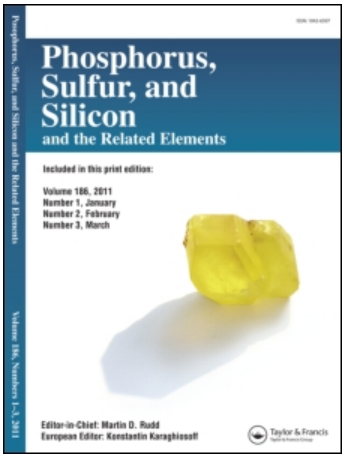

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Fused Heterocyclic Systems Derived from 2,6-Diaryl-3,5-dibenzylidenetetrahydro-4*H*-thiopyran-4-ones

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To cite this Article El-Ghanam, Abdel Moneim(2006) 'Fused Heterocyclic Systems Derived from 2,6-Diaryl-3,5-dibenzylidenetetrahydro-4*H*-thiopyran-4-ones', Phosphorus, Sulfur, and Silicon and the Related Elements, 181: 6, 1419 — 1425
To link to this Article: DOI: 10.1080/10426500500328905
URL: http://dx.doi.org/10.1080/10426500500328905

Phosphorus, Sulfur, and Silicon, 181:1419–1425, 2006

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500500328905

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Fused Heterocyclic Systems Derived from 2,6-Diaryl-3,5-dibenzylidenetetrahydro-4*H*-thiopyran-4-ones

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*The reaction of 2,6-diphenyl and 2,6-di-p-tolyltetrahydro-4H-thiopyran-4-ones with benzaldehyde afforded 2,6-diphenyl and 2,6-di-p-tolyl-3,5-dibenzy-lidenetetrahydro-4H-thiopyran-4-ones, which, on treatment with hydroxylamine hydrochloride, hydrazine hydrate and thiourea, gave thiopyrano[4,3-c]isoxazole, thiopyrano[4,3-c]pyrazole and thiopyrano[4,3-d]pyrimidine derivatives, respectively. Also, the reaction of dibenzylidenetetrahydrothiopyran-4-ones with malononitrile in piperidine and malononitrile in ammonim acetate afforded thiopyrano[4,3-b]pyran and thiopyrano[4,3-b]pyridine derivatives, respectively, while treatment with ethyl acetoacetate gave acetyl thiopyrano[4,3-b]pyran derivatives. On the other hand, treatment of 2,6-diphenyl and 2,6-di-*p-*tolyltetrahydro-4H-thiopyran-4-ones with elemental sulfur and malononitrile in the presence of diethylamine gave thieno[2,3-c]thiopyran derivatives. Structures of all compounds were confirmed from their spectral and analytical data.*

Keywords Dibenzylidenetetrahydrothiopyrones; thiopyrano[4,3-b]pyridine; thiopyrano[4,3-c]isoxazole; thiopyrano[4,3-c]pyrazole; thieno[2,3-c]thiopyran derivatives; thiopyrano[4,3-d]pyrimidine

A wide spectrum of biological activities as well as industrial importance associated with thiopyrans and their condensed derivatives. Several thetrahydro-4H-thiopyran-4-ones are known to possess significant antibacterial, parasitic, sedative, and anti-inflammatory activities.[1] Also, superior bleaching compounds for textile and porcelain contained tetrahydrothiopyran-4-one-S,S-dioxides.[2] They are also important intermediates in the synthesis of pyrylium dyes.[3,4] Moreover, tetrahydrothiopyrones are precursors of the difficulty available 4H-thiopyran-4-ones[5] which are used in the preparation of organic conductors.[6] On the basis of the previously discussed facts, new fused thiopyran derivatives

Received June 6, 2005; accepted July 28, 2005.
I would like to thank Dr. M. A. Morsy and King Fahd University of Petroleum and Minerals, Saudi Arabia, for helping measuring spectral properties of some of the compounds.

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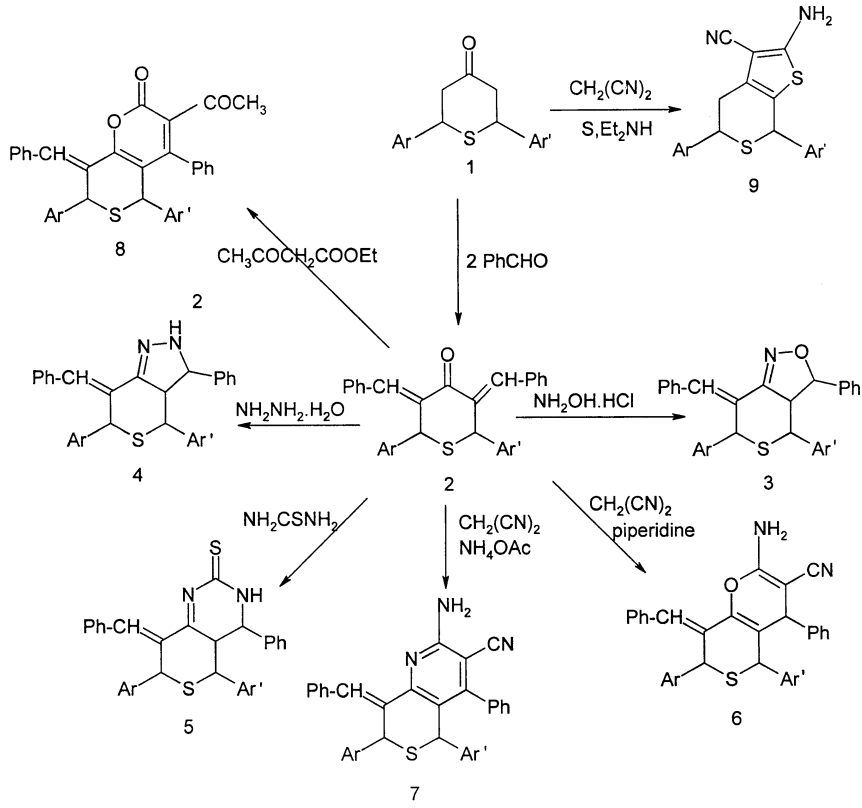
have been synthesized from 2,6-diphenyl (**2a**) and 2,6-di-*p*-tolyl (**2b**) 3,5-dibenzylidenetetrahydro-4H-thiopyran-4-ones (Scheme 1).



SCHEME 1

RESULTS AND DISCUSSION

The reaction of one molar amount of 2,6-diphenyl (**1a**) and 2,6-di-*p*-tolyl (**1b**)-tetrahydro-4H-thiopyran-4-ones, prepared according to the literature method,[7] with two molar amount of benzaldehyde in the presence of piperidine under reflux conditions afforded the corresponding 2,6-diphenyl (**2a**) and 2,6-di-*p*-tolyl (**2b**)-3,5-dibenzylidenetetrahydro-4H-thiopyran-4-ones in moderate yields, respectively (Scheme 1). The

structures of **2a**,**b** were established from their spectral and analytical data (see Experimental section). The IR spectra showed a moderately carbonyl absorption in the range of 1692–1686 cm^{-1}, while their ^{1}H-NMR spectra showed, beside other characteristics, a singlet at δ 4.28–4.22 for benzylic protons on C-2 and C-6 and a singlet at δ 7.24–7.16 for the ylidene protons on C-3 and C-5 of a thiopyran ring. On the other hand, the reaction of 3,5-dibenzylidenetetrahydro-4H-thiopyran-4-ones **2a**,**b** with bidentate reagents, hydroxylamine hydrochloride, hydrazine hydrate, and thiourea gave the fused rings thiopyrano[4,3-c]isoxazole **3a**,**b**, thiopyrano[4,3-c]pyrazole **4a**,**b**, and thiopyrano[4,3-d]pyrimidine **5a**,**b** derivatives, respectively (Scheme 1). The IR spectra of the fused heterocyclic systems **3a**,**b**–**5a**,**b** showed bands at 1640–1628 cm^{-1} for C=N and a disappearance of carbonyl absorptions. The ^{1}H-NMR spectra showed a singlet at δ 4.28–4.18 for one of the benzylic protons of a thiopyran ring, a doublet at δ 4.46–4.32 for other benzylic protons, a doublet of a doublet at δ 3.46–3.24, and a doublet at δ 4.70–4.52 (see Experimental section).

This investigation was extended to include the reactivity of **2a**,**b** with some active methylene compounds as nucleophiles. Thus, when **2a**,**b** were refluxed with malononitrile in the presence of ethanol/piperidine,[8] it gave 2-amino-5,7-diaryl-8-benzylidene-3-cyano-4-phenylthiopyrano[4,3-b]pyran **6a**,**b** in good yields (Scheme 1). The IR spectra showed a moderate absorption at 2190–2182 cm^{-1} for C≡N and a NH_2 absorption at 3368–3354 cm^{-1} and 3262–3256 cm^{-1}. The ^{1}H-NMR spectra showed, beside other characteristics, a singlet at δ 4.38–4.26 for thiopyran ring protons and a singlet at δ 4.82–4.76 for a pyran proton (see Experimental section). On the other hand, the reaction of **2a**,**b** with malononitrile in the presence of an ethanol/ammonium acetate[8] mixture under a reflux condition afforded 2-amino-5,7-diaryl-8-benzylidene-3-cyano-4-phenylthiopyrano[4,3-b]pyridine **7a**,**b** (Scheme 1). The structures of **7a**,**b** were confirmed from their spectral and analytical data (see Experimental section).

Finally, the reaction of **2a**,**b** with ethyl acetoacetate[9] in ethanol in the presence of triethylamine gave 3-acetyl-5,7-diaryl-8-benzylidene-2-oxo-4-phenylthiopyrano[4,3-b]pyran **8a**,**b** in moderate yields (Scheme 1). The ^{1}H-NMR spectra exhibited the presence of a $COCH_3$ singlet at δ 2.38–2.36 and the absence of OC_2H_5 fragment. Also, the reaction of 2,6-diphenyl **1a** and 2,6-di-*p*-tolyl **1b**-tetrahydro-4H-thiopyran-4-ones with malononitrile in the presence of sulfur and diethyl amine gave 2-amino-3-cyano-5,7-diarylthieno[2,3-c]thiopyran **9a**,**b**. The elemental analyses and spectral data were in agreement with structures **9a**,**b**.

Generally, six-member heterocyclic rings are known to be mostly in the chair conformation.[10] Sulfur heterocyclic also demonstrate the chair conformation for a heterocyclic ring from their conformational studies.[11] Assuming the chair conformation for the thiopyran ring, the two aryl groups (Ar, Ar') in compounds **3**, **4**, **5**, **6**, **7**, **8**, and **9** expected to occupy the less-hindered equatorial positions.[7]

EXPERIMENTAL

Melting points are uncorrected and were measured on a Kofler Block Infrared spectra were recorded with a Unicam SP 1025 spectrophotometer for KBr pellets. The ^{1}H-NMR spectra were recorded on Jeol Lambada-500 MHz spectrometer using TMS as an internal standard. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

Synthesis of 2,6-Diaryl-3,5-dibenzylidenetetrahydro-4H-thiopyran-4-ones 2a,b

A mixture of 2,6-diaryltetrahydro-4H-thiopyran-4-ones **1a**,**b** (1 mmol) and benzaldehyde (2 mmol) in 30 mL of absolute ethanol and piperidine (0.5 mL) was refluxed for 4 h. The reaction mixture then was poured into ice cold water and acidified with HCl to give **2a**,**b** as solids, which recrystallized from ethanol.

2a: Yield, 66%, m.p. 168°C; IR (KBr, cm^{-1}) : 3086, 1692; ^{1}H-NMR (DMSO-d_6, δ) : 4.28 (s, 2H, thiopyran protons), 7.16 (s, 2H, ylidene), 7.26–7.86 (m, 20H, arom.); MS: m/z (M^+) 444. anal. calc. for $C_{31}H_{24}SO$: C, 83.78; H, 5.41; S, 7.21. Found: C, 83.69; H, 5.28; S, 7.22.

2b: Yield, 62%, m.p. 192°C; IR (KBr, cm^{-1}) : 3082, 2886, 1686; ^{1}H-NMR (DMSO-d_6, δ): 4.22 (s, 2H, thiopyran protons), 7.24 (s, 2H, ylidene), 7.28–7.80 (m, 18H, arom.), 2.42 (s, 6H, 2 CH_3); MS: m/z (M^+) 472. anal. calc. for $C_{33}H_{28}SO$: C, 83.90; H, 5.93; S, 6.78. Found: C, 83.82; H, 5.92; S, 6.80.

Synthesis of Fused Thiopyran Compounds 3a,b–5a,b

A solution of 2,6-diaryl-3,5-dibenzylidenetetrahydro-4H-thiopyran-4-ones **2a**,**b** (0.02 mmol) in 30 mL of ethanol was treated with an equimolar amount of hydroxylamine hydrochloride, hydrazine hydrate, or thiourea and a few drops of acetic acid. The reaction mixture was refluxed for 4 h, concentrated, and cold, and the separated compounds were filtered off and recrystallized from ethanol.

3a: Yield, 71%, m.p. 240°C; IR (KBr, cm^{-1}): 3018, 1628; ^{1}H-NMR (DMSO-d_6, δ): 4.42 (d, 1H), 4.28 (s, 1H), 3.24 (dd, 1H), 4.70 (d, 1H), 7.16–7.82 (m, 21H, 20H arom. + 1H ylidene); MS: m/z (M^+) 459. anal. calc. for $C_{31}H_{25}NOS$: C, 81.05; H, 5.45; N, 3.05; S, 6.97. Found: C, 80.96; H, 5.50; N, 3.12; S, 6.88.

3b: Yield, 68%, m.p. 198°C; IR (KBr, cm^{-1}): 3186, 3064, 1640; ^{1}H-NMR (DMSO-d_6, δ): 4.36 (d, 1H), 4.26 (s, 1H), 3.30 (dd, 1H), 4.68 (d, 1H), 7.22–7.86 (m, 19H, 18H arom. + 1H ylidene), 2.46 (s, 6H, $2CH_3$). anal. calc. for $C_{33}H_{29}NOS$: C, 81.31; H, 5.95; N, 2.87. Found: C, 81.42; H, 5.92; N, 2.98.

4a: Yield, 73%, m.p. 166°C; IR (KBr, cm^{-1}): 3192, 3078, 1632; ^{1}H-NMR (DMSO-d_6): 11.22 (s, 1H, NH), 4.42 (d, 1H), 4.18 (s,1H), 3.42 (dd, 1H), 4.62 (d, 1H), 7.16–7.82 (m, 21H, 20H arom. + 1H ylidene); MS: m/z (M^+) 458. anal. calc. for $C_{31}H_{26}N_2S$: C, 81.22; H, 5.68; N, 6.11. Found: C, 81.26; H, 5.58; N, 6.26.

4b: Yield, 68%, m.p. 215°C; IR (KBr, cm^{-1}): 3168, 3058, 1632; ^{1}H-NMR (DMSO-d_6, δ): 10.98 (s, 1H, NH), 4.40 (d, 1H), 4.26 (s, 1H), 3.46 (dd, 1H), 4.54 (d, 1H) 7.16–7.88 (m, 19H, 18H arom. + 1H ylidene), 2.48 (s, 6H, $2CH_3$). anal. calc. for $C_{33}H_{30}N_2S$: C, 81.48; H, 6.17, N, 5.76. Found: C, 81.32; H, 6.08; N, 5.66.

5a: Yield, 76%, m.p. 246°C; IR (KBr, cm^{-1}): 3166, 3072, 1636, 1454; ^{1}H-NMR ($CDCl_3$, δ): 11.24 (s, 1H, NH), 4.46 (d, 1H), 4.24 (s, 1H), 3.24 (dd, 1H), 4.62 (d, 1H), 7.08–7.86 (m, 21H, 20H arom. + 1H ylidene); MS: m/z (M^+) 502. anal. calc. for $C_{32}H_{26}N_2S_2$: C, 76.49; H, 5.18; N, 5.58, S, 12.75. Found: C, 76.32; H, 5.22; N, 5.40; S, 12.81.

5b: Yield, 71%, m.p. 220°C; IR (KBr, cm^{-1}): 3152, 3066, 1630, 1450; ^{1}H-NMR ($CDCl_3$, δ): 10.86 (s, 1H, NH), 4.32 (d, 1H), 4.28 (s, 1H), 3.36 (dd, 1H), 4.60 (d, 1H), 7.12–7.84 (m, 19H, 18H arom. + 1H ylidene), 2.46 (s, 6H, $2CH_3$). anal. calc. for $C_{34}H_{30}N_2S_2$: C, 76.98; H, 5.66. Found: C, 76.80; H, 5.80.

Synthesis of Thiopyrano[4,3-b]pyran Derivatives 6a,b

2,6-diaryl-3,5-dibenzylidenetetrahydro-4H-thiopyran-4-ones **2a**,**b** (0.01 mmol) was added to an equimolar amount of malononitrile in ethanol (20 mL) and a few drops of piperidine. The reaction mixture was refluxed for 3 h, concentrated, and cold to give thiopyrano[4,3-b]pyran derivatives **6a**,**b** in good yields which recrystallized from dioxane.

6a: Yield, 76%, m.p. 256°C; IR (KBr, cm^{-1}): 3368, 3256, 3062, 2182; ^{1}H-NMR (DMSO-d_6, δ): 4.30 (s, 1H), 4.26 (s, 1H), 4.76 (s, 1H), 5.28 (b, 2H, NH_2), 7.16–7.88 (m, 21H, 20H arom. + 1H ylidene). MS: m/z (M^+) 510. Anal. calc. for $C_{34}H_{26}N_2OS$: C, 80.00; H, 5.10. Found: C, 79.88; H, 5.16.

6b: yield, 75%, m.p. 222°C; IR (KBr, cm^{-1}): 3354, 3262, 3070, 2190; ^{1}H-NMR (DMSO-d_6, δ): 4.38 (s, 1H), 4.26 (s, 1H), 4.82 (s, 1H), 5.26 (b, 2H, NH_2), 7.16–7.89 (m, 19H, 18H arom. + 1H ylidene), 2.46 (s, 6H, $2CH_3$). Anal. calc. for $C_{36}H_{30}N_2OS$: C, 80.30; H, 5.58. Found: C, 80.18; H, 5.52.

Synthesis of Thiopyrano[4,3-b]pyridine Derivatives 7a,b

A mixture of **2a**,**b** (0.01 mmol) and malononitrile (0.01 mmol) in 20 mL of ethanol was refluxed for 6 h with ammonium acetate (2 gm). The solvent was evaporated, and the solid formed was recrystallized from benzene to give **7a**,**b**.

7a: Yield, 69%, m.p. 196°C; IR (KBr, cm^{-1}): 3400, 3350, 2208; ^{1}H-NMR (DMSO-d_6, δ): 4.24 (s, 2H, thiopyran), 5.26 (b, 2H, NH_2), 7.12–7.82 (m, 21H, 20H arom. + 1H ylidene). Anal. calc. for $C_{34}H_{25}N_3S$: C, 80.47; H, 4.93; N, 8.28; S, 6.31. Found: C, 80.52; H, 5.12; N, 8.16; S, 6.28.

7b: Yield, 66%, m.p. 224°C, IR (KBr, cm^{-1}): 3412, 3360, 2214; ^{1}H-NMR (DMSO-d_6, δ): 4.26 (s, 2H, thiopyran), 5.32 (b, 2H, NH_2), 7.02–7.94 (m, 19H, 18H arom + 1H ylidene), 2.42 (s, 6H, $2CH_3$). Anal. calc. for $C_{36}H_{29}N_3S$: C, 80.75; H, 5.42; N, 7.85. Found: C, 80.76; H, 5.38; N, 7.88.

Synthesis of 3-Acetylthiopyrano[4,3-b]pyran Derivatives 8a,b

A mixture of **2a**,**b** (0.01 mmol) and ethyl acetoacetate (0.01 mmol) in absolute ethanol (20 mL) was refluxed for 2 h in the presence of triethylamine (0.5 mL). The reaction mixture was concentrated to give **8a**,**b**, which recrystallized from benzene.

8a: Yield, 71%, m.p. 245°C, IR (KBr, cm^{-1}): 3104, 2889,1696, 1668; ^{1}H-NMR (DMSO-d_6, δ): 2.38 (s, 3H, $COCH_3$), 4.26 (s, 2H, thiopyran protons), 7.04–7.82 (m, 21H, 20H arom. + 1H ylidene). Anal. calc. for $C_{35}H_{26}SO_3$: C, 79.85; H, 4.94; S, 6.08. Found: C, 79.92; H, 4.90; S, 6.12.

8b: Yield, 69%, m.p. 265°C, IR (KBr, cm^{-1}): 3096, 2908, 1698, 1672; ^{1}H-NMR (DMSO-d_6, δ): 2.36 (s, 3H, $COCH_3$), 2.42 (s, 6H, 2CH3), 4.28 (s, 2H, thiopyran protons), 7.10–7.86 (m, 19H, 18H arom. + 1H ylidene). Anal. calc. for $C_{37}H_{30}SO_3$: C, 80.14; H, 5.42; S, 5.78. Found: C, 80.22; H, 5.48; S, 5.68.

Synthesis of Thieno[2,3-c]thiopyran Derivatives 9a,b

To a solution of 2,6-diaryltetrahydro-4H-thiopyran-4-ones **1a**,**b** (0.02 mmol) in 30 mL of THF, elemental sulfur (0.02 mmol), malononitrile (0.02 mmol) and a catalytic amount of triethylamine were added. The reaction mixture was heated at reflux for 4 h and then poured into

ice water and acidified with few drops of HCl. The solid product formed was collected by filtration, washed with water, dried, and recrystallized from dioxane.

9a: Yield, 68%, m.p. 182°C, IR (KBr, cm^{-1}): 3389, 3228, 3086, 2966, 2182; ^{1}H-NMR (DMSO-d_6, δ): 3.02 (m, 2H), 4.38 (s, 1H), 4.22 (dd, 1H), 7.12-7.90 (m, 10H, arom.), 8.22 (br, 2H, NH_2). anal. calc. for $C_{20}H_{16}N_2S_2$: C, 68.97; H, 4.60; N, 8.05. Found: C, 68.82; H, 4.76; N, 8.12.

9b: Yield, 63%, m.p. 194°C; IR (KBr, cm^{-1}): 3402, 3238, 3092, 2974; ^{1}H-NMR (DMSO-d_6, δ): 2.98 (m, 2H), 4.42 (s, 1H), 4.26 (dd, 1H), 7.16-7.88 (m, 8H, arom.), 8.32 (br, 2H, NH_2), 2.48 (s, 6H, $2CH_3$). anal. calc. for $C_{22}H_{20}N_2S_2$: C, 70.21; H, 5.32. Found: C, 70.18; H, 5.38.

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