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MANNICH CONDENSATIONS OF THIOPHENOLS. REACTION OF p-HALOTHIOPHENOLS WITH PRIMARY ALIPHATIC AMINES AND FORMALDEHYDE

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ABSTRACT - The synthesis of previously unreported 1,5-di(p-halophenyl)-1,5-dithia-3-azapentanes is reported. A study of reaction conditions necessary for preparing these compounds and the N-alkylamino methyl-p-halophenyl sulfides is discussed.

INTRODUCTION

Condensation of p-chlorobenzenethiol (ClC_6H_4SH), formaldehyde, and benzylamine has been reported (Grillot and Schaffrath, 1959(as yielding an unidentified mixture, m.p. 54-55.6° and a small quantity of N-benzylaminomethyl-p-chlorophenyl sulfide. They also reported the synthesis of N-aryl-N-methylaminomethyl aryl sulfides ($ArN(CH_3)CH_2SAr$) and three other condensations yielding 1,3,5-triaryl-1,5-dithia-3-azapentanes ($ArSCH_2\underset{Ar}{N}CH_2SAr$). No reference was made to the reaction of primary aliphatic amines, other than benzylamine, mentioned above with formaldehyde and thiophenols.

In previous work (Weatherbee, Sleeter and Han, 1965) in our laboratories, good yields of products from Mannich condensations of primary aliphatic amines with 2-naphthalenethiol were secured. No other references to Mannich condensations of thiophenols, formaldehyde, and primary aliphatic amines appear in the literature.

RESULTS AND DISCUSSION

In this investigation condensation of p-chlorobenzenethiol with primary aliphatic amines and formaldehyde resulted in the isolation of previously unreported 1,5-(p-chlorophenyl)-1,5-dithia-3-alkyl-3-azapentanes ($ClC_6H_4SCH_2\text{-}\underset{R}{N}\text{-}CH_2SC_6H_4Cl$). Corresponding p-bromoderivatives were secured when p-bromobenzenethiol was used in lieu of the p-chlorobenzenethiol. The 3-alkyl-3-azapentane structure is assigned on the basis of elementary analysis, nmr spectra, and infrared spectra showing the absence of SH and NH stretching modes.

Condensation of benzylamine, formaldehyde, and p-chlorobenzenethiol in a 1:2:2 mole ratio, respectively, gave 1,5-di(p-chlorophenyl)-1,5-dithia-3-benzyl-3-azapentane, m.p. 53-54°. The "mixture" reported by Grillot and Schaffrath was probably this compound contaminated with N-benzylaminomethyl-p-chlorophenyl sulfide, m.p. 70-71°. The latter compound is very difficult to isolate in pure form.

The manner of mixing the reactants and the solvent used was found to have considerable effect on the yields. For the 1,5-di(p-halophenyl)-1,5-dithia-3-alkyl-3-azapentanes, addition of the amine dissolved in ethyl acetate to a solution formed by adding the formaldehyde to the thiophenol in ethyl acetate at 10-15°C gave the highest yields. Although the same products were obtained if formaldehyde were added to a solution of the amine and thiophenol, or if the thiophenol were added to solutions of the amine and formaldehyde, the yields were lower. The solvents methanol, ethanol, and dioxane normally used in our laboratories in Mannich condensations were found to give lower yields than when ethyl acetate was employed. The mole ratio of reactants used in the condensations influenced the yields. Use of an excess of amine or thiophenol drastically reduced yields. With some amines, solid material in addition to the desired 1,5-dithia-3-azapentanes was secured. The use of 100% excess of the formaldehyde resulted in the highest yields of the 1,5-dithia-3-azapentanes.

For the N-alkylaminomethyl-p-halophenyl sulfides, the 1:1:1 mole theoretical quantity of amines, formaldehyde, and thiophenol never gave the expected N-alkylaminomethyl-p-halophenyl sulfide. This probably accounts for the fact that Grillot and Schaffrath obtained a small quantity of N-benzylaminomethyl-p-chlorophenyl sulfide. Although considerable difficulty was encountered in obtaining the latter compound, a 64% yield of N-benzylaminomethyl-p-bromophenyl sulfide was secured when a 100% excess of the amine was used. In several reactions of benzylamine, formaldehyde, and p-chlorobenzenethiol, no condensation was observed and the only substance isolated was the salt of the amine and thiophenol N-benzylaminonium p-chlorophenyl sulfide.

EXPERIMENTAL

1,5-di(p-chlorophenyl)-1,5-dithia-3-benzyl-3-azapentane

To 28.8 g of p-chlorothiophenol (0.2 mole) in 100 ml of ethyl acetate was added dropwise 30 ml of 37% aqueous formaldehyde (0.4 mole) dissolved in 40 ml of ethyl acetate with stirring in an ice bath at 10-15°. To the resulting solution was added 11 ml (0.1 mole) of benzylamine, dropwise, with stirring. The solution was stirred for 5 minutes in the ice-water bath and then gradually warmed to gentle refluxing. The refluxing was continued for one hour under an atmosphere of nitrogen. Two layers formed. The solvents were removed under vacuum with a rotary evaporator, leaving an oil which solidified upon cooling. The solid was dissolved in 70 ml of warm heptane-octane mixture (70:30). Upon cooling, 41 g of solid (97% yield), m.p. 51-52°, was secured. After four recrystallizations from the heptane-octane mixture the m.p. was 53-54°. The experiment has been repeated several times giving similar results.

Analysis:

Calculated for $C_{21}H_{19}Cl_2NS_2$:	C 59.99	H 4.56	N 3.33	S 15.25
Found:	60.00	4.78	3.27	

Integration of nmr spectra of the compound dissolved in $CDCl_3$ gave 13 aryl hydrogens at 7.18 ppm, 4 CH_2-S hydrogens at 4.33 ppm, and 2-CH_2-N hydrogens at 3.81 ppm. The nmr spectra gave no D_2O exchange indicating the compound contains no easily replaceable proton, such as an NH or NH_2 group.

Infrared spectra of p-chlorothiophenol in CCl_4 gave an absorption at 256° cm^{-1} but this absorption was absent in the infrared spectra of the compound indicating the -SH hydrogen was involved in the condensation. The absence of N-H stretching vibrations in the area of 3310-3500 cm^{-1} shows that the amino hydrogens were involved in the reaction. Absorption at 633 cm^{-1} is indicative of the S-CH_2 stretching vibration.

1,5-di(p-chlorophenyl)-1,5-dithia-3-tert-octyl-3-azapentane
m.p. 69-70°, yield 52%.
Analysis:

Calculated for $C_{22}H_{29}Cl_2NS_2$:	C 59.71	H 6.61	
Found:	59.80	6.70	

1,5-di(p-chlorophenyl)-3-tert-butyl-1,5-dithia-3-azapentane
b.p. 170° at 3 mm, yield 44%.
Analysis:

Calculated for $C_{18}H_{21}Cl_2NS_2$:	C 55.95	H 5.48	N 3.63
Found:	55.73	5.98	3.86

1,5-di(p-bromophenyl)-3-benzyl-1,5-dithia-3-azapentane
m.p. 71-72°, yield 91%.
Analysis:

Calculated for $C_{21}H_{19}Br_2NS_2$:	C 49.52	H 3.76	N 2.75
Found:	49.75	3.82	2.72

1,5-di(p-bromophenyl)-3-tert-octyl-1,5-dithia-3-azapentane
m.p. 65-66°, yield 55%.
Analysis:

Calculated for $C_{22}H_{29}Br_2NS_2$:	C 49.72	H 5.50	N 2.64
Found:	49.93	5.43	2.52

1,5-di(p-chlorophenyl)-3-cyclohexyl-1,5-dithia-3-azapentane
b.p. 140° at 1 mm, yield 36%.
Analysis:

Calculated for $C_{20}H_{23}Cl_2NS_2$:	C 58.22	H 5.62	N 3.40
Found:	58.80	5.32	3.73

1,5-di(p-bromophenyl)-3-cyclohexyl-1,5-dithia-3-azapentane
b.p. 133° at 1 mm, yield 44%.
Analysis:

Calculated for $C_{20}H_{23}Br_2NS_2$:	C 47.91	H 4.62	N 2.79
Found:	48.53	4.40	2.56

Benzylaminomethyl p-bromophenyl sulfide

To 3.75 ml of 37% aqueous formaldehyde (0.05 mole) in 15 ml of ethyl acetate was added 11 ml (0.1 mole; 100% excess) benzylamine with stirring at 10-15°. The resulting solution was added dropwise with stirring to 9.45 g of p-bromothiophenol (0.05 mole) in 25 ml of ethyl acetate; a white solid formed during the addition. The solid dissolved as the mixture was gradually warmed to gentle refluxing over a period of 10 minutes. The solution was refluxed for one hour under nitrogen. The solvents were removed with a rotary evaporator leaving a white solid. After one recrystallization from a 70:30 heptane-octane mixture, 9.9 g of solid (64% yield), m.p. 89-94° was secured. After six recrystallizations from the heptane-octane mixture the melting point was 98°.

Analysis:

Calculated for $C_{14}H_{14}BrNS$:	C	54.55	H	4.58	N	4.54
Found:		54.13		4.89		4.85

N-Benzylammonium p-chlorophenyl sulfide

When p-chlorophenyl sulfide was used in lieu of the p-bromothiophenyl in the above experiment, 11.95g, (95% yield) N-Benzylammonium sulfide, m.p. 94-95°, was the only substance isolated.

Analysis:

Calculated for $C_6H_5CH_2NH_3^{\oplus}S^{\ominus}L_6H_4Cl$:	C	62.02	H	5.60	N	5.56	S	12.73	Cl	14.08
Found:		61.89		5.57		5.44		12.53		14.01

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FOOTNOTES AND LITERATURE CITED

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