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DIPHENYL PHOSPHORAZIDATE(DPPA) AS A 1,3-DIPOLE
—ITS REACTION WITH ENAMINES OF CYCLIC KETONES—

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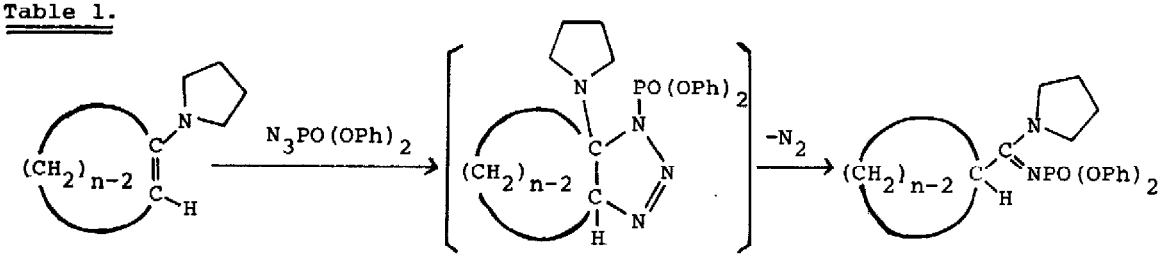
Recent publications from these laboratories have revealed that diphenyl phosphorazidate(DPPA)[1] may be used for the peptide bond formation reaction,[2,3] the modified Curtius reaction,[2,4] esterification of α-functionalized acetic acids,[4,5] preparation of thiol esters,[6] and diketopiperazine formation reaction,[7] in all of which the azide group of DPPA functions as the azide anion equivalent. Breslow and co-workers[8] reported the chemical properties of the phosphoryl nitrene generated from DPPA. Our further interests on the synthetic use of DPPA have led us to investigate the role of its azide function as a 1,3-dipole to enamines, well-known strong 1,3-dipolarophiles,[9] derived from cyclic ketones.

Although the 1,3-dipolar cycloaddition of organic azides to enamines of cyclic ketones has been proven to be a method of ring contraction, reported procedures have drawbacks such as low yields,[10] lack of functional specificity[11] or the use of poisonous, explosive azide.[12] We here report that the use of DPPA as a 1,3-dipole overcomes these difficulties and may promise a convenient ring contraction reaction of pyrrolidine enamines of cyclic ketones in preparatively satisfactory yields.

Pyrrolidine enamines from various cyclic ketones smoothly underwent the 1,3-dipolar cycloaddition with DPPA followed by ring contraction with evolution of nitrogen, summarized in Table 1. Although we have not tried to isolate labile intermediates Δ^2-triazolines, there will be no doubt about their existence.[9]

In a general procedure, a mixture of an enamine(1 eq) and DPPA(1.2 eq) in ethyl acetate was stirred at reflux for 3 hr. After dilution with benzene-ethyl acetate and usual work-up with acid(citric acid) and alkali(sodium bicarbonate), the product was purified by silica gel column chromatography, recrystallization, or distillation.

Table 1.



n	Yield, %[a]	Mp or Bp(mmHg), °C
6	76.5[b]	77-79
7	74	93-95
8	75	210(0.2)
12	60	oil
12	34[c]	81.5-82.5
16	68	109-110
16	58[d]	109-110

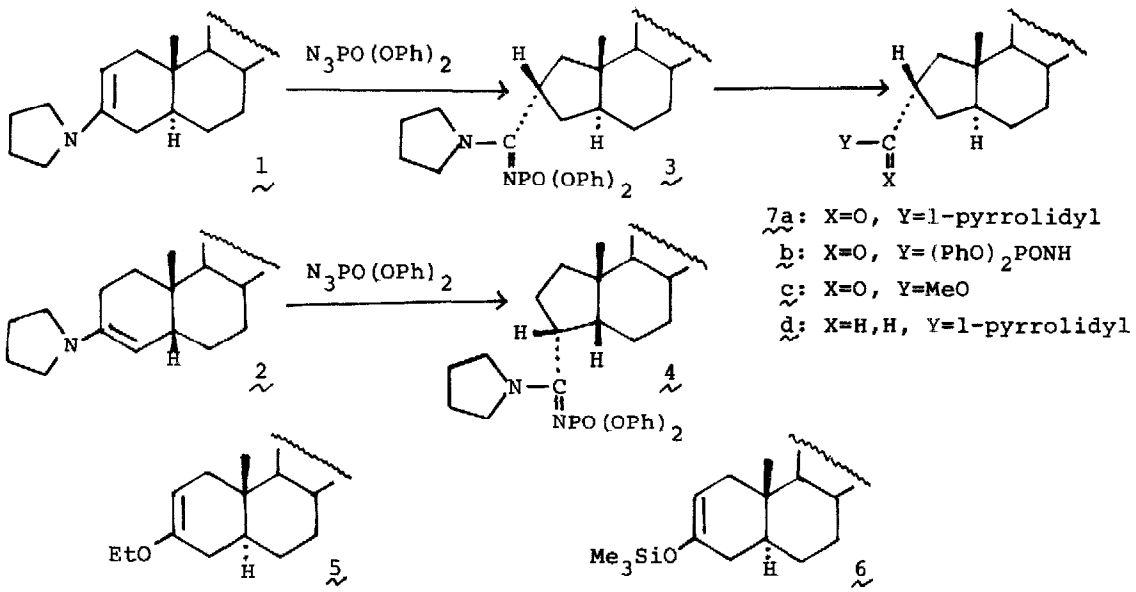
a Isolated yield.

b The reaction was carried out in tetrahydrofuran at room temp. for 0.5 hr and then at reflux for 2 hr.

c Morpholine enamine was used with 2 eq of DPPA. See the text on the other product.

d Based on cyclohexadecanone.

Cholestanone and coprostanone pyrrolidine enamines(1 and 2) also gave the corresponding A-norsteroids(3, mp 111-112°, and 4, mp 126-128°) with DPPA(2 eq) in 79 and 71% yields, respectively. Both the ethyl enol ether(5) and the trimethylsilyl enol ether(6) derived from cholestanone did not undergo the ring contraction with DPPA, exhibiting the functional specificity of DPPA as a 1,3-dipole. The phosphorylamidine(3) was hydrolyzed with 1N sodium hydroxide in dioxane to give the pyrrolidyl amide[12](7a, mp 158-159°) in 43% yield as well as the phosphoryl derivative(7b, mp 134-136°) in 28% yield, while acidic hydrolysis with 20% hydrochloric acid in dioxane followed by esterification with methanolic hydrogen chloride afforded the methyl ester[12](7c, mp 97-98°), in 88% yield. Lithium aluminum hydride reduction of 3 furnished the pyrrolidyl amine(7d, mp 157-161°), in 73% yield.



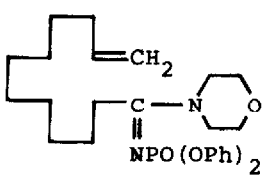
1 2 3 4 5 6

7a: X=O, Y=1-pyrrolidyl
b: X=O, Y=$(PhO)_2PONH$
c: X=O, Y=MeO
d: X=H,H, Y=1-pyrrolidyl

The ring-contracted product from cyclohexadecanone pyrrolidine enamine also underwent acidic hydrolysis to give cyclopentadecanone carboxylic acid which was isolated as its methyl ester. The ester was again hydrolyzed with alkali to recover the acid, mp 63-66°, which was already converted to the important perfume muscone via exaltone.[13]

In the reaction of cyclododecanone morpholine enamine with DPPA, the oily ring-cleavage product(8, nmr in $CDCl_3$: characteristic pattern of CH_2=CH-CH_2- at δ 2.0, 4.89, 4.94 and 5.76 ppm) was obtained in 38% yield together with the expected ring-contracted product. The former(8) will also be produced from the intermediate 1,3-dipolar adduct, but to our knowledge no precedent has been reported.

Since 1,3-dipolar cycloaddition to enamines of aromatic or conjugated cyclic ketones has seldom been reported, extension of the above DPPA method has been examined briefly. Addition of DPPA to α-tetralone pyrrolidine enamine gave the ring-contracted product(9, mp 115-116°) in only 4% yield, while β-tetralone pyrrolidine enamine afforded the same product(9) in 33% yield. In the former case, the major product(22% yield) was the oily ring-cleavage product(10, nmr in $CDCl_3$: characteristic pattern of CH_2=CH-CH_2- at δ 3.38, 4.96, 5.00 and 5.8 ppm). Cholestenone pyrrolidine enamine(11) also underwent the ring contraction with DPPA to give the A-norsteroid(12, a colorless foam) in 34% yield.



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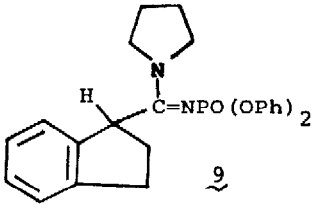

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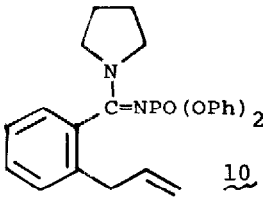

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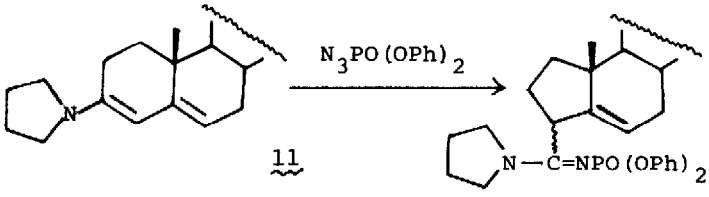

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