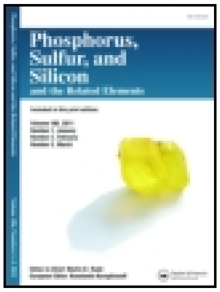

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

# Synthesis of Some New Spirothiopyran Derivatives from the Reaction of 4-Thiopyrylidenemalononitriles with Bidentate and Active Methylene Reagents

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To cite this article: Abdel Moneim El-Ghanam (2003): Synthesis of Some New Spirothiopyran Derivatives from the Reaction of 4-Thiopyrylidenemalononitriles with Bidentate and Active Methylene Reagents, Phosphorus, Sulfur, and Silicon and the Related Elements, 178:4, 863-868

To link to this article: http://dx.doi.org/10.1080/10426500307794

*Phosphorus, Sulfur and Silicon*, 2003, Vol. 178:863–868
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1042-6507/03 $12.00 + .00
DOI: 10.1080/10426500390198020

# SYNTHESIS OF SOME NEW SPIROTHIOPYRAN DERIVATIVES FROM THE REACTION OF 4-THIOPYRYLIDENEMALONONITRILES WITH BIDENTATE AND ACTIVE METHYLENE REAGENTS

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(Received June 26, 2002; accepted September 21, 2002)

*2,6-Diphenyl and 2-phenyl-6-p-tolyl-4-thiopyrylidenemalomonitriles have been synthesized as α,β-unsaturated nitriles from the condensation of 2,6-diphenyl and 2-phenyl-6-p-tolyl-4H-thiopyran-4-thiones with malononitrile. Treatment of 4-thiopyrylidenemalononitriles with hydrazine hydrate, hydroxylamine hydrochloride, thiourea, thiosemicarbazide, or guanidine hydrochloride afforded the corresponding spirothiopyran derivatives of pyrazole, isoxazole, 1,3-thiazine or pyrimidine, respectively, while treatment with acetylacetone gave the corresponding spirothiopyran derivatives of pyran.*

*Keywords:* 4-Thiopyrylidenemalononitriles; IR spectra; mass spectra; NMR spectra; spirothiopyran

The importance of thiopyran derivatives because of their importance as intermediates in the synthesis of pyrylium dyes[1] as well as their biological activities[2] promoted the present investigation.

α,β-Unsaturated nitriles have attracted much attention as potential starting materials for the synthesis of many heterocyclic compounds.[3–6] In this investigation, 4-thiopyrylidenemalononitriles are synthesized as α,β-unsaturated nitrile to study their reactivity toward some bidendate and active methylene reagents.

The author thanks Kink Fahd University of Petroleum and Minerals (Saudi Arabia) Chemistry Department for helping completing this work while working as a Research Associate in the department.

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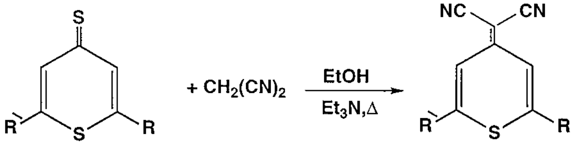
## RESULTS AND DISCUSSION

2,6-Diphenyl and 2-phenyl-6-p-tolyl-4-thiopyrylidenemalononitriles **2a**,**b** are synthesized from the reaction of 2,6-diphenyl and 2-phenyl-6-p-tolyl-4H-thiopyran-4-thiones **1a**,**b**, and prepared according to the literature method,[7] with malononitrile in refluxing ethanol in the presence of triethylamine as a catalyst (Eq. 1).



(1)

1 2

a, $R=R'=C_6H_5$

b, $R=C_6H_5$, $R'=p\text{-}CH_3C_6H_4$

The structure of 4-thiopyrylidenemalononitriles **2a**,**b** are confirmed from their spectral and analytical data (Tables I and II). The IR spectra showed a moderately C≡N absorption in the range 2192–2196 $cm^{-1}$, while their $^1$H-NMR spectra showed beside other characteristics, a singlet at 6.76–6.82 $\delta$ for H-3 and H-4 protons of thiopyran ring.

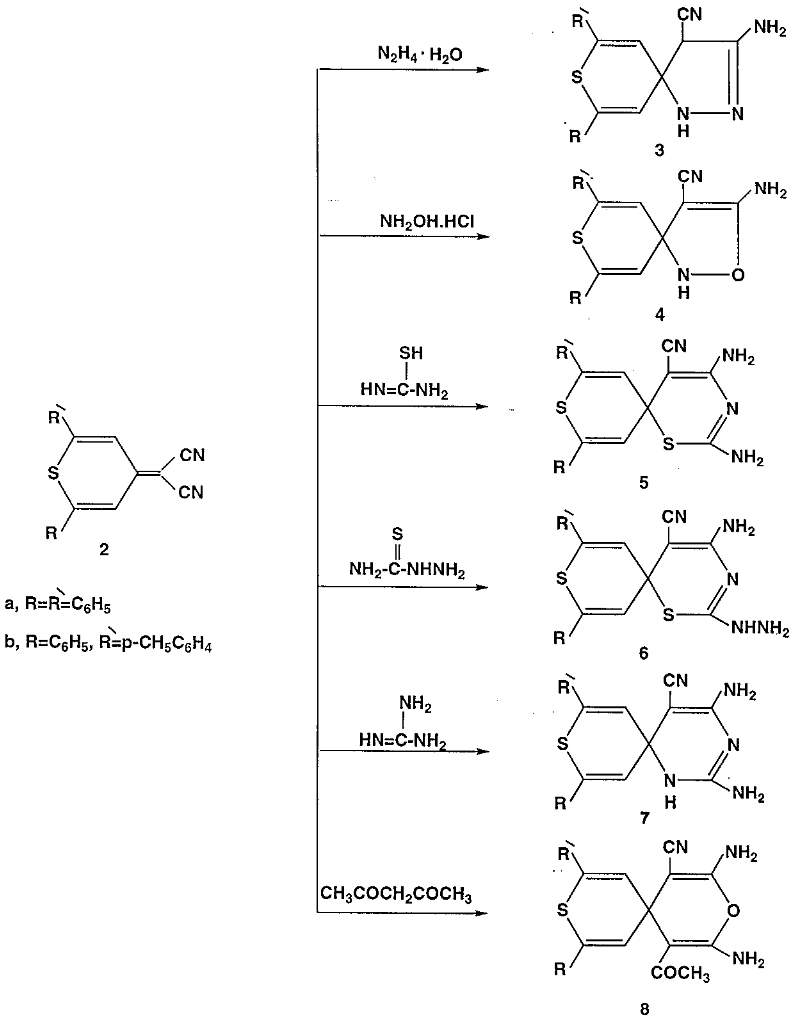
Treatment of **2a**,**b** with hydrazine hydrate, hydroxylamine hydrochloride, thiourea, thiosemicarbazide, or guanidine hydrochloride in ethanol in the presence of pipredine afforded the corresponding spirothiopyran derivatives of pyrazole, isoxazole, 1,3-thiazine or primidine **3a**,**b–7a**,**b** (Scheme 1). The reaction involve the addition of the amino or mercapto groups at the ethylenic double bond and then nucleophilic attack of the amino or imino group to give the cyclized spiro compounds.

Also, the reaction of 4-thiopyrylidenemalononitriles **2a**,**b** with active methylene compounds, acetylacetone, in ethanol in the presence of pipredine gave the corresponding spirothiopyran derivatives **8a**,**b** (Scheme 1).

A carbanion formation is assumed in these reactions followed by nucleophilic addition at the ethylenic bond and cyclization to give the spiro compounds **8a**,**b**. All spirothiopyran derivatives **3a**,**b–8a**,**b** were confirmed from their spectral and analytical data (Tables I and II).

## EXPERIMENTAL

Elemental analysis were preformed on a Perkin-Elmer 240 microanalyzer. Melting points were recorded on a Kofler Block and are uncorrected.



SCHEME 1

Infrared spectra were measured with a Unicam SP 1025 spectrophotometer for KBr pellets. The $^1$H NMR spectra were recorded on a Varian EM-390 MHz spectrometer using TMS as internal standard. Mass spectra were recorded at 70 eV with an AEI MS-9 spectrometer coupled to a DS-50 Data System using a direct insertion probe for introduction of samples.

**TABLE I** Spectral Data of the Prepared Compounds **2a**,**b**–**8a**,**b**

| Compd. | IR (KBr) $\nu$ (cm$^{-1}$) | $^1$H-NMR $\delta$ (ppm) $CDCl_3$ |
|---|---|---|
| **2a** | 3086 (CH, arom), 2192 (C≡N), 1582 (C=C). | 7.62 (m, 10H, arom), 6.76 (s, 2H, H-3 and H-5 in thiopyran) |
| **2b** | 3072 (CH, arom), 2196 (C≡N), 1579 (C=C), 2920 (CH, aliph) | 7.60 (m, 9H, arom), 6.82 (s, 2H, H-3 and H-5 in thiopyran), 2.38 (s, 3H, $CH_3$) |
| **3a** | 3392, 3326, 3214 ($NH_2$ + NH), 3094 (CH, arom), 2198 (C≡N), 1632 (C≡N), 1608 (C=C) | 10.82 (br, 1H, NH), 7.62 (m, 10H, arom), 7.22, 6.88 (s, 2H, H-3 and H-5 in thiopyran), 5.58 (br, 2H, $NH_2$) |
| **3b** | 3386, 3332, 3220 ($NH_2$ + NH), 3086 (CH, arom); 2920 (CH, aliph) 2196 (C≡N), 1628 (C=N), 1596 (C=C) | 10.90 (br, 1H, NH), 7.58 (m, 9H, arom), 7.18, 6.90 (s, 2H, H-3 and H-5 in thiopyran), 5.62 (br, 2H, $NH_2$), 2.40 (s, 3H, $CH_3$) |
| **4a** | 3398, 3322, 3232 ($NH_2$ + NH), 3093 (CH, arom), 2196 (C≡N), 1608 (C=C) | 11.22 (br, 1H, NH), 7.58 (m, 10H, arom), 7.20, 6.86 (s, 2H, H-3 and H-5 in thiopyran), 5.86 (br, 2H, $NH_2$) |
| **4b** | 3389, 3329, 3226 ($NH_2$ + NH), 3112 (CH, arom), 2920 (CH, aliph), 2206 (C≡N), 1602 (C=C) | 11.16 (br, 1H, NH), 7.62 (m, 9H, arom), 7.12, 6.82 (s, 2H, H-3 and H-5 in thiopyran), 5.86 (br, 2H, $NH_2$), 2.42 (s, 3H, $CH_3$) |
| **5a** | 3390, 3336 ($NH_2$), 3102 (CH, arom), 2202 (C≡N), 1630 (C=N), 1608 (C=C) | 7.56 (m, 10H, arom), 5.48–5.82 (br, 4H, $2NH_2$), 7.22, 6.88 (s, 2H, H-3 and H-5 in thiopyran) |
| **5b** | 3394, 3328 ($NH_2$), 3092 (CH, arom), 2932 (CH, aliph), 2196 (C≡N), 1632 (C=N), 1606 (C=C) | 7.58 (m, 9H arom), 7.26, 6.80 (s, 2H, H-3 and H-5 in thiopyran), 5.18–5.56 (br, 4H, $2NH_2$), 2.42 (s, 3H, $CH_3$) |
| **6a** | 3388, 3336, 3240 ($NH_2$ + NH), 3096 (CH, arom), 2204 (C≡N), 1636 (C=N), 1600 (C=C) | 10.82 (br, 1H, NH), 7.62 (m, 10H, arom), 7.26, 6.92 (s, 2H, H-3 and H-5 in thiopyran), 4.68–5.32 (br, 4H, $2NH_2$) |
| **6b** | 3404, 3332, 3236 ($NH_2$ + NH), 3092 (CH, arom), 2198 (C≡N), 2936 (CH, aliph), 1642 (C=N), 1606 (C=C) | 10.94 (br, 1H, NH), 7.56 (m, 9H, arom), 7.18, 6.92 (s, 2H, H-3 and H-5 in thiopyran), 4.56–5.38 (br, 4H, $2NH_2$), 2.38 (s, 3H, $CH_3$) |
| **7a** | 3406, 3336, 3240 ($NH_2$ + NH), 3102 (CH, arom), 2192 (C≡N), 1642 (C=N), 1596 (C=C) | 11.16 (br, 1H, $NH_2$), 7.60 (m, 10H, arom), 7.26, 6.98 (s, 2H, H-3 and H-5 in thiopyran), 5.16–5.58 (br, 4H, $2NH_2$) |
| **7b** | 3396, 3342, 3230 ($NH_2$ + NH), 3112 (CH, arom), 2940 (CH, aliph), 2190 (C≡N), 1638 (C=N), 1602 (C=C) | 11.10 (br, 1H, NH), 7.64 (m, 9H, arom), 7.64, 6.84 (s, 2H, H-3 and H-5 in thiopyran), 5.28–5.60 (br, 4H, $2NH_2$), 2.42 (s, 3H, $CH_3$) |
| **8a** | 3406, 3350 ($NH_2$), 3110 (CH, arom), 2966, 2942 (CH, aliph), 2192 (C≡N), 1668 (C=O), 1608 (C=C) | 7.58 (m, 10H, arom), 7.22, 6.94 (s, 2H, H-3 and H-5 in thiopyran), 5.24 (br, 2H, $NH_2$), 2.32 (s, 3H, $CH_3$), 2.20 (s, 3H, $COCH_3$) |
| **8b** | 3396, 3342 ($NH_2$), 3108 (CH, arom), 2962, 2938 (CH, aliph), 2188 (C≡N), 1672 (C=O), 1592 (C=C) | 7.52 (m, 9H, arom), 7.16, 6.82 (s, 2H, H-3 and H-5 in thiopyran), 5.30 (br, 2H, $NH_2$), 2.30 (s, 3H, $CH_3$), 2.22 (s, 3H, $COCH_3$) |

**TABLE II** Analytical Data of Compounds **2a**,**b**–**8a**,**b**

| Compd. | m.p. (°C) (cryst. solv.) | Yield (%) | Mol. form. | Analysis % calcd. (found) | | | |
|---|---|---|---|---|---|---|---|
| | | | | C | H | N | S |
| **2a** | 128 (ethanol) | 78 | $C_{20}H_{12}N_2S$ | 76.92 | 3.84 | 8.96 | 10.26 |
| | | | | (76.76 | 3.94 | 9.12 | 10.24) |
| **2b** | 146 (ethanol) | 81 | $C_{21}H_{14}N_2S$ | 77.30 | 4.29 | 8.59 | 9.82 |
| | | | | (77.42 | 4.18 | 8.71 | 9.88) |
| **3a** | 162 (ethanol) | 62 | $C_{20}H_{16}N_4S$ | 69.77 | 4.64 | 16.28 | 9.30 |
| | | | | (69.82 | 4.56 | 16.36 | 9.21) |
| **3b** | 150 (ethanol) | 66 | $C_{21}H_{18}N_4S$ | 70.39 | 5.03 | 15.64 | 8.94 |
| | | | | (70.52 | 5.22 | 15.60 | 8.76) |
| **4a** | 126 (ethanol) | 73 | $C_{20}H_{15}N_3OS$ | 69.57 | 4.35 | 12.17 | 9.28 |
| | | | | (69.64 | 4.18 | 12.08 | 9.36) |
| **4b** | 166 (ethanol) | 60 | $C_{21}H_{17}N_3OS$ | 70.19 | 4.74 | 11.70 | 8.91 |
| | | | | (70.06 | 4.72 | 11.62 | 8.76) |
| **5a** | 186 (ethanol) | 71 | $C_{21}H_{16}N_4S_2$ | 64.95 | 4.12 | 14.43 | 16.49 |
| | | | | (65.12 | 4.28 | 14.30 | 16.38) |
| **5b** | 172 (ethanol) | 66 | $C_{23}H_{20}N_4S_2$ | 65.67 | 4.48 | 13.93 | 15.92 |
| | | | | (65.48 | 4.56 | 14.06 | 15.76) |
| **6a** | 188 (benzene) | 81 | $C_{21}H_{17}N_5S_2$ | 62.53 | 4.22 | 17.37 | 15.88 |
| | | | | (62.42 | 3.98 | 17.52 | 15.82) |
| **6b** | 192 (benzene) | 73 | $C_{22}H_{19}N_5S_2$ | 63.31 | 4.56 | 16.79 | 15.35 |
| | | | | (63.48 | 4.38 | 16.88 | 15.32) |
| **7a** | 182 (ethanol) | 71 | $C_{21}H_{17}N_5S$ | 67.92 | 4.58 | 18.87 | 8.63 |
| | | | | (67.76 | 4.66 | 18.72 | 8.48) |
| **7b** | 196 (ethanol) | 66 | $C_{22}H_{19}N_5S$ | 68.57 | 4.94 | 18.18 | 8.31 |
| | | | | (68.62 | 4.78 | 18.30 | 8.29) |
| **8a** | 216 (benzene) | 62 | $C_{25}H_{20}N_2O_2S$ | 72.82 | 4.85 | 6.80 | 7.77 |
| | | | | (72.68 | 4.96 | 6.72 | 7.76) |
| **8b** | 194 (benzene) | 70 | $C_{26}H_{22}N_2O_2S$ | 73.24 | 5.16 | 6.57 | 7.51 |
| | | | | (73.36 | 5.22 | 6.70 | 7.38) |

## Synthesis of 4-Thiopyrylidenemalononitriles 2a,b

0.023 mmol of 2,6-diphenyl and 2-phenyl-6-p-tolyl-4H-thiopyran-4-thiones **1a**,**b** prepared according to the literature method[7] was added to an equimoler amount of malononitrile in 50 ml ethanol and few drops of triethylamine. The reaction mixture was refluxed for 6 h, concentrated and cooled to give **2a**,**b**, which was collected by filtration and crystallized from ethanol. MS: m/z (relative abundance) **2a** $M^+$ 312 (12), 286 (18), 280 (22), 260 (19), 236 (52), 210 (24), 183 (100), 178 (22), 77 (36).

## Synthesis of Spiro Compounds 3a,b–6a,b

### *General Procedure*

A solution of 4-thiopyrylidenemalononitriles **2a**,**b** (0.02 mmol in 40 ml ethanol) was treated with equimolar amount of hydrazine hydrate or hydroxylamine hydrochloride or thiourea or thiosemecarbazide or guanidine hydrochloride and few drops of pipridene. The reaction mixture was refluxed for 4 h, concentrated, cooled, and the separated compound was filtered off and recrystallized from the suitable solvent. MS: m/z (relative abundance) **3b** $M^+$ 358 (22), 343 (16), 332 (22), 326 (32), 315 (46), 234 (18), 202 (26), 148 (100), 135 (26), 117 (28), 103 (32), 91 (18), 77 (36); **4a** $M^+$ 345 (12), 319 (18), 313 (12), 302 (36) 268 (22), 236 (34), 134 (100), 77 (36); **5a** $M^+$ 388 (8), 362 (12), 356 (22), 346 (28), 330 (32), 253 (16), 236 (100), 134 (36), 77 (42); **6b** $M^+$ 417 (26), 402 (18). 386 (22), 360 (36), 250 (30), 148 (100), 91 (48), 77 (18).

## Synthesis of Compounds 8a,b

0.02 mmol of 4-thiopyrylidenemalononitriles **2a**,**b** was added to a stirred mixture of equimolar amount of acetylacetone in 40 ml ethanol and few drops of pipredine. The reaction mixture was refluxed for 4 h, concentrated, cooled, and the separated solid was filtered off and recrystallized from suitable solvent. MS: m/z (relative abundance) **8a** $M^+$ 412 (14), 380 (24), 369 (18), 343 (42), 335 (20), 327 (28), 236 (100), 134 (38), 77 (28).

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