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Synthesis of furan from allenic sulfide derivatives

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In this paper, we report the synthesis of furan derivatives from allenic sulfides. By the reaction with NaH, β-Hydroxyl allenic sulfides were found to generate furan products in excellent yields with the removal of phenylthio group. β-Aldehyde allenic sulfides were found to give similar furan products with one more substituent when treated with additional nucleophilic reagents. β-ketone allenic sulfides can also cyclize to give furan derivatives with the promotion of P_2O_5.

furan, allene, synthetic method, nucleophilic reaction

1 Introduction

As representative five-membered ring heterocycles, furans exist in many natural products which have important biological activities and present as key structural units in many material molecules[1]. Furans are also used as important intermediates for various transformations in organic synthesis. Therefore, the development of novel approaches to multi-substituted furan derivatives has attracted broad interests of many synthetic organic chemists over the past years[2−7].

A variety of literature have reported the synthesis of furan compounds. The classic methods include Paar-Knorr furan synthesis and Feist-Bénary furan synthesis[8,9]. Recently, new approaches based on transition metal-catalyzed processes have been developed. In 1990, Marshall et al. reported a Rh(Ⅰ)- or Ag(Ⅰ)-catalyzed reaction of α-allenic ketones to form polysubstituted furan products through intramolecular cyclization (Scheme 1)[10]. They further carried out extensive studies on this system[11,12]. Later, Hashmi et al. explored the Pd(Ⅱ)[13,14], Au(Ⅲ)[15] catalytic system and Ma et al. developed the Pd(0) [16]catalytic system. In 2006, a Au(Ⅲ) catalyst with porphyrin ligand was employed by Che and coworkers, which was also highly effective for this transformation[17].

Scheme 1 The transition-metal-catalyzed cyclization of α-allenic ketones to form furans.

We have recently reported $[RuCl_2(p\text{-cymene})]_2$- or $PtCl_2$-catalyzed rearrangement of β-allenic sulfides to form furan derivatives. We have continued to study this reaction from more easily available starting materials, the α-diazo carbonyl compounds and propargyl sulfides, which are catalyzed by two catalysts successively or only by one catalyst to form furan derivatives through two sequential rearrangements (Scheme 2)[18].

In the course of our further study, we have found that β-carbonyl allenic sulfides can cyclize to generate furan products with high efficiency when treated with base. Besides, β-ketone allenic sulfides can also cyclize to give furan derivatives under the promotion of P_2O_5 (Scheme 3).

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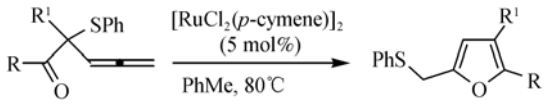
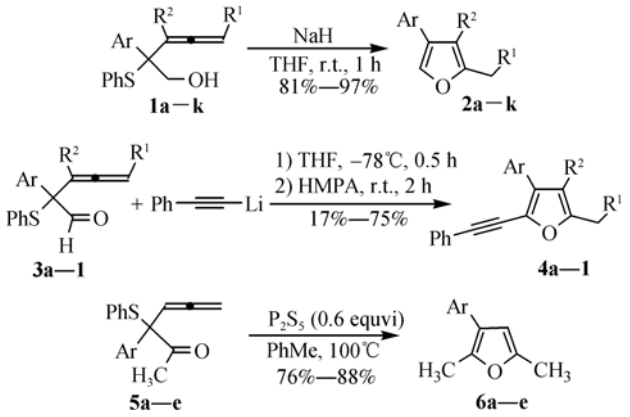
These results lead us to conceive that these reactions may be developed into useful synthetic methods of multi-substituted furan derivatives. We report here in this paper the detailed investigation on these reactions.



Scheme 2 Transition metal-catalyzed rearrangement of β-carbonyl allenic sulfides to form furans.



Scheme 3 Synthesis of furan derivatives from allenic sulfide derivatives.

2 Experimental

2.1 Reagents and instruments

2.1.1 Reagents. All solvents and reagents used in the experiment were AR degree. Petroleum ether (30—60℃) and ethyl acetate were distilled. All other general solvents were distilled prior to use. CH_2Cl_2, $ClCH_2CH_2Cl$ and acetonitrile were distilled over CaH_2. THF, Et_2O and toluene were distilled over Na.

2.1.2 Instruments. All glassware used in the experiment was flame-dried under a highly pure nitrogen atmosphere. The water and air sensitive reagents were added by syringe with strict operation to avoid water and air. Most reagents were purchased from Alfa, Aldrich and Acros. Yanaco melting point apparatus (Shibayama factory in Japan) was used to measure the melting point and the thermometer was not corrected. IR spectra were recorded with a Thermo Electron Corporation Nicolet AVATAR 330 FT-IR infrared spectrometer. Mass spectra were obtained on a VG-ZAB-HS mass spectrometer. Elemental analysis was measured with Elementar Vario apparatus. ^{1}H NMR spectra were recorded at 200 MHz or 300 MHz with Varian Mercury 200 or 300 spectrometer or recorded at 400 MHz with Brucker ARX 400 spectrometer. Chemical shifts were reported in ppm using tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 50 MHz or 75 MHz with Varian Mercury 200 or 300 spectrometer or recorded at 100 MHz with a Brucker ARX 400 spectrometer.

2.2 The preparation of β-hydroxyl allenic sulfides 1a—k

β-Ester allenic sulfides were prepared directly by the Rh(Ⅱ)- or Cu(Ⅰ)-catalyzed reaction of the α-diazo carbonyl compounds with propargyl sulfides through metal carbene-ylide-[2,3] σ rearrangement pathway[18−20]. Further reduction could transform the corresponding esters to a series of β-hydroxyl allenic sulfides **1a—k** conveniently.

2.3 The reaction of β-hydroxyl allenic sulfides 1a—k with NaH to form furans

NaH (60% in mineral oil, 0.6 mmol) was added to a 25 mL round-bottomed flask under nitrogen atmosphere. The mineral oil was washed with freshly distilled petroleum ether. Anhydrous THF (10 mL) and substrate **1** were then added. The reaction was quenched with aqueous NaCl and the mixture was extracted with diethyl ether 3 times after the starting material disappeared as monitored by TLC. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column eluted with petroleum ether to afford the furan product **2**.

2-Methyl-4-phenyl furan (**2a**). Yield: 97%. IR (film) 2922, 1127, 909, 746, 734, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 2.32 (s, 3 H), 6.30 (s, 1 H), 7.20—7.26 (m, 1 H), 7.31—7.37 (m, 2 H), 7.43—7.47 (m, 2 H), 7.58 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 13.59, 104.84, 125.65, 126.71, 127.16, 128.70, 132.83, 136.60, 153.24; EI-MS (*m*/*z*): 158 (M^+, 100), 306 (3), 129 67), 115 1), 77 (11).

4-(3,4-Dichlorophenyl)-2-methyl furan (**2b**). Yield: 90%. IR (film) 1761, 1555, 1473, 1134, 1029, 800, 652 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 2.31 (s, 3 H), 6.22 (s, 1 H), 7.23 (dd, *J*=2.1, 8.4 Hz, 1 H), 7.38 (d, *J*=8.4 Hz, 1 H), 7.49 (d, *J*=2.1 Hz, 1 H), 7.55 (d, *J*=0.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 13.52, 104.46, 124.80, 125.16, 127.29, 130.26, 130.55, 132.69, 132.97, 137.17, 153.79; EI-MS (*m*/*z*): 226 (M^+, 100), 197 (18), 162 (29),

128 (37). HRMS calcd for: $C_{11}H_8O^{35}Cl_2$ [M^+] 225.9952; Found: 225.9955.

4-(4-Methoxylphenyl)-2-methyl furan (**2c**). Yield: 92%. IR (film) 2954, 1557, 1504, 1251, 1124, 1031, 835, 805, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.30 (s, 3 H), 3.78 (s, 3 H), 6.24 (t, J=0.9 Hz, 1 H), 6.88 (dd, J=2.4, 6.6 Hz, 2 H), 7.36 (dd, J=2.4, 6.6 Hz, 2 H), 7.49 (d, J=0.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.53, 55.18, 104.84, 114.09, 125.43, 126.73, 135.72, 153.02, 158.50; EI-MS (*m*/*z*): 188 (M^+, 100), 173 (57), 159 (12), 145 (16), 115 (23).

4-(4-Chlorophenyl)-2-methyl furan (**2d**). Yield: 99%. IR (film) 2924, 1132, 1096, 908, 832, 800, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.31 (s, 3 H), 6.23 (s, 1 H), 7.28－7.36 (m, 4 H), 7.54 (d, J=0.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.52, 104.65, 126.12, 126.81, 128.82, 131.32, 132.27, 136.72, 153.50; EI-MS (*m*/*z*): 192 (M^+, 100), 163 (21), 149 (8), 129 (48).

4-(4-Bromophenyl)-2-methyl furan (**2e**). Yield: 92%. IR (film) 2924, 1131, 908, 830, 800, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.32 (s, 3 H), 6.24 (s, 1 H), 7.30 (dd, J=2.1, 6.6 Hz, 2 H), 7.46 (dd, J=2.1, 6.6 Hz, 2 H), 7.56 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.55, 104.60, 120.31, 126.16, 127.16, 131.76, 136.75, 153.53; EI-MS (*m*/*z*): 236 (M^+, 100), 207 (15), 128 (56), 111 (23), 71 (39).

2-Methyl-4-(4-methylphenyl) furan (**2f**). Yield: 94%. IR (film) 2917, 1558, 1129, 909, 805, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.31 (s, 3 H), 2.34 (s, 3 H), 6.27 (s, 1 H), 7.14－7.17 (m, 2 H), 7.33－7.36 (m, 2 H), 7.55 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.58, 21.10, 104.87, 125.54, 127.11, 129.03, 129.37, 136.24, 136.36, 153.06; EI-MS (*m*/*z*): 172 (M^+, 100), 143 (27), 129 (40), 115 (14).

4-(3-Methoxyphenyl)-2-methyl furan (**2g**). Yield: 90%. IR (film) 2958, 2835, 1604, 1579, 1228, 1166, 1128, 1043, 920, 831, 823, 779, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.30 (s, 3 H), 3.80 (s, 3 H), 6.28 (s, 1 H), 6.76－6.80 (m,1 H), 6.98－7.06 (m, 2 H), 7.23－7.28 (m, 1 H), 7.57 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.50, 55.09, 104.87, 111.39, 111.96, 118.17, 127.03, 129.66, 134.17, 136.77, 153.16, 159.85; EI-MS (*m*/*z*): 188 (M^+, 100), 159 (18), 145 (17), 129 (12), 115 (28). HRMS calcd for: $C_{12}H_{12}O_2$ [M^+] 188.0837; Found: 188.0835.

4-(3-Chlorophenyl)-2-methyl furan (**2h**). Yield: 96%. IR (film) 2921, 1599, 1132, 919, 783, 761, 686 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.32 (s, 3 H), 6.26 (s, 1 H), 7.20－7.33 (m, 3 H), 7.42－7.43 (m, 1 H), 7.58 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.52, 104.61, 123.68, 125.65, 126.63, 129.03, 129.38, 129.90, 134.54, 137.06, 153.56; EI-MS (*m*/*z*): 192 (M^+, 100), 163 (20), 149 (8), 129 (70), 110 (22). HRMS calcd for: $C_{11}H_9O^{35}Cl$ [M^+] 192.0342; Found: 192.0344.

2-Methyl-4-(1-naphthyl) furan (**2i**). Yield: 95%. IR (film) 3046, 1126, 918, 798, 776, 664 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.37 (s, 3 H), 6.29 (s, 1 H), 7.41－7.49 (m, 5 H), 7.75－7.80 (m, 1 H), 7.83－7.87 (m, 1 H), 8.16－8.20 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.57, 108.49, 125.42, 125.56, 125.70, 125.75, 126.00, 126.53, 127.50, 128.32, 131.23, 131.71, 133.82, 138.53, 152.33; EI-MS (*m*/*z*): 208 (M^+, 100), 193 (15), 179 (26), 165 (71), 152 (18), 89 (10). HRMS calcd for: $C_{15}H_{12}O$ [M^+] 208.0888; Found: 208.0887.

2,3-Dimethyl-4-phenyl furan (**2j**). Yield: 81%. IR (film) 2924, 1758, 1139, 980, 903, 751, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.03 (s, 3 H), 2.26 (s, 3 H), 7.27－7.46 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 9.20, 11.59, 113.09, 126.62, 127.75, 128.46, 128.87, 133.41, 136.65, 148.52; EI-MS (*m*/*z*): 172 (M^+, 100), 157 (11), 143 (39), 129 (67), 115 (20), 77 (11).

2-*n*-Pentyl-4-phenyl furan (**2k**). The Reaction time was 1.5 h, yield: 86%. IR (film) 2956, 2928, 2859, 1553, 1451, 1131, 927, 805, 767, 742, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.90 (t, J=7.2 Hz, 3 H), 1.32－1.38 (m, 4 H), 1.62－1.72 (m, 2 H), 2.63 (t, J=7.5 Hz, 2 H), 6.30 (s, 1 H), 7.20－7.51 (m, 5 H), 7.58 (d, J=0.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.99, 22.41, 27.62, 28.05, 31.36, 103.94, 125.62, 126.65, 126.88, 128.67, 132.90, 136.49, 157.73; EI-MS (*m*/*z*): 214 (M^+, 61), 171 (15), 157 (100), 128 (42), 115 (11), 77 (8).

2.4 The reaction of β-aldehyde allenic sulfides 3a－l with phenylethynyl lithium

Under a nitrogen atmosphere, phenylacetylene (0.45 mmol) was dissolved in anhydrous THF (5 mL) in a 50 mL three-necked flask. *t*-BuLi (1.5 M solution in pentane, 0.36 mmol) was then added dropwise by syringe to the solution at −78℃ (dry ice-acetone bath). The reaction was kept at −78℃ for 30 min, during which aldehyde **3**

(0.30 mmol) in THF (5 mL) was added by funnel. The reaction was continued for an additional 20 min until starting material disappeared as monitored by TLC. HMPA (0.90 mmol) was added to this system at last. The cooled bath was removed and the temperature of system was increased to room temperature. After the intermediate compound was found disappeared by TLC, the reaction was quenched with aqueous NH_4Cl, extracted with ether for 3 times. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column eluted with petroleum ether to afford the furan product **4**.

5-Methyl-3-phenyl-2-phenylethynyl furan (**4a**). Yield: 62%. IR (film) 3060, 2196, 1482, 1158, 958, 755, 764, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.34 (d, J = 0.9 Hz, 3 H), 6.34 (d, J = 0.9 Hz, 1 H), 7.27－7.44 (m, 6 H), 7.51－7.54 (m, 2 H), 7.80－7.84 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.87, 80.85, 95.89, 106.71, 122.66, 126.67, 127.38, 128.38, 128.43, 128.55, 130.70, 131.17, 132.26, 153.80; EI-MS (m/z): 258 (M^+, 81), 232 (20), 215 (45),123 (100), 77 (21), 45 (46). HRMS calcd for: $C_{19}H_{14}O$ [M^+] 258.1045; Found: 258.1047.

5-Methyl-3-(4-methylphenyl)-2-phenylethynyl furan (**4b**). Yield: 61%. IR (film) 2918, 2200, 1554, 1485, 1442, 1156, 958, 823, 805, 754, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.33 (d, J = 0.9 Hz, 3 H), 2.36 (s, 3 H), 6.31 (d, J = 0.9 Hz, 1 H), 7.20－7.23 (m, 2 H), 7.32－7.36 (m, 3 H), 7.51－7.54 (m, 2 H), 7.70－7.73 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.84, 21.20, 81.00, 95.88, 106.69, 122.74, 126.54, 128.34, 129.23, 129.34, 130.74, 131.10, 137.17, 153.67; EI-MS (m/z): 272 (M^+, 100), 257 (4), 229 (54),145 (16). HRMS calcd for: $C_{20}H_{16}O$ [M^+] 272.1201; Found: 207.1203.

5-Methyl-3-(3-methoxyphenyl)-2-phenylethynyl furan (**4c**). Yield: 62%. IR (film) 2953, 2204, 1603, 1465, 1284, 1266, 1233, 1166, 1048, 1014, 780, 755, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.35 (s, 3 H), 3.82 (s, 3 H), 6.34 (s, 1 H), 6.84－6.88 (m, 1 H), 7.30－7.55 (m, 8 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.85, 55.16, 80.82, 96.10, 106.75, 111.97, 113.24, 119.16, 122.59, 128.03, 128.38, 128.47, 129.52, 130.56, 131.16, 133.54, 153.79, 159.73; EI-MS (m/z): 288 (M^+, 100), 273 (16), 245 (75), 202 (24), 105 (24), 77 (12). HRMS calcd for: $C_{20}H_{16}O_2$ [M^+] 288.1150; Found: 288.1150.

5-Methyl-2-phenylethynyl-3-(2-thienyl) furan (**4f**). Yield: 66%. IR (film) 2919, 1608, 1565, 1484, 1442, 1257, 1226, 1158, 802, 754, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.34 (d, J = 0.6 Hz, 3 H), 6.31 (d, J = 0.6 Hz, 1 H), 7.06－7.09 (m, 1 H), 7.25－7.30 (m, 1 H), 7.36－7.41 (m, 4 H), 7.58－7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.83, 80.34, 98.32, 106.33, 122.63, 124.48, 124.57, 125.74, 127.25, 128.42, 128.53, 130.38, 131.11, 134.74, 153.83; EI-MS (m/z): 264 (M^+, 100), 235 (5), 221 (58),176 (9), 129 (10). HRMS calcd for: $C_{17}H_{12}OS$ [M^+] 264.0609; Found: 264.0603.

3-(4-Chlorophenyl)-5-methyl-2-phenylethynyl furan (**4g**). Yield: 62%. IR (film) 3050, 2917, 2192, 1550, 1497, 1482, 1093, 1070, 958, 833, 803, 754, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.36 (s, 3 H), 6.31 (s, 1 H), 7.35－7.40 (m, 5 H), 7.49－7.54 (m, 2 H), 7.73－7.76 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.87, 80.49, 96.28, 106.49, 122.44, 127.90, 128.45, 128.62, 128.73, 130.80, 131.20, 133.05, 154.02;

4,5-Dimethyl-3-phenyl-2-phenylethynyl furan (**4k**). Yield: 67%. IR (film) 3063, 2918, 2205, 1483, 1442, 1256, 1169, 1006, 769, 754, 699, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.02 (s, 3 H), 2.30 (s, 3 H), 7.21－7.60 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 9.40, 11.93, 80.60, 94.52, 114.70, 122.81, 127.21, 128.12, 128.27, 128.72, 131.04, 131.97, 132.59, 149.73; EI-MS (m/z): 229 (M^+, 41), 145 (20), 77 (8), 43 (11). HRMS calcd for: $C_{20}H_{16}O$ [M^+] 272.1201; Found: 272.1201.

2.5 P_2S_5-promoted reaction of β-ketone allenic sulfides 5a－e to form furans

Under a nitrogen atmosphere, ketone **5** (0.5 mmol) and P_2S_5 (0.3 mmol) were mixed in anhydrous toluene (5 mL) in a 25 mL round-bottomed flask. The reaction was continued at 100℃ (oil bath) and completed in 1－2 h as monitored by TLC. The reaction was evaporated directly and the residue was purified by silica gel column eluted with petroleum ether to afford the furan product **6**.

2,5-Dimethyl-3-(4-bromophenyl) furan (**6a**). Yield: 81%. IR (film) 3054, 2918, 1577, 1488, 1221, 1074, 1007, 981, 829, 799, 739, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.26 (s, 3 H), 2.35 (s, 3 H), 6.05 (s, 1 H), 7.18－7.21 (m, 2 H), 7.45－7.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 12.92, 13.31, 106.59, 119.76, 120.40, 128.81, 131.52, 133.41, 145.92, 149.92; EI-MS (m/z): 250 (M^+, 100), 207 (10), 170 (19), 128 (60), 43 (85).

2,5-Dimethyl-3-phenyl furan (**6b**). Yield: 88%. IR (film) 3056, 2919, 1602, 1581, 1440, 1220, 1009, 980, 926, 765, 744, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.28 (s, 3 H), 2.40 (s, 3 H), 6.11 (s, 1 H), 7.36—7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 12.94, 13.37, 106.92, 121.40, 126.01, 127.34, 128.47, 134.53, 145.76, 149.69; EI-MS (*m*/*z*): 172 (M^+, 100), 157 (21), 129 (52), 43 (49).

3-(4-Chlorophenyl)-2,5-dimethyl furan (**6c**). Yield: 87%. IR (film) 3064, 2919, 1579, 1493, 1222, 1093, 1007, 982, 927, 832, 798, 740, 687 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.27 (s, 3 H), 2.36 (s, 3 H), 6.06 (s, 1 H), 7.25—7.34 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 12.91, 13.32, 106.67, 120.41, 128.50, 128.61, 131.74, 133.00, 145.93, 149.92; EI-MS (*m*/*z*): 206 (M^+, 100), 191 (12), 163 (18), 128 (24), 43 (46).

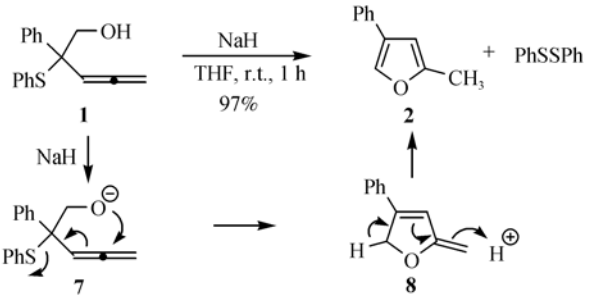
3-(3,4-Dichlorophenyl)-2,5-dimethyl furan (**6d**). Yield: 76%. IR (film) 2920, 1596, 1578, 1477, 1224, 1135, 1028, 799, 739, 687 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.27 (s, 3 H), 2.37 (s, 3 H), 6.05 (s, 1 H), 7.15—7.18 (m, 1 H), 7.39—7.43 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.00, 13.32, 106.43, 119.49, 126.49, 128.93, 130.35, 130.44, 132.48, 134.66, 146.44, 150.21; EI-MS (*m*/*z*): 240 (M^+, 100), 225 (12), 197 (16), 162 (31), 141 (23), 43 (91).

2,5-Dimethyl-3-(3-methylphenyl) furan (**6e**). Yield: 85%. IR (film) 2920, 1608, 1222, 845, 784, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.28 (s, 3 H), 2.37 (s, 3 H), 2.40 (s, 3 H), 6.10 (s, 1 H), 7.04—7.07 (m, 1 H), 7.15—7.29 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 12.94, 13.38, 21.48, 106.99, 121.44, 124.45, 126.81, 128.11, 128.38, 134.47, 138.01, 145.70, 149.60; EI-MS (*m*/*z*): 186 (M^+, 100), 171 (30), 143 (35), 128 (26), 115 (16), 43 (40).

3 Results and discussion

3.1 The investigation of the substrate scope

As described in the experimental part, the preparation of β-hydroxyl allenic sulfides was convenient. Thus, we further attempted to introduce other functional groups onto the hydroxyl group of **1a**. However, we unexpectedly observed cyclization of **1a** when **1a** reacted with NaH at room temperature for 1 h, affording a furan product **2** in 97% yield with removal of phenylthio group. The possible mechanism was proposed as follows (Scheme 4). The hydroxyl proton of **1a** is removed by NaH and the generated oxygen anion attacks the middle carbon of allene moiety, with the removal of phenylthio group. This leads to the formation of the five-membered ring intermediate **8**, which is then rearranged to give furan product **2**. The leaving phenylthio groups is dimerized to PhSSPh in this reaction.

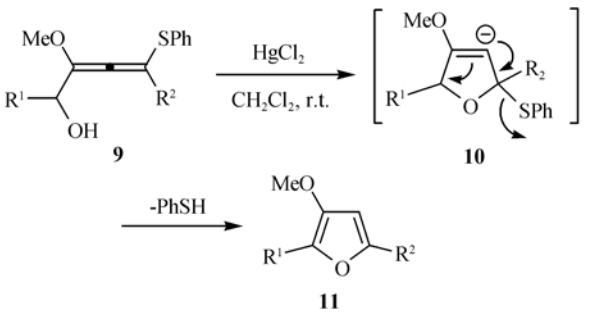


Scheme 4 The reaction of β-hydroxyl allenic sulfide with NaH to form furan.

In general, without activation by functional groups or transition metals, an allene moiety is hard to accept nucleophilic attack. In our system, the oxygen anion attacks the allene moiety intramolecularly with removal of phenylthio group, affording an aromatic conjugated furan derivative, which is thermodynamically stable. We assume that this is the driving force for this reaction.

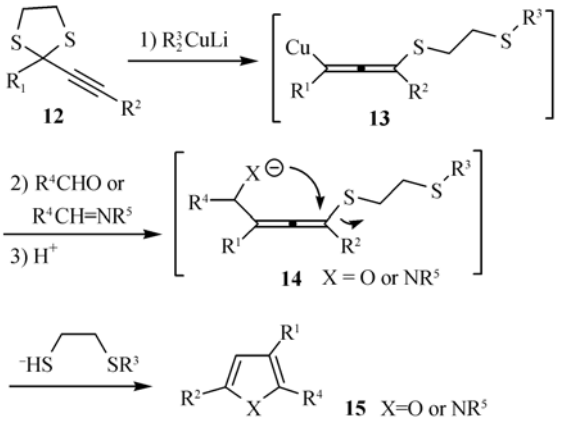
Phenylthio group is a very good leaving group. Tsay et al. have reported a reaction of phenylthio-containing α-allenic alcohol with $HgCl_2$. In that reaction, the hydroxyl group attacks the allene moiety intramolecularly, then cyclization occurs to give furan product **11** via intermediate **10**. The elimination of a phenylthio group also occurs in this reaction (Scheme 5)[21].

Another example is the reaction reported by Luh et al., in which propargylic dithioacetals **12** reacts with lithium alkylcopper to give allenic copper **13**. The intermediate **13** undergoes nucleophilic addition to yield aldehyde or



Scheme 5 The cyclization of phenylthio-containing β-allenic alcohols promoted by $HgCl_2$.

imine **14**, which is subsequently *in situ* cyclized to generate furan or pyrrole product with the removal of thiol molecule (Scheme 6) [22].



Scheme 6 Lithium alkylcopper promoted reaction of propargylic dithioacetals with aldehydes or imines.

β-hydroxyl allenic sulfides **1a**—**k** were easily prepared, and could be transferred into 2,4-disubstituted furan product in high efficiency. This may provide an excellent new methodology to synthesize furan derivative. Therefore, we started to extend the substrate scope of this reaction.

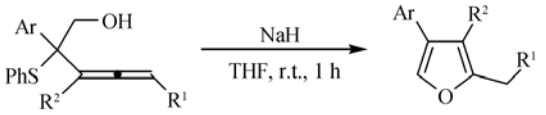
First, the substrates with various Ar groups were examined. The reaction worked similarly well for the substrates bearing either an electron-donating group or an electron-withdrawing group on the phenyl ring (**1a**—**i**). The reaction also worked when there was a substituent on the allene motif, however, the yield was slightly lower. The reaction gave a 2,3,4-trisubstitued furan product **2j** when R^2 was methyl group. When R^1 was *n*-butyl group, the reaction took a little longer time probably due to the steric effect (Table 1).

3.2 Extension of the reaction

With β-hydroxyl allenic sulfides as substrates, only 2,4-disubstituted furan derivatives could be obtained. In the reaction, the oxygen anion is the key intermediate. On the basis of this, we have considered the expansion of this reaction further. Obviously, the addition of a nucleophilic reagent to β-aldehyde allenic sulfide also form an oxygen anion. It is thus expected to obtain a furan derivative bearing one more substitute if the similar process as the above-mentioned reaction occurs.

We proceeded to prepare β-aldehyde allenic sulfide **3a**, and then to investigate the nucleophilic addition with

Table 1 The reaction of **1a**—**k** with NaH to form furans



1a—k **2a—k**

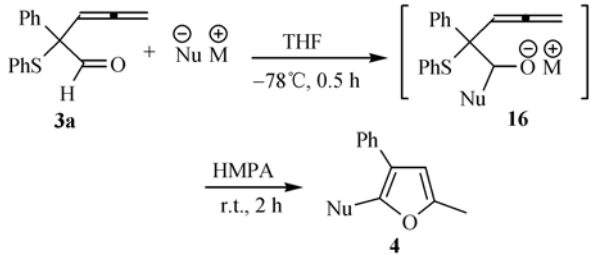
Entry	Substrate (**1**, Ar, R^1, R^2)	Yield (%) [a]
1	**1a**, Ph, H, H	97
2	**1b**, 3,4-$Cl_2C_6H_3$, H, H	90
3	**1c**, 4-$MeOC_6H_4$, H, H	92
4	**1d**, 4-ClC_6H_4, H, H	99
5	**1e**, 4-BrC_6H_4, H, H	92
6	**1f**, 4-$CH_3C_6H_4$, H, H	94
7	**1g**, 3-$MeOC_6H_4$, H, H	90
8	**1h**, 3-ClC_6H_4, H, H	96
9	**1i**, 1-Naphthyl, H, H	95
10	**1j**, Ph, H, CH_3	81
11	**1k**, Ph, *n*-Bu, H	86 [b]

a) Yield of isolated products after column chromatography. b) The reaction time was 1.5 h.

3a. We observed that the starting material decomposed when methyl lithium was added to the system. This may be due to the high reactivity of methyl lithium that can cause side reactions. When methyl Grignard reagent, acetylenyl Grignard reagent or phenylethynyl lithium was added, the first addition could go well at low temperature. However, for the second reaction, the reaction could continue to complete only by adding HMPA and by raising the reaction temperature to room temperature. The subsequent *in situ* cyclization affords the desired furan product **4a** in moderate yield. Without addition of HMPA, we could only isolate the alcohol product **16** (M = H) in high yield, which was formed through the first nucleophilic addition. We also tried phenylethynyl sodium as the nucleophilic reagent. When it was reacted with **3a** at −78℃ first, and then at gradually raising temperature up to room temperature within 0.5 h, furan product **4a** could be formed directly without the addition of HMPA. A possible explanation is that the combination of Mg(Ⅱ) or Li(Ⅰ) cation with oxygen anion is more tight than Na(Ⅰ), which makes the nucleophilicity of oxygen anion weaker when Mg(Ⅱ) or Li(Ⅰ) was the cation ion-pair compared with Na(Ⅰ). Therefore, the additive HMPA was needed to coordinate the metal cation, then the freed oxygen anion can attack the allene moiety to form furan product effectively.

In these reactions, phenylethynyl lithium was prepared

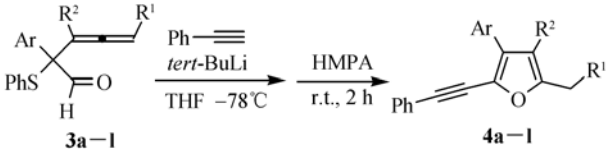
in situ by the reaction of phenylacetylene and *t*-BuLi in THF at −78℃. Phenylethynyl sodium was prepared *in situ* by the reaction of phenylacetylene and NaN(Si-$(CH_3)_3)_2$ in THF at −78℃ (Scheme 7). With **3a** as substrate and under the conditions that phenylethynyl lithium was prepared from lithiation of phenylacetylene by treatment with *t*-BuLi at −78℃, we continued to optimize this reaction by investigating the effect of additives, solvents and the order of substrate adding. It is known that TMEDA can effectively coordinate the lithium cation and promote the reactivity of the anion, providing furan products in similar yield. When diethyl ether or toluene was used as solvent, the yield of this reaction was decreased significantly. We also tried to add HMPA or TMEDA to the reaction system during the process to prepare the phenylethynyl anion, but the reaction system turned complicated. It is probably because the addition of the activated phenylethynyl anion to β-aldehyde allenic sulfide was less selective.



Scheme 7 The reaction of β-aldehyde allenic sulfide **3a** with nucleophilic reagents.

On the basis of all the previous consideration, we started to investigate the reaction of phenylethynyl lithium, prepared from lithiation of phenylacetylene by *t*-BuLi *in situ*. The phenylethynyl lithium was used as nucleophilic reagent to react with a series of β-aldehyde allenic sulfides **3b**—**l** to form 2-phenylethynyl-substituted furan products. HMPA was added after the completion of the first addition in all reactions (Table 2). We have found that the electronic effects have obvious influence over this reaction. When there was an electron-withdrawing substituent in the Ar group, the reaction was less efficient (entries 7—10). For example, when Ar is 3,4-$Cl_2C_6H_3$, only trace product can be obtained (entry 10). For all the reactions, we could isolate some byproducts of high polarity, which might be a mixture of diastereomers of *cis-trans* isomers. However, the exact

Table 2 The reaction of β-aldehyde allenic sulfides **3a**—**l** with phenylethynyl lithium



Entry	Substrate (**3**, Ar, R^1, R^2)	Yield (%) [a]
1	**3a**, C_6H_5, H, H	62
2	**3b**, 4-$CH_3C_6H_4$, H, H	61
3	**3c**, 3-$MeOC_6H_4$, H, H	62
4	**3d**, 4-$MeOC_6H_4$, H, H	66
5	**3e**, 2-Naphthyl, H, H	75
6	**3f**, 2-Thienyl, H, H	27
7	**3g**, 4-ClC_6H_4, H, H	42
8	**3h**, 4-BrC_6H_4, H, H	24
9	**3i**, 3-ClC_6H_4, H, H	17
10	**3j**, 3,4-$Cl_2C_6H_3$, H, H	trace
11	**3k**, Ph, H, CH_3	67
12	**3l**, Ph, ^{n}Bu, H	50

a) Yield of isolated products after column chromatography.

structures of these by-products are still unknown. They are probably some rearranged products generated from the adduct of phenylethynyl anion with aldehyde through other pathways due to the influence of electron-withdrawing groups. More studies on the electronic effects of Ar groups are necessary. The reaction of β-aldehyde allenic sulfides with substitute on the allene moiety went smoothly similar to the previous reaction of β-hydroxyl allenic sulfides with NaH (entries 11,12).

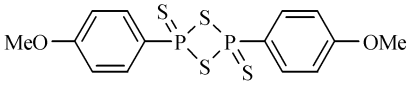
There are several limitations of this reaction. First, this reaction is not easy to handle because it includes several substrates adding steps and needs strict anhydrous conditions. The overall yields are only low to moderate, and so far we have failed to optimize better reaction conditions to improve the yield. The scope of nucleophilic reagents needs to be extended. Moreover, the purity of the furan products formed in this reaction was affected due to their low polarities, which makes it difficult to separate the furan products from the by-product PhSSPh of similar polarity. A possible resolution of this problem is to change the phenylthio group to a 4-methoxyphenylthio group, then the dimerized thioether by-product may have higher polarity and thus can be removed completely away from the furan product.

3.3 Further extension of the reaction

Next, we considered replacing the carbonyl group of the

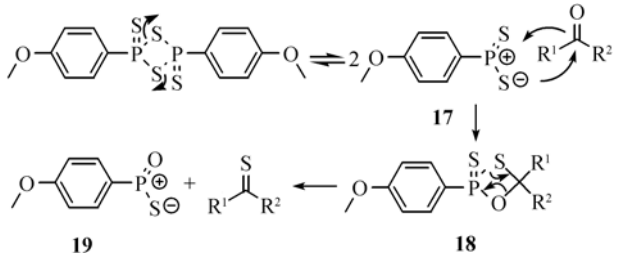
aldehyde substrate with a thiocarbonyl group. It is anticipated that such substrate can cyclize to thiophene under similar conditions through the intramolecular nucleophilic attack of β-sulfur anions to the allene moiety.

Lawesson reagent (LR; Scheme 8) is a common sulfuration reagent which can transform carbonyl group of aldehydes, ketones, amides or esters to the corresponding thiocarbonyl group. Thus, β-ketone allenic sulfide **5a** was first used as substrate. It was attempted to transform **5a** to the corresponding thiocarbonyl compound by adding 1.2 equivalents of Lawensson reagent in toluene at 100℃. Contrary to our expectation, a furan product **6a** was isolated in 97% yield after 5 h. Control experiment showed that this furan product could not be formed under the same condition without adding Lawesson reagent.



Scheme 8 Lawesson reagent.

The mechanism of transforming carbonyl group to thiocarbonyl group by Lawesson reagent is showed in Scheme 9. The dimer of LR is first cleaved to monomer **17**, **17** reacts with carbonyl compound to form four-membered ring **18**, and the retro-ring opening of **18** gives **19** and the thiocarbonyl product. In this reaction, the Lawesson reagent does not function as a sulfuration reagent, but acts in the promotion of a cyclization of the substrate through activating the carbonyl group. We presume that the role of the Lawesson reagent played in this reaction is to attack the carbonyl group of **5a** by the thio anion of **17**, which leads to the generation of an oxygen anion. The oxygen anion further attacks the middle carbon of the allene moiety to give the cyclization furan product **6a**, instead of attacking phosphine and forming four-membered ring **18**.



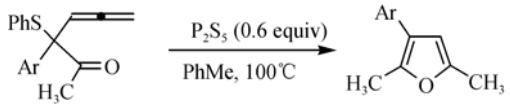
Scheme 9 The mechanism of transforming the carbonyl group to the thiocarbonyl group by the Lawesson reagent.

In this reaction, the Lawesson reagent acts as a nucleophile, which attacks the carbonyl group to generate the oxygen anion. This initiates the cyclization process to form furan product. We then decided to study whether some other simpler nucleophilic reagents could also promote this reaction and also hoped to discover more new reactions. Thus, we studied the reaction of β-ketone allenic sulfide **5b** with 1 equivalent of various nucleophiles, including inorganic nucleophiles such as I_2, KI, and Na_2S, and organic nucleophiles such as MeONa, DMSO, and P_2S_5. Finally, we found the reaction with P_2S_5, which is also a common sulfuration reagent similar to Lawesson reagent, could give furan product **6b** in 88% yield.

Since P_2S_5 is much cheaper than Lawesson reagent as sulfuration reagent, we decided to use P_2S_5 as promoter in the reaction of β-acetone allenic sulfide to form furan product. We found that at least 0.5 equivalent of P_2S_5 was needed for the complete transformation of the substrate to furan product. The P_2S_5 reagent in this reaction does not function as catalyst. It was finally determined that the optimized reaction condition was to carry out the reaction in toluene at 100℃ with 0.6 equivalent of P_2S_5.

Under the optimized reaction conditions, we briefly investigated the generality of this reaction. The reaction of a series of β-ketone allenic sulfides (R = Me) with P_2S_5 all could provide the corresponding furan products with high efficiency. The substituents on Ar did not seem to obviously affect this reaction (Table 3). However, under the same conditions, β-aldehyde allenic sulfide **3a** could not be transformed into the corresponding furan product.

Table 3 P_2S_5 promoted reaction of β-ketone allenic sulfides **5a**—**e** to form furans



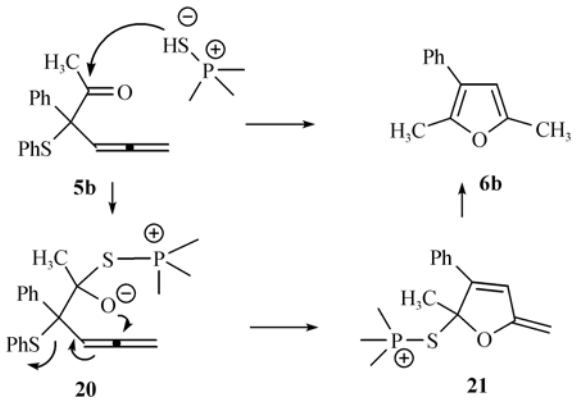
5a—**e** **6a**—**e**

Entry	Substrate (**5**, Ar)	Yield (%) [a]
1	**a**, 4-BrC_6H_4	81
2	**b**, Ph	88
3	**c**, 4-ClC_6H_4	87
4	**d**, 3,4-$Cl_2C_6H_3$	76
5	**e**, 3-MeC_6H_4	85

a) Yield of isolated products after column chromatography.

This reaction also has problems associated with the separation of the furan product from the by-product PhSSPh. Further studies are needed to improve the reaction conditions and to expand the substrate scope.

We proposed a reaction mechanism for this reaction as showed in Scheme 10. The lone pair electron first attacks the carbonyl group of substrate **5b** to form the oxygen anion intermediate **20**, and the oxygen anion then attacks the middle carbon of allene moiety to form intermediate **21**, which finally leads to the formation of furan product. However, more rigorous studies are needed to clarify the detailed mechanistic issue.



Scheme 10 The mechanistic proposal.

4 Conclusions

We have studied the reactions of various kinds of allenic sulfide derivatives which contain β-oxygen functional groups, including alcohols, aldehydes and ketones. These studies lead to the development of novel method to synthesize ploysubstituted furan derivatives under different conditions. The advantage of these reactions includes the convenience of preparing the starting materials. When β-alcohol allenic sulfides or β-ketone allenic sulfides are used as substrates, the reaction operation is simple and the yields of product are generally high.

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