Synthesis of Bullvalenes: Classical Approaches and Recent Developments

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Dedicated to the memory of Prof. Félix Serratosa, a pioneer of organic synthesis in Spain

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Abstract The goal of this short review is to provide an overview of the different synthetic methodologies applied along the years for the synthesis of bullvalenes, prototypical fluxional molecules that were key in the understanding of valence tautomerism phenomena. Some interesting applications of these unique shapeshifting compounds are also presented.

1 Introduction

Fluxional molecules are dynamic structures that rapidly interchange between a number of constitutional isomers through low-energy rearrangements. These shapeshifting molecules have been crucial in the study of the fundamental concept of valence tautomerization. This phenomenon is based on the rapid rupture and formation of single and/or double bonds without migration of atoms or groups. A classical example of a fluxional molecule is bullvalene (1), with chemical formula C_{10}H_{10}; this is also one of the most popular examples of this type of molecule. This molecule can be seen as a tetracyclic cage-type structure formed by three units of 3,4-homotropylidene that undergo rapid [3.3] sigmatropic rearrangements (Scheme 1).2,3

A molecule such as bullvalene (1), with ten distinguishable positions and three symmetry axes, possesses 1,209,600 degenerated interconvertible tautomers, thus it is a key structure in the understanding of valence tautomerization (Scheme 2).4–6 A lower number of constitutional isomers are possible for substituted bullvalenes.7–9

In bullvalene (1) all C–C bonds are in continuous movement due to multiple and fast degenerated Cope rearrangements. As a consequence, all carbon and hydrogen atoms of the molecule are equivalent on the nuclear magnetic resonance timescale, consisting of a single broad signal in the 1H NMR spectrum at room temperature and a sharp signal at high temperatures (ca. 120 °C) (Figure 1). However, at temperatures around –60 °C, the four aliphatic and the six olefinic protons of the molecule give rise to distinct signals.10

The structure and properties of bullvalene (1) were predicted by von Doering and Roth in 1963,11 as a part of a study on thermal rearrangements. These investigations led to the conclusion that the particular structure of bullvalene that forces its three 3,4-homotropylidene units to adopt a...
boatlike conformation would be ideal for fast and multiple degenerate Cope rearrangements assisted by strain release.\textsuperscript{11} Anecdotally, the name bullvalene was derived from the nickname of von Doering, known by his students as the ‘bull’, due to the feared and tough research group seminars, and was chosen to rhyme with fullvalene, another molecule of great interest for the group at that time.

Since the theoretical design of bullvalene (1) in 1963,\textsuperscript{1a} this unique molecule has attracted the curiosity of the organic synthetic community. Significant synthetic efforts have led to the development of expedient syntheses of 1 that have constituted the basis of extensive studies in bullvalene chemistry and have enabled the preparation of many substituted derivatives. The constant evolution of synthetic methodology has allowed considerably shortening of the preparation of 1 and its derivatives along the years, facilitating the access and exploration of these fluxional molecules.

## 2 Classical Syntheses of Bullvalenes

### 2.1 Preparation of Bullvalene

Shortly after the prediction of the structure and properties of bullvalene, this molecule was serendipitously obtained in 1963 by Schröder and co-workers while exploring the photochemistry of cyclooctatetraene dimers.\textsuperscript{4a–c} Despite the low overall yield (6%), this two-step synthesis of bullvalene (1), consisting of the dimerization of cyclooctatetraene (2) at 100 °C and subsequent photochemical opening of the dimer 3 (Scheme 3) with the consequential formation of benzene as byproduct, constitutes one of the shortest preparations of 1 to date.

In 1966, the von Doering group developed a different synthetic strategy for the preparation of bullvalene (1) via the UV irradiation of 4a,8a-dihydronaphthalene (5), prepared by thermal partial decomposition of the Nenitzescu hydrocarbon 4 at 301 °C.\textsuperscript{12} Although short, this synthesis...
was impractical due to the formation of naphthalene and other undetermined products that were difficult to separate from 1 (Scheme 4).

Another synthetic procedure designed by Jones and Scott was based on the UV irradiation of bicyclo[4.2.2]deca-2,4,7,9-tetraene (8a) to afford 1 cleanly in 64% yield.13 The main drawback of this protocol was the tedious synthesis of 8a, which was also low yielding.14 This preparation commenced with Cu(II)-promoted thermal decomposition of diazoacetic ester in the presence of cyclooctatetraene (2) to afford methyl bicyclo[6.1.0]nona-2,4,6-triene-9-carboxylate (6) (Scheme 5). Conversion of 6 into the sodium salt of tosylhydrazone 7 was accomplished via the corresponding acid, generation of the acid chloride, reduction to the aldehyde, and formation of the tosylhydrazone. Thermal decomposition of the tosylhydrazone sodium salt 7 at 90–120 °C led to a complex mixture of C10H10 products including 8a, which was obtained in 38% yield.

This synthesis, 1967, started with the Buchner reaction of ethyl diazoacetate with benzene under harsh conditions and long reaction times to give cycloheptatriene 11 (Scheme 8).15 Hydrolysis of the ester in 11 to the carboxylic acid, followed by reaction with SOCl2 led to the acyl chloride, which reacted with diazomethane to afford diazomethyl ketone 14. Treatment of 14 with CuSO4 in a mixture of benzene/hexane under reflux led to barbaralone (9a). In 1998, the Buchner reaction was improved by Johnston and co-workers by using a Rh salt as the catalyst, which allowed the temperature to be decreased to 45 °C and the reaction time reduced to 8–10 hours.16 One-carbon homologation of barbaralone (9a) with diazomethane led to bullvalone (10a) in 24% yield, along with isomeric aldehyde 10a′ (25% yield). Reduction of the ketone functionality of 10a with NaBH4 gave 15, which was acetylated with acetic anhydride in pyridine at 130 °C to form 16 (40%, two steps). The final step involved a challenging pyrolysis of 16 at very high temperature (345 °C) to afford bullvalene (1).

In 1972, a new synthesis of bullvalene (1) was designed by the Serratosa group (Scheme 9).17 This route allowed the preparation of 1 in three steps from tris(3-diazo-2-oxopropyl)methane [methane(tri-α-diazoacetone), 21]. Tris-diazoacetone 21 was synthesized in five steps from methyl ester 17 by Wittig reaction, reduction of the with Adams’ catalyst, hydrolysis of the esters, conversion into the acyl chloride with PCl5, and reaction with diazomethane.18 Reaction of 21 in the presence of CuSO4 in xylene at reflux under high dilution conditions afforded tricyclo[3.3.2.02,8]decane-

With the aim of improving his first synthetic design of bullvalene (1), the von Doering group envisioned a new synthetic route to 1 through barbaralone (9a) and bullvalone (10a), (Scheme 6).3b The aforementioned molecules 9a and 10a also undergo low energy Cope rearrangements, leading to two constitutional isomers respectively.6c,15

In the case of barbaralone (9a), the two possible isomers are degenerated, whereas for bullvalone (10a), the one carbon homologue of 9a, the equilibrium is dominated by the most stable isomer (Scheme 7).
3,7,9-trione (‘bullvalenetrione’, 22) in ca. 2% yield. The yield of this reaction could be improved to 4% by employing soluble copper chelates as catalysts. Despite the low yields, this is a remarkable transformation in which three C–C bonds are formed. Reaction of 22 with p-toluenesulfonyl hydrazide led to tris-tosylhydrazone 23, which was converted into bullvalene (1) in 20% yield by treatment with excess methylithium under Shapiro reaction conditions. Overall, this synthesis of 1 was completed in 8 steps and ca. 0.3% overall yield.

The Serratosa group developed another route to 1 inspired by the procedure of the von Doering group presented in Scheme 8 but applying some of the reactions employed in their first approach. In this route, barbaralone (9a) was prepared more efficiently from 14 by a modified procedure using copper(II) acetylacetonate as soluble copper catalyst (Scheme 10). Homologation of 9a with diazomethane led to 10a, which reacted with p-toluenesulfonyl hydrazide in acetic acid to give tosylhydrazone 24 in 70% yield through an unexpected rearrangement (see mechanism in Scheme 10). Anionic fragmentation of the tosylhydrazone 24 with excess methylithium gave 8a in 36% yield. Hydrocarbon 8a, reported by Jones and Scott in their approach to bullvalene (1) (see Scheme 5), was converted into 1 by UV irradiation in 82% yield. In this way, 1 was prepared in 9 steps in ca. 2% overall yield.

2.2 Syntheses of Substituted Bullvalenes

During the 1970s, progress made in the synthesis of bullvalene (1) led to numerous studies on its fluxional behavior along with the preparation of a variety of mono- and polysubstituted bullvalenes. The synthesis of substituted
bullvalenes was accompanied by interesting investigations, mainly based on NMR studies, on the study of their equilibria.21 Most substituted bullvalenes were synthesized from the parent unsubstituted bullvalene (1). Monosubstituted bullvalenes were normally derived from a common bromobullvalene intermediate 25 usually prepared in two steps by dibromination of 1 with Br₂ followed by dehydrobromination with KOTBu (Scheme 11).22 Chlorobullvalene (26) could be also synthesized similarly by chlorination with SO₂Cl₂ and subsequent elimination of HCl by reaction with KOTBu (Scheme 11).21

Phenylbullvalene (27) and methylbullvalene (28) were prepared from bromobullvalene (25) by reaction with Ph₂CuLi and Me₂CuLi, respectively (Scheme 13). Phenylbullvalene (27) was found to be in a 3:1 equilibrium between the 4- and 3-substituted isomers,24 whereas methylbullvalene (28) appeared to be in a 1:2:1 equilibrium between the 4- and 3-substituted isomers.25 Alternatively, methylbullvalene (28) was also synthesized by addition of methylmagnesium bromide and CoCl₂ to bromobullvalene.21 The preparation of (alkylthio)bullvalene 29 was achieved by refluxing bromobullvalene (25) with copper(I) mercaptides in pyridine and quinoline.26

The bullvalene Grignard derivative 30 was prepared by reaction of 25 with magnesium (Scheme 14).27 Reagent 30 was further transformed into bullvalenecarboxylic acid (31) by reaction with CO₂, dibullvalene (32) by reaction with bromobullvalene (25) in the presence of CoCl₂, and iodobullvalene (33) by reaction with I₂.21,27 Compound 33 was used as starting material for the synthesis of fluorobullvalene (34) by reaction with AgF.21

Monosubstituted bullvalenes possess around 1.2 × 10⁶ valence isomers, but in contrast to the parent bullvalene (1), all these isomers are not structurally equivalent. For monosubstituted bullvalenes there are four possible positional isomers A₁, A₂, B, and C (Scheme 12), which can be interconverted at room temperature by Cope rearrangements.21 The equilibrium between these four positional isomers is dynamic at high temperatures, although it can be frozen at low temperatures.24,22 The equilibrium composition is influenced by the nature of the substituent R.22 Although in most cases the substituent preferentially occupies an olefinic position (A₁ and/or A₂), there are some exceptions. Thus, the fluoro group stays preferentially at the methine carbon (C),21 and hydroxymethyl (CH₂OH), methoxymethyl (CH₂OMe), and acetoxyethyl (CH₂OAc) groups show a slight preference for the aliphatic positions on bullvalene (B).23
Alkoxybullvalenes (36) with methoxy, ethoxy, isopropanoxy, and tert-butoxy groups have been obtained by addition of the corresponding potassium alkoxides to bromobullvalene (25).22 These reactions presumably proceed through intriguing dehydrobullvalene intermediate 35 (Scheme 15).22 All substituted bullvalenes showed temperature-dependent NMR spectra.21

Disubstituted bullvalenes have been commonly prepared from dibromobullvalene (37), obtained from bromobullvalene (25) by another sequence of dibromination/dehydrobromination (Scheme 16).28 Interestingly, when dry KOtBu in benzene was used instead of KOTBu in tBuOH and benzene in the dehydrobromination, di-tert-butoxybullvalene (38) was obtained.21

A wide range of disubstituted bullvalenes with identical substituents were obtained by functional group transformations in dibromobullvalene (37).21,28,29 Reaction of 37 with NaCu(CN)2 led to dicyanobullvalene (39), which was further transformed by hydrolysis into bullvalenedicarboxylic acid (40) (Scheme 17). Reaction of 40 with diazomethane led to the formation of dimethyl bullvalenedicarboxylate (41).30 Bullvalenedicarbaldehyde (42) was obtained by reduction of the cyano groups in 39 with LiAlH4. Further reduction of the aldehyde groups in 42 using LiAlH4 afforded bullvalenediol (43). On the other hand, reaction of 37 with Me2CuLi or Ph2CuLi gave dimethylbullvalene (44),25 as a 2:3:3:3:1 mixture of valence, and diphenylbullvalene (45),24 as a 7:6:5:7:1 mixture of 4,5-, 3,5-, and 3,7-disubstituted isomers.

A different procedure for the synthesis of dimethyl bullvalenedicarboxylate (41) consisted of the irradiation of dimethyl cis-4a,8a-dihydroporphaphenalene-4a,8a-dicarboxylate (5') in methanol by a low-pressure mercury lamp (Scheme 18).30 This transformation was mechanistically related to that found in the synthesis of 1 by Jones and Scott (see Scheme 5).13

Diphenylbullvalene (45) was alternatively prepared by reaction of tricarbonylcyclocloctatetraeneiron (2') with diphenylacetylene at high temperatures (ca. 165 °C) to form 8b, followed by UV irradiation (Scheme 19).21
Disubstituted bullvalenes bearing two different substituents have also been synthesized. The most common approach is based on the monosubstitution of one bromine atom in dibromobullvalene (37) by a cyano group through reaction with NaCu(CN)$_2$ leading to bromocyanobullvalene (46) (Scheme 20). Further reduction of the cyano group in 46 with Dibal-H afforded bromobullvalenecarbaldehyde (47), which was reduced with LiAlH$_4$ to bromobullvalenol (48). Derivatives 49, 50, and 51 were similarly obtained.

A different procedure for the synthesis of differently disubstituted bullvalenes involves the bromination/dehydrobromination of methylbullvalene (28) to afford bromomethylbullvalene (52) (Scheme 21). The bromine in 52 was further substituted by a cyano group through reaction with NaCu(CN)$_2$ to give cyano(methyl)bullvalene (53). Hydrolysis of the cyano moiety to the carboxylic acid and subsequent reaction with diazomethane led to methyl methylbullvalenecarboxylate (54).

On the other hand, bromofluorobullvalene (55) was prepared from fluorobullvalene (34) by bromination/dehydrobromination (Scheme 22). A variety of fused disubstituted bullvalenes have been obtained by Diels–Alder reaction between the dehydrobullvalene intermediate 35, formed by reaction of bromobullvalene (25) with potassium alkoxides, and various dienes such as furan, 1,3-diphenylisobenzofuran (57), and tetraphenylcyclopentadiene (58) (Scheme 23). The expected direct Diels–Alder adducts 56a and 57a, formed by reaction of 35 with furan and 57, respectively, were not observed due to their high strain. Instead, these adducts undergo rapid rearrangement to the more stable isomers 56b and 57b. Products 56b, 57b, and 59 showed temperature-dependent NMR spectra, evidencing their dynamic situation.

Different trisubstituted bullvalenes were synthesized from parent tribromobullvalene (60), prepared by bromination/dehydrobromination of dibromobullvalene (37). Reaction of 60 with Me$_2$CuLi led to trimethylbullvalene (61), whereas treatment with Ph$_2$CuLi afforded triphenylbullvalene (62), which was found in a 1:1.96:1.04 equilibrium between the 4,5,10-, 4,5,9-, and 3,7,10-isomers (Scheme 24). The same bromination/dehydrobromination sequence was employed for the synthesis of tetra- (63), penta- (66), and hexabromobullvalenes (68) (Scheme 25). Slower rearrangements were observed for pentabromobullvalene (66).
whereas no fluxional behavior was recognized in hexabromobullvalene (68), which was obtained as a single isomer.8b Tetramethylbullvalene (64) was formed by reaction of tetrabromobullvalene (63) with Me₂CuLi.25 Tetraphenylbullvalene (65), obtained by reaction of 63 with Ph₂CuLi was found to be in a 4.2:5.9:1 equilibrium between the 1,4,5,10-, 1,3,5,10-, and 1,3,7,10-isomers.24 Penta- (67) and hexaphenylbullvalenes (69) were similarly prepared. As in the case of hexabromobullvalene (68), in hexaphenylbullvalene (69) the fluxional behavior was lost.24

3 Recent Developments in the Synthesis of Bullvalenes

The constant development in the field of synthetic organic along with the discovery of novel reactivities and methodologies has enabled ingenious new syntheses of bullvalene and highly substituted bullvalenes. An innovative syntheses of substituted bullvalenes has been developed by the Bode group, finding interesting applications of the corresponding products in supramolecular adaptive binding and sensing.9a,b,33a,d In this bullvalene synthesis, cycloheptanone (70) was used as the starting material (Scheme 26). Protection of cycloheptanone (70) with ethylene glycol gave acetal 71, which then was subjected to di-bromination to give 72. Bromide elimination and acid hydrolysis provided cycloheptadienone 73, which underwent Mukaiyama–Michael addition of silyl enol ether 74 to give enone 75. Enedione 76 was obtained from 75 by allylic oxidation of 75 with diacetoxiodobenzene and tert-butyl hydroperoxide. Conversion of 76 into the carboxylic acid 77 by treatment with trifluoroacetic acid, followed by reaction with tetrahydrothiophene-derived sulfur ylide 78, via a mixed anhydride, gave product 79, which was treated with...
scandium triflate to trigger the intramolecular cyclopropanation that provided triketone 80, a key intermediate for further functionalizations.

Triketone 80 was transformed to diallylbullvalene 84 in three steps (Scheme 27). Addition of allylmagnesium bromide to 80 afforded two diastereomeric diols, meso 81a and chiral 81b. Meso 81a was transformed into diallylbullvalone 82 by treatment with pyridine and thionyl chloride. The same reaction conditions applied to chiral 81b led to furan product 83. On the other hand, treatment of chiral 81b with disopropylethylamine and thionyl chloride followed by pyridine provided 82. Finally, enolization of diallylbullvalone 82 and trapping of the enolate with isobutyl chloroformate gave diallylbullvalene 84. Therefore, tetrasubstituted bullvalene 84, with three different substituents and 840 possible interconvertible constitutional isomers, was obtained in 11 steps from cycloheptanone (70). Diallylbullvalene 84 constitutes a versatile intermediate whose two allyl moieties can be further employed for the attachment of other relevant functional groups.

Since 2000, gold(I) catalysis has emerged as a powerful tool for the construction of molecular complexity from simple substrates. The ability of cationic gold(I) complexes to promote a wide variety of enyne cyclizations along with the versatility of the intermediates accessed through these transformations has been utilized to develop expedient and efficient synthesis of bullvalene and substituted bullvalenes through the fluxional molecules barbaralone (9a) and bullvalone (10a) from readily available 7-ethynylcyclohepta-1,3,5-trienes (85) (Scheme 28).

This new approach relies on a gold(I)-catalyzed oxidative cyclization of 85 in the presence of external oxidants such as diphenyl sulfoxide or pyridine N-oxides, to afford barbaralone (9a) and other 1-substituted barbaralones under mild conditions and good to excellent yields (Scheme 28). The barbaralone synthesis proceeds by activation of the alkyne in 85 by gold(I), followed by attack of the external oxidant to form α-oxo gold(I) carbene 86, which then undergoes intramolecular cyclopropanation to give barbaralone 9. This transformation can be also seen as a gold(I)-catalyzed cyclization of 1,6-enyne 85 to afford gold(I) carbene 87 followed by oxidation.

This new two-step approach to barbaralones constitutes one of the shortest, mildest, and most efficient synthesis of barbaralones 9 to date. Substrates 85 can be prepared in one step from the corresponding alkynes and commercially available tropylium tetrafluoroborate (Scheme 29). Reaction of 85a and 85b in the presence of gold(I) catalyst [IPrAuMe]+_SbF_6^- and diphenyl sulfoxide as external oxidant.
provided barbaralone (9a) and phenylbarbaralone (9b) in 97% and 83% yield, respectively.35

Bullvalone (10a) and phenylbullvalone (10b) were obtained in 37% and 22% yield, respectively through one-carbon homologation of the corresponding barbaralones 9a and 9b using diazo(trimethylsilyl)methane instead of explosive diazomethane employed in classic strategies (Scheme 30).36

Bullvalene (1) and phenylbullvalene (27) were prepared from the corresponding bullvalones 10a and 10b via a two-step, one-pot procedure involving the formation of the enol triflates 86 and 87 and subsequent reduction under palladium catalysis in the presence of nBu3SnH (Scheme 31).37 This strategy allowed the preparation of bullvalene (1) and phenylbullvalene (27) in 5 steps and 10% and 7% overall yield, respectively, constituting one of the most efficient synthesis of these fluxional molecules to date. Moreover, disubstituted bullvalenes 45, 88, and 89 bearing two equal or two different groups were synthesized from phenylbullvalone (10b) by formation of the enol triflate followed by Stille coupling.38 Bullvalenes 45, 88, and 89 were found to be in 7.6:5.7:1, 5.2:1.5:1, 3.8:2.3:1 equilibria, respectively, with the 3,6- and 3,7-disubstituted isomers at –40 °C.35

The latest synthesis of bullvalene (1) from 2018, as well as several mono- and disubstituted derivatives of 1, has been achieved in just two steps and good overall yields by the Fallon and Pašteka groups.39 This synthesis is based on a cobalt-catalyzed [6+2] cycloaddition of cyclooctatetraene (2) with terminal or internal alkynes to afford products 8 (Scheme 32), previously encountered as intermediates in the synthesis of bullvalenes (see Schemes 5 and 10). UV irradiation of compounds 8 provided a wide range of bullvalenes in good yields, featuring substituents such as alcohols, alkyl, benzyl, and silyl groups. Bullvalene (1) was obtained in 60% yield over two steps. This procedure constitutes the shortest and most efficient synthesis of bullvalene and mono- and disubstituted bullvalenes to date. Nevertheless, this protocol does not enable the formation of aryl-substituted bullvalenes.

Interestingly the first4a and the most recent39 synthesis of bullvalene (1) are conceptually very similar, although after more than fifty years of research, the overall yield has been increased considerably and the most recent approach is much more versatile.

4 Applications of Bullvalenes

Schröder and co-workers reported the application of crown ether functionalized bullvalenes in the selective binding of metal ions.40,33d This approach relied on the shapeshifting ability of bullvalenes and the low preference of crown ether substituents for a specific site on the bullvalene core. It was proposed that the crown ether group at-
attached to bullvalene would adopt different ring sizes as the bullvalene core interconverts into its possible constitutional isomers through Cope rearrangements, leading to selective binding of metal ions depending on their size. Nonetheless, only weak host-guest interactions were observed, leading to low selectivity in the accommodation of different alkali and ammonium cations of distinct sizes (Scheme 33).

The Bode group has described interesting applications of tetrasubstituted bullvalenes in host discovery.9b,33a,b These studies revealed that due to their shapeshifting nature, these tetrasubstituted bullvalenes could respond and adapt their shapes in order to bind suitable guests. In front of a favorable interaction with a molecular guest, such as C60, the equilibrium of bullvalene constitutional isomers was shifted towards the amplification of the isomers that are more tightly bound to the target, acting as dynamic combinatorial libraries. Moreover, boronic acid substituted bullvalenes with a 13C label have been employed in chemical sensing of polyols such as carbohydrates, flavanols, and sialic acids through covalent binding.33c These shapeshifting substituted bullvalenes adapt their structures to strongly bind polyols. Thus, distinct 13C NMR patterns were observed for each polyol bound bullvalene isomer, allowing specific analyte detection by a single NMR measurement (Scheme 34).

5 Conclusion

In summary, since the prediction of the structure and properties of bullvalene (1) in 1963 by von Doering several different approaches for the preparation of this unique fluxional molecule have been developed. Most classical syntheses of bullvalene (1) rely on long linear sequences with low overall yields. Nevertheless, these procedures constituted the base for the preparation of a wide variety of substituted bullvalenes, leading to numerous NMR studies on their dynamic fluxional behavior and isomer composition. The constant evolution and enormous advances in synthetic organic chemistry, to which organometallic chemistry has contributed considerably, have enabled the development of expedient synthesis of bullvalenes and substituted derivatives with improved overall yields and less number of steps. The most efficient synthesis of bullvalenes to date are, thus, the most recent ones, featuring Au(I)-35 and Co(II)-catalyzed39 reactions as key steps. These new synthetic developments, which have streamlined the preparation of a wide range of substituted derivatives, will allow the discovery of new applications for bullvalenes in adaptive binding and sensing.33

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