Syntheses with Ethynylphosphonium Salts; Nucleophilic Additions to Phenylethynyltriphenylphosphoniun Bromide

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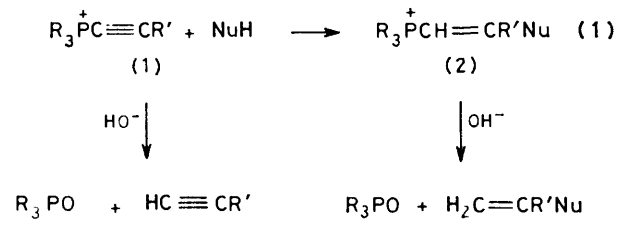
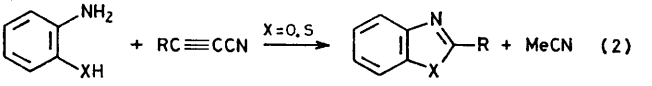
Acyclic and heterocyclic adducts have been prepared by additions to phenylethynyltriphenylphosphonium bromide of benzoylhydrazine, hydroxylamine, *o*-aminobenzophenone, *o*-aminophenol, *o*-aminobenzenethiol, *o*-aminoaniline, ethylenediamine, 2,3-diamionopyridine, 1,2-diaminonaphthalene, 1,8-diaminonaphthalene, and benzophenone hydrazone. A useful feature of the title compounds is that the triphenylphosphonium group activates the triple bond and then can be removed either as phosphine oxide or as a quaternary salt; thus, they are potential ethynyl equivalents.

In this work we use ethynylphosphonium salts (1) chiefly for synthesis of heterocyclics by double Michael additions. Although they have seen some application in syntheses since their discovery in 1962,[1] the potential of these compounds is just beginning to be disclosed.[2-5] The background for nucleophilic attacks on the triple bond, particularly the synthesis of heterocyclics from alkynes[6a] *or* from phosphonium salts[6b] has been reviewed.

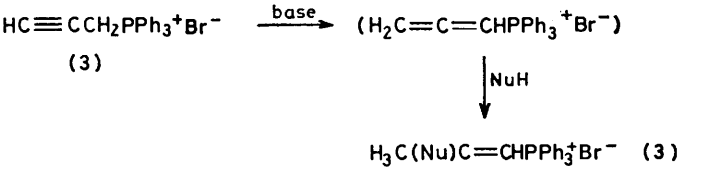


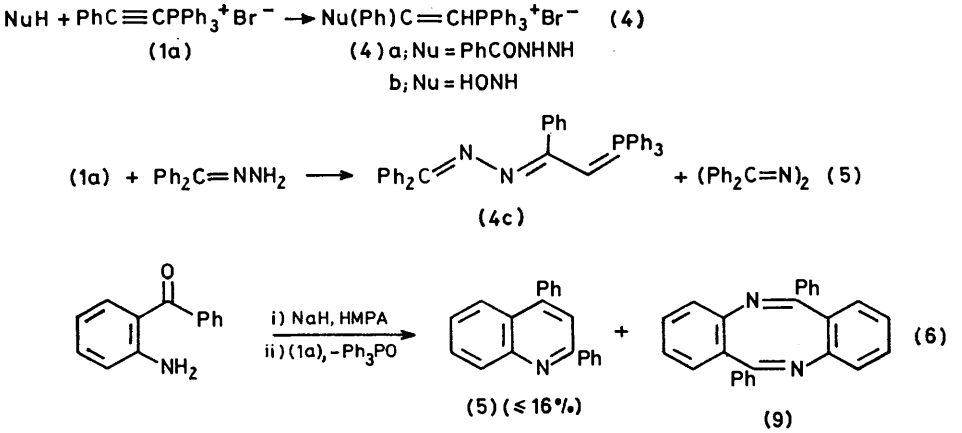
Hoffmann reported that nucleophilic additions of H_2O, R_2NH, $MeCO(EtO_2C)CH_2$, an enamine, PhSH, Ph_2PH, and Ph_3P to (1) were facile; clearly the phosphonium group was a Michael activator.[2] Further additions of phosphines (+HX) to give 1,2-diphosphonioethylenes,[2,3] of azide ion to yield triazole ylides,[4] and of pyridine *N*-oxides to give substituted pyridines, were also observed.[5]

Aqueous base strips R_3P (as R_3PO) from both the starting and product salts [equation (1)]. Thus, the ethynylphosphonium salts may be regarded as masked acetylenes with which the familiar synthetic device (principle) of activate-react-unblock may be employed.[6a] Elegant illustrations of this approach are found in an analogous system in which CN activates the triple bond and then departs after the addition is over [equation (2)].[7]



As starting materials propargyl-phosphonium and -sulphonium salts and nucleophiles may lead to similar products [equation (3)].[8,9] Process (3) differs from (1), however, in that the nucleophile attacks the allenic rather than the acetylenic form. These mechanisms have been of interest to us as well as to others.[6,9] But if one is interested only in obtaining the product, as is often the case, the question of its origins may hold little interest. Thus, propargyl is equivalent to propynyl, at least in the presence of base, and the product of equation (3) could presumably arise equally well from $H_3CC{\equiv}CPPh_3^+Br^-$. Indeed, because of the ready availability of several propargylic compounds, $RC{\equiv}CCH_2X$, synthetic



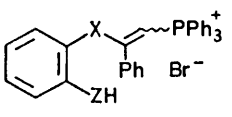


routes such as equation (3) could have a distinct advantage.[8] On the other hand, the ethynyl substituent R′ in (1) can, in principle, be any group, *e.g.*, aryl, heteroaryl, Cl, CN, *etc.*, and this makes process (1) more widely applicable. Obviously, the choice of a synthetic route will depend critically on the availability of starting materials.

Our additions to (1a) may be divided roughly into single [equation (4)] and multistep processes [equations (5) and (6)]. In equation (5), a simple adduct presumably forms which, on treatment with base, loses HBr to form (4c). Process (6) is analogous overall to several medium-yield (31—64%) processes from propargylphosphonium salts.[8a,c] Under the indicated conditions of equation (6) and several others that we tried, self-condensation, which led to dibenzodiazocine in equation (6), often seemed to predominate; the higher yields in Schweizer's procedure appear to be due to the fact that acyclic adducts were formed *before* NaH was used to close the ring.[8a,c] Reactions of (1a) with several vicinal dinucleophiles yield acyclic adducts (6) which usually react, or can be made to react, to give cyclic products (7). Where an acyclic product (6) is indicated, it was isolated and cyclized to (7), usually at higher temperatures. In other cases ring-closure to (7) accompanied by the loss of methylenephosphorane [as (8)] was competitive.

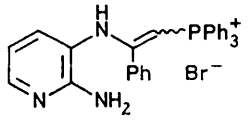
The above ' closure and cleavage ' technique was used earlier by Schweizer *et al.*, in his syntheses of heterocyclics which began with process (3).[8a,b] Besides equations (1) and (5) in which R_3PO departs, this is a second way in which intermediate products of ethynylphosphonium salt reactions shed the activating group.

With respect to our acyclic amine adducts, *e.g.*, (4) and (6) there is the possibility of enamine–imine tautomerism. Since spectral data (n.m.r., i.r.) have already been used to clarify the equilibrium condition for similar compounds,[8a] our own comments can be brief. Although we have listed our products as enamines, they might be also tautomeric mixtures or imines, depending on the solvent: in $CDCl_3$, (4a) consists of enamine and imine, while the presence of a third tautomer, the hydroxyazine, is uncertain; in [$^2H_6$]DMSO, (4b), (6a), and (6c) are essentially all imine; in $CDCl_3$, (6a and c) are mostly enamine. In some cases, chemical shifts of the mobile protons were not apparent, presumably because of exchange.

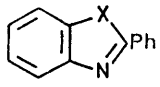


(6)

a; X = NH, Z = O
b; X = S, Z = NH
c; X = NH, Z = NH

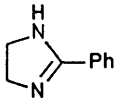


(6d)

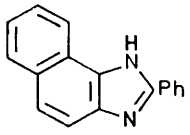


(7)

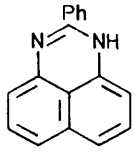
a; X = O
b; X = S
c; X = NH



(7d)



(7e)



(7f)

$(CH_3)Ph_3P^+ Br^-$

(8)

EXPERIMENTAL

The preparation of (1a) has been described.[3] In column chromatography alumina was Woelm neutral, activity grade 1. One of the solvents, hexamethylphosphoramide is carcinogenic.

1-(2-*Benzoylhydrazino*)-1-*phenyl*-2-*triphenylphosphonioethylene Bromide* (4a).—Benzoylhydrazine (136 mg, 1 mmol) and (1a) (443 mg) were heated in acetonitrile (20 ml) at 80—90° for 24 h. After the solution was cooled and the solvent evaporated, the residue was treated with ether. This yielded a *solid* (511 mg, 88%), m.p. 220—220.5°; $\nu_{max.}$ (KBr) 3 400br, 2 850, 2 760, 1 675, 1 435, 1 257, 1 106, 740, and 681 cm^{-1}; δ ($CDCl_3$) 4.43 [d(m), *J* 12 Hz], 6.33 [d(m), *J* 16 Hz], and 6.8—8.40 (m) (Found: C, 68.2; H, 4.9. $C_{33}H_{28}BrN_2OP$ requires C, 68.4; H, 4.85%).

1-(N-*Hydroxylamino*)-1-*phenyl*-2-*triphenylphosphonioethylene Bromide* (4b).—Hydroxylamine hydrochloride (80 mg, 1.2 mmol) and (1a) (0.443 g, 1 mmol) and triethylamine (1 ml) were stirred in methanol (15 ml) for 16 h. After the solvent was evaporated, the insoluble solid (0.45 g, 95%) was washed with chloroform, stirred for several days with ethanolic triethylammonium hydrogen bromide and again washed. It has m.p. 230—231°; δ [$(CD_3)_2SO$] 5.23 (2 H, d, *J* 17 Hz) and 7.1—8.2 (m); $\nu_{max.}$ (KBr) 3 050, 2 920, 2 810, 1 603 (w), 1 585, 1 437, 1 106, 959, 740br, and 687 cm^{-1} (Found: C, 65.95; H, 4.8. $C_{26}H_{23}BrNOP$ requires C, 65.55; H, 4.85%).

2,4-*Diphenylquinoline* (5).—2-Aminobenzophenone (3.94

g, 0.02 mol) was added to a stirred suspension of sodium hydride (60% in oil, 0.8 g, 0.02 mol) in dry hexamethylphosphoramide (40 ml) under nitrogen to produce a reddish solution. After *ca.* 45 min (1a) (8.86 g, 0.02 mol) was introduced, discharging the red colour. After the stirred mixture was heated at 100—110° for 22 h, it was poured into water (*ca.* 500 ml) and worked up. The crude residue in chloroform had an i.r. absorption at 3 300 cm^{-1} which was attributed to $\nu_{C\equiv CH}$ of phenylacetylene. Column chromatography of the residue over alumina yielded (5) (0.9 g, 16%), m.p. 110—112° (lit.,[10] 112°), *m/e* 281 (M^+); compound (9) (0.5 g), m.p. 189° (lit.,[11] 190°), *m/e* 358 (M^+); and triphenylphosphine oxide (2.5 g), m.p. 155—157°, which was identical with an authentic sample. An analogous preparation in dimethylformamide followed by a different mode of work-up led to rather more self-condensation of the aminobenzophenone (24%) and less quinoline (7%).

1-o-*Hydroxyanilino*-1-*phenyl*-2-*triphenylphosphonioethylene Bromide* (6a) *and* 2-*Phenylbenzoxazole* (7a).—*o*-Aminophenol (327 mg, 3 mmol) in tetrahydrofuran (20 ml), (1a) (1.11 g, 2.5 mmol), and chloroform (10 ml) were warmed to 65° for *ca.* 1.5 h and stirred overnight at *ca.* 25°. The precipitate was filtered, yielding crystals (1.20 g, 87%) of (6a), m.p. 203—204° (from methanol); $\nu_{max.}$ (KBr) 3 100br, 2 990br, 1 600, 1 500, 1 440, 1 285, 1 100, 992, 937, 867, 770, 745, and 683 cm^{-1}; δ [$(CD_3)_2SO$] 4.5 (1 H, d, *J* 13 Hz) and 6.8—7.9 (24 H, m) (Found: C, 69.6; H, 5.0. $C_{32}H_{27}BrNOP$ requires C, 69.55; H, 4.9%).

Compound (6a) (554 mg, 1 mmol) was heated at reflux temperature in chloroform (10 ml) for 24 h. After the solvent was evaporated, the residue was treated with tetrahydrofuran and the suspension was filtered. The solid (261 mg) was mostly methyltriphenylphosphonium bromide (8), m.p. 231—232° (lit.,[12] 232—233°). From the filtrate, (7a) (21 mg, 14%) was obtained by column chromatography, m.p. 97° (lit.,[13] 102.5—103.5°); *m/e* 195 (M^+).

1-o-*Aminophenylthio*-1-*phenyl*-2-*triphenylphosphonioethylene Bromide* (6b) *and* 2-*Phenylbenzo*[1,2-d]*thiazoline* (7b).—*o*-Aminobenzenethiol (*ca.* 40 mg) and (1a) (111 mg, 0.25 mmol) were stirred in chloroform (10 ml) for *ca.* 7 h. The solvent was removed and the residue was crystallized from tetrahydrofuran to give (6b) (70 mg, 49%), m.p. 162—162.5°; $\nu_{max.}$ (KBr) 3 400br, 2 940, 2 860, 1 613, 1 582, 1 477, 1 430, 1 102, 895, 755, 740, 720, and 682 cm^{-1}; δ ($CDCl_3$) 5.7 (1 H, d, *J* 15 Hz), 5.7 (2 H, m), and 6.6—7.7 (24 H, m) (Found: C, 68.0; H, 4.95. $C_{32}H_{27}BrNPS$ requires C, 67.6; H, 4.8%).

Compound (6b) (500 mg, 0.879 mmol) was heated at reflux in acetonitrile (15 ml) under nitrogen for 24 h. The solvent was removed, the residue was treated with a few ml of tetrahydrofuran and the suspension was filtered. The impure solid (331 mg) contained (8). The filtrate yielded material from which (7b) (150 mg, 80%), m.p. 112.5—114° (lit.,[14] 114°) was obtained by column chromatography.

1-(o-*Aminoanilino*)-1-*phenyl*-2-*triphenylphosphonioethylene Bromide* (6c).—*o*-Phenylenediamine (324 mg, 3 mmol) and (1a) (1.11 g, 2.5 mmol) were stirred in chloroform (20 ml) at 60° under nitrogen for 20 h. The solvent was evaporated and the residue was treated with tetrahydrofuran. Filtration of the suspension yielded (8) (322 mg, 36% yield), m.p. 231—232°, from methylene chloride–tetrahydrofuran. Compound (6c) (314 mg, 23%) was obtained from the filtrate, m.p. 193—194°; $\nu_{max.}$ (KBr) 3 470—2 770, 3 450, 3 260, 3 050, 2 950, 1 620, 1 545, 1 495, 1 435, 1 100, 941, and 748 cm^{-1}; δ [$(CD_3)_2SO$] 5.4br (<1 H), 5.7br (<1 H), 4.5 (1 H, d, *J* 14 Hz), 7.1, and 7.5—7.8 (24 H, m) (Found: C, 69.6; H, 5.05. $C_{32}H_{28}BrN_2P$ requires C, 69.7; H, 5.05%).

When (6c) was treated with aqueous alkali a yellow material was formed, m.p. 199—202°. Although the elemental analysis was not completely satisfactory, the loss of HBr from (6c) is indicated.

2-*Phenylbenzimidazole* (7c).—*o*-Phenylenediamine (272 mg, 2.5 mmol) and (1a) (1.11 g, 2.5 mmol) were heated in chloroform (20 ml) at 80° under nitrogen for 7 h and left at *ca.* 25° overnight. After the solvent was removed, the residue was treated with tetrahydrofuran and filtered. The collected solid was (8) (324 mg, 36%). The filtrate yielded material from which 2-phenylbenzimidazole (131 mg, 27%), m.p. 291—292° (lit.,[13] 287—288°) was obtained by column chromatography.

2-*Phenylimidazoline* (7d).—Ethylenediamine (1.5 ml) and (1a) (1.33 g, 3 mmol) dissolved in acetonitrile under nitrogen with evolution of heat. The solvent was removed, the residue was treated with tetrahydrofuran and the suspension of (8) (885 mg, 83% yield) was filtered. After the filtrate was evaporated, the residue was dissolved in ether. Hydrochloric acid (3M) extracted (7d) leaving some triphenylphosphine oxide in the ether portion. The aqueous portion was neutralized and (7d) (329 mg, 73%), m.p. 95—99° (lit.,[15] 101°) was extracted with methylene chloride, $\nu_{max.}$ (KBr) 3 220br, 2 930, 2 850, 1 600, 1 570, 1 500, 1 470, 1 265, 980, 780, and 695 cm^{-1}; δ ($CDCl_3$) 3.7 (4 H, s), 5.23br (1 H, s), and 7.2—7.9 (5 H, m); *m/e* 146 (M^+).

2-*Phenylnaphtho*[1,2-d]*imidazole* (7e).—1,2-Diaminonaphthalene (350 mg, 2.1 mmol) and (1a) (887 mg, 2 mmol) in acetonitrile (50 ml) under nitrogen were heated at 100° for 36 h. The solvent was evaporated, the residue was treated with tetrahydrofuran, and the suspension of (8) (365 mg) was filtered. After the filtrate was evaporated, the crystalline residue was washed successively with 3M-hydrochloric acid (10 ml) and potassium hydroxide (5%) and then extracted with chloroform. Work-up gave white (7e) (153 mg, 31%), m.p. 221.5—222° (from benzene) (lit.,[16] 217—218°); δ ($CDCl_3$) 5.0 (1 H, m) and 7.2—8.6 (11 H, m); *m/e* 244 (M^+).

Reaction of 2,3-*Diaminopyridine and* (1a).—2,3-Diaminopyridine (50 mg, 0.46 mmol), (1a) (220 mg, 0.5 mmol), and acetonitrile (20 ml) were stirred at *ca.* 25° for 2 h; crystals of (6d) (133 mg, 53%) separated in a few minutes. These were filtered and washed repeatedly. Because of its insolubility, n.m.r. data for (6d) could not be obtained in the usual solvents. It had m.p. 285—286°; $\nu_{max.}$ (KBr) 3 340br, 3 100br, 1 665, 1 640, 1 565, 1 523, 1 436, 1 104, 812, 755br, 720, and 680 cm^{-1}. This product appears to be a hydrobromide of the 1 : 1 adduct. Although the structure has been given in equation (6) as (6d), this is speculative (Found: C, 58.4; H, 4.1; Br, 24.4. Calc. for $C_{31}H_{28}Br_2N_3P$: C, 58.8; H, 4.45; Br, 25.25%).

2-*Phenylperimidine* (7f).—1,8-Diaminonaphthalene (334 mg, 2 mmol) in tetrahydrofuran (20 ml) was added dropwise over 10 min to (1a) (887 mg, 2 mmol) in chloroform (10 ml). After 24 h at reflux temperature, the reaction mixture was filtered leaving 23 mg of unknown material. The filtrate was evaporated, the residue was treated with tetrahydrofuran and the suspension of (8) (587 mg, 82% yield) was filtered. From the filtrate (7f) (227 mg, 46%) was obtained by column chromatography, m.p. 181—183° (decomp.) (lit.,[17] 186°); $\nu_{max.}$ (KBr) 3 060br, 1 637, 1 600, 1 375, 771,

and 704 cm^{-1}; δ ($CDCl_3$) 6.6 (1 H, m) and 6.9—7.83 (11 H, m); *m/e* 244 (M^+).

Reaction of Benzophenone Hydrazone with (1a).—Benzophenone hydrazone (420 mg, 2.14 mmol) and (1a) (887 mg, 2 mmol) were heated in acetonitrile (20 ml) under nitrogen at reflux temperature for 24 h. After the solvent was evaporated, the residue was treated with a small amount of chloroform, and the suspension was filtered yielding diphenylketazine, $(Ph_2C{=}N)_2$ (51 mg), m.p. 166—167° (lit.,[18] 164°), *m/e* 360 (M^+). When the filtrate was extracted with 5% aqueous potassium hydroxide (20 ml), a small amount of a red crystalline material (18 mg) could be removed by filtration. The filtrate was worked up to yield orange crystals of (4c) (223 mg, 40%), m.p. 243—244°; $\nu_{max.}$ (KBr) 3 030, 1 470, 1 430, 1 392, 1 105, 906, and 691 cm^{-1}; δ ($CDCl_3$) 7.1—7.9 (m); *m/e* 558 (M^+, parent) and 237* ($558^+ \longrightarrow 364^+ + 194$). The azine structure of (4c) is preferred on the basis of the observed mass spectrum, *i.e.*, the loss of Ph_2CN_2 which could give a metastable peak (237*) and the absence of significant expulsion of N_2, which is often found with cyclic compounds (Found: C, 83.55; H, 5.85. $C_{39}H_{31}N_2P$ requires C, 83.85; H, 5.6%). A final residue contained *ca.* 120 mg of solids (azine and triphenylphosphine oxide) and an unknown oil (384 mg).

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