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New Synthesis of Aryl β-Bromoalkyl Sulfones from Arenesulfonyl Chlorides via Cross Halogenation

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Abstract—A new procedure has been proposed for the synthesis of aryl β-bromoalkyl sulfones by radical addition of arenesulfonyl chlorides at the double bond of alkenes in the presence of copper(I) halides, sodium bromide, and phase-transfer catalyst. The key stage of the process is bromide ion insertion into intermediate copper(II) derivative formed in the initiation stage. The subsequent bromine atom transfer from copper to alkyl radical yields the addition product.

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Aryl β-haloalkyl sulfones are synthetic precursors of aryl vinyl sulfones that are important from the practical viewpoint [1]. Aryl β-chloroalkyl sulfones can readily be obtained by radical addition of arenesulfonyl chlorides at double C=C bonds of unsaturated hydrocarbons [2]. Aryl β-bromoalkyl sulfones seem to be more interesting due to their higher reactivity. These compounds can be prepared according to the procedure reported in [3]; however, the scope of this procedure is limited by accessibility of the corresponding arenesulfonyl bromides. Therefore, elaboration of methods for the synthesis of aryl β-bromoalkyl sulfones from arenesulfonyl chlorides is a practically important problem which is also interesting from the viewpoint of development of the theory of organic reaction mechanisms.

A promising method for the preparation of various halogen derivatives is based on radical addition of organohalogen reagents at multiple bonds in the presence of transition metal compounds [4]. Scheme 1 illustrates generally accepted elementary step sequence

Scheme 1.

$$M^+ + CCl_4 \longrightarrow [M]^{2+} + [CCl_4]^{\cdot -}$$

$$\longrightarrow MCl^+ + \dot{C}Cl_3 \quad (1)$$

$$\dot{C}Cl_3 + RCH{=}CH_2 \longrightarrow R\dot{C}HCH_2CCl_3 \quad (2)$$

A

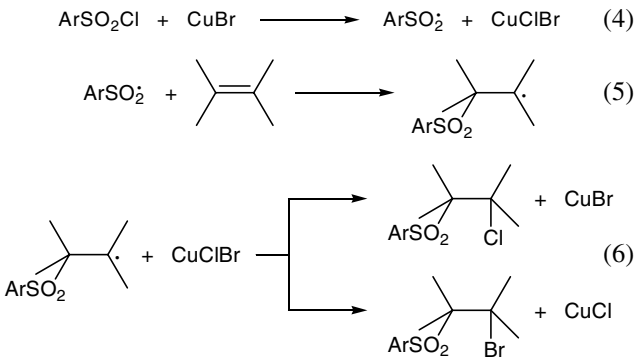
$$\mathbf{A} + MCl^+ \longrightarrow RCHClCH_2CCl_3 + M^+ \quad (3)$$

in such processes (addition of CCl_4; M = Cu) [5]. In reactions with arenesulfonyl halides, step (1) (one-electron transfer from the metal atom to sulfonyl halide molecule) leads to the formation of arylsulfonyl radical $ArSO_2^{\cdot}$ which then adds at a double bond to give radical adduct **A**. The final product is formed in step (3) involving ligand transfer from the metal to radical adduct **A**; the rate of this step approaches that controlled by diffusion, and it is effective even with weakly reactive benzyl and allyl type radicals.

On the basis of Scheme 1 we advanced a concept of "cross halogenation" [6]. It was found that addition of polychloromethanes and arenesulfonyl chlorides (RCl-like reagents) at double bonds of cycloalkenes in the presence of a large excess of copper(I) bromide gives rise to mixtures of cycloalkane derivatives containing the R substituent in position *1* and halogen atom (chlorine or bromine) in position *2*; here, the fraction of bromo derivatives can reach 85%. For example, the addition of carbon tetrachloride to norbornadiene in acetonitrile in the presence of 2 equiv of CuBr leads to predominant formation of diastereoisomeric 5-bromo-3-trichloromethyltricyclo[2.2.1.$0^{2,6}$]heptanes in an overall yield of 60%; under analogous conditions, the addition of trichloroacetonitrile to *cis*-cyclooctene produces a mixture containing 24% of (2-bromocyclooctyl)dichloroacetonitrile and 11% of (2-chlorocyclooctyl)dichloroacetonitrile; in the addition of arenesulfonyl chlorides $ArSO_2Cl$ (Ar = *p*-MeC_6H_4, *p*-FC_6H_4) to norbornadiene in the presence of more than 3 equiv of CuBr, a mixture of 3-arylsulfonyl-5-halotricyclo-

[2.2.1.$0^{2,6}$]heptanes containing 80–85% of the corresponding bromides was obtained with an overall yield of up to 55% [6] (Scheme 2).

Scheme 2.



The adduct is formed in step (6) via halogen transfer to the radical adduct from CuClBr, the latter appearing at the initiation step; therefore, the formation of chlorides cannot be avoided if the reaction follows the above scheme. In fact, the experimental chloride-to-bromide ratios are very consistent with the known rate constants for halogen transfer from $CuCl_2$ and $CuBr_2$ to alkyl radicals (1.1×10^9 and 4.3×10^9 l× mol^{-1} s^{-1}, respectively [7]).

To exclude participation of CuClBr in the halogen transfer step, in the present work we carried out the cross halogenation reaction in the presence of excess sodium bromide and phase-transfer catalyst. As a result, we isolated aryl bromoalkyl sulfones containing no impurity of the corresponding chlorides. We found that the addition of arenesulfonyl chlorides $ArSO_2Cl$ (Ar = *p*-MeC_6H_4, *p*-FC_6H_4, Ph, *p*-ClC_6H_4, β-naphthyl) to norbornene and norbornadiene in the presence of 30 mol % of copper(I) halide, tetraethylammonium bromide as phase-transfer catalyst, and a large excess of sodium bromide in acetonitrile at 80–100°C gives the corresponding bromine-containing adducts in 40–60% yield. The fact that no chlorides were formed under the above conditions is very important, for bromo and chloro derivatives of these series crystallize jointly; therefore, it is almost impossible to remove undesirable chloride impurity. The structure of the products (see table) was confirmed by the ^{1}H NMR and mass spectra and elemental analyses.

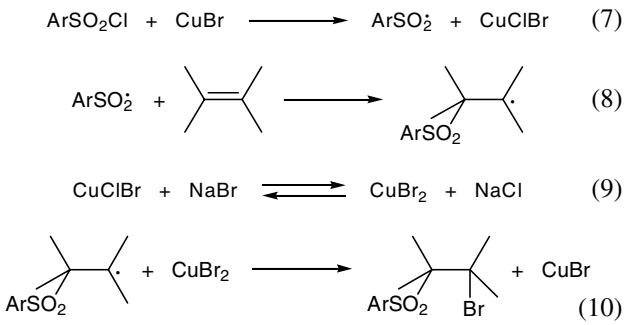
The addition products of arenesulfonyl chlorides to norbornadiene are tricyclane derivatives that are structurally related to those formed under typical radical reaction conditions (i.e., under initiation by UV light or chemical radical initiators) [8] or by radical addition of the corresponding organohalogen reagents in the presence of transition metal compounds [6, 9]. The products result from intramolecular cyclization of initially formed radical adduct [8].

It should be emphasized that the ratio of *exo*,*exo*- and *exo*,*endo*-disubstituted tricyclanes is 60:40; i.e., it is typical of common radical reactions (55:45). Therefore, the products cannot be formed via two-step process including addition of arenesulfonyl chloride to give aryl chloroalkyl sulfone and subsequent nucleophilic replacement of chlorine by bromine (from sodium bromide). Moreover, it should be kept in mind that nucleophilic substitution in such polycyclic systems is hindered. The adducts are stable under the given conditions; this follows from the fact that heating of 4-methylphenyl *exo*-3-chlorotricyclo[2.2.1.$0^{2,6}$]hept-*exo*-5-yl sulfone in acetonitrile in the presence of sodium bromide and phase-transfer catalyst gave neither the corresponding bromo derivative nor isomerization product. In some cases, the addition of arenesulfonyl chlorides to norbornadiene was accompanied by formation of traces of 5,6-disubstituted norbornenes. This is consistent with the data reported in [8] on the addition of polyhalomethanes under typical radical reaction conditions at elevated temperature.

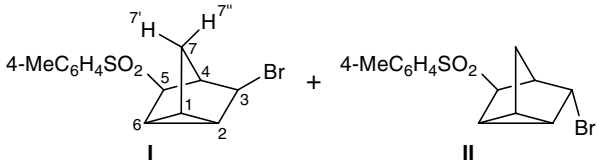
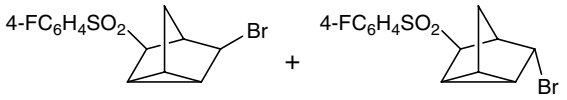
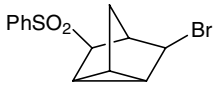
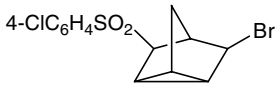
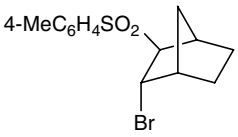
The data in table show that the bromine-containing product is formed regardless of the catalyst [copper(I) salt] and that its yield does not depend on the halogen nature therein. For example, the yield of *endo*-2-bromobicyclo[2.2.1]hept-*exo*-3-yl 4-methylphenyl sulfone (**VIII**) was 60% in the presence of 30 mol % of copper(I) chloride.

Taking into account the above stated, we propose a mechanism shown in Scheme 3. It differs from that given in Scheme 2 by the presence of equilibrium (9). Mixed copper(II) chloride bromide [or, depending on the initial copper(I) halide, copper(II) chloride] formed in step (7) is involved in fast ion exchange in acetonitrile solution in the presence of phase-transfer

Scheme 3.



Addition of arenesulfonyl chlorides to norbornadiene and norbornene (CuBr, 80°C)

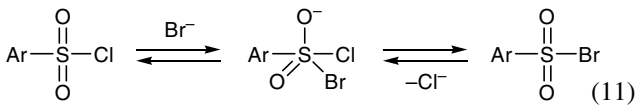
Ar in $ArSO_2Cl$	Substrate	Reaction time, h	Product	Yield, %
p-MeC_6H_4	Norbornadiene	1	 **I** + **II**	43
p-FC_6H_4	Norbornadiene	1.5	 **III** + **IV**	50
Ph	Norbornadiene	2.5	 **V**	24
p-ClC_6H_4	Norbornadiene	2.5	 **VI**	33
β-$C_{10}H_7$[a]	Norbornadiene	1	 **VII**	42
p-MeC_6H_4	Norbornene	17[b]	 **VIII**	60

[a] β-Naphthyl.
[b] CuCl, 100°C.

catalyst and sodium bromide to give copper(II) bromide. Halogen transfer from $CuBr_2$ [step (10)] leads to the cross halogenation product and regeneration of catalytically active copper(I) derivative. Therefore, it is possible to use almost catalytic amount of copper(I) halide instead of its excess over stoichiometric amount. The exclusive formation of bromides in good yields and the absence of chlorine-containing adducts among the products indicates the key role of equilibrium (9) in the process. In fact, assuming that equilibrium (9) is lacking, the reaction with 30 mol % of copper(I) chloride could give rise to a mixture of bromides and chlorides, as was observed in [6].

Equilibrium (9) is displaced to the right due to the presence of a large excess of NaBr and lower solubility of NaCl in acetonitrile. The following data support the above stated: the solubility of NaBr in acetone at 37°C is greater than the solubility of NaCl by a factor of 214 (0.075 and 0.00035 g/l, respectively); under analogous conditions the solubilities of KBr and KCl differ by a factor of 338 (3.28×10^{-2} and 9.7×10^{-5} wt %, respectively) [10]. Phase-transfer catalyst facilitates exchange process involving solid sodium bromide [11].

The formation of arenesulfonyl bromide from arenesulfonyl chloride and sodium bromide according to reaction (11) can also be presumed. The subsequent addition of arenesulfonyl bromide at double bond should follow a mechanism analogous to that shown in


(11)

Scheme 3, i.e., the final product should be formed via bromine transfer to alkyl radical from $CuBr_2$ [which is generated according to equilibrium (9)] rather than from $ArSO_2Br$.

Thus the proposed procedure ensures effective synthesis of aryl bromoalkyl sulfones containing no impurities of the corresponding chloro derivatives from accessible arenesulfonyl chlorides.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ on a Bruker AMX-300 spectrometer (300 MHz). The mass spectra were obtained on an MKh-1321 mass spectrometer.

Norbornene (99%), norbornadiene (99%), *p*-toluenesulfonyl chloride (99%), *p*-fluorobenzenesulfonyl chloride (99%), benzenesulfonyl chloride (99%), *p*-chlorobenzenesulfonyl chloride (98%), and naphthalene-2-sulfonyl chloride (98%) were commercial reagents. Acetonitrile was purified by standard procedure [12]. Copper(I) chloride [13] and copper(I) bromide [14] were prepared by known methods.

Aryl bromoalkyl sulfones I–VIII (*general procedure*). A mixture of 5.9 mmol of norbornene or norbornadiene, 5.2 mmol of the corresponding arenesulfonyl chloride, 1.57 mmol of copper(I) halide, 330 mg (1.57 mmol) of tetraethylammonium bromide, 7.21 g (72 mmol) of NaBr, and 20 ml of acetonitrile was freed from dissolved oxygen by passing a weak stream of argon over a period of 20 min. The reaction vessel was hermetically capped, and the mixture was heated under stirring at 80°C for a time indicated in table. The mixture was then cooled and poured into water, and the precipitate was filtered off and recrystallized from ethanol.

***exo*-3-Bromotricyclo[2.2.1.0^{2,6}]hept-e*xo*-5-yl 4-methylphenyl sulfone (I) and *endo*-3-bromotricyclo[2.2.1.0^{2,6}]hept-*exo*-5-yl 4-methylphenyl sulfone (II)** were obtained by addition of *p*-toluenesulfonyl chloride to norbornadiene. Stereoisomers **I** and **II** were separated by crystallization from ethanol. Overall yield 43%.

Compound **I**. mp 154–156°C. ^1H NMR spectrum, δ, ppm: 7.78 d (2H, *o*-H), 7.39 d (2H, *m*-H), 3.81 s (1H, 3-H), 3.07 s (1H, 5-H), 2.48 s (3H, CH_3), 2.46 d (1H, 7′-H), 2.39 s (1H, 4-H), 2.08 d (1H, 7″-H), 1.81–1.66 m (3H, 1-H, 2-H, 6-H). Mass spectrum, *m*/*z* (I_{rel}, %): 328 (<0.1) $[M + 2]^+$, 326 (<0.1) $[M]^+$, 247 (97), 189 (35), 187 (35), 173 (100), 171 (100), 140 (24), 139 (32). Found, %: C 51.50; H 4.65. $C_{14}H_{15}BrO_2S$. Calculated, %: C 51.39; H 4.62.

Compound **II**. mp 146–150°C (from ethanol). ^1H NMR spectrum, δ, ppm: 7.83 d (2H, *o*-H), 7.39 d (2H, *m*-H), 4.00 s (1H, 3-H), 3.83 s (1H, 5-H), 2.54–2.39 m (5H, CH_3, 7′-H, 4-H), 1.80–1.68 m (3H, 1-H, 2-H, 6-H), 1.51 d (1H, 7″-H).

***exo*-3-Bromotricyclo[2.2.1.0^{2,6}]hept-e*xo*-5-yl 4-fluorophenyl sulfone (III) and *endo*-3-bromotricyclo[2.2.1.0^{2,6}]hept-*exo*-5-yl 4-fluorophenyl sulfone (IV)** were obtained by addition of *p*-fluorobenzenesulfonyl chloride to norbornadiene. The stereoisomers were separated by crystallization from ethanol. Overall yield 50%.

Compound **III**. mp 128°C. ^1H NMR spectrum, δ, ppm: 7.93 m (2H, *o*-H), 7.28 m (2H, *m*-H), 3.83 s (1H, 3-H), 3.08 s (1H, 5-H), 2.45 m (2H, 7′-H, 4-H), 2.10 d (1H, 7″-H), 1.82–1.65 m (3H, 1-H, 2-H, 6-H). Mass spectrum, *m*/*z* (I_{rel}, %): 173 (100), 171 (100), 143 (67), 133 (33), 127 (25). Found, %: C 47.41; H 3.70. $C_{13}H_{12}BrFO_2S$. Calculated, %: C 47.14; H 3.65.

Compound **IV**. ^1H NMR spectrum, δ, ppm: 8.03–7.90 m (2H, *o*-H), 7.33–7.24 m (2H, *m*-H), 4.02 s (1H, 3-H), 3.83 s (1H, 5-H), 2.52–2.42 m (2H, 7′-H, 4-H), 1.86–1.64 m (3H, 1-H, 2-H, 6-H), 1.54 d (1H, 7″-H).

***exo*-3-Bromotricyclo[2.2.1.0^{2,6}]hept-*exo*-5-yl phenyl sulfone (V).** Yield 24%. ^1H NMR spectrum, δ, ppm: 7.92 m (2H, *o*-H), 7.70 m (1H, *p*-H), 7.60 m (2H, *m*-H), 3.83 s (1H, 3-H), 3.09 s (1H, 5-H), 2.49 d (1H, 7′-H), 2.41 s (1H, 4-H), 2.10 d (1H, 7″-H), 1.85–1.65 m (3H, 1-H, 2-H, 6-H). Mass spectrum, *m*/*z* (I_{rel}, %): 314 (0.8) $[M + 2]^+$, 312 (0.8) $[M]^+$, 233 (42), 189 (22), 187 (22), 173 (100), 171 (100). Found, %: C 49.70; H 4.31. $C_{13}H_{13}BrO_2S$. Calculated, %: C 49.85; H 4.18.

***exo*-3-Bromotricyclo[2.2.1.0^{2,6}]hept-*exo*-5-yl 4-chlorophenyl sulfone (VI).** Yield 33%. ^1H NMR spectrum, δ, ppm: 7.85 d (2H, *o*-H), 7.58 d (2H, *m*-H), 3.83 s (1H, 3-H), 3.07 s (1H, 5-H), 2.50–2.42 m (2H, 7′-H, 4-H), 2.11 d (1H, 7″-H), 1.87–1.65 m (3H, 1-H, 2-H, 6-H). Found, %: C 44.85; H 3.69. $C_{13}H_{12}BrClO_2S$. Calculated, %: C 44.91; H 3.48.

***exo*-3-Bromotricyclo[2.2.1.0^{2,6}]hept-*exo*-5-yl 2-naphthyl sulfone (VII).** Yield 42%. ^1H NMR spectrum, δ, ppm: 8.49 s (1H, α-H), 8.06–7.65 m (6H, H_{arom}), 3.82 s (1H, 3-H), 3.18 s (1H, 5-H), 2.55 d (1H, 7′-H), 2.45 s (1H, 4-H), 2.12 d (1H, 7″-H), 1.85–1.67 m (3H, 1-H, 2-H, 6-H). Mass spectrum, *m*/*z* (I_{rel}, %): 364 (18) $[M + 2]^+$, 362 (18) $[M]^+$, 283 (55), 189 (36), 187 (36), 173 (100), 171 (100), 127 (91).

Found, %: C 56.42; H 4.18. $C_{17}H_{15}BrO_2S$. Calculated, %: C 56.21; H 4.16.

***endo*-2-Bromobicyclo[2.2.1]hept-*exo*-3-yl 4-methylphenyl sulfone (VIII).** Yield 60%. ^{1}H NMR spectrum, δ, ppm: 7.80 d (2H, *o*-H), 7.40 d (2H, *m*-H), 4.43 m (1H, 2-H), 3.03 d.d (1H, 3-H), 2.86 d (1H, 1-H), 2.56 br.s (1H, 4-H), 2.48 s (3H, CH_3), 2.07–1.28 m (6H, 5-H, 6-H, 7-H). Mass spectrum, *m*/*z* (I_{rel}, %): 330 (6) $[M + 2]^+$, 328 (6) $[M]^+$, 249 (21), 175 (100), 173 (100). Found, %: C 51.20; H 5.23. $C_{14}H_{17}BrO_2S$. Calculated, %: C 51.07; H 5.20.

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