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One-pot synthesis of polysubstituted pyridine derivatives using ketene dithioacetals

Masayori Hagimori,[a] Naoko Mizuyama,[b] Yukari Hisadome,[b] Junko Nagaoka,[c] Kazuo Ueda[b] and Yoshinori Tominaga[b,*]

[a]*Faculty of Pharmaceutical Sciences, Nagasaki International University, 2825-7 Huis Ten Bosch, Sasebo 859-3298, Japan*
[b]*Faculty of Environmental Studies, 1-14, Bunkyo-machi, Nagasaki 852-8521, Japan*
[c]*Faculty of Engineering of Nagasaki University, 1-14, Bunkyo-machi, Nagasaki 852-8521, Japan*

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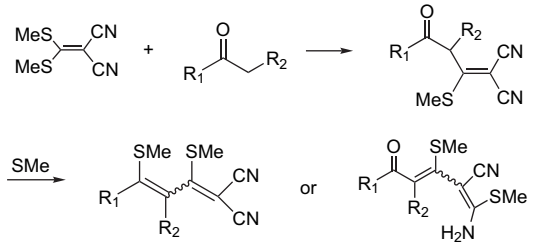
Abstract—Polysubstituted pyridine derivatives were synthesized by the reaction of ketene dithioacetal, 3,3-bis(methylsulfanyl)methylenemalononitrile **1b**, with a variety of active methylene compounds in the presence of either sodium hydroxide or potassium hydroxide as a base in DMSO. This reaction was carried out under economical one-pot reaction conditions (cheap catalyst and solvent) and solved the problem of the odor of methanethiol, commonly derived from reactions of ketene dithioacetals. This is a significant enhancement of GSC (green and sustainable chemistry) in the field of ketene dithioacetal chemistry.

1. Introduction

Pyridine derivatives have drawn much attention due to their well-documented biological activities.[1] Therefore, new and improved synthetic studies are important in the field of drug design. Ketene dithioacetals are very useful electrophilic reagents in the synthesis of heterocycles, and are typically prepared by the condensation of active methylene compounds with carbon disulfide in the presence of an appropriate base and subsequent alkylation with an alkylating agent such as dimethyl sulfate.[2] Reactions with various nucleophiles have been reported (Scheme 1). Ketene dithioacetals are especially useful as building blocks to incorporate a two- and three-carbon unit in the construction of a variety of heterocyclic compounds. Moreover, the synthesis of the polysubstituted derivative is also possible. As shown in the simplified reaction scheme given in Scheme 1, these reactions proceed through an addition–elimination mechanism, which starts with nucleophilic addition at the sp^2 sulfur-substituted carbon atom of ketene dithioacetal, followed by elimination of the methylsulfanyl group to complete the substitution reaction. During work-up of the reaction mixture, ill-smelling methanethiol is discharged from the reaction system. Generally, this bad odor can be removed easily by treatment with hypochlorous acid. If the odorous methanethiol can be removed from the reaction system than it can also be reused, enhancing the usefulness of ketene dithioacetals still further. The excellent leaving ability of the reincorporated methylsulfanyl group can be utilized again. In this case, however, the methylsulfanyl derivatives cannot be utilized per se, but it may be possible to use them after transforming the sulfur atom of the methylsulfanyl group to a sulfinyl or sulfonyl group by treatment with an oxidizing reagent such as aqueous hydrogen peroxide or *m*-chloroperbenzoic acid. In this way, the problem of bad odor can be solved, and the reactivity of the products obtained by the reaction of ketene dithioacetals with nucleophiles can be enhanced.



Scheme 1.

Many reactions of active methylene compounds with ketene dithioacetals have been reported.[3] We have succeeded in the synthesis of 2*H*-pyran-2-one derivatives, which are potentially useful as organic electroluminescence (EL) materials, via the reaction of active methylene compounds and methyl

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* Corresponding author. Tel./fax: +81 819 2748; e-mail: ytomi@nagasaki-u.ac.jp

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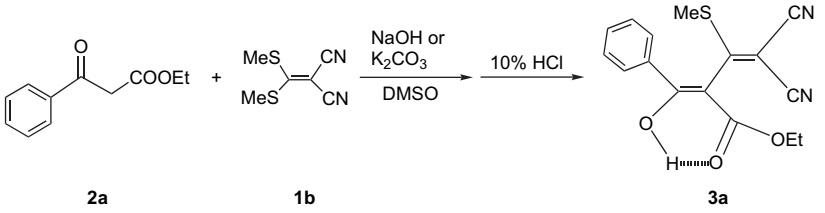
bis(methylsulfanyl)methylenecyanoacetate **1a**.[4] The electron density of a ketene dithioacetal is low at the sp^2 carbon atom substituted by methylsulfanyl groups, and this carbon atom is strongly electrophilic and susceptible to attack by nucleophilic reagents. On the other hand, the leaving ability of the methylsulfanyl group is very high. By appropriate application of these peculiar properties and with a suitable choice of nucleophilic reagents, it is theoretically possible to realize a tandem reaction consisting of an initial (common) addition reaction followed by an elimination of the methylsulfanyl group, a second addition reaction of the eliminated methylthiolate anion, and a final cyclization reaction.

2. Results and discussion

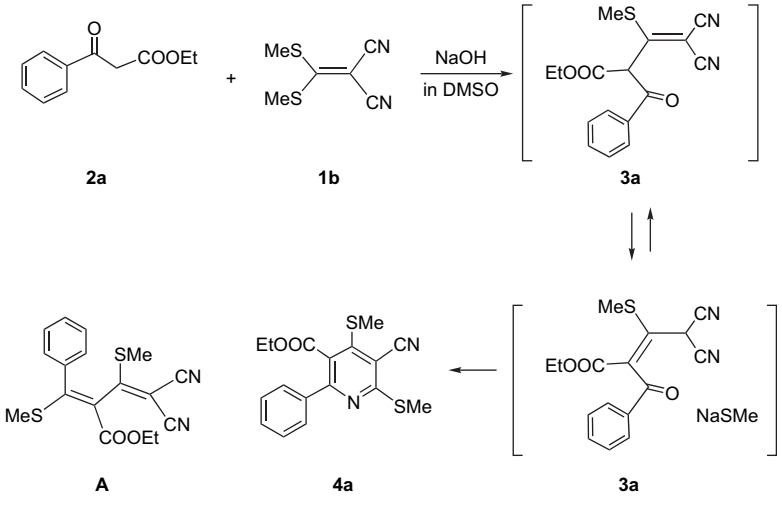
Due to the known activity of the active methylene compounds toward ketene dithioacetal, the reaction of ethyl benzoylacetate **2a**, an active methylene compound, with 3,3-bis(methylsulfanyl)methylenemalononitrile **1b** was attempted first.

First, the reaction was performed under ordinary reaction conditions: the methylene compound **2a** was dissolved in DMSO (dimethyl sulfoxide), and then ketene dithioacetal **1b** and pulverized sodium hydroxide were added, and the mixture was stirred for 2 h at room temperature. When the reaction was complete, water was added, and the mixture was acidified with hydrochloric acid, and the precipitate, which separated out on standing was collected. Recrystallization from ethanol gave the primary substitution product with the methylsulfanyl group, ethyl 2-benzoyl-4,4-dicyano-3-(methylsulfanyl), but-3-enoate **3a** in 68% yield (Scheme 2). However, for this experiment, when the reaction mixture was diluted with water and stirred at room temperature under alkaline conditions without the addition of acid, crystals gradually separated out. Stirring was continued for 5 h; the product was collected by suction filtration and recrystallized from ethanol to give colorless needles in 48% yield, mp 128–129 °C. During work-up of the reaction mixture, ill-smelling methanethiol was not confirmed. The IR spectrum of this compound clearly shows resonances characteristic of an ester carbonyl group at 1735 cm^{-1}, and a cyano group at 2220 cm^{-1}. The ^1H NMR spectrum exhibited signals corresponding to the methylsulfanyl groups at 2.67 and 2.69 ppm. The UV spectrum is very similar to that of a pyridone derivative, as described earlier.[5] Based on these spectral analyses, this compound was identified as ethyl 5-cyano-4,6-bis-(methylsulfanyl)-2-phenylpyridine-3-carboxylate **4a**. While the exact structure cannot be clearly determined through spectral analyses, such that the butadiene structure of A is entirely possible (Scheme 3), X-ray analysis conclusively established that the structure was that as shown in Figure 1.

This one-pot preparation of polysubstituted pyridines from ketene dithioacetals is significant from a synthetic point of view. The reaction conditions were therefore optimized to improve the yield of the product. As shown in Table 1, run 3, when the reaction time was extended to 15 h from the initial conditions of run 1 described above, the yield of **4a** dropped to 29%. No identifiable compounds could be isolated upon acidification of the filtrate of this reaction mixture, suggesting that either the intermediate decomposed under the alkaline conditions or the reaction proceeded further. When sodium hydroxide (used as a base) was substituted



Scheme 2.



Scheme 3.

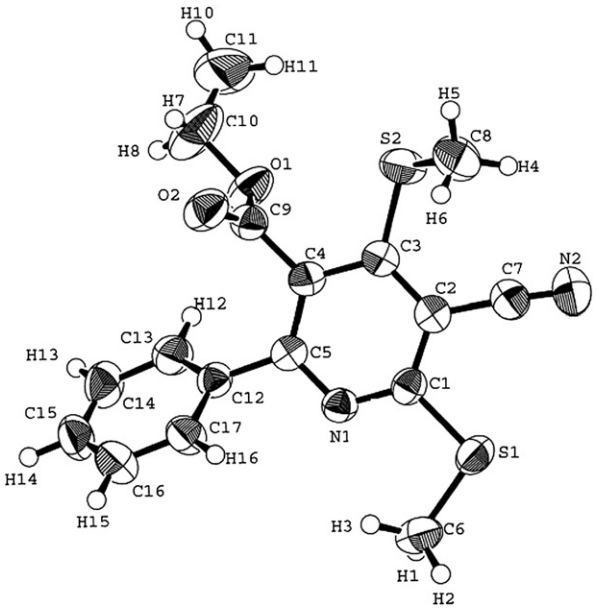
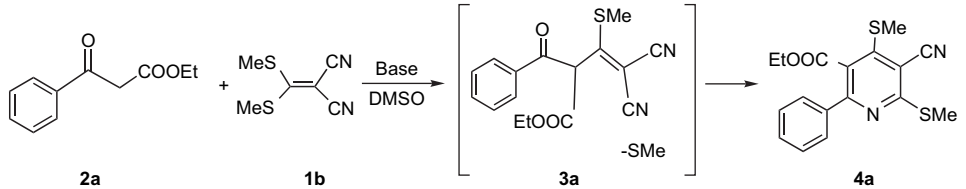


Figure 1. ORTEP drawing of **4a**.

for potassium hydroxide, the yield (56%) was improved by 10%. After completion of the first step of the reaction and following addition of water, if the resulting mixture was allowed to stand for 20 h (rather than for 4–5 h as used in the previous reactions), the yield improved to 57%. On the other hand, when the reaction was performed with potassium carbonate as the base, no products separated out, even after 4–5 h after the addition of water. When this solution was acidified with hydrochloric acid, intermediate **3a** was obtained in 84% yield. This shows that in order the nucleophilic attack of methanethiolate to occur on the cyano group, it is necessary to carry out the reaction under strongly basic conditions. It also became clear that the formation of the pyridine ring by the reaction of methanethiolate takes place in the second step, i.e., in the aqueous alkaline solution.

The yields of this reaction are only moderate up to 57%. It may be assumed that this is due in part to the instability and decomposition of intermediate **3a** under the alkaline conditions. Consideration of the stability of the intermediate led to examination of the conditions of the reaction between 1,3-indanedione **2i** and **1b**. When the reaction was performed under the same conditions as those for **2a** with **1b**, the desired product was obtained in 62% yield (Table 2; run 1). In this case, the by-product **5i** was obtained in 26% yield after the treatment of this filtrate with hydrochloric acid.[6] The fact that the combined yield of the two compounds is high suggests that the substitution reaction in the first step takes place readily and the intermediate corresponding to **3a** is stable. However, the yield of **4i** dropped when the base was changed to potassium hydroxide (run 2) or when the reaction time was prolonged (run 3). As shown in run 4, when the mixture was allowed to stand for a longer period after the addition of water, the yield increased to 72%. The use of 40 mmol sodium hydroxide also improved the yield to 71%. These results suggest that

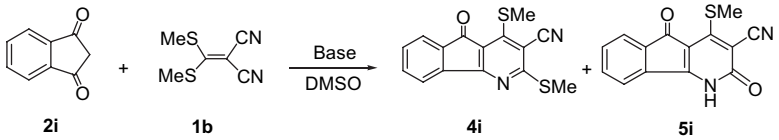
Table 1. Reaction of ethyl benzoacetate **2a** with ketene dithioacetal **1b** in the presence of base



2a **1b** **3a** **4a**

Run	**2a** (mmol)	**1b** (mmol)	Base (mmol)	Solvent	RT(A) (h)	RT(B) (h)	**4a** (Yield, %)
1	10	10	NaOH (20)	DMSO	4	4	48
2	10	10	KOH (20)	DMSO	4	4	56
3	10	10	NaOH (20)	DMSO	15	5	29
4	10	10	KOH (20)	DMSO	4	20	57
5	12	10	NaOH (20)	DMSO	4	20	45
6	12	10	K_2CO_3 (20)	DMSO	4	20	0

Table 2. Reaction of 1,3-indadione **2i** with ketene dithioacetal **1b** in the presence of base



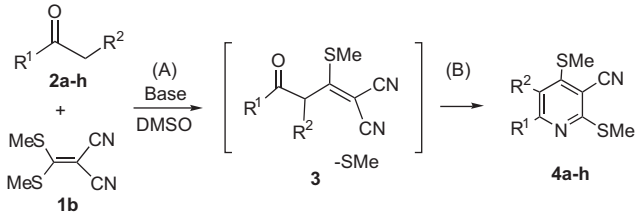
2i **1b** **4i** **5i**

Run	**2i** (mmol)	**1b** (mmol)	Base (mmol)	Solvent	RT(A) (h)	RT(B) (h)	**4i** (Yield, %)	**5i** (Yield, %)
1	10	10	NaOH (20)	DMSO	4	5	62	26
2	10	10	KOH (20)	DMSO	4	5	29	63
3	10	10	NaOH (20)	DMSO	15	5	28	65
4	10	12	NaOH (20)	DMSO	4	40	72	16
5	10	12	NaOH (40)	DMSO	4	20	71	2
6	10	12	K_2CO_3 (20)	DMSO	4	20	21	72

the addition of the methanethiolate anion and subsequent cyclization in the final step take place after the addition of water.

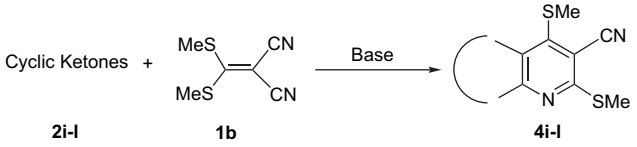
The results show that it is necessary to modify the reaction conditions to some extent depending on the structure of the active methylene compounds used in the reaction. A series of polysubstituted pyridine derivatives have been synthesized by the reaction of ketene dithioacetal with a variety of active methylene compounds. The active methylene compounds used in this study are shown in Tables 3 and 4. The initial purpose of the study has thus been realized; although,

Table 3. Reaction of active methylene compounds **2a–h** with ketene dithioacetal **1b** in the presence of base



Run		2 (10 mmol)		1b (mmol)	Base (mmol)	RT(A) (h)	RT(B) (h)	4	(Yield, %)	Mp (°C)
		R^1	R^2							
1	**2a**	C_6H_5	COOEt	10	NaOH (20)	4	4	**4a**	48	128–129
					KOH (20)	4	4		56	
2	**2b**	C_6H_5	CN	10	NaOH (20)	4	5	**4b**	49	134–136
					KOH (20)	15	5		31	
					NaOH (20)	4	30		58	
3	**2c**	C_6H_5	CO–Me	10	NaOH (20)	4	4	**4c**	23	119–120
				12	KOH (20)	4	20		46	
4	**2d**	C_6H_5	CO–C_6H_5	10	NaOH (20)	4	4	**4d**	31	142–147
						6	20		59	
5	**2e**	Me	COOMe	10	NaOH (20)	4	4	**4e**	33	37–38
						6	20		68	
6	**2f**	Me	COOEt	10	NaOH (20)	6	20	**4f**	58	58–59
7	**2g**	Me	Tolyl	10	NaOH (20)	4	4	**4g**	8	240–241
8	**2h**	Me	CO–Me	11	NaOH (20)	4	20	**4h**	44	94–95

Table 4. Reaction of cyclic ketones **2i–l** with ketene dithioacetal **1b** in the presence of base



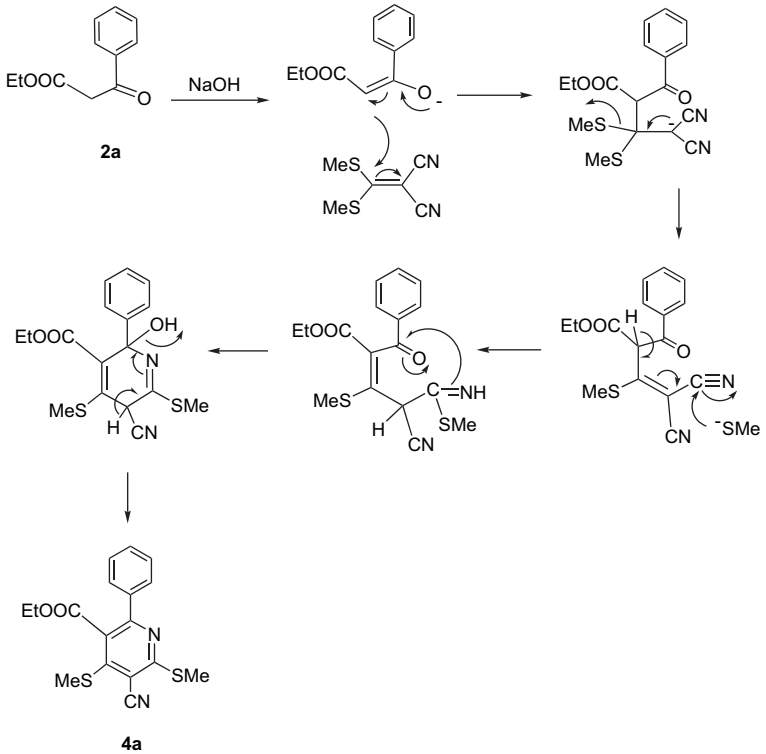
2 (mmol)		Base	4 Products	5 Products	4 (Yield, %)	5 (Yield, %)	4i–l Mp (°C)
2i	10	NaOH	**4i**	**5i**	71	2	219–220
2j	10	NaOH	**4j**	—	24	—	122–123
		KOH			37	—	
2k	10	NaOH	**4k**	—	29	—	161–162
2l	10	NaOH	**4l**	**5l**	20	38	297–298

reinvestigation may be desirable for some reactions with low yields. It is thought that the reason for the low yields is attributed to the formation of pyridone derivatives like **5i** and **5l** in Table 4. However, it is not possible to confirm by-products (reaction of **2j**,**k** with **1b**), on account of the poor water solubility.

By the reaction between an active methylene compound possessing keto-carbonyl group(s) and a ketene dithioacetal, bis(methylsulfanyl)methylenemalononitrile **1b**, the pyridine derivatives are formed by consecutive addition, elimination, addition, and cyclization reactions via the mechanism shown in Scheme 4. Since this sequence of reactions takes place in an alkaline medium, the intermediates may partly decompose into ketones causing a decrease in the product yields. One way of improving the reaction yield would be to find an appropriate strategy to stabilize the intermediates. In the final stage of the reaction, the methylthiolate anion adds to the cyano group to achieve a more stable state, and the resulting imino or amino group undergoes dehydrative condensation with a carbonyl group to complete the reaction. For these reactions, the use of potassium hydroxide as a base gave slightly better results than sodium hydroxide. The reactivity of the final reaction may be dependent upon the nucleophilicity of the methanethiolate anion. The nucleophilicity at this stage is more increased in aqueous solvent than in DMSO. This interpretation is supported by the fact that the use of potassium carbonate caused the yield to fall to 21% even in the reaction with a 1,3-indanedione, and that the cyclization product **4a** could not be obtained from benzoylacetate **2a**. The presence of a keto-carbonyl group is essential for this reaction to take place. All the active methylene compounds used in this study contain at least one keto-carbonyl group as an electron-withdrawing group and are substituted further by groups such as cyano and ester.

These reactions were generally carried out on a 10 mmol scale, but can be readily applied to experiments on 1 mmol scale. For this case, the yield of **4a** was 58%. The odor of methanethiol is not a serious problem as long as the treatment of the reaction mixture is performed under basic conditions. Even when the mixture is treated under acidic conditions, the problematic odor can be alleviated by pretreatment with sodium hypochlorite. The by-products can be removed by suction filtration, or when they are soluble in water, they can be extracted with ethyl acetate. The extracted solvent can be recycled and used many times for extraction in similar reactions. The reaction developed here not only prevents the evolution of methanethiolate, which is generally formed by the reactions with ketene dithioacetals, but also utilizes the methanethiolate generated for the construction of a pyridine ring. This reaction is considered as a significant GSC in the study field of ketene dithioacetals.

This study describes a useful synthetic method for the preparation of polysubstituted pyridine derivatives in an economical one-pot reaction condition using cheap catalysts and solvents. This method solved the problem of the odor of methanethiol, commonly derived from reactions of ketene dithioacetals, even though the yields of some of the products may appear unsatisfactory. Additionally, it should be emphasized that the pyridines prepared by this method bear methylsulfanyl groups at the 2- and 4-position of the pyridine ring. As the methylsulfanyl group is an excellent leaving group, the pyridines prepared by this route will play an important role as intermediates for the syntheses of various polysubstituted pyridine derivatives. Furthermore, we are



Scheme 4.

trying the reaction of the active methylene compounds against other ketene dithioacetals having methoxycarbonyl groups, sulfonyl groups, nitro groups, acryl groups, and so on. As a result, compounds like intermediate **3a** could be obtained. In the cases where an intermediate was not obtained, a 2-pyrone or a butadiene derivative was obtained. We are currently examining these reactions. Recently, Yoshida and co-workers reported the syntheses of polysubstituted arylpyrimidines.[7] These reactions are based on the nucleophilic substitution reactions of organometallic reagents using methylsulfanyl group. A combination of Yoshida's process and our preparation of 2,4-bis(methylsulfanyl)-pyridine derivatives may be considered highly applicable for the synthesis of potential candidates for materials of organic EL.

3. Experimental

3.1. Reaction of ketene dithioacetals with active methylene compounds: general procedure

A mixture of ketene dithioacetal (1.70 g, 10 mmol), active methylene compound (10 mmol), powdered sodium hydroxide or potassium hydroxide (20 mmol), and 20 ml of DMSO was stirred for 4–5 h (see Table 1) at room temperature. The color of the reaction mixture was changed from yellow to red brown. The reaction time is shown in Tables 1 and 2. The reaction mixture was poured into 300 ml of water and this solution was stirred for 4–20 h at room temperature. The precipitate that appeared was collected by filtration. After drying in air, the product was recrystallized from methanol or ethanol to give pure products (see Tables 1 and 2). The filtrate was acidified with 10 ml of 10% HCl solution and extracted with 200 ml of ethyl acetate. (This ethyl acetate of extract can be reused.) After evaporation, the residue (0.54 g for run 1 in Table 1; including DMSO and by-products, etc.) was disposed off. When this reaction was carried out on a 1.0 mmol scale of **1b** (0.175 g, 1.0 mmol) and **2a** (0.192 g, 1.0 mmol) in the presence of sodium hydroxide (0.14 g, 3.5 mmol) in DMSO (2.0 ml), the product **4a** was obtained in 58% (0.201 g, 0.584 mmol) yield.

3.1.1. 2-Benzoyl-4,4-dicyano-3-methylsulfanyl-but-3-enoic acid ethyl ester (3a). An analytical sample was obtained as colorless leaflets. Mp: 103–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J=7.2 Hz, 3H), 2.41 (s, 3H), 4.40 (q, J=7.2 Hz, 2H), 7.46 (m, 3H), 7.57 (m, 2H), 14.05 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.38, 19.18, 62.64, 81.61, 111.89, 112.43, 127.79, 128.65, 132.19, 132.36, 169.26, 175.44, 178.71 ppm. IR (KBr): 2220, 2217, 1654, 1561, 1264, 1016 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{14}N_2O_3S$, m/z 314.07 (M^+); found, m/z 314.0712.

3.1.2. 5-Cyano-4,6-bis(methylsulfanyl)-2-phenylnicotinic acid ethyl ester (4a). An analytical sample was recrystallized from ethanol to give colorless needles. Mp: 128–129 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, J=7.3 Hz, 3H), 2.67 (s, 3H), 2.69 (s, 3H), 4.22 (q, J=7.3 Hz, 2H), 7.44 (m, 3H), 7.66 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.13, 62.20, 108.23, 114.55, 127.94, 128.47, 128.53, 130.09, 138.01, 150.84, 157.24, 165.09, 166.43 ppm. IR (KBr): 2220, 1735, 1515, 1230, 1120 cm^{-1}. UV (ethanol) λ_{max}, nm (log ε): 278 (4.51), 347 (3.86). MS m/z: 345 (M^++1, 22), 344 (M^+, 100), 329 (49), 311 (15), 292 (55), 277 (98), 259 (50). Anal. Calcd for $C_{17}H_{16}N_2O_2S_2$: C, 59.28; H, 4.68; N, 8.13. Found: C, 59.42; H, 4.67; N, 8.12.

3.1.3. 2,4-Bis(methylsulfanyl)-6-phenylpyridine-3,5-dicarbonitrile (4b). An analytical sample was recrystallized from a mixture of methanol and toluene to give yellow needles. Mp: 219–220 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70 (s, 3H), 2.90 (s, 3H), 7.55 (m, 3H), 7.94 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.37, 18.42, 104.24, 106.53, 113.52, 115.57, 128.64, 129.34, 131.48, 135.91, 157.99, 162.38, 168.22 ppm. IR (KBr): 2215, 1510, 1480, 1320, 815 cm^{-1}. MS m/z: 298 (M^++1, 17), 297 (M^+, 49), 296 (100), 282 (158), 264 (14). Anal. Calcd for $C_{15}H_{11}N_3S_2$: C, 60.58; H, 3.73; N, 14.13. Found: C, 60.75; H, 3.58; N, 14.08.

3.1.4. 5-Acetyl-2,4-bis(methylsulfanyl)-6-phenylnicotinonitrile (4c). An analytical sample was recrystallized from methanol to give colorless leaflets. Mp: 119–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.47 (s, 3H), 2.66 (s, 3H), 7.50 (m, 2H), 7.63 (m, 1H), 7.77 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.02, 19.12, 23.34, 108.04, 114.50, 129.06, 129.19, 129.31, 133.00, 134.41, 136.35, 148.93, 157.74, 164.65, 194.55 ppm. IR (KBr): 2210, 1671, 1248 cm^{-1}. UV (ethanol) λ_{max}, nm (log ε): 273 (4.55), 331 (3.91). MS m/z: 315 (M^++1, 20), 314 (M^+, 100), 299 (25), 281 (14). Anal. Calcd for $C_{16}H_{14}N_2OS_2$: C, 61.12; H, 4.49; N, 8.91. Found: C, 61.04; H, 4.43; N, 8.94.

3.1.5. 5-Benzoyl-2,4-bis(methylsulfanyl)-6-phenylnicotinonitrile (4d). An analytical sample was recrystallized from methanol to give yellow needles. Mp: 142–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, 3H), 2.71 (s, 3H), 7.21–7.68 (m, 10H). ^{13}C NMR (100 MHz, DMSO) δ 48.47, 48.61, 91.81, 126.96, 127.80, 128.05, 129.61, 130.13, 141.34, 142.10, 183.20 ppm. IR (KBr): 2235, 1650, 1525, 1235 cm^{-1}. UV (ethanol) λ_{max}, nm (log ε): 277 (4.54), 350 (4.02). MS m/z: 377 (M^++1, 26), 376 (M^+, 100), 361 (35), 347 (11), 343 (23), 299 (15), 105 (27). Anal. Calcd for $C_{21}H_{16}N_2OS_2$: C, 66.99; H, 4.28; N, 7.44. Found: C, 66.82; H, 4.31; N, 6.98.

3.1.6. 5-Cyano-2-methyl-4,6-bis(methylsulfanyl)nicotinic acid methyl ester (4e). An analytical sample was recrystallized from methanol to give colorless plates. Mp: 37–38 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3H), 2.61 (s, 3H), 2.62 (s, 3H) 3.95 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.38, 18.69, 18.80, 52.77, 107.32, 114.26, 127.77, 149.64, 157.67, 164.78, 166.72 ppm. IR (KBr): 2219, 1726, 1531, 1432, 1262, 1134 cm^{-1}. UV (ethanol) λ_{max}, nm (log ε): 276 (3.99), 331 (3.06). MS m/z: 269 (M^++1, 15), 268 (M^+, 100), 253 (74), 237 (12), 235 (30). Anal. Calcd for $C_{11}H_{12}N_2O_2S_2$: C, 49.23; H, 4.51; N, 10.44. Found: C, 49.21; H, 4.52; N, 10.43.

3.1.7. 5-Cyano-2-methyl-4,6-bis(methylsulfanyl)nicotinic acid ethyl ester (4f). An analytical sample was recrystallized from ethanol to give colorless needles. Mp: 58–59 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, J=7.2 Hz, 3H), 2.54 (s, 3H), 2.61 (s, 3H), 2.62 (s, 3H), 4.42 (q, J=7.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.30, 14.01, 18.66, 18.79, 62.12, 107.49, 114.35, 128.21,

149.46, 157.62, 164.67, 166.24 ppm. IR (KBr): 2221, 1721, 1534, 1246, 1147 cm^{-1}. UV (ethanol) λ_{max}, nm (log ε): 276 (4.45), 331 (3.85). MS *m/z*: 283 (M^++1, 17), 282 (M^+, 100), 267 (89), 253 (22), 249 (27), 239 (45). Anal. Calcd for $C_{12}H_{14}N_2O_2S_2$: C, 51.04; H, 5.00; N, 9.92. Found: C, 51.02; H, 4.94; N, 9.93.

3.1.8. 6-Methyl-2,4-bis(methylsulfanyl)-5-(4-tolylsulfonyl)nicotinonitrile (4g). An analytical sample was recrystallized from methanol to give colorless needles. Mp: 240–241 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.44 (s, 3H), 2.65 (s, 3H), 2.08 (s, 3H), 7.31 (d, *J*=8.3 Hz), 7.84 (d, *J*=8.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.63, 20.11, 21.58, 27.11, 110.86, 114.01, 127.57, 129.34, 129.48, 133.77, 139.12, 144.53, 154.82, 161.53, 167.69 ppm. IR (KBr): 2217, 1515, 1491, 1318, 1158 cm^{-1}. UV (ethanol) λ_{max}, nm (log ε): 291 (4.35). MS *m/z*: 364 (M^+, 13), 209 (13), 300 (29), 299 (26), 286 (35), 285 (100), 270 (25). Anal. Calcd for $C_{16}H_{16}N_2O_2S_3$: C, 52.72; H, 4.42; N, 7.69. Found: C, 52.81; H, 4.34; N, 7.73.

3.1.9. 5-Acetyl-6-methyl-2,4-bis(methylsulfanyl)nicotinonitrile (4h). An analytical sample was recrystallized from methanol to give colorless needles. Mp: 94–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H), 2.58 (s, 3H), 2.60 (s, 3H), 2.63 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.41, 19.69, 19.82, 23.33, 108.41, 114.29, 132.42, 148.52, 159.98, 164.96, 191.85 ppm. IR (KBr): 2221, 1680, 1503, 1425, 1267, 1067 cm^{-1}. UV (ethanol) λ_{max}, nm (log ε): 281 (4.24), 488 (3.55). MS *m/z*: 252 (M^+, 7), 238 (14), 237 (100), 107 (33), 84 (7). Anal. Calcd for $C_{11}H_{12}N_2OS_2$: C, 52.35; H, 4.79; N, 11.10. Found: C, 52.31; H, 4.69; N, 11.05.

3.1.10. 2,4-Bis(methylsulfanyl)-5-oxo-5*H*-indeno[1,2-*b*]pyridine-3-carbonitrile (4i). An analytical sample was recrystallized from methanol to give yellow needles. Mp: 219–220 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77 (s, 3H), 2.87 (s, 3H), 7.52 (m, 1H), 7.62 (m, 1H), 7.73 (m, 1H), 7.86 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.09, 18.19, 105.48, 115.10, 123.89, 132.46, 132.53, 134.79, 134.83, 135.63, 140.80, 153.28, 166.26, 171.79, 188.92 ppm. IR (KBr): 2214, 1709, 1540, 1266, 749 cm^{-1}. UV (ethanol) λ_{max}, nm (log ε): 257 (4.21), 311 (4.35). MS *m/z*: 299 (M^++1, 20), 298 (M^+, 100), 297 (22), 283 (64), 265 (59), 237 (13). Anal. Calcd for $C_{15}H_{10}N_2OS_2$: C, 60.38; H, 3.38; N, 9.39. Found: C, 60.54; H, 3.38; N, 9.31.

3.1.11. 7,7-Dimethyl-2,4-bis(methylsulfanyl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carbonitrile (4j). An analytical sample was recrystallized from methanol to give colorless needles. Mp: 122–123 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 6H), 2.56 (s, 3H), 2.63 (s, 3H), 2.75 (s, 3H), 3.00 (s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.65, 19.76, 28.07, 32.23, 47.74, 52.95, 104.91, 115.25, 122.57, 158.88, 164.32, 168.81, 196.32 ppm. IR (KBr): 2213, 1681, 1508, 1227 cm^{-1}. UV (ethanol) λ_{max}, nm (log ε): 290 (4.35). MS *m/z*: 293 (M^++1, 19), 292 (M^+, 100), 291 (14), 277 (52), 259 (26). Anal. Calcd for $C_{14}H_{16}N_2O_3S_2$: C, 57.50; H, 5.51; N, 9.58. Found: C, 57.57; H, 5.56; N, 9.50.

3.1.12. 2,4-Bis(methylsulfanyl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carbonitrile (4k). An analytical sample was recrystallized from methanol to give colorless leaflets. Mp: 161–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (m, 2H), 2.63 (s, 3H), 2.70 (t, *J*=6.6 Hz), 2.75 (s, 3H), 3.10 (t, *J*=6.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.78, 19.82, 20.85, 34.01, 39.22, 105.11, 115.18, 123.55, 159.32, 165.63, 168.44, 196.18 ppm. IR (KBr): 2214, 1671, 1508, 1319, 1216, 810 cm^{-1}. UV (ethanol) λ_{max}, nm (log ε): 289 (4.32). MS *m/z*: 265 (M^++1, 17), 264 (M^+, 100), 249 (53), 231 (25). Anal. Calcd for $C_{12}H_{12}N_2OS_2$: C, 54.52; H, 4.56; N, 10.60. Found: C, 54.17; H, 4.43; N, 10.76.

3.1.13. 2,4-Bis(methylsulfanyl)-5,5-dioxo-benzo[4,5]-thieno[3,2-*b*]pyridine-3-carbonitrile (4l). An analytical sample was recrystallized from methanol to give yellow needles. Mp: 297–298 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.76 (s, 3H), 2.97 (s, 3H), 7.17–7.80 (m, 2H), 7.88 (m, 1H), 8.17 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.05, 18.14, 107.12, 113.87, 121.78, 123.58, 127.34, 130.15, 133.54, 134.23, 140.32, 151.33, 171.45 ppm. IR (KBr): 2216, 1526, 1314, 1173 cm^{-1}. UV (ethanol, insufficient solubility) λ_{max}, nm (log ε): 285. MS *m/z*: 335 (M^++1, 20), 334 (M^+, 100), 319 (71), 301 (54), 237 (10), 136 (12). Anal. Calcd for $C_{14}H_{10}N_2O_2S_3$: C, 50.28; H, 3.01; N, 8.38. Found: C, 50.25; H, 2.84; N, 8.33.

3.1.14. 4-Methylsulfanyl-2,5-dioxo-2,5-dihydro-1*H*-indeno[1,2-*b*]pyridine-3-carbonitrile (5i). This compound was synthesized according to the procedure in Ref. 6. An analytical sample was recrystallized from methanol to give yellow leaflets. ^{1}H NMR (400 MHz, DMSO) δ 2.81 (s, 3H), 7.49–7.70 (m, 4H), 8.01 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO) δ 17.03, 98.05, 109.56, 116.14, 122.96, 123.17, 133.71, 134.23, 134.25, 134.64, 159.20, 160.60, 161.21, 186.17 ppm.

3.1.15. 4-Methylsulfanyl-2,5,5-trioxo-2,3,4,5-tetrahydro-1*H*-5λ^6-benzo[4,5]thieno[3,2-b]pyridine-3-carbonitrile (5l). An analytical sample was recrystallized from methanol to give colorless leaflets. Mp: 300 °C with decomposition. ^{1}H NMR (400 MHz, DMSO) δ 2.91 (s, 3H), 7.86–8.09 (m, 4H), 8.34 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO) δ 17.35, 101.48, 115.21, 121.87, 124.35, 124.42, 134.51, 134.66, 139.70, 145.86, 155.13, 161.65 ppm. IR (KBr): 3432, 2218, 1653, 1315, 1167 cm^{-1}. HRMS (EI) calcd for $C_{13}H_8N_2O_3S_2$, *m/z* 303.9976 (M^+); found, *m/z* 303.9975.

3.1.16. X-ray structure of 5-cyano-4,6-bis(methylsulfanyl)-2-phenylnicotinic acid ethyl ester (4a). $C_{17}H_{16}N_2O_2S_2$, *M*=344.45, orthorhombic, *a*=7.5925(4), *b*=15.8220(8), *c*=14.6241(8) Å, *V*=1756.77(16) Å^3, space group $Pna2_1$ (no. 33), *Z*=4, D_x=1.302 g cm^{-3}. Crystal dimensions 0.40×0.25×0.20 mm^3, μ(Mo Kα)=3.126 mm^{-1}, 2278 reflections measured, 290 unique (R_{int}=0.020), which were used in all calculations. The final $\omega R(F^2)$ was 0.0733 (all data).

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