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REACTIONS OF 3-[BIS(METHYLTHIO)METHYLENE]-2(3*H*)-IMIDAZO[1,2-*a*]PYRIDINONES WITH QUINOLINIUM AND ISOQUINOLINIUM *N*-UNSUBSTITUTED AMINIDES[1]

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Abstract – 1,3-Dipolar cycloadditions of 3-[bis(methylthio)methylene]-2(3*H*)-imidazo[1,2-*a*]pyridinones with quinolinium and isoquinolinium *N*-unsubstituted aminides were investigated and the corresponding spiro[imidazo[1,2-*a*]pyridine-3,3’-pyrazolo[1,5-*a*]quinoline] and spiro[imidazo[1,2-*a*]pyridine-3,3’-pyrazolo[5,1-*a*]isoquinoline] derivatives were formed by way of the elimination of methanethiol from the primary adducts.

Ketene dithioacetals substituted with electron-withdrawing group(s) are excellent electrophiles and dipolarophiles and their reactions with various substrates were documented.[2-4] Recently, we reported a synthesis of 3-[bis(methylthio)methylene]-2(3*H*)-imidazo[1,2-*a*]pyridinones (**1**) which are novel heterocyclic ketenedithioacetals conjugated with a carbonyl group, and their transformations to 2*H*-pyrano[2’,3’:4,5]imidazo[1,2-*a*]pyridin-2-ones (**2**)[5] and ethyl 2’,3’-dihydro-2-methylthio-2’,4-dioxospiro[2-cyclopentene-1,3’-imidazo[1,2-*a*]pyridine]-3-carboxylates (**3**) (see Figure 1).[6] We were particularly interested in the formation of the spiro compounds **3** because a structurally similar 2,3-dihydrospiro[imidazo[1,2-*a*]pyridine-3,2’-indan]-2-one (**4**, ZSET1446) has been reported to act as an Alzheimer’s disease progression inhibitor and cognitive enhancer.[7-9] Therefore, we next planned to prepare new 2(3*H*)-imidazo[1,2-*a*]pyridinone derivatives having a spiro-fused five-membered heterocycle at the 3-position from the 1,3-dipolar cycloadditions of **1** with appropriate reagents. After some elaboration for such 1,3-dipoles we found that **1** smoothly reacted with the title compounds. We report here the syntheses of 2-methylthio-2-oxo-2,3,3’,3a’-tetrahydrospiro[imidazo[1,2-*a*]pyridine-3,3’-pyrazolo[1,5-*a*]quinoline] and 2-methylthio-2-oxo-2,3,3’,3a’-tetrahydrospiro[imidazo[1,2-*a*]pyridine-

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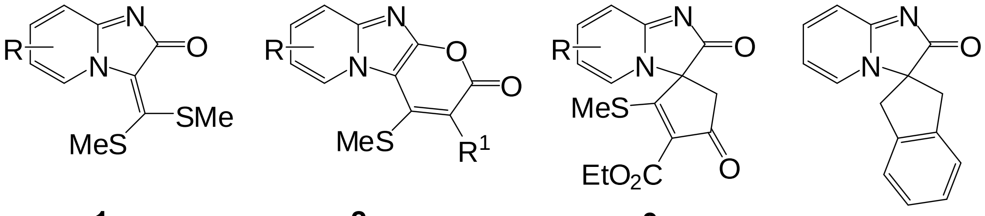
Dedicated to Professor Dr. Ei-ichi Negishi on his 77th birthday.

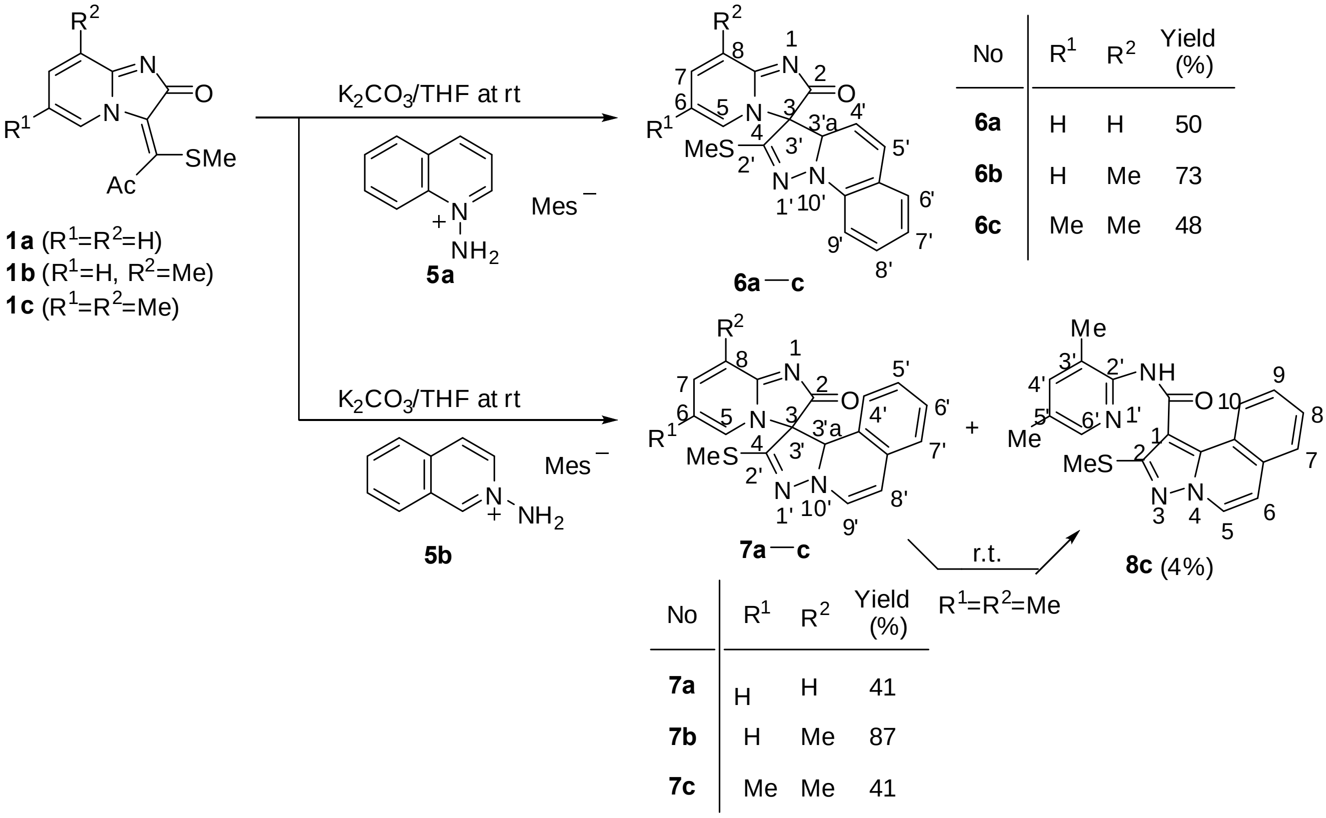
3,3’-pyrazolo[5,1-*a*]isoquinoline] derivatives in the reactions of 3-[bis(methylthio)methylene]-2(3*H*)-imidazo[1,2-*a*]pyridinones (**1**) with quinolinium and isoquinolinium *N*-unsubstituted aminides.



1 **2** **3** **4** (ZSET1446)

Figure 1

Since we earlier reported the 1,3-dipolar cycloadditions of 3-[bis(methylthio)methylene]-2(3*H*)-indolizinones whose structure is closely similar to that of 3-[bis(methylthio)methylene]-2(3*H*)-imidazo[1,2-*a*]pyridinones (**1**),[4] we examined the reactions of **1a**—**c** with monocyclic and bicyclic pyridinium*N*-unsubstituted aminides. The reactions of **1a**—**c** with 1-aminopyridinium iodide in the presence of a base did not afford any significant product, but those with 1-aminoquinolinium mesitylenesulfonate (**5a**) and 1-aminoisoquinolinium mesitylenesulfonate (**5b**) in the presence of excess potassium carbonate in THF at room temperature proceeded with the elimination of methanethiol to provide the corresponding products **6a**—**c**, **7a**,**b** and **7c**+**8c** (its ratio 10:1) respectively. (Scheme 1)



No	R1	R2	Yield (%)
6a	H	H	50
6b	H	Me	73
6c	Me	Me	48

No	R1	R2	Yield (%)
7a	H	H	41
7b	H	Me	87
7c	Me	Me	41

Scheme 1

Interestingly, compound **7c** was converted to **8c** during the recrystallization from $CHCl_3$-hexane or on standing at room temperature. On the other hand, similar reaction of **1a** with pyridinium monosubstituted methylide such as pyridinium 1-(ethoxycarbonyl)methylide or 1-phenacylide did not provide good results.

Elemental analyses and HRMS data for products **6a—c**, **7a**,**b**, and **8c** were in accord with our proposed compositions and their IR spectra of **6a—c**, and **7a**,**b** exhibited a characteristic carbonyl band of the 2(3*H*)-imidazo[1,2-*a*]pyridinone at 1698—1701 cm^{-1}. In ^1H-NMR spectra of **6a**—**c** and **7a**—**c** the signal (δ 2.50—2.55) of sole methylthio group and that (δ 5.65—5.70 for **6a**—**c** and δ 6.07—6.12 for **7a**—**c**) for the 3a'-proton attached on the sp^3-carbon were distinctly indicated.[10] In addition the large high field shift (1.71—1.88 ppm) of the 5-proton in **6a**—**c** and **7a**—**c** compared with that in **1a**—**c** was observed.[5] This fact strongly supported the presence of the spiro structure at the 3-position of the 2(3*H*)-imidazo[1,2-*a*]pyridinone skeleton in **6a**—**c** and **7a**—**c**, because the lower chemical shifts of the 5-proton in **1a**—**c** was mainly derived from the deshielding effect by the 3-exo-methylene group. The final structures of **6a**—**c** and **7a**—**c** were decided by the X-ray analysis of one compound **6a**. The ORTEP drawing of **6a** is shown in Figure 2.[11]

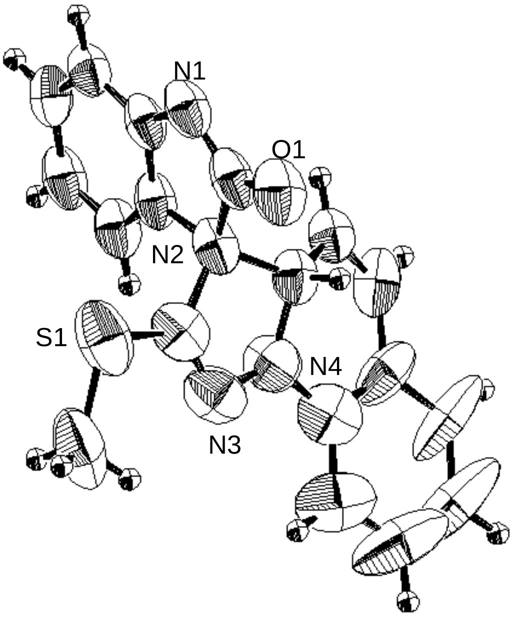


Figure 2. ORTEP drawing for **6a**

On the other hand, the ^1H-NMR spectrum of **8c** in $CDCl_3$ significantly changed the chemical shifts depending upon their concentrations. For example, the ^1H-NMR spectrum in 3.79×10^{-3} mol/L of **8c** showed the signals at δ 2.34 (3H, s, 3'-Me), 2.40 (3H, s, 5'-Me), 2.73 (3H, s, SMe), 7.11 (1H, d, *J*=7.3 Hz, 6-H), 7.47 (1H, br s, 4'-H), 7.54 (1H, ddd, *J*=8.2, 8.1, 1.4 Hz, 9-H), 7.59 (1H, ddd, *J*=8.2, 7.7, 1.4 Hz, 8-H), 7.72 (1H, br d, *J*=7.7 Hz, 7-H), 8.16 (1H, br s, 6'-H), 8.21 (1H, *J*=7.3 Hz, 5-H), 8.31 (1H, br s, NH), and 9.20 (1H, br d, *J*=8.1 Hz, 10-H) and that in 9.30×10^{-2} mol/L exhibited the corresponding signals at δ 2.30, 2.37, 2.71, 7.06, 7.42, 7.49, 7.55, 7.67, 8.08, 8.20, 8.59, 9.11. Like this all methine and methyl protons of **8c** showed the high field shifts (0.01-0.09 ppm) with the increase of the concentration but only amino proton a larger low field shift (0.28 ppm). The origins of such high or low field shifts for the proton signals of **8c** is unclear but they may be considered the shielding effect by the intermolecular arene-arene interactions to their methine and methyl protons[12] and the deshielding effect by the hydrogen bonding of the amino group respectively. In addition the presences of three sp^3-carbons and an amino group could be also confirmed in the C^{13}-NMR and IR spectra of **8c**. Though we first considered the structure of **8c** as isoquinolinium aminide **12** (see Scheme 2) formed by the retro-1,5-dipolar cyclization of **7c**, these spectral evidences refused the structure **12** and suggested an alternative structure **8c**. The structure **8c** was finally confirmed by the X-ray analysis and the ORTEP drawing is shown in Figure 3.

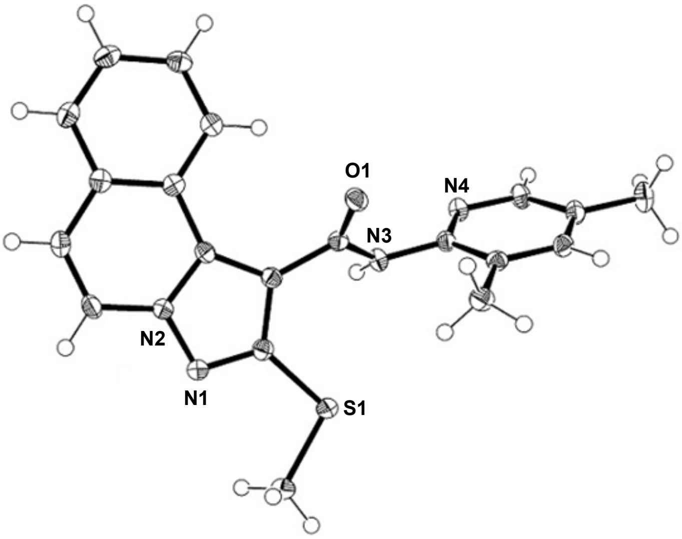
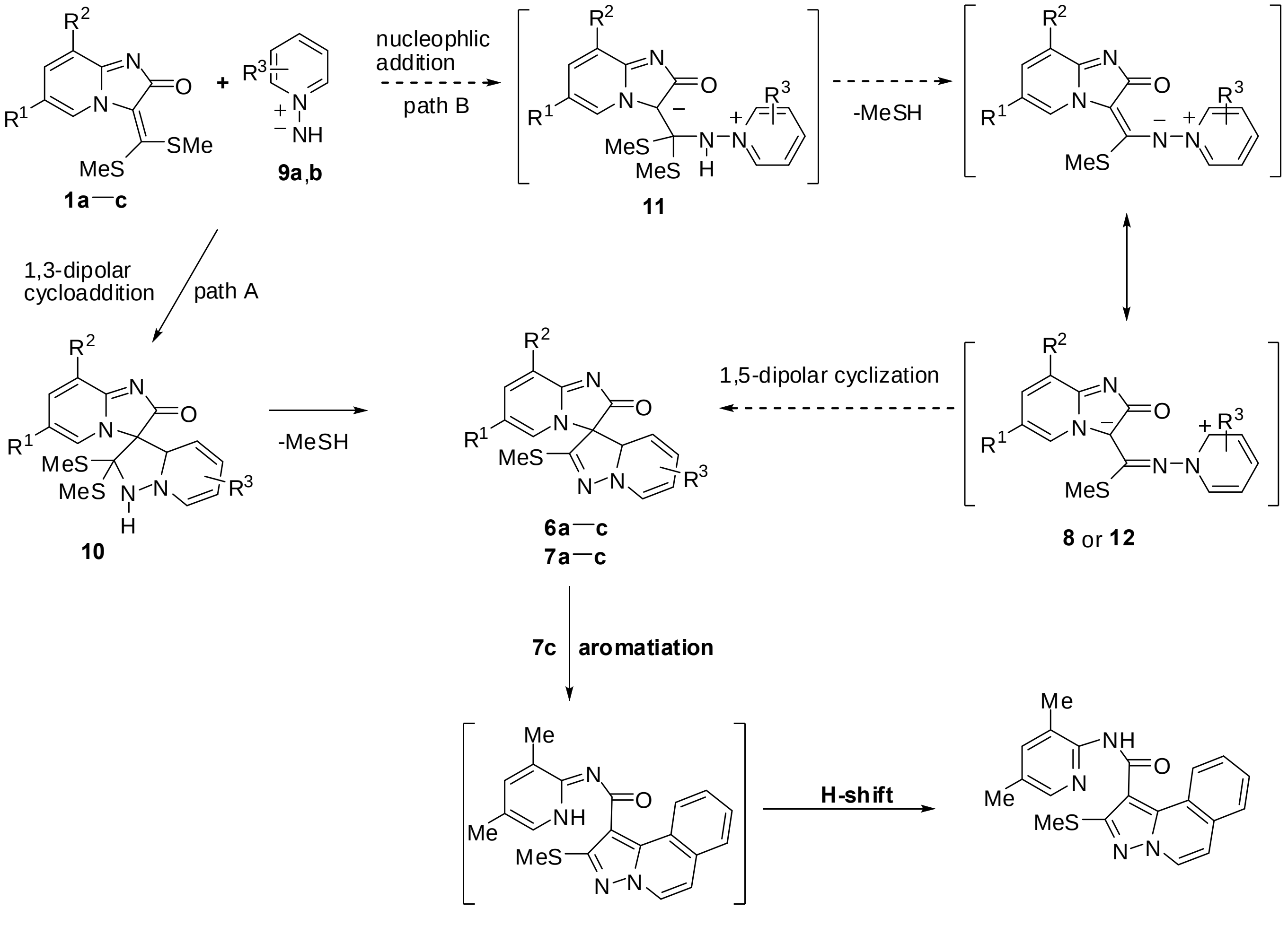


Figure 3. ORTEP drawing of **8c**

The possible mechanisms for these reactions are shown in Scheme 2. There are two possible routes for the formation of cycloadducts **6a**—**c** and **7a**—**c**. First is path A in which products **6a**—**c** and **7a**—**c** were formed via the 1,3-dipolar cycloadditions of **1a**—**c** with quinolinium (**9a**) or isoquinolinium aminide **(9b)** generated in situ from the alkaline treatment of their salts **5a**,**b**, followed by the elimination of one molecule of methanethiol from the primary adducts **10**. The second is path B in which the same products were given through the nucleophlic addition of the aminide nitrogen of **9a**,**b** to the positive carbon of ketenedithioacetals **1a**—**c**, the elimination of a methanethiol from the primary adducts **11**, and then the



Scheme 2

1,5-dipolar cyclization of the corresponding quinolinium or isoquinolinium *N*-vinylaminides **12**. We believe that above reactions proceeded by way of path A since it is known that the 1,5-dipolar cyclization of pyridinium (2,2-disubstituted vinyl)aminide derivatives is generally difficult to take place under such mild conditions.[13-16] However, we do not completely refuse the alternative route (path B) for the formation of spiro compounds **6a—c** and **7a—c** since the extremely high electrophilicity of ketenedithioacetals conjugated with electron-withdrawing group(s) is well documented.[2,3,5,6] The transformation from **7c** to **8c** can be interpreted by the aromatization of the 4,5-dihydropyrazole ring in **7c**, followed by the 1,3-shift of the amino proton in the resulting 1,2-dihydropyridine **13**.

The pharmaceutical activity for these spiro compounds **2**, **6** and **7** is now in screening.

EXPERIMENTAL

Melting points were measured with a Yanagimoto micromelting point apparatus and were not corrected. Microanalyses were carried out on a Perkin-Elmer 2400 elemental analyzer. The ^{1}H-NMR and ^{13}C-NMR spectra were determined with a JEOL JNM-LA400 (^{1}H: 400 MHz and ^{13}C: 100.4 MHz) spectrometer in deuteriochloroform with tetramethylsilane used as the internal standard; the chemical shifts are expressed in δ values. The IR and HRMS spectra were taken with JASCO FT/IR-5300 IR spectrophotometers and Agilent 6520 Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) LC/MS.

Reaction of 3-[bis(methylthio)methylene]-2(3*H*)-imidazo[1,2-*a*]pyridinones with quinolinium or isoquinolinium aminides. General method. A mixture of 3-[bis(methylthio)methylene]-2(3*H*)-imidazo[1,5-*a*]pyridinones (**1**, 1 mmol), 1-aminoquinolinium (**5a**, 0.344g (1 mmol)) or 1-aminoisoquinolinium mesitylenesulfonate (**5b**, 0.344g (1 mmol)), and potassium carbonate (5g) in THF (30 mL) was stirred at room temperature until the disappearance of **1** was confirmed by TLC monitoring. The resulting mixture was then filtered to remove insoluble inorganic substances and the filtrate was concentrated at reduced pressure. The residue was separated by column chromatography on alumina using chloroform as an eluent. The yellow fractions were combined and concentrated at reduced pressure. Recrystallization from $CHCl_3$-hexane gave the corresponding adducts **6a**—**c** and **7a**,**b**, but the reaction of **1c** with **5b** afforded a 10:1 mixture of **7c** and **8c** after the column chromatographic separation and the recrystallization of its crude products from the same solvent afforded only **8c**. The same compound **8c** could be also obtained on standing of cycloadduct **7c** at room temperature. These results and some properties of products (**6a**—**c, 7a**—**c, and 8c**) are as follows:

2’-Methylthio-2-oxo-2,3,3’,3a’-tetrahydrospiro[imidazo[1,2-*a*]pyridine-3,3’-pyrazolo[1,5-*a*]quinoline] (**6a**): 50% (from **1a** and **5a**), 2 h (reaction time), yellow prisms (from $CHCl_3$-hexane), mp 165—166 °C. IR (KBr) cm^{-1}: 1626, 1698. ^{1}H-NMR δ: 2.55 (3H, s, SMe), 5.19 (1H, dd, *J* = 10.0, 2.3 Hz, 4’-H), 5.69 (1H, dd, *J* = 2.3, 2.3 Hz, 3a’-H), 6.51 (1H, dd, *J* = 10.0, 2.3 Hz, 5’-H), 6.60 (1H, ddd, *J* = 6.8, 6.8, 1.0 Hz, 6-H), 6.83 (1H, ddd, *J* = 7.6, 7.3, 1.2 Hz, 7’-H), 7.02 (1H, dd, *J* = 7.3, 1.2 Hz, 6’-H), 7.17 (1H, br d, *J* = 6.8 Hz, 5-H), 7.21—7.27 (2H, m, 8-H, 8’-H), 7.38 (1H, br d, *J* = 8.1 Hz, 9’-H), 7.67 (1H, ddd, *J* = 9.1, 6.8, 1.0 Hz, 7-H). ^{13}C NMR ($CDCl_3$) δ: 14.27, 68.65, 79.79, 112.30, 112.92, 113.66, 113.81, 118.63, 119.93, 127.72, 130.09, 130.24, 134.93, 138.48, 142.84, 147.49, 166.37, 181.63. $C_{18}H_{15}N_4OS$ $(M+H)^+$: Calcd; 335.0961 (Found; 335.0968). *Anal.* Calcd for $C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75. Found C, 64.40; H, 4.12; N, 16.63.

8-Methyl-2’-methylthio-2-oxo-2,3,3’,3a’-tetrahydrospiro[imidazo[1,2-*a*]pyridine-3,3’-pyrazolo[1,5-*a*]-quinoline] (**6b**): 73% (from **1b** and **5a**), 2 h (reaction time), yellow prisms (from $CHCl_3$-hexane), mp 97—98 °C. IR (KBr) cm^{-1}: 1618, 1701. ^{1}H-NMR δ: 2.43 (3H, s, 8-Me), 2.54 (3H, s, SMe), 5.19 (1H, dd, *J* = 10.0, 2.3 Hz, 4’-H), 5.70 (1H, dd, *J* = 2.3, 2.3 Hz, 3a’-H), 6.50 (1H, dd, *J* = 10.0, 2.3 Hz, 5’-H), 6.53 (1H, dd, *J* = 6.8, 6.8 Hz, 6-H), 6.82 (1H, ddd, *J* = 7.6, 7.3, 1.2 Hz, 7’-H), 7.02 (1H, dd, *J* = 7.3, 1.2 Hz, 6’-H), 7.06 (1H, br d, *J* = 6.8 Hz, 5-H), 7.24 (1H, ddd, *J* = 8.1, 7.6, 1.2 Hz, 8’-H), 7.38 (1H, br d, *J* = 8.1 Hz, 9’-H), 7.48 (1H, br d, *J* = 6.8 Hz, 7-H). ^{13}C NMR ($CDCl_3$) δ: 14.44, 17.32, 68.76, 80.52, 112.09, 113.03, 114.16, 118.82, 119.97, 126.50, 127.83, 130.21, 131.27, 138.74, 141.11, 147.76, 166.45, 181.78 (one carbon is overlapping). $C_{19}H_{17}N_4OS$ $(M+H)^+$: Calcd; 349.1118 (Found; 349.1122). *Anal.* Calcd for $C_{19}H_{16}N_4OS$: C, 65.50; H, 4.63; N, 16.08. Found C, 65.47; H, 4.51; N, 15.89.

6,8-Dimethyl-2’-methylthio-2-oxo-2,3,3’,3a’-tetrahydrospiro[imidazo[1,2-*a*]pyridine-3,3’-pyrazolo-[1,5-*a*]quinoline] (**6c**): 48% (from **1c** and **5a**), 16 h (reaction time), yellow needles (from $CHCl_3$-hexane), mp 101—103 °C. IR (KBr) cm^{-1}: 1635, 1701. ^{1}H-NMR δ: 2.10 (3H, s, 6-Me), 2.40 (3H, s, 8-Me), 2.54 (3H, s, SMe), 5.20 (1H, dd, *J* = 10.0, 2.3 Hz, 4’-H), 5.65 (1H, dd, *J* = 2.3, 2.3 Hz, 3a’-H), 6.50 (1H, dd, *J* = 10.0, 2.3 Hz, 5’-H), 6.83 (1H, ddd, *J* = 7.6, 7.3, 1.2 Hz, 7’-H), 6.86 (1H, br s, 5-H), 7.04 (1H, dd, *J* = 7.3, 1.2 Hz, 6’-H), 7.25 (1H, ddd, *J* = 8.1, 7.6, 1.2 Hz, 8’-H), 7.34 (1H, br s, 7-H), 7.39 (1H, br d, *J* = 8.1 Hz, 9’-H). $C_{20}H_{19}N_4OS$ $(M+H)^+$: Calcd; 363.1274 (Found; 363.1284). *Anal.* Calcd for $C_{20}H_{18}N_4OS$: C, 66.28; H, 5.01; N, 15.46. Found C, 66.32; H, 4.79; N, 15.35.

2’-Methylthio-2-oxo-2,3,3’,3a’-tetrahydrospiro[imidazo[1,2-*a*]pyridine-3,3’-pyrazolo[5,1-*a*][isoquinoline] (**7a**): 41% (from **1a** and **5b**), 1 h (reaction time), yellow prisms (from $CHCl_3$-hexane), mp 176—178 °C. R (KBr) cm^{-1}: 1626, 1701. ^{1}H-NMR δ: 2.51 (3H, s, SMe), 5.44 (1H, d, *J* = 7.6 Hz, 8’-H), 6.12 (1H, s, 3a’-H), 6.41 (1H, ddd, *J* = 6.8, 6.8, 1.0 Hz, 6-H), 6.52 (1H, br d, *J* = 7.6 Hz, 4’-H), 6.84 (1H, dt, *J* = 7.6, 1.2 Hz, 5’-H), 6.88 (1H, d, *J* = 7.6 Hz, 9’-H), 6.96 (1H, dd, *J* = 7.6, 1.2 Hz, 7’-H), 7.05 (1H, br d, *J* = 6.8 Hz, 5-H), 7.08 (1H, br t, *J* = 7.6 Hz, 6’-H), 7.19 (1H, br d, *J* = 9.2 Hz, 8-H), 7.54 (1H, ddd, *J* = 9.2, 6.8, 1.0 Hz, (7-H). ^{13}C NMR ($CDCl_3$) δ: 14.23, 69.08, 82.02, 100.02, 112.44, 116.06, 122.86, 124.62, 125.28, 126.51, 128.75, 129.51, 132.18, 133.88, 142.68, 148.00, 166.85, 182.69. $C_{18}H_{15}N_4OS$ $(M+H)^+$: Calcd; 335.0961 (Found; 335.0968). *Anal.* Calcd for $C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75. Found C, 64.51; H, 4.21; N, 16.66.

8-Methyl-2’-methylthio-2-oxo-2,3,3’,3a’-tetrahydrospiro[imidazo[1,2-*a*]pyridine-3,3’-pyrazolo[5,1-*a*]-isoquinoline] (**7b**): 87% (from **1b** and **5b**), 3 h (reaction time), yellow prisms (from $CHCl_3$-hexane), mp 158—159 °C. IR (KBr) cm^{-1}: 1622, 1698. ^{1}H-NMR δ:2.50 (3H, s, SMe), 5.42 (1H, d, *J* = 7.6 Hz, 8’-H), 6.12 (1H, s, 3a’-H), 6.41 (1H, ddd, *J* = 6.8, 6.8, 1.0 Hz, 6-H), 6.52 (1H, br d, *J* = 7.6 Hz, 4’-H), 6.84 (1H, ddd, *J* = 7.6, 7.6, 1.2 Hz, 5’-H), 6.88 (1H, d, *J* = 7.6 Hz, 9’-H), 6.96 (1H, dd, *J* = 7.6, 1.2 Hz, 7’-H), 7.05 (1H, br d, *J* = 6.8 Hz, 5-H), 7.08 (1H, br t, *J* = 7.6 Hz, 6’-H), 7.19 (1H, br d, *J* = 9.2 Hz, 8-H), 7.54 (1H, ddd, *J* = 9.2, 6.8, 1.0 Hz, (7-H). ^{13}C NMR ($CDCl_3$) δ: 14.28, 17.32, 69.05, 82.60, 99.95, 112.18, 123.07, 124.69, 125.23, 126.39, 128.67, 129.58, 130.98, 132.27, 141.06, 148.10, 166.76, 182.68. $C_{19}H_{17}N_4OS$ $(M+H)^+$: Calcd; 349.1118 (Found; 349.1124). *Anal.* Calcd for $C_{19}H_{16}N_4OS$: C, 65.50; H, 4.63; N, 16.08. Found C, 65.38; H, 4.67; N, 15.89.

6,8-Dimethyl-2'-methylthio-2-oxo-2,3,3',3a'-tetrahydrospiro[imidazo[1,2-*a*]pyridine-3,3'-pyrazolo-[5,1-*a*]isoquinoline] (**7c**): 42% (from **1c** and **5b**), 24 h (reaction time), yellow prisms. ^{1}H-NMR δ: 1.95 (3H, S, 6-Me), 2.38 (3H, s, 8-Me), 2.50 (3H, s, SMe), 5.43 (1H, d, *J* = 7.6 Hz, 8'-H), 6.07 (1H, s, 3a'-H), 6.48 (1H, br d, *J* = 7.6 Hz, 4'-H), 6.73 (1H, br s, 5-H), 6.81 (1H, ddd, *J* = 7.6, 7.6, 1.2 Hz, 5'-H), 6.89 (1H, d, *J* = 7.6 Hz, 9'-H), 6.94 (1H, dd, *J* = 7.6, 1.2 Hz, 7'-H), 7.06 (1H, br t, *J* = 7.6 Hz, 6'-H), 7.21 (1H, br s, 7-H).[17] ^{13}C NMR ($CDCl_3$) δ: 14.13, 16.99, 17.21, 69.00, 82.81, 100.02, 122.42, 123.21, 124.61, 125.18, 125.65, 126.41, 128.71, 128.90, 129.74, 132.33, 144.04, 148.29, 165.20, 182.74.

2-Methylthiopyrazolo[5,1-*a*]isoquinoline-1-[*N*-(3,5-dimethylpyridin-2-yl)]-carboxamide (**8c**): 4% (from **1c** and **5b**), 24 h (reaction time), colorless prisms (from $CHCl_3$-Et_2O), mp 183—184 °C. IR (KBr) cm^{-1}: 3192, 1665. ^{1}H-NMR δ (3.79×10^{-3} mol/L): 2.34 (3H, s, 3'-Me), 2.40 (3H, s, 5'-Me), 2.73 (3H, s, SMe), 7.11 (1H, d, *J* = 7.3 Hz, 6-H), 7.47 (1H, br s, 4'-H), 7.54 (1H, ddd, *J* = 8.2, 8.1, 1.4 Hz, 9-H), 7.59 (1H, ddd, *J* = 8.2, 7.7, 1.4 Hz, 8-H), 7.72 (1H, br d, *J* = 7.7 Hz, 7-H), 8.16 (1H, br s, 6'-H), 8.21 (1H, d, *J* = 7.3 Hz, 5-H), 8.31 (1H, br s, NH), 9.20 (1H, br d, *J* = 8.1 Hz, 10-H). ^{1}H-NMR δ (9.30×10^{-2} mol/L): 2.30 (3H, s, 3'-Me), 2.37 (3H, s, 5'-Me), 2.71 (3H, s, SMe), 7.06 (1H, d, *J* = 7.3 Hz, 6-H), 7.42 (1H, br s, 4'-H), 7.49 (1H, ddd, *J* = 8.2, 8.1, 1.4 Hz, 9-H), 7.55 (1H, ddd, *J* = 8.2, 7.7, 1.4 Hz, 8-H), 7.67 (1H, br d, *J* = 7.7 Hz, 7-H), 8.08 (1H, br s, 6'-H), 8.20 (1H, d, *J* = 7.3 Hz, 5-H), 8.59 (1H, br s, NH), 9.11 (1H, br d, *J* = 8.1 Hz, 10-H). ^{13}C NMR ($CDCl_3$) δ (9.30×10^{-2} mol/L): 15.23, 17.72, 18.45, 109.06, 113.56, 123.52, 125.47, 126.92, 127.02, 127.84, 128.56, 129.06, 130.15, 131.38, 139.38, 140.47, 146.19, 147.19, 150.15, 162.55. $C_{20}H_{19}N_4OS$ $(M+H)^+$: Calcd; 363.1274 (Found; 363.1280). *Anal.* Calcd for $C_{20}H_{18}N_4OS$: C, 66.28; H, 5.01; N, 15.46. Found C, 66.11; H, 5.00; N, 15.43.

Crystallography of 2'-Methylthio-2-oxo-2,3,3',3a'-tetrahydrospiro[imidazo[1,2-*a*]pyridine-3,3'-pyrazolo[1,5-*a*]quinoline] (6a). A single crystal (0.92×0.52×0.04 mm) grown from ethanol was used for the unit-cell determinations and data collection by a Rigaku AFC5S four-circle diffractometer with graphite-monochromated MoK$_\alpha$ radiation (λ=0.71069 Å). Crystal data of **6a**: $C_{18}H_{14}N_4OS$; M=334.39; monoclinic, space group $P2_1$/a (#14), Z=4 with a=14.523 (14) Å, b=7.22 (3) Å, c=15.600 (18) Å, β=99.65° (8); V=1611.7 (64) Å^3, and D$_{calc.}$=1.378 g/cm^3. All calculations were performed using CrystalStructure.[18] The structure was solved by a direct method (SIR92).[19] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final R- and R$_w$-factors after full-matrix least-squares refinements were 0.074 and 0.055 for 1230 ($I>2.00\sigma(I)$) observed reflections, respectively.

Crystallography of 2-Methylthiopyrazolo[5,1-*a*]isoquinoline-1-[*N*-(3,5-dimethylpyridin-2-yl)]-carboxamide (8c). A single crystal (0.20×0.20×0.40 mm) grown from $CHCl_3$-hexane was used for the unit-cell determinations and data collection by a Bruker D8 goniometer with graphite-monochromated MoK_α radiation ($\lambda = 0.71069$ Å). Crystal data of **8c**: $C_{20}H_{18}N_4OS$; M = 362.45; orthorhombic, space group *P*bca (#61), Z = 8 with a = 16.5134 (10) Å, b = 8.9284 (5) Å, c = 23.6791 (14) Å; V = 3503.9 (4) $Å^3$, and D_{calc} = 1.374 g/cm^3. All calculations were performed using Bruker SHELXTL Software Package. The structure was solved by a direct method (SHELXL-97).[20] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final R- and R_w-factors after full-matrix least-squares refinements were 0.035 and 0.088 for 3667 (I>2.00σ(I)) observed reflections, respectively.

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