Synthesis and Reactions of *N,N'*-Dichlorodiiminosuccinonitrile

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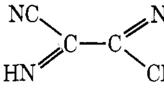
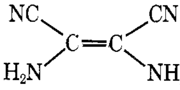
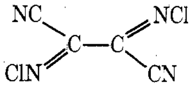
N,N'-Dichlorodiiminosuccinonitrile (Cl_2DISN) has been prepared from diaminomaleonitrile (DAMN) by an improved method in an excellent yield. Namely, Cl_2DISN reacts with thiols affording *N,N'*-disulfenyl compounds, whereas it is reduced into diiminosuccinonitrile (DISN) by diphenyl sulfide or *N*-benzyl-1,4-dihydronicotinamide. Olefins react with Cl_2DISN to yield pyrazine derivatives by simultaneous dehydrochlorination.

Oligomers of hydrogen cyanide have received intensive attention because of their relationship to chemical evolution[1,2] and the versatility of their reactions.[3] Diiminosuccinonitrile (DISN) and diaminomaleonitrile (DAMN) have been extensively studied,[4–6] and DAMN is now commercially available.[7,8] In the course of our current study to extend the reactions of DAMN,[9] we have found an improved synthesis of *N,N'*-dichlorodiiminosuccinonitrile (Cl_2DISN), which will be described in this paper together with some representative reactions of Cl_2DISN.


DISN


DAMN


Cl_2DISN

Results and Discussion

Synthesis of Cl_2DISN. The formation of Cl_2DISN from DAMN (50% yield) or DISN (quantitative) by chlorination in acetonitrile has been reported.[5] The reactions, however, required low temperature (between −40 and −20°) because liquid chlorine was employed and both DAMN and DISN are susceptible to decomposition by acids, especially in solvents contaminated with moisture. To avoid these difficulties, the reaction was carried out in carbon tetrachloride or chloroform at 0°, using *tert*-butyl hypochlorite instead of liquid chlorine (eq 1). The results are summarized in Table

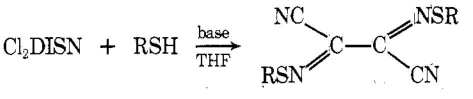
$$\text{DAMN} + 3\,t\text{-BuOCl} \longrightarrow \text{Cl}_2\text{DISN} + 3\,t\text{-BuOH} + \text{HCl} \tag{1}$$

I. DAMN is soluble in acetonitrile, sparingly soluble in chloroform, and insoluble in carbon tetrachloride or benzene, but all of these solvents readily dissolve Cl_2DISN. The data in Table I suggest that the effect of solvent rather than temperature is the most important factor increasing the yield of Cl_2DISN.

Reaction of Cl_2DISN. When Cl_2DISN in tetrahydrofuran (THF) was treated with thiols in the presence of pyridine or triethylamine, the corresponding *N,N'*-disulfenyldiiminosuccinonitriles [$(RS)_2$DISN] were obtained in excellent yields (eq 2). Similar reaction with DISN is known to afford DAMN.[5] Since chlorimine is a potential halogenating agent,[10] the reaction may proceed *via* sulfenyl chloride and DISN (eq 3) analogously to the reaction of DISN

$$\text{Cl}_2\text{DISN} + 2\text{RSH} \longrightarrow [\text{DISN} + 2\text{RSCl}] \longrightarrow (\text{RS})_2\text{DISN} \tag{3}$$

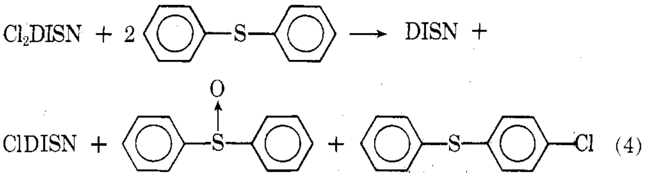
with sulfur dichloride.[6] However, the present reaction is advantageous over the reactions requiring DISN and sulfenyl chlorides in that the starting materials are easily available and a stable thiol can be used in place of an unstable sulfenyl chloride.


(2)

$(RS)_2$DISN

A solution of Cl_2DISN in dimethyl sulfoxide (DMSO) spontaneously underwent reaction to provide $(MeS)_2$DISN (37%) and dimethyl sulfone (43%).

DISN and *N*-chlorodiiminosuccinonitrile (ClDISN)[5] can be obtained by treating Cl_2DISN with diphenyl sulfide at room temperature (eq 4). Since DISN is unreactive with sulfides, excess diphenyl sulfide may be used and the present reaction constitutes a novel and convenient route to DISN. The reaction with thioanisole, however, is too fast to be controlled even at relatively lower temperatures, whereas that with anisole does not proceed even at elevated temperatures. It should be noted that normal electrophilic aromatic substitution proceeds faster with anisole than thioanisole, for which initial formation of a sulfonium ion has been proposed.[11] The observed reactivity of the sulfides, then, may be accounted for by the initial formation of a charge-transfer complex, 1 (*vide infra*). DISN is also obtained in the reaction of Cl_2DISN with *N*-benzyl-1,4-dihydronicotinamide (BNAH) at −20°. Since DISN is itself reduced (although more slowly) by BNAH into DAMN, exactly 2 molar equiv of BNAH should be used in this preparation of DISN from Cl_2DISN (eq 5). On the other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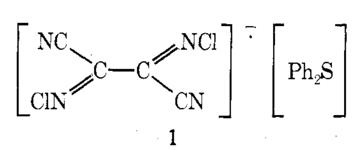
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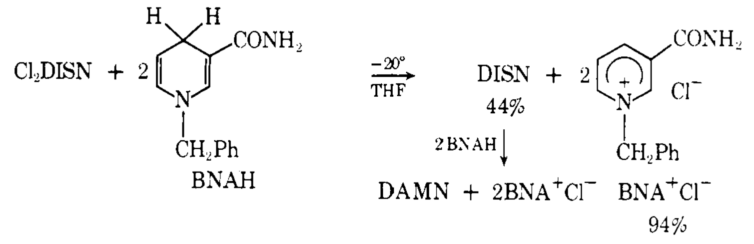
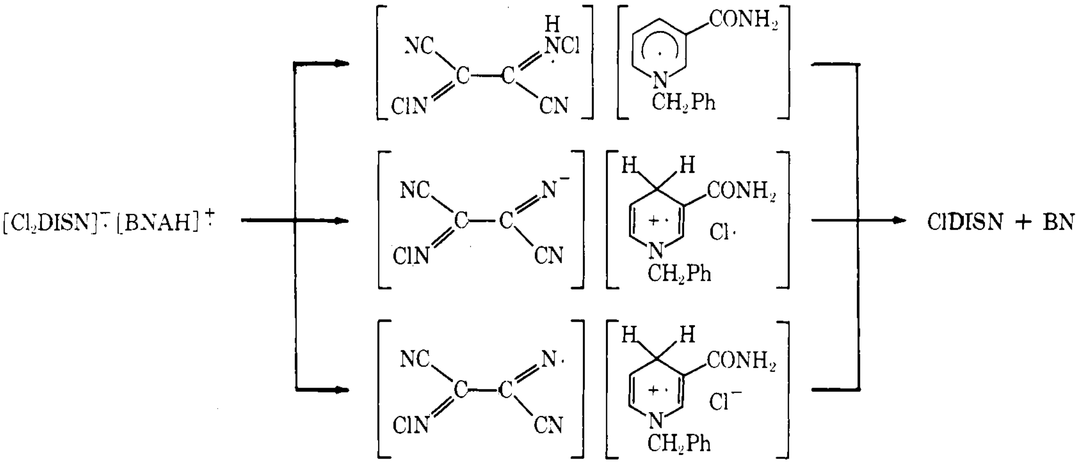
Table I
Reaction of Diaminomaleonitrile with *tert*-Butyl Hypochlorite

t-BuOCl, mmol	DAMN, mmol	Na_2CO_3, mmol	Solvent (ml)	Reaction temp, °C (time, hr)	Convn of DAMN, %	Yield of Cl_2DISN, % Crude	Isolated[a]
15.05	5.02	15.02	CCl_4 (90)	29 (1.5)	93.2	90.3	85.7
15.02	5.02	15.03	$CHCl_3$ (90)	29 (1.5)	97.8	83.2	66.1
15.09	5.01	15.42	Benzene (90)	9 (1.5)	99.3	88.7	79.8
15.09	5.02	15.00	CCl_4 (90)	3 (1.5) and −20 (15)	97.6	94.0	89.1
15.02	5.00		CCl_4 (90)	3 (1.5) and −20 (15)	97.3	76.9	73.8

[a] Purified by sublimation at 85° (1 Torr).



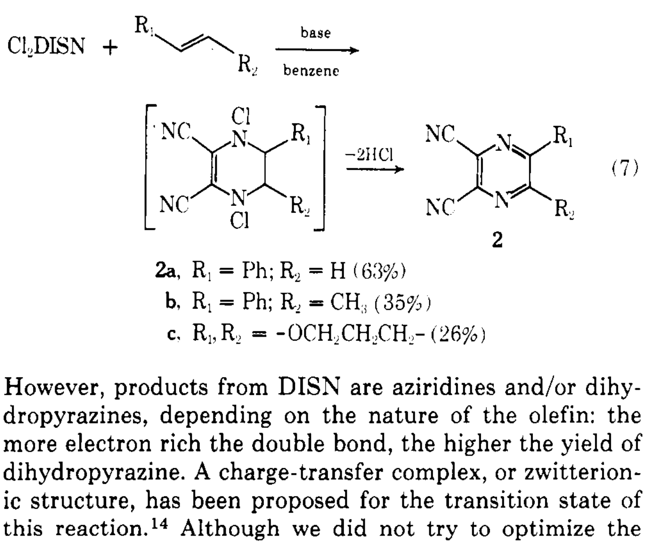
(5)



(6)

hand, sodium borohydride does not react with Cl_2DISN. This fact suggests that the mechanism of the reduction by BNAH is not a simple S_N2-type hydride attack.[12] Recently, we reported that reductions by BNAH involve an electron–proton–electron transfer process.[13] We consider the present reaction to proceed with a similar mechanism (eq 6), but a detailed discussion will be deferred until the necessary data are accumulated.

Cl_2DISN reacts with some olefins to provide pyrazine derivatives, 2 (eq 7). DISN itself also reacts with olefins.[14]



(7)

2a, R_1 = Ph; R_2 = H (63%)
b, R_1 = Ph; R_2 = CH_3 (35%)
c, R_1,R_2 = $-OCH_2CH_2CH_2-$ (26%)

However, products from DISN are aziridines and/or dihydropyrazines, depending on the nature of the olefin: the more electron rich the double bond, the higher the yield of dihydropyrazine. A charge-transfer complex, or zwitterionic structure, has been proposed for the transition state of this reaction.[14] Although we did not try to optimize the yields, the fact that styrene gave the highest yield[15] and 2,3-dihydropyran gave the lowest, as well as the fact that chlorine is more electronegative than hydrogen, seems to suggest that [2 + 4] cycloaddition is more plausible than the two-step addition at least for the reaction of Cl_2DISN. Since dehydrochlorination occurs spontaneously, the use of Cl_2DISN is superior to DISN when pyrazines are desired.

Experimental Section

Preparation of Cl_2DISN. Into a mixture of DAMN (0.54 g), $NaCO_3$ (1.59 g), and CCl_4 (60 ml), a solution of *tert*-butyl hypochlorite (1.64 g) in CCl_4 (30 ml) was added dropwise at room temperature or at a temperature of ice-water (3°). The reaction mixture was stirred for 1.5 hr; then precipitates were filtered off and washed by CCl_4. The combined solution of CCl_4 was concentrated by means of a rotary evaporator, yielding 0.805 g (94% yield) of crude Cl_2DISN, which was sublimed at 80° (1 Torr), affording pure crystals of Cl_2DISN: mp 160–161° (lit.[5] mp 164.5–165.5°).

Table II
Yield and Melting Point of $(RS)_2DISN$

R in $(RS)_2DISN$	Yield, %	Mp, °C	Registry no.
i-Pr	86.6	91–92	52109-62-3
$PhCH_2$	90.8	144–145	52109-63-4
Ph	91.4	205–207	52147-69-0
p-$CH_3OC_6H_4$	94.1	243–244	52109-64-5
p-ClC_6H_4	89.9	298–300	52109-65-6

Reaction of Cl_2DISN with Thiols. Into an ice-cooled solution of Cl_2DISN (0.35 g) and pyridine (0.16 g) or triethylamine (0.20 g) in 25 ml of anhydrous THF was added dropwise a solution of ethanethiol (0.26 g) in 10 ml of anhydrous THF. The reaction mixture was stirred for 30 min at 3°, then for an additional 30 min at room temperature (22°). Precipitates were filtered off and the solvent was evaporated from the filtrate under a reduced pressure. The solidified material thus obtained was recrystallized from ethanol, yielding *N,N'*-diethylthiodiiminosuccinonitrile [$(EtS)_2DISN$] in 80% yield: mp 114–115°; ir (KBr) 2950, 2925, 2920, 2860, 2225, 1520, 1460, 1430, 1390, 1258, 1053, 1000, 985, 965, 769, 725, and 653 cm^{-1}; mass spectrum (100°, 70 eV) *m/e* 226 ($M\cdot^+$, 37.3%), 197 ($M\cdot^+$ − Et·, 26.8%), 169, 137, and 61 (EtS^+, 100%). *Anal.* Calcd for $C_8H_{10}N_4S_2$: C, 42.48; H, 4.46; N, 24.77; S, 28.29. Found: C, 42.22; H, 4.21; N, 24.52; S, 28.22.

Other thiols were reacted similarly. The yields and melting points of the products are listed in Table II.

Reaction of Cl_2DISN with Dimethyl Sulfoxide. Cl_2DISN (0.50 g) was dissolved into 1 ml of DMSO and the solution was stirred for 1 hr at 10–15°. An exothermic reaction took place at this moment. The reaction mixture was subjected to column chromatography on silica gel with benzene as an eluent. Yellow crystals thus obtained were recrystallized from cyclohexane, affording 0.22 g (37% yield) of *N,N'*-dimethylthiodiiminosuccinonitrile [$(MeS)_2DISN$]: mp 191–192°; ir (KBr) 2915, 2230, 1510, 1435, 1325, 990, 974, 940, 720, and 695 cm^{-1}; mass spectrum (100°, 70 eV) *m/e* 198 ($M\cdot^+$, 100%), 183 ($M\cdot^+$ − Me·, 93.6%), 169, 151, 137, 99, and 47 (MeS^+, 66%). *Anal.* Calcd for $C_6H_6N_4S_2$: C, 36.37; H, 3.05; N, 28.28; S, 32.30. Found: C, 36.23; H, 3.14; N, 28.19; S, 32.30.

Elution with benzene-ethyl acetate (1:1) gave 0.25 g (43% yield) of dimethyl sulfone.

Reaction of Cl_2DISN with Diphenyl Sulfide. Cl_2DISN (0.35 g) and diphenyl sulfide (0.76 g) were dissolved into 20 ml of acetonitrile and the solution was stirred for 12 hr at room temperature

(22°). After evaporation of the solvent *in vacuo,* the residue was treated with benzene. The gray solid, which is insoluble to benzene, was found to be sufficiently pure DISN (68 mg): mp 163–165° dec (lit.[4] mp 165–166°).

Materials soluble to benzene were subjected to silica gel column chromatography. *p*-Chlorophenyl phenyl sulfide (0.60 g, 68% yield), which was contaminated by a small amount of *p,p′*-dichlorodiphenyl sulfide, and ClDISN (50 mg, 18% yield) were isolated from fractions eluted with benzene–*n*-hexane (3:2). Diphenyl sulfoxide (0.25 g, 30% yield) was obtained from fractions eluted with benzene–ethyl acetate (3:2). Furthermore, elution with benzene–ethyl acetate (1:1) gave additional 13 mg of DISN (38% total yield).

Reaction of Cl_2DISN with *N*-Benzyl-1,4-dihydronicotinamide. A solution of Cl_2DISN (0.35 g) in THF (10 ml) was cooled to −20° by a Dry Ice-CCl_4 bath. To this solution was added a solution of BNAH (0.86 g) in THF (30 ml). The solution was stirred for 30 min at −20° and crystals of BNA^+Cl^- (0.93 g, 94% yield) were filtered off. The solvent was evaporated *in vacuo* from the filtrate and the residue was purified by a column of silica gel. Elution with benzene–ethyl acetate (4:1) gave 94 mg of DISN (44% yield).

Reaction of Cl_2DISN with Sodium Borohydride. A mixture of Cl_2DISN (0.35 g) and $NaBH_4$ (0.16 g) in THF (30 ml) was stirred for 15 hr at room temperature. After usual work-up, 81% of Cl_2DISN used was recovered and no indication was obtained for the formation of DISN.

Reaction of Cl_2DISN with Olefins. A mixture of Cl_2DISN (0.35 g), Na_2CO_3 (0.42 g), and styrene (1.0 g) in benzene (10 ml) was kept at room temperature in a dark for 5 days. The residue remained after evaporation of the solvent *in vacuo* was subjected to column chromatography on silica gel, yielding 0.10 g of Cl_2DISN and pale yellow crystals, which was sublimed at 110° (1 Torr), giving white needles of 2,3-dicyano-5-phenylpyrazine (0.18 g, 63% yield): mp 164–165°; ir (Kbr) 3050, 2240, 1560, 1540, 1520, 1460, 1430, 1120, 794, 770, 693, and 510 cm^{-1}. *Anal.* Calcd for $C_{12}H_6N_4$: C, 69.89; H, 2.93; N, 27.17. Found: C, 69.84; H, 2.66; N, 27.00.

Similar reactions with β-methylstyrene and 2,3-dihydropyran gave **2b** and **2c** in 35 and 26% yields, respectively, after similar work-up described above.

Registry No.—**2a,** 52109-66-7; **2b,** 52109-67-8; **2c,** 52109-68-9; DAMN, 1187-42-4; DISN, 28321-79-1; Cl_2DISN, 33420-44-9; $(EtS)_2$DISN, 52109-69-0; $(MeS)_2$DISN, 52109-70-3; *tert*-butyl hypochlorite, 5923-22-8; ethanethiol, 75-08-1; 2-propanethiol, 75-33-2; benzenemethanethiol, 100-53-8; benzenethiol, 108-98-5; *p*-methoxybenzenethiol, 696-63-9; *p*-chlorobenzenethiol, 106-54-7; dimethyl sulfoxide, 67-68-5; diphenyl sulfide, 139-66-2; *N*-benzyl-1,4-dihydronicotinamide, 952-92-1; sodium borohydride, 16940-66-2; styrene, 100-42-5; β-methylstyrene, 637-50-3; 2,3-dihydropyran, 110-87-2.

Supplementary Material Available. Full ir, mass spectral, and elemental analyses data for compounds **2b, 2c,** and those listed in Table II as well as melting points of **2b** and **2c** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3373.

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(15) Only an azirine compound was formed by the reaction of styrene with DISN.[14]

Synthesis of α-Cyanoglycine *N*-Carboxyanhydride and α-Cyanoglycine[1]

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α-Cyanoglycine *N*-carboxyanhydride (4), a new, monomeric precursor of poly-α-cyanoglycine (2) required for chemical evolution studies, was synthesized from ethyl α-cyanoglycine (**6a**) by the following sequence of reactions, rather than by standard procedures from the highly labile amino acid, α-cyanoglycine (5). Compound **6a** was converted to its *N*-benzyloxycarbonyl (CBZ) derivative by treatment with benzyl chloroformate in refluxing ethyl acetate and then was selectively hydrolyzed with aqueous KOH to *N*-CBZ-α-cyanoglycine (**7b**). A slight change in the reaction conditions to KOH in 50% acetone–water brought about hydrolysis of both the ester and the nitrile groups and yielded *N*-CBZ-aminomalonic acid. Compound **7a** reacted with trifluoroacetic anhydride to produce α-cyanoglycine *N*-carboxyanhydride (4), which with a large excess of water gave α-cyanoglycine (5).

During the past 2 decades, extensive research on the origin of life[3] has led to the widespread belief that the prebiological formation of primitive proteins occurred in two stages, α-amino acid synthesis initiated by the action of high energy from natural sources on the components of a reducing atmosphere followed by polycondensation of the accumulated monomers in the oceans or on land. A critical examination of the evidence for the second step suggests, however, that the inherent thermodynamic barrier to spontaneous polymerization of α-amino acids has been overcome only when specific environments have been invoked (anhydrous locales, high-temperature milieu, or acidic bodies of water, for example) that are not characteristic of a young, developing planet. This objection does not apply to an alternative route for protein abiogenesis that has been proposed[4] for the direct synthesis of heteropolypeptides from hydrogen cyanide and water without the intervening formation of α-amino acids.