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Direct Introduction of CH_2SMe Group in Aromatic Ring

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Abstract—Application as a reagent of an accessible methylthiomethyl acetate in a reaction carried out under two-phase conditions and electrophilic catalysis can become a promising procedure for preparation of methylthiomethyl-substituted arenes.

Existing procedures for introduction of thioether groups, mainly CH_2SMe group, into aromatic ring of phenols, naphthols, anilines [1–4] are as a rule inconvenient and multistage. As initial reagents are used DMSO, dialkyl sulfides, thiols; the latter are employed instead of secondary amines in a process analogous to Mannich reaction [2]. The activators of reagents* transforming them into sulfonium forms are sometimes unavailable.

The yields of the target products are poor, they are contaminated with side products. With aromatic substrates possessing free *ortho*-positions the products contain only *ortho*-substituted compounds resulting from a rearrangement in the last stage of the reaction catalyzed by bases and occurring by the type of cyclic rearrangement of Sommelet–Hauser. To get higher yields the special reaction conditions are required: a low temperature, the use of liquid ammonia as a medium, amides of alkali metals as catalysts. The reaction takes several hours or even days.

In the same manner the corresponding methylthiomethyl-substituted toluene [5] and fluorene [6] were also obtained. These methods found general application to the most nucleophilic aromatic compounds, to phenols and anilines. Among indirect methods is known, for instance, the treatment of chloromethyl derivatives with thiolates. However the methods of direct, one-stage introduction of a thioether group into an aromatic ring were not developed.

The goal of this study was an attempt to develop methods of direct methylthiomethylation of arenes **II**.

The methylthiomethyl group at elevated temperature is capable to undergo intermolecular transfer from *N*-aryl-S,S-dimethylsulfinylimines to phenol ring [7]. This mode of *trans*-alkylation occurred also in some other cases [8], in particular, under acid catalysis. Cation $CH_3SCH_2^+$ (**I**) is the probable active species when the substitution occurred in the *para*- or *meta*-positions of an aromatic ring [9].

Thiomethoxymethyl cation (**I**) was synthesized and investigated in the form of hexachloroantimonate (**I**)·$SbCl_6$ [10, 11]. As stated in [10], its ^1H NMR spectrum corresponded to a structure with a distributed positive charge.

$$(Me-S-CH_2 \longleftrightarrow Me-S=CH_2)^+$$
I

Carbonium-sulfonium cation **I** is a natural reagent for direct methylthiomethylation. But its hexachloroantimonate is not convenient for preparation, storage, and application: it is highly sensitive to moisture, it is a strong oxidant and chlorinating agent [10, 11]. Sulfonium salts are also likely to be a poor source of cation **I** [8].

In this connection methylthiomethyl acetate $MeSCH_2OAc$ (**III**) may be regarded as interesting synthetic precursor of cation **I**. The protonation of compound **III** in the gas phase provides among the other ions cation **I** as the main product [12]. In the liquid phase ester **III** is protonated at the oxygen atom [13] and behaves as a methylthiomethylating agent [14]: anisole (**IIa**) with reagent **III** in benzene in the presence of hydrogen chloride affords 30% of the *para*-substituted reaction product. Thus the process proceeds as electrophilic substitution similar to aminomethylation with elimination from the

$$\mathbf{III} \xrightarrow{H^+} AcOH + \mathbf{I}$$
$$ArH + \mathbf{I} \longrightarrow ArCH_2SMe + H^+$$
II **IV**

† Deceased.

* In reaction with phenol DMSO is activated by heating [3], but it is not a general technique.

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Reaction of anisole (**IIa**), acenaphthene (**IIb**), and toluene (**IIc**) with methylthiometyl acetate (**III**) in a system toluene–aqueous H_2SO_4

Run no.	Substrate	$[H_2SO_4]$, wt%	Temperature, °C	Molar ratio (**III**)/(**II**)	Reaction time, h	Conversion of substrate, %	Yield of reaction products, %[a]			Yield of product **IV** on substrate conversion, %
							$ArCH_2SMe$ (**IV**)	Ar_2CH_2 (**V**)	Oligomer (**VI**)	
1	**IIa**	45	81	1.00	1	76	52[b]	24[c]		68
2	**IIb**	35	53	1.00	6	13	8	5	0	62
3[d]	**IIb**		73		11	43	30	11	2[e]	70
4	**IIb**	57	51	1.00	4	35	24[f]	1	6[g]	69
5	**IIb**	45	84	1.00	5	57	49[h]	2	1	86
6	**IIb**	45	84	1.35	4	72	60[i]	3	1	84
7	**IIc**[j]	45	81	0.12	3	1.6	13[k]			96

[a] By analysis data, see EXPERIMENTAL.
[b] Sum of two isomers obtained in 7:1 ratio.
[c] Sum of all products observed on the chromatogram after elution of all monosubstituted compounds.
[d] Continuation of run no. *2* at higher temperature.
[e] Soluble oligomer was isolated in amount of 25 mg.
[f] Also formed disubstituted products **VIIb** in 4% yield.
[g] Polymer insoluble in toluene (0.103 g).
[h] Yield of compound **VIIb** 6%.
[i] Yield of compound **VIIb** 10%.
[j] Substrate and solvent (83.6 mmol).
[k] Calculated on the reagent.

reagent of cation **I** as active species (and not an acetoxymethyl cation, active species in the case of the oxygen analog of reagent **III** [15]).

However it was reported in [14] that up to 30% of side product, diarylmethane Ar_2CH_2 (**Va**), Ar = *p*-$MeOC_6H_4$, formed in this reaction.

The formation of considerable amounts of type **V** side products and of substances with higher condensation degree, polyarylmethylene oligomers **VI**, is characteristic of reactions where into the aromatic ring is introduced a substituted methyl group, CH_2X (X = OH, OAc, Cl, NMe_2) [15–17]. This trend can be essentially suppressed under conditions of the phase-transfer catalysis [17]. Here also will be reduced the tendency of compound **III** to hydrolyze [18].

We tested as substrates anisole (**IIa**), acenaphthene (**IIb**), and toluene (**IIc**). The results of the experiments performed are compiled in the table. No optimization of reaction conditions was carried out. The data in the table suggest that the procedure may be optimized with respect to temperature and acidity. The factors of solvent, catalyst, the character of acid applied also could be operative. These preliminary results permit a conclusion that under conditions of electrophilic phase-transfer catalysis the methylthiomethylation can be carried out on a preparative scale with aromatic compounds considerably differing in reactivity. From the initial reaction rates the partial rate constants of substitution in position *4* of anisole, *5* of acenaphthene, *4* of toluene were calculated at 0.079, 0.010, and 0.0001 l (mol min)$^{-1}$ respectively. The methylthiomethylated compounds contained minor amounts of side products. The reaction is worth further investigation.

EXPERIMENTAL

GLC analyses were carried out on chromatograph Chrom-5 coupled with an integrator CI-100, detector flame-ionization, glass column 1.2 m, stationary phase SE-30 (30% on Inerton Super 0.16–0.2 mm), carrier gas nitrogen, oven temperature programming from 100 to 180°C at a rate 6 deg min^{-1}, from 180 to 250°C at a rate 12 deg min^{-1}. ^{1}H NMR spectra were registered on spectrometer Gemini-200 (at 200 MHz).

Methylthiomethyl acetate (III). Equimolar amounts of anhydrous DMSO and acetic anhydride were charged into a flask equipped with a reflux condenser (a vigorous reaction is possible). The reaction mixture was heated on an oil bath for 1 h at 130°C or for 7 h at 100°C. The solution obtained was

subjected to fractional distillation on Vigreux column 30–40 cm long. After distilling off the acetic acid and the traces of unreacted acetic anhydride the main fraction was collected at 54–57°C (20 mm Hg). The yield almost quantitative. n_D^{20} 1.4547 (1.4540 [19], 1.4570 [20]). ^{1}H NMR spectrum (CD_3CN, TMS), δ, ppm: 2.03 s (3H, SCH_3), 2.20 s (3H, CCH_3), 5.10 s (2H, SCH_2O). Found, %: C 40.46; H 6.88; S 25.95. $C_4H_8O_2S$. Calculated, %: C 39.98; H 6.71; S 26.68.

Methylthiomethylation under conditions of phasetransfer catalysis. Into a flask with a conical pointed bottom equipped with a thermometer and an agitator with short blades was charged 10 mmol of substrate **II**, 10 mmol of reagent **III**, internal reference (*n*-alkane), and phase-transfer agent for electrophile, sodium tetrakis(perfluorophenyl)borate or *N*,*N*-dimethyl-*N*-octadecyltaurobetaine [17] (1.5–3 mmol l^{-1}* in solvent IIc). The total volume of organic phase was 10 ml.

The reaction was initiated by adding 5 ml of heated sulfuric acid solution. Intermittently sampling of organic phase was performed, the samples of 0.15 ml were washed with saturated water solution of sodium hydrogen carbonate and analyzed by GLC.

(Methylthiomethyl)anisoles (IVa) (isomers mixture). From the final reaction mixture (see table, run no. *1*) after distilling off the solvent and unreacted substrate was collected 0.435 g of colorless distillate at 1 mm Hg and bath temperature 100°C. According to GLC the distillate contained two components in ~7 : 1 ratio and about 2% of substituted toluene (**IVc**) admixture. Found, %: C 65.23; H 7.29; S 18.76. C9H12OS. Calculated , %: C 64.24; H 7.12; S 19.05. n_D^{20} 1.5670 (1.5660 [14] for 4-substituted anisole).

5-(Methylthiomethyl)acenaphthene (IVb). A mixture of arene **IIb** (1.64 g, 10 mmol) and ester **III** (1.10 ml, 10 mmol) was heated at 55°C till the majority of crystals were dissolved, then at shaking was added dropwise conc. H_2SO_4 (0.2 ml, 3.6 mmol). The homogeneous mixture self-heated to 85°C, and it was maintained for another 15 min. The reaction mixture was quenched with water (5 ml), and the emulsion formed was twice extracted with 5 ml of benzene. The extract was washed with 20% solution of KOH, with water, and benzene was evaporated. The residue was treated with boiling hexane (6 × 2 ml), and the combined hexane solution was evaporated. The residual acenaphthene was removed by sublimation in a vacuum (1 mm Hg) at 80–100°C, and at the bath temperature 185°C was distilled off 0.18 g of reaction product **IVb** of 97% purity which crystallized at cooling. After 2-fold recrystallization from methanol mp 49.1°C. ^{1}H NMR spectrum (CD_2CI_2, TMS), δ, ppm: 2.01 s (3H, CH_3), 4.07 s (2H, SCH_2), 3.38 s (4H, CH_2CH_2), 7.30 d (2 × 1H), 7.20 d (1H), 7.48 t (1H), 7.77 d (1H). Found, %: C 77.86; H 6.54; S 15.25. $C_{14}H_{14}S$. Calculated, %: C 78.46; H 6.58; S 14.96.

Di(methylthiomethyl)acenaphthenes. After distilling off monosubstituted compound **IVb** as described above the still residue from runs nos. *5*, *6* was dissolved in CCl_4, and the solution was subjected to chromatography on silica gel (eluent CCl_4, GLC monitoring). The fraction containing no less than 98% of disubstituted acenaphthene was collected; on removal of solvent formed a wax-like substance, mp 50–65°C (0.10 g). Found, %: C 69.73; H 6.66; S 23.43. $C_{16}H_{18}S_2$. Calculated, %: C 70.02; H 6.61; S 23.37.

(Methylthiomethyl)toluene (IVc) was isolated from the final reaction mixture (see table, run no. *7*) by procedure described above for compound **IVa**. We obtained 0.148 g of product containing 5% of unidentified impurities. The ^{1}H NMR spectrum corresponded to the 4-substituted **IVc** with an admixture likely to be composed of isomeric products. Found, %: C 72.29; H 7.77; S 19.72. $C_9H_{12}S$. Calculated, %: C 71.02; H 7.95; S 21.03. n_D^{20} 1.5495 (1.5599 [5] for 2-substituted isomer).

* No phase-transfer catalysis was observed likely because of high lipophily of cation **I**.

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