Reaction of Some Alkyl Phosphite and Wittig – Horner Reagents with Derivatives of 5- Bromo-3-Cyano-Pyridone and Camphorquinone

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Abstract: 5-bromo-3-cyano-4,6-dimethyl-2-(1H)-pyridone(**1**) reacts with trialkyl phosphites **4a,b** to give the dialkyl phospates **7a,b** and the alkylated product **6**. On the other hand, Wittig-Horner reagent, diethyl (cyanomethyl) phosphonate **5a** reacts, with **1** to give product **8**. Moreover, camphorquinone **2** reacts with triethyl phosphonate **5b** to give the coupling product of type **9** and camphorquinone monoxime **3** reacts with diethyl (cyanomethyl) phosphonate **5a** to give phosphonate adduct **10**.
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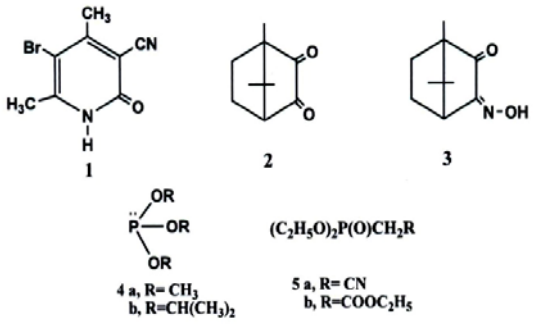
Keywords: Bromo pyridone, camphorquinone, camporquinone monoxime, phosphate, coupling product, nicotinonitrile, phosphonate.

1. Introduction

Extending our work [1-11] on the reaction of organophosphorus reagents with different carbonyl functions. We examined the reactions of organophosphorus reagents towards substituted 3-cyano-2-pyridones which are important intermediates in the pharmaceutical , dye and photo industries and they are also used as active components of drugs that increase cardiac contractility [12]. The study was extending to camphorquinone **2** and its derivative **3** which they are reported to possess a variety of pharmacological importance such a dentin bonding agents [13],dental cements [14] and in root canal filling materials [15]. The present investigation has aimed to investigate the reaction of 5-bromo-4,6-dimethyl-3-cyano-2-(1H) pyridone (5-bromo-4,6-dimethyl-2-oxo-1,2-dihydropyridine -3- carbonitrile) **1** [16-18] with trialkyl phosphites **4a,b** [19,20] and Wittig - Honer reagents [21] namely diethyl (cyanomethyl) phosphonate **5a**. Moreover, the investigation was studied the reaction of camphorquinone (1, 7, 7-trimethylbicyclo [2.2.1] - heptane-2,3 - dione) **2** [22] with triethyl phosphonoacetate **5b** and camphorquinone monoxime (3-(hydroxyimino) - 1,7,7 - trimethyl bicyclo [2.2.1] heptane-2-one) **3** [22] with diethyl (cyan-omethyl) phosphonate **5a**. A comparative study for the behavior of derivatives of pyridones **1** and camphorquinones 2, 3 towards some of organophosphorus reagents (Scheme 1).

2. Experimental

Melting points were determined in open glass capillaries using an Electrothermal IA 9000 series digital melting point apparatus (Electrothermal, Essex. UK) and were uncorrected. The IR spectra were measured in KBr pellets with a Perkin-Elmer Infracord Spectrophotometer model 157(Grating). The ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ as solvent on a Joel-500 MHz spectrometer, and the chemical shifts were recorded in δ values relative to TMS. The ^{31}P-NMR (125 MHz) spectra were taken with a Varian CFT-20 (vs. external 85% H_3PO_4 standard). The mass spectra were performed at 70 eV on a Shimadzu GCS-OP 1000 Ex spectrometer provided with a data system. Elemental analyses were performed using an Elmenter Varu EL Germany Instrument.



Scheme 1

Reaction of 5-bromo-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1) with trimethyl phosphite (4a).

An excess of trimethyl phosphite (**4a**) (≈ 3 mL) was added to **1** (0.22g , 1m mol) and was heated 2h. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on a silica gel column to give product **6** [5- bromo-2-methoxy -4,6-dimethyl nicotinonitrile] (**6** , $C_9H_9BrN_2O$).

Eluent : petroleum ether / acetone (80/20, v/v) product **6** was separated as colorless crystals , yield 25% and m.p. 80-81 °C. IR [υ , cm^{-1} , KBr] : 2219 (CN). ^{1}H-NMR (500 MHz, δ pmm, $CDCl_3$): 2.44 (s, 3H, CH_3) , 2.57 (s, 3H , CH_3) , 3.99 (s , 3H, OCH_3). ^{13}C-NMR (125 MHz, , δ pmm, $CDCl_3$): 14.8, 24.1($2CH_3$) , 54.5(OCH_3), 97.5(C-CN), 108.7(C-Br), 114.5(CN), 153.5(C-CH_3), 159.9(C-N), (163.4 (C-OCH_3). MS m/z (%) 239[M^+] (30) Anal. Calcd for $C_9H_9BrN_2O$ (239.99) : C,44.84 ; H, 3.76 ; Br, 33.14 ; N, 11.62. Found : C, 44.55 ; H 3.42 ; Br, 33.01 ; N, 11.92.

[5-bromo-3-cyano-4,6-dimethyl-1,2-dihydropyridin-2-yldimethyl phosphate]
(**7a**, $C_{10}H_{14}BrN_2O_4P$).

Eluent : petroleum ether / acetone (20/80, v/v) product **7a** was separated as yellow crystals , yield 55% and m.p. 198-199°C. IR [υ , cm^{-1} , KBr] : 1040 (P-O-CH_3) 1250 (P=O), 2211(CN), 3174 (NH). ^{1}H-NMR (500 MHz, δ pmm, $CDCl_3$): 2.38 (s, 3H, CH_3) , 2.40 (s, 3H , CH_3) , 2.43 (s , 1H, NH, exchangeable with D_2O).3.83 (d, 6H $^3J_{HP}$=11.50 Hz, $P(OCH_3)_2$), 5.04 (d, 1H, CH). ^{13}C-NMR (125 MHz, δ pmm, $CDCl_3$): 11.2, 14.9 ($2CH_3$), 54.7 (d, $^2J_{CP}$=29.30 Hz, O=$P(OCH_3)_2$), 76.7(C-O-P(O)), 91.9(Br-C), 106.3 (C-CN), 117.3(CN), 145.8 (C-NH), 152.3 ((C-CH_3). ^{31}P-NMR (δ pmm, $CDCl_3$): +2.83. MS m/z (%) 335[M^+] (65) Anal. Called for $C_{10}H_{14}BrN_2O_4P$ (335.99) : C,35.63 ; H, 4.19 ; Br, 23.70 ; N, 8.31. ; P, 9.19, Found : C, 35.33 ; H 4.55 ; Br, 23.38 ; N, 8.02 ; P, 9.50.

Reaction of 5-bromo-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1) with triisopropylphosphite (4b).

An excess of triisopropyl phosphite (**4b**) (≈3 mL) was added to **1** (0.22g , 1m mol) and was heated 1h. After evaporation of the volatile materials under reduced pressure, the residue was washed several times with petroleum ether (b.r. 40-60°C) to give product **7b**, [5- bromo-3-cyano -4,6-dimethyl-1,2-dihydropyridine-2-yldiisopropyl phosohate]
(**7a**, $C_{14}H_{22}BrN_2O_4P$).

Crystallized from ethylacetate, **7b** was separated as colorless crystals, yield 65% and m. p 158 – 159°C. IR [υ , cm^{-1} , KBr] : 997 ($P(O\text{-}ipr)_2$), 1248 (P=O), 2219(CN), 3177 (NH). ^{1}H-NMR (500 MHz, δ pmm, $CDCl_3$): 1.25 (m, 12H, (O) $P(O\text{-}ipr)_2$) , 2.38 (s, 3H , CH_3) , 2.40 (s , 3H, CH_3), 2.43 (s , 1H, NH, exchangeable with D_2O), 4.74 , 4.35 (2m, 2H, (O) $P(O\text{-}ipr)_2$), 5.07 (d , 1H, CH). ^{13}C-NMR (125 MHz, δ pmm, $CDCl_3$): 11.2, 14.9 ($2CH_3$), 22.9 ($P(OCH(\underline{CH_3})_2$), 51.5 (d, $^2J_{CP}$=7.6 Hz, $P(O\underline{CH}(CH_3)_2)$, 76.7 (C-O-P(O)), 91.8(Br-C), 106.5 (C-CN), 117.4(CN), 145.8 (C-NH), 152.3 ((C-CH_3). ^{31}P-NMR (δ pmm, $CDCl_3$): +2.79. MS m/z (%) 392 [M^+] (40) Anal. Called for $C_{14}H_{22}BrN_2O_4P$ (392.05) : C,42.76 ; H, 5.64 ; Br, 20.32 ; N, 7.12 ; P, 7.88, Found : C, 42.81 ; H 5.32 ; Br, 20.45 ; N, 7.02 ; P, 7.55.

Reaction of 5-bromo-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1) with diethyl (cyanomethyl) phosphonate (5a).

Diethyl (cyanomethyl) phosphonate (**5a**) (0.17g, 1m mol) was dissolved in very dry xylene (25mL) and then NaH (0.024, 1m mol) was added carefully. Then the pyridone **1** (0.22g, 1m mol) was added to the mixture and refluxed for 10h. After evaporation of the volatile material under reduced pressure, the residue was washed several times with petroleum ether (b.r. 60- 80°C) to give product **8** [5- bromo-2-(cyanomethyl) -4,6-dime-thylnicotinonitrile] (**8**, $C_{10}H_8BrN_3$).

Crystallized from ethylacetate, **8** was separated as colorless crystals, yield 83% and m. p 242 – 243°C. IR [υ , cm^{-1} , KBr] : 2221 (CN). ^{1}H-NMR (500 MHz, δ pmm, $CDCl_3$): 2.43 (s, 3H , CH_3) , 2.57 (s , 3H, CH_3), 4.05 (s , 2H, CH_2). ^{13}C-NMR (125 MHz, δ pmm, $CDCl_3$): 14.8, 24.2 ($2CH_3$), 22.9 (CH_2), 108.2 (C-CN), 116.4 , 117.0 (2CN), 118.8 (C-Br), 154.2(C-CH_3), 161.4 (C-CH_2), 165.0 (C=N). MS m/z (%) 250 [M^+] (100) Anal. Called for $C_{10}H_8BrN_3$ (250.09) : C,48.02 ; H, 3.22 ; Br, 31.95 ; N, 16.80 ; Found : C, 48.15 ; H 3.45 ; B, 31.75 ; N, 16.50

Reaction of camphorquinone (1,7,7-trimethylbicyclo [2.2.1] - heptane - 2,3-dione (2) with triethylphosphonoacetate (5b)

Triethylphosphonoacetate (**5b**) (0.22g, 1m mol) was dissolved in very dry xylene (25mL) and then sodium hydride (0.024, 1m mol) was added carefully. Then the compound **2** (0.16g, 1m mol) was added to the mixture and refluxed for 5h. after evaporation of the volatile material under reduced pressure, the residue was subjected to silica gel column chromatography to give **9** [4,4′,7,7′,7,7′-hexamethyl-2,2′-bi (bicyclo [2.2.1] heptan)-2(2′)-ene-3,3′-dione] (**9**, $C_{20}H_{28}O_2$).

Eluent : petroleum ether /acetone (95/5 , v/v) product **9** was separated as colorless crystals, yield 75% and m. p 220 – 221°C. IR [υ , cm^{-1} , KBr] : 1705 (C=O), 1625 (C=C). ^{1}H-NMR (500 MHz, δ pmm, $CDCl_3$): 0.99 (s, 3H , CH_3) , 1.03 (s , 6H, $2CH_3$), 1.25 - 1.43 (m , 2H, CH_2), 1.62 - 1.86 (m , 2H, CH_2), 2.33 (m , H, CH). ^{13}C-NMR (125 MHz, δ pmm, $CDCl_3$): 18.3 (CH_3), 19.9 ($2CH_2$), 26.9 , 29.9 ($2CH_3$), 39.7 (CH), 47.0 ($\underline{C}$-$(CH_3)_2$), 50.1 ($\underline{C}$-CH_3), 145.8 (C=C), 207.5 (C=O). MS m/z (%) 300 (55). Anal. Calcd for $C_{20}H_{28}O_2$ (300.44) : C,79.96 ; H, 9.39 Found : C, 79.53 ; H, 9.40.

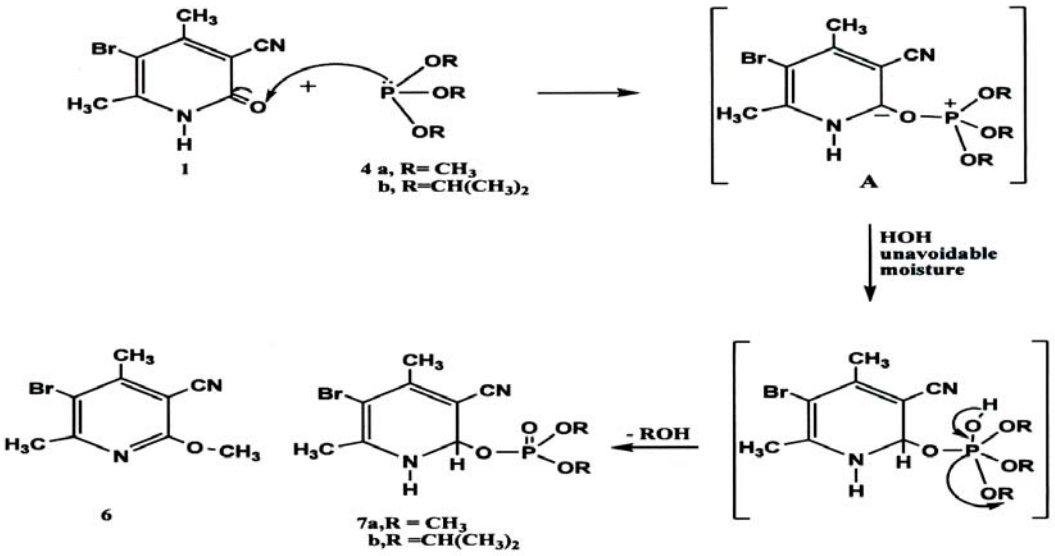
Reaction of camphorquinone monoxime (3-hydroxy imino)-1,7,7-trimethyl bicyclo [2.2.1] – heptane – 2-one(3) with diethyl (cyanomethyl) phosphonate (5a)

Diethyl (cyanomethyl) phosphonate **(5a)** (0.34g, 2m mol) was dissolved in very dry xylene (30mL) and then NaH (0.048, 2m mol) was added carefully. Then the compound **3** (0.18g, 1m mol) was added to the mixture and refluxed for 5h. after evaporation of the volatile material under reduced pressure, the residue was washed several times with petroleum ether (b.r. 60 -80°C) to give product **10** [diethyl cyano (3-(ethoxyimino)-2-hydroxy-1,7,7- trimethyl bicyclo [2.2.1] heptane -2-yl) methyl phosphonate] (**10**, $C_{18}H_{31}N_2O_5P$).

Crystallized from ethyl acetate, **10** was separated as colorless crystals, yield 55% and m. p. 153 – 154°C. IR [υ , cm^{-1} , KBr] : 3200 (C-OH), 2200 (CN), 1642 (C=N), 1230 (P=O, bonded) 1088 cm^{-1} (P-O-C_2H_5). ^{1}H-NMR (500 MHz, δ pmm, $CDCl_3$): 0.99 (s, 3H , CH_3) , 1.01 (s, 6H, $2CH_3$), 1.38 - 1.63 (m, 2H, CH_2), 1.69 - 1.89 (m, 2H, CH_2), 2.53(m, H, CH), 2.81 (d, H, CHCN) 1.10 (t, 3H, $OCH_2\underline{CH_3}$) 3.99 (q, 2H, $O\underline{CH_2}CH_3$), 1.29 (t, 6H, $P(OCH_2\underline{CH_3})_2$), 4.17 (q, 4H, $P(O\underline{CH_2}CH_3)_2$, $^{3}J_{HP}$= 12.05Hz), 8.51 (s, 1H, C-OH, exchangeable with D_2O). ^{13}C-NMR (125 MHz, δ pmm, $CDCl_3$): 18.7 (CH_3), 20.5 ($2CH_2$), 22.7 , 29.7 ($2CH_2$), 39.5 (CH), 44.5 ($\underline{C}$-$(CH_3)_2$), 49.8 ($\underline{C}$-CH_3), 12.8 (O-CH_2-CH_3), 68.5 (O-$\underline{CH_2}$-CH_3), 21.9 ($\underline{C}$H-CN), 16.3 ((O) $POCH_2CH_3$), 61.7 ((O) P-O-$\underline{CH_2}CH_3$), 78.5 (C-OH), 117.7 (CN), 164.6 (C=N). ^{31}P-NMR (δ pmm, $CDCl_3$) : +19.75. MS m/z (%) 386 [M^+] (35). Anal. Calcd for $C_{18}H_{31}N_2O_5$ P (386.42) : C,55.95 ; H, 8.09 ; N, 7.25 ; P, 8.01. Found : C, 55.44 ; H, 8.25 ; N,7.41 ; P, 8.45.

3- Results and Discussion:

We have found that when 5- bromo- 4.6 - dimethyl - 2 - oxo - 1,2 - dihydro pyridine - 3 - carbonitrile **(1)** was allowed to react with excess trimethyl phosphite **4a** without solvent to give the products 5 - bromo - 2 - methoxy - 4,6 - dimethyl nicotinonitrile **(6)** and 5 - bromo - 3 - cyano - 4,6 - dimethyl - 1,2 - dihydropyridine - 2 - yldimethyl phosphate (**7a**) (Scheme 2) .



Scheme 2

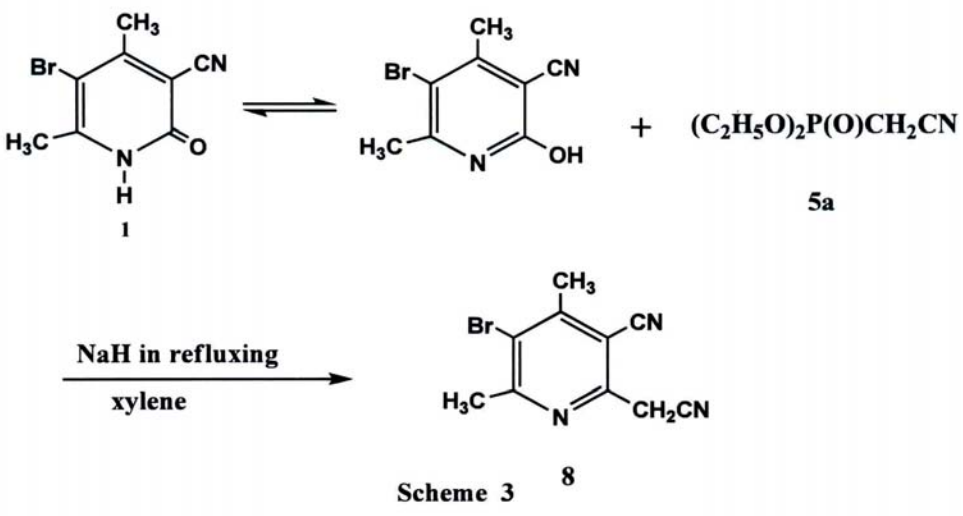
Compounds **6** and **7a** are chromatography pure and possess sharp melting points . The alkylated product **6** was deduced from its analysis IR,^{1}H, ^{13}C-NMR, and mass spectral data (cf. Experimental). The

structure of the other isolated compound **7a** was identified for the following reasons: Elemental and mass spectral analysis for compound **7a** corresponded to empirical formula of $C_{10}H_{14}BrN_2O_4P$. The IR of **7a** (KBr , cm^{-1}) revealed absence of the band at 1680 (C = O, amide , Pyridone) and exhibited the presence of the absorption band at 1250 cm^{-1} (P=O). The ^{1}H-NMR spectrum (in $CDCl_3$) of the adduct **7a** showed doublet centered at δ= 3.83 ($^3J_{HP}$= 11.50Hz) due to 6 Protons of $(OCH_3)_2$ attached to the phosphorus atom . Compound **7a** exhibited absence of signal at 160.8 due to lack of (C=O) of the ^{13}C-NMR spectrum of **1** ($CDCl_3$, δppm) . The ^{31}P-NMR spectrum for **7a** showed signal at + 2.83 ppm (85% H_3PO_4) . The mass spectrum of **7a** contained a prominent peak of M^+ at m/z (%) 335 (65) (cf. Experimental) .

Similarly triisopropyl phosphite **4b** reacted with **1** to give mainly the phosphate adduct **7b** in good yield (scheme 2). Structure assignment for **7b** was substantiated on the basis of their elemental analysis , IR , ^{1}H , ^{13}C , ^{31}P-NMR , and mass spectral data (cf. Experimental).

A possible explanation for the course of the reaction of trialkyl phosphites **4a,b** [19,20] with pyridone **1** was shown in Scheme 2 . The reaction was assigned to proceed through an initial attack of the phosphorus reagents **4 a,b** at the most reactive center in **1** and led to the formation of dipolar adduct **(A)** . The reaction was accompanied with rapid hydrolysis by the presence of unavoidable moisture and elimination of one molecule of alcohol under the applied reaction conditions to afford the dialkylphosphate products **7a,b .**

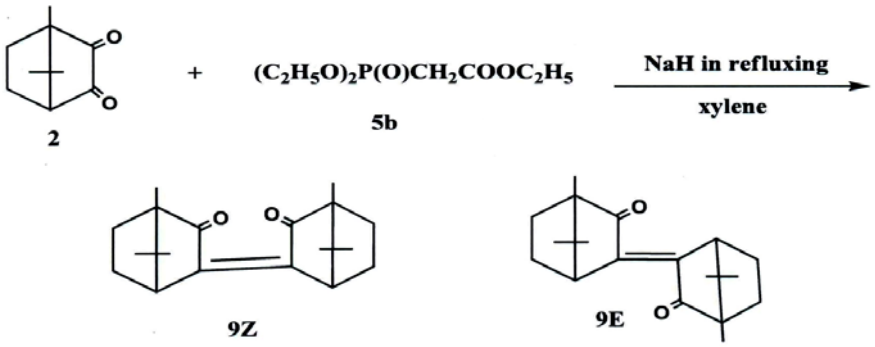
Furthermore , this study was extended to include the behavior of 5- bromo – 4,6 – dimethyl - 2 - oxo - 1,2 - dihydrpyridone **(1)** towards Wittig – Horner reagent diethyl (cyanomethyl) phosphonate **(5a)** (Scheme 3).



Scheme 3

Compound **1,** is found to be in equilibrium with tautomeric form [17] was allowed to react with one equivalent of phosphonate **5a** in very dry xylene and in the presence of sodium hydride as a base , the reaction mixture was proceeded at reflux temperature for 10 h to give a chromatographically pure adduct formulated as 5- bromo - 2 - (cyanomethyl) - 4,6 - dimethyl - nicotinonitrile **8** . The structure of **8** was deduced from its elemental analysis , IR , ^{1}H , ^{13}C-NMR and mass spectral data (cf. Experimental). The IR spectrum (KBr, cm^{-1}) of **8** revealed absence of absorption bands at 3170 (NH) and at 1680 (C=O , amide) . The ^{1}H-NMR spectrum of **8** ($CDCl_3$, δ ppm) revealed the prensence of a signal at 4.0 due to the methylene protons (s, 2H , CH_2CN). ^{13}C-NMR spectrum ($CDCl_3$, δppm) showed the absence of a signal at 160.8 (C = O). that recorded in the compound **1 .**The mass spectrum of 8 contained a prominent peak of M^+ at m/z(%) 250 [M^+] (100) . Elemental analysis and molecular weight determination (MS) of **8** Support the molecular formula C_{10} H_8 Br N_3 (Scheme 3) (cf. Experimental).

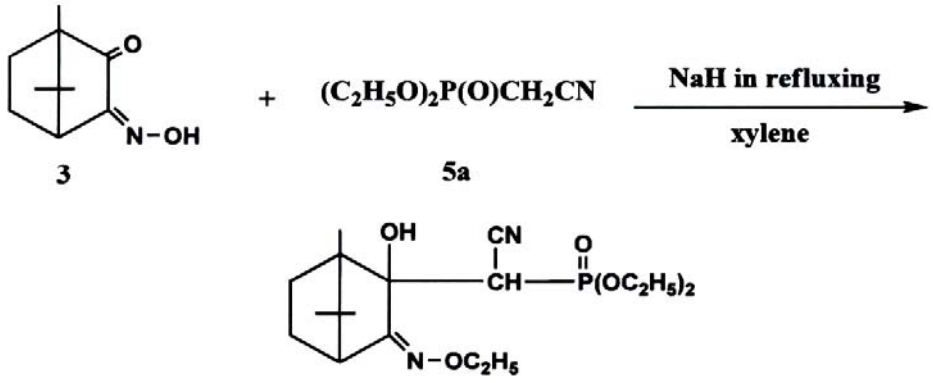
Next , the reaction of camphorquinone (1,7,7, trimethyl- bicyclo [2.2.1] – heptane-2,3 – dione) (**2**) with one mole equivalent of Wittig – Horner reagent triethylphosphonoacetate **(5b)**[24] in very dry xylene in the presence of sodium hydride as a base , proceeded at reflux temperature for 5h to give a colorless crystalline coupling product **9** , so formed was assigned structure **9 ,** that can exist either in the **Z** or **E** conformations (scheme 4).



Scheme 4

The structural assignment for 4,4\,7,7\,7,7\ - hexamethyl -2 , 2\ - bi(bicyclo [2.2.1] heptane) – 2 (2\) – ene – 3,3 - dione **(9)** is based upon analytical and molecular measurements (MS : m/z 300, M^+ ,55%) corresponded to $C_{20}H_{28}O_2$ .The IR spectrum of **9** revealed the presence of absorption band at δ = 1625 cm^{-1} (C=C) . The ^{13}C-NMR of the coupling compound lacked the signal recorded in the compound **2** at δ = 202.0 (C=O , camphorquinone) and revealed the presence of signal at 145.8 due to (C=C) of the coupling product **9** [25] (cf. Experimental).

Moreover, the reaction of 3-(hydroxyimino)-1,7,7-trimethyl bicyclo [2.2.1] heptane - 2 - one (camporquinone monoxime) **(3)** in a very dry xylene with two mole equivalents of Wittig - Horner reagent diethyl (cyanomethyl) posphonate (**5a)** in the presence of sodium hydride as a base was investigated . The reaction mixture was refluxed for 5h to give a chromatographically pure adduct formulated as diethyl cyano (3- (ethoxyimino)-2-hydroxy-1,7,7-trimethyl bicyclo [2.2.1] heptane -2-yl) methylphosphonate **(10)** based upon analytical and spectroscopic arguments (Scheme 5) (cf. Experimental). Elemental and mass spectral analyses for compound **10** corresponded to an empirical formula $C_{18}H_{31}N_2O_5P$. The isolated compound **10** in 55% yield , was established to be alkylated phosphonate [25] adduct from its elemental analysis , IR , ^{1}H , ^{13}C , ^{31}P-NMR and mass spectroscopic data. The IR spectrum in KBr of compound **10** exhibited absorption bands at 3200 (C-OH) , 2200 (CN) , 1230 (P = O , bonded) and 1088 cm^{-1} (P–O–C_2H_5) and revealed absence of band at 1700 cm^{-1} ((C=O) , camphorquinone monoxime). The ^{1}H-NMR ($CDCl_3$,δppm) spectrum of compound **10** exhibited signals at δ 1.10 (t , 3H , OCH_2 $\underline{CH_3}$) 3.99 (q,2H,OCH_2CH_3) corresponding to alkylation (ethoxy group) and signals at δ = 1.29 (t, 6H, P ($OCH_2CH_3)_2$) 4.17 (q , 4H , P ($O\underline{CH_2}CH_3)_2$) Corresponding to the phosphonate structure . ^{13}C- NMR spectrum of **10** ($CDCl_3$, δppm) revealed absence of signal at 207.5 (C=O) camphor) . The signal at δ = + 19.75 ppm (85% H_3PO_4)of ^{31}P-NMR spectrum for adduct **10** supported the phosphnate structure. The mass spectrum of compound **10** showed the prominted peack of M^+ at m/z 386 [M^+] (35%) (cf. Experimental) .



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Scheme 5

4- Conclusion:

From the results of the present investigation, it can be concluded that the reaction of the derivatives of 5-bromo-3-cyano-pyridone **1** and camphorquinones **2** and **3** with trialkyl phosphites **4** and Wittig-Horner reagents **5** led to different products depending on the nature of the phosphorus reagents used, the structure of the carbonyl compounds as well as on the stability of the addition products.

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