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# Synthesis of heterocyclic compounds by reaction of dialkyl acetylenedicarboxylates with thiourea derivatives

**Abstract:** Phosphorus ylides have been prepared in excellent yields by the three-component reaction of activated electron-deficient acetylenic esters (dimethyl and diethyl acetylenedicarboxylate) and thiourea derivatives in the presence of triphenylphosphine. In some cases, these ylides were cyclized to dihydropyrimidothiazine, thioxoimidazolidine, and thioxotetrahydropyrimidine derivatives.

**Keywords:** DEAD; DMAD; thiourea derivatives; triphenylphosphine.

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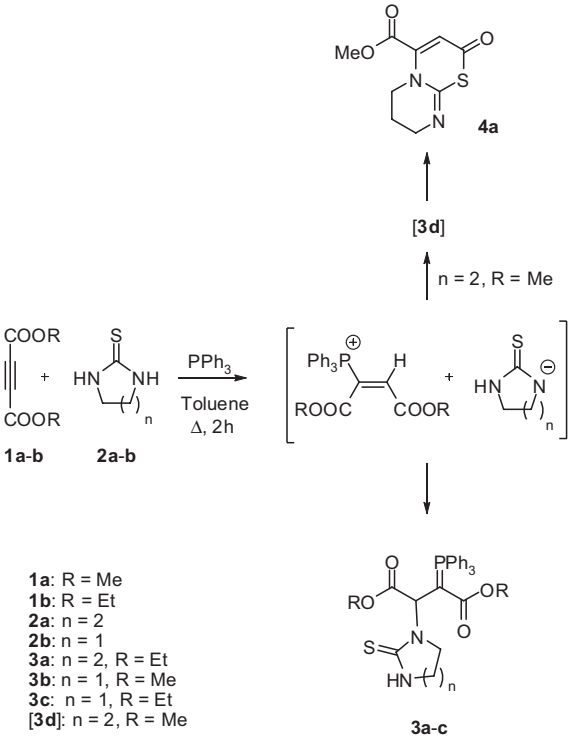
## Introduction

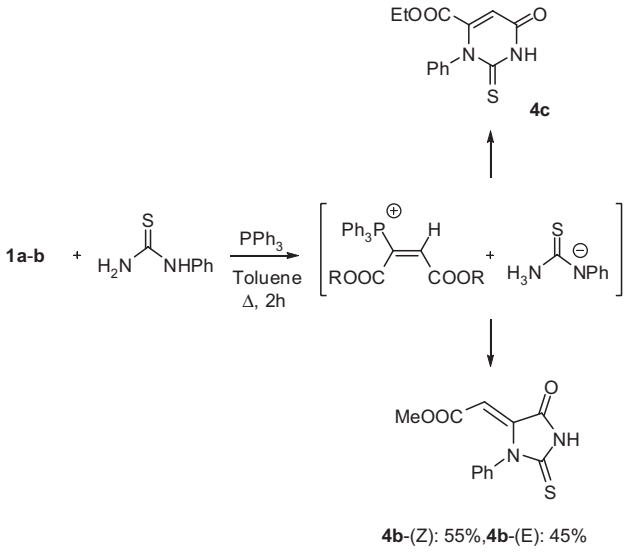
Electron-deficient acetylenic esters are versatile reagents for the preparation of stable phosphorus ylides [1, 2]. The reactions of dialkyl acetylenedicarboxylates with 2-mercaptopyrimidine and 2-mercapto-4,6-dimethylpyrimidine in the presence of triphenylphosphine leads to stable phosphorus ylides [3]. Recently, a simple synthesis of stable phosphorus ylides derived from imidazolidine-2-thione [4], one-pot synthesis of α-amino esters with β-phosphorus substituents [5], chemoselective synthesis of sulfur containing organic compounds, and three-component reaction among triphenylphosphine, dialkyl acetylenedicarboxylate, and 4-amino-5-alkyl-2,4-dihydro-1,2,4-triazole-3-thiones have been reported [6]. Several heterocyclic compounds possessing a bridgehead thiazole or thiazine moiety play a vital role in many biological activities [7]. Such heterocyclic systems have found broad application in drug development as the anti-HIV-1 and anti-herpes simplex virus HSV-1 agents [8]. An earlier report has indicated that the reaction of dimethyl acetylenedicarboxylate (DMAD) with thienopyrimidine derivatives produces thienopyrimidothiazine derivatives. Some thienopyrimidothiazines are promising antitumor agents against Hep-G2 cells with $IC_{50}$ <20 μM [9]. This study aimed to test the reactivity of dialkyl acetylenedicarboxylates towards thiourea derivatives in the presence of triphenylphosphine [10–13] (Schemes 1 and 2).

## Results and discussion

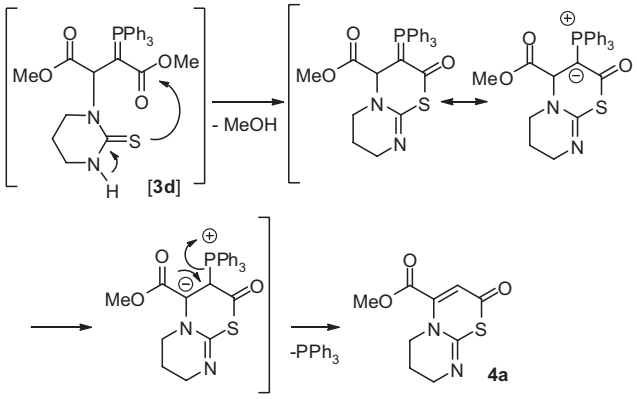
The structures of products **3a–c** and **4a–c** were deduced from their IR, $^1$H NMR, and $^{13}$C NMR spectral data. The $^1$H




**Scheme 1**



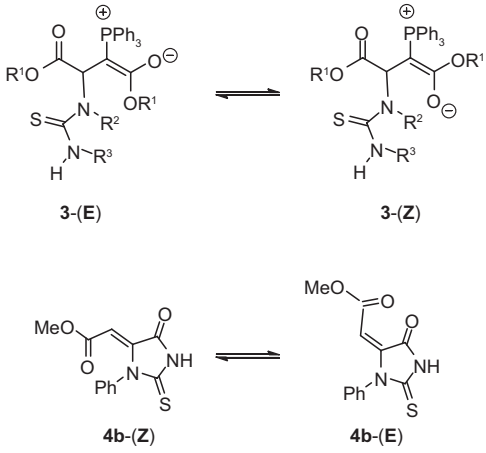

Scheme 2




Scheme 4

NMR and $^{13}$C NMR spectra of phosphorus ylides **3a–c** are consistent with a mixture of two rotational isomers. The ylide moiety of these compounds is strongly conjugated with the adjacent carbonyl group, and rotation about the partial double bond in **3-(E)** and **3-(Z)** geometrical isomers is low on the NMR timescale at ambient temperature (Scheme 3).

Stable rotamers of phosphoranes have been previously reported in the literature [14–16]. However, in cyclized products **4a–c**, only in **4b** two isomers which correlate with E and Z isomers of exo double bonds are observed. We suggest that in the intermediate product **3d** a nucleophilic attack of secondary amine is restricted and only thione attack is possible to give **4a** (Scheme 4).




Scheme 3

In other cases, nucleophilic attack of primary amine competes with thione attacks. In the case of methyl esters, the formation of a five-membered ring is favored but with ethyl esters a six-membered ring is formed by attack on the reactive carboxyl group.

The $^{1}$H NMR spectrum of **3a** is consistent with the given structure. The $^{13}$C NMR spectrum of **3a** displays 34 distinct resonances in agreement with the presence of a mixture of two rotamer structures. Although the presence of the $^{31}$P nucleus complicates both the $^{1}$H NMR and $^{13}$C NMR spectra of **3a**, it helps in the assignment of signals by long-range spin-spin couplings with $^{1}$H and $^{13}$C nuclei. The $^{1}$H NMR and $^{13}$C NMR spectra of **3b** and **3c** are similar to those of **3a**, except for the signals from the ester groups. The structural assignments made for phosphoranes **3a–c** on the basis of the $^{1}$H NMR and $^{13}$C NMR spectra are also supported by their IR spectra.

# Conclusion

The procedure described herein provides an acceptable method for preparation of highly stable phosphorus ylides. In some cases, these ylides can be cyclized to dihydropyrimidothiazine, thioxoimidazolidine, and thioxotetrahydropyrimidine derivatives.

# Experimental

## General

Melting points were measured on an Electrothermal 9100 melting point apparatus and are uncorrected. IR spectra were measured on an AVATAR 370 FT-IR Thermo Nicolet Infrared spectrophotometer. $^{1}$H

and $^{13}C$ NMR spectra were recorded on a BRUKER DRX-400 AVANCE spectrometer at 400 MHz and 100 MHz, respectively.

## General procedure for the preparation of phosphorus ylides 3a–f and compounds 4a–c

At ambient temperature, dimethyl acetylenedicarboxylate (0.24 mL, 2 mmol) was added dropwise to a stirred solution of triphenylphosphine (0.53 g, 2 mmol) and a thiourea derivative (2 mmol) in toluene (7 mL). After the addition was complete (approximately 10 min), the mixture was heated under reflux for an additional 2 h. The solvent was removed under reduced pressure and the residue was crystallized from ethyl acetate and then from ethanol.

**Diethyl 2-(2-thioxotetrahydropyrimidin-1(2*H*)-yl)-3-(triphenylphosphoranylidene) succinate (3a)** Yellowish powder; yield 96% for the mixture, 71% for major isomer **(*Z*)-3a**; mp 191–193°C; $^1H$ NMR (DMSO-$d_6$) for **(*Z*)-3a**: δ 0.33 (t, $^3J_{HH}$ = 7.2 Hz, $CH_3$), 1.33 (t, $^3J_{HH}$ = 7.2 Hz, $CH_3$), 1.81–1.90 (m, $2CH_2$), 3.01–3.10 (m, $4CH_2$), 3.45–4.13 (m, $4CH_2$), 5.79 (d, $^3J_{PH}$ = 18.8 Hz, P=C-CH), 7.53–7.66 (m, 30H, arom); $^{13}C$ NMR (DMSO-$d_6$) for **(*Z*)-3a**: δ 14.2 and 14.7 ($2CH_3$), 21.4 ($2CH_2$), 57.3, and 60.4 ($2OCH_2$), 41.9 (d, $^1J_{PC}$ = 126.4 Hz, P=C), 63.5 (d, $^2J_{PC}$ = 18.0 Hz, P=C-CH), 126.7 (d, $^1J_{PC}$ = 90.0 Hz, $C_{ipso}$), 129.4 (d, $^3J_{PC}$ = 12.0 Hz, $C_{meta}$), 132.6 (d, $^4J_{PC}$ = 2.0 Hz, $C_{para}$), 133.6 (d, $^2J_{PC}$ = 9.0 Hz, $C_{ortho}$), 169.0 (d, $^2J_{PC}$ = 13.0 Hz, 2C=O), 171.8 (d, $^3J_{PC}$ = 15.0 Hz, 2C=O), 177.4 (1C=S); yield 25% for minor isomer **(*E*)-3a**; $^1H$ NMR (DMSO-$d_6$) for **(*E*)-3a**: δ 0.98 (t, $^3J_{HH}$ = 7.2 Hz, $CH_3$), 1.28 (t, $^3J_{HH}$ = 7.1 Hz, $CH_3$), 5.83 (d, $^3J_{PH}$ = 20.4 Hz, P=C-CH) ppm; $^{13}C$ NMR (DMSO-$d_6$) for **(*E*)-3a**: δ 14.6 and 15.1 ($2CH_3$), 58.0 and 60.4 ($2OCH_2$), 41.5 (d, $^1J_{PC}$ = 128.4 Hz, P=C), 62.8 (d, $^2J_{PC}$ = 17.9 Hz, P=C-CH), 126.0 (d, $^1J_{PC}$ = 91.0 Hz, $C_{ipso}$), 177.8 (1C=S); IR: ν 3444, 1743, 1732 $cm^{-1}$. Anal. Calcd for $C_{30}H_{33}N_2O_4PS$: C, 65.68; H, 6.06; N, 5.11; S, 5.84. Found: C, 65.65; H, 6.04; N, 5.08; S, 5.81. (Data for two rotamers.)

**Dimethyl 2-(2-thioxoimidazolidin-1-yl)-3-(triphenylphosphoranylidene) succinate (3b)** White powder; yield 95% for the mixture, 58% for major isomer **(*Z*)-3b**; mp 267–271°C (dec.); $^1H$ NMR ($CDCl_3$) for **(*Z*)-3b**: δ 3.75 (s, 3H, $CH_3$), 3.78 (s, 3H, $CH_3$), 3.81–4.10 (m, 8H, $2CH_2$), 5.01 (d, $^3J_{PH}$ = 18.8 Hz, P=C-CH), 7.25–7.76 (m, 30H, arom), 7.65 (s, 1H, NH); $^{13}C$ NMR ($CDCl_3$) for: δ 39.51 and 39.86 ($2CH_3$), 43.75 and 44.03 ($2CH_2$), 49.0 (d, $^1J_{PC}$ = 125.4 Hz, P=C), 51.8 (d, $^2J_{PC}$ = 17.5 Hz, P=C-CH), 126.5 (d, $^1J_{PC}$ = 90.0 Hz, $C_{ipso}$), 129.0 (d, $^3J_{PC}$ = 11.5 Hz, $C_{meta}$), 133.4 (d, $^4J_{PC}$ = 2.0 Hz, $C_{para}$), 132.5 (d, $^2J_{PC}$ = 8.5 Hz, $C_{ortho}$), 181.3 (d, $^2J_{PC}$ = 12.5 Hz, 2C=O), 181.3 (d, $^3J_{PC}$ = 14.5 Hz, 2C=O); yield 37% for minor isomer **(*E*)-3b**; $^1H$ NMR ($CDCl_3$) for **(*E*)-3b**: δ 3.55 (s, 3H, $CH_3$), 3.76 (s, 3H, $CH_3$), 5.15 (d, $^3J_{PH}$ = 20.4 Hz, P=C-CH), 7.78 (s, 1H, NH); $^{13}C$ NMR ($CDCl_3$) for **(*E*)-3b**: δ 41.1 and 41.2 ($2CH_3$), 43.8 and 44.1 ($2CH_2$), 49.9 (d, $^1J_{PC}$ = 127.3 Hz, P=C), 51.9 (d, $^2J_{PC}$ = 17.5 Hz, P=C-CH), 125.3 (d, $^1J_{PC}$ = 92.5 Hz, $C_{ipso}$); IR: ν 3464, 1742, 1631 $cm^{-1}$. Anal. Calcd for $C_{27}H_{27}N_2O_4PS$: C, 64.02; H, 5.37; N, 5.53; S, 6.33. Found: C, 63.95; H, 5.34; N, 5.51; S, 6.35. (Data for two rotamers.)

**Diethyl 2-(2-thioxoimidazolidin-1-yl)-3-(triphenylphosphoranylidene) succinate (3c)** White powder; yield 89% for the mixture, 65% for major isomer **(*Z*)-3c**; mp 184–186°C; $^1H$ NMR (DMSO-$d_6$) for **(*Z*)-3c**: δ 0.35 (t, $^3J_{HH}$ = 7.2 Hz, $CH_3$), 1.25 (t, $^3J_{HH}$ = 7.2 Hz, $CH_3$), 2.40–2.60 (m, 8H, $4CH_2$), 3.41–4.35 (m, 8H, $4CH_2$), 4.85 (d, $^3J_{PH}$ = 18.5 Hz, P=C-CH), 7.34–7.71 (m, 30H, arom) 7.9 (s, 1H, NH); yield 35% for minor isomer **(*E*)-3c**; $^1H$ NMR (DMSO-$d_6$): δ 1.25 (t, $^3J_{HH}$ = 7.2 Hz, $CH_3$), 1.34 (t, $^3J_{HH}$ = 7.1 Hz, $CH_3$), 5.21(d, $^3J_{PH}$ =20.4 Hz, P=C-CH), 7.82 (s, 1H, NH); IR ν 3431, 1743, 1633. Anal. Calcd for $C_{29}H_{31}N_2O_4PS$: C, 65.15; H, 5.84; N, 5.24; S, 6.00. Found: C, 65.12; H, 5.81; N, 5.22; S, 5.97. (Data for two rotamers.)

**Methyl 2-oxo-2,6,7,8-tetrahydropyrimido[2,1-*b*][1,3]thiazine-4-carboxylate (4a)** Yellowish powder; yield 86%; mp 173–175°C; $^1H$ NMR ($CDCl_3$): δ 2.05 (m, 2H, $CH_2$), 3.61–3.92 (m, 4H, $CH_2$), 3.90 (s, 3H, $CH_3$), 6.90 (s, 1H, CH); $^{13}C$ NMR ($CDCl_3$): δ 19.5, 40.5, 46.8, 52.5, 115.2, 142.2, 150.3, 163.6, 166.5; IR: ν 1720, 1689. Anal. Calcd for $C_9H_{10}N_2O_3S$: C, 47.78; H, 4.45; N, 12.38; S, 14.17. Found: C, 47.80; H, 4.43; N, 12.37; S, 14.15.

**Methyl 2-(5-oxo-3-phenyl-2-thioxoimidazolidin-4-ylidene) acetate (4b)** Yellow powder; yield 84% for the mixture, 55% for major isomer **(*Z*)-4b**; mp 246–249°C $^1H$ NMR (DMSO-$d_6$) for **(*Z*)-4b**: δ 3.95 (s, 3H, $CH_3$), 6.75 (s, 1H, C=CH), 12.2 (2H, broad, NH); yield 29% for minor isomer **(*E*)-4b**; $^1H$ NMR ($CDCl_3$) for **(*E*)-4b**: δ 3.81 (s, 3H, $CH_3$), 6.65 (s, 1H, C=CH); $^{13}C$ NMR ($CDCl_3$) for **(*E*)-4b**: δ 52.0, 107.0, 128.4, 129.0, 133.0, 152.7, 164.7, 165.6, 166.4; IR: ν 3280, 1711, 1681. Anal. Calcd for $C_{12}H_{10}N_2O_3S$: C, 54.95; H, 3.84; N, 10.68; S, 12.23. Found: C, 54.94; H, 3.81; N, 10.64; S, 12.19. (Data for two isomers.)

**Ethyl 6-oxo-3-phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylate (4c)** Yellow powder; yield 85%; mp 182–185°C; $^1H$ NMR ($CDCl_3$): δ 1.31 (t, $^3J_{HH}$ = 7.2 Hz, $CH_3$), 4.25 (q, $^3J_{HH}$ = 7.5 Hz, $CH_2$), 6.9 (s, 1H, C=CH), 7.17–7.45 (m, 5H, arom), 8.57 (s, 1H, NH); $^{13}C$ NMR ($CDCl_3$): δ 14.1, 61.9, 117.6, 122.6, 125.1, 126.7, 127.8, 129.6, 130.2, 142.4, 166.1, 169.6, 181.2; IR: ν 3422–3272, 1685, 1708. Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14; S, 11.60. Found: C, 56.47; H, 4.34; N, 10.12; S, 11.57.

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# References

[1] Hassanabadi, A.; Hosseini-Tabatabaei, M. R.; Shahraki, M.; Anary-Abbasinejad, M.; Ghoroghchian, S. An efficient one-pot synthesis of 1,3,5-substituted-1H-pyrazoles derivatives. *J. Chem. Res. Syn*. **2011**, *35*, 11–14.

[2] Charati, F. R.; Moghimi, M.; Maghsoodlou, M. T.; Habibi-Khorasani, S. M.; Hossaini, Z.; Maleki, N.; Skelton, B. W.; Makha, M. Synthesis and dynamic NMR study of a functionalized sulfonamide phosphonate diester. *Phosphorus Sulfur Silicon Relat. Elem*. **2011**, *186*, 1428–1435.
[3] Saghatforoush, L.; Maghsoodlou, M. T.; Aminkhani, A.; Marandi, G.; Kabiri, R. One-pot synthesis of stable phosphonium ylides using 2-mercaptopyrimidine derivatives. *J. Sulfur Chem*. **2006**, *27*, 583–588.
[4] Mosslemin, M. H.; Anary-Abbasinejad, M.; Hassanabadi, A.; Bagheri, M. A. Three-component reaction between triphenylphosphine, dialkyl acetylenedicarboxylate and 4-amino-5-alkyl-2,4-dihydro-1,2,4-triazole-3-thiones: an efficient one-pot synthesis of stable phosphorus ylides. *J. Sulfur Chem*. **2010**, *31*,135–139.
[5] Adib, M. Simple synthesis of stable phosphorus ylides derived from imidazolidine-2-thione. *Phosphorus Sulfur Silicon Relat. Elem*. **2005**, *180*, 2701–2707.
[6] Yavari, I.; Sanaeishoar, T.; Ghazvini, M.; Iravani, N. Solvent-free synthesis of functionalized 2,3-dihydrothiazoles from isothiocyanates, primary alkylamines, and 2-chloro-1,3-dicarbonyl compounds. *J. Sulfur Chem*. **2010**, *31*, 169–176.
[7] Swarnkar, P. K.; Kriplani, P.; Gupta, G. N.; Ojha, K. G. Synthesis and antibacterial activity of some new phenothiazine derivatives. *J. Chem*. **2007**, *4*, 14–20.
[8] Hassan, N. A. Novel synthesis of S-glycosides derived from 5,6-di-substituted thieno[2,3-d]pyrimidin-4-one-2-thiones. *J. Sulfur Chem*. **2005**, *26*, 343–352.
[9] Ashraf, A. A. Thieno[2,3-d]pyrimidines in the synthesis of antitumor and antioxidant agents. *Arch. Pharm. Chem. Life Sci*. **2010**, *343*, 301–309.
[10] Anary-Abbasinejad, M.; Khaksari, Z.; Hassanabadi, A. Cheminform abstract: three-component reaction of triphenylphosphine, dialkyl acetylenedicarboxylates, and heterocyclic rings and the related iminophosphoranes. *Synth. Comm*. **2012**, *42*, 204–212.
[11] Caesar, J.; Griffiths, D. V.; Griffiths, P. A.; Tebby, T. J. Reactions of ylides formed from trialkyl phosphites with dialkyl acetylenedicarboxylates in the presence of carbon dioxide. *J. Chem. Soc. Perkin Trans. 1*, **1990**, *24,* 2329–2333.
[12] Islami, M. R.; Abedini-Torghabeh, J.; Fatemi, S. J.; Hassani, Z.; Amiry, A. An efficient and novel protocol for the synthesis of pyrazolo[5,1-*a*]isoindole derivatives. *Synlett* **2004,** *10*, 1707–1710.
[13] Mansouri, A.; Hassani, Z.; Islami, M. R. Synthesis of oxo-phosphoranylidene aminobenzoic acid derivatives by a multicomponent reaction. *Phosphorus Sulfur Silicon Relat. Elem*. **2010**, *185*, 1753–1758.
[14] Ahn, S.; Langenhahn, V.; Sperber, W.; Beck, W.; Fehlhammer, W. Reactions of "in-situ" generated Cr(CO)5CN-C(Cl)-PR3 (R = Ph, $NMe_2$) with potential dipolarophiles. New examples of [3 + 2] cycloadditions with concomitant interligand C-C bond formation. *Zeitschr. Anorg. Allgem. Chem.* **2010**, *636*, 492–498.
[15] Asghari, S.; Salimi, A.; Taghipour, V. An efficient one-pot synthesis of 2,3-dialkyl-1,1-diethyl-1-(acetylamino)-3-(1,1,1-triphenylphosphanilidene)-1,1,2,3-ropanetetracarboxylates and their temperature-dependent NMR spectra. *Phosphorus Sulfur Silicon Relat. Elem*. **2012**, *187*, 669–676.
[16] Yavari, I.; Azad, L.; Sanaeishoar, T. Triphenylphosphine-mediated chemoselective synthesis of functionalized thiazol-2(5*H*)-ones. *Monatsh. Chem*. **2011**, *142*, 177–182.