Notes

Extraordinary Formation of a Novel Butadiene Derivative, (*Z*,*E*)-1-(2-Naphthylmethyloxycarbonyl-amino)-2,4-bis(4-nitrophenyl)butadiene, and Subsequent Isomerization into the Corresponding (*E*,*E*)-Isomer

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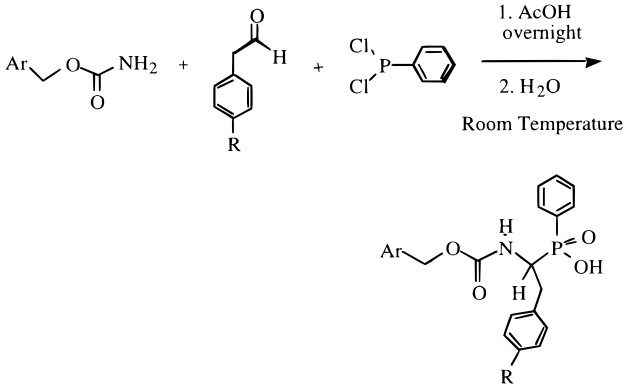
Phosphorus-containing peptide analogues have been widely utilized in designs of novel protease inhibitors because of their ability to mimic the transition state of enzymatic catalyses.

α-Amino phosphonates were most frequently incorporated in such designs;[1−4] on the other hand, α-amino phosphinates received less attention. In our ongoing program of de novo design of thrombin inhibitors, we find, as supported by molecular modeling, that the structural features of α-amino phosphinates could be beneficial to our goal of developing noncovalent active site inhibitors.

The α-amino phosphinates utilized in our design as the key building blocks are *N*-CBZ-protected [1-amino-2-(4-substituted-phenyl)ethyl]phenylphosphinates (**1**), which were synthesized by adopting a procedure of Chen and Dan[5] (Scheme 1). In a typical preparation, benzyl carbamate was treated with (4-nitrophenyl)acetaldehyde[6] and dichlorophenylphosphine in acetic acid to give a good yield (∼60%) of the desired 4-nitrophenyl compound **2**. When the benzyl carbamate was substituted by 2-naphthylmethyl carbamate in the same reaction under identical conditions, however, much less material was obtained. Moreover, an unexpected compound **4** was formed as the major product (a relative 80%, mol/mol) present in the crude material, while the desired compound **3** was produced in 20% yield. The major product was purified from the crude material and its ^{1}H NMR (Figure 1, top) showed a distinctively different pattern from that of the expected one (**3**), and elemental analysis revealed a composition of $C_{28}H_{21}N_3O_6$ with no phosphorus present, in agreement with the mass spectrometric analysis (CI mode) which showed an $[M + 1]^+$ peak at *m*/*e* 496. A

Scheme 1



1, Ar = phenyl;
R = functional group.
2, Ar = phenyl; R = nitro.
3, Ar = 2-naphthyl; R = nitro.

careful examination of the ^{1}H NMR spectrum (in DMSO-d_6) of **4** revealed the presence of an "impurity", and it was soon discovered that the peaks of this "impurity" increased as those of **4** decreased (Figure 1) while the NMR solution of the product stood at room temperature. An important characteristic of this transformation (with a half-life of ∼4 months) is that the total number of the new peaks is equal to that of the old one (**4**) and, more importantly, the new scalar coupling constants appear to remain the same. This indicates that some key structural features of the original product **4** were preserved and the transformation is an intramolecular event, such as isomerization. Compound **4** appears to be stable in its solid form when kept in the dark at room temperature. However, under somewhat elevated temperature, even the solid underwent transformation.

A scrutiny of several possible mechanisms led us to the structure of (*Z*,*E*)-butadiene **4** shown in Figure 2 as the original product, which slowly isomerizes into the (*E*,*E*)-butadiene **5** (Figure 2). The results of 1D ^{1}H NMR (Figure 1) and 2D COSY experiments[7] support the basic configuration of the product (**4**) as a butadiene. The important connectivities between neighboring protons of 1 and 2, 3, and 4 are clearly evidenced in the COSY spectrum,[7] and the same spectrum also shows that these connectivities are preserved in the isomer (**5**), as indicated by cross-peaks of 1′−2′ and 3′−4′. The coupling constant between protons 3 and 4 was found to be 16 Hz, leading to the assignment of a trans (*E*) configuration for the second double bond. The ROESY experiments,[7] on the other hand, provided crucial through-space coupling data, rendering possible the unambiguous assignment of the configurations and conformations for both **4** and its isomer, **5**. Some key ROESY cross-peaks for

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(7) The 2D COSY and ROESY experimental parameters and results (Figures 3−5) are included in the Supporting Information for this paper. However, some key ROESY cross-peaks observed in a mixture of **4** and **5** are summarized in Table 1.

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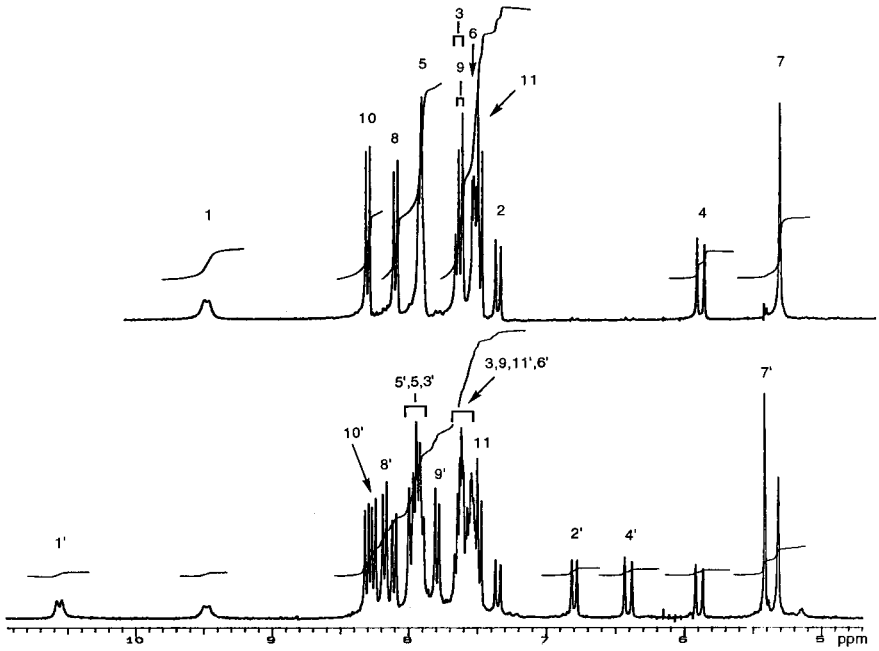
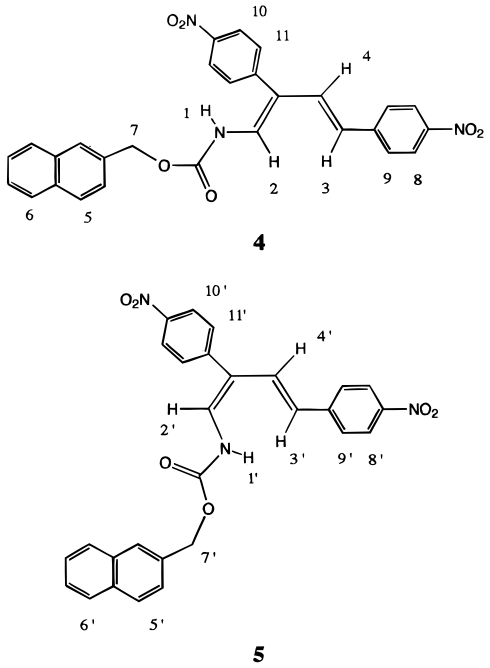


Figure 1. ^{1}H NMR spectra of **4** in DMSO-d_6 (Varian XL-300): top, immediately after dissolution (for assignment of protons, see Figure 2); bottom, after the solution stood at room temperature for approximately 4 months.



4

5

Figure 2. Structures of compound **4** and **5** and proton assignments.

Table 1. Summary of Key ROESY Cross-Peaks

compd **4**	compd **5**
1−11	1′−3′
2−3	2′−11′
4−11	4′−11′

compounds **4** and **5**, respectively, are summarized in Table 1. First of all, the presence of the cross-peak 1−11 in the ROESY spectrum established a *Z* configuration for the first double bond. Second, the overall conformation of the product **4** is determined to be *s*-*Z* by the occurrence of cross-peaks 2−3 and 4−11. The observation of these two cross-peaks also confirmed the previous assignment of an *E* configuration for the first double bond on the basis of the coupling constant. Last, as compound **4** isomerized to **5**, cross-peaks 1′−3′ and 2′−11′ occurred while neither cross-peak 1′−11′ nor 2′−3′ was observed, consistent with the proposed transformation. In both isomers, cross-peaks 4−11 and 4′−11′ remained. It is interesting to note that both **4** and **5** are locked in the *s*-*Z* conformation.

The first striking feature of the proposed mechanism (Scheme 2) is the role played by the naphthylmethyl group that diverted the reaction course leading to the predominant formation of an unexpected new structure [a reexamination of the ^{1}H NMR spectrum of the crude product of **2** revealed that the corresponding benzylbutadiene compound **7** was also formed, but as a minor product, with a relative 13% yield]. The importance of the naphthalene ring may be related to the enamine form of intermediate **8**. Presumably, the naphthalene ring facilitates the formation of the enamine **8a**, a nucleophile, possibly by an unconventional hydrogen-bonding interaction[8] involving its π orbital and the amide proton. Such an interaction may be more favored with the naphthalene ring than with the benzene ring, since the more extended π orbital of the naphthalene ring may have a stronger interaction with the amide proton. The second feature is the formation of an electrophile **9** through the putative enolization of (4-nitrophenyl)acetaldehyde; such enolization has been suggested before by the present authors to have played a central role in the oxidative degradation of 4-nitrophenethyl alcohol by the Collins reagent.[9] In the formation of both the enamine **8a** and enol **9**, the key nucleophile and electrophile in the proposed mechanism, the nitro group plays a unique and critical role, probably by inducing and/or stabilizing the more conjugated enamine and enol forms through its remarkable reso-

(8) Unconventional hydrogen bonding with a benzene ring acting as hydrogen bond acceptor was observed experimentally,[8a] and theoretical calculation indicated that it was about half as strong as normal hydrogen bonding.[8b] (a) Mitchell, J. B.; Nandi, C. L.; McDonald, I. K.; Thornton, J. M.; Price, S. L. *J. Mol. Biol.* **1994**, *239*, 315−331. (b) Levitt, M.; Perutz, M. F. *J. Mol. Biol.* **1988**, *201*, 751−754.

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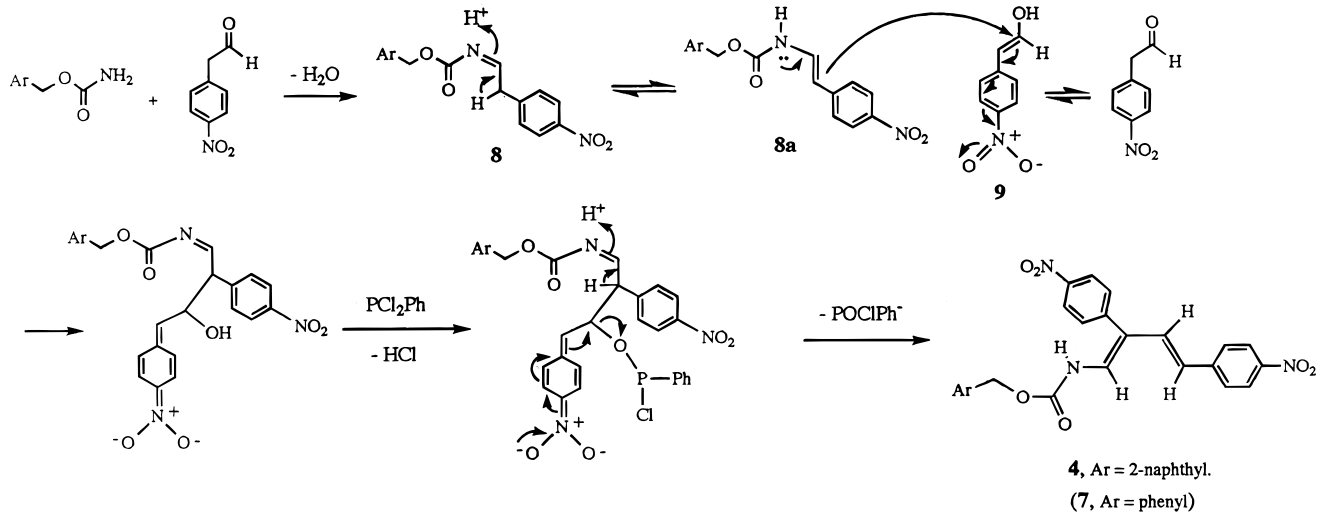
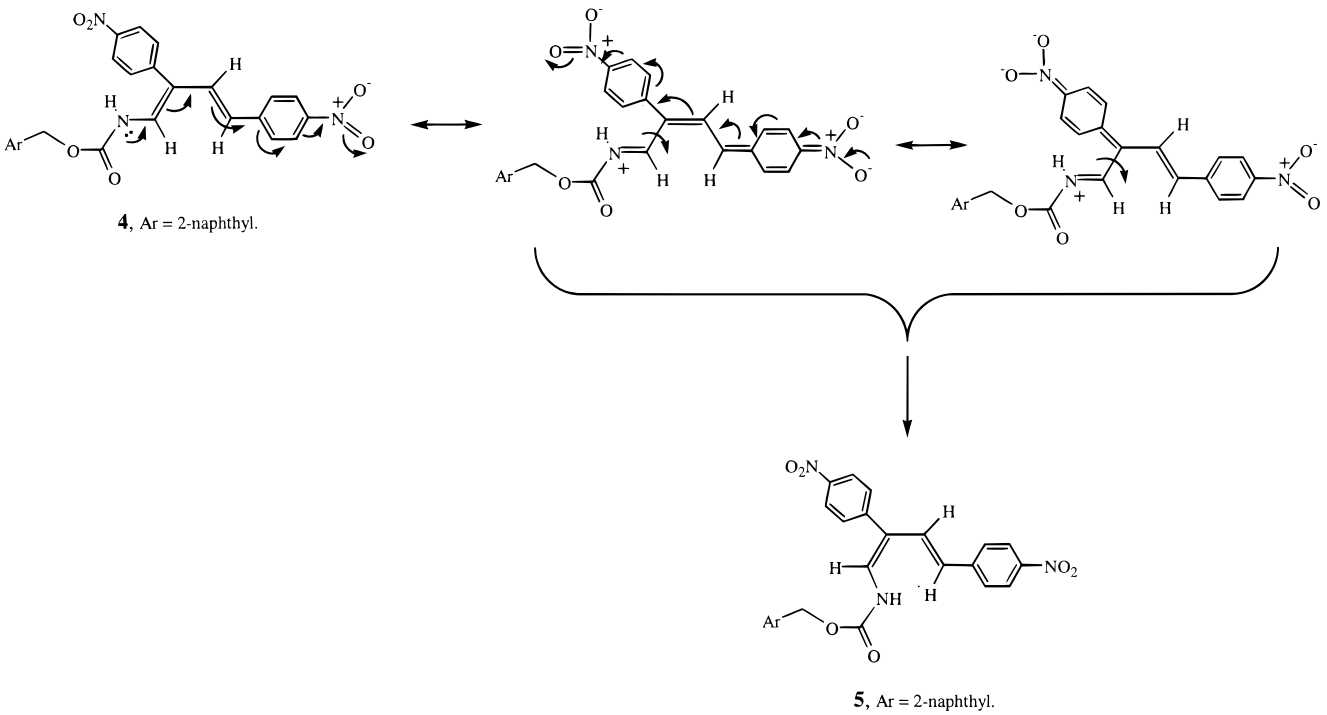
Scheme 2



Scheme 3



nance effect. The function of dichlorophenylphosphine is apparently to provide a leaving group for the hydroxyl, resulting in the formation of a highly conjugated product **4**; compound **4** could not be formed in the absence of the former.

As for the subsequent isomerization, it appears that the remarkable resonance effect of the nitro group once again comes into play as illustrated in Scheme 3. The first double bond of **4** should have significant single bond character because of the contribution from the two resonance forms. Therefore, isomerization may proceed through the rotation of the first "double bond" of the molecule (Scheme 3). The underlying driving force for the isomerization has to be the energy difference between the two isomers. However, it is not clear why the *E*,*E* isomer would be more stable than the initial *Z*,*E* isomer.

Experimental Section

General Methods. All commercial chemicals were purchased from Aldrich. ^{1}H NMR spectra were acquired on a Varian Associates XL-300 NMR spectrometer. COSY and ROESY experiments were conducted on a GE 500 MHz NMR spectrometer. Mass spectra were obtained on a Finnigan MAT-90 mass spectrometer. Elemental analysis was carried out by Midwest Microlab, Indianapolis, IN. Thin-layer chromatography (TLC) plates were obtained from E. M. Science.

2-Naphthylmethyl Carbamate. The original procedure for the preparation of *tert*-butyl carbamate[10] was modified to afford the title compound. Trifluoroacetic acid (1.56 mL, 21 mmol) was added dropwise to a mixture of 2-naphthylmethanol (1.58 g, 10.0 mmol) and sodium cyanate (1.30 g, 20 mmol) in 12.5 mL of benzene at room temperature. After being stirred at room temperature overnight, the reaction mixture was combined with 100 mL of CH_2Cl_2 and the resulting mixture was washed with 2 N NaOH (3×). The aqueous phase was extracted with CH_2Cl_2 (4×), and the organic phases were combined and washed again with water (3×) and brine (1×). The washed CH_2Cl_2 solution was dried and concentrated to about 17 mL. White plates formed were collected by filtration (1.30 g, 65%). TLC:

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R_f 0.50 (silica; ethyl acetate/hexane, 1/1, v/v). ^{1}H NMR ($CDCl_3$): δ 7.9−7.8 (4 H, m), 7.6−7.45 (3 H, m), 5.26 (2 H, s), 4.80 (2 H, s, broad).

(4-Nitrophenyl)acetaldehyde. This compound was prepared according to the method of Lethbridge et al.[6] from the oxidation, by lead tetraacetate, of 4-nitrostyrene which was in turn synthesized from 2-(4-nitrophenyl)ethyl bromide.[11] The title compound was also prepared in lower yield from 4-nitrobenzaldehyde by adapting a method for the synthesis of (4-cyanophenyl)acetaldehyde.[4] ^{1}H NMR ($CDCl_3$): δ 9.83 (1 H, t, J = 1.7 Hz), 8.23 (2 H, d, J = 8.8 Hz), 7.41 (2 H, d, J = 8.8 Hz), 3.89 (2 H, d, J = 1.7 Hz).

(*Z*,*E*)-1-(2-Naphthylmethyloxycarbonylamino)-2,4-bis(4-nitrophenyl)butadiene. A reaction mixture of 2-naphthylmethyl carbamate (560 mg, 2.78 mmol), (4-nitrophenyl)acetaldehyde (476 mg, 2.88 mmol), and dichlorophenylphosphine (373 mol) in 2.5 mL of acetic acid was stirred at room temperature overnight, and 7 mL of water was added. The resulting mixture was heated at 100 °C for ∼3 min, and the supernatant was decanted. The precipitate was washed with ether (2×) and acetone/ether (1/5) to give 110 mg (15%, based on 4-nitrophenylaldehyde) of a yellow powder. ^{1}H NMR (DMSO-d_6): δ 9.48 (1 H, d, J = 11.2 Hz), 8.30 (2 H, d, J = 8.7 Hz), 8.10 (2 H, d, J = 8.8 Hz), 7.91 (4 H, m), 7.64 (1 H, d, J = 15.8 Hz), 7.63 (2 H, d, J = 8.8 Hz), 7.54−7.51 (3 H, m), 7.48 (2 H, d, J = 8.7 Hz), 7.35 (1 H, d, J = 11.2 Hz), 5.89 (1 H, d, J = 15.8 Hz), 5.32 (2 H, s). MS (CI): $[M + 1]^+$, m/e 496. Anal. Calcd for $C_{28}H_{21}N_3O_6$: C, 67.87; H, 4.27; N, 8.48. Found: C, 67.92; H, 4.41; N, 8.31.

In another run (in which the procedure of Chen and Dan[5] was followed), after water was added, the resulting mixture was not heated. Instead, the mixture was filtered and the precipitate collected was washed only with ether. The ^{1}H NMR spectrum indicated that the dried precipitate contained approximately 80% (mol/mol) of compound **4** and 20% of compound **3**.

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Supporting Information Available: Text describing 2D NMR experiments and COSY and ROESY spectra (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the article, and can be ordered from the ACS; see any current masthead page for ordering information.

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