

Ammonium iodide-mediated electrosynthesis of unsymmetrical thiosulfonates from arenesulfonohydrazides and thiols

Alexander O. Terent'ev,^{a,b} Olga M. Mulina,^a Alexey I. Ilovaisky,^a
Vladimir A. Kokorekin^{a,c} and Gennady I. Nikishin^a

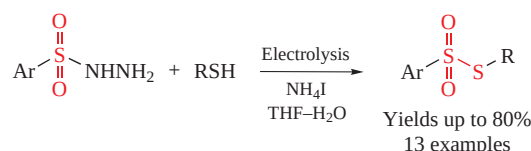
^a N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: terentev@ioc.ac.ru

^b D. I. Mendeleev University of Chemical Technology of Russia, 125047 Moscow, Russian Federation

^c I. M. Sechenov First Moscow State Medical University, 119991 Moscow, Russian Federation

DOI: 10.1016/j.mencom.2019.01.027

Unsymmetrical thiosulfonates were synthesized from thiols and arenesulfonohydrazides by their electrolysis in undivided cell equipped with graphite anode and stainless steel cathode under high current density applying NH_4I both as a redox catalyst and a supporting electrolyte. In the course of the process, oxidative formation of S–S bond occurs with the loss of hydrazine moiety.



The reactions of sulfonyl chlorides with thiols leading to thiosulfonates¹ suffer from low selectivity due to the rapid formation of disulfides as a result of nucleophilic substitution of sulfo group in thiosulfonates by the action of thiols. Oxidative methods² represent a good alternative for this approach. Thiosulfonates have been successfully synthesized by reactions between sodium sulfinates/sulfonyl hydrazides and thiols/disulfides using various oxidative systems^{3–9} or through disproportionation of sodium sulfinates.¹⁰

The application of electric current in organic synthesis is attractive due to its low price and environment-friendliness.¹¹ In this context, we report on electrosynthesis of thiosulfonates by means of electrochemical oxidative formation of S–S bond. This transformation runs fast in undivided electrochemical cell with the use of graphite anode and iron cathode, and is tolerant

to both electron-donating and electron-withdrawing groups in starting compounds.¹²

The co-electrolysis of arenesulfonohydrazides **1a–i** and thiols **2a–e** was studied in H_2O –THF, H_2O –dioxane, EtOH–THF, EtOH or DMSO solution with KI, NH_4I , NBu_4I , NH_4Br and NH_4Cl as supporting electrolytes in undivided cell at constant current (50 mA cm^{-2}) (Scheme 1). The choice of solvents is based on their high electric conductivity and low reactivity under these conditions. Halogen-containing supporting electrolytes permit formation of molecular halogens which can oxidize the starting hydrazides **1**. Current density and reaction temperature values were chosen for conducting the electrosynthesis fast enough and avoiding formation of significant quantities of side products. As a result, thiosulfonates **3a–m** were obtained (see Scheme 1).

p-Toluenesulfonohydrazide **1a** and thiophenol **2a** were selected as model reactants for the estimation of optimal conditions for the electrosynthesis of thiosulfonate **3a** (Table 1).

For the full conversion of **1a** and **2a** into **3a**, four electrons are theoretically needed. Initially we decided to conduct experiments applying slight excess of electricity passed (5 F per mole of **1a**). In entries with non-equal amounts of reactants, the yield of compound **3a** and amount of electricity passed were calculated relative to the reactant taken in less amount for more convenient comparison of the experiment results. In entries 1–5, the nature of supporting electrolyte was shown to be crucial for the reaction outcome. Only in the cases of KI and NH_4I , the target product **3a** was formed in detectable amounts (entries 1, 2), however NH_4I provided its better yield (entry 2). Entries 6–8 demonstrate that the use of 1 mol of NH_4I per 1 mol of hydrazide **1a** is optimal. Conducting the process with the excess of any of the reactants led to a significant increase of **3a** yield up to 57–70% (entries 9–13). Application of 2 mol of **2a** per 1 mol of **1a** turned out to be the most appropriate (entry 12). Raising the electric charge passed to 10 F mol^{-1} (entry 14) did not improve the yield of product **3a** and further increase in this value to 15 F mol^{-1} dropped the yield to 40% (entry 15). Decreasing of electricity passed to theoretical

1a–i	2a–e	3a–m
Ar–SO ₂ –NHNH ₂	RSH	Ar–SO ₂ –S–R
1a Ar = 4-MeC ₆ H ₄	Reactants	Product
1b Ar = 4-MeOC ₆ H ₄	1a + 2a	3a 70
1c Ar = 4-FC ₆ H ₄	1b + 2a	3b 61
1d Ar = 4-ClC ₆ H ₄	1c + 2a	3c 55
1e Ar = 4-BrC ₆ H ₄	1d + 2a	3d 46
1f Ar = 4-IC ₆ H ₄	1e + 2a	3e 66
1g Ar = 4-O ₂ NC ₆ H ₄	1f + 2a	3f 57
1h Ar = 2-naphthyl	1g + 2a	3g 25
1i Ar = 2,4,6-Me ₃ C ₆ H ₂	1h + 2a	3h 43
2a R = Ph	1i + 2a	3i 30
2b R = 4-MeC ₆ H ₄	1a + 2b	3j 68
2c R = 4-ClC ₆ H ₄	1a + 2c	3k 80
2d R = Bu ⁱ	1a + 2d	3l 35
2e R = Bu	1a + 2e	3m 55

Scheme 1 Reagents and conditions: sulfonohydrazide **1** (1 mmol), thiol **2a** (2 mmol) and supporting electrolyte NH_4I (1 mmol) in H_2O –THF (30 ml, 1:1) was electrolyzed at constant current (50 mA cm^{-2}) at 30°C .

Table 1 Optimization of the reaction conditions for the synthesis of thiosulfonate **3a** from *p*-toluenesulfonylhydrazide **1a** and thiophenol **2a**.^a

Entry	Molar ratio 1a : 2a	Supporting electrolyte (mmol)	Solvent	Electricity passed ^b / F mol ⁻¹	Yield of 3a (%) ^c
1	1:1	KI (3)	H ₂ O–THF	5	17
2	1:1	NH ₄ I (3)	H ₂ O–THF	5	43
3	1:1	NBu ₄ I (3)	H ₂ O–THF	5	trace
4	1:1	NH ₄ Br (3)	H ₂ O–THF	5	<10
5	1:1	NH ₄ Cl (3)	H ₂ O–THF	5	<10
6	1:1	NH ₄ I (2)	H ₂ O–THF	5	49
7	1:1	NH ₄ I (1)	H ₂ O–THF	5	51
8	1:1	NH ₄ I (0.5)	H ₂ O–THF	5	34
9	1.5:1	NH ₄ I (1)	H ₂ O–THF	5	57
10	2:1	NH ₄ I (1)	H ₂ O–THF	5	62
11	3:1	NH ₄ I (1)	H ₂ O–THF	5	67
12	1:2	NH ₄ I (1)	H ₂ O–THF	5	70 (68 ^d)
13	1:3	NH ₄ I (1)	H ₂ O–THF	5	68
14	1:2	NH ₄ I (1)	H ₂ O–THF	10	65
15	1:2	NH ₄ I (1)	H ₂ O–THF	15	40
16	1:2	NH ₄ I (1)	H ₂ O–THF	4	24
17	1:2	NH ₄ I (1)	H ₂ O–dioxane	5	47
18	1:2	NH ₄ I (1)	EtOH–THF	5	57
19	1:2	NH ₄ I (1)	EtOH	5	22
20	1:2	NH ₄ I (1)	DMSO	5	trace
21	1:2	LiClO ₄ (1)	H ₂ O–THF	5	14

^a General procedure: a solution of *p*-toluenesulfonylhydrazide **1a** (1–3 mmol), thiophenol **2a** (1–3 mmol) and supporting electrolyte (0.5–3 mmol) in H₂O–THF (1:1), H₂O–dioxane (1:1), EtOH–THF (1:1), EtOH or DMSO (30 ml) was electrolyzed at constant current (50 mA cm⁻²) at 30 °C under magnetic stirring with the use of graphite anode and stainless steel cathode.

^b In entries 1–8 and 12–21 the electricity passed was calculated relative to **1a**, in entries 9–11 relative to **2a**. ^c Isolated yield based on reactant taken in less amount. ^d Electrolysis with platinum electrodes.

value (4 F mol⁻¹) caused the dramatic fall in the yield (entry 16). Replacement of H₂O–THF system with other solvents resulted only in decrease of **3a** yield (entries 17–20). Change of electrode material (entry 12, in parentheses) gave compatible result. When inert electrolyte LiClO₄ (entry 21) was tested, the yield of **3a** was as low as 14%. This fact proved our initial proposal concerning the participation of generated from NH₄I molecular iodine in sulfonylhydrazide oxidation. The side reaction was the formation of diphenyl disulfide, which was a real obstacle to achieve higher yields of the target product. Therefore, the optimal conditions were as follows: 1 mol of NH₄I, 2 mol of thiol **2a** per 1 mol of sulfonylhydrazide, H₂O–THF (1:1) as the solvent, 5 F mol⁻¹ of electricity passed (see Table 1, entry 12).

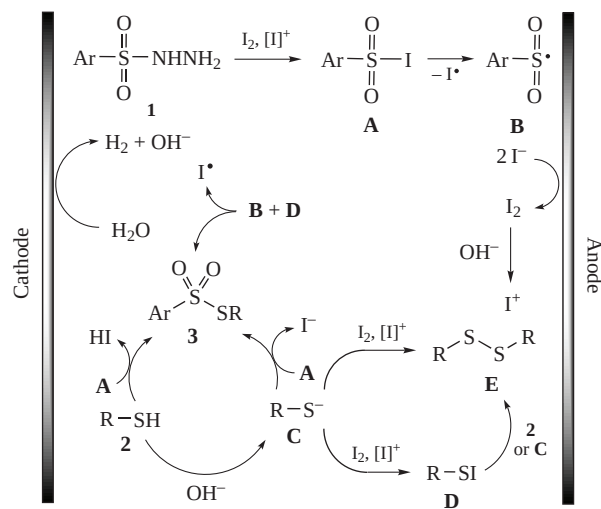
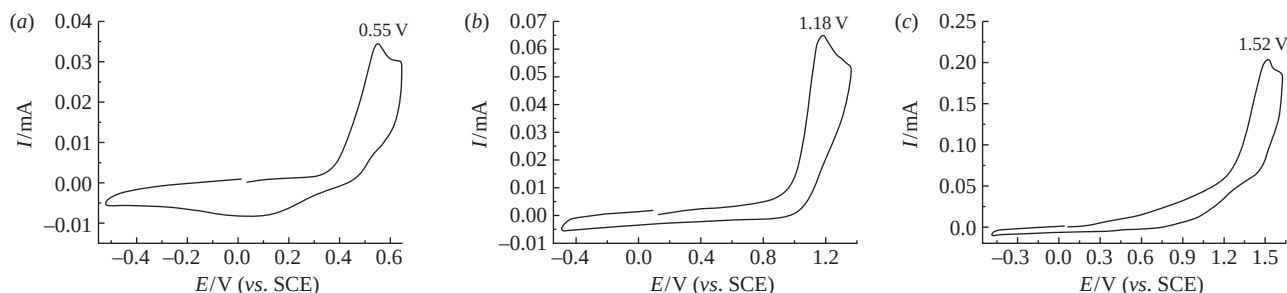
With optimized conditions in hand, we tested a wide range of arenesulfonylhydrazides **1a–i** and thiols **2a–e** in order to explore the scope of the procedure (see Scheme 1). The target thiosulfonates **3** were generally obtained in yields from moderate to high, but in the cases of compounds **1g** and **1i** the corresponding

thiosulfonates **3g** and **3i** formed in low yields (the reduction of nitro group on the cathode and bulkiness of mesitylene moiety). Arenethiols **2b,c** and alkanethiols **2d,e** also successfully enter into this reaction affording thiosulfonates **3j–m** in yields from moderate to high.

In a multigram electrosynthesis (10 mmol of hydrazide **1a** and 20 mmol of thiophenol **2a**) under the optimized conditions (see Table 1, entry 12) product **3a** was isolated in 64% yield.

Cyclic voltammetry (CV) experiments were run to get insight into the reaction mechanism. For this purpose, working glassy-carbon electrode, H₂O–THF (1:1) solvent, and tetrabutylammonium perchlorate as a non-oxidizable supporting electrolyte were chosen. The redox properties of *p*-toluenesulfonylhydrazide **1a**, thiophenol **2a** and NH₄I in H₂O–THF (1:1) solution were studied. Obtained CV curves are shown in Figure 1. Iodide-anion oxidation occurs at the earliest potentials as +0.55 V. Chemically irreversible oxidation of *p*-toluenesulfonylhydrazide **1a** proceeds at +1.18 V. Thiophenol **2a** is oxidized most difficultly at +1.52 V. According to obtained data, one may conclude that under experimental conditions NH₄I serves both as a supporting electrolyte and a redox catalyst.

On the basis of literature and experimental data we proposed a mechanism for the process in question (Scheme 2). At the first reaction step, iodide anion is oxidized on the anode to molecular iodine,¹³ which further oxidizes arenesulfonylhydrazide **1** resulting in the generation of arenesulfonyl iodide **A**.¹⁴ Hypiodites, iodates or periodates can also be involved in the processes of iodide-anion oxidation and formation of arenesulfonyl iodide **A**.¹⁵ They are mainly produced as a result of the reaction between molecular iodine and hydroxide anion formed by the cathodic reduction of H₂O.¹⁶ The thiosulfonate **3** can be formed from **A** through several different ways. The first one is nucleophilic attack of thiol **2** on the iodide **A** with the elimination of HI. Thiol **2** can

**Scheme 2****Figure 1** The CV curves obtained for 3.0 mM solutions of (a) NH₄I, (b) *p*-toluenesulfonylhydrazide **1a** and (c) thiophenol **2a** in H₂O–THF (1:1), containing Bu₄NClO₄ (0.1 mol dm⁻³), on a working glassy-carbon electrode (*d* = 1.7 mm) at a scan rate of 100 mV s⁻¹.

also be deprotonated with hydroxide anion formed on the cathode to give thiolate anion **C**, which can react with sulfonyl iodide **A** providing desired product **3**. Thiolate anion **C** can be oxidized with molecular iodine^{11(c)} or hypiodites, iodates, periodates, providing sulfonyl iodide **D**.¹⁷ Its reaction with sulfonyl radical **B**¹⁸ generated from unstable sulfonyl iodide **A** also results in thiosulfonate **3**.¹⁹ Side disulfide **E** can be produced as a result of the reaction of thiol **2**²⁰ or thiolate anion **C** with sulfonyl iodide **D**,²¹ as well as oxidation of thiolate anion **C** with molecular iodine, hypiodites, iodates and periodates followed by recombination of formed thiyl radicals.²² In addition, thiyl radical and thiolate anion **C** can be generated through the reductive cleavage of S–S bond in diorganyl disulfide **E**.

To summarize, we have demonstrated application of electric current for the synthesis of unsymmetrical thiosulfonates from arenesulfonohydrazides and thiols through oxidative S–S bond formation. The process is conducted in an undivided electrochemical cell equipped with graphite anode and stainless steel cathode. Ammonium iodide was applied both as a supporting electrolyte and a redox catalyst. A wide scope of starting compounds successfully enters into this reaction. A possible reaction mechanism was proposed with the use of cyclic voltammetry.

This work was supported by the Russian Foundation for Basic Research (grant no. 18-33-00693).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.027.

References

- (a) J.-P. Mahieu, M. Gosselet, B. Sebillé and Y. Beuzard, *Synth. Commun.*, 1986, **16**, 1709; (b) H. T. Pham, N.-L. T. Nguyen, F. Duus and T. X. T. Luu, *Phosphorus Sulfur Silicon Relat. Elem.*, 2015, **190**, 1934.
- (a) A. Lei, W. Shi, C. Liu, W. Liu, H. Zhang and C. He, *Oxidative Cross-Coupling Reactions*, 1st edn., Wiley-VCH, Weinheim, 2016; (b) T. Zhang, N.-X. Wang and Y. Xing, *J. Org. Chem.*, 2018, **83**, 7559; (c) Y. Liu, H. Yi and A. Lei, *Chin. J. Chem.*, 2018, **36**, 692; (d) S. Murarka and A. P. Antonchick, *Synthesis*, 2018, **50**, 2150; (e) H. Zhang and A. Lei, *Asian J. Org. Chem.*, 2018, **7**, 1164; (f) O. M. Mulina, A. I. Ilovaisky and A. O. Terent'ev, *Eur. J. Org. Chem.*, 2018, 4648; (g) S. Liang, K. Xu, C.-C. Zeng, H.-Y. Tian and B.-G. Sun, *Adv. Synth. Catal.*, 2018, **360**, 4266.
- K. Fujiki, N. Tanifuji, Y. Sasaki and T. Yokoyama, *Synthesis*, 2002, 343.
- Z. Peng, X. Zheng, Y. Zhang, D. An and W. Dong, *Green Chem.*, 2018, **20**, 1760.
- G. Liang, M. Liu, J. Chen, J. Ding, W. Gao and H. Wu, *Chin. J. Chem.*, 2012, **30**, 1611.
- T. Keshari, R. Kapoor and L. D. S. Yadav, *Synlett*, 2016, **27**, 1878.
- (a) N. Taniguchi, *Eur. J. Org. Chem.*, 2014, 5691; (b) N. Taniguchi, *J. Org. Chem.*, 2015, **80**, 1764.
- G.-Y. Zhang, S.-S. Lv, A. Shoberu and J.-P. Zou, *J. Org. Chem.*, 2017, **82**, 9801.
- Q. Chen, Y. Huang, X. Wang, J. Wu and G. Yu, *Org. Biomol. Chem.*, 2018, **16**, 1713.
- L. Cao, S.-H. Luo, K. Jiang, Z.-F. Hao, B.-W. Wang, C.-M. Pang and Z.-Y. Wang, *Org. Lett.*, 2018, **20**, 4754.
- (a) Y. Jiang, K. Xu and C. Zeng, *Chem. Rev.*, 2018, **118**, 4485; (b) S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe and S. R. Waldvogel, *Angew. Chem. Int. Ed.*, 2018, **57**, 6018; (c) K. Liu, C. Song and A. Lei, *Org. Biomol. Chem.*, 2018, **16**, 2375; (d) D. Pletcher, R. A. Green and R. C. D. Brown, *Chem. Rev.*, 2018, **118**, 4573; (e) A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes and S. R. Waldvogel, *Angew. Chem. Int. Ed.*, 2018, **57**, 5594; (f) D. S. P. Cardoso, B. Šljukić, D. M. F. Santos and C. A. C. Sequeira, *Org. Process Res. Dev.*, 2017, **21**, 1213; (g) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230; (h) A. S. Mendkovich, M. A. Syroeshkin, K. R. Mitina, M. N. Mikhailov, V. P. Gulyai and V. M. Pechennikov, *Mendelev Commun.*, 2017, **27**, 580; (i) Y. Yuan, Y. Cao, Y. Lin, Y. Li, Z. Huang and A. Lei, *ACS Catal.*, 2018, **8**, 10871; (j) H.-B. Zhao, P. Xu, J. Song and H. C. Xu, *Angew. Chem. Int. Ed.*, 2018, **57**, 15153; (k) B. V. Lyalin, V. L. Sigacheva, L. L. Fershtat, N. N. Makhova and V. A. Petrosyan, *Mendelev Commun.*, 2018, **28**, 518; (l) L. Li, Q. Yang, Z. Jia and S. Luo, *Synthesis*, 2018, **50**, 2924; (m) A. O. Terent'ev, O. M. Mulina, D. A. Pirgach, M. A. Syroeshkin, A. P. Glinushkin and G. I. Nikishin, *Mendelev Commun.*, 2016, **26**, 538; (n) A. O. Terent'ev, O. M. Mulina, D. A. Pirgach, A. I. Ilovaisky, M. A. Syroeshkin, N. I. Kapustina and G. I. Nikishin, *Tetrahedron*, 2017, **73**, 6871.
- O. M. Mulina and A. O. Terent'ev, in *Proceedings of the International Conference 'Frontiers in Chemistry'*, Armenia, 2018, p. PS 073.
- (a) X.-J. Pan, J. Gao and G.-Q. Yuan, *Tetrahedron*, 2015, **71**, 5525; (b) H. Huang, G. Yuan, X. Li and H. Jiang, *Tetrahedron Lett.*, 2013, **54**, 7156; (c) X. Gao, G. Yuan, H. Chen, H. Jiang, Y. Li and C. Qi, *Electrochem. Commun.*, 2013, **34**, 242; (d) G. Yuan, Z. Zhu, X. Gao and H. Jiang, *RSC Adv.*, 2014, **4**, 24300; (e) Q. Qu, X. Gao, J. Gao and G. Yuan, *Sci. China: Chem.*, 2015, **58**, 747; (f) S. Liang, C.-C. Zeng, X.-G. Luo, F.-Z. Ren, H.-Y. Tian, B.-G. Sun and R. D. Little, *Green Chem.*, 2016, **18**, 2222.
- Y.-C. Luo, X.-J. Pan and G.-Q. Yuan, *Tetrahedron*, 2015, **71**, 2119.
- (a) L. Emmanuvel, R. K. Shukla, A. Sudalai, S. Gurunath and S. Sivaram, *Tetrahedron Lett.*, 2006, **47**, 4793; (b) W.-C. Li, C.-C. Zeng, L.-M. Hu, H.-Y. Tian and R. D. Little, *Adv. Synth. Catal.*, 2013, **355**, 2884.
- (a) C. L. Mehlretter, *US Patent 2770589A*, 1956; (b) C. L. Mehlretter, *US Patent 2830941A*, 1958; (c) Y. Aiya, S. Fujii, K. Sugino and K. Shirai, *J. Electrochem. Soc.*, 1962, **109**, 419; (d) S. Yamada, D. Morizono and K. Yamamoto, *Tetrahedron Lett.*, 1992, **33**, 4329.
- A. G. Lavekar, D. Equbal, Saima and A. K. Sinha, *Adv. Synth. Catal.*, 2018, **360**, 180.
- (a) I. V. Alabugin, V. I. Timokhin, J. N. Abrams, M. Manoharan, R. Abrams and I. Ghiviriga, *J. Am. Chem. Soc.*, 2008, **130**, 10984; (b) K. Gilmore, B. Gold, R. J. Clark and I. V. Alabugin, *Aust. J. Chem.*, 2013, **66**, 336.
- Z. Guo, W.-T. Wei, G. Zhou, X.-D. Xu and G.-P. Chen, *Synlett*, 2018, **29**, 2076.
- Q. T. Do, D. Elothmani, G. Le Guillanton and J. Simonet, *Tetrahedron Lett.*, 1997, **38**, 3383.
- D. Witt, *Synthesis*, 2008, 2491.
- (a) M. Hirano, S. Yakabe, K. Ando and T. Morimoto, *J. Chem. Res.*, 1998, 816; (b) B. Zeynizadeh, *J. Chem. Res.*, 2002, 564; (c) D. R. Dreyer, H.-P. Jia, A. D. Todd, J. Geng and C. W. Bielawski, *Org. Biomol. Chem.*, 2011, **9**, 7292.

Received: 2nd October 2018; Com. 18/5702