(n-Butylsulfinyl)benzene (11)[15] [Kugelrohr oven temperature 100–105 °C (4×10^{-2} Torr)] and **1,1'-sulfinylbisbenzene (13)**,[17] mp 70–71 °C (hexane), had spectral data (^{1}H NMR and MS) which are consistent with their structure.

(n-Pentylsulfinyl)benzene (12)[16] [Kugelrohr oven temperature 105–110 °C (6×10^{-2} Torr)]: ^{1}H NMR δ 7.65–7.43 (m, 5 H), 2.81–2.73 (m, 2 H), 1.79–1.24 (m, 6 H), 0.90–0.82 (m, 3 H); MS (70 eV) *m/e* (relative intensity) 196 (M^+, 1), 179 (35), 126 (100), 110 (20), 78 (46). Anal. Calcd for $C_{11}H_{16}OS$: C, 67.30; H, 8.22; S, 16.33. Found: C, 67.02; H, 8.11; S, 16.16.

Acetylene Analysis. In the reaction between phenylmagnesium bromide and **(Z)-2**, the outlet of the reaction flask was connected to a 5-mL bulb, equipped with an inlet and an outlet, and cooled with liquid N_2. N_2 was flushed during the reaction time and after the quenching. A white crystalline solid was formed in the bulb. The bulb's inlet was then stoppered and most of the N_2 was removed at the same temperature by a vacuum pump connected to the outlet. The bulb was allowed to reach room temperature and the evolved gas was analyzed by mass spectrometry. Acetylene (M^+, 26) was found.

In another experiment, starting from 2 mmol of halovinyl sulfoxide, the reaction flask was flushed with N_2, and the gas was bubbled into cold diethyl ether (−80 °C). A cold methanolic solution of K_2HgI_4 (prepared by adding 5 g of HgI_2 to 25 mL of a 20% solution of KI in CH_3OH[27]) was added to the ethereal solution of acetylene, followed by 6 mL of a 0.5 N solution of NaOH. Titration of NaOH excess with 0.1 N H_2SO_4 gave the amount of acetylene trapped in diethyl ether (85% of the amount of the starting sulfoxide).

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Registry No. 1, 74031-48-4; 2, 74031-47-3; 3, 138286-19-8; 4, 134262-30-9; 5, 138286-20-1; 6, 138286-21-2; 7, 40110-66-5; 8, 40110-65-4; 9, 138286-22-3; 10 isomer 1, 138286-23-4; 10 isomer 2, 138286-24-5; 11, 13153-10-1; 12, 34756-51-9; 13, 945-51-7; (E)-PhSCH=CHBr, 17101-82-5; (Z)-PhSCH=CHBr, 17101-71-2; (Z)-(2-Np)SCH=CHBr, 134613-51-7; (E)-PhSCH=CHCl, 26620-11-1.

Supplementary Material Available: Spectral data of compounds 1, 2, 4, and 11 (1 page). Ordering information is given on any current masthead page.

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Preparation of 1,4-Diketones and Their Reactions with Bis(trialkyltin) or Bis(triphenyltin) Sulfide–Boron Trichloride

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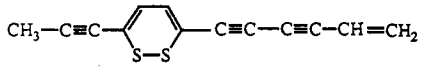
1,4-Diphenyl- and 1,4-bis(4-chlorophenyl)-1,4-butanediones (**3** and **4**), as well as 1-phenyl-, 1-(4-chlorophenyl)-, and 1-(4-methoxyphenyl)-1,4-pentanediones (**7–9**) react with bis(tributyltin), bis(tricyclohexyltin), and/or bis(triphenyltin) sulfide in the presence of boron trichloride to give, 2,5-diaryl- or 5-methyl-2-arylthiophenes. 1,8-Diphenyl-1,7-octadiyne-3,6-dione (**10**) and 1-phenyl-1,7-nonadiyne-3,6-dione (**11**), which were prepared in nine steps from 1,4-butanediol, react with the thionation reagents to give 2,5-bis(2-phenylethynyl)thiophene (**20g**) and 2-(2-phenylethynyl)-5-(1-propynyl)thiophene (**20f**), respectively.

1,4-Dicarbonyl compounds are useful synthetic intermediates, particularly in the synthesis of natural products. This report describes a nine-step procedure for the controlled and versatile synthesis of less readily available unsymmetrical alkynyl 1,4-diketones. Owing to the interest in the disulfide/dithione valence isomerization and in the synthesis of the potent antiviral natural products Thiarubrines A and B (**1** and **2**) and their derivatives,[1-7]



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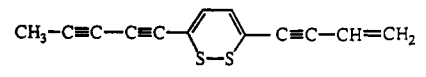

2

we decided to attempt to develop mild experimental procedures for the difficult conversion of 1,4-diketones to the corresponding 1,4-dithiones[4,5,8-20] which could be cyclized

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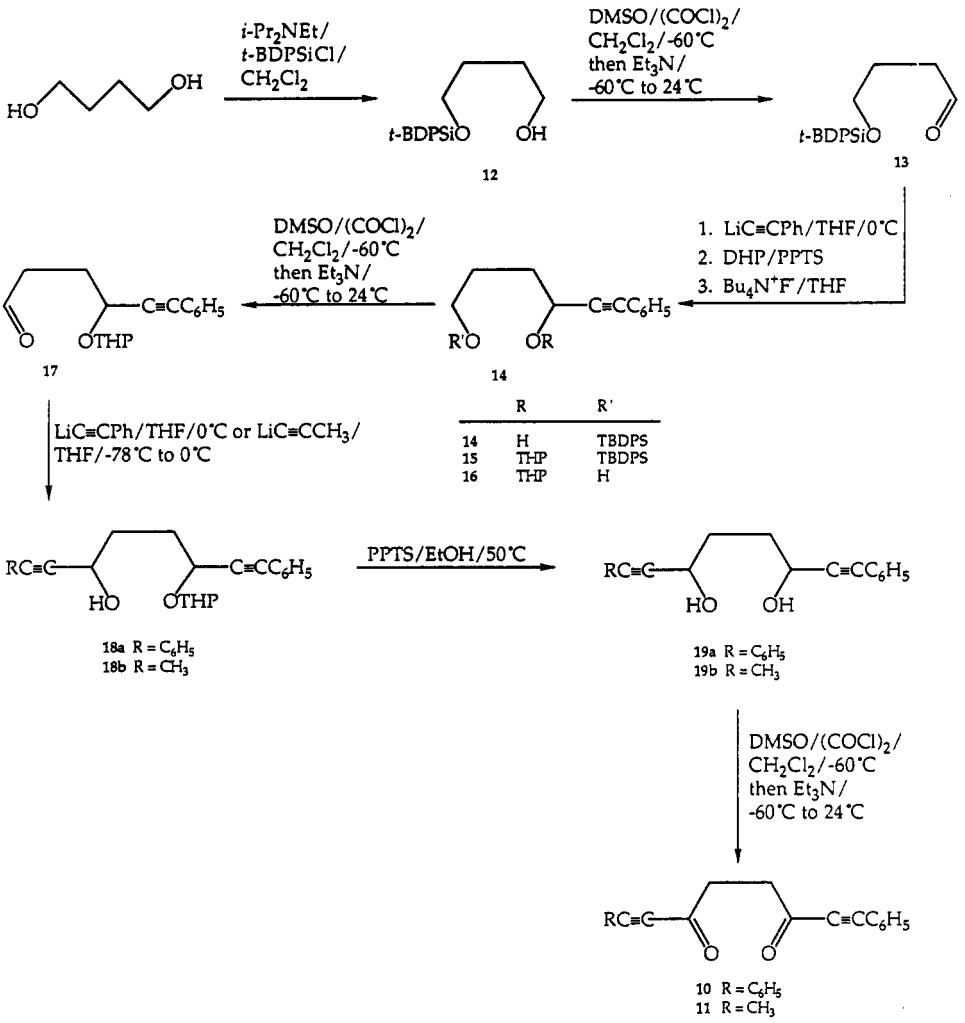
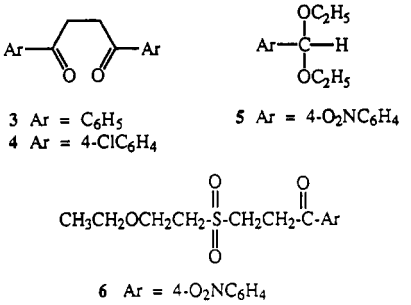
0022-3263/92/1957-1722$03.00/0

Scheme I



to 1,2-dithiins.[21] However, as described below, attempted thionation of the 1,4-diketones gave thiophenes rather than the 1,2-dithiins.

1,4-Diphenyl- and 1,4-bis(4-chlorophenyl)-1,4-butanedione (**3** and **4**)[8,16,22,23] were prepared via the Stetter's thiazolium-catalyzed addition of benzaldehyde and of 4-chlorobenzaldehyde to divinyl sulfone.[10,11] Under similar experimental conditions, 4-nitrobenzaldehyde afforded diethoxy(4-nitrophenyl)methane (**5**)[24,25] and (2-ethoxyethyl)[3-oxo-3-(4-nitrophenyl)propyl] sulfone (**6**).



3 Ar = C_6H_5
4 Ar = 4-ClC_6H_4

5 Ar = 4-$O_2NC_6H_4$

6 Ar = 4-$O_2NC_6H_4$

Diketones **7**,[22,26] **8**,[27] and **9**[28] were prepared via the thiazolium-catalyzed addition of the corresponding aromatic aldehyde to methyl vinyl ketone.[29-31]

Scheme I shows a versatile procedure for the synthesis of symmetrical and unsymmetrical 1,4-dialkynylic 1,4-

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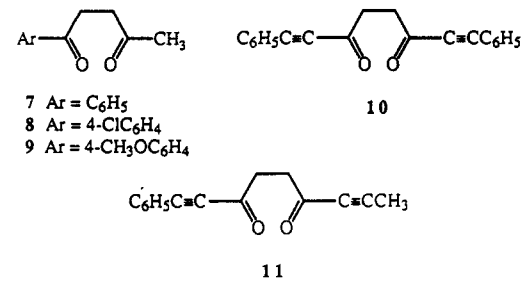

7 Ar = C_6H_5
8 Ar = 4-ClC_6H_4
9 Ar = 4-$CH_3OC_6H_4$

10

11

butanediones from readily available 1,4-butanediol. An advantage of this diketone synthesis is that structural modifications are readily introduced at various stages in the synthesis prior to ring closure. The preparation of 1,8-diphenyl-1,7-octadiyne-3,6-dione (**10**) and 1-phenyl-1,7-nonadiyne-3,6-dione (**11**) was used to demonstrate the efficacy of the nine-step synthetic sequence.[32]

Scheme I shows the general synthesis of 1,4-diketones **10** and **11**. 1,4-Butanediol was monoprotected with *tert*-butyldiphenylsilyl chloride[33] to give 4-[(*tert*-butyldiphenylsilyl)oxy]butanol (**12**, 95%) which was oxidized to 4-[(*tert*-butyldiphenylsilyl)oxy]butanal (**13**, 98%) with dimethyl sulfoxide–oxalyl chloride.[34] Pyridinium dichromate (PDC)[35,36] also oxidizes alcohol **12** to aldehyde **13** in 78% yield. Aldehyde **13** reacted with lithium phenylacetylide to afford 6-[(*tert*-butyldiphenylsilyl)oxy]-3-hydroxy-1-phenylhept-1-yne (**14**, 99%),[37] which was tetrahydropyranylated in the presence of pyridinium *p*-toluenesulfonate (PPTs)[38] to give the protected alcohol **15** (98%). Selective deprotection (desilylation)[39] of compound **15** afforded alcohol **16** (80%)[39] which was oxidized[34] to aldehyde **17** (81%). Treatment of aldehyde **17** with lithium phenylacetylide yielded alcohol **18a** (95%) which was detetrahydropyranylated in the presence of PPTs[38] to give 1,4-diol **19a** (94%). Oxidation of 1,4-diol **19a** with dimethyl sulfoxide-oxalyl chloride[34] gave 1,4-diketone **10** (80%).[40] 1,4-Diketone **11** was similarly prepared from 1,4-butanediol using the appropriate organolithium compounds.[37]

Attempted thionation of 1,4-diketones **3**, **4**, **7–10**, and **11** with the Steliou reagent gave the corresponding thiophenes instead of 1,2-dithiins. Although bis(tricyclohexyltin) and bis(triphenyltin) sulfides required refluxing toluene and bis(tributyltin) sulfide reacted at 22–24 °C, Table I shows that the excellent yields of thiophenes **20** are essentially independent of the tin sulfide used and of the substituents on the 1,4-diketones. The exception is thionation of 1-phenyl-1,7-nonadiyne-3,6-dione (**11**), which ultimately leads to thiophene **20f** in only 13–28% yields (Table I). Although it is not possible to infer the intermediacy of 1,2-dithiins from these experimental results, this thiophene synthesis from 1,4-diketones employing the Steliou reagent[15] gives higher yields in shorter reaction times than previously reported thiophene syntheses utilizing the Lawesson reagent in refluxing benzene or toluene or using tetraphosphorus decasulfide.[9,16–20]

Experimental Section

General. Melting points were determined in open capillary tubes and are uncorrected. High-resolution mass spectra (HREIMS) were obtained at 70 eV. Chemical ionization mass spectra (CIMS, 2-methylpropane) and electron impact mass spectra (EIMS) were obtained at an ionization potential of 70 or 100 eV. N_2 was dried by passing it through a column of Drierite and 5-Å molecular sieves. Solvents were dried and purified by standard procedures. THF was distilled over Na, CH_2Cl_2 was distilled over CaH_2, and both were stored under N_2. Analytical TLC was performed on Analtech Uniplate 10- × 20-cm (0.25-mm) silica gel GF prescored glass plates which were developed in a solvent mixture of 1:2 ethyl acetate/hexanes. The plates were visualized under UV light and in a diiodine chamber. Flash column chromatography was performed on 230–400-mesh silica gel.[41,42]

Bis(tributyltin) sulfide, bis(tricyclohexyltin) sulfide, and bis(triphenyltin) sulfide were prepared in over 90% yields from the corresponding $(R)_3SnCl$ and sodium sulfide nonahydrate.[15]

General Procedure for the Preparation of Lithium Acetylides. To a solution of alkyne (10 mmol) in THF (20 mL) at −10 to −20 °C was added BuLi (1 M, in THF, 11 mL, 1.1 equiv) dropwise under N_2. The solution was stirred for 1 h at 0 °C and used immediately in the subsequent reactions.

1,4-Diphenyl-1,4-butanedione (3), 1,4-bis(4-chlorophenyl)-1,4-butanedione (4), 1-phenyl-1,4-pentanedione (7), 1-(4-chlorophenyl)-1,4-pentanedione (8), and 1-(4-methoxyphenyl)-1,4-pentanedione (9) were prepared by Stetter's procedure[10,11,22] and purified by flash chromatography, giving **3** (23%, mp 143–144 °C) [lit.[22] mp 144–146 °C], **4** (63%, mp 147–148 °C) [lit.[11] mp 149–150 °C], **7** (80%, a clear oil) [lit.[22,26] mp 28–29 °C], **8** (87%, mp 74–75 °C) [lit.[27] mp 76 °C], and **9** (64%, mp 72–73 °C) [lit.[28] mp 72 °C].

Diethoxy(4-nitrophenyl)methane (5) and (2-ethoxyethyl)[3-oxo-3-(4-nitrophenyl)propyl] sulfone (6) were prepared by the Stetter procedure[10,11,22] from 4-nitrobenzaldehyde. The residue was chromatographed using 5:1 hexanes/ethyl acetate solution to isolate compound **5**[24,25] as a light brown solid (28%, mp 54–55 °C) [lit.[24a] mp 35–37 °C]: ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, 3 H, J = 7.13 Hz), 4.44 (q, 2 H, J = 7.12 Hz), 8.20–8.30 (q, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.15, 61.90, 123.41, 130.60, 135.79, 150.40, 164.62; CIMS $m + 1/z$ (relative intensity) 196 (M + 1 − CH_3–CH_3) (100), 180 (M + 1 − $HOCH_2CH_3$ or $-NO_2$) (9), 166 (M + 1 − $2CH_3CH_3$) (40).

The second compound (**6**) was isolated by eluting with 2:1 hexanes/ethyl acetate solution as clear crystals (32%, mp 131–133 °C): IR (Nujol, cm^{-1}) 2925 (CH_2, CH_3), 1702 (C=O), 1605 (C=C), 1377 and 1289 (SO_2), 1125 (SO_2); ^1H NMR (300 MHz, DMSO-d_6) δ 1.38 (t, 3 H, J = 7.15 Hz), 3.58 (t, 2 H, J = 5.65 Hz), 3.64 (t, 2 H, J = 5.89 Hz), 3.70 (t, 2 H, J = 5.71 Hz), 4.13 (t, 2 H, J = 5.74 Hz), 4.26 (q, 2 H, J = 7.03 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 14.21, 49.87, 53.15, 53.83, 60.27, 66.74, 113.57, 122.41, 130.43, 153.67, 165.36; CIMS $m + 1/z$ (relative intensity) 300 (M + 1 − O) (100), 282 (M + 1 − O, − H_2O) (22), 192 (35), 166 (9), 111 (13).

4-[(*tert*-Butyldiphenylsilyl)oxy]butanol (12). To a solution of 1,4-butanediol (5 g, 55 mmol) in CH_2Cl_2 (10 mL) containing *i*-Pr_2NEt (10 mL) was added *t*-BDPSiCl (5 mL, 18 mmol) dropwise under N_2 at 22–24 °C. The solution was stirred at 22–24 °C for 2 h, concentrated in vacuo, and chromatographed, eluting with hexanes/ethyl acetate (10:1) to give **12** (clear oil, 5.6 g, 95%); IR (neat, cm^{-1}) 3400 (OH), 3080 (aromatic CH), 1590 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9 H), 1.63–1.67 (m, 4 H), 2.30

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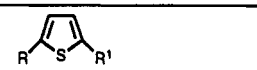
Table I. Effects of Substituents on the Formation of Thiophenes from 1,4-Dicarbonyl Compounds



compd no.	R	R¹	yield, % $(Sn(Bu)_3)_2S$	$(Sn(cyclohexyl)_3)_2S$	$(Sn(phenyl)_3)_2S$
20a	C_6H_5	C_6H_5	98	98	97
20b	4-ClC_6H_4	4-ClC_6H_4	92	96	98
20c	CH_3	C_6H_5	95		96
20d	CH_3	4-ClC_6H_4	94		97
20e	CH_3	4-$CH_3OC_6H_4$	91	93	
20f	$CH_3C{\equiv}C$	$C_6H_5C{\equiv}C$	15	13	28
20g	$C_6H_5C{\equiv}C$	$C_6H_5C{\equiv}C$	84	89	92

(s, 1 H), 3.63 (t, 2 H, J = 6.04 Hz), 3.69 (t, 2 H, J = 5.82 Hz), 7.34–7.68 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.09, 26.77, 29.16, 29.66, 62.63, 63.93, 127.59, 129.56, 133.57, 135.46; HRCIMS $m + 1/z$ 329.1936 (calcd for $C_{20}H_{29}O_2Si$ 329.1927).

General Procedure for the Dimethyl Sulfoxide–Oxalyl Chloride Oxidation.[34] A mixture of CH_2Cl_2 (25 mL) and oxalyl chloride (1 mL, 1.40 g, 11 mmol) was stirred and cooled at −50 to −60 °C as 1.72 g (1.7 mL, 22 mmol) of DMSO was added. The reaction mixture was stirred for 2 min and the alcohol (10 mmol in 10 mL of CH_2Cl_2) was added by cannula over 5 min. After the solution was stirred for 15 min, triethylamine (7.0 mL, 50 mmol) was added, and the reaction mixture was stirred for 5 min and then allowed to warm to 22–24 °C. Water (50 mL) was added, and the aqueous layer was extracted with additional CH_2Cl_2 (50 mL). The organic layers were combined, washed with saturated NaCl solution (100 mL), and dried ($MgSO_4$). The filtrate was concentrated in vacuo, and the residue was chromatographed, eluting with hexanes/ethyl acetate (10:1) to give the carbonyl product.

4-[(*tert*-Butyldiphenylsilyl)oxy]butanal (13). The monosilyl ether of 1,4-butanediol (**12**, 6.75 g, 20.1 mmol) was oxidized using the Swern oxidation procedure[34] to give silyl ether aldehyde **13** (clear oil, 6.40 g, 19.6 mmol, 98%): IR (neat, cm^{-1}) 3080 (aromatic CH), 1730 (C=O), 1590 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9 H), 1.88 (p, 2 H, J = 6.10 Hz), 2.53 (td, 2 H, J = 7.15 Hz), 3.68 (t, 2 H, J = 5.97 Hz), 7.34–7.66 (m, 10 H), 9.76 (t, 1 H, J = 1.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.11, 25.17, 26.76, 40.66, 62.83, 127.62, 129.61, 133.50, 135.45, 202.38; HRCIMS $m + 1/z$ 327.1771 (calcd for $C_{20}H_{27}O_2Si$ 327.2866).

Aldehyde **13** also could be prepared by the PDC oxidation of alcohol **12**.[35,36] To a dry CH_2Cl_2 (10 mL) solution of the alcohol **12** (2 g, 6.1 mmol) was added PDC (3.44 g, 9.15 mmol) in one portion. The mixture was stirred at 22–24 °C for 16 h under N_2. Diethyl ether (15 mL) was added and stirring continued for 10 min. The reaction mixture was filtered over silica gel, and the residue on the silica gel was washed with 100 mL of diethyl ether. The combined filtrate and wash solution was concentrated in vacuo, and the residue was chromatographed using hexanes/ethyl acetate (10:1) solution to give 1.56 g (78%) of **13**.

6-[(*tert*-Butyldiphenylsilyl)oxy]-3-hydroxy-1-phenylhept-1-yne (14). To a solution of freshly prepared lithium phenylacetylide (2.02 g, 20 mmol) in THF (10 mL) was added aldehyde **13** (6.4 g, 19.6 mmol) in THF (10 mL) at −78 °C dropwise over 5 min under N_2. The solution was warmed to 0 °C, stirred at 0 °C for 4 h, and diluted with a 1:1 solution of ethyl acetate/diethyl ether (100 mL) and saturated NH_4Cl solution (30 mL) added. The layers were separated, the organic layer was washed with water (3 × 100 mL) and dried ($MgSO_4$), the solvent was evaporated in vacuo, and the residue was chromatographed with hexanes/ethyl acetate (5:1) to give the acetylenic alcohol **14** (light brown oil, 8.40 g, 99%): IR (neat, cm^{-1}) 3400 (OH), 3080 (aromatic CH), 1590 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (d, 9 H, J = 2 Hz), 1.76 to 1.96 (m, 4 H), 3.10 (d, 1 H, J = 6 Hz), 3.73 (t, 2 H, J = 6 Hz), 4.67 (d, 1 H, J = 6 Hz), 7.25 to 7.70 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.03, 26.70, 28.14, 34.82, 62.41, 63.78, 84.65, 90.21, 122.68, 127.54, 128.06, 129.52, 131.51 133.35, 135.40; CIMS m/z (relative intensity) 411 (M + 1 − H_2O) (9), 159 (9), 157 (8), 156 (10), 155 (M + 1 − H_2O, − HOSitBuDP) (100).

Acetylenic alcohol **14** was also prepared using the Grignard reagent.[37] Phenylethyne (550 mg, 5.4 mmol) was dissolved in 40 mL of diethyl ether under N_2. Ethylmagnesium bromide (1.73 mL of 3 M ether solution, 5.2 mmol) was added dropwise under Ar during a 5-min period and the mixture stirred at 22–24 °C for 9 h. The protected aldehyde **13** (1.70 g, 5.17 mmol) dissolved in 5 mL of diethyl ether under an Ar atmosphere was slowly added (5 min) to the stirring mixture. After the mixture was stirred for 7 h, saturated NH_4Cl solution (5 mL) was added slowly to the reaction mixture. The ether layer was separated and washed with water (5 × 10 mL). The aqueous layer was extracted with diethyl ether (2 × 30 mL), the ether layers were combined and dried ($MgSO_4$), and the solvent was evaporated under vacuum. The residue was chromatographed using 8:1 hexanes/ethyl acetate to give 1.9 g (85%) of acetylenic alcohol **14** which was identical to the product described above.

Pyridinium *p*-Toluenesulfonate (PPTs).[38] *p*-Toluenesulfonic acid monohydrate (5.7 g, 30 mmol) was added to pyridine (12.1 mL, 150 mmol) with stirring at 22–24 °C. After the solution was stirred for 20 min, the excess pyridine was removed under vacuum on a water bath at approximately 60 °C to afford a quantitative yield of PPTs as colorless crystals. The product was recrystallized from propanone (7.15 g, 95%), mp 120–121 °C [lit.[35] mp 120 °C].

1,8-Diphenyl-1,7-octadiyne-3,6-dione (10). The acetylenic diol **19a** (1.5 g, 5.2 mmol) was oxidized using the Swern oxidation procedure[34] to give diketone **10** (light brown crystals, 1.11 g, 75%). The diketone **10** was recrystallized from hexanes/ethyl acetate, mp 106–8 °C [lit.[8] mp 109 °C]: IR (Nujol, cm^{-1}) 3060 (aromatic CH) 2200 (alkyne), 1670 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 3.11 (s, 4 H), 7.26–7.60 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 39.58, 78.11, 88.09, 92.26, 120.30, 129.30, 131.51, 133.75, 185.78; HREIMS (70 eV) m/z 286.09937 (calcd for $C_{20}H_{14}O_2$ 286.3340).

Diketone 10 also could be prepared by the PDC oxidation of diol **19a**. To a dry CH_2Cl_2 (15 mL) solution of the alcohol **19a** (700 mg, 2.4 mmol) was added PDC (3.0 g, 8.0 mmol) in one portion.[35] The mixture was stirred at 22–24 °C for 18 h under N_2. Diethyl ether (10 mL) was added to the reaction mixture, which was then stirred for 15 min, and filtered over silica gel. The residue on the silica gel was washed with 100 mL of diethyl ether. The filtrate was dried ($MgSO_4$), the solvent was evaporated in vacuo, and the residue was chromatographed using hexanes/ethyl acetate (10:1) solution to give 160 mg (23%) of **10**.

1-Phenyl-1,7-nonadiyne-3,6-dione (11). The acetylenic diol **19b** (1 g, 5 mmol) was oxidized using the Swern oxidation procedure[34] to give diketone **11**. The diketone **11** was chromatographed, eluting with hexanes/ethyl acetate (10:1) to give a light brown oil (690 mg, 70%): IR (neat, cm^{-1}) 3060 (aromatic CH), 2200 (alkyne), 1670 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 2.01 (s, 3 H), 2.92 to 3.05 (m, 4 H), 7.34 to 7.58 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 3.87, 38.66, 79.60, 87.18, 90.97, 91.20, 119.50, 128.44, 130.64; 132.81, 184.93, 185.03; HREIMS m/z 224.0853 (Calcd for $C_{15}H_{12}O_2$ 224.0837).

Diketone **11** also could be prepared by the PDC oxidation (vide supra) of 1,4-diol **19b**.[35] The residue was chromatographed using hexanes/ethyl acetate (10:1) solution to give 160 mg (42%) of diketone **11**.

6-[(*tert*-Butyldiphenylsilyl)oxy]-1-phenyl-3-[(2-tetrahydropyranyl)oxy]hept-1-yne (15). To a solution of the acetylenic secondary alcohol **14** (1.5 g, 3.5 mmol) in CH_2Cl_2 (10 mL) at 22–24 °C was added 3,4-dihydro-2*H*-pyran (0.479 mL, 442 mg, 5.25 mmol) and PPTs (20 mg, 0.08 mmol). The solution was stirred at 22–24 °C for 1 h and diluted with a 100-mL solution of (1:1) diethyl ether and ethyl acetate. The organic layer was separated, washed with H_2O (3 × 100 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residue was chromatographed, eluting with hexanes/ethyl acetate (20:1) to

give the THP ether **15** (clear oil, 1.75 g, 97%): IR (neat, cm^{-1}) 3070, 3050 (aromatic CH), 2940, 2857 (aliphatic CH), 1598 (aromatic C=C), 1112, 1020 (satd ethers COC); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.92, 19.09, 25.33, 26.75, 28.24, 30.37, 32.07, 61.89, 63.50, 67.37, 84.56, 89.20, 97.72, 123.00, 127.48, 127.93, 128.01, 129.42, 131.56, 133.77, 135.39; CIMS *m/z* (relative intensity) 411 (M + 1 - HOTHP) (6), 327 (2), 179 (2), 155 (M + 1 - HOTHP, - HOSitBuDP) (28), 103 (HOTHP) (13), 85 (100).

6-Phenyl-4-[(tetrahydropyranyl)oxy]-5-hexyn-1-ol (16). To a solution of the THP ether **15** (1.7 g, 3.3 mmol) in THF (10 mL) was added a 1 M solution of tetrabutylammonium fluoride in THF (5 mL, 5 mmol) at 22–24 °C. The solution was stirred for 2 h and diluted with 100 mL (1:1) of diethyl ether/ethyl acetate solution. The organic layer was separated and washed with H_2O (3 × 100 mL). The water extract was washed with 2:1 diethyl ether/ethyl acetate solution (2 × 50 mL), and the organic layers were combined and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residue was chromatographed over silica gel using (5:1) hexanes/ethyl acetate solution. Two isomers were isolated as clear oils.

Clear oil I: IR (neat, cm^{-1}) 3411 (OH), 3057 (aromatic CH), 2942, 2870 (aliphatic CH), 2226 (alkyne), 1598 (aromatic C=C), 1020 (satd ethers COC); ^1H NMR (300 MHz, $CDCl_3$) δ 1.50–1.97 (m, 10 H), 2.77 (s, 1 H), 3.57 (m, 1 H), 3.70 (t, 2 H, *J* = 5.93 Hz), 3.84 (m, 1 H), 4.70 (t, 1 H, *J* = 5.94 Hz), 5.07 (t, 1 H, *J* = 6.28 Hz), 7.26–7.44 (5 H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.19, 25.23, 28.51, 30.31, 32.18, 62.15, 62.26, 65.05, 85.45, 87.50, 95.52, 122.46, 128.04, 128.15, 131.58.

Clear oil II: IR (neat, cm^{-1}) 3411 (OH), 3057 (aromatic CH), 2945, 2870 (aliphatic CH), 2230 (alkyne), 1598 (aromatic C=C), 1021 (satd ethers COC); ^1H NMR (300 MHz, $CDCl_3$) δ 1.53–1.91 (m, 10 H), 2.60 (s, 1 Hs), 3.59 (m, 1 H), 3.68 (t, 2 H, *J* = 5.98 Hz), 4.07 (m, 1 H), 4.54 (t, 1 H, *J* = 6.18 Hz), 4.85 (t, 1 H, *J* = 3.06 Hz), 7.26–7.43 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.82, 25.19, 28.27, 30.28, 32.06, 62.01, 62.11, 67.51, 84.74, 88.76, 97.97, 122.75, 128.01, 131.49; CIMS *m/z* (relative intensity) 275 (M + 1) (0.19), 257 (M + 1 - H_2O) (6), 173 (M + 1 - HOTHP) (40), 103 (HOTHP) (6), 101 (7), 85 (100).

6-Phenyl-4-[(tetrahydropyranyl)oxy]-5-hexyn-1-al (17). Alcohol **16a** (1.45 g, 5 mmol) was oxidized using Swern oxidation procedure[34] to give aldehyde **17a**. Aldehyde **17a** was chromatographed, eluting with hexanes/ethyl acetate (10:1), to give a light brown oil (**17**, 1.25 g, 85%): IR (neat) 2950 (aliphatic CH), 2730 (aldehyde CH), 1730 (C=O), 1600 (aromatic C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 1.52–1.79 (m, 6 H). 2.17–2.24 (q, 2 H, *J* = 6.42 Hz), 2.68–2.73 (m, 2 H), 3.52–3.59 (m, 1 H), 3.75–3.83 (m, 1 H), 4.72 (t, 1 H, *J* = 6.09 Hz), 5.04 (t, 1 H, *J* = 2.83 Hz), 7.27–7.44 (m, 5 H), 9.83 (t, 1 H, *J* = 1.54 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.12, 25.30, 28.45, 30.26, 39.77, 62.26, 64.19, 86.02, 86.86, 95.54, 122.28, 128.19, 128.41, 131.71, 201.90; HREIMS *m/z* 272.1473 (calcd for $C_{17}H_{20}O_3$ 272.1412).

Aldehyde **17** was also prepared from the PDC oxidation (vide supra) oxidation of alcohol **16**.[35] The residue chromatographed using hexanes/ethyl acetate (10:1) solution to give 180 mg of **17** (25%).

6-[(Tetrahydropyranyl)oxy]-1,8-diphenyl-1,7-octadiyn-3-ol (18a). To a solution of freshly prepared lithium phenylacetylide (650 mg, 6 mmol) in THF (15 mL) was added a solution of the aldehyde **17** (1.5 g, 5.5 mmol) in THF (5 mL) dropwise at −78 °C under N_2. The solution was stirred at −78 °C for 1 h and warmed to 22–24 °C. The resulting solution was diluted with diethyl ether (50 mL) and 20 mL of saturated NH_4Cl solution added. The organic layer was separated, washed with H_2O (2 × 50 mL), and dried ($MgSO_4$), and the solvent was evaporated in vacuo. The residue was chromatographed, eluting with hexanes/ethyl acetate (5:1) to give acetylenic alcohol **18a** (1.96 g, 95%) as a clear oil: IR (neat, cm^{-1}) 3416 (OH), 3057 (aromatic CH), 2943–2868 (aliphatic CH), 2228 (alkyne), 1598, 1572 (C=C), 1117, 1021 (satd ethers COC); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25–2.14 (m, 10 H), 2.80–2.96 (m, 1 H), 3.50–3.59 (m, 1 H), 3.81–3.89 (m, 1 H), 4.73–4.80 (m, 2 H), 5.09 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.15, 19.24, 25.30, 30.36, 31.30, 31.58, 33.54, 33.76, 62.36, 62.50, 62.75, 64.89, 64.95, 84.91, 85.70, 85.78, 87.29, 87.47, 89.92, 95.60, 95.63, 122.50, 122.60, 128.12, 128.20, 128.27, 131.60, 131.72; CIMS *m/z* (relative intensity) 273 (M + 1 - HOTHP) (22), 171 (M + 1 - HOTHP, - C≡CPh) (58), 133 (100), 105 (30), 103 (HOTHP) (13).

6-[(Tetrahydropyranyl)oxy]-1-phenyl-1,7-nonadiyn-3-ol (18b): clear oil; IR (neat, cm^{-1}) 3420 (OH), 3057 (aromatic CH), 2943–2869 (aliphatic CH), 2233 (alkyne), 1598 (aromatic C=C), 1117, 1021 (satd ethers COC); ^1H NMR (300 MHz $CDCl_3$) δ 1.54–2.05 (m, 10 H), 1.83 and 1.84 (two singlets, 3 H), 2.53–2.62 (two doublets, 1 H, *J* = 5.04 Hz), 3.54–3.59 (m, 1 H), 3.80–3.88 (m, 1 H), 4.45 (br, s, 1 H), 4.69–4.74 (q, 1 H, *J* = 5.05 Hz), 5.08 (m, 1 H), 7.27–7.44 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 3.48, 19.16, 19.20, 25.31, 30.32, 31.32, 31.53, 33.83, 33.96, 62.08, 62.20, 62.28, 64.92, 80.16, 80.92, 85.55, 85.62, 87.42, 87.55, 95.47, 95.54, 122.54, 128.10, 128.23, 131.71; HREIMS *m/z* 312.1750 (calcd for $C_{20}H_{24}O_3$ 312.1725).

1,8-Diphenyl-1,7-octadiyne-3,6-diols (19a). To an ethanolic solution (30 mL) of tetrahydropyranyl ether **18** (1.87 g, 5 mmol) was added PPTS (20 mg, 0.08 mmol) in one portion. The solution was refluxed for 1 h, cooled to 22–24 °C, and diluted with a mixture of diethyl ether (100 mL) and H_2O (200 mL). The organic layer was washed with H_2O (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography over silica gel, eluting with hexanes/ethyl acetate (3:1) to give a diastereomeric mixture of dialcohols **19a** (1.36 g, 94%) as a clear oil: IR (neat, cm^{-1}) 3340 (OH), 3059 (aromatic CH), 2927–2867 (aliphatic CH), 2229 (alkyne), 1598, 1572 (aromatic C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 2.00–2.13 (m, 4 H), 3.01 (br s, 2 H), 4.70–4.73 (m, 2 H), 7.24–7.44 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 33.32, 33.58, 62.32, 62.40, 85.08, 89.59, 122.47, 128.20, 128.34, 131.64; CIMS *m/z* (relative intensity) 274 (M + 1 - OH) (14), 273 (M + 1 - H_2O) (76), 171 (M + 1 - H_2O, — C≡CPh) (68), 159 (16), 143 (17), 133 (12), 131 (19), 105 (100).

1-Phenyl-1,7-nonadiyne-3,6-diol (19b): clear oil (915 mg, 93%); IR (neat, cm^{-1}) 3356 (OH), 2920–2868 (aliphatic CH), 2235 (alkyne), 1598 (aromatic C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 1.82 and 1.83 (2 s, 3 H), 1.88–2.05 (m, 4 H), 3.19 (br s, 1 H), 3.47 (br s, 1 H), 4.45 (m, 1 H), 4.68 (m, 1 H), 7.27–7.44 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 3.45, 33.30, 33.50, 33.71, 62.04, 62.23, 62.29, 79.87, 79.93, 81.27, 84.84, 89.74, 122.50, 128.13, 128.23, 131.59; CIMS *m/z* (relative intensity) 212 (M + 1 - OH) (16), 211 (M + 1 - H_2O) (100), 195 (9), 193 (9), 186 (M + 1 - C≡CCH$_3$) (2), 183 (3) 155 (11), 109 (M + 1 - H_2O, —C≡CPh) (20), 105 (42).

General Procedure for the Preparation of 2,5-Disubstituted Thiophenes 20. Reactions involving bis(tricyclohexyltin) and bis(triphenyltin) sulfides were performed in refluxing toluene, and experiments using bis(tributyltin) sulfide were carried out at 22–24 °C. To a 10-mL dry toluene solution of bis(triphenyltin) sulfide (697 mg, 0.95 mmol) and dione **4** (100 mg, 0.48 mmol) was injected 1 M BCl_3 in CH_2Cl_2 (0.64 mL, 0.64 mmol). The reaction solution was refluxed for 2 h, cooled to 22–24 °C, and added to 100 mL of 2:1 diethyl ether/ethyl acetate. The solution was washed with H_2O (3 × 100 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography using 100:1 hexanes/ethyl acetate solution to give **2,5-bis(4-chlorophenyl)-5-methylthiophene (20b)** as a white solid (97 mg, 98%), mp 161–162 °C [lit.[36] mp 161–162 °C]: ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 2 H), 7.32–7.53, (dd, 8 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 124.39, 126.75, 129.07, 132.56, 133.37, 142.58.

2,5-Diphenylthiophene (20a): yield 96 mg (97%); mp 148–149 °C [lit.[18] mp 149–150 °C]; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (s, 2 H), 7.37–7.75 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 124.02, 125.63, 127.52, 128.94, 134.34, 143.62.

2-Methyl-5-phenylthiophene (20c): yield 95 mg (96%); mp 46–47 °C [lit.[16] mp 49–51 °C]; ^1H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 1 H), 6.69 (q, 1 H, *J* = 3.54 Hz), 7.07 (d, 1 H, *J* = 3.52 Hz), 7.20–7.54 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.35, 122.80, 125.38, 126.10, 126.91, 128.71, 134.62, 139.38, 141.90.

2-(4-Chlorophenyl)-5-methylthiophene (20d): yield 96 mg (97%); mp 108–109 °C;[43,44] ^1H NMR (300 MHz, $CDCl_3$) δ 2.49 (s, 3 H), 6.71 (q, 1 H, *J* = 2.57 Hz), 7.07 (d, 1 H, *J* = 3.56 Hz), 7.28–7.46 (m, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.43, 123.24, 126.29, 126.58, 128.89, 132.61, 133.20, 139.95, 140.57.

2-(4-Methoxyphenyl)-5-methylthiophene (20e): 92 mg; yield 93%; mp 94–95 °C [lit.[16] mp 93–94 °C]; ^1H NMR (300 MHz,

(43) Thiophene **20f** has been previously prepared[44] but no spectral data were reported.

(44) Karchenko, V. G.; Voronin, S. P.; Gubina, T. I.; Markushina, I. A.; Oleinik, A. F. *Khim. Geterotsikl. Soedin.* **1984**, *12*, 1606.

$CDCl_3$) δ 2.48 (s, 3 H), 3.81 (s, 3 H), 6.68 (d, 1 H, J = 2.39 Hz), 6.97 (d, 1 H, J = 3.49 Hz), 6.87–7.47 (dd, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.39, 55.32, 114.19, 121.79, 126.00, 126.73, 127.62, 138.41, 141.87, 158.81.

2-(2-Phenylethynyl)-5-(1-propynyl)thiophene (20f):[45] light yellow oil, yield 27 mg (28%); IR (neat, cm^{-1}) 3055 (aromatic CH), 2922 (aliphatic CH), 1597 (aromatic C≡C); ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3 H), 6.98 (d, 1 H, J = 3.77 Hz), 7.08 (d, 1 H, J = 3.81 Hz), 7.32–7.51 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 4.72, 72.67, 82.34, 91.30, 93.23, 122.63, 123.18, 125.60, 128.34, 128.49, 130.83, 131.40, 131.55; HREIMS m/z 222.0532 (calcd for $C_{15}H_{10}S$ 222.0503).

2,5-Bis(2-phenylethynyl)thiophene (20g):[45-48] brown oil, yield 91 mg (92%); IR (neat, cm^{-1}) 1598 (aromatic C≡C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 2 H), 7.34–7.53 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 82.25, 94.04, 122.56, 124.64, 128.39, 128.65, 131.45, 131.80; HREIMS m/z 284.0614 (calcd for $C_{20}H_{12}S$ 284.0660).

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Registry No. 1, 63543-09-9; 2, 71539-72-5; 3, 495-71-6; 4, 24314-35-0; 5, 2403-62-5; 6, 138695-84-8; 7, 583-05-1; 8, 53842-12-9; 9, 2108-54-5; 10, 22956-51-0; 11, 138695-85-9; 12, 130372-07-5; 13, 127793-62-8; 14, 138695-86-0; 15 (isomer 1), 138695-87-1; 15 (isomer 2), 138695-95-1; 16 (isomer 1), 138695-88-2; 16 (isomer 2), 138695-96-2; 17, 138695-89-3; 18a, 138695-90-6; 18b, 138695-93-9; 19a (isomer 1), 138695-91-7; 19a (isomer 2), 138695-97-3; 19b, 138695-94-0; 20a, 1445-78-9; 20b, 82366-97-0; 20c, 5069-26-1; 20d, 95650-85-4; 20e, 85093-01-2; 20f, 138695-92-8; 20g, 90267-18-8; $(Sn(Bu)_3)_2S$, 4808-30-4; $(Sn(cyclohexyl)_3)_2S$, 13121-76-1; $(Sn(phenyl)_3)_2S$, 77-80-5; methyl vinyl ketone, 78-94-4; divinyl sulfone, 77-77-0; 4-nitrobenzaldehyde, 555-16-8.

Supplementary Material Available: ^1H NMR of 6, 12–17, 18a, 18b, 19b, and 20f (35 pages). Ordering information is given on any current masthead page.

(45) Acetylenic thiophenes 20f and 20g are unstable in light at 22–24 °C.

(46) The thiophene 20g has been previously synthesized but no spectral data were reported.[47,48]

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Tandem S_N2–Michael Reactions for the Preparation of Simple Five- and Six-Membered-Ring Nitrogen and Sulfur Heterocycles

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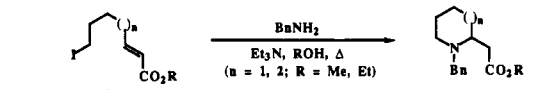
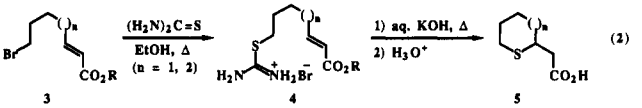
A one-pot tandem S_N2–Michael addition sequence has been developed for the preparation of five-membered- and six-membered-ring nitrogen and sulfur heterocycles from 6- or 7-halo-2-alkenoate esters. Nitrogen-containing rings are prepared by reaction of the ω-halo-2-alkenoate ester with a primary amine in the presence of triethylamine. The sulfur analogues are generated by thiourea displacement of the halide followed by base hydrolysis of the isothiouronium salt. Yields are routinely in the 60–80% range. Experiments are described which elucidate the chronology of the reaction sequences. Ring size and steric hindrance to the initial substitution reaction appear to be the only limitations of the procedure.

As part of our synthetic program aimed at the development of new approaches to functionalized ring systems, we have explored the use of a tandem S_N2–Michael addition route to nitrogen and sulfur heterocycles bearing an acetic acid residue at C-2. Previous studies by Boeckman and co-workers[2] have demonstrated the use of a sequential Gabriel amine synthesis–Michael addition for the preparation of a dihydroisoindole-1-acetic ester precursor to the lycorine alkaloids. In a different context, Vedejs and co-workers[3] have reported the formation of methyl (±)-2*H*-tetrahydrothiopyran-2-acetate from methanolysis of methyl (*E*)-7-(acetylthio)-2-heptenoate. We report here several related procedures which allow for the one-pot synthesis of five- and six-membered-ring nitrogen and sulfur heterocycles by reaction of 6- or 7-halo-2-alkenoate esters with benzylamine (eq 1) or thiourea (eq 2), respectively.



(1)

1 2



(2)

3 4 5

Synthesis of Starting Materials. The heterocyclization substrates used in this study are depicted in Scheme I. Ethyl (*E*)-2-(bromomethyl)cinnamate (6) was prepared by known methods.[4] Ethyl (*E*)-2-(2-bromoethyl)-cinnamate (8) was prepared by Wittig olefination of 2-(2-bromoethyl)benzaldehyde (7)[5] with ethyl (triphenylphosphoranylidene)acetate; treatment of 8 with sodium iodide in acetone afforded 9. Ethyl (*E*)-6-bromo-2-hexenoate (10), ethyl (*E*)-7-bromo-2-heptenoate (12), ethyl

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