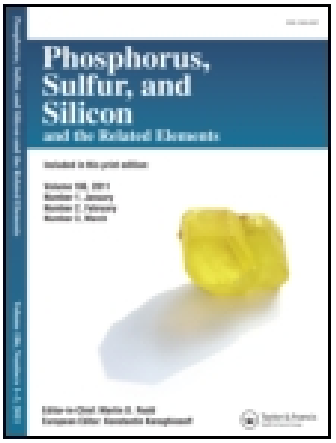

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Simple and Efficient Synthesis of 1,3-Dithioles with Pyrimidinylidene or Pyrazolylidene Substituents

Ayoob Bazgir [a] & Ali Mohammad Astaraki [a]
[a] Department of Chemistry , Islamic Azad University , Doroud Branch, Doroud, Iran
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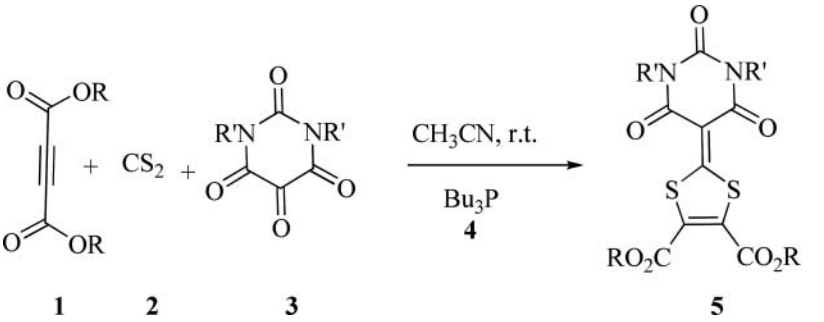
SIMPLE AND EFFICIENT SYNTHESIS OF 1,3-DITHIOLES WITH PYRIMIDINYLIDENE OR PYRAZOLYLIDENE SUBSTITUENTS

Ayoob Bazgir and Ali Mohammad Astaraki
Department of Chemistry, Islamic Azad University, Doroud Branch, Doroud, Iran

GRAPHICAL ABSTRACT



Abstract *2-Pyrimidinylidene-1,3-dithioles or 2-pyrazolylidene-1,3-dithioles are prepared by a three-component condensation reaction of pyrimidine-tetraone or 1H-pyrazole-4,5-dione, carbon disulfide, and dialkyl acetylendicarboxylates in the presence of tributylphosphine.*

Keywords 1; 3-Dithiole; acetylenic esters; 1*H*-pyrazole-3; 4-dione; pyrimidine-2; 4; 5; 6-tetraone

INTRODUCTION

Simple nitrogen heteroarenes have received much attention in the literature over the years. These compounds can be considered as potential building blocks in synthesis and are found in a wide variety of pharmacologically and biologically active compounds. The pyrimidine moiety is present in numerous natural products as well as in synthetic pharmacophores with biological activities.[1–3] Substituted pyrimidines, particularly with amino groups in the 2 and 4 positions, are known pharmacophores in several structure-based drug design approaches in medicinal chemistry.[4,5] Similarly, heterocycles containing the pyrazole ring are important targets in synthetic and medicinal chemistry because this

Received 29 November 2010; accepted 29 December 2010.
Address correspondence to Ayoob Bazgir, Department of Chemistry, Islamic Azad University, Doroud Branch, Doroud 688173551, Iran. E-mail: a_bazgir@yahoo.com

fragment is a key moiety in numerous biologically active compounds,[6–8] among them prominent drug molecules such as Celecoxib, Pyrazofurine, and many others. Recently, they have also emerged as potential atypical antipsychotics.[9]

Derivatives of sulfur heterocycles such as thiophene and 1,3-dithiole have been widely explored as new materials because of their superconducting, optical, and electronic switching properties.[10] 1,3-Dithiol-2-ylidenes have attracted much attention as building blocks for electronic materials due to their highly electron-donating properties.[11,12] Therefore, due to the importance of 1,3-dithioles, various methods have been reported for the synthesis of 1,3-dithiole derivatives.[13–19]

Therefore, as part of our program aimed at developing new methodologies for the preparation of heterocycles,[20–22] we report here an efficient synthesis of pyrimidinylidene-1,3-dithioles or pyrazolylidene-1,3-dithioles.

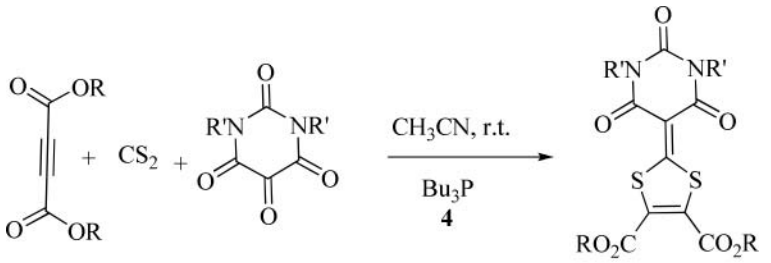
RESULTS AND DISCUSION

The one-pot, three-component condensation reaction of dialkyl acetylenedicarboxylate **1**, carbon disulfide **2**, and pyrimidine-tetraone **3** in the presence of tributylposphine **4** proceeded rapidly in acetonitrile at room temperature, and was completed after 5–8 h to afford the pyrimidinylidene-1,3-dithiole derivatives **5** in good yields (Table 1).

The good yields and purity of the products and the simplicity of the present procedure make it an interesting, convenient, and acceptable one-pot method for the preparation of functionalized pyrimidinylidene-1,3-dithioles. The compounds **5a–f** are stable solids whose structures were established by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and elemental analysis.

We have not established an exact mechanism for the formation of the pyrimidinylidene-1,3-dithioles **5**. However, a reasonable possibility is shown in Scheme 1. Reaction of the tributylphosphine adduct **6** with acetylenedicarboxylate **1** leads

Table 1 Synthesis of 2-pyrimidinylidene-1,3-dithioles **5**

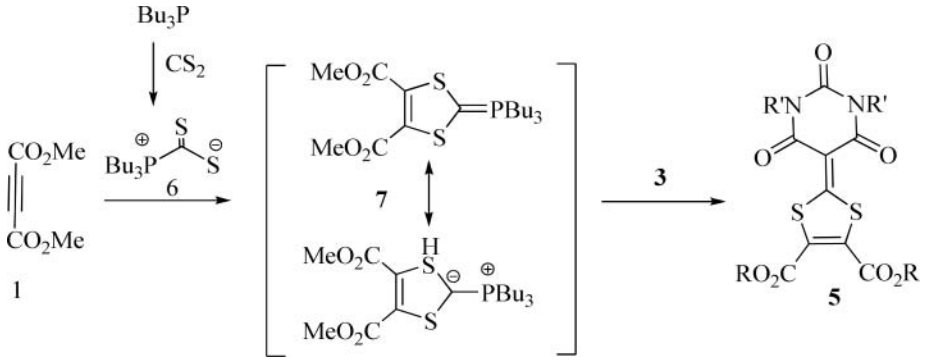


1 **2** **3** **5**

Product **5**	R	R'	Time (h)	Yield (%)[a]
a	Me	Me	5	90
b	Me	H	6	83
c	Et	Me	5	87
d	Et	H	7	79
e	^{t}Bu	Me	7	80
f	^{t}Bu	H	8	75

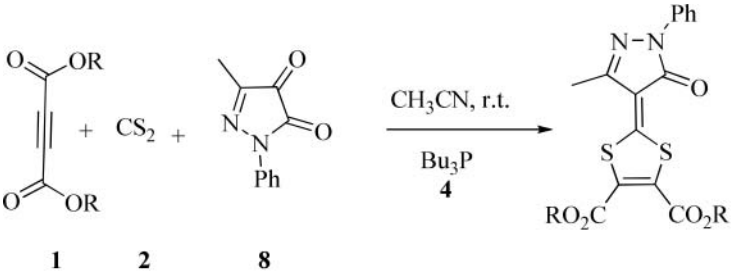
[a]Isolated yields.

to 2-tributylphosphoranylidene-1,3-dithioles **7**, which yield **5** by in situ Wittig reaction with pyrimidine-tetraone **3**.[13]



Scheme 1

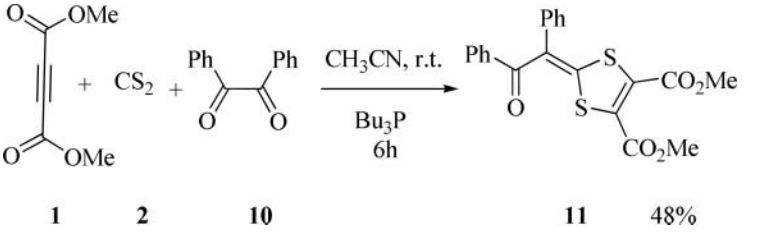
As expected, when the pyrimidine-tetraone **3** was replaced by 3-methyl-1-phenyl-1*H*-pyrazole-4,5-dione **8**, the desired pyrazolylidene-1,3-dithioles **9** were obtained with good yields under the same reaction conditions (Scheme 2).



Product **9**	R	Time (h)	Yield (%)
a	Me	5	78
b	Et	5	74
c	^{t}Bu	6	68

Scheme 2

When benzil **10** was selected as an active carbonyl compound, the desired 1,3-dithiole **11** was obtained in moderate yield (Scheme 3).



Scheme 3

In summary, we have described a mild, facile, and three-component method for the synthesis of 2-pyrimidinylidene-1,3-dithioles and 2-pyrazolylidene-1,3-dithioles using readily available starting materials. Prominent among the advantages of this new method are operational simplicity, good yields, and easy work-up procedures employed.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. IR spectra were recorded using an FTIR apparatus (KBr pellets, ν_{max}/cm^{-1}). Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. The chemicals used in this work were obtained from Fluka and Merck and were used without purification.

General Procedure for the Preparation of 1,3-Dithioles

To a magnetically stirred solution of CS_2 (1 mmol) and tributylphosphine (1 mmol) in CH_3CN (5 mL) was added pyrazole-4,5-dione or pyrimidine-2,4,5,6-tetraone (1 mmol) and dimethyl acetyenedicarboxylate (1 mmol) at room temperature. The mixture was finally stirred for an appropriate time. After completion of the reaction (TLC), the reaction mixture was filtered and the residue was washed with ether (10 mL) to afford the pure products.

Dimethyl 2-(1,3-dimethyl-2,4,6-trioxotetrahydropyrimidin-5(6*H*)-ylidene)-1,3-dithiole-4,5-dicarboxylate (5a). Cream powder (yield 90%); mp 209 °C–211 °C. IR: 1737, 1716, 1701. ^{1}H NMR: δ 3.31 (6H, s, $2CH_3$), 3.90 (6H, s, $2CH_3$). ^{13}C NMR: δ 21.5, 23.8, 28.3, 54.4, 136.4, 150.5, 159.7, 160.7, 173.2. MS: *m/z* 372 (M^+). Anal. Calcd. for $C_{13}H_{12}N_2O_7S_2$: C, 41.93; H, 3.25; N, 7.52. Found: C, 41.85; H, 3.33; N, 7.60.

Dimethyl 2-(2,4,6-trioxotetrahydropyrimidin-5(6*H*)-ylidene)-1,3-dithiole-4,5-dicarboxylate (5b). Cream powder (yield 83%); mp 232 °C–234 °C. IR: 3034, 1730, 1709, 1696. ^{1}H NMR: δ 3.88 (6H, s, $2CH_3$), 9.43 (2H, bs, 2NH). ^{13}C NMR: δ 22.4, 27.2, 56.9, 135.4, 149.6, 159.4, 161.7, 17.9. MS: *m/z* 343 (M^+). Anal. Calcd. for $C_{11}H_8N_2O_7S_2$: C, 38.37; H, 2.34; N, 8.14. Found: C, 38.44; H, 2.25; N, 8.21.

Diethyl 2-(1,3-dimethyl-2,4,6-trioxotetrahydropyrimidin-5(6*H*)-ylidene)-1,3-dithiole-4,5-dicarboxylate (5c). Cream powder (yield 87%); mp 184 °C. IR: 2975, 2928, 1733, 1633. ^{1}H NMR: δ 1.30 (6H, t, $^3J_{HH} = 7.04$ Hz, $2CH_3$), 3.20 (6H, bs, $2CH_3$), 4.48 and 4.55 (4H, AB_q, $^3J_{HH} = 6.98$ Hz, $2CH_2$). ^{13}C NMR: δ 14.1, 28.3, 63.7, 103.1, 136.4, 150.5, 159.3, 160.7, 173.1. MS: *m/z* 400 (M^+). Anal. Calcd. for $C_{15}H_{16}N_2O_7S_2$: C, 44.99; H, 4.03; N, 7.00. Found: C, 44.90; H, 4.09; N, 6.91.

Diethyl 2-(2,4,6-trioxotetrahydropyrimidin-5(6*H*)-ylidene)-1,3-dithiole-4,5-dicarboxylate (5d). Cream powder (yield 79%); mp 215 °C–217 °C. IR: 3038, 2920, 1728, 1704, 1654. ^{1}H NMR: δ 1.33 (6H, t, $^3J_{HH} = 6.87$ Hz, $2CH_3$), 4.32 and 4.34 (4H, q, $^3J_{HH} = 6.87$ Hz, $2CH_2$), 9.41 (2H, bs, 2NH). MS: *m/z* 372 (M^+). Anal. Calcd. for $C_{13}H_{12}N_2O_7S_2$: C, 41.93; H, 3.25; N, 7.52. Found: C, 41.83; H, 3.16; N, 7.44.

Due to the very low solubility of **5d–f**, we cannot report the ^{13}C NMR data for these products.

Di-*tert*-butyl 2-(1,3-dimethyl-2,4,6-trioxotetrahydropyrimidin-5(6*H*)-ylidene)-1,3-dithiole-4,5-dicarboxylate (5e). Cream powder (yield 80%); mp > 300 °C. IR: 2975, 2939, 1720, 1717, 1634. ^{1}H NMR: δ 1.54 (18H, s, $6CH_3$), 3.32 (6H, s, $2CH_3$). MS: *m/z*

456 (M^+). Anal. Calcd. for $C_{19}H_{24}N_2O_7S_2$: C, 49.99; H, 5.30; N, 6.14. Found: C, 49.83; H, 5.22; N, 6.05.

Di-*tert*-butyl 2-(2,4,6-trioxotetrahydropyrimidin-5(6*H*)-ylidene)-1,3-dithiole-4,5-dicarboxylate (5f). White powder (yield 75%); mp > 300 °C. IR: 30245, 2970, 2943, 1717, 1703, 1631. ^{1}H NMR: δ 1.43 (18H, s, $6CH_3$), 9.32 (2H, bs, 2NH). MS: *m/z* 428 (M^+). Anal. Calcd. for $C_{17}H_{20}N_2O_7S_2$: C, 47.65; H, 4.70; N, 6.54. Found: C, 47.54; H, 4.76; N, 6.62.

Dimethyl 2-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)-1,3-dithiole-4,5-dicarboxylate (9a). Cream powder (yield 78%); mp 221 °C–223 °C. IR: 3087, 1719, 1705. ^{1}H NMR: δ 2.23 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 721–7.32 (5H, m, H-Ar). ^{13}C NMR: δ 15.8, 50.3, 50.4, 117.5, 118.7, 126.7, 128.4, 139.3, 140.6, 146.2, 151.3, 165.2, 171.3. MS: *m/z* 390 (M^+). Anal. Calcd. for $C_{17}H_{14}N_2O_5S_2$: C, 52.30; H, 3.61; N, 7.17. Found: C, 52.38; H, 3.55; N, 7.08.

Diethyl 2-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)-1,3-dithiole-4,5-dicarboxylate (9b). Cream powder (yield 74%); mp 213 °C–215 °C. IR: 3081, 1715, 1711. ^{1}H NMR: δ 1.23 (6H, t, $^3J_{HH} = 7.11$ Hz, $2CH_3$), 2.26 (3H, s, CH_3), 4.11 (4H, m, $2CH_2$), 7.20–7.33 (5H, m, H-Ar). ^{13}C NMR: δ 14.3, 16.2, 57.3, 57.5, 117.7, 117.9, 125.2, 128.7, 138.6, 140.1, 145.9, 151.7, 166.0, 171.1. MS: *m/z* 418 (M^+). Anal. Calcd. for $C_{19}H_{18}N_2O_5S_2$: C, 54.53; H, 4.34; N, 6.69. Found: C, 54.41; H, 4.26; N, 6.60.

Di-*tert*-butyl 2-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)-1,3-dithiole-4,5-dicarboxylate (9c). White powder (yield 68%); mp 232 °C–234 °C. IR: 3078, 1719, 1714. ^{1}H NMR: δ 1.41 (18H, s, $6CH_3$), 2.29 (3H, s, CH_3), 7.18–7.25 (5H, m, H-Ar). ^{13}C NMR: δ 15.7, 28.3, 69.7, 116.4, 117.5, 125.9, 127.5, 138.1, 141.4, 145.3, 151.0, 166.5, 171.7. MS: *m/z* 474 (M^+). Anal. Calcd. for $C_{23}H_{26}N_2O_5S_2$: C, 58.21; H, 5.52; N, 5.90. Found: C, 58.31; H, 5.46; N, 5.99.

Di-*tert*-butyl 2-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)-1,3-dithiole-4,5-dicarboxylate (11). White powder (yield 48%); IR: 3023, 1714, 1709, 1704. ^{1}H NMR: δ 3.87 (3H, s, CH_3), 3.91 (3H, s, CH_3), 7.31–7.54 (10H, m, H-Ar). ^{13}C NMR: δ 50.3, 50.4, 120.2, 127.5, 127.8, 128.3, 132.5, 134.8, 138.7, 138.9, 139.2, 167.9, 178.5. MS: *m/z* 412 (M^+). Anal. Calcd. for $C_{21}H_{16}O_5S_2$: C, 61.15; H, 3.91. Found: C, 61.23; H, 3.84.

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