Formation and Reaction of Oxazoles. Synthesis of *N*-Substituted 2-(Aminomethyl)oxazoles

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Synopsis. The BF_3-catalyzed reaction of substituted α-diazoacetophenones with chloroacetonitrile gave 5-aryl-2-chloromethyloxazoles (**3**) in high yields. Methyl *p*-nitrophenyldiazoacetate also yielded 2-(chloromethyl)-5-methoxy-4-(*p*-nitrophenyl)oxazole. The nucleophilic substitution of **3** with primary, secondary, and tertiary amines afforded the corresponding secondary amines, tertiary amines, and quaternary ammonium salts bearing a 2-oxazolylmethyl group.

The chemistry of oxazoles has strongly been interested in these two decades in connection with the synthesis of biologically active natural products containing oxazole ring system.[1] And also, the oxazoles having an (alkylamino)methyl group or an (dialkylamino)methyl group on C-2 have been paid attention because of their pharmaceutical properties.[2]

The authors have reported the general method of the synthesis of oxazoles through the BF_3-catalyzed reaction of α-diazo carbonyl compounds with nitrile.[3,4] We wish to report here the synthesis of *N*-alkyl-substituted 2-(aminomethyl)oxazole derivatives by the combination of the following two reactions: (i) the BF_3-catalyzed reaction of α-diazo carbonyl compounds with chloroacetonitrile to give 2-(chloromethyl)-oxazoles (**3**), (ii) the nucleophilic substitution reaction of **3** with amines.

Results and Discussion

Synthesis of 2-(Chloromethyl)oxazoles. The BF_3-catalyzed decomposition of substituted α-diazoacetophenones (**1**) in a chloroacetonitrile solution at −5 °C gave BF_3 salts of the corresponding 5-aryl-2-(chloromethyl)oxazoles (**3**) with evolution of nitrogen gas. The free 5-aryl-2-(chloromethyl)oxazoles (**3**) were obtained in high yields after neutralization with sodium hydrogencarbonate (Table 1). Structure of **3** was characterized on the basis of their spectroscopic data: The ^1H NMR signals of CH_2Cl and methine proton of oxazole-C-4 were observed at δ 4.65—4.72 and 7.3—7.5, respectively (Table 1). The yields of **3** are relatively lower than those of reactions of α-diazoacetophenones with acetonitrile.[3] This seems to be attributed to the low electron density on nitrogen atom of chloroacetonitrile.

The reaction of methyl *p*-nitrophenyldiazoacetate with chloroacetonitrile also gave 2-chloromethyl-5-methoxy-4-(*p*-nitrophenyl)oxazole (**3d**; R_1=CH_3O, R_2=*p*-$NO_2C_6H_4$) in moderate yield.

Nucleophilic Substitution Reaction of 2-(Chloromethyl)oxazoles with Amines. The 2-(chloromethyl)-oxazoles (**3**) are expected to have high reactivity toward nucleophilic reagents because they have structures similar to benzyl chloride. The reaction of 2-chloromethyl-5-(*p*-nitrophenyl)oxazole (**3a**: R_1=*p*-$NO_2C_6H_4$, R_2=H) with various primary, secondary, and tertiary amines was studied. The reactions were carried out in a benzene or an alcohol solution at room temperature or 40 °C using five molar equivalents of amines. Primary and secondary amines gave the corresponding secondary and tertiary amines (**4**), having a 2-oxazolylmethyl group in high yields. Aliphatic primary amines gave products **4a—4f** in quite high yields even in the case of bulky *t*-butylamine (Table 2). The ^1H NMR signals of CH_2-N group of these products were observed at δ 3.99—4.02.

2-Aminoethanol gave 2-[(2-hydroxyethylamino)-

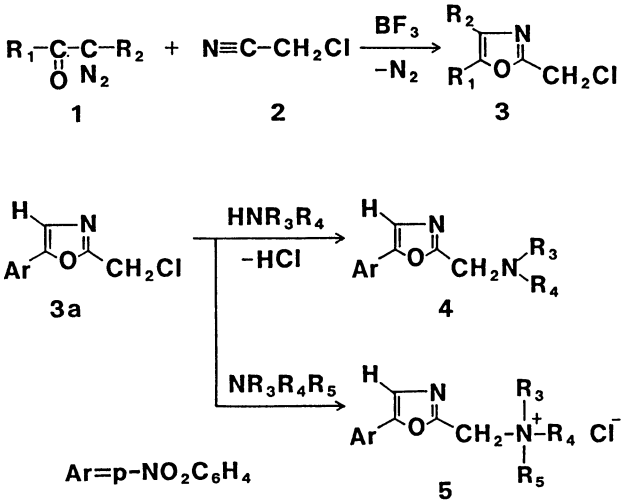


Table 1. Yields, Melting Points, and ^1H NMR Data of **3**

Run	R_1	R_2	Reaction temp/°C	Compd	Yield[a] %	Mp θ_m/°C	^1H NMR/δ CH_2-Cl	^1H NMR/δ C_4-H
a	*p*-$NO_2C_6H_4$	H	−5	**3a**	64	122—3	4.65	7.47
b	*m*-$NO_2C_6H_4$	H	−5	**3b**	64	80—1	4.72	7.49
c	C_6H_5	H	5	**3c**	84	74—5	4.65	7.30
d	CH_3O	*p*-$NO_2C_6H_4$	50	**3d**	45	163—4	4.55	—[b]

a) Yields were based on the diazo carbonyl compounds used. b) A singlet signal of OCH_3 was observed at δ 4.18.

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

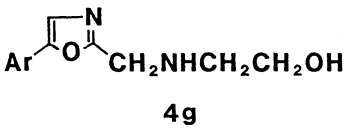
Run	Amine	Reaction Cond. Temp/°C	Time/day	Product	Yield[a] %	Mp θ_m/°C	^{1}H NMR/δ[b] CH_2[c]	C_4-H
Reaction with primary amines[d]								
a	CH_3NH_2[e]	r.t.	4	**4a**	87	61—3	4.02	7.55
b	$CH_3CH_2NH_2$[f]	r.t.	2	**4b**	94	67—8	4.02	7.47
c	$CH_3CH_2CH_2NH_2$	r.t.	16	**4c**	96	[g]	4.01	7.48
d	$(CH_3)_2CHNH_2$	r.t.	5	**4d**	97	48—9	4.02	7.49
e	$(CH_3)_3CNH_2$	40	10	**4e**	99	40—2	3.99	7.48
f	CH_2=$CHCH_2NH_2$	r.t.	10	**4f**	95	40—1	4.02	7.47
g	$HOCH_2CH_2NH_2$	40	20	**4g**	95	Oil	4.05	7.48
h	$(CH_3)_2NCH_2CH_2NH_2$	r.t.	3	**4h**	ca. 80[h,i]	[g]	4.02	7.43
Reaction with secondary amines								
i	$(CH_3CH_2)_2NH$	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	*N*-Methylpiperazine	r.t.	3	**4n**	93	116—9	3.79	7.43
o	$HOCH_2CH_2NHCH_3$	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.

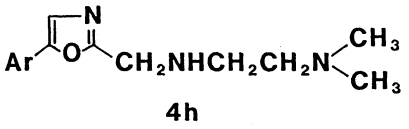
Table 3. Yields, Melting Points, and ^{1}H NMR Data of **5**

Run	Ar	Amine	Reaction time/day	Compd	Yield[a] %	Mp θ_m/°C	^{1}H NMR/δ[b] CH_2[c]	C_4-H
a	*p*-$NO_2C_6H_4$	$(CH_3CH_2)_3N$	100	**5a**	94	200—1	5.35	7.62
b	*p*-$NO_2C_6H_4$	1,4-Dimethylpiperazine[d]	12	**5b**	97	133—7	5.74	7.58
c	*p*-$NO_2C_6H_4$	DABCO[d]	1	**5c**	91	>300	4.94	8.18[e]

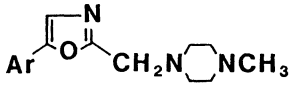
a) Isolated yields on the basis of oxazoles used. b) Measured in $CDCl_3$ unless otherwise noted. c) Methylene group attached to C_2 of oxazole ring. d) A 1 : 1-reaction product was obtained. e) Measured in DMSO-d_6 solution.



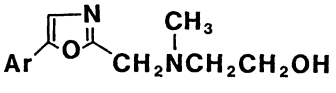
4g



4h



4n



4o

Ar=p−$NO_2C_6H_4$

methyl]-5-(*p*-nitrophenyl)oxazole (**4g**) as a sole product, which was confirmed on the basis of its ^{1}H NMR spectrum. Chemical shift (δ 4.05) of CH_2-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 ^{1}H NMR data. The chemical

Table 4. Results of the Elemental Anlysis 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	$C_{10}H_7N_2O_3Cl$
3b	50.45	2.95	11.75	50.33	2.96	11.74	$C_{10}H_7N_2O_3Cl$
3c	62.06	4.25	7.25	62.03	4.16	7.23	$C_{10}H_8NOCl$
3d	49.11	3.45	10.48	49.18	3.38	10.43	$C_{11}H_9N_2O_4Cl$
4d	59.77	5.76	15.88	59.76	5.79	16.08	$C_{13}H_{15}N_3O_3$
4l	57.91	5.18	14.47	58.12	5.28	14.53	$C_{14}H_{15}N_3O_4$

shifts of N-CH_3 of **4n** (δ 2.30) is quite similar to that of the starting *N*-methylpiperazine (δ 2.26), and CH_2 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 $CDCl_3$ 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 BF_3-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 BF_3 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 N_2 evolution ceased, the reaction mixture was cooled to −15 °C to complete the precipitate formation. The precipitate (BF_3 salt of **3**) was separated by filtration, and was neutralized with saturated aqueous solution of $NaHCO_3$. 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 Na_2SO_4, evaporation of solvent. Analitical 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

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7) 2-Chloromethyloxazoles (**3**) are strongly skin irritating.