Preparation of New Nitrogen-Bridged Heterocycles. 45.[1] Smooth Hydrolysis of 6-Membered Heterocyclic 2-Imines with Partial Aromaticity

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The treatment of 2*H*-pyrano[2,3-*b*]indolizin-2-imines and 2*H*-thiino[3,2-*a*]indolizin-2-imines with acetic acid at reflux temperature smoothly afforded the corresponding 2*H*-pyrano[2,3-*b*]indolizin-2-one and 2*H*-thiino-[3,2*a*]indolizin-2-one derivatives in moderate to good yields. An X-ray analysis of a 2*H*-thiino[3,2-*a*]indolizin-2-one derivative was also performed.

Key words 2*H*-thiino[3,2-*a*]indolizin-2-imine; acidic hydrolysis; X-ray analysis; 2*H*-thiino[3,2-*a*]indolizin-2-one; 2*H*-pyrano [2,3-*b*]indolizin-2-imine; 2*H*-pyrano[2,3-*b*]indolizin-2-one

It is well known that compounds bearing carbon-nitrogen double bonds smoothly undergo hydrolysis to provide the corresponding ketone and amine derivatives. However, the hydrolysis of some 6-membered heterocyclic 2-imines such as pyran-2-imine and thiin-2-imine (A) to the corresponding carbonyl compounds (E) is often difficult or leads to further decomposition,[2] because such compounds (A) have partial aromaticity and are present in an aromatic 2-amino form (B) under acidic conditions and as an acyclic anion form (D) *via* the deprotonated isomer (C) under strong alkaline conditions (see Chart 1).[3] Owing to these chemical features and their low solubility in common organic solvents, the handling and characterization of these pyran-2-imine and thiin-2-imine derivatives are troublesome, compared with the corresponding 2-one derivatives.

Recently, we reported a one-pot synthesis of 2*H*-pyrano-[3,2-*a*]indolizin-2-one derivatives from the thermolysis of ethyl 2-(3-cyanoallylidene)-1,2-dihydropyridin-1-ylacetates in refluxing acetic acid, and the smooth transformation of 2*H*-pyrano[3,2-*a*]indolizin-2-imine intermediates to the final derivatives during this reaction was observed.[4] In our studies to find a procedure for converting these 2-imine derivatives to the corresponding 2-one compounds, which are easier to handle, we examined application of this method to some 6-membered heterocyclic 2-imines. In this paper, we report a novel method for selective hydrolysis of the 2-imine moiety in the title compounds.

Results and Discussion

Reactions of 6-Membered Heterocyclic 2-Imines with Acetic Acid Since we previously observed that treatment of ethyl 3-(2-acetoxyindolizin-3-yl)-1-cyanoacrylates with sulfuric acid at room temperature gave the corresponding 2*H*-pyrano[2,3-*b*]indolizin-2-imines such as **2**,[2,5] we first investigated this reaction in acetic acid. As expected, the thermolyses of ethyl 3-(2-acetoxy-1-methyl- (**1a**) and 1-phenylindolizin-3-yl)-1-cyanoacrylates (**1b**)[6] in refluxing acetic acid afforded the corresponding products **3a**, **b** in 43 and 63% yields, respectively (Chart 2). Their structures were deduced to be ethyl 10-methyl- (**3a**) and 10-phenyl-2-oxo-2*H*-pyrano[2,3-*b*]indolizine-3-carboxylate (**3b**) by physical and spectral comparison with authentic samples.[2,7] Interestingly, other functional groups in the molecule were left intact during this reaction.

Similar treatment of 3-substituted ethyl 2-imino-2*H*-thiino[3,2-*a*]indolizine-10-carboxylate hydrochlorides (**4a**—**f**)[8] in acetic acid provided yellow crystalline products **5a**—**f** in 38—69% yields (Chart 3). The structures of these products **5a**—**f** were determined to be ethyl 3-cyano-2-oxo-2*H*-thiino[3,2-*a*]indolizine-1-carboxylates (**5a**—**c**) and diethyl 2-oxo-2*H*-thiino[3,2-*a*]indolizine-3,10-dicarboxylates (**5d**—**f**) by their physical and spectral data. In particular, elemental analyses of **5a**—**f** definitely indicated the loss of a nitrogen atom from the original molecules **4a**—**f**.

An X-ray analysis of diethyl 2-oxo-2*H*-thiino[3,2-*a*]in-

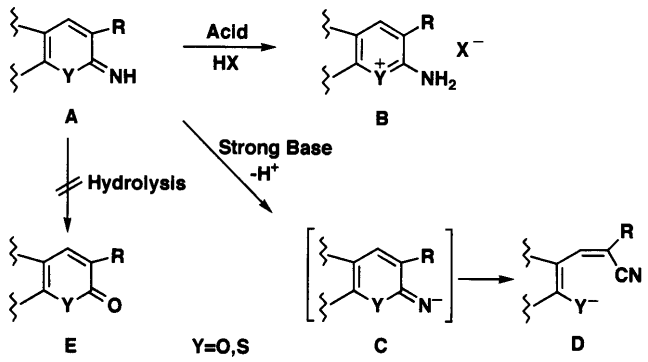

Chart 1

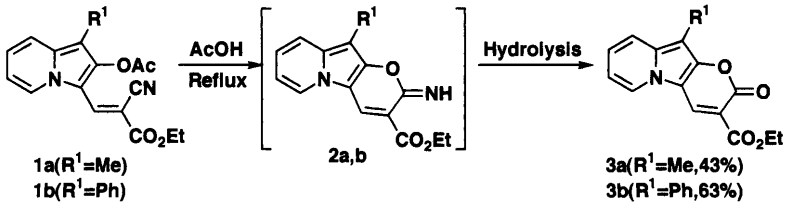

Chart 2

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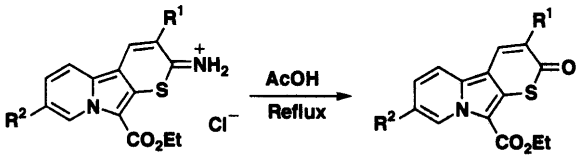

4a-f 5a-f

Prod.	React.	R^1	R^2	Yield (%)
5a	4a	CN	H	56
5b	4b	CN	Me	38
5c	4c	CN	Et	69
5d	4d	CO_2Et	H	68
5e	4e	CO_2Et	Me	51
5f	4f	CO_2Et	Et	61

Chart 3

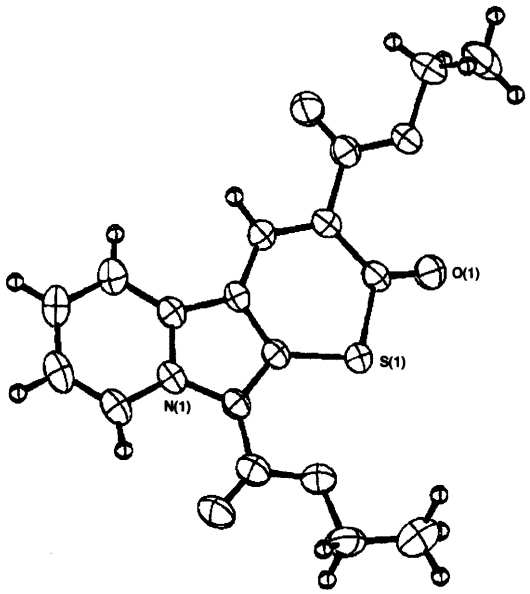

Fig. 1. ORTEP Drawing of Diethyl 2-Oxo-2*H*-thiino[3,2-*a*]indolizine-3,10-dicarboxylate

dolizine-3,10-dicarboxylate (**5d**) was also performed and the structure was finally confirmed. The ORTEP drawing[9] of **5d** is shown in Fig. 1.

On the other hand, extension of this reaction to 1,2-dihydropyrido[3,2-*a*]indolizin-2-imine and 1,2-dihydrodipyrido-[1,2-*b*:3′,2′-*d*]pyrazol-2-imine,[10] which possess a 1,2-dihydropyridin-2-imine system, was unsuccessful.[11]

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 ^{1}H-NMR spectra were determined with a Hitachi R-600 spectrometer (60 MHz) in deuteriochloroform with tetramethylsilane as an internal standard; the chemical shifts are expressed in δ values. The IR spectra were taken with a JASCO FT/IR-5300 IR spectrophotometer.

Preparation of 2*H*-Pyrano[2,3-*b*]indolizin-2-one and 2*H*-Thiino[3,2-*a*]indolizin-2-one Derivatives. General Method A solution of ethyl 3-(2-acetoxyindolizin-3-yl)-2-cyanoacrylates (**1**, 1 mmol) or 2*H*-thiino[3,2-*a*]indolizin-2-imine hydrochlorides (**4**, 1 mmol) in 30 ml of acetic acid was heated at reflux temperature until the starting material completely disappeared (TLC monitoring, 4—8 h). The resulting solution was concentrated at reduced pressure and the residue was separated by column chromatography on alumina using chloroform as an eluent. The yellow chloroform eluates were combined and concentrated at reduced pressure. Recrystallization of the crude product from chloroform or chloroform-hexane provided the corresponding 2*H*-pyrano[2,3-*b*]indolizin-2-ones **3** as orange needles or 2*H*-thiino[3,2-*a*]indolizin-2-ones **5** as yellow needles.

Data for compounds **3a,b** and **5a—f** are as follows:

Ethyl 10-Methyl-2-oxo-2*H*-pyrano[2,3-*b*]indolizine-3-carboxylate (**3a**): 43% (from **1a**), mp 240—241 °C (lit. 239—241 °C).[2,7]

Ethyl 2-Oxo-10-phenyl-2*H*-pyrano[2,3-*b*]indolizine-3-carboxylate (**3b**): 63% (from **1b**), mp 212—213 °C (lit. 212—213 °C).[2,7]

Ethyl 3-Cyano-2-oxo-2*H*-thiino[3,2-*a*]indolizine-10-carboxylate (**5a**):[12] 56% (from **4a**), mp 281—283 °C, IR (KBr) 1697, 1630 cm^{-1} (CO), 2214 cm^{-1} (CN). *Anal.* Calcd for $C_{15}H_{10}N_2O_3S$: C, 60.39; H, 3.38; N, 9.39. Found: C, 60.21; H, 3.23; N, 9.54.

Ethyl 3-Cyano-7-methyl-2-oxo-2*H*-thiino[3,2-*a*]indolizine-10-carboxylate (**5b**): 38% (from **4b**), mp >300 °C, IR (KBr) 1699, 1641 cm^{-1} (CO), 2220 cm^{-1} (CN), ^{1}H-NMR ($CDCl_3$) 1.49 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 2.50 (3H, s, 7-Me), 4.48 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.43 (1H, d, J=9.0 Hz, 6-H), 7.85 (1H, d, J=9.0 Hz, 5-H), 8.42 (1H, s, 4-H), 9.61 (1H, br s, 8-H). *Anal.* Calcd for $C_{16}H_{12}N_2O_3S$: C, 61.53; H, 3.87; N, 8.97. Found: C, 61.62; H, 3.89; N, 8.97.

Ethyl 3-Cyano-7-ethyl-2-oxo-2*H*-thiino[3,2-*a*]indolizine-10-carboxylate (**5c**): 69% (from **4c**), mp 254—256 °C, IR (KBr) 1693, 1641 cm^{-1} (CO), 2218 cm^{-1} (CN), ^{1}H-NMR ($CDCl_3$) 1.34 (3H, t, J=7.0 Hz, 7-$CH_2C\underline{H}_3$), 1.47 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 2.84 (2H, q, J=7.0 Hz, 7-$C\underline{H}_2CH_3$), 4.48 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.50 (1H, d, J=9.0 Hz, 6-H), 7.89 (1H, d, J=9.0 Hz, 5-H), 8.42 (1H, s, 4-H), 9.60 (1H, br s, 8-H). *Anal.* Calcd for $C_{17}H_{14}N_2O_3S$: C, 62.56; H, 4.32; N, 8.58. Found: C, 62.56; H, 4.39; N, 8.51.

Diethyl 2-Oxo-2*H*-thiino[3,2-*a*]indolizine-3,10-dicarboxylate (**5d**): 68% (from **4d**), mp 180—182 °C, IR (KBr) 1705, 1630 cm^{-1} (CO), ^{1}H-NMR ($CDCl_3$) 1.34 (3H, t, J=7.0 Hz, 7-$CH_2C\underline{H}_3$), 1.41, 1.48 (each 3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 4.39, 4.44 (each 2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.17 (1H, br t, J=7.0 Hz, 7-H), 7.51 (1H, br q, J=9.0, 7.0 Hz, 6-H), 7.82 (1H, d, J=9.0 Hz, 5-H), 8.78 (1H, s, 4-H), 9.67 (1H, br d, J=7.0 Hz, 8-H). *Anal.* Calcd for $C_{17}H_{15}NO_5S$: C, 59.12; H, 4.38; N, 4.06. Found: C, 59.10; H, 4.34; N, 4.11.

Diethyl 7-Methyl-2-oxo-2*H*-thiino[3,2-*a*]indolizine-3,10-dicarboxylate (**5e**): 51% (from **4e**), mp 219—221 °C, IR (KBr) 1678, 1633 cm^{-1} (CO), ^{1}H-NMR ($CDCl_3$) 1.42, 1.48 (each 3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 2.48 (3H, s, 7-Me), 4.41, 4.46 (each 2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.38 (1H, d, J=9.0 Hz, 6-H), 7.84 (1H, d, J=9.0 Hz, 5-H), 8.79 (1H, s, 4-H), 9.53 (1H, br s, 8-H). *Anal.* Calcd for $C_{18}H_{17}NO_5S$: C, 60.16; H, 4.77; N, 3.90. Found: C, 60.18; H, 4.82; N, 3.75.

Diethyl 7-Ethyl-2-oxo-2*H*-thiino[3,2-*a*]indolizine-3,10-dicarboxylate (**5f**): 61% (from **4f**), mp 146—148 °C, IR (KBr) 1687, 1628 cm^{-1} (CO), ^{1}H-NMR ($CDCl_3$) 1.35, 1.42, 1.48 (each 3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$, 7-$CH_2C\underline{H}_3$), 2.80 (2H, q, J=7.0 Hz, 7-$C\underline{H}_2CH_3$), 4.41, 4.47 (each 2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.41 (1H, d, J=9.0 Hz, 6-H), 7.89 (1H, d, J=9.0 Hz, 5-H), 8.83 (1H, s, 4-H), 9.59 (1H, br s, 8-H). *Anal.* Calcd for $C_{19}H_{19}NO_5S$: C, 61.11; H, 5.13; N, 3.75. Found: C, 60.90; H, 5.16; N, 3.48.

Crystallography of Diethyl 2-Oxo-2*H*-thiino[3,2-*a*]indolizine-3,10-dicarboxylate (5d) A single crystal (0.22×0.40×0.44 mm) grown from $CHCl_3$–hexane was used for the unit-cell determination and data collection on a Rigaku AFC5S four-circle diffractometer, with graphite-monochromated MoK_α radiation (λ=0.71069 Å). Crystal data of **5d**: $C_{17}H_{15}NO_5S$; M=345.37; monoclinic, space group $P2_1/c$ (#14), Z=4 with a=7.297 (5) Å, b=10.029 (4) Å, c=21.479 (2) Å; β=90.95 (2)°; V=1572 (1) Å^3, and $D_{calc.}$=1.459 g/cm^3. All calculations were performed using the TEXSAN program.[13] The structure was solved by a direct method (SIR).[14] The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotopically. The final R- and R_w-factors after full-matrix least-squares refinements were 0.044 and 0.049, respectively, for 2249 observed reflections.

References and Notes

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11) Other acids, such as trifluoroacetic acid, were also examined, but only the starting material was recovered.
12) ^{1}H-NMR spectrum of this compounds could not be measured because of its low solubility.
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