A NEW APPROACH TO IMIDAZO[1,2-a]PYRIDINE DERIVATIVES
AND THEIR APPLICATION TO THE SYNTHSES OF NOVEL

Takashi Abe, Yukihisa Okumura, Hiroyuki Suga, and Akikazu Kakehi*

Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380-8553. E-Mail: xkakehi@shinshu-u.ac.jp

Abstract – 3-[Bis(methylthio)methylene]-2(3H)-imidazo[1,2-a]pyridinones were prepared from the S-alkylation of pyridinium 1-[1-carbamoyl-1-[(methylthio)thiocarbonyl]]methylides with methyl iodide followed by the alkaline treatment of the resulting pyridinium salts. The reactions of these 3-methylene-2(3H)-imidazo[1,2-a]pyridinones with some ethyl cyano- or acyl-substituted acetates in the presence of a base did not afford the initially expected 2H-pyrano[2’,3’:4,5]imidazo[1,2-a]pyridine-2-one derivatives, but, instead of them, provided ethyl 3-[2-hydroxyimidazo[1,2-a]pyridin-3-yl]acrylates. The thermolyses of these acrylates without any solvent under reduced pressure gave the corresponding 2H-pyrano[2’,3’:4,5]imidazo[1,2-a]pyridine-2-one derivatives.

Imidazo[1,2-a]pyridine derivatives have a variety of biological activities and have attracted much attention as potential pharmaceutical and agricultural medicines. Thus, various constructive routes for this skeleton have been developed, but, the access by their methods to the suitably functionalized imidazo[1,2-a]pyridine derivatives which can readily lead to the fused one is usually difficult. In a continuation of our work on nitrogen-bridged heterocycles, we were interested in the preparation of such functionalized imidazo[1,2-a]pyridine derivatives, because we were familiar with the formation and the reaction of its 1-deaza analogue, indolizine derivative. For example, we have described that 2(3H)-indolizinones derivatives were useful precursors for the syntheses of some

Dedicated to Professor Akira Suzuki on his 80th birthday.
functionalized compounds such as 3-[bis(alkylthio)methylene]-2(3H)-indolizinones\textsuperscript{15} and 3-vinylindolizines,\textsuperscript{16} and which in turn were converted to the corresponding indolizine derivatives fused with a furan,\textsuperscript{17} pyran,\textsuperscript{18} and oxepine ring.\textsuperscript{18,19} So, we planned the preparation of 3-[bis(alkylthio)methylene]-2(3H)-imidazo[1,2-a]pyridinone (A, see Figure 1) as a potential precursor for a novel heterocycle, 2H-pyran[2',3':4,5]imidazo[1,2-a]pyridine-2-one. However, the brief survey of the literature\textsuperscript{20} disclosed its inaccessibility from the potential precursor, 3-[mercapto(alkylthio)methylene]-2(3H)-imidazo[1,2-a]pyridine (B), because this molecule behaved as its enolic tautomer, alkyl 2-hydroxyimidazo[1,2-a]pyridine-3-dithiocarboxylate (B'), and afforded only the O-alkylated product (C). We next looked for an alternative method for the preparation of such molecules and developed a new one for them in which the higher acidity of the amide proton in 1-(1-carbamoylvinyl)pyridinium salt (D) was utilized for the construction of the imidazole ring. In this paper, we report the preparation of 3-[bis(methylthio)methylene]-2(3H)-imidazo[1,2-a]pyridinones and their reaction with activated ethyl acetates to provide novel pyrano[2',3':4,5]imidazo[1,2-a]pyridine derivatives via the thermolyses of the resulting ethyl 3-(2-hydroxyimidazo[1,2-a]pyridin-3-yl)acrylates.

![Figure 1](image_url)

**RESULTS AND DISCUSSION**

**Preparations of 3-methylene-2(3H)-imidazo[1,2-a]pyridinones (4).** Since an amide proton has higher acidity than that of normal amino protons, we thought that the desired 3-methylene-2(3H)-imidazo[1,2-a]pyridinone derivatives such as 4 could be obtained by the deprotonation of the carbamoyl group in the corresponding 1-[1-carbamoylvinyl]pyridinium halides (3) with a base, followed by the attack of the resulting imide ion to the 2-position of the pyridine ring and the dehydrogenation of the primary bicycloadducts. In fact, although the treatment of the 1-[1-carbamoyl-2,2-bis(methylthio)-vinyl]pyridinium iodides (3a—c), readily obtainable from the reactions of pyridinium 1-[1-carbamoyl-1-[(methylthio)thiocarbonyl]]methylides (2a—c) with methyl iodide, with a comparatively weak base such
as DBU, triethylamine, or potassium carbonate did not afford the desired 3-[bis(methylthio)methylene]-
2(3H)-imidazo[1,2-a]pyridinone derivatives (4a—c) at all, the use of a stronger base such as potassium
t-butoxide in ethanol (method A) or in DMF (method B) gave the corresponding products 4a—c in
moderate yields (21—51%) as orange to reddish crystals. Interestingly, in the reaction of unsymmetrical
3-methylpyridinium iodide (3b) only the 8-methyl derivative 4b was obtained, while the alternative
6-methyl one 4b' was not. In general, it is well known that the attack at the 2-position of the pyridine
ring in the cyclization and the cycloaddition reactions of the 3-substituted pyridinium ylides or salts in the
ground state is preferred over that at the 6-position, but the observation of the exclusive mode at the
2-position is rare. These results are shown in Scheme 1.

The structural assignment of these compounds (4a—c) was accomplished mainly from physical and spectral
means, and confirmed by the X-ray analysis of one compound 4c. For example, elementary analyses of
compound (4a—c) were in good accord with the compositions of our proposed structures. The IR
spectra of these compounds showed a strong carbonyl absorption band near 1630 cm⁻¹, indicating the
contribution of a similar polarized structure as observed in 3-methylene-2(3H)-indolizinones (near
1600 cm⁻¹). ¹H-NMR spectra of 4a—c showed two

![Scheme 1](image)

Figure 2. ORTEP drawing of 4c
methylthio proton signals at separate positions (δ 2.47—2.50 and 2.67—2.69) as each singlet due to their magnetic nonequivalence. These values showed distinctly that both methyl groups are attached to the sulfur atom but not to the oxygen atom. Furthermore, that the product from the 3-methylpyridinium salt 3b was the 8-methyl derivative 4b was clearly showed by the presence of the vicinal ABC pattern signals in the 1H-NMR spectra. The numbers for the sp2- and sp3-carbons in their 13C-NMR spectra of 4a—c were well in accord with those of our proposed structures. Finally, the X-ray analysis of one compound 4c was carried out and the structure was confirmed. The ORTEP drawing24 of 4c is shown in Figure 2.

Preparation of ethyl 3-[2-hydroxyimidazo[1,2-a]pyridin-3-yl]acrylates (6) and their transformation to 2H-pyrano[2′,3′:4,5]imidazo[1,2-a]pyridine-2-ones (7). In imitation of our previous syntheses of pyrano[2,3-b]indolizines,15 the reactions of 4a—c with some activated ethyl acetates were investigated. However, these reactions of 4a—c with ethyl cyanoacetate (5a), diethyl malonate (5b), ethyl benzoylecetate (5c), and ethyl acetoacetate (5d) under various conditions did not afford the expected 2H-pyrano[2′,3′:4,5]imidazo[1,2-a]pyridin-2-one derivatives (7a—l) at all. Instead of them, many of these reactions formed ethyl 3-[2-hydroxyimidazo[1,2-a]pyridin-3-yl]acrylates. For example, when the reactions of 4a—c with 5a—c were carried out in the presence of potassium t-butoxide in t-butanol (method C) at room temperature, the smooth evolution of methanethiol was observed and the corresponding acrylate derivatives 6a—i were isolated in 55—98% yields from the reaction mixtures. On the other hand, similar reactions of 4a, b and 5d gave only complex mixtures and any significant products such as 6j, k could not be isolated from them, though the reaction of 4c with 5d afforded the normal product 6l in 75% yield. The same products 6c, l were obtained from the reactions of 4c with 5a, d in the presence of DBU in chloroform (method D) at room temperature in 62 and 75% yields respectively, but the application of method D to the reactions of 4a, b and 5d did not give good results.

Since we failed to obtain directly 2H-pyrano[2′,3′:4,5]imidazo[1,2-a]pyridin-2-one derivatives (7) from the reactions of 2(3H)-imidazo[1,2-a]pyridinones (4) and acetates 5, we next examined the elimination of ethanol from acrylates 6a—i, l obtained. Heating of acrylates 6a—i, l in various solvents or treatment with acetic acid or concentrated sulfuric acid did not provide the condensation products 7a—i, l. However, when acrylates 6a—h were heated without any solvent at reduced pressure (3 torr), the eliminations smoothly occurred to give the expected products 6a—h in 21—73% yields. On the other hand, similar treatment of 6i, l did not provide the corresponding products 7i, l, but 4-unsubstituted 7i’ and 3-unsubstituted 2H-pyrano[2′,3′:4,5]imidazo[1,2-a]pyridine-2-one derivatives (7i’) were formed in 34 and 16% yields, respectively. These results are shown in Scheme 2.

The elementary analyses of compounds 6a—i, l were in good accord with our postulated structures. The IR spectra of 6a—i, l exhibited characteristic absorption bands at 3406—3447 cm−1 and at 1608—1651 cm−1 due to the presences of the 2-hydroxy and the 3-vinyl groups respectively. Each 1H-NMR spectra
showed only one set of proton signals for 6a–i,l. Similarly, any signals of mixture were not observed in the $^{13}$C-NMR spectra of unsymmetrical acrylates 6g–i. This fact suggested that compounds 6a–i,l are the sole products, and not cis-trans mixtures in the relation of the 3-vinyl group, though we could not
determined their E/Z configurations for 6a–c,g–i,l because of the tetra-substituted mode. In addition,
the presences of one methylthio signal at $\delta$ 1.94–2.58 (3H, s) and one or two ethoxycarbonyl signals at $\delta$
0.95–1.27 (3H, t) and 3.86–4.18 (2H, q) in compounds 6a–i,l were also indicated, together with
protons and methyl group(s) on the pyridine ring. On the other hand, each proton signal for the
2-hydroxy group in 6a–i was not shown, but this must be due to the broadening of the signal because
one sp$^3$-carbon signal which should appear in its tautomeric 2(3H)-imidazo[1,2-a]pyridinone structure did
not appear in the $^{13}$C-NMR spectra. Judging from these data and their smooth transformation to
subsequent elimination products 7a–h,i,l', we concluded 6a–i,l to be ethyl 3-[2-hydroxymidazo-
[1,2-a]pyridin-3-yl]acrylates.

Similarly, compounds 7a–h afforded satisfactory elemental analyses and their $^1$H-NMR spectra
demonstrated clearly the disappearance of an ethoxy group from the precursors 6a–h. However, the
analyses for 7i',l' exhibited formulas C$_{19}$H$_{14}$N$_{2}$O$_{3}$ and C$_{13}$H$_{12}$N$_{2}$O$_{2}$S respectively and they were not in
accord with our initially expected compositions (C_{20}H_{16}N_{2}O_{3}S and C_{15}H_{14}N_{2}O_{3}S).  \textsuperscript{1}H-NMR spectral analyses of 7i',l' provided a solution for the structural question, that is, the loss of a methylthio or an acetyl group from the initially formed 7i,l and the appearance of a new olefinic proton at the 4- (7i') or 3-position (7l') were shown. These findings suggested that the cyclization products 7i,l underwent a further elimination reaction under the conditions employed here to give the observed ones 7i',l', though the detailed mechanisms for them is unclear. Finally, one (7d) of this type of compound was subjected to X-ray analysis and the skeleton was completely confirmed to be 2\textit{H}-pyrano[2',3':4,5]imidazo[1,2-\textit{a}]pyridin-2-one. The ORTEP drawing of 7d is shown in Figure 3.\textsuperscript{24}

**Reaction Mechanisms.** Possible mechanisms are shown in Scheme 3. As described above, 3-methylene-2(3\textit{H})-imidazo[1,2-\textit{a}]pyridinones (4a–c) can be created by the intramolecular nucleophilic cyclization of the imide ion 8, generated by the proton abstraction from the comparatively acidic carbamoyl group of pyridinium salts (3a–c), to the 2-position on the pyridine ring, followed by the dehydrogenation of the primary bicycloadducts 9. The production of ethyl 3-[2-hydroxyimidazo[1,2-\textit{a}]pyridin-3-yl]acrylates (6a–i,l) can be explained by the nucleophilic attack of the carbanion 10, produced in situ by the treatment of active methylene compounds 5a–d with a base, to the electron-poor 3(1)-methylene carbon in 4a–c, followed by the elimination of a methylthio anion from the resulting adduct 11 and the 1,5-shift of a hydrogen atom from the 3(2)-position to the 2-carbonyl oxygen in intermediates 12. Although the reason why the transformation from 6a–i,l to 7a–i,l was ineffective on heating in a solvent or by treatment with an acid or a base is still uncertain, the route from 6a–i,l to pyranoimidazopyridines (7a–i,l) should proceed via the nucleophilic addition of the lone pair electrons of the 2-hydroxy oxygen to the ester carbonyl carbon attached with the 3-vinyl group and subsequent elimination of a molecule of ethanol.

**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 \textsuperscript{1}H-NMR and
13C-NMR spectra were determined with a JEOL JNM-LA400 (1H: 400 MHz and 13C: 100.4 MHz) spectrometer in deuteriochloroform25 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.

Materials. 1-(Carbamoylmethyl)pyridinium chloride (1a—c) were prepared in good yields from the reaction of pyridine, 3-methylpyridine, and 3,5-dimethylpyridine with α-chloroacetamide in acetone according to the literature.26 Some physical and spectral data for the new compound 1c are as follows: 1-Carbamoylmethyl-3,5-dimethylpyridinium chloride (1c); 80%, colorless prisms, mp 250—253 °C (from CHCl3-hexane), IR (KBr) ν 1682, 3086, 3244 cm⁻¹. 1H-NMR δ: 2.59 (6H, s, 3- and 5-H), 5.68 (1H, br, NH), 5.82 (2H, s, NCH2), 8.04 (1H, br s, 4-H), 8.95 (2H, br s, 2- and 6-H), 9.66 (1H, br, NH). Anal. Calcd for C9H13ClN2O: C, 53.87; H, 6.53; N, 13.96. Found: C, 53.78; H, 6.43; N, 14.15.

Pyridinium 1-(1-carbamoyl)[1-methylthio(thiocarbonyl)]methylides 2a—c were prepared from the treatment of a mixture of pyridinium salts 1a—c, carbon disulfide, and dimethyl sulfate with aqueous sodium hydroxide, according to the procedure described by Tominaga et al.27 Some data for new pyridinium methylides 2b,c are as follows: 3-Methylpyridinium 1-(1-carbamoyl)-
[1-methylthio(thiocarbonyl)]methylide (2b), 56%, yellow prisms, mp 179—180 °C (from CHCl₃-hexane). IR (KBr): ν 1631, 3243, 3293 cm⁻¹. ¹H-NMR δ: 2.48 (3H, s, SMe), 2.58 (3H, s, 3-Me), 5.53 (1H, br, NH), 7.79 (1H, dd, J=8.0, 6.1 Hz, 5-H), 8.19 (1H, br d, J=8.0 Hz, 4-H), 8.29 (1H, br s, 2-H), 8.30 (1H, br d, J=6.1 Hz, 6-H), 10.69 (1H, br, NH). ¹³C-NMR δ: 16.67, 18.62, 126.34, 126.41, 138.20, 145.06, 146.57, 148.89, 165.11, 178.18. Anal. Calcd for C₁₀H₁₂N₂O₃S₂: C, 49.97; H, 5.03; N, 11.66. Found: C, 49.73; H, 5.27; N, 11.66.

3,5-Dimethylpyridinium 1-(1-carbamoyl)[1-methylthio(thiocarbonyl)]methylide (2c), 45%, yellow prisms, mp 199—200 °C (from CHCl₃-hexane). IR (KBr): ν 1631, 3244, 3281 cm⁻¹. ¹H-NMR δ: 2.48 (3H, s, SMe), 2.53 (6H, s, 2-, 6-Me), 5.53 (1H, br, NH), 7.98 (1H, br s, 4-H), 8.49 (2H, br s, 2-, 6-H), 10.70 (1H, br, NH). ¹³C-NMR δ: 16.68, 18.49, 126.36, 137.51, 145.82, 146.19, 165.22, 178.02. Anal. Calcd for C₁₁H₁₄N₂O₃S₂: C, 51.94; H, 5.55; N, 11.01. Found: C, 51.88; H, 5.59; N, 10.91.

Preparations of 3-[bis(methylthio)methylene]-2(3H)-imidazo[1,2-a]pyridinones (4a—c). General Method. The mixture of pyridinium methylide (2, 10 mmol) and methyl iodide (1.846 g, 13 mmol) in acetone (20 mL) was stirred at room temperature for 1 day. The precipitates of pyridinium salt 3 which separated were collected by suction and washed with acetone (20 mL). Without further purification, the salt 3 was treated with potassium t-butoxide (1.346 g, 12 mmol) in ethanol (25 mL, Method A) or DMF (25 mL, Method B) at room temperature and stirred for the time given in the description for each product. The resulting solution was concentrated under reduced pressure at a temperature below 30 °C. The residue was then separated by column chromatography on alumina using CHCl₃ as an eluent. The yellow to orange layers which eluted first were collected and the combined solution was concentrated under reduced pressure. The recrystallization from CHCl₃-Et₂O provided the corresponding product 4.

In these reactions the use of other bases such as DBU, triethylamine, or potassium carbonate did not provide the desired 2(3H)-imidazo[1,2-a]pyridinone derivative (4) at all. Furthermore, the formation of an alternative 6-methyl derivative 4b' in the alkaline treatment of unsymmetrical 3-methylpyridinium salt 3b could not be detected.

3-[Bis(methylthio)methylene]-2(3H)-imidazo[1,2-a]pyridinones (4a): From 2a, 21% (Method A, reaction time 5 h) or 24% (Method B, reaction time 5 h), orange prisms, mp 142—143 °C. IR (KBr): ν 1610 cm⁻¹. ¹H-NMR δ: 2.48 and 2.68 (each 3H, s, SMe), 6.64 (1H, ddd, J=7.0, 7.0, 1.4 Hz, 6-H), 7.14 (1H, br d, J=9.0 Hz, 8-H), 7.44 (1H, ddd, J=9.0, 7.0, 1.4 Hz, 7-H), 8.93 (1H, br d, J=7.0 Hz, 5-H). ¹³C-NMR δ: 19.63, 20,72, 110.45, 116.04, 124.46, 130.19, 137.52, 152.34, 160.91, 170.84. Anal. Calcd for C₁₀H₁₀N₂O₂S: C, 50.39; H, 4.23; N, 11.75. Found: C, 50.17; H, 4.37; N, 12.01.

3-[Bis(methylthio)methylene]-8-methyl-2(3H)-imidazo[1,2-a]pyridinones (4b): From 2b, 38% (Method A, reaction time 4 h), red prisms, mp 149—151 °C. IR (KBr): ν 1630 cm⁻¹. ¹H-NMR δ:
2.38 (3H, s, 8-Me), 2.50 and 2.69 (each 3H, s, SMe), 6.57 (1H, t, J=7.0, 6-H), 7.25 (1H, br d, J=7.0 Hz, 7-H), 8.79 (1H, br d, J=7.0 Hz, 5-H). \(^{13}\)C-NMR δ: 17.13, 19.58, 20.66, 110.25, 124.88, 125.80, 127.46, 135.69, 151.72, 160.97, 170.85.  

Anal. Calcd for C\(_{11}\)H\(_{12}\)N\(_2\)OS\(_2\): C, 52.35; H, 4.79; N, 11.10. Found: C, 52.40; H, 4.82; N, 11.03.

3-[Bis(methylthio)methylene]-6,8-dimethyl-2(3H)-imidazo[1,2-a]pyridinones (4c): From 2c, 51% (Method A, reaction time 2 h) or 30% (Method B, reaction time 4 h), red prisms, mp 209—211 °C. IR (KBr): \(\tilde{\nu}\) 1630 cm\(^{-1}\). \(^{1}H\)-NMR δ: 2.23 (3H, s, 6-Me), 2.37 (3H, s, 8-Me), 2.47 and 2.67 (each 3H, s, SMe), 7.13 (1H, br s, 7-H), 8.57 (1H, br s, 5-H). \(^{13}\)C-NMR δ: 17.19, 18.07, 19.70, 21.02, 119.77, 125.19, 125.27, 125.54, 138.62, 151.25, 160.11, 171.04. Anal. Calcd for C\(_{12}\)H\(_{14}\)N\(_2\)OS\(_2\): C, 51.94; H, 5.55; N, 11.01. Found: C, 51.88; H, 5.59; N, 10.91.

### Preparations of ethyl 3-[2-hydroxy-2(3H)-imidazo[1,2-a]pyridin-3-yl]acrylates (6a—l).

**General method.** A mixture of 3-[bis(methylthio)methylene]-2(3H)-imidazo[1,2-a]pyridinone (4, 1 mmol) and an active methylene compound (5, 1.2 mmol) was stirred with potassium \(t\)-butoxide (0.135 g, 1.2 mmol) in \(t\)-BuOH (30 mL) (method C) or with DBU (0.182 g, 1.2 mmol) in CHCl\(_3\) (30 mL) (Method D) 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 CHCl\(_3\)-EtOH (9:1) as an eluent. The yellow layers were collected and the combined solution was concentrated under reduced pressure. Recrystallization of the crude product from EtOH afforded the corresponding ethyl 3-[2-hydroxyimidazo[1,2-a]pyridine-3-yl]-acrylates (6a—l).

The reactions of 2(3H)-imidazo[1,2-a]pyridinones 4a,b with ethyl acetoacetate (5d) gave complex mixtures and the isolation of significant products such as 6j,k from them was unsuccessful. Some physical and spectral data for these products 6a—l are shown below.

**Ethyl 2-cyano-3-(2-hydroxyimidazo[1,2-a]pyridin-3-yl)-3-(methylthio)acrylate (6a):** From 4a and ethyl cyanoacetate (5a), 68% (Method C, reaction time 6 h), yellow needles, mp 260—263 °C. IR (KBr): \(\tilde{\nu}\) 1651, 1685, 2199, 3412 cm\(^{-1}\). \(^{1}H\)-NMR δ: 1.27 (3H, br, O\(\text{CH}_2\text{CH}_3\)), 4.17 (2H, br, O\(\text{CH}_2\text{CH}_3\)), 7.10 (1H, br t, J=6.8, 6.8 Hz, 6-H), 7.46 (1H, br d, J=8.5 Hz, 8-H), 7.53 (1H, br q, J=8.5, 6.8 Hz, 7-H), 8.03 (1H, br d, J=6.8 Hz, 5-H). Anal. Calcd for C\(_{14}\)H\(_{14}\)N\(_2\)O\(_3\)S: C, 55.43; H, 4.32; N, 13.85. Found: C, 55.46; H, 4.24; N, 13.91.

**Ethyl 2-cyano-3-(2-hydroxy-8-methylimidazo[1,2-a]pyridin-3-yl)-3-(methylthio)acrylate (6b):** From 4b and 5a, 72% (Method C, reaction time 3 h), yellow needles, mp 284—287 °C. IR (KBr): \(\tilde{\nu}\) 1620, 1705, 2203, 3425 cm\(^{-1}\). \(^{1}H\)-NMR δ: 1.27 (3H, br, O\(\text{CH}_2\text{CH}_3\)), 2.50 (3H, br s, SMe), 2.58 (3H, br s, 8-Me), 4.18 (2H, br, O\(\text{CH}_2\text{CH}_3\)), 7.02 (1H, br t, J=6.8, 6.8 Hz, 6-H), 7.53 (1H, br d, J=6.8 Hz, 5-H), 7.99
(1H, br d, J=6.8 Hz, 5-H). Anal. Calcd for C_{15}H_{15}N_{3}O_{3}S+1/2C_{2}H_{5}OH: C, 56.46; H, 5.33; N, 12.34. Found: C, 56.64; H, 5.04; N, 12.59.

**Ethyl 2-cyano-3-(2-hydroxy-6,8-dimethylimidazo[1,2-a]pyridin-3-yl)-3-(methylthio)acrylate (6c):** From 4c and 5a, 55% (Method C, reaction time 15 h) or 62% (Method D, reaction time 15 h), yellow needles, mp 299—302 °C. IR (KBr): ν 1633, 1693, 2200, 3437 cm⁻¹. ¹H-NMR δ: 1.26 (3H, br, OCH₂CH₃), 2.33 (3H, br s, 6-Me), 2.50 (3H, br s, 8-Me), 2.53 (3H, br s, SMe), 4.18 (2H, br, OCH₂CH₃), 7.17 (1H, br s, 7-H), 7.75 (1H, br s, 5-H). Anal. Calcd for C_{16}H_{17}N_{3}O_{3}S: C, 57.99; H, 5.17; N, 12.68. Found: C, 57.99; H, 5.17; N, 12.69.

**Diethyl [1-(2-hydroxyimidazo[1,2-a]pyridin-3-yl)-1-(methylthio)methylene]malonate (6d):** From 4a and diethyl malonate (5b), 55% (Method C, reaction time 15 h) or 62% (Method D, reaction time 15 h), yellow needles, mp 64—66 °C. IR (KBr): ν 1616, 1651, 1718, 3404 cm⁻¹. ¹H-NMR δ: 1.18 (6H, t, J=7.1 Hz, 2×OCH₂CH₃), 2.16 (3H, s, SMe), 4.17 (4H, q, J=7.1 Hz, 2×OCH₂CH₃), 6.97 (1H, br t, J=6.8 Hz, 6-H), 7.33 (1H, br q, J=8.8 Hz, 7-H), 7.43 (1H, br d, J=8.8 Hz, 8-H), 8.05 (1H, br d, J=6.8 Hz, 5-H). ¹³C-NMR δ: 13.97, 15.71, 60.99, 97.01, 109.87, 114.40, 120.04, 124.52, 127.26, 135.59, 146.83, 156.88, 164.34. Anal. Calcd for C_{16}H_{18}N_{2}O_{5}S: C, 54.84; H, 5.18; N, 7.99. Found: C, 54.54; H, 5.29; N, 8.28.

**Diethyl [1-(2-hydroxy-8-methylimidazo[1,2-a]pyridin-3-yl)-1-(methylthio)methylene]malonate (6e):** From 4b and (5b), 55% (Method C, reaction time 15 h) or 62% (Method D, reaction time 15 h), yellow needles, mp 95—98 °C. IR (KBr): ν 1608, 1638, 1697, 3423 cm⁻¹. ¹H-NMR δ: 1.18 (6H, t, J=7.1 Hz, 2×OCH₂CH₃), 2.18 (3H, s, SMe), 2.57 (3H, s, 8-Me), 4.17 (4H, q, J=7.1 Hz, 2×OCH₂CH₃), 6.88 (1H, t, J=7.0 Hz, 6-H), 7.13 (br d, J=7.0 Hz, 7-H), 7.96 (1H, br d, J=7.0 Hz, 5-H). ¹³C-NMR δ: 14.05, 15.72, 16.38, 60.94, 97.57, 114.06, 119.58, 120.81, 122.54, 127.17, 136.47, 147.47, 157.29, 164.49. Anal. Calcd for C_{17}H_{20}N_{2}O_{5}S: C, 56.03; H, 5.53; N, 7.69. Found: C, 55.93; H, 5.71; N, 7.61.

**Diethyl [1-(2-hydroxy-6,8-dimethylimidazo[1,2-a]pyridin-3-yl)-1-(methylthio)methylene]malonate (6f):** From 4c and (5b), 84% (Method C, reaction time 15 h) or 62% (Method D, reaction time 15 h), yellow needles, mp 182—185 °C. IR (KBr): ν 1610, 1705, 3447 cm⁻¹. ¹H-NMR δ: 1.17 (6H, t, J=7.1 Hz, 2×OCH₂CH₃), 2.17 (3H, s, SMe), 2.29 (3H, s, 6-Me), 2.51 (3H, s, 8-Me), 4.15 (4H, q, J=7.1 Hz, 2×OCH₂CH₃), 6.97 (1H, br s, 7-H), 7.75 (1H, br s, 6-Me). Anal. Calcd for C_{18}H_{22}N_{2}O_{5}S: C, 57.13; H, 5.86; N, 7.40. Found: C, 57.19; H, 5.87; N, 7.33.

**Ethyl 2-benzoyl-3-(2-hydroxyimidazo[1,2-a]pyridin-3-yl)-3-(methylthio)acrylate (6g):** From 4a and ethyl benzoylecetate (5c), 73% (Method C, reaction time 3 h), red prisms, mp 260—263 °C. IR (KBr): ν 1624, 1653, 1701, 3406 cm⁻¹. ¹H-NMR δ: 1.07 (3H, t, J=7.1 Hz, OCH₂CH₃), 2.02 (3H, s, SMe), 4.12 (2H, q, J=7.1 Hz, OCH₂CH₃), 7.05 (1H, t, J=6.9 Hz, 6-H), 7.31—7.47 (5H, m, 7-, 8-H, Phenyl-H),
7.86—7.91 (2H, m, Phenyl-H), 8.29 (1H, br d, J=6.9 Hz, 5-H). $^{13}$C-NMR δ: 14.09, 15.73, 60.78, 97.76, 109.86, 114.68, 124.46, 126.34, 127.39, 128.06, 128.53, 132.32, 135.70, 137.84, 145.49, 157.31, 164.24, 193.20. Anal. Calcd for C$_{20}$H$_{18}$N$_{2}$O$_{4}$S: C, 62.81; H, 4.74; N, 7.33. Found: C, 62.77; H, 5.04; N, 7.07.

**Ethyl 2-benzoyl-3-(2-hydroxy-8-methylimidazo[1,2-a]pyridin-3-yl)-3-(methylthio)acrylate (6h):**

From 4b and 5c, 98% (Method C, reaction time 17 h), red prisms, mp 209—212 °C. IR (KBr): ν 1618, 1638, 1661, 1719, 3429 cm$^{-1}$. $^1$H-NMR δ: 1.05 (3H, t, J=7.1 Hz, OCH$_2$CH$_3$), 1.94 (3H, s, SMe), 2.48 (3H, s, 8-Me), 4.10 (2H, q, J=7.0 Hz, OCH$_2$CH$_3$), 6.92 (1H, t, J=7.0, 6-H), 7.13 (1H, br d, J=7.0 Hz, 7-H), 7.31—7.37 (2H, m, Ph-H), 7.41—7.47 (1H, m, Ph-H), 7.99—8.04 (2H, m, Ph-H), 8.30 (1H, br d, J=6.8 Hz, 5-H). $^{13}$C-NMR δ: 14.11, 15.51, 16.13, 60.63, 98.20, 114.65, 120.50, 122.35, 126.52, 127.40, 128.01, 128.87, 132.33, 135.95, 137.87, 144.02, 157.76, 164.25, 193.66. Anal. Calcd for C$_{21}$H$_{20}$N$_{2}$O$_{4}$S: C, 63.62; H, 5.08; N, 7.07. Found: C, 63.53; H, 5.16; N, 7.08.

**Ethyl 2-benzoyl-3-(2-hydroxy-6,8-dimethylimidazo[1,2-a]pyridin-3-yl)-3-(methylthio)acrylate (6i):**

From 4c and 5c, 78% (Method C, reaction time 17 h), red prisms, mp 234—236 °C. IR (KBr): ν 1616, 1660, 1712, 3409 cm$^{-1}$. $^1$H-NMR δ: 1.05 (3H, t, J=7.1 Hz, OCH$_2$CH$_3$), 1.94 (3H, s, SMe), 2.32 (3H, s, 6-Me), 2.41 (3H, s, 8-Me), 4.10 (2H, q, J=7.1 Hz, OCH$_2$CH$_3$), 7.15 (1H, br s, 7-H), 7.30—7.37 (2H, m, Ph-H), 7.39—7.47 (1H, m, Ph-H), 7.97—8.04 (2H, m, Ph-H), 8.09 (1H, br s, 5-H). $^{13}$C-NMR δ: 14.11, 15.32, 15.50, 16.13, 60.63, 98.22, 114.62, 120.55, 122.35, 126.59, 126.93, 127.35, 128.01, 128.90, 132.32, 136.04, 137.89, 144.00, 157.78, 164.24, 193.63. Anal. Calcd for C$_{22}$H$_{22}$N$_{2}$O$_{4}$S: C, 64.37; H, 5.40; N, 6.82. Found: C, 64.51; H, 5.42; N, 6.68.

**Ethyl 2-acetyl-3-(2-hydroxy-6,8-dimethylimidazo[1,2-a]pyridin-3-yl)-3-(methylthio)acrylate (6l):**

From 4c and 5c, 78% (Method C, reaction time 17 h), red prisms, mp 234—236 °C. IR (KBr): ν 1616, 1660, 1712, 3409 cm$^{-1}$. $^1$H-NMR δ (DMSO-$d_6$): 0.95 (3H, t, J=7.1 Hz, OCH$_2$CH$_3$), 2.08 (3H, s, SMe), 2.09 (3H, s, 6-Me), 2.22 (3H, s, 8-Me), 2.23 (3H, s, COMe), 4.10 (2H, q, J=7.1 Hz, OCH$_2$CH$_3$), 7.09 (1H, br s, 7-H), 8.17 (1H, br s, 5-H), 8.24 (1H, s, OH). Anal. Calcd for C$_{17}$H$_{20}$N$_{2}$O$_{4}$S: C, 64.37; H, 5.40; N, 6.82. Found: C, 64.51; H, 5.42; N, 6.68.

**Preparation of 2$H$-pyrano[2’3’:4,5]imidazo[1,2-a]pyridine-2-ones (7a-h,i,l). General method.**

Ethyl 3-(2-hydroxyimidazo[1,2-a]pyridin-3-yl)-3-(methylthio)acrylate (6, 0.5 mmol) without any solvent was put in a test tube equipped with a vacuum system, and the tube was heated by an electronic furnace under reduced pressure (3 torr) at the reaction temperature and for the time described for each compound 7a—h,i,l. The resulting reaction mixture was dissolved in as small amount of CHCl$_3$ as possible and the solution was separated by column chromatography on silica gel using CHCl$_3$-EtOH (9:1). The yellow fractions which eluted first were combined and concentrated under reduced pressure. The
recrystallization of the residue from CHCl$_3$-Et$_2$O afforded the corresponding 2H-pyrano[2’,3’:4,5]imidazo[1,2-a]pyridine-2-one derivative (7).

First we examined the syntheses of these compounds 7a—i,l by the reactions of ethyl 3-[2-hydroxyimidazo[1,2-a]pyridine-3-yl]acrylates (6a—i,l) under various reaction conditions (for example, heating at 80 °C in DMF in the presence of a base such as potassium t-butoxide, heating at 80 °C in acetic acid, and treatment with concentrated sulfuric acid at room temperature), but the expected 2H-pyrano[2’,3’:4,5]imidazo[1,2-a]pyridine-2-ones (7a—i,l) could not be obtained at all.

Some physical and spectral data for these products 7a—h,i',l' are shown below.

4-Methylthio-2-oxo-2H-pyrano[2’,3’:4,5]imidazo[1,2-a]pyridine-3-carbonitrile (7a): From 6a, 21% (reaction temperature 75 °C, time 15 min), yellow needles, mp 266—270 °C. IR (KBr): $\nu$ 1715, 2216 cm$^{-1}$. $^1$H-NMR $\delta$: 3.11 (3H, s, SMe), 7.23 (1H, ddd, $J=7.0, 7.0, 1.4$ Hz, 7-H), 7.67 (1H, ddd, $J=9.0, 7.0, 1.2$ Hz, 8-H), 7.79 (1H, br d, $J=9.0$ Hz, 9-H), 9.17 (1H, br d, $J=7.0$ Hz, 6-H). Anal. Calcd for C$_{12}$H$_{17}$N$_3$O$_2$: C, 56.02; H, 2.74; N, 16.33. Found: C, 56.20; H, 2.79; N, 16.11.

9-Methyl-4-methylthio-2-oxo-2H-pyrano[2’,3’:4,5]imidazo[1,2-a]pyridine-3-carbonitrile (7b): From 6b, 50% (reaction temperature 150 °C, time 10 min), yellow needles, mp 287—291 °C. IR (KBr): $\nu$ 1705, 2214 cm$^{-1}$. $^1$H-NMR $\delta$: 2.65 (3H, s, 9-Me), 3.09 (3H, s, SMe), 7.12 (1H, t, $J=7.0$, 7-H), 7.46 (1H, br d, $J=7.0$ Hz, 8-H), 9.02 (1H, br d, $J=7.0$ Hz, 6-H). Anal. Calcd for C$_{13}$H$_{9}$N$_3$O$_2$: C, 57.55; H, 3.34; N, 15.49. Found: C, 57.44; H, 3.26; N, 15.69.

7,9-Dimethyl-4-methylthio-2-oxo-2H-pyrano[2’,3’:4,5]imidazo[1,2-a]pyridine-3-carbonitrile (7c): From 6c, 42% (reaction temperature 200 °C, time 20 min), yellow needles, mp >300 °C. IR (KBr): $\nu$ 1667, 2212 cm$^{-1}$. $^1$H-NMR $\delta$: 2.44 (3H, s, 7-Me), 2.61 (3H, s, 9-Me), 3.08 (3H, s, SMe), 7.32 (1H, s, 8-H), 8.80 (1H, br s, 6-H). Anal. Calcd for C$_{14}$H$_{11}$N$_3$O$_2$: C, 58.93; H, 3.89; N, 14.73. Found: C, 58.63; H, 3.88; N, 15.01.

Ethyl 4-methylthio-2-oxo-2H-pyrano[2’,3’:4,5]imidazo[1,2-a]pyridine-3-carboxylate (7d): From 6d, 59% (reaction temperature 100 °C, time 15 min), yellow needles, mp 172—175 °C. IR (KBr): $\nu$ 1703 cm$^{-1}$. $^1$H-NMR $\delta$: 1.42 (3H, t, $J=7.2$ Hz, OCH$_2$CH$_3$), 2.63 (3H, s, SMe), 4.43 (2H, q, $J=7.2$ Hz, OCH$_2$CH$_3$), 7.13 (1H, ddd, $J=7.0, 7.0, 1.2$ Hz, 7-H), 7.54 (1H, ddd, $J=9.0, 7.0, 1.2$ Hz, 8-H), 7.73 (1H, br d, $J=9.0$ Hz, 9-H), 9.17 (1H, br d, $J=7.0$ Hz, 6-H). $^{13}$C-NMR $\delta$: 14.01, 17.79, 62.31, 105.99, 112.06, 114.50, 117.71, 127.06, 129.49, 145.37, 145.83, 156.52, 157.42, 164.96. Anal. Calcd for C$_{14}$H$_{12}$N$_3$O$_4$: C, 55.25; H, 3.97; N, 9.21. Found: C, 55.25; H, 4.07; N, 9.50.

Ethyl 9-methyl-4-methylthio-2-oxo-2H-pyrano[2’,3’:4,5]imidazo[1,2-a]pyridine-3-carboxylate (7e): From 6e, 65% (reaction temperature 100 °C, time 20 min), yellow needles, mp 164—167 °C. IR (KBr): $\nu$ 1709 cm$^{-1}$. $^1$H-NMR $\delta$: 1.42 (3H, t, $J=7.2$ Hz, OCH$_2$CH$_3$), 2.61 (3H, s, 8-Me), 2.62 (3H, s, SMe), 4.43
(2H, q, $J$=7.2 Hz, OCH$_2$CH$_3$), 7.05 (1H, t, $J$=7.0, 7.0 Hz, 7-H), 7.35 (br d, $J$=7.0 Hz, 8-H), 9.01 (1H, br d, $J$=7.0 Hz, 6-H). $^{13}$C-NMR δ: 14.12, 17.00, 17.91, 62.32, 106.41, 112.16, 114.41, 124.73, 128.05, 128.58, 145.31, 146.05, 156.33, 157.50, 164.85. Anal. Calcd for C$_{15}$H$_{14}$N$_2$O$_4$S: C, 56.59; H, 4.43; N, 8.80. Found: C, 56.52; H, 4.34; N, 8.97.

**Ethyl 7,9-dimethyl-4-methylthio-2-oxo-2$H$-pyrano[2',3':4,5]imidazo[1,2-$a$]pyridine-3-carboxylate (7f):** From 6f, 73% (reaction temperature 100 °C, time 90 min), yellow needles, mp 181—184 °C. IR (KBr): $\nu$ 1693 cm$^{-1}$. $^1$H-NMR δ: 1.42 (3H, t, $J$=7.1 Hz, OCH$_2$CH$_3$), 2.41 (3H, s, 7 -Me), 2.60 (3H, s, 9-Me), 2.62 (3H, s, SMe), 4.43 (2H, q, $J$=7.1 Hz, OCH$_2$CH$_3$), 7.21 (1H, br s, 8-H), 8.81 (1H, br s, 6-Me). $^{13}$C-NMR δ: 14.14, 16.89, 17.91, 18.61, 62.29, 106.33, 111.76, 122.71, 124.37, 127.17, 131.63, 144.97, 145.37, 145.37, 156.28, 157.58, 165.01. Anal. Calcd for C$_{16}$H$_{26}$N$_2$O$_4$S: C, 57.82; H, 4.85; N, 8.43. Found: C, 57.78; H, 4.78; N, 8.54.

**3-Benzoyl-4-methylthio-2$H$-pyrano[2',3':4,5]imidazo[1,2-$a$]pyridin-2-one (7g):** From 6g, 59% (reaction temperature 50 °C, time 20 min), orange needles, mp 161—164 °C. IR (KBr): $\nu$ 1655, 1696 cm$^{-1}$. $^1$H-NMR δ: 2.44 (3H, s, SMe), 7.14 (1H, ddd, $J$=7.0, 7.0, 1.4 Hz, 7 -H), 7.46—7.52 (2H, m, Phenyl-H), 7.56 (1H, ddd, $J$=9.0, 7.0, 1.2 Hz, 8 -H), 7.58—7.64 (1H, m, Phenyl -H), 7.86—7.91 (2H, m, Phenyl-H), 8.29 (1H, br d, $J$=7.0 Hz, 5 -H). Anal. Calcd for C$_{18}$H$_{12}$N$_2$O$_3$+H$_2$O: C, 61.01; H, 3.98; N, 7.91. Found: C, 60.87; H, 4.24; N, 7.79.

**3-Benzoyl-9-methyl-4-methylthio-2$H$-pyrano[2',3':4,5]imidazo[1,2-$a$]pyridin-2-one (7h):** From 6h, 66% (reaction temperature 100 °C, time 15 min), orange needles, mp 193—196 °C. IR (KBr): $\nu$ 1697 cm$^{-1}$. $^1$H-NMR δ: 2.42 (3H, s, SMe), 2.67 (3H, s, 9-Me), 7.04 (1H, t, $J$=7.0 Hz, 7-H), 7.35 (br d, $J$=7.0 Hz, 8 -H), 7.44—7.51 (2H, m, Ph -H), 7.57—7.63 (1H, m, Ph -H), 7.95—8.00 (2H, m, Ph-H), 8.46 (1H, br d, $J$=7.0 Hz, 6-H). Anal. Calcd for C$_{19}$H$_{14}$N$_2$O$_3$: C, 65.13; H, 4.03; N, 7.99. Found: C, 65.04; H, 3.97; N, 8.14.

**3-Benzoyl-7,9-dimethyl-2$H$-pyrano[2',3':4,5]imidazo[1,2-$a$]pyridin-2-one (7i):** From 6i, 34% (reaction temperature 100 °C, time 45 min), orange needles, mp 250—252 °C. IR (KBr): $\nu$ 1641, 1716 cm$^{-1}$. $^1$H-NMR δ: 2.42 (3H, s, 7-Me), 2.62 (3H, s, 9-Me), 7.28 (1H, br s, 8-H), 7.36—7.48 (2H, m, Ph-H), 7.52—7.59 (1H, m, Ph-H), 7.76—7.82 (2H, m, Ph-H), 8.03 (1H, br s, 6-H), 8.56 (1H, s, 4-H). $^{13}$C-NMR δ: 16.72, 18.21, 100.37, 107.97, 113.16, 120.74, 125.12, 127.65, 128.03, 128.97, 132.49, 133.11, 133.95, 137.67, 146.33, 159.12, 160.68, 192.40. Anal. Calcd for C$_{19}$H$_{14}$N$_2$O$_3$: C, 71.69; H, 4.43; N, 3.97; H, 8.80. Found: C, 71.83; H, 4.33; N, 8.77.

**7,9-Dimethyl-4-methylthio-2$H$-pyrano[2',3':4,5]imidazo[1,2-$a$]pyridin-2-one (7l):** From 6l, 16% (reaction temperature 100 °C, time 30 min), yellow needles, mp 222—226 °C. IR (KBr): $\nu$ 1701 cm$^{-1}$. 


\(^1\)H-NMR \(\delta\) (DMSO-d\(_6\)): 2.38 (3H, s, 7-Me), 2.58 (3H, s, 9-Me), 2.64 (3H, s, SMe), 5.71 (1H, s, 3-H), 7.12 (1H, br s, 8-H), 8.35 (1H, br s, 6-H). \textit{Anal.} Calcd for C\(_{13}\)H\(_{12}\)N\(_2\)O\(_2\): C, 59.98; H, 4.65; N, 10.76. Found: C, 60.27; H, 4.64; N, 10.48.

**Crystallography of 3-[Bis(methylthio)methylene]-6,8-dimethyl-2(3H)-imidazo[1,2-a]pyridinone (4c)**

A red prismatic single crystal (0.82×0.28×0.24 mm) grown from CHCl\(_3\)-hexane was used for the unit-cell determinations and data was collected using a Rigaku AFC5S four-circle diffractometer with graphite-monochromated MoK\(_\alpha\) radiation (\(\lambda=0.71069\) Å). The crystal data of this compound are as follows: 4c: C\(_{12}\)H\(_{14}\)N\(_2\)O\(_2\)S; \(M=266.38\); monoclinic, space group \(P2_1/n\) (#14), \(Z=4\) with 

- \(a=10.95(3)\) Å,
- \(b=10.388(1)\) Å,
- \(c=11.518(1)\) Å,
- \(\beta=105.97(1)\)\(^{\circ}\),
- \(V=1259.8(38)\) Å\(^3\) and \(D_{\text{calc}}=1.404\) g/cm\(^3\). All calculations were performed using CrystalStructure.\(^{28}\) The structure was solved by a direct method (SIR).\(^{29}\) 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 0.048 and 0.039 respectively for 1897 (\(I>2.00\sigma(I)\)) observed reflections.

**Crystallography of ethyl 4-methylthio-2-oxo-2H-pyrano[2',3':4,5]imidazo[1,2-a]pyridine-3-carboxylate (7d)**

A yellow prismatic single crystal (0.82×0.68×0.32 mm) grown from CHCl\(_3\) was used for the unit-cell determinations and data was collected using a Rigaku AFC5S four-circle diffractometer with graphite-monochromated MoK\(_\alpha\) radiation (\(\lambda=0.71069\) Å). The crystal data of this compound are as follows: 3c: C\(_{14}\)H\(_{12}\)N\(_2\)O\(_4\)S; \(M=304.32\); triclinic, space group \(P-1\) (#2), \(Z=2\) with 

- \(a=7.959(13)\) Å,
- \(b=13.19(2)\) Å,
- \(c=7.116(13)\) Å,
- \(\alpha=103.98(16)\)\(^{\circ}\),
- \(\beta=104.73(14)\)\(^{\circ}\),
- \(\gamma=75.74(13)\)\(^{\circ}\),
- \(V=687.2(19)\) Å\(^3\) and \(D_{\text{calc}}=1.471\) g/cm\(^3\). All calculations were performed using CrystalStructure.\(^{28}\) The structure was solved by a direct method (SIR).\(^{29}\) 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 0.076 and 0.068 respectively for 2383 (\(I>2.00\sigma(I)\)) observed reflections.

**REFERENCES**


25. Only compound 61 was measured in DMSO-<sup>d</sup> because of its low solubility.


927.
