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Lewis Acid Promoted Electrophilic Aromatic Substitution Reaction of Nitrile Oxide: Increase of the Electrophilicity of Carbon Atom of Nitrile Oxide by Lewis Acid Complexation

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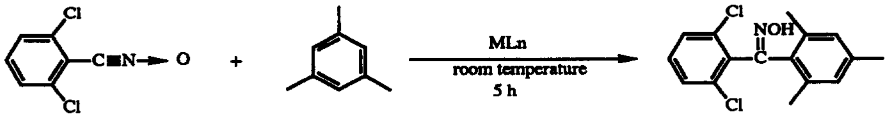
Summary: Nitrile oxides complexed with Lewis acid have their increased electrophilic character at the carbon atom and could be used as hydroxynitrilium ion equivalents toward aromatic compounds.

Nitrile oxide is an important class of 1,3-dipoles and used to form isoxazoline and isoxazole derivatives.[1] Although the catalytic activity of Lewis acid in the reactions of nitrile oxides and dipolarophiles may have intrinsic possibilities as in Diels-Alder reactions, the utility of Lewis acid in 1,3-dipolar cycloaddition reactions of nitrile oxides has been scarecely studied.[2] The most important reason for this may be due to the formation of unreactive complexes between nitrile oxides and a Lewis acid.[3, 4a]

Recently, Kanemasa et al. have reported the successful use of Lewis acids in the cycloaddition reaction of nitrile oxides[4] and nitrones.[5] Nitrile oxides, which are generated from treatment of the corresponding hydroximoyl chlorides with organometallics (*n*-BuLi, EtMgBr, or Et_2Zn), form the nitrile oxide/Lewis acid complex immediately. The nitrile oxide complexed with relatively weak Lewis acid (in these cases, LiCl, MgBrCl, or $ZnCl_2$) equilibrates with free nitrile oxide and could react with dipolarophiles.[4]

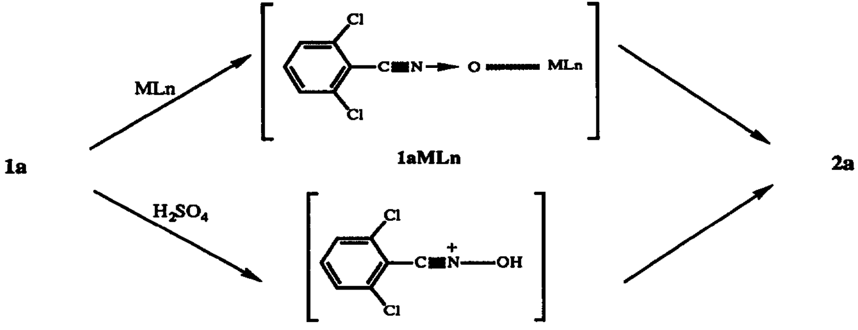
On the other hand, the reactions of various nitro compounds such as α,β–unsaturated nitro derivatives, α–carbonyl nitromethanes, nitronates of nitroalkanes, and primary nitroalkanes with aromatic compounds in strong acidic conditions (HF, H_2SO_4, or CF_3SO_3H) have been reported.[6,7] In these reactions, *N,N*-dihydroxyiminium carbenium ions[6] or hydroxynitrilium ions (*O*-protonated nitrile oxide ions)[7] have been proposed as reactive intermediates in the reaction with aromatic compounds.

Accumulation of these and related observations[8] has led us to a general premise that the complexation of nitrile oxides with strong Lewis acid should increase the electrophilicity of the carbon atom of nitrile oxides. To confirm our assumption we examined the reaction of 2,6-dichlorobenzonitrile oxide (**1a**) and mesitylene in the presence of Lewis acid (MLn). Lewis acid such as $AlCl_3$, BF_3 etherate, $SnCl_4$, and $FeCl_3$ conducted the reaction effectively at room temperature within 5 hours to give the product **2a** after workup in reasonable yields (70-85%). Concentrated sulfuric acid proved to be effective as well via the hydroxynitrilium ion species.[7,9] But, the use of $TiCl_4$, Ti(*i*-PrO)$_4$, $SnCl_4 \cdot 5H_2O$, $ZnCl_2$, or ZnI_2 did not effect the reaction, and the starting nitrile oxide **1a** was recovered in good yields after aqueous workup. The use of trifluoroacetic acid[7d] caused no reaction. Of course, the reaction proceeded not at all in the absense of Lewis acids even at elevated temperatures.[10]



1a **2a**

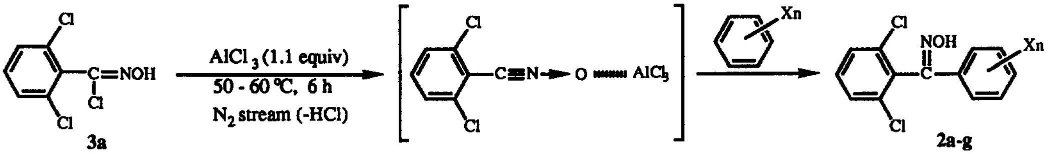
2,6-Dichlorobenzonitrile oxide (**1a**) might be complexed with Lewis acid to form **1aMLn**, or protonated to hydroxynitrilium ion by H_2SO_4 to **1aH$^+$**. These intermediates could act as electrophilic species toward mesitylene as shown in **Scheme 1**.



Scheme 1

The use of 2,6-dichlorobenzohydroximoyl chloride (**3a**) instead of isolated nitrile oxide **1a** resulted in the same product **2a** in the presense of $AlCl_3$. In this case, however, a gentle warming (50-60 °C) of the reaction mixture and successive replacement of the generated HCl gas by N_2 stream are needed. In this manner,[11] we prepared some oxime derivatives, and the results were summarized in **Table 1**.

Table 1. The reaction of 2,6-dichlorobenzohydroximoyl chloride (**3a**) with aromatic compounds.



Entry	Aromatic Nucleophile	Product	Yield (para : ortho)[a]
1	benzene	2b	70
2	benzene-d_6	2c	77
3	toluene	2d	75 (80 : 20)
4	mesitylene	2a	82
5	chlorobenzene	2e	48 (not determined)
6	anisole	2f	92 (90 : 10)
7	phenyl ether	2g	87 (not determined)

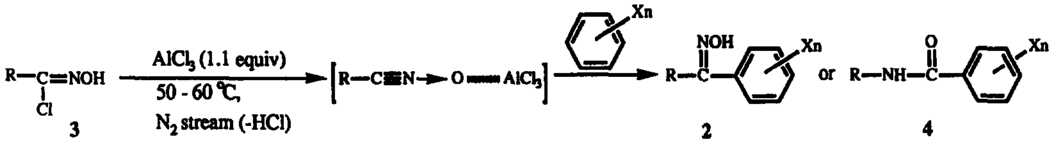
[a] The ratio was determined by ^1H NMR.

The reaction of **3a** and aromatic compounds in the presence of $AlCl_3$ did not proceed at room temperature. It is noteworthy that the reaction of **3a** and toluene in the presence of $EtAlCl_2$ instead of $AlCl_3$ afforded the corresponding oxime derivative **2d** in 80% yield at room temperature due to formation of a **1a** and $AlCl_3$ complex in situ as shown below.

$$\mathbf{3a} \quad + \quad EtAlCl_2 \quad \xrightarrow{\text{room temperature}} \quad \mathbf{1a} — AlCl_3 \quad + \quad \text{ethane}$$

The results obtained from variation of **3a** to other hydroximoyl chlorides **3** were summarized in **Table 2**.

Table 2. The reaction of hydroximoyl chloride 3 with aromatic compounds.



Entry	R	Aromatic Nucleophile	Time (h)	Product	Yield (para : ortho)^a
1	2-F, 6-ClC_6H_3-	benzene	6	2	80
2	2,3,5,6-$F_4C_6H_4$-	anisole	6	2	85 (75 : 25)
3	EtO_2C-	anisole	10	2	30 (65 : 35)
4	4-$CF_3C_6H_4$-	anisole	6	4	52 (80 : 20)
5	C_6H_5-	anisole	6	4	60 (90 : 10)
6	2,4,6-$Me_3C_6H_2$-	anisole	10	4	49 (single compound)

^{a}The ratio was determined by ^{1}H NMR.

As shown in **Table 2**, we could isolate the oxime derivatives **2** as the major products in the reaction of electrophilic nitrile oxides (entries 1-3). However, with less electrophilic nitrile oxides (entries 4-6) the reaction proceeded slowly and incompletely.[12] Moreover, in these cases, we could isolate the Beckmann rearranged products **4** as the major product. From the structure of **4**, which were confirmed from their mass[13] and proton NMR spectra, **4** might be derived from the initially formed **2** , followed by migration of R group. These results suggest that the R group and the hydroxyl group of the initially formed **2** is anti relationship. The configuration of **2** was coincident with the work of Hegarty,[14] who studied the nucleophilic addition reaction to nitrilium ion speceis.

In conclusion, we have developed a novel nucleophilic addition reaction of aromatic compounds to nitrile oxides which are electrophilically activated by Lewis acid complexation. Investigations of the reactions toward some other nucleophiles are in progress and will be published in due course.

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8. The nucleophilic addition reactions at the electrophilically activated substrates with Lewis acid is of familar tools in the current organic chemistry. Lewis basic substrates including carbonyl compounds, epoxides, imines, acetals were activated by Lewis acid, and reacted with various nucleophiles including aromatic compounds, allyltin and related derivatives. As an example see: (a)Y. Nishigaichi, M. Fujimoto, K. Nakayama, A. Takuwa, K. Hamada, and T. Fujiwara, *Chem. Lett.*, **1992**, 2339. (b) T. Sato, S. Okura, J. Otera, and H. Nozaki, *Tetrahedron Lett.*, **1987**, *28*, 6299. (c) S. K. Taylor, M. E. Davisson, B. R. Hissom, Jr., S. L. Brown, H. A. Pristach, S. B. Schramm, and S. M. Harvey, *J. Org. Chem.*, **1987**, *52*, 425. (d) M. A. Ciufolini and G. O. Spencer, *J. Org. Chem.*, **1989**, *54*, 4739.
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10. At elevated temperature only small amounts of the corresponding furoxan of **1a** was observed.
11. General procedure for the formation of **2d** from **3a** and toluene: To a stirred solution of **3a** (450 mg, 2 mmol) in dry toluene (10 mL) was added anhydrous aluminum chloride (295 mg, 2.2 mmol). The reaction mixture was warmed to 50-60 °C. During the reaction , the generated HCl gas was removed by dry nitrogen gas. After 6 hours the reaction mixture was cooled to room temperature and poured into a cold saturated aqueous NH_4Cl. Extraction with ether followed by usual workup gave a crude product. Silica gel column chromatography of the obtained crude product afforded pure **2d** as a white solid, 420 mg (75%); MS (20 eV) *m/z* (rel intensity) 92 (66), 244 (M^+-Cl, 38), 262 (37), 278 (48), 279 (M^+, 100), 280 (50), 281 (72); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.39 (s, 2.4 H), 2.53 (s, 0.6 H), 7.16-7.69 (m, 7 H), 9.90 (brs, 1H).
12. As an example, the reaction of 2,4,6-trimethylbenzonitrile oxide (the least electrophilic nitrile oxide as we studied) with benzene in the presence of $AlCl_3$ afforded the Beckmann rearranged amide derivative in 35% yield after 30 h at room temperature.
13. In mass spectra of the amide derivatives **4** base peak appeared at *m/z* = 135 corresponding to [4-$MeOC_6H_4CO^+$].
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