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REACTION OF 2-ALKYLTHIOPYRIDINIUM SALTS WITH ACTIVE METHYLENE COMPOUNDS

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Abstract — Reactions between active methylene compounds and 2-alkyllthio-1-alkylpyridinium iodides in the presence of sodium hydride, were found to occur at the 2 or 4-position. In contrast, 2-chloro-1-methylpyridinium iodide reacted at the 2-position, whereas 6-chloro-2-methylthiopyridinium iodide reacted at the 6-position to yield only one product. Chemoselectivity of the pyridinium salt was calculated using molecular orbital (MO) calculations.

Various methods for introducing an alkyl or aryl group at the 2-position of a pyridine ring have been reported to date.[1] We have previously reported on a novel method for the efficient formation of a carbon-carbon bond at the 2-position of a quinoline ring via reaction of 2-alkylthioquinolinium or 1-alkylthioisoquinolinium salts with active methylene compounds.[2] To expand upon this new and promising methodology, we carried out reactions between active methylene compounds and pyridinium salts bearing an alkylthio and/or chloro leaving group. Furthermore, the chemoselectivity of 6-chloro-1-methyl-2-methylthiopyridinium iodide, which possess both an alkylthio and a halogeno leaving group, was determined using molecular orbital (MO) calculations.

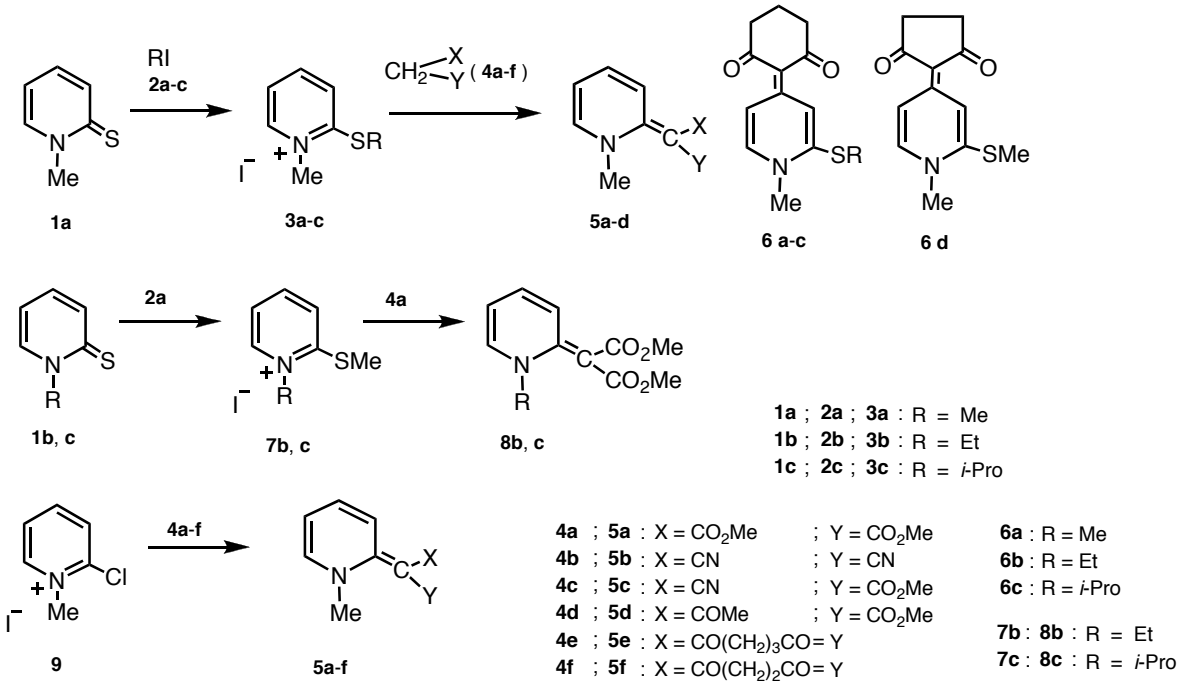
Reactions of 2-alkylthio and 2-chloropyridinium salts with active methylene compounds

First, as shown in Scheme 1, 2-alkylthio-1-alkylpyridinium iodides **3a**-**c** and **7b**,**c** were readily prepared from 1-alkyl-2(1*H*)-thiopyridones **1a**-**c**.[3] Subsequently, **3a** was reacted with straight-chain active methylene compounds **4a**-**d**, in the presence of NaH as a base, to regioselectively yield 2-alkylidene-pyridines **5a**-**d** in 64-99% yields (Table 1, Entries 1-5). Pyridinium salts **3b** and **3c**, which possess a bulky alkylthio group, reacted with **4a** under mild conditions to afford **5a** (90% yield, Entry 6;

This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

83% yield, Entry 7; respectively). Similarly, pyridinium salts **7b** and **7c**, which possess a bulky alkyl group on the nitrogen atom, reacted with **4a** to afford **8b** (95% yield, Entry 8) and **8c** (100% yield, Entry 9), respectively. As shown in Table 1, increasing steric bulkiness of the alkylthio group (MeS-, EtS-, Me_2CHS-) corresponded with lower yields. The reactions between 2-chloro-pyridinium salt (**9**)[4] and **4a**-**d** afforded corresponding **5a**-**d** (70-98% yields, Entries 10-13), which are the same products as those using **3a**. In the cases of cyclic active methylene compounds, the reaction between **3a** and cycloalkane-1,3-diones (**4e**, **f**) in DMF proceeded regioselectively at the 4-position to yield only 4-dioxo-cycloalkylidene-2-methylthiopyridines (**6a**, Entry 14 and **6d**, Entry 15), respectively, in low yields. Under similar conditions as that for **3a**, pyridinium salts **3b** and **3c**, which possess a bulky thioalkyl group, reacted with **4e** to give **6b** (32% yield, Entry 16) and **6c** (30% yield, Entry 17), respectively. In contrast, the reaction between pyridinium salt **9** and **4e** or **4f** proceeded regioselectively at the 2-position to give 2-dioxocycloalkylidenepyridines (**5e**, 76%, Entry 18; 83%, Entry 20 and **5f**, 61%, Entry 19; 53%, Entry 21), respectively.

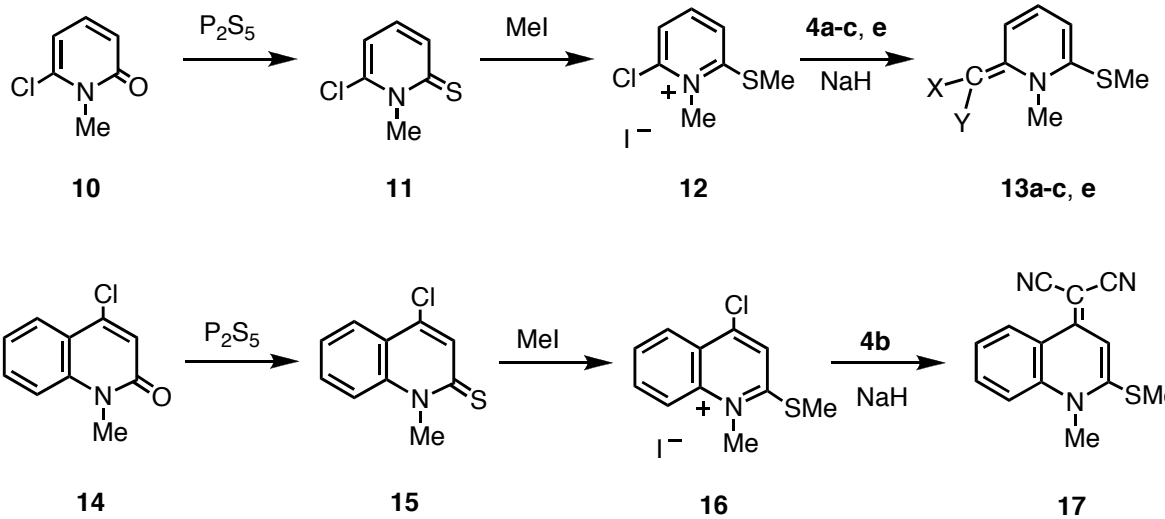
Next, as shown in Scheme 2, reactions were carried out using compounds that possess a methylthio and a chloro leaving group. Pyridinium salt **12** reacted with **4a**-**c** chemoselectively at the 6-position in 79-93% yields (Table 2, Entries 1-4, respectively). On the other hand, **12** reacted with cyclic **4e** at the 6-position to yield only **13e** in 36% yield (Entry 5), under similar reaction conditions that **3a**-**c** reacted with **4e** at the 4-position. Quinolonium salt **16** reacted with **4b** at the 4-position chemoselectively (Entries 6 and 7).



Scheme 1

Table 1. Reactions of **3a**-**c**, **7b**, **c**, **9** with **4a**-**f** in the presence of NaH

Entry	Temp. (℃)	Time (h)	Solvent	**Salt**	**4**	Product	Yield (%)
1	rt	2	THF	**3a**	**a**	**5a**	98
2	rt	1	THF	**3a**	**a**	**5a**	99
3	rt	0.5	THF	**3a**	**b**	**5b**	67
4	10	0.5	THF	**3a**	**c**	**5c**	64
5	65	3	THF	**3a**	**d**	**5d**	87
6	rt	2	THF	**3b**	**a**	**5a**	90
7	rt	3	THF	**3c**	**a**	**5a**	83
8	rt	2	THF	**7b**	**a**	**8b**	95
9	rt	3	THF	**7c**	**a**	**8c**	100
10	rt	0.5	THF	**9**	**a**	**5a**	93
11	rt	0.5	THF	**9**	**b**	**5b**	96
12	rt	0.5	THF	**9**	**c**	**5c**	98
13	rt	0.5	THF	**9**	**d**	**5d**	70
14	rt	6	DMF	**3a**	**e**	**6a**	39
15	rt	6	DMF	**3a**	**f**	**6d**	17
16	rt	6	DMF	**3b**	**e**	**6b**	32
17	rt	6	DMF	**3c**	**e**	**6c**	30
18	rt	1	DMF	**9**	**e**	**5e**	76
19	rt	1	DMF	**9**	**f**	**5f**	61
20	90	6	DMF	**9**	**e**	**5e**	83
21	90	6	DMF	**9**	**f**	**5f**	53



Scheme 2

Table 2. Reactions of **12** and **16** with **4a-c, e** in the presence of NaH

Entry	Salt	Temp. (°C)	Time (h)	Solvent	**4**	Product	Yield (%)
1	**12**	reflux	3	THF	**a**	**13a**	92
2	**12**	rt	3	THF	**a**	**13a**	93
3	**12**	rt	3	THF	**b**	**13b**	91
4	**12**	rt	3	THF	**c**	**13c**	79
5	**12**	90	3	DMF	**e**	**13e**	36
6	**16**	0	2	THF	**b**	**17**	40
7	**16**	rt	2	THF	**b**	**17**	23

Chemoselectivity

Theoretical calculations for the reactions of **12** and **16** with **4a-c**, **4e** (Scheme 2) were carried out using Gaussian 03 program package at HF/6-31G (d, p) level.[5] With the assumption that the reactions proceeded via two steps, activation energies were calculated for two processes: 1) the addition of **4a-c** and 4**e** to the 2- or 6-positions of **12** or the 2- or 4-positions of **16** (*Ea*1), and 2) the subsequent elimination of MeSH or HCl (*Ea*2). The energy diagram of the reaction between **12** and **4b** is shown in Fig. 1, and the calculated values of *Ea*1 and *Ea*2 along with the yields of adducts are summarized in Table 3. According to our calculations, *Ea*1 and *Ea*2 for the reaction on the 6-position of **12** were both smaller than those for the 2-position; similarly the energies for the 4-position of **16** were smaller than those for the 2-position. These calculations were in agreement with our experimental results, in which only adducts **13a-c**, **13e** and **17** were obtained.

Table 3. Activation enagies calculated at HF/6-31G(d, p) level and yields of adducts in reactions of **3a**, **9**, **12** and **16** with **4a**-**c**, **e** in the presence of NaH
*Ea*1 and *Ea*2 stand for activation energies for the addition and elimination processes, respectively.

Entry	Salt	**4**	*Ea*1(Kcal/mol) 2[a)]	6[a)]	*Ea*2(Kcal/mol) 2[b)]	6[b)]	Temp. (°C)	Time (h)	Product	Yield (%)
1	**12**	**a**	10.58	9.46	25.72	21.76	rt	3	**13a**	93
2	**12**	**b**	13.27	11.11	25.32	6.79	rt	3	**13b**	91
3	**12**	**c**	14.76	14.07	26.40	10.53	rt	3	**13c**	79
4	**12**	**e**	15.07	14.46	14.04	13.75	90	3	**13e**	36
5	**16**	**b**	9.58	9.21[c)]	31.24	8.81[c)]	0	2	**17**	40
6	**3a**	**b**	16.48	-----	20.43	----	rt	0.5	**5b**	67
7	**9**	**b**	11.50	-----	6.79	----	rt	0.5	**5b**	96

a) Position where the addition of **4** occures.
b) Position where the elimination process occures.
c) For addition at the 4-position.

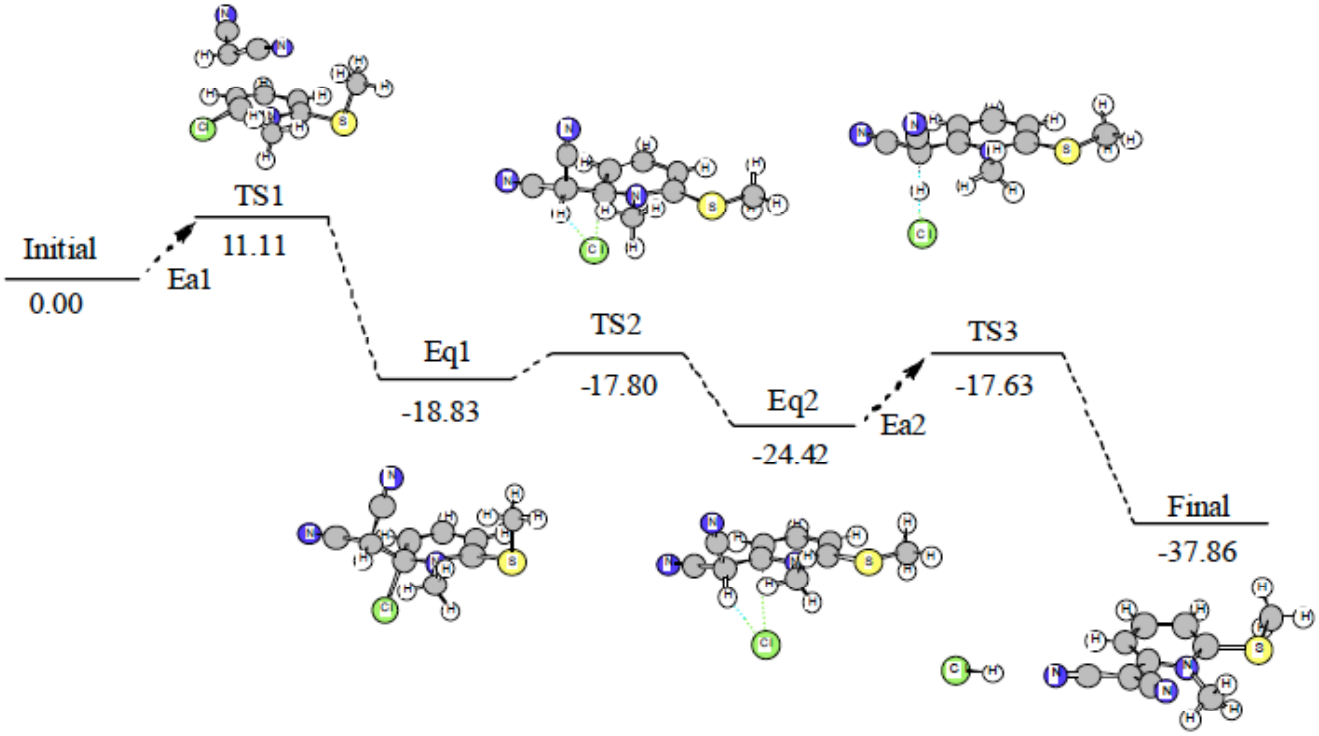


Fig.1. Schematic View of Energy Diagram Where **4b** (- ion) Added to 6-Position of **12** (+ ion) and Produced **13b** by Eliminating HCl

The energy of the initial state was set equal to zero. The energy of each state is denoted in kcal/mol. Ea1 (Ea2) stands for the activation energy of the addition (elimination) process. See text.

In summary, the 2-alkylthio leaving group of pyridinium salts **3a**-**c**, **7b**, and **7c** was regioselectively substituted with straight-chain active methylene compounds **4a**-**d** under the mild conditions. In contrast, cyclic active methylene compounds **4e**, **f** reacted with **3a**-**c** at the 4-position to give only one product, which retained the alkylthio leaving group. In the cases of **12** and **16**, the reaction with **4a**-**c** and **4e** occurred at the position that has a halogeno leaving group.

EXPERIMENTAL

The following instruments were used to obtain physical data: Melting points, Yanaco micromelting point apparatus (values are uncorrected); IR spectra, Perkin Elmer FT-IR1725X spectrophotometer; MS spectra, JEOL JMN-DX 303/JMA-DA 5000 spectrometer; NMR spectra, JNM-GSX 400 (^{1}H-NMR, 400 MHz; ^{13}C-NMR, 100 MHz), JNM-EX270 (^{1}H-NMR, 270 MHz; ^{13}C-NMR, 67.8 MHz), JEOL JNM-PMX 60SI spectrometers with tetramethylsilane (TMS) as an internal standard; elemental analyses, Perkin Elmer 2400 CHN Elemental Analyzer. For column chromatography, Merck Kieselgel silica gel 60 (230-400 mesh) was used.

General procedures for the synthesis of 1-alkyl-2-alkylthiopyridinium iodides (3c and 7c). a) An acetone solution (7 mL) of **1c** (0.306 g, 2 mmol) and **2a** (0.34 g, 2.4 mmol) was gently refluxed for 4 h. The resulting yellow precipitate was collected by filtration then recrystallized from methanol to give 2-methylthio-1-*iso*propylpyridinium iodide (**7c**, 0.570 g, 97%). b) Reaction of **1a** (0.125 g, 1 mmol) with **2c** (0.202 g, 1.2 mmol) was carried out under similar conditions to give 1-methyl-2-*iso*propylthiopyridinium iodide (**3c**, 0.220 g, 75%).

3c: Pale yellow needles (MeOH), mp 123-126 °C. IR (KBr) cm^{-1}: 1610, 1597, 1313, 1178, 780. ^{1}H-NMR (DMSO-d_6) δ : 1.55 (6H, d, *J*=7.0 Hz, CMex2), 4.20 (3H, s, NMe), 4.28 (1H, m, *J*=7.0 Hz, CH), 7.88 (1H, ddd, *J*=2.0, 7.0, 7.0 Hz, H-5), 8.25 (1H, dd, *J*=2.0, 7.0 Hz, H-3), 8.50 (1H, ddd, *J*=2.0, 7.0, 7.0 Hz, H-4), 9.10 (1H, dd, *J*=2.0, 7.0 Hz, H-6). *Anal*. Calcd for $C_9H_{14}INS$: C, 36.62; H, 4.78; N, 4.75. Found: C, 36.70; H, 4.99; N, 4.45.

7c: Pale yellow needles (MeOH), mp 165-167 °C. IR (KBr) cm^{-1}: 1660, 1620, 1590, 1360, 1140, 850, 760. ^{1}H-NMR ($CDCl_3$) δ : 1.80 (6H, d, *J*=7.0 Hz, CMex2), 3.00 (3H, s, SMe), 5.30 (1H, m, *J*=7.0 Hz, CH), 7.95 (1H, ddd, *J*=2.0, 8.0, 8.0 Hz, H-5), 8.20 (1H, dd, *J*=2.0, 8.0 Hz, H-3), 8.50 (1H, ddd, *J*=2.0, 7.0, 7.0 Hz, H-4), 9.40 (1H, dd, *J*=2.0, 7.0 Hz, H-6). *Anal*. Calcd for $C_9H_{14}INS$: C, 36.62; H, 4.78; N, 4.75. Found: C, 36.80; H, 4.90; N, 4.32.

General procedures for the reaction of the pyridinium salts (3a-c, 7b, 7c and 9) with 4a-f. a) To a suspension of NaH (15 mg, 0.6 mmol) in THF (5 mL) was added dimethyl malonate (**4a**, 79 mg, 0.6 mmol) at 0 °C under N_2. The mixture was stirred for 10 min at rt, followed by the addition of **3a** (134 mg, 0.5 mmol). After stirring for 2 h at rt, the reaction mixture was quenched with H_2O (5 mL), treated with saturated aqueous $Na_2S_2O_3$ solution (3 mL), then extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, then concentrated *in vacuo* to give 1,2-dihydro-2-dimethoxycarbonylmethylidene-1-methylpyridine (**5a**,[4] 109 mg, 98%). b) Reactions of **3b**, **3c** with **4b**-**f**, **7b**, **7c** and **9** with **4a**-**f** were carried out using similar procedures (specific conditions and yields are listed in Tables 1) to give 2-dicyanomethylidene-1,2-dihydro-1-methylpyridine (**5b**),[4] 2-cyano(methoxycarbonyl)methylidene-1,2-dihydro-1-methylpyidine (**5c**), 2-acetyl(methoxycarbonyl)methylidene-1,2-dihydro-1-methylpyidine (**5d**), 1,2-dihydro-1-methyl-2-(2,6-dioxocyclohexylidene)pyridine (**5e**), 1,2-dihydro-1-methyl-2-(2,5-di-oxocyclopentylidene)pyridine (**5f**), 1,4-dihydro-1-methyl-2-methylthio-4-(2,6-dioxocyclohexylidene) pyridine (**6a**), 2-ethylthio-1,4-dihydro-1-methyl-4-(2,6-dioxocyclohexylidene)pyridine (**6b**), 1,4-di-hydro-1-methyl-4-(2,6-dioxocyclohexylidene)-2-isopropylthiopyridine (**6c**),

1,4-dihydro-1-methyl-2-methylthio-4-(2,5-dioxocyclopentylidene)pyridine (**6d**), 1-ethyl-2-(dimethoxycarbonylmethylidene)-1,2-dihydropyridine (**8b**), 1,2-dihydro-2-(dimethoxycarbonylmethyllidene)-1-isopropylpyridine (**8c**).

5c: Yellow needles (benzene), mp 117-119 °C. IR (KBr) cm^{-1}: 2350, 1670, 775. ^{1}H-NMR ($CDCl_3$) δ: 3.67 (3H, s, OMe), 4.00 (3H, s, NMe), 6.79 (1H, dd, *J*=2.0, 7.0 Hz, H-5), 7.53 (1H, dd, *J*=2.0, 6.0 Hz, H-4), 7.73 (1H, dd, *J*=2.0, 7.0 Hz, H-3), 8.26 (1H, dd, *J*=2.0, 7.0 Hz, H-6). MS *m/z*: 190 (M^+). *Anal*. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.08; H, 5.53; N, 14.08.

5d: Yellow needles (benzene), mp 186-187 °C. IR (KBr) cm^{-1}: 1680, 1620, 790. ^{1}H-NMR ($CDCl_3$) δ: 2.56 (3H, s, COMe), 3.63 (3H, s, OMe), 4.00 (3H, s, NMe), 7.83 (2H, m, H-3, 4), 8.20 (1H, dd, *J*=2.0, 6.0 Hz, H-6). MS *m/z*: 207 (M^+). *Anal*. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.67; H, 6.46; N, 6.73.

5e: Yellow hygroscopic columns (MeOH), mp 196 °C. IR (KBr) cm^{-1}: 1635, 1590, 790. ^{1}H-NMR ($CDCl_3$) δ: 2.0 6 (2H, m, CH_2), 2.50 (4H, dd, *J*=7.0 Hz, CH_2CH_2), 4.06 (3H, s, NMe), 7.36 (1H, dd, *J*=3.0, 6.0 Hz, H-5), 7.79-8.17 (2H, m, H-3, 4), 8.33 (1H, dd, *J*=2.0, 6.0 Hz, H-6). ^{13}C-NMR ($CDCl_3$) δ: 20.85, 37.2 5(C2), 46.15, 108.08, 121.08, 133.87, 139.66, 141.42, 159.40, 192.23 (C2). MS *m/z*: 203(M^+). HRMS Calcd for $C_{12}H_{13}NO_2$ (M^+): 203.0946. Found: 203.0980.

5f: Yellow hygroscopic plates (acetone), mp 204-205 °C. IR (KBr) cm^{-1}: 1660, 1630, 770. ^{1}H-NMR ($CDCl_3$) δ: 2.56 (4H, s, CH_2CH_2), 4.23 (3H, s, NMe), 7.33 (1H, dd, *J*=2.0, 6.0 Hz, H-5), 8.00 (1H, m, *J*=2.0, 6.0 Hz, H-4), 8.06-8.39 (2H, m, H-3, 6). ^{13}C-NMR ($CDCl_3$) δ: 33.89 (C2), 47.09, 106.48, 120.15, 130.01, 140.07, 141.60, 154.92, 200.04 (C2). MS *m/z*: 189 (M^+). HRMS Calcd for $C_{11}H_{11}NO_2$ (M^+): 189.0790. Found: 189.0830.

6a: pale brown columns (MeOH), mp 217-218 °C. IR (KBr) cm^{-1}: 1630, 850, 735. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (2H, m, CH_2), 2.50 (4H, dd, *J*=6.0, 6.0 Hz, $COCH_2$x2), 2.76 (3H, s, SMe), 3.82 (3H, s, NMe), 7.56 (1H, d, *J*=8.0 Hz, H-6), 8.79 (1H, dd, *J*=2.0, 8.0 Hz, H-5), 9.23 (1H, d, *J*=2.0 Hz, H-3). ^{13}C-NMR ($CDCl_3$) δ: 15.50 (C2), 19.82, 39.78, 42.58, 109.10, 117.05, 118.72, 140.01, 153.00, 153.48, 197.03 (C2). MS *m/z*: 249 (M^+). *Anal*. Calcd for $C_{13}H_{15}NO_2S$: C, 62.64; H, 6.07; N, 5.62; S, 12.84. Found: C, 62.44; H, 6.07; N, 5.59; S, 13.15.

6b: pale yellow needles (acetone), mp 173-175 °C. IR (KBr) cm^{-1}: 1630, 1590, 840, 735. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, t, *J*=8.0 Hz, CMe), 1.95 (2H, m, *J*=6.0, 6.0 Hz, CH_2), 2.50 (4H, dd, *J*=6.0, 6.0 Hz, $COCH_2$x2), 3.2 (2H, q, *J*=8.0 Hz, SCH_2), 3.82 (3H, s, NMe), 7.50 (1H, d, *J*=6.0 Hz, H-6), 8.65 (1H, dd, *J*=2.0, 8.0 Hz, H-5), 9.14 (1H, d, *J*=2.0 Hz, H-3). ^{13}C-NMR ($CDCl_3$) δ: 13.08, 19.85, 27.41, 39.71 (C2), 42.74, 109.10, 118.99, 119.02, 140.10, 152.17, 153.49, 196.90 (C2). MS *m/z*: 263 (M^+). *Anal*. Calcd for

$C_{14}H_{17}NO_2S$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.73; H, 6.42; N, 5.22.

6c: pale brown columns (acetone), mp 162-163 °C. IR (KBr) cm^{-1}: 1625, 1580, 740. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (6H, d, *J*=8.0 Hz, C-Mex2), 1.76-2.00 (2H, m, CH_2), 2.39 (4H, dd, *J*=7.0, 7.0 Hz, $COCH_2$x2), 3.76(3H, s, NMe), 3.77 (1H, m, *J*=7.0 Hz, SCH), 7.20 (1H, d, *J*=8.0 Hz, H-6), 8.69 (1H, dd, *J*=2.0, 8.0 Hz, H-5), 9.16 (1H, d, *J*=2.0 Hz, H-3). ^{13}C-NMR ($CDCl_3$) δ: 19.85, 22.56(C2), 38.89 (C2), 39.69, 42.92, 109.08, 119.20, 119.70, 140.20, 151.60, 153.59, 196.84 (C2). MS *m/z*: 277 (M^+). *Anal*. Calcd for $C_{15}H_{19}NO_2S$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.97; H, 6.92; N, 4.96.

6d: pale brown columns (MeOH), mp 297-298 °C. IR (KBr) cm^{-1}: 1645, 840, 735. ^{1}H-NMR ($CDCl_3$) δ: 2.83 (3H, s, SMe), 2.90 (4H, s, $COCH_2$x2), 4.10 (3H, s, NMe), 8.17 (1H, d, *J*=6.9 Hz, H-6), 8.43 (1H, dd, *J*=1.8, 6.9 Hz, H-5), 8.75 (1H, d, *J*=1.8 Hz, H-3). ^{13}C-NMR ($CDCl_3$) δ: 15.52, 31.16 (C2), 44.62, 112.75, 118.22, 118.37, 143.65, 147.19, 159.37, 203.70 (C2). MS *m/z*: 235 (M^+). HRMS Calcd for $C_{12}H_{13}NO_2S$ (M^+): 235.0672. Found: 235.0677.

8b: yellow crystalline powder (acetone), mp 146-147 °C. IR (KBr) cm^{-1}: 1740, 1715, 1690, 1660, 870, 710. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, dd, *J*=8.0 Hz, CMe), 3.65 (6H, s, OMex2), 4.35 (2H, ddd, *J*=8.0 Hz, NCH_2), 7.00-7.35 (1H, m, H-5), 7.80 (2H, brd, H-4, 5), 8.15 (1H, d, *J*=6.0 Hz, H-6). ^{13}C-NMR ($CDCl_3$) δ: 15.66, 50.31 (C2), 52.71, 120.21, 134.64 (C2), 138.94, 139.09, 162.14, 167.60 (C2). MS *m/z*: 237 (M^+). HRMS Calcd for $C_{12}H_{15}NO_4$: 237.1001. Found: 237.1049.

8c: yellow needles (acetone), mp 222-223 °C. IR (KBr) cm^{-1}: 1740, 1700, 1660, 870, 790. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (6H, d, *J*=6.0 Hz, CMex2), 3.50 (6H, s, OMex2), 5.30 (1H, m, *J*=6.0 Hz, NCH), 7.16-8.85 (3H, m, H-3, 4, 5), 8.20 (1H, d, *J*=6.0 Hz, H-6). ^{13}C-NMR ($CDCl_3$) δ: 22.98 (C2), 50.11 (C2), 57.69, 121.34 (C2), 134.95, 136.35, 139.53, 162.02, 167.48 (C2). MS *m/z*: 251 (M^+). *Anal*. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.94; H, 6.93; N, 5.50.

Synthesis of 6-chloro-1-methyl-2-methylthiopyridinium iodide (12). A pyridine solution (8 mL) of 6-chloro-1-methyl-2(1*H*)-pyridone (**10**,[6] 3.99 g, 25 mmol) and phosphorus pentasufide (5.5 g, 25 mmol) was refluxed for 5 h. After cooling to rt, the reaction mixture was diluted with water (10 mL), then extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, then concentrated *in vacuo*. An acetone solution of the resulting residue (crude **11**) and MeI (**2a**, excess) was refluxed for 15 h. The resulting precipitate was collected by filtration, then recrystallized from MeOH to give 6-chloro-1-methyl-2-methylthiopyridinium iodide (**12**, 4.515 g, 60%).

12: brown powder (MeOH), mp 188-189 °C. IR (KBr) cm^{-1}: 1586, 1364, 1170. ^{1}H-NMR (DMSO-d_6) δ: 2.93 (3H, s, SMe), 4.23 (3H, s, NMe), 7.85 (1H, d, *J*=8.21 H, H-3), 8.02 (1H, d, *J*=8.21 H, H-5), 8.27 (1H, dd, *J*=8.21, 8.21 H, H-4). ^{13}C-NMR (DMSO-d_6) δ: 16.38, 43.36, 124.67, 127.45, 142.45,

150.54, 164.75. *Anal*. Calcd for C_7H_9ClINS: C, 27.88; H, 3.01; N, 4.64. Found: C, 28.14; H, 2.88; N, 4.53.

General procedure for the reaction of 12 with 4a-c and 4e. a) To a suspension of NaH (31.2 mg, 1.3 mmol) in THF (10 mL) was added dimethyl malonate (**4a**, 172 mg, 1.3 mmol) at 0 °C under N_2. The mixture was stirred for 10 min at rt, followed by the addition of **12** (302 mg, 1 mmol). After stirring for 3 h at rt, the reaction mixture was quenched with H_2O (10 mL), treated with saturated $Na_2S_2O_3$ solution (5 mL), then extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, then concentrated *in vacuo* to give 1,6-dihydro-1-methyl-2-methylthio-6-dimethoxycarbonyl-methylidenepyridine (**13a**, 250 mg, 93%). b) Reactions of **12** with **4b**-**c**, **e** were carried out by similar procedures (specific conditions and yields are listed in Table 2) to give 1,6-dihydro-1-methyl-2-methylthio-6-dicyanomethyl-idenepyridine (**13b**), 1,6-dihydro-1-methyl-2-methylthio-6-cyano(methoxycarbonyl)methylidenepyridine (**13c**), 1,6-dihydro-1-methyl-2-methylthio-6-(2,6-dioxocyclohexylidene)pyridine (**13e**).

13a: brown columns (acetone), mp 163-165 °C. IR (KBr) cm^{-1}: 1623, 1552, 1359, 780. ^{1}H-NMR (DMSO-d_6) δ : 2.70 (3H, s, SMe), 3.40 (6H, s, OMex2), 3.70 (3H, s, NMe), 7.03 (dd, *J*=2.0, 8.0 Hz, H-5), 7.51 (1H, dd, *J*=2.0, 8.0 Hz, H-3), 7.80 (1H, dd, *J*=8.0, 8.0 Hz, H-4). ^{13}C-NMR ($CDCl_3$) δ : 16.41, 42.29, 50.41 (C2), 79.70, 114.91, 128.16, 136.85, 154.98, 163.97, 167.62. MS *m*/*z*: 269 (M^+). HRMS Calcd for $C_{12}H_{15}NO_4S$ (M^+): 269.0722. Found: 269.0630.

13b: pale Brown needles (acetone), mp 168-170 °C. IR (KBr) cm^{-1}: 2196, 1606, 1540, 1329, 773. ^{1}H-NMR (DMSO-d_6) δ : 2.68 (3H, s, SMe), 3.97 (3H, s, NMe), 6.80 (1H, dd, *J*=2.0, 8.0 Hz, H-5), 7.10 (1H, dd, *J*=2.0, 8.0 Hz, H-3), 7.63 (1H, dd, *J*=8.0, 8.0 Hz, H-3). ^{13}C-NMR (DMSO-d_6) δ : 16.22, 45.35, 115.72, 118.89, 121.29, 128.39, 129.46, 130.65, 133.92, 136.79. MS *m*/*z*: 251 (M^+). HRMS Calcd for $C_{10}H_9N_3S$ (M^+): 203.0517. Found: 203.0465.

13c: pale brown plates (acetone), mp 128-131 °C. IR (KBr) cm^{-1}: 2177, 1671, 1546, 1358, 776. ^{1}H-NMR ($CDCl_3$) δ : 2.77 (3H, s, SMe), 3.10 (3H, s, OMe), 3.90 (3H, s, NMe), 6.33 (1H, dd, *J*=2.0, 8.0 Hz, H-5), 7.40 (1H, dd, *J*=8.0, 8.0 Hz, H-4), 7.85 (1H, dd, *J*=2.0, 8.0 Hz, H-3). ^{13}C-NMR ($CDCl_3$) δ : 16.31, 44.40, 51.14, 111.8 8 (C2), 121.69, 122.24, 135.70, 154.40, 161.17, 167.36. MS *m*/*z*: 269(M^+). HRMS Calcd for $C_{11}H_{12}N_2O_2S$ (M^+): 236.0619. Found: 236.0567.

13e: pale yellow Plates (THF), mp 222-223 °C. IR (KBr) cm^{-1}: 1609, 1529, 1362, 748. ^{1}H-NMR ($CDCl_3$) δ : 1.90-2.20 (2H, m, *J*=6.0 Hz, CH_2), 2.30 (4H, m, $COCH_2$x2), 2.70 (3H, s, SMe), 3.90 (3H, s, NMe), 7.10 (1H, dd, *J*=6.0, 6.0 Hz, H-4), 7.80 (1H, dd, *J*=2.0, 8.0 Hz, H-5), 7.89 (1H, d, *J*=2.0, 6.0 Hz, H-4). ^{13}C-NMR ($CDCl_3$) δ : 16.31, 20.91, 37.20 (C2), 42.03, 100.49, 108.87, 117.16, 128.00, 138.57,

156.36, 160.58, 192.05 (C2). MS *m/z*: 251 (M^+). HRMS Calcd for $C_{13}H_{15}NO_2S$ (M^+): 249.0823. Found: 249.0872.

Synthesis of 4-chloro-1-methyl-2(1*H*)-quinolone (14). To a solution of 4-chloro-1-methylquinolinium iodide (3.06 g, 10 mmol) and $K_3Fe(CN)_6$ (9.87 g, 30 mmol) in H_2O (100 mL) cooled in ice was added KOH (3.36 g, 60 mmol) for 1 h. After stirring for 4 h, the reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, then concentrated *in vacuo*. The resulting residue was recrystallized from acetone to give **14** (1.65 g, 85%).

14: pale yellow plates (acetone), mp 107 °C. IR (KBr) cm^{-1}: 1662, 1636, 1585, 768, 746. ^{1}H-NMR ($CDCl_3$) δ : 3.72 (3H, s, NMe), 6.90 (1H, s, H-3), 7.32-7.42 (2H, m, H-6,8), 7.63 (1H, ddd, *J*=1.5, 7.1, 8.1 Hz, H-7), 8.02 (1H, dd, *J*=1.5, 8.1 Hz, H-5). ^{13}C-NMR ($CDCl_3$) δ : 29.55, 114.36, 119.19, 120.98, 122.57, 126.18, 131.86, 139.75, 144.26, 160.94. MS *m/z*: 195 (M^++2), 193 (M^+). HR-MS *m/z*: Calcd for $C_{10}H_8ClNO$: 193.0294. Found: 193.0231.

Synthesis of 4-chloro-1-methyl-2-methylthioquinolinium iodide (16). A pyridine solution (8 mL) of **14** (1.16 g, 6 mmol) and phosphorus pentasufide (1.6 g, 7.2 mmol) was refluxed for 5 h. After cooling to rt, the reaction mixture was diluted with water (10 mL), then extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, then concentrated *in vacuo*. The resulting residue was dissolved in acetone (10 mL), treated with an excess amount of **2a**, then refluxed for 5h. The resulting yellow precipitate was collected by filtration, then recrystallized from methanol to give **16** (0.49 g, 23%).

16: yellow powder (MeOH), mp＞300 °C. IR (KBr) cm^{-1}: 1600. ^{1}H-NMR (DMSO-d_6) δ : 2.70 (3H, s, SMe), 4.43 (3H, s, NMe), 7.77 (1H, s, H-3), 7.95 (1H, ddd, *J*=1.5, 7.1, 7.5 Hz, H-6 or 7), 8.27 (1H, ddd, *J*=1.3, 7.1, 8.4 Hz, H-6 or 7), 8.48-8.60 (2H, m, H-5, 8). ^{13}C-NMR (DMSO-d_6) δ : 15.92, 39.00, 119.00, 121.79, 123.51, 125.79, 128.85, 135.25, 139.30, 146.86, 165.14. *Anal.* Calcd for $C_{11}H_{11}ClINS$: C, 37.57; H, 3.15; N, 3.98. Found: 37.6; H, 3.20; N, 4.13.

Reaction 16 with 4b. a) To a suspension of NaH (31.2 mg, 1.3 mmol) in THF (10 mL) was added **4b** (86 mg, 1.3 mmol) at 0 °C under N_2. The mixture was stirred for 10 min at 0 °C, followed by the addition of **16** (351 mg, 1 mmol). After stirring for 2 h at 0℃, the reaction mixture was quenched with H_2O (10 mL), treated with saturated aqueous $Na_2S_2O_3$ solution (5 mL), then extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, then concentrated *in vacuo* to give 1,4-dihydro-1-methyl-2-methylthio-4-dicyanomethylidenequinoline (**17**,[7] 96 mg, 40%).

Calculation of activation energies. As shown in Figure 1, **12** (positive ion) and **4b** (negative ion) approached each other to form the initial equilibrium state ("Initial"). Subsequently, the addition of **4b** to the 6-position (or 2-position) of **12** via a transition state (TS1) formed the intermediate state (Eq1).

Finally, HCl (or MeSH) was eliminated via TS2 and TS3. The structures at each state were optimized using *ab initio* molecular orbital method Gaussian 03 at HF/6-31G (d, p) level.[5] Solvent effects were not considered. After optimizing the TS structure, the vibrational calculations were carried out to confirm that the TS had only one imaginary vibrational frequency. The intrinsic reaction coordinate calculations were also carried out to ensure that the TS was connected to the initial and the targeted final states. The activation energy of the addition step (*Ea*1) was defined as the difference between the energies of TS1 and the Initial state. Similarly, the energy of the elimination step (*Ea*2) was defined as a difference between the energies of TS2 (or TS3) and Eq1 (or Eq2).

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