Notes

Phosphine-Catalyzed Annulation of Thioamides and 2-Alkynoates: A New Synthesis of Thiazolines

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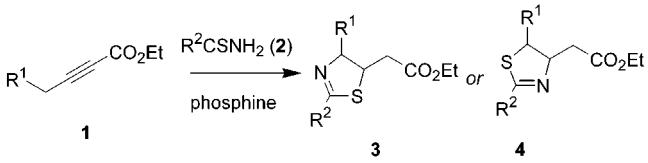
Abstract: The annulation of thioamides with 2-alkynoates and 2,3-dienoates under the catalysis of tri-*n*-butylphosphine was described. The annulation reaction provided a new entry to thiazolines, particularly those with 2-aryl substituents.

Thiazolines are important structural moieties present in many natural products that exhibit significant biological activities.[1] Notable examples are thiangazole[2] and curacin A,[3] which show antiviral and antiproliferative activities, respectively. The synthesis of thiazolines has therefore attracted much research interest.[4] A number of elegant approaches to make these heterocycles have been developed over the years. The most commonly used methods include cyclodehydration of β-hydroxythioamides[5] or cysteine amides[6] and condensation of 2-aminothiols with nitriles,[7] carboxylic acids,[8] esters,[9] or iminoesters.[10] Thiazolines have also been prepared from hydroxyamides with Lawesson's reagent.[11] Most recently, a ruthenium-catalyzed oxidation of thiazolidine to thiazoline has also been described.[12] However, we were interested in a straightforward synthesis of thiazolines from the annulation of electron-deficient alkynes and thioamides (Scheme 1).[13] Phosphines are known to impart bielectrophilic character to the electron-deficient alkynes and promote the γ-addition of nucleophiles to these alkynes.[14] Carbon,[15] nitrogen,[16] and oxygen pronucleophiles[17] have all been shown to undergo the addition reaction. We anticipated that γ-addition and subsequent cyclization would occur when binucleophilic thioamides were used in the reaction sequence, leading to thiazolines **3** or **4**.

Scheme 1. Annulation of Thioamides with 2-Alkynoates



To test the feasibility of this approach, ethyl 2-butynoate (**1a**) was reacted with 4-trifluoromethylthiobenzamide (**2a**) in the presence of phosphine catalysts. By simply heating a mixture of **1a** (1.2 equiv) and **2a** with triphenylphosphine (10 mol %) in toluene at reflux for 14 h, thiazoline **3a** was isolated in 66% yield. The more nucleophilic *n*-Bu_3P promotes the cyclization at room temperature in slightly better yield. Tricyclohexylphosphine and tri-*o*-tolylphosphine also function but offer no advantage. It appears that phosphine is essential for the annulation to occur since no reaction was detected without Ph_3P even after 48 h at reflux.[18] We finally chose *n*-Bu_3P as the catalyst for annulation of thioamides with 2-alkynoates, due to the mild conditions and operational simplicity. It is noteworthy that no simple Michael-type adduct of thioamide with 2-butynoate was observed.

The annulation reaction appears to be applicable for a variety of aromatic thioamides (Table 1). Aryl thioamides with electron-withdrawing and electron-donating substituents, heteroaryl thioamide such as 2-thienyl (**2d**) and 3-pyridyl (**2e**) all participated well to give thiazolines in good yield. Aliphatic thioamides such as thioacetamide (**2f**) did not undergo a clean cyclization with ethyl 2-butynoate, with only 21% of thiazoline **3f** isolated. However, trifluorothioacetamide (**2g**) reacted with 2-butynaote to give thiazoline **3g** in 54% yield.

Other 2-alkynoates were also studied to probe the scope of the annulation reaction. Ethyl 2-pentynoate (**1b**) underwent a smooth coupling with thiobenzamide to give two regioisomers, thiazoline **3h** (17%) and thiazoline **5a**

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(18) Tertiary amines such as DABCO did not catalyze the formation of thiazolines.

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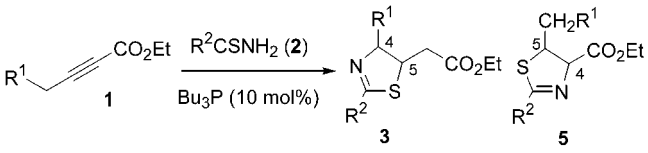
Table 1. Bu_3P-Catalyzed Annulation of Thioamides and 2-Alkynoates[a]



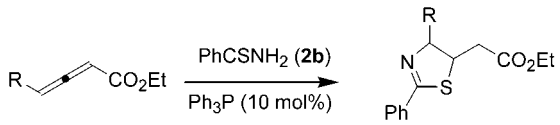
R^1	R^2	product (yield, %)
H (**1a**)	*p*-$CF_3C_6H_4$ (**2a**)	**3a** (82)
H (**1a**)	Ph (**2b**)	**3b** (64)
H (**1a**)	*p*-$MeOC_6H_4$ (**2c**)	**3c** (67)
H (**1a**)	3-pyridyl (**2d**)	**3d** (86)
H (**1a**)	2-thienyl (**2e**)	**3e** (70)
H (**1a**)	Me (**2f**)	**3f** (21)
H (**1a**)	CF_3 (**2g**)	**3 g** (54)
Me (**1b**)	Ph (**2b**)	**3h** (17, cis/trans 1:3) + **5a** (51, cis/trans 1:3)

[a] Reactions were run at 0.2 M with 1.2 equiv of alkynoate and 10 mol % of Bu_3P in toluene at room temperature for 24 h.

(51%), respectively. The reaction was not highly diastereoselective, as both **3h** and **5a** were a mixture of stereoisomers with the cis to trans ratio of 1:3. The differentiation between **3h** and its regioisomer **4** in which S and N transpose each other was achieved by HMQC and HMBC analysis. HMQC data of *trans*-**3h** indicated that the protons H-4 (δ 4.48 ppm) and H-5 (δ 3.86 ppm) were connected to carbons at δ 76.6 ppm (C-4) and δ 52.3 ppm (C-5), respectively.[19] In the HMBC spectrum, the H-5 showed a correlation to the carbonyl group (δ 170.9 ppm). Similar correlations were observed in the HMQC and HMBC spectra of *cis*-**3h**, which ruled out **4** as the regioisomer. In the HMBC spectrum of *trans*-**5a**, the resonance (δ 0.96 ppm) attributable to the methyl group (R^1) showed a correlation to C-5 (δ 55.3 ppm), which confirmed that ethyl was attached to C-5. The stereochemistry was assigned by comparison of the coupling constant values for H-4 and H-5 ($J_{4,5}$) in the thiazoline ring to those reported in the literature for trans- and cis-substituted thiazoline-5-methyl-4-carboxylic acids.[20] Accordingly, *cis*-**3h** ($J_{4,5} = 7.0$ Hz) and *cis*-**5a** ($J_{4,5} = 8.5$ Hz) have higher coupling constants than *trans*-**3h** ($J_{4,5} = 4.5$ Hz) and *trans*-**5a** ($J_{4,5} = 5.0$ Hz), respectively. Formation of **5a** prompted us to explore 2-alkynoates without γ−H because they are prone to α-addition.[21] Methyl propiolate, di-*tert*-butyl acetylenedicarboxylate, and methyl phenylpropiolate failed to participate in the annulation with thiobenzamide. In all cases, decomposition of starting materials was observed in the presence of *n*-Bu_3P, *o*-Tol_3P, or Cy_3P, indicating that 2-alkynoates with γ−H, particularly 2-butynoate, are more amenable to annulation with thioamides.

2-Alkynoates with γ-hydrogen undergo isomerization to allenoates and 2,3-dienoates in the presence of phosphine.[22] It has been shown that 2,3-butadienoates also react with carbon and oxygen pronucleophiles in a γ-addition manner.[23] We next examined the annulation of allenoates with thiobenzamide (Scheme 2). In contrast to 2-butynoate, coupling of ethyl 2,3-butadienoate (**6a**)

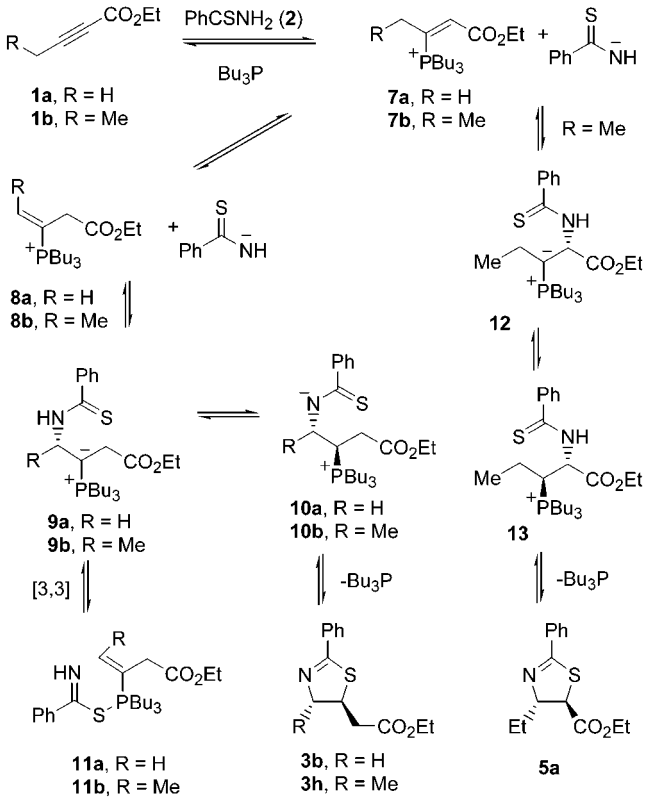
Scheme 2. Annulation of Thiobenzamide with 2,3-Dienoates



6a, R = H
6b, R = Me

3b, R = H, 54%
3h, R = Me, 28% (*cis*/*trans* 1:3)

Scheme 3. Proposed Mechanism of Annulation of Thioamides with 2-Alkynoates



with thiobenzamide occurred at room temperature even with the less nucleophilic Ph_3P as catalyst. However, the reaction led to uncharacterized byproducts, and **3b** was isolated in a significantly lower yield (23%), probably due to the higher reactivity of allenic esters. Through the slow addition of **6a** via a syringe pump over 4 h to a mixture containing thiobenzamide and Ph_3P in toluene at room temperature, annulation reaction occurred smoothly and thiazoline **3b** could be obtained in 54% yield. In the case of ethyl 2,3-pentadienoate (**6b**), thiazoline **3h** was obtained as a mixture of diastereomers (cis/trans 1:3) in modest yield, mainly due to the dimerization of 2,3-pentadienoate. Interestingly, thiazoline **5a**, the major product from the annulation of thiobenzamide with 2-pentynoate (**1b**), was not observed in the reaction of thiobenzamide and allenoate **6b**.

The formation of thiazoline in a single step from thioamides and 2-alkynoates can be rationalized mechanistically by addition of the nitrogen nucleophile to the thermodynamically more stable vinylphosphonium intermediates **8**, which is derived from the initially formed vinylphosphonium intermediates **7** directly or via 2,3-dienoates (Scheme 3). Although it is difficult to verify the involvement of allenoates as intermediates due to their

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higher reactivity, the different reaction profile of 2-pentyonate (**1b**) and 2,3-pentadienoate (**6b**) suggests the likely direct conversion of **7** to **8**. From **9**, subsequent proton exchange provides **10**, which undergoes an intramolecular substitution to give thiazolines **3**. Lack of formation of thiazoline isomers **4** possibly reflects the notion that hard nucleophiles react preferentially in the phosphine-catalyzed γ-addition. In thioamides, nitrogen is therefore more reactive toward the vinylphosphonium intermediates **8** than sulfur.

An alternative account of regioselectivity incurs a pentacoordinated phosphorus intermediate **11**.[24] Thiophilic attack of vinylphosphonium intermediates **8** on the sulfur atom of thioamides would provide **11**, from which a novel polyhetero-Claisen rearrangement occurs to generate phosphonium ylides **9**.[25] In the case of ethyl 2-pentynoate (**1b**), the vinylphosphonium intermediate **7b** reacts preferentially with thioamides, leading to **12** probably due to the slow conversion of **7b** to **8b**. Subsequent proton exchange and cyclization gave **5a** as the major product. Apparently, the diastereoselectivity arises from the proton exchange step, i.e., **9b** → **10b**, where the thermodynamically more stable zwitterionic intermediate *anti*-**10b** forms preferentially, leading to the *trans*-thiazoline **3h** upon cyclization. The low yield of thioacetamide in the thiazoline formation is probably associated with its lower acidity (pK_a 13.40) in comparison to trifluorothioacetamide **2g** (pK_a 11.02), which results in a slower formation of vinylphosphonium intermediates **7** or **8** and therefore allows other side reactions to occur.[26]

In conclusion, we have described a new annulation of thioamides with 2-alkynoates and allenoates in the presence of phosphine catalysts. The annulation works well for aromatic and heteroaromatic thioamides using 2-butynoate as the partner. Efforts to perform the annulation in an enantioselective manner are underway, and the results will be reported in due course.

Experimental Section

All commercial chemicals were used as received. ^{1}H and ^{13}C spectra were recorded using $CDCl_3$ as the solvent unless otherwise stated. Combustion analyses were performed by the Atlantic Microlab, Inc. All reactions were performed under the nitrogen atmosphere unless otherwise stated. Preparative HPLC was used to isolate the cis and trans isomers of **3h** and **5a** for NMR studies. The specific chromatographic conditions were as follows: **3h**: column, Luna C18(2) (Phenomenex), 10 μm, 21.2 × 250 mm; mobile phase (isocratic), water:acetonitrile/TFA (400:600:0.5); flow rate, 19 mL/min; detection, 280 nm; temperature, ambient; retention times, cis 10.0 min, trans 11.9 min. **5a**: column, Waters Sperisorb ODS-2, 10 μm, 20 × 250 mm; mobile phase (isocratic), water/acetonitrile (40:60); flow rate, 19 mL/min; detection, 280 nm; temperature, ambient; retention times, cis 12.5 min, trans 13.4 min.

General Procedure for the Annulation of Thioamides with Ethyl 2-Alkynoate. To a mixture containing thioamides (1 mmol) and ethyl 2-alkynoate (1.2 mmol) in toluene (5 mL) was added 20 mg (0.1 mmol) of tri-*n*-butylphosphine under nitrogen. The resulting mixture was stirred at room temperature overnight. After the removal of solvents, the residue was purified by silica gel chromatography (hexane/ethyl acetate = 9:1) to give thiazolines.

Ethyl [2-(4-trifluoromethylphenyl)-4,5-dihydrothiazol-5-yl]acetate (3a): yellow oil; IR (neat) 2981, 1725, 1320, 1165, 1122, 1064, 841 cm^{-1}; ^{1}H NMR δ 1.29 (t, 3H, J = 7.2 Hz), 2.71 (d, 1H, J = 1.2 Hz), 2.74 (s, 1H), 4.20 (q, 2H, J = 7.2 Hz), 4.30−4.52 (m, 3H), 7.68 (d, 2H, J = 8.1 Hz), 7.94 (d, 2H, J = 8.1 Hz); ^{13}C NMR δ 14.4, 41.2, 47.0, 61.2, 70.1, 125.7, 125.8, 128.8, 136.5, 166.6, 171.1. Anal. Calcd for $C_{14}H_{14}F_3NO_2S$: C, 52.99; H, 4.45; N, 4.41. Found: C, 53.22; H, 4.50; N, 4.33.

Ethyl (2-phenyl-4,5-dihydrothiazol-5-yl)acetate (3b): yellow oil; IR (neat) 2976, 1729, 1604, 1238, 1213, 1175, 1015, 943 cm^{-1}; ^{1}H NMR δ 1.26 (t, 3H, J = 7.2 Hz), 2.68 (d, 2H, J = 8.0 Hz), 4.16 (q, 2H, J = 7.2 Hz), 4.23−4.44 (m, 3H), 7.37−7.46 (m, 3H), 7.80 (d, 2H, J = 7.1 Hz); ^{13}C NMR δ 14.4, 41.3, 46.6, 61.1, 70.0, 128.5, 128.7, 131.5, 133.4, 167.8, 171.3. Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.48; H, 5.88; N, 5.37.

Ethyl [2-(4-methoxyphenyl)-4,5-dihydrothiazol-5-yl]acetate (3c): yellow oil; IR (neat) 2979, 1728, 1605, 1508, 1248, 1169, 1029, 835, 729 cm^{-1}; ^{1}H NMR δ 1.27 (t, 3H, J = 7.1 Hz), 2.68 (d, 1H, J = 0.6 Hz), 2.70 (s, 1H), 3.84 (s, 3H), 4.18 (q, 2H, J = 7.1 Hz), 4.23−4.44 (m, 3H), 6.90 (d, 2H, J = 9.0 Hz), 7.76 (d, 2H, J = 9.0 Hz); ^{13}C NMR δ 14.4, 41.3, 46.6, 55.6, 61.1, 69.9, 114.0, 126.2, 130.2, 162.2, 167.0, 171.3. Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C,59.97; H, 6.20; N, 4.98.

Ethyl [2-(pyridin-3-yl)-4,5-dihydrothiazol-5-yl]acetate (3d): yellow oil; IR (neat) 2980, 1726, 1606, 1415, 1210, 1178, 1015, 946, 703 cm^{-1}; ^{1}H NMR δ 1.24 (t, 3H, J = 7.1 Hz), 2.66 (d, 1H, J = 2.1 Hz), 2.69 (s, 1H), 4.14 (q, 2H, J = 7.1 Hz), 4.25−4.45 (m, 3H), 7.32 (dd, 1H, J = 4.8, 7.8 Hz), 8.06 (dt, 1H, J = 1.8, 7.8 Hz), 8.64 (dd, 1H, J = 1.8, 4.8 Hz), 8.99 (d, 1H, J = 1.8 Hz); ^{13}C NMR δ 14.4, 41.2, 46.9, 61.2, 67.0, 123.6, 129.2, 135.6, 149.6, 152.1, 165.2, 171.1. Anal. Calcd for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.84; H, 5.66; N, 10.95.

Ethyl [2-(thiophen-2-yl)-4,5-dihydrothiazol-5-yl]acetate (3e): yellow oil; IR (neat) 2979, 1726, 1600, 1425,1210, 1177, 1013, 836, 710 cm^{-1}; ^{1}H NMR δ 1.27 (t, 3H, J = 7.1 Hz), 2.70 (d, 1H, J = 1.2 Hz), 2.72 (s, 1H), 4.18 (q, 2H, J = 7.1 Hz), 4.27−4.42 (m, 3H), 7.06 (dd, 1H, J = 3.3, 4.8 Hz), 7.40 (d, 1H, J = 3.3 Hz), 7.46 (d, 1H, J = 4.8 Hz); ^{13}C NMR δ 14.1, 41.1, 47.4, 61.2, 69.5, 127.8, 130.0, 131.0, 137.2, 161.0, 171.2. Anal. Calcd for $C_{11}H_{13}NO_2S_2$: C, 51.74; H, 5.13; N, 5.49. Found: C, 52.04; H, 5.35; N, 5.29.

Ethyl (2-methyl-4,5-dihydrothiazol-5-yl)acetate (3f): yellow oil; IR (neat) 2981, 1729, 1633, 1372, 1179, 1147, 1027, 922, 907 cm^{-1}; ^{1}H NMR δ 1.26 (t, 3H, J = 7.2 Hz), 2.21 (s, 3H), 2.60 (d, 1H, J = 2.4 Hz), 2.62 (s, 1H), 3.98−4.06 (m, 1H), 4.15 (q, 2H, J = 7.2 Hz), 4.12−4.20 (m, 2H); ^{13}C δ NMR 14.4, 20.6, 41.4, 47.7, 61.1, 69.6, 166.5, 171.2. Anal. Cacld for $C_8H_{13}NO_2S$: C, 51.31; H, 7.00; N, 7.48. Found: C, 51.38; H, 7.11; N, 7.37.

Ethyl (2-trifluoromethyl-4,5-dihydrothiazol-5-yl)acetate (3 g): yellow oil; IR (neat) 2985, 1728, 1633, 1376, 1346, 1283, 1188, 1145, 1018, 990, 738 cm^{-1}; ^{1}H NMR δ 1.26 (t, 3H, J = 7.2 Hz), 2.68 (d, 1H, J = 1.6 Hz), 2.70 (s, 1H), 4.16 (q, 2H, J = 7.2 Hz), 4.25−4.31 (m, 1H), 4.34−4.43 (m, 2H); ^{13}C NMR δ 14.4, 40.8, 48.1, 61.5, 69.2, 116.8, 120.4, 159.8, 160.4, 170.6. Anal. Cacld for $C_8H_{10}F_3NO_2S$: C, 39.83; H, 4.18; N, 5.81. Found: C, 39.72; H, 4.23; N, 5.76.

Ethyl (2-phenyl-4-methyl-4,5-dihydrothiazol-5-yl)acetate (3h). *cis*-**3h**: pale yellow oil; IR (neat) 2976, 1729, 1240, 1222, 1175, 1155, 1027, 945, 765, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.19 (t, 3H, J = 7.0 Hz), 1.34 (d, 3H, J = 7.0 Hz), 2.48 (dd, 1H, J = 10.5, 16.5 Hz), 2.86 (dd, 1H, J = 4.5, 16.5 Hz), 4.09 (m, 2H), 4.25 (ddd, 1H, J = 4.5, 7.0, 10.5 Hz), 4.56 (dq, 1H, J = 7.0, 7.0 Hz), 7.46 (m, 2H), 7.52 (m, 1H), 7.74 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 14.0, 15.1, 35.2, 50.0, 60.3, 72.9, 127.8, 128.7, 131.4, 132.8, 164.3, 171.2. Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.52; N, 5.32. Found: C, 63.92; H, 6.52; N, 5.22. *trans*-**3h**: pale yellow oil; IR (neat) 2977, 1729, 1241, 1218, 1177, 1156, 950, 765, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.18 (t, 3H, J = 6.5 Hz), 1.26 (d, 3H, J = 6.5 Hz), 2.60 (dd, 1H, J = 9.5, 17.0 Hz), 2.87 (dd, 1H, J = 5.5, 17.0 Hz), 3.86 (ddd, 1H, J = 4.5, 5.5, 9.5 Hz), 4.09 (q, 2H, J = 6.5 Hz), 4.48 (dq, 1H, J = 4.5, 6.5 Hz), 7.45 (m, 2H), 7.51 (m, 1H), 7.75 (m, 2H). ^{13}C NMR (DMSO-d_6) δ14.0, 19.2, 40.4, 52.3, 60.2, 76.6, 127.9, 128.7, 131.3, 132.8, 163.4, 170.9.

Ethyl 2-phenyl-5-ethyl-4,5-dihydrothiazole-4-carboxylate (5a). *cis*-**5a**: colorless oil; IR (neat) 2965, 1749, 1726, 1447,

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1253, 1232, 1175, 1037, 950, 766, 689 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.92 (t, 3H, J = 7.0 Hz), 1.25 (t, 3H, J = 7.0 Hz), 1.38 (m, 1H), 1.60 (m, 1H), 4.18−4.27 (m, 3H), 5.27 (d, 1H, J = 8.5 Hz), 7.50 (m, 2H), 7.57 (m, 1H), 7.81 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 12.4, 14.1, 24.6, 54.8, 60.7, 80.4, 128.0, 128.8, 131.9, 132.4, 168.0, 168.9. Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.95; H, 6.51; N, 5.14. *trans*-**5a**: colorless oil; IR (neat) 2964, 1732, 1447, 1240, 1176, 1032, 949, 767, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.96 (t, 3H, J = 7.0 Hz), 1.23 (t, 3H, J = 7.0 Hz), 1.66 (m, 1H), 1.81 (m, 1H), 4.16−4.23 (m, 3H), 5.12 (d, 1H, J = 5.0 Hz), 7.50 (m, 2H), 7.57 (m, 1H), 7.81 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 11.8, 14.0, 29.0, 55.3, 61.1, 82.2, 128.1, 128.8, 131.8, 132.4, 168.6, 170.1.

Reaction of Ethyl 2,3-Butadienoate with Thiobenzamide. To a solution containing thiobenzamide (0.27 g, 2.0 mmol) and triphenylphosphine (52 mg, 0.2 mmol) in toluene (5 mL) was added slowly a solution of ethyl 2,3-butadienoate (0.22 g, 2.0 mmol) in toluene (5 mL) over 4 h via a syringe pump. The mixture was then stirred at room temperature overnight. After removal of solvents under reduced pressure, the residue was purified by silica gel chromatography (hexane/ethyl acetate = 9:1) to give 0.27 g (54%) of **3b** as yellow oil.

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Supporting Information Available: The HMQC and HMBC spectral data of *trans*-**3h** and *trans*-**5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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