Reactions of the Iodomethylate of *N*, *N*-Dimethylthiobenzamide with Nucleophilic Reagents

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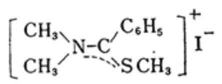
It has been reported that α-dialkylaminomethylene compounds can be prepared by the condensation of *N,N*-dialkylformamide acetals[1,2] with active hydrogen compounds, such as active methylene compounds. In the present study, the preparation of various α-dimethylaminobenzylidene compounds by reactions of the iodomethylate (I) of *N,N*-dimethylthiobenzamide with nucleophilic reagents will be examined.

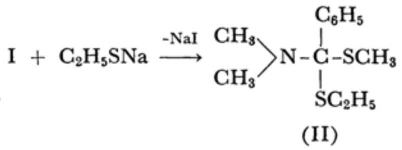
Recently, Böttcher and Bauer have isolated the iodomethylate (I) of *N,N*-dimethylthiobenzamide by treating *N*-methylisothiobenzamide-*S*-methylether with methyl iodide.[3] The iodomethylate (I) is easily hydrolyzed with alkali to give *N,N*-dimethylbenzamide and methyl mercaptan.



(I)

This result suggests that the iodomethylate (I) would yield condensation products when it is treated with nucleophilic reagents, such as sodium ethylmercaptide, potassium cyanide, amines, and the monosodium salts of active methylene compounds.

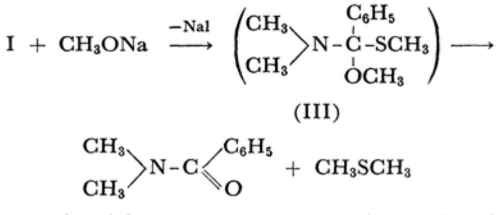
With this in mind the reaction of sodium ethylmercaptide with the iodomethylate (I) was attempted first. Sodium ethylmercaptide easily reacted with the iodomethylate (I) in dry ether at room temperature, and *N,N*-dimethylbenzamide methylethylmercaptol (II) was obtained in a fairly good yield.



$$\mathrm{I} + C_2H_5SNa \xrightarrow{-NaI} (CH_3)_2N-C(C_6H_5)(SCH_3)(SC_2H_5)$$

(II)

On the other hand, sodium methoxide could hardly react at all with the iodomethylate (I) at room temperature. When they were refluxed in dry benzene for 1 hr., however, *N,N*-dimethylbenzamide was obtained in a 41.5% yield, along with dimethyl sulfide, instead of the expected product, *N,N*-dimethylbenzamide monothioketal (III).



$$\mathrm{I} + CH_3ONa \xrightarrow{-NaI} \left((CH_3)_2N-C(C_6H_5)(SCH_3)(OCH_3)\right) \longrightarrow (CH_3)_2N-C(C_6H_5)=O + CH_3SCH_3$$

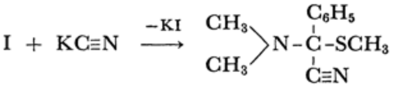
(III)

The results of the reactions of other sodium alkoxides with the iodomethylate (I) are listed in Table I.

TABLE I. REACTIONS OF I WITH SODIUM ALKOXIDES

Sodium alkoxide	Reaction condition			Yield, %	
	Solvent	Temp. °C	Time hr.	Amide	Sulfide
Methoxide	Benzene	80	1.0	41.5	—
Ethoxide	Benzene	80	1.0	46	—
Cyclohexyloxide	Toluene	110	2.0	33	16
Benzyloxide	Dioxane	100	3.0	79	65

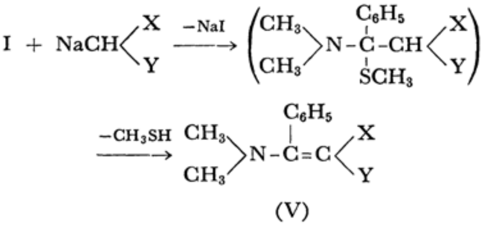
In addition, when potassium cyanide and the iodomethylate (I) were refluxed in dry benzene for 1 hr., α-dimethylamino-α-methylthiobenzyl cyanide (IV) was obtained in a 64% yield, while potassium iodide was eliminated.



$$\mathrm{I} + KC{\equiv}N \xrightarrow{-KI} (CH_3)_2N-C(C_6H_5)(SCH_3)(C{\equiv}N)$$

(IV)

Next, it was found that α-dimethylaminobenzylidene malonate was produced in a 56% yield, with the evolution of methyl mercaptan, when a suspension of the iodomethylate (I) and the monosodium salt of ethyl malonate in dry dioxane was stirred at 80°C for 2 hr. Similar results were obtained by treating the iodomethylate (I) with the monosodium salts of other active methylene compounds, such as ethyl acetoacetate, ethyl cyanoacetate, acetylacetone and nitromethane (see Table II).



$$\mathrm{I} + NaCH\langle^{X}_{Y} \xrightarrow{-NaI} \left((CH_3)_2N-C(C_6H_5)(SCH_3)-CH\langle^{X}_{Y}\right) \xrightarrow{-CH_3SH} (CH_3)_2N-C(C_6H_5)=C\langle^{X}_{Y}$$

(V)

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[1] H. Meerwein, W. Florian, N. Schön and G. Stopp, *Ann.*, **641**, 1 (1961).

[2] H. Eilingsfeld, M. Seefelder and H. Weidinger, *Chem. Ber.*, **96**, 2671 (1963).

[3] B. Böttcher and F. Bauer, *Ann.*, **568**, 218 (1950).

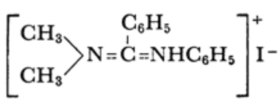
TABLE II. THE YIELDS, PHYSICAL PROPERTIES AND ANALYSES FOR α-DIMETHYLAMINOBENZYLIDENE DERIVATIVES OF ACTIVE METHYLENE COMPOUNDS

Active Methylene Compound	Yield %	B. p. °C/mmHg	M. p. °C	Found %	Calcd. %
Ethyl Malonate	56	136—137/0.11		C, 65.84	C, 65.95
				H, 7.38	H, 7.27
				N, 5.00	N, 4.81
Ethyl Acetoacetate	60	144—145/0.06		C, 67.94	C, 68.44
				H, 7.75	H, 7.33
				N, 5.25	N, 5.36
Ethyl Cyanoacetate	72	164—166/0.02	87—88[a]	C, 68.67	C, 68.83
				H, 6.86	H, 6.60
				N, 11.72	N, 11,47
Acetylacetone	52		115—117[b]	C, 72.45	C, 72.70
				H, 7.41	H, 7.41
				N, 6.26	N, 6.06
Nitromethane	57		128—129[c]	C, 62.37	C, 62.48
				H, 6.54	H, 6.29
				N, 14.66	N, 14.58

a) Recrystallized from benzene-ligroin. b) from ethyl acetate. c) from ethanol or benzene.

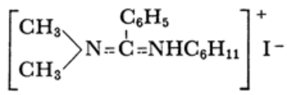
Further, the reactions of the iodomethylate (I) with primary amines were examined. When an ethanol solution of aniline was added to a suspension of the iodomethylate (I) in ethanol at room temperature, the evolution of methyl mercaptan was observed, and after stirring had been continued for 3 hr., *N, N*-dimethyl-*N'*-phenylbenzamidine hydroiodide was obtained in a 68% yield. Similarly, cyclohexylamine reacted with the iodomethylate (I) at room temperature to give *N,N*-dimethyl-*N'*-cyclohexylbenzamidine hydroiodide in a high yield.

$$\text{I} + C_6H_5NH_2 \xrightarrow{-CH_3SH}$$



$$\left[(CH_3)_2N{=}\overset{C_6H_5}{C}{=}NHC_6H_5 \right]^+ I^-$$

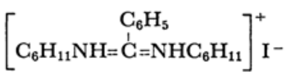
$$\text{I} + C_6H_{11}NH_2 \xrightarrow{-CH_3SH}$$



$$\left[(CH_3)_2N{=}\overset{C_6H_5}{C}{=}NHC_6H_{11} \right]^+ I^-$$

On the other hand, when a mixture of 2 mol. of cyclohexylamine and 1 mol. of the iodomethylate (I) was refluxed in ethanol for 2 hr., *N, N'*-dicyclohexylbenzamidine hydroiodide was given in a 49% yield, along with methyl mercaptan and dimethylamine.

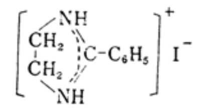
$$\text{I} + 2\,C_6H_{11}NH_2 \xrightarrow[-(CH_3)_2NH]{-CH_3SH}$$



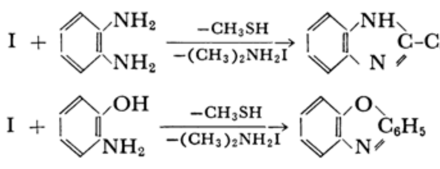
$$\left[C_6H_{11}NH{=}\overset{C_6H_5}{C}{=}NHC_6H_{11} \right]^+ I^-$$

Further, when ethylenediamine and the iodomethylate (I) were refluxed in ethanol for 2 hr., 2-phenylimidazoline hydroiodide was produced in a high yield. Free 2-phenylimidazoline was obtained by treating the hydroiodide with alkali.

$$\text{I} + H_2NCH_2CH_2NH_2 \xrightarrow[-(CH_3)_2NH]{-CH_3SH}$$



o-Phenylenediamine reacted with the iodomethylate (I) at room temperature in ethanol to give 2-phenylbenzimidazole in a good yield, with the elimination of methyl mercaptan and dimethylamine hydroiodide. In a similar way, 2-phenylbenzoxazole was prepared in a good yield by the reaction between *o*-aminophenol and the iodomethylate (I).



Experimental[4]

The Iodomethylate (I) of *N, N*-Dimethylthiobenzamide.—This compound was prepared by the following method. A solution of 83 g. (0.5 mol.) of *N, N*-dimethylthiobenzamide and 100 g. (0.7 mol.) of methyl iodide in 400 ml. of acetone was refluxed on a water-bath for 1 hr. After the mixture had then been cooled, the iodomethylate (I) was separated and recrystallized from acetone. Yield, 140 g. (92%); m. p. 148—149°C.

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[4] All melting points and boiling points are uncorrected.

The Reaction of I with Sodium Ethylmercaptide.—A suspension of 28 g. (0.1 mol.) of I and 9.8 g. (0.11 mol.) of sodium ethylmercaptide in 150 ml. of dry ether was stirred at room temperature for 1 hr. The precipitate of sodium iodide was then removed by filtration and washed with dry ether. After ether had been evaporated from the filtrate, the residual liquid was distilled in vacuo to give 11.1 g. (52%) of *N, N*-dimethylbenzamide methylethylmercaptol (II). B. p. 94—97°C/0.08 mmHg.

Found: C, 59.93; H, 8.14; N, 6.08. Calcd. for $C_{11}H_{19}NS_2$: C, 59.73; H, 7.94; N, 5.81%.

The Reaction of I with Sodium Methoxide.—A suspension of 3.0 g. (0.01 mol.) of I and 0.6 g. (0.01 mol.) of sodium methoxide in 20 ml. of dry benzene was refluxed for 1 hr. Then the reaction mixture was filtered to remove the precipitate of sodium iodide. After the benzene had been removed from the filtrate, the residual liquid was distilled under reduced pressure to give 0.62 g. (41.5%) of *N, N*-dimethylbenzamide. B. p. 133°C/12 mmHg.

By similar procedures, *N, N*-dimethylbenzamide and sulfides were obtained by the reactions of I with sodium ethoxide, sodium cyclohexyloxide and sodium benzyloxide (see Table I).

The Reaction of I with Potassium Cyanide.—A suspension of 3.0 g. (0.01 mol.) of I and 0.65 g. (0.01 mol.) of potassium cyanide in 20 ml. of dry benzene was refluxed for 1 hr. After the solution had cooled, the precipitated potassium iodide was filtered off and the benzene was removed from the filtrate in vacuo. The distillation of the residue under reduced pressure gave 1.33 g. (64%) of α-dimethylamino-α-methylthiobenzyl cyanide (IV). B. p. 93—94°C/2 mm Hg.

Found: C, 63.82; H, 7.13; N, 13.55. Calcd. for $C_{11}H_{14}N_2S$: C, 64.06; H, 6.84; N, 13.58%.

The infrared spectrum showed an absorption at 2230 cm^{-1}(C≡N).

The Reactions of I with the Monosodium Salts of Active Methylene Compounds.—Into a solution of an excess amount of an active methylene compound in 20 ml. of dry dioxane, 0.23 g. (0.01 mol.) of sodium metal was added in portions. Then the mixture was heated to the boiling point, when all the sodium parts disappeared. To the resulting suspension of the monosodium salt of the active methylene compound in dioxane was then added 3.0 g. (0.01 mol.) of I and the mixture was stirred for 2 hr. at 80°C. The α-dimethylaminobenzylidene derivatives (V) of the active methylene compounds obtained were purified by distillation or recrystallization. Their properties are listed in Table II.

The Reaction of I with Aniline.—A solution of 0.9 g. (0.01 mol.) of aniline in 20 ml. of ethanol was added to a suspension of 3.0 g. (0.01 mol.) of I in 20 ml. of ethanol. Soon the evolution of methyl mercaptan was observed and the suspended I was dissolved. After the solution had been stirred for 3 hr. at room temperature, the ethanol was removed in vacuo, giving *N, N*-dimethyl-*N'*-phenylbenzamidine hydroiodide as a white crystal; this was then recrystallized from ethanol-ether. Yield, 2.3 g. (68%). m. p. 122—124°C. Free *N, N*-dimethyl-*N'*-phenylbenzamidine (m. p. 72°C) was obtained by treating the hydroiodide with a 20% aqueous solution of potassium hydroxide.

The Reaction of 1 mol. of I with 1 mol. of Cyclohexylamine.—A suspension of 3.0 g. (0.01 mol.) of I and 1.0 g. (0.01 mol.) of cyclohexylamine in 20 ml. of ethanol was stirred at room temperature. The suspended I was soon dissolved completely, and the evolution of methyl mercaptan was observed. After stirring had been continued for 3 hr., the ethanol was evaporated and *N, N*-dimethyl-*N'*-cyclohexylbenzamidine hydroiodide was obtained as a white crystal. The hydroiodide was then recrystallized from ethanol-ether. Yield, 3.4 g. (91.5%); m. p. 189—190°C.

Found: C, 50.33; H, 6.17; N, 7.85. Calcd. for $C_{15}H_{23}N_2I$: C, 50.37; H, 6.41; N, 7.81%.

The Reaction of 1 mol. of I with 2 mol. of Cyclohexylamine.—A suspension of 3.0 g. (0.01 mol.) of I and 2.0 g. (0.02 mol.) of cyclohexylamine in 20 ml. of ethanol was refluxed for 3 hr. Then the ethanol was removed from the reaction mixture, and the resulting *N, N'*-dicyclohexylbenzamidine hydroiodide was recrystallized from ethanol-ether. Yield, 2.0 g. (49%); m. p. 173—174°C.

Found: C, 55.50; H, 7.04; N, 7.02. Calcd. for $C_{19}H_{29}N_2I$: C, 55.34; H, 7.08; N, 6.79%.

The Preparation of 2-Phenylimidazoline from I and Ethylenediamine. — Into a suspension of 3.0 g. (0.01 mol.) of I in 20 ml. of ethanol was added a solution of 0.6 g. (0.01 mol.) of ethylenediamine in 10 ml. of ethanol; the mixture was then refluxed on a water-bath. Soon the I was dissolved completely, and the evolution of methyl mercaptan was observed. After 2 hr., the solvent was removed and the resulting 2-phenylimidazoline hydroiodide monohydrate was recrystallized from acetonitrile-ether. Yield, 2.4 g. (89%); m. p. 105—107°C.

Found: C, 37.44; H, 4.50; N, 9.89. Calcd. for $C_9H_{13}N_2OI$: C, 37.00; H, 4.45; N, 9.59%.

Free 2-phenylimidazoline (m. p. 100—101°C) was obtained by treating the hydroiodide with a 10% aqueous solution of potassium hydroxide.

The Preparations of 2-Phenylbenzimidazole and 2-Phenylbenzoxazole from I.—A suspension of 3.0 g. (0.01 mol.) of I and 1.0 g. (0.01 mol.) of *o*-phenylenediamine in 20 ml. of ethanol was stirred at room temperature. The suspended I was thus dissolved completely, and methyl mercaptan was evolved. After stirring had been continued for 4 hr., about 50 ml. of water was added to the reaction mixture giving 1.45 g. (74.5%) of 2-phenylbenzimidazole. This was then recrystallized from acetonitrile. M. p. 285—286°C.

Similarly, when a suspension of 3.0 g. (0.01 mol.) of I and 1.1 g. (0.01 mol.) of freshly-refined *o*-aminophenol in 20 ml. of ethanol was stirred for 3 hr. at room temperature, 1.3 g. (67%) of 2-phenylbenzoxazole was obtained; it was then recrystallized from ethanol-ether. M. p. 101—102°C.

Summary

The reactions of the iodomethylate (I) of *N, N*-dimethylthiobenzamide with nucleophilic reagents have been examined. The iodomethylate I reacted with sodium ethylmercaptide and potassium

cyanide to give *N,N*-dimethylbenzamide methylethylmercaptol and α-dimethylamino-α-methylthiobenzyl cyanide respectively. When primary amines and the monosodium salts of active methylene compounds were treated with the iodomethylate I, benzamidine hydroiodides and α-dimethylaminobenzylidene derivatives of the active methylene compounds were, respectively, obtained, and methyl mercaptan was eliminated. Further, it has been found that diamines, such as *o*-phenylenediamine, easily condensed with the iodomethylate I to yield such heterocyclic compounds as 2-phenylbenzimidazole, while methyl mercaptan and dimethylamine were eliminated.

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