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Dill and parsley seed extracts in scale up synthesis of aminopolyalkoxybenzenes – beneficial synthons for fused nitrogen polyalkoxyheterocycles

Irina B. Karmanova,[a] Sergei I. Firgang,[a] Leonid D. Konyushkin,[a] Victor N. Khrustalev,[b,c] Alexander V. Ignatov,[d] Leonid A. Kuznetsov,[d] Yuriy A. Pinchuk,[a] Ivan A. Kozlov[d] and Victor V. Semenov*[a]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: vs@zelinsky.ru*
[b] *Peoples' Friendship University of Russia, 117198 Moscow, Russian Federation*
[c] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation*
[d] *'Russkii Katalizator' CJSC, 603004 Nizhnii Novgorod, Russian Federation*

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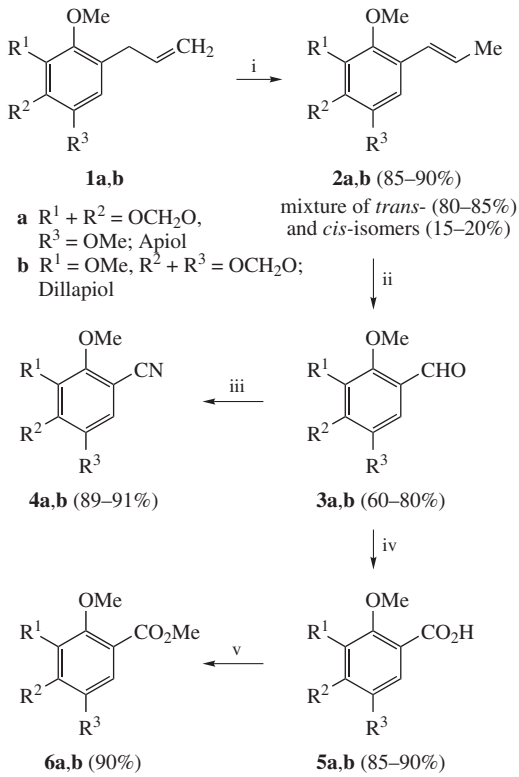
Ecologically friendly transformation of readily accessible plant allylpolyalkoxybenzenes to hardly available aminotetraalkoxybenzenes has been developed. The efficacy of hydrogenation stage is substantially increased by the application of highly porous ceramic block Pd-catalysts featuring a large surface area, low hydraulic resistance, significant thermal and mechanical stabililty, multiple cycling and easy regeneration.

Polyalkoxy-substituted heterocycles with multiple biological activities are abundant in nature. Numerous natural cytostatics (colchicine, combretastatins, steganacine, podophyllotoxin, noscapine, shizandrins, some polyalkoxyflavanoids) and their semisynthetic analogues that contain polymethoxybenzene fragment are widely known as potent antimitotic and anticancer agents.[1–4] The pronounced antiproliferative effects of these molecules is associated with inhibition of tubulin polymerization and microtubule damage.

Nitrogen-containing polyalkoxy-substituted fused heterocycles, both natural and synthetic, such as indoles,[2] quinolones,[3] acridones,[4–6] furoquinolines,[7] *Cactaceae* tetrahydroisoquinolines,[8] *etc.*, often exhibit significant cytotoxicity against human cancer cells, providing a promising starting point in synthesis of biologically active molecules. However, such N-heterocycles have been poorly studied mostly due to the limited availability of the souce material, namely, polyalkoxy-substituted aminobenzenes. Such compounds with four and more alkoxy groups are quite expensive and easily undergo oxidation during their synthesis and/or storage.

In the present study we have developed effective preparative methods for the synthesis of diverse aminotetraalkoxybenzenes from readily available plant allylpolyalkoxybenzenes apiol **1a** and dillapiol **1b**. They can be easily isolated from *Umbelliferae* plants essential oils by high-vacuum distillation. Liquid CO_2 extraction technology developed by Karawan Ltd. (Krasnodar, Russia, http://kuban-karawan.ru/) allows one to produce ~100 dm^3 of the essential oils that contain 15–70% of alkoxybenzenes from 2500 kg of parsley and dill seeds.[9] Natural allylbenzenes can be considered as starting material in environmentally friendly and selective syntheses in drug development. However, side reactions in oxidizing medium, for instance, dimerization, Baeyer–Villiger rearrangement, intra- and intermolecular condensations, present a significant challenge to the selective polyalkoxybenzene transformations.[1(*d*)] To overcome these difficulties, we have proposed a combination of the specialized equipment and optimized protocols.[10] This technology allowed us to perform transformation of propenylbenzenes **2a**,**b** to the aldehydes **3a**,**b** in 60–85% yields on a scale of 100 g (Scheme 1).

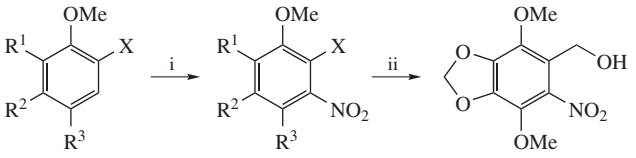


Scheme 1 *Reagents and conditions*:[10] i, KOH, 100 °C, 40 min; ii, O_3, $CHCl_3$–MeOH–pyridine (80:20:3 v/v), 15 °C, 1–2 h; iii, I_2–NH_4OH (28%)–H_2O, room temperature, 16 h; iv, $CO(NH_2)_2 \cdot H_2O_2$, MeOH, reflux, 1.5 h; v, $SOCl_2$, MeOH, reflux, 3 h.

Propenylbenzenes **2a**,**b** were prepared by heating **1a**,**b** for 40 min in the presence of KOH on a water bath in 90–95% yield. Ozonolysis of **2a**,**b** was conducted using a custom-designed apparatus with a maximal capacity of 10 g of O_3 per hour from O_2. Polyalkoxybenzonitriles **4a**,**b** were obtained in >90% yields *via* oxidation of aldehydes with iodine I_2 (molar ratio 1:1.1) in aqueous NH_4OH at room temperature as described recently.[10,11] Polyalkoxybenzoic acids **5a**,**b** were synthesized in high yields

(80–90%) from aldehydes **3a**,**b** using the urea–hydrogen peroxide complex in water.[10] Synthesis of polyalkoxybenzoic acids methyl esters **6a**,**b** (85–95% yield) was reported earlier.[10] The above conditions made it possible both to avoid side reactions[9,10,12] and to access the key building blocks **4**–**6** for the synthesis of aminopolyalkoxybenzenes in high yields on a 100 g scale.

In our hands, the nitration of the starting tetraalkoxyallylbenzenes **1a**,**b** in different reaction media, including pure HNO_3 as well as HNO_3 mixture with H_2SO_4, AcOH, Ac_2O, $CHCl_3$, yielded mixtures of different nitrobenzenes which were difficult to separate. The replacement of allyl fragment in tetraalkoxybenzenes **1a**,**b** with electron-withdrawing group raised the tolerance to oxidation. Thus, compounds **3**, **4**, **6** were nitrated to corresponding nitroaromatic nitriles **7**, esters **8**, and aldehydes **9** in solution of 98% HNO_3 in $CHCl_3$ (Scheme 2).†



3, **9** X = CHO
4, **7** X = CN
6, **8** X = CO_2Me

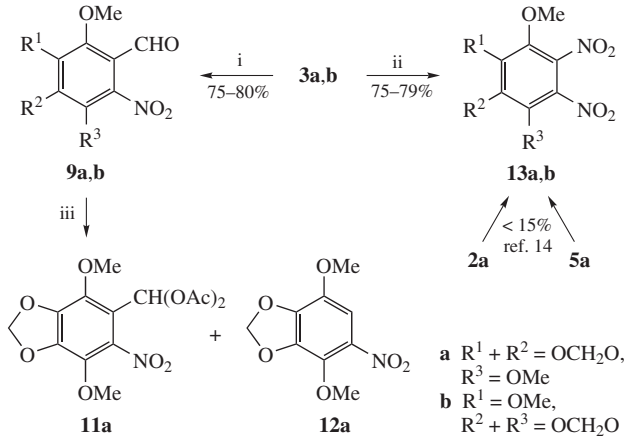
a $R^1 + R^2 = OCH_2O$, R^3 = OMe
b R^1 = OMe, $R^2 + R^3 = OCH_2O$

Scheme 2 *Reagents and conditions*: i, $CHCl_3$–HNO_3 (98%), 0 °C, 30–60 min; ii, $NaBH_4$, Pr^iOH–MeOH, 40 °C, 2 h.

Aldehyde moiety in **9a** was selectively reduced with $NaBH_4$ to afford nitrobenzyl alcohol **10a**.

Apiol nitrobenzoic acid methyl ester **8a** was prepared previously by nitration of the corresponding ester **6a** in Ac_2O solution using $Cu(NO_3)_2 \cdot 6H_2O$.[13]

Apiol nitrobenzaldehyde **9a** was obtained in high yield by nitration of the corresponding arene **3a** with 62% HNO_3 in AcOH, although minor by-products nitroapiolacylal **11a** and nitroapiol **12a** (~10%) were also formed. Benzaldehydes **3a**,**b** were transformed efficiently to corresponding nitrobenzaldehydes **9a**,**b** in solution of 98% HNO_3 in $CHCl_3$ at 0 °C within 30–40 min. On the other hand, the use of excess 70% HNO_3 and prolongation of the reaction time to 4 h gave directly dinitro derivatives **13a**,**b**. The synthesis of dinitroapiol **13a** by nitration of isoapiol **2a** and apiolic acid **5a** was described previously without specifying the yield.[14–16] Following these procedures, we failed to prepare **13a** in more than 15% yield. In our hands the nitration of carboxy arenes **5** resulted in decarboxylation affording a mixture of nitroapiol[2,17] **12a** and dinitroapiol **13a** (Scheme 3). The structure of compound **13a** was unambigously established by X-ray diffraction (see Online Supplementary Materials).



Scheme 3 *Reagents and conditions*: i, $CHCl_3$–HNO_3 (98%), 0 °C, 40 min, ii, $CHCl_3$–HNO_3 (71–79%), room temperature, 5 h; iii, AcOH–Ac_2O–HNO_3 (62%), 30–40 °C.

We further examined hydrogenation of nitroalkenes **7**, **8**, **13** to access the target aminopolyalkoxybenzenes. In case of compounds **13**, the process was complicated by side reactions. Generally, aminobenzenes with several electron-donating substituents (NH_2, OMe) were obtained by hydrogenation over Raney nickel[18] and tin dichloride reduction.[19–21] However, these products were readily oxidized in air and largely lost during isolation. In addition, the formation of polyaminobenzene complexes with tin and nickel salts also hindered their purification, especially when tin salts were removed by hydrogen sulfide.[21] Formation of diaminoapiol **14a** upon reduction of **13a** with $SnCl_2$ was accompanied by the loss of product due to its oxidation and by appearance of impurities.[22] Further studies showed that polyamine synthesis proceeded efficiently by hydrogenation of dinitroanilines in a custom-designed reactor using granulated graphite Sibunit with 2–5% Pd as a catalyst placed into stainless steel mesh boxes.[23]

Highly porous ceramic blocks (Figure 1) as catalytic systems are currently under active development. Due to a wide choice of construction, large surface area, low hydraulic resistance, and significant thermal and mechanical stabililty highly porous catalytic systems become more and more abundant.[24] Block catalysts with cellular structure are promising candidates for application in different liquid-phase catalytic syntheses of a wide range of organic compounds.[25]

Our studies revealed that these catalysts markedly facilitated hydrogenation of polyalkoxynitrobenzenes (Scheme 4).‡

As an example, aminopolyalkoxybenzens **14**–**16** were obtained under mild conditions at room temperature and hydrogen pressure of 30 atm during 3 h. The process required lesser amount of the catalyst, namely, 1% Pd/6% γ-Al_2O_3, as compared to the typical 5% Pd/C. Moreover, the conventional hydrogenation of

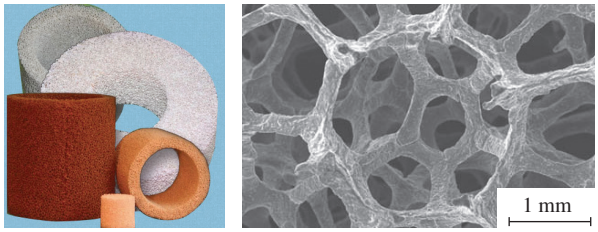
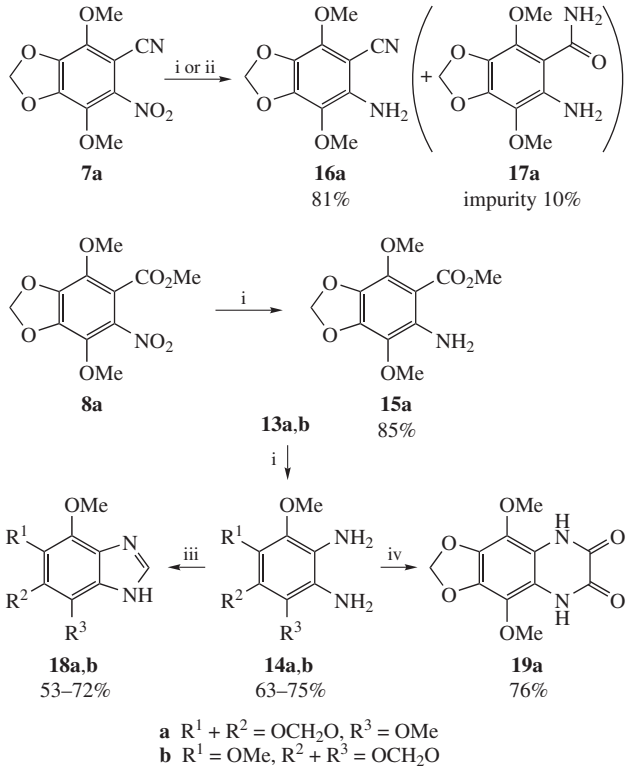


Figure 1 Typical highly porous cellular block catalyst manufactured by company 'Russkii Katalizator CJSC', www.rus-cat.com, www.chemblock.com.

† *General procedure for the nitration of tetraalkoxybenzenes* **3**, **4**, **6** *to mononitro derivatives* **7**–**9**. Nitric acid (98%, 4 ml, 96 mmol) was added dropwise on stirring to the solution of aldehyde **3** (nitrile **4** or methyl ester **6a**,[10] 20 mmol) in dry $CHCl_3$ (50 ml) at 0–5 °C (ice bath). The reaction mixture was stirred at 0–5 °C for 30–60 min and diluted with ice-water (100 g). The organic phase was separated and the water phase was extracted with $CHCl_3$ (2×40 ml). The combined extracts were washed with water (40 ml), aqueous solution of $NaHCO_3$ (10%, 40 ml), again with water (40 ml), and evaporated *in vacuo*. The residue was crystallized from MeOH to afford products **7**–**9**. Yields 75–97%.

General procedure for the nitration of tetraalkoxybenzaldehydes **9a**,**b** *to tetraalkoxydinitrobenzenes* **13a**,**b**. Nitric acid (72%, 190 ml, 3.1 mol) was added dropwise on stirring within 2 h to the solution of aldehyde **3a** or **3b** (40 g, 0.19 mol) in dry $CHCl_3$ (180 ml) at 0–5 °C. The mixture was stirred for additional 3 h at 0–5 °C, 5 h at room temperature, and diluted with ice-water (400 g). The water phase was extracted with $CHCl_3$ (2×100 ml), the combined extracts were washed with water (100 ml), aqueous solution of $NaHCO_3$ (100 ml), and again with water (100 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was crystallized from EtOH to afford **13a** or **13b**. Yields 72–79%.



Scheme 4 *Reagents and conditions*: i, H_2 (30 bar), block highly porous ceramic catalyst (1% Pd/6% γ-Al_2O_3), MeOH, room temperature, 3 h; ii, H_2 (30 bar), granulated 5% Pd/C, MeOH, 40–45 °C, 4.5 h; iii, HCOOH, reflux, 3 h; iv, $(HO_2C)_2$, 2 N HCl, reflux, 3 h.

7a with 5% Pd/C brought about 10% of aminobenzamide **17a** as a by-product. This type of block catalysts can be repeatedly regenerated by hydrogen directly in the reactor at 400 °C up to 30–40 times without activity loss.

The reaction mixture could be quickly extracted from the reactor without filtration devices. Diamines **14a**,**b** were separated as stable diaminobenzene hydrochlorides. Diamines **14a**,**b** can be condensed with HOOCH–$CH(OEt)_3$ to afford benzimidazoles **18a**,**b** directly in the course of hydrogenation in a stainless steel reactor. Diamine **14b** cannot be isolated and purified due to its instability in air, but can be converted *in situ* to benzimidazole **18b** in high yield (72% starting from **13b** in one pot). Similarly, **18a** was also obtained without separation of **14a** in higher yield (53% on 2 steps in one pot starting from **13a**) than synthesized by two stages (45% on 2 steps with separation). Diamine dihydrochloride **14a**·2HCl was transformed to 1,4-dihydroquinoxaline-2,3-dione **19a** on reflux with oxalic acid in 2 N HCl.

In conclusion, dill and parsley seed extracts represent suitable starting material for the large-scale synthesis of fused nitrogen polyalkoxyheterocycles with strong antimitotic activity. The intermediate polyalkoxyarenediamines can be considered as promising synthons for the preparation of polymethoxy-substituted fused heterocycles.

‡ *Hydrogenation of polyalkoxynitrobenzenes* **7a**, **8a** *and* **13a** *with block highly porous ceramic catalyst*. The process employed block highly porous cellular catalyst.[25(b)] Highly porous ceramic material (α-Al_2O_3) covered by sol γ-Al_2O_3 with pores no less than 70–95% was used as catalyst carrier, readily permeable to air and water. This catalyst carrier was impregnated with $Pd(NO_3)_2$ and heated at 450 °C to provide PdO-coating, which was hydrogenated to metallic Pd with hydrogen at 50–55 °C, yielding the target block highly porous ceramic catalyst with 1% Pd/6% γ-Al_2O_3.

Block highly porous ceramic catalyst cylinder (1% Pd/6% γ-Al_2O_3, 50 mm diameter, 50 mm height, 10 ppi cell, 33.9 g, 70–95% pores) was fixed in the middle of stainless steel cylinder autoclave (50 mm inner diameter) equipped with thermocouple, hydrogen inlet tube, and electric heating system. The stirring of the reaction mixture was provided by shaking device (capacity 120–160 min^{-1}).

The solution of nitroarene **7a**, **8a** or **13a** (20 mmol) in MeOH (200 ml) was hydrogenated at room temperature for 3 h at hydrogen pressure of 30 bar. The reaction mixture was removed from autoclave, the solvent was evaporated, and the residue was recrystallized from a proper solvent to afford **15a** (or **16a**). In case of separation of **14a**, HCl (36.5%, 7 ml) was added immediately to autoclave, the reaction mixture was removed, diluted with additional portion of HCl to pH 2, evaporated to dryness. The residue was mixed with CH_2Cl_2 (120 ml) within 5–10 min, filtered, washed with CH_2Cl_2 (100 ml), and dried in air to afford **14a**·2HCl as brown crystals.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.01.026.

References

1 (*a*) A. Jordan, J. A. Hadfield, N. J. Lawrence and A. T. McGown, *Med. Res. Rev.*, 1998, **18**, 259; (*b*) S. Desbene and S. Giorgi-Renault, *Curr. Med. Chem.: Anti-Cancer Agents*, 2002, **2**, 71; (*c*) N.-H. Nam, *Curr. Med. Chem.*, 2003, **10**, 1697; (*d*) V. V. Semenov and M. N. Semenova, *Russ. Chem. Rev.*, 2015, **84**, 134.

2 M. J. Piggott and D. Wege, *Aust. J. Chem.*, 2000, **53**, 749.

3 A. Maiti, P. V. N. Reddy, M. Sturdy, L. Marler, S. D. Pegan, A. D. Mesecar, J. M. Pezzuto and M. Cushman, *J. Med. Chem.*, 2009, **52**, 1873.

4 F. Dallacker and G. Adolphen, *Liebigs Ann. Chem.*, 1966, **691**, 138.

5 S. Habtemariam, P. G. Waterman and T. G. Hartley, *Phytochemistry*, 1996, **43**, 291.

6 M. W. Muriithi, A.-K. Abraham, I. Scowen, S. L. Croft, P. M. Gitu, H. Kendrick, W. Njagi and W. Colin, *J. Nat. Prod.*, 2002, **65**, 956.

7 V. S. P. Chaturvedula, J. K. Schilling, J. S. Miller, R. Andriantsiferana, V. E. Rasamison and D. G. I. Kingston, *J. Nat. Prod.*, 2003, **66**, 532.

8 A. T. Shulgin and A. Shulgin, *Tinkal: The Continuation*, Transform Press, Berkeley, 1977, p. 646.

9 V. V. Semenov, V. A. Rusak, E. M. Chartov, M. I. Zaretskii, L. D. Konyushkin, S. I. Firgang, A. O. Chizhov, V. V. Elkin, N. N. Latin, V. M. Bonashek and O. N. Stas'eva, *Russ. Chem. Bull., Int. Ed.*, 2007, **56**, 2448 (*Izv. Akad. Nauk, Ser. Khim.*, 2007, 2364).

10 V. V. Semenov, A. S. Kiselyov, I. Y. Titov, I. K. Sagamanova, N. N. Ikizalp, N. B. Chernysheva, D. V. Tsyganov, L. D. Konyushkin, S. I. Firgang, R. V. Semenov, I. B. Karmanova, M. M. Raihstat and M. N. Semenova, *J. Nat. Prod.*, 2010, **73**, 1796.

11 L. D. Konyushkin, T. I. Godovikova, S. K. Vorontsova, D. V. Tsyganov, I. B. Karmanova, M. M. Raihstat, S. I. Firgang, M. A. Pokrovskii, A. G. Pokrovskii, M. N. Semenova and V. V. Semenov, *Russ. Chem. Bull., Int. Ed.*, 2010, **59**, 2268 (*Izv. Akad. Nauk, Ser. Khim.*, 2010, 2212).

12 D. V. Tsyganov, N. B. Chernysheva, L. K. Salamandra, L. D. Konyushkin, O. P. Atamanenko and V. V. Semenov, *Mendeleev Commun.*, 2013, **23**, 147.

13 F. Dallacker and F. Gohlke, *Liebigs Ann. Chem.*, 1961, **644**, 30.

14 J. Ginsberg, *Chem. Ber.*, 1888, **21**, 1192.

15 G. Ciamician and P. Silber, *Chem. Ber.*, 1890, **20**, 35.

16 G. Ciamician and P. Silber, *Chem. Ber.*, 1889, **22**, 2489.

17 F. Dallacker, L. Erkens and O. Kim, *Z. Naturforsch. C*, 1978, **33C**, 459.

18 H. Gilman and H. S. Broadbent, *J. Am. Chem. Soc.*, 1948, **70**, 2619.

19 R. E. Lyle and J. L. LaMattia, *J. Org. Chem.*, 1975, **40**, 438.

20 J. R. E. Hoover and A. R. Day, *J. Am. Chem. Soc.*, 1955, **77**, 4324.

21 B. C. Platt and T. M. Sharp, *J. Chem. Soc.*, 1948, 2129.

22 G. Ciamician and P. Silber, *Chem. Ber.*, 1890, **23**, 2283.

23 V. V. Elkin, L. N. Tolkacheva, N. B. Chernysheva, I. B. Karmanova, L. D. Konyushkin and V. V. Semenov, *Russ. Chem. Bull., Int. Ed.*, 2007, **56**, 1216 (*Izv. Akad. Nauk, Ser. Khim.*, 2007, 1171).

24 (*a*) A. I. Kozlov and E. S. Lukin, *RF Patent 2233700*, 2004; (*b*) A. I. Kozlov, E. S. Lukin, I. A. Kozlov, V. P. Kolesnikov and V. N. Grunskii, *Glass and Ceramics*, 2005, **62**, 206 (*Steklo i Keramika*, 2005, no. 7, 12); (*c*) A. S. Shaimardanov, E. M. Kol'tsova, A. I. Kozlov, A. V. Zhensa, V. A. Kostikov and L. S. Gordeev, *Theor. Found. Chem. Eng.*, 2007, **41**, 137 (*Teor. Osnovy Khim. Tekhnol.*, 2007, **41**, 148).

25 (*a*) N. I. Vavilov, V. L. Zbarsky, A. I. Kozlov, E. S. Lukin, E. N. Mizgunova, P. I. Fedotov and V. A. Chashtin, *RF Patent 2164222*, 2001; (*b*) V. L. Zbarsky, N. V. Khodov, A. I. Kuimov and A. I. Kozlov, *RF Patent 2333795*, 2008; (*c*) A. I. Kozlov, V. N. Grunskii, A. V. Bespalov, A. S. Novoselov, D. S. Grakova, A. A. Merkin and A. A. Komarov, *Usp. Khim. Khim. Tekhnol.*, 2008, **22** (2), 49 (in Russian).

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