

Substitution reactions between arenethiolate anions and 1,3-dihalo-2,2-dimethylpropanes. Synthetic scope and mechanistic aspects

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Abstract

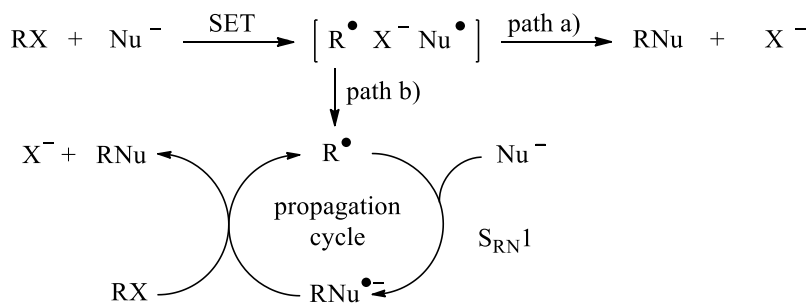
The synthetic scope of the reactions between benzenethiolate, 4-methoxybenzenethiolate, 2-naphthalenethiolate, and 2-pyridinethiolate anions with 1,3-dihalo-2,2-dimethylpropane was studied. These reactions render mono and disubstituted products from good to excellent yields. For all the substrates studied the monosubstituted halogenated product is the intermediate or the main product depending on the nature of the second leaving group. Aryl cyclopropyl sulfides were found as side products and their yields strongly depend on the base concentration (*tert*-BuOK). Finally, using neopentyl iodide as a model, the mechanism of these reactions was evaluated based on non-kinetic evidence, demonstrating that the reactions switch from S_{RN}1 to polar S_N2 according to the solvent employed.

Keywords: Aliphatic substitution, S_{RN}1, arenethiolate anions, neopentyl halides

Introduction

Aliphatic nucleophilic substitution can proceed through the classical polar S_N2, S_N1, and related mechanisms, all of them visualized as the transfer of electrons by pairs. Electron transfer (ET) substitution reactions appear as an alternative for many systems which are low reactive or even unreactive through polar mechanisms. Their absence of reactivity is usually given by different structural factors, namely, strain (*e.g.*, cycloalkyl and polycycloalkyl halides), steric (*e.g.*, cycloalkyl, polycycloalkyl, and neopentyl halides); and electronic factors such as the presence of a perfluoroalkyl chain in aliphatic halides (R_fX). For these compounds, which can be substituted

by ET, their radicals have to be formed by an initial ET as a single-electron-transfer (SET) process which can be reached by different means. The most commonly used include electrochemical initiation, thermal ET and photoinduced electron transfer (PET) from a charged nucleophile (Nu^-). Once the pairs of radicals are formed ($\text{R}\cdot$ and $\text{Nu}\cdot$), they can react in a cage reaction (Scheme 1, path a). However, the diffusion of the radical offers a new alternative where the addition of $\text{R}\cdot$ to the Nu^- triggers a $\text{S}_{\text{RN}}1$ chain mechanism in which radical and radical anions are intermediates (Scheme 1, path b). Although these two possible pathways can be present, the $\text{S}_{\text{RN}}1$ is the one which has been widely studied and shown to operate in most systems.¹

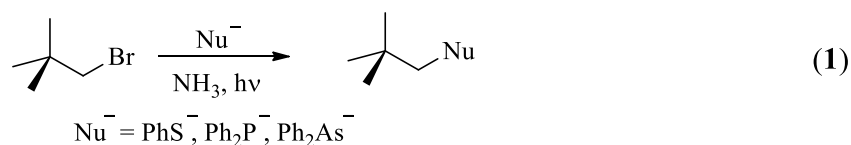


Scheme 1. General picture for electron transfer substitution reactions of aliphatic compounds.

For aliphatic halides with no low-lying π^* orbital, a concerted dissociative ET approach is considered as an initiation step, where ET from the Nu^- to substrate RX gives $\text{R}\cdot$ and X^- in a single step. A stepwise ET pathway involves another possibility through which the radical anion of the substrate is formed as an intermediate. This radical anion cleaves in a subsequent step. The $\text{R}\cdot$ can react with the Nu^- to give $\text{RNu}\cdot^-$ which, by ET to the substrate, forms the neutral substitution product and regenerates the intermediate radical needed to continue the propagation cycle (Scheme 1). The process affords, on the whole, a nucleophilic substitution. The mechanism has termination steps that depend on RX , Nu^- , and experimental conditions.

Inhibition by radical traps or radical anion scavengers has been extensively used to provide non-kinetic mechanistic evidence. The most commonly employed are di-*tert*-butylnitroxide (DTBN), 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), together with good electron acceptors such as *p*-dinitrobenzene (*p*-DNB) or *m*-dinitrobenzene (*m*-DNB).¹

Neopentyl halides have been studied in ET substitution reactions because of their low reactivity in polar $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ mechanisms. Most of these studies have been carried out under irradiation in liquid ammonia as a solvent. In these reaction conditions, anions PhS^- , Ph_2P^- , and Ph_2As^- react with neopentyl bromide giving 60, 76, and 82% yields of substitution, respectively (Equation 1).² The rate constant for the reaction between a neopentyl radical and Ph_2P^- and PhS^- anions were found to be $1.3 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ and $1.2 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$, respectively in MeCN as solvent, by using a neopentyl halide derivative containing a cyclizable probe of the 5-hexenyl type.³

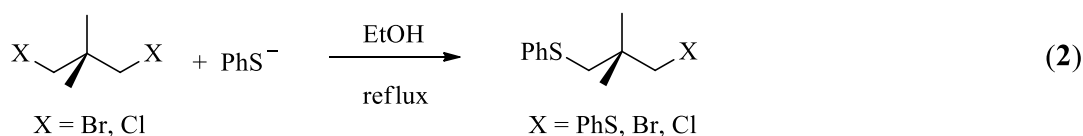


In contrast with the aromatic thiolate anion, PhS^- , the aliphatic $i\text{-PrS}^-$ anion rendered quantitative straightforward substitution with 6-iodo-5,5-dimethyl-1-hexene as a probe. However, the same reaction, in the presence of dicyclohexylphosphine (DCHP), yielded up to 22% hydrocarbon products suggesting a SET mechanism for this anion. No evidence for this mechanistic pathway was observed with the bromide probe.⁴

The effects of leaving groups, solvent, and hydrogen atom donors have been investigated in the reaction of $\text{BzCH}(\text{Me})^-$ with 6-X-5,5-dimethyl-1-hexenes (X = I, Br, or OTs) in HMPA.⁵ It is suggested that the reaction of the iodo derivative takes place in part with radicals as intermediates while the bromide and tosylate compounds appear to react via the $\text{S}_{\text{N}}2$ pathway.⁵ Neopentyl iodide affords substitution with BzCH_2^- ions and with the anion of anthrone under irradiation in DMSO (65 and 52%, respectively). Furthermore, substitution by the $^- \text{CH}_2\text{NO}_2$ ion, which fails to photoinitiate the process, succeeds (69%) under entrainment conditions (in the presence of AcCH_2^- ions); the $\text{S}_{\text{RN}}1$ mechanism is proposed to account for these results.⁶

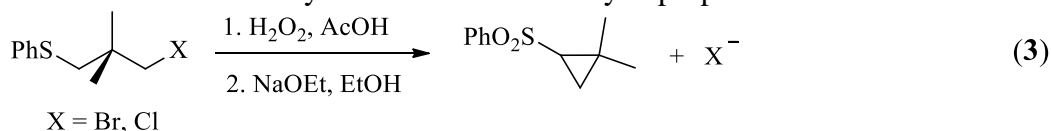
When the substrate has two leaving groups, disubstitution by the same Nu^- is possible. The most studied aliphatic system bearing two leaving groups has been the gem-dihalocyclopropanes and dihalopolycycloalkanes.^{1a,b} To the best of our knowledge there are just a few examples of this reaction in the neopentyl system. Thus, disubstituted (36%) and monosubstituted reduced (16%) compounds are obtained by reaction of 1,3-diiodo-2,2-dimethylpropane with BzCH_2^- ion in DMSO.⁶

1,3-Dihalo-2,2-dimethylpropanes (X = Br and Cl) have been used as starting material for the preparation of several cyclopropyl sulfides, sulfoxides and sulfones.⁷ Therefore, when 1,3-dibromo-2,2-dimethylpropane is treated with PhS^- (1 or 2 equiv) in refluxing ethanol, 3-bromo-2,2-dimethylpropyl phenyl sulfide (X = Br, 46%) or 2,2-dimethyl-1,3-bis(phenylthio)propane (X = PhS, 74%) are obtained after 15 or 52 h, respectively. Following the same methodology up to 23% yield of 3-chloro-2,2-dimethylpropyl phenyl sulfide (X = Cl) can be prepared, starting from 1,3-dichloro-2,2-dimethylpropane under reflux for 20 h (Equation 2).⁷



Cyclopropyl derivatives can be obtained in excellent yields by treatment of 3-halo-2,2-dimethylpropyl phenyl sulfones with NaOEt in ethanol (Equation 3). Another approach consists

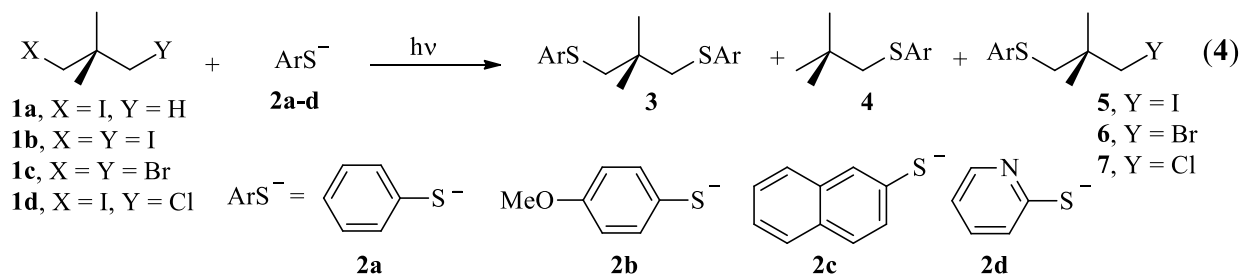
in the use of the aryl (3-chloropropyl) sulfides, but strong basic conditions such as sodium amide in liquid ammonia are necessary for the formation of cyclopropane.⁸



As stated before, it is difficult to perform nucleophilic substitution at C-1 and C-3 in the neopentyl system as 1,3-dihalo-2,2-dimethylpropane, and extreme reaction conditions are necessary (refluxing solvent and several reaction hours). We are interested in developing a methodology using arenethiolate anions in DMSO as solvent and under irradiation, in order to obtain the substitution products under mildest conditions. We will also consider the synthesis of the aryl cyclopropyl sulfides in a one-pot procedure by the addition of an extra amount of a strong base.

Results and Discussion

In an S_{RN1} reaction of neopentyl dihalides **1b-d** with arenethiolate anions **2a-d**, three possible reaction products can be found, namely, disubstituted **3**, reduced monosubstituted **4** and monosubstituted with halogen retention (**5**, Y = I; **6**, Y = Br; **7**, Y = Cl) derivatives (Equation 4). Compounds **3** and **4** are straightforwardly assigned to an intramolecular ET in the reaction mechanism, while products **5-7** are formed by ET from **5-7** radical anions to a molecule of substrate **1** (intermolecular ET). The product distributions depend on the nucleophile, the halogen and their space distribution in the substrate skeleton.⁹



To explore the reaction between neopentyl halides with ArS⁻ anions, four different substrates were chosen, 1-iodo-2,2-dimethylpropane **1a** (neopentyl iodide), 1,3-diiodo-2,2-dimethylpropane **1b**, 1,3-dibromo-2,2-dimethylpropane **1c** and 1-chloro-3-iodo-2,2-dimethylpropane **1d**. The arenethiolate anions **2a-d** were generated *in situ* by deprotonation using *tert*-BuOK and thiophenol, *p*-methoxythiophenol, 2-naphthalenethiol and 2-pyridinethiol, respectively.

Reactions of neopentyl iodide (**1a**), effect of the solvent and the additives

Neopentyl bromide reacts with several nucleophiles by the $S_{RN}1$ mechanism in different solvents such as liquid ammonia and MeCN.^{2,3} However, the reactivity of the iodo derivative with ArS^- anions was not investigated yet. As such, the photoinduced reactions between neopentyl iodide and anions **2a-d** were first studied. All the ArS^- anions gave high yields of substitution products **4a-d** after 1 h of reaction (Equation 5), benzenethiolate anion **2a** was the most reactive giving the substitution product almost in quantitative yield (Table 1, entry 1). *p*-Methoxybenzenethiolate **2b** and 2-naphthalenethiolate **2c** anions had similar reactivity affording 83 and 86% yields of sulfides **4b** and **4c**, respectively (Table 1, entries 2 and 3). Among the ArS^- anions studied, 2-pyridinethiolate anion **2d** showed the less reactivity rendering product **4d** in 68% yield (Table 1, entry 4). This result can be ascribed to the further stabilization of anion **2d** by delocalization of the negative charge on the electron-withdrawing group pyridine, lowering its reactivity.

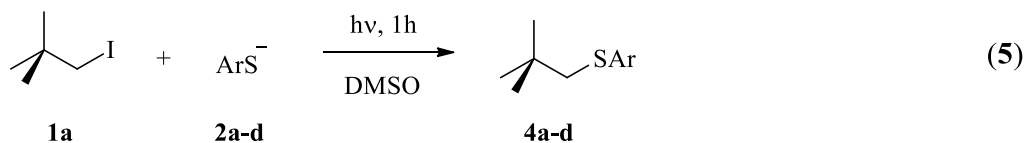
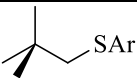


Table 1. Reactions of sulfur nucleophiles **2** with neopentyl iodide **1a** in DMSO^a

Entry	Ar-S ⁻	Product (%) ^b
	Ar =	
1	2a Ph	4a 96
2	2b <i>p</i> -MeOC ₆ H ₄	4b 83
3	2c 2-C ₁₀ H ₇	4c 86
4	2d 2-C ₅ H ₄ N	4d 68

^a**1a** = 0.05 M; ArS^- = 0.25 M in DMSO under nitrogen atmosphere, irradiation time = 1 h.

^bDetermined by GC using the internal standard method, error 5%.

The reaction between **1a** and *p*-methoxybenzenethiolate anion **2b** was chosen as a model for the mechanistic studies. First, the addition of ET quenchers and radical scavengers were evaluated at low reaction conversion in order to assess the inhibition effect of such additives. In DMSO after 10 min of irradiation of a mixture of **1a** and anion **2b**, 44% of **4b** was formed; the same result was observed in the dark (Table 2, entries 1 and 2). This last observation is not in agreement with an ET reaction since a catalytic effect of light is expected for this type of process. In relation to this, the photo-ejection from the excited arenethiolate anions to 1-iodo-adamantane was previously proposed to trigger a non-chain $S_{RN}1$ reaction leading to

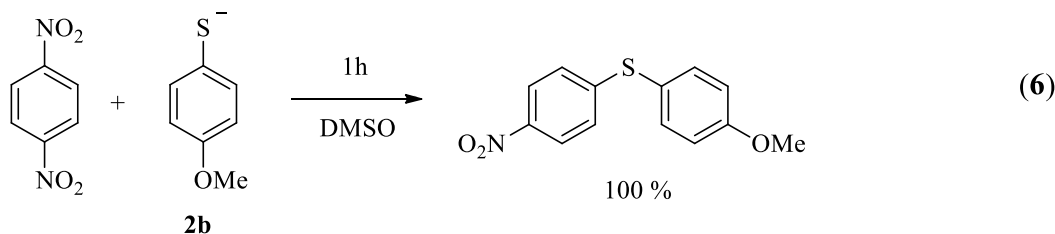
1-adamantyl aryl sulfide. The quantum yield for this photo-ejection ranges from 0.43 to 0.75 at 308 nm in MeCN.¹⁰

The dark reaction was slightly inhibited in the presence of 40 mol% of TEMPO and the yield of product **4b** dropped to 37% (Table 2, entry 3). The addition of a strong electron acceptor was also evaluated; thus, a 20 mol% of *p*-DNB reduced the amount of product **4b**. By increasing the amount of *p*-DNB up to 100 mol%, the formation of sulfide **4b** was completely inhibited. However, in this condition a 100% of 4-methoxyphenyl 4-nitrophenyl sulfide was found, arising from a nucleophilic aromatic substitution with one of the nitro substituents acting as a leaving group (Equation 6) (Table 2, entries 4 and 5). For this particular case, *p*-DNB competes with **1a** as a better electrophile for a substitution reaction rather than a better electron acceptor. In order to avoid the aromatic substitution, *m*-DNB was chosen since, if the Meiseinheimer complex were formed, the latter would not be productive.¹¹ Nevertheless, the use of a 100 mol% of *m*-DNB had little or no effect on the formation of **4b** (Table 2, entry 6).

Table 2. Effect of additives and solvents in the reaction of neopentyl iodide **1a** with *p*-methoxybenzenethiolate anion **2b**^a

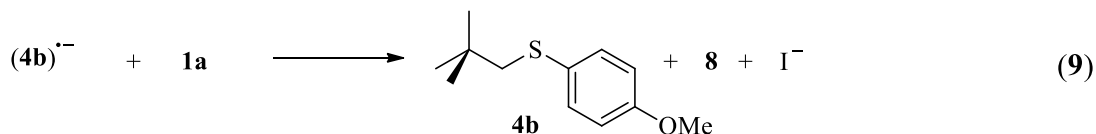
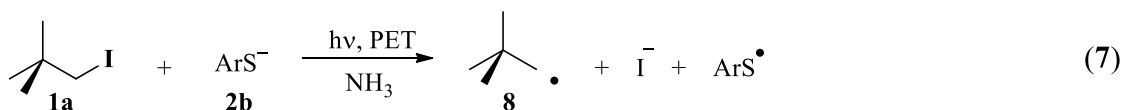
Entry	Conditions	Additive	4b (%) ^b
1	DMSO, 25 °C, 10 min, hv		44
2	DMSO, 25 °C, 10 min, dark		44
3	DMSO, 25 °C, 10 min, dark	TEMPO 0.02 M	37
4	DMSO, 25 °C, 10 min, dark	<i>p</i> -DNB 0.01 M	33
5	DMSO, 25 °C, 10 min, dark	<i>p</i> -DNB 0.05 M	- ^c
6	DMSO, 25 °C, 10 min, dark	<i>m</i> -DNB 0.05 M	39
7 ^d	NH ₃ , -33 °C, 1 h, hv		50
8 ^d	NH ₃ , -33 °C, 1 h, dark		-
9 ^d	NH ₃ , -33 °C, 1 h, hv	TEMPO 0.0018 M	27
10 ^d	NH ₃ , -33 °C, 1 h, hv	<i>p</i> -DNB 0.0018 M	-

^a**1a** = 0.05 M, *p*-methoxybenzenethiolate anion = 0.05 M. ^bDetermined by GC using the internal standard method, error 5%. ^c100% of 4-methoxyphenyl 4-nitrophenyl sulfide was found. ^d**1a** = 0.008 M, *p*-methoxybenzenethiolate anion = 0.008 M.



Changing the solvent from DMSO to liquid ammonia the behavior of the reaction was completely different. Thus, after 1 h of irradiation a mixture of neopentyl iodide **1a** and anion **2b**

rendered 50% yield of the substitution product **4b** (Table 2, entry 7); there was no reaction in the dark and the yield of product **4b** dropped significantly in the presence of both the radical trap TEMPO and the electron scavenger *p*-DNB (Table 2, entries 8, 9 and 10, respectively). All these results are in agreement with a $S_{RN}1$ mechanism, where the neopentyl radical **8** is formed after a PET reaction from the *p*-methoxybenzenethiolate anion to iodide **1a** (Equation 7). Radical **8** added to anion **2b** to give radical anion **(4b)^{•-}** (Equation 8), which is able to generate the substitution product **4b** and neopentyl radical by dissociative ET to the neutral substrate (Equation 9).



The results suggest that in DMSO, the reaction follows a polar mechanism with a minor, if any, contribution of a radical pathway. Another mechanistic possibility involves an initial dissociative ET within a solvent cage followed by coupling of the R^\bullet radicals with Nu^\bullet to give the substitution product by a geminate or cage collapse process (Scheme 1, path a).

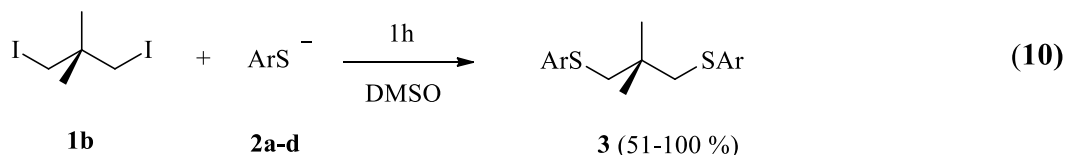
A cage collapse mechanism has also been proposed in the substitution of neopentyl halides by alkylthiolate anions. The main evidence in favor of this mechanistic option involves no inhibition by the presence of radical or radical anion traps and the increase of reduction product by decreasing the solvent viscosity in the presence of good hydrogen donors such as DCHP, despite the fact that in some systems DCHP can also act as an anion trap. Moreover, the role of the radical of DCHP, formed after hydrogen donation, has not been clearly established, and in some cases it has been proposed as the initiator of a propagation cycle.⁴

On the other hand, when liquid ammonia is used as a solvent, the low temperature slows down the polar pathway and the ET path prevails under irradiation triggering a radical chain substitution reaction ($S_{RN}1$).

Despite the operating mechanism, the reaction conditions employing DMSO as solvent were selected to explore the reactivity and product distribution of dihalogenated neopentyl derivatives **1b-d**. The selection of the solvent has been based on the simplicity of the procedure since reactions using liquid ammonia as solvent are not accessible in many organic chemistry laboratories.

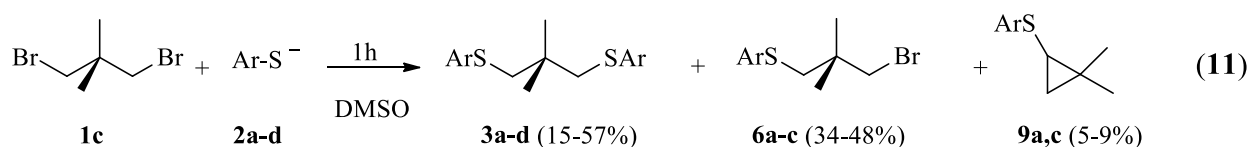
Reactions of arenethiolate anions (**2**) with 1,3-diiodo-2,2-dimethylpropane (**1b**)

Dihalide **1b** rendered exclusively disubstituted products 1,3-bis(arylthio)propanes **3** when the potassium *tert*-butoxide (*tert*-BuOK) was used in stoichiometric amounts for the *in situ* formation of the arenethiolate anions (Equation 10). After 1 h of reaction, dihalide **1b** gave a 100% yield of disubstitution product **3a** with benzenethiolate anion (Table 3, entry 1). Almost quantitative yields of products **3b** and **3c** were found for anions **2b** and **2c** (Table 3, entries 3 and 4). The presence of small amounts of a monosubstitution halogenated product **5c** in addition to **3c** strongly suggests its participation as intermediate for the formation of the final product observed. Pyridinethiolate anions **2d** showed the lower reactivity giving only 51% yield of product **3d** (Table 3, entry 6).



Reactions of arenethiolate anions with 1,3-dibromo-2,2-dimethylpropane (**1c**)

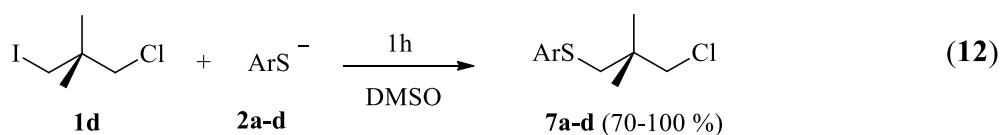
When dibromide **1c** was allowed to react with arene thiolate anions, a mixture of disulfide products **3a-d**, together with monosubstitution with retention of bromide **6a-d** and cyclopropane derivatives **9a-d** in low amounts, was found (Equation 11). Benzenethiolate anion afforded 17% yield of **3a**, 48% yield of sulfide **6a** and small amounts of 2,2-dimethylcyclopropyl phenyl sulfide **9a** (Table 3, entry 7). In the same conditions anion **2b** gave a mixture of **3b** and **6b** in a 54 and 36% yield, respectively (Table 3, entry 9). 2-Naphthalenethiolate anion **2c** after 1 h of reaction with dibromoalkane afforded a mixture of disulfide **3c**, 3-bromo-2,2-dimethylpropyl 2'-naphthyl sulfide **6c** and 2,2-dimethylcyclopropyl 2-naphthyl sulfide **9c** in 15, 45 and 5% yields, respectively (Table 3, entry 10).

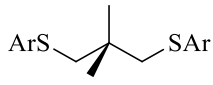
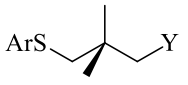



Finally, heterocyclic anion **2d** afforded only product **3d** in 20% yield; as previously stated, this anion showed the lowest reactivity of the arenethiolate anions studied.

Reactions of arenethiolate anions with 1-chloro-3-iodo-2,2-dimethylpropane (**1d**)

The large difference in reactivity between iodide and chloride as leaving groups was evidenced in the reaction employing substrate **1d** where, regardless of the nucleophile used, only the iodide was replaced by the arenethiolate anion with completed retention of the chloride atom. Benzenethiolate, *p*-methoxybenzenethiolate, 2-naphthalenethiolate and 2-pyridinethiolate anions gave aryl 3-chloro-2,2-dimethylpropyl sulfides **7a-d** in 85, 100, 92 and 70% yield, respectively (Equation 12, Table 3, entries 13, 15, 16 and 18).

**Table 3.** Reactions of sulfur nucleophiles **2** with 1,3-dihalo-2,2-dimethylpropane in DMSO^a

Entry	Substrate	ArS ⁻	Products (%) ^b		
					
	1	2 (Ar)	3	5-7	9
1	X = I, Y = I	2a (Ph)	100	-	-
2 ^c	1b	2a (Ph)	2	-	19
3		2b (<i>p</i> -MeOC ₆ H ₄)	96	-	-
4		2c (2-C ₁₀ H ₇)	95	5c 2	-
5 ^c		2c (2-C ₁₀ H ₇)	6	-	12
6		2d (2-C ₅ NH ₄)	51	-	-
7	X = Br, Y = Br	2a (Ph)	17	6a 48	9
8 ^c	1c	2a (Ph)	-	-	93
9		2b (<i>p</i> -MeOC ₆ H ₄)	54	6b 36	-
10		2c (2-C ₁₀ H ₇)	15	6c 45	5
11 ^c		2c (2-C ₁₀ H ₇)	-	6c 8	44
12		2d (2-C ₅ H ₄ N)	20	-	-
13	X = I, Y = Cl	2a (Ph)	-	7a 85	-
14 ^c	1d	2a (Ph)	-	7a 17	83
15		2b (<i>p</i> -MeOC ₆ H ₄)	-	7b 100	-
16		2c (2-C ₁₀ H ₇)	-	7c 92	-
17 ^c		2c (2-C ₁₀ H ₇)	-	7c 25	63
18		2d (2-C ₅ H ₄ N)	-	7d 70	-

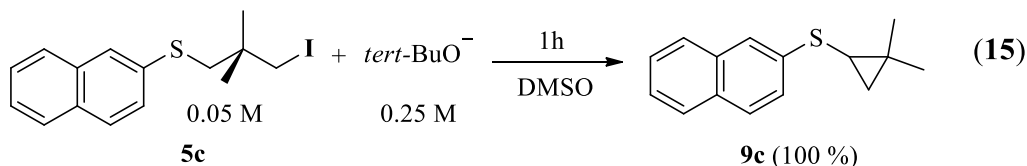
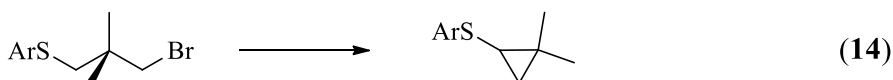
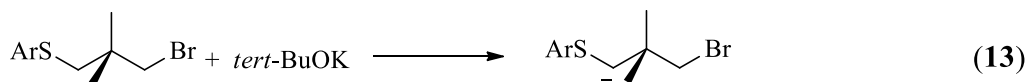
^aSubstrate = 0.05 M, ArS⁻ = 0.25 M in DMSO, under laboratory light, the conversion was completed after 1 h reaction. ^bDetermined by GC using the internal standard method, error 5%.

^cIn the presence of 0.25 M of *tert*-BuOK.

Development of aryl cyclopropyl sulfides (**9a-c**) in the reaction

The formation of aryl cyclopropyl sulfides can be explained by deprotonation of the halo-monosubstituted intermediates **5-7** followed by an intramolecular substitution reaction

(Equations 13 and 14). Similar results were previously reported for 3-bromo-2,2-dimethylpropyl phenyl sulfone using NaOEt as a base (Equation 3); in this specific case, deprotonation was facilitated by the phenylsulfonyl group (PhSO_2).⁸ In order to support the mechanism proposed, the halo-monosubstituted compound was isolated and treated with a strong base. Particularly, 3-iodo-2,2-dimethylpropyl 2-naphthyl sulfide **5c** was isolated from the reaction between **1b** and **2c**. When the latter iodo sulfide was treated with a five-molar excess of *tert*-BuOK in DMSO, cyclopropane derivative **9c** was formed quantitatively (Equation 15).

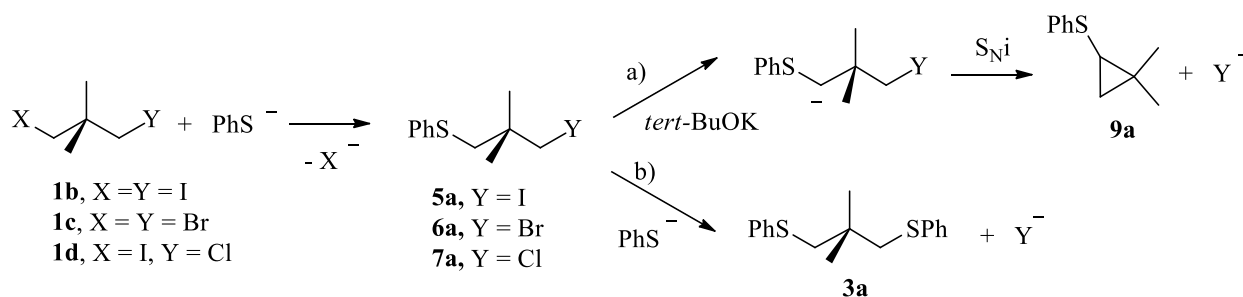


Effect of the excess of *tert*-BuOK on the reactions

It is worth mentioning that aryl cyclopropyl sulfides **9** are observed always in small amounts in the reactions of halides **1b** and **1c** with arenethiolate anions. Nevertheless, their formation can be avoided with the use of stoichiometric amounts of *tert*-BuOK. In addition, 2,2-dimethylcyclopropyl 2-naphthyl sulfide **9c** was obtained by deprotonation of the isolated aryl-iodo intermediate **5c** (Equation 15). Taking these results into account, we evaluated the possibility of the selective synthesis of aryl cyclopropyl sulfides in a one-pot procedure.

When diiodoalkane **1b** was treated with 0.25 M of benzenethiolate anion **2a** and 0.25 M of *tert*-BuOK, cyclopropane **9a** was obtained in very low yield (19%), however, the formation of disulfide **3a** (2%) could not be suppressed (Table 3, entry 2). This result indicates that 3-iodo-2,2-dimethylpropyl phenyl sulfide (**5a**, Y = I) is an intermediate in the reaction for the formation of **9a** even we were not able to detect the presence of **5a** from the reaction mixture (Scheme 2, path a). Furthermore, the second substitution affording **3** is as fast as the deprotonation followed by cyclization to yield **9** (Scheme 2, paths b and a, respectively). Although we succeeded in changing the product distribution to render **9a** by adding an extra amount of *tert*-BuOK, the mass balance of this reaction was very poor. To check the stability of the substrate in the reaction media, a solution of **1b** was stirred in the presence of 0.25 M of *tert*-BuOK. After 1 h, the substrate disappeared, leaving no detectable product by GC chromatography. This finding reveals that substrate **1b** is not stable in such strong basic conditions. Similar results were found with 2-naphthalenethiolate anion **2c** which, in the presence of **1b** and with an extra amount of base, afforded the cyclopropane derivative **9c** in only a 12% and the disulfide **3c** in 6% yields (Table 3, entry 5). As a result, using substrate 1,3-diiodo-2,2-dimethylpropane, the reaction was

not selective with a low mass balance due to the instability of the alkyl diiodide and the fast second substitution reaction. This withdraw can be solved by two approaches, namely, decreasing the rate of the second substitution by reducing the nucleophile concentration or by changing the leaving group. Regarding the second alternative, dibromide **1c** was selected. By mixing 1,3-dibromo-2,2-dimethylpropane **1c** with anion **2a** and *tert*-BuOK in the same concentration, 93% yield of the desired cyclopropane derivative **9a** was found (Table 3, entry 8). The naphthyl cyclopropyl thioderivative **9c** was obtained in a 44% yield together with a remaining 8% of the monosubstituted compound with retention of one bromide atom **6c** (Y = Br) (Table 3, entry 11). Neither PhS⁻ nor 2-C₁₀H₇S⁻ afforded disulfides **3a** and **3c** in the presence of an excess of *tert*-BuOK. These results clearly point out that cyclization can be selectively obtained by delaying the second substitution, changing the second leaving group. In this condition deprotonation is faster and aryl cyclopropyl sulfides are formed in very good yields (Scheme 2, exclusive path a). This procedure can be extended to iodo chloro derivative **1d** affording cyclic compounds **9a** and **9c** in 89 and 63% yields with PhS⁻ and 2-C₁₀H₇S⁻ anions respectively (Table 3, entries 14 and 17).



Scheme 2

Conclusions

The synthetic scope of the reactions between mono- and di-haloneopentyl derivatives with benzenethiolate **2a**, 4-methoxybenzenethiolate **2b**, 2-naphthalenethiolate **2c**, and 2-pyridinethiolate **2d** anions has been established and the results are summarized as follows:

Neopentyl iodide **1a** reacted with thiolate anions **2a-d** to afford the corresponding substitution products from moderate to excellent yields (68-96%). Based on non-kinetic evidence, the mechanism for these reactions goes from S_{RN}1 to polar S_N2 by changing the solvent from NH₃ to DMSO, respectively.

1,3-Diiodo-2,2-dimethylpropane **1b** gave disubstitution products **3a-c** with thiolate anions **2a-c** in excellent yields (95-100%) and with anion **2d**, disulfide **3d** was obtained in moderate yield (51%).

After reaction with thiolate anions **2a-d**, 1,3-dibromo-2,2-dimethylpropane **1c** rendered a mixture of disubstitution products **3a-d** (15-54%) and monosubstituted derivatives with retention of one bromide atom **6a-c** (36-48%), whereas 1-chloro-3-iodo-2,2-dimethylpropane **1d** afforded exclusively mono-halosubstituted derivatives **7a-d** in good yields (70-100%).

Finally, it was possible to synthesize novel aryl cyclopropyl sulfides **9a,c** in good yields (44-93%) when the reactions between **1c-d** and thiolate anions **2a,c** were performed in the presence of an excess of *tert*-BuOK.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded at 400.16 and 100.62 MHz respectively on a Bruker Advance II - 400 spectrometer, and all spectra are reported in δ (ppm) relative to Me_4Si , with CDCl_3 as solvent. Gas chromatographic analyses were performed on a Hewlett Packard 6890 A with a flame-ionization detector, on a HP-5 30 m capillary column of a 0.32 mm \times 0.25 mm film thickness. Mass spectra were performed on a Shimadzu GC-MS QP 5050 spectrometer. HRMS spectra were recorded on a Bruker, MicroTOF Q II equipment, operated with an ESI source operated in (positive/ negative) mode, using nitrogen as nebulizing and drying gas and sodium formate 10 mM as internal calibrant.

Materials. *tert*-BuOK, benzenethiol, *p*-methoxybenzenethiol, 2-naphthalenethiol, 2-pyridinethiol, neopentyl iodide, *p*-dinitrobenzene, *m*-dinitrobenzene and DTBN were all high-purity commercial samples used without further purification. DMSO was distilled under vacuum and stored over molecular sieves (4 Å). Arenethiolate anions (ArS^-) were generated *in situ* by deprotonation using *tert*-BuOK. The 1,3-dihalo-2,2-dimethylpropanes **1b-d**, were synthesized following the procedures previously reported.¹²

Neopentyl phenyl sulfide, **4a**;² *p*-methoxyphenyl neopentyl sulfide, **4b**; neopentyl 2-pyridyl sulfide, **4d**;¹³ 2,2-dimethyl-1,3-bis(phenylthio)propane, **3a**;⁷ 3-bromo-2,2-dimethylpropyl phenyl sulfide, **6a**;⁷ 3-chloro-2,2-dimethylpropyl phenyl sulfide, **7a**⁷ and 2,2-dimethylcyclo-propyl phenyl sulfide **9a**¹⁴ are known and exhibited physical properties identical to those reported in the literature. They were also isolated by radial chromatography on silica gel 60 containing gypsum from the reaction mixture and characterized by ^1H and ^{13}C NMR and mass spectrometry.

Reactions of anions ArS^- with neopentyl halides. General procedure

The reaction was carried out in a three-necked, 10 mL Schlenk tube equipped with a nitrogen gas inlet and a magnetic stirrer. The flask was dried under vacuum, filled with nitrogen and then charged with 10 mL of dried DMSO. Then 2.5 mmol of *tert*-BuOK, 2.5 mmol of the nucleophile and 0.5 mmol of substrate were added to the degassed solvent under nitrogen. After 1 h of irradiation with a high pressure Hg lamp or under laboratory light, the reaction was quenched by the addition of MeI (6 equiv) in excess and poured in 30 mL of water, and then the mixture was

extracted with methylene chloride (3 × 20 mL). The organic extract was washed twice with water, dried and the products were quantified by GC with diphenyl disulfide or cinnamyl phenyl sulfide as internal standard.

Reactions of anion (2c) with neopentyl iodide (1a) in liquid ammonia. The following procedure is representative of these reactions. *p*-MeOC₆H₄SH (1 mmol) and *tert*-BuOK (1.01 mmol) were added to 125 mL of distilled ammonia; after 10 min the substrate neopentyl iodide (1 mmol) was added to the solution and the reaction mixture irradiated for 1 h. Next, the reaction was quenched with an excess of MeI (6 equiv) and the ammonia allowed to evaporate. The residue was dissolved in water and then extracted with methylene chloride (3 × 20 mL), the products were quantified by GC using the internal standard method as indicated above.

2-Naphthyl neopentyl sulfide (4c). Isolated by radial chromatography techniques with petroleum ether as eluent from the crude product reaction mixture of anion **2c** and **1a**. Colorless solid, mp 122-125 °C. ¹H NMR: δ 1.05 (s, 9H), 2.96 (s, 2H), 7.34-7.42 (m, 3H), 7.65-7.71 (m, 4H); ¹³C NMR: δ 29.1, 32.6, 48.3, 125.7, 126.3, 126.6, 126.8, 127.5, 127.8, 129.0, 132.5, 133.5, 134.3; MS: 230 (M⁺, 73%), 215 (2), 173 (44), 160 (100), 129 (17), 115 (41), 57 (19); HRMS (ESI) for C₁₅H₁₈S [M]⁺ calcd: 231.1202; found: 231.1198.

1,3-Bis(4-methoxybenzenethio)-2,2-dimethylpropane (3b). Was isolated as oil by radial chromatography techniques with petroleum ether/diethyl ether (90:10) as eluent from the crude product reaction mixture of anion **2b** and **1b**. ¹H NMR: δ 1.07 (s, 6H), 2.96 (s, 4H), 3.78 (s, 6H), 6.81 (d, 4H, 8.8 Hz), 7.33 (d, 4H, 8.8 Hz). ¹³C NMR: δ 26.6, 37.2, 48.1, 55.3, 114.5, 128.1, 132.8, 158.6; MS: 348 (M⁺, 52%), 209 (51), 195 (17), 153 (46), 140 (22), 139 (100), 109 (14); HRMS (ESI) for C₁₉H₂₄NaO₂S₂ [M+Na]⁺ calcd: 371.1110; found: 371.1159.

1,3-Bis(2-naphthylthio)-2,2-dimethylpropane (3c). Was isolated by radial chromatography techniques with petroleum ether/diethyl ether (90:10) as eluent from the crude product reaction mixture of anion **2c** and **1b**. White solid, mp 99-101 °C. ¹H NMR: δ 1.19 (s, 6H), 3.17 (4H, s), 7.37-7.43 (m, 6H), 7.62-7.75 (m, 8H); ¹³C NMR: δ 26.9, 37.2, 45.7, 125.5, 126.5, 126.8, 127.0, 127.6, 127.7, 128.3, 131.7, 133.8, 135.1; MS: 388 (M⁺, 100%), 387 (85), 229 (61), 215 (51), 173 (71), 159 (55), 115 (37); HRMS (ESI) for C₂₅H₂₄NaS₂ [M+Na]⁺ calcd: 411.1212; found: 411.1214.

1,3-Bis(2-pyridylthio)-2,2-dimethylpropane (3d). Was isolated as oil by radial chromatography techniques with petroleum ether/diethyl ether (90:10) as eluent from the crude product reaction mixture of anion **2d** and **1b**. ¹H NMR: δ 1.12 (s, 6H), 3.38 (s, 4H), 6.94 (ddd, 2H, 0.8 Hz, 5.2 Hz, 6.0 Hz), 7.19 (d, 2H, 8.0 Hz), 7.43 (dt, 2H, 1.6 Hz, 8.0 Hz), 8.39 (d, 2H, 0.8 Hz); ¹³C NMR: δ 26.3, 36.3, 40.7, 119.3, 122.42, 135.8, 149.2, 159.3; MS: 243 (23%), 212 (6), 180 (79), 179 (68), 166 (78), 164 (26), 136 (21), 125 (21), 124 (43), 111 (39), 112 (100), 78 (71), 67 (18), 55 (28). HRMS (ESI) for C₁₅H₁₈N₂S₂ [M+H]⁺ calcd: 291.0984; found: 291.1002.

3-Iodo-2,2-dimethylpropyl 2-naphthyl sulfide (5c). Was isolated as oil by radial chromatography techniques with petroleum ether/diethyl ether (90:10) as eluent from the crude product reaction mixture of anion **2c** and **1b**. ¹H NMR (400.16 MHz, CDCl₃): δ 1.17 (s, 6H), 3.10 (s, 2H), 3.31 (s, 2H), 7.38-7.47 (m, 3H), 7.71-7.79 (m, 4H); ¹³C NMR: δ 22.2, 26.7, 35.7,

45.8, 125.8, 126.6, 127.1, 127.4, 127.7, 127.8, 128.5, 131.8, 133.8, 134.7; MS: 356 (M^+ , 45%), 229 (16), 173 (100), 159 (13), 129 (22). HRMS (ESI) for $C_{15}H_{17}S$ $[M-I]^+$ calcd: 229.1045 found: 229.1044.

3-Bromo-2,2-dimethylpropyl 4-methoxyphenyl sulfide (6b). Was isolated as oil by radial chromatography techniques with petroleum ether/diethyl ether (90:10) as eluent from the crude product reaction mixture of anion **2b** and **1c**. 1H NMR: δ 1.10 (s, 6H), 2.95 (s, 2H), 3.43 (s, 2H), 3.79 (s, 3H), 6.83 (d, 2H, 8.8 Hz), 7.39 (d, 2H, 8.8 Hz); ^{13}C NMR: δ 25.7, 36.7, 44.9, 47.2, 55.4, 114.6, 127.6, 130.2, 133.3, 158.9; MS: 290 (M^+ , 43%), 288 (M^+ , 50), 153 (100), 140 (41), 139 (42), 138 (31), 109 (34), 107 (28), 69 (14), 55 (12).

3-Bromo-2,2-dimethylpropyl 2-naphthyl sulfide (6c). Was isolated as oil by radial chromatography techniques with petroleum ether/diethyl ether (90:10) as eluent from the crude product reaction mixture of anion **2c** and **1c**. 1H NMR: δ 1.15 (s, 6H), 3.13 (s, 2H), 3.47 (s, 2H), 7.40-7.47 (m, 3H), 7.72-7.80 (m, 4H); ^{13}C NMR: δ 25.8, 36.7, 44.6, 44.8, 125.7, 126.6, 127.1, 127.4, 127.7, 127.8, 128.5, 131.8, 133.8, 134.7; MS: 310 (M^+ , 27%), 308 (M^+ , 27), 173 (100), 160 (19), 129 (20), 115 (29); HRMS (ESI) for $C_{15}H_{18}BrS$ $[M+H]^+$ calcd: 309.0307, found: 309.0302.

3-Chloro-2,2-dimethylpropyl 4-methoxyphenyl sulfide (7b). Was isolated as oil by radial chromatography techniques with petroleum ether/diethyl ether (90:10) as eluent from the crude product reaction mixture of anion **2b** and **1d**. 1H NMR: δ 1.08 (s, 6H), 2.95 (s, 2H), 3.51 (s, 2H), 3.79 (s, 3H), 6.85 (d, 2H, 8.8 Hz), 7.39 (d, 2H, 8.8 Hz); ^{13}C NMR: δ 25.0, 37.4, 46.4, 54.1, 55.3, 114.8, 127.7, 133.2, 158.8; MS: 246 (M^+ , 31%), 244 (M^+ , 73), 188 (18), 153 (100), 140 (62), 139 (48), 138 (32), 125 (21), 109 (34), 107 (28); HRMS (ESI) for $C_{12}H_{18}ClOS$ $[M+H]^+$ calcd: 245.0761; found: 245.0819.

3-Chloro-2,2-dimethylpropyl 2-naphthyl sulfide (7c). Was isolated as oil by radial chromatography techniques with petroleum ether/diethyl ether (90:10) as eluent from the crude product reaction mixture of anion **2c** and **1d**. 1H NMR: δ 1.18 (s, 6H), 3.19 (s, 2H), 3.59 (s, 2H), 7.48-7.54 (m, 3H), 7.78-7.87 (m, 4H); ^{13}C NMR: δ 25.2, 37.4, 43.9, 54.2, 125.8, 126.7, 127.2, 127.3, 127.8, 127.8, 128.5, 131.8, 133.9, 134.9; MS: 266 (M^+ , 30%), 264 (M^+ , 68), 208 (26), 173 (100), 160 (52), 129 (38), 128 (22), 115 (54); HRMS (ESI) for $C_{15}H_{18}ClS$ $[M+H]^+$ calcd: 265.0812, found: 265.0810.

3-Chloro-2,2-dimethylpropyl 2-pyridyl sulfide (7d). Was isolated as oil by radial chromatography techniques with petroleum ether/diethyl ether (90:10) as eluent from the crude product reaction mixture of anion **2d** and **1d**. 1H NMR: δ 1.09 (s, 6H), 3.36 (s, 2H), 3.49 (s, 2H), 6.96 (dd, 1H, 5.2 Hz, 6.8 Hz), 7.20 (d, 1H, 8 Hz), 7.39 (dt, 1H, 1.7 Hz, 7.7 Hz), 8.40 (d, 1H, 4.4 Hz); ^{13}C NMR: δ 24.8, 36.9, 38.6, 54.4, 119.5, 122.5, 135.9, 149.2, 158.7; MS: 215 (M^+ , 22%), 200 (7), 166 (74), 125 (71), 124 (100), 112 (30), 111 (30), 79 (38), 78 (63), 67 (26), 55 (27), 51 (27).

2,2-Dimethylcyclopropyl 2-naphthyl sulfide (9c). Was isolated as oil by radial chromatography techniques with petroleum ether as eluent from the crude product reaction mixture of anion **2c** and **1c**, in the presence of 0.25M excesses of *tert*-BuOK. 1H NMR: δ 0.58 (t, 1H, 4.8 Hz), 1.03

(dd, 1H, 4.8 Hz, 8.4 Hz), 1.22 (s, 3H), 1.33 (s, 3H), 2.16 (dd, 1H, 4.8 Hz, 8.4 Hz), 7.36-7.45 (m, 3H), 7.67-7.78 (m, 4H) ^{13}C NMR: δ 20.0, 20.1, 21.3, 25.8, 26.5, 123.0, 125.0, 126.5, 126.8, 127.8, 128.1, 131.2, 133.9, 137.1; MS: 228 (M^+ , 77%), 172 (100), 128 (22); HRMS (ESI) for $\text{C}_{15}\text{H}_{17}\text{S}$ [$\text{M}+\text{H}$] $^+$ calcd: 229.1045; found: 229.1040.

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