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The Action of Boron Trifiuoride on Aromatic Nitrile Oxides

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Synopsis. The action of boron trifluoride etherate on stable aromatic nitrile oxides effected the isomerization of nitrile oxides into isocyanates competitively with their dimerization to 1,4,2,5-dioxadiazines and/or (1,2,4-oxadiazol-4-io) oxytrifluoroborates. Quenching the reaction with methanol at an earlier stage of the reaction gave methyl benzohydroximate. The reacion was interpreted in terms of the initial coordination of BF_3 with the nitrile-oxide-oxygen atom.

We found the catalytic isomerization of stable aromatic nitrile oxides (NO, **1**) into isocyanates with some Lewis acids. Morrocchi and his co-workers reported the reaction of 2,4,6-trimethylbenzonitrile oxide (**1b**) with BF_3 forming 3,5-bis-(2,4,6-trimethylphenyl)-1,2,4-oxadiazol-4-io]oxytrifluoroborate (**5b**) and 3,6-bis(2,4,6-trimethylphenyl)-1,4,2,5-dioxadiazine (**4b**),[1] but they did not mention the formation of isocyanate. No catalytic isomerization of nitrile oxides has been reported except that with sulfur dioxide, which has been established to proceed *via* a 1,3-dipolar cycloadduct.[2] Here we report the multiplicity of the action of boron trifluoride on stable nitrile oxides.

Results and Discussion

An equimolar reaction of 2,3,5,6-tetramethylbenzonitrile oxides (**1a**) with $BF_3 \cdot OEt_2$ in refluxing dichloromethane gave 2,3,5,6-tetramethylphenylisocyanate (**2a**) in 55% yield. The treatment of the reaction mixture with methanol improved the recovery of **2a** up to 78% as methyl 2,3,5,6-tetramethylphenylcarbamate (**3a**). Various Lewis acids were also found to effect the isomerization of NO (Table 1), though in unsatisfactory yields because of the formation of a sticky mass. The reaction with $BF_3 \cdot OEt_2$ was rather clean, though, and so a detailed investigation was conducted on it (Table 2). The products varied with the reaction conditions employed. In the reaction in dichloromethane, **3a** was obtained as the sole isolable product, but in benzene, 2,4-bis-(2,3,5,6-tetramethylphenyl)-1,4,2,5-dioxadiazine (**4a**) was obtained along with **3a**. In toluene or xylene, a small amount of [3,5-bis(2,3,5,6-tetramethylphenyl)-1,2,4-oxadiazol-4-io]oxytrifluoroborate (**5a**) was obtained in aditdion to **3a** and **4a**. On the contrary, **5a** was the main product in ether, accompanied by a small amount of **3a**. In diisopropyl ether, the three products were obtained in comparable yields. It is noteworthy that the formation of **5a** was favorable compared with that of **4a** in a more polar solvent and that of **4a** in a less polar one. Table 2 also shows that the molar ratio of BF_3/NO influences on the products composition in the reactions in benzene or ether. Morrocchi *et al.* reported the reaction of **1b** with gaseous BF_3 or $BF_3 \cdot OEt_2$ forming **4b** and **5b**.[1] They suggested that **4b** was formed by the bimolecular cyclization of BF_3 coordinated NO. This speculation seems inconsistent with our experimental results. If it were the case, **4a** should be formed favorablly at a higher BF_3/NO ratio, but our result was the opposite as seen in the reactions in benzene. Furthermore, when the reaction was quenched with methanol soon after the addition of $BF_3 \cdot OEt_2$ in the solution of **1b**, methyl 2,4,6-trimethylbenzohydroximate (**9b**) was obtained in a moderate yield in the reaction in either benzene or ether. **9b** was obtained by Grundmann and Frommeld[3] by the methanolysis of **1b** with sulfuric acid. The result implies that the reaction proceeds through the initial coordination of BF_3 with the NO oxygen atom. A subsequent reaction of the free NO with the BF_3-coordinated one (**6**) is considered to afford **4** and **5**. At this stage, two conformers, **7** and **8**, are conceivable for the intermediate; **8** is more stable in polar solvents, and **7** in less polar ones. **7** and **8** may lead to **4** and **5** respectively.

Table 1. Yield of the urethane in the reaction of the nitrile oxide with various Lewis acids

Nitrile oxide	Lewis acid	Product	Yield/%
1a	$BF_3 \cdot OEt_2$	**3a**	78
1a	$TiCl_4$	**3a**	55
1a	$SnCl_4$	**3a**	43
1a	BBr_3	**3a**	25
1b	$BF_3 \cdot OEt_2$	**3b**	72
1b	$SnCl_4$	**3b**	22

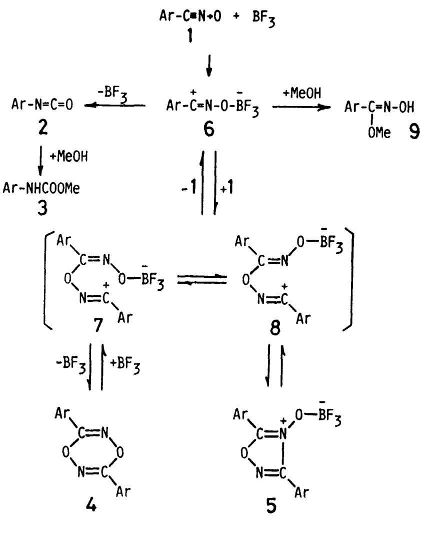
In refluxing dichloromethane. for 2 h Lewis acid/**1**=1.

Table 2. Yields of the urethane (**3a**), the dioxadiazine (**4a**) and the oxadiazoliooxytrifluoroborate (**5a**) in the reaction of the nitrile oxide (**1a**) with BF_3OEt_2 in various solvents at 25°C

Solvent	Molar ratio BF_3/**1a**	Yield/%		
		3a	**4a**	**5a**
Dichloromethane	1.0	80	0	0
	0.50	81	0	0
Benzene	2.0	38	29	0
	1.0	37	43	0
	0.55	33	47	0
	0.40	29	44	0
	0.20	28	49	0
Toluene	1.0	38	26	5
	0.50	33	33	3
Xylene	1.0	39	40	3
	0.50	39	38	1
Diisopropyl ether	1.0	31	0	25
	0.50	33	10	25
Ether	1.0	10	0	59
	0.75	9	0	65
	0.50	7	0	57[a)]
	0.38	7	0	39[b)]
	0.20	0	0	27[c)]

a) A small amount of **9a** was also obtained. b) Unreacted **1a** and **9a** were recovered in 19 and 15% yields respec tively. c) **9a** and **1a** were also recovered in 36 and 16% yields respectively.

The treatment of **4a** with $BF_3 \cdot OEt_2$ in benzene and subsequently with methanol gave **3a** in 75% yield, but in ether no change was observed. Nor was change observed in diisopropyl ether, where the treatment of **1a** with BF_3 gave **3a** as well **4a** and **5a**. Furthermore, **5a** was confirmed not to be affected by $BF_3 \cdot OEt_2$ in either benzene or ether. This indicates that no interconversion between **2a**, **4a**, and **5a** in the ethereal solvents takes place and that the unimolecular rearrangement fo **6** may be a route to **2** except in benzene, where



1~9: Ar = a) 2,3,5,6-$(CH_3)_4C_6H$, b) 2,4,6-$(CH_3)_3C_6H_2$

Scheme 1.

a route *via* **4** cannot be definitely ruled out.

The reaction of **1a** with $BF_3\cdot OEt_2$ in anisole gave *p*-methoxybenz-2,3,5,6-tetramethylanilide (**10a**) in 68% yield. This may be formed by a Friedel-Crafts reaction of the isocyanate formed with anisole.[4]

Experimental

The melting points are uncorrected. The column chromatography was conducted on silica gel (Waco-gel C-200) with chloroform as the eluent. The IR and ^{1}H NMR were measured in a KBr disk and in $CDCl_3$ respectively.

Materials. The nitrile oxides (**1a**) and (**1b**) were prepared according to Grundmann and Richter's procedure.[5] The Lewis acids were distilled under nitrogen before use. The solvents were purified and dried by usual methods.

Reactions of **1a** *with* $BF_3\cdot OEt_2$. *In Dichloromethane*: Into a solution of **1a** (351 mg, 2.0 mmol) in dichloromethane (50 ml) $BF_3\cdot OEt_2$ (250 μl, 2.0 mmol) was added. The solution was then heated to reflux for 2 h. The subsequent evaporation of the solvent gave an oil, which was treated with column chromatography to give 192 mg (55%) of **2a**, mp 24—25 °C. IR(neat): 2200 cm^{-1} (N=C=O). Treating it with methanol at room temperature (r.t.) overnight gave 224 mg (99%) of **3a**: mp 156—157 °C. IR: 3920 (NH), 1720 cm^{-1} (C=O). ^{1}H-NMR: δ 2.15 (6H, s, Me), 2.26 (6H, s, Me), 3.75 (3H, s, OMe), 6.96 (1H, s, ArH). Found: C, 69.40; H, 8.38, N, 6.89%; M$^+$, 207.1294. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76%, M$^+$, 207.1258.

The addition of methanol (10 ml) to the reaction mixture after the reaction and subsequently letting it stand at r.t. overnight gave **3a** in 78% yield on column chromatography. This methanol treatment was applied to all the working-up steps hereafter for the full recovery of the **2** in the form of **3**.

Reactions with the other Lewis acids and working-up were conducted similarly. The results are summarized in Table **1**.

In Benzene: A solution of **1a** (1.0 mmol) and $BF_3\cdot OEt_2$ (1.0 mmol) in benzene (20 ml) was allowed to stand at 25 °C for 3 d under nitrogen. After methanol treatment of the reaction mixture without separating a solid precipitate a precipitate was taken by filtration (67 mg). The filtrate was evaporated to give an oil, column chlomatography of which gave 9 mg of the same solid as was separated above from an earlie elute, **4a**; mp 195—198 °C (from methanol). The total yield was 43%. From the later elute, 76 mg (37%) of **3a** were obtained. **4a**: IR: 2860—3000, 1635, 1615, 1590, 1460, 1330, 1025, 820 cm^{-1}. ^{1}HNMR: δ 2.26 (12H, s, Me), 2.33 (12H, s, Me), 7.06 (2H, s, ArH). Found: C, 75.41; H, 7.74; N, 7.89%; M$^+$, 350.1954. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99%; M$^+$, 350.1993.

In Ether: A solution of **1a** (2.0 mmol) and $BF_3\cdot OEt_2$ (0.40 mmol) in ether (20 ml) was kept at 25 °C for 3 d. The white needles of **5a** which precipitated were collected by filtration, 113 mg (27%); mp 203—205 °C (from benzene-pet. ether). Methanol treatment of the filtrate and working-up with column chromatography gave 55 mg (16%) of **1a** and 150 mg (36%) of **9a** mp 198—200 °C. Neither **3a** nor **4a** was obtained. **5a**: IR: 2840—3000, 1580, 1050, 860 cm^{-1}. ^{1}H NMR: δ 2.18 (6H, s, Me), 2.20 (6H, s, Me), 2.32 (12H, s, Me), 7.19 (1H, s, ArH), 7.26 (1H, s, ArH). Found: C, 62.95; H, 6.23; N, 6.56%. Calcd for $C_{22}H_{26}BF_3N_2O_2$: C, 63.17; H, 6.27; N, 6.70%. **9a**: IR: 3200—4000 (OH), 1650 cm^{-1}(C=N). ^{1}H NMR: δ 2.18 (6H, s, Me), 2.23 (6H, s, Me), 3.74 (3H, s, OMe), 7.00 (1H, s, ArH), 7.90 (1H, broad, OH). Found: C, 69.54; H, 8.34; N, 6.83%; M$^+$, 207.1257. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76%; M$^+$, 207.1258.

The reaction in toluene, xylene, or diisopropyl ether was conducted and worked-up in almost the same manner.

In Anisole: The reaction was conducted using 1 mmol each of **1a** and $BF_3\cdot OEt_2$ in 10 ml of anisole at r.t. for 3 d. Methanol treatment and solvent evaporation gave an oil, the trituration of which with ether and subsequent filtration gave 123 mg of *p*-methoxybenz-2,3,5,6-tetramethylanilide (**10a**). From the filtrate, 16 mg (9%) of **4a** and 71 mg of **10a** were obtained on column chromatography. The total yield of **10a** was 68%. **10a**, mp 225—227 °C (from benzene–pet. ether): IR: 3285 (NH), 2840—3020, 1630 cm^{-1} (C=O). ^{1}H NMR: δ 2.11 (6H s, Me), 2.21(6H, s,Me), 3.28 (3H,s, OMe), 6.84(1H, s,ArH), 6.92 (2H, d, ArH), 7.35 (1H, broad, NH), 7.83 (2H, d, ArH). Found: C, 75.84, H, 7.40; N, 4.55%; M$^+$, 283.1581. Calcd for $C_{18}H_{21}NO_2$: C, 76.30, H, 7.47; N, 4.94; M$^+$, 283.1571.

Quenching with Methanol. Ten minutes after the addition of $BF_3\cdot OEt_2$ (0.5 mmol) to a solution of **1b** (161 mg, 1.0 mmol) in ether (50 ml), methanol (5 ml) was added to the solution. The mixture was kept standing at r.t. for 3 d. The subsequent solvent evaporation and column chromatography gave 13 mg (8%) of **1b** and 116 mg (60%) of **9b**; mp 140—141 °C (lit,[3]) 140—141 °C). A similar reaction in benzene gave 4% of **1b**, 14% of **4b** (mp 171—174 °C (lit,[1]) 172—173 °C)), and 54% of **9b**.

A similar reaction of **1a** in ether afforded 74% of **9a** as the sole isolable product.

Reaction of **4a** *with* $BF_3\cdot OEt_2$. A solution of **4a** (88 mg, 0.25 mmol) and $BF_3\cdot OEt_2$ (65 μl, 0.50 mmol) in benzene (20 ml) was let stand at 25 °C for 3 d. The subsequent methanol treatment of the solution and evaporation of the solvent gave a solid, which afforded 12 mg (14%) of **4a** and 78 mg (75%) of **3a** on column chromatography. A similar treatment of **4a** in ether or diisopropyl ether only resulted in no change.

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