ORGANIC LETTERS

2003
Vol. 5, No. 2
129−131

Novel Phosphine-Catalyzed Zipper Cyclization of Aliphatic Diyne–Dione and Yne–Dione Systems

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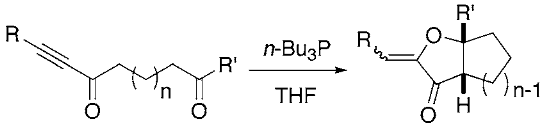
Received September 30, 2002

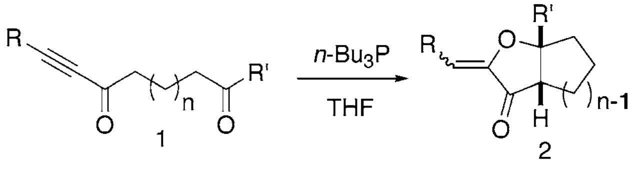
ABSTRACT



An unexpected tri-*n*-butylphosphine-catalyzed zipper cyclization of diyne–diones (1a–d) or yne–diones (1e and 1f) is described. Bicyclic ketones (2a, 2b, 2c, 2e, and 2f) with five- or six-membered rings fused to the five-membered ring were obtained from both aliphatic diyne–diones (1a–c) and yne–diones (1e and 1f) having tetra- or pentamethylene spacers. The bicyclic products (2) were produced with high diastereoselectivity.

Trialkylphosphines are useful mild reagents in various organic reactions[1] such as the addition of alcohols to acetylenes having electron-withdrawing substituents[2] and the isomerization of ynones, ynoates, and ynamides to the corresponding (2*E*,3*E*)-diene[3] and polyenes.[4] Trost et al. have reported a phosphine-catalyzed cyclization of ω-hydroxyynoates to the corresponding tetrahydrofuran or tetrahydropyran derivatives.[5] We previously reported a convenient synthetic method for the α-vinylfurans by the phosphine-initiated tandem reaction.[6] The phosphine-catalyzed addition of heteronucleophiles made it possible to design novel polyaddition methods of diyne monomers.[7] As a candidate of the diyne monomer for the novel polyaddition with bifunctional heteronucleophiles, aliphatic bisynones were subjected to the reaction which, however, was found to undergo an unexpected highly regio- and stereoselective zipper cyclization (Scheme 1).

Scheme 1



The reaction of ynones with alcohols provides the corresponding β-alkoxyenones in the presence of tri-*n*-butylphosphine (n-Bu_3P) under mild conditions.[7c] The analogous

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10.1021/ol020198n CCC: $25.00 © 2003 American Chemical Society
Published on Web 12/28/2002

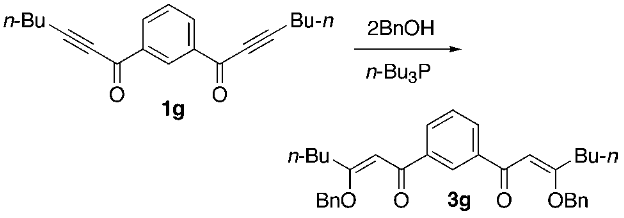
Table 1. Tri-*n*-butylphosphne-Catalyzed Cyclization of **1**[a]

run	R	R′	*n*	**1** and **2**	**1** → **2** yield (%)[b]
1	*n*-Bu	*n*-BuC≡C	2	**a**	59
2	Ph	PhC≡C	2	**b**	63
3	Ph	PhC≡C	3	**c**	73
4	Ph	PhC≡C	4	**d**	0
5	Ph	H	2	**e**	50
6	*n*-Bu	CH_3	3	**f**	41

[a] The reaction was carried out at room temperature in THF (0.5 M) in the presence of *n*-Bu_3P (20 mol %) as a catalyst. [b] Isolated yield by SiO_2 column.

reaction also took place with bisynone **1g** and benzyl alcohol in the presence of *n*-Bu_3P (20 mol %) giving rise to *β*-alkoxyenone (**3g**) in 87% yield (Scheme 2). In the case of bifunctional ynones **1a**, **1b**, and **1c**, however, unexpected bicyclic products **2a**, **2b**, and **2c**, respectively,[8] were obtained in good yields.[9]

Scheme 2



As summarized in Table 1, the same bicyclic products could be obtained without benzyl alcohol (runs 1−3). Although **2a** was contaminated with a small amount of the geometric isomer (run 1) (*Z*:*E* 92:8),[11] **2b** and **2c** proved to be composed of a single isomer (runs 2 and 3)[12] indicating that the zipper cyclization reaction proceeds in a highly diastereoselective fashion.

In the case of a bisynone (**1d**) containing a hexamethylene spacer, a bicyclic product could not be obtained due to oligomerization (run 4). Ynones possessing *ω*-aldehyde and *ω*-ketone substituents (**1e** and **1f**, respectively) also provided bicyclic ketones (**2e** and **2f**, respectively) in 50% and 35% yields by means of the zipper cyclization (runs 5 and 6). In these cases, the high diastereoselectivity was also established by the ^1H NMR spectra.[13] The NOE difference spectra of **2e** and **2f** indicate that two methine protons in **2e** and the methine proton and the methyl group in **2f** on the fused carbons are in a *cis* relationship (Figure 1).

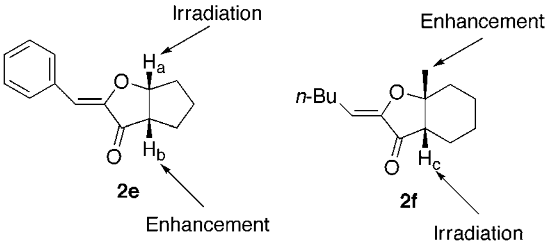
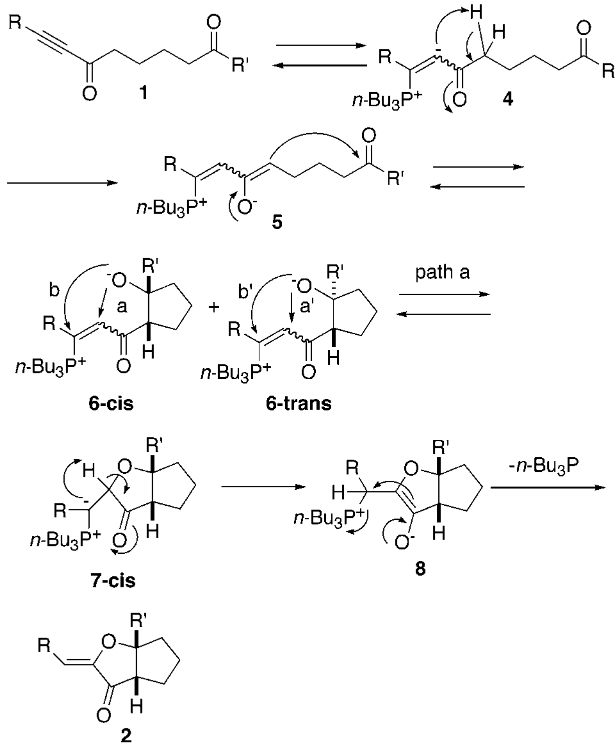


Figure 1. NOE experiments for **2e** and **2f**.

One possible reaction pathway is shown in Scheme 3. A zwitterionic intermediate (**4**) produced by the conjugate addition of the phosphine catalyst undergoes an intramolecular proton migration (1,3-proton shift) from the inner α-methylene. A nucleophilic attack of the resulting enolate

Scheme 3



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(8) The structure of **2c** was confirmed by ^1H NMR, ^{13}C NMR, IR, and mass analyses (see ref 10). Aliphatic five- or six-membered-ring moieties were assigned by the $^1H-^1H$ COSY and the $^{13}C-^1H$ COSY spectra. The carbon skeleton in the bicyclic system was supported by the INADEQUATE and HMBC techniques.

(9) For example, the reaction of **1c** provides **2c** in 75% yield in the presence of benzyl alcohol.

(10) A typical experimental procedure: To a solution of **1c** (200 mg, 0.610 mmol) in THF (1.2 mL) was added tri-*n*-butylphosphine (25 mg, 0.124 mmol) at room temperature. After being stirred for 12 h, the reaction mixture was concentrated under vacuum. The product (**2c**) was isolated by column chromatography on silica gel (hexane/ethyl acetate = 20/1) in 72.5% (145 mg, 0.442 mmol) yield. **2c**: R_f 0.65 on TLC (SiO_2, hexane/ethyl acetate 4/1); IR (neat) 3059, 2940, 2232, 1736, 1638, 1491, 1447, 1329 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm) 1.21 (m, 1 H, $-CH-$), 1.58 (m, 2 H, $-CH_2-$), 1.67 (m, 2 H, $-CH_2-$), 1.85 (m, 1 H, $-CH-$), 2.20 (m, 1 H, $-CH-$), 2.31 (m, 1 H, $-CH-$), 2.93 (t, J = 4.40 Hz, 1 H, $-COCH<$), 6.45 (s, 1 H, $PhCH=$), 7.2−7.4 (6 H, C_6H_5-), 7.48 (m, 2 H, C_6H_5-), 7.81 (d, J = 8.80 Hz, 2 H, C_6H_5-); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) 21.9, 22.0, 36.6, 51.9, 79.2, 86.6, 88.3, 106.9, 121.7, 128.2, 128.4, 128.8, 130.2, 131.8, 133.4, 145.6, 198.9; MS (EI) m/z 328 (M^+).

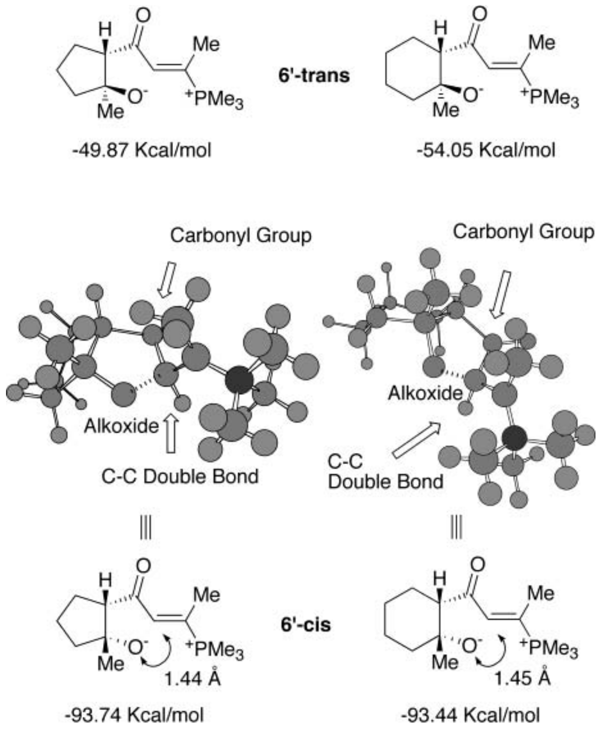

Figure 2. Heat of formation for model compounds containing trimethylphosphonium moieties (PM3 semiempirical minimization).

(**5**) to the carbonyl group at the ω-position produces alkoxide intermediates (**6**-*cis* and **6**-*trans*). On the basis of the results obtained by the PM3 molecular orbital calculations of model compounds (**6′**) containing trimethylphosphonium moieties,[14] all **6′**-*cis* forms are thermodynamically more stable than trans isomers (Figure 2). It is also of note that the distance between the alkoxide and the olefinic carbon adjacent to the carbonyl group (1.44~1.45 Å) is shorter than that between the alkoxide and the other olefinic carbon (2.44 Å). Therefore, the addition of the alkoxide produces the ylide (**7**-*cis*), which undergoes an intramolecular protonation from the methylene group adjacent to the carbonyl group, followed by the elimination[15] of the phosphine to produce **2**.

In summary, the tri-*n*-butylphosphine-catalyzed highly stereoselective zipper cyclization of diyne−dyones and yne−diones via double proton migrations has been demonstrated. Further work on the application of the present reaction is currently being investigated.

Acknowledgment. We are grateful to Dr. Y. Nakamura at Chemical Resources Laboratory (Tokyo Institute of Technology) and the NMR Application Laboratory of JEOL Ltd., Japan, for the INADEQUATE, HMBC, and NOE experiments.

Supporting Information Available: Full characterization (IR, ^{1}H NMR, ^{13}C NMR, and MS spectra) for **2c** and some DNOE spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) In the ^{1}H NMR spectrum of **2a**, two olefinic protons attributed to *E*- and *Z*-isomers were observed at 5.38 ppm (minor) and 5.44 ppm (major). For the determination of the stereochemistry of the products, the major isomer was reduced by DIBAL-H to the corresponding secondary alcohol. In the NOE differential experiment of the alcohol, an NOE was observed between the carbinol proton and the olefinic proton. Therefore, this major isomer was determined as a *Z*-isomer.

(12) In the ^{1}H and ^{13}C NMR spectra of **2b** and **2c**, no peak assignable to diastereoisomers was observed.

(13) In the case of **2f**, the geometric isomer ratio was determined as *E*:*Z* 90:10. The product (**2e**) proved to be composed of a single isomer (*Z*) as is the case for **2b**.

(14) Molecular orbital calculations were performed with MacSpartan Plus ver. 1.2.1; Wavefunction Inc.

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