REACTION OF AMINES WITH DIMETHYLTHIOFORMAMIDE[1,2]

GEORGE R. PETTIT AND LORRIN R. GARSON

Formylation of aromatic amines has been accomplished by the use of dimethylformamide in the presence of sodium methoxide (1). The reaction was found to proceed in a comparable manner with sodium amide or hydride in place of sodium methoxide.[3] However, acylation was not observed employing dimethylformamide alone or in the presence of sodium hydroxide. Subsequently, it became of interest to determine whether substitution of dimethylformamide by a thioamide would provide a route to thioformanilides or follow a different reaction pathway. Thioamides are known (2) to react with amines yielding amidines and in special cases, for example, with 5-thioformamido-6-aminopyrimidines, to produce cyclic formamidines[4] characteristic of the imidazole (in the example cited a purine) ring system. Thus, reaction between an amine and dimethylthioformamide might be expected to yield an N-substituted-N′,N′-dimethylformamidine. The following experiments were undertaken to ascertain the course of reaction between primary amines and dimethylthioformamide in the presence of sodium methoxide.

Dimethylthioformamide, prepared essentially as described by Willstätter (4) in 1909 by treating dimethylformamide with phosphorus pentasulphide,[5] was allowed to react at reflux with 1-aminonaphthalene and sodium methoxide. After 1.5 h, the mixture was cooled, diluted with water, and separated into neutral and basic fractions. When the neutral fraction was found to represent only dimethylthioformamide, thereby eliminating 1-thioformamidonaphthalene from further consideration, the basic fraction was further characterized by conversion to a red crystalline 1,3,5-trinitrobenzene derivative. The base was also found to form bright yellow picrate and styphnate salts. A pure specimen of the basic product (I), m.p. 40–40.5°, was obtained by destroying the trinitrobenzene π-complex with dilute hydrochloric acid. Infrared spectra of both the π-complex and free base (I) displayed a strong absorption band at 1 630 cm^{-1} which was initially assigned and later found to represent a C=N stretching frequency. An infrared band at 1 706 cm^{-1}, reminiscent of carbonyl-type absorption, appeared in infrared spectra of both the picrate and styphnate salts and was eventually attributed to a protonated form of the amidine group.

Employing (7) mass spectral data and results of elemental microanalyses, the base (I) was assigned empirical formula $C_{13}H_{14}N_2$. Considering the composition, chemical properties, and infrared spectra of the base and three derivatives, the substance was readily assumed to be N-(1-naphthyl)-N′,N′-dimethylformamidine (I). Assignments for the positively charged fragments believed to result from simple C–N bond cleavage (8) of the formamidine sidechain have been suggested in structure II. As might be expected,

[1]*The present contribution may be considered Part XVI of our series on Antineoplastic agents. For Part XV, refer to a paper by G. R. Pettit, D. S. Blonda, and R. A. Upham, Can. J. Chem. 43, 1798 (1965).*

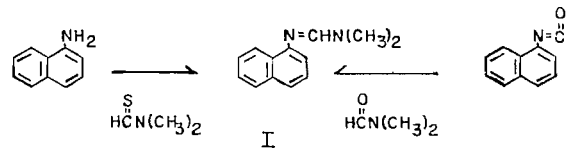
[2]*Abstracted in part from the Master of Science thesis submitted by L. R. Garson to the Graduate School, University of Maine, June, 1964.*

[3]*Later the acylation reaction was extended to certain aliphatic amines and to substitution of dimethylacetamide (found to yield acetamides) for dimethylformamide: unpublished experiments by G. R. Pettit and M. V. Kalnins.*

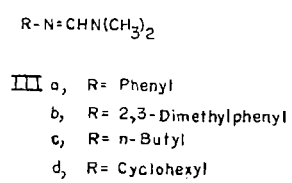
[4]*Cyclization of appropriately substituted 5-thioformamidopyrimidines has been shown (3) to occur readily in hot pyridine or quinoline solution or in methanol containing sodium methoxide. Synthesis of linear formamidines employing an analogous (but intermolecular) reaction between a thioformamide and amine does not appear to have been reported.*

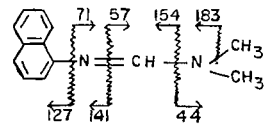
[5]*Recently (5) dimethylthioformamide has been prepared from dimethyl-amine, chloroform, and sodium hydrogen sulfide. Several less convenient methods (6) have also been used in attempts to obtain dimethylthioformamide.*

fragments corresponding to *m/e* 57 and 71 were found in relatively small abundance, in fact less than 10%, as a result of further fragmentation. Further support for the formamidine structure (I) was obtained by partially hydrolyzing (9*a*) the base to 1-formamidonaphthalene and the assignment was finally confirmed by direct comparison with an authentic sample (I) prepared (9*b*) from dimethylformamide and naphthyl isocyanate.[6]

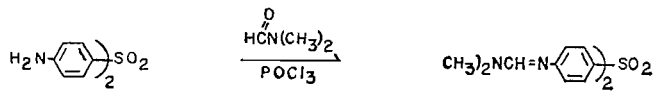


I





II



IV

Meanwhile, the dimethylthioformamide – sodium methoxide reaction sequence was applied to three aromatic and two aliphatic-type amines. Further study of the reaction was terminated when each amine was found to yield a formamidine (III*a*–III*d* and IV). Except for 2,3-dimethylaniline derivative III*b*, the structure of each formamidine was confirmed by comparison with an authentic sample prepared (9*a*, 10, or 11) employing either the dimethylformamide (cf. IV) or isocyanate route. Finally, reaction between dimethylthioformamide and 1-naphthylamine was studied in respect to base requirements. Substituting sodium hydroxide for the alkoxide led to a 90% yield of formamidine I (as the trinitrobenzene derivative). Under similar conditions, 1-aminonaphthalene and dimethylthioformamide alone provided a 97% yield of formamidine (I). At this point the investigation's original objectives had been satisfied and no further attempt was made to extend the scope of the reaction.

In view of the preceding experiments involving 1-aminonaphthalene and dimethylthioformamide, reaction between suitably constituted amines and thioformamides may provide a useful route to certain formamidines.

EXPERIMENTAL

All solvents were redistilled and both dimethylformamide, b.p. 36° (5.5 mm), and dimethylthioformamide were stored over molecular sieve (Fisher type 4A, see reference 1, footnote 9). Dry sodium methoxide was

[6]*Other trisubstituted formamidines have been prepared by this method or by allowing an amine to react with a formamide in the presence of phosphorous oxychloride (10), sulfonyl chloride (11), or phosphorous pentachloride (12). A variety of other methods (13) have been employed for synthesis of the parent system formamidine (14), symmetrically di-substituted formamidines (15), and unsymmetrically disubstituted formamidines (13, 16).*

prepared in this laboratory. The purity of each analytical specimen was assessed by thin-layer chromatography on silica gel G (E. Merck, AG., Darmstadt, Germany) containing calcium sulfate as binder. Thin-layer chromatograms of the 1,3,5-trinitrobenzene complexes and the picrate and styphnate salts were prepared using 15:85 water–tetrahydrofuran as mobile phase (and developed with iodine). Substituting, for example, 1:9 water–tetrahydrofuran or 1:1 chloroform–methanol as eluant led to considerable streaking of the chromatogram.

Melting points were observed employing a Kofler melting point apparatus and are corrected. The infrared spectra were recorded (using potassium bromide) by Dr. R. A. Hill of these laboratories. Microanalytical determinations were provided by Dr. A. Bernhardt, Max-Planck Institut, Mülheim, Germany.

Dimethylthioformamide

Quantities of dimethylformamide amounting to 500 ml (56% yield) were prepared from dimethylformamide (770 ml, 10 moles) and phosphorus pentasulfide (888 g, 4 moles) as described by Willstätter and Wirth (4). The thioformamide was distilled *in vacuo* through a 4-ft vacuum-jacketed column packed with glass helices. The fraction boiling at 77.0–77.6° (3.4 mm) was collected and stored over molecular sieve.

Anal. Calcd. for C_3H_7NS: C, 40.44; H, 7.92; N, 15.72; S, 35.92. Found: C, 40.25; H, 7.67; N, 15.99; S, 35.73.

Several new physical constants including a proton magnetic resonance spectrum of dimethylthioformamide have recently been recorded by Walter and Maerten (5).

N-(1-Naphthyl)-N′,N′-dimethylformamidine (I)

Procedure A

A mixture of dimethylthioformamide (10 ml), 1-aminonaphthalene (0.5 g), and sodium methoxide (0.38 g) was heated at reflux 1.5 h. After it had cooled, the mixture was poured into water (25 ml) and carefully acidified (litmus) with 12 *N* hydrochloric acid. The acidic solution was extracted with diethyl ether and next made basic (litmus) with 6 *N* sodium hydroxide and extracted with diethyl ether. The latter combined and dry (magnesium sulfate) ethereal extract was concentrated (*in vacuo*, steam bath) to a viscous oil. A solution of the product in absolute ethanol (30 ml) was treated with a saturated ethanolic solution of 1,3,5-trinitrobenzene. The solution turned red immediately and approximately 2 minutes later a red crystalline complex began to separate. The *trinitrobenzene complex* weighed 0.89 g (94%) and melted at 142–142.5°. Five recrystallizations from absolute ethanol caused no change in the melting point but produced a pure specimen as fibrous red needles; ν_{max} 1 630, 1 565, and 1 545 cm^{-1}.

Anal. Calcd. for $C_{19}H_{17}N_5O_6$: C, 55.45; H, 4.17; N, 17.02. Found: C, 55.25; H, 4.50; N, 17.09.

A specimen of the 1,3,5-trinitrobenzene complex was treated with 5% hydrochloric acid. The red coloration disappeared at once and the acidic solution was successively extracted with benzene, made basic with potassium hydroxide, and extracted with diethyl ether. The combined ethereal extract was dried (magnesium sulfate) and evaporated (steam bath) to a viscous oil. A specimen of *N-(1-naphthyl)-N′,N′-dimethylformamidine (I)*[7] crystallized from 2-propanol–water as colorless needles melting at 39.5–40.5° (lit. m.p. 40–40.5°, ref. 11); ν_{max} 3 000, 2 900, 1 630 (broad), 1 570, 1 500, 1 460, 1 440, 1 380, 1 270, 1 230, 1 110, 1 080, 1 043, 1 015, 970, 800, and 775 cm^{-1}; mass spectrometry: *m/e* 198 (M^+), 197, 183, 170, 156, 154, 153, 141, 129, 128, 127, 126, 99, 44, 42, 28.[8] Based on an isotope abundance of 15 at M + 1 (199) and 0.8 at M + 2 (200), the product was found consistent with empirical formula $C_{13}H_{14}N_2$.

The *picrate derivative* (prepared in absolute ethanol) of formamidine I recrystallized from absolute ethanol as bright yellow needles melting at 212–213°; ν_{max} 1 705, 1 625, and 1 610 cm^{-1}.

Anal. Calcd. for $C_{19}H_{17}N_5O_7$: C, 53.39; H, 4.00; N, 16.39. Found: C, 52.94; H, 4.04; N, 16.03.

Recrystallizing (3 times) the *styphnate derivative* (prepared in absolute ethanol employing styphnic acid) from absolute ethanol yielded a pure sample of fine yellow needles; m.p. 214–215°; ν_{max} 1 705, 1 635, and 1 565 cm^{-1}.

Anal. Calcd. for $C_{19}H_{17}N_5O_8$: C, 51.47; H, 3.86; N, 15.80. Found: C, 51.82; H, 4.12; N, 15.43.

When reaction between 1-aminonaphthalene and dimethylthioformamide was repeated as described above substituting sodium hydroxide (0.28 g) for sodium methoxide and the basic reaction product treated with 1,3,5-trinitrobenzene, a 1.3 g yield (90%), m.p. 142–143°, of the formamidine (I) complex was isolated. Repeating the same experiment using only 1-aminonaphthalene and dimethylthioformamide led to 1.4 g (97%) of the formamidine (I) 1,3,5-trinitrobenzene complex melting at 142–142.5°. In both cases the trinitrobenzene derivative was found to be identical[7] with the corresponding samples noted above and with that prepared below in Procedure B.

Procedure B

By the general method described by Jovtscheff and Falk (10) formamidine I was prepared (in 82% yield) from 1-naphthyl isocyanate (6.2 g) and dimethylformamide (15 ml). The product (6.4 g) was converted

[7]*Identity was established by mixture melting point determination and infrared spectral comparison with an authentic sample.*

[8]*All values less than 10% of the base peak (198) were omitted.*

to the 1,3,5-trinitrobenzene complex in ethanol solution. Two recrystallizations from ethanol gave a pure specimen melting at 142–142.5°.

N-Phenyl-N',N'-dimethylformamidine (IIIa)

The crude formamidine obtained by allowing aniline (0.65 g) to react with dimethylthioformamide (20 ml) as described in procedure A (for formamidine I) was treated with a saturated solution of styphnic acid in absolute ethanol. The yellow styphnate was collected, washed with ethanol, and dried; the yield was 0.61 g (18%). One recrystallization from ethanol led to bright yellow platelets melting at 169–170°. The same substance (III*a*, styphnate, m.p. 169–170°) was obtained as previously reported (10), using phenyl isocyanate and dimethylformamide. The styphnate salts were found to be mutually identical.[7]

N-(2,3-Dimethylphenyl)-N',N'-dimethylformamidine (IIIb)

Dimethylthioformamide (15 ml) was allowed to react with 2,3-dimethylaniline (5.0 g) as noted for preparation of formamidine I (procedure A). A solution of the crude oily formamidine in absolute ethanol was treated with a saturated ethanolic solution of picrate acid. The yellow solid which separated weighed 1.5 g (16%). Four recrystallizations from absolute ethanol gave bright yellow platelets melting at 177–178°.

Anal. Calcd. for $C_{17}H_{19}N_5O_7$: C, 50.37; H, 4.72; N, 17.28. Found: C, 50.32; H, 5.03; N, 17.54.

4,4-Bis(N',N'-dimethylguanyl)diphenyl Sulfone (IV)

A solution of phosphorous oxychloride (13.0 g) in tetrahydrofuran (30 ml) was added dropwise (during 0.5 h) to a solution composed of dimethylformamide (12.4 g) and tetrahydrofuran (50 ml). Stirring was continued at room temperature for 0.5 h and a solution of 4,4'-diaminodiphenyl sulfone (7.0 g) in tetrahydrofuran (50 ml) was next added dropwise to the reaction mixture. The solid hydrochloride salt which separated was collected and washed with diethyl ether. An aqueous solution of the hydrochloride was treated with potassium hydroxide until the solution became basic (litmus). The mixture was extracted with chloroform and the combined extract was dried and solvent removed *in vacuo*. The crystalline residue weighed 8.1 g. Two recrystallizations from tetrahydrofuran yielded a sample of colorless platelets melting at 146–148°. Additional recrystallization (3 times) from tetrahydrofuran – diethyl ether provided an analytical specimen melting at 149–150°.

Anal. Calcd. for $C_{18}H_{22}N_4O_2S$: C, 60.32; H, 6.19; N, 15.63; O, 8.93; S, 8.93. Found: C, 60.14; H, 6.07; N, 15.67; S, 9.11.

Reaction between dimethylthioformamide and 4,4'-diphenyl sulfone (3.0 g) as illustrated for the preparation of formamidine I proved less satisfactory for preparation of amidine IV. A thin-layer chromatogram (methanol as mobile phase with sulfuric acid development) indicated that less than 30% of the required formamidine (IV) was formed. When the same reaction was repeated in absence of sodium methoxide, only starting amine was isolated.

N-Butyl-N',N'-dimethylformamidine (IIIc)

Applying the general procedure described by Bredereck (11), for reaction between *n*-butylamine (13.2 g) and the dimethylformamide (41.0 g) – phosphorous oxychloride (34.6 g) reagent, afforded 7.1 g (31%) of formamidine III*c* boiling at 61–62° (15 mm). Conversion of 1-butylamine (10.0 g) to formamidine III*c* (2.1 g, 12%) was even less rewarding by use of the dimethylthioformamide (10 ml) route (see I, procedure A). Here, the reaction mixture was heated at reflux 48 h. The identical composition of both products was confirmed by infrared spectral comparison.

N-Cyclohexyl-N',N'-dimethylformamidine (IIId)

Both procedures summarized in the preceding experiment (see III*c*) were repeated with cyclohexylamine (10 g), and essentially analogous yields of oily cyclohexylformamidine III*d* were obtained. Both specimens (III*d*) were converted to styphnate salt derivatives (m.p. 186–187°, ref. 11 reports m.p. 186–187°) and the salts were found to be identical.[7]

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DEPARTMENT OF CHEMISTRY,
UNIVERSITY OF MAINE,
ORONO, MAINE.

ERRATUM: THE SYNTHESIS AND REACTIONS OF DIVINYL CARBONIUM IONS

T. S. SORENSEN

(Ref. Can. J. Chem. 42, 2768 (1964))

The compound referred to as 4-methylene-2,6-dimethyl-2,5-heptatriene on page 2769, under Results and Discussion, line 3, should be 4-methylene-2,6-dimethyl-2,5-heptadiene.

DEPARTMENT OF CHEMISTRY,
UNIVERSITY OF ALBERTA,
CALGARY, ALBERTA.