Chem. Pharm. Bull.
22(9)2118—2122(1974)

UDC 547.491.4.04 : 547.7.04

Studies on Organic Sulfur Compounds. XVI.[1] Nucleophilic Reaction of Heterocyclic Bases with Alkoxycarbonyl Isothiocyanates[2]

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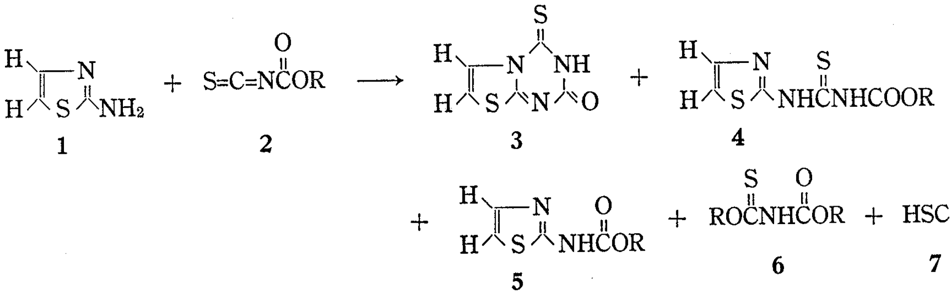
(Received March 7, 1974)

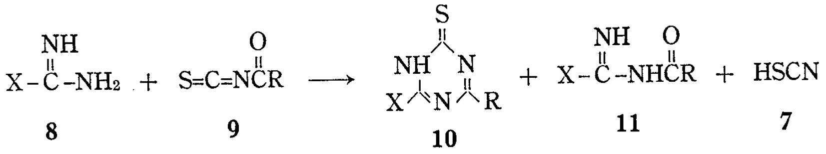
Reactions of ethoxycarbonyl isothiocyanate (**2a**) with heterocyclic amines whose pK_a values range from 2.95 to 9.17 were examined. Regardless of the base strengths, the heterocyclic amines except 4-aminopyridine afforded the addition products in a good yield in the nucleophilic reactions with **2a**. 4-Aminopyridine (**14**) which afforded no addition product with **2a** yielded ethyl N-(4-pyridyl)carbamate (**16**). Probably the nucleophilic substitution of **14** occurs at the ring nitrogen atom and the pyridinium salt (**15**) formed in the initial stage of the reaction rearranged intermolecularly and resulted in the formation of **16**.

Previous works[4] in this series have shown that the nucleophilic reaction of 2-aminothiazole (**1**) with alkoxycarbonyl isothiocyanates (**2**) afforded thiazolo[3,2-*a*]-s-triazin-4-one (**3**), N-alkoxycarbonyl-N′-(2-thiazolyl)thioureas (**4**), and alkyl N-(2-thiazolyl)carbamates (**5**).

The formation of these three types of compounds, **3**, **4** and **5** means that the nucleophilic reactions of **1** took place at the two electrophilic centers of isothiocyanato and carbonyl carbon atoms of **2** and resulted in cycloaddition and addition reactions with the isothiocyanato moiety and nucleophilic substitution at the carbonyl carbon atom.



Similar results were obtained by Goerdeler, *et al.*[5-7] in the reaction of amidines (**8**) and acyl isothiocyanates (**9**), which lead to triazinethiones (**10**) and characteristic side reactions resulting in the formation of acylamidines (**11**) and HSCN (**7**).



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[1] Part XV: T. Matsui, M. Nagano, and T. Kinoshita, *Yakugaku Zasshi*, **94**, 533 (1974).

[2] This was presented in part at the 14th Annual Meeting of Kanto Branch, Pharmaceutical Society of Japan, Tokyo, November, 1972.

[3] Location: *Hiromachi, Shinagawa-ku, Tokyo.*

[4] *a*) M. Nagano, J. Tobitsuka, T. Matsui, and K. Oyamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 2618 (1972); *b*) M. Nagano, T. Matsui, J. Tobitsuka, and K. Oyamada, *ibid.*, **20**, 2626 (1972).

[5] J. Goerdeler, *Quarterly Reports on Sulfur Chemistry*, **5**, 169 (1970).

[6] J. Goerdeler and J. Neuffer, *Tetrahedron Letters*, **1967**, 2791.

[7] J. Goerdeler and J. Neuffer, *Chem. Ber.*, **104**, 1580, 1605 (1971).

Goerdeler, *et al.* have reported that the lower the basicity of **8** and the carbonyl activity of **9** are, the greater is the yield of **10**; on the other hand, the greater the basicity of **8** and the carbonyl activity of **9** are, the more those side reactions predominate. We have examined the relationship between pK_a values of 2-aminothiazoles and the nature and yields of the reaction products from **2**.[4b)] However, a definite conclusion concerning the relation of basicity to the type of reaction product from each reagent could not be obtained in previous works.

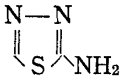
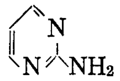
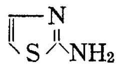
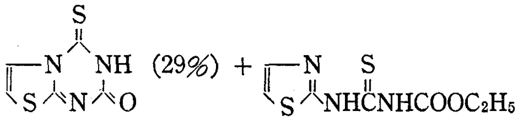
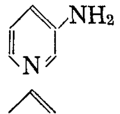
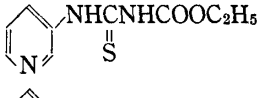
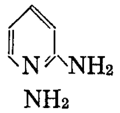
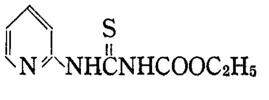
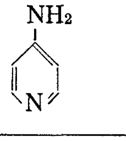
In this paper we wish to report additional results on the reaction of **2** with some heterocyclic bases, whose pK_a values range from 2.95 to 9.17.

The reaction of ethoxycarbonyl isothiocyanate (**2a**) with 2-aminopyridine (**12**) whose pK_a value is greater than that of 2-aminothiazole (see Table I) afforded ethyl 4-(2-pyridyl)-3-thioallophanate (**13**) in a good yield,[8)] which means the nucleophilic addition of amino substituent to the isothiocyanato moiety is favored regardless of the higher basicity.

More interesting results were noted in the nucleophilic reaction of 4-aminopyridine (**14**) which afforded no addition product, with **2a** yielding the thiocyanic salt (**15**) of ethyl N-(4-pyridyl)carbamate (**16**), which means the nucleophilic substitution at the carbonyl carbon is predominant.

pK_a values and the yields of addition products from aminopyridines with **2a** are summarized in Table I together with those of some heterocyclic amines.

Table I. PKa Values of Heterocyclic Bases and Yields of Addition Products with **2a**

Heterocyclic Bases	pK_a[a)]	Addition products	Yield (%)
	2.95[b)]		68.9
	3.54		77.4
	5.39	 (50%)	79.0[c)]
	5.98		71.1
	6.86		80.0
	9.17	—	—

a) A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, **1948**, 2240
b) The pK value was determined by the spectrophotometric method in aqueous solution containing 4% alcohol at 27°.[4b)]
c) ref. 4)

Regardless of base strength, the heterocyclic amines except 4-aminopyridine have shown the tendency to afford the addition products in a good yield in the nucleophilic reaction with **2a**. Any correlations between pK_a values of heterocyclic amines and the yields of the addition products were not apparent.

[8)] Thiocyanic acid was detected by the color reaction with ferric chloride. There appeared no doubt the nucleophilic substitution at the carbonyl carbon may take place to some extent.

In the case of **14** the nucleophilic substitution probably occurs at the ring nitrogen[9] in the initial stage of the reaction. The ultraviolet (UV) absorption spectrum of the reaction mixtures of **14** and **2a** underwent a remarkable change during the reaction as is shown in Fig. 1. Immediately after mixing the reagents[10] the maximum absorption observed at 288 mμ soon disappeared in the diluted solution of dioxane and a new peak appeared at 239 mμ, which corresponds the maximum absorption of **16**. Another peak at 260 mμ may possibly be attributed to that of a 4-aminopyridinium salt.[11]

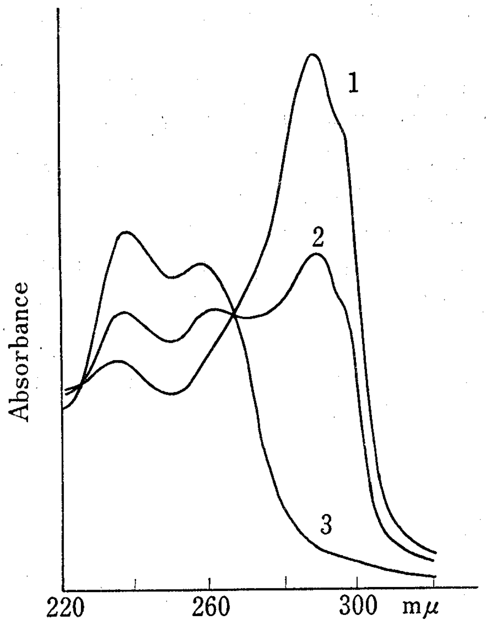


Fig. 1. UV Spectra of the Reaction Mixture of Ethoxycarbonyl Isothiocyanate (**2a**) and 4-Aminopyridine (**14**) in Dioxane

1 imme diately after mixing
2 5 minutes later
3 30 minutes later

The carbonyl absorption in the infrared (IR) spectrum which was taken after removal of the solvent also showed a considerable shift from 1780 cm^{-1} to 1725 cm^{-1}, which is identical with that of **16**. After standing overnight the reaction mixtures afforded the thiocyanic salt of **16** as pale yellow needles, which show a maximum UV absorption at 264.5 mμ, and after treating with the base gives **16**. Probably the salt (**15**) formed in the initial stage of the reaction rearranged intermolecularly in basic media and resulted in the formation of **16**.

Remarkable differences exist in the nucleophilic reaction of 2- and 4-substituted aminopyridines (see Chart 1) and some differences may also exist between the basicities of 2-aminosubstituted pyridines and thiazoles. The amidine moiety of **1** gave the cycloaddition product of **3**, but no cycloaddition reaction occurred in the nucleophilic reaction of **12**.

There are many reports[11–14] relative to the differences in the physico-chemical behavior of aminopyridines and aminothiazoles which can undergo a similar tautomerism. The previous interpretations of this difference were based on the tautomerism. However, most of the heterocyclic amines proved to exist predominantly in the amino forms.[15–18]

The reason which makes such differences in nucleophilic behavior must be due to another factors of the molecules. In the next paper we will discuss in detail the difference in nucleophilic behavior of heterocyclic amines and mechanism of ambident reactivities of **2a**.

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9) R.A. Jones and A.R. Katritzky, *J. Chem. Soc.*, **1959**, 1317.

10) The starting materials **14** and **2a** have the absorption maximum at 245—260 mμ[11] and 258 mμ respectively.

11) E.A. Steck and G.W. Ewing, *J. Am. Chem. Soc.*, **70**, 3397 (1948).

12) A. Weissberger, "The Chemistry of Heterocyclic Compounds: Pyridine and Its' Derivatives," Part 3, ed. by E. Klinsberg, Interscience Publishers, New York, 1962.

13) *a*) S.J. Angyal, W.O. Morris, and W.K. Warburton, *Austral. J. Sci. Res.*, **A5**, 368 (1952); *b*) S.J. Angyal, *ibid.*, **A5**, 374 (1952).

14) *a*) T. Kato, H. Yamanaka, and H. Moriya, *Yakugaku Zasshi*, **84**, 1201 (1964); *b*) T. Kato, H. Yamanaka, T. Niitsuma, K. Wagatsuma, and M. Oizumi, *Chem. Pharm. Bull.* (Tokyo), **12**, 910 (1964); *c*) T. Kato, H. Yamanaka, N. Katagiri, and S. Masuda, *ibid.*, **20**, 133 (1972).

15) L.C. Anderson and N.V. Seeger, *J. Am. Chem. Soc.*, **71**, 340 (1949).

16) *a*) S.J. Angyal and C.L. Angyal, *J. Chem. Soc.*, **1952**, 1461; *b*) C.L. Angyal and R.L. Werner, *ibid.*, **1952**, 2911.

17) J.D.S. Goulden, *J. Chem. Soc.*, **1952**, 2939.

18) *a*) N. Mataga and S. Mataga, *Bull. Chem. Soc. Japan*, **32**, 600 (1959); *b*) M.J.S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill Book Co., New York, 1969, p. 387; *c*) H. Konishi, H. Kato, and T. Yonezawa, *Theoret. Chim. Acta* (Berl.), **19**, 71 (1970).

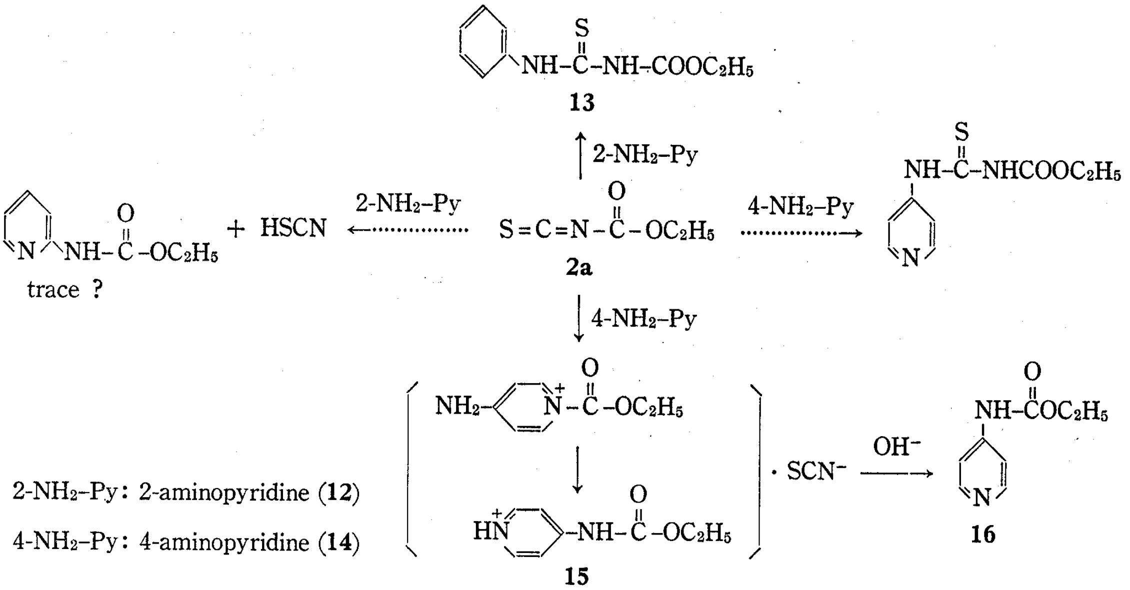

Chart 1

Experimental[19]

General Method for the Reactions of Ethoxycarbonyl Isothiocyanate (2a) with Heterocyclic Bases——To a solution of heterocyclic base (0.01 mole), a solution of **2a** (0.011 mole) was added dropwise at room temperature and the mixture was allowed to stand 5 hr. In some cases, crystals of the reaction product were precipitated. After removal of the solvent under reduced pressure, the residues were recrystallized from appropriate solvents. Polar aprotic solvents, such as ethyl acetate, acetone, dioxane, *etc.* are favorable for the above reactions and gave similar results.

Ethyl 4-(1,3,4-Thiadiazol-2-yl)-3-thioallophanate——1.01 g of 2-amino-1,3,4-thiadiazole was allowed to react with 1.45 g of **2a** in 50 ml of acetone. After removal of solvent, the residue was recrystallized from EtOH to give 1.6 g of ethyl 4-(1,3,4-thiadiazol-2-yl)-3-thioallophanate as colourless leaflets, mp 230—235° (decomp.). *Anal.* Calcd. for $C_6H_8O_2N_4S$: C, 31.02; H, 3.47; N, 24.11; S, 27.60. Found: C, 31.30; H, 3.61; N, 23.92; S, 27.03. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1715 (>C=O). NMR (DMSO-d_6) ppm (J=Hz): 1.30 (3H, triplet, J=7.0), 4.26 (2H, quartet, J=7.0), 9.14 (1H, singlet), 11.90 (2H, broad).

Ethyl 4-(2-Pyrimidinyl)-3-thioallophanate——0.95 g of 2-aminopyrimidine was allowed to react with 1.45 g of **2a** in 50 ml of acetone. After removal of solvent, the residue was recrystallized from EtOH to give 1.75 g of ethyl 4-(2-pyrimidinyl)-3-thioallophanate as pale yellow needles, mp 199—200° (decomp.). *Anal.* Calcd. for $C_8H_{10}O_2N_4S$: C, 42.47; H, 4.46; N, 24.76; S, 14.17. Found: C, 42.57; H, 4.42; N, 24.75; S, 14.43. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1765 (>C=O). NMR (DMSO-d_6) ppm (J=Hz): 1.28 (3H, triplet, J=7.0), 4.25 (2H, quartet, J=7.0), 8.86—7.20 (3H, multiplet), 11.66 (1H, broad), 12.60 (1H, broad).

Ethyl 4-(3-Pyridyl)-3-thioallophanate——0.94 g of 3-aminopyridine was allowed to react with 1.45 g of **2a** in 50 ml of acetone. After removal of solvent, the residue was recrystallized from EtOH to give 1.6 g of ethyl 4-(3-pyridyl)-3-thioallophanate as pale yellow needles, mp 173—174°. *Anal.* Calcd. for $C_9H_{11}O_2N_3S$: C, 47.99; H, 4.92; N, 18.65; S, 14.23. Found: C, 47.91; H, 4.86; N, 18.57; S, 14.56. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1720 (>C=O). NMR (DMSO-d_6) ppm (J=Hz): 1.28 (3H, triplet, J=7.0), 4.26 (2H, quartet, J=7.0), 7.3—8.8 (4H, multiplet), 11.38 (1H, broad), 11.56 (1H, broad).

Ethyl 4-(2-Pyridyl)-3-thioallophanate (**13**)——0.94 g of 2-aminopyridine was allowed to react with 1.45 g of **2a** in 25 ml of acetone. After removal of solvent, the residue was recrystallized from EtOH to afford 1.8 g of ethyl 4-(2-pyridyl)-3-thioallophanate as pale yellow prisms, mp 104—105°. *Anal.* Calcd. for $C_9H_{11}O_2N_3S$: C, 47.99; H, 4.92; N, 18.65; S, 14.24. Found: C, 47.82; H, 4.81; N, 18.49; S, 14.13. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1715 (>C=O). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 243.5 (4.25), 297 (4.21). NMR (DMSO-d_6) ppm (J=Hz): 1.30 (3H, triplet, J=7.0), 4.28 (2H, quartet, J=7.0), 7.0—8.9 (4H, multiplet), 12.0 (2H, broad).

Reaction of 4-Aminopyridine (14) with 2a——a) 0.94 g of **14** was allowed to react with 1.45 g of **2a** in 25 ml of acetone. After removal of solvent the residue was allowed to stand overnight. (A part of the residue was submitted to the measurement of IR spectra.) The precipitated crystals (0.9 g) were collected

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[19] All melting points are uncorrected. NMR spectra were obtained in the specified solvents on a Varian A-60 D spectrometer with tetramethylsilane as an internal standard. IR spectra were determined on a Hitachi EPI-G3 spectrometer.

and recrystallized from EtOH–acetone to give HSCN salt (**15**) of ethyl N-(4-pyridyl)carbamate (**16**) as pale yellow needles, mp 158—161° (decomp.). *Anal.* Calcd. for $C_9H_{11}O_2N_3S$ (as HSCN salt): C, 47.99; H, 4.92; N, 18.65; S, 14.23. Found: C, 47.84; H, 4.91; N, 18.62; S, 14.41. IR ν_{max}^{Nujol} cm^{-1}: 2025 (SCN), 1725 (>C=O). UV λ_{max}^{EtOH} mμ (log ε): 264.5 (4.25). NMR (DMSO-d_6) ppm (*J*=Hz): 1.30 (3H, triplet, *J*=7.0), 4.28 (2H, quartet, *J*=7.0), 7.86—8.8 (4H, multiplet), 9.0–10.0 (1H, broad), 11.23 (1H, broad singlet).

b) 0.9 g of **15** was dissolved in 10 ml of water and neutralized to pH 7 with dropwise addition of 2N NaOH aqueous solution. After cooling, the precipitated crystals (0.6 g) were collected and recrystallized from MeOH–water to give 0.4 g of **16** as colourless prisms, mp 130—131° (lit.[20] mp 128—129°). *Anal.* Cacld. for $C_8H_{10}O_2N_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.58; H, 6.16; N, 16.85. IR ν_{max}^{Nujol} cm^{-1}: 1725 (>C=O). UV λ_{max}^{EtOH} mμ (log ε): 239.5 (4.26).[21] NMR (DMSO-d_6) ppm (*J*=Hz): 1.26 (3H, triplet, *J*=7.0), 4.24 (2H, quartet, *J*=7.0), 7.3—8.5 (4H, multiplet), 10.0 (1H, broad singlet).

Time-Course Measurement of UV Spectra——0.94 g of **14** was mixed with 1.45 g of **2a** in 50 ml of dioxane. A portion of the reaction mixture was used for the measurement of UV absorption after diluting with a proper amount of dioxane. UV absorption spectra were made on a Beckman DB spectrophotometer and absorbances were recorded from a wavelength of 220 mμ to 320 mμ, at intervals of 5 minutes. As the reaction mixture gave an emulsion and was separated into two layers after standing few minutes, only the qualitative features of the spectra were recorded.

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20) C. Richter and P. Sieber, Swiss Patent 324439 (1957) [*C.A.* 52, 18475*g* (1958)].

21) When the hydrogen ion content of the solution is increased, the maximum absorption is shifted to 264.5 mμ (log ε: 4.43).