Preparation of New Nitrogen-Bridged Heterocycles. 42.[1] Synthesis and the Reaction of Pyridinium *N*-Ylides Using Bifunctional Ethyl Thiocyanatoacetates

Akikazu Kakehi,* Suketaka Ito, and Yasunobu Hashimoto

Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380

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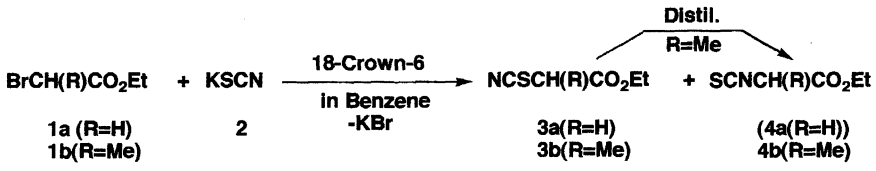
Various pyridinium (monosubstituted methylide)s were smoothly attacked to the cyano group in ethyl thiocyanatoacetate or ethyl 2-thiocyanatopropionate to afford the corresponding pyridinium (substituted cyanomethylide)s in low-to-moderate yields, while pyridinium (unsubstituted amidate)s reacted with the ester carbonyl group in the same reagents to give pyridinium (thiocyanatoaceto)- or (2-thiocyanatopropiono)amidates in considerable yields. The 1,3-dipolar cycloadditions of some pyridinium (unsymmetrically substituted cyanomethylide)s with dimethyl acetylenedicarboxylate (DMAD) in various solvents afforded only dimethyl 3-cyanoindolizine-1,2-dicarboxylate, except a few examples. On the other hand, the treatment of pyridinium (thiocyanatoaceto)- or (2-thiocyanatopropiono)amidates with a strong base, such as potassium *t*-butoxide, gave new bicyclic mesoionic compounds, *N*-[2-(1,3,4-thiadiazolo[3,2-*a*]pyridinio)]acetamidate derivatives, in moderate yields. The intermediacy of *N*-[1-(2-thiocyanatopyridinio)]acetamidates in the formation reactions of the latter compounds was also proven by independent syntheses.

It is well known that pyridinium *N*-ylides are strong dipolar and nucleophilic species. For example, their 1,3-dipolar cycloadditions with various electron-deficient alkenes and alkynes are useful and versatile methods for preparing some nitrogen-bridged heterocycles[2] and their reactions with various electrophiles afford a variety of interesting compounds, such as extended dipoles,[3] heterocycles,[4] and enamines.[5] In a continuation of our studies to preparing new nitrogen-bridged heterocycles, we are especially interested in the synthesis of new pyridinium *N*-ylides, which can be starting materials for them, and may show novel reactivities. For this purpose we recently planned the development of bifunctional reagents which can introduce a more reactive substituent onto the anion atom in pyridinium *N*-ylides. The reagents designed by us were ethyl thiocyanatoacetate and ethyl 2-(thiocyanato)propionate, which have two electrophilic centers in the molecules. These reagents were prepared from the reactions of potassium thiocyanate with ethyl bromoacetate or ethyl 2-bromopropionate and their reactions with some pyridinium methylides and amidates were investigated. In this paper we report on novel synthetic methods for various pyridinium (substituted cyanomethylide)s and pyridinium thiocyanatoacetamidates using these bifunctional reagents and the reactions of pyridinium *N*-ylides thus obtained with DMAD or a strong base.

Results and Discussion

Preparations of Ethyl Thiocyanatoacetates. Ethyl thiocyanatoacetate (**3a**) was prepared in 80% yield from the reaction of potassium thiocyanate (**2**) with ethyl bromoacetate (**1a**) in benzene in the presence of 18-crown-6 at room temperature. In this reaction an alternative possible products, ethyl isothiocyanatoacetate (**4a**), was not formed at all. On the other hand, although a similar treatment of **2** with ethyl 2-bromopropionate (**1b**) in benzene did not give any significant product, at the reflux temperature it formed the corresponding ethyl 2-(thiocyanato)propionate (**3b**), accompanied by a small amount of ethyl 2-(isothiocyanato)propionate (**4b**) (Scheme 1). Compounds **3a,b** were very stable at room temperature, but **3b**, upon heating at near 120 ° C, was smoothly converted to the 2-isothiocyanato derivative **4b**.

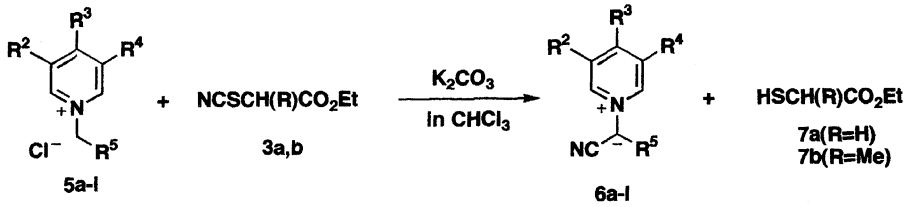
The structures of these compounds could be readily assigned by the indication of each characteristic absorption band for the thiocyanate group (2160 cm^{-1}) or the isothiocyanato group (2072 cm^{-1}) as well as for the saturated ester carbonyl group (1735 and 1740 cm^{-1}) in their IR spectra.



Scheme 1.

Reactions of Ethyl Thiocyanatoacetates (3a,b) with Pyridinium Methylides and Amidates. When ethyl thiocyanatoacetate (**3a**) and 1-(cyanomethyl)pyridinium chlorides (**5a—c**) were treated with excess potassium carbonate in chloroform at room temperature, yellow crystalline pyridinium dicyanomethylides (**6a—c**) were isolated in 7, 15, and 18% yields, respectively. Although the same pyridinium dicyanomethylides (**6a—c**) were also formed from the reactions of pyridinium salts **5a—c** with ethyl 2-(thiocyanato)propionate (**3b**) in the presence of a base, their yields were lower than those in cases using ethyl thiocyanatoacetate (**3a**). Similar treatment of **3a** and 1-(ethoxycarbonylmethyl)- (**5d—f**), 1-acetonyl- (**5g—i**), and 1-phenacylpyridinium chlorides (**5j—l**) gave the corresponding pyridinium (substituted cyanomethylide)s (**6d—l**) in 28—63% yields. In the above-mentioned reactions the generation of ethyl mercaptoacetate (**7a**) or ethyl 2-mercaptopropionate (**7b**) could also be confirmed (Scheme 2). The reason why the yields for pyridinium dicyanomethylides (**6a—c**) were lower than those for other pyridinium (substituted cyanomethylide)s is unclear, but may have been due to the low reactivity or the instability of pyridinium cyanomethylides generated in situ from the alkaline treatment of 1-(cyanomethyl)pyridinium chlorides (**5a—c**).

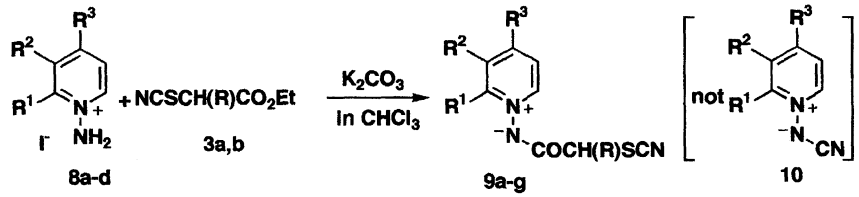
On the other hand, the reactions of reagents **3a,b** with 1-aminopyridinium iodides (**8a—d**) in the presence of a base gave a quite different type of products. These reactions did not afford the initially expected pyridinium cyanamidates, such as **10**, at all, but, instead of them, yielded the corresponding pyridinium (thiocyanatoaceto)- (**9a—d**) and (2-



5,6	R^2	R^3	R^4	R^5	Yield(%)[a]	5,6	R^2	R^3	R^4	R^5	Yield(%)
a	H	H	H	CN	7(3)	g	H	H	H	COMe	58
b	H	Me	H	CN	15(4)	h	H	Me	H	COMe	40
c	Me	H	Me	CN	18(7)	i	Me	H	Me	COMe	42
d	H	H	H	CO_2Et	63	j	H	H	H	COPh	45
e	H	Me	H	CO_2Et	53	k	H	Me	H	COPh	37
f	Me	H	Me	CO_2Et	51	l	Me	H	Me	COPh	28

a) The yield in the parenthesis is for the reaction using 3b.

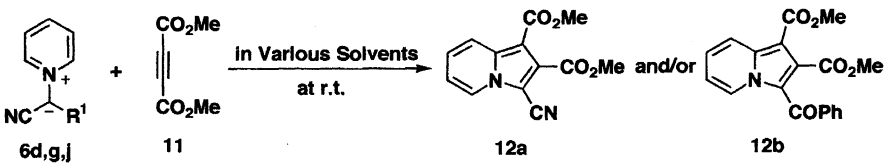
Scheme 2.



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

9	R^1	R^2	R^3	R	Yield(%)
a	H	H	H	H	63
b	Me	H	H	H	69
c	H	Me	H	H	80
d	H	H	Me	H	65
e	H	H	H	Me	44
f	Me	H	H	Me	42
g	H	H	Me	Me	60

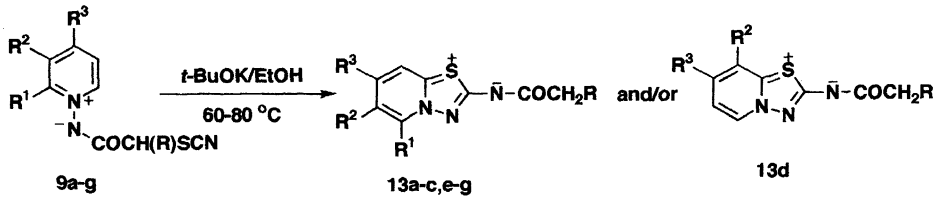
Scheme 3.

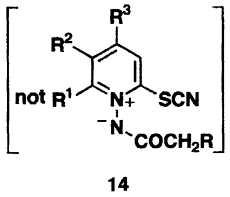


Ylide/Solvent	$CHCl_3$	CH_3CN	THF	Dixane	DMF
6d	12a(26%)	12a(70%)	12a(44%)	12a(44%)	121a(39%)
6g	12a(30%)	12a(49%)	12a(35%)	12a(43%)	12a(34%)
6j	12a(55%)	12a(55%)	12a,b(*ca.* 37%)[a]	12a(34%)	12a,b(*ca.* 24%)[b]

a) The ratio of **12a** to **12b** is 1 : 18.
b) The ratio of **12a** to **12b** is 1 : 6.

Scheme 4.





React.	Prod.	R^1	R^2	R^3	R	Yield(%)
9a	13a	H	H	H	H	26
9b	13b	Me	H	H	H	28
9c	13c	H	Me	H	H	12
	13d	--	Me	H	H	25
9d	13e	H	H	Me	H	34
9e	13f	H	H	H	Me	38
9f	13g	Me	H	H	Me	17
9g	13h	H	H	Me	Me	23

Scheme 5.

thiocyanatopropiono)amidates **9e—g** in considerable yields (42—80%) (Scheme 3).

Both structures of pyridinium (substituted cyanomethylide)s (**6a—l**) and pyridinium (2-thiocyanatoaceto)amidates (**9a—g**) could be determined by physical and spectral inspections and by comparisons with known pyridinium methylides **6a—d,g**.[6—8] The elemental analyses for all compounds **6a—l** and **9a—g** were in good accord with our proposed compositions. The IR spectra for compounds **6a—l** definitely exhibited one or two cyano absorption bands characteristics of the pyridinium 1-cyanomethylides at considerably lowered regions (2143—2182 cm^{-1}).[6] On the other hand, those for compounds **9a—g** showed each lower-shifted absorption band (1649—1676 cm^{-1}) due to the carbonyl groups conjugated with the ylidic anion, but did not show any absorption band for the thiocyanate group. Although the reason why the thiocyanato absorption band was absent is unclear, the dipole structure ($Py^+N^-CO–CH_2–SCN$) around the central methylene group may be balanced. The chemical shifts and signal patterns due to the protons on the pyridine ring in products **6a—l** or **9a—g** in their ^1H NMR spectra were very similar to each other and to those in known pyridinium methylides and amidates.[3] Furthermore, inspections of their peak areas in these ^1H NMR spectra exhibited that no attack of these reagents **3a,b** onto the pyridine ring of the corresponding pyridinium ylides took place. Some physical and spectral data for known compounds **6a—d,g** coincided with those reported earlier.[6,8] Mechanistically, it is clear that pyridinium (substituted cyanomethylide)s (**6a—l**) and pyridinium thiocyanatoacetamidates (**9a—g**) were formed via a nucleophilic attack of the ylidic anion atoms of the corresponding pyridinium ylides generated from salts **5a—l** and **8a—d** on the cyano carbon and the ester carbonyl carbon in **3a,b**, respectively. The reason for the definite difference in the reactivities between the pyridinium methylides and the amidates employed here may be explained by the hard and soft acids and bases principle.[9] That is, its harder anionic nitrogen of the pyridinium amidates attacks to its harder ester carbonyl carbon of **3a,b** and its softer anionic carbon of the pyridinium methylides to its softer thiocyanato carbon of the same reagents. We have already observed similar reactions of the pyridinium amidates toward the ester carbonyl

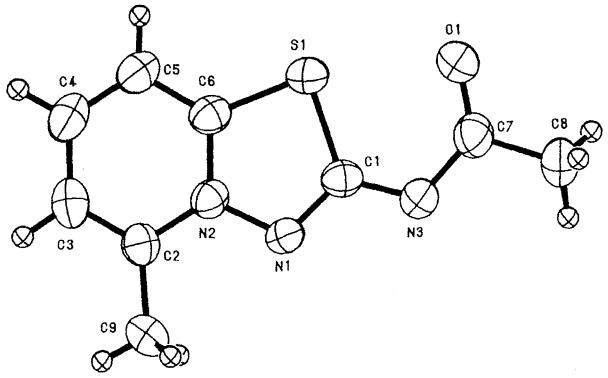


Fig. 1. ORTEP drawing of *N*-[2-(5-methyl-1,3,4-thiadiazolo[3,2-*a*]pyridinio)]acetamidate (**13b**) showing the atom labeling scheme and 50% probability thermal ellipsoids.

carbon.[10]

Some Reactions of Pyridinium Ylides. Although the usefulness of 3-unsubstituted indolizine derivatives for preparing 3,5-fused indolizines, such as pyrrolo[2,1,5-*cd*]-indolizine derivatives, has been well documented,[11] many 3-unsubstituted indolizines are considerably unstable and can not necessarily be used for all such reactions. Recently, the effective use of more stable 3-cyanoindolizines in pyrrolo-[2,1,5-*cd*]indolizine synthesis has been reported;[12] in turn, the utility for the precursors, pyridinium dicyanomethylides, has been realized. Although our preparative method of pyridinium dicyanomethylides (**6a—c**) has only used low-cost, readily available materials, **5a—c** and **3a,b**, their yields are considerably low. On the other hand, higher yields for **6a,b** have been reported using the conventional procedure;[6a] however, tetracyanoethylene of the starting material employed there is very expensive. These facts prompted us to examine the effective transformation method from pyridinium (unsymmetrically substituted cyanomethylide)s, which were obtained in higher yields than those for pyridinium dicyanomethylides **6a—c**, to the 3-cyanoindolizine derivatives. For this purpose, pyridinium cyano(ethoxycarbonyl)methylide (**6d**), pyridinium acetyl(cyano)methylide (**6g**), and pyridinium benzoyl(cyano)methylide (**6j**) were selected as candidates for 1,3-dipoles and their 1,3-dipolar cycloadditions with DMAD (**11**) were examined in chloroform, acetonitrile, tetrahydrofuran (THF), dioxane, and *N*,*N*-dimethylformamide (DMF) at room temperature (Scheme 4). The isolation of the reaction mixtures clearified that most of the reactions afforded dimethyl 3-cyanoindolizine-1,2-dicarboxylate (**12a**); in only two cases (**6j** and **11** in THF and DMF), mixture (its ratio was 1 : 16 in THF or 1 : 6 in DMF) of the same product **12a** and dimethyl 3-benzoylindolizine-1,2-dicarboxylate (**12b**) was obtained. This fact, that the ability to eliminate the acyl groups from primary 1,3-dipolar bicycloadducts is much higher than that of the cyano group, must have realistically reflected the difference in the bond-dissociation energies between the sp^3C–sp^2C and sp^3C–spC single bonds.[13]

On the other hand, the reactions of pyridinium thiocyanatoacetamidates (**9a—g**) with dipolarophiles, such as DMAD (**11**), did not afford any significant products at all. The

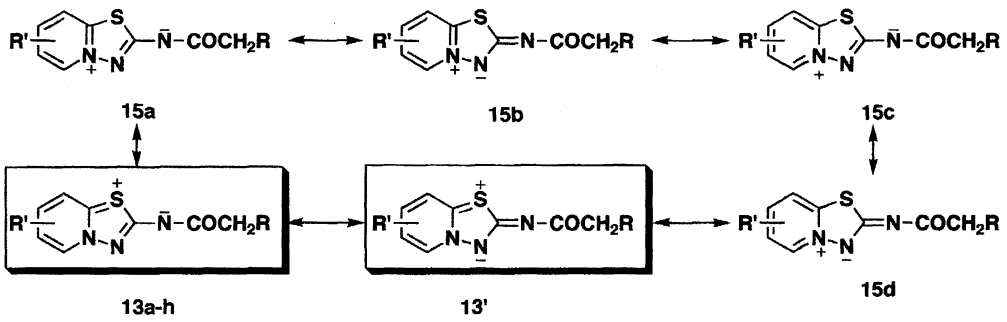
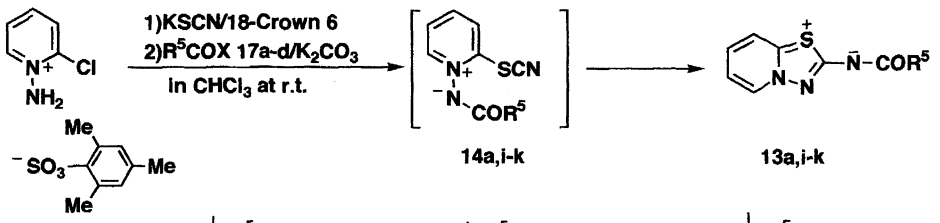


Fig. 2. Main resonance hybrids for *N*-[2-(1,3,4-thiadiazolo[3,2-*a*]pyridinio)]acetamidates (**13a—h**).

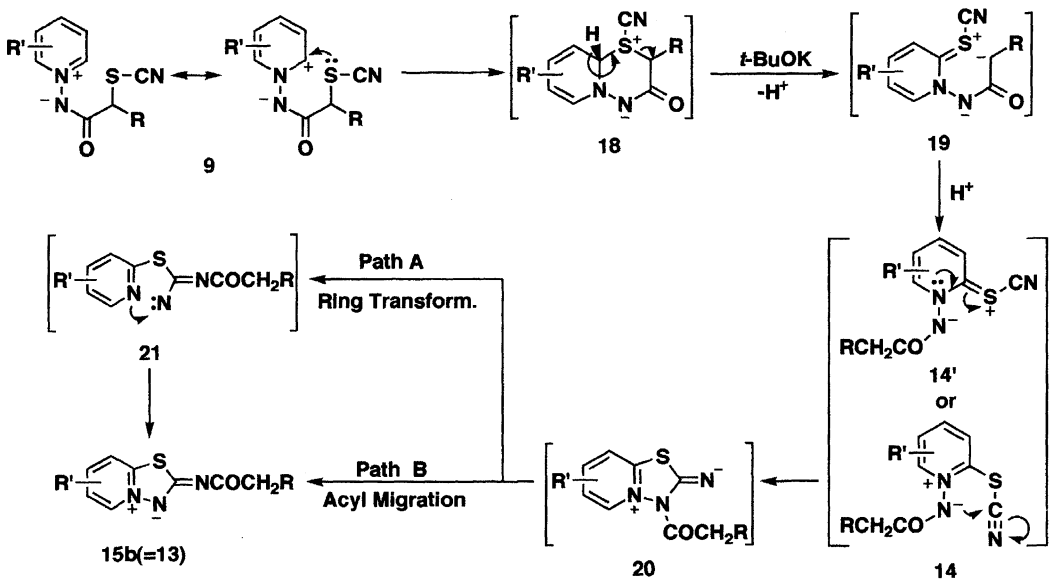


17	R^5COX
a	Ac_2O
b	$(PrCO)_2O$
c	PhCOCl
d	EtOCOCl

14	R^5
a	Me
i	Pr
j	Ph
k	EtO

13	R^5	Yield(%)
a	Me	63
i	Pr	50
j	Ph	80
k	EtO	80

Scheme 6.



Scheme 7.

treatment of **9a**,**b**,**d**—**g** with a strong base (potassium *t*-butoxide) in ethanol at 60—80 °C, however, afforded colorless crystalline compounds **13a**,**b**,**e**—**h** in low-to-moderate yields (12—38%). In the reactions of unsymmetrical pyridinium amidate **9c** two products **13c**,**d** were formed in 12 and 25% yields, respectively (Scheme 5).

The structures of products **13a**—**h** were initially presumed to be 2- thiocyanatopyridinium acetamidates and propionamidates (**14**), since their elemental analyses showed that they have the same compositions with the original amidates **9a**—**g** and their ^{1}H NMR spectra showed the disappearance of an α-proton signal of the pyridine ring and the new appearance of an acetyl (δ = 2.32—2.37 (3H, s)) or a propionyl proton signals (δ = 1.26 or 1.27 (3H, t, J = 7.0 Hz) and 2.63—2.66 (2H, q, J = 7.0 Hz)). However, we still had some doubts about this structural assignment because of the absence of the 2-thiocyanato absorption band in their IR spectra. Hence, an X-ray analysis for one compound **13b** was carried out, and its rearranged bicyclic mesoionic structure, *N*-[2-(5-methyl-1,3,4-thiadiazolo[3,2-*a*]pyridinio)]acetamidate, was finally determined. An ORTEP drawing[14] for **13b** is shown in Fig. 1.[15] Interestingly, the structural data showed the high double-bonded character of the S1–C6 bonds (its bond length is 1.719 Å and this value is fairly shorter than that (1.780 Å) for the S1–C1 bond (see Fig. 1)) and the delocalized structure in the N1–C1–N3 sequence (the lengths of the N1–C1 and C1–N3 bonds are 1.310 and 1.336 Å, respectively). These data clearly show the larger contribution of the 1,3,4-thiadiazolium structures (**13** and **13′**) than that of pyridinium structures **15a**—**d** (See Fig. 2).

The transformation mechanism of the pyridinium thiocyanatoacetamidates (**9**) to *N*-[2-(1,3,4-thiadiazolo[3,2-*a*]-pyridinio)]acetamidates (**13**) involves very complicated features, and is not straightforward. From a consideration of the function of the strong base employed here and of the high nucleophilicity of the anion atom in pyridinium *N*-ylide, however, we presumed 2-thiocyanatopyridinium acetamidates (**14**) to be a possible intermediate. Here, this intermediate **14** has a structure proposed initially for products **13a**—**h**. In order to confirm of this assumption, an unequivocal synthesis of 2-thiocyanatopyridinium acetamidates (**14a**) was investigated. Interestingly, the treatment of 1-amino-2-chloropyridinium mesitylenesulfonate (**16**) with potassium thiocyanate (**2**) in chloroform in the presence of 18-crown-6 at room temperature followed by the addition of acetic anhydride (**17a**) and potassium carbonate to the resulting mixture did not give the expected substitution product **14a**, but directly yielded the rearranged compound **13a** in 63% yield. Similar reactions of salt **16** with propionic anhydride (**17b**), benzoyl chloride (**17c**), and ethyl chloroformate (**17d**) as acylating agents provided the corresponding mesoionic compounds **13i**—**k** in 50, 80, and 80% yields, respectively. (Scheme 6)

The possible reaction mechanisms deduced by the above experimental results are shown in Scheme 7. First, the intramolecular nucleophilic addition of the sulfur lone pair in pyridinium amidate (**9**) to the 2-position of the pyridine ring take place, and subsequent abstraction of the bridgehead proton of the resulting pyrido[2,1-*b*][1,3,4]thiadiazine intermediate **18** by a strong base proceeds with the ring opening of the 1,3,4-thiadiazine ring to give intermediate **19**, and then 2-thiocyanatopyridinium acetamidates (**14′** or **14**). The intramolecular recyclization of **14**, followed by a ring transformation (path A) or the acyl migration (path B) of the resulting 3-acyl-2-imido-1,3,4-thiadiazolo[3,2-*a*]pyridinium (**20**) should provide the final products **13**. At present, whether this reaction proceeds via path A or path B is unclear.

Furthermore, although we were interested in the reactivity of these mesoionic compounds **13a**—**k**, their reactions with dimethyl acetylenedicarboxylate (**11**) gave only complex mixtures, and no significant products could be isolated.

Experimental

The melting points were measured with a Yanagimoto micromelt-

ing point apparatus and were not corrected. Microanalyses were carried out on a Perkin–Elmer 2400 elemental analyzer. The ^{1}H NMR spectra were determined with a Hitachi R-600 spectrometer (60 MHz) in deuteriochloroform with tetramethylsilane used as an internal standard; the chemical shifts are expressed in δ values. The IR spectra were taken with a JASCO FT/IR-5300 infrared spectrophotometer.

Ethyl Thiocyanatoacetate (3a). A suspension of ethyl bromoacetate (**1a**, 83.5 g, 0.5 mol), potassium thiocyanate (**2**, 58.2 g, 0.6 mol), and 18-crown-6 (0.5 g) in dry benzene (200 ml) was stirred at room temperature until the growth of the characteristic thiocyanato absorption band (2160 cm^{-1}) in the IR spectra is stopped (ca. 7 d). The reaction mixture was then filtered and the separated insoluble inorganic substances were washed two times with 20 ml portions of benzene. The combined filtrate was concentrated at reduced pressure and vacuum distillation of the residual oil gave ethyl thiocyanatoacetate (**3a**), 80%, colorless oil, bp 122—123 °C/14 mmHg (1 mmHg = 133.322 Pa), IR (neat) 2160 (SCN) and 1740 cm^{-1} (CO), ^{1}H NMR ($CDCl_3$) δ = 1.34 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 3.81 (2H, s, CH_2), and 4.33 (2H, q, J = 7.0 Hz, $CO_2CH_2CH_3$). Found: C, 41.40; H, 4.86; N, 9.80%. Calcd for $C_5H_7NO_2S$: C, 41.37; H, 4.86; N, 9.65%.

Ethyl 2-Thiocyanatopropionate (3b) and Ethyl 2-Isothiocyanatopropionate (4b). Since a similar treatment of ethyl 2-bromopropionate (**1b**, 90.5 g, 0.5 mol), potassium thiocyanate (**2**, 58.2 g, 0.6 mol), and 18-crown-6 (0.5 g) in dry benzene (200 ml) at room temperature did not provide any significant products at all, the reaction solution was heated under reflux for 3 d. The resulting mixture was then filtered to remove any insoluble inorganic substances and the concentration of the filtrate gave ethyl 2-thiocyanatopropionate (**3b**), including a small amount of ethyl 2-isothiocyanatopropionate (**4b**).

We used this crude material for the below reactions because vacuum distillation at near to 120 °C caused a smooth transformation of **3b** to **4b**. Its isolation was also unsuccessful, since the mixture of **3b** and **4b** was azeotropically distilled off at 50 °C/3 mmHg.

3b; 45% (crude), colorless oil, IR (neat) 2160 (SCN) and 1735 cm^{-1} (CO), ^{1}H NMR ($CDCl_3$) δ = 1.31 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 1.73 (3H, d, J = 7.0 Hz, $CH(CH_3)$), 3.95 (1H, q, J = 7.0 Hz, $CH(CH_3)$), and 4.28 (2H, q, J = 7.0 Hz, $CO_2CH_2CH_3$).

4b; colorless oil, IR (neat) 2072 (NCS) and 1735 cm^{-1} (CO), ^{1}H NMR ($CDCl_3$) δ = 1.35 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 1.75 (3H, d, J = 7.0 Hz, $CH(CH_3)$), 3.99 (1H, q, J = 7.0 Hz, $CH(CH_3)$), and 4.31 (2H, q, J = 7.0 Hz, $CO_2CH_2CH_3$). Found: C, 45.06; H, 5.82; N, 8.89%. Calcd for $C_6H_9NO_2S$ (**3b** is also included): C, 45.27; H, 5.70; N, 8.80%.

Reactions of Pyridinium Methylides or Aminides with Ethyl Thiocyanatoacetates (3a,b). General Procedure. A mixture of pyridinium salts (**5** or **8**, 5 mmol), ethyl thiocyanatoacetate (**3a** or **3b**, 5 mmol), and potassium carbonate (5 g, 36 mmol) was allowed to react under stirring in chloroform (30 ml) at room temperature until the spot of salt **5** or **8** disappeared based on TLC monitoring (about 3—7 d). The reaction mixture was then filtered to remove insoluble substances, and the filtrate was concentrated at reduced pressure. The residue was separated by column chromatography on alumina using ether, and then chloroform, as eluents. Evaporation of the chloroform layers and the recrystallization from chloroform–ether afforded the corresponding pyridinium cyanomethylide (**6**) or pyridinium thiocyanatoacetamidates (**9**).

In the reactions of pyridinium salts **5** and **3a,b** the formations of ethyl mercaptoacetate (**7a**) and ethyl 2-mercaptopropionate (**7b**) could be confirmed by their characteristic unpleasant odor and ^{1}H NMR spectral inspections. These results and some properties for products **6a—l** and **9a—g** are given below.

6a; pale yellow needles, 7% (from **5a** and **3a**) or 3% (from **5a** and **3b**), mp 247—248 °C (Lit,[6a] 245—246 °C), IR (KBr) 2182 and 2148 cm^{-1} (CN).

6b; pale yellow needles, 15% (from **5b** and **3a**) or 4% (from **5b** and **3b**), mp 226—227 °C (Lit,[6a] 223—224 °C), IR (KBr) 2180 and 2143 cm^{-1} (CN).

6c; yellow needles, 18% (from **5c** and **3a**) or 7% (from **5c** and **3b**), mp 262—263 °C (Lit,[8] 256—257 °C), IR (KBr) 2182 and 2151 cm^{-1} (CN).

6d; pale yellow needles, 63%, mp 115—116 °C (Lit, 112—113 °C[6b] and 113.5—114 °C[6c]), IR (KBr) 2178 (CN) and 1647 cm^{-1} (CO).

6e; yellow needles, 53%, mp 132—133 °C, IR (KBr) 2170 (CN) and 1641 cm^{-1} (CO), ^{1}H NMR ($CDCl_3$) δ = 1.26 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 2.43 (3H, s, 4-CH_3), 4.12 (2H, q, J = 7.0 Hz, $CO_2CH_2CH_3$), 7.3—7.6 (2H, almostly d, J = 6.0 Hz, 3- and 5-H), and 8.9—9.3 (2H, almostly d, J = 6.0 Hz, 2- and 6-H). Found: C, 64.60; H, 5.87; N, 13.73%. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72%.

6f; orange prisms, 51%, mp 137—138 °C, IR (KBr) 2168 (CN) and 1655 cm^{-1} (CO), ^{1}H NMR ($CDCl_3$) δ = 1.26 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 2.37 (6H, s, 3- and 5-CH_3), 4.13 (2H, q, J = 7.0 Hz, $CO_2CH_2CH_3$), 7.37 (1H, br s, 4-H), and 8.98 (2H, br s, 2- and 6-H). Found: C, 66.10; H, 6.55; N, 12.89%. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84%.

6g; orange needles, 58%, mp 159—160 °C (Lit,[6d] 143—144 °C), IR (KBr) 2166 (CN) and 1570 cm^{-1} (CO).

6h; yellow needles, 40%, mp 145—146 °C, IR (KBr) 2166 (CN) and 1562 cm^{-1} (CO), ^{1}H NMR ($CDCl_3$) δ = 2.22 (3H, s, $COCH_3$), 2.29 (3H, s, 4-CH_3), 7.3—7.6 (2H, almostly d, J = 6.0 Hz, 3- and 5-H), and 8.9—9.3 (2H, almostly d, J = 6.0 Hz, 2- and 6-H). Found: C, 68.83; H, 5.83; N, 16.38%. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08%.

6i; yellow needles, 42%, mp 145 °C, IR (KBr) 2162 (CN) and 1550 cm^{-1} (CO), ^{1}H NMR ($CDCl_3$) δ = 2.22 (3H, s, $COCH_3$), 2.44 (6H, s, 3- and 5-CH_3), 7.51 (1H, br s, 4-H), and 8.92 (2H, br s, 2- and 6-H). Found: C, 70.02; H, 6.46; N, 15.13%. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88%.

6j; yellow needles, 45%, mp 146—147 °C, IR (KBr) 2168 (CN) and 1541 cm^{-1} (CO), ^{1}H NMR ($CDCl_3$) δ = 7.1—7.8 (3H, m, 3-, 4-, 5-H, and phenyl) and 9.0—9.5 (2H, m, 2- and 6-H). Found: C, 75.77; H, 4.82; N, 12.30%. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60%.

6k; yellow needles, 37%, mp 182—184 °C, IR (KBr) 2164 (CN) and 1527 cm^{-1} (CO), ^{1}H NMR ($CDCl_3$) δ = 2.35 (3H, s, 4-CH_3), 7.1—8.0 (7H, m, 3-, 5-H, and phenyl), and 8.9—9.2 (2H, almostly d, J = 6.0 Hz, 2- and 6-H). Found: C, 76.16; H, 5.06; N, 12.00%. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86%.

6l; yellow needles, 28%, mp 159—160 °C, IR (KBr) 2164(CN) and 1537 cm^{-1} (CO), ^{1}H NMR (CDCl3) δ = 2.38 (6H, s, 3- and 5-CH_3), 7.1—8.0 (6H, m, 4-H and phenyl), and 8.87 (2H, br s, 2- and 6-H). Found: C, 76.62; H, 5.61; N, 11.38%. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19%.

9a; colorless flakes, 63%, mp 212—214 °C, IR (KBr) 1657 cm^{-1} (CO), ^{1}H NMR ($CDCl_3$) δ = 3.89 (2H, s, SCH_2), 7.6—8.3 (3H, m, 3-, 4-, and 5-H), and 8.7—9.0 (2H, m, 2- and 6-H). Found: C, 49.50; H, 3.58; N, 21.21%. Calcd for $C_8H_7N_3OS$: C, 49.73; H, 3.65; N, 21.75%.

9b; colorless needles, 69%, mp 214—215 °C, IR (KBr) 1662 cm^{-1} (CO), ^{1}H NMR ($CDCl_3$) δ = 2.70 (3H, s, 2-CH_3), 3.91 (2H,

s, SCH_2), 7.4—8.2 (3H, m, 3-, 4-, and 5-H), and 8.54 (1H, almostly d, J = 6.0 Hz, 6-H). Found: C, 52.20; H, 4.30; N, 20.52%. Calcd for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.28%.

9c; colorless needles, 80%, mp 207—208 °C, IR (KBr) 1662 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ = 2.53 (3H, s, 3-CH_3), 3.89 (2H, s, SCH_2), 7.4—8.1 (2H, m, 4- and 5-H), and 8.5—8.8 (2H, m, 2- and 6-H). Found C, 52.00; H, 4.24; N, 20.45%. Calcd for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.28%.

9d; colorless needles, 65%, mp 228—230 °C, IR (KBr) 1670 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ = 2.58 (3H, s, 4-CH_3), 3.87 (2H, s, SCH_2), 7.4—7.6 (2H, almostly d, J = 6.0 Hz, 3- and 5-H), and 8.5—8.8 (2H, almostly d, J = 6.0 Hz, 2- and 6-H). Found: C, 52.12; H, 4.29; N, 20.21%. Calcd for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.28%.

9e; colorless needles, 44%, mp 161—163 °C, IR (KBr) 1653 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ = 1.67 (3H, d, J = 7.0 Hz, SCHCH_3), 4.18 (1H, q, J = 7.0 Hz, S$CH$$CH_3$), 7.6—8.3 (3H, m, 3-, 4-, and 5-H), and 8.7—9.0 (2H, m, 2- and 6-H). Found: C, 49.98; H, 4.60; N, 19.63%. Calcd for $C_9H_9N_3OS+1/2H_2O$: C, 49.99; H, 4.66; N, 19.43%.

9f; colorless needles, 42%, mp 72—73 °C, IR (KBr) 1649 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ = 1.66 (3H, d, J = 7.0 Hz, SCHCH_3), 2.70 (3H, s, 2-CH_3), 4.18 (1H, q, J = 7.0 Hz, S$CH$$CH_3$), 7.5—8.2 (3H, m, 3-, 4-, and 5-H), and 8.52 (1H, almostly d, J = 6.0 Hz, 6-H). Found: C, 50.21; H, 5.40; N, 17.65%. Calcd for $C_{10}H_{11}N_3OS+H_2O$: C, 50.19; H, 5.48; N, 17.56%.

9g; colorless needles, 60%, mp 197—199 °C, IR (KBr) 1670 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ = 1.66 (3H, d, J = 7.0 Hz, SCHCH_3), 2.58 (3H, s, 4-CH_3), 4.17 (1H, q, J = 7.0 Hz, S$CH$$CH_3$), 7.4—7.7 (2H, almostly d, J = 6.0 Hz, 3- and 5-H), and 8.5—8.8 (2H, almostly d, J = 6.0 Hz, 2- and 6-H). Found: C, 54.24; H, 5.00; N, 18.99%. Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99%.

Reactions of Pyridinium (Unsymmetrically Substituted Cyanomethylide)s 6d,g,j with DMAD (11). General Procedures. To a solution (20 ml) in which pyridinium cyanomethylide (**6**, 2 mmol) was dissolved in various solvents, such as chloroform, acetonitrile, THF, dioxane, and DMF, DMAD (**11**, 0.312 g, 2.2 mmol) was added. The resulting mixture was allowed to react under stirring at room temperature for 1 d. The reaction solution was then concentrated at reduced pressure, and the residue was separated by column chromatography on alumina using chloroform as an eluent. The evaporation of the chloroform layers and the recrystallization from chloroform–hexane afforded dimethyl 3-cyanoindolizine-1,2-dicarboxylate (**12a**), mp 130—131 °C (Lit,[6a] 130—131.5 °C) and/or dimethyl 3-benzoylindolizine-1,2-dicarboxylate (**12b**), mp 166—167 °C (Lit,[11b] 165—166 °C) as colorless needles (See Scheme 4 for these results).

Reactions of Pyridinium Thiocyanatoacetamidates(9a—g) with Potassium *t*-Butoxide. General Procedures. An ethanolic solution (10 ml) of pyridinium thiocyanatoacetamidate (**9**, 1 mmol) and potassium *t*-butoxide (0.134 g, 1.2 mmol) was heated at 60—80 °C for 3 h. The reaction solution was concentrated at reduced pressure, and the residue was separated by column chromatography on alumina using chloroform. The evaporation of the chloroform layers and the recrystallization from chloroform–ether gave a colorless crystalline product **13**.

In the reaction of unsymmetrical 3-methylpyridinium thiocyanatoacetamidates **9c** with the base, a mixture of *N*-[2-(6- and 8-methyl-1,3,4-thiadiazolo[3,2-*a*]pyridino)]acetamidates **13c,d** was obtained in 37% yield (the ratio of **13c** to **13d** was about 1 : 2), but their separations by column chromatography were unsuccessful.

These results and some properties for *N*-[2-(1,3,4-thiadiazolo-[3,2-*a*]pyridinio)]acetamidates **13a—h** are given below.

13a; colorless needles, 26%, mp 290—293 °C, IR (KBr) 1575 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ = 2.37 (3H, s, $COCH_3$), 7.3—8.2 (3H, m, 6-, 7-, and 8-H), and 8.86 (1H, br d, J = 7.0 Hz, 5-H). Found: C, 49.43; H, 3.62; N, 21.58%. Calcd for $C_8H_7N_3OS$: C, 49.73; H, 3.65; N, 21.75%.

13b; colorless needles, 28%, mp 284—287 °C, IR (KBr) 1577 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ = 2.37 (3H, s, $COCH_3$), 2.92 (3H, s, 5-CH_3), and 7.2—8.1 (3H, m, 6-, 7-, and 8-H). Found: C, 52.33; H, 4.19; N, 20.30%. Calcd for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.28%.

13c + 13d; 37%, colorless needles, Found: C, 49.80; H, 4.63; N, 19.35%. Calcd for $C_9H_9N_3OS+1/2H_2O$: C, 49.99; H, 4.66; N, 19.43%. ^1H NMR ($CDCl_3$) δ = 2.35 (3H, s, $COCH_3$), 2.54 (3H, s, 6-CH_3), 7.3—8.1 (2H, m, 7- and 8-H), and 8.67 (1H, br s, 5-H) (**13c**). ^1H NMR ($CDCl_3$) δ = 2.35 (3H, s, $COCH_3$), 2.65 (3H, s, 8-CH_3), 7.3—8.1 (2H, m, 6- and 7-H), and 8.71 (1H, br d, J = 7.0 Hz, 5-H) (**13d**).

13e; colorless needles, 34%, mp 286—288 °C, IR (KBr) 1574 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ = 2.32 (3H, s, $COCH_3$), 2.58 (3H, s, 7-CH_3), 7.35 (1H, br d J = 7.0 Hz, 6-H), 7.71 (1H, br s, 8-H), and 8.70 (1H, d, J = 7.0 Hz, 5-H). Found: C, 51.90; H, 4.44; N, 20.48%. Calcd for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.28%.

13f; colorless needles, 38%, mp 217—219 °C, IR (KBr) 1595 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ = 1.26 (3H, t, J = 7.0 Hz, $COCH_2CH_3$), 2.63 (2H, q, J = 7.0 Hz, $COCH_2CH_3$), 7.3—8.2 (3H, m, 6-, 7-, and 8-H), and 8.85 (1H, br d, J = 7.0 Hz, 5-H). Found: C, 47.98; H, 4.87; N, 18.81%. Calcd for $C_9H_9N_3OS+H_2O$: C, 47.99; H, 4.92; N, 18.65%.

13g; colorless needles, 17%, mp 211—213 °C, IR (KBr) 1587 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ = 1.27 (3H, t, J = 7.0 Hz, $COCH_2CH_3$), 2.66 (2H, q, J = 7.0 Hz, $COCH_2CH_3$), 2.94 (3H, s, 5-CH_3), and 7.3—8.2 (3H, m, 6-, 7-, and 8-H). Found: C, 54.01; H, 4.92; N, 18.85%. Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99%.

13h; colorless needles, 23%, mp 249—251 °C, IR (KBr) 1602 cm^{-1} (CO), ^1H NMR ($CDCl_3$) 1.27 (3H, t, J = 7.0 Hz, $COCH_2CH_3$), 2.59 (3H, s, 7-CH_3), 2.64 (2H, q, J = 7.0 Hz, $COCH_2CH_3$), 7.34 (1H, br d, J = 7.0 Hz, 6-H), 7.79 (1H, br s, 8-H), and 8.68 (1H, d, J = 7.0 Hz, 5-H). Found: C, 54.08; H, 4.94; N, 19.03%. Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99%.

Independent Syntheses of *N*-[2-(1,3,4-Thiadiazolo[3,2-*a*]-pyridinio)]acylamidates. General Procedures. A chloroform suspension (20 ml) of 1-amino-2-chloropyridinium mesitylenesulfonate (**16**, 0.329 g, 1 mmol) and excess potassium thiocyanate (0.156 g, 1.5 mmol) was allowed to react in the presence of 18-crown-6 (0.7 g) at room temperature for 2 d. To the mixture an acylating agent (**7**, 1.2 mmol) and excess potassium carbonate (3 g) were added, and the resulting mixture was then stirred for an additional 2 d. The mixture was filtered and the insoluble inorganic substances which were separated were washed two times with 20 ml portions of chloroform. The combined chloroform layer was concentrated at reduced pressure, and the residue was separated by column chromatography on alumina using chloroform as an eluent. Evaporation of the solvent and recrystallization from chloroform–ether gave the corresponding *N*-[2-(1,3,4-thiadiazolo-[3,2-*a*]pyridinio)]acylamidates **13**.

In the reaction in which acetic anhydride (**17a**) was used as an acylating agent *N*-[2-(1,3,4-thiadiazolo[3,2-*a*]pyridinio)]-acetamidates (**13a**), mp 290—293 °C, was formed in 63% yield. This product was completely in accord with **13a** prepared above. The results and some properties for other products **13i—k** are given

below.

13i; colorless needles, 50%, mp 204—205 °C, IR (KBr) 1614 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ = 1.00 (3H, t, J = 7.0 Hz, $COCH_2CH_2CH_3$), 1.4—2.1 (2H, m, $COCH_2CH_2CH_3$), 2.61 (2H, t, J = 7.0 Hz, $COCH_2CH_2CH_3$), 7.3—8.2 (3H, m, 6-, 7-, and 8-H), and 8.85 (1H, br d, J = 7.0 Hz, 5-H). Found: C, 54.20; H, 5.20; N, 18.94%. Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99%.

13j; colorless needles, 80%, mp >300 °C, IR (KBr) 1593 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ = 7.4—8.1 (8H, m, 6-, 7-, 8-H, and phenyl), and 8.91 (1H, br d, J = 7.0 Hz, 5-H). Found: C, 61.09; H, 3.51; N, 16.57%. Calcd for $C_{13}H_9N_3OS$: C, 61.16; H, 3.55; N, 16.46%.

13k; colorless needles, 80%, mp 238—240 °C, IR (KBr) 1614 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ = 1.36 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 4.30 (2H, q, J = 7.0 Hz, $CO_2CH_2CH_3$), 7.3—8.2 (3H, m, 6-, 7-, and 8-H), and 8.85 (1H, br d, J = 7.0 Hz, 5-H). Found: C, 48.42; H, 3.98; N, 18.90%. Calcd for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82%.

Crystallography of *N*-[2-(5-Methyl-1,3,4-thiadiazolo[3,2-*a*]-pyridinio)]acetamidate (13b). A single crystal (0.04×0.22×0.64 mm) grown from chloroform was used for the unit-cell determinations and the data collections of a Rigaku AFC5S four-circle diffractometer, with graphite-monochromated Mo $K\alpha$ radiation (λ = 0.71069 Å). This crystal was monoclinic, space group $P2_1/n$, Z = 4 with a = 7.376 (2), b = 18.403 (3), c = 7.361 (2) Å; β = 107.41 (2)°; V = 953.4 (4) $Å^3$, and D_{calcd} = 1.444 g cm^{-3}. All calculations were performed using the TEXSAN program.[16] The structure was solved by a direct method (MITHRIL).[17] The non-hydrogen atoms were refined anisotropically and the hydrogen atoms isotropically. The final R-factors after full-matrix least-squares refinements were 0.045 for 985 observed reflections.

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