

Polarized Ketene Dithioacetals. Part 65.¹ Studies on Additions of 2-Aroyl-3-cyano-1,1-bis(methylthio)propenide Anions to Hetero-multiple Bonds¹

Laitonjam W. Singh, Hiriakkanavar Ila, and Hiriakkanavar Junjappa*

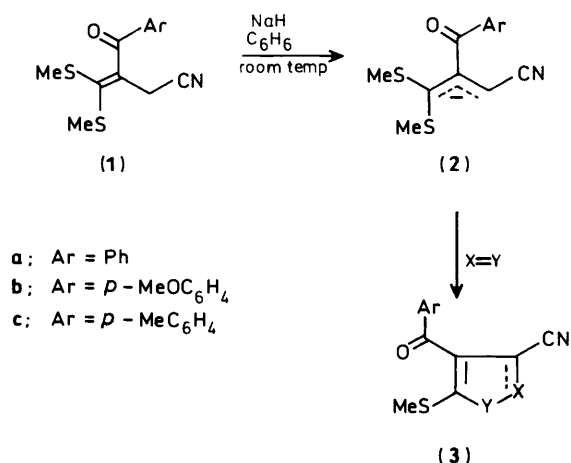
Department of Chemistry, North-Eastern Hill University, Shillong 793 003, Meghalaya, India

2-Aroyl-3-cyano-1,1-bis(methylthio)propenide anions (**2a** and **b**) undergo stepwise [3 + 2] cyclocondensation with aryl isothiocyanates followed by elimination of a methylthio group to give the corresponding 4-aryloxy-2-arylamino-5-(methylthio)thiophene-3-carbonitriles (**5a—c**). Addition of the anion (**2a**) (Ar = Ph) to 4-chlorobenzaldehyde under similar conditions yielded the cyclic hemiacetal (**8**), which in the presence of BF₃·Et₂O and methanol afforded the *O*-methyl derivative (**12**) and 2-(4-chlorophenyl-3-bis(methylthio)methyl-5-phenylfuran-3-carbonitrile (**13**). Addition of the propenide anions (**2a** and **c**) to benzonitrile gave only dimeric products (**14a** and **b**), respectively. Mechanisms for these reactions are suggested.

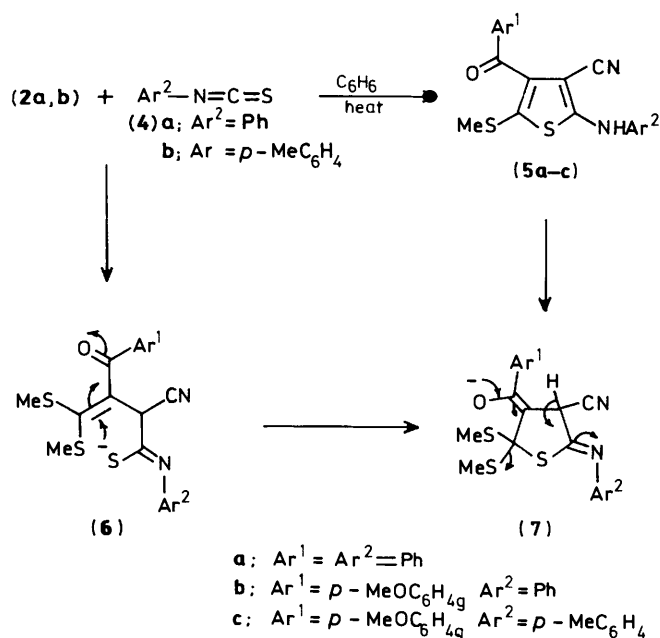
We have previously reported that the α -oxoketene dithioacetals derived from propiophenones readily undergo a base-catalysed 1,3-alkylthio shift to give the corresponding 3-alkylthio-2-alkylthiomethylacrylophenones.^{2,3} Mechanistic studies have revealed that the rearrangement involves initial (reversible) formation of 2-aryloxy-1,1-bismethylthiopropenide anions. Other cyclic α -methylene and α -allyl oxoketene dithioacetals afforded either rearrangement products from 1,3- and 1,5-alkylthio shifts, respectively, or products derived from subsequent transformation of bis(methylthio)-2-oxopropenide anions.^{4,5} We now report that when the dithioacetal (**1a**), having more acidic methylene protons, is treated with sodium hydride in dimethylformamide (or benzene) under identical conditions, the red-coloured 3-cyanopropenide anion (**2a**) is formed, which on quenching in dilute acid yields the starting material (**1a**) in nearly quantitative yield. No trace of any other product (rearranged or not) was detected in the reaction mixture. The propenide anions (**2**) appeared to be suitable three-carbon fragments for an anionic [3 + 2] cyclocondensation process;⁶ we therefore decided to study their reactions with hetero-multiple bonds, in the hope of developing new synthetic routes to five-membered heterocycles (Scheme 1).^{7,8} We report here our studies of the reactions of the anions (**2**) with aryl isothiocyanates, 4-chlorobenzaldehyde, and benzonitrile.

Results and Discussion

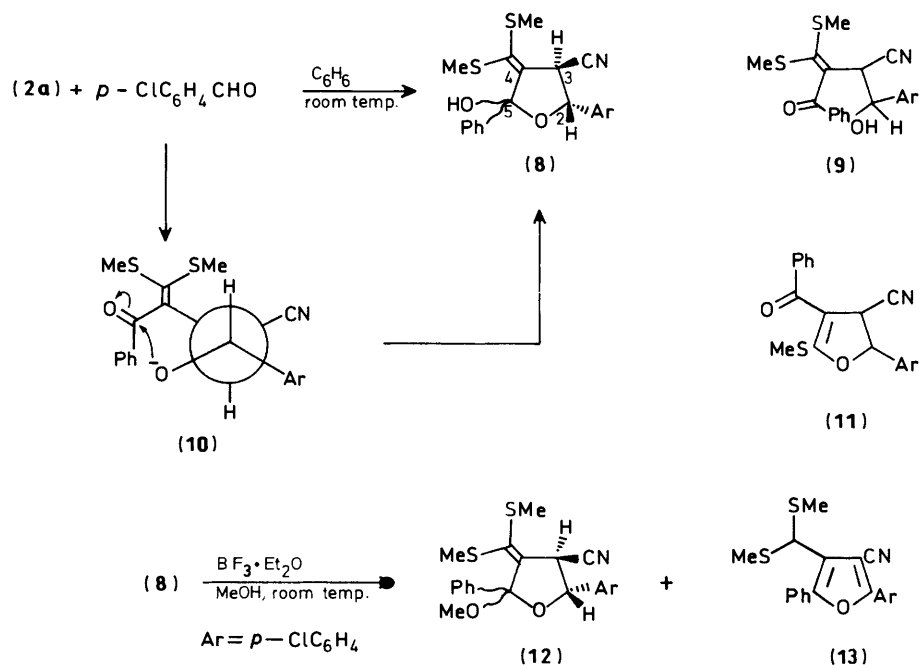
(a) *Reaction of the Anions (2) with Aryl Isothiocyanates.*—The dithioacetals (**1a—c**) were prepared according to the reported procedure.⁹ The anion (**2a**) was generated from (**1a**) by sodium hydride in benzene at room temperature (3–4 h) and treated with phenyl isothiocyanate. Work-up yielded only starting material (**1a**) along with some polymeric product. However, in another experiment, when the reaction mixture was refluxed for 2 h, a light yellow crystalline solid (65%) was obtained, which was characterized as 2-anilino-4-benzoyl-5-(methylthio)thiophene-3-carbonitrile (**5a**). The mass spectrum of (**5a**) exhibited a molecular ion peak at *m/z* 350, and its i.r. spectrum (KBr) displayed sharp bands at 3 295m (NH), 2 210m (CN), and 1 630 (CO) cm⁻¹. The 4-methoxydithioacetal (**1b**) similarly reacted with phenyl and 4-methylphenyl isothiocyanates to give the corresponding thiophenes (**5b** and **c**), respectively, under identical conditions. The probable mechanism of formation of (**5**) is shown in Scheme 2. Nucleophilic addition of (**2**) to the aryl isothiocyanate gives the intermediate thioimide (**6**); this is followed by intramolecular conjugate addition by sulphur and subsequent elimination of a methylthio group. The overall process is thus a stepwise anionic [3 + 2] cycloaddition of the



Scheme 1.



Scheme 2.



Scheme 3.

propenide anion (**2**) to a C=S bond, providing a novel route to substituted thiophenes.*

(b) *Reaction of the Anion (2a) with 4-Chlorobenzaldehyde.*—A suspension of (**2a**) in benzene (generated as earlier) and 4-chlorobenzaldehyde was stirred at room temperature (18 h); work-up gave a colourless solid (62%) characterized as the cyclic hemiacetal (**8**). The i.r. spectrum (KBr) exhibited a strong absorption at 3 350 cm⁻¹ (ν_{OH}) along with a medium-intensity absorption at 2 250 cm⁻¹ (ν_{CN}). The open-chain hydroxy ketone structure (**9**) was eliminated by the absence of carbonyl bands between 1 500 and 1 800 cm⁻¹. The ¹H n.m.r. spectrum showed (**8**) to exist as a diastereoisomeric mixture (1:1) in solution. The relative stereochemistry at C-2 and C-3 was tentatively assigned as *trans* because of the absence of vicinal coupling^{11,12,13a} between 2-H and 3-H [δ 6.04 (s, 0.5 H) and 6.08 (s, 0.5 H), and δ 4.08 (s, 0.5 H) and 4.16 (s, 0.5 H), respectively].[†] The ¹³C n.m.r. spectrum further supported the existence of diastereoisomeric hemiacetals in solution. Each ring carbon atom (except C-1 of the two aryl groups) gave rise to a pair of peaks of unequal intensities, and the absence of signals beyond δ 160 (carbonyl carbon) further ruled out the open-chain structure (**9**). In the formation of the hemiacetal (**8**) the initially formed alkoxide ion (**10**) preferentially adds to carbonyl carbon in 5-*exo-trig* fashion to give the expected product (**8**) rather than following the high-energy 5-*endo-trig* pathway to the corresponding dihydrofuran (**11**).¹⁴ In another experiment, when (**2a**) was treated with 4-chlorobenzaldehyde in refluxing benzene (1 h), only a polymeric mixture was obtained. However, when (**8**) was treated with methanol in the presence of a catalytic amount of BF₃·Et₂O, work-up and column chromatography gave the corresponding

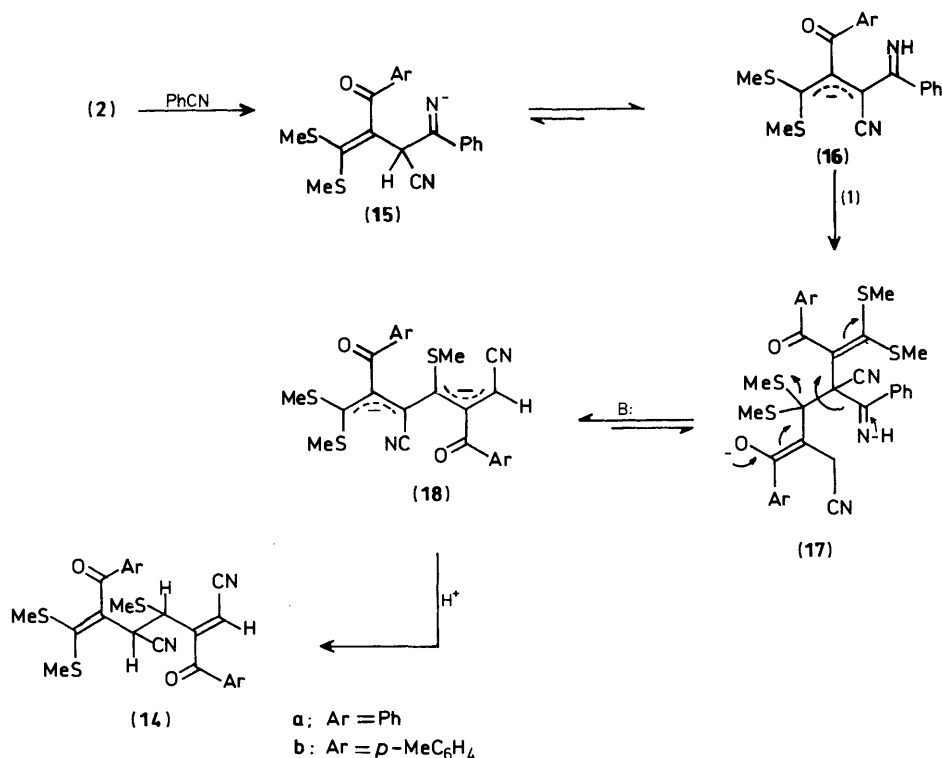
diastereoisomeric *O*-methyl derivatives (**12**) (55%) along with a colourless solid (40%). The solid was characterized as the substituted furan (**13**) (Scheme 3). The formation of the furan (**13**) from (**8**) evidently involves dehydration preceded by a 1,3-prototropic shift.

(c) *Reaction of the Anion (2a) with Benzonitrile.*—A suspension of (**2a**) and benzonitrile in benzene was stirred at room temperature for 32 h. Work-up then gave a colourless solid identified as the dimer (**14a**) on the basis of spectral and analytical data. Elemental analysis was in agreement with the molecular formula C₂₅H₂₂N₂O₂S₃, and the mass spectrum exhibited a peak at m/z 431 ($M^+ - 47$, 18%). The ¹H n.m.r. spectrum displayed three singlets, at δ 2.06 (3 H), 2.43 (3 H), and 2.52 (3 H) due to the three methylthio groups. The two allylic methine proton signals appeared as sharp doublets (J 12 Hz) at δ 5.00 (1 H, CHSCH₃) and 5.90 (1 H, CHCN). The vicinal coupling constant (12 Hz) agrees with an *erythro*-configuration,^{13b} with the bulkier groups in *anti*-conformation. The olefinic proton signal was merged with the aromatic multiplet between δ 7.20 and 7.95 (11 H). However in the case of 4-methyl substituted dimer (**14b**), the olefinic signal was located at δ 7.60 (s, 1 H); its low-field position points to a *Z*-configuration about the double bond, with the proton *cis* to the aryl group.³ The ¹³C n.m.r. spectrum (CDCl₃) of (**14b**) supported the dimeric structure [δ 33.80 (d, CHSCH₃) and 36.57 (d, CHCN)].

The dimers (**14**) appear to be formed by self-condensation of (**1**) through initial Michael addition of the carbanion (**2**). However (**1a**) was recovered unchanged when stirred with sodium hydride in the absence of benzonitrile under identical conditions. Thus benzonitrile has a role to play in the formation of (**14**) from (**1**). The probable mechanism is shown in Scheme 4. The carbanion (**2**) adds to benzonitrile to give the intermediate anion (**15**), which by a subsequent 1,3-proton shift gives the more stable propenide anion (**16**). Subsequent Michael addition of (**16**) to (**1**), followed by elimination of a methylthio group and benzonitrile, gives, after equilibration, the thermodynamically stable dianion (**18**),³ which yields the more stable *erythro*-product (**14**) on acidification.

* A similar approach to the synthesis of 2-anilino-6-methylthiopyran-4-ones through base-catalysed [4 + 2] cyclocondensation of acylketene dithioacetals with aryl isothiocyanates has been reported recently by us.¹⁰

† A Dreiding model revealed that the torsion angle for the *trans*-isomer was 100–110°, whereas that for the *cis*-isomer was 0–10°; this further supports the *trans*-stereochemistry at C-2 and C-3.



Scheme 4.

The reaction of (2a) with benzonitrile in refluxing benzene did not give any identified product.

Experimental

M.p.s were determined with a Thomas Hoover apparatus. I.r. spectra were recorded with a Perkin-Elmer 297 spectrometer and ¹H n.m.r. spectra with a Varian EM-390 90 MHz spectrometer (tetramethylsilane as internal reference). ¹³C N.m.r. spectra were recorded with a Bruker WM-400 spectrometer, and mass spectra with a JEOL JMS-D 300 spectrometer by direct insertion at 70 eV.

Reactions of the Anions (2) with Aryl Isothiocyanates.—*2-Anilino-4-benzoyl-5-(methylthio)thiophene-3-carbonitrile (5a)*. To a stirred suspension of sodium hydride (1.44 g, 0.03 mol; 50% suspension in mineral oil) in dry benzene (15 ml) a solution of the dithioacetal (1a) (2.63 g, 0.01 mol) in benzene (15 ml) was added dropwise, and the mixture was further stirred at room temperature for 5 h. A solution of phenyl isothiocyanate (2.02 g, 0.015 mol) in benzene (20 ml) was added slowly (0.5 h) with stirring, which was continued for a further 2 h at room temperature. The mixture was refluxed for 2 h, poured into crushed ice, and neutralized with 20% acetic acid (5 ml); the organic layer was separated and the aqueous layer was extracted with CHCl₃ (3 × 50 ml). The combined extracts were washed with water (3 × 50 ml), dried (Na₂SO₄), and concentrated. The viscous residue was purified by column chromatography over silica gel. Elution with hexane–benzene (3:1) gave the *thiophene (5a)* (2.30 g, 65%) as light yellow crystals, m.p. 136–137 °C (from chloroform–hexane) (Found: C, 65.4; H, 4.3; N, 7.8. C₁₉H₁₄N₂O₂S₂ requires C, 65.1; H, 4.0; N, 8.0%); δ_H(CDCl₃) 2.35 (3 H, s, SMe) and 7.08–7.82 (11 H, m, NH, ArH); λ_{max}(MeOH) 295 (log ε 3.88), and 325 nm (3.72); *m/z* 350 (*M*⁺, 100%) and 325 (*M*⁺ – 15, 90).

2-Anilino-4-(4-methoxybenzoyl)-5-(methylthio)thiophene-3-

carbonitrile (5b). This was prepared from (1b) and (4a) as for (5a) as light yellow crystals (52%), m.p. 122 °C (from chloroform–hexane) (Found: C, 63.4; H, 4.5; N, 7.1. C₂₀H₁₆N₂O₂S₂ requires C, 63.2; H, 4.2; N, 7.4%); ν_{max}(KBr) 3 200 (NH), 2 220 (CN), and 1 610 cm⁻¹ (CO); δ_H(CDCl₃) 2.45 (3 H, s, SMe), 3.96 (3 H, s, OMe), and 7.05–8.12 (10 H, m, NH, ArH); λ_{max}(MeOH) 380 (log ε 3.75) and 325sh nm (3.80); *m/z* 380 (*M*⁺, 7%).

4-(4-Methoxybenzoyl)-2-(4-methylanilino)-5-(methylthio)thiophene-3-carbonitrile (5c). This was prepared from (1b) as for (5a) as light yellow crystals (76%), m.p. 102–103 °C (from chloroform–hexane) (Found: C, 64.0; H, 4.8; N, 6.9. C₂₁H₁₈N₂O₂S₂ requires C, 64.0; H, 4.6; N, 7.1%); ν_{max}(KBr) 3 275 (NH), 2 205 (CN), and 1 605 cm⁻¹ (CO); δ_H(CDCl₃) 2.32 (6 H, s, SMe, Me), 3.80 (3 H, s, OMe), and 6.87–7.85 (9 H, m, NH and ArH); λ_{max}(MeOH) 284 (log ε 3.67) and 328sh nm (3.90); *m/z* 394 (*M*⁺, 15%).

Reaction of the Anion (2a) with 4-Chlorobenzaldehyde.—*4-Bis(methylthio)methylene-2-(4-chlorophenyl)-5-hydroxy-5-phenyltetrahydrofuran-3-carbonitrile (8)*. To a stirred suspension of sodium hydride (50% suspension in mineral oil; 1.44 g, 0.03 mol) and the dithioacetal (1a) (2.63 g, 0.01 mol) in benzene (30 ml) [as for (5a)], 4-chlorobenzaldehyde (2.1 g, 0.015 mol) in benzene (20 ml) was added dropwise during 0.5 h, and the mixture was stirred at room temperature for a further 18 h. Work-up and column chromatography as for (5a) gave the *furan (8)* as a colourless solid (2.40 g, 62%), m.p. 194–195 °C (from chloroform–hexane) (Found: C, 59.7; H, 4.7; N, 3.1. C₂₀H₁₈ClNO₂S₂ requires C, 59.5; H, 4.5; N, 3.5%); δ_H[(CD₃)₂SO–CDCl₃] 1.75 (1.5 H, s, SMe), 1.87 (1.5 H, s, SMe), 2.21 (1.5 H, s, SMe), 2.28 (1.5 H, s, SMe), 4.08 (0.5 H, s, 3-H), 4.16 (0.5 H, s, 3-H), 6.03 (0.5 H, s, 2-H), 6.08 (0.5 H, s, 2-H), and 7.30–7.75 (9 H, m, ArH); δ_C[(CD₃)₂SO] 14.47 (q, SMe), 15.50 (q, SMe), 45.77 and 46.53 (d, CHCN), 82.94 and 84.74 (d, C-2), 109.69 and 110.54 (s, C-5), 112.56 and 112.70 (s, C-4), 126.38 and 126.82 (s, CN), 127.86, 128.49, 128.78, 128.96, (CHAR) 129.24

(C—Cl), 156.71 and 158.24 [s, (Me₂S)₂C=C]; *m/z* 357 (17%), 355 (45, M⁺ - MeSH), 339 (17), and 337 (43, M⁺ - MeSH + H₂O).

Reaction of the Furan (8) with Boron Trifluoride-Ether Complex and Methanol.—To an ice-cold solution of the furan (8) (2.0 g, 0.005 mol) in methanol (10 ml), BF₃·Et₂O (1 ml) was added slowly (20 min) and the mixture was stirred at 5–10 °C for 3 h, poured into cold water, and extracted with CHCl₃ (3 × 25 ml). The extracts were washed successively with saturated aqueous NaHCO₃ (3 × 25 ml), saturated brine (2 × 25 ml), and water (25 ml), dried (Na₂SO₄), and concentrated. The viscous residue was purified by column chromatography over silica gel. Elution with hexane gave 4-bis(methylthio)methyl-2-(4-chlorophenyl)-5-phenylfuran-3-carbonitrile (13) as a colourless solid (0.77 g, 40%), m.p. 162–163 °C (from chloroform-hexane) (Found: C, 62.4; H, 4.0; N, 3.3. C₂₀H₁₆ClNOS₂ requires C, 62.3; H, 4.15; N, 3.6%; *v*_{max}(KBr) 2 210 cm⁻¹; δ_H 2.00 (6 H, s, SMe), 5.00 [1 H, s, (Me₂S)CH], and 7.20–8.19 (9 H, m, ArH); *m/z* 385 (M⁺, 2%), 340 (39), and 338 (100), (M⁺ - 47). Further elution, with benzene-hexane (1:3) gave the *O*-methyl derivative (12) as a viscous semisolid (1.1 g, 55%) (Found: C, 60.4; H, 5.0; N, 3.1. C₂₁H₂₀ClNO₂S₂ requires C, 60.4; H, 4.9; N, 3.35%; *v*_{max}(CCl₄) 2 220 cm⁻¹; δ_H 1.67 (1.5 H, s, SMe), 1.79 (1.5 H, s, SMe), 2.13 (1.5 H, s, SMe), 2.16 (1.5 H, s, SMe), 3.17 (1.5 H, s, OMe), 3.25 (1.5 H, s, OMe), 3.95 (0.5 H, s, 2-H), 4.06 (0.5 H, s, 2-H), 5.82 (0.5 H, s, 3-H), 5.88 (0.5 H, s, 3-H), and 7.32 (9 H, m, ArH); *m/z* 417 (M⁺, 6%).

Reactions of the Anions (2a and c) with Benzonitrile.—To a stirred suspension of sodium hydride (50% suspension in mineral oil; 1.44 g, 0.03 mol) and (1a) (2.63 g, 0.01 mol) in benzene (30 ml) [as for (5a)], a solution of benzonitrile (1.0 g, 0.01 mol) in benzene (20 ml) was added (0.5 h) and stirring was continued for a further 32 h. Work-up as for (5a) gave crude material which was purified by column chromatography over silica gel. Elution with hexane-benzene (1:1) afforded 3-benzoyl-5-[α-bis(methylthio)methylenephenacyl]-4-methylthiohex-2-enedinitrile (14a) as a colourless solid (2.00 g, 83%), m.p. 191–192 °C (from benzene-hexane) (Found: C, 63.0; H, 4.8; N, 5.6. C₂₅H₂₂N₂O₂S₃ requires C, 62.8; H, 4.6; N, 5.9%; *v*_{max}(KBr) 2 250 (CN), 1 630 (CO), and 1 620 cm⁻¹ (CO) (¹H n.m.r. data in text).

3-(4-Methylbenzoyl)-5-[4-methyl-α-bis(methylthio)methylene-phenacyl]-4-methylthiohex-2-enedinitrile (14b) was similarly obtained (yield 76%); m.p. 109–110 °C (from benzene-hexane)

(Found: C, 64.1; H, 5.3; N, 5.3. C₂₇H₂₆N₂O₂S₃ requires C, 64.0; H, 5.1; N, 5.5%; *v*_{max}(KBr) 2 235 (CN) and 1 640 cm⁻¹ (CO); δ_H(CDCl₃) 2.12 (3 H, s, SMe), 2.39 (6 H, s, SMe), 2.42 (3 H, s, SMe), 2.50 (3 H, s, SMe), 4.94 (1 H, d, *J* 12 Hz, CHSMe), 5.90 (1 H, d, *J* 12 Hz, CHCN), 7.10–7.35 (4 H, m, ArH), 7.60 (1 H, s, olefinic), and 7.38–7.92 (4 H, A₂B₂, m, ArH); δ_C(CDCl₃) 16.91, 17.79, and 18.21 (SMe), 21.31 and 21.50 (Me), 33.80 (d, CHSMe), 36.57 (d, CHCN), 115.38 and 115.86 (s, CN), 128.32, 128.67, 128.95, and 129.05 (CH of Ph); 126.23, 132.10, 134.44, and 134.56 (C-1 and C-4 of Ph), 142.59 [s, (Me₂S)₂C=CCO], 144.24 (s, C=CHCN); 150.50 [s, (Me₂S)₂C=CCO], 157.04 (d, C=CH-CN), 191.40 (s, C=O), and 193.95 (s, C=O); *m/z* 459 (M⁺ - 47, 4%).

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References

- 1 Part 64, C. V. Asokan, S. Bhattacharji, H. Ila, and H. Junjappa, *Synthesis*, 1988, 281.
- 2 S. Apparao, A. Rahman, H. Ila, and H. Junjappa, *Tetrahedron Lett.*, 1982, **23**, 971.
- 3 S. Apparao, H. Ila, and H. Junjappa, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2837.
- 4 S. Apparao, A. Datta, H. Ila, and H. Junjappa, *J. Chem. Soc., Perkin Trans. 1*, 1984, 921.
- 5 S. Apparao, S. S. Bhattacharji, H. Ila, and H. Junjappa, *J. Chem. Soc., Perkin Trans. 1*, 1985, 641.
- 6 P. Beak and K. D. Wilson, *J. Org. Chem.*, 1987, **52**, 218, and references therein.
- 7 W. Bannwarth, R. Eidenschink, and T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 468.
- 8 T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 627.
- 9 S. Apparao, H. Ila, and H. Junjappa, *Synthesis*, 1981, 65.
- 10 L. W. Singh, H. Ila, and H. Junjappa, *Synthesis*, 1985, 531.
- 11 L. E. Erickson, *J. Am. Chem. Soc.*, 1965, **87**, 1867.
- 12 A. Banerji, M. Sarkar, T. Ghoshal, S. C. Pal, and J. N. Shoolery, *Tetrahedron*, 1984, **40**, 5047.
- 13 L. M. Jackman and S. Sternhell in 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon, Oxford, 1969, (a) pp. 283–288; (b) pp. 291–292.
- 14 J. E. Baldwin and M. J. Husch, *Tetrahedron*, 1982, **38**, 2939, and references cited therein.

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