Application of Ruppert's reagent in preparing novel perfluorinated porphyrins, chlorins and bacteriochlorins

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A first report to demonstrate the utility of (trifluoromethyl)trimethylsilane as an efficient reagent for the synthesis of perfluorinated porphyrins, chlorins and bacteriochlorins is presented.

Photodynamic therapy (PDT) has now emerged as one of the promising strategies in cancer treatment.[1] In this therapy, patients are given intravenous injections of a porphyrin-based drug that accumulates in cancer cells in generally higher concentrations than in surrounding tissue. The photosensitizing agent is then activated by a visible or near IR light to cancer sites through fiber optics which following energy transfer to molecular oxygen produces the singlet state oxygen, the putative cytotoxic agent. PDT is thus a novel and potentially important form of cancer therapy. The worldwide approval of Photofrin (a porphyrin-based photosensitizer) for the treatment of various types of cancers has created considerable interest among physicians, chemists, biologists and physicists. This interest has spawned considerable research in understanding the basic structural and chemical characteristics of effective photosensitizers for photodynamic therapy. Our group and others have been carrying out research in this area for several years to understand how pharmacokinetic and pharmacodynamic characteristics of photosensitizers control their photosensitizing activity.[2]

The importance of the effect of fluorinated substituents in general, and the trifluoromethyl group in particular, on biological activity is well known, but efficient selective methods for the incorporation of the group into a substrate are few in number.[3] In recent years, with an increased understanding of the behavior of organofluorine compounds, considerable progress has been made in the development of new synthetic methodologies.[3] Many organofluorine derivatives have been used as probes for studying biochemical processes. First, fluorine and hydrogen are comparable in size (the van der Waal's radii of F and H are 1.35 and 1.1 Å, respectively). Thus, whereas a particular molecule and its fluoro analogs would be sterically almost indistinguishable to a guest molecule, their chemical behavior could be different from one another. Second, the high C–F bond energy, which averages about 116 kcal mol^{-1}, leads to enhanced thermal stability.[3,4] Finally, fluorine substitution can increase lipid solubility, and this increases the rate of transport of biologically active compounds across lipid membranes.[5] Thus, various non-porphyrin based perfluoroalkyl, especially trifluoromethyl-substituted compounds have been examined for their ability to enhance transport rate *in vivo*.

For quite some time one of our objectives has been to develop an efficient methodology which can be utilized to prepare a wide variety of fluorinated porphyrin-based photosensitizers. Our interest in these compounds was to determine their utility in investigating the pharmacokinetic profile by ^{19}F NMR studies[6] as well as understanding the effects of fluoroanalogs on photodynamic activity. While photosensitizer concentration in tissue may be determined by chemical extraction techniques, these methods are invasive, time consuming, and clinically not feasible. *In vivo* NMR is noninvasive, safe and the effect of photodynamic therapy can be monitored over time in a single living system.

In porphyrin chemistry, most of the fluorinated analogs (in which perfluoroalkyl groups are substituted at the peripheral or at the *meso*-positions) have been prepared by total synthesis.[7] Compared to the non-fluorinated analogs the corresponding fluorinated derivatives generally have shown improved PDT efficacy.[8] For making PDT more effective as well as economical, efforts are being made by various investigators to prepare long wavelength photosensitizers (650–800 nm) with required photophysical properties.

Encouraged with the results obtained from the fluorinated porphyrin derivatives, we were interested in developing an efficient methodology for the preparation of fluorinated chlorin and bacteriochlorin analogs as improved photosensitizers for PDT. Although there are several examples for introducing perfluoroalkyl groups into compounds containing carbonyl substituents, these procedures are seldom applicable to trifluoromethylation in porphyrin systems. However, we found that trifluoromethyltrimethylsilane ($TMSCF_3$), a reagent developed by Prakash and Olah,[9] also known as Ruppert's reagent[10] is quite efficient in converting the carbonyl porphyrins into the corresponding fluorinated analogs. In our initial attempts, *meso*-formyl-octaethyl porphyrin [Ni(II) complex **1**, free base **2**] were used as substrates and reacted with $TMSCF_3$ in the presence of a catalytic amount of tetrabutylammonium fluoride (Scheme 1). After standard workup, the corresponding fluorinated trimethylsiloxy analogs **3a** and **4a** were obtained in 98% and 95% yield respectively. Reaction of **4b** with tetrapropylammonium perruthenate–*N*-methylmorpholine *N*-oxide[11] furnished a novel *meso*-trifluoroacetylporphyrin **5** in quantitative yield.

Having established that (perfluoroalkyl)trimethylsilane is an efficient reagent to prepare perfluoroalkyl-substituted porphyrins, we set out to explore the utility of this reaction with other substrates. In the chlorin system, we first examined 3-formyl *N*-hexyl purpurin imide **6**,[12] which on reaction with $TMSCF_3$ produced the corresponding trifluoro analog **7** as a sole product in 93% yield (Scheme 2); the trifluoromethylation of the fused imide ring system did not occur.

To further illustrate the viability of this reaction as a practical strategy for the preparation of fluorinated analogs of hindered ketones, ketochlorin **9** and diketobacteriochlorin **13** were used as substrates which in turn were prepared from octaethylporphyrin and etioporphyrin I respectively.[13] Reaction of compounds either as a free base or as the related metal analog afforded the expected trifluoromethyl derivatives in 82% and 74% yield respectively. Interestingly, Zn(II) bacteriochlorins **13** and the related free base analog **14** containing two keto groups at the diagonal pyrrole units, under various reaction conditions afforded only the monotrifluoromethyl analog and the expected corresponding bis(trifluoromethyl) bacteriochlorin was not isolated (Scheme 3).

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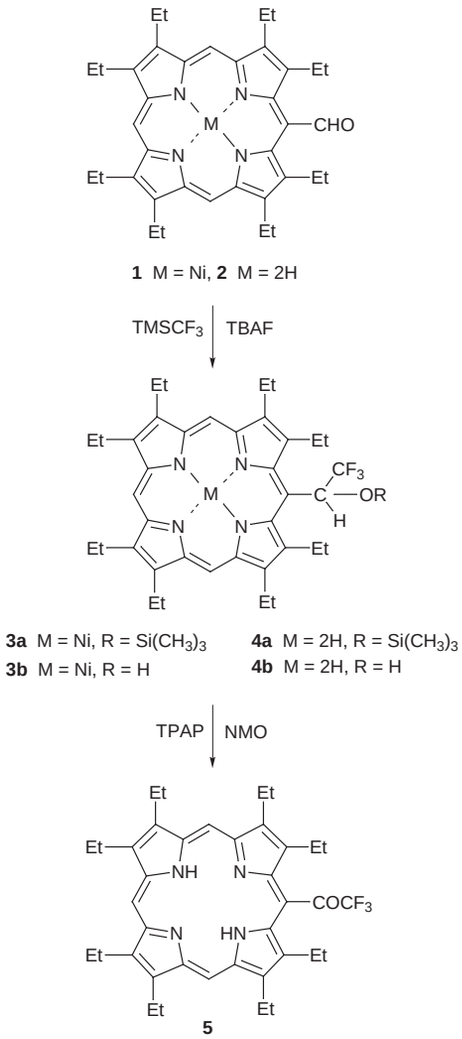
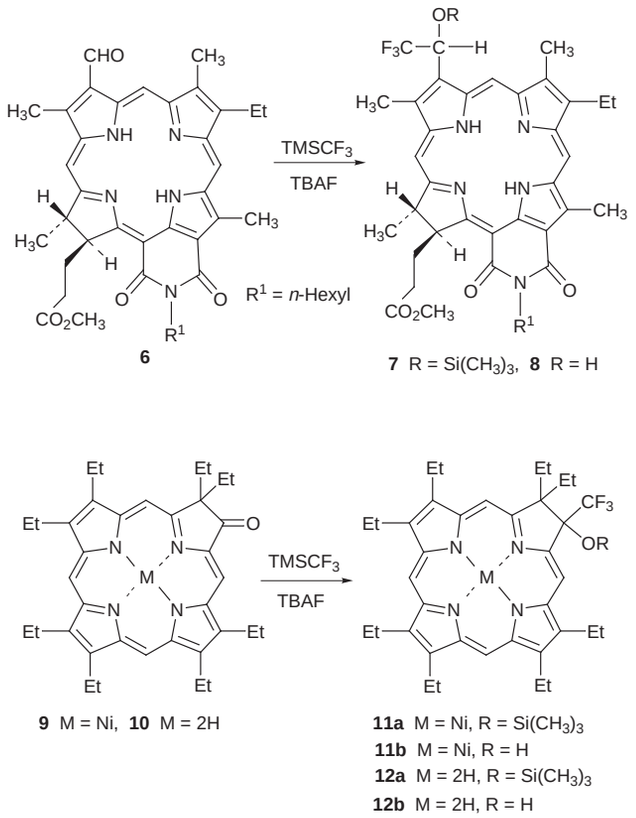


Scheme 1 Preparation of fluorinated porphyrins.

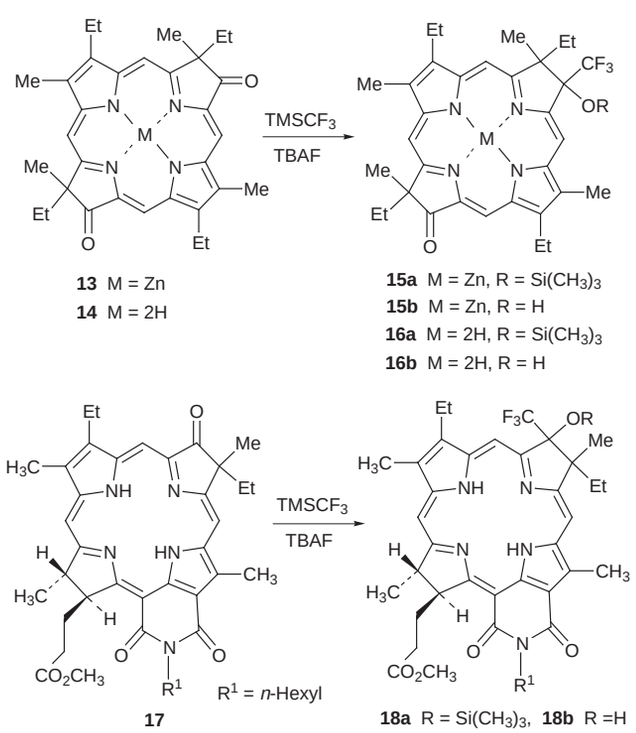
The utility of this reaction was further explored in keto-bacteriochlorins **17** isolated from the isomeric mixture obtained *via* the pinacol–pinacolone reaction of 7,8-*vic*-dihydroxy-bacterio-chlorin.[14] Reaction of 7-ketobacteriochlorin **17** with $TMSCF_3$ produced the corresponding trifluoromethylsiloxy analogs **18** in 92% yield. In all these compounds, the siloxy analogs could easily be converted into the corresponding hydroxy derivatives by reacting either with a large excess of tetrabutylammonium fluoride or hydrolyzing with aqueous HCl. The mechanism for the formation of various fluorinated porphyrins is similar to that discussed by Olah and co-workers for other carbonyl compounds.[3]

In porphyrin and chlorin systems we have shown that overall lipophilicity of the molecules plays an important role in PDT efficacy, and can be altered by introducing alkyl ether side chains with a variable number of carbon units.[2,15] The availability of various fluorinated chlorins and bacteriochlorins containing hydroxy groups has now provided us a unique opportunity to synthesize a series of alkyl ether analogs for comparison with the non-fluorinated analogs. ^{19}F NMR can be used to provide the pharmacokinetic profiles of an entire series of congeneric photosensitizers including both active and inactive analogs, thus, greatly increasing our ability to study mechanistic aspects of *in vivo* photodynamic therapy.

The methodology discussed here also illustrates the first example of the utility of the $TMSCF_3$ reagent for introducing a trifluoromethyl group at the *meso*-position of the porphyrin macrocycle. Electron deficiency created at the metal center has been shown to increase the catalytic activity of porphyrinato-iron(III) complexes towards hydroxylation of alkanes by oxygen and other oxidants.[16] The electron-withdrawing groups most commonly employed at the *meso* positions of the porphyrins



Scheme 2 Preparation of fluorinated chlorins.



Scheme 3 Preparation of fluorinated bacteriochlorins.

are the perhalophenyls and perfluoroalkyl groups obtained by total synthesis.[17] However, the reaction of porphyrin **4b** (obtained by treating the related formyl analog with $TMSCF_3$), with tetrapropylammonium perruthenate (TPAP)–*N*-methyl-morpholine *N*-oxide (NMO) provides the first example of introducing the trifluoroacetyl group at the *meso* position of the porphyrin system **5**.

In summary, the procedure described here allows a straightforward synthesis of various fluorinated porphyrin-based systems, which are otherwise difficult to synthesize. This is also

the first example to show the importance of (trifluoromethyl)-trimethylsilane as a versatile fluorinating reagent in porphyrin-based systems. Efforts aimed at exploring the utility of this methodology for the preparation of other fluorinated chlorin and bacteriochlorin compounds and their use as photosensitizers in PDT are currently underway.

All new compounds were characterized by NMR (^{1}H, ^{19}F, ^{13}C) and mass spectrometry analyses.

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