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Chemistry in Hydrogen Fluoride. Preparation of Aromatic Amides and Thioamides

Andrew E. Feiring

Contribution No. 2305 from the Central Research and Development Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

Received August 19, 1975

The electrophilic substitution reactions of aromatic compounds using a wide variety of substrates, electrophiles, and catalysts have been extensively investigated.[1] The direct introduction of the amide or thioamide moiety into an aromatic ring by electrophilic substitution has received little attention. Gattermann[2] observed formation of aromatic amides by the aluminum chloride catalyzed reaction of aromatic compounds with carbamoyl chloride.[3] More recently, Russian workers[4] observed the formation of aromatic amides in the reaction of aromatic hydrocarbons with alkali metal cyanate in concentrated sulfuric acid in the presence of aluminum chloride.[5] In this note the direct amidation and thioamidation of aromatic compounds with potassium cyanate or potassium thiocyanate using anhydrous hydrogen fluoride as solvent and catalyst are reported.

Aromatic amides were obtained by treating aromatic compounds with dry potassium cyanate in liquid HF at temperatures of 25–100°. The results are presented in Table I. In all cases the only organic materials observed were the monoamides and unreacted substrate with no tar formation. Control experiments demonstrated that the change in isomer ratio with temperature in the case of toluene was not due to isomerization of initially formed species at the higher temperature. With the more reactive aromatic compounds, anisole and toluene, replacement of the cyanate salt with potassium thiocyanate resulted in thioamide formation in high yield and moderate conversion (Table II).

A possible mechanism for the reaction is outlined in Scheme I. In a first step the cyanate salt reacts with HF to generate carbamoyl fluoride (1). Generation of the relative unstable carbamoyl fluoride (1, X = O) from reaction of KOCN with HF has been previously reported.[5] Subsequent acylation of the aromatic by 1 affords the observed products. The ability of HF to function as a Friedel–Crafts catalyst is well known.[1] Alternatively, partial amidation may occur via one or more intermediates in the reversible[5] for-

Scheme I

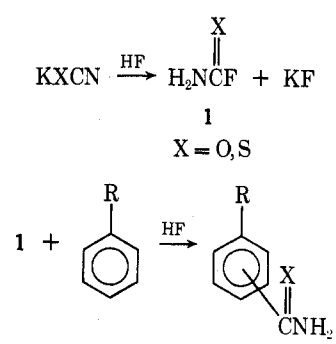

Table I
Reaction of Aromatic Compounds with Potassium Cyanate in HF

Substrate (mol)	Registry no.	KOCN, (mol)	Temp, °C	Conversion,[a] %	Product	Registry no.
Toluene (0.14)	108-88-3	0.030	100	70	45% *o*-toluamide[b]	527-85-5
					18% *m*-toluamide	618-47-3
					37% *p*-toluamide	619-55-6
Toluene (0.054)		0.040	25	50	26% *o*-toluamide[b]	
					74% *p*-toluamide	
Benzene (0.17)	71-43-2	0.030	100	63	Benzamide[c]	55-21-0
Anisole (0.74)	100-66-3	0.050	25	42	34% *o*-anisamide[d]	2439-77-2
					66% *p*-anisamide	3424-93-9
Naphthalene (0.05)	91-20-3	0.040	25	51	89% 1-naphthamide[e]	2243-81-4
					11% 2-naphthamide	2243-82-5
Chlorobenzene (0.08)	108-90-7	0.040	100	9	Chlorobenzamide[f]	619-56-7
Fluorobenzene (0.08)	462-06-6	0.040	100	20	*p*-Fluorobenzamide[g]	824-75-9
Pyridine (0.10)	110-86-1	0.050	100			
Aniline (0.05)	62-53-3	0.050	100			
Benzotrifluoride (0.06)	98-08-8	0.05	100			

[a] Based on KOCN. [b] Analyzed by GLC (6 ft × 0.125 in. 10% SE-30 on Chromosorb W column at 175°). [c] Mp 127–128° (lit.[7] mp 132.5–133.5°). [d] Analyzed by NMR, ratios by integration of methoxy singlets. [e] Isomer distribution by GLC analysis (10 ft × 0.25 in. 10% Carbowax on Chromosorb W at 150°) of the methyl esters formed by acid hydrolysis of the crude product, followed by diazomethane. Unreacted naphthalene (3.7 g) was recovered. [f] Mostly para (by NMR), not quantitatively analyzed. [g] Mp 150–152° (lit.[8] mp 152–153°).

Table II
Reaction of Aromatic Compounds with Potassium Thiocyanate in HF

Substrate (g)	KSCN, g, mol	Temp, °C	Conversion,[a] %	Product (g)	Registry no.
Toluene (6.4)	4.9, 0.050	25	36	*p*-Methylthiobenzamide[b] (2.7)	2362-62-1
Anisole (7.6)	4.9, 0.050	25	61	*p*-Methoxythiobenzamide[c] (5.1)	2362-64-3
Benzene (5.5)	4.9, 0.050	25			

[a] Based on potassium thiocyanate. [b] Recrystallized from benzene–petroleum ether, mp 169–171° (lit.[9] mp 172°). [c] Recrystallized from benzene, mp 145–147° (lit.[10] mp 148.5–149.5°).

mation of 1 from KXCN and HF. These species might well have different selectivities. The striking difference in isomer distribution obtained in the reaction with toluene at 25 and 100° might be due to a change in the relative proportion of reactive species with temperature.

Several aspects of the data in Tables I and II deserve further comment. The isomer ratios and relative conversions obtained in the amidation reactions are, in general, normal for electrophilic aromatic substitution reactions.[1] In particular, the exclusive formation of *p*-fluorobenzamide from fluorobenzene is in line with previous observations[6] for this compound. The failure of aniline and pyridine to react is reasonable as their protonation in HF would result in strong deactivation toward electrophilic attack. The exclusive formation of the para isomers with the thiocyanate reagent may reflect a less reactive, more selective nature of this species relative to KOCN, although the greater size of the sulfur reagent relative to the oxygen reagent could account for the exclusive formation of the para isomers.

Experimental Section

General. Potassium cyanate and potassium thiocyanate (Fisher) were dried in a vacuum oven at 105°. Anhydrous hydrogen fluoride was obtained in a cylinder from Air Products and used as received. The aromatic substrates were reagent grade and used without purification. GLC analyses were performed on a Hewlett-Packard 5700 instrument with thermal conductivity detector using the indicated column and conditions. Peak areas are not corrected for relative detector response. Melting points were measured on a Thomas-Hoover melting point apparatus and are corrected.

Caution. Hydrogen fluoride is extremely corrosive to human tissue, contact resulting in painful, slow-healing burns. Laboratory work with HF should be conducted only in an efficient hood with operator wearing full face shield and protective clothing.[11]

Procedure. Reactions at room temperature were run in a 170-ml Kel-F vessel. Higher temperature reactions were run in an 80-ml Hastelloy pressure bomb. Potassium cyanate or thiocyanate (0.03–0.05 mol) and excess aromatic were introduced into the reaction vessel. The vessel was cooled in dry ice–acetone or liquid N_2, evacuated, and charged with 40 g of liquid HF. The vessel was closed, warmed to the reaction temperature, and shaken (Hastelloy bomb) or stirred (Kel-F vessel) for 4 hr. The HF and excess aromatic were removed by aspirator vacuum. The residue was partitioned between water and ether. The ether solution was dried ($MgSO_4$) and concentrated. The residue was analyzed by NMR, ir, and GLC comparison with authentic samples. Results are summarized in Tables I and II.

Registry No.—Potassium cyanate, 590-28-3; HF, 7664-39-3; potassium thiocyanate, 333-20-0.

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Synthesis of Tertiary Amines by Selective Diborane Reduction

Pamela L. Russ and Edward A. Caress*

Department of Chemistry, The George Washington University, Washington, D.C. 20052

Received September 5, 1975

The preparation of tertiary amines containing functionality in the substituent groups has frequently presented a challenge to the synthetic organic chemist. A survey of the literature shows that there are few methods of preparing such tertiary amines and that many of them have limited scope, or poor yield, or both.[1] For example, the reduction of N,N-disubstituted amides with lithium aluminum hydride is one of the more common methods of preparing tertiary amines. The use of this reagent rather severely limits the type of functionality that can be permitted elsewhere in the amide. Also, an aldehyde is often obtained instead of, or along with, the desired amine.[2]

During the past 15 years, diborane has been developed as a reagent for reducing a variety of functional groups.[3] Its usefulness lies in the property that, while most functional groups can be reduced with the reagent, the rates of reduction vary greatly. This permits the reduction of certain groups in a polyfunctional molecule while leaving others intact, if conditions are properly chosen. The relative activity of diborane toward different functional groups is carboxylic acids and amides > olefins > ketones > nitriles > epoxides > esters > acid chlorides.[4] This order of reactivity suggests the possibility of reducing an amide with diborane to obtain an amine while leaving a variety of other functional groups untouched. Thus, with proper protection of a carboxyl function, an amide can be reduced to an amine that carries the carboxyl function.

The purpose of this paper is to suggest a new general approach, shown in Scheme I, to the synthesis of polyfunctional tertiary amines and to report the synthesis of *N*-ethyl-*N*-(2-tosylaminoethyl)glycine hydrochloride (**6a**) using this approach.

In the synthesis of **6a**, the starting material was glycylglycine 1 and it is necessary to protect both the amine and the carboxylic acid functions of this molecule. The amine function was protected by the tosyl group as the tosylamide is known to be inert to diborane reduction.[5] The choice of protecting group for the carboxyl function posed a greater problem.