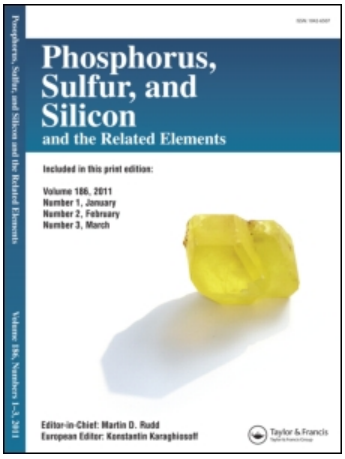

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SULFUR CONTAINING ACTIVATED NITRILES: SYNTHESIS OF THIOPHENE, PYRIDINE-2,6-DITHIONE,3,5-DIARYLANILINE AND PYRID0[2,3-z]PYRIMIDINE DERIVATIVES

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SULFUR CONTAINING ACTIVATED NITRILES: SYNTHESIS OF THIOPHENE, PYRIDINE-2,6-DITHIONE,3,5-DIARYLANILINE AND PYRIDO[2,3-D]PYRIMIDINE DERIVATIVES

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[1-(4-N,N-dimethylaminosulfonephenyl)ethylidene]malononitrile **2a** was used as starting material in the synthesis of thiophene, pyridine-2,6-dithione, pyrido[2,3-d]pyrimidine, 3,5-diarylaninline, enamine and enol ether derivatives.

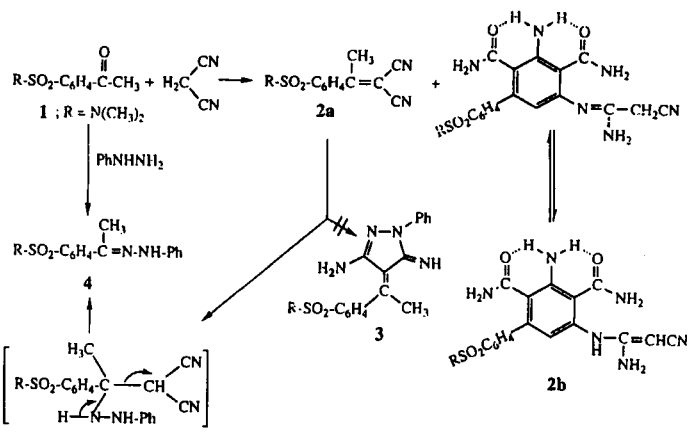
Keywords: Arylidenemalononitrile; pyridinedithione; pyridopyrimidine; diarylaniline; enamine; enol ether

Activated nitriles have attracted considerable interest as potential building blocks for many nitrogen containing heterocyclic system[1–3]. In previous work[4] it was reported that the methyl function in (1-phenylethylidene)malononitrile is extermely reactive towards electrophilic reagents. The reactivity of this methyl function was decreased by replacing the phenyl substituent with a 2-furyl or 2-thienyl substituent[5].

The aim of the present work is the synthesis of [1-(4-N,N-dimethylaminosulfonephenyl) ethylidene]malononitrile to study the effect of the sulfonyl group on the reactivity of the methyl function and their behavior towards cinnamonitrile derivatives, carbon disulfide, phenyl isocyanate, diazonium chloride, triethyl formate and DMF acetal.

Condensation of 4-N,N-dimethylaminosulfoneacetophenone[6] **1** with malononitrile afforded [1-(4-N,N-dimethylaminosulfonephenyl)ethylidene]malononitrile **2a** together with a pentasubstituted benzene derivative **2b** as a by-product.

In contrast to the anticipated formation of the pyrazoline derivative[7] **3**, the reaction of **2a** with phenylhydrazine gave the hydrazone derivative **4**. The formation of **4** is assumed to proceed via nucleophilic addition and subsequent malononitrile elimination. The proposed structure **4** was supported by independent synthesis from **1** with phenylhydrazine (m.p. and m.m.p.) (Scheme 1).



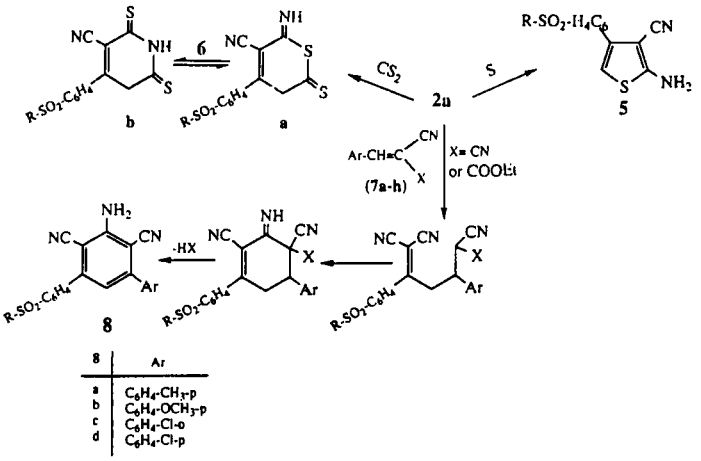
SCHEME 1

Treatment of **2a** with elemental sulfur under the Gewald reaction condition[8] furnished 2-amino-3-cyano-4-(4-N,N-dimethylaminosulfonephenyl)thiophene **5**. When **2a** was heated with carbon disulfide it gave 2H-thiin derivative **6a** which underwent rearrangement into pyridine-3,6-dithione derivative **6b**.

Interaction **2a** with α-cyanocinnamonitrile or ethyl α-cyanocinnamate derivatives **7a–h** furnished 1-amino-5-aryl-3-(4-N,N-dimethylaminosulfonephenyl)-2,6-benzene-dicarbonitrile **8a–d**. The formation of **8** is assumed to proceed via addition of the methyl function of **2a** to the activated double bond in **7** followed by cyclization through HCN/or ethyl formate elimination (Scheme 2).

Reaction of **2a** with phenyl isocyanate provided N-phenylpyridone derivative **9** as an intermediate which reacted with an additional mole of phenyl isocyanate to afford pyrido[2,3-d]pyrimidine derivative **10**.

The trans- N,N-dimethylenamine **11** was obtained via interaction of **2a** with N,N-dimethylformamide dimethyl acetal, while β,γ-unsaturated enol ethers **12** and **13** were obtained respectively by interaction of **2a** with triethyl orthofor-



SCHEME 2

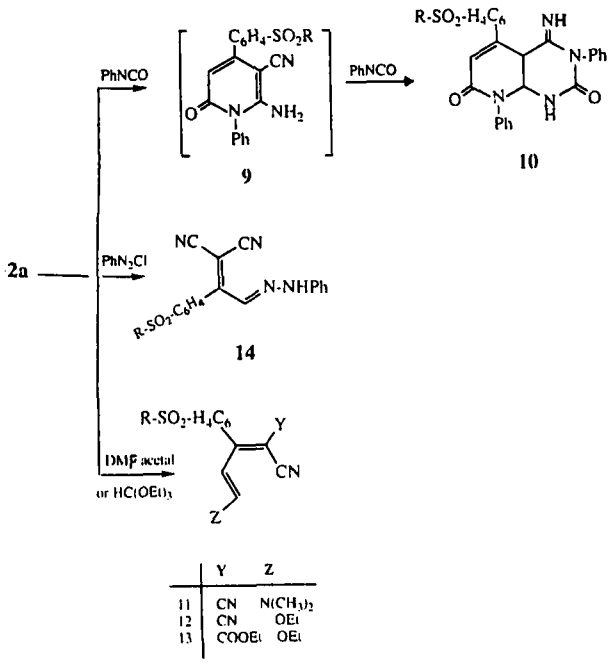
mate. It appears that the enol ether **12** is formed first and then undergoes alcoholysis to give ethyl-2-cyano-3(4-N,N-dimethylaminosulfonephenyl)-5-ethoxy-2,4-pentadienoate **13**.

Coupling of **2a** with benzenediazonium chloride in ethanolic sodium acetate solution afforded the deep violet coupling product **14** (Scheme 3).

From the above findings, it was concluded that the poorer electron attracting group (Me_2 NSO_2-) at the p-position deactivates the reactivity of the β-methyl group by induction not by delocalization[9], while the β-carbanion is established with a conjugated double bond and two terminal activating groups (2CN), therefore this anion which is formed initially undergoes nucleophilic addition to afford the by-product **2b**.

EXPERIMENTAL

All m.p.'s are uncorrected. Microanalyses were carried out at the Microanalytical Center of Cairo University. IR spectra (KBr) were measured on a Shimadzu IR 440 spectrophotometer. ^{1}H NMR spectra using a FX 90Q Fourier-transform spectrometer and the mass spectra on a Shimadzu GC-MS-QP 1000 EX using the direct inlet system.



SCHEME 3

Reaction of 1 with Malononitrile

To a solution of (1; 0.1 mole) in dry benzene (100 ml) was added malononitrile (0.1 mole), ammonium acetate (2g) and acetic acid (2ml). The reaction mixture was refluxed using a Dean-Stark water separator until water ceased to be collected. The solution was cooled, washed with water, dried over anhydrous sodium sulfate and diluted with n-hexane. The product was crytallized from an appropriate solvent to give **2a** (50–55% yield) and a biproduct **2b** (30% yield) (Table I). **2a**: ν_{max}/cm^{-1} 2900 (CH_3), 1600(C=C), 2200 (CN); δ_H [$(CD_3)_2SO_4$] 2.78 (9H,s,3CH_3), 8.2–8.4 (4H, m, arom.); m/z 275 (M^+ 24.59%), 231(10), 167(62), 140(100), 113(34.9). **2b**: ν_{max}/cm^{-1} 3225, 2290 (NH_2), 2200 (CN), 1610 (C=O amide); δ_H [$(CD_3)_2SO_4$] 2.65, 2.68 (6H, 2s,-$N(CH_3)_2$), 1.88 (2H, s,-CH_2CN), 1.82 (2H, s, NH_2aliphatic), 4 (6H, br, NH_2 aromatic, 2NH_2-CO-(hydrogen bonded), exchangeable by D_2O), 7.8–8.25 (5H,m,arom); m/z 443 (M^+53.2%), M + 1 (43.9), M + 2 (19.4), 428 (100), 320 (78.4), 258 (51.1), 103 (25.2), 77 (63.3).

TABLE I Physical data for the newly synthesized compounds

Compd. no.	*M.P. T/°C*	*Formula*	*Found (required%)*	
			C	*H*
2a	140[a]	$C_{13}H_{13}N_3O_2S$	56.60(56.73)	4.70(4.73)
2b	193[c]	$C_{19}H_{21}N_7O_4S$	51.50(51.47)	4.80(4.74)
4	200[a]	$C_{16}H_{19}N_3O_2S$	60.60(60.57)	6.00(5.99)
5	195[c]	$C_{13}H_{13}N_3O_2S_2$	50.70(50.81)	4.20(4.23)
6	272[a]	$C_{14}H_{13}N_3O_2S_3$	47.80(47.86)	3.70(3.70)
8a	331[a]	$C_{23}H_{20}N_4O_2S_2$	66.40(66.35)	4.80(4.81)
8b	240[a]	$C_{23}H_{20}N_4O_3S$	63.70(63.89)	4.50(4.63)
8c	266[b]	$C_{22}H_{17}ClN_4O_2S$	60.50(60.48)	3.90(3.89)
8d	162[a]	$C_{22}H_{17}ClN_4O_2S$	60.40(60.48)	3.80(3.89)
10	230[a]	$C_{27}H_{23}N_5O_4S$	63.20(63.16)	4.50(4.48)
11	265[b]	$C_{16}H_{18}N_4O_2S$	58.20(58.18)	5.50(5.45)
12	175[b]	$C_{16}H_{17}N_3O_3S$	58.10(58.03)	5.00(5.14)
13	110[a]	$C_{18}H_{22}N_2O_5S$	57.00(57.14)	5.8(5.82)
14	203[a]	$C_{19}H_{17}N_5O_2S$	60.10(60.16)	4.50(4.49)

[a]from ethanol
[b]from benzene
[c]from acetic acid

Reaction of 2a with Phenylhydrazine

(a) A mixture of (**2a**; 0.01 mole) and phenylhydrazine (0.01 mole) in ethanol (50 ml) was refluxed for 2h. to give the hydrazone **4** (85% yield) (Table I): ν_{max}/ cm^{-1} 3300, 3275(NH), 1680(C=N); m/z 317 (M^+76.5%), 194(2.5), 167 (9), 77(13).

(b) To a solution of **1** (0.01 mol) in ethanol (50 ml) was added phenylhydrazine (0.01 mole). The reaction mixture was refluxed for 2h. to give the hydrazone **4** (90% yield) (Table I).

Reaction of 2a with Sulfur

(**2a**; 0.05 mole) and elemental sulfur (0.05 mole) in ethanol (50 ml) treated with a few drops of piperidine. The reaction mixture was refluxed for 2h. to give the thiophene derivative **5** (60% yield) (Table I): ν_{max}/cm^{-1} 3340, 3300 (NH_2), 2200 (CN).

Reaction of 2a with Carbon Disulfide

To a solution of (**2a**; 0.1 mole) in pyridine (10 ml), carbondisulfide was added and the resulting solution was heated at reflux temperature for 8h. After cooling, methanol (30 ml) was added and the precipitated solid was collected and recrys-

tallized from a suitable solvent to give the pyridine-2,6-dithione derivative (**6**) (35% yield) (Table I). **6b**: ν_{max}/cm^{-1} 3310, 3250 (NH), 2200(CN), 1080 (C=S); m/z 351 (M^+ 45.53%), 307(37), 243(10.88), 210(10.58), 177(11.44), 125(12.79), 87(13.58) (Chart 1).

Reaction of 2a with Cinnamonitrile Derivatives

Equimolar amounts of **2a** and (**7a–h**) (0.01 mole) were refluxed for 3h in ethanol (50 ml) containing a catalytic amount of piperidine (0.5 ml) and then cooled. The solid product was collected and crystallized from the appropriate solvent (Table I). **8b**: ν_{max}/cm^{-1} 3480, 3370 (NH_2), 2200 (CN); δ_H [$(CD_3)_2SO_4$] 2.8 (6H,s,$2CH_3$), 3.9(3H,-s,OCH_3), 7.2–8.4 (11H, m, aromatic H and NH_2); m/z 432 (M^+ 0.14%), 393(100), 367(11), 286 (80.3), 214(36.3), 108 (26). **8c**: ν_{max}/cm^{-1} 3460, 3350 (NH_2), 2200(CN); δ_H [$(CD_3)_2SO_4$] 2.8 (6H,s,$2CH_3$), 7.1–8.3 (11H,m,aromatic H and NH_2). **10d**: ν_{max}/cm^{-1} 3440, 3350 (NH_2), 2200 (CN); m/z 436.8 (1.5%), 410.6 (4.7), 383.3 (6.78), 319.5 (25.7), 267(12.4), 237.5(23), 211.8(15), 171(38), 112(55.8).

Reaction of 2a with Phenyl Isocyanate

A mixture of (**2a**; 0.01 mole) and phenyl isocyanate was refluxed for 8h in pyridine (20 ml) then allowed to cool. The precipitate was filtered off and crystallized from an appropriate solvent to give **10** (40% yield) (Table I): ν_{max}/cm^{-1} 3380, 3220 (NH), 1670(C=N), 1680 (CO); m/z 513 (M^+ 0.22%) 399 (0.33), 343 (2.2), 283 (1.5), 212 (10.5), 119 (8), 93 (100).

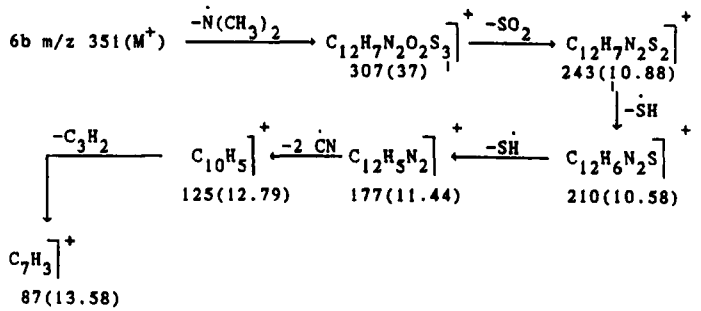


CHART 1 Mass fragmentation pattern of compound 6b.

1,1-Dicyano-2-(4-N,N-dimethylaminosulfonephenyl)-4-(N,N-dimethylamino)1,3-butadiene (11)

DMF acetal (0.01 mole) was added to a solution of (**2a**; 0.01mole) in anhydrous DMF (30 ml). The solution was heated at reflufor 6h and then evaporated to dryness. The solid product was crystallized from the appropriate solvent to give N,N-dimethylenamine **11** (55% yield) (Table I): ν_{max}/cm^{-1} 1610(C=C), 2200(CN); δ_H [$(CD_3)_2SO_4$] 2.78 (6H,s,$SO_2N(CH_3)_2$), 3.18, 3.22 (6H,2s,$N(CH_3)_2$), 6,7.2 (2H,2d, CH=CH) (J = 14.4 Hz), 7.8–8.3 (4H,m,arom); m/z 330 (M^+ 28%), 323 (100), 152 (10.4), 70 (10.2).

Preparation of β,γ-unsaturated Enol Ethers using Triethyl Orthoformate

A mixture of (**2a**; 0.01 mole), triethyl orthoformate (0.05 mole) was refluxed for 5h. The solid obtained on heating was filtered off and crystallized to give **12** (40% yield). The unreacted triethylorthoformate was removed under reduced pressure and the separated solid crystallized from the suitable solvent to give **13** (35% yield) (Table I). **12**: ν_{max}/cm^{-1} 600(C=C), 2200(CN); m/z 331 (M^+ 2.5%), 274(6.4), 210(100), 177(47.6), 140(38.4), 113(14.9). **13**: ν_{max}/cm^{-1} 1710(COester), 2200(CN); δ_H [$(CD_3)_2SO_4$] 2,1.3 (6H, 2t, $2OCH_2CH_3$), 3.7, 3.9(4H, 2q, $2OCH_3$), 6.7, 7.1(2H, 2d, CH=CH), .8(6H, s, $N(CH_3)_2$), 7.6-8(4H,m,arom); m/z 378 (M^+ 0.23%), 332(4.52), 288 (2.46), 224(37.43), 196(21.77), 168(15.32), 140(44.27), 113(13.4), 87(3.79) (Chart 2).

1-(4-N,N-Dimethylaminosulfonephenyl)-2-(Phenylhydrazono)Ethylidene Malononitrile (14)

A cold solution of (**2a**; 0.01 mole) in ethanol (50 ml) was treated with a saturated sodium acetate solution (10 ml) and then with benzenediazonium chloride (0.01 mol). The reaction mixture was left in the refrigerator for 24 h. The

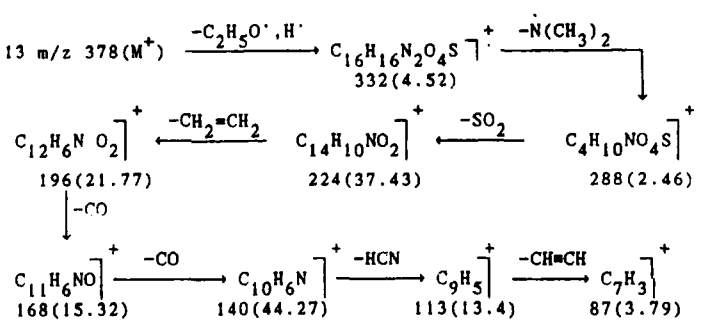


CHART 2 Mass fragmentation pattern of compound 13.

resulting product was collected and crystallized from the appropriate solvent to give **14** (65% yield) (Table I). **14**:ν_{max}/cm^{-1} 3300, 3260 (NH), 1680 (C=N), 2200(CN); δ_H ($CDCl_3$) 2.8 (6H,s,$N(CH_3)_2$), 7.6–8.4 (11H, m, aromatic H, NH, HC=N). 7.6-8(4H,m,arom); m/z 378 (M^+ 0.23%), 332(4.52), 288 (2.46), 224(37.43), 196(21.77), 168(15.32), 140(44.27), 113(13.4), 87(3.79) (Chart 2).*

1-(4-N,N-Dimethylaminosulfonephenyl)-2-(Phenylhydrazono)Ethylidene Malononitrile (14)*

A cold solution of (**2a**; 0.01 mole) in ethanol (50 ml) was treated with a saturated sodium acetate solution (10 ml) and then with benzenediazonium chloride (0.01 mol). The reaction mixture was left in the refrigerator for 24 h. The resulting product was collected and crystallized from the appropriate solvent to give **14** (65% yield) (Table I). **14**:ν_{max}/cm^{-1} 3300, 3260 (NH), 1680 (C=N), 2200(CN); δ_H ($CDCl_3$) 2.8 (6H,s,$N(CH_3)_2$), 7.6–8.4 (11H, m, aromatic H, NH, HC=N).

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