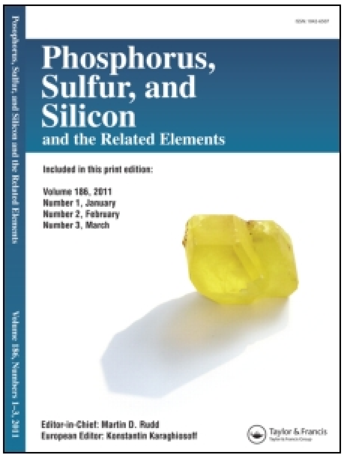

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# Studies With Pyridinethiones: A Convenient Synthesis of Polyfunctionally Substituted Pyridine Ring Systems

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# STUDIES WITH PYRIDINETHIONES: A CONVENIENT SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED PYRIDINE RING SYSTEMS

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1-Benzoyl-1-phenylsulfone-2-ethoxyethene **3** has been prepared *via* reaction of phenacyl sulfone **1** with triethylorthoformate. Compound **3** can be used for prepration of pyridinethione, which could be annulated into fused various heterocyclic ring systems.

*Keywords:* Phenacyl sulfone; Pyridine thione; thienopyridine

## INTRODUCTION

Sulfones have proven to be valuable synthons for the preparation of a wide variety of biologically active heterocyclic systems [1–5]. As an extension of our efforts directed towards the development of convenient synthetic approaches for the construction of biological active heterocycles [6–8].

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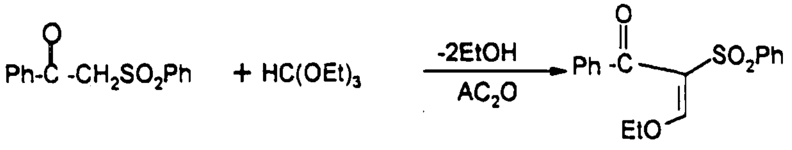
## RESULTS AND DISCUSSION

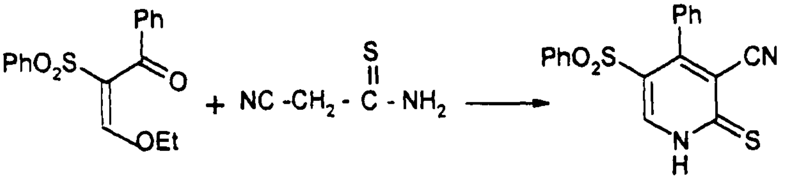
The reaction of phenacylphenyl sulfone **1** with triethylorthoformate **2** in acetic anhydride furnished exclusively 1-benzoyl-1-phenylsulfonyl-2-ethoxyethene **3**.

5-phenylsulfonyl pyridinethione **5** was obtained in 75% yield from the reaction of **3** with an equimolar amount of cyanothioacetamide **4** in refluxing acetonitrile solution.



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

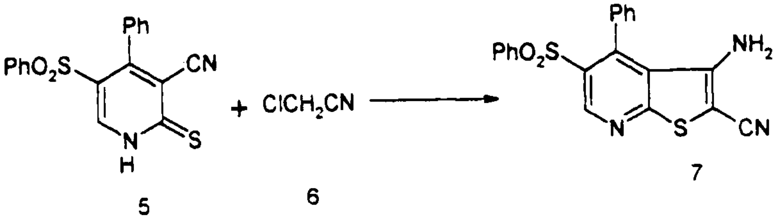
The pyridinethione **5** reacted with α-chloroacetonitrile **6** in ethanol in the presence of $K_2CO_3$ to afford the corresponding thienopyridine derivative **7**.



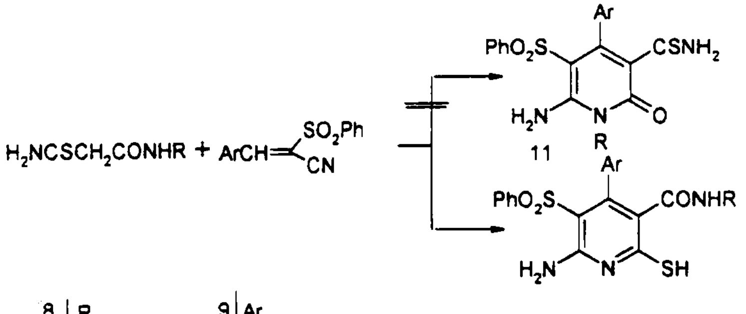
**3** **4** **5**

When equimolar amounts of **8a** or its anilide analogue **8b** and each of the cinnamonitrile derivatives **9a-c** in ethanolic triethylamine solutions were heated under reflux, a single product was isolated in 65–78% yield. On the basis of elemental analyses and spectral data, the products were assigned the structure of 6-amino-4-aryl-2-mercaptopyridine-3-carbamide **10a** or 6-amino-4-aryl-2-oxo-1-substituted-1,2-dihydro pyridine-3-thiocarbamide **11**. Thus, the $^1H$ NMR spectrum showed three types of exchangeable protons in accordance with structure **10** and δ values of the

$NH_2$ groups in **10** are consistent with those of compounds with a somewhat similar structure [9]. Structure **10** was further confirmed based on its behavior towards different chemical reagents.



Methylation of **10d-e** with methyl iodide in cold methanolic potassium carbonate solutions resulting in the formation of the corresponding S-methyl derivatives **12a-c**. That methylation took place at the sulphur atom was proved by removal of the S-methyl group upon treatment of the methylated products **12b,c** with hydrazine hydrate to produce **13a,b** (cf. Scheme 2).

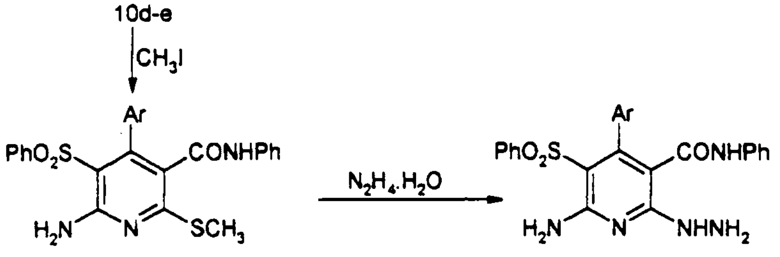


| 8 | R |
|---|---|
| a | H |
| b | $C_6H_5$ |

| 9 | Ar |
|---|---|
| a | $C_6H_5$ |
| b | $C_6H_4$ - $OCH_3$-p |
| c | $C_6H_4Cl$-p |

| 10 | R | Ar |
|---|---|---|
| a | H | $C_6H_5$ |
| b | H | $C_6H_4$-$OCH_3$-p |
| c | H | $C_6H_4$ Cl-p |
| d | $C_6H_5$ | $C_6H_5$ |
| e | $C_6H_5$ | $C_6H_4$ $OCH_3$-p |

SCHEME 1



| 12 | Ar |
|---|---|
| a | $C_6H_5$ |
| b | $C_6H_4$-$OCH_3$-p |
| c | $C_6H_4$-Cl-p |

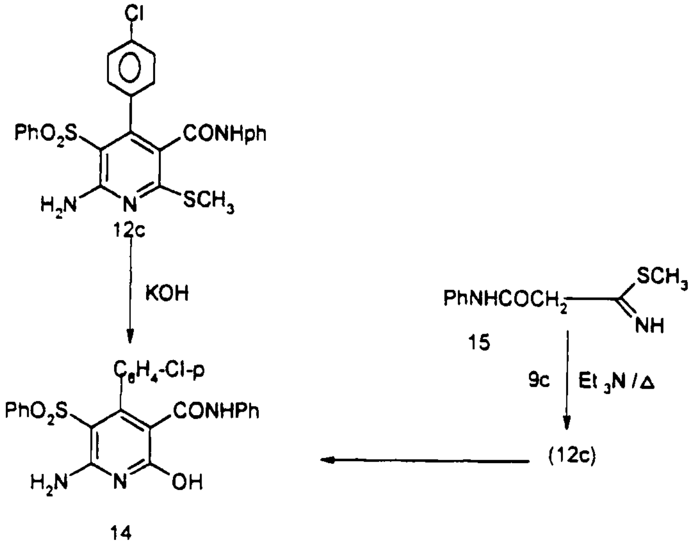
| 13 | Ar |
|---|---|
| a | $C_6H_4$-$OCH_3$-p |
| b | $C_6H_4$-Cl-p |

SCHEME 2

Treatment of **12c** with an aqueous potassium hydroxide solution resulted in the formation of **14**. Assignment of structure **14** to the reaction product was based on analytical and spectral data. Thus, the $^1H$ NMR spectrum (DMSO-$d_6$) of **14** showed in addition to the aromatic signals, signals at δ (ppm) 4.42 (s, 2H, $NH_2$), 6.15 (s, 1H, OH), and 12.12 (s, 1H, NH). In support of structure **14** for the reaction product, *S*-methylmonothiomalonanilide, **15** [9] reacted with **9c** in boiling ethanol in the presence of a catalytic amount of triethylamine to yield a product identical in all respects (m.p., and IR spectrum) with **14**. Formation of **14** from the reaction of **15**with **9c** most probably took place *via* the intermediate **12c** (cf. Scheme 3).

## EXPERIMENTAL

All melting points were taken on a Thomas-Hoover appratus in open capillary tubes and are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. $^1H$ NMR spectra were obtained on an EM - 390 spectrophotometer using TMS as internal standered and chemical shifts are expressed as δ ppm. Analytical data were obtained from Analytical data unit at Cairo University, Egypt.



SCHEME 3

**1-Benzoyl-1-phenylsulfonyl-2-ethoxyethene (3)**

A solution of phenacyl sulfone **1** (2.6 g, 0.01 mol) and triethyl orthoformate **2**(1.4 g, 0.01 mol) in acetic anhydride(20 ml) was refluxed for 30 min. The solid product was collected after removal of the excess of acetic anhydride under reduced pressure and crystallized from absolute ethanol.

Yellow crystals (65%). m.p. = 145°C. IR (KBr); 2290 (CH), 1715(C=O), 1620(C=C)cm$^{-1}$. $^1$H NMR; δ: 0.90(t, *J*=6.9Hz, 3H,$CH_3$), 3.82 (q, *J*=6.9Hz, 2H,$CH_2$); 6.21(s, 1H, olefinic proton); 6.81–7.80 (m, 10H, aromatic protons).

Analysis for $C_{17}H_{16}O_4S$ (316.31)

Calcd. C; 64.6, H, 5.1; S, 10.1%

Found C; 64.2, H, 5.1; S, 10.0%

**1,2-Dihydro-4-phenyl-5-phenylsulfonyl-2-thioxopyridine-3-carbonitrile (5)**

To a solution of **3** (3.1 g, 0.01 mol) in (30 ml) of a cetonitrile, cyanothioacetamide (1.og, 0.01 mol) and a catalytic amount of triethylamine were added. The reaction mixture was heated at reflux for 3h. and poured on to ice/water. The solid product was recrystallized from absolute ethanol.

Brown crystals (60%) -m.p = 195°C – IR (KBr); 3320 (NH), 2218(C=N), 1620 (C=C) $cm^{-1}$. $^1H$ NMR; δ= 4.25(s, 1H, NH), 6.78 – 7.80(m, 11 H, aromatic protons).

Analysis for $C_{18}H_{12}N_2O_2S_2$ (352.39)

Calcd. C; 61.4; H, 3.4; N, 8.0; S, 18.2 %

Found C; 61.5, H, 3.3; N, 7.5; S, 18.4 %

### 3-Amino-4-phenyl-5-phenylsulfonylthieno[2,3-b]pyridine-2-carbonitrile (7)

A solution of **5** (3.2 g, 0.01 mol) in (30 ml) absolute ethanol, 2-chloroacetonitrile (0.75 g, 0.01 mol) and (0.5 g) $K_2CO_3$ were added. The reaction mixture was heated at reflux for 2h. The solid product formed on dilution with water was collected by filtration and recaystallized from ethanol.

Orange crystals (55%) – m.p = 176°C – IR (KBr); 3450–3320 ($NH_2$); 2216 (C=N) $cm^{-1}$ -$^1H$ NMR; δ: 4.43 (s, 2H, $NH_2$). 6.72–782 (m, 11H, aromatic protons).

Analysis for $C_{20}H_{13}N_3O_2S_2$ (391.43)

Calcd C; 61.4, H; 3.3, N; 10.7, S; 16.4 %

Found C; 61.3, H; 3.3, N; 10.3, S; 16.3 %

### 6-Amino-4-aryl-5-phenylsulfonyl-3-thiohydroxypyridine-3-carbamide (10a-e)

To a solution of anilide **8a-b** (0.01 mol) in ethanol (50 ml), α-cyanocinnamonitriles **9a-c** (0.01 mol) and a catalytic amount of triethylamine were added. The reaction mixture was heated at reflux for 2h. and poured on to ice/water and then neutralized by HCl to pH 7. The solid product was recrystallized from absolute ethanol.

**10a**: yellow crystals (60%) m.p = 212 °C IR (KBr); 3400 – 3320 ($NH_2$, NH), 1670(C=O) $cm^{-1}$. $^1H$ NMR δ: 4.25 (br, 2H, $NH_2$); 4.46 (s, 2H, $NH_2$), 6.50 (s, 1H, SH), 6.75–792 (m, 10H, aromatic protons), Analysis for $C_{18}H_{15}N_3O_3S_2$ (385.38)

Calcd C; 56.1, H, 3.9; N, 10.9, S; 16.6 %

Found C; 56.4, H, 3.8; N, 10.5, S, 16.3 %

**10b**: yelow crystals (60%) m.p. = 220 °C IR (KBr); 3450–3320 ($NH_2$, NH); 1675 (C=O) $cm^{-1}$. $^1H$ NMR; δ: 2.93 (s, 3H, $OCH_3$); 4.23 (s, 2H. $NH_2$); 4.45 (s, 2H, $NH_2$), 6.2 (s, 1H, SH), 6–8–7.8 (m, 9H, aromatic protons)

Analysis for $C_{19}H_{17}N_3O_4S_2$ (415.4)

Calcd C; 54.9, H, 4.1, N; 10.1, S, 15.4 %

Found C; 54.6, H, 4.0, N; 10.3, S, 15.6 %

**10c**: yellow crystals (65%) m.p = 190 °C- IR (KBr); 3450–3320 ($NH_2$); 1668 (C=O) $cm^{-1}$. $^1H$ NMR; δ: 4.21 (br, 2H, NH2), 4.45 (s, 2H, $NH_2$); 6.60 (s, 1H, SH), 6.68–7.81 (m, 9H, aromatic protons). Analysis for $C_{18}H_{14}N_3O_3S_2Cl$ (419.83)

Calcd. C; 51.5, H; 3.4, N, 10.0, S, 15.3 %

Found C; 51.6, H, 3.5, N, 9.5, S, 15.4%

**10d**: yellow crystal (73 %) m.p = 250 °C IR (KBr); 3450–3320 ($NH_2$, NH); 1670 (C=O) $cm^{-1}$. $^1H$ NMR; δ: 4.25 (s, 2H, $NH_2$); 6.50 (s, 1H, SH); 6.72–7.81 (m, 15H, aromatic protons); 12.23 (s, 1H, NH) Analysis for $C_{24}H_{19}N_3O_3S_2$ (461.49)

Calcd. C; 62.5, H, 4.1, N, 9.1, S, 13.9 %

Found C; 62.1, H, 4.5, N, 9.4, S, 13.4 %

**10e**: yellow crystal (81%) m.p =200 °C IR (KBr); 3440–3350 ($NH_2$, NH); 1680 (C=O)$cm^{-1}$. $^1H$ NMR; δ: 2.90 (s, 3H, $OCH_3$); 4.25 (s, 2H, $NH_2$); 6.52 (s, 1H, SH), 6.80–7.95 (m, 14H, aromatic protons), 12.22 (s, 1H, NH).

Analysis for $C_{25}H_{21}N_3O_4S_2$ (491.5)

Calcd. C; 61.1, H, 4.3; N, 8.5; S, 13.0 %

Found C; 61.3, H, 4.6; N, 8.8; S, 13.2 %

### 6-Amino-4-aryl-5-phenylsulfonyl-2-methylthiopyridine-3-carbanilide (12a-e)

To a solution of **10d-e**(0.01 mol) in methanol (30 ml), methyl iodide (0.01 mol) and (5 g) $K_2CO_3$ were added. The reaction mixture was heated at reflux for 2 h. and poured on to water. The solid product was collected by filtration and recrystallized from absolute ethanol.

**12a**: yellow crystal (55%). m.p = 180 °C. IR (KBr); 3450–3320 ($NH_2$, NH); 1670 (C=O) 1650 (C=C). $^1H$ NMR; δ = 2.93 (s, 3H, $CH_3$); 4.42 (s, 2H, $NH_2$), 6.75–7.81 (m, 15H, aromatic protons) 12.41 (s, 1H, NH).

Analysis for $C_{25}H_{21}N_3O_3S_2$ (475.51)

Calcd. C 63.1; H, 4.4; N, 8.8; S, 13.5%

Found C 63.3; H, 4.5; N, 8.4; S, 13.6%

**12b**: yellow crystals (70%) -m.p = 210 °C. IR (KBr); 3440–3320 ($NH_2$, NH); 1675 (C=O) $cm^{-1}$. $^1H$ NMR; δ: 2.93 (s, 3H, $CH_3$); 2.95 (s, 3H, $CH_3$), 4.40 (s, 2H, $NH_2$), 6.70–7.79 (m, 14H, aromatic protons),12.22 (s, 1H, NH).

Analysis for $C_{26}H_{23}N_3O_4S_2$ (505.60)

Calcd. C 61.8; H, 4.6; N, 8.3; S, 12.7 %

Found C 61.5; H, 4.4; N, 8.5; S, 12.4 %

**12c**: orange crystals (65%) -m.p = 190 °C. IR (KBr); 3450–3320 ($NH_2$, NH); 1670 (C=O) 1640 (C=C)$cm^{-1}$. $^1H$ NMR;: 2.89 (s, 3H, $CH_3$), 4.40 (s, 2H, $NH_2$), 6.71–7.79 (m, 14H, aromatic protons), 12.23 (s, 1H, NH). Analysis for $C_{25}H_{20}N_3O_3S_2$ Cl (509.89)

Calcd. C 58.9; H, 3.9; N, 8.2; S, 12.6 %

Found C 58.5; H, 3.6; N, 8.4; S, 12.3 %

### 6-Amino-4-aryl-2-hydrazino-5-phenylsulfonylpyridine-3-carbaanilide (13)

Hydrazine hydrate (0.01 mol) was added to a solutioon of **12a-c** (0.01 mol) in ethanol (20 ml). The reaction mixture was heated at reflux for 3 h and pour onto ice/water. The solid product was collected by filtration and recrystallized from DMSO.

**13a**: yellow crystals (82%) -m.p = 156°C. IR (KBr); 3450–3240 ($NH_2$, NH), 1670 (C=O), 1650 (C=C) $cm^{-1}$. $^1H$ NMR; δ = 3.45 (s, 3H, $CH_3$), 4.32 (br, 4H, $2NH_2$), 6.72–7.89 (m, 14H, aromatic protons), 12.21 (s, 1H, NH), 13.40 (s, 1H, NH) ppm.

Analysis for $C_{25}H_{23}N_5O_4S$ (489.48)

Calcd. C 61.3; H, 4.7; N, 14.3; S, 6.5 %

Found C 61.2; H, 4.5; N, 14.1; S, 6.3 %

**13b**: yellow crystal (61%) -m.p = 18°C. IR (KBr); 3450–3240 ($NH_2$, NH), 1670 (C=O), 1650 (C=C)$cm^{-1}$. $^1H$ NMR;: 4.31 (br, 4H, $2NH_2$), 6.75–7.88 (m, 14H, aromatic protons), 12.22 (s, 1H, NH), 13.01 (s, 1H, NH).

Analysis for $C_{24}H_{20}N_5O_3SCl$ (493.91)

Calcd. C 58.4; H, 4.1; N, 14.2; S, 6.5%

Found C 58.1; H, 4.1; N, 14.0; S, 6.5%

### 6-Amino-4-[4-chlorophenyl]-2-hydroxy-5-phenylsulfonylpyridine-3-carbanilide (14)

To a solution of **12c** (0.01 mol) in ethanol (20ml) and (0.5 g) KOH were added. The reaction mixture was heated for 30 min., pour onto water. and neutralize until pH 7. The solid product was collected by filtration and recrystallized from absolute ethanol.

yellow crystal (64%)- m.p. = 182°C. IR (KBr); 3550–3320 (OH, $NH_2$, NH), 1640 (C=O), 1600 (C=C)$cm^{-1}$. $^1H$ NMR; δ: 4.42 (s, 2H, $NH_2$), 6.15 (s, 1H, OH), 6.72–7.81 (m, 14H, aromatic protons), 12.12 (s, 1H, NH), ppm.

Analysis for $C_{24}H_{18}N_3O_4S$ (444.41)
Calcd C 64.9; H, 4.1; N, 9.5; S, 7.2 %
Found C 64.5; H, 4.2; N, 9.3; S, 7.4 %

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