Notes

The Thiomethylation of Ammonia

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Following a study of the reactions of Grignard reagents with arylthiomethyl- and bis(arylthiomethyl)-amines,[1] it became of interest to extend this study to the tris(alkylthiomethyl)- and -(arylthiomethyl)amines.

Dougherty and Taylor[2] synthesized a variety of tris-(thiomethyl)amines by refluxing thiols with hexamethylenetetramine in *anhydrous* dioxane for 24 hr. To avoid disulfide formation during the long reaction time, the process had to be carried out under a nitrogen atmosphere. From β-thionaphthol these investigators obtained the supposed tris(thiomethyl)amine as an oil. They reported no analytical data for this compound, although analyses were listed for the product obtained from thiophenol, which was also an oil.

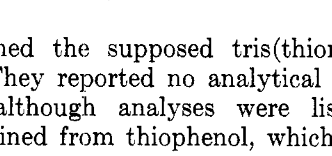
Table I

Condensation Products of Thiols with Formaldehyde and Ammonia in a 3:3:1 Ratio

R in $(RSCH_2)_3N$	Registry no.	Mp, °C	Reflux time, min	Yield,[d] %	Chemical shift of SCH_2N, ppm	Formula	Analyses[a] Calcd, % C	H	N	Found, % C	H	N
Phenyl	13084-04-3	31–32[b]	60[c]	75 (89)	4.38[e]	$C_{21}H_{21}NS_3$	65.75	5.52	3.65	66.29	5.55	3.51
p-t-Butylphenyl	13084-05-4	Oil	20	66 (89)	4.37[e]	$C_{33}H_{45}NS_3$	71.83	8.22	2.54	72.11	8.19	2.76
β-Naphthyl	13084-06-5	67–68[b]	20	80.5	4.49[e]	$C_{33}H_{27}NS_3$	74.26	5.10	2.62	74.54	4.95	2.91
p-Chlorophenyl	13100-23-7	112–114	15	67 (78)	4.37[f]	$C_{21}H_{18}Cl_3NS_3$	51.90	3.73	2.88	52.01	3.57	3.09[g]
m-Tolyl	13084-07-6	Oil	20	85	4.40[f]	$C_{24}H_{27}NS_3$	67.87	6.39	3.29	68.06	6.42	2.96
										67.67	6.44	3.12
Mesityl	13095-01-7	68.5–69.5	20	46.5 (84)	4.12[f]	$C_{30}H_{39}NS_3$	70.67	7.71	2.75	69.63	7.55	2.38
p-Nitrophenyl	13084-08-7	149–151	30	21.5 (72)	4.78[h]	$C_{21}H_{18}N_4O_6S_3$	48.64	3.49	10.80	48.39	3.56	10.89
Benzyl	13084-09-8	45–47	15	55 (70)	3.92[f]	$C_{24}H_{27}NS_3$	67.87	6.34	3.29	67.61	6.15	3.30

[a] Elemental analyses performed by Drs. Strauss and Weiler, 164 Banbury Road, Oxford, England. [b] Reported to be oils by Dougherty and Taylor.[2] [c] Stirred without external heating. [d] Values in parentheses are crude yields. [e] In carbon tetrachloride. [f] In deuterated chloroform. [g] Calcd.: Cl, 21.84. Found: 21.45. [h] In dimethyl sulfoxide–chloroform (both deuterated).

Galimberti[3] has reported the preparation of tris-(2,5-dimethylphenylthiomethyl)amine by refluxing hexamethylenetetramine with 2,5-dimethylthiophenol in absolute alcohol–glacial acetic acid for 30 min. With α- and β-thionaphthol in alcohol, he obtained the bis-(naphthylthiomethyl)amines instead of the tris compounds. However, when the reaction was carried out with β-thionaphthol in acetic acid instead of alcohol, Galimberti claimed that he obtained 1,3-bis-(β-mercapto-α-naphthyl)-2-azapropene.



Asinger, *et al.*,[4] obtained tris[(2,4-dimethylpentan-3-on-2-yl)thiomethyl]amine, $(Me_2CHCOCMe_2SCH_2)_3N$, from gaseous ammonia and a mixture of α-mercaptodiisopropyl ketone and formalin and reported this as an unusual reaction product, since, with other α-mercapto ketones, Δ³-thiazoline derivatives were usually obtained.

Since in the course of our work we found that tris-(phenylthiomethyl)amine could be obtained much more simply than by any of the methods described in the literature, namely, by condensing thiophenol with 37% formaldehyde and aqueous ammonia in an alcoholic solution, it was considered worthwhile to check the generality of this reaction by using a variety of available thiols. The results obtained with the reactants in 3:3:1 ratio are summarized in Table I.

Thus, it is seen that indeed this condensation is a general one and even β-thionaphthol yields the corresponding tris(arylthiomethyl)amine. The fact that this compound was obtained as a crystalline solid, melting at 67–68°, whereas Dougherty and Taylor[2] claimed to have obtained it as an oil, makes their claim subject to suspicion.

Experimental Section

Tris(arylthiomethyl)amines. General Procedure.—The thiophenol or mercaptan, 37% formaldehyde, and aqueous ammonia (sp gr 0.90) in a molar ratio of 3:3:1 were dissolved in a suitable quantity of 95% alcohol. Stirring was begun and, if an initial heating occurred, external heat was not applied until the temperature subsided. Stirring was then continued for an additional 15–30 min at the reflux temperature of the solution.

If crystallization occurred upon chilling the reaction mixture, the crystals were removed by filtration and the solid material was suspended in 100 ml of 10% NaOH, filtered, and washed with water until neutral to litmus and then with ether. The resulting residue was recrystallized from a benzene or a benzene–alcohol solvent. If crystallization of the crude tris(thiomethyl)amine did

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(1) I. E. Pollak, A. D. Trifunac, and G. F. Grillot, *J. Org. Chem.*, **32**, 272 (1967).

(2) G. Dougherty and W. H. Taylor, *J. Am. Chem. Soc.*, **55**, 4588 (1933).

(3) P. Galimberti, *Gazz. Chim. Ital.*, **77**, 375 (1947); *Chem. Abstr.*, **42**, 4558 (1948).

(4) F. Asinger, M. Thiel, and V. Tesar, *Ann. Chem.*, **619**, 169 (1958).

not occur upon chilling, the lower layer that formed in the reaction was separated, washed with 10% NaOH, and then dissolved in ether. The resulting ether extract was then washed with base and water and was then dried over KOH pellets. The ether was removed and, in certain cases, crystallization of the resulting oil occurred upon chilling. If crystallization occurred, a recrystallization from a benzene–alcohol solvent was employed. In all cases the infrared and nmr spectra, which are not reported in this Note, agreed with the structures assigned to these compounds. However, the chemical shifts of the SCH_2N group in parts per million are recorded in Table I.

Registry No.—Ammonia, 7664-41-7.

The Reaction of Grignard Reagents with Arylthiomethylarylamines and with Tris(phenylthiomethyl)amines

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In a previous communication,[1] we have noted that Grignard reagents, in analogy with their action upon alkoxymethylamines,[2] cleave the C–S bond rather than the C–N bond in the phenylthiomethylalkylamines. The latter might be the expected cleavage if, as suggested by Grillot and Lau[3] in their study of the acid-catalyzed rearrangement of the arylthiomethylamines, the C–N bond should be a more labile bond than the C–S bond.

The study of the action of Grignard reagents on the S,N-acetals has now been extended to the N-(arylthiomethyl)arylamines, to N,N-bis(phenylthiomethyl)aniline, and to tris(phenylthiomethyl)amine. The reaction of Grignard reagents on the two former types of compounds appears to be an excellent method of preparing N,N-dialkylanilines, while reaction with the latter compound leads to the synthesis of tertiary aliphatic amines if an excess of Grignard reagent is used.

In Table I are listed the N-alkylated anilines obtained from N-(phenylthiomethyl)N-methylaniline and N-(phenylthiomethyl)N-methyl-*p*-toluidine according to eq 1.

$$C_6H_5SCH_2N(CH_3)Ar + RMgX \longrightarrow RCH_2N(CH_3)Ar + C_6H_5SMgX \quad (1)$$

In Table II are listed the N,N-dialkylated anilines that were obtained from N,N-bis(phenylthiomethyl)aniline according to eq 2, while in Table III are listed

$$(C_6H_5SCH_2)_2NC_6H_5 + 2RMgX \longrightarrow (RCH_2)_2NC_6H_5 + 2C_6H_5SMgX \quad (2)$$

the N-monoalkylated anilines that were obtained from N-(phenylthiomethyl)aniline, according to eq 3 and 4.

$$C_6H_5SCH_2NHC_6H_5 + 2RMgX \longrightarrow RCH_2N(MgX)C_6H_5 + C_6H_5SMgX + RH \quad (3)$$

$$RCH_2N(MgX)C_6H_5 + H_2O \longrightarrow RCH_2NHC_6H_5 + Mg(OH)X \quad (4)$$

Reaction of 3 moles of the Grignard reagent with 1 mole of tris(phenylthiomethyl)amine, according to eq 5, produces tertiary alkylmethylamines, as noted in Table IV.

$$(C_6H_5SCH_2)_3N + 3RMgX \longrightarrow (RCH_2)_3N + 3C_6H_5SMgX \quad (5)$$

In order to check the feasibility of using the reaction of tris(phenylthiomethyl)amine with Grignard reagents for the preparation of primary and secondary amines by a stepwise replacement of the thiophenoxy groups and subsequent acid hydrolysis of the unreplaced thiomethyl groups according to Scheme I and II, the Grignard reagent prepared from 0.1 mole of bromobenzene was added to 0.1 mole of tris(phenylthiomethyl)amine and the products (before acid hydrolysis) were analyzed by nmr spectroscopy. The results indicated that the reaction product was a mixture in which the components were in the following relative order of concentrations: $(PhSCH_2)_3N > (PhCH_2)_3N > (PhCH_2)_2NCH_2SPh > PhCH_2N(CH_2SPh)_2$. Thus, it seems impossible to replace selectively the thiophenoxy groups. In fact, it appears that the order of ease of replacing a single thiophenoxy group is $R_2NCH_2SPh > RN(CH_2SPh)_2 > N(CH_2SPh)_3$.

SCHEME I

$$RMgX + (PhSCH_2)_3N \xrightarrow[-PhSMgX]{} RCH_2N(CH_2SPh)_2 \xrightarrow[\substack{-2PhSH \\ -2CH_2O}]{H^+} RCH_2NH_2$$

SCHEME II

$$2RMgX + (PhSCH_2)_3N \xrightarrow[-2PhSMgX]{} (RCH_2)_2NCH_2SPh \xrightarrow[-PhSH,\ -CH_2O]{H^+} (RCH_2)_2NH$$

Experimental Section

Infrared spectra obtained on a Perkin-Elmer Infracord and nmr spectra obtained on a Varian A-60 spectrometer for the compounds prepared in this study are in agreement with the structures assigned.

The method used in the preparation of the N-(arylthiomethyl)-arylamines and of the N,N-bis(phenylthiomethyl)aniline has been reported by Grillot and Schaffrath[4] while the synthesis of tris(phenylthiomethyl)amine has been described by Pollak and Grillot.[5] The preparation of N-*n*-propyl-N-methylaniline is typical of the preparation of all the amines studied. The Grignard reagent was prepared from 24 g (1 g-atom) of magnesium turnings in 100 ml of dry tetrahydrofuran (THF) to which was added over a period of 2 hr a solution of 48 g (0.44 mole) of ethyl bromide in 50 ml of THF. At the completion of the addition of ethyl bromide, the reaction mixture was refluxed for an additional 30 min.

To the thus prepared Grignard reagent was gradually added a solution of 93 g (0.4 mole) of N-phenylthiomethyl-N-methylaniline[4] in 50 ml of THF. A vigorous exothermic reaction ensued. At the end of the addition, the reaction mixture was stirred for 1 hr. Following the usual work-up (See the Experimental Section entitled Reactions of Phenylthiomethylamines with Grignard Reagents in ref 1), 47.5 g (79.5% of theory) of N-*n*-propyl-N-methylaniline was obtained as a colorless liquid that boiled at 58–60° (1–2 mm). Pertinent data concerning all the amines prepared in this study appear in Tables I, II, III, and IV (p 2893).

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[1] I. E. Pollak, A. D. Trifunac, and G. F. Grillot, *J. Org. Chem.*, **32**, 272 (1967).

[2] G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **123**, 532 (1923).

[3] G. F. Grillot and P. T. S. Lau, *J. Org. Chem.*, **30**, 28 (1965).

[4] G. F. Grillot and R. E. Schaffrath, *ibid.*, **24**, 1035 (1959).

[5] I. E. Pollak and G. F. Grillot, *ibid.*, **32**, 2891 (1967).