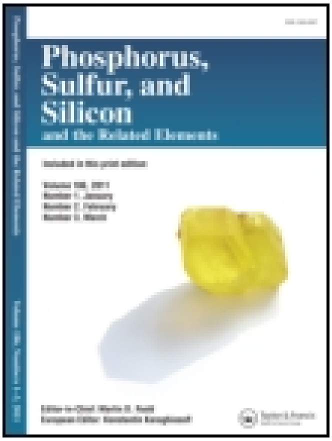

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Activated Nitriles with Ammonium Benzyldithiocarbamate, Synthesis of Thietane Derivatives

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*4-Aryl-2-iminothietane-3-carbonitriles **3** were obtained in a moderate yield via the reaction of substituted arylidene malononitriles with ammonium benzyldithiocarbamate. The reaction of **3a** with hydrazine hydrate, ethyl carbazate, phenylisothiocyanate, and carbon disulphide have been investigated.*

Keywords Activated nitriles; ammonium benzyldithiocarbamate; pyrimidine; 1,3-thiazine derivatives; thietane

INTRODUCTION

Thietanes have received somewhat less attention than their synthetically five- or six-membered heterocyclic rings. Thus, while there are a variety of syntheses of thietanes with particular substitution patterns, there is no simple and completely general method for preparing thietanes of a wide range of ring substitution patterns. Thietanes have been considered as odorants for natural gas.[1] Other thietane derivatives with physiological activity are useful as anti-inflammatory agents,[2] sedatives,[3] and insecticides.[4] Furthermore, thietanes may be involved as intermediates in the photochemical cross linking of 4-thiouridine and cytidine units in bacterial transfer-RNA[5] and patented as a stabilizer for polyvinyl chloride.[6]

In conjunction with our program that aims to explore the synthetic potential of activated nitriles and their derivatives,[7–16] we report here on the reaction of substituted arylidene malononitrile **1** with ammonium benzyldithiocarbamate **2**. The reaction of a 1:1 mixture of **1** and **2** in absolute ethanol afforded a colored solid for which the two

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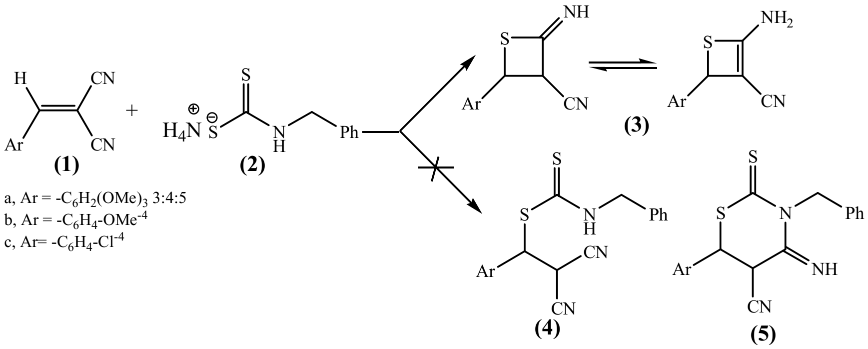
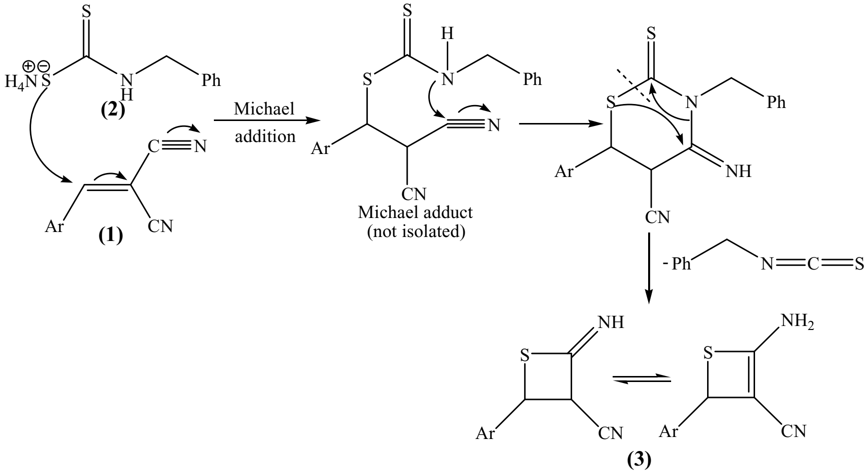


SCHEME 1

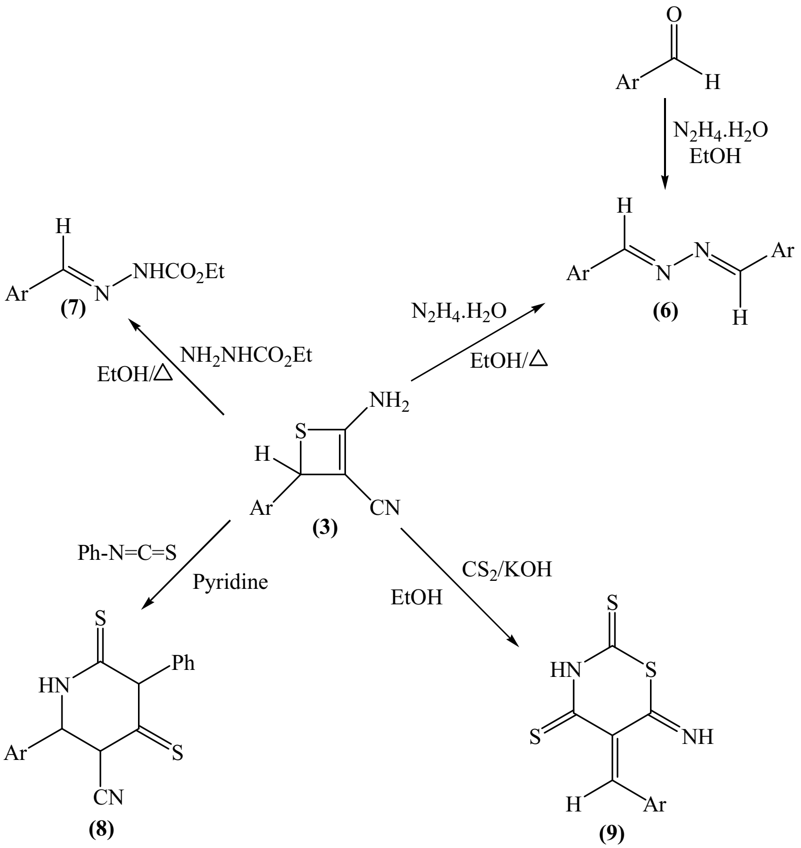
theoretically possible structures **4** and **5** were eliminated based on microanalytical and spectroscopic data. These data can only be intelligibly interpreted in terms of structure **3** (Scheme 1).

The structure of **3** is substantiated from microanalytical data and was confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopy (c.f. Exp.).

Formation of **3** may be rationalized in terms of the route shown in Scheme 2. However, independent chemical proof for compound **3** seemed necessary. Thus, the reaction of **3a** with hydrazine hydrate, ethyl carbazate, phenylisothiocyanate, and carbon disulfide in ethanolic potassium hydroxide solution were also investigated (Scheme 3).

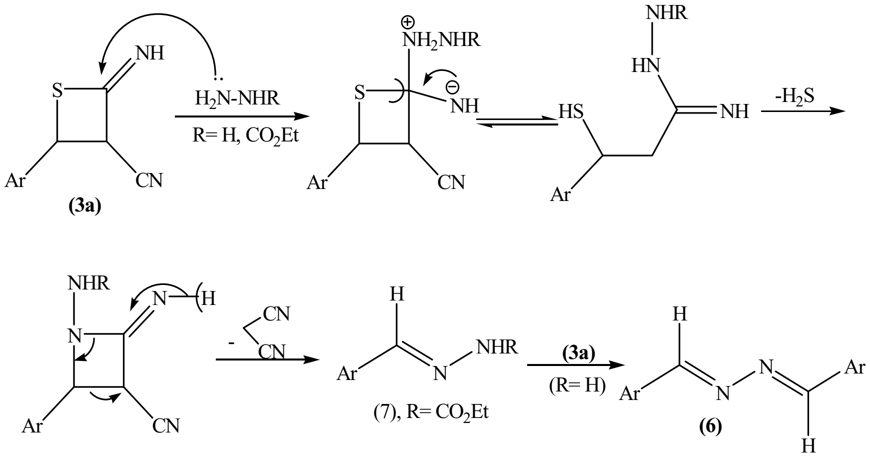


SCHEME 2



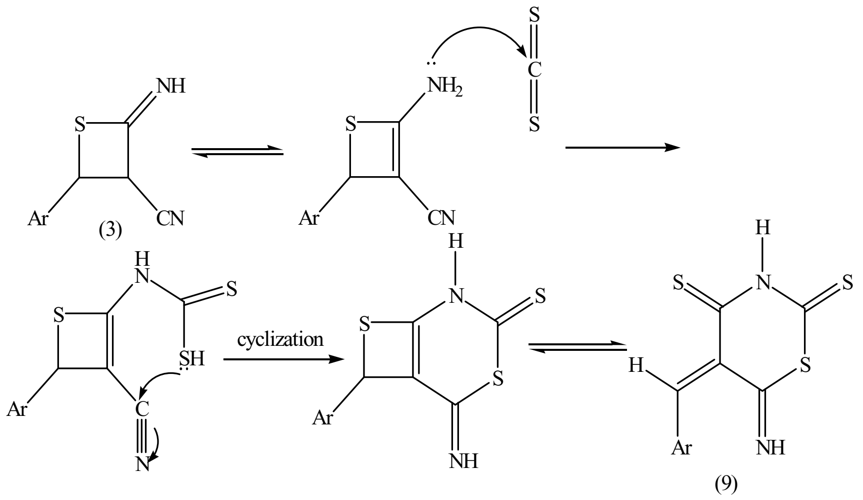
SCHEME 3

Treatment of **3a** with hydrazine hydrate in boiling ethanol afforded the sulfur free compound which was identified to be the azine derivative **6**. The structure of **6** was confirmed by comparison (m.p., mixed m.p., IR, and TLC) with an authentic sample obtained from the reaction of 3,4,5-trimethoxybenzaldehyde with hydrazine hydrate in ethanol with 2:1 molar ratio. In a typical procedure, an equimolar amount (1:1) of compound **3a** and ethyl carbazate were refluxed in ethanol for 3 h, and removal of the solvent followed by trituration with methanol left a solid product, identified to be the diazoester **7**. Conversion of **3** to **6** and **7** could be visualized as shown in Scheme 4. When compound **3a** was refluxed with phenylisothiocyanate in boiling pyridine, an insoluble product was isolated and identified to be 3-phenyl-2,4-dithioxo-6-(3,4,5-trimethoxyphenyl)-1,2,3,



SCHEME 4

4-tetrahydropyrimidine-5-carbonitrile **8**. The assigned structure **8** is deduced from analytical data and confirmed from the spectroscopic analysis (c.f. Exp.). Refluxing **3a** with carbon disulfide in ethanolic KOH solution affords the thermodynamically stable product 2,4-dithioxo-6-imino-5-(3,4,5-trimehoxybenzyl-idine)3H-1,3-thiazine **9**. The structure features of **9** were elucidated from the spectroscopic analysis (Scheme 3). Conversion of **3** to **9** could be explained as shown in Scheme 5.



SCHEME 5

EXPERIMENTAL

All melting points are uncorrected. The infrared spectra are recorded on FTIR Maltson (infinity series) spectrometers as KBr discs. The ^{1}H-NMR spectra were measured on Varian Gemini 200 MHz instrument with chemical shift (δ) expressed in ppm downfield from TMS. Mass spectra were recorded on Shimaduzu GC-MS, QP 1000 EX instrument operating at 70 eV. TLC was run using TLC aluminum sheets silica gel F_{254} (Merck).

General Method for Synthesis of 4-Aryl-2-imino-thietane-3-carbonitriles (3a–c)

A mixture of ammonium benzyldithiocarbamate (2 g, 10 mmol) and arylidene malononitrile (10 mmol) was refluxed in 30 mL ethanol for 1 h until there was no more substrate (TLC). The solid deposited on hot was filtered off, dried, and recrystallized from suitable solvent to give compounds **3a–c**.

2-Imino-4-(3,4,5-trimethoxyphenyl) thietane-3-carbonitrile (3a)

Recrystallized from benzene as orange crystals, m.p. 198–200°C, yield 50%. IR (KBr): 3393, 3262, 3153 cm^{-1} (NH_2), 2978, 2942, 2836 cm^{-1} (C-H), 2208 cm^{-1} (C≡N), 1636 cm^{-1} (C=N). ^{1}H-NMR (DMSO-d_6, δ ppm) 10.12 (s, 1H), 9.6 (s, 1H), 8.1 (s, 1H), 7.4 (s, 2H), 3.9 (s, 6H), 3.8 (s, 3H).^{13}C-NMR (DMSO-d_6) 159.7 (C_2), 60.2 (C_3), 115.1 (C≡N), 42.2 (C_4), 134.8 ($C_{1'}$), 108.3 ($C_{2'}$, $C_{6'}$), 153 ($C_{3'}$, $C_{5'}$), 136.2 ($C_{4'}$), 56.3, 58.4, 55.3 (3OMe). EI-MS m/z (%): 278 (100) [$M^{+\cdot}$], 246 (78.2), 219 (16.2), 204 (20.7), 188 (10.7). Anal. Calcd. for $C_{13}H_{14}N_2O_3S$ (278): C, 56.11; H, 5.03; N, 10.07; S, 11.52. Found: C, 55.92; H, 4.83; N, 9.66; S, 11.08.

2-Imino-4-(4-methoxyphenyl) thietane-3-carbonitrile (3b)

Recrystallized from dioxane as yellow crystals, m.p. 210–219°C, yield 39%. IR (KBr): 3410, 3274, 3166 cm^{-1} (NH_2), 2918, 2900 cm^{-1} (C-H), 2216 cm^{-1} (C≡N), 1632 cm^{-1} (C=N). ^{1}H-NMR (DMSO-d_6, δ ppm) 9.6 (s, 1H), 9.1 (s, 1H), 7.8 (s, 4H), 6.8 (s, 1H), 3.76 (s, 3H). ^{13}C-NMR (DMSO-d_6) 161.7 (C_2), 59.7 (C_3), 40.1 (C_4), 133.3 ($C_{1'}$), 128.3 ($C_{2'}$, $C_{6'}$), 115.6 ($C_{3'}$, $C_{5'}$), 159.7 ($C_{4'}$), 55.2 (OMe), 114.7 (C≡N). EI-MS m/z (%): 218 (78.7) [$M^{+\cdot}$], 203 (100) [M – CH_3]. Anal. Calcd. for $C_{11}H_{10}N_2OS$ (218): C, 60.55; H, 4.59; N, 12.84; S, 14.68. Found: C, 60.08; H, 4.33; N, 12.64; S, 14.57.

4-(4-Chlorophenyl)-2-imino-thietane-3-carbonitrile (3c)

Recrystallized from benzene as yellow crystals, m.p. 230–232°C, yield 53%. IR (KBr): 3402, 3281, 3160 cm^{-1} (NH_2), 2922, 2900, 2870 cm^{-1} (C-H), 2208 cm^{-1} (C≡N), 1642 cm^{-1} (C=N). ^{1}H-NMR (DMSO-d$_6$, δ ppm) 9.8 (s, 1H), 8.9 (s, 1H), 7.3 (m, 4H), 6.3 (s, 1H). EI-MS m/z (%): 223 (100), 224 (5.7) [M + 1], 225 (32) [M + 2]. Anal. Calcd. for $C_{10}H_7ClN_2S$ (222.5): C, 53.93; H, 3.15; N, 12.58; S, 14.38; Cl, 15.95. Found: C, 54.31; H, 3.36; N, 11.99; S, 14.72; Cl, 16.21.

Action of hydrazine hydrate on 3a: Formation of the azine 6

A mixture of **3a** (1.3 g, 3 mmol) and hydrazine hydrate (1 g, 30 mmol) was refluxed in 20 mL ethanol for 1 h (TLC). Evaporation of excess ethanol left a dark brown solid which recrystallized from ethanol to give the azine **6** as dark brown crystals, m.p. 188–190°C, yield 33%. IR (KBr): 2910 cm^{-1} (C-H), 1627 cm^{-1} (C=N). ^{1}H-NMR (DMSO-d$_6$, δ ppm) 8.1 (s, 2H, N=CH), 6.8 (s, 4H$_{\text{arom.}}$), 3.9 (s, 12H, 4OMe), 3.8 (s, 6H, 2OMe). EI-MS m/z (%): 388 (100) [M^{+}], 194 (31.4), 167 (12.7). Anal. Calcd. for $C_{20}H_{24}N_2O_6$ (388): C, 61.85; H, 6.18; N, 7.22. Found: C, 62.09; H, 5.86; N, 7.43.

Authentic sample 6

To a solution of 3,4,5-trimethoxybenzaldehyde (0.39 g, 2 mmol) in ethanol (10 mL), hydrazine hydrate (0.5 mL) was added dropwise with stirring at room temperature for 0.5 h. The solid deposited was collected by filtration, dried, and recrystallized from ethanol.

Reaction of 3a with ethyl carbazate: Formation of ethyl-2-(3,4,5-trimethoxybenzyl-idine) hydrazine carboxylate 7

A mixture of **3a** (2.78 g, 10 mmol) and ethyl carbazate (1.04 g, 10 mmol) was refluxed in 50 mL ethanol for 4 h (TLC). The reaction mixture was concentrated, left to cool and the solid deposited was filtered off and recrystallized from ethanol to give the diazoester **7** as pale yellow crystals, m.p. 140–142°C, yield 45%. IR (KBr): 3268 cm^{-1} (NH), 1719 cm^{-1} (C=O). ^{1}H-NMR (CDCl$_3$, δ ppm) 8.7 (s, 1H), 8.2 (s, 1H), 7.2 (s, 2H$_{\text{arom.}}$), 4.1 (q, 2H, J = 8.2 Hz), 1.59 (t, 3H, J = 6.1 Hz).^{13}C-NMR (CDCl$_3$) 14.1 (Me), 59.2 (CH$_2$), 156.2 (CO), 144.8 (CH=N), 130.1, 108.6, 154.6, 139.6 (C$_{\text{arom.}}$), 55.1, 59.3, 56.1 (3OMe). EI-MS m/z (%): 282 (76.5) [M$^{+\cdot}$], 193 (100, M-EtOH, –HN=C=O), 192 (87.68), 181 (40.6), 91 (30.3), 65 (23.7). Anal. Calcd. for $C_{13}H_{18}N_2O_5$ (282): C, 55.32; H, 6.38; N, 9.93. Found: C, 55.14; H, 6.36; N, 10.16.

Formation of 3-phenyl-2,4-dithioxo-6-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile 8

To a solution of **3a** (2.78 g, 10 mmol) in 20 mL pyridine, phenylisothiocyanate (2 mL, 15 mmol) was added, and the reaction mixture was refluxed for 6 h (TLC) then left to cool and acidified with cold dilute hydrochloric acid. The crud solid obtained was collected by suction, washed with water, dried, and recrystallized from ethanol to give compound **8** as brown powder, m.p. 230–232°C, yield 70%. IR (KBr): ν_{NH} centered at 3446 cm^{-1}, $\nu_{C=S}$ at 1133 cm^{-1}, 1634 cm^{-1} for $\nu_{C=N}$. ^{1}H-NMR (DMSO-d_6, δ ppm) 11.8 (s, 1H), 7.2-6.8 (m, 7$H_{arom.}$), 3.93 (s, 6H, 2OMe), 3.84 (s, 3H, OMe). EI-MS m/z (%): 387 (43.6) [M-CN], 79 (81) for the molecular ion peak $C_4H_3N_2^{+\cdot}$, 52 (100). Anal. Calcd. for $C_{20}H_{19}N_3O_3S_2$ (413): C, 58.11; H, 4.60; N, 10.17; S, 15.49. Found: C, 58.71; H, 4.62; N, 9.93; S, 15.08.

2,4-Dithioxo-6-imino-5-(3,4,5-trimethoxybenzylidine)3H-1,3-thiazine 9

A mixture of **3a** (2.78 g, 10 mmol) and carbon disulfide (5 mL) in potassium hydroxide (10%) (20 mL) was refluxed in a water bath for 6 h (TLC). The excess solvent was collected by distillation, and the reaction mixture was left to cool, then acidified with cold dilute hydrochloric acid. The deposited solid was collected by suction, washed with cold water, dried, and recrystallized from benzene to give the thiazine derivative **9** as brown crystals, m.p. 142–144°C, yield 38%. IR (KBr): 3394, 3207 cm^{-1} (NH), 2933, 2847 cm^{-1} (C-H), 1630 cm^{-1} (C=N), 1339 cm^{-1} (C=S). ^{1}H-NMR ($CDCl_3$, δ ppm) 8.6 (s, 1H), 8.1 (s, 1H), 6.9 (s, 1H), 6.7 (s, 2$H_{arom.}$), 3.93 (s, 6H, 2OMe), 3.81 (s, 3H, OMe).^{13}C-NMR ($CDCl_3$) 204 (C_2, C=S), 198.2 (C_4, C=S), 122.3 (C_5), 162.6 (C_6, C=NH), 141.3 (C_5, $= \underline{CH}$), 129.1 ($C_{1'}$), 107.7 ($C_{2'}$, $C_{6'}$), 157.1 ($C_{3'}$, $C_{5'}$), 139.2 ($C_{4'}$), 54.9, 58.9, 55.1 (3OMe). EI-MS m/z (%): 354 (11.7) [$M^{+\cdot}$], 278 (39.8, M-CS_2), 93 (100). Anal. Calcd. for $C_{14}H_{14}N_2O_3S_3$ (354): C, 47.46; H, 3.95; N, 7.91; S, 27.12. Found: C, 47.08; H, 4.32; N, 8.26; S, 26.83.

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