

a) Yields were based on the diazo carbonyl compounds used. b) A singlet signal of OCH₃ was observed at δ 4.18.

Table 2. Yields, Melting Points, and ^1H NMR Data of **4**

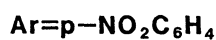
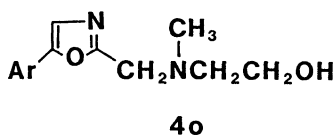
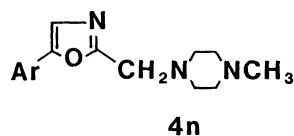
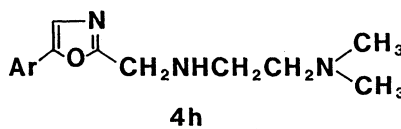
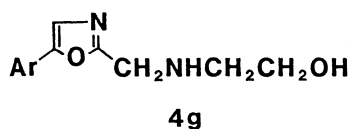
Run	Amine	Reaction Cond.		Product	Yield ^{a)}	Mp $\theta_{\text{m}}/^{\circ}\text{C}$	¹ H NMR/ $\delta^{\text{b)}$	
		Temp/ $^{\circ}\text{C}$	Time/day		%		$\text{CH}_2^{\text{c)}$	$\text{C}_4\text{-H}$
Reaction with primary amines ^{d)}								
a	$\text{CH}_3\text{NH}_2^{\text{c)}$	r.t.	4	4a	87	61—3	4.02	7.55
b	$\text{CH}_3\text{CH}_2\text{NH}_2^{\text{f)}$	r.t.	2	4b	94	67—8	4.02	7.47
c	$\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2$	r.t.	16	4c	96	^{g)}	4.01	7.48
d	$(\text{CH}_3)_2\text{CHNH}_2$	r.t.	5	4d	97	48—9	4.02	7.49
e	$(\text{CH}_3)_3\text{CNH}_2$	40	10	4e	99	40—2	3.99	7.48
f	$\text{CH}_2=\text{CHCH}_2\text{NH}_2$	r.t.	10	4f	95	40—1	4.02	7.47
g	$\text{HOCH}_2\text{CH}_2\text{NH}_2$	40	20	4g	95	Oil	4.05	7.48
h	$(\text{CH}_3)_2\text{NCH}_2\text{CH}_2\text{NH}_2$	r.t.	3	4h	ca. 80 ^{h,i)}	^{g)}	4.02	7.43
Reaction with secondary amines								
i	$(\text{CH}_3\text{CH}_2)_2\text{NH}$	r.t.	9	4i	98	Oil	3.92	7.50
j	Pyrrolidine	r.t.	1	4j	89	71—2	3.89	7.47
k	Piperidine	r.t.	1.5	4k	95	^{g)}	3.76	7.49
l	Morpholine	r.t.	1.5	4l	99	142—3	3.76	7.44
m	Piperazine	r.t.	1.8	4m	96	^{g)}	3.76	7.44
n	<i>N</i> -Methylpiperazine	r.t.	3	4n	93	116—9	3.79	7.43
o	$\text{HOCH}_2\text{CH}_2\text{NHCH}_3$	r.t.	5	4o	95 ^{j)}	Oil	3.92	7.51

a) Isolated yields on the basis of oxazoles used. b) Measured in CDCl_3 . c) Methylene group attached to C_2 of oxazole ring. d) Reaction was carried out in a benzene solution otherwise cited. e) Methanol was used as a solvent. f) Ethanol was used as a solvent. g) Pure compound showing sharp melting point was not obtained. h) Reaction site was primary amine. i) Separation of the reaction product from starting amine was unsuccessful. j) Reaction site was secondary amine.

Table 3. Yields, Melting Points, and ^1H NMR Data of **5**

Run	Ar	Amine	Reaction time/day	Compd	Yield ^{a)}	Mp $\theta_m/^\circ\text{C}$	^1H NMR/ $\delta^b)$	
					%		$\text{CH}_2^c)$	$\text{C}_4\text{-H}$
a	<i>p</i> - $\text{NO}_2\text{C}_6\text{H}_4$	$(\text{CH}_3\text{CH}_2)_3\text{N}$	100	5a	94	200—1	5.35	7.62
b	<i>p</i> - $\text{NO}_2\text{C}_6\text{H}_4$	1,4-Dimethylpiperazine ^{d)}	12	5b	97	133—7	5.74	7.58
c	<i>p</i> - $\text{NO}_2\text{C}_6\text{H}_4$	DABCO ^{d)}	1	5c	91	>300	4.94	8.18 ^{e)}

a) Isolated yields on the basis of oxazoles used. b) Measured in CDCl_3 unless otherwise noted. c) Methylene group attached to C_2 of oxazole ring. d) A 1 : 1-reaction product was obtained. e) Measured in $\text{DMSO}-d_6$ solution.



methyl]-5-(*p*-nitrophenyl)oxazole (**4g**) as a sole product, which was confirmed on the basis of its ^1H NMR spectrum. Chemical shift (δ 4.05) of $\text{CH}_2\text{-N}$ group attached to oxazole ring of **4g** is quite similar to those of reaction products (δ 3.99—4.02) of other primary amines (Table 2). This indicates that the reaction site of 2-aminoethanol is not the hydroxyl group but the amino group as is predicted from the difference in nucleophilicities of amino and hydroxyl groups. Similarly, *N,N*-dimethylethylenediamine clarified not to react at the tertiary amine but to react at the primary

amine to give secondary amine (**4h**).

Secondary amines also react with **3a** to yield the tertiary amines (**4**) in high yields (Table 2, Runs i—o). Diethylamine is shown to be less reactive than most primary amines listed in Table 2. However, cyclic secondary amines such as pyrrolidine, piperidine, morpholine, and piperazine are indicated to have higher reactivity than the usual primary amines. *N*-Methylpiperazine reacted with **3a** at the site of secondary amine to give tertiary amine (**4n**) which was characterized on the basis of ^1H NMR data. The chemical

Table 4. Results of the Elemental Analysis of **3** and **4**

Compound	Found			Calcd			Molecular formula
	C	H	N	C	H	N	
3a	50.38	3.00	11.68	50.33	2.96	11.74	C ₁₀ H ₇ N ₂ O ₃ Cl
3b	50.45	2.95	11.75	50.33	2.96	11.74	C ₁₀ H ₇ N ₂ O ₃ Cl
3c	62.06	4.25	7.25	62.03	4.16	7.23	C ₁₀ H ₈ NOCl
3d	49.11	3.45	10.48	49.18	3.38	10.43	C ₁₁ H ₉ N ₂ O ₄ Cl
4d	59.77	5.76	15.88	59.76	5.79	16.08	C ₁₃ H ₁₅ N ₃ O ₃
4l	57.91	5.18	14.47	58.12	5.28	14.53	C ₁₄ H ₁₅ N ₃ O ₄

shifts of N-CH₃ of **4n** (δ 2.30) is quite similar to that of the starting *N*-methylpiperazine (δ 2.26), and CH₂ group attached to oxazole-C-2 of **4n** (δ 3.79) shows a signal in the same region as those of other cyclic secondary amines products (δ 3.76–3.89). 2-(Methylamino)ethanol also reacts at the nitrogen atom to give *N*-methyl-*N*-[[5-(*p*-nitrophenyl)-2-oxazolyl]-methyl]-2-hydroxyethylamine (**4o**) in 95% yield.

Tertiary amines such as triethylamine, 1,4-dimethylpiperazine, and 1,4-diazabicyclo[2.2.2]octane (DABCO) gave the corresponding quaternary ammonium chlorides (**5**) in high yields (Table 3). The reaction with triethylamine was very slow at room temperature. Although 1,4-dimethylpiperazine and DABCO have two reaction sites in each molecule, they afforded a 1:1-adduct even when half equivalent amount of amine was used.

Experimental

Melting points were measured with Yanagimoto Melting Point Apparatus and described without correction. The IR spectra were recorded on Hitachi Perkin Elmer Infrared Spectrometer model 983 in KBr mull. The ¹H NMR spectra were recorded in CDCl₃ solution at 90 MHz on a Varian Spectrometer model EM390 using TMS as an internal standard.

Materials. α -Diazoacetophenones were synthesized by the reaction of the corresponding acid chlorides with excess of diazomethane in the presence of triethylamine according to Newman's method.⁵⁾ Methyl *p*-nitrophenyldiazoacetate was synthesized by the diazo group transfer reaction reported by Regitz.⁶⁾ Chloroacetonitrile and amines were purified by distillation just before use.

General Procedure of the BF₃-Catalyzed Reaction of Diazo Carbonyl Compounds with Chloroacetonitrile. Diazo carbonyl compound (**1**; 5 mmol) was added in small portions to 20 ml of chloroacetonitrile containing BF₃ etherate (1.0 ml) at –5 °C or 0 °C under magnetic stirring. The reaction proceeded with vigorous evolution of nitrogen gas and gave a gray precipitate. After the N₂ evolution ceased, the reaction mixture was cooled to –15 °C to complete the precipitate formation. The precipitate (BF₃ salt of **3**) was separated by filtration, and was neutralized with saturated aqueous solution of NaHCO₃. Free 2-(chloromethyl)oxazole (**3**)⁷⁾ was

extracted with ether (50 ml) twice. The oxazoles (**3**) were obtained from ether layer, after drying over anhydrous Na₂SO₄, evaporation of solvent. Analytical data of **3** were shown in Table 4.

General Procedure of the Nucleophilic Substitution of **3 with Amines.** A benzene or an ethanol solution (only for methylamine and ethylamine) of 2.0 mmol of 2-chloromethyloxazole (**3a**) was treated with 10 mmol of amine at room temperature or 40 °C. The end point of the reaction was determined by the disappearance of the spot of **3a** in TLC. In the case of primary and secondary amine, solvent and excess amine were evaporated, and the residue was purified by recrystallization from benzene–hexane. The reaction products of tertiary amines were separated by filtration from benzene solution, washed with benzene, and recrystallized from dichloromethane.

References

- 1) J. M. Liesch and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **99**, 1645 (1977); D. A. Evans, C. E. Sacks, W. A. Kleschick, and T. R. Taber, *ibid.*, **101**, 6789 (1979); A. I. Meyers and R. A. Amos, *ibid.*, **102**, 870 (1980); B. H. Lipshutz and R. W. Hungate, *J. Org. Chem.*, **46**, 1410 (1981); A. I. Meyers, J. P. Lawson, and D. R. Carver, *ibid.*, **46**, 3119 (1981); Y. Nagao, S. Yamada, and E. Fijita, *Tetrahedron Lett.*, **24**, 2291 (1983); C. Schregenberger and D. Seebach, *Tetrahedron Lett.*, **25**, 5881 (1984); M. J. Kukla and J. M. Fortunato, *J. Org. Chem.*, **49**, 5003 (1984).
- 2) Many patents have been issued on this subject as shown below; S. Inoue, K. Ohata, T. Tsutsui, and T. Nomura, *Jpn. Kokai Tokkyo Koho*, **79**, 30161 (*Chem Abstr.*, **91**, 56988z); **79**, 30162 (**91**, 56986x); **79**, 30163 (**91**, 74592v); **79**, 30164 (**91**, 74593w); **79**, 30165 (**91**, 74594x); **79**, 30166 (**91**, 74597a); **79**, 30169 (**91**, 56987y); **79**, 30170 (**91**, 91632a); **79**, 30186 (**91**, 39464h); **79**, 30191 (**91**, 91633b); **79**, 30192 (**91**, 39463g); etc.
- 3) T. Ibata and R. Sato, *Chem. Lett.*, **1978**, 1129; *Bull. Chem. Soc. Jpn.*, **52**, 3597 (1979).
- 4) T. Ibata, T. Yamashita, M. Kashiuchi, S. Nakano, and H. Nakawa, *Bull. Chem. Soc. Jpn.*, **57**, 2450 (1984).
- 5) M. S. Newman and P. F. Beal III, *J. Am. Chem. Soc.*, **71**, 1506 (1949).
- 6) M. Regitz, *Chem. Ber.*, **98**, 1210 (1965).
- 7) 2-Chloromethyloxazoles (**3**) are strongly skin irritants.