

FACILE SYNTHESSES OF PYRIDO[2,1-c]-1,4-THIAZINE DERIVATIVES¹

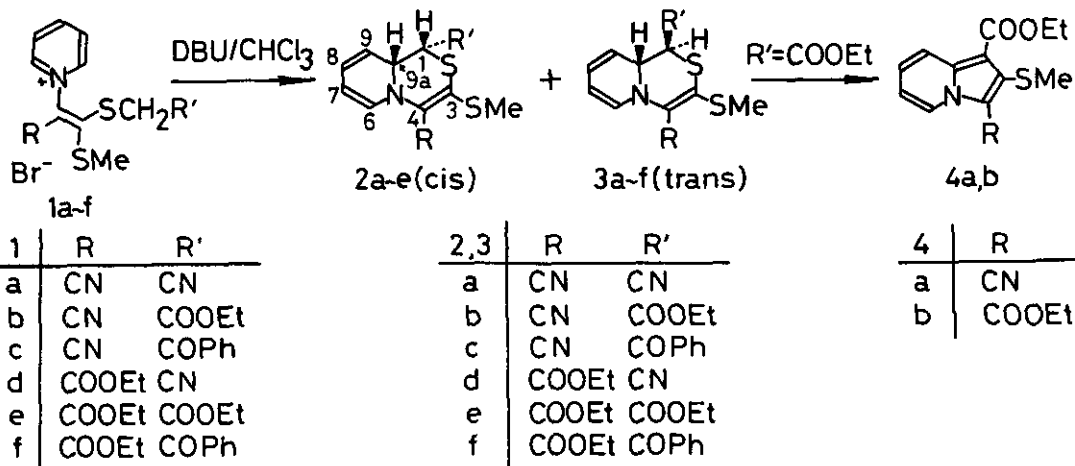
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Abstract — Alkaline treatment of 1-[2-(cyano- or acylmethylthio)-vinyl]pyridinium bromides gave smoothly new heterocyclic compounds, 1-cyano- or 1-acyl-1,9a-dihydropyrido[2,1-c]-1,4-thiazine derivatives.

In our preceding paper², we described a preparative method for 3-acyl or 3-(acylthio)pyrazolo[1,5-a]pyridine derivatives from the reactions of 1-[(acylmethylthio)methyleneamino]pyridinium bromides with base. In particular, the usefulness of these reactions and their mechanistic interest prompted us to examine the possibility of an extension of this method to other heterocyclic systems. In this communication we wish to report smooth syntheses of 1,9a-dihydropyrido[2,1-c]-1,4-thiazine derivatives from the reactions of 1-[(2-cyano- or acylmethylthio)vinyl]pyridinium bromides with a base and the transformation of some pyrido-thiazines to aromatic indolizines.

The treatment of 1-[1-cyano-2-(cyanomethylthio)-2-(methylthio)vinyl]pyridinium bromide 1a³ with a small excess of DBU in chloroform at 0 °C gave instantly a cis-trans mixture (the ratio of 2a to 3a was 8 : 1) of 1,4-dicyano-3-methylthio-1,9a-dihydropyrido[2,1-c]-1,4-thiazines 2a⁴, mp 137–138 °C (Dec), ν (KBr) 2230 and 2210 cm^{-1} (CN), δ (CDCl_3) 2.50 (3H, s, SMe), 4.02 (1H, d, $J=2.0$ Hz, 1-H), 4.60 (1H, q, $J=4.0$ and 2.0 Hz, 9a-H), 4.99 (1H, br t, $J=7.0$, 6.0, and 1.5 Hz, 7-H), 5.41 (1H, br q, $J=10.0$ and 4.0 Hz, 9-H), 6.41 (1H, br q, $J=10.0$ and 6.0 Hz, 8-H), and 6.72 (1H, d, $J=7.0$ Hz, 6-H), and 3a, δ (CDCl_3) 2.50 (3H, s, SMe), 4.03 (1H, d, 8.0 Hz, 1-H), 4.41 (1H, q, $J=8.0$ and 4.0 Hz, 9a-H), and 6.92 (1H, d, $J=7.0$ Hz, 6-H)⁵. Similar treatment of pyridinium salts 1b-f³ with DBU gave the corresponding yellow or orange products 2b+3b, 2c+3c, 2d+3d, 2e+3e, and 3f in 62, 30, 46, 50, and 80% yields^{4,6}, respectively. On the other hand, the use of potassium



carbonate in place of DBU as a base in these reactions leads always to the formation of intractable tarry materials. These dihydropyridothiazines 2a-e and 3a-f are

extremely unstable at room temperature, but pure samples of 2a, 2c+3c, 2d+3d, and 3f can be stored at a lowered temperature (-10~-20 °C). Mixtures 2b+3b and

2e+3e were decomposed smoothly even in a freezer to afford aromatic ethyl

1-indolizinecarboxylates 4a (76%), mp 152-153 °C, ν (KBr) 2205 (CN) and 1682 cm^{-1} (CO), δ (CDCl_3) 1.44 (3H, t, $J=7.0$ Hz, OCH_2CH_3), 2.81 (3H, s, SMe), 4.42 (2H, q, $J=7.0$ Hz, OCH_2CH_3), 6.98 (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, 7-H), 8.25 (1H, br d, $J=9.0$ Hz, 8-H), and 8.29 (1H, d, $J=7.0$ Hz, 5-H), and 4b (15%), mp 59 °C, ν (KBr) 1680 and 1660 cm^{-1} (CO), while compounds

2a+3a, 2c+3c, 2d+3d, and 3f were decomposed completely on standing at room temperature and any significant product could not be isolated.

The structural elucidation of compounds 2a-e and 3a-f was accomplished mainly by their nmr spectral inspection. In particular, both values of the cis coupling

($J=2.0$ Hz) and the trans coupling constants ($J=8.0$ Hz) between the 1 and 9a protons supported strongly this 1,9a-dihydropyrido[2,1-c]-1,4-thiazine structure, since

these values are in good accord those expected for the cis and trans configurations in such molecule from the consideration of their dihedral angles using a Dreiding model. Furthermore, the nmr spectra of these products 2a-e and 3a-f are very

similar to those of their 4-aza-analogs, 4,4a-dihydropyrido[1,2-d]-1,3,4-thiadiazine derivatives, which were described recently by us². The structures of indolizines

4a,b were determined by their nmr spectral inspection and partly by the comparison of 4b with an authentic specimen prepared independently⁷. Further investigation

for the scope and the limitation of this reaction is now in progress.

REFERENCES AND NOTES

1. Preparation of new nitrogen-bridged heterocycles. 10. For part of this Series, see ref. 2.
2. A. Kakehi, S. Ito, M. Ito, and T. Yotsuya, this journal, 1984, 22, 2237.
3. These pyridinium Salts 1a-f were prepared in nearly quantitative yields from the alkylations of the corresponding pyridinium N-ylides with bromoacetonitrile, with ethyl bromoacetate, and with phenacyl bromide in chloroform at room temperature. For the syntheses of pyridinium N-ylides, see Y. Tominaga, Y. Miyake, H. Fujito, Y. Matsuda, and G. Kobayashi, Yakugaku Zasshi, 1977, 97, 927.
4. Compounds 2a, 2c+3c, 2d+3d, 3f, 4a, and 4b gave satisfactory elemental analyses.
5. Other proton signals of 3a were overlapped with those of the major cis isomer 2a.
6. Some data of these products are as follows: 2b+3b (the ratio of 2b to 3b was 10 : 7), ν (Neat) 2211 (CN) and 1730 cm^{-1} (CO). 2c+3c (the ratio of 2c to 3c was 7 : 10), ν (KBr) 2208 (CN) and 1677 cm^{-1} (CO). 2d+3d (the ratio of 2d to 3d was 2 : 1), ν (KBr) 2235 (CN) and 1710 cm^{-1} (CO). 2e+3e (the ratio of 2e to 3e was 8 : 5), ν (Neat) 1720 cm^{-1} (CO). 3f, mp 94 °C (Dec), ν (KBr) 1675 cm^{-1} (CO).
7. Indolizine 4b was prepared in a 89% yield from the reaction of 1-(ethoxycarbonylmethyl)pyridinium chloride and 1-[1-ethoxycarbonyl-2,2-bis(methylthio)vinyl]pyridinium iodide in the presence of potassium carbonate.

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