Dihydrofurans via an Intramolecular Alkoxide Addition to an Allenylphosphine Oxide

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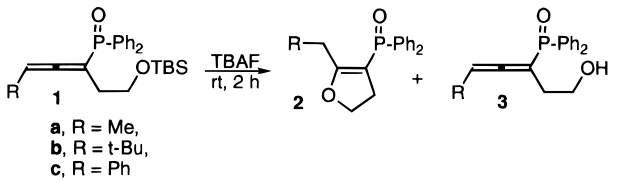
Our research interests involve the development of new synthetic strategies for the synthesis of heterocyclic ring systems through the reactions of allenes with tethered nucleophiles. Allenes have recently become important in the synthesis of five- and six-member carbocyclic[1] and heterocyclic[2] ring systems. However, relatively little work has been performed on the addition of nucleophiles to allenyl phosphates.[3] In this paper we would like to report our findings on the intramolecular cyclization of tethered alkoxides to allenylphosphine oxides to afford good to excellent yields of 2-alkyl- and 2-aryl-3-(diphenylphosphinoyl)-4,5-dihydrofurans (DHFs). To examine the potential of the cyclization (Scheme 1), a series of TBDMS protected allenylphosphine oxides **1** were prepared in two steps from conveniently accessible starting materials. It was originally envisioned that the deprotection of **1** would afford the free alcohols **3**. Then, using methods similar Marshall's furan syntheses, the alcohols would be cyclized to dihydrofurans **2** using base or Lewis acid.[4] Surprisingly, deprotection with TBAF afforded directly the DHFs **2** in excellent yields.

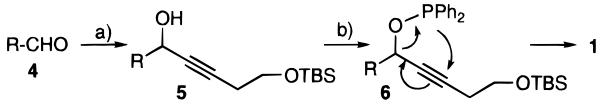
Synthesis of the starting allenes began with the coupling of appropriate aldehydes with the lithium salt of 1-(*tert*-butyldimethylsilyloxy)-3-butyne to afford proparglylic alcohols **5a**−**c** (Scheme 2).[5] Treatment of the proparglylic alcohols with chlorodiphenylphosphine afforded, after a [2,3]-sigmatropic rearrangement, allenyl phosphine oxides **1a**−**c** in excellent yields.[6] Reaction of **1a**−**c** with tetrabutylammonium fluoride in dry THF at room temperature for 1 h initiated cyclization to DHFs **2a**−**c**.[7]

When the substituents R were sterically small on the allenylphosphine oxides, such as **1a** (R = Me) or **1c** (R = Ph), only DHFs **2a** (91%) and **2c** (84%) were isolated. Neither allenols **3a** or **3c** were observed in the ^{1}H-NMR spectra of the crude material. Cyclization occurred in less than 1 h and was found not to require an inert atmosphere or rigorous anhydrous conditions. Inspection of the ^{1}H NMR spectrum of the crude material showed the near quantitative conversion of **1a** to dihydrofuran **2a** with little to no side products. Even deprotection of allenes **1a** and **1c** in wet THF failed to afford the corresponding allenols **3**. When 1 M TBAF in THF was diluted with ∼20% water, protected allenols were quantitatively recovered. Deprotection of **1b** (R = t-Bu) afforded, after workup and HPLC purification, dihydrofuran **2b** (36%) and allenol **3b** (54%). Reaction conditions, including exclusion of a proton source, concentration, and temperature effects had nominal effect on product ratio or overall reaction yield. Cyclization is clearly hindered by the steric bulk of the t-Bu group in **1b**. Attempts to cyclize allenol **3b** under a variety of conditions, such as deprotonation with *tert*-butoxide,[8] potassium hydride,[9] or reaction with $AgNO_3$[10] proved unproductive, affording only trace amounts of DHFs by ^{1}H-NMR analysis.

Scheme 1

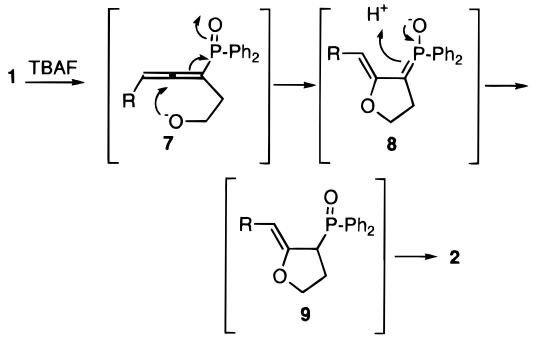


Scheme 2



a) LiCCCH$_2$CH$_2$OTBS, THF, -78 °C, b) ClPPh$_2$, DMAP, Et$_2$O, 36 h.

Scheme 3



One mechanistic proposal for the formation of the DHFs involves deprotection of the silyl ether to afford alkoxide **7**, followed by its conjugate addition to the sp-hybridized carbon of the allenylphosphine oxide to afford the phosphorus enolate **8**. Tautomerization of enolate **8** afforded only dihydrofuran **2**. No exocyclic enol ether **9** was ever observed. Attempts to trap **8** or **9** with electrophilic methyl iodide proved futile. We therefore propose that the enolate **8** directly protonates to afford the dihydrofuran **2**. However, a second possible mechanism would involve addition of alkoxide **7** in an 5-exo-dig manifold to afford directly DHF **2**.[11]

We have developed a short and efficient synthesis of sterically unhindered 2,3-disubstituted dihydrofurans using an intramolecular addition reaction of a tethered alkoxide to an allenylphosphine oxide. Future studies on this potentially important new synthetic methodology are currently in progress. Studies to determine the effects of ring size and electronic and steric effects of both

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allenyl and phosphorus substitutents and mechanism will be reported in due course.

Experimental Section

1-(*tert*-Butyldimethylsilyloxy)-3-(diphenylphosphinoyl)-3,4-hexadiene (1a). To a solution of proparglylic alcohol **5a** (951 mg, 4.16 mmol), dry ethyl ether (20 mL), and DMAP (2.04 g, 16.6 mmol) was added chlorodiphenylphosphine (1.84 g, 8.32 mmol). After stirring for 48 h at rt, the reaction was quenched with water (20 mL) and the aqueous layer extracted with ether (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and chromatographed (80% EtOAc/hexane) to afford 1.48 g (86%) of allene **1a**. ^{1}H-NMR (270 MHz, $CDCl_3$): δ −0.01 (6H, s), 0.84 (9H, s), 1.42 (3H, t, $J \sim 6.9$ Hz), 2.3−2.3 (2H, m), 3.71 (2H, t, $J \sim 7$ Hz), 5.0 (1H, m), 7.3−7.5 (6H, m), 7.6−7.7 (4H, m).

1-(*tert*-Butyldimethylsilyloxy)-6,6-dimethyl-3-(diphenylphosphinoyl)-3,4-heptadiene (1b). Using the procedure for the synthesis of **1a**, to proparglylic alcohol **5b** (400 mg, 1.48 mmol), dry diethyl ether (9 mL), and DMAP (723 mg, 5.92 mmol) was added chlorodiphenylphosphine (651 mg, 2.96 mmol). Workup and chromatography (80% EtOAc/hexane) afforded 618 mg (92%) of allene **1b**. ^{1}H-NMR (270 MHz, $CDCl_3$): δ −0.06 (6H, s), 0.68 (9H, s), 0.81 (9H, s), 2.3−2.5 (2H, m), 3.71 (2H, dt, $J \sim 1.7$ Hz, 8.6 Hz), 5.0 (1H, dt, $J \sim 11.1$ Hz,1.7 Hz), 7.2−7.5 (6H, m), 7.6−7.8 (4H, m).

1-(*tert*-Butyldimethylsilyloxy)-5-phenyl-3-(diphenylphosphinoyl)-3,4-pentadiene (1c). Using the procedure for the synthesis of **1a**, to proparglylic alcohol **5c** (643 mg, 1.35 mmol), dry diethyl ether (10 mL), and DMAP (394 mg, 5.42 mmol) was added chlorodiphenylphosphine (596 mg, 2.71 mmol). Workup and chromatography (80% EtOAc/hexane) afforded 5.97 mg (86%) of allene **1c**. ^{1}H-NMR (270 MHz, $CDCl_3$): δ −0.05 (3H, s), −0.03 (3H, s) 0.82 (9H, s), 2.5−2.6 (2H, m), 3.81 (2H, t, $J \sim 6.7$ Hz), 6.37 (1H, dt, $J \sim 11.1$, Hz, 3.0 Hz,), 7.0−7.4 (11H, m), 7.6−7.7 (4H, m).

2-Ethyl-3-(diphenylphosphinoyl)-4,5-dihydrofuran (2a). A solution of (n-Bu)$_4$NF (3.5 mL, 1 M in THF, 3.5 mmol) was added dropwise to the TBDMS allene **5a** (391 mg, 94 mmol) in dry THF (3.5 mL) under a nitrogen atmosphere. The mixture was stirred for 1 h at rt, quenched with brine (3 mL), and extracted with ether (3 × 3 mL). The combined organic layers were washed with saturatated $NaHCO_3$ (5 × 10 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed (80% EtOAC/hexanes) to afford 257 mg (91%) of dihydrofuran **2a**. ^{1}H-NMR (270 MHz): ($CDCl_3$): δ 2.94 (3H, t, $J \sim 7.5$ Hz), 2.33 (2H, q, $J \sim 7.5$ Hz), 2.62 (2H, t, $J \sim 9.4$ Hz), 4.36 (2H, t, $J \sim 9.4$ Hz), 7.5−7.6 (6H, m), 7.6−7.8 (4H, m). ^{13}C-NMR (67.95 MHz): ($CDCl_3$) δ 11.6, 21.3, 33.4 (d, $J \sim 10$ Hz), 70.1 (d, $J \sim 10$ Hz), 95.3 (d, $J \sim 123$ Hz), 128.4, 128.6, 131.4, 131.5, 131.6, 131.7, 132.8, 134.3, 173.4 (d, $J \sim 20$ Hz). IR: (CCl_4) ν 3058, 2973, 2939, 2898, 1623, 1438, 1365, 1199,1118, 1064, 721, 698 cm^{-1}. HRMS (70 ev EI): 298.1122 calcd for $C_{18}H_{19}O_2P$, 298.1114). LRMS; *m*/*z* 298(74, M^+), 283(11), 269(11), 241(7), 227(3), 201(34), 183(14), 173(4), 155(8), 141(10), 129(21), 115(14), 91(10), 84(base), 77(54).

2-(2,2-Dimethylpropyl)-3-(diphenylphosphinoyl)-4,5-dihydrofuran (2b). Following the procedures for the deprotection of **2a**, (n-Bu)$_4$NF (3.2 mL, 1 M in THF, 3.2 mmol) was added dropwise to TBDMS allene **1b** (473 mg, 1.04 mmol) to afford after workup and purification, 134 mg (36%) of dihydrofuran **2b** ^{1}H-NMR (270 MHz): ($CDCl_3$): δ 0.92 (9H, CH_3, s), 2.46 (2H, CH_2, s), 2.60 (2H, H_3, t, $J \sim 9.2$ Hz), 4.35 (2H, H_3, t, $J \sim 9.2$ Hz), 7.4−7.5 (6H, ArH, m), 7.6−7.8 (4H, ArH, m), and 191 mg (54%) of uncyclized allenol **3b** ^{1}H-NMR (270 MHz, $CDCl_3$): δ 0.72 (9H, s), 2.46−2.55 (2H, m), 3.82−3.74 (2H, m), 5.10 (1H, dt, $J \sim 10.9$ Hz,1.7 Hz), 7.4−7.6 (6H, m), 7.6−7.8 (4H, m).

2-Phenyl-3-(diphenylphosphinoyl)-4,5-dihydrofuran (2c). Following the procedures for the deprotection of **2a**, (n-Bu)$_4$NF (2.8 mL, 1 M in THF, 2.8 mmol) was added dropwise to TBDMS allene **1c** (443 mg, 0.93 mmol) in dry THF (3 mL) to afford after workup and purification 282 mg (84%) of dihydrofuran **2c**. ^{1}H-NMR (270 MHz, $CDCl_3$): δ 2.62 (2H, t, $J \sim 9.2$ Hz), 3.80 (2H, s), 4.35 (2H, t, $J \sim 9.2$ Hz), 7.1−7.2 (5H, m), 7.4−7.5 (6H, m), 7.6−7.8 (4H, m).

1-(*tert*-Butyldimethylsilyloxy)-3-pentyn-5-ol (5a). A solution of 4-(*tert*-butyldimethylsilyloxy)-1-butyne (6.78 g, 36.8 mmol) in dry THF (100 mL) was cooled to −78 °C, and *n*-butyllithium (25 mL, 1.55 M , 38.8 mmol) was added dropwise. The solution was stirred for 5 min at −78 °C, warmed to rt for 20 min, and then recooled to −78 °C. A solution of acetaldehyde (**4a**) (5.00 g, 58.1 mmol) in 100 mL of THF was added dropwise via cannula. After stirring for 1 h at −78 °C, the reaction was warmed to rt and quenched with water. The organic layer was separated and the aqueous layer extracted with ether (3 × 100 mL). The combined organic layers were washed with saturated NH_4Cl, dried over $MgSO_4$, and concentrated. Distillation of the crude residue (Kugelrohr (165−170 °C, 1 mm) afforded 11.9 g of the proprogyl alcohol **5a** (82%) as a clear oil. ^{1}H-NMR (270 MHz, $CDCl_3$): δ −0.01 (6H, s), 0.82 (9H, s), 1.31 (3H, d, J ∼ 7.4 Hz), 2.32 (2H, dt, $J \sim 1.1$ Hz, 7.9 Hz), 3.62 (2H, t, $J \sim 7.9$ Hz), 4.39 (1H, tq, $J \sim 1.1$ Hz, 7.4 Hz).

1-(*tert*-Butyldimethylsilyloxy)-6,6-dimethyl-3-heptyn-5-ol (5b). Using the procedure for the preparation of **5a**, *n*-butyllithium (25 mL, 1.55 M in hexanes, 38.8 mmol) was added to 4-(*tert*-butyldimethylsilyloxy)-1-butyne (6.56 g, 35.6 mmol) in THF (100 mL), followed by trimethylacetaldehyde (**4b**) (5.00 g, 58.1 mmol) in THF (100 mL) to afforded after workup and distillation (165−170 °C, 1 mm), 11.9 g of the proprogyl alcohol **5b** (82%) as a clear oil. ^{1}H-NMR (270 MHz, $CDCl_3$): δ 0.05 (6H, s), 0.88 (9H, s), 0.96 (9H, s), 2.42 (2H, dt, $J \sim 1.8$ Hz, 7.1 Hz), 3.70 (2H, t, $J \sim 7.1$ Hz), 3.97 (1H, dt, $J \sim 1.8$ Hz, 5.9 Hz).

5-(*tert*-Butyldimethylsilyloxy)-1-phenyl-2-pentyn-1-ol (5c). Using the procedure for the preparation of **5a**, *n*-butyllithium (24 mL, 1.55 M , 37.2 mmol) was added to 4-(*tert*-butyldimethylsilyloxy)-1-butyne (6.30 g, 34.2 mmol) in THF (100 mL), followed by benzaldehyde (**4c**) (5.00 g, 59.0 mmol) in THF (100 mL) to afforded after workup and distillation (200−210 °C, 1 mm), 11.4 g of the proprogyl alcohol **5c** (85%) as a clear oil. ^{1}H-NMR (270 MHz, $CDCl_3$): δ 0.08 (6H, s), 0.91 (9H, s), 2.50 (2H, dt, $J \sim 1.8$ Hz, 7.1 Hz), 3.76 (2H, t, $J \sim 7.0$ Hz), 5.40 (1H, s) 7.3−7.6 (5H, m).

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Supporting Information Available: Spectroscopic data (^{1}H-NMR, ^{13}C-NMR, IR, HRMS, and LRMS) for all new compounds (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered form the ACS: see any current masthead page.

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