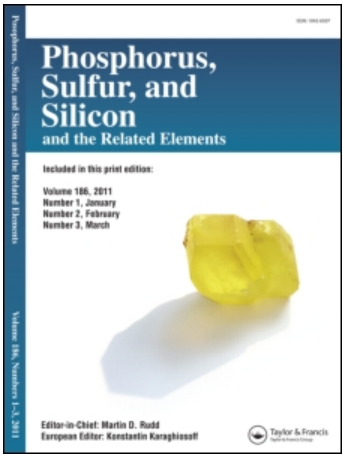

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS AND REACTIONS OF SOME 1,3-(2-THIENYL)-1,3 OXOPROPANE NITRILE DERIVATIVES

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To cite this Article El-shafei, A. K. , Sultan, A. A. , Soliman, A. M. and Metzger, J.(1992) 'SYNTHESIS AND REACTIONS OF SOME 1,3-(2-THIENYL)-1,3 OXOPROPANE NITRILE DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 72: 1, 121 — 125
To link to this Article: DOI: 10.1080/10426509208031545
URL: http://dx.doi.org/10.1080/10426509208031545

Phosphorus, Sulfur, and Silicon, 1992, Vol. 72, pp. 121–125
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SYNTHESIS AND REACTIONS OF SOME 1,3-(2-THIENYL)-1,3 OXOPROPANE NITRILE DERIVATIVES

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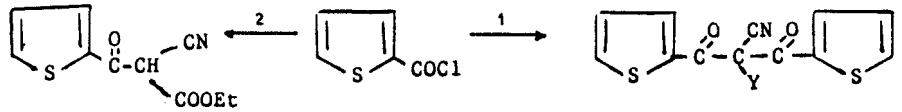
(Received April 29, 1992; in final form July 16, 1992)

The reactions of a variety of bidentate nucleophiles with mono- or dithienoyl compounds derived from active nitriles were studied. The structure of the obtained new compounds was assigned.

Key words: Oxoalkanenitriles; mono-thienoyl; dithienoyl.

1,3-Oxoalkanenitriles are proved to be important intermediates for the synthesis of otherwise difficulty accessible, synthetically useful, and/or novel heterocyclic systems.[1] The present work is planned to study the synthesis and reactions of some 1,3-(2-thienyl)-1,3 oxoalkane nitriles using different substrates with different reagents and under different reactions conditions.

The reaction of 2-thienoyl chloride with either malononitrile or ethyl cyanoacetate in refluxing benzene in the presence of triethylamine gave dithienoyl malononitrile **1** and dithienoyl ethyl cyanoacetate **2**. Attempts to obtain the α-cyano- or the α-ethoxycarbonyl-2-thienoyl acetonitriles following this procedure were unsuccessful. However, we were able only to obtain the ethyl 2-thienoylmalonitrile **3** by reacting an equivalent amounts of ethyl sodiocyanoacetate[2] and 2-thienoyl chloride in benzene at room temperature, ch. Scheme 1.



3

1, Y= CN

2, Y= COOEt

SCHEME 1 1: $CNCH_2Y$/TEA/benzene; 2: NaCH(CN)CODEt/benzene.

The reaction of Compound **1** with mercaptoacetic acid, hydrazine hydrate or hydroxylamine hydrochloride in refluxing ethanol in the presence of a basic catalyst was performed where 2-[1′-(2-thienoyl)-1′-cyano]methylene-4-thiazolidinone **4**, 5-

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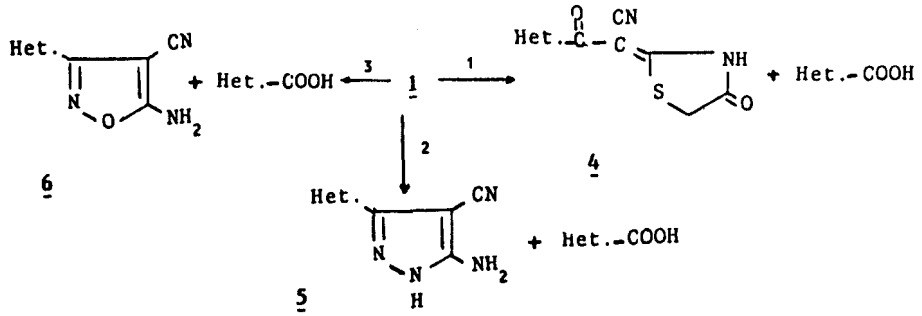
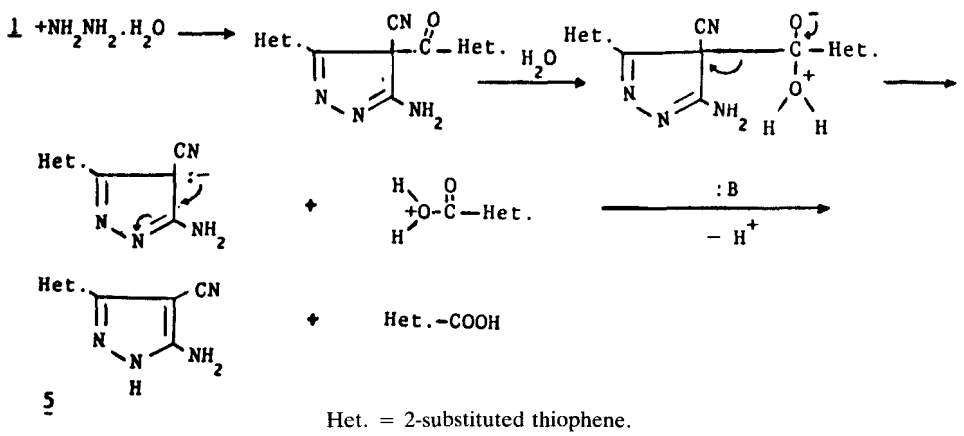
amino-4-cyano-3-(2-thienyl)pyrazole **5** or 5-amino-4-cyano-3-(2-thienyl)isoxazole **6** were obtained, respectively, cf. Scheme 2.



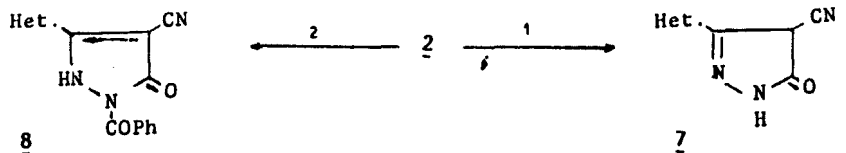
SCHEME 2 1:$HSCH_2COOH$/EtOH/Pip.; 2: $NH_2NH_2.H_2O$/EtOH/Pip., 3: NH_2OH/EtOH/TEA, Het. = 2-substituted thiophene.

Since we were able to identify the corresponding thiophene-2-carboxylic acid as a byproduct; the key step of the reaction mechanism was assumed to involve a preliminary nucleophilic attack at either the cyano group[3] to give compounds **4** or at the carbonyl function to give compounds **5**[4] or **6**,[5–9] respectively. The following steps involve a cleavage of the (—C—CO—) bond with thiophene-2-carboxylic acid elimination in the case of compound **5**;



Het. = 2-substituted thiophene.

The reaction of compound **2** with hydrazine hydrate or benzoyl hydrazide was carried out in refluxing ethanol in the presence of a catalytic amount of piperidine, where 4-cyano-3-(2-thienyl)-(4H)-pyrazol-5-one **7** and 1-benzoyl-4-cyano-3-(2-thienyl)pyrazol-5-one **8**, respectively were obtained by a mechanism similar to that described above, cf. Scheme 3.

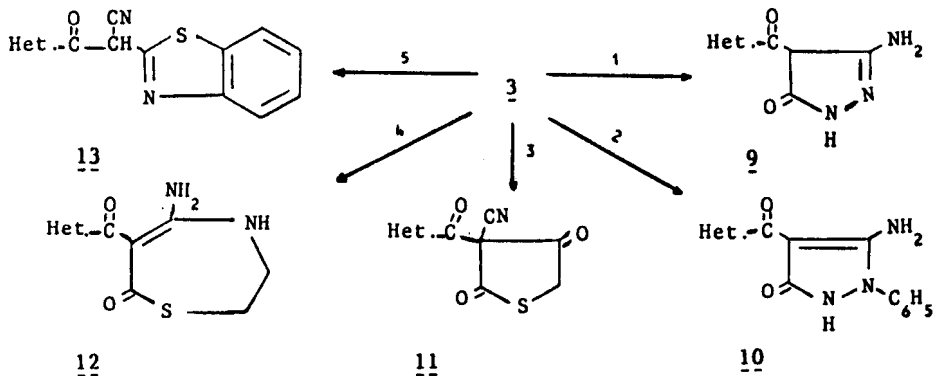


SCHEME 3 1: $NH_2NH_2.H_2O$/EtOH/Pip.; 2: $PhCONHNH_2$/EtOH/Pip.; Het. = 2-substituted thiophene.

The presence of compound **3** in a keto-enol form affects to a great deal its reactivity towards hydrazines. Nucleophilic attacks were found to take place mainly at both the carbonyl ester and the cyano function rather than the other carbonyl group.

The reaction of hydrazine hydrate and phenylhydrazine with compound **3** in refluxing ethanol was performed in presence of piperidine catalyst where 3-amino-4-(2-thienoyl)-(4H)-pyrazol-5-one **9** and 3-amino-2-phenyl-4-(2-thienoyl)pyrazol-5-one **10**, respectively, were obtained. The stirring of an equimolar mixture of mercaptoacetic acid and compound **3** in ethanol containing a catalytic amount of piperidine at room temperature gave 3-(2-thienoyl)-3-cyano-(2H,4H)-thiophene-2,4-dione **11**, via a nucleophilic attack at the carbonyl ester group and dehydration. cf. Scheme 4.

Novel heterocyclic ring structures were obtained according to the same reaction pathways of formation of monosubstituted nitriles; thus when compound **3** is allowed to react with cystamine or 2-aminobenzenthiol in refluxing pyridine in the presence of a few drops of piperidine it afford Δ^5-5-amino-6-(2-thienoyl)-1,4-thiazepin-7-one **12** and 2-[1′-(2-thienoyl)-1′-cyano]-methylbenzthiazole **13**, respectively. cf. Scheme 4.



SCHEME 4 1: $NH_2NH_2.H_2O$/EtOH/Pip.; 2: $PhNHNH_2$/EtOH/Pip.; 3: $HSCH_2COOH$/EtOH/Pip.; 4: $HSCH_2CH_2COOH$/Pyridine/Pip.; 5: 2-aminobenzenthiol/pyridine/Pip.; Het. = 2-substituted thiophene.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Kofler plate. The infrared spectra were measured on a Pye Unicam Sp 1200 spectrometer and ^{1}H-NMR spectra were measured on a Varian EM 360L spectrometer at 60 M Hz using TMS as internal standard. Microanalyses, IR and ^{1}H-NMR spectra were performed at the Central Laboratory, Faculty of Science and Technology, University of Aix-Marseille III, France. cf. Table I.

Dithienoyl malononitrile **1** *and ethyl dithienoylcyanoacetate* **2**: To a mixture of either malononitrile or ethyl cyanoacetate (0.05 mol) and triethylamine (0.1 mol) in 50 ml of benzene, 0.1 mol of 2-thienoyl chloride was gradually added with stirring at room temperature. The reaction mixture was then heated at reflux for 2 h. The cooled mixture was filtered off, washed with water and ethanol and recrystallized.

Ethyl 2-thienoylmalonitrile **3**: To a stirred solution of 0.1 mol of ethyl sodiocyanoacetate in benzene, 0.1 mol of thienoyl chloride was added dropwise at room temperature. The reaction mixture was stirred for an additional one hour and was then heated on a water bath at 80°C for 2 hours. The cooled reaction mixture was concentrated, filtered off, washed with water, dilute ethanol and recrystallized.

2-[1′-(2-Thienoyl)-1′-cyano]methylene-4-thiazolidinone **4**; *5-amino-4-cyano-3-(2-thienyl)pyrazole* **5** *and 5-amino-4-cyano-3-(2-thienyl)isoxazole* **6**: An equimolar mixture (0.02 mol) of compound **1**, along

TABLE I

Analytical and spectral data of the reported new compounds

No.	Yield %	m.p °c	Molecular formula[a]	IR $\upsilon(cm^{-1})$	^{1}H-NMR(DMSO-d_6)[b] δ(ppm)
1	33	150-1 (THF/EtOH)	$C_{13}H_6N_2O_2S_2$ (287.4)	3120,2210, 1730	8.30-8.10(m,2H,α,α')8.05-7.85 (m,2H,γ,γ'),7.50-7.20(m,2H,β, β'),$CDCl_3$.
2	41	92-5 (THF/EtOH)	$C_{15}H_{11}NO_4S_2$ (334.7)	3100,2980, 2210,1725	8.35-8.00(m,2H,α,α'),7.95-7.95-7.76(m,2H,γ,γ'),7.50-7.05(m,2H,β,β'),4.45-4.10(q, 2H,CH_2),1.60-1.10(t,3H,CH_3), $CDCl_3$.
3[c]	84	78-9 (EtOH)	$C_{10}H_9NO_3S$ (223.2)	3080,2997, 2220,1650	14.55(s,1H,OH),8.55-8.35(d, 1H,α),7.90-7.78(d,1H,γ),7.42-7.25(t,1H,β),4.65-4.28(q,2H, CH_2),1.60-1.32(t,3H,CH_3).
4[d]	72	245-8 (EtOH)	$C_{10}H_6N_2O_2S_2$ (250.2)	3450,3340, 2215,1700	8.10-7.75(m,2H,α,γ),7.60-7.30(m,2H,β+tautomeric OH and NH),3.90(s,2H,CH_2).
5	65	220-2 (EtOH)	$C_8H_6N_4S$ (190.2)	3420,3320 3200,2200	11.60(br,1H,NH),7.40-7.10(m, 2H,α,γ),6.90-6.75(t,1H,β), 6.00(br,2H,NH_2).
6	62	225-6 (EtOH)	$C_8H_5N_3O_5$ (191.2)	3320,3220 2200,1600	8.65(br,2H,NH_2),7.90-7.70(m, 2H,α,γ),7.40-7.15(t,1H,β).
7	71	245-7 (EtOH)	$C_8H_5N_3OS$ (191.9)	3630,3490 2240,1630, 1610	7.95(m,4H,α,γ+OH,NH),7.45-7.10(t,1H,β).
8	63	255-6 (EtOH)	$C_{15}H_9N_3O_2S$ (296.6)	3200,2200, 1705,1620	10.50(br,1H,NH),8.28-7.78(m, 3H,thienyl),7.70-7.42(m,5H, arom.).
9	62	145-6 (EtOH)	$C_8H_7N_3O_2S$ (209.2)	3335,3260, 3180,1650, 1560	9.80-9.25(br,1H,NH),7.80-7.68 (d,1H,α),7.58-7.40(d,1H,γ), 7.22-6.92(t,1H,β),4.40-3.90 (br,2H,NH_2).
10	77	190-1 ($CHCl_3$)	$C_{14}H_{11}N_3O_2S$ (286.5)	3310,3280, 3100,1630	10.45(br,1H,NH),8.10-7.85(m, 2H,α,γ),7.45-7.00(m,5H,arom.) 6.95-6.85(t,1H,β).
11	43	205-8 (pyridine)	$C_{10}H_9N_3O_2S$ (220.1)	3080,2230, 1715,1665	8.00-7.65(m,2H,α,γ),7.45-7.15 (m,1H,β),3.65(s,2H,CH_2).
12	32	204-5 (EtOH)	$C_{10}H_{12}N_2O_2S_2$ (257.2)	3320 broad, 3060,1720, 1680	8.80-8.45(br,1H,NH),7.88-7.72 (d,2H,α,γ),7.30-7.10(t,1H,β), 6.80-6.40(br,2H,NH_2).
13	60	255-8 (EtOH)	$C_{14}H_8N_2OS_2$ (285.6)	3120-3070, 2160,1600	8.25-7.22(m,8H,thienyl+ arom.),3.15(s,1H,CHCN).

[a]Satisfactory microanalyses obtained: C, ±0.4%; H, ±0.2%; N, ±0.4%; S, ±0.3%

[b]Unless otherwise stated.

[c]Present in keto-enol forms.

[d]Present in different tautomeric forms.

with mercaptoacetic acid, hydrazine hydrate or hydroxylamine hydrochloride in 50 ml ethanol was heated at reflux temperature for 2 hours. These reactions were catalyzed with a few drops of piperidine or with an equimolar amount of triethylamine in case of reactions with hydroxylamine hydrochloride. After cooling, the precipitated solid was filtered off, washed with hot water and dilute ethanol and was recrystallized. The filtrate was evaporated *in vacuo* and the residual mass was crystallized from hot water to give the corresponding thiophene-2-carboxylic acid.

4-Cyano-3-(2-thienyl)-(4H)-pyrazol-5-one **7** *and 1-benzoyl-4-cyano-3-(2-thienyl)pyrazol-5-one* **8**: An equimolar mixture (0.02 mol) of compound **2** with hydrazine hydrate or benzoylhydrazide in 50 ml ethanol was heated under reflux for 2 hours. The reaction with benzoylhydrazide was catalyzed with few drops of piperidine. The cooled reaction mixture was filtered off and the obtained solid was recrystallized.

3-Amino-4-(2-thienoyl)-(4H)-pyrazol-5-one **9** *and 3-amino-2-phenyl-4-(2-thienoyl)pyrazol-5-one* **10**: An equimolar mixture (0.02 mol) of compound **3** along with hydrazine hydrate and phenylhydrazine in 50 ml ethanol containing few drops of piperidine was heated under reflux for 2 hours. The cooled reaction mixture was filtered off and the obtained product was recrystallized.

3-(2-Thienoyl)-3-cyano-(2H,4H)-thiophene-2,4-dione **11**: An equimolar mixture (0.02 mol) of compound **3** and mercaptoacetic acid in 50 ml ethanol containing few drops of piperidine was dissolved by stirring at room temperature for ½ hour. The reaction mixture was left overnight at room temperature and the precipitated solid was filtered off and recrystallized.

Δ^5-5-Amino-6-(2-thienoyl)-1,4-thiazepin-7-one **12** *and 2-[1'-(2-thienoyl)-1'-cyano]-methylbenzothiazole* **13**: An equimolar mixture (0.02 mol) of compound **3** along with cystamine or 2-aminobenzenthiol in 50 ml pyridine was heated at reflux temperature for 3 hours. The reaction mixture was concentrated, left to cool, filtered off, washed with dilute ethanol and recrystallized.

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