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Chemistry of Phosphonium Ylides. Part 35. Reaction of Trimethyl Tinazide with Phosphonium Ylides. Synthesis of Antitumor Phosphanylidene Stannanyl Triazole and Triazene Compounds

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ABSTRACT

*The reaction of 4-azidotrimethylstannane **(1)** with the nucleophilic active phosphacumulene ylides **2a-c**, took place by 1,3-dipolar cycloaddition to give phosphanylidene triazole derivatives **3a-c**. Furthermore, the reaction of the azide **1** with hexaphenylcarbodiphosphorane **(4)** behaves differently and afforded the corresponding phosphanylidene triazene **6** and triphenylphosphane. Treatment of the azide **1** with the stabilized phosphonium ylide, methoxycarbonylmethylenetriphenylphosphorane **(8)** afforded the triazole **(10)** along with triphenylphosphine oxide. The antitumor activity of compounds **3b** and **3c** was evaluated, in vitro against (breast: MCF 7 and liver: HEPG 2) human solid tumor cell lines. They showed values closed to that recorded by the reference drug Doxorubicin.*

Keywords: Tinazide, Phosphoranes, Triazoles, Triazene, Antitumor activity.

INTRODUCTION

The cycloaddition of azides with double bonds to yield heterocyclic structures has been evolved into a powerful tool in organic synthesis, material sciences, life sciences and novel applications [1,2]. The bifunctionality of azides enable them to undergo 1,3-dipolar cycloaddition reactions [3-5]. Triazole derivatives have found wide pharmacological applications as anticancer [6-8], anal- gesic [9], anti-inflammatory [10], anticonvulsant [11] and antiviral agents [12,13]. Besides, they are used as chaperones for Gaucher disease [14], and their metal complexes have biological and pharmacological significance [15]. On the industrial scale, some triazole compounds were tested as corrosion inhibitors of bronze covered with patina layer [16]. On the other hand, triazene derivatives are used as antimicrobial agents [17].

EXPERIMENTAL SECTION

Melting points were determined with an electrothermal digital melting point apparatus (electrothermal Engineering Ltd., Essex, United Kingdom) and are uncorrected. The IR spectra were recorded in KBr disks on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers (Pye Unicam Ltd. Cambridge, England and Shimadzu, Tokyo, Japan, respectively). ^{1}H- and ^{13}C-NMR spectra were obtained from a JEOl ECA 500 MHz NMR spectrometer (Tokyo, Japan) using deuterated dimethylsulphoxide (d_6-DMSO) as a solvent and (TMS) as internal reference at 500, 125 MHz, respectively and ^{31}P NMR spectra were obtained from a JEOl ECA 500 MHz NMR spectrometer at 200 MHz NMR spectrometer, too. Mass spectra (EI-MS) were obtained at 70 eV with A Finnigan MAT SSQ 7000 spectrometer (England). Elemental analyses (C, H, N) results were recorded with Elementar Vario EL Germany (Germany), P was measured by spectrophotometric methods and both of them agreed satisfactory with the calculated values. The using reported yields are of pure isolated materials obtained by column chromatography silica gel 60 (Merck). 4-Azidotrimethylstannane was purchased from Aldrich Company for chemicals under Lot. S 28241-316.

Reaction of (*N*-phenyliminovinylidene)triphenylphosphorane (2a) with 4-azidotrimethylstann- ane (1)

A solution of the (*N*-phenyliminovinylidene)triphenylphosphorane **(2a)** [32] (0.001 mol, 0.377 g) in 20 ml of *THF*, was added drop by drop with stirring at room temperature, to a solution of 4- azidotrimethylstannane **(1)** (0.001 mol, 0.205 g) in 20 ml of *THF*. The reaction mixture was stirred for 6 hrs during which the color changed from white to yellow (the progress of the reaction was controlled by TLC). *THF* was distilled off under reduced pressure and the residue was subjected to silica gel column chromatography using pet.ether (60-80 °C)/ ethyl acetate as eluent (70:30, *v/v*), to give **3a**.

5-(Triphenyl-λ^5-phosphanylidene)-3-(trimethyl-λ^4-stannannyl)-3,5-dihydro-4*H*-1,2,-3-triazol-4-ylidene]aniline (3a).

Colorless crystal, yield 90 %, mp: 98-100 °C, IR (KBr, *cm^{-1})* 1638 (C=N), 1547 (C=P), 1485, 1467 (P-aryl). ^{1}H NMR (500 MHz, d_6-DMSO, *δ*, ppm): 2.53 (s, 9H, $3CH_3$), 7.26 -7.66 (m, 20H, arom.). MS *m/z* 585 $[M+2H]^+$. Anal. Calcd. for $C_{29}H_{29}N_4PSn$ (583.2) : C, 59.72; H, 5.01; N, 9.61; P, 5.31; Sn, 20.35; Found: C, 59.64; H, 4.55; N, 9.89, P, 5.51; Sn, 20.35.

Reaction of (2-oxovinylidene)- (2b) or (2-thioxovinylidene)-triphenylphosphorane (2c) with azidotrimethylstannane (1).

A mixture of (2-oxovinylidene)- **(2b)** [33] (0.001 mol, 0.302 g) or (2-thioxovinylidene)-triphenylphosphorane **(2c)** (0.001 mol, 0.318 g), with 4-azidotrimethylstannane **(1)** (0.001 mol, 0.205 g), in toluene (40 ml) was refluxed for 8 hrs in case of **2b** and 12 hrs in case of **2c**. Toluene was distilled off and the residue was subjected to silica gel column chromatography using pet.ether (60-80 °C)/ ethyl acetate as an eluent (20:80, *v/v*), to give **3b** and **3c**.

5-(Triphenyl-λ^5-phosphanylidene)-3-(trimethyl- λ^4-stannanyl)-3,5-dihydro-4*H*-1,2,3-triazol-4-one (3b).

Colorless crystals, yield 85%, mp: 110-112 °C. IR, (KBr, cm^{-1}): 1696 (C=O), 1636 (C=P), 1448, 1351 (P-aryl). ^{1}H NMR (500 MHz, d_6-DMSO, *δ*, ppm): 1.96 (s, 9H, $3CH_3$), 7.45-7.71 (m, 15H, arom.); ^{13}C NMR (125 MHz, d_6-DMSO, *δ*, ppm): 185.02 (C=O), 160.26 (C=P), 16.90 ($3CH_3$).^{31}P- NMR: δ = 30.54 ppm. MS *m/z*: 506 $[M-2H]^+$, 493 $[M-CH_3]^+$ 478 $[M-2CH_3]^+$. Anal. Calcd. for $C_{23}H_{24}N_3OPSn$ (508.1): C, 54.36; H, 4.76; N, 8.27; P, 6.10; Sn, 23.36; Found: C, 54.16 H, 4.60; N, 8.27; P, 6.00; Sn, 23.36.

5-(Triphenyl-λ^5-phosphanylidene)-3-(trimethyl-λ^4-stannanyl)-3,5-dihydro-4H-1,2,3-triazole-4-thione (3c).

Colorless crystals, yield 90 %, mp: 132-134 °C. IR, (KBr, *cm^{-1})*: 1588 (C=P), 1476, 1432 (P-aryl), 1185 (C=S). ^{1}H NMR (500 MHz, d$_6$-DMSO, *δ*, ppm): 2.68 (s, 9H, 3CH$_3$), 7.39-7.60 (m, 15H, arom.); ^{13}C NMR (125 MHz, d$_6$-DMSO, *δ*, ppm) : 194.96 (C=S), 154.19 (C=P), 16.61 (3CH$_3$). ^{31}P- NMR: δ = 29.93 ppm. MS *m/z*: 525 [M+H]$^+$, 509 [M-CH$_3$]$^+$,478 [M-3CH$_3$]$^+$. Anal. Calcd. for $C_{23}H_{24}N_3PSSn$ (524.2): C, 52.70; H, 4.61; N, 8.02; P, 5.91; S, 6.12; Sn, 22.65; Found: C, 52.64; H, 4.26; N, 8.02; P, 5.51; S, 6.26; Sn, 22.65.

Interaction of hexaphenylcarbodiphosphorane (4) with azidotrimethylstannane (1)

To a solution of 4-azidotrimethylstannane **(1)** (0.001 mol, 0.205 g), in 20 ml *THF* was added, hexaphenylcarbodiphosphorane **(4)** [34] (0.001 mol, 0.536g) in 20 ml *THF*. The reaction mixture was refluxed for 12 hrs during which the color changed from colorless to yellow then brown. *THF* was distilled off under reduced pressure and the remained residue was chromatographed on silica gel using pet.ether (60-80 °C): ethyl acetate as an eluent (2:8, *v/v*), to give **6** and triphenylphosphane (m.p. and mixed m.p. 78 °C).

1-[(Triphenyl-λ^5-phosphanylidene)methyl]-3-(trimethyl-λ^4-stannanyl)triaz-1-ene (6)

Colorless crystals yield 60 %, mp: 114-116 °C. IR, (KBr, *cm^{-1})*: 1541(C=P), 1431, 1370 (P-aryl). ^{1}H NMR (500 MHz, d$_6$-DMSO, *δ*, ppm): 2.02 (s, 9H, 3CH$_3$), 7.52-7.77 (m, 15H, arom.). ^{31}P NMR: 30.52. MS *m/z*: 479 [M-H]$^+$, 434 [M-3CH$_3$]$^+$. Anal. Calcd. for $C_{22}H_{24}N_3PSn$ (480.1): C, 55.03; H, 5.04; N, 8.75; P, 6.45; Sn, 24.72; Found: C, 53.04; H, 5.06; N, 8.30; P, 5.45; Sn, 24.72.

Reaction of methoxycarbonylmethylenetriphenylphosphorane (8) and azidotrimethylstannane (1)

A mixture of methoxycarbonylmethylenetriphenylphosphorane **(8)** [35] (0.001 mol, 0.334 g) and 4-azidotrimethylstannane **(1)** (0.001 mol, 0.205 g), in toluene (40 ml) was refluxed for 12 hrs during which the color changed from yellow to dark brown. Toluene was distilled off and the residue was subjected to silica gel column chromatography using pet.ether (60-80 °C)/ ethyl acetate as eluent (30:70, *v/v*), to give **10** together with triphenylphosphine oxide (m.p. and mixed m.p.151^{0}C).

5-Methoxy-1-(trimethylλ^4-stannanyl)-1H-1,2,3-triazole (10).

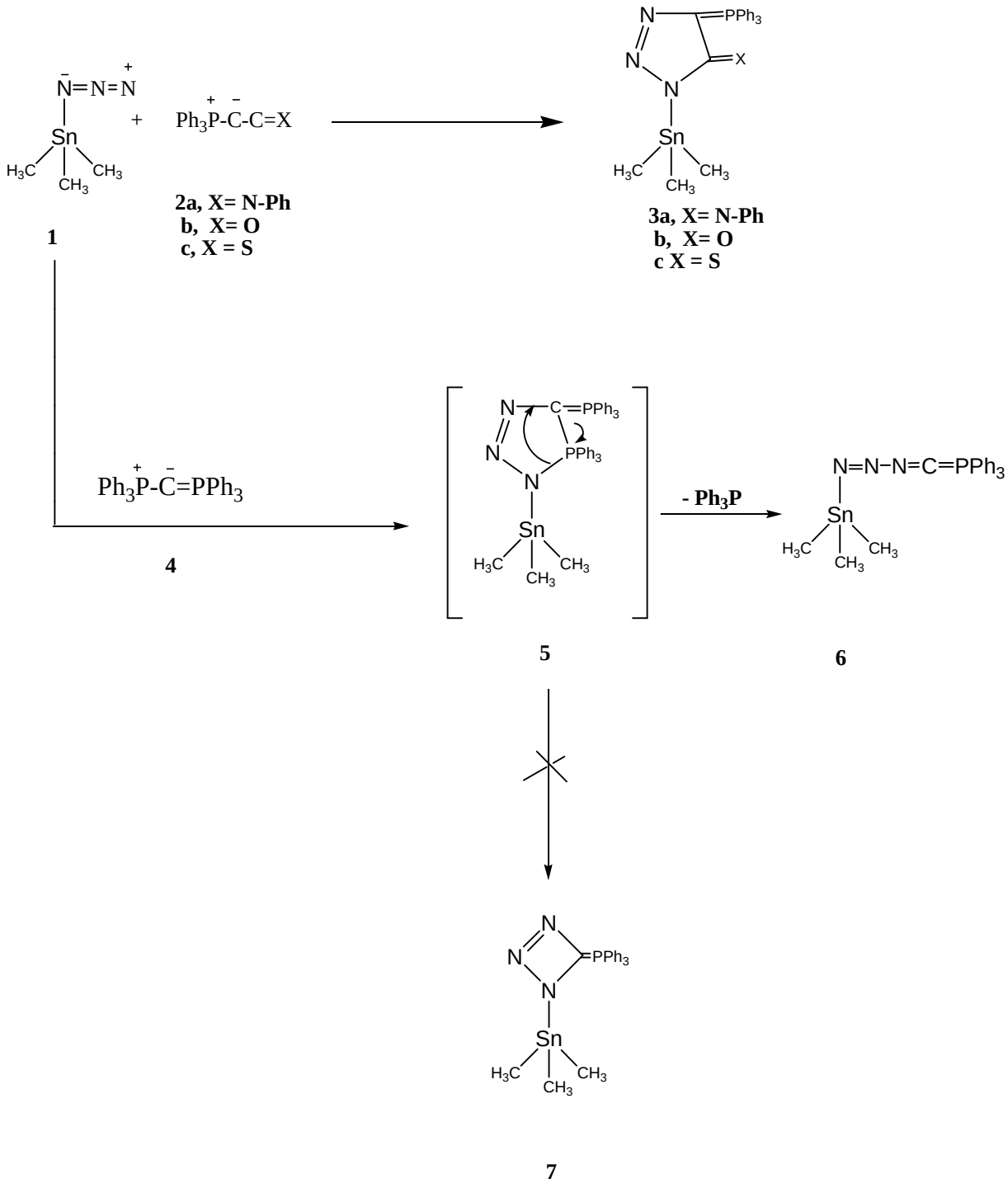
Colorless crystals, yield 30 %, mp: 252-254 °C. IR, (KBr, *cm^{-1})*: IR revealed the absence of ylidic (C=O). ^{1}H NMR (500 MHz, d$_6$-DMSO, *δ*, ppm): 2.08 (s, 9H, 3CH$_3$), 3.99 (s, 3H, OCH$_3$) 7.43 (s, 1H, CH); MS *m/z*: 262 [M]$^+$, 217 [M-3CH$_3$]$^+$, 185[M-3CH$_3$+OCH$_3$]$^+$. Anal. Calcd. for $C_6H_{13}N_3OSn$ (261.9): C, 27.52; H, 5.00; N, 16.04; Sn, 45.33; Found: C, 27.64; H, 5.00; N, 16.04; Sn, 42.03.

Chemicals

All the chemicals and reagents used in this study were of analytical grade and purchased from (Sigma Chemical Co., St. Louis, Mo, and U.S.A): It was used in cryopreservation of cells.

Cells culture

The cells of MCF-7 human breast cancer and HEPG2 liver carcinoma were maintained and grown in RPMI-1640 medium supplemented with 10% heat inactivated fetal borine serum (Sigma Chemical Co., St. Louis, Mo, and U.S.A), penicillin and streptomycin at 37^{0}C in humidified atmosphere containing 5 % CO2.

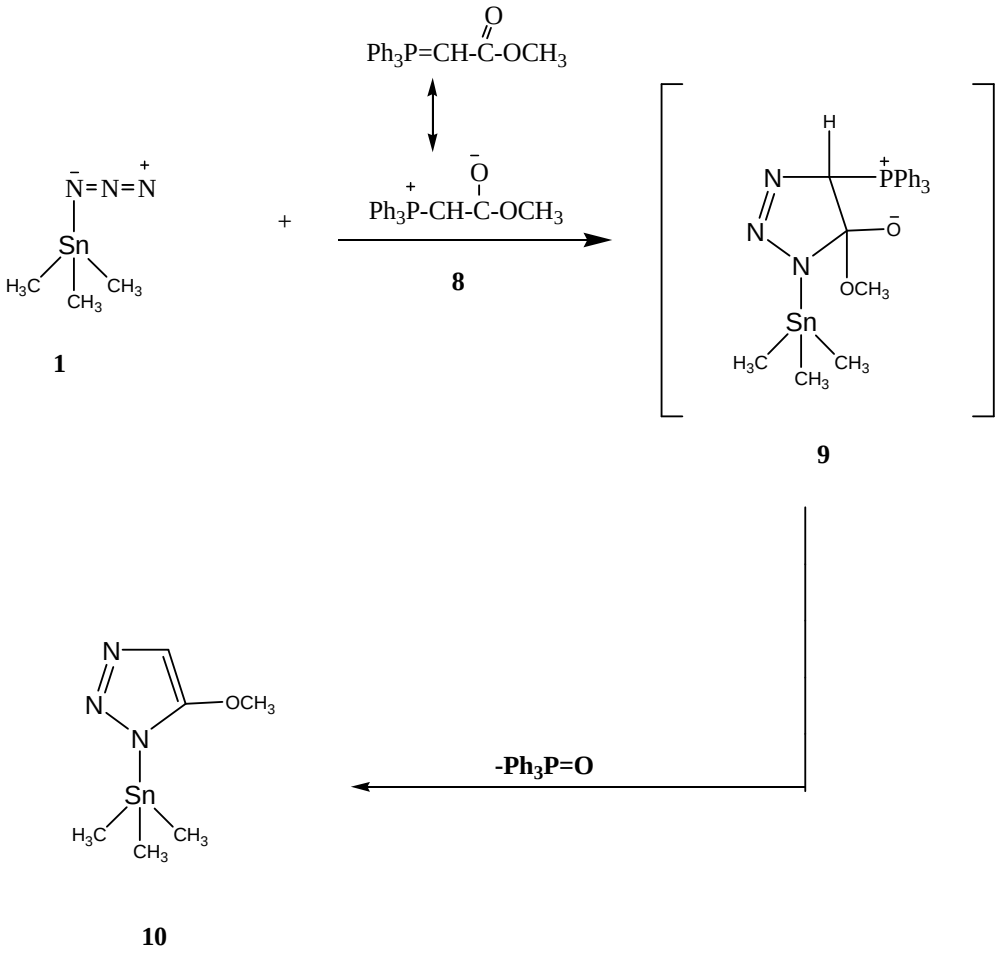


Scheme (1)

In Vitro Cytotoxicity Assay

For in vitro short term cytotoxicity evaluation of prepared compounds, MCF-7 and HEPG2 cells were plated a concentration of 5 x10^4-10^5 cells per well, in complete culture medium in 96 – well flat-bottomed culture plates (Falcon) for 24 h to assure total attachment. Then various concentration of test compounds were added to the cell suspended in 0.10 ml of phosphate buffered saline (FBS) (0.20 M, PH 7.4), the control cells without the test compounds were also cultured, then the plate was incubated for 24 h at 40 $^{\circ}$C and 72 hrs at 37 $^{\circ}$C, in a humidified 5%

CO_2 atmosphere. Cell survival was evaluated at the end of the incubation period with Sulphorhodmine-B (SRB) colorimetric assay according to *Skehan et al* (1990) [36]. This test is based on the sensitivity of the human tumor cell lines to thymoquinone was determined by the SRB assay. SRB is a bright pink aminoxanthrene dye with two sulphonic groups. It is a protein stains that binds to the amino groups of intracellular proteins under mildly acidic conditions to provide a sensitive index of cellular protein content. After incubation, media were removed and 50 ul of 0.4 % SRB dissolved in 1 % acetic acid solution well were. The wells were then washed 4 times with 1 % acetic acid. The absorbance was determined photometrically at 564 nm with ELISA microplate reader (Meter tech. Σ 960, U.S.A.).



Scheme (2)

Calculation

The percentage of cell survival was calculated as follows:

Survival fraction = O.D. (treated cells)/ O.D. (control cells) where (O. D.) is the optical density. The IC_{50} values (the concentrations of thymoquinone required to produce 50 % inhibition of cell growth). The experiment was repeated 3 times for each cell line.

RESULTS AND DISCUSSION

Chemistry

Recently [18-22], we reported the successful utilization of the active nucleophilic phospha-cumulene ylides **2a-c**, for the synthesis of heterocyclic compounds, which are not easily

available through conventional methods. It was of interest to investigate and compare the behavior of the active phosphacumulenes **2a-c**, phosphallene **4** and the stabilized phosphonium ylide **8**, towards 4-azidotrimethylstannane **(1)**.

We have found that the reaction of (*N*-phenyliminovinylidene)triphenylphosphorane **(2a)** with 4-azidotrimethylstannane **(1)** proceeds in tetrahydrofuran at room temperature, for 6 hrs to give 5-(triphenyl-λ^5-phosphanylidene)-3-(trimethyl-λ^4-stannanyl)3,5-dihydro-*4H*-1,2,3-triazol-4-lidene]-aniline **(3a)**. The reaction can be considered as a 1,3-dipolar cycloaddition of the bifunctional 4-azidotrimethylstannane **(1)** to the nucleophilic phosphorane **2a** to form the triazoline **3a**. The structure of the new triazoline **3a** was proved from analytical and spectroscopic data. The most important features in the spectroscopic data of the triazoline **3a**, is that the IR spectrum lack the presence of the azide moiety which appeared in the starting material **1** at 2053 cm^{-1}. Moreover, a signal at δ 30.9 ppm was observed in its ^{31}P NMR spectrum, which is in agreement with a phosphorane on 5-membered system [23-25]. In the MS of **3a**, the *m/z* 585 $[M+2H]^+$ (2.5 %).

Next, when 4-azidotrimethylstannane **(1)** was treated with (2-oxovinylidene)-**(2b)** or (2-thioxo-vinylidene)-triphenylphosphorane **(2c)** in boiling toluene for 8 hrs in the case of **2b** and 12 hrs when **2c** was used, the corresponding triazoles **3b** and **3c** were obtained. Their elemental analyses and spectroscopic results were consistent with the assigned structures, namely 5-(triphenyl-λ^5-phos- phanylidene)-3-(trimethyl-λ^4-stannanyl)-3,5-dihydro-*4H*-1,2,3-triazol-4-one **(3b)** and 5-(triphenyl-λ^5-phosphanylidene)-3-(trimethyl-λ^4-stannanyl)-3,5-dihydro-*4H*-1,2,3-triazole-4-thione **(3c)** respec-tively. The IR spectrum of **3b** showed the C=O at 1696 cm^{-1} and a signal at δ 30.54 ppm was observed in its ^{31}P NMR spectrum. The ^{13}C NMR of **3b** disclosed the presence of the C=O at δ 185.02 and CH_3 at δ 16.90 ppm and a signal was found at *m/z* 506 $[M-2H]^+$ (6.5%) in the MS. On the other hand, the IR spectrum of **3c** showed the C=S band at 1185 cm^{-1} and a signal was observed at δ 29.93 ppm in its ^{31}P NMR spectrum. Moreover, the thiocarbonyl function appeared at δ 194.96 ppm in the ^{13}C NMR spectrum of **3c** and an ion peak at *m/z* 525 $[M+H]^+$ (3.8%) was observed in the MS.

Furthermore, the reaction of 4-azidotrimethylstannane **(1)** with the phosphallene ylide, namely, hexaphenylcarbodiphosphorane **(4)**, was investigated, too. Compounds **1** and **4** react in equimolar ratio in boiling *THF* to give 1-[(triphenyl-λ^5-phosphanylidene) methyl]-3-(trimethyl-λ^4-stannanyl)- triaz-1-ene **(6)**, together with triphenylphosphane. It is evident that formation of compound **6** involves the intermediate formation of 4,4,4-triphenyl-5-(triphenyl-λ^5-phosphanylidene)-3-(trimeth- yl-λ^4-stannanyl)-4,5-dihydro-*3H*-1,2,3,4-λ^5-triazaphosphole **(5)** *via* intermolecular cycloaddition. After extrusion of triphenylphosphane, which is a good leaving group, the linear triazene **6** was obtained (Scheme1). The cyclic structure 4-(triphenyl-λ^5-phosphanylidene)-1-(trimethyl-λ^4-stannan- yl)-1,4-dihydrotriazete **(7)** is ruled out since the triazete derivatives are unstable [26, 27]. The linear triazene **6** showed a peak around 2115 cm^{-1} in its IR spectrum assigned to the cumulated double bond. Moreover, a single singlet was observed in the ^{31}P NMR at δ 30.52 ppm which is assigned to the phosphorane structure **6**. Besides, the MS showed a peak at 479 $[M-H]^+$ (8.6%).

4-Azidotrimethylstannane **(1)** was found to react with the stabilized phosphonium ylide namely, methoxycarbonylmethylene triphenylphosphorane **(8)** in boiling toluene for 12 hrs, to give 5-methoxy-1-(trimethyl-λ^4-stannanyl)-*1H*-1,2,3-triazole **(10)**, along with triphenylphosphine oxide. 1,3-Dipolar cycloaddition of the azide **1** to the enol betaine form of the phosphorane **8**, allowed the formation of the unstable 5-methoxy-4-(triphenylphosphonio)-1-(trimethyl-λ^4-stannanyl)4,5-dihy-dro-*1H*-1,2,3-triazol-5-olate **(9)**. Elimination of triphenylphosphine oxide, which is a good leaving group, leads to the stannanyl triazole **10**. In the spectroscopic data of compound **10**, the

most important features is that ^{1}H NMR spectrum showed the presence of singlet signal of OCH_3 at δ 3.99 ppm and in the mass spectrum, the M^+ was found at *m/z* 262 (11.57 %) (Scheme 2).

Pharmacological evaluation

Chemotherapy is a major approach for both localized and metastasized cancers [28]. Therefore, two of the newly synthesized compounds were screened for their *in- vitro* cytotoxic and growth inhibi- tory activities against human breast carcinoma cell line (MCF-7) and liver carcinoma cell line (HEPG 2), in comparison with the activity of the utilized anticancer doxorubicin (DXR) (fig.1) as a reference drug. The cytotoxic activities of the tested compounds were expressed as the median growth inhibitory concentration (IC_{50}) which is the dose that reduces survival to 50%. The screening results are complined in table 1. According to the American National Cancer Institute guidelines drugs with $IC_{50} < 30$ are active. From Table 1, it is evident that the tested compounds show antitumor activities with IC_{50} values 12.6 and 18.2 μg/ml, while DXR (IC_{50}: 2. 97 μg/ml). It is clear from the data that the comparison of the cytotoxicity against MCF-7 cells of prepared compounds has shown that the cells killing potency follows the order **3c** > **3b**. This may be attributable to presence of phosphanylidene-triazolthione moiety in the molecular structure of **3c** and phosphanylidene-triazolone in **3b**, which may contribute to the cytotoxic activity that may interact with DNA by intercalation and inhibition of macromolecular biosynthesis. This inhibits the progression of the enzyme topoisomerase II, which unwinds DNA for transcription and otherwise stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being released and thereby stopping the process of replication as act Doxorubicin [29], suppressing agent, inhibit the formation and growth of tumors from initiated cells [30].

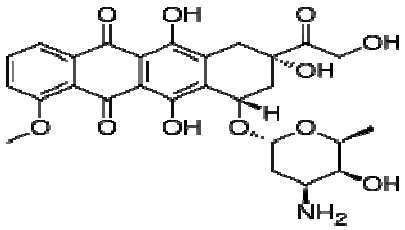


Fig. 1: DXR, Doxorubicin

Moreover, the same two compounds **3b** and **3c** were screened for their *in vitro* for their cytotoxic and growth inhibitory activities towards liver carcinoma (HEPG2) cell line. The IC_{50} after short time exposure was 12.1, and 13.0 ug/ml for compounds **3b** and **3c**, respectively, i.e the cell killing potency follows the order, **3b > 3c** (Table 1). The results showed that compounds **3b** and **3c** are pronounced antitumor activity.

Table 1: Effect of the tested compounds on MCF-7 and HEPG2 tumor cell lines

Compound No.	MCF-7	HEPG2
Doxorubicin (st.)	2.97	3.73
3b	18.2	12.1
3c	12.6	13.0

CONCLUSION

The reaction of the active phosphacumulenes **2a-c**, phosphallene **4** and stable phosphonium ylide **8** with 4-azidotrimethylstannane **(1)** represent an interesting approach to the construction of new nitrogen heterocycles. It leads to different products depending on the nature of the reagent

used. This process can be considered as a simple route for the formation of phosphanylidene stannanyl- triazoylideneaniline **3a**, triazolone **3b**, triazolthione **3c** and triazene **6** which are difficult to obtain by other conventional methods. Moreover, the difference in the nucleophilic character of **2a** >**2b** > **2c** > **4** can be noticed, too [31]. While **2a** reacts smoothly with the azide **1**, the oxo and thioxo analogue and allylic phosphorane **4**, react less rapidly respectively. On the other hand, the stabilized phosphorane behaves differently towards **1**, affording the stannanyl triazole along with triphenyl- phosphine oxide. Compounds **3b** and **3c** showed pronounced antitumor activity.

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