[CONTRIBUTION FROM THE CALIFORNIA RESEARCH CORP.]

The Formation of Nitriles by Reaction of Terminal Methyl Groups with Sulfur and Anhydrous Ammonia

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Methyl groups activated by an aromatic ring can be converted to the corresponding nitriles or thioamides in good yields by reaction with elemental sulfur and anhydrous ammonia at elevated temperature. Higher alkyl groups give lower yields. Either product may be favored by control of terminal hydrogen sulfide pressure. The over-all reaction is reversible. Irreversible side reactions are minimized under optimum reaction conditions.

The simpler alkylbenzenes can be oxidized with sulfur as well as with oxygen. With the former, direct reaction yields bibenzyls, stilbenes, and substituted thiophenes.[1,2] In the presence of water and a base, carboxylates are favored almost exclusively.[3] Other inorganic sulfur species, including certain sulfates, function equally well when properly initiated.[4] Even sulfur and water alone will favor carboxylic acid formation over condensations and dehydrogenations if adequately controlled.[5] The present study was made to determine the effect of substituting anhydrous ammonia for water in the reaction of sulfur with various hydrocarbons. It was found that thioamides or nitriles could be favored as the principal products, particularly from the lower alkylbenzenes, thiophenes, and pyridines.

RESULTS AND DISCUSSION

Kindler first demonstrated that thioamides were formed from certain ketones by reaction with sulfur and various amines, including anhydrous ammonia[6]; but formation of thioamides from hydrocarbons, sulfur, and ammonia has not been demonstrated. The direct synthesis of nitriles with these reagents is also apparently new. However, this is not surprising since many thioamides upon heating will dissociate to nitriles and hydrogen sulfide. The reaction of sulfur, ammonia, and hydrocarbon to give nitriles is paralleled by that of oxygen, ammonia, and hydrocarbon, carried out catalytically in the vapor phase.[7] Overoxidation in the latter is difficult to control, while conversion of sulfur to hydrogen sulfide, with its lower heat of reaction than that of oxygen to water, gives no such problem. Some side reactions occur but can be minimized.

While reactions begin at about 230°, reasonable rates are attained in the range 300–350°, under autogenous pressures of 100–350 atmospheres. Reaction times range between 15 minutes and 2 hours. An excess of hydrocarbon over sulfur serves as a useful medium for the reaction, although an inert solvent such as benzene can be used.

The reaction is most successful with the alkylaromatics such as toluene, xylene, ethylbenzene, and cumene. Yields decrease with increasing size of the alkyl groups. Xylenes yield both mono- and dinitriles, and the former can react further if desired. The alkylpyridines and alkylthiophenes behave much like the alkylbenzenes but give lower yields of nitriles and thioamides. β-Picoline yielded nicotinonitrile which was converted directly to the amide by quenching the hot reaction mixture in water. 2,3-Dimethylbutane first formed 3,4-dimethylthiophene by reaction with sulfur alone, and then with ammonia participation gave 3-cyano-4-methylthiophene, a new compound. Other paraffins, olefins, and alicyclic compounds gave much less satisfactory results under these reaction conditions. Typical results are summarized in Table I.

In the case of the methylbenzenes, it was established that the reaction with sulfur and anhydrous ammonia to give thioamides and nitriles was reversible and can be written for toluene:

$$\mathrm{C_6H_5CH_3 + 3\,S + NH_3} \rightleftharpoons \mathrm{C_6H_5CSNH_2 + 2\,H_2S} \rightleftharpoons \mathrm{C_6H_5CN + 3\,H_2S} \quad (1)$$

Benzonitrile was reduced to toluene in the presence of hydrogen sulfide. The yield was poor, however, due to side reactions. This reversibility probably holds for pyridines and thiophenes as well. It is thus analogous to the reversible alkylbenzene, sulfur, water system which yields carboxylic acids.[5]

The temperature at which thioamides dissociate varies among the compounds studied. In all cases, it was found to be below reaction temperature, suggesting that under reaction conditions the equilibrium favors nitrile over thioamide.

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[1] L. Aronstein and A. S. Van Nierop, *Rec. trav. chim.*, 21, 448 (1902).

[2] (a) W. G. Toland, Jr., J. B. Wilkes, and F. J. Brutschy, *J. Am. Chem. Soc.*, **25**, 2265 (1953); (b) W. G. Toland, Jr., and J. B. Wilkes, *J. Am. Chem. Soc.*, **76**, 307 (1954).

[3] W. G. Toland, Jr., D. L. Hagmann, J. B. Wilkes, and F. J. Brutschy, *J. Am. Chem. Soc.*, **89**, 5423 (1958).

[4] W. G. Toland, *J. Am. Chem. Soc.*, **82**, 1911 (1960).

[5] W. G. Toland, *J. Org. Chem.*, **26**, 2929 (1961).

[6] K. Kindler, *Chem. Zentr.*, **96**, I, 1529 (1925).

[7] (a) J. N. Cosby and M. Erchak, Jr., U. S. Patent **2,499,055**, February 28, 1950. (b) D. J. Hadley, *Chem. and Ind.*, 238 (1961).

TABLE I

ANHYDROUS AMMONIA–SULFUR REACTIONS WITH HYDROCARBONS

Compound (C)	$C/S/NH_3$ Molar	Solvent, C_6H_6 Mole/Mole C	Temp.	Time, Min.	Phase Released at Temp., °C.[a]	Conversion of C, Mole %[b]	Product	Yield, Mole %[c]
Toluene	2/6.2/10	5	293	60	Both 20	72.5	$C_6H_5CSNH_2$	46.5
	1/3.1/20	10	332	30	Vapor 316	84.8	C_6H_5CN	79.6
p-Xylene	10/4.2/7	None	316	50	Both 20	27.3	$CH_3C_6H_4CSNH_2$	60+
o-Xylene	0.5/3.1/20	10	332	50	Liquid 330	92.8	$CH_3C_6H_4CN$	38.8
m-Xylene	1/6.2/10	10	316	60	Vapor 270–304	100	$CH_3C_6H_4CSNH_2$	33.0
							$C_6H_4(CSNH_2)_2$	3.5
							$CH_3C_6H_4CN$	24.0
	10/6/20	None	330	60	Liquid >308	21.6	$CH_3C_6H_4CN$	78.2
							$C_6H_4(CN)_2$	5.1
m-Tolunitrile	1/3/30	None	343	15	Liquid >332	9.1	$C_6H_4(CN)_2$	75.3
							$C_6H_4(CSNH_2)_2$	16.0
Ethylbenzene	10/2/5	None	288	90	Both 20	36	$C_6H_5CH_2CSNH_2$	5.5
Cumene	1/3/5	5	288	120	Vapor 260–270	62	$C_6H_5CHCH_3CN$	28
	1/6/35	None	343	30	Liquid 316	95.9	$C_6H_5CHCH_3CN$	54.8
							$C_6H_5CH(CN)_2$	11.2
p-Tolunitrile	1/5.6/20	20	330	90	Vapor 310–327	85	$C_6H_4(CN)_2$	73
β-Picoline	1/3/20	10	332	80	Vapor 288–316	100	C_5H_4NCN	15
2,3-Dimethylbutane	10/3.1/10	None	316	60	Both 20	16.5	3,4-Dimethylthiophene	15.3
							3-Cyano-4-methylthiophene	0.4
	1/3.1/10	10	315	60	Both 315	60.5	3,4-Dimethylthiophene	25.3
							3-Cyano-4-methylthiophene	14.3

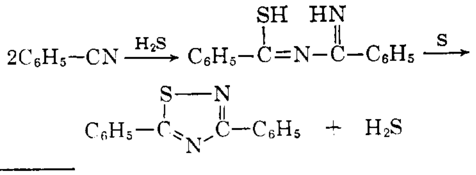
[a] See Experimental section for explanation. [b] Conversion $= \frac{\text{Moles C charged} - \text{Moles C recovered}}{\text{Moles C charged}} \times 100$. [c] Yield $= \frac{\text{Moles product}}{\text{Moles C consumed}} \times 100$.

Four factors become important in the successful use of this nitrile synthesis. First, excess ammonia is desirable to drive the reaction toward completion by mass action. Second, reaction times are best kept to a minimum to prevent irreversible reactions from draining away products in equilibrium with starting materials. Third, the threshold temperature for side reactions of sulfur and hydrocarbon is in some cases lower than that at which the ammonia takes part in the desired reaction. It is therefore advantageous to preheat reagents separately to the desired reaction temperature and then mix, to avoid side reactions. In the case of particularly reactive hydrocarbons such as olefins, their rate of reaction with sulfur is so fast that ammonia has little chance to participate, and yields of nitrogen-containing products are very low. The fourth factor is the method of recovering reaction products. Simply cooling the reaction vessel under pressure yields thioamides. However, by releasing hydrogen sulfide at full temperature and pressure, nitriles are formed exclusively.

Several nonreversible reactions may direct yields to other products. Side reactions are of several types: hydrocarbon with sulfur to yield stilbenes, biphenyls, and thiophenes; nitriles with sulfur and hydrogen sulfide to give substituted 1,2,4-thiadiazoles; and trimerization of nitriles catalyzed by hydrogen sulfide and ammonia yielding substituted 1,3,5-triazines. Initial evidence was based on high mass spectrographic results. Later, an example of each of these classes of compounds was isolated, and then synthesized from either reactants or products and the above reagents.

Dimerization of methylbenzenes with sulfur to stilbenes, biphenyls, and thiophenes has been studied previously.[1] The presence of ammonia is not required.

Formation of the thiadiazole ring from benzonitrile and thiobenzamide, *via* an intermediate condensation product cyclized by mild oxidation with iodine was reported by Ishikawa.[8] In the present study, sulfur served the same purpose, yielding the heterocycle in one step from benzonitrile, hydrogen sulfide, and sulfur. Sulfur alone failed to produce this reaction:



(2)

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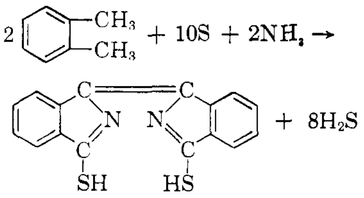
(8) S. Ishikawa, *J. Chem. Soc. Japan*, **42**, 579 (1921); *Chem. Abstr.*, **16**, 1588 (1921).

When starting from toluene, some benzonitrile precursor may yield the thiadiazole directly.

Trimerization of nitriles to 1,3,5-triazines can be induced by many catalysts.[9] Ammonia alone induced no trimer formation from benzonitrile; but when present with hydrogen sulfide, 2,4,6-triphenyl-1,3,5-triazine was formed. The same dimeric intermediate as shown in Equation 2 may be involved, followed by further reaction with another molecule of nitrile.

The formation of dithia-β-isoindigo(dithiodiphthalimidine) from *o*-phthalodinitrile, hydrogen sulfide, and alcoholic ammonia has been described.[10] Its presence might be expected in the products of the reaction of *o*-xylene, sulfur, and ammonia, but it could not be isolated in pure enough form for positive identification.



(3)

EXPERIMENTAL

Reagents. Toluene, ethylbenzene, and cumene were Baker's C.P.; xylenes were Oronite 95% pure, β-picoline was Eastman practical grade, and 2,3-dimethylbutane was Phillips' technical grade.

Reactants were charged to either a 2.5-l. or 4.5-l. 316 steel autoclave with an electrically heated shaker. After completion of the reaction as indicated by attainment of a constant pressure, the autoclave was allowed to cool to the desired temperature for pressure release, shaking was stopped, and the desired phase released. Effluent vapors passed through a water-cooled condenser, receiver, and water scrubber.

All liquid and/or solid products, including autoclave residues, were combined, extracted with water to remove ammonium sulfide, and distilled through an 18-in. long by 1-in. diameter helices packed column. Solvent, if present, and unchanged hydrocarbon were distilled. If thioamides were present, which was the case if hot release of hydrogen sulfide had not been employed or had been attempted at too low a temperature to avoid its combination with nitrile, a pot temperature was reached at which hydrogen sulfide was evolved due to thioamide dissociation. Reflux was continued until hydrogen sulfide evolution ceased; and the distillation was then completed under vacuum, taking the nitrile overhead. By-products concentrated in the pot as heavy, dark residues.

In the case of toluene products, a high mass spectrographic analysis of this residue showed the presence of large peaks at 238 and 309, suggesting 3,5-diphenyl-1,2,4-thiadiazole and 2,4,6-triphenyl-1,3,5-triazine, respectively. Both were isolated and identified by the procedures used in the specific experiments which follow.

The residue from *o*-xylene reaction products, after extraction with boiling xylene, had such well defined crystals of deep red to purple that it was purified as described by Drew and Kelly[10] for dithia-β-isoindigo. The analysis failed to identify it as such, although it may be present.

Anal. Calcd. for $C_{16}H_{10}N_2S_2$: C, 65.3; H, 3.4. Found: C, 66.10, 66.27; H, 3.30, 3.39.

3-Methyl-4-cyanothiophene from 2,3-dimethylbutane. The autoclave was charged with 780 g. (10 moles) of benzene, 86.2 g. (1 mole) of 2,3-dimethylbutane, 100 g. (3.1 moles) of sulfur in an oversized test tube wired to the thermowell to avoid mixing until shaking began, and 170 g. (10 moles) of anhydrous ammonia. At 315° shaking began and was continued for 1 hr. Products were released directly into ice. Residue in the autoclave consisted of 6.3 g. of black solids, largely carbon. The organic phase (768 g.) was separated from the aqueous layer and steam distilled to give 749 g. of organic condensate which was distilled to recover benzene, 34.2 g. of 2,3-dimethylbutane, 17.1 g. of 3,4-dimethylthiophene, and 10.7 g. of 3-methyl-4-cyanothiophene, a new compound, b.p. 87° at 10 mm. Recrystallized twice from alcohol and dried over concd. sulfuric acid, it was characterized as follows: m.p. 34.7–35.1°; n^{80}_{D} 1.5237.

Anal. Calcd. for C_6H_5NS: C, 58.49; H, 4.09; N, 11.4; S, 26.03. Found: C, 58.4, 58.8; H, 4.3, 4.4; N, 11.8; S 25.0.

Mass spectrography showed a parent peak at 123; and infrared indicated the thiophene ring (3100 cm.$^{-1}$), the cyano group (2225 cm.$^{-1}$), a methyl group (1365 cm.$^{-1}$), and ring hydrogens (800 cm.$^{-1}$). Only traces of organic materials were found in other fractions from this run.

Reduction of benzonitrile to toluene. A 2.5-l. autoclave was charged with 780 g. (10 moles) of benzene, 103 g. (1 mole) of benzonitrile, and 235 g. (6.9 moles) of hydrogen sulfide, and heated to 330° with shaking for 30 min. Products were released directly into ice and the phases separated. Distillation of the organic phase gave 8.8 g. of toluene.

Trimerization of benzonitrile. A 260-ml. autoclave was charged with 31 g. (0.3 mole) of benzonitrile, 3.4 g. (0.1 mole) of hydrogen sulfide, and 25.5 g. (1.5 moles) of anhydrous ammonia. After heating with shaking at 250° for 1 hr., the mixture was depressured before cooling. The liquid and solid products remaining behind were then dissolved in hot xylene. Upon cooling, 5.2 g. of white solids crystallized. After recrystallization from xylene, they had a melting point of 233–234° and gave an infrared spectrum identical with the known 2,4,6-triphenyl-1,3,5-triazine (cyaphenine), m.p. 232°.[9]

A duplicate experiment in a sulfur-free autoclave, in the absence of hydrogen sulfide, gave no trimer.

Synthesis of 3,5-diphenyl-1,2,4-triadiazole. A 260-ml. autoclave was charged with 80.6 g. (0.78 mole) of benzonitrile, 10.0 g. (0.31 mole) of sulfur, and 12.0 g. (0.35 mole) of hydrogen sulfide. Upon heating with shaking to 190–215°, an exothermic reaction occurred during a 15-min. period; and the pressure dropped from 36 to 14 atm. The reaction was continued for 1 hr. Products were cooled before depressuring. A 40-g. aliquot of autoclave products was dissolved in 200 cc. of hot ethanol, and on cooling to 25° crystallized 3.3 g. of sulfur. Further chilling of the filtrate to 2° gave 8.5 g. of crystals which were recrystallized, washed, and dried. This was 3,5-diphenyl-1,2,4-thiadiazole, m.p. 86–87.2°, lit., 86–87°.

Anal. Calcd. for $C_{14}H_{10}N_2S$: C, 70.7; H, 4.2; N, 11.7; S, 13.4. Found: C, 68.43, 68.62; H, 4.16, 4.27; N, 10.99, 11.13; S, 13.61, 13.57.

Additional thiadiazole and thiobenzamide were recovered from the filtrate by dilution with water.

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(9) V. Migrdichian, *The Chemistry of Organic Cyanogen Compounds*, New York, Reinhold Publishing Corp., 1947, p. 356.

(10) H. D. K. Drew and D. B. Kelly, *J. Chem. Soc.*, 625–637 (1941).