REGIOSELECTIVE SYNTHESIS OF NOVEL BIFUNCTIONAL *NEO*-COMPOUNDS *VIA* C–H ACTIVATION OF AN ALKYL CHAIN OF LINEAR ACYL HALIDES

Cite this: *INEOS OPEN*, **2022**, *5 (3)*, 66–69
DOI: 10.32931/io2213a

Received 10 February 2023,
Accepted 6 April 2023

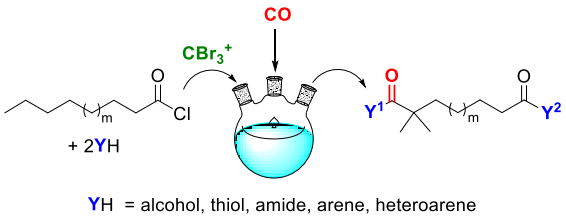
http://ineosopen.org

I. S. Akhrem,† D. V. Avetisyan, L. V. Afanas'eva, O. I. Artyushin, N. D. Kagramanov, and V. V. Burlakov*

Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, str. 1, Moscow, 119334 Russia

Abstract

The regioselective one-pot sp^3 C–H bond functionalization of an alkyl unit in organic molecules already bearing functional groups is of great interest for the synthesis of bifunctional compounds. This report describes the unprecedented regioselective synthesis of otherwise inaccessible bifunctional *neo*-compounds *via* C–H activation of an alkyl chain of linear acyl halides in the presence of CO and two different sequentially introduced nucleophiles.



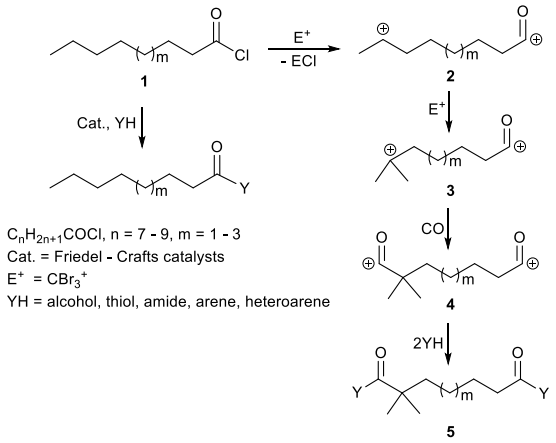
Key words: superelectrophilic complex, C–H functionalization, bifunctional compounds, *neo*-structure.

Introduction

Recent decades have seen the emergence of a new burgeoning area of research in chemistry aimed at further functionalization of monofunctional compounds *via* sp^3 C–H bond activation [1–3]. Considerable progress has been made in the development of new methods for obtaining the target organic molecules from chemically inert substrates by the functionalization of their sp^3 C–H bonds with transition metal complexes and radical initiators [1]. Superelectrophiles occupy a special niche among the reagents and catalysts capable of functionalizing C–H bonds, often enabling otherwise inconceivable chemical transformations.

The functionalization of sp^3 C–H bonds in various long-chain organic compounds can be performed in the presence of the exceptionally reactive superelectrophilic complex $CBr_4 \cdot 2AlBr_3$, CO, and nucleophiles [3–6]. A salient feature of these reactions is their high regioselectivity in the absence of special directing groups in substrates. The latter are converted to a new type of compounds that have *neo*-structures, with functional groups being remote from each other.

There are two types of products that can be derived from the sp^3 C–H bond functionalization with CO and a nucleophile in the presence of $CBr_4 \cdot 2AlBr_3$: (1) those in which the originally present functional group is not affected and (2) those in which the present group is modified under the action of the superelectrophile during the reaction. The products of the first type are derived from methyl alkyl ketones, alkanoates, esters, and carbonyl derivatives of adamantanes [3–5]. Bromoadamantanes, adamantanes, and acyl halides compose a family of substrates that are transformed into the second-type products [4, 6]. Obviously, both types of the products are bifunctional compounds. However, while the products of the first type contain one new and one originally present functional groups, both functionalities in the molecules of the products of the other type are new. The second-type reactions include, in particular, recently described bifunctionalization of linear acyl chlorides with CO and nucleophiles in the presence of $CBr_4 \cdot 2AlBr_3$ (Scheme 1) [4, 6b].



Scheme 1. Comparison of the classical Friedel–Crafts catalysts and $CBr_4 \cdot 2AlBr_3$ in the reactions of acyl halides.

Unlike the Friedel–Crafts catalysts that can ionize only the acid chloride group C(O)–Cl of linear acyl halides (**1**), $CBr_4 \cdot 2AlBr_3$ can ionize both the C(O)–Cl and sp^3 C–H bonds, affording a dication (**2**). The ionization of sp^3 C–H bonds with the superelectrophile leads preferentially to the most stable tertiary cation (**3**). The isomerization of linear alkanes under the action of the Lewis superacids was described by Vol'pin *et al.* as early as 1988 [7]. Due to the repulsion of the positive charges, the carbocation and, consequently, the new functional group tend to adopt the most remote position from the originally present functional group. In the presence of CO, these cations convert to the corresponding acyl cation (**4**) which then, upon addition of a nucleophile, gives rise to the final bifunctional product (**5**).

† Deceased 19 October, 2021

The present work reports a new method for the synthesis of bifunctional compounds from linear acyl halides, CO, and two different sequentially introduced nucleophiles. This transformation furnishes a new type of products featuring *neo*-structures and two maximally remote functionalities.

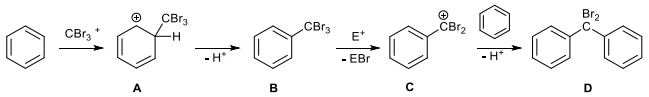
Results and discussion

In a diacylium dication with an unbranched methylene chain, both cationic centers are equivalent. That is why it is impossible to obtain an individual product with two different functional groups from a linear dicarboxylic acid dichloride using two different nucleophiles added sequentially.

In contrast, the diacylium cationic centers in **1** (Scheme 1) are not equivalent. Due to the presence of two adjacent donor groups, the electrophilicity of the acyl cation bound with the *neo* carbon is lower than that of the unbranched carbon atom. Therefore, the nucleophilic addition to the latter will be facilitated compared to the former one. The addition of one equivalent of a nucleophile to generated diacylium **1** was expected to occur quite selectively at the unbranched acyl center. However, the introduction of a second nucleophile to the monoacyl cation produced in the reaction with the first nucleophile could be complicated by scrambling of the already introduced and incoming functionalities. To avoid this undesired process, it was necessary to ensure that the initially introduced nucleophile could form a stronger bond with the acyl group than the second one. Therefore, to synthesize the products with two different functional groups from a linear acid chloride selectively, the first nucleophile (Y^1H) should be a more electron-deficient arene or an alcohol, while the second nucleophile (Y^2H), should be a more electron-rich aliphatic alcohol or a thiol.

Another important point to consider was the fact that benzene and activated arenes readily react with $CBr_4{\cdot}2AlBr_3$ to form trihalomethylalkylated derivative **B** or the products of their further arylation **C** and **D** (Scheme 2).

The reaction of benzene even with less electrophilic $CCl_4{\cdot}AlCl_3$, which leads to product **D**, has been known since the



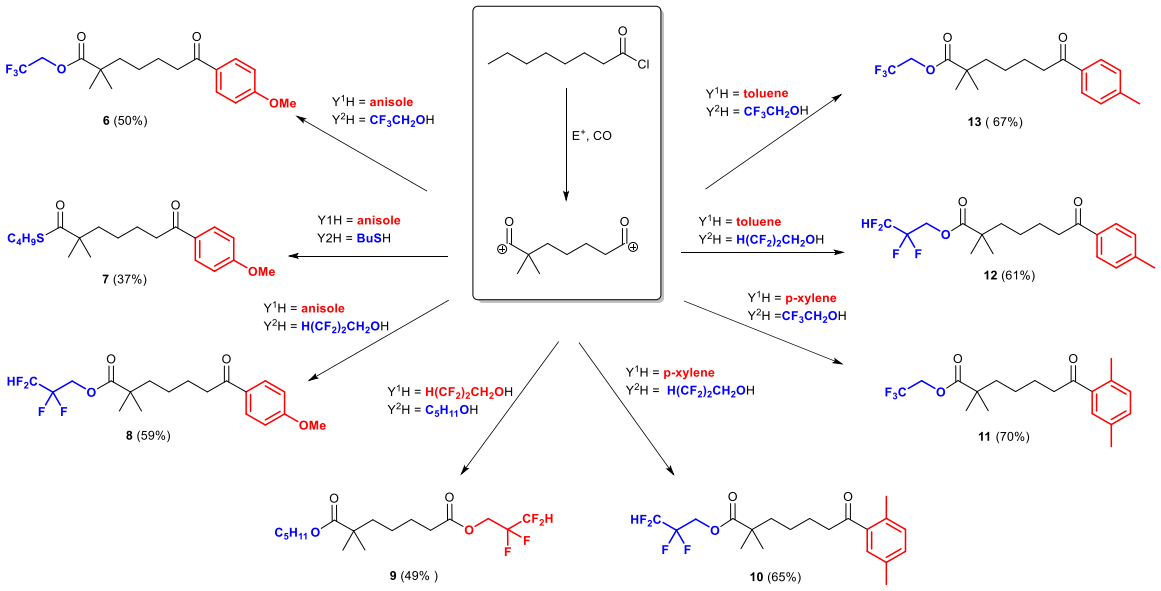
Scheme 2. Reaction of benzene with CBr_3^+.

beginning of the last century [8]. Recently, we have used this reaction for the effective synthesis of valuable tritylmethanols [9] and Schiff bases [10]. The DFT B3LYP/6-31+G calculations for the reactions of benzene with $CBr_4{\cdot}2AlBr_3$ showed that the transformations of benzene into **A**, **B**, and **C** in the gas phase are virtually barrierless (E_a = 0–1 kcal/mol), and the formation of **A**–**C** is exothermic (ΔH = –4 ÷ –17 kcal/mol) [11]. The GLC-MS studies revealed that the reaction of $C_7H_{15}COCl$ with xylene (Y^1H) and hexanol (Y^2H) in the presence of $CBr_4{\cdot}2AlBr_3$ (1:1:1:2) performed by Method 1 (see the Electronic Supplementary Information (ESI)) afforded after the hydrolytic workup compound **C** (M^+–Br = 277, main product), the product of its hydrolysis, 1,4-dimethylbenzoic acid (M^+ = 150), and $C_7H_{15}COOC_6H_{13}$, and the monoalkylated product from $C_7H_{15}COCl$ (M^++1 = 229, in a small amount). Therefore, the synthesis of bifunctional compounds can be accomplished only with the arenes that do not react with $CBr_4{\cdot}2AlBr_3$. For more nucleophilic benzene and alkylbenzene substrates, another method (Method 2) was developed, in which CO and CBr_4 were introduced into the reaction mixture in 0.5–1 h after the reaction beginning (see the Experimental section and ESI).

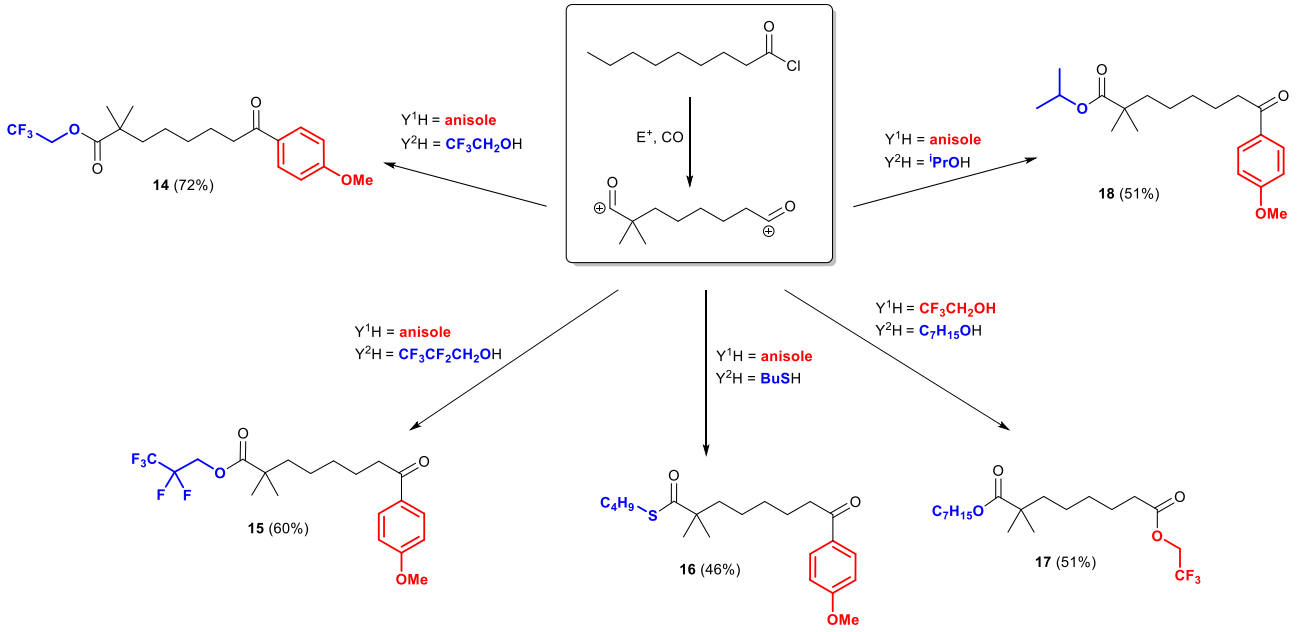
Scheme 3 depicts the structures of the *neo*-bifunctional products obtained from $C_7H_{15}COCl$, CO (1 atm), and two sequentially introduced nucleophiles in the presence of $CBr_4{\cdot}2AlBr_3$.

In general, the yields of products **6**–**9** synthesized by Method 1 ranged within 49–59%. Only in the reaction with HSBu, the yield of product **7** was 37%. The yields of compounds **10**–**13** obtained by Method 2 were 61–70% (Scheme 4).

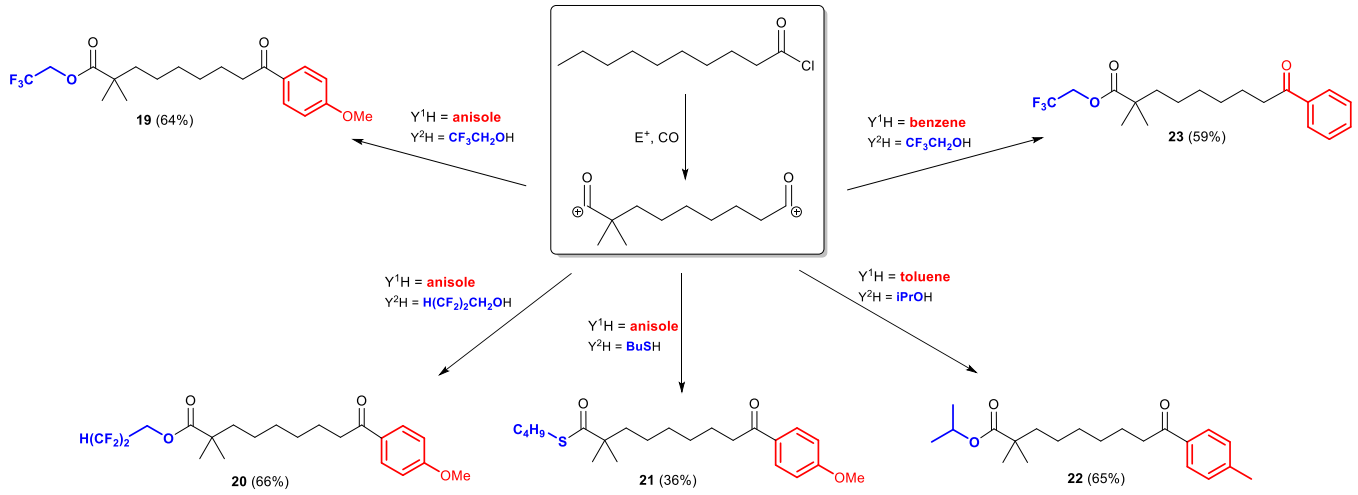
Analogously, the bifunctional *neo*-products with different groups were obtained from nonanoic (Scheme 4) and decanoic acid chlorides (Scheme 5).



Scheme 3. Bifunctional products obtained from $C_7H_{15}COCl$, CO, and two sequentially introduced nucleophiles in the presence of $CBr_4{\cdot}2AlBr_3$ (**6**–**9**: Method 1; **10**–**13**: Method 2). The yields refer to the pure products.



Scheme 4. Bifunctional products **14**–**18** obtained from $C_8H_{17}COCl$ and two different sequentially introduced nucleophiles in the presence of $CBr_4{\cdot}2AlBr_3$ by Method 1.



Scheme 5. Bifunctional products obtained from $C_9H_{19}COCl$ and two sequentially introduced nucleophiles in the presence of $CBr_4{\cdot}2AlBr_3$ (**19**–**21**: Method 1, **22**–**23**: Method 2).

Experimental

All reagents were purchased from commercial sources and dried over anhydrous $CaCl_2$. The samples were weighed and introduced into the reactions in the air. The reactions were monitored by GC using a Focus GC Thermo Scientific instrument. All products were characterized using elemental analysis, ^1H, ^{13}C, and ^{19}F NMR spectroscopy, as well as MS spectrometry. The NMR spectra were recorded on a Bruker AMX-400 spectrometer (operating frequencies: 400.13, 100.61, and 376.49 MHz, respectively). The chemical shifts (^1H, ^{13}C) were referenced internally by the residual or deuterated solvent signals (benzene-d_6: δ_H 7.23 ppm, δ_C 128.0 ppm; $CDCl_3$: δ_H 7.32 ppm, δ_C 76.91 ppm) relative to $SiMe_4$. The $^{13}C\{^1H\}$ NMR spectra of all compounds except for decanoic acid chloride (Fig. S6a in the ESI) were registered using the *J*MODECHO mode; the signals for the C nuclei bearing odd and even numbers of protons had opposite polarities. The $^{13}C\{^1H\}$ spectrum of decanoic acid chloride was registered in the usual mode. The ^{19}F NMR spectra were recorded under ^1H broad-band decoupling. The GC–MS spectra were registered on a Finnigan Polaris GCO Plus instrument. The atom numbering schemes used for the assignment are presented in the ESI.

The reactions were carried out using two methods.

Method 1 was used for the reactions in which anisole or a polyfluorinated alcohol was used as the first nucleophile (Y^1H).

The corresponding acid chloride was added to a stirred solution of $CBr_4{\cdot}2AlBr_3$ (freshly prepared from CBr_4 and $AlBr_3$) in anhydrous CH_2Br_2 at –20 °C under an atmospheric pressure of CO. The molar ratio $[RCOCl]/[CBr_4{\cdot}2AlBr_3]$ was 1/2. After stirring for 2 h at the same temperature under CO atmosphere, the corresponding nucleophile Y^1H was added to the *in situ* generated carbonylation intermediate. The molar ratio $[RCOCl]/[Y^1H]$ was 1/1. The mixture was stirred at –20 °C for

10–20 min. Then the second nucleophile (Y^2H) was added with the molar ratio [RCOCl]/[Y^2H] = 1/(1–5). The reaction mixture was left to warm to 0 °C over 20–30 min. Then water (10 mL) and $CHCl_3$ (30 mL) were added. The organic layer was separated. The aqueous phase was extracted with $CHCl_3$ (10 mL). The combined organic phase was washed with water until neutral pH, dried over Na_2SO_4, and concentrated under reduced pressure. The target products were purified by column chromatography on silica gel using a hexane/acetone (5/1) mixture as an eluent. The yields of the products were determined by ^1H NMR spectroscopy using mesitylene as an internal standard.

Method 2 was used for the reactions in which toluene or *p*-xylene was used as the first nucleophile (Y^1H).

The corresponding acid chloride, Y^1H (benzene, toluene, or *p*-xylene), and $AlBr_3$ were stirred in anhydrous CH_2Br_2 at –20 °C for 0.5–1 h (with the molar ratio [RCOCl]/[arene]/[$AlBr_3$] of 1/1/(2–4)). Then, under an atmospheric pressure of CO, CBr_4 or $CBr_4{\cdot}2AlBr_3$ was added (with the total molar ratio [RCOCl]/[$CBr_4{\cdot}2AlBr_3$] of 1/2). After stirring for 2 h, the corresponding nucleophile Y^2H was added at –20 °C. Then the reaction mixture was left to warm to 0 °C over 20–30 min. The total molar ratio [RCOCl]/[$CBr_4{\cdot}2AlBr_3$]/[Y^1H]/[Y^2H] was 1/2/1/(1–5). The target products were isolated similarly to Method 1.

Conclusions

In summary, we developed a novel methodology for the synthesis of a new type of bifunctional compounds *via* C–H activation of linear acyl halides. The sequential treatment of the latter with two different nucleophiles in the presence of CO selectively afforded bifunctional compounds having *neo*-structures and two different functional groups. The new method significantly expands the possibilities of the regioselective synthesis of bifunctional products bearing different functionalities.

Acknowledgements

This work was performed using the equipment of the Center for Molecular Composition Studies of INEOS RAS with financial support from the Ministry of Science and Higher Education of the Russian Federation (agreement no. 075-03-2023-642).

Corresponding author

* E-mail: vvburl@ineos.ac.ru. Tel: +7(499)702-5870 (1189)

Electronic supplementary information

Electronic supplementary information (ESI) available online: experimental details, elemental analyses, ^1H and ^{13}C NMR as well as MS spectra for all the compounds obtained. For ESI, see DOI: 10.32931/io2213a

References

1. See for examples: (a) K. Godula, D. Sames, *Science*, **2006**, *312*, 67–172. DOI: 10.1126/science.1114731; (b) Selective Functionalization of C–H Bonds, *Chem. Rev.*, **2010**, *2*, 575−1211 (special issue); (c) *Handbook of C–H Transformations: Applications in Organic Synthesis*, G. Dyker (Ed.), Wiley, Weinheim, **2005**; (d) C–H Functionalization in Organic Synthesis, *Chem. Soc. Rev.*, **2011**, *4*, 1845–2040 (special issue).
2. J. C. K. Chu, T. Rovis, *Angew. Chem., Int. Ed.*, **2018**, *57*, 62–101. DOI: 10.1002/anie.201703743 and references cited therein.
3. I. S. Akhrem, A. V. Orlinkov, *Chem. Rev*., **2007**, *107*, 2037–2079. DOI: 10.1021/cr970005n and references cited therein.
4. I. S. Akhrem, *J. Organomet. Chem.*, **2015**, *793*, 54–77. DOI: 10.1016/j.jorganchem.2014.12.012 and references cited therein.
5. (a) I. S. Akhrem, D. V. Avetisyan, L. V. Afanas'eva, *Tetrahedron Lett.*, **2012**, *53*, 3493–3496. DOI: 10.1016/j.tetlet.2012.04.125; (b) I. S. Akhrem, L. V. Afanas'eva, I. M. Churilova, O. I. Artyushin, N. D. Kagramanov, *Mendeleev Commun.*, **2015**, *25*, 124–125. DOI: 10.1016/j.mencom.2015.03.015; (c) I. S. Akhrem, D. V. Avetisyan, L. V. Afanas'eva, O. I. Artyushin, N. D. Kagramanov, *Tetrahedron Lett.*, **2015**, *56*, 562–566. DOI: 10.1016/j.tetlet.2014.11.115; (d) I. S. Akhrem, D. V. Avetisyan, L. V. Afanas'eva, O. I. Artyushin, N. D. Kagramanov, *Tetrahedron Lett.*, **2016**, *57*, 1863–1866. DOI: 10.1016/j.tetlet.2016.03.056; (e) I. S. Akhrem, D. V. Avetisyan, L. V. Afanas'eva, A. A. Tyutyunov, O. I. Artyushin, N. D. Kagramanov, *Mendeleev Commun.*, **2018**, *28*, 651–652. DOI: 10.1016/j.mencom.2018.11.030
6. (a) I. S. Akhrem, D. V. Avetisyan, L. V. Afanas'eva, E. I. Goryunov, I. M. Churilova, P. V. Petrovskii, N. D. Kagramanov, *Mendeleev Commun.*, **2011**, *21*, 259–261. DOI: 10.1016/j.mencom.2011.09.009; (b) I. S. Akhrem, D. V. Avetisyan, L. V. Afanas'eva, O. I. Artyushin, N. D. Kagramanov, A. L. Sigan, *Tetrahedron Lett.*, **2017**, *58*, 4014–4019. DOI: 10.1016/j.tetlet.2017.09.019
7. A. V. Orlinkov, I. S. Akhrem, L. V. Afanas'eva, M. E. Vol'pin, *Dokl. Akad. Nauk SSSR*, **1988**, *299*, 890–894.
8. (a) M. Gomberg, *Chem. Ber.*, **1900**, *33*, 3144–3149. DOI: 10.1002/cber.19000330368; (b) J. Boeseken, *Recl. Trav. Chim. Pays-Bas*, **1905**, *24*, 1–3; (c) M. Gomberg, *J. Am. Chem. Soc.*, **1913**, *35*, 1035–1042. DOI: 10.1021/ja02197a016; (d) M. Gomberg, R. L. Jickling, *J. Am. Chem. Soc.*, **1915**, *37*, 2575–2591. DOI: 10.1021/ja02176a017
9. I. S. Akhrem, D. V. Avetisyan, L. V. Afanas'eva, O. I. Artyushin, *ChemistrySelect*, **2020**, *5*, 7835–7839. DOI: 10.1002/slct.201904255
10. I. S. Akhrem, L. V. Afanas'eva, D. V. Avetisyan, O. I. Artyushin, N. D. Kagramanov, *Mendeleev Commun*., **2020**, *30*, 238–240. DOI: 10.1016/j.mencom.2020.03.037
11. (a) Yu. A. Borisov, I. S. Akhrem, *J. Mol. Catal. A: Chem.*, **2017**, *426*, 610–617. DOI: 10.1016/j.molcata.2016.10.027; (b) Yu. A. Borisov, S. S. Kiselev, I. S. Akhrem, *Mol. Catal.*, **2022**, *529*, 112539. DOI: 10.1016/j.mcat.2022.112539