Accepted Manuscript

Transalkylation of alkyl aryl sulfides with alkylating agents

Daria Nawrot, Marek Kolenič, Jiří Kuneš, Filip Kostelansky, Miroslav Miletin, Veronika Novakova, Petr Zimcik

PII: S0040-4020(17)31313-3

DOI: 10.1016/j.tet.2017.12.039

Reference: TET 29195

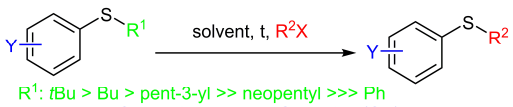
To appear in: *Tetrahedron*

Received Date: 15 November 2017

Revised Date: 13 December 2017

Accepted Date: 19 December 2017

Please cite this article as: Nawrot D, Kolenič M, Kuneš Jiří, Kostelansky F, Miletin M, Novakova V, Zimcik P, Transalkylation of alkyl aryl sulfides with alkylating agents, *Tetrahedron* (2018), doi: 10.1016/j.tet.2017.12.039.



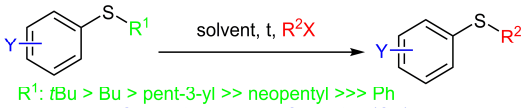
R^1: *t*Bu > Bu > pent-3-yl >> neopentyl >>> Ph
Y: H = Me = OMe = 3,4-benzo > CF_3 > 3,4-$(CN)_2$
solvent: DMF = NMP > dioxane >>> cyclohexane
R^2X = MeI > EtI > BuI > DMS >>> DMC

Graphical Abstract

Transalkylation of alkyl aryl sulfides with alkylating agents

Leave this area blank for abstract info.

Daria Nawrot, Marek Kolenič, Jiří Kuneš, Filip Kostelansky, Miroslav Miletin, Veronika Novakova and Petr Zimcik



R^1: *t*Bu > Bu > pent-3-yl >> neopentyl >>> Ph
Y: H = Me = OMe = 3,4-benzo > CF_3 > 3,4-$(CN)_2$
solvent: DMF = NMP > dioxane >>> cyclohexane
R^2X = MeI > EtI > BuI > DMS >>> DMC

Tetrahedron
journal homepage: www.elsevier.com

Transalkylation of alkyl aryl sulfides with alkylating agents

Daria Nawrot[a], Marek Kolenič[a], Jiří Kuneš[b], Filip Kostelansky[a], Miroslav Miletin[a], Veronika Novakova[c] and Petr Zimcik[a,*]

[a] *Department of Pharmaceutical Chemistry and Pharmaceutical Analysis, Faculty of Pharmacy in Hradec Kralove, Charles University, Akademika Heyrovskeho 1203, 500 05, Hradec Kralove, Czech Republic*
[b] *Department of Organic and Bioorganic Chemistry, Faculty of Pharmacy in Hradec Kralove, Charles University, Akademika Heyrovskeho 1203, 500 05, Hradec Kralove, Czech Republic.*
[c] *Department of Biophysics and Physical Chemistry, Faculty of Pharmacy in Hradec Kralove, Charles University, Akademika Heyrovskeho 1203, 500 05, Hradec Kralove, Czech Republic.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Alkylation
Sulfide
Sulfonium
Substituent effect
S-transalkylation

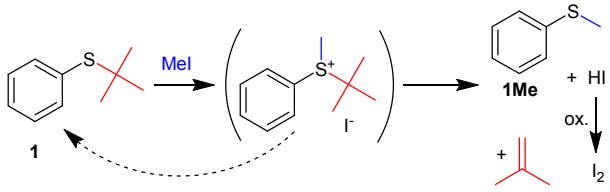
ABSTRACT

The reaction of methyl iodide with *tert*-butylphenylsulfide in DMF leads to a transalkylation that produces methylphenylsulfide. This transalkylation reaction was further studied by ^{1}H NMR spectroscopy. The polarity of the solvent, the electron density on the sulfur atom, and the strength of the alkylating agent (MeI, EtI, BuI, dimethyl sulfate, or dimethyl carbonate) played important roles in the reaction. The suggested mechanism of the reaction involves the formation of a dialkyl aryl sulfonium salt that subsequently eliminates the radical. This mechanism was supported by the observation of higher conversion rates for compounds with more branched alkyl groups on the sulfur atom, which may lead to the formation of more stable radicals.

1. Introduction

Alkyl aryl sulfides are an important group of synthetic molecules that are used in different fields of organic chemistry with various applications, including drugs,[1] photosensitizers and materials science.[4, 5] Typically, their stability is sufficient for further synthetic modification, including alkylation (e.g., quaternization of nitrogens and formation of ethers). In our continuous synthetic efforts to find new potential photosensitizers, we conducted a study to synthesize phthalocyanines bearing both alkyl aryl sulfide and quaternary ammonium moieties. The last step of the synthetic procedure was alkylation using methyliodide (MeI), in which an unexpected transalkylation on the sulfur atom was observed (data not shown). The transalkylation was confirmed in a model reaction of 2,3,9,10,16,17,23,24-octakis(*tert*-butylsulfanyl)phthalocyaninato zinc(II) with MeI. The *tert*-butyl groups were partially replaced by methyl groups, which was revealed by the ladder of products visible upon examination with thin layer chromatography (TLC) and the analysis of the mass spectra (see Supplementary Data, Figure S1). A plausible explanation is the S-transalkylation reaction that may involve an unstable dialkyl aryl sulfonium salt, as suggested in Scheme 1. The S-transalkylation of various sulfides with alkylating agents has previously been reported in the literature with a similar suggested mechanism.[6-11] The reaction has also found practical applications, e.g., in the synthesis of thia-crown ethers[12, 13] and the homologation of primary halides.[14] Transalkylation between sulfides and sulfonium salts has also been reported as a pathway for the synthesis of poly(thioether) vitrimers.[15]

In this work, the S-transalkylation reaction was examined more closely by varying the reaction conditions (temperature, equivalents, and solvents), alkylating agents, and starting materials to reveal the optimal reaction parameters.



Scheme 1 Suggested mechanism of S-transalkylation

2. Results and Discussion

Simple *tert*-butylphenylsulfide (**1**, Scheme 1) was selected as the primary model compound to study the effect of different reaction conditions. The mechanism suggested in Scheme 1

* Corresponding author. Tel.: +420-49-5067257; e-mail: zimcik@faf.cuni.cz

involves the formation of a dialkylarylsulfonium salt as an unstable intermediate. The salt then eliminates the *tert*-butyl cation, immediately forming isobutene and a proton. The latter then forms hydrogen iodide that is most likely oxidized to iodine by oxygen in air, as indicated by observation of the typical iodine yellow-brown color of the reactions when performed at higher temperatures and not protected from light. Elimination of the second alkyl group ("methyl" in Scheme 1) from the dialkylarylsulfonium intermediate is also possible but much less probable due to the very low stability of the potential methyl radical.

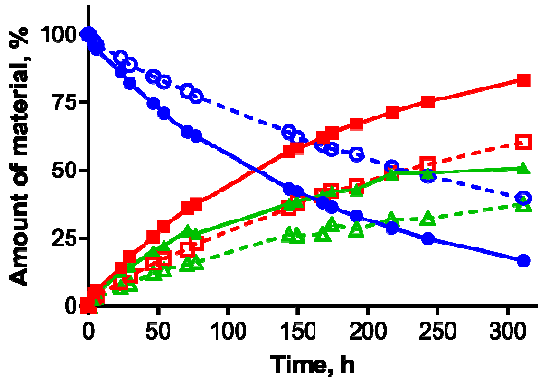
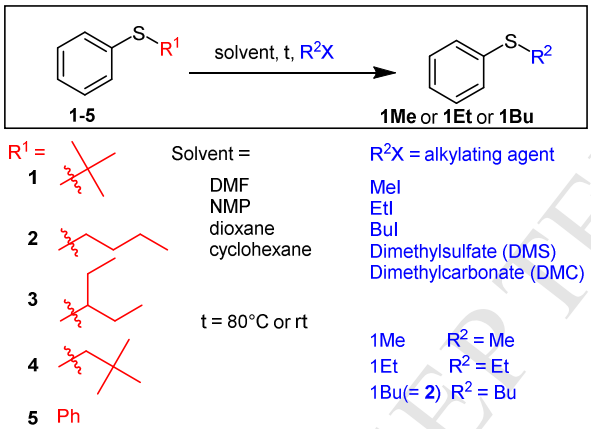


Figure 1 Progress of the reaction of **1** with 5 eq (full symbols, full lines) or with 2 eq (open symbols, dashed lines) of MeI in DMF-d_7 in NMR tube. The amount of material was calculated from the corresponding proton integrals for **1** (blue dot), **1Me** (red square) and isobutene (green triangle).



Scheme 2 General reaction conditions applied in the study of the transalkylation reaction.

First, the reaction was studied in a closed NMR tube in DMF-d_7 at room temperature (rt) with 5 or 2 equivalents of MeI to confirm the presence of the suggested intermediates or products. The NMR spectra taken at different times revealed the unequivocal presence of the product **1Me** and the eliminated isobutene (Figure S2, S3). The amount of isobutene produced correlated well with amount of **1Me** detected (Figure 1); however, it was not exactly the same as a result of the volatile character of isobutene, which causes its release into the gaseous phase. No other intermediates or side products were identified (Figure S3), including the dialkylsulfonium salt that has been often suggested as an unstable intermediate but never detected.[6-11]

Subsequent studies were performed in flasks that enabled a wider variation of the synthetic conditions (e.g., changes in the temperature). For these studies, sulfide **1** was treated with the alkylating agent, the reaction was stopped at selected times, and all lipophilic products were isolated by flash chromatography (Scheme 2). The mixture was then analyzed by ^{1}H NMR spectroscopy, and the progress of the transalkylation was easily observable in both the aliphatic and aromatic regions (Figure 2, as an example). The integrated area under the aliphatic signals, which were always well separated (including in reactions with other starting materials **2-14**), was used to calculate the conversion ratio and plot the reaction progress against the reaction time (Figure 3). The isolated yields of the reactions were calculated only upon full conversion and were typically above 70%. It must be noted that the calculated yields might be partially influenced by the lower boiling point of some of the starting materials and products. The amount of the material may have thereby been reduced during evaporation of the solvents, but care was taken to limit this problem.

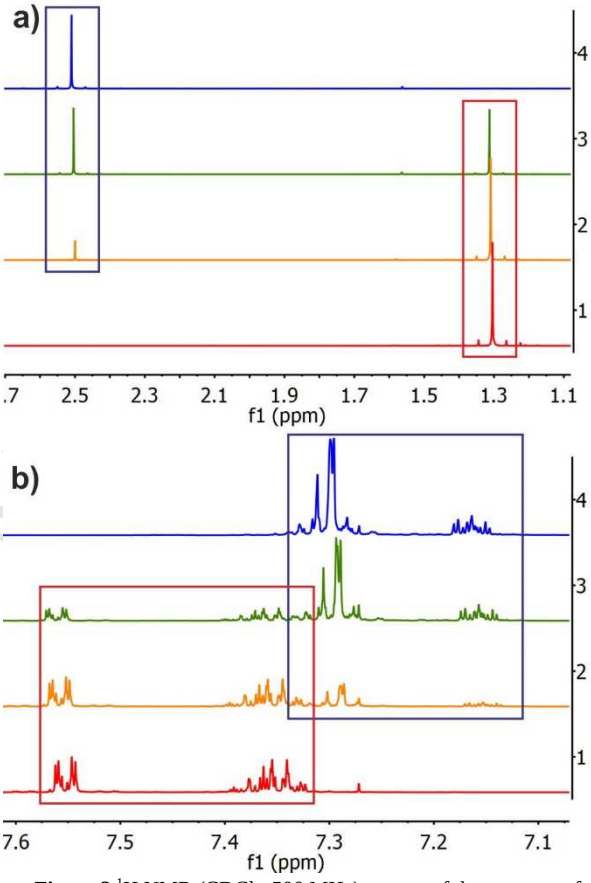


Figure 2 ^{1}H NMR ($CDCl_3$, 500 MHz) spectra of the progress of the transalkylation reaction of **1** (red spectrum) to **1Me** (blue spectrum) with 10 eq of MeI at 80 °C in DMF: a) aliphatic region, b) aromatic region. Spectra were taken before the reaction (1, red) and after 30 min (2, yellow), 2 h (3, green), and 24 h (4, blue) of reaction time.

The first set of experiments focused on the effect of an excess of the alkylating agent—in this case, MeI—and variations in the reaction temperature (Figure 3a) using DMF as the solvent. DMF was chosen as the solvent and the temperature was set to 80 °C as the starting point since these are the conditions that have been used for the alkylation of some nitrogen-containing compounds in literature. We used conditions close to those commonly used, where some sulfur side reactions could be expected if the compound contained both a sulfur atom and an alkyl group.[16-18] It seems that 10 eq of MeI *per* sulfide at 80 °C allowed the reaction to run very efficiently. Almost a full conversion was achieved after 6 h, and 100% conversion of **1** to **1Me** was obtained after 24 h. A further increase to 20 eq of MeI did not substantially enhance the progress. It should be noted that a very high

conversion rate was also obtained using only 2 eq of MeI at 80 °C. In addition to the concentration of the alkylating agent, the temperature seems to play important role in the reaction progress since only a 12% conversion was obtained at rt with 10 eq of MeI after 24 h (Figure 3a). A similar level of conversion was obtained with 5 eq at rt, and only 9% conversion was achieved with 2 eq of MeI at rt after 24 h (Figure 1).

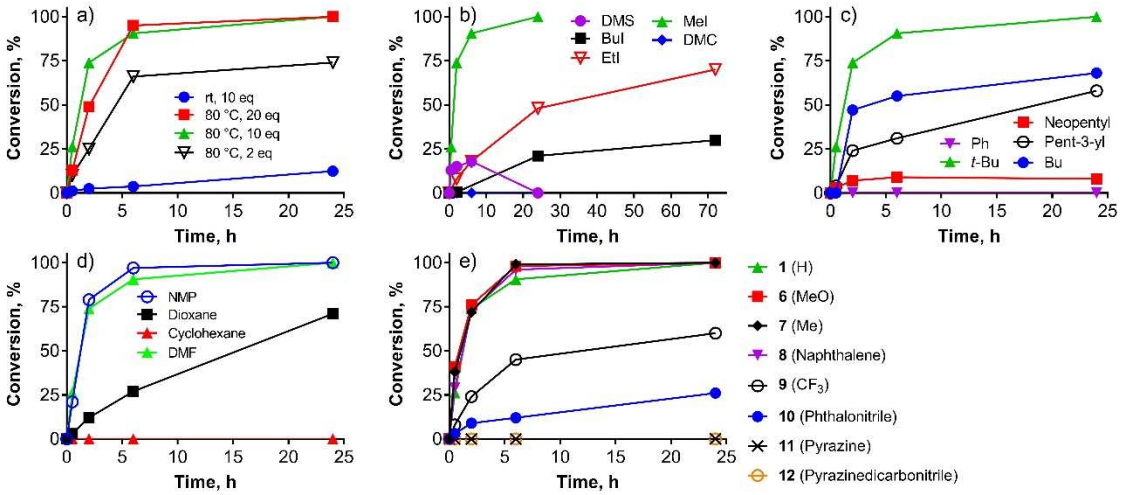


Figure 3 Progress of the transalkylation reaction. a) starting material: **1**, alkylating agent: MeI, solvent: DMF. b) starting material: **1**, alkylating agent: various (10 eq), solvent: DMF, 80 °C. c) starting material: **1-5**, alkylating agent: 10 eq MeI, solvent: DMF, 80 °C. d) starting material: **1**, alkylating agent: 10 eq MeI, solvent: various, 80 °C. e) starting material: **1,6-12**, alkylating agent: 10 eq MeI, solvent: DMF, 80 °C. The reference reaction (**1**, DMF, MeI (10 eq), 80 °C) is always indicated by a green color.

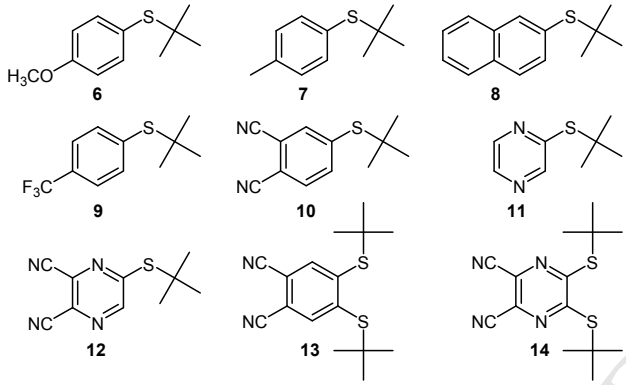


Figure 4 Structures of compounds **6-14**.

The solvent also plays an important role in the reaction kinetics when highly polar intermediates are involved. This was also shown to be valid in our experiments (Figure 3d). The reaction of **1** with 10 eq of MeI at 80 °C was the best in the highly polar solvents DMF and NMP (the reaction kinetics were almost the same), while much slower reaction kinetics were observed for the reaction in the less polar solvent dioxane. However, dioxane may partly stabilize the intermediate through donation of its oxygen electron pairs. No conversion was detected for the reaction in non-polar cyclohexane, and the starting amount of **1** was fully recovered even after 24 h of heating. This clear dependence on the solvent polarity indirectly supported the suggested presence of dialkyl aryl sulfonium salts as the intermediate.

MeI is one of the strongest alkylating agents. Decreasing the strength of the alkylating agent substantially slowed the reaction, as seen from the reaction of **1** with 10 eq of ethyliodide (EtI) and butyliodide (BuI) in DMF at 80 °C (Figure 3b). In these cases, a full conversion was not obtained even after 72 h of reaction. Reaction with dimethylsulfate (DMS) under the same conditions was also slower than that with MeI. Additionally, decomposition of the starting material and/or products seemed to occur with the prolonged reaction times in DMS since the amount of isolated material from the reaction under these conditions was substantially less. No starting material or product was detectable by NMR after 24 h of heating. Dimethylcarbonate (DMC) is a mild and eco-friendly alkylating agent. Its reactivity is tunable, i.e., at T ~ 90 °C, methoxycarbonylation occurs, whereas at higher reaction temperatures (T ~ 160 °C), methylation reactions are observed with a variety of nucleophiles.[19] In our experiments, no reaction occurred with 10 eq DMC in DMF at 90 °C or at reflux (156 °C). Even heating **1** in pure DMC at 160 °C in a closed vessel in a microwave for 24 h did not yield any transalkylation, and the starting material was always fully recovered.

In addition to the strength of the alkylating agent, the electron density on the sulfur atom may also significantly influence the first step of the reaction mechanism, *i.e.*, formation of the dialkyl aryl sulfonium salt. To investigate this effect, starting materials with substituents with different electron-donating/withdrawing abilities that can substantially influence the electron density on the sulfur were introduced to the study. Compounds **6-12** (Figure 4) were reacted with 10 eq of MeI in DMF at 80 °C (Figure 3e). Changing the aromatic ring from benzene to naphthalene (**8**) or introducing electron-donating substituents (**6**, **7**) did not speed up the conversion process, and the reactions of these compounds were comparable with those of the unsubstituted compound **1**. It seems, therefore, that the electron density was already sufficient in the case of the unsubstituted phenyl ring in **1** and was not the rate-limiting step. On the other hand, lowering the electron density on the sulfur through electron-withdrawing substituents (**9**, **10**) led to a substantial slowing of the conversion rate. Upon the change of the aromate to an electron-deficient pyrazine ring (**11**), the most susceptible part of the molecule for alkylation was the nitrogen in position 4 of the pyrazine ring. Heating of **11** with 10 eq MeI for 30 min gave 1-methyl-3-*tert*-butylpyrazinium iodide as the only product. The position of the methyl group on the pyrazine nitrogen was unequivocally confirmed using 2D NMR experiments (see Supplementary Data, Figures S10-S12). Quaternization of the nitrogen made the pyrazine ring even more electron-deficient, and no transalkylation was detected even after 24 h of heating. Similarly, substitution of pyrazine with two electron-withdrawing carbonitriles (compound **12**) made it fully resistant against MeI attack, and no transalkylation or *N*-methylation were detected. Additionally, compounds **13** and **14** bearing two *tert*-butylsulfanyl groups were also investigated through reaction with 20 eq MeI (*i.e.*, 10 eq per sulfide) in DMF at 80 °C. Similarly to the effect observed with the pyrazine-containing compound **12**, no reaction occurred for pyrazine **14**. In

the case of phthalonitrile **13**, two of the expected products were detected by ^{1}H NMR in the reaction mixture after 24 h along with the unreacted starting material in a ratio of 37:53:10 for **13**:mono:ditransalkylated compound..

The cleavage of sulfonium salts (the second part of the suggested mechanism) has been reported in the literature to proceed either electrochemically,[20] with a catalyst[21] or with a reducing agent (e.g., potassium in graphite[22]). It should also be noted that cleavage of sulfonium salts is part of the natural *S*-adenosyl-l-methionine reduction process.[23] An excellent review summarizing the ways sulfonium salts can be reduced has been published recently.[24] The important factor in this cleavage seems to be the stability of the eliminated radical.[22] Hence, while the electron density on the sulfur atom may influence the first step of the reaction mechanism, the stability of the eliminated radical influences the second part of the reaction. For this reason, we also focused on the type of substituent attached to sulfur (**1**-**5**). The selection of substituents was intended to allow a comparison of the effects of the type of carbon attached to the sulfur (primary (**2**), secondary (**3**), tertiary (**1**), secondary attached to quaternary (**4**) and aromatic (**5**)). As seen from the results of the reactions of these materials with 10 eq of MeI in DMF at 80 °C (Figure 3c), the conversion rate of the starting compounds decreased in the following order **1** > **2** > **3** > **4**. No reaction was detected for diphenylsulfide **5**. The highest reactivity was observed for *tert*-butylphenylsulfide **1**, which is understandable because it formed the most stable elimination product. The second most stable elimination product was expected to be formed from compound **3** with the pent-3-yl substituent (pent-2-ene). However, in the case of compound **2**, the elimination product was expected to be almost the same (the expected product was but-2-ene, which is more stable than but-1-ene); therefore, their ability to eliminate should be comparable. The bulkiness of the alkyl group in **3** may make the sulfur less accessible for MeI attack in the first part of the reaction mechanism, explaining the observed slightly lower reactivity. The neopentyl substituent of **4** cannot form a stable elimination product due to its quaternary central carbon, which explains its observed low rate of the transalkylation, as seen in Figure 3c, and the associated elimination is potentially possible only if some rearrangement occurs. Diphenylsulfide **5** did not react at all due to the hardly decreased electron density on sulfur, and the electrons were delocalized on both aromatic rings. The observed order of reactivity in this work was in good accordance with the published leaving group propensity for the chemical reduction of dialkyl phenyl sulfonium salts.[22]

3. Conclusion

In conclusion, we studied the S-transalkylation reaction of alkyl aryl sulfides with alkylating agents. The reaction mechanism seems to involve sulfonium salts as the intermediate with a subsequent elimination of the alkyl radical that may form alkenes. Isobutene was unequivocally confirmed by NMR as the elimination product from *tert*-butyl sulfide. The first part of the reaction can be influenced by the electron density of the sulfur atom, the polarity of the solvent and the strength of the alkylating agent. The second part of the reaction can be affected by the stability of the eliminated radical. The optimized conditions may be useful in providing an alternative pathway for the synthesis of some alkyl aryl sulfides.

4. Experimental section

All organic solvents used in the synthesis were of analytical grade. All other chemicals for the syntheses were purchased from certified suppliers (*i.e.*, Sigma-Aldrich, TCI Europe, Acros, and Merck) and used as received. TLC was performed on Merck aluminum sheets coated with silica gel 60 F254. Merck Kieselgel 60 (0.040−0.063 mm) was used for column chromatography. The melting points were measured on an Electrothermal IA9200-series digital melting-point apparatus (Electrothermal Engineering, Southend-on-Sea, Essex, Great Britain). The infrared spectra were measured on a Nicolet 6700 spectrometer in ATR mode. The ^{1}H and ^{13}C NMR spectra were recorded on a VNMR S500 NMR spectrometer (Varian Inc., Palo Alto, CA). The chemical shifts are reported as δ values in ppm and are indirectly referenced to $Si(CH_3)_4$ via the signal from the solvent. J values are given in Hz. Elemental analysis was carried out using a Vario Micro Cube Elemental Analyzer (Elementar Analysensysteme GmbH, Hanau, Germany). High-resolution mass spectra (HR MS) were measured on a Synapt G2Si high-resolution mass spectrometer (Waters, Manchester, UK) based on Q-TOF.

The starting materials were prepared by three different published methods: reaction of the corresponding thiophenol with *tert*-butanol (**1**,**6**-**9**),[25, 26] alkylation of thiophenol (**2**-**4**) or nucleophilic substitution of arylchlorides by thiolate (**10**-**12**). Compound **5** was obtained commercially, and compounds **13** and **14** were previously prepared in our laboratory.[27]

*4.1. General procedure for the synthesis of compounds **1** and **6**-**9***

Acetic acid (5 mL), perchloric acid (65%, 2 mL) and acetic anhydride (3 mL) were mixed in a round-bottom flask cooled in an ice bath, and the mixture was stirred for 20 min. *Tert*-butyl alcohol (2.48 g, 3.2 mL, 33.5 mmol) and the corresponding thiophenol (28 mmol) were then added to the mixture, and the volume was adjusted with acetic acid to 25 mL. The mixture was stirred at room temperature for 2 h and then diluted with brine (ca 15 mL). The mixture was transferred to a separatory funnel and washed 3 times with diethyl ether. The combined ether phases were then washed with K_2CO_3 solution (3 times 25 mL) until the pH of the water phase was basic and then with water (ca 40 mL). Care was taken in this process due to the strong gas evolution during neutralization. Alternatively, a 10% water solution of NaOH could be used for neutralization. The ether phase was dried with Na_2SO_4, and the solvent was evaporated.

*4.2. General procedure for the synthesis of compounds **2**-**4**.*

Thiophenol (1.76 g, 16 mmol) was added to a suspension of sodium hydride (60% suspension in mineral oil, 0.7 g, 18 mmol) in anhydrous DMF (15 mL) under an argon atmosphere, and the mixture was stirred at rt for 30 min. A solution of the particular alkylbromide (16 mmol) dissolved in DMF (11 mL) was then added. The resulting mixture was heated at 80 °C for 1 h, and then, water (45 mL) was added after cooling. The mixture was transferred to a separatory funnel and washed with diethyl ether (3 × 25 mL). The organic phase was dried over Na_2SO_4, evaporated and purified by column chromatography on silica with hexane as the mobile phase.

*4.3. Tert-butylphenylsulfide (**1**)*

Compound **1** was prepared according to above mentioned general procedure. The data obtained in the analysis of the compound corresponded well to that previously published.[25] Yield: 87%; colorless liquid; δ_H ($CDCl_3$, 500 MHz) 7.58–7.52 (m, 2H, ArH), 7.43–7.29 (m, 3H, ArH), 1.31 (s, 9H, *t*Bu); δ_C ($CDCl_3$, 126 MHz) 137.5, 132.7, 128.6, 128.4, 45.8, 31.0.

*4.4. Butylphenylsulfide (**2**)*

Compound **2** was prepared according to above mentioned general procedure. The data obtained in the analysis of the

compound corresponded well to that previously published.[28] Yield: 71%, colorless liquid; δ_H ($CDCl_3$, 500 MHz) 7.38–7.23 (m, 3H, ArH), 7.27–7.14 (m, 2H, ArH), 2.95 (t, *J* = 7.4 Hz, 2H, SCH_2), 1.66 (p, *J* = 7.5 Hz, 2H, CH_2), 1.48 (sex, *J* = 7.5 Hz, 2H, CH_2), 0.95 (t, *J* = 7.4 Hz, 3H, CH_3); δ_C ($CDCl_3$, 126 MHz) 137.0, 129.4, 129.0, 128.8, 128.7, 125.6, 33.2, 31.2, 21.9, 13.6.

*4.5. Pent-3-ylphenylsulfide (**3**)*

Compound **3** was prepared according to above mentioned general procedure. The data obtained in the analysis of the compound corresponded well to that previously published.[29] Yield: 63%, colorless liquid; δ_H ($CDCl_3$, 500 MHz) 7.48–7.39 (m, 2H, ArH), 7.32–7.26 (m, 2H, ArH), 7.24–7.19 (m, 1H, ArH), 3.01 (p, *J* = 6.5 Hz, 1H, CH), 1.71–1.53 (m, 4H, CH_2), 1.03 (t, *J* = 7.4 Hz, 6H, CH_3); δ_C ($CDCl_3$, 126 MHz) 135.9, 131.7, 128.7, 126.4, 52.2, 26.7, 11.2.

*4.6. Neopentylphenylsulfide (**4**)*

Compound **4** was prepared according to above mentioned general procedure. The data obtained in the analysis of the compound corresponded well to that previously published.[30] Yield: 87%, colorless liquid; δ_H ($CDCl_3$, 500 MHz) 7.40–7.34 (m, 2H, ArH), 7.32–7.21 (m, 2H, ArH), 7.20–7.11 (m, 1H, ArH), 2.92 (s, 2H), 1.07 (s, 9H); δ_C ($CDCl_3$, 126 MHz) 138.4, 129.4, 129.0, 128.8, 128.7, 125.4, 48.6, 32.44, 29.02.

*4.7. Tert-butyl(4-methoxyphenyl)sulfide (**6**)*

Compound **6** was prepared according to above mentioned general procedure. The data obtained in the analysis of the compound corresponded well to that previously published.[26] Yield: 95%, colorless liquid; δ_H ($CDCl_3$, 500 MHz) 7.45 (d, *J* = 8.8 Hz, 2H, ArH), 6.87 (d, *J* = 8.8 Hz, 1H, ArH), 3.82 (s, 3H, OCH_3), 1.27 (s, 9H, *t*Bu); δ_C ($CDCl_3$, 126 MHz) 160.2, 138.9, 123.6, 114.0, 55.3, 45.5, 30.8.

*4.8. Tert-butyl(4-methylphenyl)sulfide (**7**)*

Compound **7** was prepared according to above mentioned general procedure. The data obtained in the analysis of the compound corresponded well to that previously published.[26] Yield: 98%, colorless liquid; δ_H ($CDCl_3$, 500 MHz) 7.46–7.40 (m, 2H, ArH), 7.18–7.12 (m, 2H, ArH), 2.37 (s, 3H, CH_3), 1.29 (s, 9H, *t*Bu); δ_C ($CDCl_3$, 126 MHz) 138.7, 137.4, 129.2, 129.1, 45.5, 30.9, 21.2.

*4.9. Tert-butylnapht-2-ylsulfide (**8**)*

Compound **8** was prepared according to above mentioned general procedure. The data obtained in the analysis of the compound corresponded well to that previously published.[26] Yield: 68%, white solid; δ_H ($CDCl_3$, 500 MHz) 8.09 (t, *J* = 1.2 Hz, 1H), 7.87 (dt, *J* = 9.6, 3.8 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.62 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.57–7.48 (m, 2H), 1.36 (s, 9H, *t*Bu); δ_C ($CDCl_3$, 126 MHz) 137.0, 134.3, 133.4, 133.0, 130.2, 127.9, 127.7, 127.6, 126.6, 126.2, 46.3, 31.0.

*4.10. Tert-butyl(4-trifluoromethylphenyl)sulfide (**9**)*

Compound **9** was prepared according to above mentioned general procedure. The data obtained in the analysis of the compound corresponded well to that previously published.[26] Yield: 88%, colorless liquid; δ_H ($CDCl_3$, 500 MHz) 7.69–7.63 (m, 2H, ArH), 7.62–7.56 (m, 2H, ArH), 1.32 (s, 9H, *t*Bu); δ_C ($CDCl_3$, 126 MHz) 137.6, 137.3, 130.6 (q, *J* = 32.6 Hz), 125.2 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.0 Hz), 46.7, 31.0.

*4.11. 4-(tert-butylsulfanyl)phthalonitrile (**10**)*

4-Nitrophthalonitrile (2.0 g, 11.5 mmol) and 2-methylpropane-2-thiol (1.9 g, 20.7 mmol) were dissolved in anhydrous DMF (35 mL) under an argon atmosphere. The mixture was stirred and sonicated for 10 min at rt, and K_2CO_3 (4.3 g, 31 mmol) was added in several small portions. The reaction mixture was then stirred at 45 °C for 24 h under an argon atmosphere. The reaction mixture was poured onto ice, and the resulting precipitate was filtered and washed with a mixture of methanol and water (1:1). The solid was then recrystallized from methanol/water. The data obtained in the analysis of the compound corresponded well to that previously published.[31] Yield: 2.15 g (86%); white-greenish solid; m.p. 63-67 °C; δ_H ($CDCl_3$, 500 MHz) 7.91 (d, *J* = 1.7 Hz, 1H, H-3), 7.85 (dd, *J* = 8.1, 1.7 Hz, 1H, H-5), 7.75 (dd, *J* = 8.1, 0.5 Hz, 1H, H-6), 1.37 (s, 9H, *t*Bu); δ_C ($CDCl_3$, 126 MHz) 141.9, 140.2, 140.0, 133.1, 116.0, 115.1, 114.9, 114.8, 48.5, 31.0.

*4.12. 2-tert-butylsulfanylpyrazine (**11**)*

Sodium hydride (60% suspension in mineral oil, 1.01 g, 25.3 mmol) was dissolved in anhydrous THF (40 mL) under an argon atmosphere, and 2-methylpropane-2-thiol (2.83 mL, 2.26 g, 25 mmol) was added. 2-Chlorpyrazine (2.31 g, 20 mmol) was dissolved in anhydrous THF (5 mL) and added dropwise into the reaction. The mixture was refluxed for 4.5 h, diluted with water (20 mL) and extracted twice with ethylacetate (50 mL). The combined organic phases were washed with brine (20 mL), dried with Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography on silica with hexane:ethylacetate (9:1) as the mobile phase. Yield: 2.4 g (71%); colorless oil; ν_{max} (ATR) 3065, 2963, 2921, 1505, 1453, 1378, 1363, 1280 cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 8.46 (d, *J* = 1.6 Hz, 1H, H-3), 8.40 (dd, *J* = 2.6, 1.6 Hz, 1H, H-5), 8.24 (d, *J* = 2.6 Hz, 1H, H-6), 1.51 (s, 9H, *t*Bu); δ_C ($CDCl_3$, 126 MHz) 156.8, 146.7, 143.7, 140.4, 48.3, 30.7; HRMS (ESI): MH^+, found 169.0798. $C_8H_{12}N_2S + H^+$ requires 169.0794.

*4.13. 5-(tert-butylsulfanyl)pyrazine-2,3-dicarbonitrile (**12**)*

2-Methylpropane-2-thiol (0.86 g, 1.05 mL, 9.6 mmol) was added to a 1 M aq. NaOH solution (10 mL, 10 mmol) and stirred at rt for 15 min. Subsequently, a solution of 5-chloropyrazine-2,3-dicarbonitrile[32] (1.28 g, 7.8 mmol) in THF (10 mL) was added, and the reaction was stirred at rt for 1.5 h. Then, water (30 mL) was added, and the product was extracted with ethylacetate (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered and purified by column chromatography on silica with hexane:ethylacetate (8:1) as the mobile phase to produce a slightly brown solid. Yield: 1.1 g (64%); slightly brown solid; m.p. 65.6-66.6 °C; δ_H ($CDCl_3$, 500 MHz) 8.50 (s, 1H, ArH), 1.66 (s, 9H, *t*Bu); δ_C ($CDCl_3$, 126 MHz) 164.8, 146.9, 132.2, 126.9, 113.4, 113.0, 51.6, 29.6; ν_{max} (ATR) 2972 (CH), 2240 (CN), 1539, 1490, 1473, 1419, 1366, 132, 1232 cm^{-1}; [Found: C, 54.97; H, 4.52; N, 25.59. $C_{10}H_{10}N_4S$ requires: C, 55.03; H, 4.62; N, 25.67%].

4.14. 1-Methyl-3-(tert-butylsulfanyl)pyrazinium iodide

Compound **11** (212 mg, 1.26 mmol) was dissolved in DMF (2 mL), and MeI (785 µL, 1.79 g, 12.6 mmol) was added. The reaction was heated at 80 °C for 2 h. Water (5 mL) was added, and the mixture was washed with diethyl ether (3 × 20 mL). The water phase was collected and evaporated to dryness. The brown-red oil that remained after evaporation turned into a dark yellow solid after the addition of diethyl ether. The solid was collected and crystallized from methanol/diethyl ether. The dark yellow crystals were collected and washed slightly with acetone. Yield: 300 mg (77%); dark yellow solid. Yield: 300 mg (77%); dark

yellow solid; m.p. 156.8-158.1 °C (dec.); ν_{max} (ATR) 3091, 3021, 2982, 2986, 2919, 1462, 1407, 1389, 1227 cm^{-1}; δ_H ($(CD_3)_2SO$, 500 MHz) 9.26–9.20 (m, 1H, H-5), 9.12 (s, 1H, H-2), 8.71 (d, *J* = 3.6 Hz, 1H, H-6), 4.23 (s, 3H, N^+CH_3), 1.57 (s, 9H, *t*Bu); δ_C ($(CD_3)_2SO$, 126 MHz) 163.0 (C-3), 149.4 (C-5), 138.8 (t, *J* = 9.4 Hz, C-2), 132.6 (t, *J* = 8.9 Hz, C-6), 51.1 (C, *t*Bu), 48.8 (t, *J* = 4.8 Hz, N^+CH_3), 30.2; [Found: C, 35.30; H, 4.89; N, 9.15. $C_9H_{15}IN_2S$ requires: C, 34.85; H, 4.87; N, 9.03%].

4.15. General procedure for monitoring the transalkylation reaction.

The starting material (typically 200 mg, 1 eq) was dissolved in DMF (or an alternative solvent) (2 mL), and the alkylating agent (typically 10 eq, but in some experiments 2 eq or 20 eq) was added. The reaction was then typically heated to 80 °C (or stirred at rt or heated to reflux in some experiments) under a condenser. After the selected time (typically 30 min, 2 h, 6 h or 24 h), the solution was cooled, quantitatively transferred to a beaker containing water (5-10 mL) and then extracted with diethyl ether (3 × 20 mL) in a separatory funnel. The organic phases were collected, dried with Na_2SO_4 and evaporated. Subsequently, the products were subjected to flash column chromatography on silica with dichloromethane as the mobile phase. All fractions containing the product and starting material were combined (no attempt was made to separate the starting material and product), evaporated and analyzed by ^{1}H NMR spectroscopy. Evaporation at any stage of the work was performed at 75 mbar and 40 °C to avoid/limit the loss of volatile material (e.g., the b.p. of methylphenylsulfide (**1Me**) is 188 °C). In the transalkylation of **11**, the water phase was also collected during extraction and analyzed by ^{1}H NMR. No product was observed in the organic phase in this latter experiment. ^{1}H NMR data of the products of transalkylation are given in the supplementary data..

Acknowledgments

The work was supported by Czech Science Foundation [grant No. 17-19094S] and by Charles University [SVV 260 401]. Authors would like to thank Lucie Nováková for HR MS measurements.

References

1. Block, J. H.; Beale, J. M. J., *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry* 11th ed.; Lippincott Williams and Wilkins: Baltimore, 2004.
2. Machacek, M.; Cidlina, A.; Novakova, V.; Svec, J.; Rudolf, E.; Miletin, M.; Kučera, R.; Simunek, T.; Zimcik, P. *J. Med. Chem.* **2015,** 58, (4), 1736-1749.
3. Zorlu, Y.; Kumru, U.; Isci, U.; Divrik, B.; Jeanneau, E.; Albrieux, F.; Dede, Y.; Ahsen, V.; Dumoulin, F. *Chem. Commun.* **2015,** 51, (30), 6580-6583.
4. Belviso, S.; Cammarota, F.; Rossano, R.; Lelj, F. *J. Porphyrins Phthalocyanines* **2016,** 20, (01n04), 223-233.
5. Wang, Q.; Zhang, S.; Xu, B.; Li, S.; Yang, B.; Yuan, W.; Hou, J. *J. Phys. Chem. C* **2017,** 121, (9), 4825-4833.
6. Labuschagne, A. J. H.; Malherbe, J. S.; Meyer, C. J.; Schneider, D. F. *J. Chem. Soc.-Perkin Trans. 1* **1978**, (9), 955-961.
7. Eames, J.; Kuhnert, N.; Jones, R. V. H.; Warren, S. *Tetrahedron Lett.* **1998,** 39, (10), 1247-1250.
8. Eames, J.; Kuhnert, N.; Warren, S. *J. Chem. Soc.-Perkin Trans. 1* **2001**, (13), 1504-1510.
9. Aggarwal, V. K.; Eames, J.; de las Heras, M. A.; McIntyre, S.; Warren, S. *J. Chem. Soc.-Perkin Trans. 1* **2000**, (24), 4456-4461.
10. Eliel, E. L.; Pearson, W. H.; Jewell, L. M.; Abatjoglou, A. C. *Tetrahedron Lett.* **1980,** 21, (4), 331-334.
11. Branowska, D.; Rykowski, A.; Wysocki, W. *Tetrahedron Lett.* **2005,** 46, (37), 6223-6226.
12. Branowska, D.; Lawecka, J.; Wysocki, W.; Rykowski, A. *Arkivoc* **2009**, 71-77.
13. Branowska, D.; Buczek, I.; Kalinska, K.; Nowaczyk, J.; Rykowski, A. *Tetrahedron Lett.* **2005,** 46, (49), 8539-8541.
14. Corey, E. J.; Jautelat, M. *Tetrahedron Lett.* **1968**, (55), 5787-5788.
15. Hendriks, B.; Waelkens, J.; Winne, J. M.; Du Prez, F. E. *ACS Macro Lett.* **2017,** 6, (9), 930-934.
16. Makhseed, S.; Machacek, M.; Alfadly, W.; Tuhl, A.; Vinodh, M.; Simunek, T.; Novakova, V.; Kubat, P.; Rudolf, E.; Zimcik, P. *Chem. Commun.* **2013,** 49, (95), 11149-11151.
17. Ghazal, B.; Machacek, M.; Shalaby, M. A.; Novakova, V.; Zimcik, P.; Makhseed, S. *J. Med. Chem.* **2017,** 60, (14), 6060-6076.
18. Machacek, M.; Demuth, J.; Cermak, P.; Vavreckova, M.; Hruba, L.; Jedlickova, A.; Kubat, P.; Simunek, T.; Novakova, V.; Zimcik, P. *J. Med. Chem.* **2016,** 59, (20), 9443-9456.
19. Tundo, P.; Selva, M. *Acc. Chem. Res.* **2002,** 35, (9), 706-716.
20. Kjærsbo, T.; Daasbjerg, K.; Pedersen, S. U. *Electrochim. Acta* **2003,** 48, (13), 1807-1816.
21. McCurdy, A.; Jimenez, L.; Stauffer, D. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1992,** 114, (26), 10314-10321.
22. Beak, P.; Sullivan, T. A. *J. Am. Chem. Soc.* **1982,** 104, (16), 4450-4457.
23. Farrar, C. E.; Siu, K. K. W.; Howell, P. L.; Jarrett, J. T. *Biochemistry* **2010,** 49, (46), 9985-9996.
24. Fensterbank, L.; Goddard, J. P.; Malacria, M.; Ollivier, C. *Chimia* **2012,** 66, (6), 425-432.
25. Gibson, S. E.; Guillo, N.; White, A. J. P.; Williams, D. J. *J. Chem. Soc.-Perkin Trans. 1* **1996**, (21), 2575-2581.
26. Gelat, F.; Lohier, J.-F.; Gaumont, A.-C.; Perrio, S. *Adv. Synth. Catal.* **2015,** 357, (9), 2011-2016.
27. Zimcik, P.; Miletin, M.; Novakova, V.; Kopecky, K.; Nejedla, M.; Stara, V.; Sedlackova, K. *Austr. J. Chem.* **2009,** 62, (5), 425-433.
28. Murthy, S. N.; Madhav, B.; Reddy, V. P.; Nageswar, Y. V. D. *Eur. J. Org. Chem.* **2009,** 2009, (34), 5902-5905.
29. Scholz, R.; Hellmann, G.; Rohs, S.; Raabe, G.; Runsink, J.; Özdemir, D.; Luche, O.; Heß, T.; Giesen, A. W.; Atodiresei, J.; Lindner, H. J.; Gais, H.-J. *Eur. J. Org. Chem.* **2010,** 2010, (24), 4559-4587.
30. O'Mahony, G. E.; Eccles, K. S.; Morrison, R. E.; Ford, A.; Lawrence, S. E.; Maguire, A. R. *Tetrahedron* **2013,** 69, (47), 10168-10184.
31. Kaipova, S.; Dinçer, H.; Altindal, A. *J. Coord. Chem.* **2015,** 68, (4), 717-731.
32. Nakamura, A.; Ataka, T.; Segawa, H.; Takeuchi, Y.; Takematsu, T. *Agric. Biol. Chem.* **1983,** 47, (7), 1555-1560

Highlights:

- Alkyl aryl sulfides are transalkylated using various alkylating agents
- Reaction depends on polarity of the solvent and electron density on the sulfur
- Suggested mechanism involves formation of sulfonium salts as intermediate