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The Acid Catalyzed Decomposition of Diazo Compounds. I. Synthesis of Oxazoles in the BF_3 Catalyzed Reaction of Diazo Carbonyl Compounds with Nitriles

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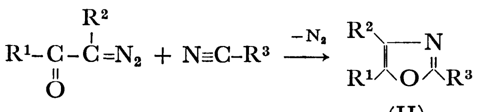
The BF_3-catalyzed decomposition of diazo carbonyl compounds in nitriles have afforded the corresponding oxazoles in high yields. This method is applicable to diazo carbonyl compounds such as *m*- and *p*-substituted diazoacetophenones, ethyl diazoacetate, 1,2-diphenyl-2-diazoethanone, dibenzoyldiazomethane, and dimethyl diazomalonate. Bis(diazo ketone)s such as terminal bis(diazoacetylated) alkanes (III_{1-4}: $n=6$, 8, 10, 12) and *m*- and *p*-bis(diazoacetyl)benzenes also gave the corresponding bisoxazoles in a similar reaction. The reaction has been interpreted in terms of a stepwise mechanism *via* betaine intermediates initiated by the attack of BF_3 on the carbonyl oxygen of diazo carbonyl compounds. The emission spectra of oxazoles are described.

The synthesis of oxazoles has been the subject of numerous studies in connection with the pharmaceutical properties of oxazole derivatives.¹⁾ Most of the methods reported however are not satisfactory as a general method for the synthesis of oxazoles because of the low yield of oxazoles and the difficulties in obtaining the starting materials.



(I) (II)

The 1,3-dipolar cycloaddition of carbonylcarbene to the carbon-nitrogen triple bond of the cyano group was first proposed by Huisgen *et al.* to give oxazoles (II) having arbitrary substituents on C-2, C-4, and C-5 positions.²⁾ In accordance with this working hypothesis, the thermal,²,³⁾ phtochemical,⁴⁾ and transition metal catalyzed²,³⁾ decomposition of diazo carbonyl compounds in nitriles were studied. The yields of oxazoles were not high even though the use of copper²,³ᵃ⁾ and π-allylic palladium⁵⁾ catalysts which were employed to prevent the Wolff rearrangement of the diazo carbonyl compound. Nozaki *et al.* improved the yield (up to 66%) using WCl_6 as a catalyst.⁶⁾ The by-product formation of α-chlorinated ketones was not inevitable in this reaction. Recently Doyle *et al.* reported the $AlCl_3$-catalyzed reaction of α-unsubstituted diazo ketones and nitriles giving oxazoles in high yields.⁷⁾ In a previous paper in this series the BF_3-catalyzed decomposition of diazo carbonyl compounds in nitriles to give oxazoles in high yields was reported.⁸⁾ In this paper this method has been employed to the synthesis of several substituted oxazoles.

Results and Discussion

The BF_3-catalyzed decomposition of α-diazoacetophenone in an excess of acetonitrile proceeded with vigorous evolution of nitrogen and gave 2-methyl-5-phenyloxazole (II_1) in 94% yield. This method is applicable to other nitriles. Propionitrile, isobutyronitrile, phenylacetonitrile, benzonitrile, *p*-methoxybenzonitrile, cinnamonitrile, and chloroacetonitrile gave oxazoles in high yields. (Phenylthio)acetonitrile afforded *N*-phenacyl-α-(phenylthio)acetamide (12%) together with 2-phenylthiomethyl-5-phenyloxazole (II_9). Under these circumstances neither the expected cyanomethylphenylsulfonium phenacylide nor the (cyanomethyl)phenacylphenyl sulfonium salt was obtained despite a detailed inspection of the reaction mixture by column chromatography.⁹⁾ This indicates the higher reactivity of the cyano group towards the diazonium type intermediate (VII) than that of the sulfur atom. Methyl cyanoacetate yielded oxazole (II_{10}) in moderate yields with accompanying intractable oily products. The electron attracting substituent on the nitrile lowered the yield of oxazole, *e.g.*, *p*-nitrobenzonitrile gave the oxazole (II_7) in lower yield than in the cases of benzonitrile and *p*-methoxybenzonitrile.

The *m*- and *p*-substituted α-diazoacetophenones, 12-cyano-1-diazo-2-dodecan-2-one, ethyl diazoacetate, and 1,2-diphenyl-2-diazoethanone also gave 5-aryl-2-methyloxazoles (II_{12-23}), 5-(*p*-methoxyphenyl)-2-ethyloxazole (II_{24}), 5-(ω-cyanodecyl)-2-methyloxazole (II_{25}), 5-ethoxy-2-methyloxazole (II_{26}), and 3,5-diphenyl-2-methyloxazole (II_{27}) respectively. Both the electron-attracting and electron-releasing substituents on a benzene ring of diazoacetophenones do not effect the yield of the oxazoles and the rate of the reaction. A benzoyl group or a methoxycarbonyl group attached to a diazomethyl carbon atom however suppressed the reaction and consequently elevated temperatures were necessary for completion of the reaction. Some dimethyl diazomalonate was recovered even after prolonged heating of the reaction mixture (80 °C, 50 h) and caused a low yield of oxazole (II_{29}).

The NMR data shows that the chemical shift of the oxazole ring proton (C_4–H) is effected by the substituent on C_5 rather than that on C_2 (Table 1). Electron-attracting groups on the benzene ring attached to C_5 deshielded the C_4–H and an alkyl group on C_5 shielded the C_4–H.

Bis(diazo ketone)s such as α,ω-bis(diazoacetyl)alkanes (III_{1-4}: $n=6$, 8, 10, 12) and *m*- and *p*-bis(diazoacetyl)benzenes ($V_{1,2}$) gave bisoxazolyl compounds (IV_{1-4}) and ($VI_{1,2}$: $R=CH_3$; VI_3: $R=Ph$) in the reaction with acetonitrile or benzonitrile.

In the experimental work conducted here an excess of BF_3 was used although a catalytic amount of BF_3 is

Table 1. Yields, melting points, and NMR data of oxazoles (II)

Compd	R^1	R^2	R^3	Reaction temp/°C	Yield %	Mp/°C	NMR(δ/ppm, $CDCl_3$)		
							C_4-**H**	C_2-$\mathbf{CH_3}$	Others[a]
II_1	C_6H_5	H	CH_3	5	94	58—59	7.15	2.48	
II_2	C_6H_5	H	CH_3CH_2	5	99	oil	7.13	—	1.33(t), 2.80(q) C_2H_5
II_3	C_6H_5	H	$(CH_3)_2CH$	5	82	oil	7.15	—	1.35(d), 3.12(sep) *i*-Pr
II_4	C_6H_5	H	$C_6H_5CH_2$	5	77	91—92	7.20	—	4.10 CH_2
II_5	C_6H_5	H	C_6H_5	5	92	74—75	b)	—	
II_6	C_6H_5	H	*p*-$CH_3OC_6H_4$[c]	5	82	104—105	b)	—	3.85 OCH_3
II_7	C_6H_5	H	*p*-$NO_2C_6H_4$[c]	5	17	215—216	b)	—	
II_8	C_6H_5	H	$C_6H_5CH{=}CH$	10	76	103—104	7.05	—	d)
II_9	C_6H_5	H	$C_6H_5SCH_2$	10	44	48—49	b)	—	4.20 SCH_2
II_{10}	C_6H_5	H	CH_3OOCCH_2	10	46	oil	7.24	—	3.90 CH_2, 3.73 OCH_3
II_{11}	C_6H_5	H	$ClCH_2$	5	86	74—75	7.30	—	4.65 CH_2Cl
II_{12}	*p*-$CH_3OC_6H_4$	H	CH_3	5	95	107—108	7.08	2.50	3.83 OCH_3
II_{13}	*p*-$CH_3C_6H_4$	H	CH_3	5	96	56—57	7.08	2.45	2.30 CH_3
II_{14}	*p*-ClC_6H_4	H	CH_3	5	83	86—87	7.17	2.47	
II_{15}	*p*-BrC_6H_4	H	CH_3	5	88	98—100	7.18	2.52	
II_{16}	*p*-CNC_6H_4	H	CH_3	5	76	125—126	7.33	2.53	
II_{17}	*p*-$NO_2C_6H_4$	H	CH_3	5	84	167—168	7.45	2.42	
II_{18}	*m*-$CH_3OC_6H_4$	H	CH_3	5	94	oil	7.12	2.40	3.77 OCH_3
II_{19}	*m*-$CH_3C_6H_4$	H	CH_3	5	93	oil	7.13	2.45	2.32 CH_3
II_{20}	*m*-ClC_6H_4	H	CH_3	5	91	oil	7.20	2.48	
II_{21}	*m*-BrC_6H_4	H	CH_3	5	83	oil	7.20	2.43	
II_{22}	*m*-CNC_6H_4	H	CH_3	5	95	95—96	7.28	2.55	
II_{23}	*m*-$NO_2C_6H_4$	H	CH_3	5	89	100—101	7.35	2.50	
II_{24}	*p*-$CH_3OC_6H_4$	H	C_2H_5	5	87	61—62	7.12	—	3.83 OCH_3 1.37(t), 2.84(q) C_2H_5
II_{25}	$NC(CH_2)_{10}$	H	CH_3	5	83	oil	6.58	2.38	d)
II_{26}	C_2H_5O	H	CH_3	20	62	oil	5.95	2.02	1.40(t), 4.08(q) C_2H_5
II_{27}	C_6H_5	C_6H_5	CH_3	5	68	oil	—	2.55	
II_{28}	C_6H_5	C_6H_5CO	CH_3	80	79	oil	—	2.50	
II_{29}	CH_3	CH_3OOC	CH_3	80	32	oil	—	2.35	3.85, 4.13 OCH_3

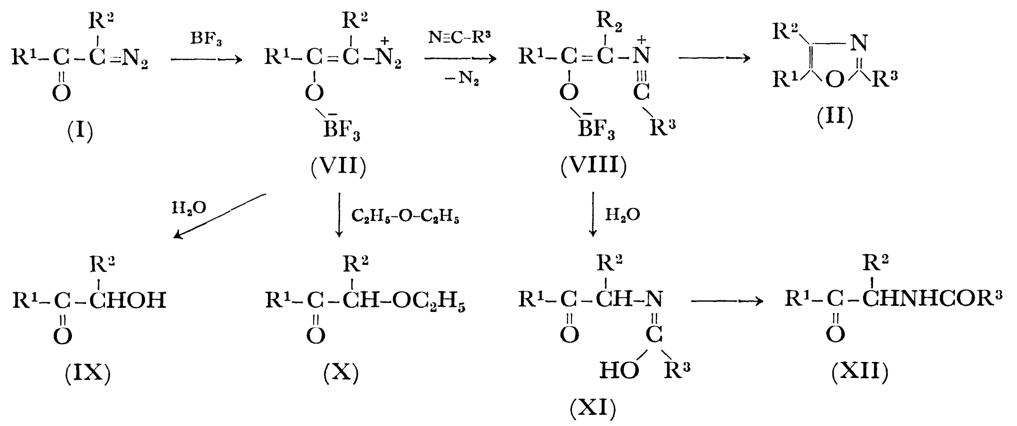
a) The signals of aromatic protons are omitted, and the signal patterns are singlet unless otherwise indicated. b) The signal of C_4–H was not distinguishable from those of the aromatic protons. c) Five molar amount of nitrile was reacted in benzene solution. d) The signals of vinyl and polymethylene protons are omitted.

Table 2. Yields, melting points, and NMR data of bisoxazolyl compounds

Oxazole	Diazocarbonyl Compound	R-CN	Reaction temp/°C	Yield %	Mp/°C	NMR (δ/ppm, $CDCl_3$)	
						C_4-**H**	C_2-$\mathbf{CH_3}$
IV_1	$N_2CHCO(CH_2)_6COCHN_2$	CH_3CN	5	95	60—61	6.58	2.40
IV_2	$N_2CHCO(CH_2)_8COCHN_2$	CH_3CN	5	96	70—71	6.55	2.38
IV_3	$N_2CHCO(CH_2)_{10}COCHN_2$	CH_3CN	5	95	70—71	6.57	2.37
IV_4	$N_2CHCO(CH_2)_{12}COCHN_2$	CH_3CN	5	95	73—75	6.55	2.40
IV_1	*m*-$N_2CHCOC_6H_4COCHN_2$	CH_3CN	5	98	103—104	7.27	2.53
VI_2	*p*-$N_2CHCOC_6H_4COCHN_2$	CH_3CN	60	78	233—234	7.28	2.55
VI_3	*p*-$N_2CHCOC_6H_4COCHN_2$	C_6H_5CN	60	80	236—237	b)	—

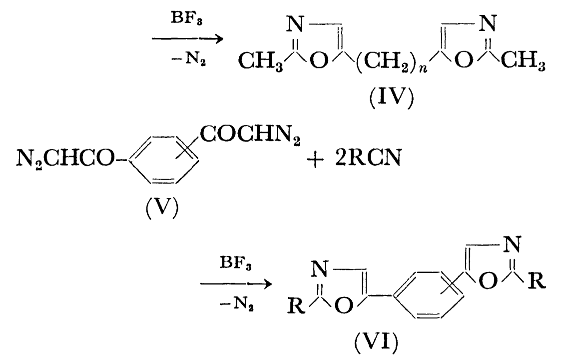
a) Signals of aromatic and polymethylene protons are omitted. b) Signal of C_4–H was not distinguishable from those of the aromatic protons.

sufficient for completion of the reaction. The reaction is reasonably explained by a stepwise mechanism *via* betaine intermediates, unlike the 1,3-dipolar cycloaddition of carbonylcarbene towards the carbon-nitrogen triple bond of nitrile proposed for the thermal and transition metal catalyzed reactions.[2,3] The reaction is initiated by the attack of BF_3 on the carbonyl-oxygen of the diazo carbonyl compound affording a diazonium type intermediate (VII).[9] The intermediacy of VII was supported by the facts that α-hydroxy or α-ethoxy ketones (IX, X) were obtained when the reaction was conducted in the presence of water or diethyl ether.[10,11] The electrophilic attack of the intermediate (VII) on the nitrogen atom of the nitrile may form a betaine intermediate (VIII) with the elimination of nitrogen. The electron-attracting substituent on the nitrile may retard this step and subsequently lower the yield of oxazole (Table 1 run 7). The reaction conducted in



Scheme 1.

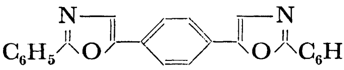
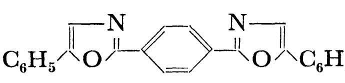
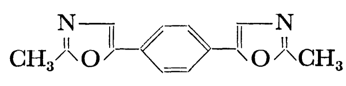
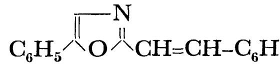
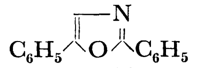
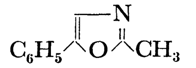
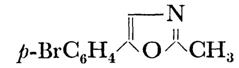
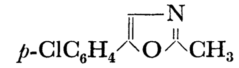
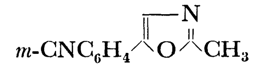
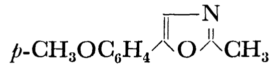
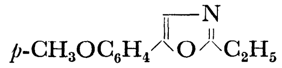
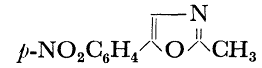
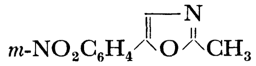
$N_2CHCO\text{-}(CH_2)_n\text{-}COCHN_2 + 2CH_3CN$
(III: n=6, 8, 10, 12)



acetonitrile containing a trace amount of H_2O gave N-(aroylmethyl)acetamide (XII: R^1=Ar, R^2=H, R^3=CH_3) together with oxazole and α-hydroxyacetophenone (IX). The formation of XII supports the existence of an intermediate (VIII) as shown in Scheme 1. The attack of VIII on a water molecule competes with the intramolecular cyclization of VIII which gives the oxazole.

Several oxazole derivatives have been found to exhibit fluorescence properties and have been used as liquid scintillators.[1b)] The bisoxazolyl compound, 1,4-bis(5-phenyl-2-oxazolyl)benzene (VI_3), is an isomer of the well known scintillator POPOP, 1,4-bis(2-phenyl-5-oxazolyl)benzene, and shows strong emission bands at 405 nm. The UV and fluorescence spectral data of oxazoles are listed in Table 3.

Table 3. UV and emission data of oxazoles

Oxazole	UV λ_{max}/nm	UV log ε	Emission λ/nm
	341 353	4.67 4.74	405
	346 360 369	4.68 4.74 4.52	417
	298 310 325	4.61 4.70 4.56	348
	261 338	3.75 4.22	405
	305 316	4.41 4.38	360
	265 272	4.29 4.29	315
	273 279	4.33 4.35	320
	271 280	4.36 4.37	326
	274	4.29	342
	275	4.32	332
	275	4.36	332
	233 327	4.02 4.26	a)
	262	4.42	a)

a) Emission spectrum was not measured.

Experimental

All melting points were taken with a Yanagimoto Melting Point Apparatus and are uncorrected. The IR spectra were measured on a Hitachi Infrared Spectrometer model 215. The ^1H-NMR spectra were recorded in $CDCl_3$ solution at 60 MHz on a Varian Spectrometer model EM-360 using TMS as an internal standard. UV spectra were measured on a Hitachi Spectrometer model 323 in ethanol solution. Emission spectra were recorded on Hitachi Emission Spectrometer model MPE-2A in ethanol solution (1—5×10^{-6} mol/l).

Materials. Diazoacetophenones,[12)] ethyl diazoacetate,[13)] 1,2-diphenyl-2-diazoethanone,[14)] dibenzoyldiazomethane,[15)] and dimethyl diazomalonate[16)] were synthesized by the methods described in the literature. Liquid nitriles were purified by distillation of commercial reagents after refluxing over P_2O_5. p-Methoxybenzonitrile and p-nitrobenzonitrile were purified by recrystallization.

General Procedure of the BF_3 Catalyzed Reaction of Diazo Carbonyl Compounds in Acetonitrile. A solution of the diazo carbonyl compound (3 mmol) in acetonitrile (3 ml) was added dropwise to acetonitrile (10 ml) containing BF_3–etherate (1.0 ml) under magnetic stirring at temperatures described in the Tables. After the vigorous evolution of N_2 ceased the reac-

TABLE 4. ANALYTICA DATA OF OXAZOLES

Compd	Molecular formula	Found (%)			Calcd (%)		
		C	H	N	C	H	N
II$_4$	$C_{16}H_{13}ON$	81.58	5.65	5.98	81.68	5.57	5.95
II$_6$	$C_{16}H_{13}O_2N$	76.43	5.22	5.53	76.47	5.22	5.57
II$_7$	$C_{15}H_{10}O_3N_2$	67.87	3.86	10.38	67.66	3.79	10.52
II$_8$	$C_{17}H_{13}ON$	82.52	5.27	5.76	82.57	5.30	5.66
II$_9$	$C_{16}H_{13}ONS$	72.04	4.89	5.20	71.88	4.90	5.24
II$_{11}$	$C_{10}H_8ONCl$	62.06	4.25	7.25	62.03	4.16	7.23
II$_{12}$	$C_{11}H_{11}O_2N$	69.85	5.90	7.48	69.82	5.86	7.40
II$_{13}$	$C_{11}H_{11}ON$	76.27	6.34	8.09	76.27	6.40	8.09
II$_{14}$	$C_{10}H_8ONCl$	62.08	4.16	7.30	62.03	4.17	7.23
II$_{15}$	$C_{10}H_8ONBr$	50.60	3.42	5.88	50.44	3.39	5.88
II$_{16}$	$C_{11}H_8ON_2$	71.93	4.40	15.31	71.72	4.38	15.21
II$_{17}$	$C_{10}H_8O_3N_2$	58.54	3.91	13.75	58.82	3.95	13.72
II$_{22}$	$C_{11}H_8ON_2$	71.70	4.44	15.17	71.72	4.38	15.21
II$_{23}$	$C_{10}H_8O_3N_2$	59.06	4.05	13.72	58.82	3.95	13.72
II$_{24}$	$C_{12}H_{13}O_2N$	70.78	6.46	6.97	70.91	6.45	6.89
II$_{29}$	$C_7H_9O_4N$	49.38	5.45	8.25	49.12	5.30	8.18
IV$_1$	$C_{14}H_{20}O_2N_2$	67.59	8.00	11.12	67.71	8.12	11.28
IV$_2$	$C_{16}H_{24}O_2N_2$	69.32	8.74	9.87	69.53	8.75	10.14
IV$_3$	$C_{18}H_{28}O_2N_2$	70.73	9.10	9.11	71.01	9.27	9.20
IV$_4$	$C_{20}H_{32}O_2N_2$	71.97	9.58	8.30	72.25	9.70	8.43
VI$_1$	$C_{14}H_{12}O_2N_2$	70.06	4.97	11.68	69.99	5.03	11.66
VI$_2$	$C_{14}H_{12}O_2N_2$	70.01	4.95	11.66	69.99	5.03	11.66
VI$_3$	$C_{24}H_{16}O_2N_2$	79.10	4.43	7.72	79.10	4.43	7.96

tion mixture was poured into H_2O (50 ml) and ether (50 ml). The ether layer was extracted twice with 3 M HCl and the combined aqueous solution made basic with $NaHCO_3$. The separated oxazole was extracted with ether and purified by recrystallization.

General Procedure of the BF_3 Catalyzed Reaction of Diazo Carbonyl Compounds in Liquid Nitriles. The Diazo carbonyl compound (3 mmol) was treated in the similar manner described above in an excess of liquid nitrile. The oxazoles ($R^3 \neq CH_3$) could not be extracted with 3 M HCl and therefore the reaction mixture was treated with H_2O and extracted twice with ether (2×20 ml) after the solution was made basic with $NaHCO_3$. The ether extract was dried over Na_2SO_4, the ether evaporated, and column chromatographed over silica gel.

Reaction with Solid Nitriles. A five molar equivalent of the nitrile was reacted with α-diazoacetophenone in dried benzene (20 ml). The reaction mixture was separated by column chromatography after the usual work up.

Reaction of m-*Chloro-α-diazoacetophenone in Water Containing Acetonitrile.* *m*-Chloro-α-diazoacetophenone (1 mmol) was decomposed in water containing acetonitrile[17] (20 ml) at 5 °C. Column chromatography of the reaction mixture gave three products: 5-(*m*-chlorophenyl)-2-methyloxazole (II$_{20}$, 55 %), α-hydroxy-*m*-chloroacetophenone (12%), and *N*-(*m*-chlorophenacyl) acetamide (XII: R^1=*m*-ClC_6H_4, R^2=H, R^3=CH_3): colorless crystals; mp 118—119 °C; yield 0.057 g, 27 %; IR (KBr) 1690 (C=O), 1650, 3280 cm^{-1} (amide); NMR ($CDCl_3$) δ 2.41 (s, 3H, CH_3), 4.97 (d, 2H, CH_2), 6.8 (broad s, 1H, NH), 7.4—8.2 ppm (m, 4H, Ar). Found: C, 56.66; H, 4.80; N, 6.63%. Calcd for $C_{10}H_{10}O_2NCl$: C, 56.75; H, 4.76; N, 6.62%.

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