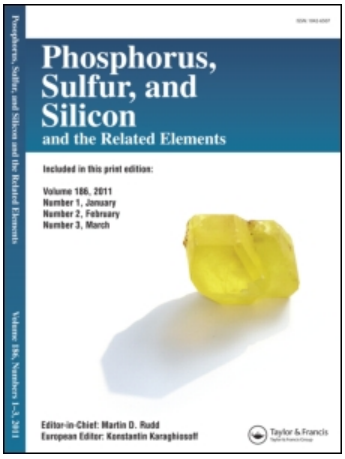

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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El-Sayed M. A. Yakoup[a]; Dalal B. Giurgius[b]; L. S. Boulos[a]
[a] National Research Centre, Cairo, Egypt [b] Faculty of Science, Ain-Shams University, Cairo, Egypt

To cite this Article Yakoup, El-Sayed M. A. , Giurgius, Dalal B. and Boulos, L. S.(1999) 'THE BEHAVIOR OF 6-METHYL-2-THIOURACIL TOWARDS WITTIG-HORNER REAGENTS', Phosphorus, Sulfur, and Silicon and the Related Elements, 148: 1, 177 — 187
To link to this Article: DOI: 10.1080/10426509908037009
URL: http://dx.doi.org/10.1080/10426509908037009

Phosphorus, Sulfur and Silicon, 1999, Vol. 148, pp. 177-187
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THE BEHAVIOR OF 6-METHYL-2-THIOURACIL TOWARDS WITTIG-HORNER REAGENTS

EL-SAYED M.A. YAKOUT[a], DALAL B. GIURGIUS[b] and L.S. BOULOS[a*]

[a]*National Research Centre, Dokki, Cairo, Egypt and* [b]*Faculty of Science, Ain-Shams University, Cairo, Egypt*

(Received 17 August, 1998; In final form 30 November, 1998)

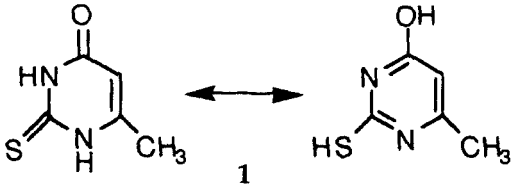
6-Methyl-2-thiouracil (**1**) reacts with Wittig-Horner (**2a-e**) reagents to give the new products **3, 4, 6, 7** and **9** along with the alkylated derivatives **5, 8** and **10**. When **1** was treated with **2e** and/or **2f,** the alkylated compound **10** is the sole reaction prduct. Possible reaction mechanism are considered and the structural assignments are based on compatible analytical and spectroscopic results.

Keywords: Wittig-Horner reagents; 6-methyl-2-thiouracil; the olefinic compounds; the phosphorane adduct and the alkylated products

INTRODUCTION

It has been reported that substituted pyrimidines in general and uracils in particular possess antiviral, antitumor effect and pharmacological characteristics.[1–4] As a prelude to the current work on the behavior of the Wittig and Wittig-Horner reagents toward different unsaturated systems,[5–11] we have now investigated the reaction of 6-methyl-2-thiouracil (**1**) with Wittig-Horner reagents (**2a-f**). This is to determine the preferential site of attack by these reagents and for the production of new phosphorane and alkylated products of expected therapeutic significance.[12–14]

* To whom correspondence should be addressed.



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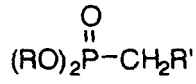
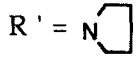
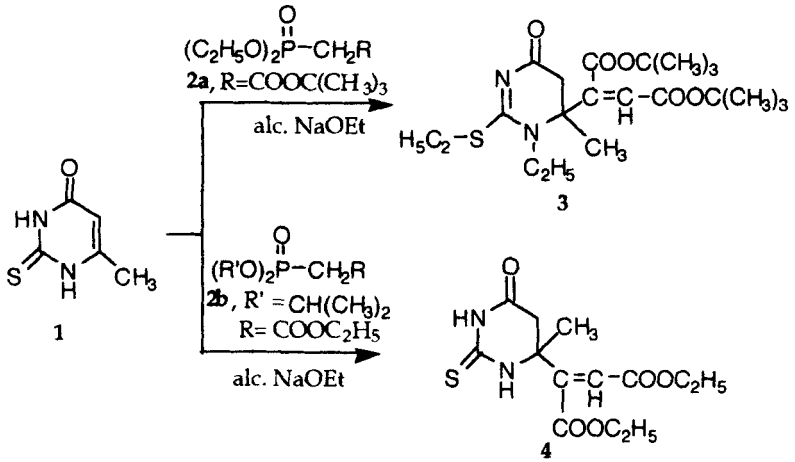


2a, $R=C_2H_5$, $R'= COOC(CH_3)_3$
b, $R=CH(CH_3)_2$, $R' = COOC_2H_5$
c, $R= CH_3$, $R' = COOCH_3$
d, $R = C_2H_5$, R ' = 
e, $R = C_2H_5$, $R' = COOCH_3$
f, $R = C_2H_5$, $R' = COOC_2H_5$

RESULTS AND DISCUSSION

When 6-methyl-2-thiouracil (**1**) was allowed to react with one equivalent of **2a** in the presence of alcoholic sodium ethoxide solution at reflux temperature for 8 hours, adduct **3** and some unchanged thiouracil (**1**) were isolated. Carrying out the reaction using three moles of the Wittig-Horner reagent **2a** instead of one mole, led to the formation of product **3** in good yield (Scheme 1). Elemental microanalysis and mass spectral data for compound **3** corresponds to an empirical formula of $C_{21}H_{34}N_2O_2S$. The IR (cm^{-1}) spectrum of **3** revealed the characteristic absorption bands at 1680 (C=O, amide), 1740 and 1745 (C=O, ester). Moreover, the IR spectrum of compound **3** indicated the absence of thioamidic carbonyl group present in the spectrum of **1** at 1424 cm^{-1}. The ^{1}H-NMR ($(CD_3)_2CO$) of compound **3** disclosed the presence of two triplets centered at $\delta = 1.12$ ppm (3H, N-$CH_2\underline{CH_3}$), 1.21 (3H, S-$CH_2\underline{CH_3}$) and two quartets at 3.2 (2H, N-$\underline{CH_2}$-CH_3), 3.45 (2H, S-$\underline{CH_2}$-CH_3). The tert-butyl groups appeared as a broad singlet centered at $\delta = 1.9$ ppm [18H, $2C(CH_3)_3$]. Moreover, the

^{1}H-NMR of adduct **3** exhibits signals at 2.2 ppm (s, 3H, C6-CH_3), 3.9 (s, 2H, cyclic CH_2) and at 5.95 ppm (s, 1H, C=CH-$COOC(CH_3)_3$). The chemical shift recorded for the methine proton suggested the Z form rather than the E form, which would require a down field chemical shift[15]. Actually, the mass spectrum of adduct **3** yielded a prominent ion peak M^+ at m/z 426 which is in support of structure **3** (Scheme 1).

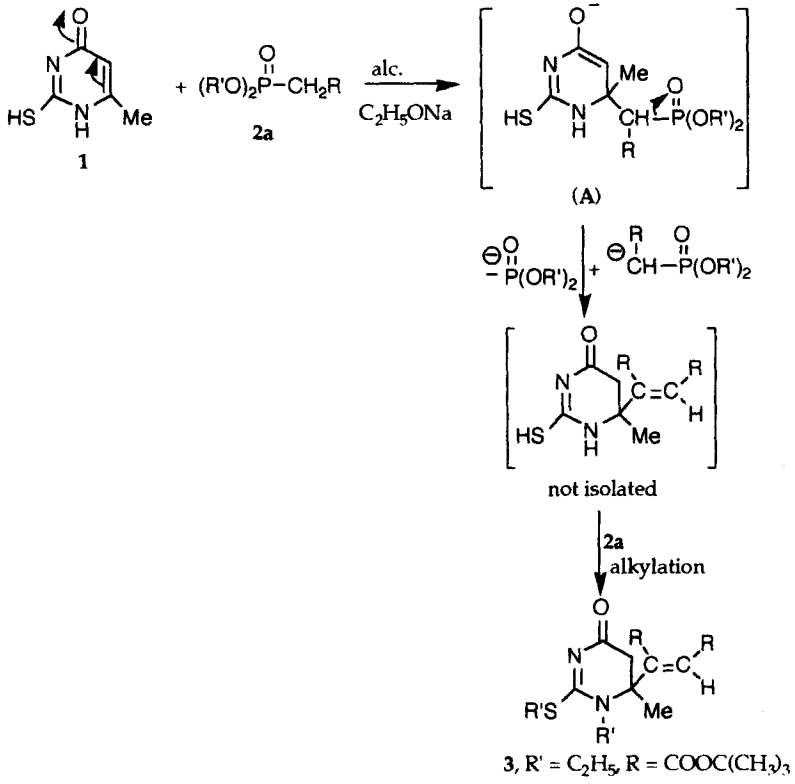


SCHEME 1

The formation of adduct **3** can be explained by the initial 1,4-addition by the carbanion center in the phosphonate anion **2a** on C_6 in the α,β-unsaturated system to give intermediate **(A)** which could then be attacked by another molecule of the phosphonate anion **2a** to give the final product **3,** possibly via successive alkylation (Scheme 2). The alkylation was also observed in the reaction of Wittig-Horner reagents with pyrroles[16], quinoneimines[8], and nitroso-naphthols[9].

Similarly, the reaction of **1** with **2b** was performed in alcoholic sodium ethoxide solution in 1:2 molar ratio to give 6-methyl, 6(1′,2′-diethoxycarbonylethylene)-2-thiouracil **4** in 70% yield (Scheme 1). The structure of compound **4** is deduced from its analysis, IR, ^{1}H-NMR and mass spectral data (cf. Experimental).

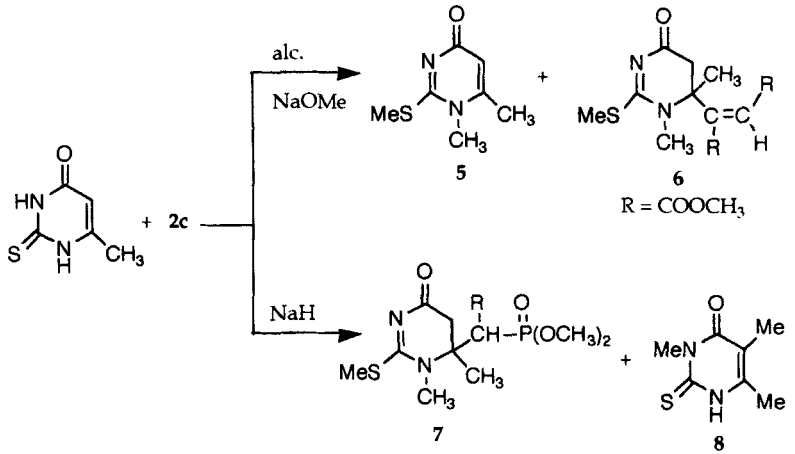
Next, the reaction of 6-methyl-2-thiouracil **(1)** with trimethylphosphonoacetate **(2c)** was performed in alcoholic sodium methoxide solution in



SCHEME 2

1:3 molar ratio to give two adducts formulated as compounds **5** and **6** (Scheme 3). Compound **5** was formulated as the known 1,6-dimethyl-2-methylthio-1H-pyrimidin-4-one[17]. The structure of the other isolated compound **6** was based on this evidence: (a) Elemental microanalysis and mass spectral data for compound **6** corresponds to an empirical formula $C_{13}H_{18}N_2O_5S$. (b) The IR (cm^{-1}) spectrum of **6** revealed the presence of strong absorption bands at 1595, 1610 cm^{-1} (C=C), 1680 (C=O, amide) and 1730, 1735 cm^{-1} (2C=O, ester). Moreover, the absorption band at 1445 cm^{-1} recorded for the C=S group in the thiouracil **1** is absent in the IR spectrum of **6.** (c) The ^{1}H-NMR spectrum of compound **6** (in $CDCl_3$) showed signals at δ = 2.1 ppm (s, 3H, C-CH_3), 2.5 (s, 3H, S-CH_3), 3.5 (s, 3H, N_1-CH_3), 3.8 (s, 3H, $COOCH_3$), 3.85 (s,

3H, $COOCH_3$), 6.1 (s, 1H, C_5-CH) and the signal at 3.95 (s, 2H) was attributed to the methylene proton (C-CH_2). In the mass spectrum of **6,** the ion peak appears at m/z 314. The formation of adduct **6** could be rationalized in terms of nucleophilic attack of the phosphonate anion **2c** on C_6 in the α,β-unsaturated system via 1:4 addition followed by alkylation to give compound **6** and dialkyl phosphite. The dialkyl phosphite was detected in the water layer by development of a violet color reaction on addition of 3,5-dinitrobenzoic acid[18]. Such an observation has been made for the reaction of N,N′-cyclohexandiene -1,2-diylidene bis (benzamide) with Wittig-Horner reagents[8]. We have found that the reaction of 6-methyl-2-thiouracil (**1**) in dry toluene with two mole equivalents of trimethylphosphonoacetate (**2c**) in the presence of sodium hydride as a base, instead of sodium methoxide, proceeds at reflux temperature for 3 hours to give two adducts formulated as compounds **7** and **8** (Scheme 3).



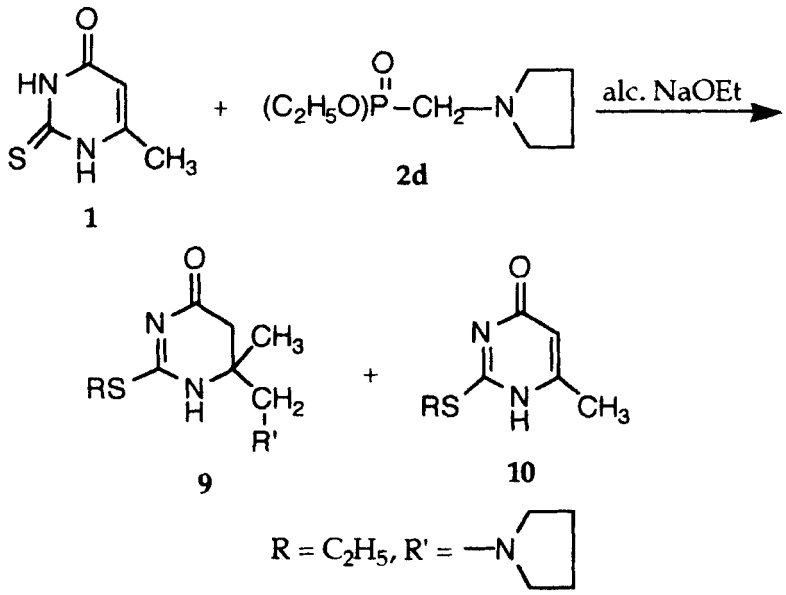
SCHEME 3

Compound **7** was obtained chromatographically in a pure form and the structure elucidation is due to : (a) Correct elemental analysis and molecular weight determination by the mass spectrum. (b) Its IR spectrum in KBr exhibits strong absorption bands at 1680 (C=O, amide), 1740 cm^{-1} (C=O, ester), 1235 cm^{-1} (P=O, bonded)[19] and at 1047 cm^{-1} (P-O-alkyl). (c) Adduct **7** possesses the phosphonate structure since it exhibits a positive shift in its ^{31}P-NMR spectrum (δ = + 20.7 ppm, vs 85% H_3PO_4) and

absorbs in the region characteristic for this class of compounds[20,21]. (d) The ^{1}H-NMR spectrum ($CDCl_3$) of compound **7** shows signals at δ = 2.01 ppm (d, 3H, C-CH_3), 2.5 (s, 3H, S-CH_3), 3.5 (s, 3H, N_1-CH_3), 3.8 (s, 3H, OCH_3). The two methoxy groups attached to the phosphorus atom appeared as a doublet centered at δ = 3.9 ppm (6H, P-OCH_3, ^{3}JHP = 10 Hz). Moreover, the ^{1}H-NMR of compound **7** showed signals at 3.3 ppm (d, 1H with ^{2}JHP= 12 Hz), 4.05 (s, 2H, cyclic CH_2). (e) ^{13}C-NMR spectrum ($CDCl_3$) of adduct **7** gave a doublet (J_{cp} = 125 Hz) at δc = 148.5 (C-P) and at 59.5 ppm (P-O-C, J_{cp} = 7.3 Hz). Moreover, the ^{13}C-NMR of compound **7** showed signals at δc = 38 (N_1-CH_3), 52.8 (OCH_3, 2d, J_{cp} = 7.3 Hz), 22 (S-CH_3) and at 11.28 (C-CH_3).

Formation of compound **7** can be explained via addition of the Wittig-Horner reagent **2c** to C_6 in the α,β-unsaturated system followed by successive alkylation to give the end product **7.** The other isolated product **8** proved to be the known[22] 1,4,5-trimethyl-2-thiouracil.

Next, the reaction of **1** with diethyl pyrrolidinomethanephosphonate **2d** was performed in alcoholic sodium ethoxide in 1:2 molar ratio to give two adducts formulated as **9** and **10** (Scheme 4).



SCHEME 4

The structure of compound **9** was based on these evidences. Elemental analysis and mass spectral data for compound **9** correspond to an empirical formula $C_{12}H_{21}N_3OS$. The IR (cm^{-1}) spectrum of **9** revealed the absence of the absorption band at 1445 cm^{-1} recorded for the C=S group in the thiouracil **1.** Moreover, the spectrum of compound **9** revealed the characteristic absorption band attributed to the stretching frequency of NH at 3500 cm^{-1}. The ^{1}H-NMR spectrum of **9** ($CDCl_3$) showed signals at 1.75 (d, 4H) and 2.55 ppm (d, 4H) corresponding to the methylene protons of the pyrrolidine ring. Also the ^{1}H-NMR of **9** revealed the presence of signals at 2.2 ppm (s, 3H, C_6-CH_3), 1.21 (t, 3H, S-$CH_2\underline{CH_3}$), 3.45 (q, 2H, S-$C\underline{H_2}$-CH_3). 2.8 (s, 2H, $C\underline{H_2}$-N), 3.95 (s, 2H, cyclic CH_2). ^{1}H-NMR of compound **9** showed signal at 11.2 for the NH proton. The other isolated compound **10** was formulated as the known 2-ethylsulfanyl-6-methyl-3H-pyrimidin-4-one[23].

The reaction of **1** with alkyl diethylphosphonoacetate **2e,f** was also investigated. When **1** was allowed to react with **2e** and/or **2f** in the presence of alcoholic sodium ethoxide solution at reflux temperature for 6 hours, the alkylated product 2-ethylsulfanyl-6-methyl-3H-pyrimidin-4-one **(10)**[23] is the sole reaction product.

Noteworthy that when 6-methyl-2-thiouracil **(1)** is allowed to react with Wittig reagents [$(C_6H_5)_3P$=CHR)] in boiling toluene, the thiouracil **1** remained practically unchanged even after 30 hours.

CONCLUSION

From the results of the present investigation, it can be concluded that whereas 6-methyl-2-thiouracil **(1)** is inactive towards Wittig reagents, it reacts with Wittig-Horner reagents to give different products depending on the nature of the phosphonate anion as well as the stability of the addition products. These findings clearly indicate that Wittig-Horner reagents preferentially attack the carbon atom in the α,β-unsaturated system rather than the thiocarbonyl in the thiouracil **(1).** Moreover, biological activity of the synthesized new products is under consideration and will be published elsewhere.

EXPERIMENTAL

All melting points are uncorrected. Wittig-Horner reagents were prepared by means of the Michaelis-Arbusov reaction[24]. Elemental analyses were

carried out at the Microanalysis Department, National Research Centre. The IR spectra were measured in KBr on a Perkin Elmer infrared Spectrometer model 157 (Grating). The 1H- and ^{13}C-NMR spectra were run on a Varian Spectrometer at 200 M Hz using TMS as an internal reference. The ^{31}P-NMR spectra were recorded on $CDCl_3$ (vs. H_3PO_4 as an external standard) with a JNM-PS-100Fa Spectrometer. The mass spectra were run at 70 ev on a Kratos MS-50 equipment provided with a data system.

Reaction of tert-butyl diethylphosphonoacetate (2a) with 6-methyl-2-thiouracil (1)

Three moles of sodium ethoxide in alcohol were added to a solution of an equimolar amount of tert-butyl phosphonoacetate **(2a),** and then one mole of the starting material **(1)** was added. The reaction mixture was heated to reflux temperature for 8 hrs. Then the mixture was allowed to cool, poured into a small amount of water, extracted with ethyl acetate (3×20 ml), and the extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residual material was recrystallized from ethyl acetate to give the new product **3** in 65% yield, m.p. 225 °C. Anal. Calcd. for $C_{21}H_{34}N_2O_5S$ (426.58); C, 59.13; H, 8.03; N, 6.57; S, 7.52%. Found: C, 58.82; H, 7.79; N, 6.15; S, 7.21%.

Reaction of ethyl diisopropylphosphonoacetate (2b) with 6-methyl-2-thiouracil (1)

The reaction of ethyl diisopropylphosphonoacetate **(2b)** (3 moles) and 6-methyl-2-thiouracil **(1)** (mole) in the presence of sodium ethoxide (3 moles) in absolute ethanol was carried out in the same manner as previously described. The reaction was finished after reflux for 6 hours, then the volatile materials were evaporated and water was added to dissolve the solid residue. Ethyl acetate (20 ml) was used three times to extract the product from the water, the extracts were dried over anhydrous sodium sulfate, evaporated under reduced pressure till dryness, and the residue recrystallized from cyclohexane to produce colourless crystals of compound **4** in 70% yield, m.p. 78 °C. Anal. Cald. for $C_{13}H_{18}N_2O_5S$ (314.36) : C, 49.67; H, 5.77; N, 8.91; S, 10.20%. Found: C, 49.82; H, 5.49; N, 8.73; S, 9.94%. IR (in KBr) cm^{-1}; 1680 (C=O, amide), 1740, 1745 (C=O, ester), 1424 (C=S), 3420 (NH). ^{1}H-NMR ($CDCl_3$, δ ppm): 12.0 (s,

NH), 2.2 (C-CH_3), 1.2 (t, 6H, 2 $COOCH_2CH_3$), 3.4 (q, 4H, $2COOCH_2CH_3$), 3.9 (s, 2H, cyclic CH_2), 5.9 (s, 1H, $C{=}CHCOOC_2H_5$). MS: m/z 314 (80%).

Reaction of trimethylphosphonoacetate (2c) with 6-methyl-2-thiouracil (1) in presence of sodium methoxide

The reaction of trimethylphosphonoacetate **(2c)** (3 moles) with 6-methyl-2-thiouracil **(1)** (1 mole) was carried out in ethanolic sodium methoxide solution (from the reaction of 3 moles of Na in 25 ml CH_3OH). The reaction mixture was refluxed and controlled by TLC till the starting material was disappeared aftr 8 hrs. Then the mixture was poured into water and extracted with chloroform to provide two compounds **5** and **6** which have been isolated by means of fractional recrystallization, i.e. compound **5** was extracted and crystallized from methanol to give the known 1,6-dimethyl-2-methylsulfanyl-1H-pyrimidin-4-one in 60% yield (mixed m.p. 224 °C, comparative IR spectra)[9] and compound **6** (70% yield) was recrystallized from ethyl acetate to give pale yellow crystals, m.p. 162–64 °C. Anal. Calcd. for $C_{13}H_{18}N_2O_5S$ (314.36); C, 49.67; H, 5.77; N, 8.91; S, 10.20%. Found: C, 49.30; H, 5.53, N, 8.62; S, 9.75%.

Reaction of 2c with 1 in presence of sodium hydride

Trimethylphosphonoacetate **(2c)** (2 moles) was dissolved in very dry toluene (25 ml) and then sodium hydride (2 mole) was added carefully with stirrig. Then, the starting thiouracil **(1)** (1 mole) was added to the mixture which was refluxed for 6 hrs. The volatile materials were evaporated under reduced pressure to give a mixture of two compounds **7** and **8** which have been isolated by column chromatography using silica gel and ethyl acetate / n-hexane as an eluent. Compound **7** was obtained in yield 45%, m.p. 85–87 °C and recrystallized from cyclohexane. Anal. Calcd. for $C_{12}H_{21}N_2O_6PS$ (352.35); C, 40.91; H, 5.85; N, 7.50; P, 8.44; S, 8.72%; Found: C, 41.23; H, 6.21; N, 7.48; P, 8.20. The second isolated compound **8** was recrystallized from ethyl acetate / pet. ether in yield 40%, m.p. and mixed m.p. (265 °C) to give the known 1,4,5-trimethyl-2-thiouracil (mixed m.p. 256)[14].

Reaction of diethyl pyrrolidinomethanephosphonate (2d) with 6-methyl-2-thiouracil (1)

The reaction of diethyl pyrrolidinomethanephosphonate (2d) (2 moles) with 6-methyl-2-thiouracil **(1)** (1 mole) was carried out in ethanolic sodium ethoxide solution (from the reaction of 2 moles of sodium metal in 25 ml absolute ethanol). The reaction mixture was refluxed for 7 hrs till the starting material was disappeared on TLC, then the solvent was evaporated and the residue was dissolved in small amount of water, extracted with chloroforom (3×20 ml), and the extracts were dried over anhydrous Na_2SO_4. The extracts were evaporated and fractional crystallization was carried out to isolate products **9** and **10,** respectively.

Compound **9** was recrystallized from ethyl acetate / pet. ether in 40% yield m.p. 60 C. Anal. Calcd. for $C_{12}H_{21}N_3OS$ (255.38) : C, 56.44; H, 8.29; N, 16.45; S, 12.55%. Found : C, 56.19; H, 8.05; N, 16.01; S, 12.32%.

Compound **10** was isolated in 45% yield and formulated as the known 2-ethylsulfanyl-6-methyl-3H-pyrimidin-4-one[23] (mixed m.p. 156 °C).

Reaction of alkyl diethylphosphonoacetate (2e,f) with 6-methyl-2-thiouracil (1)

The reaction of methyl diethyl phosphonoacetate **(2e)** and/or triethyl phosphonoacetate **(2f)** (3 moles) and 6-methyl-2-thiouracil **(1)** (1 mole) in the presence of sodium ethoxide (3 moles) in absolute ethanol, was carried out in the same manner as previously described. The reaction was finished after reflux for 6 hours, and then the reaction mixture was poured into small amount of water, extracted with ethyl acetate (3×20 ml), dried over anhydrous Na_2SO_4, evaporated under reduced pressure till dryness and the residue recrystallized from cyclohexane to produce colourless crystals of the known compound **10** (yield 75%), m.p. and mixed m.p. 156 °C[23].

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