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The Vilsmeier-Haack Reaction of Lactams: Chloroformylation of 1,3,4,5-Tetrahydro-2H-1-benzazepin-2-one and 2H-1,4-Thiazin-3-ones

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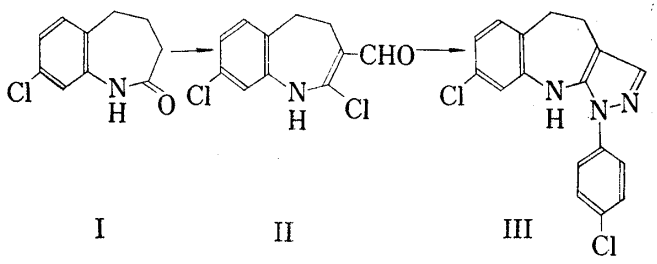
Recently Morita, *et al.*[2] of these laboratories reported a novel one-step synthesis of some fused heterocyclic compounds by the reaction of lactams with formamide in the presence of phosphorus oxychloride in a sealed vessel. The reaction is very likely to proceed through the Vilsmeier-Haack reaction.[3] Although recent publications[4] disclosed a variety of applications of the Vilsmeier-Haack reaction to the field of heterocyclic chemistry, only a few examples were reported on the introduction of the α,β-unsaturated β-chloroaldehyde moiety to five- and six-membered lactams. Thus α-pyrrolones[5] and 2H-1,4-benzoxazin-3-ones[6] were shown to give 2-chloro-3-formylpyrroles and 2-dimethylaminoformylidene-3-chloro-1,4-benzoxazines respectively.

In this paper will be described the first application of this reaction to the seven-membered lactam and some 2H-1,4-thiazin-3-ones, the conversion of the α,β-unsaturated β-chloroaldehyde derivatives thus obtained to some new fused heterocyclic systems and other related matters.

The reaction of 8-chloro-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (I) with phosphorus oxychloride ($POCl_3$) and dimethylformamide (DMF) gave 2,8-dichloro-3-formyl-4,5-dihydro-1H-1-benzazepine (II). The structure was confirmed by the infrared and nuclear magnetic resonance spectra. The α,β-unsaturated β-chloroaldehyde moiety of II is susceptible to nucleophilic attack as exemplified by the facile conversion to 1-(*p*-chlorophenyl)-8-chloro-4, 5-dihydro-pyrazolo-[3,4-*b*][1]benzazepine[7] (III) on treatment with *p*-chlorophenylhydrazine in ethanol (Chart 1).



I II III

Chart 1

As an extension of the reaction the introduction of the α,β-unsaturated β-chloroaldehyde moiety to a six-membered lactam containing other hetero atom was tried. Thus 2H-1, 4-benzothiazin-3-one (IV) was treated with an excess of the Vilsmeier reagent ($POCl_3$-DMF) at room temperature. Nuclear magnetic resonance and infrared spectra of the product were in good agreement with the anticipated 3-chloro-2-formyl-1,4-benzothiazine (V). This compound is also susceptible to various nucleophilic attack to afford a novel fused hetero-

1) Location: *Juso-nishino-cho, Higashiyodogawa-ku, Osaka, Japan.*
2) K. Morita, S. Kobayashi, H. Shimadzu and M. Ochiai, *Tetrahedron Letters*, **1970**, 861.
3) M. Ochiai, *Kagaku No Ryoiki*, **19**, 900 (1965); C.H. Jutz and W. Muller, *Angew. Chem. Intern. Ed. Engl.*, **5**, 1042 (1966).
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cyclic compound such as 1-(*p*-chlorophenyl)pyrazolo[4,3-*b*][1,4]benzothiazine derivative[7] (VI), and a variety of 3-(N-substituted)amino-2-formyl-1,4-benzothiazine derivatives (VIIa, b, c and d) as shown in Chart 2. Formation of the Schiff base was not observed with aniline.

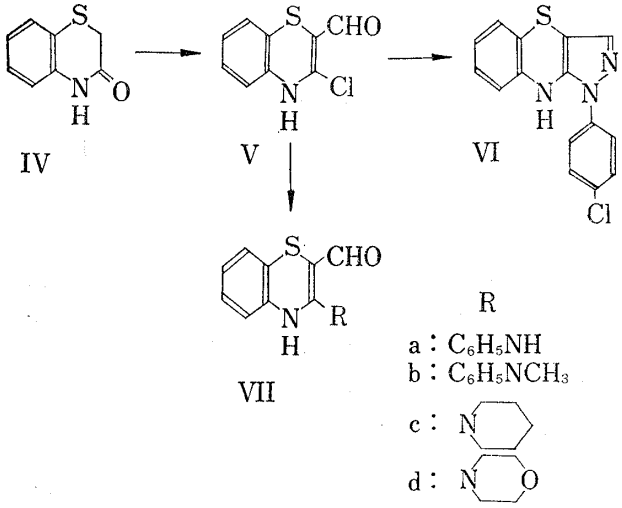


Chart 2

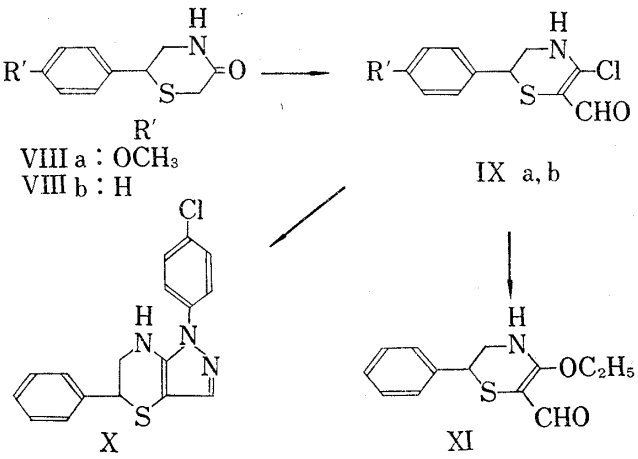


Chart 3

Similarly, 6-aryl-2,3,4,5-tetrahydro-1,4-thiazin-3-ones (VIIIa and b) were treated with $POCl_3$-DMF at 110° to give 3-chloro-2-formyl-6-aryl-5,6-dihydro-1,4-thiazine (IXa and b). Treatment of IXb with *p*-chlorophenylhydrazine gave 1-(*p*-chlorophenyl)-5-phenyl-5, 6-dihydro-pyrazolo[4,3-*b*][1,4]thiazine (X).[7] The reaction of IXb with sodium ethoxide in ethanol under reflux furnished 3-ethoxy-2-formyl-6-phenyl-5,6-dihydro-1,4-thiazine (XI) (Chart 3).

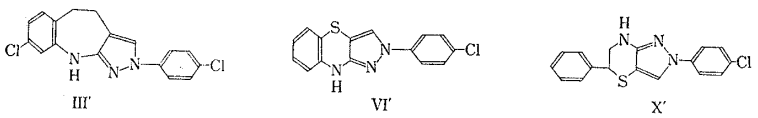
Thus the introduction of α,β-unsaturated β-chloroaldehyde moiety to various lactams by means of the Vilsmeier-Haack reaction appears to be quite general and provides a versatile synthetic utility for new fused heterocyclic systems.

Experimental

All melting points were determined in capillary tube and uncorrected. NMR spectra were measured with a Varian A-60 Spectrometer using tetramethylsilane as an internal standard.

2,8-Dichloro-3-formyl-4,5-dihydro-1H-1-benzazepine (II)——To a solution of $POCl_3$ (60 ml) and DMF (15 ml) was added 8-chloro-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one[10] (I, 5.85 g), and the mixture was stirred at 85° for 4 hr. After cooling the solvent was evaporated under reduced pressure, the residual oil was poured onto crushed ice and left overnight. The precipitates were collected, washed with ligroin and dried. Recrystallization from benzene gave colorless needles, 1.65 g (22.8%), mp 156—156.5°. *Anal.* Calcd. for $C_{11}H_9ONCl_2$: C, 54.56; H, 3.74; N, 5.78. Found: C, 54.81; H, 3.70; N, 5.68. IR (KBr): 1640 cm^{-1}. NMR ($CDCl_3$): δ 2.85 (q, CH_2CH_2), 7.00 (m, aromatic), 7.37 (s, CHO) and 9.84 ppm (s, NH).

7) The structures III, VI and X were given to the condensation products taking into consideration that aryl hydrazines generally react with alkyl halides at their α-nitrogen[8] and that β-chloro vinylketone derivatives react with hydrazine derivatives to give hydrazones.[9] However it should be noted that isomeric structures III', VI' and X' cannot be ruled out.



8) "The Chemistry of Open-Chain Organic Nitrogen compounds, P.A.S. Smith ed." Vol. 2, W.A. Benjamin, Inc., New York, N.Y., 1966, p126—127.
9) A.E. Pohland and W.R. Benson, *Chem. Rev.*, **66**, 161 (1966).
10) M. Tomita, S. Minami and S. Uyeo, *J. Chem. Soc.* (*C*), **1969**, 183.

1-(*p*-Chlorophenyl)-8-chloro-4,5-dihydro-pyrazolo[3,4-*b*][1]benzazepine (III)——A mixture of II (1.21 g), *p*-chlorophenylhydrazine (1.1 g) and AcONa (1.1 g) in EtOH (30 ml) was heated under reflux for 1 hr. To the mixture was added H_2O (10 ml) and the separated solid was collected, washed with water and dried. Recrystallization from MeOH gave colorless prisms, 0.4 g (24.2%), mp 190—192°. *Anal.* Calcd. for $C_{17}H_{13}N_3Cl_2$: C, 61.83; H, 3.96; N, 12.72. Found: C, 61.81; H, 4.02; N, 12.85. NMR (d_6-DMSO): δ 2.84 (q, CH_2-CH_2), 6.70—7.30 (m, aromatic and =CH-), 7.85 (s, *p*-chlorophenyl) and 8.05 ppm (broad, NH).

3-Chloro-2-formyl-1,4-benzothiazine (V)——A solution of 2H-1,4-benzothiazin-3-one[11] (IV, 33.0 g) in $POCl_3$ (200 ml) and DMF (50 ml) was stirred at room temperature for 26 hr and then the excess of $POCl_3$ was evaporated under reduced pressure. The residue was poured onto crushed ice and allowed to stand overnight at room temperature. The precipitates were collected, washed with water and dried, 28.9 g (47.6%) of 3-chloro-2-formyl-1,4-benzothiazine which was used for the following experiments without further purification. IR (KBr): 1645 cm^{-1} and NMR (d_6-DMSO): δ 6.74—7.40 (m, aromatic), 7.70 (s, CHO) and 10.16 ppm (broad, NH).

1-(*p*-Chlorophenyl)-pyrazolo[4,3-*b*][1,4]benzothiazine (VI)——A mixture of V (5.25 g), *p*-chlorophenylhydrazine (5.0 g) and AcONa (8.2 g) in EtOH (150 ml) was heated under reflux for 2.5 hr. The solvent was evaporated *in vacuo*, and the resulting solid was collected, washed with water and dried. Recrystallization from benzene gave 3.05 g (39.4%) of VI, mp 170—171°. *Anal.* Calcd. for $C_{15}H_{10}N_3SCl$: C, 58.17; H, 3.25; N, 13.56. Found: C, 57.79; H, 3.59; N, 12.96. NMR (d_6-DMSO): δ 6.68—7.40 (m, aromatic and =CH-) and 10.75 ppm (broad, NH).

2-Formyl-3-phenylamino-1,4-benzothiazine (VIIa)——To a solution of V (1.05 g) in AcOH (20 ml) was added aniline (0.93 g). The mixture was heated at 80° for 30 min. On cooling the solid was obtained and washed with water. Recrystallization from EtOH gave 1.05 g (78.3%) of VIIa, mp 124—125°. *Anal.* Calcd. for $C_{15}H_{12}ON_2S$: C, 67.14; H, 4.50; N, 10.44. Found: C, 67.36; H, 4.50; N, 10.24.

2-Formyl-3-(N-methyl-N-phenyl)amino-1,4-benzothiazine (VIIb)——To a solution of V (1.05 g) in EtOH (20 ml) was added N-methylaniline (1.35 g). The mixture was heated at 80° for 2 hr. After cooling the precipitates were collected and recrystallized from ligroin–hexane to give 1.30 g (86.6%) of VIIb, mp 135—136°. *Anal.* Calcd. for $C_{16}H_{14}ON_2S$: C, 68.05; H, 4.99; N, 9.92. Found: C, 67.96; H, 4.72; N, 9.94. Similarly the reaction of V with piperidine gave 2-formyl-3-piperidino-1,4-benzothiazine (VIIc) in 42.3% yield, mp 223—225° (from EtOH). *Anal.* Calcd. for $C_{14}H_{16}ON_2S$: C, 64.57; H, 6.19; N, 10.75. Found: C, 64.46; H, 6.14; N, 10.90, and with morpholine gave 2-formyl-3-morpholino-1,4-benzothiazine (VIId) in 81.7% yield, mp 238—240° (from dioxane). *Anal.* Calcd. for $C_{13}H_{14}O_2N_2S$: C, 59.51; H, 5.37; N, 10.67. Found: C, 59.66; H, 5.36; N, 10.59.

3-Chloro-2-formyl-6-(*p*-methoxyphenyl)-5,6-dihydro-1,4-thiazine (IXa)——To a solution of $POCl_3$ (25 ml) and DMF (3 ml) was added 6-(*p*-methoxyphenyl)-2,3,4,5-tetrahydro-1,4-thiazin-3-one[12] (VIIIa, 2.23 g). The mixture was heated at 110° for 2 hr and left overnight. After removal of $POCl_3$ the residue was poured onto crushed ice, the precipitates were collected and washed with water. Recrystallization from dilute MeOH gave colorless needles, 1.1 g (40.7%), mp 161—162°. *Anal.* Calcd. for $C_{12}H_{12}O_2NSCl$: C, 53.42; H, 4.48; N, 5.19. Found: C, 53.14; H, 4.65; N, 5.04. IR (KBr): 1640 cm^{-1}. NMR (d_6-DMSO): δ 3.76 (s, OCH_3), 3.20—4.30 (m, $CHCH_2$), 7.14 (q, aromatic), 8.80 (broad, NH) and 9.62 ppm (s, CHO).

3-Chloro-2-formyl-6-phenyl-5,6-dihydro-1,4-thiazine (IXb)——To a solution of $POCl_3$ (70 ml) and DMF (10.5 ml) was added 6-phenyl-2,3,4,5-tetrahydro-1,4-thiazin-3-one[12] (VIIIb, 6.75 g). The mixture was stirred at room temperature for 6 hr. The excess of $POCl_3$ was evaporated *in vacuo*, the residue was poured onto crushed ice and left overnight. The precipitates were collected, washed with water and crystallized from EtOH to give colorless needles, 6.3 g of IXb (84.0%), mp 185° (decomp.). *Anal.* Calcd. for $C_{11}H_{11}ONSCl$: C, 55.11; H, 4.20; N, 5.84. Found: C, 55.33; H, 4.06; N, 5.64.

1-(*p*-Chlorophenyl)-5-phenyl-5,6-dihydro-pyrazolo[4,3-*b*][1,4]thiazine (X)——To a solution of *p*-chlorophenylhydrazine (2.7 g) and AcONa (3.3 g) in 30% EtOH (80 ml) was added a solution of IXb (2.4 g) in hot EtOH (100 ml). The mixture was heated under reflux for 45 min. After cooling the precipitates were collected and recrystallized from EtOH to give 2.42 g (74%) of X, mp 182—184°. *Anal.* Calcd. for $C_{17}H_{14}N_3SCl$: C, 62.28; H, 4.30; N, 12.81. Found: C, 62.27; H, 4.23; N, 12.68.

3-Chloro-2-ethoxy-6-phenyl-5,6-dihydro-1,4-thiazine (XI)——To a sodium ethoxide solution (prepared from 0.37 g of sodium and 25 ml of EtOH) was added IXb (1.2 g) and the mixture was heated under reflux for 1 hr. After removal of EtOH under reduced pressure H_2O was added to the residue. The precipitates were collected and recrystallized from dilute MeOH to give colorless needles, 0.55 g (44.0%) of XI, mp 185—187° (decomp.). *Anal.* Calcd. for $C_{13}H_{15}O_2NS$: C, 62.62; H, 6.06; N, 5.61. Found: C, 62.60; H, 6.18; N, 5.63. NMR (d_6-DMSO): δ 1.28 (t, $CH_2C\underline{H}_3$). 3.20—4.30 (m, $CHCH_2$). 4.15 (q, $C\underline{H}_2CH_3$), 7.32 (s, aromatic) and 9.41 ppm (s, CHO).

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11) G. Traverso and C.B. Riolo, *Ann. Chim.* (Rome), **45**, 668 (1955).
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