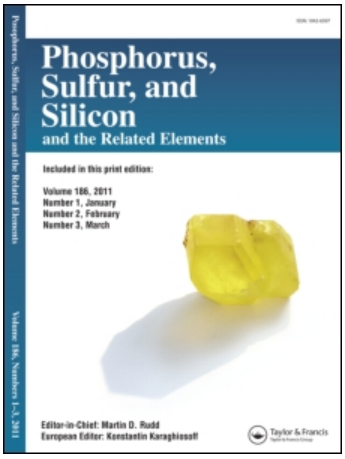

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MODERN FRIEDEL-CRAFTS CHEMISTRY. XIV. ON THE CYCLIZATION OF SELECTED ARYL HYDROXYALKYL SULFIDES

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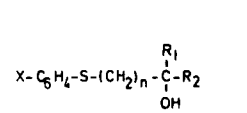
The feasibility of cycloalkylation reactions in the presence of Friedel–Crafts catalysts was demonstrated in a number of aryl hydroxyalkyl sulfides (**1–5**), and benzyl hydroxyalkyl sulfides (**6–7**). Treatment of compounds (**1–7**) with Friedel-Crafts catalysts gave diaryl disulfides, diaryl sulfides, arene thiols, chlorohydrins, aryl chloroalkyl sulfides, aryl alkenyl sulfides and cyclization products. It is noteworthy to mention that cyclization products were isolated only in cases where the hydroxyl group is linked to a tertiary carbon atom as in compounds **3** and **7**.

A suitable reaction pathway is suggested to rationalize the formation of the various reaction products.

In the last two decades Khalaf and Roberts exerted continuous efforts to explore the various factors governing the course of the Friedel-Crafts ring closure of a variety of organic compounds.[1–7] Their extensive studies on the cyclodehydration of arylalkanols answered many questions in this area. They concluded that conversion of arylalkanols into tetralins could be achieved readily by treating primary, secondary, and tertiary alcohols with Friedel-Crafts catalysts. However, cyclodehydration to indanes could only occur in cases of secondary benzylic or tertiary arylalkanols.[8]

In continuation of these studies and due to our interest in sulfur chemistry,[9–13] we extended the scope of Friedel–Crafts cycloalkylation to aryl haloalkyl sulfides, aryl halo-alkyl sulfones, arylsulfonylacyl halides and their corresponding sulfides.[9] We found that heterocyclic sulfur compounds could be prepared in fair yields from aryl haloalkyl sulfides and arylthioacyl halides.[9]

The promising results we got concerning the Friedel–Crafts cyclization of arylalkanols[8] and aryl haloalkyl sulfides[9] prompted us to investigate the possibility of heterocyclization of aryl hydroxyalkyl sulfides, the precursors of aryl haloalkyl sulfides. For this purpose, a number of aryl hydroxyalkyl sulfides (**1–7**) were prepared as reported[14] and subjected to Friedel–Crafts conditions.



Comp.	n	R_1	R_2	X
1	1	H	H	p-Cl
2	1	H	H	p-CH_3
3	1	CH_3	CH_3	p-CH_3
4	2	H	H	p-CH_3
5	2	H	H	p-Cl
6	1	H	H	H
7	1	CH_3	CH_3	H

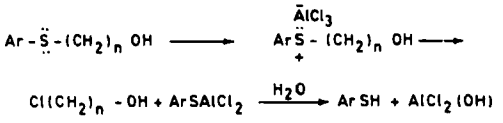
RESULTS AND DISCUSSION

Examination of the results depicted in Table I showed that *p*-chlorophenyl-2-hydroxyethyl-sulfide (**1**), 2-hydroxyethyl-*p*-tolyl-sulfide (**2**), 3-hydroxypropyl-*p*-tolyl-sulfide (**4**), *p*-chlorophenyl-3-hydroxypropyl-sulfide (**5**) and benzyl-2-hydroxyethyl-sulfide (**6**) resisted cyclization to dihydrobenzothiophenes, or thiochromans or isothiochromans upon treatment with different Friedel–Crafts catalysts. This behaviour is in sharp contrast with the previously reported ready cyclization of 4-aryl-1-butanols into tetralins or methylindanes.[15] It is clear from these results that upon treatment of aryl *n*-hydroxyalkyl-sulfides (**1**, **2**, **4**, **5**, and **6**) with Friedel–Crafts catalysts the complex formed does not cyclodehydrate to heterocyclic compounds but instead suffers carbon–sulfur bond breaking to give different cleavage products (sulfides, disulfides and thiols), dehydration to aryl alkenyl sulfides, or chlorination to aryl chloroalkyl sulfides and chlorohydrins.

Being unable to achieve the cyclodehydration process we designed some starting aryl-hydroxyalkyl-sulfides so that they contain tertiary hydroxyl group. Thus we prepared 2-hydroxy-2-methylpropyl *p*-tolyl-sulfide (**3**) and benzyl-2-hydroxy-2-methylpropyl sulfide (**7**) and subjected them to the action of Friedel–Crafts catalysts under the same previous conditions. Analysis of the reaction products showed that **3** and **7** gave among other products cyclization products, in 11–14% (Table 1, Exps. 3, 4) and 50% (Table 1, Exps. 14, 15), respectively. The higher percentage conversion of compound **7** into cyclic product compared with **3** may be attributed to preference of six-membered ring virsus five-membered ring formation.

The tendency of compounds **3** and **7** to cyclize and the resistance of compounds **1**, **2**, **4**, **5** and **6** to behave similarly could be interpreted in terms of the relative stability of the intermediate tertiary and primary carbocations formed therefrom, respectively, along with the stability of the ring expected to be formed.

To account for the formation of the different cleavage products, for example thiophenol is suggested to be formed, as reported by Harnish and Tarbell[16] through C—S bond cleavage of the sulfide-$AlCl_3$ complex.



The possibility of air oxidation of thiols into disulfides was eliminated by stirring thiophenol in carbon disulfide for 40 hours, where the starting thiol was recovered and no diphenyl disulfide or diphenyl sulfide could be isolated or detected in the reaction mixture.

Interestingly, when thiophenol was reacted with $AlCl_3$ at the same reaction conditions reported for method B, diphenyl disulfide was obtained in 60% yield. Accordingly the formation of α-disulfides could be attributed to the action of $AlCl_3$, present in excess in the reaction mixture, on the produced arene thiol and/or the attack of its precursor $ArSAlCl_2$ on the starting sulfide-$AlCl_3$ complex

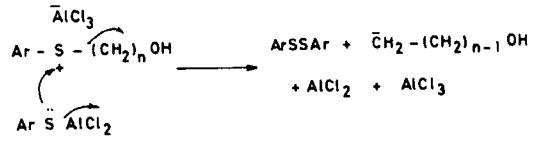
TABLE I

Reaction of Aryl hydroxyalkyl sulfides (**1–7**) with Friedel–Crafts Catalysts

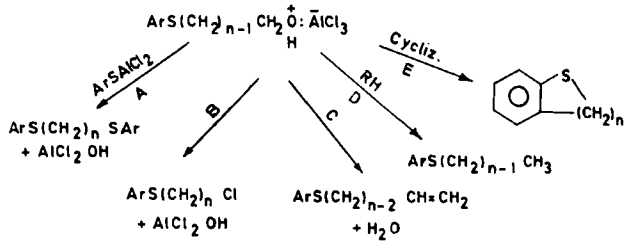
Exp.	Starting Sulfide	Method	Conversion (%)	Main products (% yield)
1	*p*-$ClC_6H_4S(CH_2)_2OH$	A[a]	96	*p*-$ClC_6H_4S(CH_2)_2Cl$ (61), Cl_2-C_6H_3-S-$(CH_2)_2Cl$ (35)
2	*p*-$CH_3C_6H_4S(CH_2)_2OH$	A	100	*p*-$CH_3C_6H_4SH$(0.3), *p*-$CH_3C_6H_4(CH_2)_2Cl$ (54), *p*-$CH_3C_6H_4SSC_6H_4$-CH_3-*p* (2.1)., *p*-$CH_3C_6H_4S(CH_2)_2SC_6H_4CH_3$-*p* (43).
3	*p*-$CH_3C_6H_4SCH_2C(CH_3)_2OH$	A	100	*p*-$CH_3C_6H_4SCH{=}C(CH_3)_2$ (33), 3,3,5-Dimethylbenzthiophene (11), *p*-$CH_3C_6H_4CH_2SC(CH_3)_2Cl$ (43), *p*-$CH_3C_6H_4SSC_6H_4CH_3$-*p* (9).
4	*p*-$CH_3C_6H_4SCH_2C(CH_3)_2OH$	D[b]	100	*p*-$CH_3C_6H_4SCH{=}C(CH_3)_2$ (5), 3,3,5-trimethylbenzothiophene (14), *p*-$CH_3C_6H_4SSC_6H_4$-CH_3*p* (39), unidentified, M/e = 232 (23).
5	*p*-$CH_3C_6H_4S(CH_2)_3OH$	B[c]	50	*p*-$CH_3C_6H_4SSC_6H_4CH_3$-*p* (40), unidentified (40), *p*-$CH_3C_6H_4SO_2(CH_2)_3OH$ (8).
6	*p*-$CH_3C_6H_4S(CH_2)_3OH$	D	49	*p*-$CH_3C_6H_4SH$ (3), *p*-$CH_3C_6H_4SC_2H_5$ (4), *p*-$CH_3C_6H_4SSC_6H_4$—CH_3-*p* (45), *p*-CH_3—C_6H_4—$SSC_6H_3(C_3H_7)$—CH_3-*p* (42).
7	*p*-$CH_3C_6H_4S(CH_2)_3OH$	E[d]	32	*p*-$CH_3C_6H_4SH$ (9), *p*-CH_3—$C_6H_4SC_3H_7$ (10), *p*-CH_3—$C_6H_4SSC_6H_4$—CH_3-*p* (80).
8	*p*-$CH_3C_6H_4S(CH_2)_3OH$	F[e]	80	*p*-$CH_3C_6H_4SH$ (4), *p*-CH_3—$C_6H_4SC_3H_7$ (21), *p*-$CH_3C_6H_4SSC_6H_4CH_3$-*p* (72).
9	*p*-$ClC_6H_4S(CH_2)_2OH$	A	50	*p*-ClC_6H_4SH (2), *p*-$ClC_6H_4SO_2H$ (8), 3-hydroxypropylthiophenol (40), *p*-$ClC_6H_4SSC_6H_4$—Cl-*p* (40)
10	*p*-$ClC_6H_4S(CH_2)_3OH$	D	90	*p*-$ClC_6H_4SCH_2CH_3$ (5), *p*-Cl—$C_6H_4SSC_6H_4$—Cl-*p* (50), *p*-Cl—$C_6H_4SSC_6H_3(C_3H_7)$—Cl-*p* (10).
11	$C_6H_5CH_2S(CH_2)_2OH$	A	100	$C_6H_5CH_2Cl$ (13), $C_6H_5CH_2SCl$ (2), $C_6H_5CH_2SCH_2CH_2Cl$ (30), $C_6H_5CH_2SCH_2C_6H_5$ (15), $C_6H_5CH_2SSCH_2C_6H_5$ (20).
12	$C_6H_5CH_2S(CH_2)_2OH$	C[f]	60	$C_6H_5CH_2Cl$ (6), $C_6H_5CH_2SCH_2C_6H_5$ (44), $C_6H_5CH_2SSCH_2C_6H_5$ (36), $Cl(CH_2)_2OH$ (12).
13	$C_6H_5CH_2S(CH_2)_2OH$	D	85	$C_6H_5CH_2SCH{=}CH_2$ (5), $C_6H_5CH_2SCH_2CH_3$ (15), $C_6H_5CH_2SCH_2C_6H_5$ (65), $C_6H_5CH_2S(CH_2)_2SCH_2C_6H_5$ (3).
14	C_6H_5—$CH_2SCH_2C(CH_3)_2$ | OH	A	100	$ClCH_2C(CH_3)_2OH$ (10), $C_6H_5CH_2SCH{=}C(CH_3)_2$ (30), $C_6H_5CH_2SCH_2C{=}C(CH_3)_2$ (2), 4,4-dimethylisothiochroman (50), 4,4,6-trimethylisothiochroman (2).
15	C_6H_5—$CH_2SCH_2C(CH_3)_2$ | OH	D	100	4,4-Dimethylisothiochroman (50), $C_6H_5CH_2SCH_3$ (5), Unidentified (45).

[a] Using $AlCl_3/CH_3NO_2$ as catalyst; [b] Using H_2SO_4 as catalyst; [c] Using $AlCl_3$ as catalyst; [d] Using H_3PO_4 as catalyst; [e] Using PPA as catalyst; [f] Using $FeCl_3$ as catalyst.

as follows:



Complexation of $AlCl_3$ with the hydroxyl group of the starting material and subsequent attack of the complex by $ArSAlCl_2$ gives an explanation for the production of other disulfides (Exp. 2 and 13, Scheme 2-A). Also, the generation of aryl haloalkyl sulfides, aryl alkenyl sulfides and aryl alkyl sulfides is expressed in the same way (Scheme 2-B, C and D).



It is noteworthy to mention that the yield of the aforementioned C—S cleavage, chlorination and elimination products increased markedly in all cases where cyclization products are not fairly produced.

In conclusion, the competition between cyclodehydration and cleavage of the aryl hydroxyalkyl sulfides was in sharp contrast to the reported ease of cyclization of aryl haloalkyl sulfides,[9] this may be explained in terms of kinetic rather than thermodynamic factors as ionization of C-halogen bond is faster if compared to ionization of C—OH bond. Thus, cyclization in the former case is rapid while the slower ionization in case of aryl hydroxyalkyl sulfides will give enough chance for the other competing reactions to occur.

EXPERIMENTAL

All melting points were uncorrected and were determined on a Kofler melting point apparatus. Chromatographic separation was carried out also using 100×2 cm silica gel column as well as 15×5 cm glass plates covered with thin film of silica gel. IR spectra were obtained using a Pye-Unicam SP 200 G spectrophotometer. GC/MS data were obtained using a Finnigan MAT 4023 spectrometer with an INCOS data system and a J & W Scientific, Inc., 50-m DBI bonded-phase capillary column (0.25-μm film thickness).

STARTING MATERIALS

Aryl hydroxyalkyl sulfides (**1–7**) were prepared by the alkylation of the thiols (*p*-chlorothiophenol, *p*-thiocresol, and benzylthiol) with chlorohydrins (ethylenechlorohydrin, 3-hydroxychooropropane and 2-hydroxy-2-methylchloropropane) as reported.[14]

CYCLIZATION PROCEDURES

The cyclization behaviour of the investigated compounds (**1–7**) was attempted through six general procedures A–F.

A. *Using $AlCl_3/CH_3NO_2$ as catalyst*

A 100 ml 3-necked flask equipped with thermometer, dropping funnel, reflux condenser capped with calcium chloride tube and magnetic stirrer was charged with 0.044 mole of anhydrous $AlCl_3$, 0.044 mole of nitromethane and subsequently 50 ml of CS_2 as solvent. To this mixture was added dropwise 0.01 mole of the sulfide to be investigated (**1–7**). The reaction mixture was stirred for 40 hours at room temperature, then decomposed with cold 5% hydrochloric acid solution. The organic layer was separated, washed with water, with 5% solium bicarbonate solution, again with water, dried over anhydrous magnesium sulfate and filtered. The solvent was distilled using rotatory evaporator and the residue was analyzed.

B. *Using $AlCl_3$ as catalyst*

As in procedure A without the addition of nitromethane.

C. *Using $FeCl_3$ as catalyst*

As in procedure B with the replacement of $AlCl_3$ with $FeCl_3$.

D. *Using H_2SO_4 as catalyst*

To a 0.01 mole of the investigated compound 20 ml of 96% H_2SO_4 were added over a period of 5 minutes. The reaction mixture was stirred at room temperature for 40 hours. It had become dark in colour and was decomposed by pouring onto ice. The products were separated as before.

E. *Using H_3PO_4 as Catalyst*

As in procedure D but H_2SO_4 was replaced by H_3PO_4. Only cyclization of **4** was attempted under these conditions.

F. *Using PPA (Polyphosphoric acid) as catalyst*

As in procedure E, but PPA was used as catalyst.

Analyses of the reaction mixtures of methods A, B, C, D, E and F were carried out mainly using GC/MS technique and using authentic samples. Results are tabulated in Table I.

Attempted autoxidation of thiophenol

A solution of thiophenol (1.1 g, 0.01 mole) in 50 ml carbon disulfide was stirred for 40 hours at room temperature. At the end of the reaction period, thiophenol was recovered unchanged in 95%.

Treatment of thiophenol with $AlCl_3$

A mixture of thiophenol (1.1 g., 0.01 mole) and aluminium chloride (0.04 mole) in 50 ml. carbon disulfide was treated as in procedure B. Analysis of the product mixture gave diphenyl disulfide in 60% yield.

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