A Generalized and Proton-Catalyzed Synthesis of Amidines from Thioimidates

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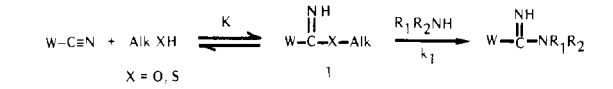
A generalized synthesis of amidines[1,2] prepared from thioimidate, using a buffered protonic catalysis in nonaqueous medium, is herein described. The classic and most important access to amidines lies in the modification of imidates and thioimidates[3] (Scheme I), as exploited by Pinner.[2,4] Although it is expected that k_1 should increase with increasing basicity of the nucleophile, the resulting more basic reaction medium causes a shift in the equilibrium position such that K becomes very small. Thus retronitrile formation may occur when strongly basic nucleophiles are used in the amidine formation step, especially for imidates when W is electron donating[5] and generally for thioimidates.[6] Our results are in accord with those of Reynaud who showed that nitrile formation from thioimidates is found not to be significant generally when aromatic amines are used as nucleophiles, but it is dominant when aliphatic amines are employed.[6] For example, treatment of the hydrochloride of 1 (W = *m*-$(C_{16}H_{33})_2NCH_2C_6H_4$; X = S) with aniline led to amidine in 88% recrystallized yield with no nitrile formation (Table I), while treatment with alkylamine, e.g., isopropylamine, led to nitrile recovery in 90% yield with formation of only trace amounts of amidine. Thus far no exceptions to nitrile formation have been observed in reaction of **2** with any of the more basic amines.

It has now been shown that the course of thioimidate reactions with strongly basic amines can be modulated, using a buffered organic reaction media. Hydrochloride 1 (W = *m*-$(C_{16}H_{33})_2NCH_2C_6H_4$; X = S) was converted quantitatively to amidine with methylamine at room temperature in chloroform containing acetic acid/acetate buffer. This buffer system was chosen because of the similarity of pK_a of acetic acid and aniline.[7] More strongly acidic conditions, i.e., treatment of thioimidate as HCl salt with amine hydrochloride, failed to yield any products under the mild reaction conditions employed above. However, addition of acetic acid/sodium acetate to this reaction mixture also led to complete amidine formation. Table I[8] shows the results of the reactions of amines or

Scheme I



Scheme II

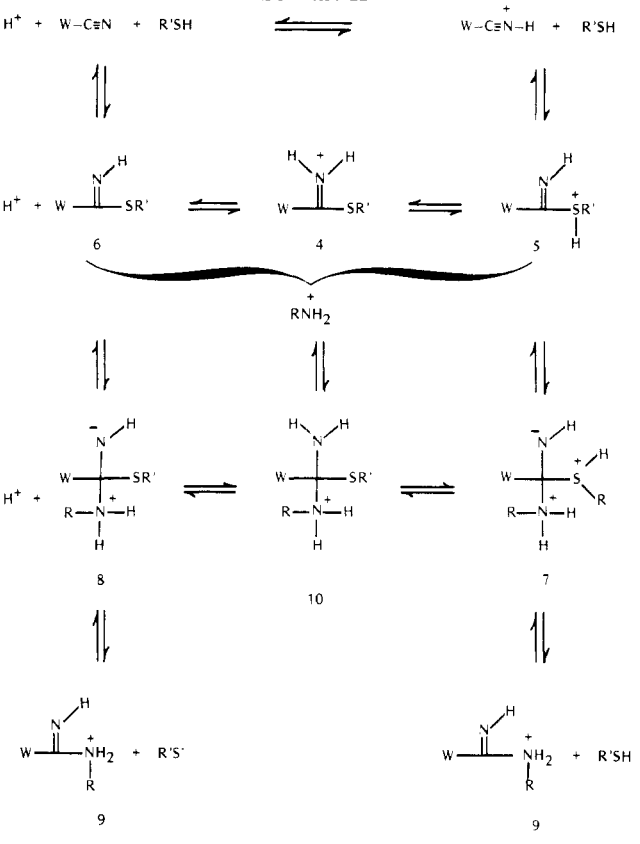
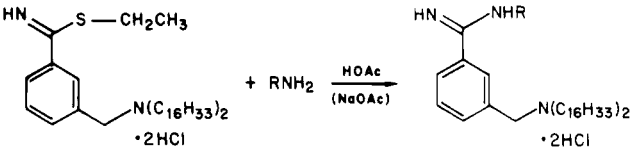


Table I. Amidine Preparation in Buffered Medium



R	time,[a] h	yield[b]	mp,[c] °C
CH_3[d]	72	90	106
CH_2CH_3[d]	72	84	91
$CH(CH_3)_2$	48	55	95
$CH_2CH{=}CH_2$	16	77*	70
c-C_5H_9	72	77	78
$CH_2C_6H_5$	1.5	88	154-157
CH_2CF_3[e]	12	86	125-127
CH_2-c-C_3H_5[e]	24	57	77-79
3-CH_3-4-OH-C_6H_3[e]	48	60*	115-118
C_6H_5[f]	16	88	86-88

[a] 1.0 equiv of thioimidate dihydrochloride was added at 20 °C to 2.0 equiv of amine and 3.5 equiv of acetic acid in chloroform comprising thus a solution 0.15 M in thioimidate. [b] All yields are of pure products recrystallized from 1,2-dimethoxyethane except as noted by an asterisk where 1,2-dimethoxyethane-acetonitrile was used. [c] Temperatures recorded are for gel formation of the lipid amidine. [d] Added as a weighed gas initially. [e] 2.0 equiv of amine·HCl and 2.0 equiv of NaOAc present initially. [f] No acetic acid present in reaction.

(1) The target compounds are antiviral agents and interferon inducers: Kraska, A. R.; Schnur, R. C. U.S. Patent 4 025 555 (1977).

(2) For general reviews see: Pinner, A. "Die Imidoather and Ihre Derivate"; R. Oppenheim: Berlin, 1892 (reprinted University Microfilms: Ann Arbor, Mich., 1961). Patai, S. "The Chemistry of Amidines and Imidates"; Wiley: New York, 1975.

(3) The thioimidate route has been less frequently exploited in synthetic strategies than the imidate path in spite of the fact that thiols are better nucleophiles and better leaving groups than the corresponding alcohols (March, J. "Advanced Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1977; pp 322–331). These properties generally should render thioimidates more easily accessible under milder conditions and more reactive to nucleophiles than the corresponding imidates. Furthermore, as in the present case, enhanced crystallinity is sometimes observed for thioimidate salts over the imidate salts.

(4) Imidates and thioimidates also readily form by reaction of strong alkylating agents, e.g., $Me_3O + BF_4$, $MeOSO_2F$, and amides or thioamides, respectively.

(5) Schaefer, F. C.; Peters, G. A. *J. Org. Chem.* **1961**, *26*, 412.

(6) Reynaud, P.; Moreau, R. C.; Gousson, T. *C. R. Hebd. Seances Acad. Sci.* **1964**, *259*, 4067–4070. Reynaud, P.; Moreau, R. C.; Thu, NH. *Ibid.* **1961**, *253*, 1968–1970. *Ibid.* **1961**, *253*, 2540–2541.

(7) The pK_a of aniline HCl is 4.58 and that of acetic acid is 4.76. Breslow, R. "Organic Reaction Mechanisms"; W. A. Benjamin: New York, 1969; p 15. Mechanisms of buffer-catalyzed hydrolysis of imidates and thioimidates have been described by Jencks and by Schmir. See: Jencks, W. P. *Prog. Phys. Org. Chem.* **1964**, *2*, 63–128. Lee, Yin-Nam; Schmir, G. L. *J. Am. Chem. Soc.* **1978**, *100*, 6700–6707; references therein.

(8) Satisfactory combustion analyses were reported for all new compounds listed in Table I.

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amine hydrochlorides with ethyl *m*-[(*N*,*N*-di-*n*-hexadecylamino)methyl]thiobenzimidate dihydrochloride, **2**, leading to amidines, **3**.

It is likely that the mechanism of this reaction involves tetrahedral intermediates possibly similar to the well-known $A_{AC}2$ acid catalyzed ester hydrolysis mechanism described by Ingold.[9] The thioimidate analogy to the $A_{AC}2$ ester hydrolysis mechanism is shown in Scheme II.

The rate of formation of **9** should be a function of the concentrations of protonated thioimidate[10] **5** (or **4** which would be in rapid tautomerism) and free amine, R_1R_2NH, which is in equilibrium with its conjugate acid. At low acid concentration, neutral thioimidate **6** fragments to nitrile and thiol, decreasing the concentration of **5** (or **4**). A strongly acidic medium decreases the concentration of free nucleophile RNH_2. The adduct **7** is analogous to the $A_{AC}2$ hydrolysis intermediate.[9] Intermediate **8** probably does not contribute significantly to the generation of amidine **9**, since it corresponds to the $B_{AC}2$ intermediate generated during base-catalyzed ester hydrolysis, as described by Ingold.[9] Controlling the acid concentration with a buffer in this otherwise aprotic organic solvent thus provides for significant concentration of free amine, while preventing rapid base-catalyzed reversion of thioimidate to nitrile. A similar principle has been employed in the preparation of guanidines, using pyridinium hydrochloride/pyridine buffers.[11]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra of $CDCl_3$ solutions (Me_4Si, δ 0) were recorded on a Varian A60 spectrometer. IR spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer, using the stipulated solvents, and are reported in reciprocal centimeters. Microanalyses were performed by Pfizer Central Research microanalysis laboratory, Groton, Conn.

Starting amines were commercially available and used without further purification. Amidines were prepared by the procedure given below, except for variations as defined in the footnotes to Table I. NMR and IR spectra of all compounds prepared were consistent with the proposed structures.

Preparation of *N*-Cyclopentyl-*n*-[(di-*n*-hexadecylamino)methyl]benzamidine Dihydrochloride. Ethyl *m*-[(di-*n*-hexadecylamino)methyl]thiobenzimidate dihydrochloride (**2**) (1.074 g; 1.5 mmol) was added to a solution of cyclopentylamine (2.55 mg; 3.0 mmol) and glacial acetic acid (0.3 mL; 5.3 mmol) in 10 mL of $CHCl_3$. The mixture was held at room temperature for 72 h, diluted to 300 mL with $CHCl_3$, washed with 3 × 50 mL of saturated $NaHCO_3$ and 3 × 50 mL of brine, dried (Na_2SO_4), and filtered. The filtrate was acidified with a 10% solution of anhydrous HCl in 5 mL of dioxane and then evaporated in vacuo to an oil. The oil was crystallized from warm 1,2-dimethoxyethane: 850 mg (77%); R_f 0.30 (4:1 benzene–ethanol on silicic acid); mp 78 °C (gel formation); IR (KBr) 1681, 1626, 1471 cm^{-1}; NMR δ 0.8–2.5 (m, 70), 2.6–3.5 (m, 4), 4.3–4.8 (m, 3), 7.3–8.6 (m, 4), 9.1–12.0 (m, 4). Anal. Calcd for $C_{45}H_{83}N_3 \cdot 2HCl \cdot 0.5H_2O$: C, 72.24; H, 11.39; N, 5.62. Found: C, 72.16; H, 11.63; N, 5.75.

Preparation of Ethyl *m*-[(Di-*n*-hexadecylamino)methyl]thiobenzimidate Dihydrochloride (2). A mixture of *m*-[(di-*n*-hexadecylamino)methyl]benzonitrile[12] (23.2 g; 0.04 mol), ethanthiol (6.0 mL; 0.08 mol) and chloroform (100 mL) was saturated with dry hydrogen chloride for 30 min at 20–25 °C. It was then stoppered and held for 6 days at 5 °C. The mixture was evaporated in vacuo to a foam which was crystallized by trituration with 1,2-dimethoxyethane. The crude product was recrystallized from hot 1,2-dimethoxyethane–chloroform: 24.6 g (88%); R_f 0.72 (4:1 benzene–ethanol on silicic acid); mp 109–111 °C; IR (CH_2Cl_2) 1620 cm^{-1}; NMR δ 0.6–2.2 (m, 65 [0.89 broad s]), 2.8–3.4 (m, 4), 3.74 (q, J = 8 Hz, 2), 4.2–4.7 (m, 2), 7.4–8.8 (m, 4). Anal. Calcd for $C_{42}H_{78}N_2S \cdot 2HCl$: C, 70.45; H, 11.26; N, 3.91. Found: C, 70.34; H, 10.94; N, 3.89.

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Registry No. **2**, 63290-29-9; **3** (R = CH_3), 71359-33-6; **3** (R = CH_2CH_3), 71393-18-5; **3** (R = $CH(CH_3)_2$), 71359-34-7; **3** (R = $CH_2CH{=}CH_2$), 71359-35-8; **3** (R = c-C_5H_9), 71359-36-9; **3** (R = $CH_2C_6H_5$), 71359-37-0; **3** (R = CH_2CF_3), 71359-38-1; **3** (R = CH_2-c-C_3H_5), 71359-39-2; **3** (R = 3-CH_3-4-OHC_6H_3), 71359-40-5; **3** (R = C_6H_5), 71359-41-6; CH_3NH_2, 74-89-5; $CH_3CH_2NH_2$, 75-04-7; $CH_2{=}CHCH_2NH_2$, 107-11-9; c-$C_5H_9NH_2$, 1003-03-8; $C_6H_5CH_2NH_2$, 100-46-9; $CF_3CH_2NH_2$, 753-90-2; C_3H_5-c-CH_2NH_2, 2516-47-4; 3-CH_3-4-$OHC_6H_3NH_2$, 2835-96-3; $C_6H_5NH_2$, 62-53-3; $(CH_3)_2CHNH_2$, 75-31-0; *m*-[(di-*n*-hexadecylamino)methyl]benzonitrile, 59050-99-6; ethanethiol, 75-08-1.

(9) Tetrahedral intermediates have been described in the bimolecular acid-catalyzed acyl–oxygen cleavage, $A_{AC}2$, mechanism for ester formation

or hydrolysis, as well as the corresponding base-catalyzed, $B_{AC}2$, mechanism for ester hydrolysis. Ingold, C. K. "Structure and Mechanism in Organic Chemistry", 2nd ed.; Cornell University Press: Ithaca, N. Y., 1969; pp 1129–1157.

(10) Thioimidate formation likely proceeds via addition of thiol to the protonated nitrile. For other examples of nitrilium ions see: Borch, R. F. *Chem Commun.* **1968**, 442–3. Borch, R. F. *J. Org. Chem.* **1969**, *34*, 627–9.

(11) Unpublished results.

(12) This nitrile was prepared from *m*-(bromomethyl)benzonitrile, di-*n*-hexadecylamine, and K_2CO_3 in dimethylacetamide at 80 °C (mp 26–7 °C, *i*-PrOH) as described in U.S. Patent 3 872 171 (March 1975).

Convenient Conversion of Alcohols into Formaldehyde Acetals or Ethers

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In our development of new methods for the conversion of alcohols into trimethylsilyl (Me_3Si) ethers,[1] we wished to explore the potential use of various neutral catalysts. In particular, we reasoned that chlorotrimethylsilane (Me_3SiCl) and dimethyl sulfoxide (Me_2SO) would react to give an adduct which might silate alcohols (eq 1).

$$Me_2SO + Me_3SiCl \rightarrow [CH_3S^+(OMe_3Si)CH_3Cl^-] \xrightarrow{ROH} ROMe_3Si + Me_2SO \quad (1)$$

This would be of great significance because of the anticipated mild conditions of the conversion.

Indeed, Me_3SiCl and Me_2SO do give a solid when mixed in either ether or benzene, but when this is allowed to react with an alcohol in refluxing benzene overnight, the product is not the Me_3Si ether but rather the formaldehyde acetal (eq 2).

$$Me_2SO + Me_3SiCl \rightarrow \xrightarrow{ROH} ROCH_2OR \quad (2)$$

This reaction is a general one and gives respectable yields of pure products (see Table I). The acetals can be obtained at room temperature in ether, but 4 days are needed

(1) For example, see Pinnick, H. W.; Bal, B. S.; Lajis, N. H. *Tetrahedron Lett.* **1978**, 4261.

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