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Regiospecific Formations of Thieno[3,2-a]indolizine and Thieno[2,3-b]indolizine Derivatives[1,2)]

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The alkaline treatment of ethyl 1-cyano-2-(ethoxycarbonylmethylthio)indolizine-3-carboxylates and diethyl 2-(ethoxycarbonylmethylthio)indolizine-1,3-dicarboxylates afforded the corresponding diethyl 1-aminothieno[3,2-a]indolizine-2,4-dicarboxylates and diethyl 3-hydroxythieno[2,3-b]indolizine-2,9-dicarboxylates in good yields.

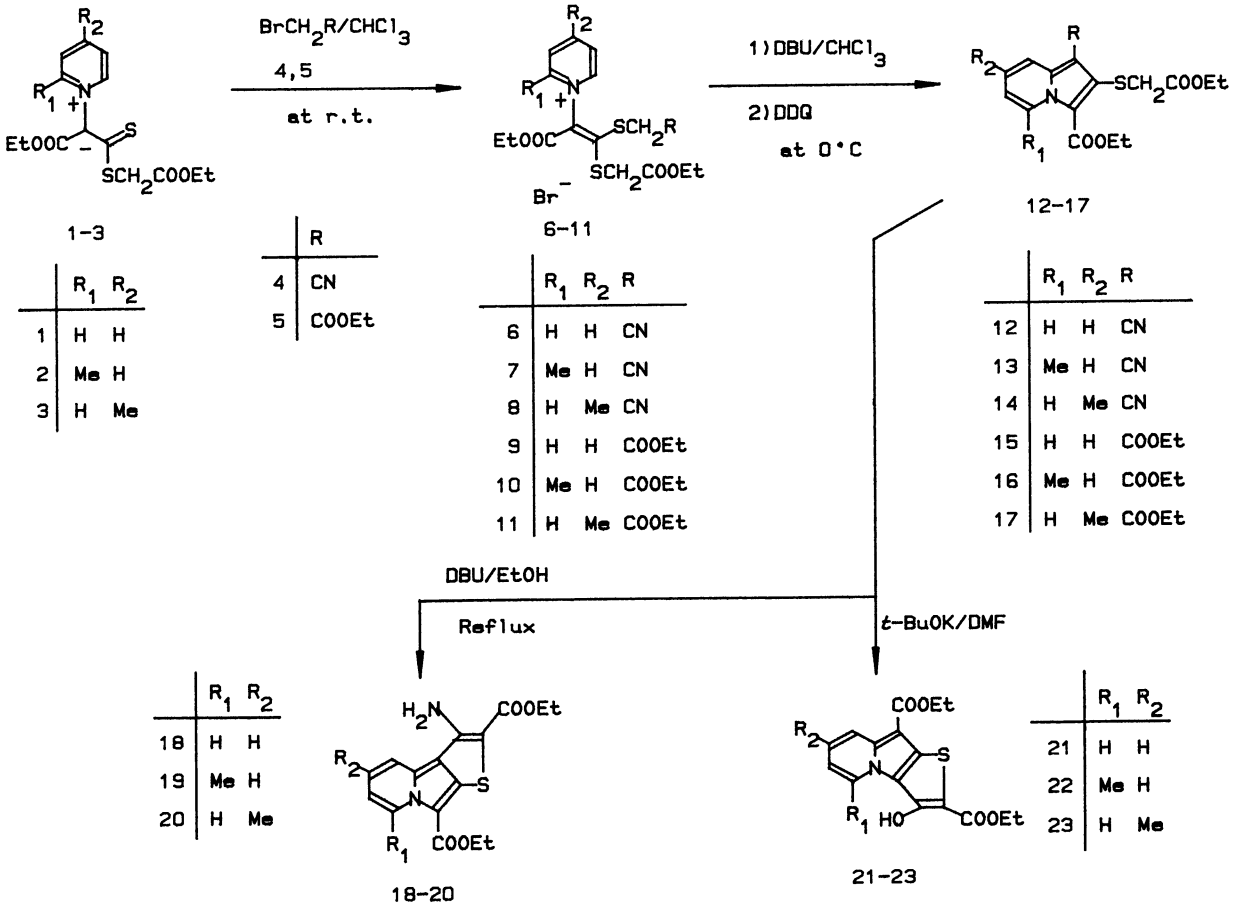
Recently, we have reported that 1,9a-dihydropyrido[2,1-c][1,4]thiazines, readily obtainable from the alkaline treatment of 1-[2-(substituted methylthio)-vinyl]pyridinium halides, were smoothly converted to aromatic indolizine derivatives in the presence of a dehydrogenating agent such as 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) or lead tetraacetate.[1,3)] This reaction has a high synthetic value for various indolizine derivatives which can not be obtained by other methods; this feature of the reaction prompted us to investigate new approaches to some fused indolizines. In this communication, we wish to report the preparations of polyfunctionalized indolizines and their intramolecular cyclizations to thieno[3,2-a]- and thieno[2,3-b]indolizines.

The treatment of 1-[2-(cyanomethylthio)-1-ethoxycarbonyl-2-(ethoxycarbonylmethylthio)vinyl]pyridinium bromide 6, which was prepared from the S-alkylation of the corresponding pyridinium N-ylide 1 with bromoacetonitrile 4, with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in chloroform at 0 °C followed by the addition of DDQ to the reaction solution afforded ethyl 1-cyano-2-(ethoxycarbonylmethylthio)indolizine-3-carboxylate 12, 68%, mp 88-89 °C, ν(KBr) 2208 (CN), 1726 (CO), and 1676 cm^{-1} (CO), δ($CDCl_3$) 1.22 and 1.42 (each 3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$),

4.01 (2H, s, SCH_2), 4.19 and 4.47 (each 2H, q, J=7.0 Hz, OCH_2CH_3), 7.00 (1H, dt, J=7.0, 7.0, and 2.0 Hz, 6-H), 7.35 (1H, br t, J=9.0 and 7.0 Hz, 7-H), 7.70 (1H, br d, J=9.0 Hz, 8-H), and 9.54 (1H, br d, J=7.0 Hz, 5-H). Similar reactions of pyridinium bromides 7 and 8 gave the corresponding 1-cyanoindolizine derivatives 13 (40%, mp 69-70 °C, ν(KBr) 2200 (CN) and 1701 cm^{-1} (CO)), and 14 (87%, mp 101-102 °C, ν(KBr) 2190 (CN), 1723 (CO), and 1653 cm^{-1} (CO)), respectively. On the other hand, the reactions of 1-[2,2-bis(ethoxycarbonylmethylthio)vinyl]pyridinium bromides 9-11 prepared from N-ylides 1-3 and ethyl bromoacetate 5 formed diethyl 2-(ethoxycarbonylmethylthio)indolizine-1,3-dicarboxylates 15 (31%, mp 53 °C, ν(KBr) 1723 (CO) and 1669 cm^{-1} (CO), δ($CDCl_3$), inter alia, 3.79 (2H, s, SCH_2), 6.99 (1H, dt, J=7.0, 7.0, and 2.0 Hz, 6-H), 7.33 (1H, br t, J=9.0 and 7.0 Hz, 7-H), 8.38 (1H, br d, J=9.0 Hz, 8-H), and 9.52 (1H, br d, J=7.0 Hz, 5-H)), 16 (47%, mp 70-71 °C, ν(KBr) 1723 (CO) and 1678 cm^{-1} (CO)), and 17 (57%, mp 59-60 °C, ν(KBr) 1724 (CO) and 1670 cm^{-1} (CO)), respectively.

The structural assignments of these indolizine derivatives 12-17 were accomplished mainly by their ^{1}H-NMR spectral comparisons with those of some indolizines reported by us[3] and other investigators.[4,5] In particular, the chemical shifts and the signal patterns in the ^{1}H-NMR spectra of compounds 12-17 were very similar to those of 2-(methylthio)indolizine analogs.[3]

Since these compounds 12-17 have an active methylene, an ester, and or a cyano group which are situated at appropriate positions in the molecule, the interactions between them should be lead to the indolizine derivatives fused with a thiophene ring. When 1-cyanoindolizines 12-14 were allowed to react with DBU in ethanol at the reflux temperature and the resulting solution were chilled in a freezer, the expected diethyl 1-aminothieno[3,2-a]indolizine-2,4-dicarboxylates 18 (94%, mp 211-213 °C, ν(KBr) 3442 and 3330 (NH_2), and 1650 cm^{-1} (CO), δ($CDCl_3$) 1.38 and 1.46 (each 3H, t, J=7.0 Hz, OCH_2CH_3), 4.34 and 4.43 (each 2H, q, J=7.0 Hz, OCH_2CH_3), 6.08 (2H, br s, NH_2, disappeared with D_2O), 7.01 (1H, dt, J=7.0, 7.0, and 2.0 Hz, 7-H), 7.29 (1H, br t, J=9.0 and 7.0 Hz, 8-H), 7.78 (1H, br d, J=9.0 Hz, 9-H), and 9.63 (1H, br d, J=7.0 Hz, 6-H)), 19 (50%, mp 170-172 °C, ν(KBr) 3398 and 3320 (NH_2), and 1652 cm^{-1} (CO)), and 20 (75%, mp 198-200 °C, ν(KBr) 3438 and 3333 (NH_2), and 1677 cm^{-1} (CO)) were collected as pale yellow prisms with a strong fluorescence. On the other hand, similar treatment of diethyl 1,3-indolizinedicarboxylates 15-17 with DBU did not give any significant products, but



their reactions under the conditions for Dieckmann reaction (t-BuoK/DMF)[6] gave diethyl 3-hydroxythieno[2,3-b]indolizine-2,9-dicarboxylates 21 (86%, mp 159-161 °C, ν(KBr) 1674 cm^{-1} (CO), δ($CDCl_3$), inter alia, 6.83 (1H, dt, J=7.0, 7.0, and 2.0 Hz, 6-H), 7.31 (1H, br t, J=9.0 and 7.0 Hz, 7-H), 8.27 (1H, br d, J=9.0 Hz, 8-H), 8.59 (1H, br d, J=7.0 Hz, 5-H), and 10.53 (1H, br s, OH, disappeared with D_2O)), 22 (87%, mp 190-192 °C, ν(KBr) 1660 cm^{-1} (CO)), and 23 (84%, mp 139-140 °C, ν(KBr) 1685 cm^{-1} (CO)), as only isolable products. An alternative product such as diethyl 1-hydroxythieno[3,2-a]indolizine-2,4-dicarboxylate could not be detected in these reactions at all.

The structures of these thienoindolizines 18-23 were determined mainly by the appearance of primary amino group or a hydroxyl group[7] and by each loss of an active methylene and a cyano or an ester groups. The distinction between thieno[2,3-b]indolizine such as 21-23 and an alternative structure, diethyl 1-hydroxythieno[3,2-a]indolizine-2,4-dicarboxylate, was accomplished by the observation of the reduced anisotropic effect (high field shift) onto the proton (5-H) faced to the hydroxyl group in the ^{1}H-NMR spectra. Further scopes and

limitation of this reaction will be given in the near future.

References

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2) New compounds 12-23 afforded satisfactory elemental analyses, but pyridinium salts 6-11 were used in next reactions without further purification.

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7) The distinct absorptions due to the hydroxyl group in their IR spectra were not exhibited in the range at 3100-4000 cm^{-1}.

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