Synthesis of 3-Aroylnicotinonitriles from Aroylketene Dithioacetals

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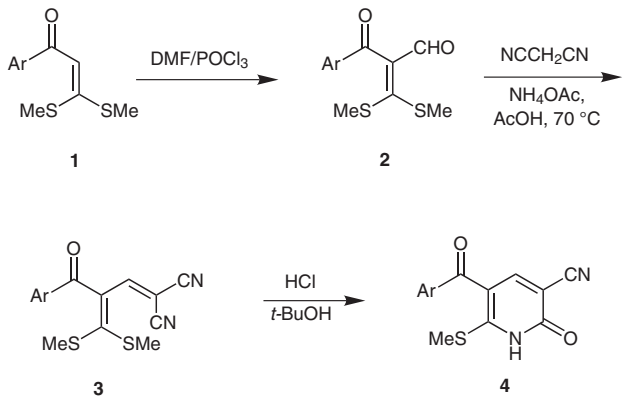
Abstract: The Knoevenagel adducts of 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes and malononitrile were cyclized in the presence of diisopropylamine to afford 5-aroyl-2,6-bis(methylsulfanyl)nicotinonitriles. Cyclization in the presence of aqueous ammonia gave 2-amino-5-aroyl-6-(methylsulfanyl) nicotinonitriles. A multicomponent reaction involving aroylketene dithioacetals, malononitrile and Vilsmeier reagent gave 5-aroyl-2-chloro-6-(methylsulfanyl)nicotinonitrile.

Key words: ketene dithioacetals, Knoevenagel condensation, Vilsmeier–Haack reaction, nicotinonitriles, multicomponent reaction

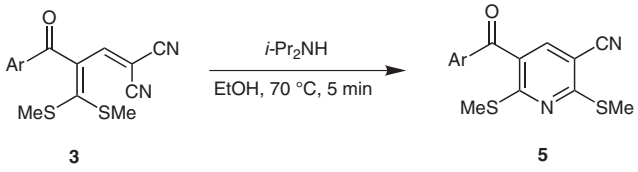
α-Oxoketene dithioacetals are highly versatile intermediates in organic synthesis.[1–4] Recently we disclosed that the reaction of aroyl ketene dithioacetals with Vilsmeier–Haack reagent afford 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes in excellent yields.[5] Rudorf et al. have explored the synthetic utility of ketene dithioacetals, having an aldehyde functionality at the α-position, in the construction of functionalized heterocycles.[6,7] We have also reported that the Knoevenagel adducts **3** derived from the α-formyl ketene dithioacetals **2** undergo acid-catalyzed cyclization to give 2-pyridone derivatives (Scheme 1).[5]



Scheme 1

The cyclization of 1,3-butadienes, with a cyano group at one terminal and alkoxy, amino or alkylthio groups at the other terminal, to pyridines is initiated by addition of a nucleophile at the carbon of the nitrile group.[8–11] Synthesis of pyridine derivatives with a halo, amino or alkylthio group at the 2-position can be achieved by such cyclizations. In this paper we report the cyclization of 2-aroyl-2-[3,3-bis(methylsulfanyl)-2-propylidene]malononitriles **3** to give 5-aroyl-2,6-bis(methylsulfanyl)nicotinonitriles **5** and 2-amino-5-aroyl-6-(methylsulfanyl)nicotinonitriles **6**. A one-pot three-component reaction involving aroyl ketene dithioacetals, malononitrile and Vilsmeier reagent to afford 5-aroyl-2-chloro-6-(methylsulfanyl)nicotinonitriles **7** has also been described. The pyridine moiety is present in numerous biologically active compounds, which have found applications as pharmaceuticals and agrochemicals.[12–14] Nicotinonitriles are valuable for their synthetic applications as well as their medicinal importance and the development of new synthetic methods to synthesize them continues to be important.

The attempted cyclization of propylidene malononitriles **3**, in the presence of potassium carbonate and methanethiol in *N*,*N*-dimethylformamide at 110 °C under the conditions reported by Peseke et al.[8] gave only the aroylketene dithioacetals **1** instead of the expected pyridines **5** apparently by a reaction involving an addition elimination mechanism. We envisioned that the desired cyclization might proceed in the presence of sterically-hindered secondary amines.[15] Thus 2-aroyl-2-[3,3-bis(methylsulfanyl)-2-propylidene] malononitriles **3** were treated with one equivalent of diisopropylamine at 70 °C for five minutes in a closed vessel to give the 5-aroyl-2,6-bis(methylsulfanyl) nicotinonitriles **5** in 30–60% yields (Scheme 2, Table 1).



Scheme 2

Table 1 Synthesis of 5-Aroyl-2,6-bis(methylsulfanyl)nicotinonitriles

5	Ar	Yield (%)
a	Ph	40
b	4-MeOC$_6$H$_4$	34
c	4-MeC$_6$H$_4$	42
d	4-ClC$_6$H$_4$	60

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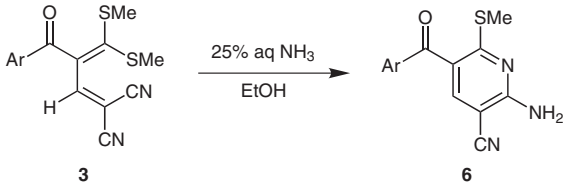
Table 1 Synthesis of 5-Aroyl-2,6-bis(methylsulfanyl)nicotinonitriles

5	Ar	Yield (%)
e	2-naphthyl	30

The cyclization induced by addition of ammonia to the nitrile group of the push-pull diene **3** was examined next. When 2-aroyl-2-[3,3-bis(methylsulfanyl)-2-propylidene]malononitriles **3** were treated with an excess of aqueous ammonia[16,17] in ethanol at 70 °C in a closed vessel for 5 min, 2-amino-5-aroyl-6-(methylsulfanyl)nicotinonitriles **6** were formed in 54–67% yields (Scheme 3, Table 2).



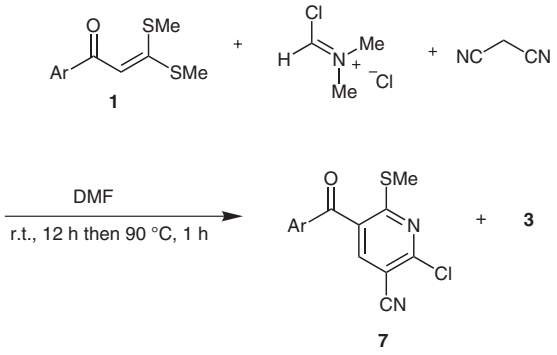
3 6

Scheme 3

Table 2 Synthesis of 2-Amino-5-aroyl-6-methylsulfanylnicotinonitriles

6	Ar	Yield (%)
a	Ph	63
b	4-$MeOC_6H_4$	59
c	4-MeC_6H_4	56
d	4-ClC_6H_4	67

The reaction of suitably substituted alkylidene malononitriles with Vilsmeier–Haack reagent leads to iminoalkylation followed by cyclization to give functionalized 2-chloropyridines. We envisioned a multicomponent[18–20] strategy in which a mixture of α-oxoketene dithioacetal and malononitrile is treated with Vilsmeier reagent. Iminoalkylation at the α-position of the ketene dithioacetals would be followed by condensation with malononitrile and subsequent cyclization of the adduct to afford 2-chlorosubstituted nicotinonitriles. The Vilsmeier–Haack reagent was prepared by the slow addition of phosphorus oxychloride to *N,N*-dimethylformamide at 0 °C, followed by stirring at room temperature for 15 minutes. To this a mixture of malononitrile and benzoylketene dithioacetal **1a** was added and stirred at room temperature for 12 hours followed by heating at 90 °C for one hour. Usual work-up using aqueous saturated potassium carbonate solution, and purification by chromatography gave 5-benzoyl-2-chloro-6-(methylsulfanyl) nicotinonitrile **7a** in 47% yield along with the adduct **3a** in 15% yield. The reaction was extended to other substituted ketene dithioacetals to obtain substituted nicotinonitriles **7b–d** in 21–76% overall yields (Scheme 4, Table 3).



Scheme 4

Table 3 Synthesis of 5-Aroyl-2-chloro-6-methylsulfanylnicotinonitriles **7a–d**

	Ar	Yield (%)	
		7	**3**
3a, **7a**	Ph	47	15
3b, **7b**	4-$MeOC_6H_4$	27	52
3d, **7c**	4-ClC_6H_4	21	45
3f, **7d**	4-$NO_2C_6H_4$	76	–

In conclusion, we have shown that the Knoevenagel adducts of 2-aroyl-3,3-bis(alkylsulfanyl)arylaldehydes undergo cyclization in the presence of diisopropyl amine to give 5-aroyl-2,6-bis(methylsulfanyl)nicotinonitriles and in the presence of aqueous ammonia to give 2-amino-5-aroyl-6-(methylsulfanyl)nicotinoniriles. We have also demonstrated that a multicomponent reaction involving aroylketene dithioacetals, malononitrile and Vilsmeier reagent lead to the formation of 5-aroyl-2-chloro-6-(methylsulfanyl)nicotinonitriles.

Melting points were determined on a Buchi-530 melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-470 spectrometer. The ^1H NMR spectra were recorded on a Bruker WM 300 (300 MHz) using TMS as internal standard and $CDCl_3$ as solvent. The ^{13}C NMR spectra were recorded on a Bruker WM 300 (75.47 MHz) spectrometer using $CDCl_3$ as solvent. Both ^1H NMR and ^{13}C NMR values are expressed as δ (ppm). The Electron Impact Mass spectra were obtained on a Finnigan-Mat 312 instrument or Schimadzu GCMS 5050 model instrument. The CHN analyses were done on an Elementar Vario EL III Carlo Erba 1108 instrument.

All reagents were commercially available and were purified before use. The previously reported aroylketene dithioacetals were prepared by the known procedure.[21] The 2-[3,3-bis(methylsulfanyl)-2-aroyl-2-propylidene] malononitriles **3** were prepared according to our recently reported procedure.[5] Anhydrous sodium sulfate was used as the drying agent.

2-[3,3-Bis(methylsulfanyl)-2-(2-naphthoyl)-2-propylidene]malononitrile (3e)

Obtained by the Knoevenagel condensation reaction[5] of 3,3-bis(methylsulfanyl)-2-(2-naphthoyl)acrylaldehyde (1.51 g, 5 mmol) with

malononitrile (495 mg, 7.5 mmol) in the presence of ammonium acetate (1.5 g, 20 mmol) and AcOH (5 mL).

Deep yellow crystals; yield: 1.44 g (82%); mp 122–124 °C.

IR (KBr): 2214, 1657, 1532, 1451, 1288, 1162, 912, 812 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.46 (s, 6 H, SCH_3), 7.26–7.64 (m, 2 H, ArH), 7.88–8.01 (m, 4 H, ArH), 8.17 (s, 1 H, ArH), 8.29 (s, 1 H, vinylic).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 18.82, 81.80, 111.31, 114.51, 124.19, 127.10, 128.02, 129.25, 129.80, 132.54, 133.89, 136.20, 136.31, 151.34, 166.32, 192.10.

MS (EI): *m*/*z* (%) = 350 (12) [M^+], 335 (9), 155 (100), 127 (98), 115 (4), 77 (23).

Anal. Calcd for $C_{19}H_{14}N_2OS_2$: C, 65.12; H, 4.03; N, 7.99. Found: C, 65.31; H, 4.05; N, 7.04.

Synthesis of 5-Aroyl-2,6-bis(alkylsulfanyl)nicotinonitriles 5; General Procedure

The appropriate 2-[2-aroyl-3,3-bis(methylsulfanyl)-2-propylidene]malononitrile **2** (1.7 mmol) and diisopropylamine was taken up in EtOH (10 mL), equipped with a reflux condenser, flushed with nitrogen and closed with a nitrogen-filled balloon. The solution was heated at 70 °C for 5 min and then cooled to r.t.. The EtOH was evaporated and the residue was dissolved in $CHCl_3$, washed with H_2O, dried over anhyd Na_2SO_4 and the solvent was evaporated. The crude product obtained was purified by column chromatography over silica gel using hexane–EtOAc (19:1) as the eluent.

5-Benzoyl-2,6-bis(methylsulfanyl)nicotinonitrile (5a)

Yellow crystals; yield: 200 mg (40%); mp 124–126 °C.

IR (KBr): 3052, 2919, 2217, 1646, 1560, 1481, 1288, 997 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.54 (s, 3 H, SCH_3), 2.65 (s, 3 H, SCH_3), 7.43 (t, *J* = 8 Hz, 2 H, ArH), 7.55 (t, *J* = 8 Hz, 1 H, ArH), 7.59 (d, *J* = 8 Hz, 2 H, ArH), 7.69 (s, 1 H, H-4).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 13.99, 14.87, 100.35, 115.81, 125.195, 129.21, 129.98, 133.65, 137.26, 142.35, 165.76, 167.17, 193.63.

MS (EI): *m*/*z* (%) = 300 (100) [M^+], 288 (3.8), 286 (20.9), 268 (23.8), 253 (10.3), 224 (8.5), 210 (3.9), 105 (22), 91 (7), 77 (42).

Anal. Calcd for $C_{15}H_{12}N_2OS_2$: C, 59.97; H, 4.03; N, 9.33. Found: C, 59.23; H, 4.07; N, 9.41.

2,6-Bis(methylsulfanyl)-5-(4-methylbenzoyl)nicotinonitrile (5b)

Yellow crystals; yield: 170 mg (32%); mp 126–128 °C.

IR (KBr): 3427, 2922, 2365, 2216, 1647, 1566, 1481, 1285, 1050 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 2.62 (s, 3 H, SCH_3), 2.74 (s, 3 H, SCH_3), 7.28 (d, *J* = 8 Hz, 2 H, ArH), 7.60 (d, *J* = 8 Hz, 2 H, ArH), 7.79 (s, 1 H, H-4).

MS (EI): *m*/*z* (%) = 314 (27) [M^+], 281 (38), 149 (20), 119 (40), 105 (22), 91 (54), 69 (100).

Anal. Calcd for $C_{16}H_{14}N_2OS_2$: C, 61.12; H, 4.49; N, 8.91. Found: C, 61.24; H, 4.51; N, 8.96.

2,6-Bis(methylsulfanyl)-5-(4-methoxybenzoyl)nicotinonitrile (5c)

Yellow crystals; yield: 190 mg (34%); mp 110–112 °C.

IR (KBr): 2930, 2216, 1650, 1607, 1566, 1369, 1258, 1167, 1015 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, SCH_3), 2.54 (s, 3 H, SCH_3), 3.87 (s, 3 H, OCH_3), 6.48 (d, *J* = 8 Hz, 2 H, ArH), 7.26 (d, *J* = 8 Hz, 2 H, ArH), 7.31 (s, 1 H, H-4).

MS (EI): *m*/*z* (%) = 330 (22) [M^+], 315 (18), 297 (15), 283 (24), 279 (7), 239 (8), 228 (11), 208 (12), 185 (26), 171 (14), 157 (22), 149 (81), 135 (100), 121 (53), 111 (58).

Anal. Calcd for $C_{16}H_{14}N_2O_2S_2$: C, 58.16; H, 4.27; N, 8.48. Found: C, 58.21; H, 4.25; N, 8.43.

2,6-Bis(methylsulfanyl)-5-(4-chlorobenzoyl)nicotinonitrile (5d)

Yellow crystals; yield: 340 mg (59%); mp 188–190 °C.

IR (KBr): 2929, 2360, 2226, 1652, 1574, 1481, 1357, 1279, 1238, 1129, 1010 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.62 (s, 3 H, SCH_3), 2.97 (s, 3 H, SCH_3), 7.49 (d, *J* = 9 Hz, 2 H, ArH), 7.64 (d, *J* = 9 Hz, 2 H, ArH), 7.90 (s, 1 H, H-4).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 13.53, 14.35, 100.10, 109.21, 115.19, 124.60, 129.16, 129.81, 130.94, 135.09, 139.86, 141.52, 165.59, 191.93.

MS (EI): *m*/*z* (%) = 336 (18) [M^+ + 2], 334 (56) [M^+], 319 (21), 301 (68), 286 (12), 273 (8), 257 (6), 237 (9), 223 (16), 209 (54), 179 (8), 141 (11), 139 (61), 113 (33), 111 (100), 97 (13), 75 (78).

Anal. Calcd for $C_{15}H_{11}ClN_2OS_2$: C, 53.80; H, 3.31; N, 8.37. Found: C, 53.99; H, 3.33; N, 8.40.

2,6-Bis(methylsulfanyl)-5-(2-naphthoyl)nicotinonitrile (5e)

Yellow crystals; yield: 180 mg (30%); mp 188–190 °C.

IR (KBr): 3053, 2924, 2218, 1643, 1560, 1477, 1358, 1286, 1225, 1022 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.64 (s, 3 H, SCH_3), 2.76 (s, 3 H, SCH_3), 7.63 (m, 3 H, ArH), 7.82 (s, 1 H, ArH), 7.85 (m, 3 H, ArH), 8.12 (s, 1 H, H-4).

MS (EI): *m*/*z* (%) = 350 (38) [M^+], 335 (14), 317 (19), 257 (9), 209 (34), 183 (22), 155 (32), 127 (100), 97 (53), 84 (71), 69 (98).

Anal. Calcd for $C_{19}H_{14}N_2OS_2$: C, 65.12; H, 4.03; N, 7.99. Found: C, 64.87; H, 3.99; N, 7.95.

Synthesis of 2-Amino-5-aroyl-6-(alkylsulfanyl)nicotinonitriles 6; General Procedure

Aqueous ammonia (25%, 1.5 mL) was added to 2-[2-aroyl-3,3-bis(methylsulfanyl)-2-propylidene]malononitrile 2 (1.7 mmol) in EtOH (10 mL), equipped with a reflux condenser and closed with a nitrogen-filled balloon. The solution was heated at 70 °C for 5 min and then cooled to r.t.. The EtOH was evaporated and the residue was dissolved in $CHCl_3$, washed with H_2O, dried over anhyd Na_2SO_4. The solvent was evaporated under vacuum and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (19:1) as the eluent.

2-Amino-5-benzoyl-6-(methylsulfanyl)nicotinonitrile (6a)

Yellow crystals; yield: 290 mg (63%); mp 162–164 °C.

IR (KBr): 3496, 3383, 3052, 2919, 2210, 1640, 1580, 1514, 1302, 1262 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, SCH_3), 5.50 (s, 2 H, NH_2), 7.42 (t, *J* = 8 Hz, 2 H, ArH), 7.49–7.57 (m, 3 H, ArH), 7.74 (s, 1 H, H-4).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 14.2, 84.0, 116.3, 122.0, 128.6, 129.3, 132.4, 137.8, 144.8, 146.0, 158.2, 169.3, 192.4.

MS (EI): *m*/*z* (%) = 269 (54) [M^+], 254 (70), 236 (47), 192 (30), 178 (20), 105 (46), 77 (100).

Anal. Calcd for $C_{14}H_{11}N_3OS$: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.13; H, 4.26; N, 15.79.

2-Amino-5-(4-methylbenzoyl)-6-(methylsulfanyl)nicotinonitrile (6b)
Yellow crystals; yield: 270 mg (56%); mp 168–170 °C.

IR (KBr): 3425, 3306, 3200, 2230, 1637, 1585, 1518, 1304 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 2.47 (s, 3 H, SCH_3), 5.52 (s, 2 H, NH_2), 7.27 (d, *J* = 8 Hz, 2 H, ArH), 7.53 (d, *J* = 8 Hz, 2 H, ArH), 7.77 (s, 1 H, H-4).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 14.1 (SCH_3), 21.9 (CH_3), 83.8, 116.1 (CN), 120.6, 129.1, 129.7, 134.8, 143.3, 144.2, 158.0, 169.1, 192.1 (CO).

MS (EI): *m*/*z* (%) = 283 (43) [M^+], 268 (100), 257 (4), 241 (6), 236 (12), 210 (4), 179 (11), 153 (18), 132 (5), 106 (9), 63 (32).

Anal. Calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.59; H, 4.65; N, 14.88.

2-Amino-5-(4-methoxybenzoyl)-6-(methylsulfanyl)nicotinonitrile (6c)
Yellow crystals; yield: 300 mg (59%); mp 166–168 °C.

IR (KBr): 3451, 3351, 3230, 2221, 1635, 1567, 1525, 1247, 1160 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.46 (s, 3 H, SCH_3), 3.88 (s, 3 H, OCH_3), 5.46 (s, 2 H, NH_2), 6.94 (d, *J* = 8 Hz, 2 H, ArH), 7.64 (d, *J* = 8 Hz, 2 H, ArH), 7.73 (s, 1 H, H-4).

MS (EI): *m*/*z* (%) = 299 (46) [M^+], 284 (100), 266 (42), 241 (24), 192 (26), 178 (34), 149 (18), 135 (65), 121 (19), 107 (36), 92 (52), 77 (66).

Anal. Calcd for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04. Found: C, 60.41; H, 4.39; N, 14.08.

2-Amino-5-(4-chlorobenzoyl)-6-(methylsulfanyl)nicotinonitrile (6d)
Yellow crystals; yield: 340 mg (67%); mp 188–190 °C.

IR (KBr): 3514, 3467, 3054, 2219, 1648, 1567, 1483, 1366, 1283, 1239, 1008 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.62 (s, 3 H, SCH_3), 5.56 (br s, 2 H, NH_2), 7.41 (d, *J* = 8 Hz, 2 H, ArH), 7.54 (d, *J* = 8 Hz, 2 H, ArH), 8.39 (s, 1 H, H-4).

MS (EI): *m*/*z* (%) = 305 (27) [M^+ + 2], 303 (83) [M^+], 286 (16), 273 (14), 237 (19), 223 (22), 209 (71), 139 (56), 111 (100), 89 (11), 75 (73).

Anal. Calcd for $C_{14}H_{10}ClN_3OS$: C, 55.35; H, 3.32; N, 13.83. Found: C, 55.10; H, 3.32; N, 13.89.

5-Aroyl-2-chloro-6-(alkylsulfanyl)nicotinonitriles 7; General Procedure
The Vilsmeier–Haack reagent was prepared by mixing DMF (15 mL, 200 mmol) and $POCl_3$ (1.92 mL, 20 mmol) at 0 °C followed by stirring at r.t. for 15 min. To the Vilsmeier–Haack reagent a mixture of aroylketene dithioacetal **1** (4.5 mmol) and malononitrile (450 mg, 6.75 mmol) was added at r.t. and stirred well for 12 h. The reaction mixture was then heated to 100 °C for 1 h, cooled, poured over ice-cold K_2CO_3 solution and extracted with Et_2O (3 × 50 mL). The organic layer was washed with H_2O, dried over Na_2SO_4 and the solvent was removed by evaporation. The crude reaction mixture was purifed by column chromatography using hexane–EtOAc (97:3) as the eluent to give **3** and **7** (see Table 3). We have recently reported spectral data of **3**.[5]

2-[2-Benzoyl-3,3-bis(methylsulfanyl)-2-propylidene]malononitrile (3a)
Yellow crystals; yield: 200 mg (15%); mp 112–114 °C (Lit.[5] 112–114 °C).

5-Benzoyl-2-chloro-6-(methylsuphanyl)nicotinonitrile (7a)
Yellow crystals; mp 158–160 °C mp; yield: 610 mg (47%).

IR (KBr): 2929, 2234, 1646, 1578, 1492, 1374, 1209, 1231, 1004 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, SCH_3), 7.54 (t, *J* = 8 Hz, 2 H, ArH), 7.64 (t, *J* = 8 Hz, 1 H, ArH), 7.68 (t, *J* = 8 Hz, 2 H, ArH), 7.87 (s, 1 H, H-4).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 14.38 (SCH_3), 103.59, 114.54 (CN), 128.93, 129.19, 129.69, 133.98, 135.88, 142.24, 153.24, 167.49.

MS (EI): *m*/*z* (%) = 290 (6) [M^+ + 2], 288 (21) [M^+], 273 (23), 257 (11), 255 (35), 245 (9), 197 (15), 152 (8), 105 (48), 77 (100).

Anal. Calcd for $C_{14}H_9ClN_2OS$: C, 58.23; H, 3.14; N, 9.70. Found: C, 58.52; H, 3.18; N, 9.77.

2-[3,3-Bis(methylsulfanyl)-2-(4-methoxybenzoyl)-2-propylidene]malononitrile (3b)
Yellow crystals; yield: 770 mg (52%); mp 114–116 °C (Lit.[5] 114–116 °C).

2-Chloro-5-(4-methoxybenzoyl)-6-(methylsulfanyl)nicotinonitrile (7b)
Yellow crystalline solid, yield: 380 mg (27%); mp 152–154 °C.

IR (KBr): 2926, 2232, 1601, 1573, 1379, 1275, 1120, 1011 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.58 (s, 3 H, SCH_3), 3.90 (s, 3 H, OCH_3), 6.97 (d, *J* = 8 Hz, 2 H, ArH), 7.71 (d, *J* = 8 Hz, 2 H, ArH), 7.78 (s, 1 H, H-4).

MS (EI): *m*/*z* (%) = 318 (5) [M^+], 305 (2), 303 (6), 287 (4), 285 (5), 199 (5), 165 (5), 135 (18), 121 (19), 107 (13), 97 (17), 81 (29), 69 (100).

Anal. Calcd for $C_{15}H_{11}ClN_2O_2S$: C, 56.52; H, 3.48; N, 8.79. Found: C, 56.73; H, 3.51; N, 8.85.

2-[3,3-Bis(methylsulfanyl)-2-(4-chlorobenzoyl)-2-propylidene]malononitrile (3c)
Yellow crystals; yield: 315 mg (21%); mp 132–134 °C (Lit.[5] 132–134 °C).

2-Chloro-5-(4-chlorobenzoyl)-6-(methylsulfanyl)nicotinonitrile (7c)
Yellow crystalline solid; yield: 660 mg (45%); mp 168–170 °C.

IR (KBr): 3049, 2220, 1653, 1576, 1489, 1382, 1286, 1234, 1010 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.59 (s, 3 H, SCH_3), 7.48 (d, *J* = 8 Hz, 2 H, ArH), 7.65 (d, *J* = 8 Hz, 2 H, ArH), 7.81 (s, 1 H, H-4)

MS (EI): *m*/*z* (%) = 326 (5) [M^+ + 4], 324 (16) [M^+ + 2], 322 (23) [M^+], 309 (12), 307 (21), 291 (52), 289 (73), 197 (42), 141 (20), 139 (63), 113 (31), 111 (100), 85 (21), 75 (84).

Anal. Calcd for $C_{14}H_8Cl_2N_2OS$: C, 52.03; H, 2.49; N, 8.67. Found: C, 52.21; H, 2.51; N, 8.70.

2-Chloro-5-(4-nitrobenzoyl)-6-(methylsulfanyl)nicotinonitrile (7d)
Yellow crystalline solid; yield: 1.1 g (76%); mp 200–202 °C.

IR (KBr): 2930, 2221, 1653, 1522, 1279, 1011 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.6 (s, 3 H, SCH_3), 7.86 (m, 3 H, ArH, H-4), 8.36 (d, *J* = 8 Hz, 2 H, ArH).

MS (EI): *m*/*z* (%) = 333 (14) [M^+], 302 (12), 288 (16), 256 (14), 214 (15), 183 (35), 159 (10), 129 (18), 120 (29), 97 (83), 71 (87), 57 (100).

Anal. Calcd for $C_{14}H_8ClN_3O_3S$: C, 50.38; H, 2.42; N, 12.59. Found: C, 50.11; H, 2.47; N, 12.63.

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References

(1) Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423.
(2) Ila, H.; Junjappa, H.; Mohanata, P. K. In *Progress in Heterocyclic Chemistry*, Vol. 13; Gribble, G. W.; Gilchrist, T. L., Eds.; Pergamon: New York, **2001**, Chap. 1, 1–24.
(3) Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029.
(4) Kolb, M. *Synthesis* **1990**, 171.
(5) Anabha, E. R.; Asokan, C. V. *Synthesis* **2006**, 151.
(6) Rudorf, W. D.; Koditz, J.; Tersakian, A.; Chatterjee, S. K. *Liebigs. Ann. Chem.* **1992**, 387.
(7) Koditz, J.; Rudorf, W. D.; Hartung, H.; Heinemann, F. *Liebigs. Ann. Chem.* **1993**, 1003.
(8) Peseke, K.; Michalik, M.; Schonhusen, U. *J. Prakt. Chemie* **1986**, *328*, 856.
(9) Peseke, K.; Michalik, M.; Schonhusen, U.; Quincoces, J. *J. Prakt. Chem./Chem.-Ztg.* **1987**, *329*, 877.
(10) Peseke, K.; Heide, G.; Fiest, H.; Michalik, M. *J. Prakt. Chem./Chem.-Ztg.* **1991**, *333*, 119.
(11) Peseke, K. *Z. Chem.* **1977**, *17*, 288.
(12) Kilama, J. J.; Iyengar, B. S.; Remer, W. A. *J. Heterocycl. Chem.* **1990**, *27*, 1437.
(13) Aadil, M.; Kirsch, G. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *82*, 91.
(14) Raghukumar, V.; Thirumalai, D.; Ramakrishnan, V. T.; Karunakara, V.; Ramamurthy, P. *Tetrahedron* **2003**, *59*, 3761.
(15) Das, S.; George, M.; Mathew, T.; Asokan, C. V. *J. Chem. Soc., Perkin Trans. 2* **1996**, 731.
(16) Kambe, S.; Saito, K.; Sakurai, A.; Midorikawa, H. *Synthesis* **1980**, 366.
(17) Rudolf, I.; Michalik, M.; Montero, A.; Peseke, K. *Synthesis* **2001**, 1686.
(18) Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.
(19) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899.
(20) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471.
(21) Chauhan, S. M. S.; Junjappa, H. *Tetrahedron* **1976**, *32*, 1911.