Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 2577–2581
Tetrahedron

Effect of halogens on the activity of halonitrobenzenes in reactions with carbanions

Mieczysław Mąkosza,* Olga Lobanova† and Andrzej Kwast

Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, 01-224 Warszawa 42, POB 58, Poland

Received 10 September 2003; revised 11 December 2003; accepted 15 January 2004

Abstract—On the basis of competition experiments using a model VNS reaction of chloromethyl phenyl sulfone with halonitrobenzenes it was shown that halogen substituents activate electron-deficient nitroarenes for the addition of carbanions whereas they protect the positions they occupy against the addition.

1. Introduction

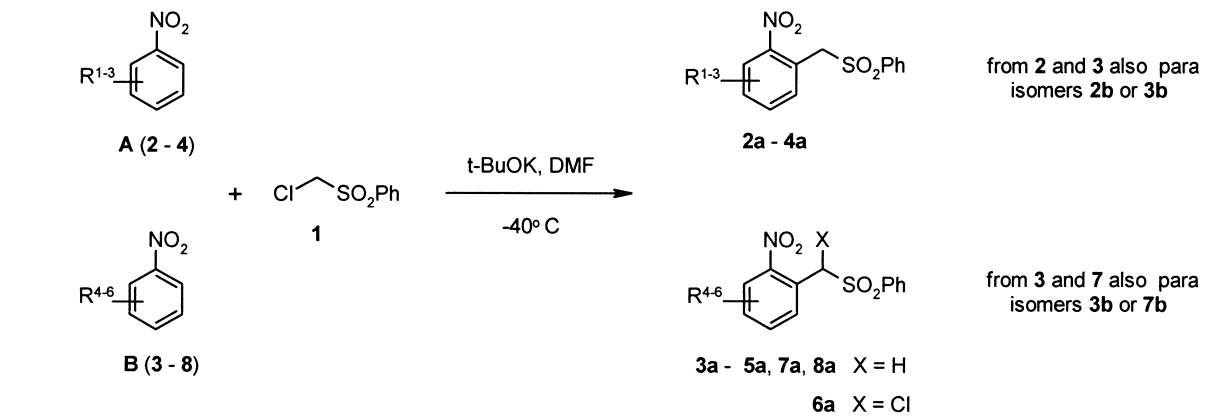
It is well documented, that the addition of nucleophiles to nitroaromatic rings proceeds faster at positions occupied with hydrogen than at the analogous positions occupied with halogen, thus reactions proceeding via σ^H adducts such as vicarious,[1] oxidative[2] and other type of nucleophilic substitution of hydrogen are favored over conventional aromatic nucleophilic substitution of halogen (S_NAr). A similar situation is observed for other electron-deficient arenes: transition metal complexes of arenes,[3] quinone derivatives[4] and even electron-deficient alkenes.[5] Since this is a general rule and numerous qualitative observations indicate that rate of the formation of σ^H adducts is substantially higher than of σ^X adducts one can consider that a halogen in a given position of electron-deficient π-systems protects that position against nucleophilic attack. This statement, although contradicting the common opinions, is entirely correct. On the other hand, halogens being in general electron-withdrawing substituents per nature, should increase total electron-deficiency of the system and accelerate the addition of nucleophilic agents to electron deficient arenes.[6] Thus, a general effect of ring halogens on reactions of electron-deficient arenes with nucleophiles should be somewhat controversial—general activation of the ring, namely acceleration of the addition in positions occupied with hydrogen, but deceleration of the addition in positions they occupy. Such a clear-cut situation was already observed for the reactions of 1,4-naphthoquinone derivatives with carbanions.[4] In simple competitive experiments, it was shown that carbanions of methyl acetoacetate and malonate add to 2-chloro-1,4-naphthoquinone exclusively in the 3-position, occupied by hydrogen, and that this reaction proceeds much faster than addition to 1,4-naphthoquinone itself. On the other hand, the reaction of these carbanions with 2,3-dichloro-1,4-naphthoquinone proceeds much more slowly than with 1,4-naphthoquinone. Thus the chloro substituent activates the electron-deficient π-system of 1,4-naphthoquinone in reactions with nucleophilic agents, but protects positions they occupy against nucleophilic attack. It is therefore of substantial interest to confirm this hypothesis and collect semi-quantitative data concerning the effect of halogen substituents on reactions of carbanions with nitrobenzene derivatives.

2. Results and discussion

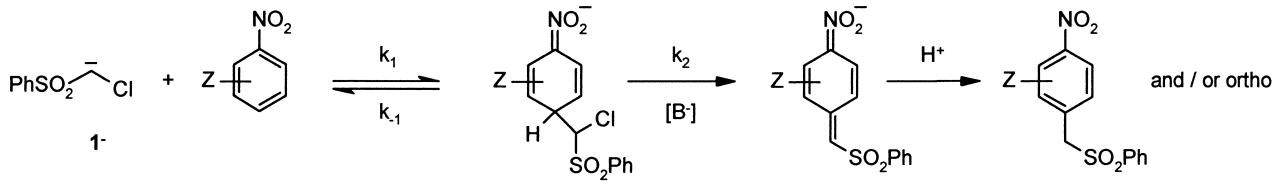
In order to estimate the effect of halogens on the activity of halonitrobenzenes with carbanions we have studied relations of rates of nucleophilic addition of carbanionic nucleophiles to nitrobenzene (**2**), 2-chloronitrobenzene (**3**), 4-chloronitrobenzene, (**4**), 2,4-dichloronitrobenzene (**5**), 2,4,6-trichloronitrobenzene (**6**), 2-bromonitrobenzene (**7**) and 4-bromonitrobenzene (**8**). As the model reaction, we chose vicarious nucleophilic substitution, VNS with the carbanion of chloromethyl phenyl sulfone (**1**) carried out in the presence of an excess of *t*-BuOK. The relationship of rates of the reactions of various halonitroarenes with this carbanion was estimated on the basis of competitive experiments in which a pair of different nitroarenes **A** and **B** was treated with sub-equimolar amount of **1** and excess of *t*-BuOK. After acidification of the reaction mixture, the ratio of the VNS products was determined by GC. These experiments are presented in Scheme 1.

Keywords: Carbanions; Halonitrobenzenes; Vicarious substitution.
* Corresponding author. Tel.: +48-22-6318788; fax: +48-22-6326681; e-mail address: icho-s@icho.edu.pl
† On leave from Institute of Physico-Organic Chemistry UAN, Donietsk, Ukraine.

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.01.038



Scheme 1.



Scheme 2.

The goal of this study required that the VNS reactions should proceed under kinetic control, namely the conditions should assure high rate of conversion of the intermediate σ^H adducts into products of the VNS reaction. According to the mechanism of this reaction shown in Scheme 2[1d] value of $k_2[B^-]$ should be very high, hence the kinetic equation of VNS (Eq. 1) can be simplified (Eq. 2).

$$\text{rate}_{VNS} = k_1k_2[\text{nitroarene}][\mathbf{1}^-][\text{base}]/(k_{-1} + k_2[\text{base}]) \quad (1)$$

$$\text{rate}_{VNS} = k_1[\text{nitroarene}][\mathbf{1}^-] \quad (2)$$

According to the results of our earlier study, the VNS reaction is kinetically controlled, namely the rate of the overall process is determined by the rate of the addition, when the process is carried out in the presence of strong base (*t*-BuOK) used in sufficiently high concentration, in aprotic dipolar solvent (DMF) at low temperature (−40 °C).[1e,f] However, under such conditions some chloronitroarenes, especially those containing more than one chloro substituent, are of limited stability, thus the concentration ratio of the competing nitroarenes becomes not constant. After some experimentation we have found procedures, which assure both the kinetic control of the process and reproducible results of the competition experiments. Observation that the orientation (*ortho*/*para* ratio) for **2** and **3** is not affected when the base concentration was substantially varied, and the value of the kinetic isotope effect KIE, found in 2-D-4-chloronitrobenzene under the conditions applied for the competitive reactions is close to unity, have confirmed the assumed kinetic scheme.

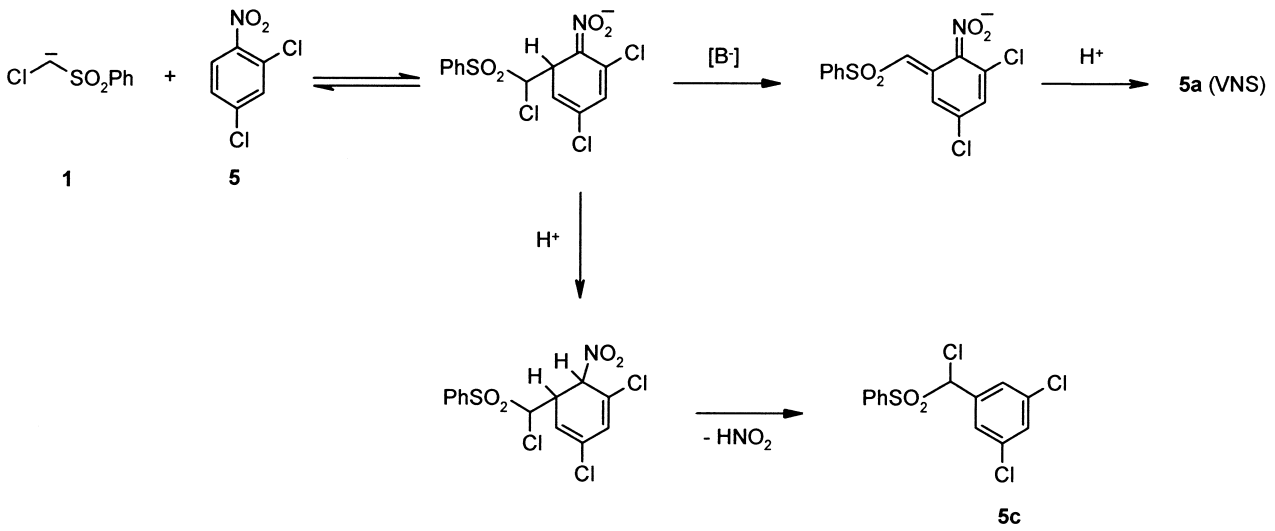
In the competitive experiments of **5** with **3** or **4** we have made a peculiar observation that the ratio of the products depends to some extend on the reaction time. When the reaction mixture was acidified after a very short time (5 s), **5a** was formed in a relatively smaller quantity whereas another product **5c** was also detected in the reaction mixture. Longer reaction time (10–15 s) assured the absence of **5c** and a higher yield of **5a**. The unexpected product **5c** was isolated in a separate experiment and identified as chloro(3,5-dichlorophenyl)methyl phenyl sulfone—a product of the *cine* substitution of the nitro group—formed during the work-up of the reaction mixture containing some amount of σ^H-adducts (Scheme 3). Apparently, addition of the carbanion to the highly electrophilic aromatic ring of **5** produces the σ-adduct which can attain a noticeable concentration due to the relatively hindered β-elimination step.

This situation seems to contradict our requirements concerning the kinetic scheme of the reaction. However, a closer inspection of the reaction course suggests that under the applied conditions, formation of σ-adducts is an irreversible process, thus the relationship of k_1 observed for a particular pair of nitroarenes after a time when the adducts are completely transformed into the VNS products reflects the genuine relation of the addition rates.[7]

Assuming equal, and constant during the course of the reaction, concentration of the both starting nitroarenes **A** and **B** ($[A]_0=[B]_0$) the observed ratio of the respective products is equal to ratio of the rates of the competing VNS reactions, which directly reflect relative rate constants of the nucleophilic addition step (Eq. 3)

$$\text{rate}^B_{VNS}/\text{rate}^A_{VNS} = [P_B]/[P_A] = k_1^B/k_1^A \quad (3)$$

In our experiments, in order to maintain comparable concentrations of the products, starting concentrations of the particular competing nitroarenes were chosen appropriately to their relative reactivity. Moreover, the molar excess of each nitroarene over **1** was usually only 2- to 6-fold, so the requirements for Eq. 3 were not met. Therefore the k_1^B/k_1^A ratio was calculated using appropriate mathematics (see Section 3) and the final results are presented in Table 1.



Scheme 3.

Table 1. Rate constants ratio in competitive reactions of nitroarenes **A** and **B** with **1**[a]

Nitroarene **A**[b]		Nitroarene **B**[b]		k_1^B/k_1^A (compared positions)
No	R_{1-3}	No	R_{4-6}	
2	H	**3**	2-Cl	8.5 (o/o), 12.6 (p/p)
2	H	**4**	4-Cl	130 (o/o)
2	H	**6**	2,4,6-Cl_3[c]	1.6 (o/o)
3	2-Cl	**4**	4-Cl	14 (o/o)
3	2-Cl	**5**	2,4-Cl_2	75 (o/o)
4	4-Cl	**5**	2,4-Cl_2	6.2 (o/o)
3	2-Cl	**7**	2-Br	0.8 (o/o), 0.7 (p/p)
4	4-Cl	**8**	4-Br	1.2 (o/o)

[a] Calculated on the basis of the observed products ratio, starting nitroarenes concentrations and number of reacting positions (see Section 3).
[b] Description according to Scheme 2.
[c] Nucleophilic substitution of 2-chlorine occurs. Substitution of chlorine in *para* position was not observed.

In the case of **6**, which was found to be exceptionally unstable in the presence of strong base, such that its concentration dropped quickly during the reaction course, another procedure was applied. The reaction was carried out for a very short time in order to achieve low conversion. The use of both nitroarenes in 1:1 proportion in considerable excess over the carbanion allows us to consider the observed product ratio directly as k_1^B/k_1^A.

The results were then re-calculated to reflect the reactivity of particular positions in the aromatic rings of nitroarenes **2**–**8** in relation to that of the *ortho* position in nitrobenzene and are presented in Figure 1. In the cases of **4**, **5** and **8** the relative rates are shown as a range of values as they were calculated from reactions of different pairs of competing nitroarenes.

For compound **4**, there is satisfactory agreement of the results obtained in direct competition of **4**+**2** and of that calculated from competition **4**+**3** then **3**+**2**. In the case of **5**, the results of direct competition were not reliable due to the large difference in reactivity of **2** and **5**. The range of values shown comprises those calculated from results of three competition sequences: **5**+**4** then **4**+**2**, **5**+**3** then **3**+**2** and also **5**+**4** then **4**+**3** then **3**+**2**.

The results in Figure 1 clearly demonstrate the expected influence of the chloro substituents on the reactivity of the nitrobenzene ring at the activated positions *ortho* and *para* to the nitro group. Activation of positions 2- and 6- by 4-Cl is substantial and much higher than that of position 4- and 6- by 2-Cl. Much weaker activation in the latter case is apparently due to a secondary steric effect, i.e., partial loss of activating effect of the nitro group caused by the bulky *ortho* substituent. Although one could not expect strict additivity of the effects in **5**, the observed reactivity of the position 6-activated by two chloro substituents seems to be in a reasonably good relation to that of **3** and **4**. Of great importance in that respect is the relative reactivity of position 2-substituted by chlorine in **6**. Although activation of this position by two other chloro substituents should be similar to that in **5**, the observed reactivity, i.e. rate constant of the addition at this position is *ca*. 400–500 times smaller than in **5**. Thus, the formulated earlier supposition concerning the deactivating effect of a halogen substituent on the position which it occupies seems to be justified. Effects of bromo substituents in 2-bromo- and

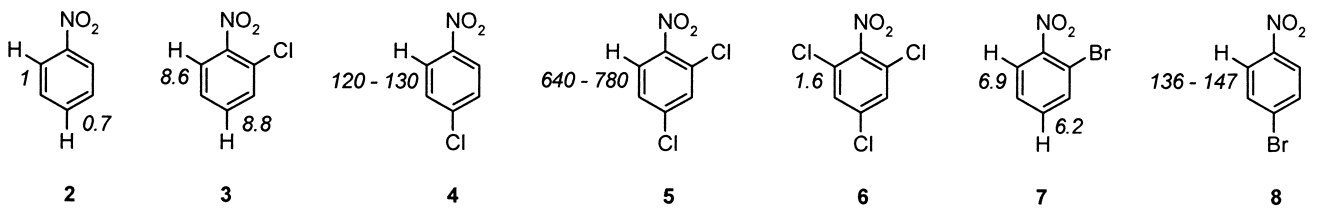


Figure 1.

4-bromonitrobenzenes **7** and **8** were similar to those of chloro substituents. The secondary steric effect in **7** was somewhat stronger than in **3**, but less than one might expect.

3. Experimental

3.1. General

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury 400 (400 MHz) or a Brucker DRX 500 (500 MHz) instruments. Chemical shifts are expressed in ppm referred to TMS, coupling constants in Hertz. Mass spectra were obtained on an AMD-604 spectrometer. GC analyses were performed on a HP 6890 chromatograph with HP-5 capillary column. Silica gel Merck 60 (230–400 mesh) was used for column chromatography.

All starting materials and reagents were commercially available. Authentic samples of the VNS products of nitroarenes **1**–**5** and **8** were obtained according to the published procedures.[8,9] The products of the VNS in **7** (**7a** and **7b**) were obtained analogously in reaction of **7** with **1** in the KOH/DMSO system.[9] A sample of **6a** was isolated from the competitive reaction mixture by column chromatography (SiO_2, hexane/AcOEt).

3.2. General procedure for competition reactions of nitroarenes 2–5, 7 and 8 with 1

To a solution of chlorosulfone **1** (0.12 mmol) and a mixture of two nitroarenes (0.15–1.3 mmol each) in DMF (7 mL) cooled to −40±0.1 °C under argon, was added rapidly a solution of *tert*-BuOK (0.5 mmol) in DMF (1 mL) from a stock solution kept at −40 °C. After 15 s. the reaction mixture was quenched at −40 °C with aqueous HCl (1:10, 2 mL), then diluted with water and extracted with CH_2Cl_2. Combined extracts were washed with water, dried with Na_2SO_4 and analyzed by GC using internal standards and calibration curve prepared for authentic samples of the products. In all instances, conversion of **1** was over 90%. The reactions were repeated 3–5 times for each pair of nitroarenes, and the results were averaged.

The relative reactivity for particular pairs of nitroarenes (Table 1) were calculated from the observed products ratios by combining integrated kinetic equation 4, with 5 and 6 involving some simplifications derived from the fact of almost complete (>90%) conversion of **1**. Further calculations according to equations 7 and 8 provided ratios of rate constants for *ortho* and *para* substitution, which were then re-calculated to obtain relative rate constants referred to that of the VNS *ortho* substitution in nitrobenzene, shown in Figure 1:

$$(k_1^{oB} + k_1^{pB})/(k_1^{oA} + k_1^{pA}) = \ln(1 - ([P^{oB}] + [P^{pB}])/[\mathbf{B}]_0)/\ln(1 - ([P^{oA}] + [P^{pA}])/[\mathbf{A}]_0) \quad (4)$$

$$[P^{oA}] + [P^{pA}] = [\mathbf{1}]_0/(1 + ([P^{oB}] + [P^{pB}])/([P^{oA}] + [P^{pA}])) \quad (5)$$

$$[P^{oB}] + [P^{pB}] = [\mathbf{1}]_0 - [\mathbf{1}]_0/(1 + ([P^{oB}] + [P^{pB}])/([P^{oA}] + [P^{pA}])) \quad (6)$$

$$k_1^{oB}/k_1^{oAB} = ((k_1^{oB} + k_1^{pB})/(k_1^{oA} + k_1^{pA}))(((1 + (p/o)^A)n^A)/(1 + (p/o)^B)n^B)) \quad (7)$$

$$k_1^{pB}/k_1^{pA} = ((k_1^{oB} + k_1^{pB})/(k_1^{oA} + k_1^{pA}))((1 + 1/(p/o)^A)/(1 + 1/(p/o)^B)) \quad (8)$$

where: $[\mathbf{A}]_0$ and $[\mathbf{B}]_0$ are starting concentrations of nitroarenes; $[P^{oA}]$, $[P^{pA}]$, $[P^{oB}]$, and $[P^{pB}]$ are concentrations of *ortho* and *para* reaction products of nitroarenes **A** and **B** respectively; $(p/o)^A$ and $(p/o)^B$ are ratios of *ortho* and *para* isomeric products observed in the reactions; n^A and n^B are numbers of reactive *ortho* positions in nitroarenes **A** and **B**.

3.1.1. (3-Bromo-2-nitrophenyl)methyl phenyl sulfone 7a. White crystals, mp 140–141 °C (EtOH), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (s, 2H), 7.38 (t, J=7.9 Hz, 1H), 7.50–7.55 (m, 2H), 7.59 (dd, J=7.9 Hz, 1.0, 1H), 7.66–7.71 (m, 4H). MS (EI) *m*/*z* 357 (1), 355 (2), 311 (20), 309 (19), 216 (99), 214 (100), 158 (31), 156 (32), 77 (68); HRMS (EI) calcd for $C_{13}H_{10}O_4NS^{79}Br$ 354.9514. Found 354.9526.

3.1.2. (3-Bromo-4-nitrophenyl)methyl phenyl sulfone 7b. White solid, mp 173 °C (EtOH), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (s, 2H), 7.23 (dd, J=8.3 Hz, 1.8, 1H), 7.46 (d, J=1.8 Hz, 1H), 7.52–7.57 (m, 2H), 7.67–7.73 (m, 3H), 7.77 (d, J=8.3 Hz, 1H). MS (EI) *m*/*z* 357 (28), 355 (27), 216 (97), 214 (100), 186 (35), 184 (35), 141 (40), 89 (40), 77 (68); HRMS calcd for $C_{13}H_{10}O_4NS^{79}Br$ 354.9514. Found 354.9516.

3.1.3. Chloro(3,5-dichloro-2-nitrophenyl)methyl phenyl sulfone 6a. White crystals, mp 174–176 °C (EtOH), ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (s, 1H), 7.59–7.65 (m, 3H), 7.75–7.80 (m, 1H), 7.83 (d, J=2.2 Hz, 1H), 7.87–7.91 (m, 2H). MS (EI) *m*/*z* 240 (97), 238 (100), 212 (30), 210 (32), 141 (30), 77 (34). HRMS (EI) calcd for $C_7H_3O_2N^{35}Cl_3$ (M^+−$PhSO_2$) 237.9229. Found 237.9232.

3.3. Competitive reactions of nitroarenes 6 and 2 with 1

To a solution of **6** (0.38–0.40 mmol) and **2** (0.43–0.47 mmol) in DMF (7 mL) cooled to −40±0.1 °C under argon, was added a stock solution (1 mL) containing carbanion of **1** (0.2 mmol) and *tert*-BuOK (0.4 mmol) in DMF. The reaction was quenched after 4–5 s with dilute HCl_{aq} (1:10), and extracted with CH_2Cl_2. Combined extracts were washed with water, dried with Na_2SO_4 and analysed by GC using internal standards as indicated earlier. Conversion of **1** was always under 20%, which means *ca* 5% conversion of the nitroarenes. The regular product of S_NAr in **6** (**6a**) was accompanied by a small amount of its dechlorinated derivative, identical to **5a**. Since the latter was formed under the reaction conditions directly from **6a** in a subsequent process, both products were counted as products of the chlorine substitution in **6**.

3.3.1. Chloro(3,5-dichlorophenyl)methyl phenyl sulfone (5c). To a solution of **5** (440 mg, 2.3 mmol) in DMF (5 mL) cooled to -40 ± 0.1 °C under argon, was added a stock solution (2 mL) containing carbanion of **1** (0.54 mmol) in DMF, prepared by addition of **1** in DMF to a solution of equimolar amount of *tert*-BuOK in DMF at -40 °C under argon. The reaction was quenched after 5 s with aqueous HCl_{aq} (1:10), diluted with water and extracted with CH_2Cl_2. Combined extracts were thoroughly washed with water, dried with Na_2SO_4 and the solvent was evaporated. The crude mixture of starting reagents, the VNS product, and **5c** were separated by column chromatography on SiO_2 using hexane/AcOEt to give **5c**, 51 mg (28%).

White crystals, mp 157–158 °C (EtOH), ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (s, 3H), 5.56 (s, 1H), 7.28 (d, J=1.9 Hz, 1H), 7.42 (t, J=1.9 Hz, 2H), 7.55–7.59 (m, 2H), 7.71–7.75 (m, 1H), 7.77–7.81 (m, 2H); MS (EI) m/z 334 (M^+, 1), 195 (96), 193 (100), 159 (6), 123 (7), 77 (11); HRMS (EI) calcd for $C_{13}H_9O_2S^{35}Cl_3$ 333.9389. Found 333.9374.

References and notes

1. (a) Goliński, J.; Mąkosza, M. *Tetrahedron Lett.* **1978**, 3495–3498. (b) Glinka, T.; Mąkosza, M. *J. Org. Chem.* **1983**, *48*, 3860–3861. (c) Mąkosza, M. J. *Acc. Chem. Res.* **1987**, *20*, 282–289. (d) Mąkosza, M.; Kwast, A. *J. Phys. Org. Chem.* **1998**, *11*, 341–439. (e) Mąkosza, M.; Lemek, T.; Kwast, A. *Tetrahedron Lett.* **1999**, *40*, 7541–7544. (f) Mąkosza, M.; Lemek, T.; Kwast, A.; Terrier, F. *J. Org. Chem.* **2002**, *67*, 394–400.
2. (a) Mąkosza, M. *Russ. Chem. Bull.* **1996**, *45*, 491–503. (b) Mąkosza, M.; Staliński, K. *Chem. Eur. J.* **1997**, *3*, 2025–2031. (c) Mąkosza, M.; Staliński, K. *Pol. J. Chem.* **1999**, *73*, 151–161.
3. (a) Semmelhack, M. F.; Clark, G. R.; Garcia, J. L.; Harrison, J. J.; Thebtaramonth, Y.; Wulff, W.; Yamashita, A. *Tetrahedron* **1981**, *37*, 3957–3965. (b) Ostrowski, S.; Mąkosza, M. *J. Organomet. Chem.* **1989**, *367*, 95–100.
4. Mąkosza, M.; Nizamov, S. *Tetrahedron* **2001**, *57*, 9615–9621.
5. Mąkosza, M.; Nizamov, S.; Kwast, A. *Tetrahedron*, submitted.
6. (a) Terrier, F. *Nucleophilic aromatic displacement*; Chemie: Weinheim, 1991. (b) Chupakhin, O. N.; Charushin, V. N.; van der Plas, H. C. *Nucleophilic aromatic substitution of hydrogen*; Academic: San Diego, 1994.
7. Lemek, T.; Mąkosza, M.; Stephenson, D. S.; Mayr, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 2793–2795.
8. Makosza, M.; Glinka, T.; Kinowski, A. *Tetrahedron* **1984**, *40*, 1863–1868.
9. Makosza, M.; Goliński, J.; Baran, *J. Org. Chem.* **1984**, *49*, 1488–1494.