Tetrahedron 74 (2018) 3707–3711

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Facile iodination of the vinyl groups in protoporphyrin IX dimethyl ester and subsequent transformation of the iodinated moieties

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ARTICLE INFO

Article history:
Received 18 April 2018
Received in revised form
10 May 2018
Accepted 15 May 2018
Available online 18 May 2018

Keywords:
Acetylation
Chlorophyll-a
Iodination
Iodoether
Protoporphyrin-IX

ABSTRACT

Iodination of protoporphyrin IX dimethyl ester using phenyliodine bis(trifluoroacetate) (PIFA) and I_2 was studied. Iodine added to both the C3- and C8-vinyl groups equally to afford the iodohydrin or iodoether in the presence of water or alcohol, respectively. Any *meso*-hydrogen atom was not substituted by an iodine atom under these conditions, although both the vinyl group and one of the *meso* positions of methyl pyropheophorbide-*a* bearing a chlorin π-system, a chlorophyll-*a* derivative, was modified with PIFA and I_2. The reaction intermediates derived from the porphyrin were more reactive than those from the chlorin and liable to form intermolecular linkages. The obtained 2-iodo-1-hydroxyethyl group was transformed into a formyl group by a mild treatment. The corresponding iodoether moiety was readily converted into the acetyl group under basic conditions. These transformations were also applicable to smaller olefins such as styrene.

1. Introduction

Iodination is a key reaction in organic synthesis and medicinal chemistry. Organoiodine compounds are employed in various reactions, including substitution and cross-coupling reactions.[1–3] Furthermore, ioversol, which contains a triiodophenyl group, is used as an X-ray contrast agent for computed tomography. Thyroid hormones thyroxine and triiodothyronine also contain iodophenyl groups. Consequently, new iodination methods with improved applicability, efficiency, and green chemistry are still extensively researched.[4–13]

Natural tetrapyrroles such as chlorophylls (Chls), protoporphyrin IX (PP-IX), and their derivatives have been studied as photosensitizers for photodynamic therapy,[14–16] artificial photosynthesis, and dye-sensitized solar cells.[17–21] Alteration of the C3-vinyl group in Chls is of considerable interest because this group has great influence on the photophysical properties of Chls.[22–28] However, there are few reports on the iodination of the vinyl groups of these tetrapyrroles. Although introduction of ^{131}I to the C3[2] and C8[2] positions of PP-IX and the pharmacokinetics of this iodinated porphyrin in mice were reported in 1960,[29] details of the pigment were not provided.

Wang et al. reported that the C20 position (one of the *meso* positions) of Chl derivative **1** (Scheme 1) was iodinated using phenyliodine bis(trifluoroacetate) (PIFA) and I_2 while leaving the C3-vinyl group unreacted.[30] Furthermore, there are no reports on the transformation of the peripheral iodinated groups derived from natural tetrapyrroles except for our late observation.

We have recently published some reports on the iodination of Chl derivative **1** (Scheme 1).[31–33] It was demonstrated that an iodine atom was selectively introduced at the C3-vinyl group or the C20 position of **1** by simply changing the reaction stoichiometry of PIFA and I_2. Furthermore, iodohydrin **4** was transformed to the epoxide **5** by treatment with ethylenediamine, and **5** was reacted with an acid and $NaIO_4$ to afford 3-formyl-chlorin **6**. Interestingly, the treatment of iodoether **7** with a base converted to **8** bearing the C3-acetyl group, which had, to the best of our knowledge, not been previously reported. These are useful alternatives to previous synthetic routes. For examples, hazardous OsO_4 was previously required to prepare **6** from **1**[34]; direct epoxidation of **1** to **5** with mCPBA is impossible, so the synthesis of **5** was accomplished using the Corey-Chaykovsky reaction of **6**[35]; and tetrapropylammonium perruthenate (TPAP) was required for oxidation of the 1-

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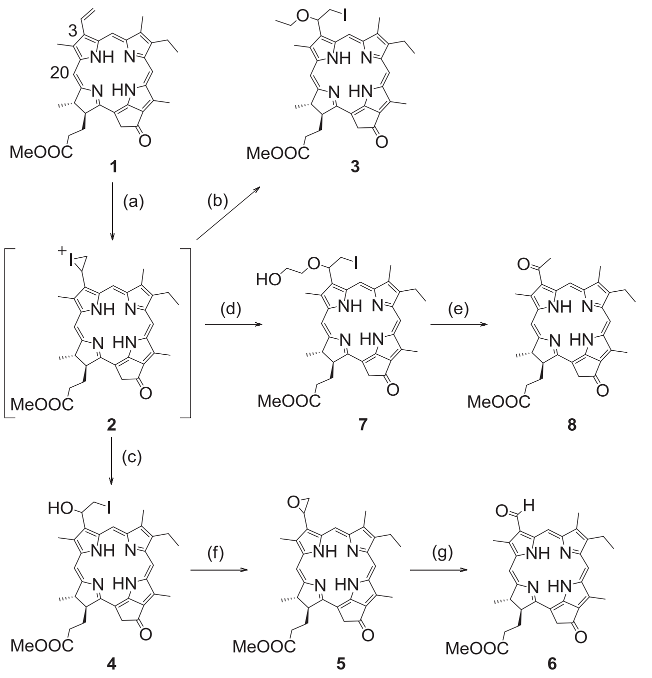
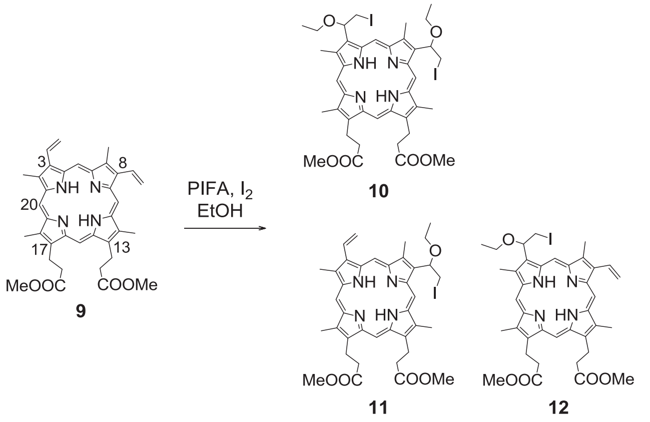
https://doi.org/10.1016/j.tet.2018.05.040



Scheme 1. Conversions of the vinyl group in chlorophyll derivative **1**. (a) PIFA (0.5 eq.), I_2 (1 eq.), 1,2-dichloroethane, r.t.; (b) EtOH, r.t.; (c) morpholine, r.t.; (d) ethylene glycol, r.t.; (e) (i) NaOH, THF/H_2O, r.t., (ii) H_2SO_4/MeOH, r.t.; (f) ethylenediamine, 1,2-dichloroethane, r.t.; (g) TsOH, $NaIO_4$, THF/H_2O, r.t.

hydroxyethyl derivative obtained by hydrobromination and subsequent hydration of **1** to prepare **8**.[36]

Despite the fact that the iodination of the two vinyl groups in PP-IX would potentially widen the application of cyclic tetrapyrroles and their related compounds, very little has been published on such a transformation. Furthermore, derivatization of the resultant peripheral iodinated groups has not been explored. Based on their structural similarities, we expect that PP-IX would undergo the same reactions that Chl derivatives did. Although their reactivities are not the same. Consequently, herein we report our findings on the iodination of a PP-IX derivative **9** (Scheme 2) as well as the subsequent epoxidation, formylation, and acetylation of the product. Visible absorption and fluorescence spectra of the iodinated porphyrin are presented. Styrene was employed to investigate the scope of these reactions, and a possible mechanism of the acetylation *via* the iodoether is also discussed.



Scheme 2. Iodoetherification of protoporphyrin-IX dimethyl ester (**9**). PIFA (0.5 eq.), I_2 (1.0 eq.), EtOH/1,2-dichloroethane.

2. Results and discussion

First, we investigated the iodoetherification of the vinyl groups in PP-IX dimethyl ester (**9**) using the homogeneous conditions under which chlorin **1** was found to be iodinated efficiently (Table S1). Accordingly, compound **9** was stirred with PIFA (0.5 eq.) and I_2 (1 eq.) in 1,2-dichloroethane for 1 h at room temperature. Ethanol (EtOH) was then added, and the mixture was additionally stirred for 2 h at room temperature. Unexpectedly, whereas chlorin **1** was successfully iodinated under these conditions, we obtained very little of the iodinated porphyrins **10**, **11**, or **12**. The ^{1}H NMR signals of the products were too broad to be resolved, suggesting oligomerization of **9**. Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF-MS) analysis indicated the presence of some iodinated porphyrins ($m/z = 763$ and 935) as well as iodinated dimeric and trimeric components (*e.g.* $m/z = 1526$, 1698, 2288, and 2461; Fig. S1). Interestingly, the reaction of **1** did not give dimers and trimers under the same conditions.

We assumed that the iodonium intermediates derived from porphyrin **9** are more reactive than those from chlorin **1**. Consequently, we reacted **9** in the presence of EtOH to immediately trap the unstable intermediates and suppress the oligomerization. The reaction mixture was purified using silica gel column chromatography. The MS spectrum of the black products clearly showed ion peaks with m/z increments of 172 and 344 units, indicating addition of 1 and 2 eq. of EtOI to **9**, respectively. Reaction with double the amount of reagents (1 eq. of PIFA and 2 eq. of I_2) and EtOH afforded the 3,8-di(1-ethoxy-2-iodoethyl) derivative **10** in 80% isolated yield after purification with chromatography.

Fig. 1 shows the ^{1}H NMR spectra of these samples, thus obtained di-iodinated compound **10** and the mixture of **10** and the mono-iodinated porphyrins **11** and **12**. The spectrum for **10** lacks the vinyl proton signals observed for **9**, around 6.15–6.40 (C3^2 and C8^2) and 8.20–8.30 ppm (C3^1 and C8^1), while the broadened proton signal at 6.13 ppm (2H) is assignable to the C3^1 and C8^1 protons in 1-ethoxy-2-iodoethyl group. The two multiplets at 4.10 and

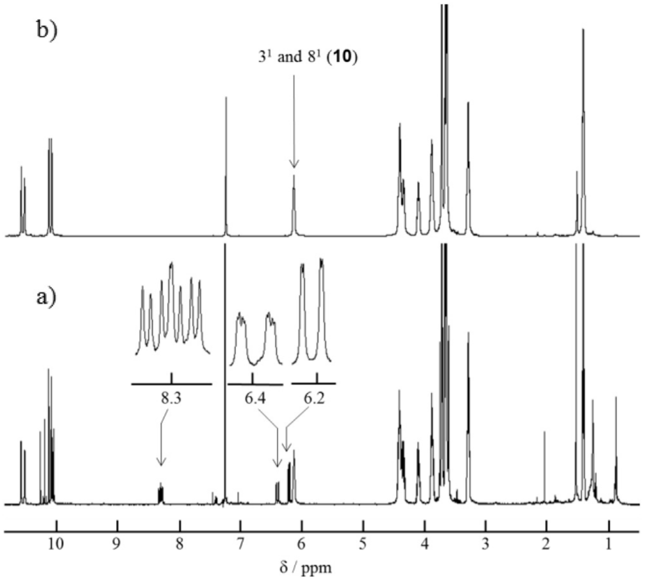


Fig. 1. ^{1}H NMR spectra of (a) **10** and (b) a mixture of **10**, **11** and **12**. The expanded portions show the vinyl proton signals for **11** and **12** in $CDCl_3$.