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A novel, one-pot and three-component synthesis of α-quinoxalinyl triphenylphosphoranes

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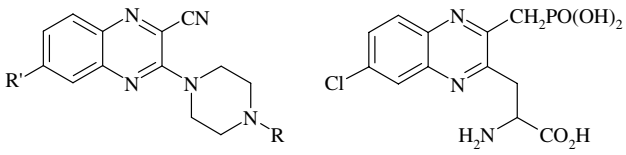
Abstract—The reactive 1:1 zwitterionic intermediate formed by the addition of triphenylphosphine to diaroylacetylenes was trapped with 1,2-benzenediamines to produce triphenylphosphorane intermediates. Intramolecular cyclization and subsequent oxidation of the intermediate afforded functionalized α-quinoxalinyl triphenylphosphoranes in good to excellent yields.

Phosphorus ylides are reactive intermediates, which take part in many valuable reactions in organic synthesis.[1–4] Several methods have been developed for the preparation of phosphorus ylides. These ylides are usually prepared by treatment of a phosphonium salt with a base, and phosphonium salts are usually prepared from phosphines and alkyl halides.[1,2] Phosphonium salts can also be prepared by Michael addition of phosphorus nucleophiles to activated olefins.[1]

Quinoxalines are of interest because of the occurrence of their saturated and partially saturated derivatives in biologically active compounds and natural products.[5] Compounds containing the quinoxaline ring system have been shown to possess anticancer,[6a] antituberculosis,[6b] antimicrobial,[6c] anti-HIV,[6d] antiprotozoal,[6e] antimalarial,[6f] antiinflammatory,[6g] and anticonvulsant[6h] activities. Furthermore, some examples have been reported as telomerase inhibitors,[7] PDGF receptor tyrosine kinase inhibitors,[8] cyclophilin A&D inhibitors,[9] angiotensin II receptor antagonists,[10] A(1) and A(3) adenosine receptor antagonists,[11] 5-HT_3 antagonists (Fig. 1, **1**),[12] monoamine oxidase A inhibitors,[13] poly(ADP-ribose) polymerase-1 inhibitors,[14] AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor antagonists,[15] NMDA (*N*-methyl-D-aspartic acid) receptor antagonists (Fig. 1, **2**),[16] and selective photo-induced DNA cleaving and cytotoxic agents.[17] In addition, some quinoxalines are used in polymer and supramolecular chemistry.[18] Due to their unique properties, development of synthetic methods, which enable easy access to functionalized quinoxalines is desirable.[5,19]



1, a new class of 5-HT_3 antagonists **2**, an NMDA receptor antagonist

Figure 1. Examples of biologically active quinoxalines.

As part of our current studies on the development of efficient methods for the preparation of heterocyclic compounds,[20] we report herein a novel, one-pot and three-component synthesis of α-quinoxalinyl triphenylphosphoranes. Thus, triphenylphosphine, diaroylacetylenes **3** and 1,2-benzenediamines **4** undergo a smooth 1:1:1 addition reaction in dichloromethane at ambient temperature to produce 2-(2-quinoxalinyl)-2-triphenylphosphoranylidene-1-ethanones **5a–i** in 89–97% yields (Scheme 1).

The reactions were carried out by first mixing triphenylphosphine and the diamine in CH_2Cl_2. Then the

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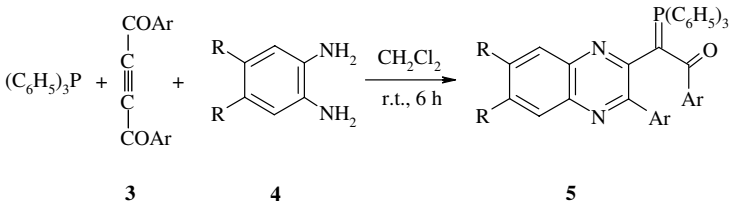


3 **4** **5**

3	Ar
a	C_6H_5
b	4-$CH_3C_6H_4$
c	2,5-$(CH_3)_2C_6H_3$

4	R
a	H
b	CH_3
c	Cl

5	Ar	R	%Yield
a	C_6H_5	H	96
b	C_6H_5	CH_3	95
c	C_6H_5	Cl	97
d	4-$CH_3C_6H_4$	H	96
e	4-$CH_3C_6H_4$	CH_3	94
f	4-$CH_3C_6H_4$	Cl	93
g	2,5-$(CH_3)_2C_6H_3$	H	89
h	2,5-$(CH_3)_2C_6H_3$	CH_3	90
i	2,5-$(CH_3)_2C_6H_3$	Cl	92

Scheme 1.

diaroylacetylene in CH_2Cl_2 was slowly added to the reaction mixture at ambient temperature, and the reaction was complete within a few hours. TLC and NMR analysis of the reaction mixtures clearly indicated formation of quinoxaline derivatives **5** in good to excellent yields.[21]

The structure of **5a** was assigned on the basis of IR, ^1H, ^{13}C and ^{31}P NMR spectroscopies, mass spectrometry and elemental analysis. The mass spectrum of **5a** displayed the molecular ion (M^+) peak at m/z 584, which is consistent with the 1:1:1 adduct of triphenylphosphine, dibenzoylacetylene and 1,2-diaminobenzene, losing two hydrogen atoms. The ^1H NMR spectrum of **5a** exhibited characteristic multiplets with appropriate chemical shifts and coupling constants for the 29 aromatic protons. The ^1H-decoupled ^{13}C NMR spectrum of **5a** showed a doublet at $\delta = 76.12$ ppm ($^1J_{PC} = 109.9$ Hz) arising from the ylide carbon atom, as well as 21 other characteristic resonances with appropriate chemical shifts in agreement with the proposed structure. The ^1H-decoupled ^{31}P NMR spectrum of **5a** exhibited a sharp signal at $\delta = 20.98$ ppm readily confirming the ylide identity of the isolated product. Partial assignment of these resonances is given.[21] Single-crystal X-ray analysis conclusively confirmed the structure of these compounds. An ORTEP diagram of **5a** is shown in Figure 2.[22]

On the basis of the well-established chemistry of trivalent phosphorus nucleophiles,[1–4] it is reasonable to assume that phosphorus ylide **5** results from the initial addition of triphenylphosphine to the acetylenic diketone and formation of the 1:1 zwitterionic intermediate **6**, which is protonated with the NH-acid **4**. Next, the positively charged ion **7** is attacked by the conjugate base **8** of the NH-acid to form phosphorane **9**. This intermediate cyclizes to 1,2-dihydroquinoxaline intermediate **10**, which is finally oxidized under the reaction conditions to produce quinoxaline **5** (Scheme 2).

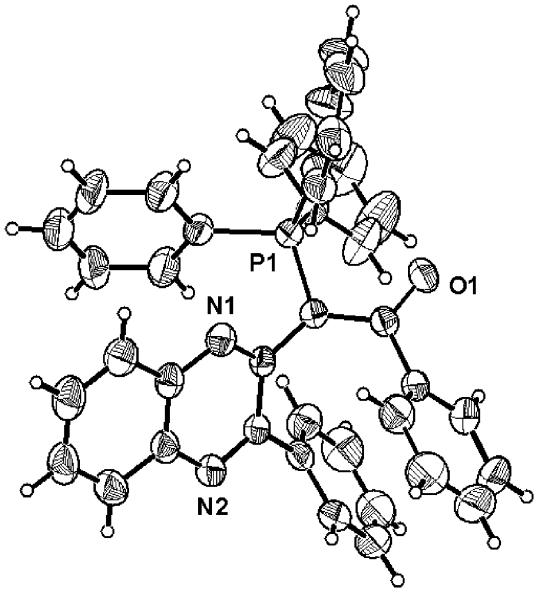
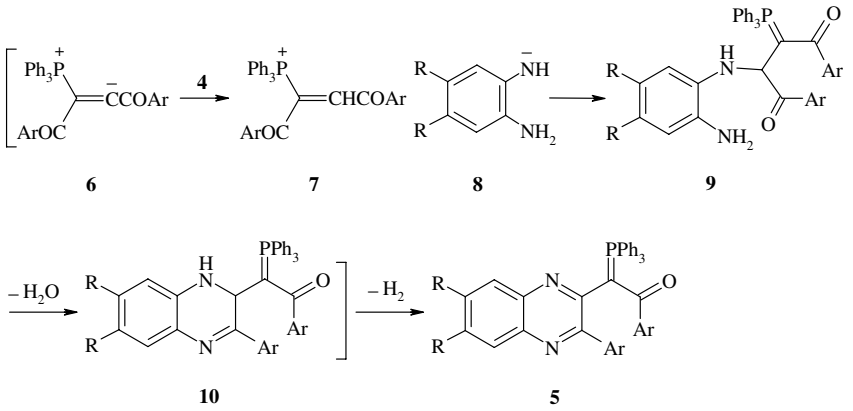


Figure 2. Molecular structure of **5a**, with 50% probability displacement ellipsoids, H atoms with arbitrary radii.

In conclusion, we have developed a novel, one-pot and three-component synthesis of α-quinoxalinyl triphenylphosphoranes of potential synthetic and pharmacological interest. These phosphoranes are potentially useful synthetic targets as well as interesting intermediates. The present method carries the advantage that, not only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modification. This procedure may provide a method for the preparation of quinoxalines with various functionalities.



Scheme 2.

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21. The procedure for the preparation of 1-phenyl-2-(3-phenyl-2-quinoxalinyl)-2-triphenylphosphoranylidene-1-ethanone **5a** is described as an example. To a magnetically stirred solution of triphenylphosphine (0.262 g, 1 mmol) and 1,2-diaminobenzene (0.108 g, 1 mmol) in dry CH_2Cl_2 (4 mL) was added dropwise a solution of dibenzoylacetylene (0.234 g, 1 mmol) in dry CH_2Cl_2 (2 mL) at −5 °C for 5 min. The reaction mixture was then allowed to warm to room temperature and stirred for 6 h. The solvent was removed and the residue was crystallized from 1:2 hexane–ethyl acetate. The product was obtained as yellow crystals, mp 227–229 °C, yield 0.56 g, 96%. IR (KBr) (ν_{max}/cm^{-1}): 1580, 1510, 1482, 1435, 1393, 1364, 1337, 1302, 1215, 1180, 1101, 1072, 1018, 949, 879, 847, 773, 748, 717, 690, 594, 561, 516, 502. MS, *m*/*z* (%): 584 (M^+, 25), 562 (20), 455 (18), 417 (15), 379 (10), 105 (17), 77 (30), 40 (100). Anal. Calcd for $C_{40}H_{29}N_2OP$ (584.66): C, 82.17; H, 5.00; N, 4.79. Found: C, 82.1; H, 5.1; N, 4.7. ^{1}H NMR (500.13 MHz, $CDCl_3$): δ 6.85 (2H, d, $J = 7.4$ Hz, 2CH), 6.95 (2H, t, $J = 7.7$ Hz, 2CH), 7.14 (1H, t, $J = 7.3$ Hz, CH), 7.26 (2H, t, $J = 7.5$ Hz, 2CH), 7.32 (2H, d, $J = 7.1$ Hz, 2CH), 7.35 (1H, t, $J = 7.3$ Hz, CH), 7.44 (6H, dt, $J = 3.1$ and $J = 7.7$ Hz, 6CH$_{meta}$ of PPh_3), 7.48–7.55 (6H, m, 6CH), 7.82 (6H, dd, $J = 7.4$ Hz and $J = 12.6$ Hz, 6CH$_{ortho}$ of PPh_3), 7.94 (1H, d, $J = 8.0$ Hz, CH). ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 76.12 (d, $^1J_{PC} = 109.9$ Hz, P=C), 126.67, 127.41, 127.42, 127.58, 127.71, 127.73 and 128.05 (7CH), 128.34 (d, $^1J_{PC} = 91.2$ Hz, C$_{ipso}$ of PPh_3), 128.41 (CH), 128.48 (d, $^3J_{PC}$ 12.5 Hz, CH$_{meta}$ of PPh_3), 128.68 and 129.16 (2CH), 131.65 (d, $^4J_{PC} = 1.9$ Hz, CH$_{para}$ of PPh_3), 134.20 (d, $^2J_{PC}$ 10.1 = Hz, CH$_{ortho}$ of PPh_3), 139.21 and 140.03 (2C), 140.98 (d, $J_{PC} = 1.2$ Hz, C), 142.10 (d, $J_{PC} = 10.1$ Hz, C), 152.93 (d, $J_{PC} = 9.7$ Hz, C), 156.96 (d, $J_{PC} = 7.9$ Hz, C), 186.29 (d, $^2J_{PC} = 3.4$ Hz, C=O). ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 20.98 (Ph_3P^+–C).
22. *Selected X-ray crystallographic data for compound* **5a**: $C_{40}H_{29}N_2OP$, orthorhombic, space group = *Pna*2$_1$ (No. 33), $a = 20.059(4)$ Å, $b = 12.566(3)$ Å, $c = 12.308(2)$ Å, $V = 3102.5(11)$ Å^3, $T = 290(2)$ K, $Z = 4$, $D_{calcd} = 1.252$ g cm^{-3}, μ(Mo-Kα) = 0.124 mm^{-1}, 23,320 reflections measured, 6005 unique reflections ($R_{int} = 0.0985$), 4685 observed reflections, final $R_1 = 0.0441$, $wR_2 = 0.1000$ and for all data $R_1 = 0.0589$, $wR_2 = 0.1068$. CCDC 622747 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.