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Studies on Conjugated Nitriles. V.[1] Reaction of 3-Benzoyl- and 3-Ethoxycarbonylacrylonitriles with Enamines

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The reactions of 3-benzoylacrylonitrile (**1a**) with 3-amino-5,5-dimethyl-2-cyclohexenone (**2**) and ethyl 3-aminocrotonate (**4**) gave the corresponding pyridine derivatives, **3** and **5**, respectively. 3-Ethoxycarbonylacrylonitrile (**1b**) also reacted with ethyl 3-benzylaminocrotonate (**6**) and 1-ethoxycarbonylmethylene-1,2,3,4-tetrahydroisoquinoline (**9**) to give the pyrrolin-5-one derivatives, **7** and **10**, respectively.

Keywords——acrylonitrile derivative; enamine derivative; pyridine derivative; pyrrolin-5-one derivative; stannic chloride

Recently, we reported that the reaction of acyl cyanides with tautomeric imines gave pyrroline derivatives[2] and related compounds.[3] The results prompted us to examine the reaction of vinylogous acyl cyanides such as 3-benzoyl- (**1a**) and 3-ethoxycarbonylacrylonitrile (**1b**) with tautomeric imines. Although several reactions of **1** have been reported,[4] little work has been done on the synthesis of heterocyclic compounds by using **1**. The only known examples are 1,3-dipolar addition with metal azides to give triazole[5] and tetrazole,[6] and hydrolysis to give maleimides.[7] In this paper we wish to describe the reactions of **1a** and **1b** with enamines **2**, **4**, **6**, and **9**.

Tteatment of *trans*-**1a** with 3-amino-5,5-dimethyl-2-cyclohexenone (**2**) in toluene under reflux for 6 h gave 7,7-dimethyl-5-oxo-2-phenyl-5,6,7,8-tetrahydroquinoline (**3**) in 55% yield, together with a 24% yield of recoverd **1a**. The structure of **3** was assigned on the basis of elemental and spectral data as described in the experimental section. Treatment of both *trans*-**1a** and *cis*-**1a** with **2** in acetic acid similarly gave **3**. The reaction proceeds *via* formation of the Michael adduct (A),[4a] which cyclizes and releases HCN to give **3**. Similarly, the reaction of **1a** with ethyl 3-aminocrotonate (**4**) gave a 64% yield of ethyl 2-methyl-6-phenylnicotinate (**5**). The reaction of **1a** with ethyl 3-benzylaminocrotonate (**6**) gave complex mixtures. On the other hand, no reaction of **1b** with these enamines **2**, **4**, and **6** occurred under the same

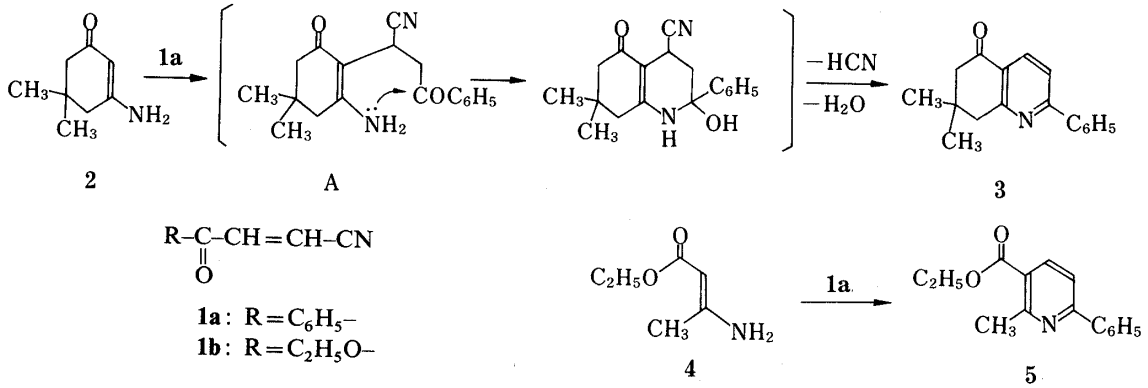

Chart 1

conditions, and the starting materials were recovered. The failure seems to result from the lower electrophilicity of **1b**.

Recently, Ohno's[8] and our groups[9] have reported that the electrophilicity of the cyano group of ethyl cyanoformate is increased by Lewis acids. This observation led us to use Lewis acids in the reaction of **1b** with **2**, **4**, and **6**. Treatment of **1b** with **6** in the presence of stannic chloride and triethylamine at room temperature for 24 h gave a 35% yield of ethyl 1-benzyl-4-cyanomethyl-2-methyl-5-oxo-3-pyrrolinecarboxylate (**7**). The structure of **7** was confirmed by its elemental and spectral data and by conversion of **7** to its acetate (**8**). The infrared (IR) spectrum showed a nitrile band at 2240 cm^{-1} and strong ester and five-membered ring lactam bands at 1720 and 1690 cm^{-1}.[10] The nuclear magnetic resonance (NMR) spectrum of **7** showed a methyl proton signal at δ 2.33 as a doublet (J=2 Hz) due to a homoallylic coupling with a methine proton. After acetylation of **7** with acetic anhydride in dry pyridine to **8**, the homoallylic coupling disappeared. When **1b** was treated with **6** in the absence of stannic chloride or triethylamine, no reaction took place. The formation of **7** can be well interpreted as follows; stannic chloride combined with the cyano group of **1b** to generate an activated intermediate (B),[11] in which the β-position to the cyano group was attacked by the C-2 site of **6** to form a Michael adduct (C), followed by cyclization to **7**.

Similar reaction of **1b** with an enamine (**9**) in the presence of stannic chloride and triethylamine gave the corresponding product (**10**) in 28% yield. However, our attempts to react **1b** with **2**, **4**, and 1-phenylpropylideneaniline in the same manner failed to give any detectable amount of the desired products.

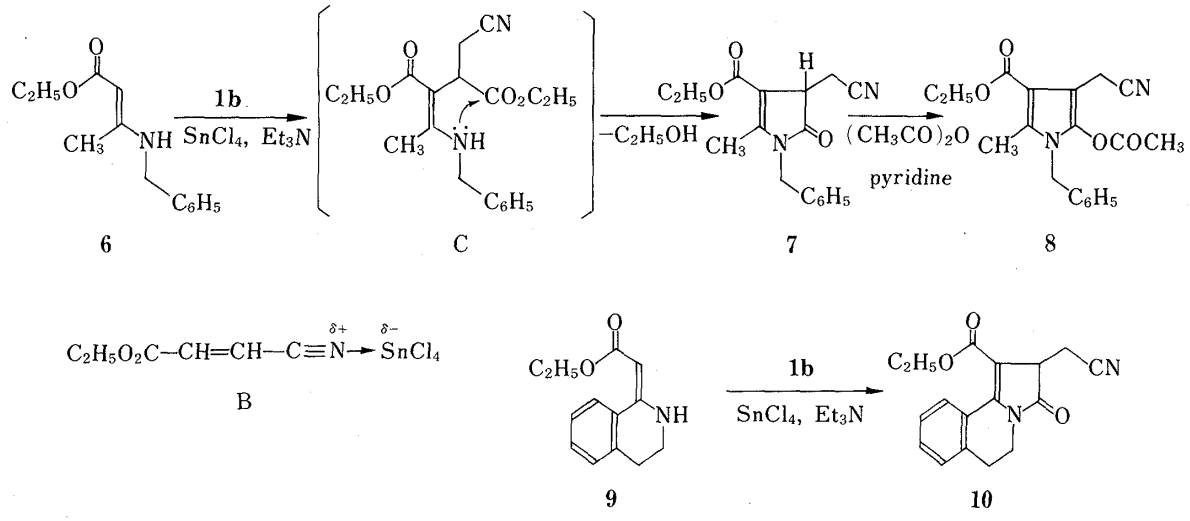

Chart 2

Experimental

All melting points are uncorrected. The IR spectra were recorded on a Hitachi 260-10 spectrophotometer, ^{1}H-NMR spectra on a JEOL JNM-PMX 60 spectrometer, ^{13}C-NMR spectra on a JEOL FX-60 spectrometer, and mass spectrum (MS) on a JEOL D-300 spectrometer operating at 70 eV.

Materials——3-Benzoylacrylonitrile (**1a**),[12] 3-ethoxycarbonylacrylonitrile (**1b**),[13] 3-amino-5,5-dimethyl-2-cyclohexenone (**2**),[14] ethyl 3-benzylaminocrotonate (**6**),[15] and 1-ethoxycarbonylmethylene-1,2,3,4-tetrahydroisoquinoline (**9**)[16] were prepared according to the literature. Ethyl 3-aminocrotonate (**4**) was obtained from Aldrich Chemical Company, Inc.

7,7-Dimethyl-5-oxo-2-phenyl-5,6,7,8-tetrahydroquinoline (3)——(a) A suspension of *trans*-3-benzoylacrylonitrile (**1a**) (230 mg, 1.5 mmol) and 3-amino-5,5-dimethylcyclohex-2-enone (**2**) (225 mg, 1.6 mmol) in toluene (5 ml) was refluxed for 6 h. Evaporation of the reaction mixture *in vacuo* followed by silica-gel column chromatography of the residue using CH_2Cl_2 as an eluent gave a solid. Recrystallization from H_2O gave **3** (208 mg, 55%), mp 65—67 °C.

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.10; H, 6.77; N, 5.58. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (C=O). ^{1}H-NMR (in $CDCl_3$) δ: 1.13 (6H, s, $CH_3 \times 2$), 2.54 and 3.08 (4H, 2s, $-CH_2- \times 2$), 7.3—7.5 (3H, m, H-Ar), 7.60 (1H, d, J=8.5 Hz, H-C(3)), 7.9—8.1 (2H, m, H-Ar), 8.23 (1H, d, J=8.5 Hz, H-C(4)). ^{13}C-NMR (in $CDCl_3$) δ: 28.3 (q, CH_3-C(7)), 33.0 (s, C-7)), 46.8 and 52.1 (2t, C(6) and C(8)), 118.8 (d, C(3)), 125.5 (s, C(4a)), 127.3, 128.8 and 129.9 (3d, phenyl), 138.4 (s, phenyl), 135.2 (d, C(4)), 161.1 and 162.3 (2s, C(2) and C(8a)), 197.8 (s, C(5)). MS *m/e*: 251 (M^+).

The starting nitrile (**1a**) was recovered in 24% yield.

(b) A suspension of *trans*-**1a** (314 mg, 2.0 mmol) and **2** (292 mg, 2.1 mmol) in CH_3CO_2H (5 ml) was refluxed for 6 h. Work-up as described above gave **3** (220 mg, 44%) and recovered **1a** (56 mg, 18%).

(c) A suspension of *cis*-**1a** (314 mg, 2.0 mmol) and **2** (292 mg, 2.1 mmol) in CH_3CO_2H (5 ml) was refluxed for 6 h. Work-up as described above gave **3** (136 mg, 27%) and recovered **1a** (119 mg, 38%).

Ethyl 2-Methyl-6-phenylnicotinate (5)——A solution of **1a** (139 mg, 0.9 mmol) and ethyl 3-aminocrotonate (**4**) (125 mg, 1.0 mmol) in toluene (5 ml) was refluxed for 9 h. Evaporation of the reaction mixture *in vacuo* followed by preparative silica-gel thin layer chromatography of the residue using benzene as a developing solvent gave an oil. Distillation gave **5** (154 mg, 64%), bp 165—168 °C (2 mmHg) [both temperature]. *Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.90; H, 6.29; N, 5.79. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 ($CO_2C_2H_5$). ^{1}H-NMR (in $CDCl_3$) δ: 1.37 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.90 (3H, s, CH_3), 4.37 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.1—7.7 (4H, m, H-Ar), 7.8—8.4 (3H, m, H-Ar). MS *m/e*: 241 (M^+).

Ethyl 1-Benzyl-4-cyanomethyl-2-methyl-5-oxo-3-pyrrolinecarboxylate (7)——3-Ethoxycarbonylacrylonitrile (**1b**) (0.75 g, 6 mmol) was added to $SnCl_4$ (1.60 g, 6 mmol) at room temperature, and then the mixture was allowed to stand overnight to solidify. A solution of ethyl 3-benzylaminocrotonate (**6**) (1.31 g, 6 mmol) and Et_3N (0.61 g, 6 mmol) in dry benzene (20 ml) was added to the solid at room temperature. The mixture was stirred for 24 h at the same temperature, and concentrated *in vacuo* to give a residue, which was extracted with $CHCl_3$ (100 ml). The extract was washed with H_2O (50 ml), dried over Na_2SO_4, and concentrated *in vacuo* to give a syrup, which was purified by silica-gel column chromatography using $CHCl_3$ as an eluent to give crystals. Recrystallization from ether–*n*-hexane gave **7** (0.63 g, 35%), mp 93.5—95 °C. *Anal.* Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.29; H, 6.13; N, 9.38. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (C≡N), 1720 (NC=O), 1690 ($CO_2C_2H_5$). ^{1}H-NMR (in $CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.33 (3H, d, J=2 Hz, CH_3), 3.0—3.7 (3H, m, CH and CH_2CN), 4.33 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.73 and 4.80 (2H, each d, J=15 Hz, $C\underline{H}_2Ph$), 7.33 (5H, s, H-Ar). MS *m/e*: 298 (M^+).

Acetylation of 7——A solution of **7** (53 mg, 0.18 mmol) and acetic anhydride (0.3 ml) in dry pyridine (0.5 ml) was kept at room temperature for 24 h, then poured into 10% HCl aqueous solution (10 ml), and extracted with ether (60 ml). The extract was washed with H_2O (30 ml), dried over Na_2SO_4, and concentrated to give a solid. Recrystallization from benzene–*n*-hexane gave ethyl 5-acetoxy-1-benzyl-4-cyanomethyl-2-methyl-3-pyrrolecarboxylate (**8**) (51 mg, 81%), mp 122—123 °C. *Anal.* Calcd for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23. Found: C, 67.23; H, 5.94; N, 8.17. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (C≡N), 1780 ($OCOCH_3$), 1685 ($CO_2C_2H_5$). ^{1}H-NMR (in $CDCl_3$) δ: 1.37 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.22 (3H, s, $COCH_3$), 2.42 (3H, s, CH_3), 3.73 (2H, s, CH_2CN), 4.32 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.92 (2H, s, $C\underline{H}_2Ph$), 6.8—7.5 (5H, m, H-Ar).

Ethyl 2-Cyanomethyl-3-oxo-2,3,5,6-tetrahydrobenzo[*g*]indolizine-1-carboxylate (10)——3-Ethoxycarbonylacrylonitrile (**1b**) (0.625 g, 5 mmol) was added to $SnCl_4$ (1.30 g, 5 mmol) at room temperature, and then the mixture was allowed to stand overnight to solidify. A solution of 1-ethoxycarbonylmethylene-1,2,3,4-tetrahydroisoquinoline (**9**) (1.302 g, 6 mmol) and triethylamine (0.606 g, 6 mmol) in dry benzene (20 ml) was added to the solid at room temperature. The mixture was stirred for 18 h at the same temperature, and concentrated *in vacuo* to give a residue. The residue was extracted with $CHCl_3$ (100 ml). The extract was washed with H_2O (50 ml), dried over Na_2SO_4, and concentrated *in vacuo* to give a syrup, which was purified by silica-gel column chromatography using CH_2Cl_2 as an eluent to give crystals. Recrystallization from CH_3OH gave **10** (0.41 g, 28%), mp 138—140 °C. *Anal.* Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.99; H, 5.40; N, 9.39. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (C≡N), 1720 (NC=O), 1700 ($CO_2C_2H_5$). ^{1}H-NMR (in $CDCl_3$) δ: 1.32 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.8—3.3 (4H, m, Ar-CH_2 and CH_2CN), 3.5—4.0 (3H, m, CH_2-N and CH), 4.26 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.2—7.6 (3H, m, H-Ar), 8.5—8.6 (1H, m, H-Ar). MS *m/e*: 296 (M^+).

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