261 (M^+); NMR (CD_3CN) δ 4.02 (s).

1-Isopropyl- (4b) and 1-*tert*-Butyl-2,3,4-trinitropyrroles (4c). The synthesis of **3b** and **3c** was carried out by the procedure described for **3a**, starting from the appropriate amines.[5]

3b: mp 95.5–96 °C; mass spectrum, *m/e* 199 (M^+); NMR [$(CD_3)_2CO$] δ 1.60 (d, J = 6.5 Hz, 6 H), 4.68 (septet, 1 H, J = 6.5 Hz), 8.06 (s, 2 H).

3c: mp 150–151 °C; mass spectrum, *m/e* 213 (M^+); NMR [$(CD_3)_2CO$] δ 1.75 (s, 9 H), 8.07 (s, 2 H).

The nitration of **3b** and **3c** in H_2SO_4 at 0 °C yielded **4b** (76%) and **4c** (66%), respectively.

4b: mp 139–140 °C; NMR [$(CD_3)_2CO$] δ 1.75 (d, J = 7 Hz, 6 H), 5.55 (septet, 1 H, J = 7 Hz), 8.53 (s, 1 H).

4c: mp 121.5–122 °C; NMR [$(CD_3)_2CO$] δ 1.88 (s, 9 H), 8.31 (s, 1 H).

Nitration of 3-Nitro-1-R-pyrroles. The starting materials were prepared from 1-R-pyrroles[9] upon nitration with 1 equiv of 100% HNO_3 in acetic anhydride at −20 (R = alkyl) or 0 °C (R = Ar).[8] The nitrations yielded mixtures of 2-nitro- and 3-nitro-1-R-pyrroles. These isomers were easily separated by chromatography (silica gel, benzene–ethyl acetate or petroleum ether–benzene) and identified from their NMR spectra. 2-Nitro derivatives were eluted more rapidly than 3-nitro derivatives. The relative ratios of 2- and 3-nitro isomers are reported in Table II together with the overall yields. 3-Nitropyrroles (0.50 g) were nitrated in H_2SO_4 at 0 °C or room temperature (R = *o*-nitrophenyl) with 1 equiv of 100% HNO_3. The crude reaction mixture (0.35–0.40 g) was poured into water and extracted with ether or ethyl acetate. When R was an alkyl group, the composition of the crude reaction mixture was determined by TLC and NMR spectroscopy. When R was an aryl group, the NMR spectrum of the crude reaction mixture was much less simple. Therefore, the reaction products were isolated by chromatography on silica gel with petroleum ether (30–50 °C) continuously enriched with benzene and characterized by their spectra. The relative rates of elution were as follows: 2,4-dinitro >2,3,4-trinitro >3,4-dinitro.

Melting Points and Spectral Features of Dinitro- and Trinitropyrroles (d, R = *p*-Nitrophenyl; e, R = *o*-Nitrophenyl).[10]

3d: mp 188–189 °C; NMR [$(CD_3)_2SO$] δ 8.08 (d, J = 10 Hz, 2 H), 8.40 (d, 2 H, J = 10 Hz), 8.90 (s, 2 H).

3e: mp 120–122 °C; mass spectrum, *m/e* 278 (M^+); NMR [$(CD_3)_2SO$] δ 7.7–8.5 (m, 4 H), 8.59 (s, 2 H).

4d: mp 60–63 °C; mass spectrum, *m/e* 323 (M^+); NMR [$(CD_3)_2CO$] δ 8.05 (d, J = 10 Hz, 2 H), 8.48 (d, 2H, J = 10 Hz), 8.55 (s, 1 H).

6b: mp 107–108 °C; NMR (CCl_4) δ 1.67 (d, 6 H, J = 7 Hz), 5.53 (septet, 1 H, J = 7 Hz), 7.62 (d, 1 H, J = 2 Hz), 7.73 (d, 1 H, J = 2 Hz).

6c: mp 141–142 °C; NMR (CCl_4) δ 1.78 (s, 9 H), 7.53 (d, 1 H, J = 2 Hz), 7.71 (d, 1 H, J = 2 Hz).

6d: mp 195–196 °C; NMR [$(CH_3)_2SO$] δ 7.86 (d, 2 H, J = 8 Hz), 7.95 (d, 1 H, J = 2 Hz), 8.33 (d, 2 H, J = 8 Hz), 8.58 (d, 1 H, J = 2 Hz).

6e: mp 154–155 °C; NMR [$(CD_3)_2SO$] δ 7.7–8.6 (m, 4 H), 8.13 (d, 1 H, J = 2 Hz), 8.69 (d, 1 H, J = 2 Hz).

Acknowledgments. The authors thank Professor G. Illuminati for helpful discussions.

Registry No.—**1,** 56350-95-9; **2,** 69726-47-2; **2b,** 69726-48-3; **3a,** 68712-54-9; **3b,** 69726-49-41; **3c,** 69726-50-7; **3d,** 69726-51-8; **3e,** 69726-52-9; **4a,** 69726-53-0; **4b,** 69726-54-1; **4c,** 69726-55-2; **4d,** 69726-56-3; **6a,** 2948-69-8; **6b,** 2881-71-2; **6c,** 69726-57-4; **6d,** 53256-10-3; **6e,** 69726-58-5; 1-methyl-2-nitropyrrole, 823-37-0; 1-isopropyl-2-nitropyrrole, 69726-59-6; 1-*tert*-butyl-2-nitropyrrole, 69726-60-9; 1-(*p*-nitrophenyl)-2-nitropyrrole, 69726-61-0; 1-(*o*-nitrophenyl)-2-nitropyrrole, 69726-62-1; 1-methyl-3-nitropyrrole, 823-72-3; 1-isopropyl-3-nitropyrrole, 69726-63-2; 1-*tert*-butyl-3-nitropyrrole, 69726-64-3; 1-(*p*-nitrophenyl)-3-nitropyrrole, 69726-65-4; 1-(*o*-nitrophenyl)-3-nitropyrrole, 69726-66-5; 1-methyl-2,3,4,5-tetranitropyrrole, 69726-67-6; 1-methylpyrrole, 96-54-8; 1-isopropylpyrrole, 7057-97-8; 1-*tert*-butylpyrrole, 24764-40-7; 1-(*p*-nitrophenyl)pyrrole, 4533-42-0; 1-(*o*-nitrophenyl)pyrrole, 33265-60-0.

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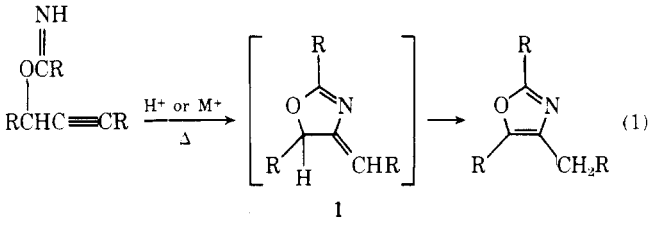
Communications

4-Methylene-4,5-dihydrooxazoles: Isolation, Properties, and Use for the Preparation of Substituted Oxazoles

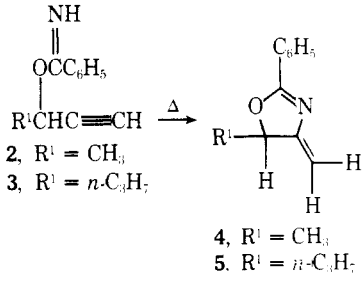
Summary: 4-Methylene-4,5-dihydrooxazoles are prepared from benzimidic esters of 1-alkyn-3-ols, and serve as useful intermediates for the synthesis of highly functionalized oxazoles.

Sir: Several natural products[1] and pharmacologically active compounds[2] contain oxazole rings. Substituted oxazoles also derive significant importance as azadiene components for Diels–Alder synthesis,[1,3,5] with their use in the total synthesis of pyridoxine (vitamin B_6)[1,4] being a notable example. One method of preparing substituted oxazoles, which is described most extensively in the patent literature, is the intramolecular cyclization of propargylic imidates (eq 1).[6] Concentrated sulfuric acid[6a] and Ag(I)[6b] and Hg(II)[6b] salts have been reported as catalysts for this conversion, which presumably[7] involves the intermediacy of a 4-alkylidene-4,5-dihydrooxazole (**1**). In this communication we report that when the solution thermolysis of benzimidic esters of 1-alkyn-3-ols is conducted under *basic* or *neutral* conditions the initially formed 4-methylene-4,5-dihydrooxazoles may be isolated in good yield (eq 2). We also report a preliminary study of the



(1)

1



(2)

2, $R^1 = CH_3$
3, $R^1 = n\text{-}C_3H_7$
4, $R^1 = CH_3$
5, $R^1 = n\text{-}C_3H_7$

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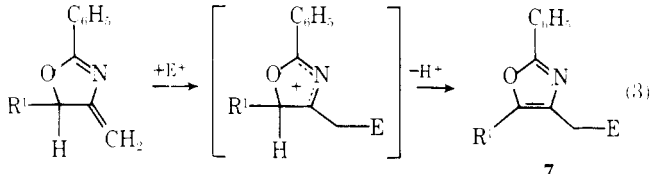
stability and chemical reactivity of these unusual[8-11] oxazolines, which prove to be useful intermediates for the regiospecific synthesis of substituted oxazoles.

Heating a benzene solution (90 mg/mL) of 3-butyn-2-yl benzimidate (**2**) (prepared from 3-butyn-2-ol in 60–90% yield)[6a] at reflux for 48 h in the presence of 1 equiv of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) afforded, after *rapid*[12] silica gel chromatography (4:1 hexane/ethyl acetate) and bulb-to-bulb distillation [bath temperature 70 °C (0.08 mm)], 5-methyl-4-methylene-2-phenyl-4,5-dihydrooxazole (**4**)[13b] in 45–50% yield. Benzimidate **2** underwent partial fragmentation to 3-butyn-2-ol and benzonitrile under these conditions, and **4** isolated in this fashion was contaminated with 20–30% of benzonitrile.[14] Pure methylene oxazoline **4**[14] showed characteristic terminal methylene absorption in the ^{1}H NMR spectrum at δ 4.4 and 5.1 and the expected signals for the methine (δ 5.2, m) and methyl (δ 1.5, d, J = 6 Hz) groups. In a similar manner, benzimidate **3** was converted to oxazoline **5** in 44% isolated yield. Methylene oxazolines **4** and **5** may also be prepared under essentially neutral conditions in higher yield, but on much smaller scales, by heating dilute hexane solutions of **2** and **3** at 140 °C for 4–8 h in sealed pressure bottles.[15]

Oxazoline **4** was remarkably stable under basic conditions and was converted only slowly (half-life ≈ 12 h) to 4,5-dimethyl-2-phenyloxazole[6a,13b] when treated with potassium *tert*-butoxide (0.3 M) in refluxing benzene. This irreversible tautomerization was rapid, however, under acidic conditions, and **4** had a half-life of only 3.5 min at 27 °C in a 0.15 M solution of trifluoroacetic acid in deuteriochloroform. Preparatively, the isomerization of **4** and **5** to oxazoles **7** [E = H; R^1 = CH_3 (98% yield), R^1 = n-C_3H_7 (84% yield)] was most conveniently accomplished by adsorption and subsequent (12 h later) chromatography on silica gel.

The facile tautomerization of **4** and **5** to the corresponding oxazoles under acidic conditions (eq 3) presumably reflects



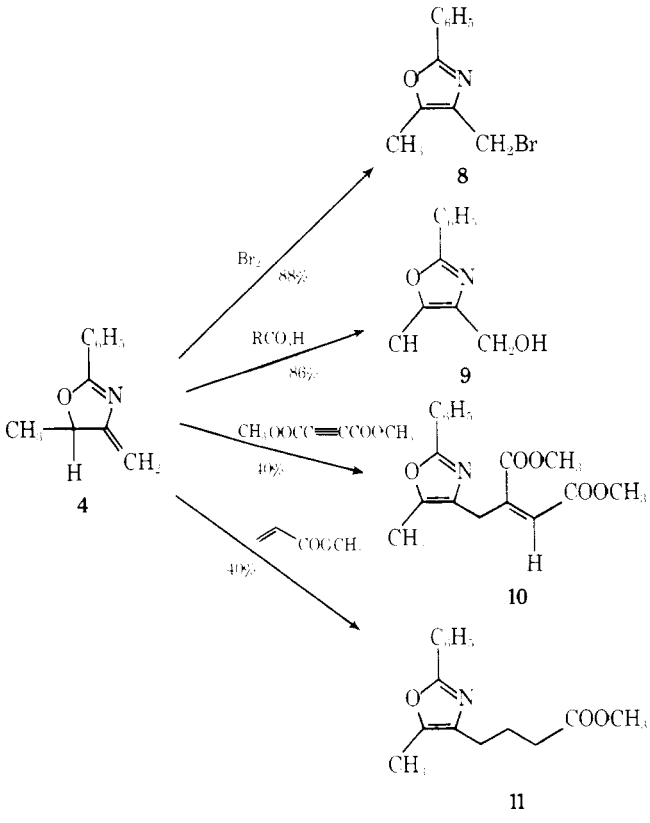
(3)

6 **7**

the stability of the delocalized cation **6** (E = H). We anticipated the other electrophiles would react similarly, and the results of this investigation are summarized in Scheme I. Oxazoline **4** rapidly decolorized Br_2/CCl_4 at room temperature to yield the bromomethyl oxazole **8**[13a] which had been previously prepared[16] in lower yield by bromination of 4,5-dimethyl-2-phenyloxazole. Treatment of **4** with *m*-chloroperbenzoic acid at 25 °C proceeded similarly to produce the crystalline alcohol **9**,[13a] mp 118–119 °C, in 86% isolated yield. As expected, **4** underwent ene reaction when treated with dimethyl acetylenedicarboxylate (80 °C, 2.5 h) or methyl acrylate (110 °C, 18 h) to afford the crystalline adduct **10**[13b,17] (mp 65–67 °C) and the oily adduct **11**[13a] both in 40% yield. To prevent competing aromatization it was essential to conduct the reaction of **4** with methyl acrylate in the presence of a few drops of triethylamine. Not unexpectedly, attempted Prins reaction of **4** with formaldehyde (boron trifluoride etherate catalyst)[18] failed completely as 4,5-dimethyl-2-phenyloxazole was rapidly produced under these acidic conditions.

The utility of 4-methylene-4,5-dihydrooxazoles as intermediates for preparing substituted oxazoles (eq 3, Scheme I) is limited by their acid stability. However, this regiospecific route to substituted oxazoles may find applications in synthesis, since it is one of few methods[1] for preparing oxazoles with highly functionalized carbon chains at position 4.

Scheme I



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(13) New compounds were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectra. Molecular composition was determined by (a) combustion or (b) mass spectral analysis.
(14) The reported yield of **4** is corrected for benzonitrile contamination. Since benzonitrile did not interfere with subsequent reactions of **4** it was typically not removed. Oxazoline **4** can be purified on a large scale by silica gel chromatography using a Waters Prep LC-500.
(15) For example, heating a hexane solution of **2** (1.9 mg/mL, containing 0.04 mg/mL of 4-*tert*-butylcatechol) at 140 °C for 5 h in a glass pressure bottle equipped with a stainless steel needle valve adaptor (Fisher Porter Co.) gave oxazoline **4** (>95% pure) in 70–90% yield after concentration and rapid[12] bulb-to-bulb distillation. Pure oxazoline **5** was prepared similarly in 80% isolated yield. The facile formation of oxazolines **4** and **5** under

these conditions results in part from surface catalysis obtained with the partially stainless steel pressure bottles we employed. Thus, thermolysis of **2** in a sealed, base washed, pyrex tube (3 mg/mL in hexane) for 8 h at 140 °C resulted in only 20% conversion to **4**. The addition of stainless steel, iron powder, or powdered pyrex (less effective) to identical reaction mixtures produced significant rate accelerations and afforded **4** in good yield.

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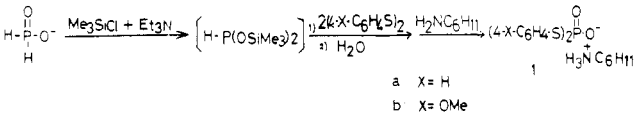
Synthesis and Properties of *S,S*-Diaryl Nucleoside Phosphorodithioates in Oligonucleotide Synthesis

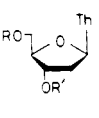
Summary: A new class of phosphorylating agents, *S,S*-diaryl phosphorodithioates, for the synthesis of oligothymidylates is described and properties of the bis(phenylthio) and bis(4-methoxyphenylthio) groups are also discussed.

Sir: In oligonucleotide synthesis, the so-called "triester approach" has recently been generalized and reported in a number of laboratories.[1-12] However, only a few examples are known of the synthesis of oligonucleotides bearing the 5′-phosphate end group utilizing this method.[13] Recently, we have investigated the chemical synthesis[14] of 5′-terminal regions of mRNAs from cytoplasmic polyhedrosis virus ($m^7G^{5'}$pppAmpGpUp... discovered by Furuichi and Miura[15]). For the large-scale synthesis of the terminal structure of mRNAs, an "activatable" protecting group for the 5′-terminal phosphate is required to construct the triphosphate structure.

In this paper we wish to report the synthesis of oligothymidylates bearing 5′-terminal phosphate by use of *S,S*-diaryl phosphorodithioates as the preliminary study for the chemical synthesis of defined mRNAs. Two kinds of cyclohexylammonium *S,S*-diaryl phosphorodithioates (**1a** and **1b**) were

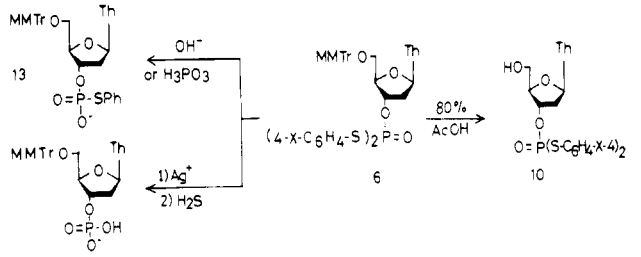


readily prepared by the reaction of bis(trimethylsilyl) hypophosphite, formed by the silylation of hypophosphorous acid, with 2.05 equiv of diaryl disulfide in 83 and 55% yields, respectively.[16] Compounds **1a** and **1b** (1.1–1.2 equiv) were condensed with appropriately protected thymidine derivatives (**2–4**) by the use of 2,4,6-triisopropylbenzenesulfonyl chloride



2 R = MMTr, R′ = H
3 R = Tr, R′ = H
4 R = H, R′ = Ac
5 R = H, R′ = H
6 R = MMTr, R′ = (4-X-C6H4-S)2P(O)
7 R = Tr, R′ = (4-X-C6H4-S)2P(O)
8 R = (4-X-C6H4-S)2P(O), R′ = Ac
9 R = (4-X-C6H4-S)2P(O), R′ = H
11 R = H, R′ = (HO)(PhS)P(O)
16 R, R′ = (4-X-C6H4S)2PTp(SC6H4-X-4)2

(TPS) (2.2–2.4 equiv)[17] in pyridine for 20–24 h. The phosphorylated products (**6–8**) were obtained in 88–96% yields. In a similar manner, unprotected thymidine was phosphorylated selectively on the 5′-hydroxyl group of the sugar moiety to afford *S,S*-diaryl thymidine 5′-phosphorodithioates (**9a** and **9b**) in 66 and 71% yields, respectively.[18] The products **9a** and **9b** were found to be quite stable in dry or aqueous pyridine and also in alcohols for several weeks. Selective removal of the monomethoxytrityl or trityl group from **6a, 6b, 7a,** and **7b** was performed without any loss of the arylthio group by treatment

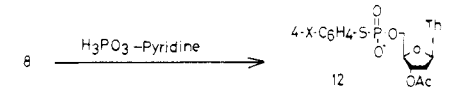


with 80% acetic acid at room temperature for 6 h or at 100 °C for 15 min. The corresponding detritylated products (**10a** and **10b**) were obtained in more than 94% yields in each case. Even when **6a** was heated in 80% acetic acid at 100 °C for 1 h, **10a** was isolated in 91% yield.[19]

Contrary to facile removal of the phenylthio group from *S*-phenyl nucleoside phosphorothioates (diester-type) by treatment with iodine in aqueous pyridine,[20] the bis(arylthio) groups of **6–9** were extremely stable toward oxidizing agents such as iodine, sodium periodate, hydrogen peroxide, iodosobenzene, and *N*-chlorosuccinimide. However, both phenylthio groups of **6a–9a** could be readily removed from **6a–9a** by treatment with 16 equiv of silver acetate or silver nitrate in aqueous pyridine at room temperature for 16 h to afford the corresponding thymidylates in quantitative yields.[21] For complete removal of the two 4-methoxyphenylthio groups from **6b–9b,** 20 equiv of silver acetate was required.[22]

S-Ethyl[23] and *S*-phenyl[20] nucleoside phosphorothioates are known to react with oxidizing agents and metal salts to generate metaphosphate intermediates, which react with nucleophiles to give the corresponding phosphorylated products. Accordingly, selective removal of one arylthio group from **6–9** is important in connection with the chemical synthesis of the 5′-terminus of mRNAs.

One of the arylthio groups could be removed from *S,S*-diaryl nucleoside phosphorodithioates (for example, **6a** and **6b**) by treatment with 0.2 N NaOH–dioxane (1:1, v/v) at room temperature for 15 min.[24] However, these conditions are similar to those for removal of acyl groups used often in oligonucleotide synthesis. Therefore, we have developed an alternative method for selective deprotection of one arylthio group from **6–9.** It was found that a solution of phosphorous



acid in pyridine was remarkably effective for this purpose. When **8a** was treated with 4 equiv of phosphorous acid in pyridine at room temperature for 24 h, *S*-phenyl 3′-*O*-acetylthymidine 5′-phosphorothioate (**12a**) was obtained quantitatively. On the other hand, on treatment of **6a** under the same conditions, the monomethoxytrityl group remained intact and *S*-phenyl 5′-*O*-monomethoxytritylthymidine 3′-phosphorothioate (**13**) was isolated in 86% yield.[25] *It is noteworthy that no deacylation and no detritylation occurred under these conditions.*[26] The specific effect of phosphorous acid should be emphasized because monoalkyl phosphates such as 2,2,2-trichloroethyl phosphate had only negligible effect.

Next, the synthesis of thymidylyl(3′→5′)thymidine 5′-phosphate (pTpT) was examined starting from **9a** and **9b.** For this purpose, the 2,2,2-trichloroethyl group[2] was chosen as the protecting group of the internucleotidic phosphate. First, **9a** was condensed with 1.2 equiv of 2,2,2-trichloroethyl phosphate at room temperature for 8 h and then the phosphorylated product (**14a**) was coupled with thymidine using two kinds of condensing agents, TPS and (4-nitrobenzenesulfonyl)triazole (NBST),[6] at room temperature for 18 h. TPS gave a better yield (92%) of the fully protected dinucleotide (**15a**) than

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