REACTIONS OF 1,2,4-TRIAZINE AZIDES WITH α-KETO AND α-ESTER PHOSPHORUS YLIDES. SYNTHESIS OF SOME NEW 1-TRIAZINO-1,2,3-TRIAZOLES

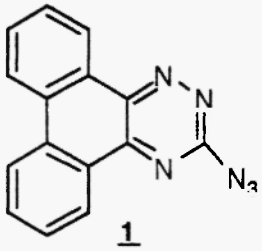
YEHIA O. EL-KHOSHNIEH
National Research Centre, Dokki, Cairo, Egypt.

Abstract : 3-Azidotriazines 1 and 2 react with acetylmethylenetriphenylphosphorane 3a to give 1-triazino-5-substituted-1,2,3-triazoles 6 and 7, respectively. The regiochemistry of the reaction was resolved by comparison of the triazole product 6 with an authentic sample, prepared by the Dimroth reaction. On the other hand, azides 1 and 2 react with ethoxycarbonylmethylenetriphenylphosphorane 3b to afford the corresponding iminophosphoranes 12 and 13. Possible reaction mechamsms are proposed for the formation of the new products.

Introduction

1,2,4-Triazines possess a wide spectrum of biological activities whereas their numerous derivatives are in clinical use (1-6). A slight variation in nuclear substitution causes a marked difference in the biological activities and therefore it has been considered worthwhile to synthesize new heterocyclic compounds incorporating 1,2,4-triazine moiety.

As an extension of our work in the 1,2,4-triazine field (7-9), the present investigation was undertaken to examine the reaction of 3-azido-phenanthro[9,10-e]-1,2,4-triazine 1 and 3-azido-5,6-diphenyl-1,2,4-triazine 2 with Wittig reagents 3. The condensation of azidotriazine 1 with the active methylene compound 4 in the presence of a base was also examined.



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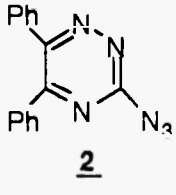

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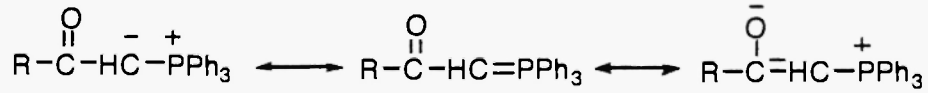
$Ph_3P=CH-R$

3a, $R=COCH_3$
b, $R=COOC_2H_5$

$CH_3CO-CH_2-COOC_2H_5$

4

Phosphorus ylides 3a,b are commonly represented in three resonance forms (A, B and C) and can, a priori, react with azides (10-15) either as carbanions (3A) or as unsaturated systems C=P (3B) as well as C=C (3C).

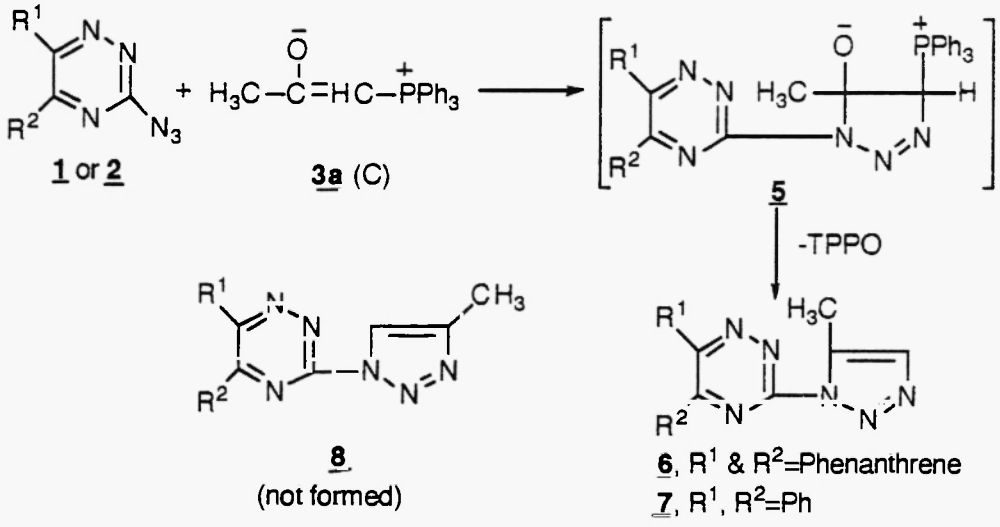


3A 3B 3C

Results and Discussion

3-Azidotriazine **1** reacts with acetylmethylenetriphenylphosphorane **3a** in toluene solution at reflux temperature for 10 h to give a brown crystalline product formulated as **6** (Scheme 1). Triphenylphosphine oxide (TPPO) was also isolated from the reaction medium. The triazole structure **6** was deduced from the following: (a) Correct elemental analysis and molecular weight determination (MS) correspond to $C_{18}H_{12}N_6$; (b) The IR spectrum of **6**, in KBr, reveals the presence of the triazole absorption band at 1180 cm^{-1}(16) (c) The ^{1}H-NMR spectrum of **6** showed signals at δ 2.60 (d, 3H, CH_3, J_{HH}=1 Hz) and at 7.8 (q, 1H, J_{HH}=1 Hz). The aromatic protons appeared as a multiplet in the range 7.33-7.72 ppm (8H).

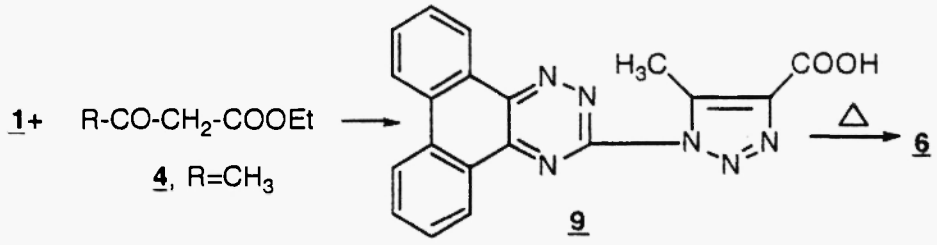
A mechanism which accounts for the reaction of azidotriazine **1** with acetylmethylene-triphenylphosphorane **3a** is depicted in Scheme1. The reaction can be visualized as 1,3-dipolar cycloaddition of the azide **1** onto the C=C bond of the ylide **3a** (form C) followed by the loss of triphenylphosphine oxide (TPPO) from the cyclic intermediate **5** to give N-1 substituted 5-methyl-1,2,3-triazole (11) (Scheme 1).



Scheme 1

Azidotriazine **2**, similarly, reacts with acetylmethylenetriphenylphosphorane **3a** to give N-1 substituted 5-methyl-1,2,3-triazole **7** in 85% yield (Scheme 1), based on correct elemental, spectroscopic data and by analogy with **6** (*cf.* Experimental).

Further structural proof for the triazole product **6** was obtained through an independent synthesis by reacting the β-keto ester : ethyl acetoacetate **4**, with azidotriazine **1** in ethanol in the presence of sodium ethoxide, followed by decarboxylation of the formed triazole-4-carboxylic acid **9** (Scheme 2) (*cf.* Experimental). This reaction, Dimroth reaction (11,17) is known to afford a triazole with the R substituent (-CH_3) in the 5-position. The identity of the triazole obtained from **3a** with that from **4** adequately demonstrates the regiochemistry of the reaction (**1**, **2** + **3a**) whereby an exclusive formation of 1,5- instead of 1,4-**8** disubstituted triazoles (*cf.* Scheme 1).

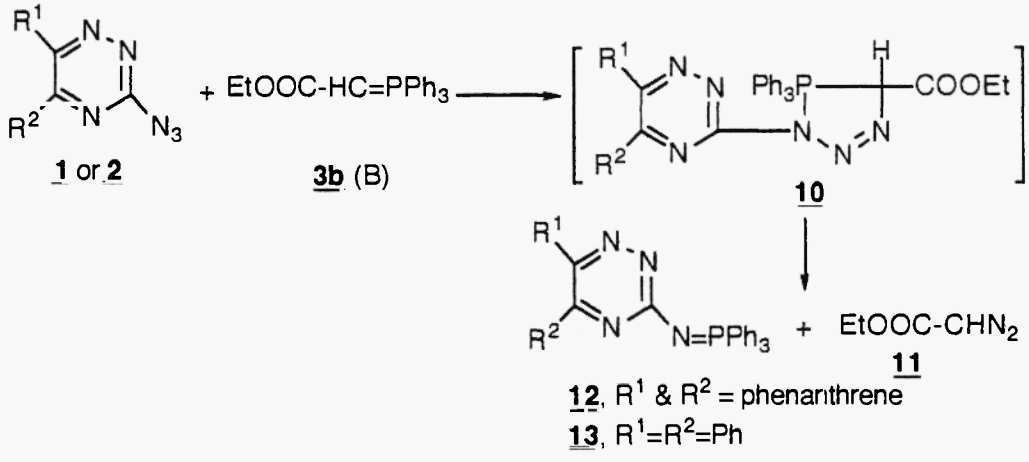


Scheme 2

Conversely, the reaction of azidotriazine **1** with ethoxycarbonylmethylenetriphenylphosphorane **3b** in dry toluene at 50 °C affords the iminophosphorane **12** and ethyl diazoacetate **11** (Scheme 3). The iminophosphorane structure **12** is assigned for the following reasons : (a) Correct elemental analysis and molecular weight determination (MS) correspond to $C_{33}H_{23}N_4P$. (b) Its ^{31}P-NMR spectrum has one signal at δ = 18.5 ppm (vs. 85% H_3PO_4) which clearly indicates an iminophosphorane structure (18), (c) The IR spectrum of **12** reveals the presence of an absorption band at 1355.7 cm^{-1} characteristic for N=P group absorption (19) and the absence of N_3 group absorption which is recorded in the starting material at 2135.3 cm^{-1} (9), (d) The ^1H-NMR spectrum ($CDCl_3$) showed only a multiplet in the range δ 7.25-7.98 ppm (Ar-**H**).

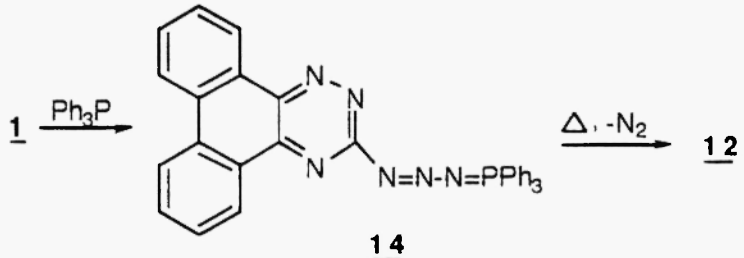
The iminophosphorane **13** was likewise obtained from the reaction of **2** and **3b**. Assignment of **13** was based on analytical, spectroscopic data and by analogy with **12**. The ^{31}P-NMR measurement of **13** exhibited one signal at δp = 17.6 ppm (vs. 85% H_3PO_4).

A possible explanation for the course of the reaction of azidotriazine **1** with ethoxycarbonyltriphenylphosphorane **3b** is shown in Scheme 3. The reaction can be regarded to proceed by a concerted 1,3-dipolar cycloaddition of the azide **1** or **2** onto the C=P bond of the ylide **3b** (form B) in the first step of the reaction, followed by collapse of the cyclic intermediate **10** to afford ethyl diazoacetate **11** and the iminophosphoranes **12** or **13** (12-14). The success of the reaction depends upon the phosphinimine formed being unreactive toward ethyl diazoacetate.



Scheme 3

Moreover, compound **12** was further synthesized by unequivocal route, namely by heating of the phosphazene **14** (9), initialy produced by reacting azidotriazine **1** with triphenylphosphine (Staudinger reaction) to give rise the corresponding iminophosphorane **12** accompanied with loss of nitrogen (20) (Scheme 4) (*cf.* Experimental).



14

Scheme 4

Experimental

All melting points are uncorrected. Ethoxycarbonylmethylene- (21) and acetylmethylene-triphenylphosphorane (22) were prepared according to established procedure. IR spectra were recorded on a Perkin-Elmer Spectrophotometer model 197 (Grating) using KBr disk. ^{1}H-NMR spectra were recorded on a Jeol-270 MHz Spectrometer, using TMS as an internal reference. ^{31}P-NMR were carried out on a Varian CFT-20 Spectrometer (vs. external 85% H3PO4). Mass spectra were performed at 70 eV on MS-50 Kratos (A.E.I.) Spectrometer provided with a data system. The appropriate precutions in handling moisture-sensitive compounds were observed. Solvents were dried by standard techniques.

Reaction of ylide 3a with azidotriazine 1 and 2. the ylide **3a** (22) (0.01 mol) was allowed to react with 3-azidotriazine **1** or **2** (9) (0.01 mol) in 50 ml of refluxing toluene. After the reaction was completed (TLC, 10 h) the solvent was evaporated in vacuo and the residual substance was crystallized from the suitable solvent to give triazoles **6** and **7**. The mother liquors from the crystallization were concentrated and the residue (2.5 g, 90%) crystallized from hexane and proved to be triphenylphosphine oxide (mp, mixed mp and comparative IR spectra) (23).

Compound **6**, brown needles (2.18 g, 70%), m.p. 194 °C (chloroform). Anal. Calcd. for $C_{18}H_{12}N_6$ (312.336) : C, 69.22; H, 3.87; N, 26.91. Found : C, 69.16; H, 3.82; N, 26.84. Mol. wt. (MS) = 312. IR (KBr) cm^{-1} : 1180 (triazole). ^{1}H-NMR ($CDCl_3$) : δ 2.60 (d, 3H, CH_3, J_{HH}=1 Hz), 7.80 (q, 1H, J_{HH}=1 Hz), 7.33-7.72 (m, 8H, Ar-H).

Compound **7**, yellow needles (2.67 g, 85%), m.p. 147 °C (chloroform). Anal. Calcd. for $C_{18}H_{14}N_6$ (314.352) : C, 68.78; H, 4.49; N, 26.73. Found : C, 68.75; H, 4.44; N, 26.70. Mol. wt. (MS) = 314. IR (KBr) cm^{-1} : 1189.86 (triazole). ^{1}H-NMR ($CDCl_3$) : δ 2.55 (d, 3H, CH_3, J_{HH}=1 Hz), 7.1 (q, 1H, J_{HH}=1 Hz), 7.25-7.75 (m, 10H, Ar-H).

Synthesis of triazole 6 by the Dimroth method. Equimolecular amounts (0.01 mol) of 3-azidotriazine **1** (9), ethyl acetoacetate **4** and sodium ethoxide were refluxed in 75 ml ethanol for 2 h. The product was

dissolved in the minimum of hot water and heated under reflux for further 1 h. The reaction mixture was poured into cold water, acidified with conc. HCl. 1-Triazino-5-methyl-1,2,3-triazole-4-carboxylic acid **9** separated (2.56 g, 72%) and was crystallized from water and dried, m.p. 212 °C. Anal. Calcd. for $C_{19}H_{12}N_6O_2$ (356.347) : C, 64.04; H, 3.40; N, 23.58. Found : C, 64.00; H, 3.32; N, 23.56. IR (KBr) cm^{-1} : 1695 (C=O). The triazole-4-carboxylix acid **9** was converted quantitatively into triazole **6**, (mp, mixed mps and comparative IR spectra) when heated above its m.p. until gas evolution ceases.

*Reaction of ylide **3b** with azidotriazines **1** and **2**.* A mixture of 3-azidotriazine **1** or **2** (9) (0.01 mol) and ylide **3b** (21) (0.01 mol) was heated in dry toluene (50 ml) at 50 °C. After the reaction was completed (TLC, 50-60 h), the volatile materials were evaporated in vacuo and the residual substance was treated with petroleum ether (b.r. 60-80 °C) in order to precipitate the iminophosphoranes **12** or **13**. The mother liquor was concentrated to give ethyl diazoacetate **11** as light yellow oil, 0.8 g (70%), which was identified by comparison its IR(24) and ^{1}H-NMR (13) spectra.

Compound **12**, yellow substance (3.9 g, 78%), m.p. 178 °C (chloroform-light petroleum). Anal. Calcd. for $C_{33}H_{23}N_4P$ (506.55) : C, 78.25; H, 4.58; N, 11.06; P, 6.11. Found : C, 78.19; H, 4.53; N, 11.02; P, 6.07. Mol. wt. (MS) = 506. IR (KBr) cm^{-1} : 1355.7 (N=P), 1027.87 (P-C, phenyl). ^{31}P-NMR ($CDCl_3$) : δ =18.5 ppm.

Compound **13**, yellow substance (4.4 g, 88%), m.p. 125 °C (chloroform-light petroleum). Anal. Calcd. for $C_{33}H_{25}N_4P$ (508.57) : C, 77.94; H, 4.95; N, 11.02; P, 6.09. Found : C, 77.90; H, 4.89; N, 10.97; P, 6.00. Mol. wt. (MS) = 508. IR (KBr) cm^{-1} : 1369.21 (N=P), 1025.94 (P-C, phenyl). ^{31}P-NMR ($CDCl_3$) : δ =17.6 ppm.

*Action of heat on **14**. Adduct **14** (9).* (0.5 g) was heated in a cold Finger sublimation at 150 °C (bath temperature) under reduced pressure (2mm/Hg) for 10 min. The substance that sublimed was collected, crystallized from chloroform-pet. ether (60-80 °C) to give a yellow substance proved to be iminophosphorane **12** in 85% yield (mp, mixed mps and comparative IR spectra).

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