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Efficient synthesis of calix[4]resorcinol *rccc* diastereoisomers using high amount of trifluoroacetic acid in the chloroform medium

Irina R. Knyazeva,*[a] Nikita P. Romashov,[b] Victor V. Syakaev,[a] Daria P. Gerasimova,[a] Olga A. Lodochnikova[a] and Alexander R. Burilov[a]

[a] *A. E. Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. E-mail: ihazieva@mail.ru*
[b] *Kazan National Research Technological University, 420015 Kazan, Russian Federation*

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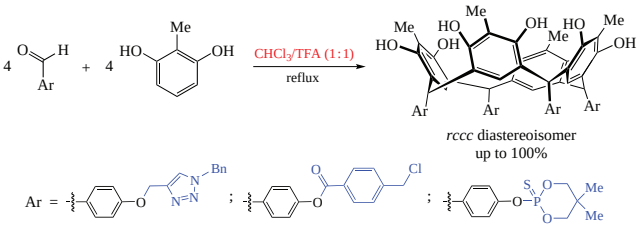
The use of excess of trifluoroacetic acid in chloroform (1 : 1, v/v) in a one-pot acid-catalyzed cyclocondensation of functionalized benzaldehydes with 2-methylresorcinol significantly improves the yield of calix[4]resorcinol *rccc* diastereoisomers compared to *rctt* ones. The fraction and yield of the *rccc* isomers sometimes approach 100% along with shortening the reaction time. The structure of new *rccc* diastereoisomer of chlorine-containing calix[4]resorcinol has been established by single crystal X-ray diffraction.



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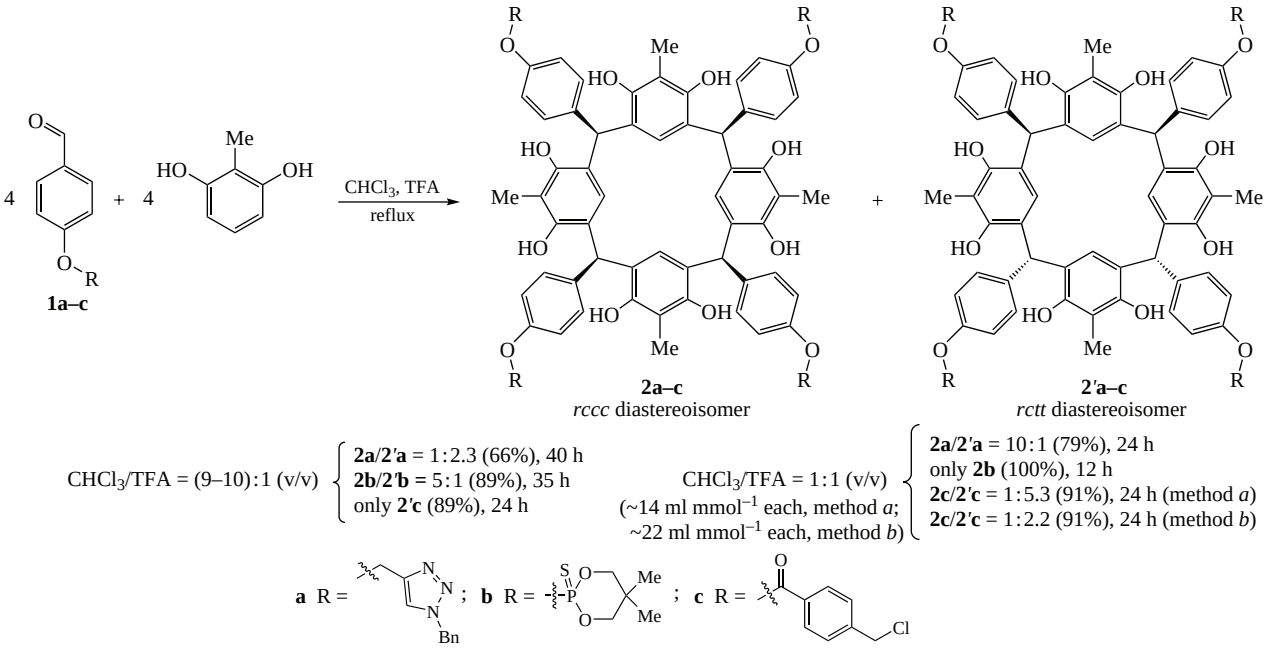
Calixarenes, in particular, calix[4]resorcinols have long been of interest in various fields of modern organic chemistry.[1–8] A conventional route for their synthesis is the acid-catalyzed cyclocondensation of resorcinols with various aliphatic and aromatic aldehydes, as well as acetals under reflux in water–alcohol mixtures in the presence of concentrated hydrochloric acid, the yields varying from moderate to high.[9–15] Non-trivial methods for the preparation of calix[4]resorcinols are also documented.[4,5]

Calix[4]resorcinols are nonplanar molecules and can exist in diverse stereoisomeric forms, which differ by spatial arrangement of substituents at methylene bridges relative to macrocyclic scaffold: all-*cis* (*rccc*), *cis-trans-trans* (*rctt*), *cis-cis-trans* (*rcct*), and *trans-cis-trans* (*rtct*); nevertheless, they usually adopt either *rccc* or *rctt* isomeric form. The formation of a particular isomer of calix[4]resorcinol depends on condensation conditions and the structure of starting compounds. One example is the predominant formation of *rccc* isomers of calix[4]resorcinols when using aliphatic aldehydes or acetals in the reactions with resorcinols under conventional conditions (water–alcohol mixtures in the presence of concentrated hydrochloric acid). Another example is the mixture of *rccc* and *rctt* isomers in the case of aromatic aldehydes. When the conditions are other than conventional, the reactions can proceed stereoselectively to provide exclusively *rccc* or *rctt* isomers of calix[4]resorcinols; only few works report the formation of other isomeric forms.[11–19]

Our research group has discovered that condensation of resorcinol and its derivatives with functionalized benzaldehydes in chloroform in the presence of trifluoroacetic acid (TFA) was an effective route for the preparation of a large number of new calix[4]resorcinols, which are formed as the mixture of *rccc* and *rctt* diastereomers. These reactions are occasionally stereoselective and normally give *rctt* isomer.[20–24] We have recently[25] found that an increase in the content of TFA in chloroform in the reaction of 4-(prop-2-yn-1-yloxy)benzaldehyde with 2-methylresorcinol alters the ratio of formed *rccc* and *rctt* diastereomers and significantly increases the yield of *rccc* isomer. Optimization of the conditions revealed that equal volumes of chloroform and TFA are optimal for the predominant formation of *rccc* isomer, whereas a small amount of TFA in chloroform led mostly to *rctt* isomer.

We associated the discovered effect of the increased content of TFA in chloroform on the *rccc*/*rctt* ratio with the relative solubility of the formed *rctt* isomer.[25] More specifically, when there was a low content of TFA, namely $CHCl_3$/TFA = 15 : 1 (v/v), the less soluble *rctt* isomer, the product of kinetic control, was precipitated and the reaction stopped. When the content of TFA was raised up to $CHCl_3$/TFA = 1 : 1 (v/v), the relative solubility of the *rctt* isomer grew, the equilibrium condensation continued to give a higher yield of thermodynamically preferred *rccc* isomer. An increase in the yield of *rccc* isomer with an increase in the content of TFA in the reaction mixture has also been rationalized by the fact that a conversion of the kinetic *rctt* isomer into the product of thermodynamic control (*rccc* isomer) occurred upon prolonged heating under homogeneous conditions. In that case, no back conversion of *rccc* into *rctt* was observed. Thus, the employed conditions of $CHCl_3$/TFA = 1 : 1 (v/v) became more solubilizing for the formed *rctt* isomer, whose solubility affected the outcome of the reaction.[25] Those results are highly promising for the target synthesis of *rccc* isomers of various calix[4]resorcinols, which are more convenient macrocyclic compounds for subsequent molecular design, because they possess improved solubility in various organic solvents as compared to corresponding *rctt* isomers and, consequently, high reactivity in subsequent reactions.

In this paper, we extended our studies and investigated the condensation of some functional derivatives of benzaldehyde with 2-methylresorcinol at the increased content of TFA in the reaction mixture. In fact, the suggested method is found to be promising as a universal approach: the reaction leads mainly to



Scheme 1

rccc isomers of corresponding calix[4]resorcinols, the yield of which may become quantitative; moreover, the rate of reaction increases and the time of reaction decreases.

We previously reported[22] that the condensation of equimolar quantities of 2-methylresorcinol and 4-(1-benzyl-1*H*-[1,2,3]-triazol-4-ylmethoxy)benzaldehyde **1a** in $CHCl_3$ media in the presence of small amount of TFA ($CHCl_3$/TFA = 10:1) under reflux for 40 h afforded a mixture of *rccc* **2a** and *rctt* **2′a** isomers in 1:2.3 ratio with a total yield of 66% (Scheme 1). Herein we found that the same reaction in the mixture of $CHCl_3$/TFA = 1:1 (v/v) under 24 h reflux gave the mixture of the same diastereomers with the preferential content of *rccc* isomer (**2a**/**2′a** = 10:1) in a total yield of 79%.†

Condensation of thiophosphorylated aldehyde **1b**, namely 2-(4-formylphenoxy)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-sulfide, with 2-methylresorcinol under the conditions studied gives only *rccc* isomer **2b** of corresponding calix[4]resorcinol with quantitative yield while the time of reaction was only 12 h. Previously,[20] when the $CHCl_3$/TFA ratio in the medium was 9:1, the *rccc*-**2b**/*rctt*-**2′b** product ratio was 5:1 with a total yield of 89% while the reaction time was 35 h.

In the previous study[23] with the use of $CHCl_3$/TFA = 10:1 system, chlorine-containing aldehyde, namely, 4-formylphenyl 4-(chloromethyl)benzoate **1c**, when reacted (24 h) with 2-methylresorcinol provided only a *rctt* isomer of calix[4]-resorcinol **2′c** in the *chair* conformation in 89% yield. Herein, employment of $CHCl_3$/TFA = 1:1 (v/v) afforded the mixture of *rccc* **2c** and *rctt* **2′c** isomers at a 1:5.3 ratio in total yield of 94% after the same time of reaction; in this case, *rccc* diastereomer **2c** was prepared for the first time (see Scheme 1, method *a*). Such a low fraction of *rccc* isomer **2c** can be rationalized by the very poor solubility of the corresponding *rctt* isomer **2′c** under the conditions studied. We supposed that an increase in the total volume of the solvent and the acid would increase the yield of *rccc* isomer providing a better dissolution of the formed *rctt* isomer. In fact, a 1.6-fold increase in the volume of $CHCl_3$/TFA at a 1:1 (v/v) ratio and the same time of reaction (24 h) led to the increase in the content of *rccc* diastereomer (*rccc*-**2c**/*rctt*-**2′c** = 1:2.2). In this case, the total yield of the products remains the same (91%) in spite of dilution of the reaction mixture (see Scheme 1, method *b*).

The structure of new *rccc* isomer of chlorine-containing calix[4]resorcinol **2c** was elucidated using ^{1}H and ^{13}C NMR spectroscopy and HSQC, HMBC, and 2D NOESY experiments. ^{1}H and ^{13}C NMR spectra show individual signals of each group of protons and carbon atoms, which indicates high symmetry of the structure of this compound and existence of only one isomer with C_{4v} symmetry (*cone* conformation) in solution. The structure and conformation of **2c** were also confirmed by single

† *General procedure for synthesis of calix[4]resorcinols* **2a**, **2′a**, **2b**. A mixture of 2-methylresorcinol (1.82 mmol) and aldehyde **1a–c** (1.82 mmol) in $CHCl_3$ (25 ml) and TFA (25 ml) was stirred under reflux for 12–24 h under an argon atmosphere. Then solvent was evaporated to dryness, and the residue was sequentialy recrystallized from acetone and ethanol to give the corresponding pure *rccc* and/or *rctt* isomers. The characteristics of compounds **2a**, **2′a**, **2b** are identical to those reported.[20,22]

‡ *Crystallographic data* for **2c**. $C_{88}H_{68}Cl_4O_{16}\cdot 8(C_2H_6OS)$, colorless plate crystal, M = 2148.24, triclinic, $P\bar{1}$, a = 13.4946(8), b = 13.8974(9) and c = 29.5591(17) Å, α = 83.247(2), β = 79.878(2) and γ = 69.859(2)°, V = 5113.7(5) Å^3, Z' = 1, d_{calc} = 1.395 g cm^{-3}, μ(MoKα) = 0.353 mm^{-1}. F(000) = 2256, 272849 reflections collected, 22312 unique, R_{int} = 0.0611, full-matrix least-squares on F^2, 1313 parameters, 0 restraints. Final indices R_1 = 0.0833, wR_2 = 0.1966 for 21162 reflections with $I > 2\sigma(I)$, goodness-of-fit on F^2 = 1.088, largest difference in peak and hole (2.953 and –1.650 e Å^{-3}), data completeness 0.999.

Single-crystal X-ray diffraction was performed on a Bruker D8 QUEST three-circle diffractometer with a PHOTON III area detector and an IμS DIAMOND microfocus X-ray tube at 100(2) K: λ(MoKα) = 0.71073 Å, ω/φ scanning mode with a step of 0.5°. Data collection and indexing, determination, and refinement of the unit cell parameters were carried out using the APEX3 software package. Numerical absorption correction based on the crystal shape, additional spherical absorption correction, and systematic error correction were performed using the SADABS-2016/2 software.[26] The structures were solved by the intrinsic phasing method using the SHELXT-2018/2 program[27] and refined by full-matrix least-squares on F^2 using the SHELXL-2018/3 program.[28] Nonhydrogen atoms were refined anisotropically. Positions of H(O) hydrogen atoms were determined from difference electron density maps and refined isotropically. The positions of hydrogen atoms of methyl groups were inserted using the rotation of the group with idealized bond angles. The remaining hydrogen atoms were refined using a riding model. Most calculations were performed using the WinGX-2021.3 software package.[29]

CCDC 2263882 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

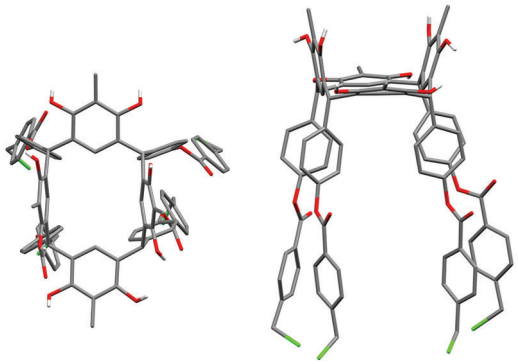


Figure 1 Two projections of the molecule in the crystal of **2c**. Hydrogen atoms (excluding those of the hydroxyl groups) and solvent molecules are omitted for clarity.

crystal X-ray diffraction (Figure 1).‡ Compound **2c** crystallizes in the $P\bar{1}$ space group with eight DMSO molecules. The molecule in the unit cell is located in the *boat* conformation. All the DMSO molecules are located outside the pseudocavities of the calixarene molecule and seven of them form hydrogen bonds with hydroxy groups of horizontally directed resorcinol moieties and vertically directed ones.

In conclusion, we have demonstrated that the condensation of 2-methylresorcinol with some functionalized benzaldehydes in chloroform with the increased content of TFA (1 : 1, v/v) increases the total yield of *rccc* and *rctt* diastereomers of the corresponding calix[4]resorcinols due to the improvement of the solubilizing ability of such reaction medium, increases the content of *rccc* isomer (up to quantitative), and decreases the time of reaction. Thus, the mentioned conditions can be recommended for the synthesis of various functional derivatives of calix[4]resorcinols in order to enhance the process and preferentially obtain *rccc* diastereomers of these macrocyclic compounds, which are highly promising for subsequent studies as compared to corresponding *rctt* isomers.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.10.035.

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