An Amino-3,4-Dihydro-2*H*-1,3,5-thiadiazin-2-one Synthesis *via* a Novel Carbamoyl Chloride

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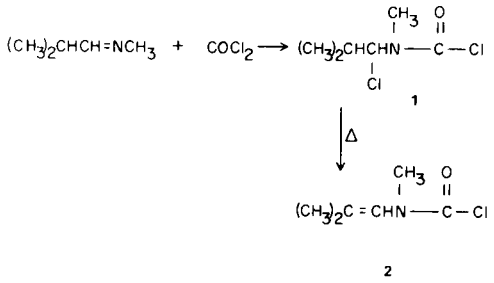
The formation and subsequent reactions of *N*-(1-enecarbamoyl) chlorides derived from cyclohexylidene amines have been reported (1,2,3). Isobutyraldehyde also readily forms enolizable imines, and several interesting reactions of these materials with electrophiles have been reported (4). Phosgene would be expected in like manner to form *N*-(1-enecarbamoyl) chlorides (**2**), quite analogous to those derived from the cyclohexylidene amines.

Although eventually **2** is formed, the initial reaction of phosgene with imine gives the dichloride, **1**. This material is surprisingly stable and can be distilled (5). Good yields of **2** may be obtained by dehydrohalogenation of **1** in high boiling inert solvents such as chlorobenzene.



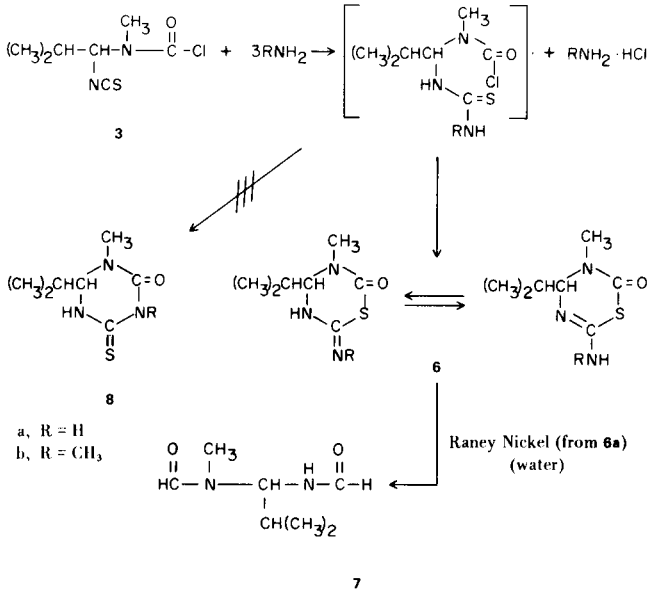
Dichloride **1** possesses two reactive chlorines, separated by three atoms and thus should be capable of reaction with nucleophiles to form substitution products, including heterocyclic compounds. Similar systems such as RC(COCl) = CClNR′$_2$ (**4**) and RCH = CClN(R′)COCl (**5**), derived from reaction of phosgene with tertiary and secondary amides respectively, have been investigated (6,7) in this manner.

A principal object of this report is to reveal one such novel heterocyclic synthesis from **1**, employing thiocyanates as the nucleophile.

Material **1** reacts with ammonium thiocyanate to give **3**. This material was of adequate purity for further synthesis, although in small quantities it could be distilled. Isolation of **3** revealed the lesser reactivity of the acyl chlorine and **1** thus has a reverse order of halogen lability to that for **4** (6) or **5**.

The isothiocyanate moiety in **3** was confirmed by the strong ir absorption at 2060 cm^{-1}. The position of thionation at the *alpha*-rather than acyl-carbon was shown not only by the appreciable difference in nmr absorption for the α-proton in **2** and **3**, but also the identical ir carbonyl absorption of these compounds (8). Carbamoyl isothiocyanates would be expected to absorb at lower frequencies (*i.e. ca.* 1705 cm^{-1}) (9).

Reaction of **3** with ammonia or primary amines gave the thiadiazinone **6** in one or both of its tautomeric forms.



Identification of **6** was achieved by consideration of the reaction mode, analyses, and spectral characteristics. Although **8** would be expected to possess nearly the same spectral features, the observed ir absorption frequencies at 1626-1618 cm^{-1} was slightly higher than that normally expected for a thioamide I band (10), and more closely resembles a normal imino absorption.

To differentiate between **6** and **8**, the material (R = H) was treated with Raney nickel to give **7** as sharp melting crystals from ethyl acetate. The bisformamide structure, quite consistent with both secondary and tertiary form-

amides, displayed non-equivalent multiple absorptions from rotational isomers caused by restricted rotation about the carbonyl carbon-nitrogen bond. Confirmation of this was achieved by observing the coalescence above 140° of these multiple absorptions in the nmr spectra of **7**.

The structure of **7** was also confirmed by its characteristic mass spectrum. The parent molecular ion at m/e 158 was quite small compared with the base peak (m/e 115) formed by loss of isopropyl radical. Loss of either CO or CHO, an important decomposition mode for formyl compounds, was readily apparent, both from the parent and base peak.

Remaining spectral properties as well as elemental analyses of **7** were entirely consistent with the assigned structure.

It would be difficult to rationalize the formation of **7** from **8**. Replacement of the thiono sulfur with two hydrogens would still require selective hydrogenolysis for ring cleavage; such ring opening would still not provide a second formyl group, even with hydrolysis. On the other hand, cleavage of sulfur bonds by hydrogen in **6** would give directly a formamido-formamidine compound, the latter hydrolyzing to give the bisformamide **7**.

The structure of **6** very likely arose from initial reaction of amine with isothiocyanate to form the adduct shown, with subsequent ring closure *via* acylation on the ureido sulfur.

EXPERIMENTAL

(1-Chloro-2-methylpropyl)methylcarbamoyl Chloride (**1**).

N-Isobutylidenemethyl amine (**11**) (0.5 mole, 42.5 g.) was dissolved in benzene and added to *ca.* 0.55 mole of phosgene contained in benzene at 5-10°. After all the imine had been added dropwise, the material was refluxed for 1 1/2 hours, with no evidence of appreciable salt formation. The benzene was removed to give a clear white liquid which was distilled at b.p. 67-75° (1.8 mm) to give 73 g. (79% yield)., ir (film) 1730 (C=O); nmr (carbon tetrachloride) δ 0.94, 1.18 (2d, 6 protons, J = 7 Hz, $CH(CH_3)_2$), *ca.* 2.13 (m's, 1 proton, $CH(CH_3)_2$), 3.12 (s, 3 protons, NCH_3), 5.82 (d, 1 proton, J = 10 Hz, *CH*Cl).

Anal. Calcd. for $C_6H_{11}Cl_2NO$: C, 39.10; H, 5.99; Cl, 38.60; N, 7.62. Found: C, 39.14; H, 6.08; Cl, 38.63; N, 7.96.

Methyl (2-Methylpropenyl)carbamoyl Chloride (**2**).

Material **1** was heated at reflux in chlorobenzene. Hydrogen chloride was given off over six hours. The residue was vacuum treated to remove solvent, then distilled at b.p. 70° (6 mm) to give 15 g. (77% yield), ir (film) 1725 (C=O), 1655 (C=C); nmr (carbon tetrachloride) δ 1.62 (s, 3 protons, $=CCH_3$), 1.72 (d, 3 protons, J < 1 Hz, $=CCH_3$), 3.02 (s, 3 protons, NCH_3), 5.8 (m, 1 proton, =*CH*).

Anal. Calcd. for $C_6H_{10}ClNO$: Cl, 24.02. Found: Cl, 24.17.

1-(1-Chloro-*N*-methylformamido)-2-methylpropyl Isothiocyanate (**3**).

Material **1** (18.4 g.) was charged into acetone and cooled to 5°. Ammonium thiocyanate (7.6 g.) dissolved in acetone was added dropwise. During addition there was continuous precipitation of ammonium chloride. The material was permitted to warm to room temperature, vacuum treated to remove solvent and the residue taken up in ether, washed with water and dried over magnesium sulfate. The ether solution was filtered, and the filtrate vacuum treated to remove ether. The yellow oil (70% yield) showed a clean nmr spectra and could be used without further purification. Small portions of the oil could be distilled, b.p. 105-110° (2 mm), but larger quantities decomposed upon attempted distillation; ir (film) 2062 (-N=C=S), 1730 (C=O); nmr (carbon tetrachloride) δ 0.98, 1.2 [2d, 6 protons, J = 7 Hz, $CH(CH_3)$], *ca.* 2.15 [m's, 1 proton, $CH(CH_3)_2$], 3.12 (s, 3 protons, NCH_3), 5.58 (d, 1 proton, J = 10 Hz, -*CH*NCS).

Anal. Calcd. for $C_7H_{11}ClN_2OS$: Cl, 17.15; N, 13.55. Found: Cl, 16.95; N, 13.46.

6-Amino-3,4-dihydro-4-isopropyl-3-methyl-2*H*-1,3,5-thiadiazin-2-one (**6a**).

Material **3** (20 g.) was dissolved in methylene chloride and gaseous ammonia sparged in, beginning at room temperature. The ammonia sparge was discontinued after it was evident that an excess had been charged as shown by further lack of exotherm and presence of ammonia in the exit gases (litmus test). The reaction mixture was filtered, the methylene chloride solution washed with water, then dried over magnesium sulfate. Upon evaporation of the methylene chloride, and ether trituration of the residue, 12 g. of solid was obtained, m.p. 122-125° dec. Recrystallization from tetrahydrofuran gave white crystals, m.p. 134-135° dec.; ir (chloroform) 3560, 3436 (N-H), 1667 (C=O), 1630 (C=N); nmr (d_6-acetone) δ 0.89, 0.97 [2d, 6 protons, J = 7 Hz, $CH(CH_3)_2$], 2.15 [m's, 1 proton, $CH(CH_3)_2$], 3.02 (s, 3 protons, NCH_3), 4.75 (d, 1 proton, J = 7 Hz, CH-).

Anal. Calcd. for $C_7H_{13}N_3OS$: C, 44.90; H, 7.00; N, 22.44. Found: C, 45.31; H, 7.32; N, 22.40.

3,4-Dihydro-4-isopropyl-3-methyl-6-(methylamino)-2*H*-1,3,5-thiazin-2-one (**6b**).

The same method to prepare **6a** was employed, substituting methyl amine for ammonia. A 35 percent yield of **6b** was obtained starting with 12 g. of **3**. Material **6b** was recrystallized from methylcyclohexane, m.p. 67-75° dec.; ir (chloroform) 3497 (N-H), 1661 (C=O), 1623 (C=N); nmr (deuteriochloroform) 0.94, 0.96 [2d, 6 protons, J = 7 Hz, $CH(CH_3)_2$], *ca.* 2.2 [m's, 1 proton, $CH(CH_3)_2$], 2.83 (s, 3 protons, NCH_3), 3.06 (s, 3 protons, NCH_3) 4.67 (d, 1 proton, J = 7 Hz, CH- ).

Anal. Calcd. for $C_8H_{15}N_3OS$: N, 20.88. Found: N, 20.90.

N-Methyl-*N*,*N*′-isobutylidenebisformamide (**7**).

Wet Raney nickel (*ca.* 15 g.) was stirred twice with fresh 2-propanol. The catalyst was then slurried with a third 100 ml. portion of 2-propanol, and to this was added 2 g. of material **6a**. The material was refluxed 4 hours, cooled and the 2-propanol solution decanted from the catalyst. The catalyst was washed several times with more 2-propanol, and the different portions of this solvent combined and filtered. The filtrate was vacuum treated to give *ca.* 0.5 g. of oil which solidified on scratching. The material was recrystallized twice from ethyl acetate to give white crystals, soluble in water, m.p. 145-145.5°; ir (chloroform)

3448 (N-H), 3311 (bonded water, this band nearly disappears on thoroughly dried samples), 1695-1639 (C=O); nmr (deuteriochloroform) δ 0.90, 1.01 [2d, 6 protons, J = 7 Hz, $CH(CH_3)_2$], 2.04 (m's, 1 proton, $CH(CH_3)_2$), 2.7 (75%), 2.72 (5%), 2.85 (5%), 2.91 (15%), (4s, 3 protons, NCH_3), 4.86, 5.03 (*ca.* 80%) (2d, 1 proton, J = 7 Hz, -CHCH-NH), 5.2 (20%) (2d, or Q, 1 proton, J = 7 Hz, -CH-CH-NH), *ca.* 7.7 (broad, 1 proton, N-H), 8.12 (10%), 8.3 (40%), 8.35 (40%) (4s, 2 protons, both C-H). Upon heating to 140° and higher, the nmr peaks for NCH_3, CH-CH-NH, C-H coalesced to a singlet, quartet (or 2 doublets) and singlets respectively; mass spectrum (70 eV): important m/e, (rel intensity), (possible fragmentation mode): 159, (trace), (158 + 1); 158, (1.6), (parent molecular ion); 129, (5), (158-CHO); 115, (100), (158-isopropyl); 100, (28) (158-2 CHO); 87, (59), (115-CO); 70 (21); 59 (35).

Anal. Calcd. for $C_7H_{14}N_2O_2$: C, 53.14; H, 8.92; N, 17.71. Found: C, 53.40; H, 9.05; N, 17.85.

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(5) A clue to its unusual stability may be revealed by the very large (*ca.* 10 Hz) coupling constant for the vicinal protons. The large J value observed would, from the Karplus equation, arise from a fairly rigid, skeletal structure with the 1,2-protons positioned *trans* (or 180°) to each other. This conformation, with the chlorine *cis*, rather than *trans* to the β-hydrogen would inhibit dehydrohalogenation *via* an energetically less favorable *cis* elimination.

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(8) The preferential lability of the α-chlorine in **1** is clearly demonstrated by its reaction with salts of *O,O*-diethyl phosphorodithioic acid. The resulting phosphorodithioate ester displays a typically prominent coupling of the α-proton with phosphorus; such H/P splitting would not be evident had reaction occured at the acyl-carbon.

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