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Synthesis of fluorinated acid-functionalized, electron rich nickel porphyrins

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Abstract

In this study, novel fluorinated, carboxylic acid esters of the generic structure: $TfO\text{-}CH_2\text{-}(CF_2)_n\text{-}COOCH_3$ (n = 2,4,6, Tf = triflate) were synthesized. The triflates were reacted with 2-hydroxy-3,4,5-trimethoxybenzaldehyde via Williamson ether syntheses. The resulting electron-rich compounds were used as aldehydes in the Rothemund reaction with pyrrole to form ester-substituted porphyrins. After metalation with $Ni(acac)_2$ and hydrolysis electron-rich porphyrins were obtained, that are equipped with covalently attached long chain acid substituents. The target compounds have potential applications in catalysis, sensing, and materials science. The fluorinated aliphatic carboxylic acids ($TfO\text{-}CH_2\text{-}(CF_2)_n\text{-}COOCH_3$) with triflate as leaving group in terminal position are easily accessible and versatile building blocks for binding long chain acids (pK_a 0-1) to substrates in Williamson ether-type reactions.

Keywords

Nickel porphyrin; acid-functionalized porphyrin; electron-rich porphyrin; perfluorinated aliphatic carboxylic acids; porphyrin synthesis.

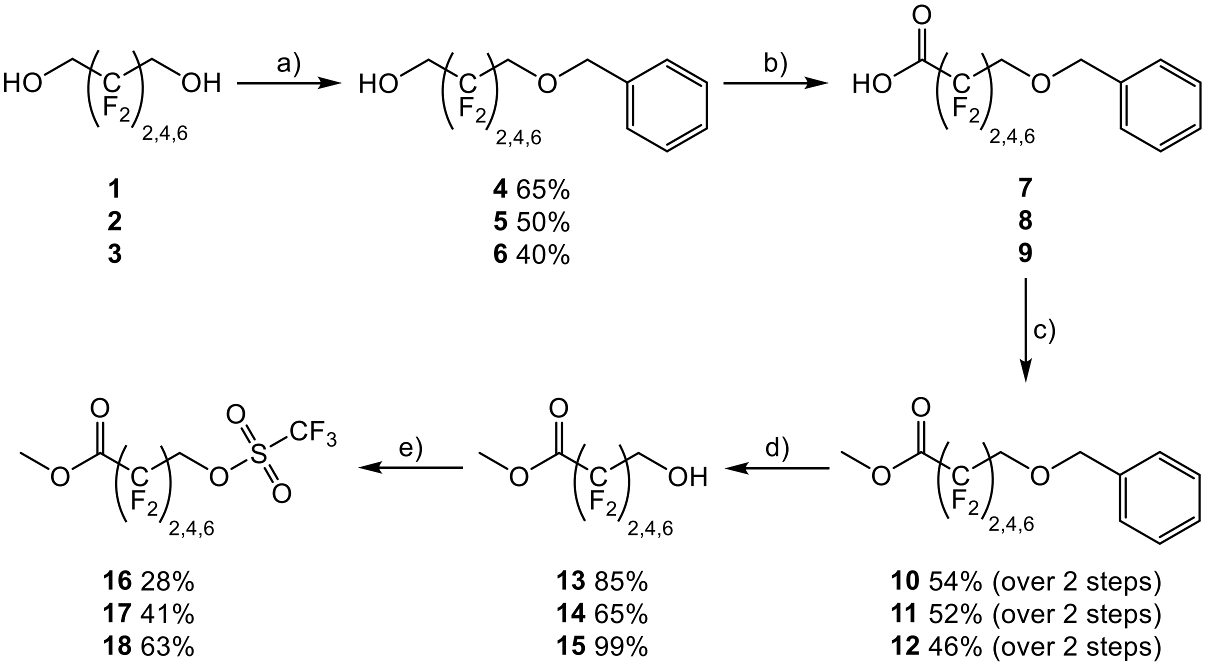
Introduction

Metal-porphyrins are prosthetic groups in a number of essential biomolecules, including hemoglobin, chlorophyll, and cytochromes, supporting processes such as oxygen transport, photosynthesis, and electron transfer.[1–5] Beyond their essential biological roles, porphyrins and their derivatives are employed in a number of applications, acting as catalysts in numerous reactions, including oxidation, reduction, and cycloaddition.[6–10] Particularly when electron rich porphyrins act as reducing agents, e.g. in electrocatalytic hydrogen evolution reactions, a proton source is needed.[11] Trifluoroacetic acid is very frequently chosen as the proton source, because it is a strong acid but just not strong enough to destroy (demetallate) the Ni porphyrin.[10] Covalent attachment of acids facilitates proton transfer and increases the efficiency.[12] Three conditions should be met for the target porphyrins of this study. 1. the acid covalently bound to the porphyrin should have an acid strength similar to trifluoroacetic acid. 2. the length of the tether with which the acid group is bound should be sufficient to serve as a proton source for redox reactions at the metal. 3. the electronic properties of the porphyrin, especially the low oxidation potential, should not be increased. We have chosen fourfold meso 3,4,5-trimethoxyphenyl-substituted Ni-porphyrin as the electron-rich system. The post-synthetic modification of this porphyrin proved to be difficult. Therefore, we have integrated the acid groups into the aldehyde component and prepared the porphyrin according to Rothemund. In initial tests, we have established that trifluoroacetic acid can be replaced by perfluorinated alkyl carboxylic acids (JACS paper). It was therefore obvious to use a perfluoroalkyl chain as a tether.

However, a perfluoroalkyl chain as a substituent on the porphyrin has an electron-withdrawing effect and thus a negative influence on the oxidation potential. We have therefore inserted an O-CH2 group between the phenyl group of the porphyrin and the perfluoroalkyl chain. The oxygen atom, especially in the 2-position, should even improve the electronic properties of the porphyrin.

Results and Discussion

Our synthesis starts with the readily available fluorinated symmetric diols HO-CH2-(CF2)*n*-CH2-OH (*n* = 2,4,6, see Scheme 1).

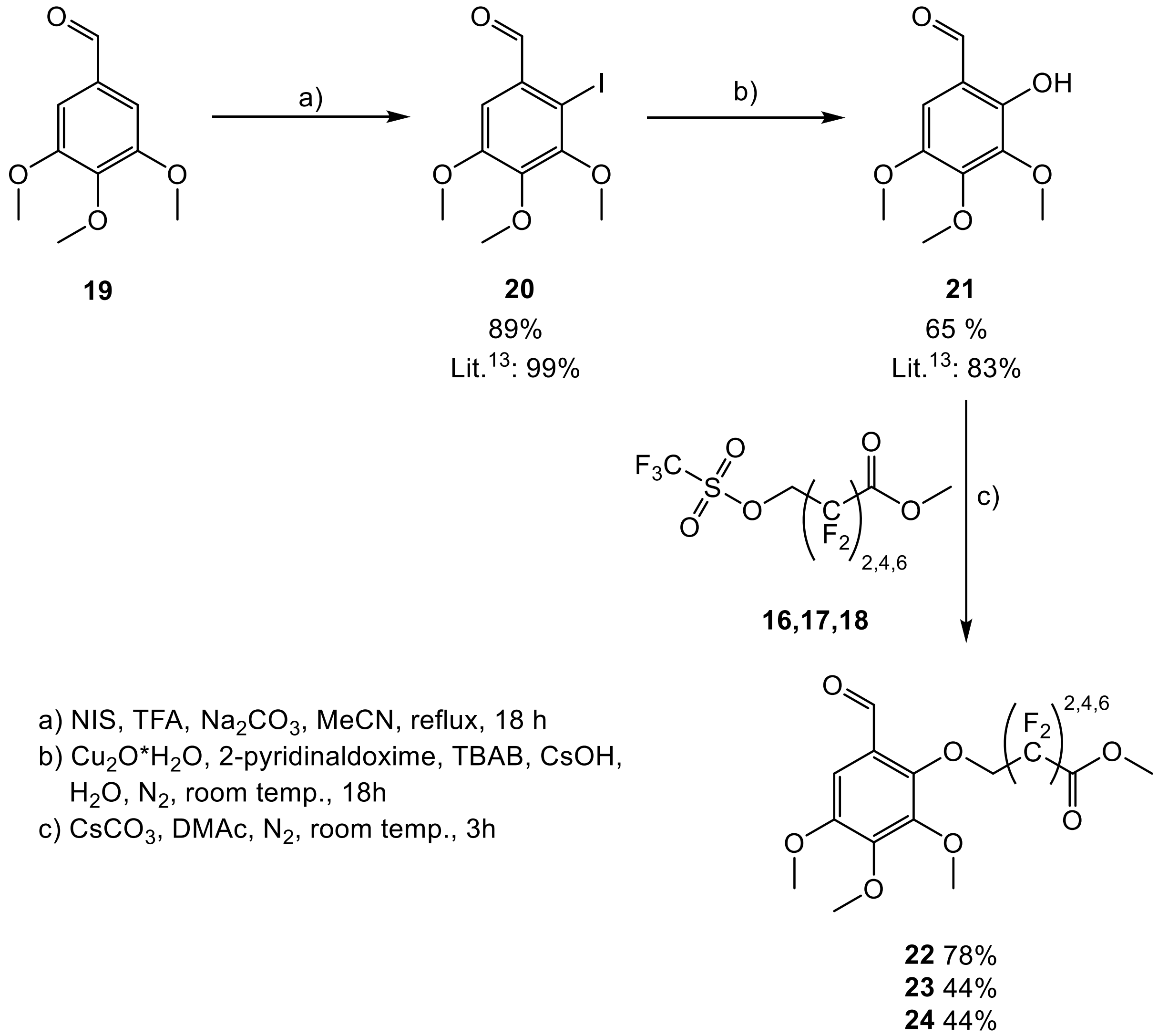


a) K_2CO_3, benzyl bromide, abs. MeCN, N_2, reflux, 18h
b) TEMPO, KBr, NaOCl, $NaHCO_3$, MeCN, room temp., 76h
c) MeOH, H_2SO_4, Reflux, 2h
d) Pd/C, H_2, EtOH, room temp., 20 h
e) Tf_2O, pyridine, DCM, room temp., 18h

Scheme 1: Synthesis of the starting materials **16**, **17**, **18** for the subsequent Williamson ether synthesis with 2-hydroxy-3,4,5-trimethoxybenzaldehyde **21**.

In order to break the symmetry and to generate the acid function only on one side, benzyl protection was performed. From diols **1**, **2** and **3** statistical mixtures of unprotected, mono- and di-protected products were obtained. However, isolation of the mono-protected products **4** (65%), **5** (50%) and **6** (40%) by chromatography was straightforward. However, the subsequent oxidation of the alcohol with the usual oxidizing agents (Jones reagent, $KMnO_4$ etc.) was not successful. A radical oxidation with TEMPO, potassium bromide (KBr), sodium hypochlorite (NaOCl), and sodium bicarbonate ($NaHCO_3$) provided the free acids **7**, **8** and **9**. Work-up and isolation proved to be difficult, therefore the acids were converted into the methyl esters **10** (54%), **11** (52%) and **12** (46%). The benzylidene protecting group was removed hydrogenolytically to give the products **13** (85%), **14** (65%) and **15** (99%). The alcohols were converted to the triflates **16** (28%) **17** (41%) and **18** (63%).

We have chosen 3,4,5-trimethoxybenzaldehyde (**19**) as the aldehyde component due to its commercial availability. An OH group was introduced to serve as the nucleophile in a Williamson ether synthesis with the triflates (**16**, **17** and **18**, see Scheme 2).

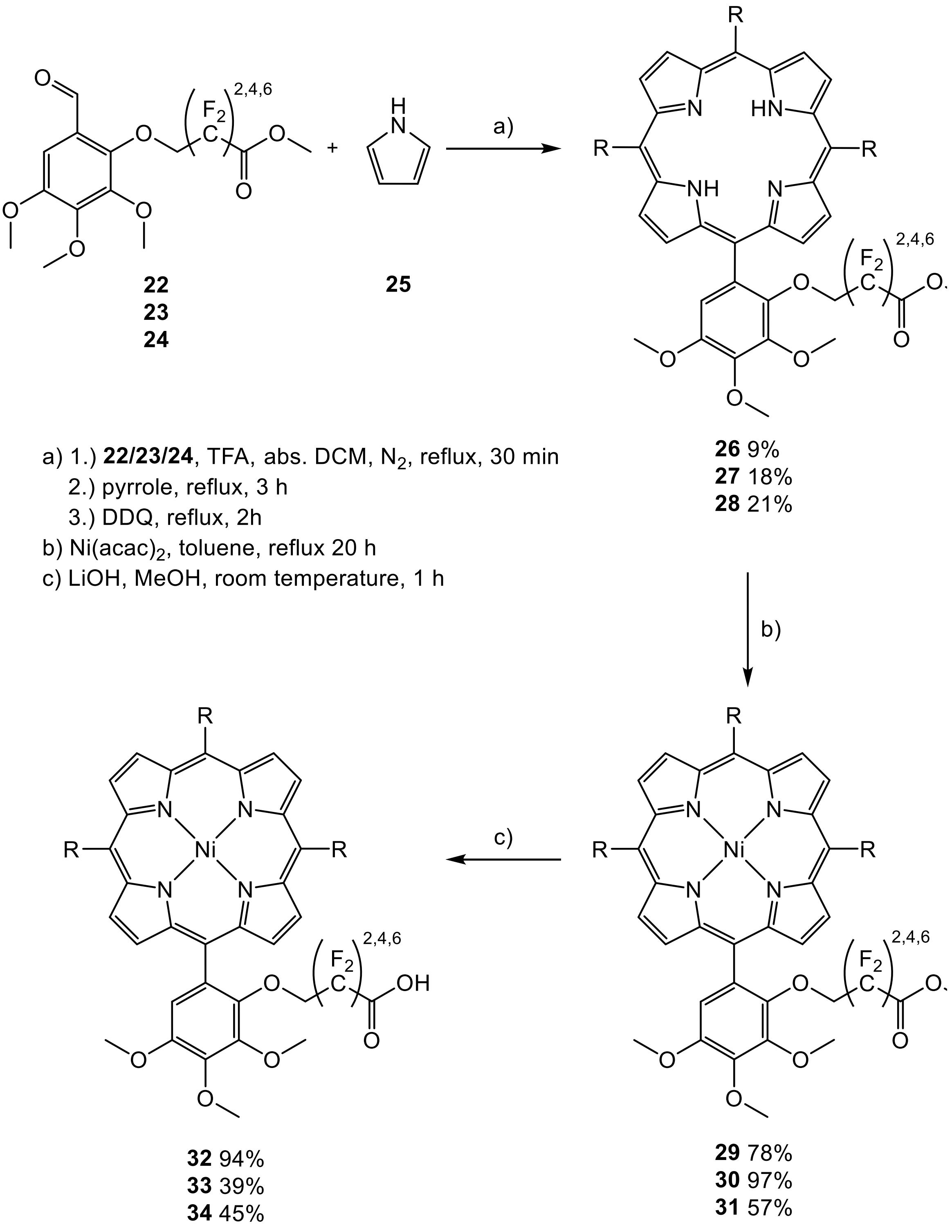


a) NIS, TFA, Na_2CO_3, MeCN, reflux, 18 h
b) Cu_2O*H_2O, 2-pyridinaldoxime, TBAB, CsOH, H_2O, N_2, room temp., 18h
c) $CsCO_3$, DMAc, N_2, room temp., 3h

Scheme 2: Synthesis of perfluoroalkyl ester functionalized aldehydes (**22**, **23** and **24**).

Towards this end, 3,4,5-trimethoxybenzaldehyde **19** was iodinated using *N*-iodosuccinimide (NIS) in *ortho* position in a yield of 89% (**20**).[13] To convert the iodo to an OH group, (**20**) was reacted with Cu(I)O, 2-pyridinaldoxime and CsOH to give 2-hydroxy-3,4,5-trimethoxybenzaldehyde (**21**, 65%).[13] In a subsequent nucleophilic substitution, the fluorinated alkyl chains of **16**, **17** and **18** were linked via a Williamson ether synthesis to yield **22** (78%), **23** (44%) and **24** (44%).

22, **23** and **24** were used as aldehyde components in the Rothemund-type synthesis of metal-free porphyrins **26** (9%), **27** (18%) and **28** (21%) (see Scheme 3).



22
23
24

25

26 9%
27 18%
28 21%

29 78%
30 97%
31 57%

32 94%
33 39%
34 45%

a) 1.) **22/23/24**, TFA, abs. DCM, N_2, reflux, 30 min
2.) pyrrole, reflux, 3 h
3.) DDQ, reflux, 2h
b) $Ni(acac)_2$, toluene, reflux 20 h
c) LiOH, MeOH, room temperature, 1 h

Scheme 3: a) Rothemund porphyrin synthesis of metal free porphyrins **26**, **27** and **28**; b) metalation of porphyrins with $Ni(acac)_2$; c) ester hydrolysis to generate the free acids **32**, **33**, **34**.

Metalation was achieved with nickel acetylacetonate to obtain the ester-substituted Ni-porphyrins **29** (78%), **30** (97%) and **31** (57%). The free acids were obtained with LiOH and HCl to give the free acids **32** (94%), **33** (39%) and **34** (45%).

Conclusion

This study reports the synthesis of perfluoro alkyl carboxylic esters with CH_2-OTf groups in ω position of the type: $TfO-CH_2-(CF_2)_n-COOCH_3$ (n = 2,4,6, Tf = triflate). The latter compounds were used in Williamson ether reactions with 2-hydroxy-3,4,5-trimethoxybenzaldehyde (**21**) to prepare the aldehyde component for a Rothemund-type porphyrin synthesis of acid functionalized electron rich porphyrins. The corresponding Ni porphyrins are potential compounds for electrocatalysis and sensor applications. The ω-triflated, perfluoroalkylated carboxylic acids (**16**, **17** and **18**) are easily accessible and versatile building blocks for binding long chain acids (pK_a range between 0 and 1) to substrates in Williamson ether-type reactions.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data of all products, copies of ^{1}H, ^{13}C and ^{19}F spectra, https://www.Beilstein-journals .org/bjoc……….

Acknowledgements

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Author Contributions

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Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information to this article.

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