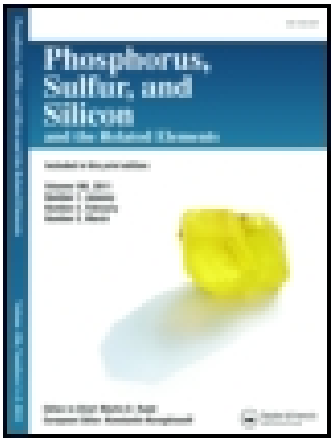

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

NEW ROUTES TO POLYFUNCTIONALLY SUBSTITUTED BENZENE. PYRIDAZINES AND THIOPHENE DERIVATIVES

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Published online: 04 Oct 2006.

Phosphorus, Sulfur, and Silicon, 1999, Vol. 155, pp. 147-155
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NEW ROUTES TO POLYFUNCTIONALLY SUBSTITUTED BENZENE, PYRIDAZINES AND THIOPHENE DERIVATIVES

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(Received July 09, 1998; In final form April 08, 1999)

Diethyl 2-phenyl-3-thiocyanopropene-1,1-dicarboxylate (**3**) as a key precursor in heterocyclic synthesis. The applicability and synthetic potency of **3** are studied to afford unique heterocyclic compounds.

Keywords: Pyridazines; thiophene; π-deficient compounds; heterocycles

One of the major characteristics of alkyl π-deficient compounds is their ability to form carbanions under mild conditions in contrast to alkyl aromatic hydrocarbons.[1,2] As part of our program directed towards developing synthetic approaches to polyfunctionally substituted condensed heterocycles of potential biological activites.[3–6] We report here a novel synthesis of a new reagent **3** in heterocyclic synthesis and its utility for the synthesis of heterocycles.

Attempts to prepare diethyl 2-phenyl-3-thiocyanatopropene-1,1-dicarboxylate (**3**) *via* direct condensation of diethyl malonate (**1**) with phenacyl thiocyanate (**2**) by using a variety of acid or base conditions failed. Compound **3** could be prepared in 80% yield *via* the condensation of diethyl malonate with acetophenone (**4**) to give the condensate product **5**. The bromination of **5** by the use of *N*-bromosuccinimide in carbon tetrachloride afforded the α-bromo compound **6** which on treatment with sodium thio-

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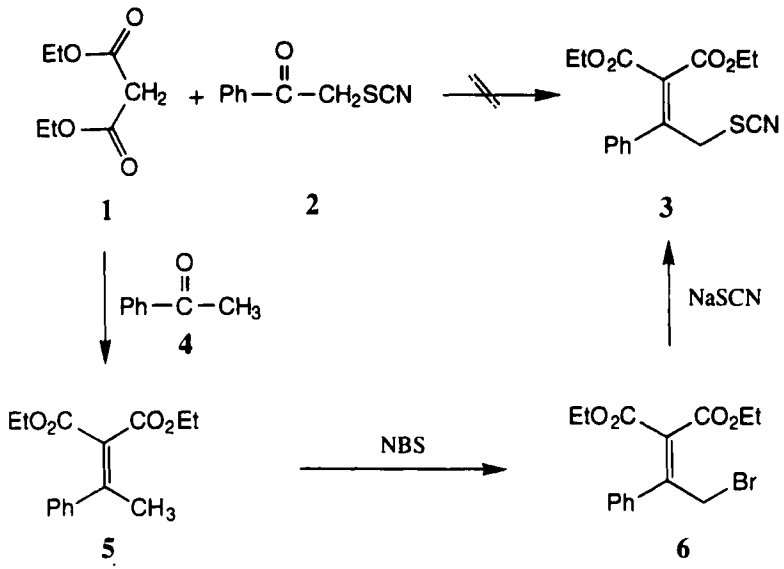
cyanate in ethanol gave the target molecule **3**. Structure of **3** was established by elemental analysis and spectroscopic methods.

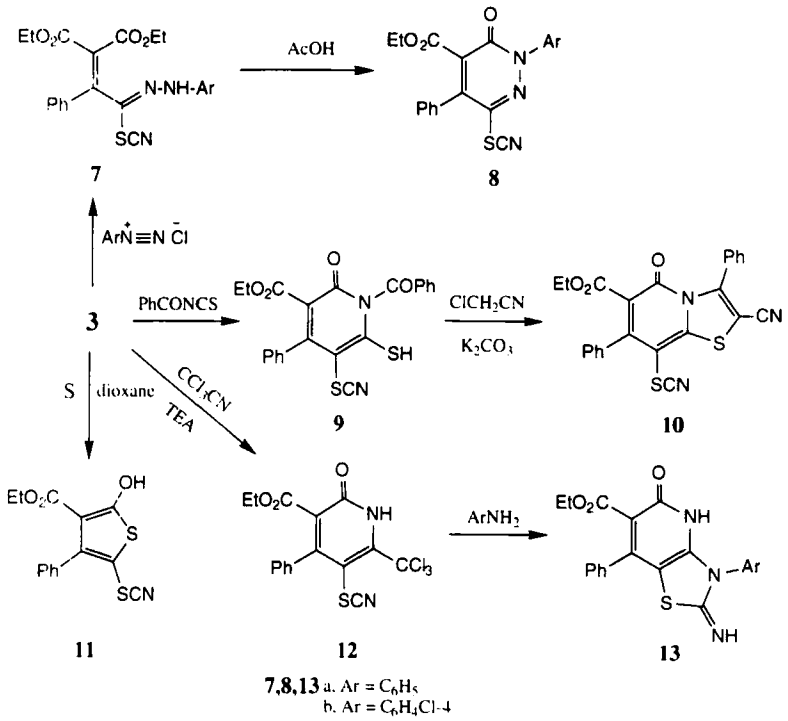
Compound **3** exhibited high reactivity towards various reagents and underwent numerous chemical transformations which led to a wide range of aromatic sulfur compounds. Compound **3** readily coupled with aryldiazonium salts in ethanol to yield a coupling product which may be formulated as hydrazone form **7** or its cyclic pyridazine form **8**. The hydrazone form **7** is preferred on the basis of its ^{1}H NMR spectrum which revealed multiplet signals for two ester groups. Furthermore on boiling the hydrazone **7** in acetic acid afforded directly the pyridazinone **8**.



SCHEME 1

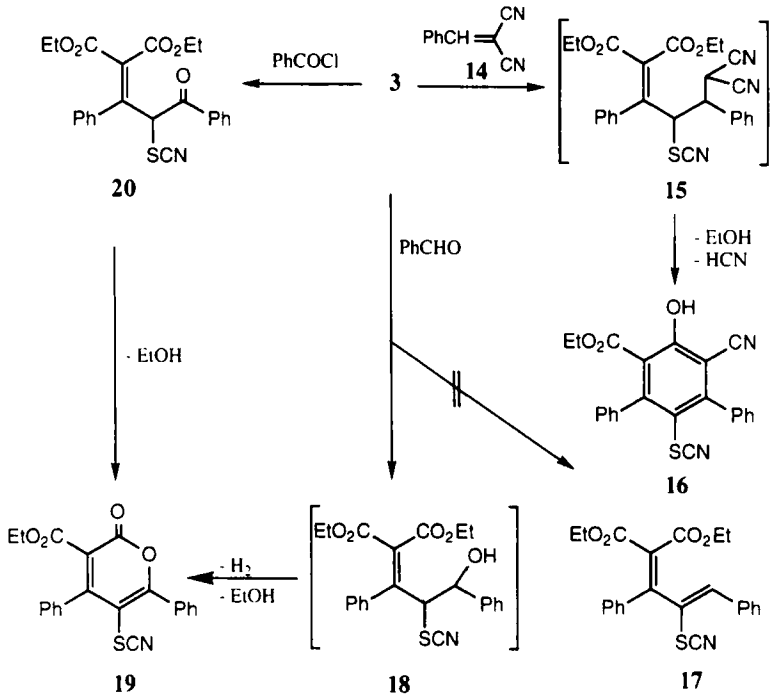
The *N*-benzoylpyridine-6-thiol (**9**) was obtained in 90% yield from the reaction of **3** with benzoyl isothiocyanate in boiling dioxane. Compound **9** reacted further with chloroacetonitrile in the presence of potassium carbonate to yield the thiazolo[3,2-*a*]pyridine derivative **10**. When compound **3** was heated with sulfur under reflux in dioxane the thiophene derivative **11** was produced. Compound **3** reacted with trichloroacetonitrile[5] in dioxane in the presence of few drops of triethylamine to produce exclusively

the pyridine derivative **12**. The trichloromethyl group in **12** shows a high reactivity towards the aromatic amines which led to the thiazolopyridine derivatives **13a,b** (Scheme 2)



SCHEME 2

Compound **3** reacted with benzylidenemalononitrile (**14**) to yield the benzene derivative **16**. Compound **16** is assumed to be formed *via* addition of **3** to the double bond in the benzylidenemalononitrile to yield a *Michael* adduct **15** which cyclizes and aromatizes by loss of hydrogen cyanide to give the final isolable benzene derivative **16**. Attempts to prepare **16** by reaction of **3** with benzaldehyde and subsequent addition of malononitrile to the so-formed benzylidene compound **17** failed. Instead the reaction of **3** with benzaldehyde afforded only the 1:1 condensate pyranone derivative **19**. The reaction apparently involves the formation of a hydroxy intermediate **18**. Treatment of **3** with benzoyl chloride in pyridine solution gives the same pyranone **19** *via* the benzoyl intermediate **20** (Scheme 3).



SCHEME 3

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were recorded with a FTIR-8201 PC spectrophotometer Shimadzu. ^{1}H NMR spectra were obtained on a Varian Germini 200 MHz spectrometer in *DMSO*-d_6 as solvent and *TMS* as an internal reference. Mass spectra were performed on a Shimadzu GCMS-Qp-1000 EX using the direct inlet system and EI + QI MSLMRUPLR. Microanalysis were performed by the Microanalytical Unit at Cairo University.

Diethyl 2-phenyl-3-bromopropene-1,1-dicarboxylate (6)

To a solution of diethyl malonate **1** (17.4 g, 0.1 mol) and acetophenone (12.0 g, 0.1 mol) in benzene (200 nl), 5 g ammonium acetate and acetic

acid (3 ml) were added. The reaction mixture was refluxed for 7 h with isotropic water separator. The solid obtained after evaporation was washed several times with water then added o 250 ml carbon tetrachloride and dried over calcium chloride. Filter then add to the filtrate *N*-bromosuccinimide (21.36 g, 0.12 mol) and dibenzoyl peroxide (50 mg). The reaction mixture was refluxed for 2 h, then evaporated under vacuum. The remaining residue was crystallized from benzene. mp 56 °C. yield 75%, yellow crystals. ν_{max}/cm^{-1} (KBr) 3000–2950 (CH_3), 1715–1695 C=O), 1630 (C=C); δ_H = 0.95–1.00 (m, 6 H, $2CH_3$), 3.95–4.23 (m, 4 H, 2 CH_2), 4.40 s, 2H, CH_2) 6.79–7.00 (m, 5 H, aromatic protons); *m/z* 341 (Found: C, 52.80; H, 5.10; Br, 23.30. $C_{15}H_{17}O_4Br$ requires C, 52.78; H, 4.98; Br, 23.46%)

Diethyl 2-phenyl-3-thiocyanatopropene-1,1-dicarboxylate (3)

To a solution of **6** (24. g, 0.1 mol) in absolute ethanol (200 ml), potassium thiocyanate (9.8 g, 0.1 mol) was added. The reaction mixture was refluxed for 3 h, then poured onto cold water. The solid product. was filtered and crystallized from ethanol. mp 78°C, yield 80%; ν_{max}/cm^{-1} (KBr) 3000–2950 (CH_2), 2214 (SCN), 1715–1695 (C=O ester); δ_H = 1.12–1.35 (m, 6 H, $2CH_3$), 4.05–4.23 (m, 4 H, 2 CH_2), 4.62 (s, 2 H, CH_2), 6.71–7.12 (m. 5 H, aromatic protons), *m/z* 319 (Found: C, 60.20; H, 5.30; N, 4.40; S, 10.00. $C_{16}H_{17}NO_4S$ requires C, 60.18; H, 5.32; N, 4.38; S, 10.03%).

Diethyl 3-arylhydrazono-2-phenyl-3-thiocyanatopropane-1,1-dicarboxylate (7a,b)

A clear diazonium salt solution was added dropwise to a solution of **3** (3.41 g, 0.01 mol) in ethanol (50 ml) containing sodium acetate (4 g) at 0–5°C. The pH of the coupling mixture was maintained at 5–6°C through the coupling process by adding sodium acetate. After the addition of the diazonium salt was complete the reaction mixture was stirred at room temperature overnight. The precipitated reddish-brown dye was filtered off, washed with water several imes. dried and crystallized from chloroform. np 152 °C, yield 85%, red crystals, ν_{max}/cm^{-1} (KBr) 2218 (SCN), 1715, 1695 (C=O); δ_H = 1–1.40 (m, 6 H, 2 CH_3), 4.00–4.23 (m, 4 H, 2 CH_2), 6.72–7.24 (m, 5 H, aromatic protons), 7.28–7.49 (m. 5 H, aromatic protons), 12.6 (s, 1H, NH); *m/z* 423 (Found: C, 62.40, H, 4.90; N, 9.90; S, 7.50. $C_{22}H_{21}N_3O_4S$ requires C, 62.41; H, 4.96; N, 9.92; S, 7.56%). **7b**: mp 198 °C. yield 90%, red crystals, ν_{max}/cm^{-1} (KBr) 2214 (SCN), 1710–1700

(C=O); δ_H = 1.00–1.36 (m, 6 H, 2 CH_3), 4.00–4.24 (m, 4 H, 2 CH_2), 6.78–7.19 (m, 5 H, aromatic protons). 7.41–7.49 (m, 5 H, aromatic protons), 12.4 (s, 1 H, NH); *m/z* 457; (Found: C, 57. 90; H, 4.50; N, 4.20; S, 7.10. $C_{22}H_{20}N_3O_4SCl$ requires C, 57.70; H, 4.37; N. 9.18; S, 6.99%).

Ethyl 1-aryl-1,6-dihydro-4-phenyl-3-thiocyanato-6-oxopyridazine-5-carboxylate (8a,b)

A solution of either (**5a** or **5b**) 2.1g or 2.3 g, 0.005 mol) in glacial acetic acid (15 ml) was refluxed for 30 min, then poured onto ice/cold water. The solid product so formed was collected by filtration and crystallized from acetic acid. **8a**: mp 210 °C, yield 87%, yellow crystals, ν_{max}/cm^{-1}(KBr) 2219 (SCN), 1710 (C=O ester), 1665 (C=O); δ_H = 1.20 (t, 3 H, CH_3); 4.20 (q, 2 H, CH_2), 6.85–7.34 (m, 10 H, aromatic protons); *m/z* 377; (Found: C, 63.60; H, 3.90; N, 1.20; S, 8.30. $C_{20}H_{15}N_3O_3S$ requires C, 63.66; H. 3.97; N, 11.14; S, 8.48%). **8b**: mp 218 °C, yield 85%, yellow crystals. ν_{max}/cm^{-1} (KBr) 2214 (SCN), 1710 (C=O ester), 1665 (C=O); *m/z* 411; (Found: C, 58.20; H. 3.40; N, 9.90; S, 7.60.$C_{20}H_{14}N_3O_3SCl$ requires C, 58.32; H, 3.40; N, 10.20; S, 7.77%).

Ethyl 1-benzoyl-1,2-dihydro-2-oxo-4-phenyl-6-thiol-5-thiocyanatopyridine-3-carboxylate (9)

To a solution of benzoyl isothiocyanate [(prepared from 1.5 ml. 0.01 mol) benzoyl chloride and (0.98 g, 0.01 mol) potassium thiocyanate in dry dioxane (30 ml)] *in situ* (3.1 g, 0.01 mol) of **3** was added and the reaction nixture was refluxed for 1 h, then evaporated under vacuum. The remaining residue was triturated with ethanol. mp 185 °C, yield 79%; yellow crystals; ν_{max}/cm^{-1} (KBr) 2215 (SCN), 1715 (C=O ester), 1675 (C=O), 1660 (C=O); δ_H =1.20 (t, 3 H, CH_3), 3.10 (s, 1 H, SH), 4.14 (q, 2 H, CH_2), 6.76–7.21 (m, 8 H, aromatic protons), 7.25–7.42 (m, 2 H, aromatic protons), m/z 436; (Found: C, 60.50; H, 3.70; N, 6.30; S, 14.50. $C_{22}H_{16}N_2O_4S_2$ requires C, 60.55; H, 3.66; N. 6.42; S. 14.67%).

Ethyl 2-cyano-4,5-dihydro-3,7-diphenyl-1-oxo-8-thiocyanatothiazolo [3,2-*a*]pyridine-6-carboxylate (10)

To a solution of **7** (2.18 g, 0.005 nol) in ethanol (50 nl), chloroacetonitrile (0.38 g, 0.005 mol) and potassium carbonate (1 g) were added. The reac-

tion mixture was refluxed for 3 h, then filtered and evaporated under vacuum. The solid product obtained was crystallized from ethanol. mp 218 °C. yield 80%, brown crystals, ν_{max}/cm^{-1} (KBr) 2222 (CN), 2215 (SCN), 1715–1695 (C=O ester), 1665 (C=O); δ_H = 1.15 (t, 3 H, CH_3), 4.05 (q, 2 H, CH_2), 6.80–7.41 (m. 10 H, arom. protons; *m/z* 457 (Found: C. 63.00; H, 3.10; N, 9.00; S, 14.00. $C_{24}H_{15}N_3O_3S_2$ requires C, 63.01; H, 3.28; N, 9.19; S, 14.00%).

Ethyl 2-hydroxyl-4-phenyl-5-thiocyanatothiophene-3-carboxylate (11)

To a solution of **3** (1.6 g, 0.005 mol) in dioxane (30 ml), elemental sulfur (0.16 g, 0.005 mol) was added. The reaction mixture was refluxed for 3 h, the solid product formed was collected by filtration and crystallized from ethanol. mp 210 °C, yield 75%, buff crystals, ν_{max}/cm^{-1} (KBr) 3400–3350 (OH), 2214 (SCN), 1710 (C=O ester); δ_H = 1.20 (t, 3 H, CH_3), 4.22 (q, 2 H, CH_2), 6.81–7.21 (m, 5 H, aromatic protons); *m/z* 305. (Found: C, 55.10; H, 3.50; N, 4.50; S, 20.90. $C_{14}H_{11}NO_3S_2$ requires C, 55.08; H, 3.60; N, 4.59; S, 20.98%).

Ethyl 1-H-2-oxo-4-phenyl-5-thiocyanato-6-trichloromethylpyridine-3-carboxylate (12)

A solution of equimolecular amount of **3** (3.2 g, 0.01 mol) and trichloroacetonitrile (1.4 g, 0.01 mol) in dioxane (30 ml) containing a few dropes of Et_3N (0.5 ml) was heated under reflux for 3 h. The reaction mixture was poured over water and neutralized with dilute HCl. The solid product formed was filtered off and crystallized from ethanol. mp 169 °C, yield 80%, yellow crystals. ν_{max}/cm^{-1} (KBr) 3300 (NH), 2414 (SCN), 1715 (C=O ester), 1675 (C=O); δ_H = 1.20 (t, 3 H, CH_3), 4.21 (q, 2 H, CH_2), 6.81–7.21 (m, 5 H, aromatic protons). 8.5 (s, 1 H, NH); *m/z* 417 (Found: C, 46.16; H, 2.60; N, 6.70; S, 7.70. $C_{16}H_{11}N_2O_3SCl_3$ requires C. 45.98; H, 2.63; N, 6.70; S, 7.66%).

Ethyl 3-aryl-2-imino-5-oxo-7-phenyl-2,3,4,5-tetrahydrothiazolo [2,3-d]pyridine-6-carbohydrate (13a,b)

General procedure

A mixture of **12** (2.08 g, 0.005 nol) and appropriate aromatic amine (0.005 mol) in ethanol (30 ml) was heated under reflux in the presence of a

few drops of Et_3N for 6 h. The reaction mixture was cooled at room emperature, poured into ice/water and neutralized with dilute HCl. The solid product formed was collected by filtration and crystallized from ethanol. **13a**: mp 180 °C, yield 75%, yellow crystals, ν_{max}/cm^{-1} (KBr) 3400, 3350 (2 NH), 1715 (C=O ester), 1670 (C=O); δ_H = 1.20 (t, 3 H, CH_3), 4.20 (q. 2 H, CH_2), 6.75–7.41 (m, 10 H, aromatic protons). 8.59 (s, 1 H, NH); (Found : C, 64.40; H, 4.30; N, 10.70; S. 8.10. $C_{21}H_{17}N_3O_3S$ requires C, 64.45; H, 4.34; N, 10.74; S, 8.18%). **13b**: mp 202 °C, yield 74%, orange crystals. ν_{max}/cm^{-1} (KBr) 3400–3370 (2NH), 1715 (C=O ester), 1670 (C=O); (Found: C, 59.20; H, 3.70; N, 9.80; S, 7.50. $C_{21}H_{16}N_3O_3SCl$ requires C, 59.22; H, 3.76; N, 9.87; S, 7.52%).

Ethyl 3-cyano-4,6-diphenyl-2H-5-thiocyanatobenzoate (16)

A solution of compound **3** (1.6 g, 0.005 mol) and benzylidenemalononitrile (0.77 g, 0.005 mol) in ethanol (50 ml) was triturated with Et_3N (0.5 ml) and carried out under reflux for 3 h. The reaction mixture was then evaporated under vacuum and the remaining residue was triturated with ethanol. The solid product formed was filtered off and crystallized from dioxane, mp 175 °C, yield 72%, yellow crystals, ν_{max}/cm^{-1} (KBr) 3400–3350 (OH), 2222 (CN), 2214 (SCN), 1712 (C=O ester); δ_H = 1.20 (t, 3 H, CH_3), 4.24 (q, 2 H, CH_2), 3.50 (s, 1H, OH), 6.71–7.48 (m, 10 H, aromatic protons); (Found: C, 68.98; H, 4.03; N, 7.00; S, 8.01 $C_{23}H_{16}N_2O_3S$ requires C, 69.00; H, 4.00; N, 7.00; S, 8.00%).

Ethyl 4,6-diphenyl-2-oxo-5-thiocyanatopyrane-3-carboxylate (19)

Method A

A solution of **3** (3.2 g, 0.01 mol) and benzaldehyde (1.10 g, 0.01 mol) in ethanol (50 ml) was treated with Et_3N (0.5 ml). The reaction mixture was heated under reflux for 6 h, then cooled, poured over ice/water and neutralized with HCl. The solid product formed was collected by filtration and crystallized from ethanol. mp 198 °C, yield 70%, yellow crystals. ν_{max}/cm^{-1} (KBr) 2214 (SCN). 1710 (C=O ester), 1665 (C=O); δ_H =1.20 (t, 3 H, CH_3), 4.20 (q, 2 H, CH_2), 6.75–7.21 (m, 10 H, aromatic protons); *m/z* 377; (Found: C, 66.80; H, 4.00; N, 3.60; S, 8.50. $C_{21}H_{15}NO_4S$ requires C, 66.84; H, 3.97; N, 3.71; S, 8.48%).

Method B

A mixture of **3** (3.2 g, 0.01 mol) and benzoyl chloride (1.5 g, 0.01 mol) in pyridine (20 ml) was refluxed for 2h, then cooled, poured into ice/H_2O and neutralized with dilute HCl. The solid product formed was collected by filtration and crystallized from ethanol, yield 62%; identical (mp, mixed mp, IR) with authentic sample prepared according to method A.

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