

## Reactions of 5-Bromo-4,6-Dimethyl-2-Thioxo-1,2-Dihydropyridine -3- Carbonitrile with Organophosphorus Reagents

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**Abstract:** The reaction of 5-bromo-4,6-dimethyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**1**) with phosphorus ylides **2a,b** afforded the new phosphonium ylides **7a,b**. Wittig – Honer reagent **3** reacts with **1** to give the olefinic product **8**. On the other hand, the dimeric compound **9** and the alkylated products **10**, **11** were isolated from the reaction of **1** with dialkyl phosphite **4**, trialkyl phosphite **5** and tris(dimethylamino) phosphine **6**. Possible reaction mechanisms are considered, and the structural assignments are based on analytical and spectroscopic evidence.

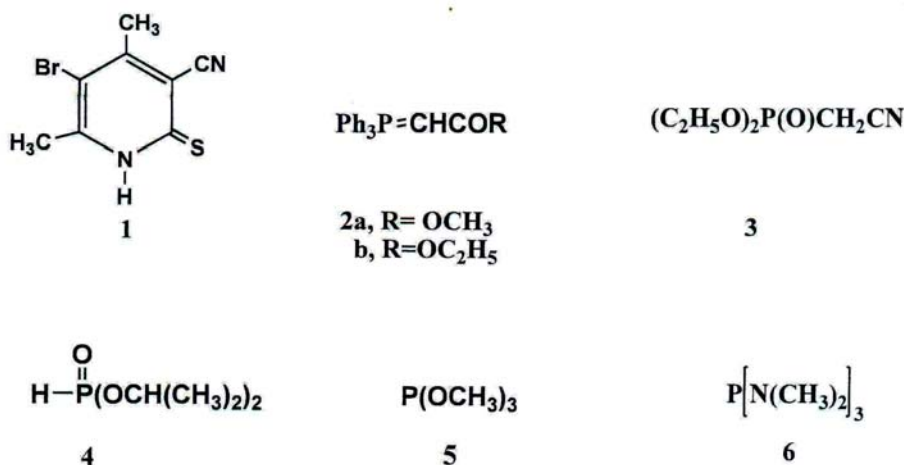
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**Keywords:** Phosphorus ylides, Wittig-Horner reagent, phosphites, dihydropyridines, nicotinonitriles.

### Introduction:

It has been reported that pyridine carbonitrile derivatives exhibit a wide spectrum of biological and pharmacological activities [1-3]. This together with our interest in organophosphorus chemistry [4-11] has encouraged the synthesis of new organophosphorus compounds incorporating such

important nuclei that may possibly lead to further biological activity. The present study deals with the reaction of 5-bromo-4,6-dimethyl 2-thioxo-1,2-dihydropyridine-3-carbonitrile (**1**) with phosphorus ylides **2a,b** Wittig – Horner reagent **3** , dialkyl phosphite **4**, trialkyl phosphite **5** and tris(dimethylamino) phosphine **6** (Scheme 1).



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 <sup>1</sup>H and <sup>13</sup>C-NMR spectra were recorded in

CDCl<sub>3</sub> as solvent on a Joel-500 MHz spectrometer, and the chemical shifts were recorded in δ values relative to TMS. The <sup>31</sup>P-NMR (125 MHz) spectra were taken with a Varian CFT-20 (vs. external 85% H<sub>3</sub>PO<sub>4</sub> 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.

**Reaction of 5-bromo-4,6-dimethyl-2-thioxo-1,2-dihydropyridine -3- carbonitrile (1)[12] with carbmethoxymethylenetriphenylphosphorane (2a).**

A mixture of **1** (0.24g , 1 m mol ) and the phosphonium ylide **2a** ( 0.32g , 1 m mol) was refluxed in boiling DMF (20 mL) for 6h. The reaction mixture was evaporated under reduced pressure. The residue was washed several times with petroleum ether (b.r. 60-80 °C) to give product **7a** [ methyl (5-bromo-3-cyano-4,6-dimethyl-2- sulfanyl -1,2- dihydropyridin-2-yl) (triphenyl - $\lambda^5$ -phosphanylidene) acetate (**7a**, C<sub>29</sub>H<sub>26</sub>BrN<sub>2</sub>O<sub>2</sub>PS). Crystallized from ethyl acetate **7a** was separated as colorless crystals, yield 78%, and m. p. 240 – 241 °C. IR [  $\nu$ , cm<sup>-1</sup>, KBr] : 3420 (NH), 2219 (CN), 1700, (C=O, ester), 1630, 1515 (C=P), and at 1435, 990 ( P-C-phenyl). <sup>1</sup>H-NMR (500 MHz,  $\delta$  ppm, CDCl<sub>3</sub>) : 2.46, 2.54 (2s, 6H, CH<sub>3</sub>), 2.22 (s, H, NH), 2.32 (s, 1H, SH), 3.20 (s, 3H, COOCH<sub>3</sub>), 7.68 – 7.74 (m, 15H, Ar) <sup>13</sup>C-NMR (125 MHz,  $\delta$  ppm, CDCl<sub>3</sub>): 12.3 , 13.5 (2CH<sub>3</sub>), 45.6 (d, <sup>2</sup>J<sub>CP</sub> = 16.4 Hz, HS-C-C=P), 53.4 (d, <sup>3</sup>J<sub>CP</sub> = 7.5 Hz, OCH<sub>3</sub>), 91.9 (C-Br), 100.10 (  $\bar{C}$ -CN), 118.91 (CN) 126.3 ((d, <sup>1</sup>J<sub>C-P</sub> =89.2 Hz, P=C), 127.5 – 133.8 (Ar), 145.8 ( $\bar{C}$ =C-Br), 152.1 (CH<sub>3</sub>-C=C), 168.3 (d, <sup>2</sup>J<sub>CP</sub> =14.5 HZ, C=O, ester), <sup>31</sup>P-NMR ( $\delta$  ppm, CDCl<sub>3</sub>): 22.52. MS m/z (%) 574 [M-3]<sup>+</sup> (50). Anal. Calcd. for C<sub>29</sub>H<sub>26</sub>BrN<sub>2</sub>O<sub>2</sub>PS(576.06) : C, 60.32 ; Br, 13.84 ; N, 4.85 ; P, 5.36 ; S, 5.55. Found: C, 60.62 ; Br, 13.54 ; N, 4.45 ; P, 5.58 ; S, 5.84.

**Reaction of 1 with carbethoxymethylene triphenyl phosphorane (2b).**

A mixture of **1** (0.24g, 1 m mol) and the phosphonium ylide **2b** (0.34g , 1 m mol) was refluxed in boiling DMF (20 mL) for 6 h. The reaction mixture was evaporated under reduced pressure. The residue was washed several times with petroleum ether (b. r. 60 – 80 °C) to give product **7b** [ ethyl (5-bromo-3-cyano-4,6-dimethyl-2-sulfanyl-1,2- dihydro pyridin -2-yl) (triphenyl -  $\lambda^5$ - phosphanylidene) acetate) (**7b**, C<sub>30</sub>H<sub>28</sub>BrN<sub>2</sub>O<sub>2</sub>PS).

Crystallized from ethylacetate, **7b** was separated as colorless crystals, yield 66%, m. p 293 – 294 °C. IR [  $\nu$ , cm<sup>-1</sup>, KBr] : 3420 (NH), 2219 (CN), 1700 , (C=O), 1630, 1515 (C=P), 1434, 990 ( P-C-phenyl). <sup>1</sup>H-NMR (500 MHz,  $\delta$  ppm, CDCl<sub>3</sub>) : 2.40, 2.50 (2s, 6H, 2CH<sub>3</sub>), 2.21 (s, H, NH), 2.3 (s, 1H, SH), 1.29 (t, 3H, COOCH<sub>2</sub>CH<sub>3</sub>), 4.21 (q, 2H, COOCH<sub>2</sub>CH<sub>3</sub>), 7.68 – 7.74 (m, 15H, Ar). <sup>13</sup>C-NMR (125 MHz,  $\delta$  ppm, CDCl<sub>3</sub>): 12.3 , 13.5 (2CH<sub>3</sub>), 45.6 (d, <sup>2</sup>J<sub>CP</sub> = 16.4 Hz,

HS-C-C=P), 14.1 (OCH<sub>2</sub>CH<sub>3</sub>), 61.6 (OCH<sub>2</sub>CH<sub>3</sub>), 100.1 (  $\bar{C}$ -CN), 118.9 (CN) 126.3 (d, <sup>1</sup>J<sub>C-P</sub> =90.24 Hz, P=C). 127.4 – 133.8 (Ar), 168.42 (d, <sup>2</sup>J<sub>CP</sub> =14.5 HZ, C=O, ester), <sup>31</sup>P-NMR ( $\delta$  ppm, CDCl<sub>3</sub>): 22.55. MS m/z (%) 517 [M-COOC<sub>2</sub>H<sub>5</sub>]<sup>+</sup> (55). Anal. Calcd. for C<sub>30</sub>H<sub>28</sub>BrN<sub>2</sub>PO<sub>2</sub>S(590.08) : C, 60.92 ; H, 4.77 ; Br, 13.51 ; N, 4.74 ; P, 5.24 ; S, 5.42. Found : C, 60.58 ; H, 4.53 ; Br, 13.76 ; N, 4.95 ; P, 5.31 ; S, 5.45.

**Reaction of 1 with diethyl (cyano methylene) phosphonate (3).**

Diethyl (cyanomethylene) phosphonate (**3**) (0.17, 1m mol) was dissolved in very dry xylene (25mL) and the sodium hydride (0.024g, 1m mol) was added carefully with stirring. The carbonitrile **1** (0.24g , 1m mol) was added to the mixture and refluxed for 10h. after evaporation of the volatile materials under reduced pressure, the residue was washed several times with petroleum ether (b.r. 60-80 °C) to give product **8** [ 5-bromo-3-cyano-4,6-dimethyl -1,2-dihydropyridine-2-yl) maleonitrile] (**8**, C<sub>12</sub>H<sub>9</sub>BrN<sub>4</sub>). Crystallized from ethylacetate, **8** was separated as colorless crystals, yield 75% and m.p 253 – 254 °C. IR [  $\nu$ , cm<sup>-1</sup>, KBr] : 3422 (NH), 2220 (CN), 1644 , (C=C). <sup>1</sup>H-NMR (500 MHz,  $\delta$  ppm, CDCl<sub>3</sub>) : 2.46, 2.54 (2s, 6H, 2CH<sub>3</sub>), 2.22 (s, H, NH), 3.99 (s, 1H, CH), 5.97 (s, 1H, CH=C). <sup>13</sup>C-NMR (125 MHz,  $\delta$  ppm, CDCl<sub>3</sub>): 11.6 , 15.3 (2CH<sub>3</sub>), 47.0 (CH), 91.9 (C-Br), 102.8 ( $\bar{C}$ -CN), 108.3(CH-CN), 117.3 (CN), 145.8 ( $\bar{C}$ =C-Br), 152.1 (CH<sub>3</sub>- $\bar{C}$ =C). MS m/z (%) 288 [M<sup>+</sup>] (45). Anal. Calcd. for C<sub>12</sub>H<sub>9</sub>BrN<sub>4</sub>(288.00) : C, 49.85 ; H, 3.14 ; Br, 27.64 ; N, 19.38. Found : C, 49.49 ; H, 3.25 ; Br, 27.55 ; N, 19.72.

**Reaction of 1 with diisopropyl phosphite (4)**

Excess of diisopropyl phosphite (**4**) ( $\approx$  3 mL). was added to **1** ( 0.24g , 1 m mol) without solvent and reaction mixture was refluxed for 3h. After evaporation the volatile material under reduced pressure, the residue washed several times with petroleum ether (b.r. 60-80 °C) to give product **9** [ 2,2'-thiobis (5-bromo-4,6-dimethylnicotinonitrile] (**9**, C<sub>16</sub>H<sub>12</sub>Br<sub>2</sub>N<sub>4</sub>S).

Crystallized from ethyl acetate, **9** was separated as colorless crystals, yield 70% and m. p 190 - 191°C. IR [  $\nu$ , cm<sup>-1</sup>, KBr] : 2219. <sup>1</sup>H-NMR (500 MHz,  $\delta$  ppm, CDCl<sub>3</sub>) : 2.46, 2.54 (2s, 6H, 2CH<sub>3</sub>), <sup>13</sup>C-NMR (125 MHz,  $\delta$  ppm, CDCl<sub>3</sub>): 14.1 , 23.5 (2CH<sub>3</sub>), 103.9 ( $\bar{C}$ -CN), 117.0 (CN), 119.8 (C-Br), 155.0 (CH<sub>3</sub>- $\bar{C}$ =C). 165.4 ( $\bar{C}$ =C-Br), 182.6 (N=C-S). MS m/z (%) 449 [M<sup>+</sup>] (40). Anal. Calcd. for C<sub>12</sub>H<sub>9</sub>BrN<sub>4</sub>(449.91) : C, 42.50 ; H, 2.67 ; Br, 35.34 ; N, 12.39 ; S, 7.09 Found : C, 42.73 ; H, 2.29 ; Br, 35.76 ; N, 12.43 ; S, 7.18.

Similarly, the reaction of carbonitrile **1** with excess of trimethyl phosphite ( $\approx 3$  mL) was refluxed for 3h to give product **10** [5-bromo-4,6-dimethyl-2-(methylthio) nicotinonitrile] (**10**,  $C_9H_9BrN_2S$ ).

Crystallized from ethyl acetate, **10** was separated as colorless crystals yield 73% and m.p  $268 - 269^\circ C$ . IR [ $\nu$ ,  $cm^{-1}$ , KBr]: 2220 (CN)  $^1H$ -NMR (500 MHz,  $\delta$  ppm,  $CDCl_3$ ): 2.36, 2.53 (2CH<sub>3</sub>), 2.51 (S-CH<sub>3</sub>)  $^{13}C$ -NMR (125 MHz,  $\delta$  ppm,  $CDCl_3$ ): 14.1, 23.5 (2CH<sub>3</sub>), 13.1 (S-CH<sub>3</sub>), 106.7 (C-CN), 117.0 (CN), 117.4 (C-Br), 154.0 (C=C-CN), 162.7 (C=S-CH<sub>3</sub>), 164.9 (C=C-Br), MS m/z (%) 255 [ $M^+$ ] (23), [ $M-15$ ]<sup>+</sup> (70). Anal. Calcd. for  $C_9H_9BrN_2S$  (255.97): C, 42.04; H, 3.53; Br, 31.07; N, 10.89; S, 12.47 Found: C, 42.33; H, 3.59; Br, 31.47; N, 11.03; S, 12.53.

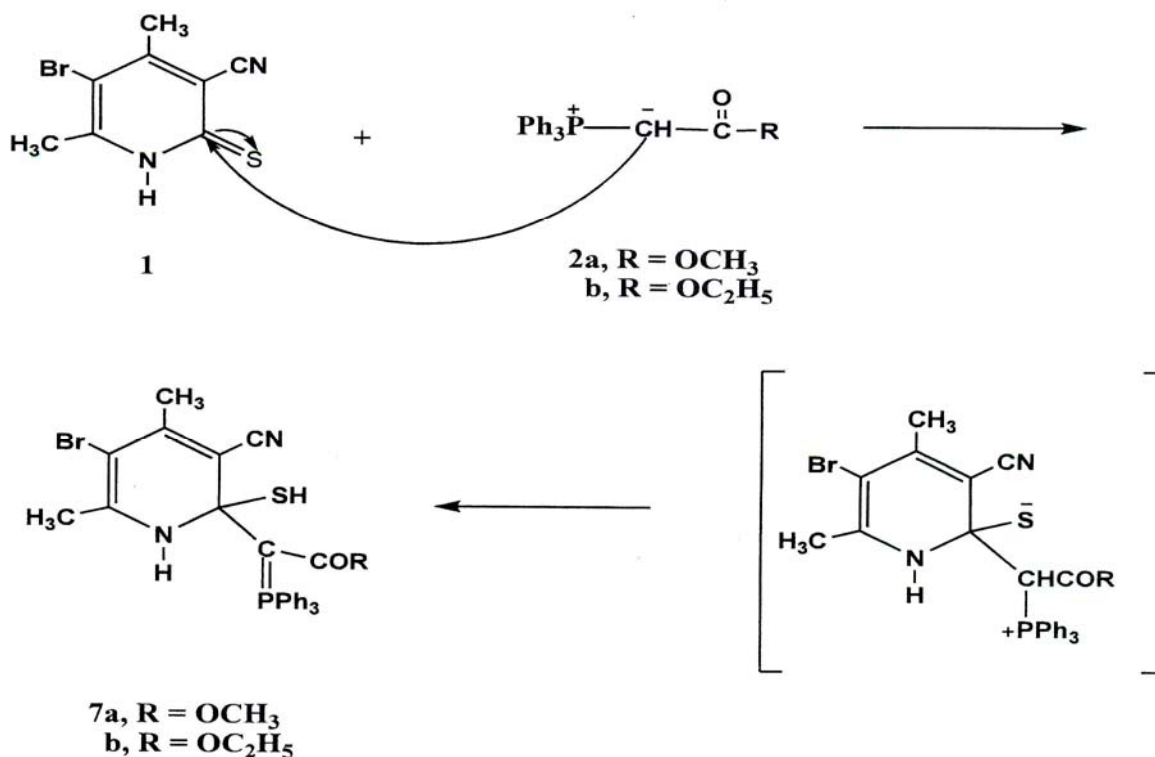
Similarly, carbonitrile **1** was reacted with excess tris (dimethylamino) phosphine (**6**) to give product **11** [5-bromo-2-(dimethylaminothio)-4,6-dimethylnicotinonitrile] (**11**,  $C_{10}H_{12}BrN_3S$ ).

Crystallized from ethyl acetate, **11** was separated as colorless crystals yield 75% and m.p  $95 - 96^\circ C$ . IR [ $\nu$ ,  $cm^{-1}$ , KBr]: 2219 (CN).  $^1H$ -NMR (500 MHz,  $\delta$  ppm,  $CDCl_3$ ): 2.36, 2.53 (2s, 6H, CH<sub>3</sub>), 2.47 (s, 6H, N(CH<sub>3</sub>)<sub>2</sub>)  $^{13}C$ -NMR (125 MHz,  $\delta$  ppm,  $CDCl_3$ ): 14.1

, 25.5 (2CH<sub>3</sub>), 43.1 (N(CH<sub>3</sub>)<sub>2</sub>), 103.9 (C-CN), 117.0 (CN), 119.8 (C-Br), 155.0 (CH<sub>3</sub>-C=C), 165.4 (C=C-Br), 182.6 (C-S). MS m/z (%) 284 [ $M^+$ ] (75). Anal. Calcd. for  $C_{10}H_{12}BrN_3S$  (284.99): C, 41.97; H, 4.23; Br, 27.92; N, 14.68; S, 11.20. Found: C, 41.88; H, 4.29; Br, 27.53; N, 14.93.

### 3- Results and Discussion

We have found that carbmethoxymethylene-triphenylphosphorane (**2a**) reacts with 5-bromo-4,6-dimethyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**1**), in boiling dimethylformamide, to give the new phosphorane product **7a** as the sole reaction product. Triphenylphosphine and / or triphenylphosphine oxide are neither isolated nor detected in the reaction medium (Scheme 2). Compound **7a** consists of pure crystals and has a sharp melting point. Structure elucidation of the new phosphorus ylide **7a** is based on the following evidence: elemental analyses and molecular weight determination (MS) of **7a** support the molecular formula  $C_{29}H_{26}BrN_2O_2PS$  (576.06); accordingly, MS: m/z = 574 [ $M-3$ ]<sup>+</sup>, 50%.



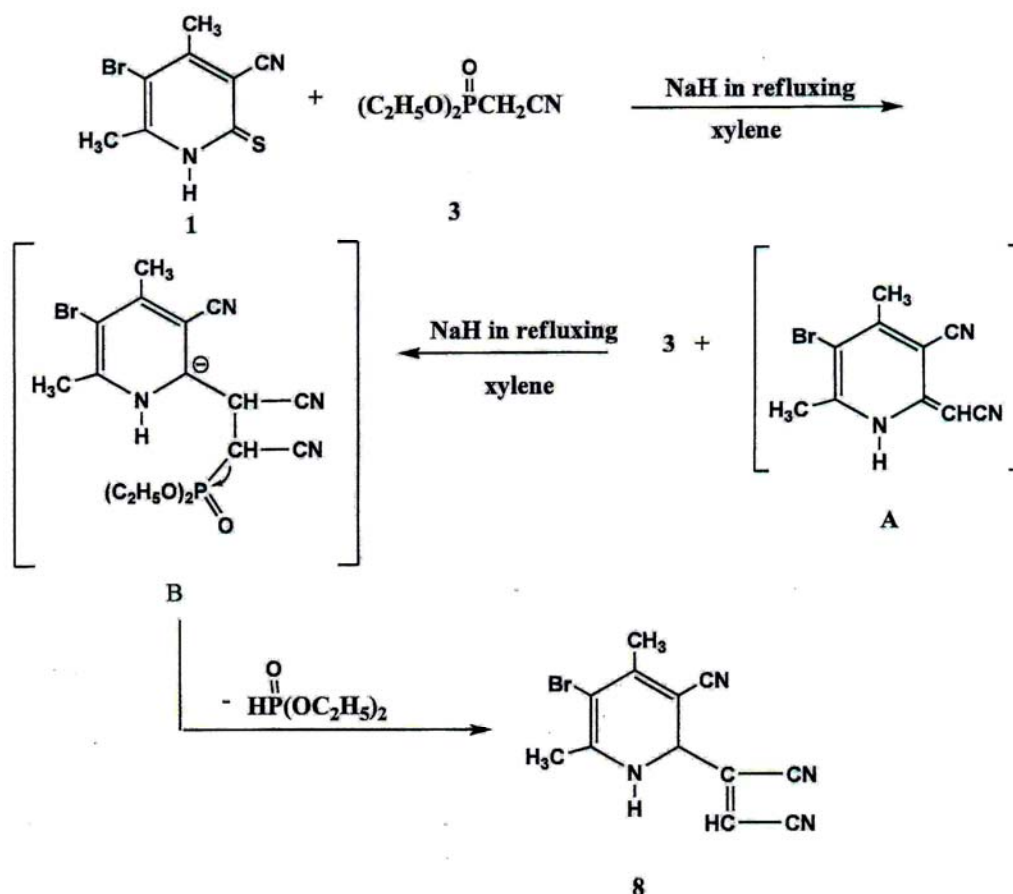
Scheme 2

Its IR spectrum, in KBr, exhibits strong absorption band at  $1700\text{ cm}^{-1}$  (C=O, ester),  $1630$ ,  $1515\text{ cm}^{-1}$  (C=P), and at  $1435$ ,  $990\text{ cm}^{-1}$  (P-C-phenyl) [13]  $^{31}\text{P}$ -NMR  $\delta = 22.52$ , a value that falls in the range frequently recorded for this class of compounds [13, 14]. The  $^1\text{H}$ -NMR spectrum of **7a** in  $\text{CDCl}_3$  discloses the presence of signals at  $\delta = 3.20$  ppm (s, 3H,  $\text{COOCH}_3$ ), 2.46, 2.54 ppm (2s, 6H,  $2\text{CH}_3$ ), 2.20 (s, H, NH), 2.30 (s, 1H, SH), 7.68 – 7.74 (m, 15H, aromatic). Actually, the structure assigned for compound **7a** is based on  $^{13}\text{C}$ -NMR spectroscopy, which indicate the presence of signals at 168.3 (d,  $^2J_{\text{CP}} = 14.5\text{ Hz}$ ) allocated to the C=O of the ester group, at 53.4 ppm (d,  $^3J_{\text{CP}} = 7.5\text{ Hz}$  for the  $\text{OCH}_3$  group), at 126.3 (d,  $^1J_{\text{CP}} = 89.22\text{ Hz}$ , P=C) [15], at 45.6 ppm (d,  $^2J_{\text{CP}} = 16.4\text{ Hz}$  ( $\text{HS-C-C=PPh}_3$ ) at

118.9 (CN) 100.1 ppm ( $\text{C-CN}$ ), 12.3, 13.5 ppm ( $2\text{CH}_3$ ).

Similarly, the reaction product of **1** with carbethoxymethylene triphenylphosphorane **2b** was assigned analogous structure **7a** on the basis of comparable spectroscopic arguments (cf. Scheme 2, Experimental section). Products **7a,b** are presumably formed via addition of the ylide species **2a,b** to the active methine carbon in compound **1** to afford the new phosphonium ylides **7a,b** (Scheme 2).

Next, when **1** was allowed to react with one mol equivalent of diethyl (cyanomethyl) phosphonate (**3**), in the presence of sodium hydride in xylene, at reflux temperature for 10h, adduct **8** was isolated in 75% yield (scheme 3). The structure of 2-(5-bromo-3-cyano-4,6-dimethyl-1,2-dihydropyridin-2-yl) maleonitrile is derived from its spectral data (cf. Experimental Section).



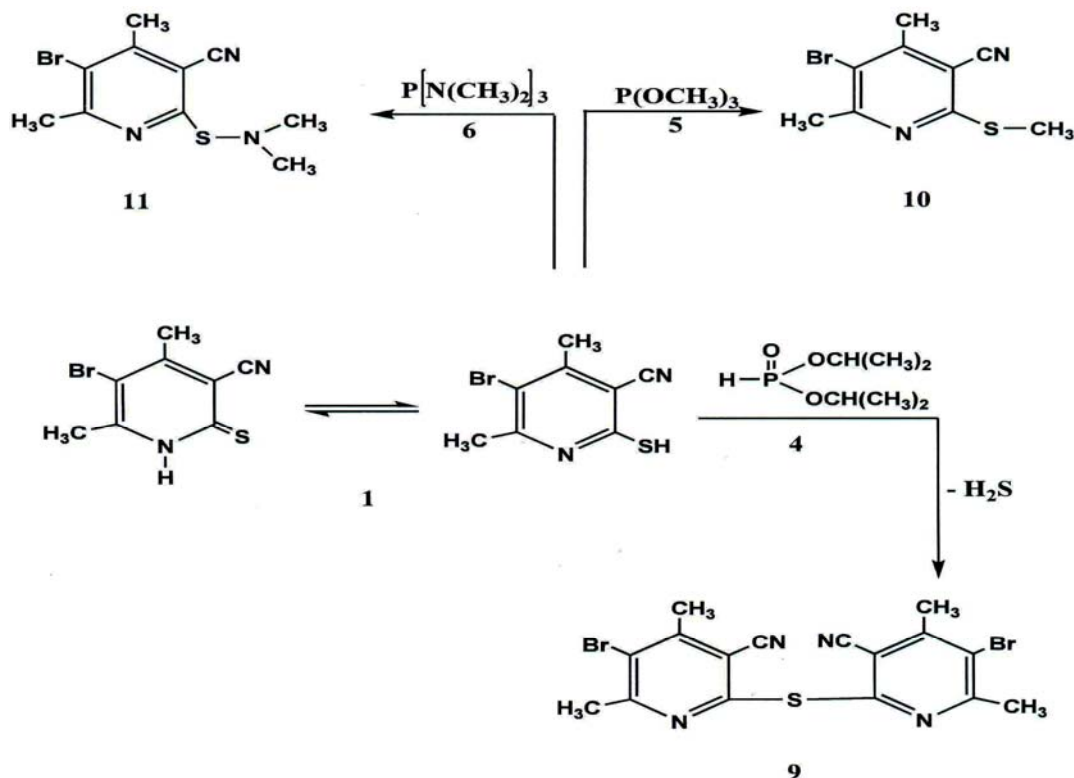
**Scheme 3**

A possible explanation for the reaction course of **1** with Wittig – Horner reagent **3** in the presence of sodium hydride as base is shown in Scheme 3. Thio-olefination of compound **1** with Wittig – Horner reagent **3** gave the intermediate (**A**) which reacted

with another molecule of **3** to give intermediate (**B**). Under the influence of the base present in the reaction medium, elimination of dialkyl phosphite after a suitable proton transfer gives the final product **8** (scheme 3).

The reaction of 5-bromo-4,6-dimethyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**1**) with diisopropyl phosphite (**4**), trimethyl phosphite (**5**), and tris (dimethylamino) phosphine (**6**) was also investigated. We have found that the reaction of diisopropyl phosphite (**4**) with **1** proceeds without solvent at reflux temperature to give the dimeric product **9** in 70% yield (Scheme 4). Structure

elucidation for compound **9** was attested by the following evidence (a) elemental analyses and molecular weight determination (MS) for compound **9** correspond to  $C_{16}H_{12}Br_2N_4S$ . (b) The IR spectrum of **9**, in KBr, discloses the absence of both NH and C=S bands appeared at  $3419\text{ cm}^{-1}$  and  $1165\text{ cm}^{-1}$  in the starting material.



**Scheme 4**

Moreover, the  $^1H$  and  $^{13}C$ -NMR of 2,2' – thiobis ( 5-bromo-4,6-dimethyl nicotinonitrile) furnish strong evidence in support of the dimeric structure **9** ( cf. Experimental Section). Trimethyl phosphite (**5**) and tris(dimethylamino) phosphine (**6**) on the other hand, reacted with **1** without solvent at reflux temperature to give the alkylated [16] products **10**, **11**, respectively ( Scheme 4). The structures of the new compounds **10**, **11** are assigned on the basis of the full set of their spectral data (cf. Experimental Section ).

#### 4- Conclusion

From the results of the present investigation, it could be concluded that the Wittig reagent **2a,b** preferentially attacked the thiocarbonyl carbon in **1** to give the phosphonate products **7a** and **7b**. Meanwhile, it has been found that the reaction of **1** with Wittig-Horner reagent **3** proceeds according to

the Wittig reaction to give the olefinic product **8**, where as, in the reaction of **1** with dialkyl phosphite, trialkyl phosphite, and tris(dialkylamino) phosphine the dimeric compound **9** and the alkylated products **10**, **11** are the sole reaction products.

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