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ORGANOPHOSPHORUS COMPOUNDS XVI. SYNTHESIS OF SOME NOVEL 2,3-DIHYDRO-1*H*-1,2-BENZAZAPHOSPHOLE 2-OXIDES AND -SULPHIDES

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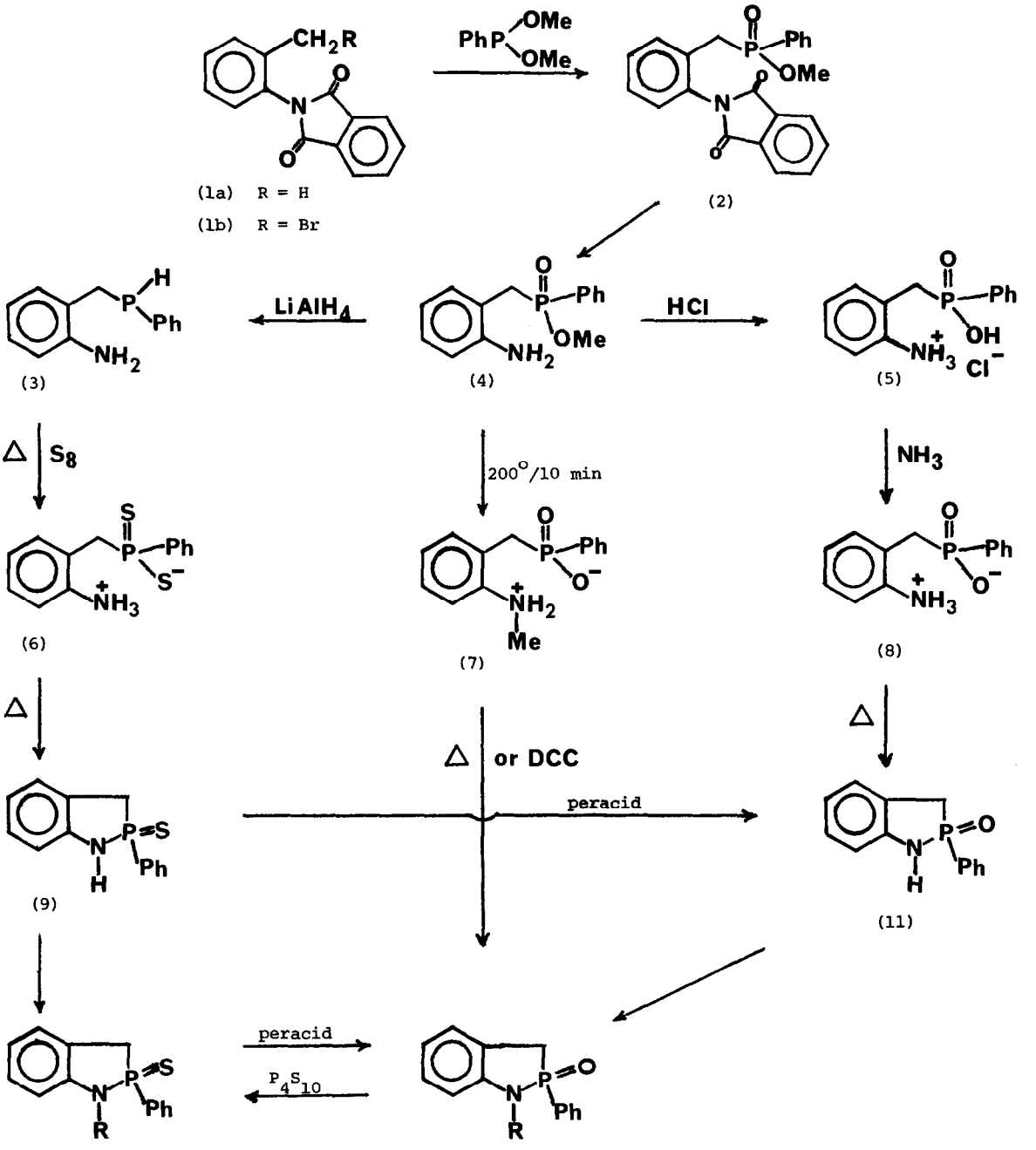
SUMMARY Several derivatives of 2,3-dihydro-1*H*-1,2-benzazaphosphole, a new class of benz-fused N-P heterocycle, have been synthesised by thermal and DCC-promoted N-P ring closure from zwitterionic intermediates.

Previously we described[1] the synthesis of 2-ethoxy-1-methyl-1,2-azaphospholidine 2-oxide in which the final ring closure to a 5-ring heterocycle involved formation of the carbon-nitrogen bond. For the related benz-annelated compounds this strategy was inappropriate, but an alternative nitrogen to phosphorus ring closure was achieved by the sequence summarised below (Scheme 1).

Reaction of o-N-phthalimidobenzyl bromide (1b) with dimethyl phenylphosphonite yielded the phosphinate ester (2). Hydrazinolysis[2] of (2) gave the amino compound (4), the key intermediate for three different procedures for N-P ring closure. In the first sequence compound (4) was reduced with lithium aluminium hydride to the amino phosphine (3), and reaction of this with sulphur gave the dithiophosphinate zwitterion (6) which underwent thermal elimination of hydrogen sulphide to yield 2,3-dihydro-2-phenyl-1*H*-1,2-benzazaphosphole 2-sulphide (9), m.p. 83-85°. ^{1}H n.m.r. δ (90 MHz, $CDCl_3$) 3.59, d ($J_{H,P}$ 10.9 Hz), benzylic CH_2; 5.33, bd ($J_{H,P}$ 9.1 Hz), NH (exch); 6.88-8.16, m, 9H aromatic. ^{13}C n.m.r. δ (22.63 MHz, $CDCl_3$) 39.9, dt (J_{CP} 67.7 Hz), C3; 111.7, dd (J_{CP} 10.3 Hz), C7; 120.6, d, C5; 122.4, s, C3a; 126.9, dd (J_{CP} 13.2 Hz), C6; 128.5, d, C4 and dd (J_{CP} 13.3 Hz), C3', C5'; 130.9, dd (J_{CP} 11.8 Hz), C2', C6';, 132.2, dd (J_{CP} 2.9 Hz), C4'; 135.1, d (J_{CP} 97.1 Hz), C1'; 145.1, d (J_{CP} 11.8 Hz), C7a. ^{31}P n.m.r. (36.4 (MHz, $CDCl_3$) δ -72.2 (i.e. downfield from phosphoric acid). Mass spectrum: m/z 245 (M, 68%), 212(100), 136(13), 135(16); m* 183.4, (245→212).


CH2R
PhP(OMe)2
Ph
OMe
(1a) R = H
(1b) R = Br
(2)
LiAlH4
HCl
(3)
(4)
(5)
S8
200°/10 min
NH3
(6)
(7)
(8)
or DCC
peracid
(9)
(11)
peracid
P4S10
(12a) R = Me
(12b) R = Et
(12c) R = CH2Ph
(10a) R = Me
(10b) R = Et
(10c) R = CH2Ph

SCHEME 1

The doublet at δ 5.33 for the single proton on nitrogen indicates the presence of an N-P bond in (9). This is corroborated in the ^{13}C n.m.r. spectrum by the magnitude of the C7a-P coupling (11.8 Hz); this figure was larger in the corresponding oxide (11) (14.7 Hz), and was as high as 28.0 Hz in the 2-methoxy 2-oxide (15). The aminophosphinate precursor (4) shows the corresponding carbon atom at δ 146.7 with J_{CP} only 4.4 Hz.

N-Alkylation of the heterocycle (9) (NaH, DMF, RX) afforded the derivatives (12a-c) in high yields.

In a second sequence, bulb-to-bulb distillation of (4) at 200-220°/0.6 mm yielded 51% of the N-methyl heterocycle (10a) together with smaller amounts of the N-methyl zwitterion (7) and the N-H heterocycle (11). Alternatively, the aminophosphinate ester (4) was heated at 200° at atmospheric pressure for 10 minutes to give mainly the N-methyl zwitterion (7). Bulb-to-bulb distillation of pure (7) gave the N-methyl heterocycle (10a) in almost quantitative yield. Cyclisation of (7) using dicyclohexylcarbodiimide (DCC) produced (10a) in 98% yield.

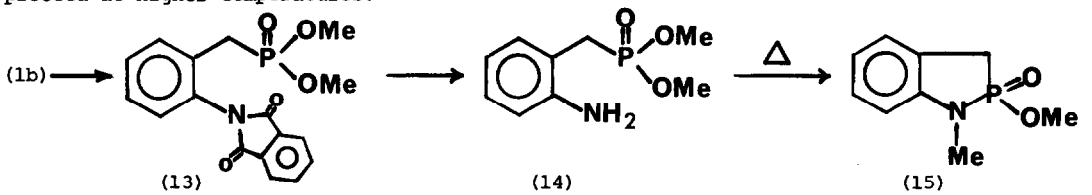
A third ring closure involved hydrolysis of the phthalimido phosphinate (2) or the corresponding aminophosphinate (4) with concentrated HCl to give the aminophosphinic acid hydrochloride salt (5). Treatment of this with dilute aqueous alcoholic ammonia gave the zwitterion (8), which upon bulb-to-bulb distillation (230°/0.6 mm) yielded the 1-unsubstituted heterocycle (11), m.p. 254-260°. Compound (11) was also obtained in good yield by oxidation of the corresponding sulphide (9) with m-chloroperoxybenzoic acid. N-Alkylation of (11) gave the compounds (10a-c).

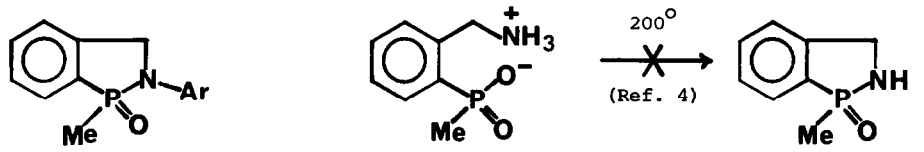
Treatment of (10a) with phosphorus pentasulphide afforded (12a), identical with the compound obtained via the zwitterion (6), and the reverse reaction was achieved with m-chloroperoxybenzoic acid. Compounds (10b,c) and (12b,c) were similarly interconverted.

Reaction of (1b) with trimethyl phosphite gave (13), hydrazinolysis of which afforded the known amino phosphonate (14)[3], m.p. 78-80° in 58% overall yield from o-toluidine, an improvement on the literature procedure[3]. When the aminophosphonate (14) was heated at 200-210° at atmospheric pressure for 10 minutes trans-methylation occurred, and bulb-to-bulb distillation of the resulting N-methyl zwitterion at 220-230°/2 mm afforded 34% of the 2-methoxy heterocycle (15) as a liquid, b.p. 155°/0.5 mm. The proton n.m.r. spectrum showed

δ (90 MHz, $CDCl_3$) 2.67, s, (small wing of signal due to diastereotopic benzylic hydrogens); 2.98, d ($\underline{J}_{HP}$ 8.2 Hz), N-Me; 3.01, bs ($\underline{J}_{HP}$ 12.9 Hz), major wing of signal for diastereotopic benzylic methylene); 3.70, d ($\underline{J}_{HP}$ 11.4 Hz), P-OMe; 6.45-7.38, m, 9 aromatic H. ^{31}P n.m.r. δ -47.9 p.p.m. Mass spectrum: m/z 197(M, 58%), 182(10), 166(7), 118(100), 119(58), 91(21), 58(32).

The compounds (9), (10a-c), (11), (12a-c) and (15) are the first examples of benz-fused 1,2-azaphospholes. Miles *et al.*[4] recently reported the synthesis by C-N cyclisation of compounds (16) in which the positions of the N and P atoms are reversed. They stated that the zwitterionic aminophosphinic acid (17) failed to undergo thermal cyclisation to (18) at 200° in a vacuum. In the light of our results the conversion of (17) → (18) might proceed at higher temperatures.





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