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The Reaction of 1,3,5-Triazine with Aromatic Nitrile Oxides. A New Synthesis of 3-Substituted 1,2,4-Oxadiazoles

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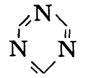
The cycloaddition of aromatic nitrile oxides(**2a**=benzo-; **2b**=*p*-tolu-; **2c**=mesitylenecarbo-) with 1,3,5-triazine(**1**) is reported. The corresponding 3-substituted 1,2,4-oxadiazoles(**3a**,**b**,**c**) are obtained in fair yields only when BF_3 is added. It was stoichiometrically confirmed that one mol of **1** behaves so as to supply three mols of azomethine radicals. A reaction scheme initiated from a two-step cycloaddition of **2** to **1** activated by BF_3 is suggested. The mixture, **1** : **2c** : BF_3 = 1 : 3 : 1, afforded a better yield of **3c**(69%) than an equimolar mixture of **2c** with ethyl formimidate or formamidine.

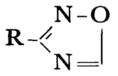
Grundmann and Kreutzberger[1—5] have investigated a variety of reactions of 1,3,5-triazine(**1**) with many kinds of nucleopiles. This paper is concerned with an unpublished reaction of **1** with nitrile oxides(**2**) which are well-known 1,3-dipoles for cycloaddition.[6a] Several aromatic **2** were treated with **1**, but 3-substituted 1,2,4-oxadiazoles(**3**), potential intermediates for organic synthesis, were obtained in fair yields only when boron trifluoride diethyl etharate(BF_3) was added to the mixtures.



1

$R\text{-}CN{\rightarrow}O$

2



3

2a, **3a**: $R=C_6H_5$
2b, **3b**: $R=p\text{-}CH_3C_6H_4$
2c, **3c**: $R=2,4,6\text{-}(CH_3)_3C_6H_2$

Experimental

Materials. **1** was prepared by Schaefer's method,[3] mp 81.6 °C(85—86),[3] N, 51.83% (52.13). Benzohydroximoyl chloride, mp 51.7 °C(49—50),[7] and *p*-toluhydroximoyl chloride, mp 67.2 °C, Cl, 20.90%(20.90) were obtained from the corresponding aldoximes by the usual manner.[7] **2c** was obtained by the previously reported method[8] from 2,4,6-trimethylbenzaldehyde oxime, mp 112.5—113.5 °C (114).[6] Hydrogen cyanide was generated from potassium cyanide and sulfuric acid and distilled over posphorus pentaoxide, bp 26 °C.

*Typical Procedure for the Reaction of **1** with **2**.* An equivalent amount of triethylamine is added to a tetrahydrofuran (THF) solution of a few grams of benzohydroximoyl chloride and *p*-toluhydroximoyl chloride, respectively, to generate **2a** and **2b**, and thus precipitated triethylamine hydrochloride is removed by filtration. These procedures and the handling of the resulting solutions of **2a** and **2b** are carried out under cooling with salt and ice mixture. **2c** is stable for a long time in both solid and solution at room temperature.[6]

In the case of *Method A*, BF_3 is added dropwise to a mixture of **1** and the smallest amount of solvent under stirring. To the resulting slurry a solution of **2** is added within half an hour. In the case of *Method B*, BF_3 is added to a solution of **1** and **2**. After the stirring has been continued according to the time and temperature schedule given in Figs. 1 and 2 and Table 2, the reaction mixture is neutralized with an aqueous potassium carbonate solution, separated from the solvent by means of mild evacuation, and then shaken with heptane. The extract is analyzed by the use of gas-liquid phase chromatography(GLC) to determine the yield of **3**, and then distilled *in vacuo*. A fraction of **3** underwent further

Table 1. Analytical data of 3-substituted 1,2,4-oxadiazoles(**3**) (1 Torr = 133.322 Pa)

3	Bp, t/°C (Torr)	Mp, t/°C	M_W[a]	C %	H %	N[b] %
3a	70 (71—2)[11]	19.2 (15.5)[11]	146 (146.2)	65.77 (65.74)	4.13 (4.14)	19.07 (19.17)
3b	81	34.0	160 (160.2)	67.38 (67.48)	5.05 (5.03)	17.53 (17.49)
3c	91.5	62.4	188 (188.2)	70.07 (70.18)	6.45 (6.43)	14.92 (14.88)

	IR, cm^{-1} [c]					NMR ($CDCl_3$), ppm[d]			
3a	3125	1520—1320	1100	880	788	7.5 (t, 3) Ph-3,4,5	8.1 (d, 2) Ph-2,6	8.8 (s, 1) C_2ON_2-5	
3b	3115	1530—1320	1100	880	745	2.4 (s, 3) 4-Me	7.3 (d, 2) Ph-3,5	8.0 (d, 2) Ph-2,6	8.7 (s, 1) C_2ON_2-5
3c	3115	1530—1315	1108	852	722	2.2 (s, 6) 2,6-Me	2.3 (s, 3) 4-Me	7.0 (s, 2) Ph-3,5	8.9 (s, 1) C_2ON_2-5

a) From the parent peak of MS. Theoretical values are given in parentheses. b) From elemental analysis. Calculated values are given in the parentheses. c) Be common in 3-substituted oxadiazole group. d) Assignments are shown under each peak.

Table 2. Reaction of aromatic nitrile oxides(**2**) with 1,3,5-triazine(**1**)[a]

2	Solvent (cm^3/mol of **1**)	Reaction[b] method	Temp t/°C Initial	Temp t/°C End	Yield[c] %
2a	THF (1650)	*A*	−20	60	26.6
2b	THF (1350)	*A*	−20	60	11.9
2c	THF (3000)	*A*	40	60	51.8
2c	Benzene (3000)	*B*	40	80	35.2
2c	Benzene (900)	*B*	40	80	69.0

a) All the reactions were carried out with the molar ratio, **1** : **2** : BF_3 = 1 : 3 : 1. b) See Experimental. c) Theoretical yield of **3** based on **2**.

purification on preparative GLC for supplying the analytical data given in Table 1.

Results and Discussion

The following was confirmed by a preliminary test: **1** is stable to BF_3 in inert solvents at temperatures up to 60 °C and produces an adduct of fine needles with BF_3. **2c** is unstable under the same conditions and rapidly converted into mesitylenecarbonitrile and a caramel-like polymer. When **1**, **2c**, and BF_3 are put together, the self-conversion of **2c** competes with the cycloaddition leading to **3c**.

The yield of **3c** is its maximum when the molar ratio of BF_3 to **1** is 0.3—0.5, as shown in Fig. 1; when the ratio is increased beyond this range, the yield is decreased, probably because of the extensive advance of the self-conversion of **2c**. Increase in the concentrations of the reactants and a molar ratio of **1** to **2** are effective for suppressing the self-conversion of **2**, and as a result, an increase in the yield of **3**, and also the dropwise addition of **2** to a mixture of **1** and BF_3 is similarly effective (Table 2). Use of BF_3 is also effective in the case of **2a** and **2b** in spite of their smaller steric hindrances than **2c**. The yields of **3a** and **3b** were both poor presumably because of the poor stability of **2a** and **2b**.[6b)]

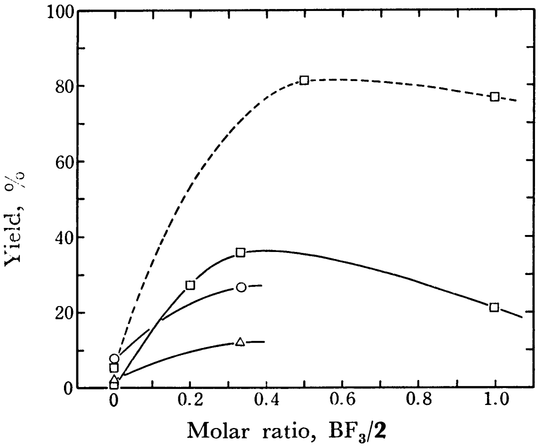


Fig. 1. Plots of yield of **3** based on **2** *vs.* molar ratio of BF_3 to **2**. —○—: **1** : **2a** : THF = 1 mol : 3 mol 1500 cm^3 by reaction *Method A*, —△—: **1** : **2b** : THF = 1 mol : 3 mol : 1500 cm^3 by reaction *Method A*, —□—: **1** : **2c** : benzene = 1 mol : 3 mol : 3000 cm^3 by reaction *Method B*, --□--: **1** : **2c** : benzene = 1 mol : 1 mol : 1000 cm^3 by reaction *Method B*.

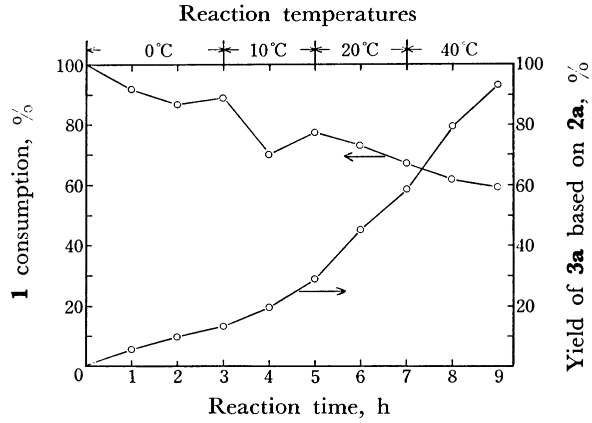
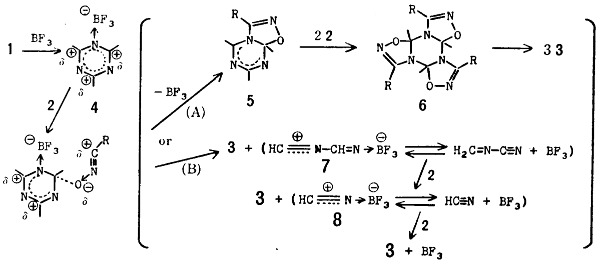


Fig. 2. Time dependence of the composition of the reaction mixture started with the ratio, **1** : **2c** : BF_3 : benzene = 1 mol : 1 mol : 0.5 mol : 1000 cm^3.

Equation 1 satisfies the experimental fact that the yield of **3c** amounted to 69% when the reaction was started with the molar ratio of **1** to **2c** as one-third (see Table 2).

$$\mathbf{1} + 3\ \mathbf{2} \longrightarrow 3\ \mathbf{3} \tag{1}$$

It is noticeable that several dipolarophiles such as aliphatic carbonyls and nitriles without electron attractive moieties can be activated by an addition of BF_3 to undergo cycloaddition with **2**.[9)] The role of BF_3 in the cycloaddition in this study is thought to activate the dipolarophile, **1**, too. The reaction scheme is inferred as Eq. 2.



(2)

4 presumed to be an activated form of **1** by BF_3 is attacked on the carbon atom by the oxygen atom of **2** and then derived to the 1:1 adduct, **5**, or split to **3** and **7** by way of a two-step cycloaddition. Additional two moles of **2** may attack the intermediates, **5** or **7** and **8**, resulting in three molecules of **3** by the route A or B. When the initial molarities of **1** and **2c** have been made equal, merely one-third mole of **1** is consumed for the formation of every one mole of **3c** during the reaction (Fig. 2). This shows that the intermediate systems containing **5** or **7** and **8** are more susceptible to the attack of **2** than **4**. Whether route A or B prevails could not be verified,[10)] since these intermediates have never been isolated.

The formation of maximal 3 mol of **3** from 1 mol of **1** demonstrates the usefulness of **1** as a starting material

TABLE 3. REACTION OF **2c** WITH HYDROGEN CYANIDE AND ITS DERIVATIVES TO FORM **3c**[a)]

Dipolarophile (mol/mol-**2c**)	Catalyst (mol/mol-**2c**)	Solvent	Reaction temp t/°C	Yield[b)] %
HCN (3)[c)]	BF_3 (0.5)	Benzene	0—60	0
$HC(NH)OC_2H_5$ (1)[d)]	—	EtOH	17—40	33.4
$HC(NH)NH_2$ (1)[e)]	—	EtOH	11—60	59.0

a) 2000 cm^3 of solvent was used for one mol of **2c**. b) Theoretical yield of **3c** based on **2c**. c) Hydrogen cyanide was mostly recovered unreacted. d) An equiv. amount of 1,8-diazabicyclo[5,4,0]undec-7-ene was added to the mixture of ethyl formimidate hydrochloride and **2c**. e) An equiv. amound of triethylamine was added to the mixture of formamidine hydrochloride and **2c**.

for **3**. As a comparison, hydrogen cyanide and its two derivatives were subjected to cycloaddition with **2c**.

$$\left.\begin{array}{l} HCN \\ HC(NH)OC_2H_5 \\ HC(NH)NH_2 \end{array}\right\} \xrightarrow{\mathbf{2c}} \mathbf{3c} \qquad (3)$$

The results are given in Table 3. It is seen that formamidine is comparative to **1** with respect to the yield of **3c**. However, formamidine is usually prepared from hydrogen cyanide *via* formimidate. Thus it is less accessible than **1** which is prepared directry from hydrogen cyanide.[3)] As regards synthesis of **3** without use of **2**, the reactions of amidoxime with acetic formic unhydride,[11)] formamide,[12)] trialkyl orthoformates,[14,15)] and *N*,*N*-dimethyl-α,α-dimethoxymethylamine[15)] have been reported to give sometimes good yields.

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