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SYNTHESIS OF SPIRO[2-CYCLOPENTENE-1,3'-IMIDAZO[1,2-*a*]-PYRIDINE] DERIVATIVES AND THEIR INTERESTING BEHAVIOR IN ¹H-NMR SPECTRA IN DEUTERIOCHLOROFORM¹

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Abstract – Ethyl 2',3'-dihydro-2-methylthio-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates were synthesized from the reactions of 3-[bis(methylthio)methylene]-2(3*H*)-imidazo[1,2-*a*]pyridinones with ethyl 4-chloroacetoacetate in the presence of a base. The 2-methylthio group in these spiro compounds was easily replaced with some primary and secondary amines to afford the corresponding 2-amino derivatives. Very interestingly, the proton signals of these spiro compounds in the ¹H-NMR spectra in deuteriochloroform (CDCl₃) changed with an increase in the sample concentration, and the analysis for the magnitude and the direction of each proton shift disclosed the conformational change of the cyclopentenone moiety in this molecule.

INTRODUCTION

For many years, imidazo[1,2-*a*]pyridine ring has been known to be core structural unit of bioactive molecules in synthetic and natural products.² Thus the development of a novel synthetic route and the structural modifications for this scaffold have been intensively investigated with the aim of developing novel active agents. Recently, 2(3*H*)-imidazo[1,2-*a*]pyridinone derivatives bearing a spiro ring at the 3-position were shown to possess some important pharmacological activities. For example, spiro[imidazo[1,2-*a*]pyridine-3,2-indan]-2(3*H*)-one (**A**, ZSET1446) was reported to act as an Alzheimer's disease progression inhibitor and cognitive enhancer,³⁻⁵ and spiro[cyclopentane-1,3-imidazo[1,2-*a*]pyridine]-2'(3'*H*)-one (**B**) was shown to act as a progesterone receptor modulator (see Figure 1).⁶

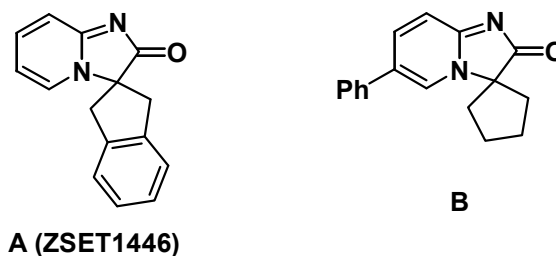


Figure 1

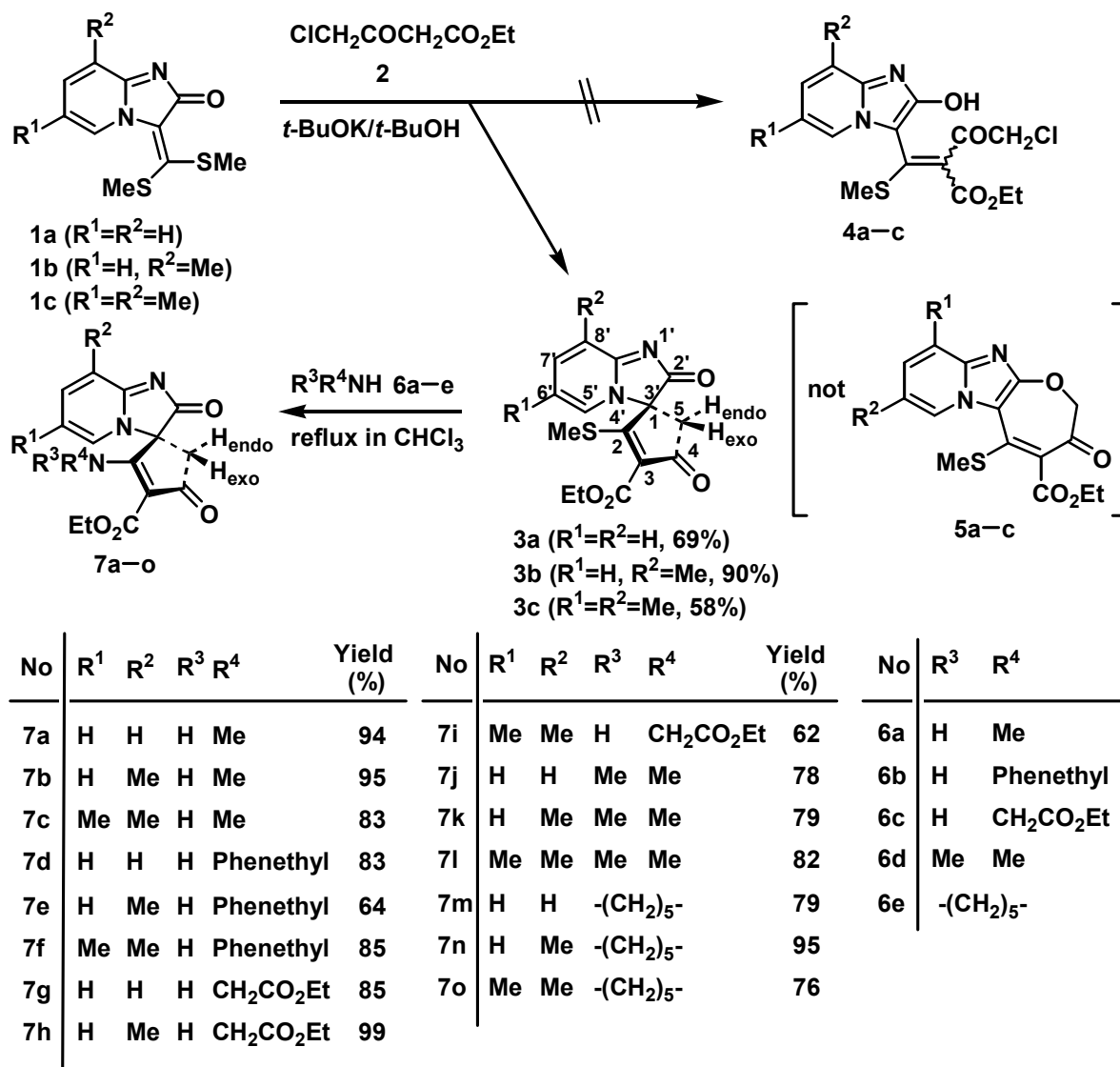
In general, these spiro compounds have been prepared from the reactions of 2(3*H*)-imidazo[1,2-*a*]pyridinones, readily obtainable from the alkaline treatment of the corresponding 2-amino-1-(ethoxycarbonylmethyl)pyridinium halides, with 1,4-dihalides such as α,α -dibromo-*o*-xylene or 1,4-dibromobutane under alkaline conditions.⁷

Recently we developed a construction method for new types of 2(3*H*)-imidazo[1,2-*a*]pyridinones, 3-[bis(methylthio)methylene]-2(3*H*)-imidazo[1,2-*a*]pyridinones, from the alkaline treatment of 1-[1-carbamoyl-2,2-bis(methylthio)vinyl]pyridinium iodides, which were readily obtained from the *S*-alkylation of pyridinium 1-carbamoyl-1-[(methylthio)thiocarbonyl]methylides with iodomethane.⁸ We also described the first synthesis of 2*H*-pyrano[2',3':4,5]imidazo[1,2-*a*]pyridin-2-one derivatives through the electrophilic substitution of these 3-methylene-2(3*H*)-imidazo[1,2-*a*]pyridinones with the carbanion species generated from some activated ethyl acetates, followed by the intramolecular cyclization of the resulting ethyl 3-[2-hydroxyimidazo[1,2-*a*]pyridin-3-yl]acrylates with the elimination of an ethanol. Since a high electrophilicity of the 3(1)-position in 3-[bis(methylthio)methylene]-2(3*H*)-imidazo[1,2-*a*]pyridinones in these reactions was demonstrated, we were interested next in their reactions with other bifunctionalized reagents. In this paper we report the smooth formation of the title compounds, spiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine] derivatives, from the reactions of 3-[bis(alkylthio)methylene]-2(3*H*)-imidazo[1,2-*a*]pyridinones with ethyl 4-chloroacetoacetate, and their transformation to the corresponding 2-amino derivatives by nucleophilic reactions with some amines. In addition we also describe the interesting behavior in the ¹H-NMR spectra of the title compounds in CDCl₃.

RESULTS AND DISCUSSION

When the reaction of 3-[bis(methylthio)methylene]-2(3*H*)-imidazo[1,2-*a*]pyridinones (**1a**) with ethyl 4-chloroacetoacetate (**2**) were carried out in the presence of potassium *t*-butoxide in *t*-butanol at room temperature, the initially expected ethyl 2-chloroacetyl-3-[2-hydroxyimidazo[1,2-*a*]pyridin-3-yl]-3-(methylthio)acrylate (**4a**) was not formed at all but, instead of it, the colorless crystalline ethyl 2',3'-dihydro-2-methylthio-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylate (**3a**) was obtained in a 69 % yield. Similar treatment of **1b,c** with **2** afforded the corresponding products **3b,c** in 90 and 58% yields respectively. Furthermore, the 2-methylthio group in **3a—c** was smoothly replaced by the treatment with primary and secondary amines such as methylamine (**6a**), phenethylamine (**6b**), ethyl glycinate (**6c**), dimethylamine (**6d**), and piperidine (**6e**) in chloroform at the reflux temperature to afford the corresponding 2-amino derivatives **7a—o** in good yields (62—99%) with the elimination of a molecule of methanethiol. These results are shown in Scheme 1.

Elemental analyses for products **3a—c** and **7a—o** supported our proposed compositions and the fact that



Scheme 1

former products **3a—c** do not involve a chlorine atom in the molecule was also indicated by the negative Bilstein test. The IR spectra of **3a—c** and **7a—o** exhibited the lowered carbonyl band (1602—1640 cm^{-1}) characteristic of the 2(3*H*)-imidazo[1,2-*a*]pyridinones such as **1a—c**⁸ and α,β -unsaturated carbonyl bands at 1635—1732 cm^{-1} , together with an amino absorption band (3221—3249 cm^{-1}) for **7a—i** and a saturated ester carbonyl band (1738—1746 cm^{-1}) for **7g—i**. In addition, the AB type signals for the 5-methylene protons in the ¹H-NMR spectra (See Table 1) of **3a—c** and **7a—o** appeared near δ 2.6 (H_{endo}) and 3.2 (H_{exo}) and these values are consistent with that (near δ 3.0) expected for such a system, but they are considerably higher than that (near δ 5.1) expected for the methylene protons in the alternative structure, oxepino[2',3':2,3]imidazo[1,2-*a*]pyridine (**5**).⁹ In addition the NOE measurement of **3a** made sure the assignment of the *endo*- and *exo*-protons at the 5-position. That is, the irradiation on the 5'-H signal caused the NOE interaction to the signals of the 6'-H, 5- H_{endo} , and 3-methylthio, and that on the 5- H_{endo} to the 5- H_{exo} and 5'-H. To obtain further information for the structures of **3a—c** and **7a—o**, we

carried out a single crystal X-ray analysis of compound (**3b**) obtained by the recrystallization from CHCl_3 -ether and we could finally confirm this structure. ORTEP drawing of **3b** involving a molecule of CHCl_3 is shown in Figure 2.¹⁰ From this crystal data the presence of a significant interaction (hydrogen bonding) between the carbonyl oxygen in 2(3*H*)-imidazo[1,2-*a*]pyridinone moiety and the methine hydrogen of CHCl_3 could also be presumed, since the distance between the oxygen and the hydrogen is 2.299 Å and is considerably close. Very interestingly, we

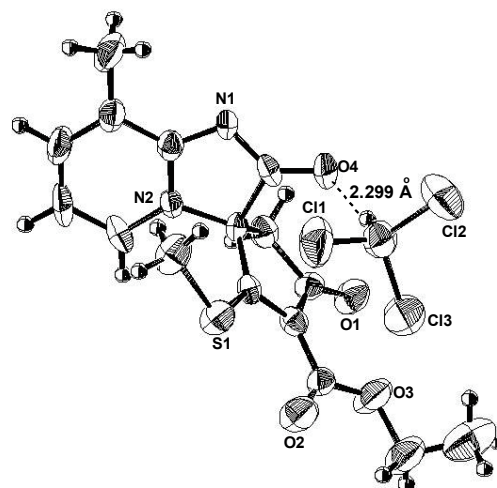


Figure 2. ORTEP drawing of **3b**: CHCl_3

observed the shifts of each proton signal with an increase in the concentration of **3a**—**c** and **7a**—**o** during the measurement of their ^1H -NMR spectra in CDCl_3 . For example, the signals due to the 5- H_{endo} , 5- H_{exo} , 6'- H , 8'- H , 5'- H , and 7'- H , the methylthio and the ethoxy protons of **3a** (its concentration was 0.67×10^{-2} mol/L) appeared at δ 2.66 (d, $J=18.0$ Hz), 3.28 (d, $J=18.0$ Hz), 6.80 (ddd, $J=6.8, 6.8, 0.8$), 7.24 (br d, $J=9.2$ Hz), 7.51 (br d, $J=6.8$ Hz), 7.74 (ddd, $J=9.2, 6.8, 1.2$ Hz), 2.27 (s), and 1.38 (t, $J=7.2$ Hz) and 4.37 (q, $J=7.2$ Hz) respectively. When the concentration of **3a** was increased to 15.06×10^{-2} mol/L, these signals appeared at δ 2.76, 3.22, 6.87, 7.23, 7.74, 7.77, 2.25, and 1.36 and 4.34 respectively. That is, the signals of the 5'- H , 6'- H , 7'- H , and 5- H_{endo} shifted to a lower magnetic field in the range of 0.04—0.23

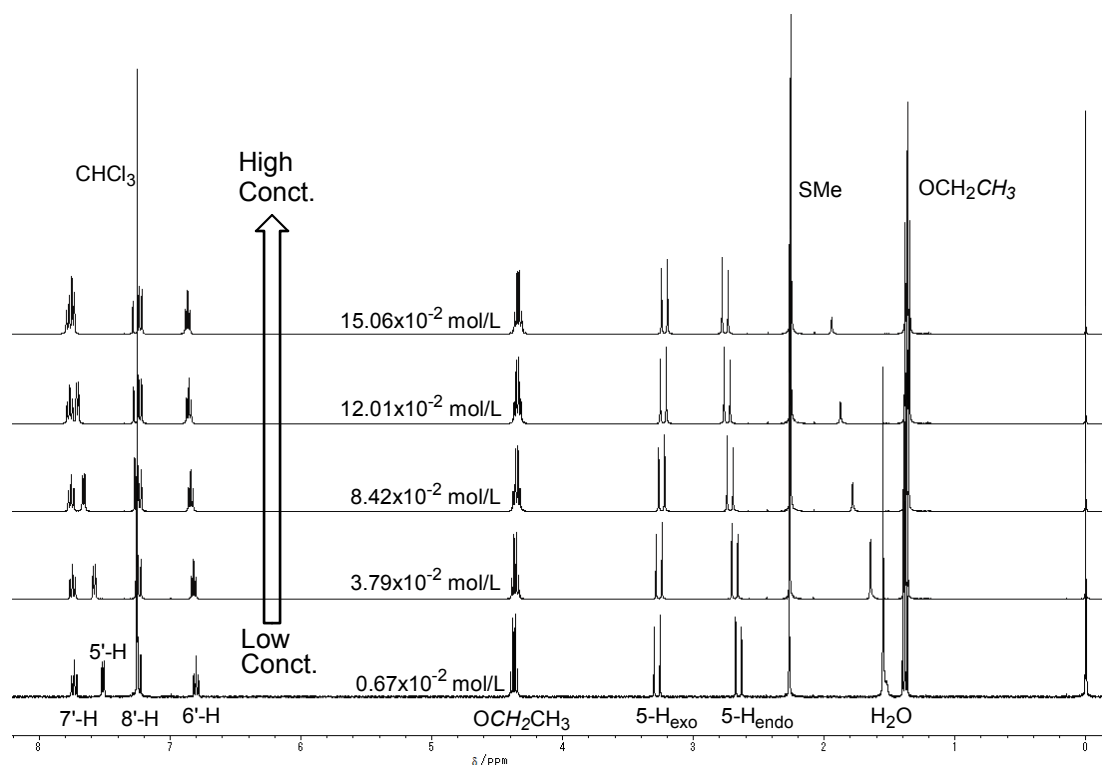


Figure 3. The signal changes in the ^1H -NMR spectra of **3a** in some concentrations

ppm and the order of their shift values was $5'\text{-H} > 5\text{-H}_{\text{endo}} > 6'\text{-H} > 7'\text{-H}$, while those of $8'\text{-H}$, 5-H_{exo} , methylthio, and ethoxy protons moved to a higher magnetic field but the magnitudes were not large (< 0.06 ppm). In addition, the shifts in the proton signals of CHCl_3 and H_2O in the solvent were also observed and the movement distance (0.39 ppm) of the latter protons was maximum. The ^1H -NMR spectral changes for some concentrations (0.67, 3.79, 8.42, 12.01, and 15.06×10^{-2} mol/L) of **3a** are shown in Figure 3 and the plots of the shift values for the principal protons are exhibited in Figure 4. An examination of the magnitudes and the directions of their shifts for both the pyridine ring protons and the 5-methylene protons indicated that these shifts were caused by the conformational

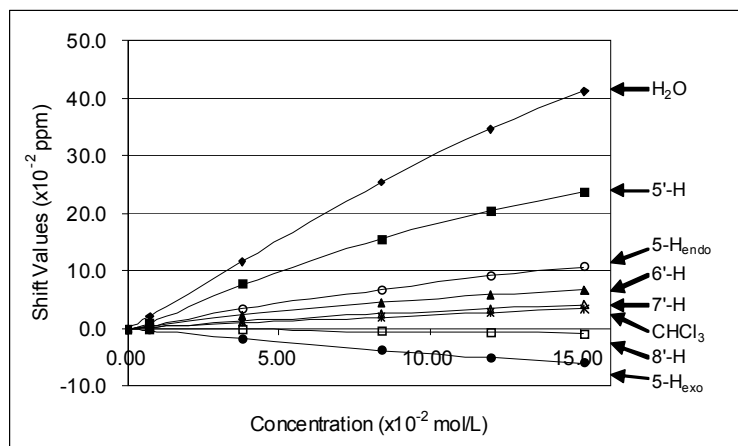


Figure 4. Plots of the shift values of principal protons

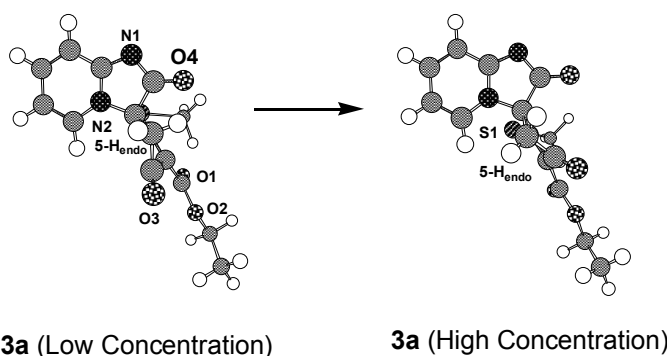


Figure 5. Conformational change of the cyclopentenone ring

change (the movement from inside to outside, see Figure 5) of the cyclopentenone ring.¹¹ That is, the shieldings of the $5'\text{-H}$, $6'\text{-H}$, and $7'\text{-H}$ on the pyridine ring due to the enone system of the cyclopentenone ring decreased with an increase in the concentration of compound **3a**. Similarly, both the low field shift of the 5-H_{endo} and the high field shift of the 5-H_{exo} with an increase in the concentration can be well explained by considering the anisotropy effect of the imidazo[1,2-*a*]pyridinone ring accompanied with the same motion of the cyclopentenone ring. In contrast, when the ^1H -NMR spectra in some concentrations in the range of 0.55–10.58 mol/L of **3a** in $\text{DMSO-}d_6$ was measured, such signal shifts were no longer observed. These facts strongly suggest that this phenomenon was caused by the interaction between **3a** and CDCl_3 or **3a** itself. It is seemed that the partner of the interaction with **3a** is not water in solvent (CDCl_3), even though the shift quantity by the water were maximum, because 1) the participation of water is the weakest when the concentration was the highest one to **3a**, 2) the chemical shift (δ 1.55 ppm) when the concentration of **3a** in CDCl_3 is 0.67×10^{-2} mol/L is close to that of free water, 3) the addition of water (20 mg)¹² in the CDCl_3 solution (0.6 mL) of **3a** (0.66×10^{-2} mol/L) did not provide any change in the ^1H -NMR spectrum. As seen in the X-ray analysis for **3b**: CHCl_3 , the interaction between the carbonyl oxygen and deuterium atom of CDCl_3 which is a solvent and present in

Table 1. ^1H -NMR spectral data for 3a—c and 7a—o in CDCl_3

No ^{a)}	Conc. ^{b)}	C-5'	C-6'	C-7'	C-8'	5-H _{endo}	5-H _{exo}	C-2	CO ₂ Et	NH	CHCl ₃	H ₂ O
3a	0.67	7.51	6.80	7.74	7.24	2.66	3.28	2.27	1.38 4.37	---	7.25	1.55
	15.06	7.74	6.87	7.77	7.23	2.76	3.22	2.25	1.36 4.34	---	7.29	1.94
3a^{c)}	---	8.41	6.98	7.94	7.22	2.86	3.13	2.21	1.28 4.28	---	---	---
3b	0.80	7.39	6.74	7.54	2.41	2.65	3.28	2.24	1.38 4.37	---	7.26	1.56
	11.64	7.52	6.78	7.57	2.41	2.71	3.24	2.23	1.37 4.35	---	7.29	1.86
3c	1.08	7.17	2.24	7.41	2.40	2.63	3.27	2.23	1.38 4.37	---	7.26	1.58
	13.00	7.32	2.25	7.44	2.39	2.68	3.23	2.22	1.37 4.35	---	7.29	1.93
7a^{d)}	0.79	7.52	6.81	7.75	7.27	2.54	3.22	2.74	1.39 4.36	9.21	7.26	1.54
7b	0.83	7.40	6.74	7.55	2.43	2.53	3.21	2.71	1.39 4.36	9.19	7.26	1.57
	5.54	7.47	6.76	7.57	2.43	2.55	3.20	2.70	1.37 4.34	9.19	7.27	1.75
7c	0.60	7.18	2.22	7.42	2.40	2.51	3.21	2.71	1.39 4.36	9.20	7.26	1.57
	10.75	7.34	2.24	7.45	2.40	2.55	3.18	2.71	1.37 4.33	9.20	7.29	2.02
7d	0.50	7.38	6.68	7.72	e)	2.47	3.20	f)	1.38 4.26–4.43	9.27	7.26	1.56
	5.05	7.50	6.72	7.73	e)	2.50	3.18	f)	1.35 4.22–4.40	9.26	7.27	1.76
7e	0.47	e)	6.64	7.52	2.41	2.48	3.21	f)	1.37 4.26–4.43	9.28	7.26	1.56
	4.00	7.34	6.66	7.53	2.41	2.49	3.19	f)	1.36 4.25–4.41	9.28	7.27	1.72
7f	0.48	7.05	2.16	7.37	2.39	2.45	3.20	f)	1.38 4.27–4.42	9.27	7.26	1.56
	7.83	7.22	2.16	7.38	2.38	2.47	3.18	f)	1.35 4.20–4.40	9.25	7.27	1.86
7g	0.97	7.55	6.82	7.75	7.27	2.54	3.22	f)	1.40 4.31–4.46	9.63	7.26	1.58
	9.28	7.74	6.86	7.78	7.28	2.59	3.18	f)	1.37 4.27–4.44	9.60	7.27	1.85
7h	0.88	7.40	6.75	7.55	2.43	2.53	3.22	f)	1.40 4.32–4.46	9.63	7.26	1.58
	9.83	7.54	6.78	7.57	2.43	2.57	3.18	f)	1.38 4.28–4.44	9.59	7.28	1.86
7i	1.10	7.19	2.21	7.42	2.41	2.51	3.22	f)	1.40 4.32–4.46	9.63	7.26	1.58
	5.86	7.30	2.23	7.43	2.41	2.53	3.19	f)	1.39 4.29–4.44	9.61	7.28	1.74
7j^{d)}	1.10	7.63	6.81	7.74	7.24	2.51	3.25	2.91	1.37 4.33	---	7.26	1.57
7k	0.47	7.46	6.73	7.53	2.41	2.49	3.25	2.89	1.36 4.33	---	7.26	1.56
	8.17	7.58	6.77	7.56	2.41	2.54	3.21	2.89	1.35 4.31	---	7.28	1.98
7l	0.54	7.23	2.22	7.40	2.39	2.46	3.24	2.90	1.37 4.34	---	7.26	1.56
	10.62	7.34	2.24	7.42	2.39	2.50	3.21	2.90	1.36 4.32	---	7.27	1.99
7m	0.56	7.63	6.82	7.73	7.25	2.49	3.22	f)	1.36 4.32	---	7.26	1.57
	11.14	7.88	6.88	7.76	7.25	2.58	3.16	f)	1.34 4.29	---	7.28	1.85
7n	0.44	7.49	6.74	7.53	2.42	2.47	3.22	f)	1.36 4.32 4.32	---	7.26	1.56
	12.03	7.67	6.79	7.55	2.41	2.53	3.18	f)	1.35 4.23–4.37	---	7.29	1.94
7o	0.68	7.28	2.23	7.40	2.39	2.45	3.21	f)	1.37 4.33		7.26	1.57
	7.81	7.43	2.25	7.42	2.39	2.50	3.18	f)	1.36 4.31		7.28	1.92

a) The coupling constants are as follows; $J_{5(\text{gem})}=17.6\text{--}18.1\text{ Hz}$, $J_{5',6'}=J_{6',7'}=6.8\text{--}7.0\text{ Hz}$, $J_{7',8'}=9.0\text{--}9.2\text{ Hz}$, $J_{5',7'}=1.2\text{--}2.0\text{ Hz}$, $J_{6'-8'}=1.0\text{--}1.2\text{ Hz}$, $J_{\text{Et}}=7.0\text{--}7.2\text{ Hz}$, $J_{\text{NHCH}}=5.6\text{--}6.6\text{ Hz}$. b) $\times 10^{-2}\text{ mol/L}$. c) The chemical shifts in $\text{DMSO}-d_6$. d) Low solubility. e) Overlapped with the phenyl proton signals. f) These data are described in the Experimental section.

the highest concentration may be an alternative selection for such interaction, though it is not certain. Such interaction and the concomitant approach of a bulky trichloromethyl group may force the cyclopentenone ring inside.

In summary, we have synthesized some spiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine] derivatives

and observed an interesting behavior in their ^1H -NMR spectra in CDCl_3 .

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 ^1H -NMR and ^{13}C -NMR spectra were determined with a JEOL JNM-LA400 (^1H : 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 spectra were taken with JASCO FT/IR-5300 IR spectrophotometers.

Preparation of ethyl 2',3'-dihydro-2-methylthio-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (3a—c). General method. A mixture of 3-[bis(methylthio)-methylene]-2(3*H*)-imidazo[1,2-*a*]pyridinone (**1**, 1 mmol) and ethyl 4-chloroacetoacetate (**2**, 1.2 mmol) was stirred with potassium *t*-butoxide (0.135 g, 1.2 mmol) in *t*-BuOH (30 mL) at room temperature for the time indicated in the description for each product. The solution was then concentrated under reduced pressure, and the residue was separated by column chromatography on alumina using benzene-EtOH (9:1) for **3a,b** or CHCl_3 for **3c** as an eluent. The first pale yellow layers were collected and the combined solution was concentrated under reduced pressure. Recrystallization of the crude product from CHCl_3 -ether afforded the corresponding spiro compounds (**3a—c**).

The ^1H -NMR spectral data of **3a—c** are shown in Table 1 and the other data are as follows.

Ethyl 2',3'-dihydro-2-methylthio-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (3a); From **1a** and **2**, 69% (reaction time 3 h), colorless powder, mp 191—194 °C. IR (KBr): ν 1624, 1711 cm^{-1} . ^{13}C -NMR δ : 14.17, 14.21, 47.60, 61.81, 73.45, 113.73, 116.28, 132.75, 133.18, 143.33, 162.01, 168.32, 174.80, 182.68, 192.73. *Anal.* Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$: C, 56.59; H, 4.43; N, 8.80. Found: C, 56.37; H, 4.47; N, 9.08.

Ethyl 2',3'-dihydro-8-methyl-2-methylthio-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (3b); From **1b** and **2**, 90% (reaction time 11 h), colorless powder, mp 167—171 °C. IR (KBr): ν 1622, 1709 cm^{-1} . ^{13}C -NMR δ : 14.16, 14.20, 17.28, 47.72, 61.80, 74.05, 113.45, 126.94, 129.88, 132.73, 141.37, 162.09, 168.32, 174.81, 182.69, 192.70. *Anal.* Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$: C, 57.82; H, 4.85; N, 8.43. Found: C, 57.88; H, 4.82; N, 8.40.

Ethyl 2',3'-dihydro-6,8-dimethyl-2-methylthio-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (3c); From **1c** and **2**, 58% (reaction time 26 h), colorless prisms, mp 191—193 °C. IR (KBr): ν 1639, 1696 cm^{-1} . ^{13}C -NMR δ : 14.07, 14.20, 17.14, 17.56, 47.88, 61.74,

74.17, 123.70, 126.28, 127.57, 144.14, 162.13, 166.73, 175.46, 182.71, 192.85. *Anal.* Calcd for $C_{17}H_{18}N_2O_4S$: C, 58.94; H, 5.24; N, 8.09. Found: C, 59.06; H, 5.22; N, 7.99.

Reactions of ethyl 2',3'-dihydro-2-methylthio-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (3a—c) with some amines. General method. A chloroform solution (15 mL) of **3** (1 mmol) and amine (**6a,b,d,e**, 3 mmol) was heated under the refluxing temperature until the TLC spot of **3** disappears or the generation of methanethiol ceases (1—12 h). After the completion of the reaction, the resulting solution was concentrated at reduced pressure and the residue was purified by the recrystallization from chloroform-ether to afford the corresponding substitution products **7a—f,j—o**.

Similar reactions of **3** (1 mmol) with ethyl glycinate hydrochloride (**6c**) were performed in the presence of triethylamine (0.253g, 2.5 mmol) to yield products **7g—i**, respectively.

The 1H -NMR spectral data of **7a—o** are shown in Table 1 and the other data are as follows.

Ethyl 2',3'-dihydro-2-methylamino-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (7a); From **3a** and methylamine (**6a**), 94% (reaction time 1 h), colorless powder, mp 191—194 °C. IR (KBr): ν 1626, 1666, 1711, 3227 cm^{-1} . *Anal.* Calcd for $C_{15}H_{15}N_3O_4$: C, 59.80; H, 5.02; N, 13.95. Found: C, 59.96; H, 4.73; N, 14.07.

Ethyl 2',3'-dihydro-8-methyl-2-methylamino-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (7b); From **3b** and **6a**, 95% (reaction time 1 h), colorless powder, mp 270—273 °C. IR (KBr): ν 1620, 1670, 1705, 3227 cm^{-1} . ^{13}C -NMR δ : 14.43, 17.36, 29.82, 47.52, 60.74, 69.53, 104.94, 113.52, 127.07, 129.57, 141.33, 165.85, 167.93, 174.14, 182.65, 191.04. *Anal.* Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 61.20; H, 5.42; N, 13.09.

Ethyl 2',3'-dihydro-6,8-dimethyl-2-methylamino-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (7c); From **3c** and **6a**, 83% (reaction time 1 h), colorless powder, mp 257—260 °C. IR (KBr): ν 1607, 1635, 1995, 3249 cm^{-1} . ^{13}C -NMR δ : 14.37, 17.17, 17.51, 29.79, 47.49, 60.65, 69.68, 104.75, 123.86, 126.28, 127.42, 144.14, 165.80, 166.24, 174.29, 182.62, 191.33. *Anal.* Calcd for $C_{17}H_{19}N_2O_4 + H_2O$: C, 58.78; H, 6.09; N, 12.10. Found: C, 59.06; H, 6.01; N, 11.90.

Ethyl 2',3'-dihydro-2',4-dioxo-2-(phenethylamino)spiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (7d); From **3a** and phenethylamine (**6b**), 83% (reaction time 12 h), colorless powder, mp 192—196 °C. IR (KBr): ν 1602, 1662, 1703, 3221 cm^{-1} . 1H -NMR (0.50×10^{-2} mol/L) δ : 2.65 (1H, ddd, $J=13.9, 7.6, 7.6$ Hz), 2.79 (1H, ddd, $J=13.9, 6.2, 6.2$ Hz), 2.96 (1H, m), 3.46 (1H, m), 7.03 (2H, br d, $J=8.1$ Hz), 7.20—7.30 (3H, m); (5.05×10^{-2} mol/L) δ : 2.65 (1H, ddd, $J=13.9, 6.2, 6.2$ Hz), 2.79 (1H, ddd, $J=13.9, 6.2, 6.2$ Hz), 2.96 (1H, m), 3.45 (1H, m), 7.03 (2H, br d, $J=8.1$ Hz), 7.19—7.33 (4H, m). ^{13}C -NMR δ : 14.42, 35.79, 45.16, 47.74, 60.76, 68.91, 105.05, 113.65, 116.41, 127.06, 128.46, 128.85,

132.43, 136.40, 143.03, 165.67, 167.84, 172.87, 182.98, 190.99. *Anal.* Calcd for $C_{22}H_{21}N_3O_4 + H_2O$: C, 64.54; H, 5.66; N, 10.26. Found: C, 64.82; H, 5.64; N, 10.00.

Ethyl 2',3'-dihydro-8-methyl-2',4-dioxo-2-(phenethylamino)spiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (7e); From **3b** and **6b**, 64% (reaction time 8 h), colorless powder, mp 212—215 °C. IR (KBr): ν 1620, 1661, 1699, 3231 cm^{-1} . 1H -NMR (0.47×10^{-2} mol/L) δ : 2.59 (1H, ddd, $J=13.9, 7.6, 7.6$ Hz), 2.78 (1H, ddd, $J=13.9, 6.4, 6.4$ Hz), 2.96 (1H, m), 3.40 (1H, m), 7.02 (2H, br d, $J=8.1$ Hz), 7.19—7.31 (3H, m); (4.00×10^{-2} mol/L) δ : 2.59 (1H, ddd, $J=13.9, 6.4, 6.4$ Hz), 2.78 (1H, ddd, $J=13.9, 6.2, 6.2$ Hz), 2.96 (1H, m), 3.40 (1H, m), 7.02 (2H, br d, $J=8.1$ Hz), 7.19—7.30 (4H, m). ^{13}C -NMR δ : 14.44, 17.37, 35.86, 45.16, 47.80, 60.77, 69.53, 104.92, 113.51, 127.05, 127.07, 128.42, 128.79, 129.35, 136.43, 141.27, 165.76, 167.75, 172.99, 183.02, 191.08. *Anal.* Calcd for $C_{23}H_{23}N_3O_4 + H_2O$: C, 65.24; H, 5.95; N, 9.92. Found: C, 65.49; H, 5.93; N, 9.69.

Ethyl 2',3'-dihydro-6,8-dimethyl-2',4-dioxo-2-(phenethylamino)spiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (7f); From **3c** and **6b**, 85% (reaction time 12 h), colorless powder, mp 243—247 °C. IR (KBr): ν 1611, 1665, 1709, 3237 cm^{-1} . 1H -NMR (0.48×10^{-2} mol/L) δ : 2.59 (1H, ddd, $J=13.9, 7.6, 7.6$ Hz), 2.79 (1H, ddd, $J=13.9, 6.2, 6.2$ Hz), 2.98 (1H, m), 3.42 (1H, m), 7.02 (2H, br d, $J=8.1$ Hz), 7.18—7.30 (3H, m); (7.83×10^{-2} mol/L) δ : 2.59 (1H, ddd, $J=13.9, 6.2, 6.2$ Hz), 2.79 (1H, ddd, $J=13.9, 6.2, 6.2$ Hz), 2.98 (1H, m), 3.44 (1H, m), 7.02 (2H, br d, $J=8.1$ Hz), 7.13—7.29 (4H, m). ^{13}C -NMR δ : 14.40, 17.19, 17.56, 35.82, 45.12, 47.82, 60.65, 69.69, 104.77, 123.77, 126.32, 126.93, 127.32, 128.39, 128.68, 136.50, 144.04, 165.74, 166.17, 173.22, 183.05, 191.35. *Anal.* Calcd for $C_{24}H_{25}N_3O_4$: C, 68.72; H, 6.01; N, 10.02. Found: C, 69.01; H, 6.08; N, 9.75.

Ethyl 2',3'-dihydro-2-(ethoxycarbonylmethyl)amino-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (7g); From **3a**, glycine ethyl ester hydrochloride (**6c**), and triethylamine, 85% (reaction time 12 h), colorless powder, mp 217—221 °C. IR (KBr): ν 1606, 1662, 1705, 1742, 3246 cm^{-1} . 1H -NMR (0.97×10^{-2} mol/L) δ : 1.21 (3H, t, $J=7.1$ Hz), 3.50 (1H, dd, $J=18.1, 6.6$ Hz), 3.99—4.20 (3H, m); (9.28×10^{-2} mol/L) δ : 1.21 (3H, t, $J=7.1$ Hz), 3.47 (1H, dd, $J=18.0, 6.2$ Hz), 3.99—4.20 (3H, m). ^{13}C -NMR δ : 14.02, 14.39, 43.88, 47.38, 60.95, 62.44, 69.06, 106.29, 113.91, 116.29, 133.43, 143.31, 165.07, 167.05, 167.80, 172.57, 182.33, 191.27. *Anal.* Calcd for $C_{18}H_{19}N_3O_6$: C, 57.90; H, 5.13; N, 11.25. Found: C, 57.90; H, 5.40; N, 10.99.

Ethyl 2',3'-dihydro-2-(ethoxycarbonylmethyl)amino-8-methyl-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (7h); From **3b**, **6c**, and triethylamine, 99% (reaction time 3 h), colorless powder, mp 230—233 °C. IR (KBr): ν 1607, 1662, 1703, 1738, 3244 cm^{-1} . 1H -NMR (0.88×10^{-2} mol/L) δ : 1.21 (3H, t, $J=7.1$ Hz), 3.50 (1H, dd, $J=18.1, 6.6$ Hz), 3.97—4.19 (3H, m):

(9.83×10^{-2} mol/L) δ : 1.21 (3H, t, $J=7.1$ Hz), 3.47 (1H, dd, $J=18.1, 6.4$ Hz), 3.95—4.19 (3H, m). ^{13}C -NMR δ : 13.98, 14.38, 17.32, 43.84, 47.41, 60.67, 62.32, 69.62, 106.13, 113.70, 126.90, 130.26, 141.47, 165.11, 166.98, 167.65, 172.69, 182.32, 191.29. *Anal.* Calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_6$: C, 58.91; H, 5.46; N, 10.85. Found: C, 59.05; H, 5.59; N, 10.58.

Ethyl 2',3'-dihydro-2-(ethoxycarbonylmethyl)amino-6,8-dimethyl-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (7i); From **3c**, **6c**, and triethylamine, 62% (reaction time 12 h), colorless powder, mp 216—220 °C. IR (KBr): ν 1640, 1669, 1713, 1746, 3225 cm^{-1} . ^1H -NMR (1.10×10^{-2} mol/L) δ : 1.21 (3H, t, $J=7.1$ Hz), 3.47 (1H, dd, $J=18.1, 6.3$ Hz), 3.97—4.20 (3H, m): (5.86×10^{-2} mol/L) δ : 1.21 (3H, t, $J=7.1$ Hz), 3.46 (1H, dd, $J=18.1, 6.3$ Hz), 3.97—4.20 (3H, m). ^{13}C -NMR δ : 14.02, 14.42, 17.23, 17.55, 43.82, 47.49, 60.88, 62.31, 69.84, 106.10, 123.99, 126.31, 127.94, 144.15, 165.22, 166.16, 167.08, 172.88, 182.36, 191.50. *Anal.* Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_6$: C, 59.84; H, 5.78; N, 10.47. Found: C, 50.70; H, 5.94; N, 10.44.

Ethyl 2',3'-dihydro-2-dimethylamino-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (7j); From **3a** and dimethylamine (**6d**), 78% (reaction time 9 h), colorless powder, mp 270—273 °C. IR (KBr): ν 1626, 1659, 1720 cm^{-1} . *Anal.* Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 61.11; H, 5.46; N, 13.14.

Ethyl 2',3'-dihydro-2-dimethylamino-8-methyl-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (7k); From **3b** and **6d**, 79% (reaction time 1 h), colorless powder, mp 238—242 °C. IR (KBr): ν 1620, 1678, 1699 cm^{-1} . ^{13}C -NMR δ : 14.39, 17.27, 35.07, 48.84, 61.17, 71.77, 110.96, 113.54, 126.90, 129.64, 141.19, 163.68, 167.18, 167.84, 183.43, 192.37. *Anal.* Calcd for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_4$: C, 62.00; H, 5.81; N, 12.76. Found: C, 62.12; H, 5.83; N, 12.62.

Ethyl 2',3'-dihydro-2-dimethylamino-6,8-dimethyl-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (7l); From **3c** and **6d**, 82% (reaction time 3 h), colorless powder, mp 197—200 °C. IR (KBr): ν 1635, 1699, 1732 cm^{-1} . ^{13}C -NMR δ : 14.36, 17.12, 17.52, 17.58, 48.91, 61.14, 71.92, 110.88, 123.75, 126.26, 125.30, 143.92, 163.78, 165.58, 167.84, 183.47, 192.57. *Anal.* Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.99; H, 6.13; N, 12.11.

Ethyl 2',3'-dihydro-2',4-dioxo-2-piperidinospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (7m); From **3a** and piperidine (**6e**), 79% (reaction time 7 h), colorless powder, mp 210—214 °C. IR (KBr): ν 1626, 1663, 1723 cm^{-1} . ^1H -NMR (0.56×10^{-2} mol/L) δ : 1.50—1.62 (6H, m), 3.11—3.18 (4H, m): (11.14×10^{-2} mol/L) δ : 1.47—1.63 (6H, m), 3.07—3.25 (4H, m). ^{13}C -NMR δ : 14.43, 17.36, 29.82, 47.52, 60.74, 69.53, 104.94, 113.52, 127.07, 129.57, 141.33, 165.85, 167.93, 174.14, 182.65, 191.04. *Anal.* Calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_4$: C, 64.21; H, 5.96; N, 11.82. Found: C, 64.43; H, 6.04; N,

11.52.

Ethyl 2',3'-dihydro-8-methyl-2',4-dioxo-2-piperidinospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]-pyridine]-3-carboxylates (7n); From **3b** and **6e**, 95% (reaction time 6 h), colorless powder, mp 212—216 °C. IR (KBr): ν 1622, 1674, 1709 cm^{-1} . $^1\text{H-NMR}$ (0.44×10^{-2} mol/L) δ : 1.50—1.59 (6H, m), 3.10—3.19 (4H, m): (12.03×10^{-2} mol/L) δ : 1.48—1.64 (6H, m), 3.06—3.21 (4H, m). $^{13}\text{C-NMR}$ δ : 14.38, 17.27, 23.10, 25.49, 48.82, 60.94, 71.81, 110.30, 113.41, 126.75, 130.11, 141.06, 163.46, 166.89, 167.98, 183.67, 192.49. *Anal.* Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_4$: C, 65.03; H, 6.28; N, 11.37. Found: C, 65.09; H, 6.57; N, 11.12.

Ethyl 2',3'-dihydro-6,8-dimethyl-2',4-dioxo-2-piperidinospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]-pyridine]-3-carboxylates (7o); From **3c** and **6e**, 76% (reaction time 4 h), colorless powder, mp 250—252 °C. IR (KBr): ν 1633, 1699, 1726 cm^{-1} . $^1\text{H-NMR}$ (0.68×10^{-2} mol/L) δ : 1.50—1.63 (6H, m), 3.09—3.16 (4H, m): (7.81×10^{-2} mol/L) δ : 1.50—1.63 (6H, m), 3.06—3.24 (4H, m). $^{13}\text{C-NMR}$ δ : 14.37, 17.17, 17.51, 29.79, 47.49, 60.65, 69.68, 104.75, 123.86, 126.28, 127.42, 144.14, 165.80, 166.24, 174.29, 182.62, 191.33. *Anal.* Calcd for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_4 + \text{H}_2\text{O}$: C, 62.83; H, 6.78; N, 10.47. Found: C, 62.95; H, 6.91; N, 10.22.

Crystallography of ethyl 2',3'-dihydro-8-methyl-2-methylthio-2',4-dioxospiro[2-cyclopentene-1,3'-imidazo[1,2-*a*]pyridine]-3-carboxylates (3b): CHCl_3 . A single crystal ($0.06 \times 0.32 \times 1.00$ mm) grown from CHCl_3 -ether was used for the unit-cell determinations and the data collection by a Rigaku AFC5S four-circle diffractometer with graphite-monochromated MoK_α radiation ($\lambda = 0.71069$ Å). Crystal data of **3b-CHCl₃**: $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_4\text{SCl}_3$; $M = 451.75$; monoclinic, space group $P2_1/n$ (#14), $Z = 4$ with $a = 18.98$ (2) Å, $b = 8.90$ (3) Å, $c = 17.003$ (14) Å, $\beta = 107.83^\circ$ (9); $V = 2013$ (7) Å³, and $D_{\text{calc}} = 1.490$ g/cm³. All calculations were performed using CrystalStructure.¹³ The structure was solved by a direct method (SIR).¹⁴ 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 0.064 and 0.063 for 1915 ($I > 2.00\sigma(I)$) observed reflections, respectively.

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