Preparation of New Nitrogen-Bridged Heterocycles 72.[1] A New Approach to 1-Acyl-3-(substituted methylthio)thieno[3′,4′:4,5]imidazo[1,5-*a*]-pyridine Derivatives

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The alkaline treatment of the pyridinium salts, readily available from the *S*-alkylations of 3-amino-4-(1-pyridinio)thiophene-5-thiolates with various alkyl halides, in chloroform at room temperature afforded the corresponding thieno[3′,4′:4,5]imidazo[1,2-*a*]pyridine derivatives in low to moderate yields *via* the intramolecular cyclization of the resulting 1,5-dipoles followed by the aromatization of the primary cycloadducts. Interestingly, the reactions using unsymmetrical 3-amino-4-[1-(3-methylpyridinio)]thiophene-5-thiolates afforded only 8-methylthieno[3′,4′:4,5]imidazo[1,2-*a*]pyridines and the other 6-methyl derivatives were not formed at all. In addition the isolation of a byproduct in the condensation reaction of pyridinium salt with the solvent ($CHCl_3$) is also discussed.

Key words synthesis; thieno imidazo pyridine; arene–arene interaction

Imidazo[1,2-*a*]pyridine derivatives have been synthesized by several methods and shown to have a variety of pharmacological actions such as antibacterial, antifungal, antiviral, antiinflammatory, hypnotic, and antiulcer activities.[2—12] In contrast, imidazo[1,2-*a*]pyridine derivatives fused with a hetero ring at the 2- and 3-positions have been scarcely reported because of the absence of a suitable preparative method for them. We have recently described the syntheses of 3-alkylthio-1-arylcarbonyl-6,8-dimethylthieno[3′,4′:4,5]imidazo[1,2-*a*]pyridines[13] and 3-acyl-4-methylthio-2*H*-pyrano[2′,3′:4,5]imidazo[1,2-*a*]pyridine-2-ones.[14] The former compounds were unexpectedly obtained together with 2-alkylthio-1-arylcarbonylthio-6,8-dimethylindolizine-3-carbonitriles in the alkaline treatment of 1-[1-cyano-2-(phenacylthio)vinyl]-3,5-dimethylpyridinium bromides. The plausible reaction mechanisms (Fig. 1) were proposed by considering the respective reactivities of pyridinium salts (**A** and **A′**) and by analogy with the only preparative example of 3-(methylthio)thieno[3′,4′:4,5]imidazo[1,2-*a*]pyridine-1-carboxamide from the reaction of 1-[3-amino-2-cyano-5-(methylthio)thiophen-4-yl]pyridinium iodide with sodium amide in tetrahydrofuran (THF).[15] We were interested in the development of a more practical procedure for the preparation of the title compounds and the mechanistic demonstration in which the key intermediates **D** prepared from an independent route lead to the corresponding thieno[3′,4′:4,5]imidazo[1,2-*a*]pyridine derivatives. We report here a new and practical preparative method for the title compounds, 1-acyl-3-(substituted methylthio)thieno[3′,4′:4,5]imidazo[1,5-*a*]pyridine derivatives.

Results and Discussion

Preparation of 3-Amino-4-(1-pyridinio)thiophene-5-thiolate Derivatives We thought that the *S*-alkylations of 3-amino-4-(1-pyridinio)thiophene-5-thiolates with various alkylating agents should smoothly lead to the key intermediates such as **D** described above. Hence, the syntheses of pyridinium betaines **4a**—**p** were investigated according to Tominaga's method.[15] However, the reactions of 1-(cyanomethyl)pyridinium chlorides (**1a**—**c**), carbon disulfide, and phenacyl bromides (**2a**—**c**) or chloroacetone (**2d**) in the presence of a base always afforded the mixtures of the

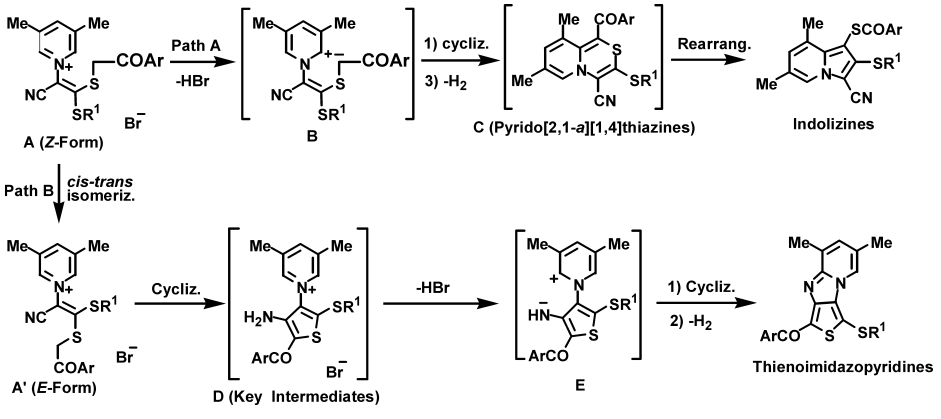

Fig. 1. Plausible Reaction Mechanisms

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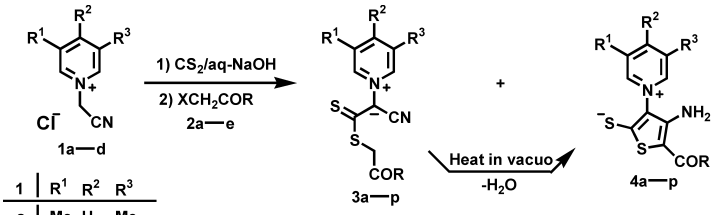


1	R^1	R^2	R^3
a	Me	H	Me
b	H	H	H
c	Me	H	H
d	H	Me	H

2	R	X
a	Ph	Br
b	4-ClC_6H_4	Br
c	4-BrC_6H_4	Br
d	Me	Cl
e	EtO	Br

4	R^1	R^2	R^3	R	Yield[a] (%)
a	Me	H	Me	Ph	83
b	Me	H	Me	4-ClC_6H_4	80
c	Me	H	Me	4-BrC_6H_4	73
d	Me	H	Me	Me	59
e	Me	H	Me	EtO	83[b]
f	H	H	H	Ph	87
g	H	H	H	4-ClC_6H_4	89
h	H	H	H	4-BrC_6H_4	79

4	R^1	R^2	R^3	R	Yield[a] (%)
i	H	H	H	Me	88
j	H	H	H	EtO	84[b]
k	Me	H	H	Ph	88
l	Me	H	H	4-ClC_6H_4	79
m	Me	H	H	4-BrC_6H_4	78
n	Me	H	H	Me	80
o	Me	H	H	EtO	93[b]
(p)	H	Me	H	Ph	0

a) The yield from 1 to 4. b) The yield from 3 to 4.

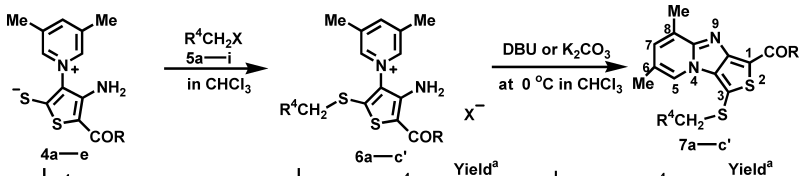
Chart 1

expected pyridinium betaines **4a**—**d**, **f**—**i**, **k**—**n** and pyridinium 1-cyano-2-thioxoethylides (**3a**—**d**, **f**—**i**, **k**—**n**) and similar reactions of **1a**—**c**, carbon disulfide, and ethyl bromoacetate provided only pyridinium 1-cyano-2-ethoxycarbonylmethylthio-2-thioxoethylides (**3e**, **j**, **o**). The dehydration reactions of these pyridinium ylides **3a**—**o** to the corresponding pyridinium betaines **4a**—**o** were accomplished by heating them at reduced pressure. On the other hand, similar treatment of 1-cyanomethyl-4-methylpyridinium chloride (**1d**) and phenacyl bromide (**2a**) gave only a complex polymeric substance and the expected pyridinium betaine **4p** could not be obtained. These results are shown in Chart 1.

The structural assignment of these pyridinium betaines **4a**—**o** were performed by their physical and spectral means, and by the comparison with those of known compounds **4f**, **j**. For example, the elementary analyses of new compounds **4a**—**e**, **g**—**i**, **k**—**o** were in good accordance with our proposed compositions and their IR spectra exhibited two absorption bands each in the range of 3235—3402 cm^{-1} due to the primary amino group, together with a lowered shifted ketone (1541—1582 cm^{-1}) or ester carbonyl band (1653 (**4e**) or 1645 cm^{-1} (**4o**)).

Preparation of Thieno[3′,4′:4,5]imidazo[1,2-*a*]pyridine Derivatives In general, many of 3-amino-4-(1-pyridinio)thiophene-5-thiolates (**4a**—**o**) were almost insoluble in many solvents such as acetone, ethanol, and chloroform and their *S*-alkylation reactions with various alkyl halides were quite sluggish. However, the treatment of 3-amino-4-(3,5-dimethyl-1-pyridinio)thiophene-5-thiolate (**4a**—**c**) with dimethyl sulfate (**5a**) in chloroform at 50 °C proceeded slowly to afford the corresponding pyridinium salts **6a**—**c**. After the removal of the unaltered alkylating agent the pyridinium salts **6a**—**c** were treated with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) in chloroform at 0 °C for 1 h (Method A) to provide the expected 1-arylcarbonyl-6,8-dimethyl-3-(methylthio)thieno[3′,4′:4,5]imidazo[1,2-*a*]pyridine (**7a**—**c**) in 69, 36, and 38% yields, respectively. Similar treatment of **4a**—**c** with diethyl sulfate (**5b**), phenethyl bromide (**5c**), benzyl bromide (**5d**), 4-methylbenzyl bromide (**5e**), 4-bromobenzyl bromide (**5f**), 4-chlorobenzyl bromide (**5g**), 4-fluorobenzyl bromide (**5h**), and 4-cyanobenzyl bromide (**5i**) gave the corresponding 1-arylcarbonyl-6,8-dimethyl-3-(substituted methylthio)thieno[3′,4′:4,5]imidazo[1,2-*a*]pyridines (**7f**—**h**, **k**—**m**, **p**—**r**, **u**—**c′**) in 14—59% yields. The reactions of pyridinium salts **6d**, **e**, **i**, **j**, **n**, **o**, **s**, **t**, which were prepared from the *S*-alkylation of pyridinium betaines **4d**, **e** with alkylating agents **5a**—**d**, with potassium carbonate in chloroform (Method B) provided the corresponding 1-acetyl-**7d**, **i**, **n**, **s** and 1-ethoxycarbonyl derivatives **7e**, **j**, **o**, **t** in 27—38% yields. When the ^{1}H-NMR spectral investigation for these reaction mixtures were performed to examine the origin of the comparatively low yields (14—59%) of products **7a**—**c′**, the presence of any product having a 3,5-dimethyl-1,4-dihydropyridine moiety (δ *ca.* 2.1 (6H, s, 3- and 5-Me), 3.9 (1H, s, 4-H), and 6.3 (2H, br s, 2- and 6-H)) in the molecue could often be detected. However, we could not isolate such products in the pure state except for only one compound **8e**, since almost all compounds were very unstable and smoothly decomposed during their separations.

On the other hand, the treatment of 1-(2-acyl-5-alkylthio-3-aminothiophen-4-yl)pyridinium salts **9a**—**c′** and 1-(2-acyl-5-alkylthio-3-aminothiophen-4-yl)-3-methylpyridinium salts **11a**—**c′**, obtained from the reactions of **4f**—**j** and **4k**—**o** with **5a**—**i**, with DBU in chloroform at 0 °C (Method A) yielded the corresponding products **10a**—**c′** and **12a**—**c′**, but their yields were very low (<5%) and their isolations in the pure state were very difficult. After some effort to improve the procedure, we found that these reactions and the products are extremely photosensitive and the bases employed also affected these reactions. Replacing the base from DBU to potassium carbonate and the interruption of as much light as possible in these reactions gave satisfactory results. Interestingly, the exclusive formation of 8-methylthieno[3′,4′:4,5]imidazo[1,2-*a*]pyridine derivatives (**12a**—**c′**) in the reactions using unsymmetrical 3-methylpyridinium betaines **4k**—**o** was observed and the alternative 6-methyl derivatives **13a**—**c′** could not be obtained at all. We have already observed an exclusive cyclization mode to the 8-methyl isomers in the alkaline treatment of 1-[1-carbamoyl-2,2-bis(methylthio)vinyl]-3-methylpyridinium iodides, and we presumed the larger steric repulsion between the 3-methyl



5	R^4	X
a	H	OSO_3Me
b	Me	OSO_3Et
c	$PhCH_2$	Br
d	Ph	Br
e	$4\text{-}MeC_6H_4$	Br
f	$4\text{-}BrC_6H_4$	Br
g	$4\text{-}ClC_6H_4$	Br
h	$4\text{-}FC_6H_4$	Br
i	$4\text{-}NCC_6H_4$	Br

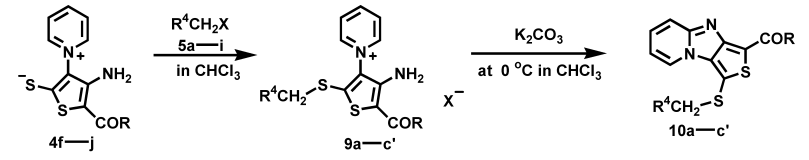
6,7	R	R^4	Yield[a] (%)
a	Ph	H	69
b	$4\text{-}ClC_6H_4$	H	36
c	$4\text{-}BrC_6H_4$	H	38
d	Me	H	36
e[b]	OEt	H	28
f	Ph	Me	53
g	$4\text{-}ClC_6H_4$	Me	14
h	$4\text{-}BrC_6H_4$	Me	34
i	Me	Me	37
j	OEt	Me	38
k	Ph	$PhCH_2$	46
l	$4\text{-}ClC_6H_4$	$PhCH_2$	33
m	$4\text{-}BrC_6H_4$	$PhCH_2$	42
n	Me	$PhCH_2$	31
o	OEt	$PhCH_2$	32

6,7	Ar	R^4	Yield[a] (%)
p	Ph	Ph	43
q	$4\text{-}ClC_6H_4$	Ph	43
r	$4\text{-}BrC_6H_4$	Ph	33
s	Me	Ph	27
t	OEt	Ph	32
u	Ph	$4\text{-}MeC_6H_4$	56
v	$4\text{-}ClC_6H_4$	$4\text{-}MeC_6H_4$	39
w	$4\text{-}BrC_6H_4$	$4\text{-}MeC_6H_4$	28
x	Ph	$4\text{-}BrC_6H_4$	52
y	$4\text{-}ClC_6H_4$	$4\text{-}BrC_6H_4$	39
z	$4\text{-}BrC_6H_4$	$4\text{-}BrC_6H_4$	27
a'	Ph	$4\text{-}ClC_6H_4$	53
b'	Ph	$4\text{-}FC_6H_4$	45
c'	Ph	$4\text{-}NCC_6H_4$	59

8e (14%)

a) The yields from **4** to **7**. b) Plus **8e** (14%).

Chart 2



9,10	R	R^4	Yield[a] (%)
a	Ph	H	27
b	$4\text{-}ClC_6H_4$	H	29
c	$4\text{-}BrC_6H_4$	H	22
d	Me	H	22
e	OEt	H	15
f	Ph	Me	34
g	$4\text{-}ClC_6H_4$	Me	33
h	$4\text{-}BrC_6H_4$	Me	26
i	Me	Me	21
j	OEt	Me	20
k	Ph	$PhCH_2$	46
l	$4\text{-}ClC_6H_4$	$PhCH_2$	27
m	$4\text{-}BrC_6H_4$	$PhCH_2$	17
n	Me	$PhCH_2$	14
o	OEt	$PhCH_2$	24

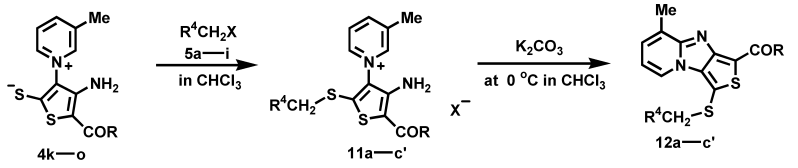
9,10	Ar	R^4	Yield[a] (%)
p	Ph	Ph	24
q	$4\text{-}ClC_6H_4$	Ph	23
r	$4\text{-}BrC_6H_4$	Ph	23
s	Me	Ph	15
t	OEt	Ph	12
u	Ph	$4\text{-}MeC_6H_4$	43
v	$4\text{-}ClC_6H_4$	$4\text{-}MeC_6H_4$	24
w	$4\text{-}BrC_6H_4$	$4\text{-}MeC_6H_4$	10
x	Ph	$4\text{-}BrC_6H_4$	25
y	$4\text{-}ClC_6H_4$	$4\text{-}BrC_6H_4$	30
z	$4\text{-}BrC_6H_4$	$4\text{-}BrC_6H_4$	17
a'	Ph	$4\text{-}ClC_6H_4$	37
b'	Ph	$4\text{-}FC_6H_4$	32
c'	Ph	$4\text{-}NCC_6H_4$	35

a) The yields from 4 to 10.

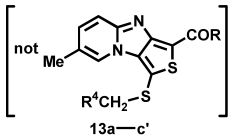
Chart 3

and the methylthio groups as its factor.[14] These results are shown in Charts 2—4.

All of thieno[3′,4′:4,5]imidazo[1,2-*a*]pyridines **7a**—**c**′, **10a**—**c**′, and **12a**—**c**′ are crystalline substances with a very strong green fluorescence. Compounds **7a**—**c**, **f**—**h** obtained here were completely in accord with those synthesized earlier by us.[13] The elemental analyses of all new products **7d**, **e**, **i**—**c**′, **10a**—**c**′, and **12a**—**c**′ confirmed our proposed compositions and the IR spectra showed the presence of a characteristic α,β-unsaturated ester carbonyl band (1659—1701 cm^{-1}) or a lowerly shifted arylcarbonyl one (1576—1612 cm^{-1}) and the absence of primary and/or secondary amino bands. Their signal patterns and shift values in the ^{1}H-NMR spectra (Table 1) of new products **7d**, **e**, **i**—**c**′, **10a**—**c**′, and **12a**—**c**′ were also not inconsistent with those expected for respective thieno[3′,4′:4,5]imidazo[1,2-*a*]pyridine derivatives in comparison with known 6,8-dimethyl compounds **7a**—**c**, **f**—**h**. Interestingly, the significant high field shifts (0.1—0.5 ppm) on the 5- and 6-protons in the ^{1}H-NMR spectra of 3-benzylthio derivatives **7p**—**c**′, **10p**—**c**′, and **12p**—**c**′ in comparison with those of 3-alkylthio and 3-phenethylthio derivatives **7a**—**o**, **10a**—**o**, and **12a**—**o**. These high field shifts must be caused by the predominant gauche conformation of the sulfide linkage leading to the intramolecular arene–arene interaction, since similar effects of the 9-deaza compounds, 3-(benzylthio)thieno[3,4-*b*]indolizine derivatives, are well known and the quantities of the chemical shift changes were also comparable to them.[16,17] Final structural confirmation for these products was carried out by the X-ray analyses of ethyl 3-phenethylthio-8-methylthieno[3′,4′:4,5]imidazo[1,2-*a*]pyridine-1-carboxylate (**12o**) and ethyl 3-benzylthio-8-methylthieno[3′,4′:4,5]imidazo[1,2-*a*]pyridine-1-carboxylate



11,12	R	R^4	Yield[a] (%)	11,12	Ar	R^4	Yield[a] (%)
a	Ph	H	48	p	Ph	Ph	34
b	4-ClC_6H_4	H	30	q	4-ClC_6H_4	Ph	20
c	4-BrC_6H_4	H	34	r	4-BrC_6H_4	Ph	24
d	Me	H	42	s	Me	Ph	43
e	OEt	H	34	t	OEt	Ph	38
f	Ph	Me	38	u	Ph	4-MeC_6H_4	32
g	4-ClC_6H_4	Me	42	v	4-ClC_6H_4	4-MeC_6H_4	36
h	4-BrC_6H_4	Me	40	w	4-BrC_6H_4	4-MeC_6H_4	41
i	Me	Me	41	x	Ph	4-BrC_6H_4	20
j	OEt	Me	26	y	4-ClC_6H_4	4-BrC_6H_4	25
k	Ph	$PhCH_2$	35	z	4-BrC_6H_4	4-BrC_6H_4	23
l	4-ClC_6H_4	$PhCH_2$	38	a'	Ph	4-ClC_6H_4	20
m	4-BrC_6H_4	$PhCH_2$	42	b'	Ph	4-FC_6H_4	25
n	Me	$PhCH_2$	36	c'	Ph	4-NCC_6H_4	30
o	OEt	$PhCH_2$	39				



a) The yields from 4 to 12.

Chart 4

Table 1. ^{1}H-NMR Spectral Data for Compounds **7a**—**c**′, **10a**—**c**′, and **12a**—**c**′

No.[a)]	C-5	C-6	C-7	C-8	SCH_2R	COR
7a	8.23	2.30	7.09	2.49	2.73	7.49, 7.56, 8.35
7b	8.26	2.33	7.14	2.51	2.76	7.47, 8.39
7c	8.26	2.34	7.14	2.52	2.77	7.63, 8.30
7d	8.25	2.33	7.14	2.57	2.70	2.87
7e	8.35	2.32	7.12	2.61	2.65	1.44, 4.44
7f	8.41	2.33	7.13	2.52	1.43, 3.13	7.50, 7.57, 8.33
7g	8.38	2.33	7.13	2.51	1.45, 3.15	7.47, 8.37
7h	8.38	2.34	7.14	2.52	1.45, 3.15	7.63, 8.30
7i	8.37	2.33	7.14	2.57	1.40, 3.07	2.88
7j	8.46	2.33	7.14	2.61	1.35, 3.01	1.44, 4.44
7k	8.26	2.28	7.11	2.51	3.04, 3.37, 7.14, 7.16—7.27	7.50, 7.57, 8.34
7l	8.26	2.29	7.16	2.52	3.06, 3.39, 7.14, 7.18—7.29	7.48, 8.38
7m	8.26	2.29	7.16	2.52	3.06, 3.39, 7.14, 7.18—7.30	7.64, 8.30
7n	8.25	2.29	7.14	2.57	3.01, 3.32, 7.13, 7.18—7.28	2.89
7o	8.28	2.26	7.11	2.60	2.96, 3.25, 7.11, 7.16—7.27	1.45, 4.45
7p	7.94	2.18	7.03	2.49	4.15, 7.05—7.17	7.50, 7.57, 8.30
7q	7.95	2.19	7.04	2.48	4.16, 7.05—7.19	7.47, 8.35
7r	7.94	2.18	7.03	2.47	4.16, 7.00—7.17	7.63, 8.28
7s	7.89	2.18	7.04	2.52	4.11, 7.02—7.16	2.89
7t	7.82	2.13	7.00	2.56	4.04, 6.93—7.11	1.46, 4.45
7u	7.92	2.19	7.06	2.51	2.18, 4.11, 6.89—6.98	7.50, 7.58, 8.28
7v	7.93	2.19	7.06	2.49	2.18, 4.14, 6.91—6.99	7.48, 8.35
7w	7.92	2.19	7.05	2.48	2.19, 4.14, 6.91—6.99	7.64, 8.28
7x	7.83	2.20	7.06	2.50	4.05, 6.87, 7.21	7.51, 7.58, 8.30
7y	7.84	2.21	7.08	2.49	4.07, 6.89, 7.22	7.48, 8.34
7z	7.85	2.21	7.08	2.49	4.07, 6.89, 7.22	7.65, 8.28
7a′	7.86	2.20	7.06	2.50	4.07, 6.95, 7.07	7.51, 7.58, 8.30
7b′	7.93	2.20	7.05	2.49	4.11, 6.81, 7.03	7.50, 7.58, 8.30
7c′	7.87	2.21	7.07	2.49	4.13, 7.13, 7.40	7.51, 7.59, 8.31
10a	8.63	6.79	7.43	7.50	2.76	7.51, 7.58, 8.24
10b	8.62	6.82	7.46	7.51	2.78	7.48, 8.25
10c	8.62	6.82	7.47	7.51	2.78	7.65, 8.16
10d	8.62	6.82	7.49	7.57	2.73	2.85
10e	8.68	6.77	7.44	7.58	2.67	1.44, 4.47
10f	8.75	6.78	7.43	7.50	1.44, 3.13	7.51, 7.58, 8.24
10g	8.74	6.80	7.46	7.50	1.46, 3.16	7.49, 8.25
10h	8.75	6.81	7.46	7.51	1.46, 3.16	7.65, 8.16
10i	8.75	6.80	7.49	7.57	1.42, 3.10	2.86
10j	8.80	6.76	7.44	7.59	1.36, 3.01	1.44, 4.48
10k	8.62	6.73	7.43	7.50	3.07, 3.39, 7.16, 7.18—7.25	7.53, 7.60, 8.24
10l	8.60	6.74	7.44	7.49	3.07, 3.40, 7.16, 7.18—7.27	7.49, 8.25
10m	8.60	6.74	7.45	7.49	3.07, 3.41, 7.16, 7.18—7.27	7.66, 8.17
10n	8.57	6.73	7.46	7.54	3.02, 3.33, 7.12, 7.16—7.26	2.85

Table 1. Continued

No.[a]	C-5	C-6	C-7	C-8	SCH_2R	COR
10o	8.56	6.67	7.42	7.56	2.96, 3.25, 7.09, 7.14—7.25	1.45, 4.48
10p	8.41	6.63	7.40	[b]	4.17, 7.03—7.17	7.51, 7.59, 8.22
10q	8.41	6.60	7.38	7.45	4.20, 7.06—7.19	7.48, 8.22
10r	8.41	6.60	7.38	7.44	4.20, 7.09—7.19	7.65, 8.13
10s	8.36	6.59	7.40	7.50	4.15, 7.03—7.18	2.88
10t	8.27	6.48	7.32	7.48	4.06, 6.95—7.11	1.45, 4.48
10u	8.35	6.55	7.35	7.43	2.18, 4.14, 6.88—6.99	7.52, 7.59, 8.21
10v	8.37	6.59	7.39	7.44	2.19, 4.16, 6.91—7.02	7.49, 8.22
10w	8.36	6.58	7.38	7.43	2.18, 4.16, 6.91—7.02	7.65, 8.15
10x	8.32	6.59	7.39	7.45	4.09, 6.92, 7.24	7.52, 7.60, 8.21
10y	8.35	6.64	7.44	[b]	4.12, 6.95, 7.25	7.48, 8.20
10z	8.34	6.62	7.42	7.45	4.12, 6.95, 7.25	7.66, 8.13
10a′	8.35	6.60	7.39	7.45	4.12, 6.99, 7.09	7.52, 7.59, 8.21
10b′	8.42	6.63	7.40	7.49	4.15, 6.84, 7.07	7.51, 7.59, 8.19
10c′	8.37	6.63	7.41	7.49	4.17, 7.18, 7.42	7.51, 7.59, 8.18
12a	8.50	6.71	7.24	2.54	2.75	7.50, 7.58, 8.35
12b	8.50	6.75	7.28	2.55	2.78	7.48, 8.38
12c	8.49	6.74	7.27	2.54	2.77	7.64, 8.31
12d	8.48	6.71	7.27	2.60	2.71	2.88
12e	8.57	6.69	7.25	2.63	2.66	1.44, 4.44
12f	8.60	6.69	7.23	2.52	1.41, 3.11	7.50, 7.57, 8.34
12g	8.63	6.73	7.27	2.54	1.44, 3.15	7.48, 8.37
12h	8.63	6.73	7.27	2.55	1.45, 3.15	7.65, 8.30
12i	8.62	6.70	7.27	2.60	1.39, 3.07	2.89
12j	8.69	6.68	7.24	2.64	1.35, 3.00	1.45, 4.45
12k	8.50	6.65	[b]	2.54	3.05, 3.37, 7.15, 7.18—7.28	7.51, 7.58, 8.35
12l	8.48	6.67	[b]	2.53	3.06, 3.39, 7.16, 7.18—7.28	7.48, 8.39
12m	8.47	6.66	[b]	2.53	3.05, 3.38, 7.16, 7.17—7.28	7.64, 8.31
12n	8.47	6.64	[b]	2.59	3.01, 3.31, 7.13, 7.15—7.28	2.90
12o	8.49	6.61	[b]	2.61	2.96, 3.24, 7.10, 7.15—7.30	1.45, 4.45
12p	8.27	6.50	[b]	2.50	4.16, 7.06—7.17	7.50, 7.57, 8.31
12q	8.29	6.53	7.19	2.51	4.20, 7.09—7.17	7.48, 8.34
12r	8.30	6.53	7.19	2.51	4.20, 7.09—7.17	7.64, 8.27
12s	8.25	6.50	7.18	2.56	4.13, 7.06—7.17	2.90
12t	8.16	6.42	7.13	2.57	4.04, 6.94—7.10	1.44, 4.44
12u	8.26	6.50	7.18	2.52	2.19, 4.14, 6.91—7.02	7.51, 7.58, 8.30
12v	8.26	6.53	7.19	2.51	2.20, 4.16, 6.91—7.03	7.48, 8.34
12w	8.28	6.54	7.20	2.52	2.20, 4.17, 6.92—7.04	7.65, 8.27
12x	8.20	6.51	7.19	2.51	4.07, 6.91, 7.22	7.51, 7.58, 8.31
12y	8.25	6.57	7.24	2.54	4.13, 6.95, 7.25	7.49, 8.34
12z	8.23	6.55	7.22	2.52	4.11, 6.94, 7.24	7.65, 8.27
12a′	8.18	6.46	7.13	2.54	4.04, 6.93, 7.03	7.44, 7.52, 8.24
12b′	8.22	6.47	7.13	2.45	4.07, 6.76, 6.99	7.44, 7.52, 8.24
12c′	8.22	6.53	7.20	2.51	4.15, 7.16, 7.41	7.51, 7.60, 8.31

a) The principal coupling constants are as follows: $J_{5,6}=J_{6,7}=6.7$—6.9 Hz, $J_{6,8}=1.2$—1.4 Hz, $J_{7,8}=9.3$—9.7 Hz, $J_{SEt}=7.3$—7.4 Hz, $J_{OEt}=7.0$—7.2 Hz. *b*) Overlapped with phenyl proton signals.

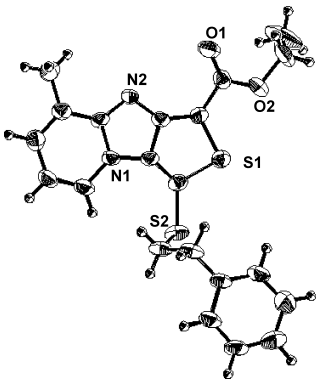


Fig. 2. ORTEP Drawing of Compound **12o**

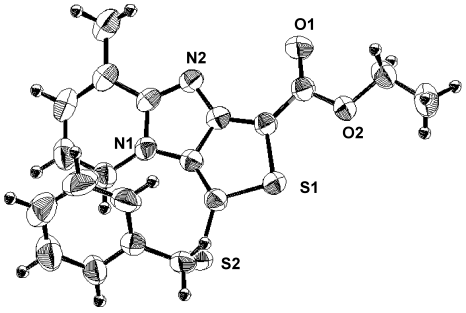


Fig. 3. ORTEP Drawing of Compound **12t**

(**12t**). ORTEP drawings of **12o** and **12t** are shown in Figs. 2 and 3.[18] As expected, the sulfide bond in compound **12t** had a gauche conformation in which the phenyl group overlaps on the C5—C6 double bond of thieno[3′,4′:4,5]imidazo[1,2-*a*]pyridine skeleton.

The structure of byproduct **13e** was first presumed to be the coupling reaction product between two molecules of pyridinium salt **6e**, but its elementary analysis was clearly incon-

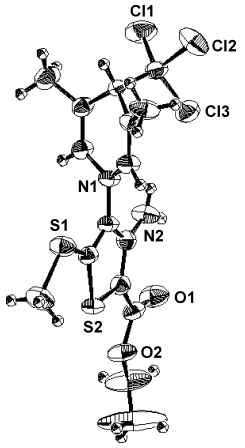


Fig. 4. ORTEP Drawing of Compound **8e**

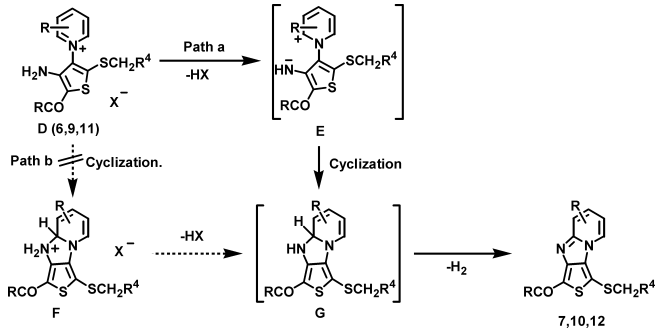


Fig. 5. Possible Routes for the Cyclization Starting from Pyridinium Salts

sistent with the proposed composition. From its elemental analysis and positive Beilstein test we suspected that this compound **13e** may be a condensation product between the pyridinium salt **6e** and the solvent ($CHCl_3$). The X-ray analysis (see Fig. 4) confirmed that compound **13e** is 1-[3-amino-2-ethoxycarbonyl-5-(methylthio)thiophen-4-yl]-3,5-dimethyl-4-trichloromethyl-1,4-dihydropyridine.

Mechanistically, the formation of thieno[3′,4′:4,5]imidazo[1,2-*a*]pyridine derivatives **7**, **10**, and **12** can be also considered by an alternative route (path b in Fig. 5) other than the 1,5-dipolar cyclization one (path a) described earlier in Fig. 1. That is, the intramolecular nucleophilic attack of the 3-amino group onto the 2-position of the pyridinium ring of 1-[2-acyl-5-alkylthio-3-aminothiophen-4-yl]pyridinium salts such as **D**, followed by the elimination of each one molecule of HX and hydrogen from the cycloadducts (**F**) should give the same products **7**, **10**, and **12**. However, the possibility of the path b is not so high, because we could not detect the presence of any cycloadduct (**F**) in the ^{1}H-NMR spsctra of some pyidinium salts. Perhaps, the higher acidity of the aromatic amines in the pyridinium salts **D** than that of aliphatic amines may be the driving force of these reactions.

In conclusion, we could develop a new and practical preparative method for 1-acyl-3-(substituted methylthio) thieno[3′,4′:4,5]imidazo[1,2-*a*]pyridine derivatives, though their yields were not so high.

Experimental

Melting points were measured on a Yamagimoto micro melting point apparatus and were not corrected. IR spectra were measured on a JASCO FT/IR-5300 IR spectrophotometer from samples as KBr pellets. NMR spectra were measured on a JEOL JNM-GX400 (400 MHz for ^{1}H and 100.4 MHz for ^{13}C) in deuteriochloroform solutions. Tetramethylsilane was used as the internal standard and *J* values were given in Hz. Elemental analyses were performed on a Perkin-Elmer 2400 elemental analyzer.

Preparation of 2-Acyl-3-amino-4-(1-pyridinio)thiophene-5-thiolates 4a—o The preparation of compounds **4a**—**o** was carried out by modifying Tominaga's procedure.[15] *Typical procedure*: A solution of 1-(cyanomethyl) pyridinium chloride (**1**, 0.10 mol), and carbon disulfide (11.4 g, 0.15 mol) in ethanol (50 ml) was treated with aqueous sodium hydroxide (10 g, 0.25 mol in 15 ml of water) under stirring in an ice bath for 20 min, and then an alkylating agent (**2**, 0.1 mol) was added to the reaction mixture. The resulting solution was allowed to react at room temperature for a further 4 h. The solution was then poured into ice water (300 ml) and the precipitates which separated were collected by suction and then dried. The products thus obtained were only pyridinium ylides **3e**, **j**, **o** or the expected 2-acyl-3-amino-4-(1-pyridinio)thiophene-5-thiolates (**4a**—**d**, **f**—**i**, **k**—**n**) involving various amounts of **3a**—**d**, **f**—**i**, **k**—**n**. These mixtures of **3** or/and **4** were heated without any solvent at 60—80 °C at a reduced pressure (3 Torr) until the generation of water completely ceased (*ca.* 2—7 d). These compounds **4a**—**o** were purified by the recrystallization from acetone. On the other hand, a similar reaction of 1-cyanomethyl-4-methylpyridinium chloride (**1d**) and phenacyl bromide (**2a**) provided only intractable polymeric substances and the structural analysis was unsuccessful because of its low solubility.

The physical and spectral data of known compounds **3f**, **j** and **4f**, **j** were in accord with those described earlier by us[19] and Tominaga *et al.*[15] and some data for the new compounds which were isolated are shown below.

3-Methylpyridinium 1-(1-Cyano-2-ethoxycarbonylmethylthio-2-thioxo) ethylide (**3o**): 59%; yellow needdles (from $CHCl_3$–Et_2O); mp 94—96 °C. IR (KBr) cm^{-1}: 1723, 2151. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 2.59 (6H, s, 3,5-diMe), 3.75 (2H, s, CH_2), 4.15 (2H, q, J= 7.1 Hz, $OC\underline{H}_2CH_3$), 7.43 (2H, m, Ph-H), 7.51 (1H, m, Ph-H), 7.83 (2H, m, Ph-H), 8.04 (1H, br s, 4-H), 8.47 (2H, br s, 2,6-H). *Anal.* Calcd for $C_{13}H_{14}N_2O_2S_2$: C, 53.04; H, 4.79; N, 9.52%. Found: C, 53.10; H, 4.93; N, 9.75%.

3-Amino-2-benzoyl-4-(3,5-dimethyl-1-pyridinio)thiophene-5-thiolate (**4a**): 83%; red prisms; mp 292—294 °C. IR (KBr) cm^{-1}: 1582, 3250, 3358. ^{1}H-NMR ($CDCl_3$) δ: 2.61 (6H, s, 3,5-diMe), 6.31 (br, NH), 7.35—7.67 (3H, m, Ph-H), 7.79 (2H, br d, J=6.2 Hz, Ph-H), 8.01 (1H, s, 4-H), 8.49 (2H, s, 2,6-H). *Anal.* Calcd for $C_{18}H_{16}N_2OS_2$: C, 63.50; H, 4.74; N, 8.23%. Found: C, 63.30; H, 4.72; N, 8.45%.

3-Amino-2-(4-chlorobenzoyl)-4-(3,5-dimethyl-1-pyridinio)thiophene-5-thiolate (**4b**)[20]: 80%; red prisms; mp >300 °C. IR (KBr) cm^{-1}: 1576, 3258, 3372. *Anal.* Calcd for $C_{18}H_{15}ClN_2OS_2$: C, 57.67; H, 4.03; N, 7.47%. Found: C, 57.60; H, 4.05; N, 7.52%.

3-Amino-2-(4-bromobenzoyl-4-(3,5-dimethyl-1-pyridinio)thiophene-5-thiolate (**4c**)[20]: 73%; red prisms; mp 296—298 °C. IR (KBr) cm^{-1}: 1574, 3254, 3364. *Anal.* Calcd for $C_{18}H_{15}BrN_2OS_2$: C, 51.55; H, 3.61; N, 6.68%. Found: C, 51.55; H, 3.60; N, 6.67%.

2-Acetyl-3-amino-4-(3,5-dimethylpyridinio)thiophene-5-thiolate (**4d**): 59%; red prisms; mp >300 °C. IR (KBr) cm^{-1}: 1574, 3248, 3376. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s, Ac), 2.60 (6H, s, 3.5-diMe), 5.90 (br, NH), 7.99 (1H, s, 4-H), 8.48 (2H, s, 2,6-H). *Anal.* Calcd for $C_{13}H_{14}N_2OS_2$: C, 56.09; H, 5.07; N, 10.06%. Found: C, 56.42; H, 4.95; N, 9.85%.

3-Amino-4-(3,5-dimethyl-1-pyridinio)-2-(ethoxycarbonyl)thiophene-5-thiolate (**4e**): 83%; red prisms; mp 284—286 °C. IR (KBr) cm^{-1}: 1653, 3233, 3397. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 2.59 (6H, s, 3,5-diMe), 4.25 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 5.12 (br, NH), 7.95 (1H, s, 4-H), 8.52 (2H, s, 2,6-H). *Anal.* Calcd for $C_{14}H_{16}N_2O_2S_2$: C, 54.52; H, 5.23; N, 9.08%. Found: C, 54.62; H, 5.40; N, 8.82%.

3-Amino-2-(4-chlorobenzoyl)-4-(1-pyridinio)thiophene-5-thiolate (**4g**)[20]: 89%; red prisms; mp 294—296 °C. IR (KBr) cm^{-1}: 1543, 3229, 3348. *Anal.* Calcd for $C_{16}H_{11}ClN_2OS_2$: C, 55.41; H, 3.20; N, 8.08%. Found: C, 55.69; H, 3.10; N, 7.86%.

3-Amino-2-(4-bromobenzoyl)-4-(1-pyridinio)thiophene-5-thiolate (**4h**)[20]: 79%; red prisms; mp 300 °C. IR (KBr) cm^{-1}: 1576, 3239, 3345. *Anal.* Calcd for $C_{16}H_{11}BrN_2OS_2$: C, 49.11; H, 2.83; N, 7.16%. Found: C, 49.27; H, 2.99; N, 6.87%.

2-Acetyl-3-amino-4-(1-pyridinio)thiophene-5-thiolate (**4i**)[20]: 88%; red prisms; mp >300 °C. IR (KBr) cm^{-1}: 1572, 3244, 3337. *Anal.* Calcd for $C_{11}H_{10}N_2OS_2$: C, 52.78; H, 4.03; N, 11.19%. Found: C, 52.86; H, 4.25; N, 10.88%.

3-Amino-2-benzoyl-4-(3-methyl-1-pyridinio)thiophene-5-thiolate (**4k**)[20]: 88%; red prisms; mp 289—291 °C. IR (KBr) cm^{-1}: 1582, 3252, 3360. *Anal.* Calcd for $C_{17}H_{14}N_2OS_2$: C, 62.55; H, 4.32; N, 8.58%. Found: C, 62.68; H,

Table 2. Some Data for Compounds **7a**—**c′**, **10a**—**c′**, and **12a**—**c′**

No.	Method	Yield (%)	mp (°C)	Appearance	IR (KBr) cm^{-1}	Formula	Calcd C (%)	H (%)	N (%)	Found C (%)	H (%)	N (%)
7a	**A**	69	221—223	Orange prisms	1589, 1555, 1464	Known[a)]						
7b	**A**	36	222—223	Yellow needles	1607, 1561, 1474	Known[a)]						
7c	**A**	38	225—228	Yellow needles	1586, 1561, 1472	Known[a)]						
7d	**B**	36	217—218	Yellow needles	1612, 1572, 1470	$C_{14}H_{14}N_2OS_2$	57.90	4.86	9.65	57.61	5.02	9.78
7e	**B**	18	170—172	Yellow needles	1694, 1582, 1476	$C_{15}H_{16}N_2O_2S_2$	56.22	5.03	8.74	56.36	5.03	8.61
7f	**A**	53	199—201	Orange needles	1589, 1554, 1464	Known[a)]						
7g	**A**	14	209—211	Orange prisms	1580, 1560, 1464	Known[a)]						
7h	**A**	34	230—232	Orange prisms	1578, 1537, 1464	Known[a)]						
7i	**B**	37	184—186	Yellow needles	1611, 1572, 1470	$C_{15}H_{16}N_2OS_2$	59.18	5.30	9.20	59.19	5.24	9.25
7j	**B**	38	132—134	Yellow needles	1659, 1575, 1472	$C_{16}H_{18}N_2O_2S_2$	57.46	5.42	8.38	57.54	5.43	8.29
7k	**A**	46	168—169	Yellow needles	1589, 1558, 1464	$C_{26}H_{22}N_2OS_2$	70.56	5.01	6.33	70.76	5.05	6.09
7l	**A**	33	166—167	Yellow needles	1586, 1551, 1466	$C_{26}H_{21}ClN_2OS_2$	65.46	4.44	5.87	65.76	4.19	5.69
7m	**A**	42	194—195	Yellow needles	1591, 1561, 1447	$C_{26}H_{21}BrN_2OS_2$	59.88	4.06	5.37	59.85	4.08	5.38
7n	**B**	31	183—184	Orange needles	1602, 1572, 1470	$C_{21}H_{20}N_2OS_2$	66.28	5.30	7.36	66.25	5.27	7.43
7o	**B**	32	156—157	Orange needles	1695, 1577, 1470	$C_{22}H_{22}N_2O_2S_2$	64.36	5.40	6.82	64.39	5.37	6.83
7p	**A**	43	163—164	Yellow needles	1597, 1568, 1460	$C_{25}H_{20}N_2OS_2$	70.06	4.70	6.54	70.32	4.68	6.31
7q	**A**	43	22—214	Yellow needles	1586, 1551, 1462	$C_{25}H_{19}ClN_2OS_2$	64.85	4.14	6.05	64.91	4.13	6.00
7r	**A**	33	115—117	Yellow needles	1581, 1547, 1462	$C_{25}H_{19}BrN_2OS_2$	59.17	3.77	5.52	59.39	3.53	5.35
7s	**B**	27	194—195	Yellow needles	1599, 1570, 1468	$C_{20}H_{18}N_2OS_2$	65.54	4.95	7.64	65.74	4.86	7.54
7t	**B**	32	171—172	Yellow needles	1698, 1582, 1470	$C_{21}H_{20}N_2O_2S_2$	63.61	5.08	7.06	63.76	5.03	6.97
7u	**A**	56	174—176	Yellow needles	1589, 1559, 1466	$C_{26}H_{22}N_2OS_2$	70.56	5.01	6.33	70.62	5.10	6.18
7v	**A**	39	229—231	Yellow needles	1582, 1549, 1466	$C_{26}H_{21}ClN_2OS_2$	65.46	4.44	5.87	65.56	4.39	5.82
7w	**A**	28	237—239	Yellow needles	1580, 1547, 1464	$C_{26}H_{21}BrN_2OS_2$	59.88	4.06	5.37	60.08	3.94	5.30
7x	**A**	52	189—191	Yellow needles	1589, 1561, 1466	$C_{25}H_{19}BrN_2OS_2$	59.17	3.77	5.52	59.43	3.78	5.25
7y	**A**	39	242—243	Yellow needles	1586, 1551, 1462	$C_{25}H_{18}BrClN_2OS_2$	55.41	3.35	5.17	55.12	3.34	5.18
7z	**A**	27	241—243	Yellow needles	1584, 1547, 1487	$C_{25}H_{18}Br_2N_2OS_2$	51.21	3.09	4.78	51.24	3.06	4.78
7a′	**A**	53	178—180	Yellow needles	1591, 1560, 1466	$C_{25}H_{19}ClN_2OS_2$	64.85	4.14	6.05	65.11	4.10	5.83
7b′	**A**	45	183—185	Yellow needles	1591, 1562, 1464	$C_{25}H_{19}FN_2OS_2$	67.24	4.29	6.27	67.02	4.29	6.49
7c′	**A**	59	171—173	Orange needles	1591, 1568, 1466, 2226	$C_{26}H_{19}N_2OS_2$	68.85	4.22	9.26	69.14	4.04	9.16
10a	**B**	27	212—213	Yellow needles	1597, 1570, 1467	$C_{17}H_{12}N_2OS_2$	62.94	3.73	8.64	62.98	3.73	8.48
10b	**B**	29	241—242	Yellow needles	1589, 1562, 1464	$C_{17}H_{11}ClN_2OS_2$	56.90	3.09	7.81	56.82	3.11	7.87
10c	**B**	22	257—259	Yellow needles	1586, 1561, 1454	$C_{17}H_{11}BrN_2OS_2$	50.63	2.75	6.95	50.91	2.65	6.72
10d	**B**	22	263—264	Yellow needles	1611, 1570, 1470	$C_{12}H_{10}N_2OS_2$	54.94	3.84	10.68	54.81	3.99	10.66
10e	**B**	15	134—136	Yellow needles	1682, 1576, 1470	$C_{13}H_{12}N_2O_2S_2$	53.41	4.14	9.58	53.40	4.12	9.61
10f	**B**	34	158—160	Orange needles	1599, 1568, 1467	$C_{18}H_{14}N_2OS_2$	63.88	4.17	8.28	63.92	4.17	8.24
10g	**B**	33	185—196	Yellow needles	1597, 1467	$C_{18}H_{13}ClN_2OS_2$	57.98	3.51	7.51	57.98	3.42	7.23
10h	**B**	26	180—183	Yellow needles	1596, 1562, 1466	$C_{18}H_{13}BrN_2OS_2$	51.80	3.14	6.71	52.07	3.37	6.42
10i	**B**	21	204—206	Yellow needles	1605, 1576, 1468	$C_{13}H_{12}N_2OS_2$	56.49	4.38	10.14	56.50	4.36	10.15
10j	**B**	10	140—142	Yellow needles	1694, 1582, 1470	$C_{14}H_{14}N_2O_2S_2$	54.88	4.61	9.14	54.81	4.69	9.12
10k	**B**	46	178—180	Yellow needles	1589, 1562, 1458	$C_{24}H_{18}N_2OS_2$	69.54	4.38	6.76	69.45	4.41	6.75
10l	**B**	27	141—143	Orange needles	1583, 1562, 1458	$C_{24}H_{17}ClN_2OS_2$	64.20	3.82	6.24	64.32	3.71	6.23
10m	**B**	17	133—134	Orange needles	1582, 1562, 1456	$C_{24}H_{17}BrN_2OS_2$	58.42	3.47	5.68	58.65	3.29	5.62
10n	**B**	14	137—138	Yellow needles	1602, 1568, 1468	$C_{19}H_{16}N_2OS_2$	64.74	4.58	7.95	64.96	4.46	7.84
10o	**B**	24	98—100	Yellow needles	1698, 1580, 1472	$C_{20}H_{18}N_2O_2S_2$	62.80	4.74	7.32	63.02	4.59	7.26
10p	**B**	24	171—173	Yellow needles	1597, 1566, 1458	$C_{23}H_{16}N_2OS_2$	68.97	4.03	6.99	69.04	4.03	6.93
10q	**B**	23	158—161	Orange powder	1585, 1560, 1456	$C_{23}H_{15}ClN_2OS_2$	63.51	3.48	6.44	63.64	3.47	6.32
10r	**B**	23	132—134	Orange powder	1587, 1562, 1460	$C_{23}H_{15}BrN_2OS_2$	57.62	3.15	5.84	57.33	3.15	6.14
10s	**B**	15	131—132	Yellow needles	1607, 1566, 1470	$C_{18}H_{14}N_2OS_2$	63.88	4.17	8.28	63.84	4.20	8.28
10t	**B**	12	97—99	Orange needles	1694, 1578, 1474	$C_{19}H_{16}N_2O_2S_2$	61.93	4.38	7.60	61.84	4.54	7.54
10u	**B**	43	181—183	Yellow needles	1612, 1464	$C_{24}H_{18}N_2OS_2$	69.54	4.38	6.76	69.62	4.33	6.73
10v	**B**	24	184—186	Yellow needles	1610, 1464	$C_{24}H_{17}ClN_2OS_2$	64.20	3.82	6.24	64.29	3.82	6.15
10w	**B**	10	192—194	Yellow needles	1608, 1589, 1462	$C_{24}H_{17}BrN_2OS_2$	58.42	3.47	5.68	58.32	3.61	5.64
10x	**B**	25	110—113	Yellow needles	1590, 1562, 1460	$C_{23}H_{15}BrN_2OS_2$	57.62	3.15	5.84	57.67	3.17	5.79
10y	**B**	30	124—127	Yellow needles	1589, 1560, 1458	$C_{23}H_{14}BrClN_2OS_2$	53.76	2.75	5.45	53.64	2.83	5.49
10z	**B**	17	88—91	Orange powder	1585, 1485, 1446	$C_{23}H_{14}Br_2N_2OS_2$	49.48	2.53	5.02	49.62	2.61	4.80
10a′	**B**	37	93—95	Yellow needles	1589, 1561, 1462	$C_{23}H_{15}ClN_2OS_2$	63.51	3.48	6.44	63.34	3.37	6.36
10b′	**B**	32	181—184	Orange powder	1587, 1558, 1458	$C_{23}H_{15}FN_2OS_2$	66.01	3.61	6.69	65.77	3.81	6.74
10c′	**B**	35	192—193	Yellow needles	1593, 1568, 1456, 2228	$C_{24}H_{15}N_3OS_2$	67.74	3.55	9.88	67.94	3.65	9.58
12a	**B**	48	218—219	Yellow prisms	1595, 1466	$C_{18}H_{14}N_2OS_2$	63.88	4.17	8.28	64.07	4.06	8.20
12b	**B**	30	258—259	Yellow needles	1595, 1468	$C_{18}H_{13}ClN_2OS_2$	57.98	3.51	7.51	58.26	3.30	7.35
12c	**B**	34	222—224	Yellow needles	1593, 1572, 1466	$C_{18}H_{13}BrN_2OS_2$	51.80	3.14	6.71	51.82	3.17	6.48
12d	**B**	42	242—243	Yellow needles	1572, 1518, 1470	$C_{13}H_{12}N_2OS_2$	56.49	4.38	10.14	56.68	4.23	10.11
12e	**B**	23	144—146	Yellow needles	1692, 1578, 1472	$C_{14}H_{14}N_2O_2S_2$	54.88	4.61	9.14	54.86	4.69	9.09
12f	**B**	38	169—171	Yellow needles	1603, 1563, 1466	$C_{19}H_{16}N_2OS_2$	64.74	4.58	7.95	64.82	4.57	7.87
12g	**B**	42	192—193	Yellow needles	1601, 1564, 1468	$C_{19}H_{15}ClN_2OS_2$	58.98	3.91	7.24	59.27	3.63	7.12
12h	**B**	40	199—200	Yellow needles	1602, 1562, 1466	$C_{19}H_{15}BrN_2OS_2$	52.90	3.51	6.49	53.21	3.21	6.70

Table 2. Continued

No.	Method	Yield (%)	mp (°C)	Appearance	IR (KBr) cm^{-1}	Formula	Calcd C (%)	H (%)	N (%)	Found C (%)	H (%)	N (%)
12i	**B**	41	173—175	Yellow needles	1576, 1522, 1470	$C_{14}H_{14}N_2OS_2$	57.90	4.86	9.65	58.03	4.70	9.68
12j	**B**	26	104—105	Yellow needles	1693, 1580, 1470	$C_{15}H_{16}N_2O_2S_2$	56.22	5.03	8.74	56.40	4.99	8.62
12k	**B**	35	148—149	Orange prisms	1584, 1557, 1460	$C_{25}H_{20}N_2OS_2$	70.06	4.70	6.54	70.00	4.70	6.60
12l	**B**	38	159—163	Yellow needles	1584, 1555, 1460	$C_{25}H_{19}ClN_2OS_2$	64.85	4.14	6.05	65.03	3.96	6.05
12m	**B**	42	165—167	Yellow needles	1584, 1555, 1460	$C_{25}H_{19}BrN_2OS_2$	59.17	3.77	5.52	59.37	3.61	5.48
12n	**B**	36	139—140	Yellow needles	1568, 1510, 1470	$C_{20}H_{18}N_2OS_2$	65.54	4.95	7.64	65.36	5.03	7.75
12o	**B**	39	82—84	Yellow prisms	1698, 1580, 1472	$C_{21}H_{20}N_2O_2S_2$	63.61	5.08	6.99	63.68	5.09	6.99
12p	**B**	34	129—130	Yellow needles	1597, 1570, 1464	$C_{24}H_{18}N_2OS_2$	69.54	4.38	6.76	69.62	4.17	6.88
12q	**B**	20	201—203	Orange needles	1582, 1543, 1460	$C_{24}H_{17}ClN_2OS_2$	64.20	3.82	6.24	64.45	3.60	6.21
12r	**B**	24	212—214	Orange needles	1580, 1561, 1491	$C_{24}H_{17}BrN_2OS_2$	58.42	3.47	5.68	58.49	3.35	5.72
12s	**B**	43	171—173	Yellow needles	1574, 1520, 1466	$C_{19}H_{16}N_2OS_2$	64.74	4.58	7.95	64.51	4.76	8.00
12t	**B**	38	133—134	Yellow needles	1701, 1576, 1470	$C_{20}H_{18}N_2O_2S_2$	62.80	4.74	7.32	62.55	4.97	7.35
12u	**B**	32	171—173	Yellow needles	1572, 1514, 1466	$C_{25}H_{20}N_2OS_2$	70.06	4.70	6.54	70.33	4.48	6.50
12v	**B**	36	230—232	Orange needles	1582, 1543, 1460	$C_{25}H_{19}ClN_2OS_2$	64.85	4.14	6.05	65.03	4.02	5.98
12w	**B**	41	238—239	Orange needles	1580, 1543, 1460	$C_{25}H_{19}BrN_2OS_2$	59.17	3.77	5.52	59.23	3.70	5.54
12x	**B**	20	168—169	Orange needles	1595, 1510, 1485	$C_{24}H_{17}BrN_2OS_2$	58.42	3.47	5.68	58.28	3.53	5.76
12y	**B**	25	229—230	Orange needles	1580, 1561, 1487	$C_{24}H_{16}BrClN_2OS_2$	54.61	3.06	5.31	54.78	2.87	5.32
12z	**B**	23	236—238	Orange needles	1578, 1539, 1487	$C_{24}H_{16}Br_2N_2OS_2$	50.36	2.82	4.89	50.67	2.62	4.79
12a′	**B**	20	148—150	Orange flakes	1595, 1510, 1491	$C_{24}H_{17}ClN_2OS_2$	64.20	3.82	6.24	64.12	3.79	6.35
12b′	**B**	25	161—163	Orange needles	1570, 1508, 1462	$C_{24}H_{17}FN_2OS_2$	66.64	3.96	6.48	66.75	3.81	6.52
12c′	**B**	30	179—182	Orange needles	1589, 1510, 1490, 2222	$C_{25}H_{17}N_3OS_2$	68.31	3.90	9.56	68.24	3.97	9.56

a) See ref. 13.

4.17; N, 8.61%.

3-Amino-2-(4-chlorobenzoyl)-4-(3-methyl-1-pyridinio)thiophene-5-thiolate (**4l**)[20]: 79%; red prisms; mp >300 °C. IR (KBr) cm^{-1}: 1576, 3241, 3353. *Anal.* Calcd for $C_{17}H_{13}ClN_2OS_2$: C, 56.58; H, 3.63; N, 7.76%. Found: C, 56.66; H, 3.71; N, 7.60%.

3-Amino-2-(4-bromobenzoyl-4-(3-methyl-1-pyridinio)thiophene-5-thiolate (**4m**)[20]: 78%; red prisms; mp >300 °C. IR (KBr) cm^{-1}: 1574, 3248, 3364. *Anal.* Calcd for $C_{17}H_{13}BrN_2OS_2$: C, 50.38; H, 3.23; N, 6.91%. Found: C, 50.11; H, 3.10; N, 6.64%.

2-Acetyl-3-amino-4-(3,5-dimethylpyridinio)thiophene-5-thiolate (**4n**): 80 %[20]; red prisms; mp >300 °C. IR (KBr) cm^{-1}: 1574, 3243, 3347. *Anal.* Calcd for $C_{12}H_{12}N_2OS_2$: C, 54.52; H, 4.58; N, 10.60%. Found: C, 54.60; H, 4.54; N, 10.55%.

3-Amino-4-(3,5-dimethylpyridinio)-2-(ethoxycarbonyl)thiophene-5-thiolate (**4o**): 93%; red prisms; mp 221—223 °C. IR (KBr) cm^{-1}: 1645, 3275, 3391. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 2.04 (3H, s, 3-Me), 4.25 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 5.12 (br, NH), 7.90 (1H, br q, J= 7.8, 6.1 Hz, 5-H), 8.15 (1H, br d, J=7.8 Hz, 4-H), 8.71 (1H, br d, J=6.1 Hz, 6-H), 8.78 (1H, br s, 2-H). *Anal.* Calcd for $C_{13}H_{14}N_2O_2S_2$: C, 53.04; H, 4.79; N, 9.52%. Found: C, 53.03; H, 4.79; N, 9.52%.

Preparation of 1-Acyl-3-(alkylthio)thieno[3′,4′:4,5]imidazo[1,2-*a*]pyridines (7a—c′), (10a—c′), and (12a—c′). General Method A A chloroform suspension (20 ml) of 3-amino-4-(3,5-dimethyl-1-pyridinio)thiophene-5-thiolates (**4a**—**e**) (2.0 mmol) and an alkylating agent (**5**, 2.5 mmol) was kept at room temperature or heated at 50 °C in a water bath until the low soluble thiolate **4** underwent the *S*-alkylation to dissolve completely in the resulting chloroform solution (*ca.* 4—10 d). The solution was then concentrated at reduced pressure and the crude salt **6** was washed 3 times with ether (each 10 ml) to remove the unaltered alkylating agent. The residue was dissolved in chloroform (30 ml) and then DBU (0.364 g, 2.4 mmol) was added at 0 °C in an ice bath and stirred for a further 1 h.[21] The reaction mixture was then concentrated at reduced pressure, and the residue was separated by column chromatography on alumina using chloroform as an eluent. The fractions with very strong fluorescence were combined and the resulting solution was concentrated at reduced pressure. Recrystallization of the crude materials from chloroform–hexane gave the corresponding 1-acyl-3-alkylthio-6,8-dimethylthieno[3′,4′:4,5]imidazo[1,5-*a*]pyridines (**7a**—**c′**).

General Method B A mixture of *S*-alkylated pyridinium salts **8a**—**c′** or **10a**—**c′**, which were prepared from 3-amino-4-(1-pyridinio)thiophene-5-thiolates (**4f**—**j**, 2 mmol) or 3-amino-4-(3-methyl-1-pyridinio)thiophene-5-thiolate (**4k**—**o**, 2.0 mmol) and **5a**—**i** according to method A above, potassium carbonate (**5g**), and chloroform (30 ml) were put in a flask covered with aluminum foil to shield any light, and stirred at room temperature for 1 d. All operations of work-ups (the concentration of the reaction mixtures, the column separation of the residues on alumina, and the purification by recrystallization from chloroform–hexane) were carried out in dark to afford the corresponding thieno[3′,4′:4,5]imidazo[1,5-*a*]pyridines (**9a**—**c′** and **11a**—**c′**).

In general, the reactions of salts **9a**—**c′** or **11a**—**c′** with a base were very photosensitive, though those of salts **6a**—**c′** were not so much. In addition the products **7a**—**c′**, **10a**—**c′**, and **12a**—**c′** were also photosensitive to some extent in the solution state. Hence, the exposure of any light to the reaction solutions of salts **9a**—**c′** or **11a**—**c′** caused the extremely diminished yields of the expected products **10a**—**c′** and **12a**—**c′**. The use of DBU as a base in the reactions of salts **9a**—**c′** or **11a**—**c′** did not provide good results. On the other hand, the replacement of DBU by potassium carbonate as a base was no problem in the reactions of salts **6a**—**c′** but a more prolonged reaction time was necessary.

The physical and spectral data for compounds **7a**—**c**, **f**—**h** were well in accord with those reported earlier by us. ^{1}H-NMR spectral data for compounds **7a**—**c′**, **10a**—**c′**, and **12a**—**c′** are shown in Table 1 and some other data are listed in Table 2. The ^{13}C-NMR spectral data for some products are as follows: **7e**, 14.59, 17.36, 18.00, 21.61, 60.90, 108.48, 118.61, 119.77, 122.17, 127.31, 134.00, 134.27, 152.38, 158.20, 161.46. **7k**, 17.08, 18.11, 35.65, 39.79, 119.97, 120.90, 121.65, 122.36, 126.65, 127.25, 127.78, 128.48, 129.92, 131.96, 134.07, 135.55, 138.00, 138.74, 150.87, 157.80, 185.11 (one carbon is overlapping). **9e**, 14.65, 21.43, 60.91, 110.12, 117.98, 118.06, 119.58, 127.25, 132.27, 133.34, 151.93, 158.20, 161.39. **9n**, 28.30, 35.65, 39.90, 110.30, 117.69, 121.04, 121.45, 126.61, 127.52, 128.35, 128.38, 132.73, 134.53, 138.50, 151.59, 158.04, 189.16. **11e**, 14.55, 17.46, 21.46, 60.91, 110.23, 119.21, 124.77, 127.97, 130.69, 134.06, 152.08, 158.88, 161.31 (one carbon is overlapping). **11x**, 17.10, 43.47, 110.02, 118.39, 121.82, 122.71, 124.15, 127.76, 127.83, 129.90, 130.12, 130.64, 131.55, 132.10, 135.41,136.80, 137.73, 150.39, 158.40, 185.32.

Isolation of the Reaction Product of Salt 6e with Chloroform in the Presence of a Base A chloroform solution of salt (**6e**), prepared from the *S*-methylation of 3-amino-4-(3,5-dimethyl-1-pyridinio)-2-(ethoxycarbonyl) thiophene-5-thiolate (**4e**, 2 mmol), was allowed to react in the presence of excess potassium carbonate (**5g**) at 0 °C, and the resulting reaction mixture was separated in the usual manner. A byproduct, ethyl 3-amino-4-(3,5-dimethyl-4-trichloromethyl-1,4-dihydropyridin-1-yl)-5-(methylthio)thiophene-2-carboxylate (**8e**), was obtained in 14% yield, together with the expected ethyl 6,8-dimethyl-3-(methylthio)thieno[3′,4′:4,5]imidazo[1,5-*a*]pyridine-1-carboxylate (**7e**, 28%).

Some Physical and Spectral Properties of **7e** as Follows: Colorless prisms; mp 140—142 °C. IR (KBr) cm^{-1}: 3472, 3362, 1665. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 2.09 (6H, s, 3′,5′-diMe), 2.48 (3H, s, SMe), 3.89 (1H, s, 4′-H), 4.28 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 5.36 (2H, br, NH_2), 6.30 (2H, s, 2′,6′-H). *Anal.* Calcd for $C_{16}H_{19}Cl_3N_2O_2S_2$: C, 43.50; H,

4.33; N, 6.34%. Found: C, 43.57; H, 4.41; N, 6.18%.

Crystallography of Ethyl 8-Methyl-3-(phenethylthio)thieno[3′,4′:4,5]imidazo[1,5-*a*]pyridine-1-carboxylate (11o) A single crystal (0.92×0.88×0.40 mm) grown from $CHCl_3$–hexane was used for the unit-cell determinations and the data collection by a Rigaku RAXIS RAPID imaging plate area detector with graphite-monochromated Cu$K\alpha$ radiation (λ=1.54187 Å). Crystal data of these compounds are as follows: **11o**: $C_{21}H_{20}N_2O_2S_2$; M=396.52; monoclinic, space group $P2_1/n$ (#14), Z=4 with a=12.697 (11) Å, b=8.36 (2) Å, c=18.875 (17) Å, β=103.33° (8); V=1949.3 (56) Å^3, and $D_{calc.}$=1.351 g/cm^3. All calculations were performed using CrystalStructure.[22] The structure was solved by a direct method (SIR92).[23] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final R- and Rw_2-factors after full-matrix least-squares refinements were 0.0820 for (I>2.00σ(I)) and 0.0778 for all observed reflections (5224).

Crystallography of Ethyl 3-Benzylthio-8-methylthieno[3′,4′:4,5]imidazo[1,5-*a*]pyridine-1-carboxylate (11t) A single crystal (0.84×0.44×0.42 mm) grown from $CHCl_3$–hexane was used for the unit-cell determinations and the data collection by a Rigaku AFC5S four-circle diffractometer with graphite-monochromated Mo$K\alpha$ radiation (λ=0.71069 Å). Crystal data of these compounds are as follows: **11t**: $C_{20}H_{18}N_2O_2S_2$; M=382.49; monoclinic, space group $P2_1/c$ (#14), Z=4 with a=9.20 (2) Å, b=10.86 (4) Å, c=18.46 (2) Å, β=91.05 (13)°; V=1843.9 (81) Å^3, and $D_{calc.}$=1.378 g/cm^3. All calculations were performed using CrystalStructure.[22] The structure was solved by a direct method (SIR92).[23] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final R- and Rw-factors after full-matrix least-squares refinements were 0.0612 and 0.0492 respectively for 2462 (I>2.00σ(I)) observed reflections.

Crystallography of 1-[3-Amino-2-ethoxycarbonyl-4-(methylthio)thiophen-4-yl]-3,5-dimethyl-4-trichloromethyl-1,4-dihydropyridine (8e) A single crystal (0.88×0.42×0.18 mm) grown from $CHCl_3$–hexane was used for the unit-cell determinations and the data collections by Rigaku AFC5S four-circle diffractometer with graphite-monochromated Mo$K\alpha$ radiation (λ=0.71069 Å). Crystal data of **8e**: $C_{16}H_{44}C_{l3}N_2O_2S_2$; M=441.82; triclinic, space group P-1 (#2), Z=2 with a=10.259 (18) Å, b=10.98 (3) Å, c=10.03 (3) Å, α=107.94° (19), β=112.13° (17), γ=73.70° (18); V=978.4 (39) Å^3, and $D_{calc.}$=1.500 g/cm^3. All calculations were performed using the CrystalStructure.[22] The structure was solved by a direct method (SIR92).[23] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final R- and Rw-factors after full-matrix least-squares refinements were 0.0772 and 0.0803 for 2721 (I>2.00σ(I)) observed reflections, respectively.

References and Notes

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