

NOVEL SYNTHESIS OF PYRAZOLO[1,5-a]PYRIDINE DERIVATIVES VIA
PYRIDO[1,2-d]-1,3,4-THIADIAZINE INTERMEDIATES¹

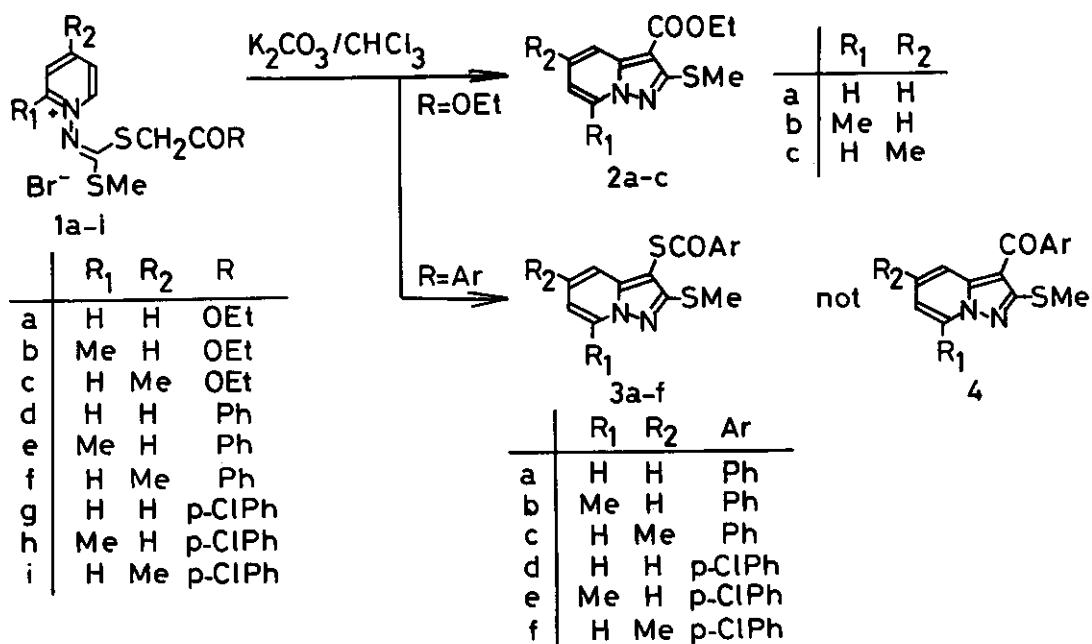
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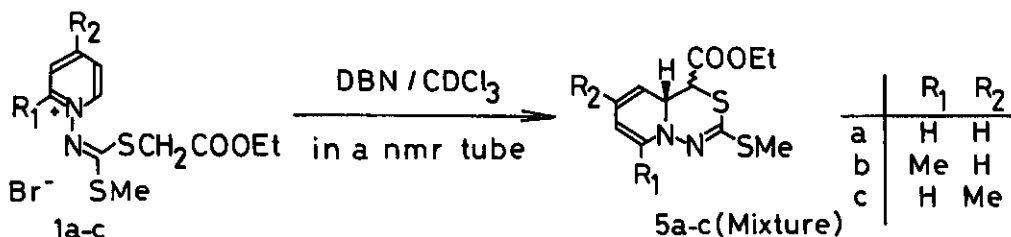
Abstract — Alkaline treatment of 1-[(ethoxycarbonylmethylthio)-methyleneamino]- and 1-[(phenacylthio)methyleneamino]pyridinium bromides afforded 3-ethoxycarbonyl- and 3-arylthiopyrazolo[1,5-a]pyridine derivatives, respectively, in good yields. The intermediacy of pyrido[1,2-d]-1,3,4-thiadiazine derivatives was confirmed by the nmr follows of these reactions.

During the course of our studies on the preparation of condensed heterocycles, the usefulness of vinyl-substituted indolizines and pyrazolo[1,5-a]pyridines as precursors for such heterocycles was extensively realized¹⁻⁶. However, these methods can be applied only to the pyridinium salts possessing a 2-methyl or a 2-methylene group. In our recent attempts to prepare 2-(acylmethylthio)-3-vinylpyrazolo[1,5-a]pyridines via the 2-allylidene-1,2-dihydropyridine route²⁻⁵ from the corresponding 1-[(acylmethylthio)methyleneamino]-2-methylpyridinium halides and activated ethoxymethylene compounds, we found a new type of the formation reaction of pyrazolo[1,5-a]pyridine derivatives which was independent of the presence of such 2-substituents and proceeded via the desulfurization and the unstable pyrido[1,2-d]-1,3,4-thiadiazine derivatives. In this communication we wish to report novel formations of 2-alkylthio-3-ethoxycarbonyl- and 3-(arylthio)-pyrazolo[1,5-a]pyridines from the alkaline treatment of 1-[(acylmethylthio)methyleneamino]pyridinium halides.

The treatment of 1-[(ethoxycarbonylmethylthio)methylthiomethyleneamino]pyridinium bromides 1a-c⁷ with excess potassium carbonate in chloroform at room temperature for 1 day afforded 3-ethoxycarbonyl-2-methylthiopyrazolo[1,5-a]pyridine derivatives: 2a (75%): mp 102-103 °C, ν (KBr) 1671 cm^{-1} (C=O), δ (CDCl_3) 1.43 (3H, t, $J=7.0$ Hz, OCH_2CH_3), 2.65 (3H, s, SMe), 4.41 (2H, q, $J=7.0$ Hz, OCH_2CH_3), 6.84 (1H, dt, $J=7.0$,

7.0, and 1.5 Hz, 6-H), 7.37 (1H, br t, J=9.0 and 7.0 Hz, 5-H), 8.05 (1H, br d, J=9.0 Hz, 4-H), and 8.45 (1H, br d, J=7.0 Hz, 7-H); 2b (82%): mp 120–122 °C, ν (KBr) 1666 cm^{-1} (C=O); 2c (79%): mp 139–140 °C, ν (KBr) 1675 cm^{-1} (C=O), all as pale yellow needles⁸. On the other hand, similar reactions of 1-[(phenacylthio)-methylthiomethyleneamino]pyridinium bromides 1d–i⁷ gave the products, 3-aroylethio-2-methylthiopyrazolo[1,5-a]pyridines: 3a (77%): mp 136–138 °C, ν (KBr) 1668 cm^{-1} (C=O), δ (CDCl₃) 2.67 (3H, s, SMe), 6.76 (1H, dt, J=7.0, 7.0, and 1.5 Hz, 6-H), 7.0–8.3 (7H, m, 4-H, 5-H, and phenyl protons), and 8.47 (1H, br d, J=7.0 Hz, 7-H), 3b (72%): mp 94–95 °C, ν (KBr) 1667 cm^{-1} (C=O); 3c (68%): mp 126–128 °C, ν (KBr) 1675 cm^{-1} (C=O); 3d (87%): mp 158–160 °C; 3e (64%): mp 136–138 °C; 3f (73%): mp 162–164 °C, respectively⁸. Furthermore, the tlc follows of these reactions indicated that compounds 2a–c and 3a–f were secondary products derived from certain substances which were generated rapidly at the early reaction stages. Since these intermediates were too unstable to be isolated in usual manner, the reactions of salts 1a–c in deuteriochloroform using DBN as a base were monitored by nmr and the formation of two isomers of 4,4a-dihydropyrido[1,2-d]-1,3,4-thiadiazines 5a–c could be detected. For example, the nmr spectrum of 5a showed the proton signals at δ 2.45 (3H, s, SMe), 4.56 (1H, br t, J=7.0 and 6.0 Hz, 7-H), 5.15 (1H, br d, J=9.0 Hz, 5-H), 5.80 (1H, br t, J=9.0 and 6.0 Hz, 6-H), and 6.52 (1H, br d, J=7.0 Hz, 8-H), together with the signals at δ 2.41 (3H, s, SMe), 4.64 (1H, br t, J=7.0 and 6.0 Hz,





7-H), and 6.48 (1H, br d, $J=7.0$ Hz, 8-H) attributable to the minor isomer⁹.

The structures of products 2a-c were smoothly determined by means of their physical and spectral inspection and by comparison with the samples prepared independently¹⁰.

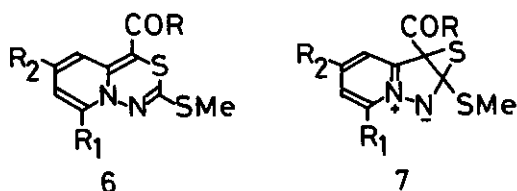
The signals due to the skeletal protons in their nmr spectra were always in the aromatic region (δ 6.5–8.5) and their chemical shifts and the signal patterns were close to those of known 3-alkoxycarbonylpyrazolo[1,5-a]pyridine derivatives^{11,12}.

On the other hand, the structures of 3a-f were confirmed on the basis of the structure of 3e determined by its X-ray analysis as well as the spectral similarity to 3e.

The structures of 5a-c were determined by their nmr spectral comparisons with those of 3,3a-dihydropyrazolo[1,5-a]pyridines¹² and 1,9a-dihydro-2H-pyrido-[1,2-b]-as-triazines^{13,14}.

Although detailed mechanisms of these reactions are still unclear, the structural features of 2a-c and 3a-f and the detection of dihydropyridothiadiazines 5a-c suggested strongly the intermediacy of non-aromatic pyridothiadiazines 6 and their cyclized thiranes 7, which may be converted then to 2a-c via the desulfurization, and to 3a-f via the opening of the thirane ring with the aroyl migration¹⁵.

Further mechanistic consideration for these reactions is now in progress.



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7. These salts 1a-i were prepared in nearly quantitatively yields from the alkylations of the corresponding pyridinium N-ylides. See Ref. 4.
8. All new compounds 2a-c and 3a-f gave satisfactory elemental analyses and mass spectra.
9. The signals for 4- and 4a-protons could not be assigned because of their overlapping with the signals of DBN (and its hydrobromide) and the ethoxycarbonyl group.
10. Compounds 2a-c were prepared by the reactions of 1-aminopyridinium iodides with 1-[1-ethoxycarbonyl-2,2-bis(methylthio)vinyl]pyridinium iodide in the presence of base. Our private communication from Dr. Y. Tominaga, Nagasaki University.
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