The solution was stirred under N_2 at rt for 24 h, washed with 30 mL of saturated $NaHCO_3$, 10% (wt/wt) aqueous $NaHSO_3$ (2 × 30 mL), and saturated NaCl (20 mL), dried (Na_2SO_4), filtered, and evaporated. Low-pressure chromatography ($CHCl_3$/Et_2O, 19/1) yielded 12.08 g (81%) of pyrrolylcarbinol **24** as a viscous orange oil, which eventually solidified: ^{1}H NMR δ 8.83 (br s, 1 H), 5.10 (d, 1 H, J = 3.9), 3.44 (d, 1 H, J = 4.1), 3.67 (s, 3 H), 3.00 (t, 2 H, J = 7.7), 2.51 (t, 2 H, J = 7.5), 2.03 (s, 3 H), 1.56 (s, 9 H), 1.44 (s, 9 H). Anal. Calcd for $C_{20}H_{31}NO_7$: C, 60.4; H, 7.9; N, 3.5. Found: C, 60.4; H, 7.8; N, 3.5.

***tert*-Butyl α-(Triphenylphosphoranylidene)-α-(5-(*tert*-butoxycarbonyl)-4-(2'-(methoxycarbonyl)ethyl)-3-methylpyrrol-2-yl)acetate (13).** To 215 mL of CH_2Cl_2 and 11.63 g (250 mol %) of *N*-chlorosuccinimide at 0 °C was added 7.0 mL (275 mol %) of dimethyl sulfide over 10 min. Pyrrolylcarbinol **24** (13.85 g, 34.8 mmol) dissolved in 150 mL of CH_2Cl_2 was added dropwise over 30 min. The solution was stirred under N_2 in the dark for 6 h at 5 °C, triphenylphosphine (63.98 g, 700 mol %) dissolved in 400 mL of CH_2Cl_2 was added in one portion, and the solution was stirred for 24 h in the dark at room temperature. The solution was washed with 50% (wt/wt) aqueous Na_2CO_3 (2 × 300 mL), H_2O (50 mL), and saturated NaCl (50 mL). The organic phase was evaporated, removing the dimethyl sulfoxide by Kugelrohr distillation (0.05 mm, 45 °C), and the residue, dissolved in 100 mL of EtOAc, was filtered and applied to an LPC column. The product was eluted with hexanes/EtOAc, 3/1 to 1/1, yielding 12.42 g (50%) of a yellowish solid: mp 71–73 °C; ^{1}H NMR δ 8.09 (br s, 1 H), 7.40–7.54 (m, 15 H), 3.63 (s, 3 H), 2.79 (br t, 2 H, J = 7.5), 2.29 (br t, 2 H, J = 7.5), 1.62 (s, 9 H), 1.49 (s, 3 H), 1.47 (s, 9 H); high-resolution FAB MS m/z calcd for $C_{38}H_{45}NO_6P$ (MH^+) 642.2985, found 642.2969.

On exposure to silica gel, slow transformation of the ylide to the higher R_f methylene derivative **27** (mp 91–93 °C) was observed. The amount of contaminent appeared to be <5% by NMR: ^{1}H NMR δ 9.23 (br s, 1 H), 3.67 (s, 3 H), 3.49 (s, 2 H), 2.99 (t, 2 H, J = 8.3), 2.52 (t, 2 H, J = 8.3), 1.95 (s, 3 H), 1.56 (s, 9 H), 1.47 (s, 9 H). Anal. Calcd for $C_{20}H_{31}NO_6$: C, 63.0; H, 8.2; N, 3.7. Found: C, 62.8; H, 8.3; N, 3.6.

Condensation of Ylide 1 and Thioimide 2. To 25 mL of *p*-xylene was added 894 mg (150 mol %) of ylide **1** and 137 mg (0.88 mmol) of monothiosuccinimide **2**.[15] The solution was brought to reflux under N_2 with magnetic stirring until **2** was no longer detectable by TLC (isooctane/Et_2O, 1/1; 5 h). The solution was then evaporated and purified by LPC (hexanes/EtOAc, 3/1), affording three products. The least polar material was triphenylphosphine sulfide; the most polar was excess ylide. The second fraction was mostly pyrromethenone **3**,[3,6] which could be recrystallized from hexanes/Et_2O, providing 285.4 mg (61%) of a light yellow powder: mp 131–133 °C (lit.[3] mp 137–138 °C); ^{1}H NMR δ 10.81 (br s, 0.5 H), 10.73 (br s, 0.5 H), 8.62 (br s, 0.5 H), 8.49 (br s, 0.5 H), 7.19–7.32 (m, 5 H), 5.05–5.34 (m, 3 H), 3.65 (s, 3 H), 3.13 (br q, 1 H, J = 7.0), 3.03 (br t, 2 H), 2.54 (t, 2 H, J = 7.6), 1.80 (s, 3 H), 1.69 (d, 3 H, J = 7.2), 1.57 (s, 9 H), 1.36 (d, 3 H, J = 7.7).

Condensation of Ylide 13 and Thioimide 2. Monothiosuccinimide **2**[15] (192 mg, 1.24 mmol) and 1.190 g (150 mol %) of ylide **13** were treated as described for the condensation of **1** and **2** (TLC: hexanes/EtOAc, 1/1). After 5 h, evaporation and LPC (isooctane/Et_2O, 19/1 gradient to 3/1) gave the following five products in order of elution: (1) triphenylphosphine, 217 mg (67%); (2) triphenylphosphine sulfide, 138 mg (38%); (3) thioimidate **29**, 357 mg (54%) a viscous orange oil as a 1.5/1 mixture of diastereomers: ^{1}H NMR δ 9.71, 9.57 (br s, 1 H), 7.21 (m, 1 H), 6.79, 6.62 (s, 1 H), 3.66, 3.65 (s, 3 H), 3.41 (br q, 1 H), 2.94 (br t, 2 H, J = 7.4), 2.50, 2.34 (t, 2 H, J = 7.4), 2.10, 2.08 (s, 3 H), 1.94, 1.93 (d, 3 H, J = 7.6), 1.55 (s, 9 H), 1.46 (d, 3 H, J = 7.0), 1.43, 1.42 (s, 9 H); high-resolution EI MS m/z calcd for $C_{27}H_{38}N_2O_7S$ (M^+) 534.2400, found 534.2415. Anal. Calcd for $C_{27}H_{38}N_2O_7S$: C, 60.7; H, 7.2; N, 5.2. Found: C, 60.9; H, 7.2; N, 5.3.

The fourth product was pyrromethenone (*Z*)-**28**, 236 mg (38%). This thio-Wittig product was a yellow powder: mp 184.5–186 °C; ^{1}H NMR (1/1 mixture of rotamers, severely broadened) δ 10.84 (br s, 0.5 H), 10.74 (br s, 0.5 H), 8.90 (br s, 0.5 H), 8.72 (br s, 0.5 H), 5.28 (br q, 0.5 H), 5.05 (br s, 0.5 H), 3.66 (s, 3 H), 3.11 (q, 1 H, J = 7.4), 3.03 (br t, 2 H, J = 7.8), 2.52 (br t, 2 H, J = 7.6), 1.81 (s, 1.5 H), 1.84 (s, 1.5 H), 1.67 (d, 3 H, J = 7.2), 1.57 (s, 9 H), 1.39 (s, 9 H), 1.36 (m, 3 H). Anal. Calcd for $C_{27}H_{38}N_2O_7$: C, 64.5; H, 7.6; N, 5.6. Found: C, 64.9; H, 7.6; N, 5.6.

The fifth product was recovered ylide **13** (132 mg, 11%).

Photoisomerization of (*Z*)-28 to (*E*)-28. A solution of (*Z*)-**28** (0.87 g, 1.6 mmol) in 90 mL of EtoAc was placed in a Pyrex photochamber and irradiated (400-W Hanovia lamp) for 1 h with magnetic stirring as a stream of N_2 was bubbled through the solution. Further irradiation did not change the ratio of (*Z*)-**28** (R_f 0.66) to (*E*)-**28** (R_f 0.61) (TLC, hexane/EtOAc, 1/1). After two repetitions of this process with recovered (*Z*)-**28**, a total of 0.47 g, 54% yield, of (*E*)-**28** was obtained after LPC: mp 166–167 °C; ^{1}H NMR δ 8.63 (s, 1 H), 7.12 (br q, 1 H, J = 7.4), 7.04 (s, 1 H), 3.27 (br q, 1 H, J = 7.6), 2.94 (t, 2 H, J = 8.4), 2.43 (t, 2 H, J = 8.3), 1.90 (d, 3 H, J = 7.4), 1.89 (s, 3 H), 1.57 (s, 9 H), 1.454 (s, 9 H), 1.448 (s, 9 H), 1.39 (d, 3 H, J = 7.4). Anal. Calcd for $C_{30}H_{44}N_2O_7$: C, 66.2; H, 8.1; N, 5.1. Found: C, 66.3; H, 8.2; N, 5.0.

When (*E*)-**28** (10 μmol) was dissolved in CH_2Cl_2 (5 mL) and exposed to acid (TFA, 300 mol %) or base (DBU, 20 mol %), complete isomerization of (*E*)-**28** back to (*Z*)-**28** was observed in 5 min at 0 °C in base and at rt in acid, by TLC and NMR.

Attempted Sulfur Contraction of 29. Thioimidate **29** (176 mg, 0.33 mmol) was dissolved in 5.3 mL of benzene, and 0.22 g (255 mol %) of triphenylphosphine was added followed by 0.17 mL (290 mol %) of diisopropylethylamine. After refluxing for 48 h under nitrogen, the solution was evaporated and the residue was redissolved in 5.3 mL of toluene. The solution was heated to reflux for 24 h. A higher R_f material was detected by TLC (isooctane/Et_2O, 1/1) along with unreacted starting materials. After concentration, the mixture was purified by LPC (isooctane/Et_2O, 5/1), yielding 37 mg (22%) of double-bond regioisomer **30** as an orange oil: ^{1}H NMR (two rotomers) δ 9.59,

9.14 (br s, 1 H), 6.48, 4.93 (s, 1 H), 3.66 (s, 3 H), 2.97, 2.96 (t, 2 H, J = 8.0), 2.59 (q, 2 H, J = 7.8), 2.49 (t, 2 H, J = 7.9), 2.10, 2.05 (s, 3 H), 1.97, 1.94 (s, 3 H), 1.56, 1.55 (s, 9 H), 1.40 (s, 9 H), 1.11 (t, 3 H, J = 7.6); high-resolution EI MS m/z calcd for $C_{27}H_{38}N_2O_7S$ 534.2400, found 534.2398.

Condensation of Ylide 13 and Thioimide 9. *cis*-Dihydromonothiosuccinimide **9**[15] (67 mg, 0.43 mmol) and 413 mg (150 mol%) of ylide **13** were treated as described for the condensation of **1** and **2** for 8 h (TLC: isooctane/Et_2O, 1/1; anisaldehyde stain). After concentration, the four least polar products were isolated by LPC (isooctane/Et_2O, 4/1 gradient to 1/1). In order of elution: (1) triphenylphosphine, 112 mg (26%); (2) monothiomaleimide **11**, 22 mg (34%);[15] (3) a mixture of triphenylphosphine sulfide and adduct (*Z*)-**31** [the latter product was synthesized and characterized separately (see below)]; (4) methylenepyrrole **27**, 51 mg (32%). This product had been previously isolated and characterized (see above).

Condensation of Ylide 13 and Thioimide 10. *trans*-Dihydromonothiosuccinimide **10**[15] (60 mg, 0.38 mmol) and 367 mg (150 mol%) of ylide **13** were treated as described for the condensation of **1** and **2** for 8 h. The mixture was then evaporated, and the residue was purified by LPC (isooctane/Et_2O, 1/1). The higher R_f material was 66 mg (67%) of triphenylphosphine, while the more polar material, 149 mg (73%) of a yellow oil, was identified as thioimidate **32**: ^{1}H NMR (1/1 mixture of diastereomers) δ 9.60, 9.58 (br s, 1 H), 6.61, 6.59 (s, 1 H), 3.66 (s, 3 H), 2.97 (br t, 2 H, J = 8.3), 2.84, 2.78 (m, 1 H, J = 7.1, 4.5), 2.51, 2.50 (t, 2 H, J = 7.9), 2.36 (m, 1 H), 2.07, 2.06 (s, 3 H), 1.89, 1.68 (m, 2 H), 1.55 (s, 9 H), 1.49, 1.45 (d, 3 H, J = 7.2), 1.42 (s, 9 H), 1.05, 1.00 (t, 3 H, J = 7.5); high-resolution EI MS m/z calcd for $C_{27}H_{40}N_2O_7S$ (M^+) 536.2556, found 536.2560. Anal. Calcd for $C_{27}H_{40}N_2O_7S$: C, 60.4; H, 7.5; N, 5.2. Found: 60.3; H, 7.5; N, 5.2.

Condensation of Ylide 13 and Thioimide 11. Freshly prepared monothiomaleimide **11**[15] (20 mg, 0.134 mmol) and 126 mg (150 mol %) of ylide **14** were treated as described for the condensation of **1** and **2** for 8 h. After evaporation, the two products were isolated by LPC (isooctane/Et_2O, 1/1). The higher R_f spot was triphenylphosphine sulfide. The lower R_f product, (*Z*)-**31**, was isomerized under these purification conditions to an approximately 1/1 mixture of double bond isomers (*Z*)-**31** and (*E*)-**31**: 64.2 mg, 97% yield; ^{1}H NMR δ 9.72, 9.66 (br s, 1 H), 8.96, 8.85 (br s, 1 H), 3.69, 3.66 (s, 3 H), 3.01 (br t, 2 H), 2.54, 2.52 (t, 2 H, J = 7.4), 2.37, 2.35 (q, 2 H, J = 7.1), 2.15, 1.97, 1.88, 1.53 (s, 6 H), 1.56 (s, 9 H), 1.41, 1.37 (s, 9 H), 1.10, 1.06 (t, 3 H, J = 7.6); high-resolution FAB MS m/z calcd for $C_{27}H_{39}N_2O_7$ (MH^+) 503.2757, found 503.2728. Anal. Calcd for $C_{27}H_{38}N_2O_7$: C, 64.5; H, 7.6; N, 5.6. Found: C, 64.7; H, 7.8; N, 5.2.

Condensation of Ylide 14 and Monothiosuccinimide 12. Monothiosuccinimide **12**[15] (74 mg) and 215 mg (100 mol %) of ylide **14**[49] were treated as described for the condensation of **1** and **2** for 4 h. By TLC (hexanes/EtOAc, 1/1) a small amount of starting material **12** was observed as well as a large quantity of a black, base-line precipitate. After concentration, two products were isolated by LPC (hexanes/EtOAc, 1/1). The higher R_f material was triphenylphosphine sulfide. The lower R_f material was identified as 16 mg (17%) of vinylogous carbamate (*Z*)-**33**. Prolonged exposure to silica gel resulted in slow isomerization to the more polar *E* isomer.

^{1}H NMR (for (*Z*)-**33**), δ 8.00 (br s, 1 H), 5.32 (d, 1 H, J = 2.0), 3.69 (s, 3 H), 3.30 (dt, 2 H, J = 5.0, 2.0), 2.57 (t, 2 H, J = 5.0); high-resolution EI MS m/z calcd for $C_7H_9NO_3(M^+)$ 155.0582, found 155.0577.

^{1}H NMR (for (*E*)-**35**): 9.86 (br s, 1 H), 5.02 (d, 1 H, J = 1.1), 3.71 (s, 3 H), 2.89 (t, 2 H, J = 5.0), 2.55 (dt, 2 H, J = 5.2, 0.9); high-resolution EI MS m/z calcd for $C_7H_9NO_3$ (M^+) 155.0582, found 155.0584.

Condensation of Ylide 14 and Thioimide 10. *trans*-Dihydromonothiosuccinimide **10**[15] (104 mg, 0.66 mmol) and 222 mg (100 mol %) of ylide **14**[49] were treated as described for the condensation of **1** and **2** for 4 h. The solution was concentrated, and the residue was purified by LPC (isooctane/Et_2O, 4/1). The high R_f band was recrystallized from isooctane/Et_2O, and 26.0 mg (13%) of triphenylphosphine sulfide was obtained. The mother liquors contained 68 mg (65%) of starting material **10**. A lower R_f product band contained 11 mg (9%) of adduct **34**: ^{1}H NMR δ 8.98 (br s, 1 H), 5.36 (s, 1 H), 3.78 (s, 3 H), 2.38 (q, 2 H, J = 7.6), 2.01 (s, 3 H), 1.11 (t, 3 H, J = 7.6); high-resolution EI MS m/z calcd for $C_{10}H_{13}NO_3$ (M^+) 195.0895, found 195.0898.

Condensation of Ylide 14 and Thioimide 5. To 5.0 mL of toluene were added 78 mg (0.51 mmol) of thioimide **5** and 188 mg (111 mol %) of ylide **14**.[49] The solution was brought to reflux for 3.5 h under N_2. Thioimide **5** was no longer detectable by TLC (hexanes/EtOAc, 1/1). After concentration, the residue was purified by LPC (hexanes/EtOAc, 5/1), affording the high R_f triphenylphosphine sulfide and the lower R_f, double bond isomerized coupling product **34** (44 mg, 45%), identical with material reported above.

Condensation of Ylide 14 and Thioimide 2. To 5 mL of toluene were added 77 mg (0.5 mmol) of monothiosuccinimide **2** and 184 mg (110 mol %) of ylide **14**.[49] The mixture was brought to reflux for 3.5 h under N_2. TLC (hexanes/EtOAc, 1/1) showed no remaining **2** and the presence of triphenylphosphine sulfide and coupling product **35**, obtained as a yellow oil after concentration and LPC (hexanes/EtOAc, 5/1): 19.3 mg, 20% yield; ^{1}H NMR δ 9.01 (br s, 1 H), 5.33 (s, 1 H), 3.72 (s, 3 H), 2.36 (q, 2 H, J = 7.5), 1.88 (s, 3 H), 1.08 (t, 3 H, J = 7.6); high-resolution EI MS m/z calcd for $C_{10}H_{13}NO_3$ (M^+) 195.0895, found 195.0890.

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Supplementary Material Available: ^{1}H NMR spectra for **13**, **23**, **30**, (*E*)-**33**, (*Z*)-**33**, **34**, and **35** (7 pages). Ordering information is given on any current masthead page.