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Formation of β-(diphenylphosphoryl)pyrroles via reactions of dibromocyclobutenylphosphine oxides with aniline

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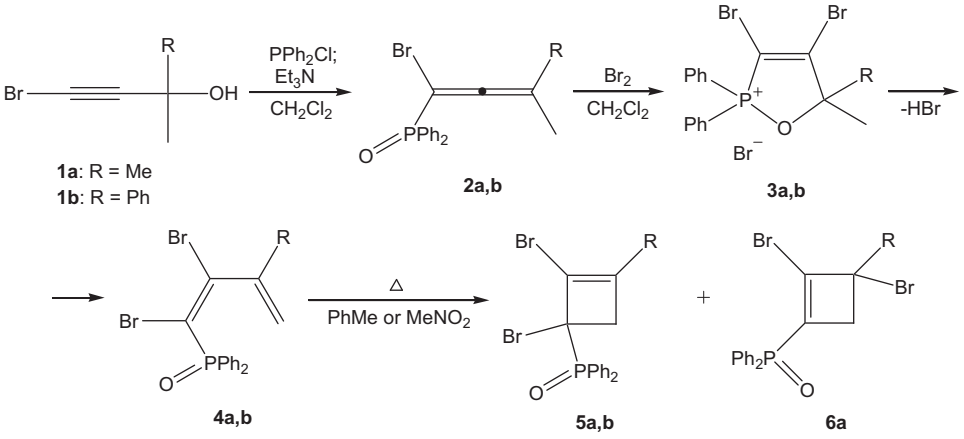
ABSTRACT

1-Phenyl-2-methyl(phenyl)-4-(diphenylphosphoryl)pyrroles are obtained, unexpectedly instead of the 1-phenyl-4-methyl(phenyl)-2-(diphenylphosphoryl)pyrrole regioisomers from a series of reactions between 1,4-dibromo-2-methyl(phenyl)-4-diphenylphosphorylcyclobutenes and aniline via nucleophilic substitution accompanied by an allylic shift, subsequent retro electrocyclization and pyrrole ring closure.

Pyrroles are widely used in synthetic organic chemistry and material science.[1,2] Among pyrrole derivatives, there are a large number of known natural biologically active compounds and drugs.[3] It is also known that phosphorylated heterocycles regulate important biological functions.[4] From this point of view, phosphorylated pyrroles are of particular interest. While a number of methods have already been documented for the preparation of 2-phosphonopyrroles,[5] there appear to be a few practical procedures available for the synthesis of 3-phosphonopyrroles. These are based on the addition of enolates and enamines to phosphonoazoalkenes,[6]



Scheme 1. Route to the synthesis of dibromocyclobutenylphosphine oxides.

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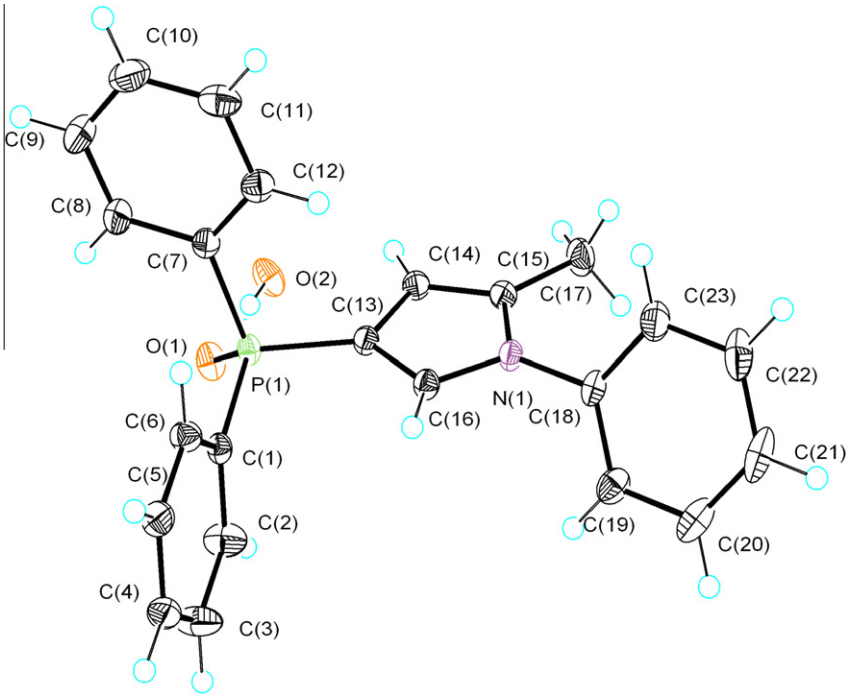


Figure 1. X-ray crystal structure (ORTEP) of **7a**-hydrate.

and nucleophilic addition of CH acids to azoalkenes[7] or ethynylphosphonates.[8]

Recently we reported the synthesis of 2-chloro-3-*tert*-butyl-1-dialkyl(aryl)phosphorylcyclobut-2-enes with the purpose of investigating the potential reactivity of these compounds.[9] However, we found that their double bond was poorly reactive towards electrophilic reagents (bromination and epoxidation), and when the reaction was carried out under harsh conditions, cleavage of the cyclobutene ring occurred leading to the formation of the original 1,3-butadiene, sometimes with its geometric isomer at the 1-position. A sequence of transformations starting with propargylic alcohols allows the preparation of various sterically hindered 1,3-butadienes, some of which underwent thermal transformation into cyclobutenes. In continuation of our interest in the chemistry of cyclobutenylphosphine oxides, we report here a study on the reactions of bromine-containing phosphorylcyclobutenes with aniline, which resulted in the discovery of a new strategy for the preparation of β-(diphenylphosphoryl)pyrroles through a series of one-pot reactions.

We applied our approach described earlier[9] to the synthesis of cyclobutene **5b** possessing bromine atoms at the double bond and the saturated carbon atom, which also bears a diphenylphosphoryl group (Scheme 1).

The starting γ-bromopropargylic alcohols **1a**,**b** and allenes **2a**,**b** were prepared according to the literature procedure.[10] Bromination of **2a** led to stable salt **3a**,[10] whereas in the case of **2b**, the

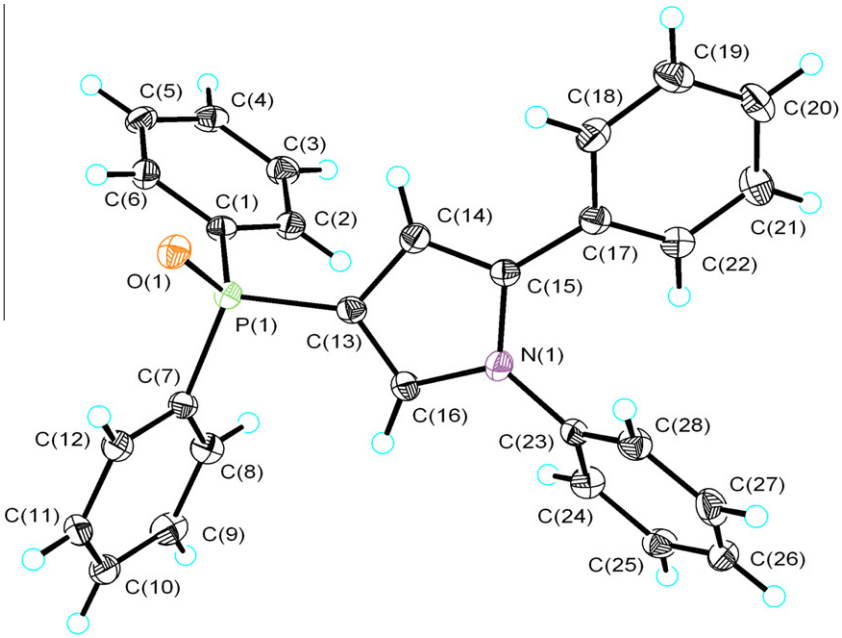
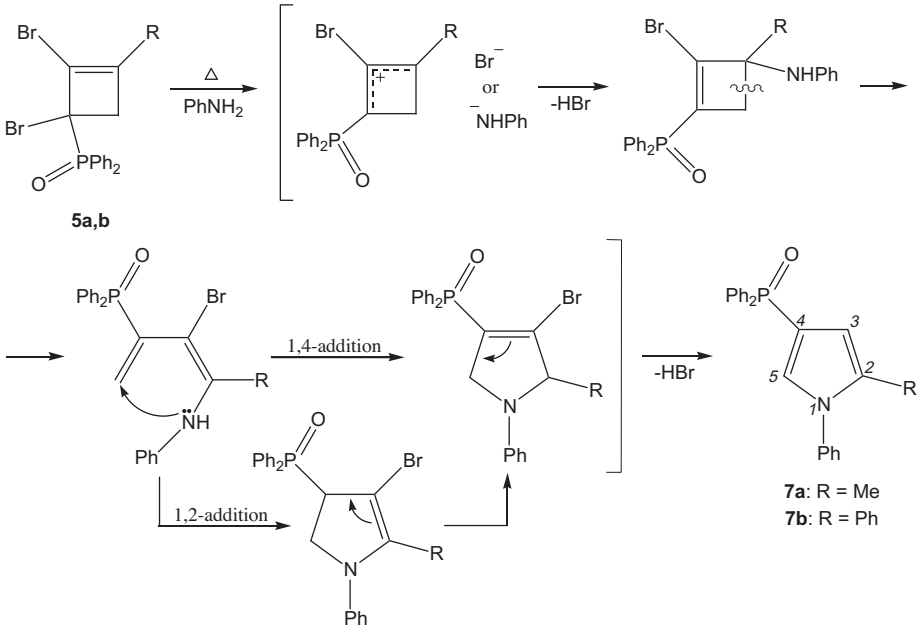


Figure 2. X-ray crystal structure (ORTEP) of **7b**.



Scheme 2. Proposed mechanism for the formation of pyrroles **7a**,**b**.

corresponding salt **3b** decomposed immediately, even upon cooling, with liberation of hydrogen bromide to form diene **4b**.[11] Heating the reaction mixture in refluxing toluene for about half an hour afforded cyclobutene **5b**. It is interesting to note that the salt **3a** was found to be sufficiently stable, so our attempts to isolate **4a** failed. We therefore decided to prepare **5a** bypassing **4a**, based on the fact that oxophospholenic salts such as **3a** decompose readily in polar solvents such as nitromethane.[12] Thus, heating **3a** in refluxing nitromethane followed by column chromatography afforded an inseparable mixture of two isomeric cyclobutenes, **5a** and **6a** in a 1:1 ratio.

All the cyclobutenes obtained seemed to be reactive in nucleophilic substitution reactions due to the presence of the bromine atom attached to a tertiary carbon atom. Actually, we found that these compounds readily underwent a thermal reaction with excess aniline, however, the reaction proceeded unexpectedly, with the formation of 1-phenyl-2-methyl (phenyl)-4-diphenylphosphoryl pyrroles **7a**,**b** instead of the expected 1-phenyl-4-methyl(phenyl)-2-diphenylphosphoryl regioisomers.

The structures of the obtained pyrroles were confirmed unambiguously by XRD crystal structure analysis[13] (Figs. 1 and 2). Compound **7a** was isolated as the monohydrate (**7a**-hydrate).

Obviously, the thermal reaction proceeds through nucleophilic substitution combined with an allylic shift, with subsequent retro electrocyclization of the cyclobutene intermediate. Pyrrole ring-closure probably proceeds via the intramolecular Michael addition of aniline to the double bond, activated by the phosphoryl group, followed by a prototropic shift and hydrogen bromide elimination (Scheme 2).

To the best of our knowledge, allylic rearrangement of cyclobutenyl halides has not previously been observed. Kiefer reported that attempted isomerization of 3-bromo-3-methylcyclobutene met with failure.[14]

Thus, we have described a novel allylic transformation of bromocyclobutenes and have proposed a new approach to the synthesis of pyrrole derivatives via a series of reactions between phosphorylated dibromocyclobutenes and aniline, which involves nucleophilic substitution with double bond migration, Michael addition, a prototropic shift and hydrogen bromide elimination. The structures of the formed pyrroles, together with the isolation of two isomeric dibromocyclobutenes, **5a** and **6a**, point to the possibility of allylic nucleophilic substitution and allylic anionotropic isomerization.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.067. These data include MOL files and InChiKeys of the most important compounds described in this article.

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11. *Procedure for the synthesis of compounds **4b** and **5b**:* To a stirred solution of allene **2b** (2.05 g, 5 mmol) in dry CH_2Cl_2 (20 ml) at 0 °C was slowly added dropwise bromine (0.80 g, 5 mmol) such that the temperature did not exceed 4 °C. The mixture was allowed to warm to room temperature over 1 h with stirring (TLC monitoring). The solvent was carefully removed by rotary evaporation. The resulting yellow oil was chromatographed on silica gel using a mixture of CH_2Cl_2/MeOH (99:1) as the eluent, to yield **4b**. Next, **4b** was suspended in toluene (12 ml) and the suspension was heated until a clear solution was obtained. This solution was heated at reflux for another 30 min then cooled to room temperature during which **5b** precipitated.
*Procedure for the synthesis of compounds **5a** and **6a**:* A solution of oxophospholenic salt **3a** (2.03 g, 4 mmol) in $MeNO_2$ (20 ml) was heated at reflux for 1 h (TLC monitoring). The solvent was removed under reduced pressure to afford a yellow oily material, which was chromatographed on silica gel using a mixture of CH_2Cl_2/MeOH (98:2) as the eluent, to yield a mixture of **5a** and **6a** (1:1).
*Procedure for the synthesis of compounds **7a**,**b**:* A solution of 1.9 mmol of the corresponding cyclobutene (a mixture of **5a** and **6a**, or **5b**) in dry aniline (5 ml, 55 mmol) was heated at 160 °C for 0.5 h (TLC monitoring). The mixture was cooled to room temperature. A precipitate formed which was filtered and washed with CH_2Cl_2 (2 × 5 ml). The combined filtrate and washings were concentrated to afford a yellow oily material, which was chromatographed on silica gel using a mixture of CH_2Cl_2/MeOH (99:1) as the eluent and increasing the polarity gradually by adding MeOH, to yield **7a**,**b**.
*1-Phenyl-2-methyl-4-diphenylphosphoryl-1H-pyrrole monohydrate (**7a**-hydrate):* Yield 0.38 g (57%), colorless crystals, mp 58–61 °C, R_f = 0.26 (CH_2Cl_2/MeOH, 96:4). IR (KBr, cm^{-1}): 608, 640, 734, 813, 956, 1029, 1069, 1119, 1165, 1210, 1391, 1437, 1502, 1597, 1657, 1821, 1897, 1971, 2916, 3060, 3124, 3439, 3500. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 2.16 (s, 3H, CH_3), 6.18–6.22 (br m, 1H, C^3-H), 6.96 (dd, 1H, C^5-H, $^4J_{HH}$ 1.8 Hz, $^3J_{HP}$ 3.5 Hz), 7.24–7.29 (m, 2H, 2*o*-H, N(Ph)), 7.36–7.54 (m, 3H, N(Ph); 4*m*-H, 2*p*-H, P(Ph)), 7.80 (dd, 4H, 4*o*-H, P(Ph), $^3J_{HH}$ 7.3 Hz, $^3J_{HP}$ 12.3 Hz). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 12.8 (s, CH_3), 111.2 (d, C^3, $^2J_{CP}$ 10.1 Hz), 113.0 (d, C^4, $^1J_{CP}$ 128.8 Hz), 125.8 (s, 2*o*-C, Ph(N)), 127.9 (s, *p*-C, Ph(N)), 128.3 (d, 4*m*-C, Ph(P), $^3J_{CP}$ 13.1 Hz), 128.9 (d, C^5, $^2J_{CP}$ 19.1 Hz), 129.3 (d, 2*m*-C, Ph(N)), 131.5 (d, 2*p*-C, Ph(P), $^4J_{CP}$ 1.0 Hz), 131.7 (d, 4*o*-C, Ph(P), $^2J_{CP}$ 10.1 Hz), 131.8 (d, C^2, $^3J_{CP}$ 12.4 Hz), 134.1 (d, 2*ipso*-C, Ph(P), $^1J_{CP}$ 107.7 Hz), 139.1 (s, *ipso*-C, Ph(N)). ^{31}P NMR (161.98 MHz, $CDCl_3$): δ 22.6. ESI-MS: calcd for $C_{23}H_{20}NOP$ (**7a**): 358.1355; found: 358.1371 $(M+H)^+$.
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13. The X-ray crystal structure for compound **7a**-hydrate has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 910127. Formula: $C_{23}H_{22}N_1O_2P_1$. Crystal system triclinic, space group P$\bar{1}$. Unit cell parameters: a = 10.372(4) Å, b = 10.495(4) Å, c = 10.806(5) Å, α = 61.841(10)°, β = 80.684(10)°, γ = 73.171(10)°, V = 992.3(7) Å^3; T = 100(2) K; Z = 2; ρ_{calc} = 1.256 g cm^{-3}; μ = 0.156 mm^{-1} (for MoKα, λ = 0.71073 Å); F(000) = 396; full-matrix least-squares on F^2; parameters = 248; restraints = 0; R(all) = 0.0503; wR(all) = 0.1127; GooF(all) = 1.075.
The X-ray crystal structure for compound **7b** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 910126. Formula: $C_{28}H_{22}N_1O_1P_1$. Crystal system orthorhombic, space group $P\ 2_12_12_1$. Unit cell parameters: a = 6.0991(7) Å, b = 16.4127(18) Å, c = 21.066(2) Å, α = 90°, β = 90°, γ = 90°, V = 2108.8(4) Å^3; T = 100(2) K; Z = 4; ρ_{calc} = 1.321 g cm^{-3}; μ = 0.151 mm^{-1} (for MoKα, λ = 0.71073 Å); F(000) = 880; full-matrix least-squares on F^2; parameters = 280; restraints = 0; R(all) = 0.0751; wR(all) = 0.1056; GooF(all) = 0.982.
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