Review Article

Methods for the synthesis of symmetrical and unsymmetrical benzoporphyrins
(A Review)

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Abstract: Benzoporphyrin derivatives have an enormous potential for application in natural and applied sciences. They act as excellent model for photosynthetic reaction center. They are an intermediate between porphyrins and phthalocyanines. Synthesis of benzoporphyrins have remained a big challenge in the field of research. Various synthetic methodologies are used in the past thirty to forty years, several advances have been developed to overcome the previously used procedure. This review is intended to cover the important synthetic utility of TBPs.

Keywords: Benzoporphyrins; isoindoles; Diels-Alder reaction; CH acids

INTRODUCTION

Porphyrin and their complexes have received considerable attention, because of their interesting excited state chemical properties, electron-transfer processes, biological processes, photo-physics and catalytic behaviours [1]. Porphyrins exist in various states in nature and act as centres of energy transfer and charge transfer processes. In nature, the photosynthetic reaction centers perform multistep electron transfer processes with high quantum efficiency and long lifetimes of the final charge separated states of around 1s [2]. From the structural point of view, the simplest representative of this class, tetrabenzoporphyrin (TBP), is an intermediate between “regular” nonextended porphyrins and phthalocyanines, partially retaining properties of both and providing a useful point in structure/property comparative studies. Tetrabenzoporphyrins have been studied substantially more than other extended porphyrins. Their unique photophysical [3,4], optoelectrochemical [5,6] and other physicochemical properties [7,8] have attracted interest in different areas.


Benzoporphyrin acts as a photochemical hole-burning material, since it gets oxidized easily than other porphyrins due to enlargement of π-conjugated system; therefore, it becomes a better photochemical hole-burning material. The synthesis and properties for photosynthetic reaction center model compounds was a subject of intensive research [14-16]. Because the electronic spectrum of benzoporphyrin is similar to that of chlorophyll [17], benzoporphyrin may become a better model compound of the photosynthetic reaction center than tetraphenylporphyrin.

Compared to regular porphyrins and phthalocyanines, the chemistry of tetrabenzoporphyrins and related
compounds has been little investigated. The meso-
substituted tetrabenzoporphyrins are now intensively
studied. However, studies on the properties and
applications of these macrocyclic compounds have often
been faced with difficulties because of the low solubility
in common organic solvents [18] and the poor
compatibility with polymeric materials. These solubility
problems may be overcome by introducing meso-
substituents as in the case of porphyrin, the solubility of
which is improved by tetraphenyl-substitution at the
meso-positions.

The symmetrical and unsymmetrical benzoporphyrins
can be synthesized by different approaches. Approaches to
the TBP system [19] can be divided as follows.

**Low-temperature synthetic approaches**

The first approach mimics the standard porphyrin
synthesis, i.e., condensation of pyrroles with meso-carbon
donors. This includes low-temperature synthesis of
tetrabenzoporphyrins by the condensation of aromatic
aldehydes with isoindole synthons where the benzene ring
is present in the latent form. The subsequent disclosure via
retro-Diels-Alder reaction [20-22] or oxidation [23] is
accomplished after formation of porphyrin ring (Scheme
1). However, the corresponding isoindole synthons (e.g.,
tetrahydroisoindoles) are fairly unstable and difficulty
accessible. So the use of such unstable synthons should be
avoided. To overcome such problem another approaches
were given in which use of bicyclooctadiene-fused pyrrole
were oxidized by thermal retro-Diels-Alder reaction [24].
But these methods still suffered from a common serious
drawback, which was the harsh conditions required for the
aromatization step (either prolonged heating of metallated
hexadecahydroTBP precursors with DDQ leading to
partial overoxidation in the tetrahydroisoindole method, or
heating over 200 °C to effect ethylene extrusion). Thus,
the scope of these approaches was limited, which resulted
in losses of valuable target porphyrins at the final stage of
a long synthesis. Use of 4,7-dihydroisoindole which is a
sofar-unknown simple pyrrole derivative as the precursor
for the synthesis of TBPs led to the spontaneous
aromatization of aneled rings and avoid the mild
reaction conditions of the final aromatization step [25]. Ito
et al proposed the synthesis of meso-Chlorinated
bicyclo[2.2.2]octadiene-fused porphyrins by chlorination
of the free base TBCODP-H₂ using N-chlorosucinimide
(NCS) followed by thermal retro-Diels-Alder reaction
[26].

**High temperature assisted template directed synthetic
approach:**

First representatives of this group of compounds
were reported in 1981 by Kopratenkov et al [27] who
synthesized the zinc complex of meso-
tetraphenyltetrabenzoporphine from phthalimide and
phenylacetic acid in the presence of zinc acetate. The
authors assumed formation of partially meso-substituted
products also, i.e., zinc complexes of mono-, di-, and
triphényltetrabenzoporphanines. Since the reaction mixture
consists of acetate ion as a source of methylene
component which explained the formation of side
products. Later on, the synthesis of meso-phenyl-
substituted tetrabenzoporphines was studied in detail by
Ichimura et al [28] By fusion of potassium phthalimide
with zinc phenylacetate at 360 °C for 1 h; the authors
obtained a mixture of zinc complexes of meso-
phenylsubstituted tetrabenzoporphines.

Moreover, the nature of such precursors and the
possibility for further transformations restricts the number
of substituents that could be introduced. The second group
of methods, which subsequently led to a much wider array
of TBP’s, stemmed from basic phthalocyanine
synthesis[3,29-30] In these methods the meso-carbons in
the porphyrin skeleton come not from electrophilic
carbons, as in traditional porphyrin condensations
(Rothmund/Adler-Longo/Lindsey), but from nuleophilic
CH acids. As a result, unstable isoindoles can be replaced
by readily available phthalimidines or their derivatives. One
version of this approach, developed by Lukyanets and co-
workers [31], appeared useful for the synthesis of
Ar₄TBP’s. According to their method, phthalimide is
condensed with CH acids (e.g. acrylatic acids) in the
presence of metal salts, which act as templates (Scheme 2
& 3).

However, the conditions required for the
condensation were so harsh (fusation at 350-400 °C) that
only inert substituents in the starting materials, such as
alkyl or halogen could sustain the procedure.

Zinc complexes of meso-tetraalkyltetra
benzoporphyrins were synthesized for the first time in
1984 following a three-step procedure utilizing
monoalkylmalonic acids as starting compounds [32].
However, the large number of steps and low accessibility
of the initial reagents stimulated search for more practical
methods for the synthesis of meso-
tetraalkyltetrabenzoporphyrins. It is known that metal
complexes of mesotetraaryltetrabenzoporphyrins can be
obtained by template condensation of phthalimide with
excess acrylatic acid in the presence of zinc(II)
hydroxide[33]. To synthesize zinc complexes of meso-
tetraalkyltetrabenzoporphyrins in such a way, i.e., by
reaction of phthalimide with excess aliphatic carboxylic
acid zinc salt, were successful only in the case of lower
carboxylic acids, propionic and butyric, while the
reactions with zinc(II) octanoate, decanoate, and
dodecanooate failed. Presumably, the reason is that it was
impossible to attain sufficiently high temperature (320–
330°C) which was necessary to complete the process
because of the low boiling point of the reaction mixture
(250–270°C). Various derivatives of TBPs such as alkyl,
alkoxy, aryl and triphenyl arloxy TBPs have been
synthesized via this method [34-35]
D-A denotes Diels-Alder reaction

Scheme 1: Reterosynthetic analysis of TBP systems

Scheme 2: Synthesis of benzoporphyrins
Synthetic approach of unsymmetrical tetrabenzoporphyrins

The available information on unsymmetrical tetrabenzoporphyrins is concerned mainly with meso-aryl-substituted derivatives [36-38] while those having no substituents in the meso positions have been studied to a considerably lesser extent. Monobenzoporphyrin and its metal complexes (which were detected for the first time in oil [39] and were then prepared by synthetic methods [40] may be regarded as first representatives of that group of compounds. The procedure proposed [41] is based on the Diels–Alder reaction of protoporphyrin IX dimethyl ester with dimethyl acetylenedicarboxylate, followed by elimination of the angular methyl group from the adduct. However, this procedure has a limited applicability; therefore, Sapunov et al [42] later proposed to obtain unsymmetrical benzoporphyrins by joint condensation of imides derived from two different ortho-dicarboxylic acids.
Scheme 4: Reagents and conditions: a, DMM, Py, 140 °C, pressure tube, 85%; b1, (i) PhSCI, CH₂Cl₂; (ii) Et₃N; (iii) Oxone, MOH, 86% for three steps; b2, (i) PhSCI, CH₂Cl₂; (ii) MCPBA; (iii) DBU, 81% for three steps; c, CNCH₂CO₂tBu, tBuOK, THF, Ar, 0 °C, 80–95%; d, TFA–CH₂Cl₂, Ar, rt, 35–40%; e, (i) Y = C₆H₄CHO, BF₃·Et₂O, CH₂Cl₂; (ii) DDQ, 25–35% for two steps; d + e, Y = C₆H₄CHO (X = H), AcOH, TosOH, CH₂Cl₂, 8–12%; f, (i) M(OAc)₂, MeOH–CHCl₃; (ii) DDQ, THF or MeCN, reflux, M = Zn, Cu, Ni, 98% for two steps.

A drawback of this method is that the reaction gives a mixture of porphyrins which are often difficult to separate on a preparative scale. The most reasonable procedure for the synthesis of unsymmetrical benzoporphyrines is likely to be stepwise condensation [44]. It is known that structurally related unsymmetrical porphyrazines containing both electron-donor and electron-withdrawing substituents and possessing a high dipole moment are very promising for use in various fields of science and techniques.

Gottumukkala et al synthesized water-soluble nido-carboranyl-TBP in six steps and 43% overall yield from butanopyrrole and carboranylbenzaldehyde using above mentioned approach [43].

Aza-derivatives of meso-alkyl substituted tetrabenzo[4]phenazines have been synthesized in literature with the purpose to determine the influence of nitrogen atoms in meso-positions of the tetrabenzo[4]phenazine macrocycle on the physico-chemical properties of porphyrines [45].


The molecular structure of the metallo-tetrabenzo[4]phenazines and H₂TBP are as follows. Benzene rings attached to the pyrroles provide the structural similarity of the tetrabenzo[4]phenazines to the phthalocyanines. The symmetric structure of MgTBP and ZnTBP puts them in the point group D₄h. According to Gouterman, the four-orbital model predicts a degenerate S₀ → S₁ transition (Q band) and a degenerate S₀ → S₂ transition (Soret or B band), where both transitions are localized in the molecular plane [46]. The strong Soret and Q bands arise in part from the delocalized nature of the π-electrons shared by the 18 or 16 conjugated bonds in the ring. The Q transition is made possible by configuration interaction mixing. The addition of the benzo groups to the basic porphyrin ring presumably plays an important role in the nature of the bands. The increased size of the TBPs over the basic porphyrin ring results in a predicted red shift of the Soret and Q bands by about 50 nm, utilizing the modified free electron molecular orbital method [47].

CONCLUSIONS

We have described the various synthetic approaches for tetrabenzo[4]phenazines. Above all mentioned methodology two major approaches came into light, one is low temperature and another is high temperature method. However high temperature is a harsh condition and gives rise to several side products but it is a one pot condensation while synthesis at low temperature includes number of steps which further reduces the yield of desired product. So synthesis of TBP is still a challenging field for researchers.

REFERENCES

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