Formation of α-[Bis(dimethylamino)phosphoryl]-Substituted Stable Enols and N,N-Dialkyldiarylacetamides from Diarylketenes and MeLi in HMPA

Ella B. Nadler, Elana S. Zipory, and Zvi Rappoport*

Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

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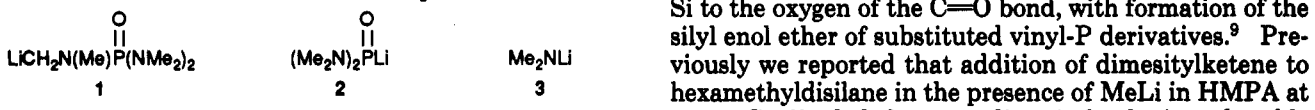
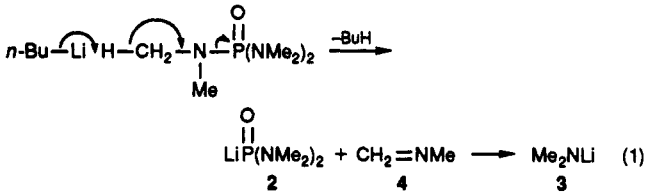
The reaction of an MeLi/HMPA mixture in ether with dimesityl- and mesitylphenylketene yielded the enols $MesC(Ar)=C(OH)PO(NMe_2)_2$ and $MesC(Ar)=CHOH$ and the amides $MesCH(Ar)CON(Me)R$ (Ar = Mes, Ph; R = Me, Et) together with other products. An initial cleavage of the HMPA by the MeLi, followed by addition of the formed anionic species $(Me_2N)_2PO^-$, Me_2N^-, or MeN^-Et to the diarylketene, is proposed.

Although hexamethylphosphoric triamide (HMPA) frequently serves as a medium for metalation by strong bases such as alkali amides and Grignard reagents, it is not always inert in these reactions. Beak et al. summarized the reactions of various electrophilic species, including carbonyl derivatives with the *N*-(α-lithio)phosphoramides such as **1** derived from the deprotonation of the nitrogen methyl group in phosphoric triamides with alkyllithium reagents such as *n*-BuLi or *s*-BuLi.[1] Reagent **1**, formed by lithiation of HMPA, generates a new C–C bond adjacent to the nitrogen on reaction with electrophiles.[2] In another instance, addition of MeLi to HMPA gave methane and the solution turned yellow.[3] Reactions leading to loss of a dialkylamino group, with the formation of the lithium derivative **2** have also been reported. HMPA



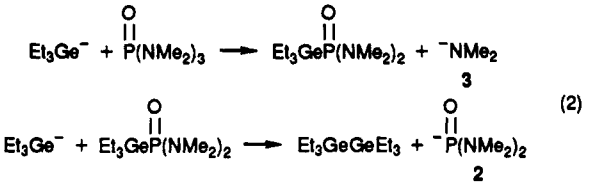
treated with *n*-BuLi instantaneously yielded red solutions containing **2** and apparently also **3** which was trapped as Me_2NH.[4] The formation of **3** by short exposure of HMPA to MeLi is suggested by Stanger and Apeloig's discovery of *N,N*-dimethyl-*p*-nitrobenzamide on treating *p*-nitrobenzoyl chloride with MeLi/HMPA.[5] The sodium salt analogues of both **2** and **3** have also been obtained from the reaction of NaH with HMPA.[6a] Evidence for the intermediacy of **2** was the formation of its adducts with azobenzene[6b] or chalcone.[6c]

Two mechanisms for the cleavage reaction have been proposed: one involving an electron transfer from *n*-BuLi to HMPA and the second involving proton abstraction yielding intermediate **4** (eq 1).[4] However, the formation of **3** from **4** has not been explained.

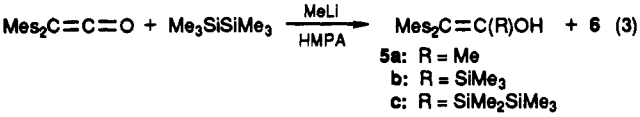


Abatjuglou and Eliel showed that **4** reacted with the lithium reagent to give a secondary amine. Formation of **2** and **4** by decomposition of initially formed **1** rather than by a concerted reaction was suggested.[7]

Another possible mechanism for the formation of **2** is a double nucleophilic displacement as suggested for the reaction with Et_3Ge^- (eq 2).[8]



Addition of silylated phosphorous reagents to ketenes is known to give addition of the P to the carbon and of the Si to the oxygen of the C=O bond, with formation of the silyl enol ether of substituted vinyl-P derivatives.[9] Previously we reported that addition of dimesitylketene to hexamethyldisilane in the presence of MeLi in HMPA at ca. 0 °C afforded three 2,2-dimesityl-substituted stable enols **5a–c** together with solvent-derived product **6** (eq 3).[10]



Here we demonstrate that the silicon reagent is irrelevant to the reaction and that both anions derived from the HMPA, when treated with the ketene, afford the stable α-phosphorus-substituted enol **6** as well as *N,N*-dialkylacetamides. No enol silyl ether was observed. We also report a similar reaction with mesitylphenylketene.

Results and Discussion

When dimesitylketene was added to a MeLi/HMPA/$Me_3SiSiMe_3$ solution after being stirred for more than 2 min or when the reaction temperature was slightly above −1 °C, the yield of the solvent-derived product **6** was increased at the expense of that of **5b**. Microanalysis gives the empirical formula $C_{24}H_{35}N_2O_2P$ for **6** and, since silicon is absent, the reaction was repeated in the absence of $Me_3SiSiMe_3$; indeed **6** was obtained.

Two structures can be considered, i.e., **6** and **7**. **7** is the product of an initial addition of $^-NMe_2$ (**3**) to the ketene

(1) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471.
(2) (a) Savignac, P.; Druex, M.; Leroux, Y. *Tetrahedron Lett.* **1974**, 2651. (b) Savignac, P.; Leroux, Y.; Normant, H. *Tetrahedron* **1975**, *31*, 877. (c) Savignac, P.; Druex, M. *Tetrahedron Lett.* **1976**, 2025. (d) Magnus, P.; Roy, G. *Synthesis* **1980**, 575.
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(4) Kaiser, E. M.; Petty, J. D.; Solter, L. E. *J. Organomet. Chem.* **1973**, *61*, C1.
(5) Stanger, A.; Apeloig, Y. Unpublished results. Stanger, A., Ph.D. Thesis, Technion, Haifa, 1985.
(6) (a) Proni, A.; Roggero, A.; Mazzei, A.; Bruzzone, M. *Inorg. Chim. Acta* **1977**, *21*, 47. (b) Normant, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 12, 1064. (c) Normant, J. F. *Bull. Soc. Chim. Fr.* **1966**, 3601.
(7) Abatjoglou, A. G.; Eliel, E. L. *J. Org. Chem.* **1974**, *39*, 3042.
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(9) Couret, J.; Satge, J.; Couret, F. *J. Organomet. Chem.* **1973**, *47*, 67. Ponomarev, S. V.; Moskalenko, A. I.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1978**, *78*, 298 (*Engl. Transl.* **1978**, *78*, 263). Kolodyazhnyl, O. I.; Kukhar, V. P. *Ibid.* **1981**, *51*, 2189 (*Engl. Transl.* **1981**, *51*, 1883). Markovski, L. N.; Romanenko, V. D.; Pidrarko, T. V. *Ibid.* **1983**, *53*, 1672 (*Engl. Transl.* **1983**, *53*, 1502). Romanenko, V. D.; Shulğin, V. F.; Scopenko, V. V.; Markovski, L. N. *J. Chem. Soc. Chem. Commun.* **1983**, 808.
(10) (a) Nadler, E. B.; Rappoport, Z.; Arad, D.; Apeloig, Y. *J. Am. Chem. Soc.* **1987**, *109*, 7873. (b) Nadler, E. B.; Rappoport, Z. *Tetrahedron Lett.* **1990**, *31*, 555.

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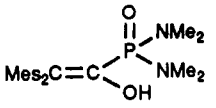
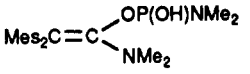
and subsequent reaction of the resultant enolate with HMPA. However, it is excluded by the X-ray analysis and the spectral data, which are consistent with structure 6 derived by nucleophilic addition of 2 to the ketene.



6

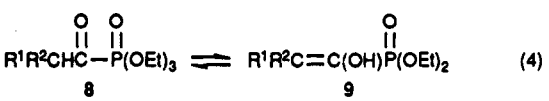


7

Compound 6 displays a $\delta(^{31}P)$ signal at 24.2 ppm (δ(85% H_3PO_4) = 0). $\delta(^{31}P)$ depends on the phosphorus coordination number,[11a] and the value resembles the values of 23.4–25.6 reported for HMPA.[11b] The OH group appears in the ^1H NMR spectrum as a doublet at 5.59 ppm with $^3J_{PCOH}$ = 18.4 Hz, which disappears on shaking the solution with D_2O. The ^1H and ^{13}C NMR spectra indicate a $Mes_2C{=}C$ unit. In the ^1H NMR spectrum the mesityl groups appear as three sharp methyl singlets at 2.16, 2.19, and 2.23 ppm with relative intensities of 2:3:1 and two aromatic protons appear in a 1:1 ratio at 6.75 and 6.83 ppm. The integration is consistent with accidental isochrony of a signal of one of the *p*-Me groups with a two *o*-Me groups signal at δ 2.19. This is reasonable in view of the frequent proximity of *p*-Me and one of the *o*-Me signals as in **5b** and **5c**.[10] The sharp signals indicate a rapid rotation of the mesityl groups in the $Mes_2C{=}C$ moiety at room temperature, as found with several other α-substituted-β,β-dimesitylethenols.[12] The *N*-methyl doublet at δ 2.53 ($^3J_{PNCH}$ = 12 Hz) resembles the HMPA doublet centered at 2.66 ppm[13] and indicates free rotation around the P(O)–N bonds on the NMR time scale. The ^{13}C NMR spectrum displays four methyl signals, again indicating identical *o*-Me groups of each ring at room temperature, and 10 aromatic and vinylic carbons with $^1J_{PC\text{-}\alpha}$, $^2J_{PC\text{-}\beta}$, and $^3J_{PC\text{-}ipso}$ values of 175, 21.3, 12.1 (trans), and 2.5 (cis) Hz, respectively. The *J* values, including the difference between the $^3J_{PC\text{-}ipso}$ values for the cis and trans ipso carbons and their magnitudes fit literature values,[14] e.g., for diphenylstyrylphosphine $^3J_{PC\text{-}ipso}$ = 0 (cis) and 17.4 (trans).[15]

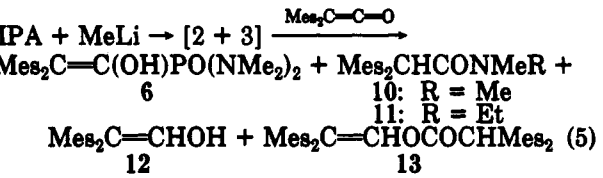
Several α-phosphorylated enols are known[16] e.g., $(RO)_2P(O)CHMeCH{=}C(OH)P(O)(OR)_2$, which display α-^{31}P at 13.7 ppm and ^{13}C–C_α at 144 ppm.[17] In enols having intramolecular P=O···HO hydrogen bonds, e.g., $Ph_2P(O)CR^1R^2CR^2{=}C(OH)P(O)Ph_2$ and others, ν_{OH} appears at 2300–2790 (br) cm^{-1},[18] and its absence in **6** indicates the absence of such bonding in solution.

Several enols,[18,19] e.g., **9**, are in equilibrium with the keto phosphonates **8** (eq 4), and when R^1 = H, R^2 = Ar the enols are favored in the equilibria.[19]



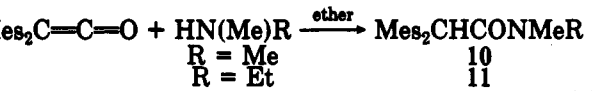
(4)

Addition of dimesitylketene to the black-green mixture formed by treatment of HMPA with MeLi in the absence of $Me_3SiSiMe_3$ and stirring for 10 min afforded mainly **6**, but several other Mes_2C-containing products were isolated as well. Three of them were identified as *N,N*-dimethyl- and *N*-ethyl-*N*-methyldimesitylacetamides (**10** and **11**, respectively) and enol **12**. Mass spectral evidence indicates the possible formation of ester **13**[20] (eq 5).



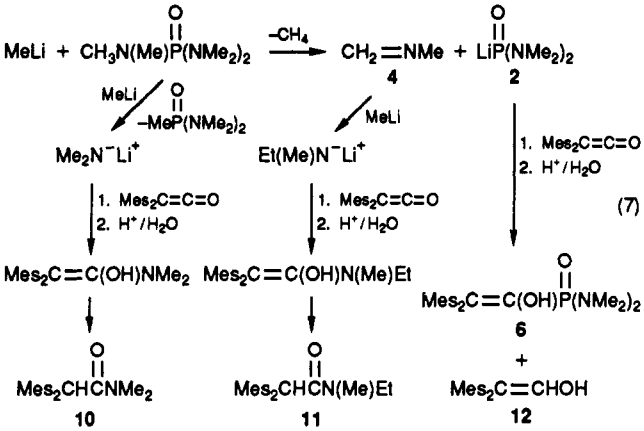
(5)

The identification of **10** and **11** was corroborated by an independent synthesis from dimesitylketene with the corresponding amines (eq 6). The ^1H NMR of both amines indicate restricted rotation around the CO–N bond.



(6)

Formation of **6** and **10–12** is rationalized by eq 7. MeLi and HMPA form **4** and **2** in analogy to eq 1 whereas Me_2N^- can be generated according to eq 1 or similarly to the first step of eq 2. If the former possibility applies, it most likely



(7)

occurs by reduction of **4** to Me_2NH. Since **12** rather than **5a** is obtained by reduction of the ketene, MeLi is apparently completely consumed at this stage and hence the reducing agent is probably anion **2**. Addition of Me_2N^- to the ketene affords **10**.[21] Capture of **4** by MeLi gives lithium ethylmethylamide in a reaction analogous to that described earlier,[7] and the latter adds to the ketene to form **11**. The fact that only adducts of **2** and no adduct of **1** with the ketene was observed (although many precedents for the formation of the latter adducts are known[1,2]) deserves further study.

The α-(*N,N*-dialkylamino) enols are apparently unstable compared with their *N,N*-dialkylamide tautomers **10** and **11**, whereas the analogous phosphoryl derivatives **6** and

(11) (a) Crutchfield, M. M.; Dungan, C. H.; Letcher, J. H.; Mark, V.; Van Wazer, J. R. *^{31}P Nuclear Magnetic Resonance*; Wiley: New York, 1967, (a) pp 173–177; (b) pp 190, 357.

(12) Biali, S. E.; Nugiel, D. A.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 846.

(13) *Handbook of Proton NMR Spectra and Data*; Edited by Ashai Research Center, Academic Press: Tokyo, Japan, 1985; Vol. 2, p 185.

(14) (a) *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J. D., Quin, L. D., Eds.; VCH Publishers: Deerfield Beach, FL, 1987; pp 391–424. (b) Kalinowski, H.-O.; Berger, S.; Braun, S. *C-13 NMR Spectroscopy*; Wiley: Chichester, 1988; pp 586–593.

(15) Xue, C.-B.; Yin, Y.-W.; Zhao, Y.-F.; Wu, J.-Z. *J. Chem. Soc., Perkin Trans. 2* **1990**, 431.

(16) For summary of the IR and NMR spectra of enols including phosphorylated enols, see: Floris, B. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, 1990; Chapter 4, p 147.

(17) Szpala, A.; Tebby, J. C.; Griffiths, D. V. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1363.

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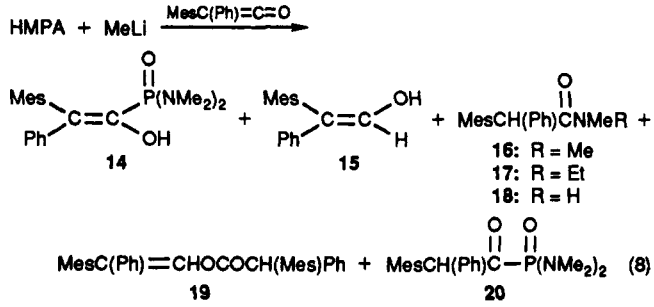
(20) Nugiel, D. A.; Rappoport, Z. *J. Am. Chem. Soc.* **1985**, *107*, 3669.

(21) In an attempt to generate the 1,1-enediol $Mes_2C{=}C(OH)_2$, water was added to dimesitylketene and neutralization of the mixture that contained unreacted ketene with aqueous NH_4Cl gave $Mes_2CHCONH_2$, showing that even the neutral NH_3 (from the dissociation of NH_4Cl) adds to the ketene (Nadler, E. B.; Biali, S. E.; Rappoport, Z., unpublished results).

14 (see below) are stable isolable enols.

The reaction of the ketene with MeLi/HMPA was extended to the unsymmetrical mesitylphenylketene. Again, an analogous phosphorus-containing enol 14 (identified by spectroscopic methods and crystallography) was formed (eq 8). Six other products (eq 8) included enol 15 obtained



by reduction of the ketene and the two amides 16 and 17 formed as the main products. The mechanism of formation of 14–17 is analogous to that given in eq 7. Another product, formed in 0.5% yield and identified tentatively by mass spectrometry, is amide 18. The mechanism of its formation is unclear. The ketone isomer of 14, i.e. 20, is probably also formed in <1% yield as evidenced by the NMR and CI mass spectra. Although keto ⇌ enol equilibria exist in related systems (eq 4), this has not yet been investigated in our system.[22] An additional product formed in 2% yield is the ester 19, tentatively assigned on the basis of its IR, NMR, and CI mass spectra. It is the product of the reaction of 2-mesityl-2-phenylethenolate and mesitylphenylketene, in analogy to the formation of 13 from 2,2-dimesitylethenolate with dimesitylketene.[20]

The structure of 14 was determined by X-ray crystallography (see below).[22] The configuration is *Z* with bulky mesityl and $PO(NMe_2)_2$ groups cis to each other. The formation of the apparently more bulky isomer is relevant to the stereochemistry of nucleophilic additions to mesitylphenylketene and to the "actual relative bulk" of phenyl and mesityl rings at the reaction site. It suggests that a perpendicular mesityl group is smaller than a phenyl group. This point will be discussed in detail together with other examples in a future paper.

The complete absence of the keto isomer of 6 among the products and the formation of <1% of 20 in the reactions leading to the isomeric enols 6 and 14 can be due either to kinetic or thermodynamic stability of the enols compared with the keto isomers. An independent investigation of this point is worthwhile. We note that many enols 5 (e.g., R = H, Mes or 5b) or MesC(Ph)=C(OH)Mes are thermodynamically more stable than the keto isomers, whereas others, e.g., 5a are less stable than the isomeric ketones but still isolable due to kinetic stability.[23]

Crystal Structures of 6 and 14.[24] The structures of 6 and 14 were solved unequivocally by X-ray crystallography. As stated, the structure of the dimesitylketene adduct is 6. Selected bond lengths and angles are given in Table I and the numbering scheme is given in the ORTEP drawing in Figure 1. Other bond lengths and angles, thermal and positional parameters, and structural factors are given in supplementary Tables S1–S4, and stereoscopic views (which demonstrate the hydrogen bonding) are given in supplementary Figures S1 and S2.

Table I. Bond Lengths and Angles for 6 and 14

	6	14
	Bond Length (Å)	
P–O(2)	1.469 (6)	1.479 (2)
P–N	1.641 (6), 1.639 (7)	1.637 (3), 1.624 (2)
P–C(1)	1.803 (6)	1.822 (3)
C_1–O(1)	1.388 (8)	1.372 (3)
4N–C	1.45 (1)–1.48 (1)	1.443 (5)–1.479 (6)
C(1)–C(2)	1.344 (8)	1.346 (4)
C(2)–C(3)	1.513 (9)	1.489 (4)
C(2)–C(12)	1.508 (9)	1.502 (4)
O(1)–H(1)		0.764
6C(Ar)–C(Me)	1.501 (9)–1.522 (9)	1.499 (5)–1.522 (6)
C(3)–C(4)	1.420 (8)	1.387 (4)
C(6)–C(7)	1.36 (1)	1.354 (6)
8C(Ar)–C(Ar)	1.38 (1)–1.410 (8)	
5C(Ar)–C(Ar) (Ph ring)		1.375 (6)–1.387 (4)
4C(Ar)–C(Ar) (Mes ring)		1.391 (4)–1.396 (5)
	Bond Angle (deg)	
P–C(1)–O(1)	108.4 (4)	112.0
P–C(1)–C(2)	128.8 (5)	129.5
C(1)–C(2)–C(12)	123.9 (6)	124.2 (2)
C(3)–C(2)–C(12)	117.8 (5)	114.4 (2)
C(1)–C(2)–C(3)	118.3 (6)	121.4 (2)
O(1)–C(1)–C(2)	121.6 (6)	118.4 (2)
O(2)–P–N(1)	110.6 (3)	109.2 (1)
O(2)–P–N(2)	117.5 (4)	117.3 (1)
C–C–C (ring cis to OH)	117.6 (7)–122.8 (6)	117.1 (2)–121.5 (3)
C–C–C (ring trans to OH)	117.3 (7)–123.0 (6)	117.7 (3)–122.9 (3)
C(1)–O(1)–H(1)		112.6

An interesting structural feature of this compound is the long P=O(2)—O(1)—H distance, which eliminates intramolecular hydrogen bonding as also observed in solution (see above). However, the presence of intermolecular hydrogen bonding is evident from the O(1)···O(2) distance of 2.52 Å, where O(1) and O(2) belong to neighboring molecules.

The C–C bond lengths resemble those in other 2,2-dimesityl-α-substituted-ethenols.[25] Of the six bond angles around the double bond, the largest is P–C(1)–C(2) [128.8 (5)°] and the smallest is P–C(1)–O(1) [108.4 (4)°], a situation reminiscent of that in 2,2-dimesityl-1-*tert*-butylethenol.[25] The torsional angle of the double bond is 11.55° and those of planes of the mesityl groups cis and trans to the OH with the C(2)C(3)C(12) plane are 62.35° and 62.77°. The two aryl groups are at an angle of 80° to each other.

The *R* factor for 14 is lower than that for 6 and most of the hydrogens, including the enolic one, were located. As stated, the configuration of 14 is *Z* with the bulkier mesityl group and the bis(dimethylamino)phosphoryl entity in a cis relationship. Selected bond lengths are given in Table I and additional bond lengths and angles and positional, structural, and thermal parameters are given in supplementary Tables S5–S8. The packing arrangement and stereoscopic views are given in supplementary Figures

(22) On standing for several hours in $CDCl_3$, the solution of 14 turns yellow and TLC and ^1H and ^{13}C NMR show the formation of a new compound. This compound is identical with the compound formed during the chromatographic purification of the reaction mixture of mesitylphenylketene and HMPA/MeLi and their separation therefore failed. It is probable that this compound is formed from 14 on the Si-60 column. Microanalysis of the mixture (Calcd for $C_{21}H_{29}N_2O_2P$: C, 67.72; H, 7.85; N, 7.52. Found: C, 67.45; H, 7.77; N, 7.32) show that the new product is an isomer of 14. Whether it is the *E* isomer or a rearranged product is under investigation.

(23) For discussions of the keto–enol equilibria of 1-substituted β,β-di(bulky)aryl ethenols, see: Hart, H.; Rappoport, Z.; Biali, S. E. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, 1990; Chapter 8, p 481.

(24) Other known crystal structures of α-phosphorylated enols are those of (*E*)-*p*-$MeOC_6H_4CH$=$C(OH)P(O)OEt)_2$[19] and (*E*)-$Ph_2P(O)$-CMe_2=$C(OH)P(O)Ph_2$.[18a]

(25) Kaftory, M.; Nugiel, D. A.; Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 8181.

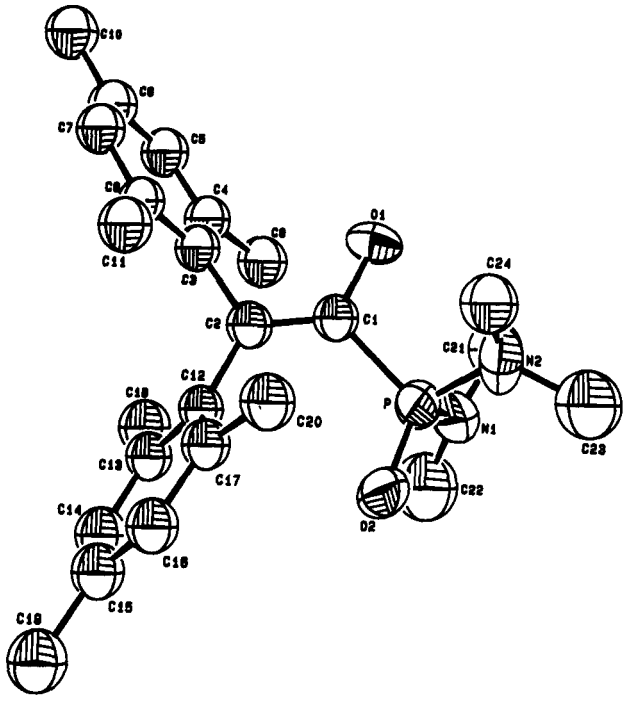


Figure 1. ORTEP drawing and numbering scheme of **6**. The numbering of **14** is identical, except that C-9, C-10, and C-11 are absent on the phenyl ring.

S3 and S4. In general the bond lengths and bond angles of **6** and **14** are very similar. An additional feature determined for **14** is the C(2)–C(1)–O(1)–H torsional angle, which is 174.8°, i.e., the arrangement around the C–O single bond is anti. The molecules are packed in pairs, related by inversion centers through hydrogen bonds. As in **6**, the O–H group of one molecule in **14** is hydrogen bonded intermolecularly to the phosphoryl oxygen of a neighboring molecule as shown by the O···O distance of 2.644 Å.

In contrast with the almost identical torsional angles of the mesityl rings of **6**, the torsional angles of the different aryl groups in **14** differ strongly. Since the torsional angle of the double bond is 8.1° [average of the values for P-(1)–C(1)–C(2)–C(3) (7.7°), P(1)–C(1)–C(2)–C(9) (9.5°), O(1)–C(1)–C(2)–C(3) (6.6°), and O(1)–C(1)–C(2)–C(9) (8.4°)], the torsional angles are given in relation to the C(3)–C(2)–C(12) plane. The torsional angle of the phenyl ring is 38.1° [average of C(1)–C(2)–C(3)–C(4) (39.3°) and C(1)–C(2)–C(3)–C(8) (36.9°)], whereas that of the mesityl ring is 76.8° [average of C(1)–C(2)–C(9)–C(14) (72.6°) and C(1)–C(2)–C(9)–C(10) (80.9°)]. The two aryl rings are at an angle of 78.5° [average of C(3)–C(2)–C(9)–C(10) (82.6°) and C(3)–C(2)–C(9)–C(14) (74.3°)] to each other, similar to the value in **6**. The smaller PhC=C torsional angle is reminiscent of a similar observation in other 2-mesityl-2-phenylethenols and their derivatives.[26]

Experimental Section

General Methods. Details concerning the determination of melting points and IR, UV, ^{1}H NMR, and mass spectra have been previously described.[27] ^{13}C NMR spectra were recorded on Bruker WP 200 SV and AMX 400 spectrometers operating at 50.32 and 100.62 MHz.

Materials. HMPA (dried with 4A molecular sieves), MeLi (1.4 M solution in ether), ethylmethylamine, and 26% aqueous dimethylamine (w/w) were commercial samples. Dimesitylketene[28a] and mesitylphenylketene[28b] were prepared according to Fuson et al. or by a modification of their method.[28c]

2,2-Dimesityl-1-[bis(dimethylamino)phosphoryl]ethenol (6) from HMPA/MeLi in the Presence of Hexamethyldisilane. The procedure before workup resembles that described for the preparation of 2,2-dimesityl-1-trimethylsilylethenol,[10b] except that the reaction temperature was 0–1 °C instead of –1° to 0 °C and the dimesitylketene was added after 4 rather than after 2 min. These minor differences in the reaction temperature and the timing of reagent addition apparently affect strongly the product distribution. The yield of **6**, mp 152 °C, after recrystallization (EtOH) was 20%.

Reaction of Dimesitylketene with MeLi in HMPA. To stirred dry HMPA (2.2 mL) at 0 °C under Ar was added MeLi (1.8 mL, 1.4 M in ether, 2.5 mmol). The solution was stirred for 10 min during which time it became blackish-green. Dimesitylketene (0.47 g, 1.7 mmol) in dry ether (5 mL) was quickly added and the mixture was stirred for 1 h at 0 °C. The mixture was decomposed with 3% HCl (100 mL), extracted with ether (3 × 40 mL), dried ($MgSO_4$), and evaporated, giving a yellowish solid (0.48 g). Ether (6 mL) was added and the white solid obtained, mp 146 °C (235 mg, 34%), was recrystallized (EtOH), giving **6**, mp 152 °C: UV λ_{max} (hexane) (ϵ) 199 nm (35 700), 246 (12 500), 261 sh (8600); IR ν_{max} (CCl_4) 3579 (OH), 2925, 2852, 2804 (C—H), 1692 (w), 1610 (C=C), 1306 (P=O), 1225, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.16 (6 H, s, Mes-Me), 2.19 (9 H, s, Mes-Me), 2.23 (3 H, s, Mes-Me), 2.53 (12 H, d, $^3J_{PH}$ = 12 Hz, N-Me), 5.59, 5.62 (1 H, d, OH, J_{POH} = 18.4 Hz, disappears on addition of D_2O), 6.75, 6.83 (2 × 2 H, 2s, Mes-H); ^{13}C NMR ($CDCl_3$) δ 20.76, 20.84, 21.17, 21.82 (*o*- and *p*-Mes-Me), 36.25 (N-Me, d, $^2J_{PC}$ = 4.2 Hz), 125.84 (C_β, d, $^2J_{PC}$ = 21.3 Hz), 128.90, 129.92, 132.35 (C-ipso, Mes trans to P, $^3J_{PC}$ = 12.1 Hz), 133.48 (C-ipso, Mes cis to P, d, $^3J_{PC}$ = 2.5 Hz), 136.11, 136.91, 138.31, 138.55, 144.97 (C_α, d, $^1J_{PC}$ = 175 Hz); ^{31}P NMR ($CDCl_3$, proton decoupled, 85% H_3PO_4 external reference) δ 24.2; mass spectrum (70 eV, 165 °C) *m/z* (relative abundance, assignment) 369 (2, M – $HNMe_2$), 350 (7, Mes_2C=$C(NMe_2)_2$), 324 (33, $Mes_2CHCH(OH)NMe_2$), 278 (99, Mes_2C=C=O), 251 (90, Mes_2CH), 236 (50, Mes_2CH – Me), 235 (100, Mes_2C – Me), 220 (97, Mes_2C – 2Me), 205 (26, Mes_2C – 3Me), 189 (11, Mes_2C – 3Me – CH_4), 165 (9, $CH(OH)PO(NMe_2)_2$), 152 (6, $PO(OH)(NMe_2)_2$), 135 (25, $PO(NMe_2)_2$), 119 (12, Mes), 91 (23, C_7H_7), 77 (7, Ph); *m/z* (CI, Me_3CH) 415 (69, M + 1), 414 (4, M), 329 (18, $Mes_2CHCH(OH)NMe_2$), 279 (100, Mes_2C=COH), 278 (25, Mes_2C=C=O), 251 (21, Mes_2CH), 137 (22, $HP(OH)(NMe_2)_2$), 92 (65, C_7H_8).

Anal. Found: C, 69.70; H, 8.24; N, 6.95; P, 7.50. Calcd for $C_{24}H_{35}N_2O_2P$: C, 69.54; H, 8.51; N, 6.76; P, 7.47.

Evaporation of the filtrate gave a yellow oil (234 mg), which was chromatographed on a Si-60 N_2-pressure column (230–400 mesh), using successively 5:95 AcOEt/petroleum ether (40–60 °C) (v/v) and 98:2, 95:5, and 90:10 (v/v) AcOEt/EtOH eluents. Fraction I (a yellow oil, 19 mg) was impure by ^{1}H NMR: IR (neat) 1730 (C=O), 1640 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.06–2.29 (6s), 5.01 (s), 6.79, 6.84, and 6.98 (3s, Ar). Aliphatic/aromatic ratio = 2.7. The mass spectrum [(CI, NH_3) *m/z* (relative abundance, assignment) 576 (21, MNH_4^+), 502 (28), 470 (15), 458 (33), 456 (27, MNH_3^+ – MesH), 437 (100, M, MesH – H), 298 (99.7, $Mes_2CHCOOH$ + 2H), 295 (24, Mes_2CHCOO), 279 (28, Mes_2CHCO), 264 (27, Mes_2CO), 251 (79, Mes_2CH), 233 (26), 219 (64), 209 (15), 147 (10, MesCO)] suggests that it contains some of the ester **13**.[20]

Fraction II (29 mg, 6%) was mostly enol **12** according to its ^{1}H NMR.[28c]

Fraction III (a colorless oil, 70 mg): ^{1}H NMR ($CDCl_3$) δ aliphatic multiplets centered at (a) 0.92, 1.42, 1.62 and (b) 4.21 ppm, and aromatic multiplets centered at 7.52 and 7.72 ppm; the (a)/(b)/Ar ratio is 8:1:1. The mass spectrum (EI, 50 °C, 70 eV)

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(28) (a) Fuson, R. C.; Armstrong, L. J.; Chadwick, D. H.; Kneisley, J. W.; Rowland, S. P.; Shenk, W. J., Jr.; Soper, Q. F. *J. Am. Chem. Soc.* **1945**, *67*, 386. (b) Fuson, R. C.; Armstrong, L. J.; Kneisley, J. W.; Shenk, W. J., Jr.; *Ibid.* **1944**, *66*, 1464. (c) Biali, S. E.; Rappoport, Z. *Ibid.* **1984**, *106*, 5641.

showed a substantial mass at m/z 279 ($Mes_2C{=}CHO^+$). The compound was not identified.

Chromatography of fraction IV (a yellowish oil, 65 mg) on a Si-60 column with a 2:8 (v/v) AcOEt/petroleum ether eluent yielded two compounds. The first (47 mg, 8%), a white solid, mp 135 °C, is amide 11 according to its ^{1}H NMR, IR, MS and independent synthesis: ^{1}H NMR ($CDCl_3$) δ 1.12–1.19 (3 H, 2t, J = 7.2 Hz, NCH_2CH_3), 2.07 (12 H, s, Mes-*o*-Me), 2.22 (6 H, s, Mes-*p*-Me), 2.86, 2.97 (3 H, 2s, N-Me), 3.13–3.24, 3.43–3.54 (2 H, 2q, J = 7.2 Hz, NCH_2CH_3), 5.27, 5.29 (1 H, 2s, Mes_2CH), 6.77 (4 H, s, Mes-H). The multiplicity of the NMe, CH_2, and CH signals suggests two conformers due to hindered rotation around the CO–N bond in a 1.4:1 ratio. Mass spectrum (CI, CH_4), m/z (assignment, relative abundance): 338 (M – 1, 100), 251 (Mes_2CH^+, 11), 218 (MesCHCONMeEt, 7).

The second compound (6 mg, 1%) is amide 10 according to ^{1}H NMR, MS, IR, and its independent synthesis: ^{1}H NMR ($CDCl_3$) δ 2.06 (12 H, s, Mes-*o*-Me); 2.22 (6 H, s, Mes-*p*-Me); 2.89, 3.02 (2 × 3 H, 2s, NMe), (due to hindered C–N rotation), 5.32 (1 H, s, Mes_2CH); 6.77 (4 H, s, Mes-H); mass spectrum (CI, CH_4), m/z (relative abundance, assignment) 391 (4, M + 4 NH_3 ?), 338 (15, M + CH_3), 324 (100, M + 1), 323 (3, M), 251 (3, Mes_2CH^+), 204 (1, $MesCHCONMe_2$).

Reaction of Mesitylphenylketene with MeLi/HMPA. To stirred dry HMPA (5.5 mL) at 0 °C under argon was added MeLi (1.4 M in ether, 4.5 mL, 6.4 mmol). While stirring for 10 min, the color became greenish-black. Mesitylphenylketene (1 g, 4.2 mmol), in dry ether (10 mL) was then added at once and the color changed to dark yellowish-black. The mixture was stirred for 1 h at 0 °C under Ar and then decomposed with 3% aqueous HCl (200 mL), extracted with ether (3 × 50 mL), rinsed with water (2 × 50 mL), dried ($MgSO_4$), filtered, and evaporated, giving a yellow orange oil (1.23 g). Chromatography on a Si-60 column with an eluent ranging from 2:98 to 20:80 ether/petroleum ether (40–60 °C) (v/v) to 1:9 EtOH/AcOEt yielded several fractions. Fraction I (18 mg, 2%) was a yellowish solid, which was tentatively assigned as 19: IR ν_{max} (Nujol) 1740 (COOR, s), 1620, 1600 (C=C, w) cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 1.98, 2.16, 2.20, 2.29, and 2.36 (18 H, 5s, Me), 5.56 (1 H, s, CH), 6.85–7.33 (15 H, m, Ar + =CH) [A few other minor impurity signals were also observed.]; mass spectrum (CI, Me_3CH) m/z (relative abundance, assignment) 475 (100, M + 1), 474 (5, M), 295 (5), 293 (3), 239 (25, MesCH(Ph)-CHOH), 238 (5, MesC(Ph)=CHOH), 237 (25, MesC(Ph)=CHO), 236 (4, MesC(Ph)=CO), 211 (8), 209 (14, MesCHPh), 113 (18), 112 (11).

Fraction II (colorless oil, 11 mg): mass spectrum (CI, CH_4) m/z (relative abundance, assignment) 450 (12.5), 297 (5.6), 255 (6.2), 255 (100, PhCH(Me)Mes + 1). ^{1}H NMR [(CD_2Cl_2) δ 2.04–2.33 (5s, Me), 6.91–7.79 (m, Ar)] shows that the compound is impure. It was not identified.

Fraction III, a white solid (11 mg, 1%), mp 112 °C was mostly 2-mesityl-2-phenylethenol (15) (mp 124 °C[26b]) according to ^{1}H NMR, TLC, and IR.

Fraction IV (yellow orange oil, 5 mg) was tentatively assigned structure 18 on the basis of the molecular peak at m/z 267 and the approximate integration: IR (neat) ν_{max} 1640 cm^{-1} (CO). The ^{1}H NMR (CD_2Cl_2) shows that the compound is not pure: δ 1.15–1.26 (t + other s, NH), 2.12, 2.16, 2.28 (9 H, 3s, Mes-Me), 2.74, 2.76 (ca. 2 H, d, NCH_3, J = 4.8 Hz), 5.21 (0.6 H, s, CHCO), 6.90–7.30 (7 H, s + m, Ar-H). Mass spectrum (CI, CH_4) m/z (relative abundance, assignment): 296 (8, M + C_2H_5), 268 (100, M + 1), 267 (7, M), 266 (4, M – 1), 251 (3, M – CH_4), 237 (Mes(Ph)CHCO), 255 (4, MesCHPh + 1), 209 (3, MesCHPh).

Fraction V (530 mg) was further purified by chromatography (Si-60 column; 30:70 ether/petroleum ether eluent). The main product, a white solid (370 mg, 30%), was pure *N*-ethyl-*N*-methylmesitylphenylacetamide (17), mp 117 °C: UV λ_{max} (hexane) 208 nm (ϵ 51 000), 235 sh (16 300), 268 (700); IR ν_{max} (Nujol) 1640–1620 (C=O, s), cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 0.85–0.92, 1.09–1.16 (3 H, 2t, J = 7.1 Hz, NCH_2CH_3), 2.15 (6 H, s, Mes-*o*-Me), 2.26 (3 H, s, Mes-*p*-Me), 2.74, 2.92 (3 H, 2s, NMe), 3.06–3.17, 3.39–3.50 (2 H, 2q, J = 7.1 Hz, NCH_2CH_3), 5.30 (1 H, s, CHCO), 6.87 (2 H, s, Mes-H), 6.97–7.02 (2 H, m, Ph-H), 7.15–7.29 (3 H, m, Ph) [The two sets of NCH_2 and NCH_2CH_3 signals in a 1.2:1 ratio are due to two rotamers]; mass spectrum (EI, 70 eV, 80 °C) m/z (relative abundance, assignment) 295 (91, M), 236 (2, MesC(Ph)=C=O), 209 (100, MesCHPh), 204 (25, MesC(Ph)=C=O – MeOH), 193 (26, $MesCH_2Ph$ – Me – H), 179 (41, MesCHPh – 2Me), 165 (11, MesCHPh – Et), 119 (4, Mes), 91 (8, tropyliuum), 86 (94, CONEtMe), 77 (4, Ph), 58 (52, NEtMe); CI (CH_4) 324 (9, M + Et), 296 (100, M + 1), 295 (10, M), 294 (6, M – 1), 209 (2, MesCHPh), 176 (5, M – Mes), 148 (2.5, (M + 1)/2).

Anal. Found: C, 81.39; H, 8.44; N, 4.53. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74.

Fraction VI, a light yellow solid (132 mg, 12%), was almost pure *N*,*N*-dimethylmesitylphenylacetamide (16). Chromatography on Si-60 with 6:4 petroleum ether/ether as eluent gave pure 16 as a white solid, mp 166 °C: UV λ_{max} (hexane) 204 nm (ϵ 46 100), 258 (360), 264 (360); IR ν_{max} (Nujol) 1640–1620 (C=O, s) cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 2.14 (6 H, s, Mes-*o*-Me), 2.26 (3 H, s, Mes-*p*-Me), 2.75, 2.97 (6 H, 2s, NMe), 5.26 (1 H, s, CHCO), 6.87 (2 H, s, Mes-H), 7.00–7.01 (2 H, m, Ph-H), 7.21–7.26 (3 H, m, Ph-H) [The signal pairs for NCH_2 and NCH_2CH_3 demonstrate a 1:1 ratio for the two conformers.]; mass spectrum (EI, 70 eV, 85 °C) m/z (relative abundance, assignment) 281 (100, M), 236 (7, MesC(Ph)=C=O), 209 (100, MesCHPh), 194 (34, MesCHPh – Me), 179 (70, MesCHPh – 2Me), 165 (21, MesC(Ph)=C=O – MeOH), 119 (9, Mes), 105 (4, PhCO), 91 (16, tropylium), 77 (10, Ph), 72 (100, $CONMe_2$), 46 (27, Me_2NH_2), 44 (7, NMe_2); CI (CH_4) 310 (8, M + Et), 296 (4, M + Me), 282 (100, M + 1), 281 (10, M), 280 (6, M – 1), 209 (3, MesCHPh), 162 (6, M – Mes).

Anal. Found: C, 81.03; H, 8.24; N, 4.84. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.84.

Fraction VII, a red clear oil (11 mg; 0.7%), was tentatively identified as the keto phosphonamide 20 by its IR, ^{1}H NMR, and CI mass spectrum: IR ν_{max} (Nujol) 1680 (C=O, s) cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 2.17 (6 H, d, J = 10.2 Hz, NMe), 2.19 (9 H, s, Mes-*o*-Me + NMe), 2.28 (3 H, s, Mes-*p*-Me), 2.60 (6 H, d, J = 10.2 Hz, NMe),[29] 6.27 (1 H, s, CHCO), 6.27–6.94 (4 H, m, Mes-H + Ph-H), 7.23–7.27 (3 H, m, Ph-H); mass spectrum (CI, CH_4), m/z (relative abundance, assignment) 401 (8, M + Et), 387 (4, M + Me), 373 (100, M + 1), 372 (3, M), 371 (6, M – 1), 345 (19, M + 1 – C=O), 344 (8, M – CO), 296 (2, M – 1 – C=O – P=O), 282 (4, M – 1 – C=O – P=O – CH_4), 237 (s, MesCH(Ph)CO), 225 (4, Mes-(Ph)Et), 209 (13, MesCHPh).

Fraction VIII, a reddish oil (350 mg), yielded 2-mesityl-2-phenyl-1-[bis(dimethylamino)phosphoryl]ethenol (14) (195 mg, 12%) on addition of ether. Crystallization (AcOEt) gave pure 14, mp 136.5 °C. The filtrate was a mixture of 14 and another compound, which repeated chromatography failed to separate.[22] 14: UV λ_{max} (hexane) 216 sh nm (ϵ 23 500), 274 (17 900); IR ν_{max} (CCl_4) 3288 (OH, w), 3054, 3004, 2925, 2851, 2806 (C—H), 1610 (C=C, m) cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 2.14 (6 H, s, *o*-Me), 2.27 (3 H, s, *p*-Me), 2.35, 2.40 (12 H, d, NMe), 6.89 (2 H, s, Mes-H), 7.15–7.28 (3 H, m, Ph-H), 7.42 (2 H, d, Ph-H); mass spectrum (90 °C, 70 eV) m/z (relative abundance, assignment) 372 (17, M), 236 (57, Mes(Ph)C=C=O), 207 (23, MesCHPh), 193 (100, $MesCH_2Ph$ – Me), 178 (36, $MesCH_2Ph$ – 2Me), 135 (37, PO-$(NMe_2)_2$), 92 (26, C_7H_8).

Anal. Found: C, 67.47; H, 7.68; N, 7.40. Calcd for $C_{21}H_{29}H_2O_2P$: C, 67.72; H, 7.85; N, 7.52.

When a similar reaction was conducted in the presence of hexamethyldisilane, 45% of 14 was obtained.

***N*-Ethyl-*N*-methyldimesitylacetamide (11).** To a stirred solution of dimesitylketene (600 mg, 2.16 mmol) in dry ether (10 mL) under Ar at 0 °C was added ethylmethylamine (0.38 mL, 4.4 mmol). The mixture was stirred at 0 °C for 20 min and then overnight at room temperature. The ether was evaporated, giving a deep red solid. Chromatography of 384 mg on a Si-60 column with 6:4 petroleum ether (40–60 °C)/ether as eluent afforded light-orange crystals (172 mg, 39%), which on recrystallization (ether/petroleum ether (40–60 °C)) gave *N*-ethyl-*N*-methyldimesitylacetamide (11) as a light beige solid, mp 135 °C: UV λ_{max} (hexane) 228 sh nm (ϵ 37 600); IR ν_{max} (Nujol) 1620–1640 (s, C=O), cm^{-1}. The ^{1}H NMR, TLC, and IR of this product are identical with those of 11 obtained from $Mes_2C{=}C{=}O$ with MeLi/HMPA.

Anal. Found: C, 81.54; H, 9.56; N, 4.18. Calcd for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.18.

(29) We ascribe the appearance of two groups in 20 to their diastereotopic nature due to the chiral MeCHPh group.

N,N-Dimethyldimesitylacetamide (10). To a stirred solution of dimesitylketene (610 mg, 2.2 mmol) in THF (10 mL) at 0 °C was added a solution of 26% Me_2NH in water (w/w) (6.5 mL, approximately 36 mmol). After stirring overnight at room temperature, the THF was evaporated. The solution was extracted with ether (3 × 30 mL) and separated, and the organic phase was dried ($MgSO_4$) and evaporated, giving an orange oil (0.59 g). The ^1H NMR ($CDCl_3$) indicated the presence of 10 along with several other compounds. Chromatography on a Si-60 column with 1:1 (v/v) petroleum ether (40-60 °C)/ether eluent gave a light orange solid (325 mg, 46%). Further chromatography of 175 mg of this solid yielded a light orange solid (141 mg). Recrystallization (ether-petroleum ether) gave N,N-dimethyldimesitylacetamide (10), mp 144.5 °C: UV λ_{max} (hexane) 233 nm sh (ϵ) (14 500), 250 (260), 268 (480); IR ν_{max} (Nujol) 1620-1640 (s) cm^{-1}. The ^1H NMR, TLC, and IR are identical with those of 10 obtained above in HMPA.

Anal. Found: C, 81.42; H, 9.01; N, 4.34. Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33.

X-ray Crystal Structure Analysis. Data were measured on a Philips PW1100 four-circle computer-controlled diffractometer. The method is identical with that described previously,[29] except that the unit cell dimensions were obtained by a least squares fit of 24 centered reflections in the range of 21° < θ < 28°. Intensity data were collected by the ω-2θ technique to a maximum of 2θ of 110°. The scan width $\Delta\omega$ for each reflection was 0.80 ± 0.15 tan θ with a scan speed of 8.24°/min. All non-hydrogen atoms were found by using the results of the SHELX5-86 direct method analysis.[30]

Crystallographic data for 6: $C_{24}H_{35}N_2O_2P$, M 414.5, space group $P_{ca}2_1$; a = 20.520 (4) Å, b = 10.064 (2) Å, c = 11.426 (4) Å; V = 2359.6 (7) Å^3; Z = 4; ρ_{calcd} = 1.17 g cm^{-3}; μ(Cu K$_\alpha$) = 11.02 cm^{-1}; no. of unique reflections 1547, reflections with $I > 2\sigma_I$ = 1475; R = 0.058; R_w = 0.093; $w^{-1} = \sigma_F^2 + 0.00045F^2$.

14: $C_{21}H_{29}N_2O_2P$, M = 456.5, monoclinic, space group $P2_{1/n}$; a = 13.278 (7) Å, b = 15.630 (8) Å, c = 10.049 (5) Å; β = 91.56 (2)°; Z = 4; R = 0.067, R_w = 0.059. For 2520 reflections [$F_o > 1.5\sigma(F_o)$; $w = 1.530[\sigma^2(F) + 0.0002F^2]$].

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Supplementary Material Available: Tables of X-ray data of 6 and 14 (12 pages). Ordering information is given on any current masthead page.

(30) (a) Sheldrick, G. M. *Crystallographic Computing 3*, Oxford University Press: 1985; pp 175-189. (b) All the crystallographic computing was done on a Cyber 74 computer at the Hebrew University of Jerusalem, by using the SHELX 1977 structure determination package.

A New Route to 3,5-Disubstituted Isoxazolidines via the Iodocyclization of Homoallylic Hydroxylamines

Fabrizio Mancini, Maria Giulia Piazza, and Claudio Trombini*

Dipartimento di Chimica "G.Ciamician", Università di Bologna, via Selmi, 2 I-40126 Bologna, Italy

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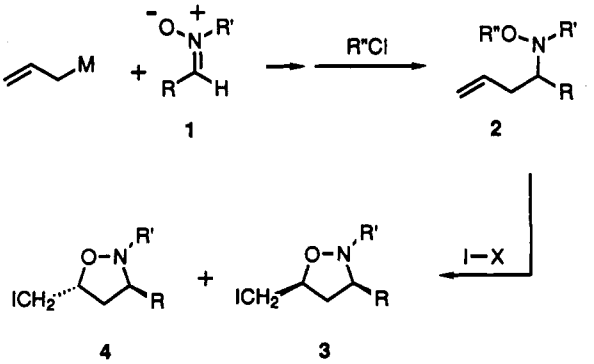
N,N-Dialkyl-*O*-trialkylsilyl homoallylic hydroxylamines reacted with iodine, *N*-iodosuccinimide, or iodine chloride to give 3,5-disubstituted isoxazolidines in good yield. The relative configuration that was generated at C3 and C5 was controlled by the nature of the nitrogen substituent of the parent hydroxylamine: the presence of a primary alkyl group favored the formation of a *cis*-isoxazolidine, whereas the presence of a *tert*-butyl group favored the formation of a *trans*-isoxazolidine. The effects that the *N*- and *O*-substituents and the nature of the iodinating agent exerted on the stereoselectivity of the cyclization were examined. The synthesis of enantiomerically pure isoxazolidines from hydroxylamines carrying a chiral *N*-mannofuranosyl group is described.

Introduction

Isoxazolidines[1] are important intermediates in the synthesis of such naturally occurring substances as Biotin,[2] amino glycosides,[3] alkaloids,[4] and the antibiotics Thienamycin[5] and Negamycin.[6] The usefulness of isoxazolidines arises from the transformations possible for these versatile compounds. For example, they can be readily converted to 1,3-amino alcohols. The most general route to isoxazolidines involves the 1,3-dipolar cycloaddition of nitrones to alkenes. This reaction was first described by Lebel,[7] was later studied by Huisgen,[8] and has been extensively

Scheme I



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