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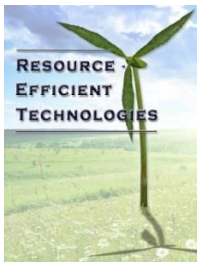

Review Article

FUNDAMENTAL AND APPLIED ASPECTS OF THE CHEMISTRY OF ACETYLENYLQUINONES

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Abstract

In addition to the reported synthetic routes for the acetylene derivatives of quinones, a detailed analysis of the fundamental chemical, physicochemical, and biological properties of this class of compounds is presented herein. The advantages of Pd- and Cu-catalyzed cross-coupling of terminal alkynes with iodarenes *via* the Sonogashira reaction to produce new acetylenylquinones with predetermined properties are examined. Here, combining quinoid and acetylene residues into one molecule gives the resulting compounds chemical specificity, as demonstrated by several reported examples of non-trivial transformations. In particular, the presence of the quinoid cycle significantly increases the electrophilicity of the triple bond and determines the range of transformation possibilities. Moreover, acetylenylquinones have heightened sensitivity to both external (such as the reaction temperature and the nature of the solvent) and internal (e.g., the structure of substituents in the nucleus and the acetylene fragment) factors. For example, regioselective cleavage of a strong triple bond under the action of amines is possible in the absence of a metal catalyst. *Peri*-substituted acetylenyl-9,10-anthraquinones are most suited for the synthetic route because of the proximity of the acetylene and carbonyl groups. Mechanisms of reactions of selective alkynylquinones are described.

Keywords: Cross-coupling, acetylenes, 9,10-anthraquinone analogs, heterocyclization, biological property.

1. Introduction

Quinones, including conjugated cyclohexadienones (1,2- and 1,4-quinones) and their annelated analogs (1,2- and 1,4-naphthoquinones and 9,10-anthraquinones), are an important and unique class of organic compounds widely used in a variety of applications. For example, alizarin (1,2-dioxoanthraquinone) is used in photographic materials and dyes, whereas condensed anthraquinoid derivatives are capable of intercalation into duplex DNA [1]. Ubiquinones, which are fat-soluble derivatives of *para*-quinones, participate in oxidation processes in the body as coenzymes for a number of oxidoreductases. On the other hand, the reactivity of acetylene compounds predetermines their use for diverse applications in organic synthesis, medicinal chemistry, and materials science [2]. In addition, many acetylene derivatives play significant roles in numerous processes in nature and are well-known for their anticancer activity [3]. Therefore, coupling of these two highly reactive residues to create a single molecule is of fundamental and practical interest to researchers as the presence of a conjugated system of carbonyl groups and triple bonds (TB) facilitates a wide range of new chemical transformations. Since they contain two pharmacophores, alkylquinones are promising agents for critical biohybrid applications in medicinal chemistry.

Since the last review featuring quinone–acetylene derivatives was published in 2004 [4], it is only fitting that this current review covers the period from 2005 to 2019 as many new advancements in this area of chemistry have occurred over the past

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15 years. The previous review [4] focused mainly on the synthesis of alkynylquinones and the traditional reactions typically associated with these compounds, including the Michael reaction and the heterocyclization of vicinal alkynylquinones. However, this current review features emerging synthetic strategies and unconventional, non-trivial transformations [5], thereby making it relevant to the ongoing scientific discourse.

2. Synthesis of acetylenequinones

The Sonogashira reaction, which features the cross-coupling of iodine- or bromine-substituted 9,10-anthraquinone and diverse terminal acetylenes, has become the main method for synthesizing acetylene derivatives of quinones in recent years. Through this reaction, a wide range of *peri*-substituted acetylenyl-9,10-anthraquinones have been prepared *via* the simple condensation of 1-iodo-9,10-anthrachine with various terminal acetylenes, including alkynes with aryl, hetaryl, and aliphatic substituents with both donor and acceptor systems, in the presence of a metal complex such as $PdCl_2(PPh_3)_2$–CuI–PPh_3 [6, 7] (Fig. 1). Generally, the cross-coupling reaction proceeded smoothly, and the yields of the alkynylquinone products were between 80 and 98 %.

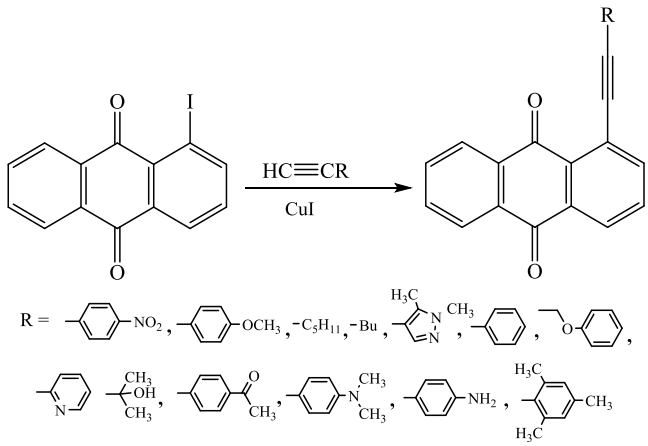


Fig. 1. Synthesis of *peri*-substituted acetylenyl-9,10-anthraquinone analogs

By using the diethyl derivative as an acetylene component in the Sonogashira reaction, researchers synthesized model compounds for studying the molecular and supramolecular properties of this series of analogs. This was accomplished by looking at the intramolecular hydrogen bonds of the individual molecules [8] (Fig. 2).

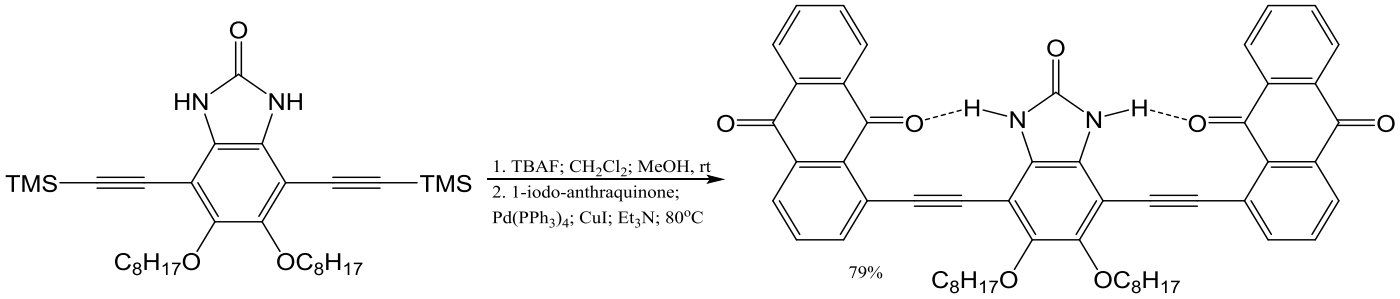


Fig. 2. Synthesis of bis-(acetylenyl-9,10-anthraquinone) with intramolecular hydrogen bonds

As shown above, the Pd-catalyzed reaction was conducted at 80 °C and resulted in a yield of 79 % of the diacetylene derivative. Despite the low activity associated with bromarenes (when compared with that of their iodarene counterparts), research has revealed that bromo-9,10-anthraquinones could be successfully introduced due to the molecular activation triggered by the presence of the halogen atoms and the fact that the halogen atoms were excellent leaving groups.

Another route utilized anthraquinone analogs bearing acetylene and sulfur-containing residues in the presence of diisopropylamine (DIPA) [9]. Here, the yield of the 2,6-bis(thiophene-3-ylethynyl)-9,10-anthraquinone product was 90 %, depending on the available dibromide starting material that was used (Fig. 3).

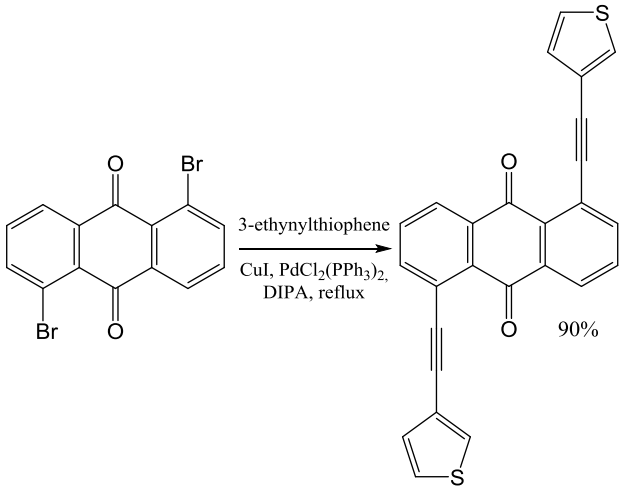
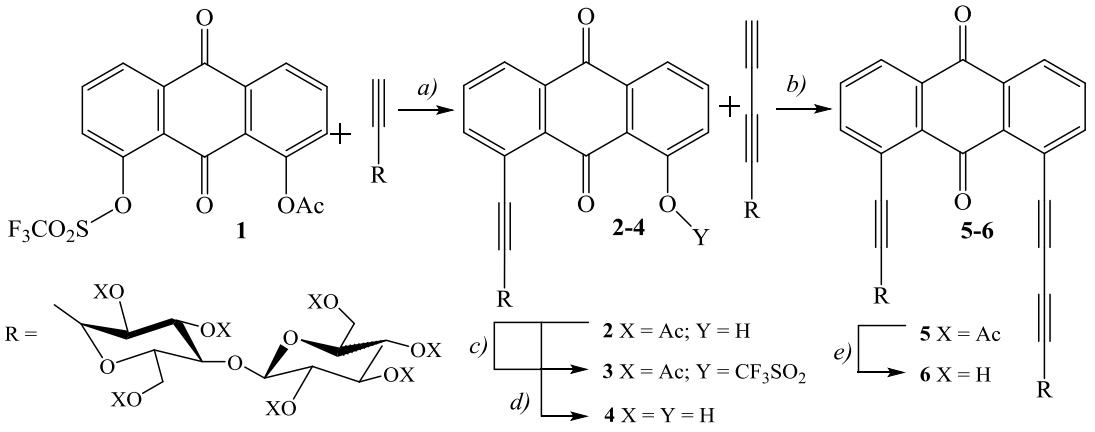


Fig. 3. Synthesis 1,5-di(acetylenyl-9,10-anthraquinone) bearing thiophene residues



a) $[Pd(PPh_3)_2]Cl_2$, CuI, Et_3N/DMF 1 : 5, 60°C, then $(NH_4)_2CO_3$; 74%.
b) As a, but at 24°C and without $(NH_4)_2CO_3$; 87%.
c) Tf_2O, Et_3N, CH_2Cl_2 ; 96%. d) MeONa, MeOH; 95%.
e) KCN, MeOH/CH_2Cl_2 ; 70%.

Fig. 4. Synthesis of unsaturated bis-C-cellobiosylated anthraquinone

In addition to halogen atoms, such as iodine and bromine, a triflate group was also used as the leaving group; this allowed for the sequential introduction of ethynyl and butadienyl groups [10]. Under the Sonogashira reaction conditions, the anthraquinone triflate derivative **1** smoothly reacted with cellobiosyl acetylene at 60 °C. The subsequent selective deacetylation of the phenolic AcO group by the action of $(NH_4)_2CO_3$ in DMF resulted in the C-glycoside **2** in a yield of 74 %, which was then converted into the aryl triflate **3** (96 %) under standard conditions (Fig. 4).

Tosylate **3** was condensed using cellobiosylbutadiyne at room temperature to give bis-C-cellobiosylated anthraquinone **5** in a yield of 87 %. The deacetylation of **2** *via* MeONa in MeOH produced the mono-C-glycoside **4** in a yield of 96 %, whereas the corresponding bis-C-cellobiosyl derivative **6** was obtained in a 70 % yield through treatment with **5** in the presence of KCN in MeOH/CH_2Cl_2 followed by column chromatography. In addition to the traditional technique employed for the synthesis of acetylenylanthraquinone analogs, Tan et al. proposed a fundamentally different way of alkynylating 9,10-anthraquinone *via* the substitution of a hydride [11]. Here, substrates that possessed electron-accepting substituents, such as carbonyls, esters, and other similar groups, could be used for the alkynylation of C(sp^2)–H bonds with bromalkines under Rh-catalyzed cross-coupling (pseudo–Sonogashira) reactions (Fig. 5).

This was the first report on the alkynylation of CH acids using a Rh catalyst under mild conditions ($[Cp^*RhCl_2]_2$ and Ag_2CO_3 at 45 °C–70 °C for esters and 25 °C–90 °C for ketones). Mechanistic studies revealed that the reaction proceeded *via* electrophilic substitution through the activation of the C–H bond.

In the same vein, the synthesis of acetylenylquinones was also possible *via* hydrolysis of the corresponding dimethoxynaphthalene analogs containing a C≡C TB as a part of their structure (Fig. 6) [12].

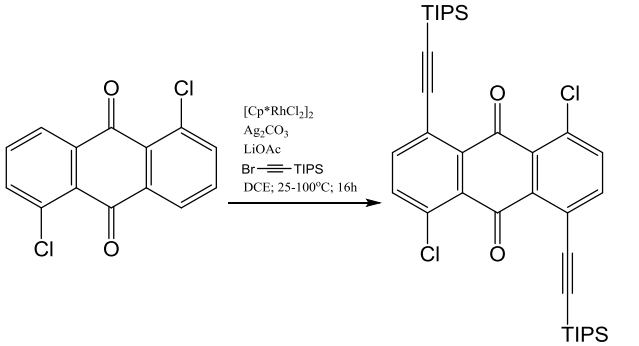


Fig. 5. Rh-catalyzed cross-coupling (pseudo–Sonogashira) through activation of the C–H bond

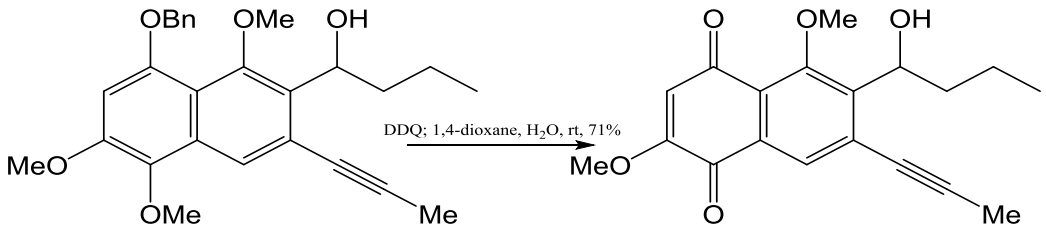


Fig. 6. Synthesis of acetylenyl-1,4-naphthoquinone *via* hydrolysis of the corresponding dimethoxynaphthalene

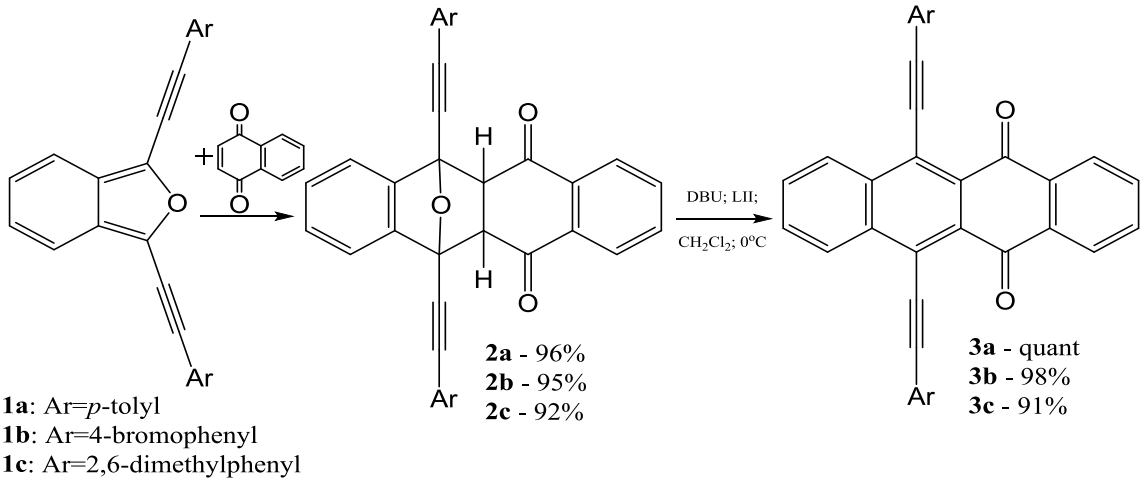


Fig. 7. Synthesis of di(acetylenyltetracenquinone) analogs *via* the [4+2] cycloaddition of benzofuran to form 1,4-naphthoquinone followed by aromatization

Selective hydrolysis resulted in acetylenylnaphthoquinone in a 71 % yield and was accomplished through the action of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) at room temperature. A fundamentally different route for obtaining 5,6,11,12-tetraarylethynyltetracene analogs made use of the [4+2] cycloaddition of benzofuran to form 1,4-naphthoquinone followed by aromatization (Fig. 7) [13].

Treating the cycloadducts with LiI and DBU-1,8-diazabicyclo[5.4.0]undec-7-ene at low temperatures in CH_2Cl_2 led to complete aromatization, and the yields of tetracenquinone products ranged from 98 % to quantitative.

3 Chemical properties

The conjugation of the C≡C bond and its favorable spatial arrangement relative to the carbonyl group in *peri*-R-ethynyl-9,10-anthraquinones increased the electrophilicity of the triple bond. This, in turn, facilitated nucleophilic addition that led to further heterocyclization.

These ethynylanthraquinone–nucleophile dyads were convenient models for more detailed examination of the regioselectivity of the reaction process. It was determined that the reaction's mechanism could be controlled by changing both the nature of the substituent associated with the TB (i.e., changing the degree and the direction of polarization) and the nature of the mono- or binucleophiles present (Fig. 8).

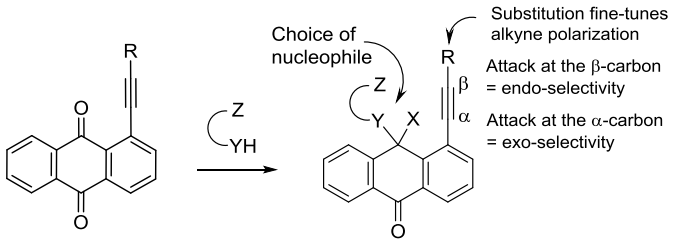


Fig. 8. Influence of the triple bond substituent on the regioselectivity of the reaction

Vasilevsky et al. extensively investigated the reactions of 1-alkynyl-9,10-anthraquinones with nitrogenous polynucleophiles [14]. Thus, *peri*-acetylenyl-9,10-anthraquinones reacted with guanidine *via* a complex series of cascade reactions starting with an addition stage followed by cyclization, elimination, and, finally, rearrangement. The interaction between guanidine and 1-phenylethynyl-9,10-anthraquinone, **1a**, in boiling *n*-butanol caused the formation of three annelated heterocycles (Fig. 9) [14].

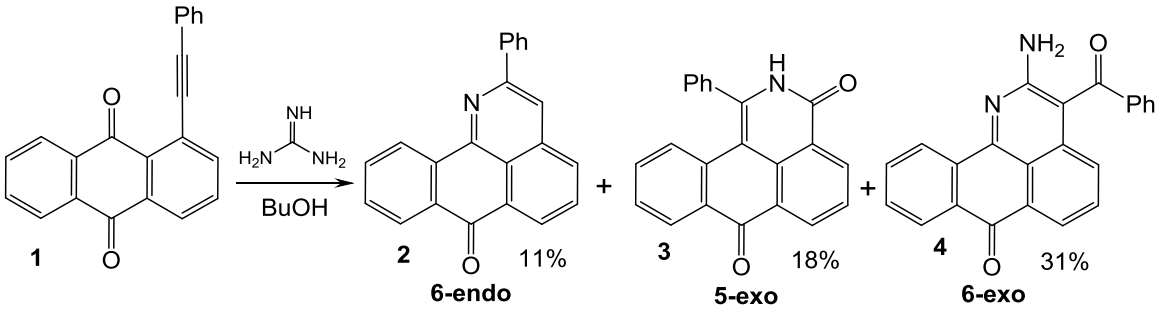


Fig. 9. Heterocyclization of 1-phenylethynyl-9,10-anthraquinone in the presence of guanidine

Phenyl-7*H*-dibenzo[*de*,*h*]quinolin-7-one, **4a**, was formed by a regioselective attack of the hemiamine nitrogen atom at the β-carbon of the C≡C TB, followed by the elimination of water and NH_2CN (or hydroxylamine and HCN). The regioselectivity of the 6-*endo*-*dig* cyclization process corresponded to the polarization of the TB.

Of these types of reactions, the most intriguing one resulted in the formation of the substituted product **3**. One proposed mechanism included a 5-*exo*-*dig*-cyclization reaction, followed by fragmentation and rearrangement. The introduction of a nitrogen atom obtained from the guanidine residue between the two acetylene carbon atoms was a previously unknown step (Fig. 10).

It was revealed that the ratio of the products from the reaction with guanine was caused by the occurrence of three competing types of cyclization reactions, namely, the attack of both the nucleophilic 6-*endo* and 5-*exo* derivatives on the electrophilic alkyne fragment and the 6-*exo*-cyclization reaction in which the alkine acted as a nucleophile. A study on the reactivity of the dyad *peri*-ethynylanthraquinone-thiourea was of particular interest since the presence of two different nucleophilic centers (S and N) in the reagent brought into question the overall chemoselectivity of the reaction [7]. It was found that the interaction between 1-R-ethynyl-9,10-anthraquinone analogs of **1** and excess thiourea in boiling pyridine for 8 to 26 h under the influence of sodium ethylate resulted in the formation of two heterocyclic products, namely, analogs of 2-R-7*H*-dibenzo[*de*,*h*]quinolin-7-one **2** and analogs of 2-R-anthra[2,1-*b*]thiophen-6,11-diones **3** with a predominance for the latter. In the case of **1f** and **1g**, only the 2-R-7*H*-dibenzo[*de*,*h*]quinolin-7-one analogs were formed (Fig. 11).

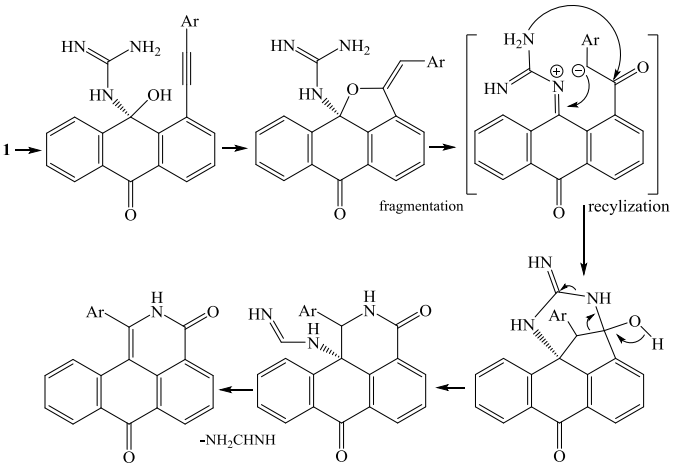


Fig. 10. A possible route for the formation of **3**

In this mechanism, it should be noted that the sulfur atom first attacked the TB which subsequently led to the activation of the C–H bond of the quinone nucleus. Aromatization and oxidation at the final stage led to the creation of the desired product (Fig. 12).

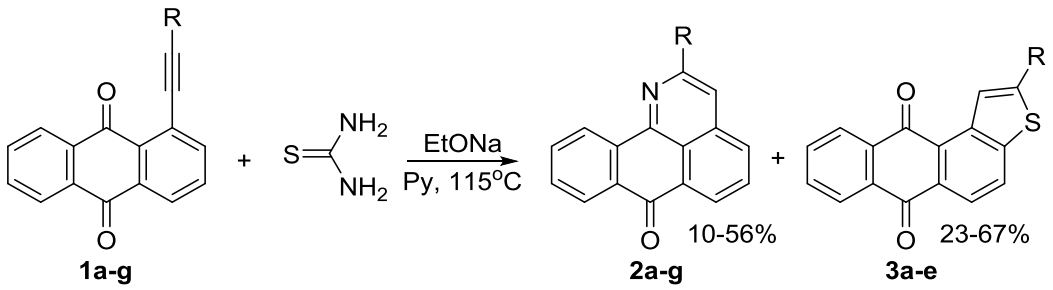


Fig. 11. The reaction of 1-R-ethynyl-9,10-anthraquinone analogs with thiourea produced 2-R-7*H*-dibenzo[*de*,*h*]quinolin-7-ones **2** and 2-R-anthra[2,1-*b*]thiophen-6,11-diones **3**

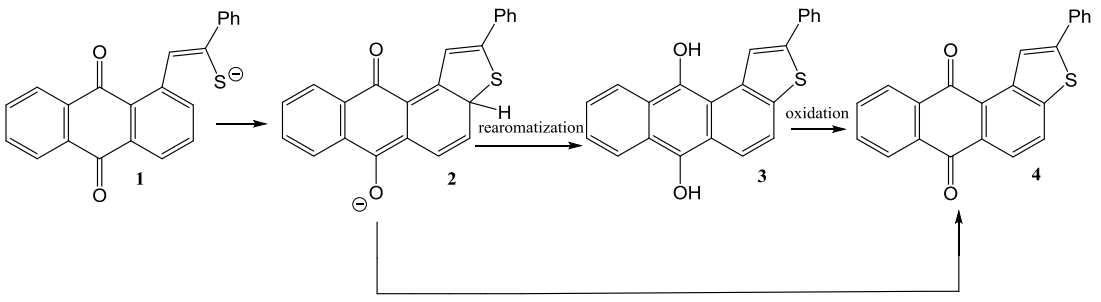


Fig. 12. Formation of anthra[2,1-*b*]thiophene through activation of the C–H bond and subsequent aromatization

In the reaction between 1-acetylenyl-9,10-anthraquinone and ethylenediamine, partial cleavage of the TB (which was atypical of acetylenes) was observed. This was followed by the formation of methyl aryl ketones and the corresponding 2-substituted imidazoline derivatives. This case was of theoretical interest as an example of how the complete cleavage of a strong C≡C bond could be achieved under mild conditions through the action of ethylenediamine (Fig. 13) [15].

Another example of an energy-efficient process featured an open reaction in which a strong TB was easily broken and no metal catalyst was required. In the study conducted by Alabugin et al., the activation of the C+C bond was shown to have a significant synthetic potential as it could be used to produce the target molecule.

In a series of studies, Japanese scientists reported the electrophilic cyclization of 1-aryl ethynylanthraquinones [16–18]. Here, protonation was performed on a wide range of substrates *via* the addition of bis(trifluoromethanesulfone)imide acid (TFSIH) in dichloromethane to give products that were stable in air. Oxodihydrodibenzochromenylium cations were formed in excellent yields (82–97 %). It was theorized that the intramolecular cyclization of the ethynyl quinone fragment proceeded *via* the protonation of the acetylene fragment followed by the attack of carbonyl oxygen on the carbon of the ethynyl group (Fig. 14).

A novel variation of the Sonogashira reaction featured carbonylation, which resulted in annelated heterocycles that were related to the well-known antibiotic and antitumor compound, (±)-BE–26554A, as described by Rixson [19]. Here, a domino reaction in which sequential ethynylation–carbonylation–*O*-acylation led to stereoisomeric anthrapiran-2-one analogs (Fig. 15).

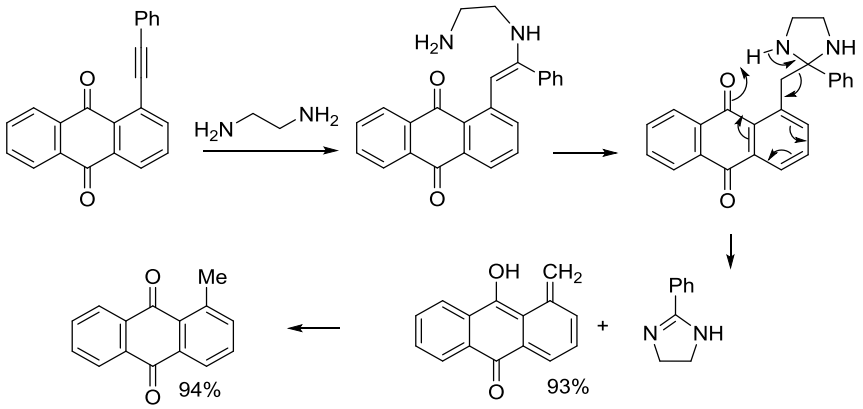


Fig. 13. Cleavage of a strong C≡C bond through the action of ethylenediamine

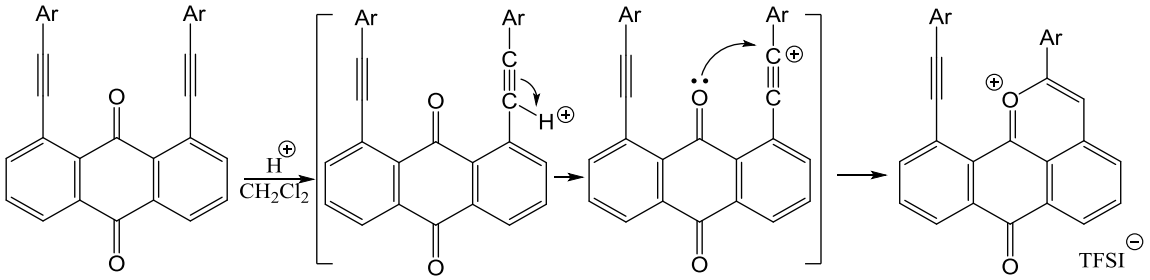


Fig. 14. The intramolecular cyclization of the ethynyl quinone fragment. Here, Ar represents ferrocenyl (Fc), 4-N,N-bis(4-methoxyphenyl)aminophenyl (Am), platinadithiolene, phenyl, *m*-tolyl, and *p*-tolyl. TFSIH is bis-(trifluoromethanesulfone)imide

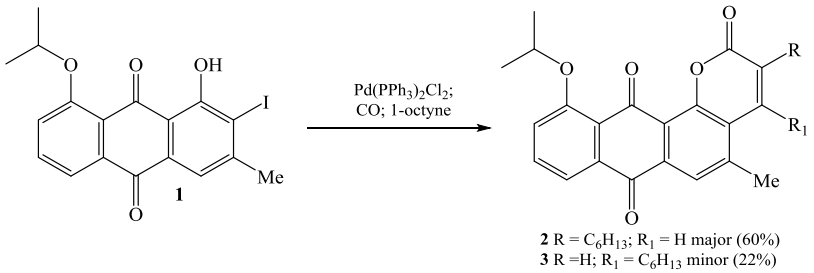


Fig. 15. Synthesis of anthrapiran-2-ones *via* a domino ethynylation–carbonylation–*O*-acylation reaction

The simplicity of this route toward the formation of anthrapyran-2-ones allowed for the production of an analog series for the antitumor compound BE–26554AA and facilitated the subsequent study of their biological activity.

In another study, it was established that the TB could undergo significant changes in its polarity and electrophilicity, depending on the associated substituent. This, in turn, streamlined the synthesis of multiple analogs. Here, the reactive capacity of the diazo-salts of *vic*-acetylenyl-9,10-anthraquinones [20] was used to demonstrate that the structure of the transformation products during diazotization of 1-amino-2-acetylenyl-9,10-anthraquinones was strongly dependent on the nature of the substituents in the alkynes and the anthraquinone nucleus (Fig. 16).

In this case, the donor substituent (OH) in the fourth position stabilized the diazonium salt and prevented electrophilic cyclization of the arylethynyl substituent at C2. This, in turn, ensured that substitution of the diazonium by azide group and the subsequent cyclization into the isoxazole ring occurred while maintaining the TB. The advantage of this process was that it offered a new synthetic route to the formation of 3-ethynyl-[1,9-*cd*]isoxazol-6-ones that would have otherwise been difficult to obtain *via* other techniques.

On the contrary, 5-*exo-dig* cyclization into condensed pyrazoles was observed between the donor substituents in the arylalkine fragment and the OAc substituent at nucleus position 40. Carbocyclization, which is the reductive dimerization of acetylenyl-9,10-anthraquinones, is described in [21]. Here, the reaction of the alkynes **1a**–**c** with guanidine was carried out in boiling *n*-butanol and resulted in the formation of O-5-*exo*-dig- and N-6-*exo-dig*-products **2** and **3**, respectively. In addition, 9,18-diaryl tetrabenzo[a,*de*,*j*,*mn*]tetracene-4,13-diones **4** were obtained in yields ranging from 12 to 24 %; these highly unusual products were the results of reductive polycondensation. The structure of the tetracycline **4** was accurately established using NMR, mass spectrometry, and X-ray crystallography (Fig. 17).

The reductive dimerization of acetylene anthraquinones under very basic conditions provided rapid access to flexible non-planar polyaromatic products with a tetracycline core, which exhibited interesting electrochemical properties.

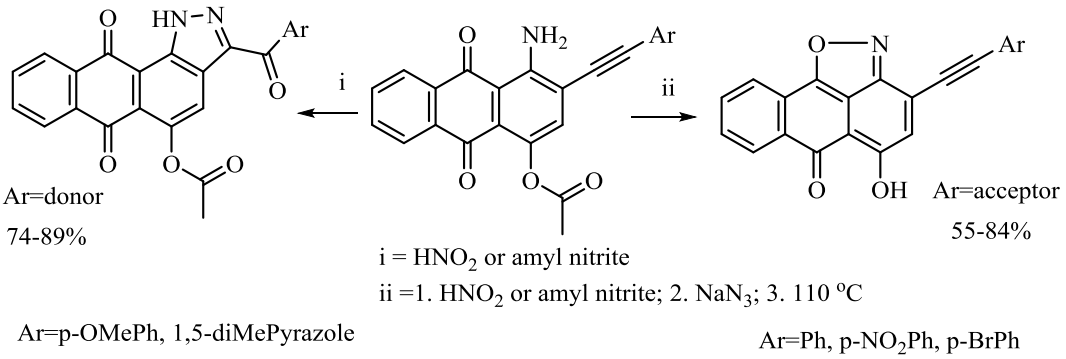


Fig. 16. Two alternative routes for the cyclization of diazo-salts of *vic*-acetylenyl-9,10-anthraquinones

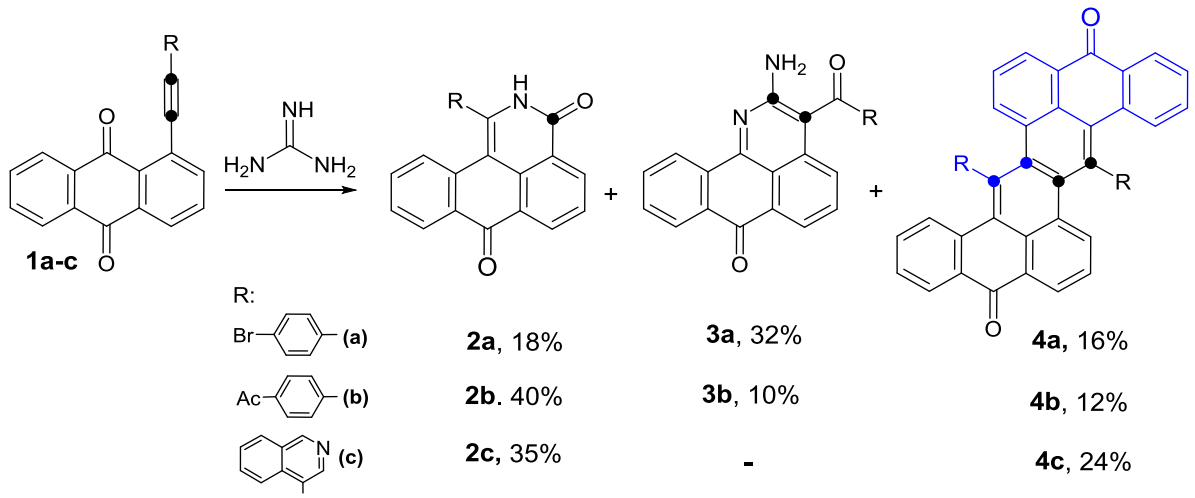


Fig. 17. Synthesis of *O*-5-*exo-dig*- and *N*-6-*exo-dig*-heterocycles and the highly unusual 9,18-diaryl tetrabenzo[a,*de,j,mn*]tetracene-4,13-diones **4**

4 Physico-chemical

Herein, research on the physico-chemical properties of alkynylquinones and their transformation products are presented along with examples of their unique properties in practical applications. Dijk et al. conducted the streamlined synthesis of an alkynylanthraquinone series in which the thioacetyl terminal groups were used for binding to a gold electrode (Fig. 18) [22].

This anthraquinone model system could be reversibly switched from a cross-conjugated system (low conductivity "off") to a linearly conjugated one (high conductivity "on") *via* two-electron redox reactions. This trait was shown to be particularly useful in applications that featured molecular electronic devices. Compounds with a thioacetyl end group were shown to be capable of binding to gold and have been the subject of studies in which the MCBJ technique was highlighted. Anthraquinones bearing acetylene and sulfur-containing residues have been reported for other practical applications (Fig. 19) [9].

These compounds formed monolayers on Au (111) or on a semiconductor surface and were efficient redox switches that could overcome the natural size limitations of their silicon-based counterparts. Yao et al. studied the possibility of using alkynylanthraquinone-based oligomers as durable organic electrodes for rechargeable batteries (Fig. 20) [23].

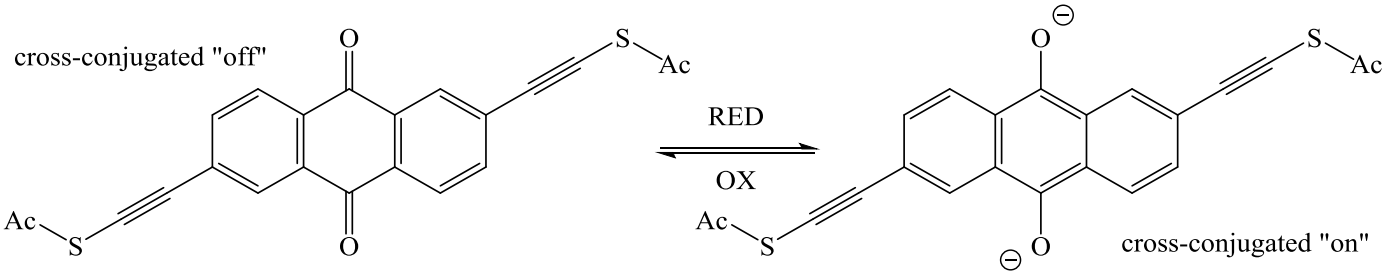


Fig. 18. 2,6-Dialkynylanthraquinone system in which the reversible transformation from a cross-conjugated system to a conjugated one is conducted *via* two-electron redox reactions

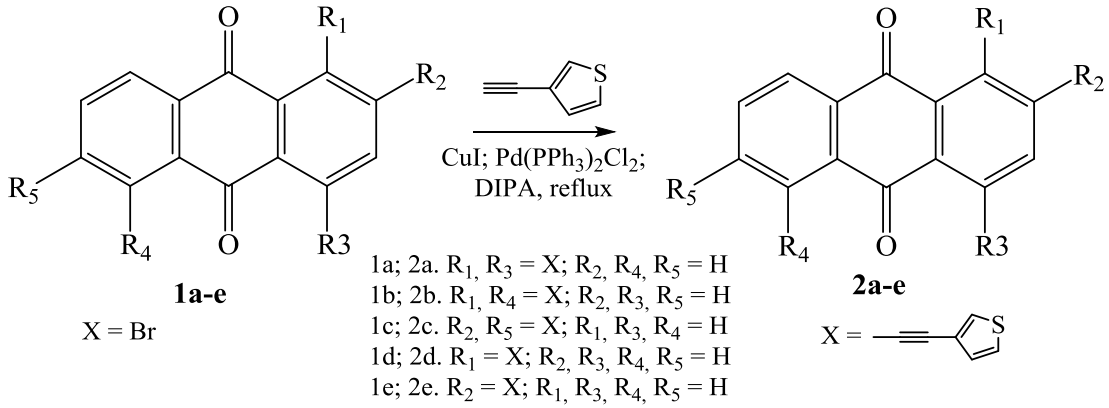


Fig. 19. Synthesis of anthraquinones bearing acetylene and sulfur-containing residues

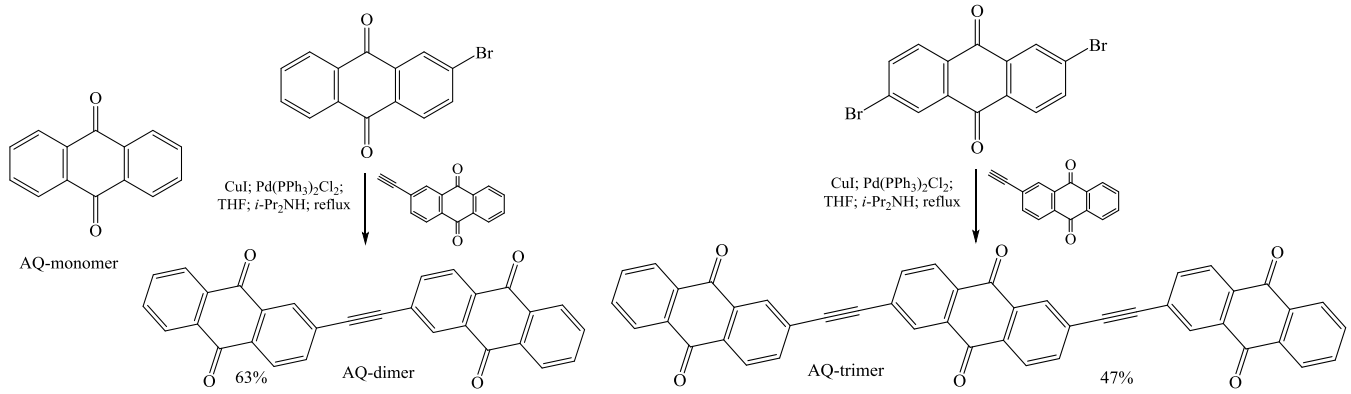


Fig. 20. The structures of 9,10-anthraquinone (AQ) as well as the corresponding dimer and trimer

AQ-dimer and AQ-trimer with acetylene bridges were synthesized (63 and 47 %, respectively) *via* the Pd-catalyzed cross-coupling of 2-ethynylanthraquinone with monobromo- and dibromanthraquinones. Even though the capacity of the AQ monomer rapidly decreased, the trimer maintained an almost constant capacity over the course of 100 cycles. A theoretical calculation of the associated quantum chemistry revealed that the extensive intermolecular π–π interaction observed was the result of oligomerization. These studies, thus, could be perceived as a guide for the development of new organic compounds that exhibited high reaction capacity and ease of cyclization [24].

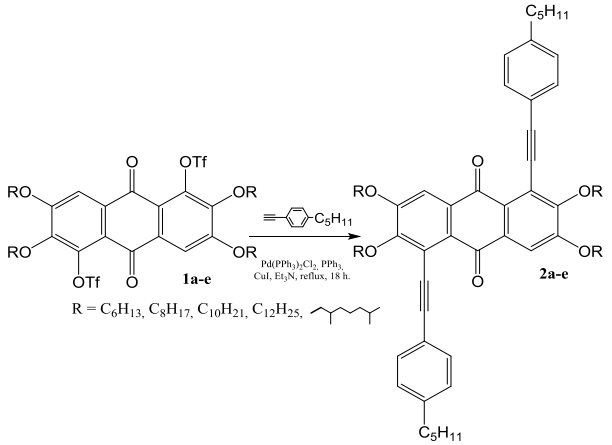


Fig. 21. Synthesis of alkyl and alkoxy derivatives of 1,5-di(1-ethynyl-(4-pentylphenyl))-9,10-anthraquinone

In another study, five new liquid crystalline alkyl and alkoxy derivatives of 1,5-di(1-ethynyl-(4-pentylphenyl))-9,10-anthraquinone (Fig. 21) were synthesized, and their phase transitions were subsequently studied using small and wide-angle X-ray scattering (SAXS/WAXS) spectroscopy. This was done in an effort to define the exact nature of the mesophases and their corresponding electron density maps. The crystal columnar rectangular (Crcolrec) phases were shown to be stable at low temperatures for the derivatives with the shortest peripheral alkoxy group (R = *n*-C_6H_{13}). At higher temperatures, however, these compounds existed in the columnar hexagonal (Colh) phase and then the discotic nematic (ND) phase. Thus, the authors investigated the effects of different types of chains on the molecule's capacity for self-assembly and how these effects inevitably influenced molecular packing as these two characteristics directly facilitated the formation of new functional materials and expanded the range of practical applications for this class of compounds.

Japanese chemists used the Sonogashira reaction to synthesize and study the structures and properties of macrocycles that had anthracene nuclei interconnected by rigid acetylene bridges, **1**, as well as the corresponding anthraquinone analogs, **2**, (Fig. 22) [25, 26].

XRD analysis revealed that compounds **2a**–**d** were peculiar in that an out-of-plane deformation of the internal carbonyl fragment was observed in all cases, and the dimer was readily formed both as crystals and in solution. Additionally, XRD studies revealed the dimeric pairs that were formed both as single crystals and in solution were caused by intermolecular interactions between the anthracene and the anthraquinone fragments, in particular, for compounds **2a** and **2b**, which were folded as dimeric pairs within a single crystal *via* intramolecular π–π interactions between the aforementioned fragments. Cyclic analogs of **2** tended to self-associate in $CHCl_3$. Such acetylenic macrocycles attracted the attention of chemists because they could be used as novel π-conjugated compounds in supramolecular and functional molecular chemistry applications for the design of nanocars, gyroscopes, and other molecular machines. Conformational control, which was implemented in a conjugated system using intramolecular hydrogen bonds, was often used to obtain individual molecular and supramolecular properties [8] (Fig. 23).

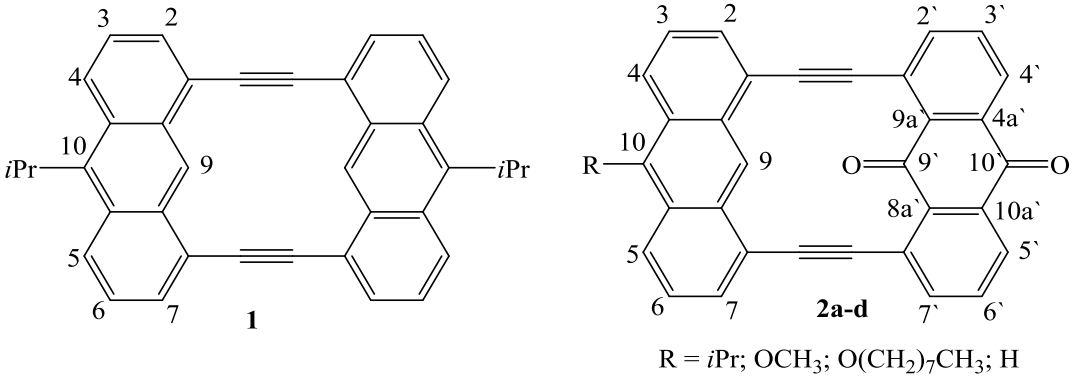


Fig. 22. Synthesis of macrocycles with their anthracene nuclei interconnected by rigid acetylene bridges **1** and the corresponding anthraquinone analogs **2**

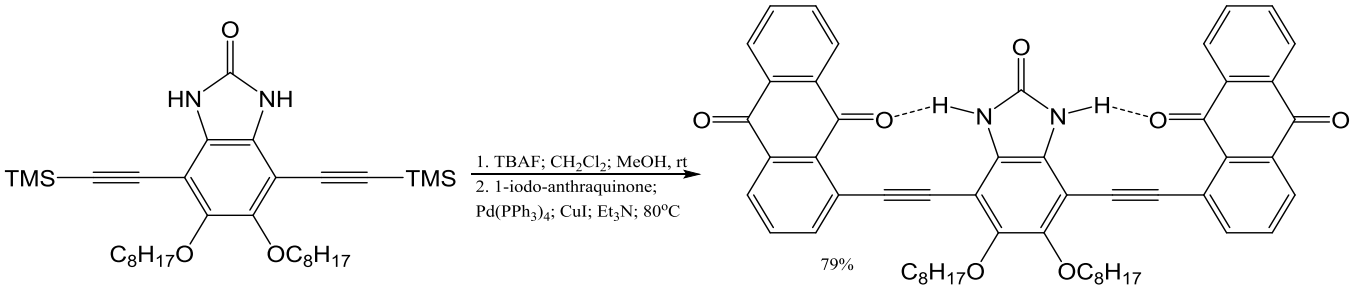


Fig. 23. The conjugated anthraquinone system with intramolecular hydrogen bonds

In this case, a completely coplanar conformation of the π-system led to short π–π distances which facilitated molecular self-assembly. Thus, this study was able to demonstrate the efficiency and significance of intramolecular non-covalent bonds for conformational control and molecular self-assembly. Hydrogen bonds such as these provided thermodynamic stability of the coplanar conformation [27], as clearly evidenced through the influence exerted by the substituent in the anthraquinone diimine fragment on the properties of trans-(ethynyl-bis(tributylphosphinyl)platinum-containing polymers (Fig. 24).

In this investigation, it was obvious that there were significant differences in the physical properties of P0, P1, and P2. First, the polymer P2 was larger than P1 and P0 because of the presence of soluble side chains, such as $–OC_4H_9$ instead of NO_2 groups. At the same time, P2 exhibited a higher fluorescence intensity and a longer lifetime than P1. Second, P2 exhibited a rare case of higher energy emission, which was not observed in P1. Third, of the lot, only P0 was phosphorescent [26, 28].

The anthrahydroquinone/anthraquinone (AHQ/AQ) system was used as a switching mechanism for molecular devices (Fig. 25). In that study, the synthesis and properties of dinuclear molecular switches, such as AcAHQ and AQ, which had associated redox-active $Ru(dppe)_2$ fragments, were investigated, and it was revealed that organometallic systems, such as the AcAHQ/AQ–Ru system, were very effective bimodal molecular switches. These complexes could be potential components for dual reversible switches and irreversible fuse systems in molecular electronics.

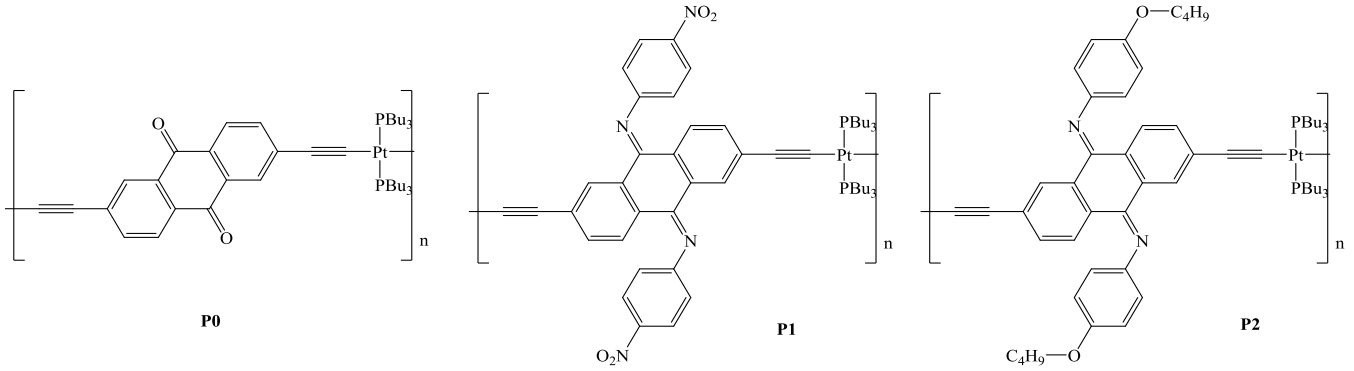


Fig. 24. A comparative series of trans-(ethynyl-bis(tributylphosphinyl)platinum and trans-(ethynyl-bis(tributylphosphinyl)platinum-containing polymers bearing different substituents

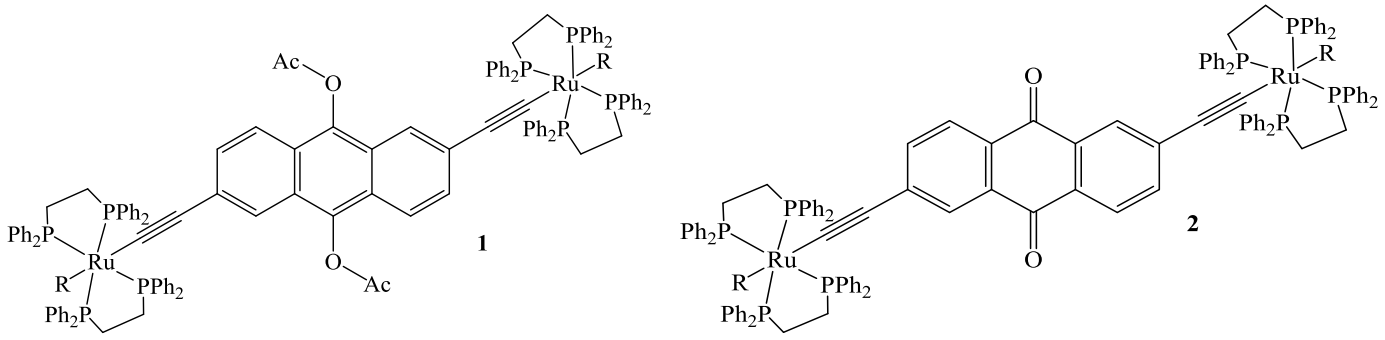


Fig. 25. An anthrahydroquinone and anthraquinone system exhibiting molecular switching capabilities

5 The biological activity of acetylenylquinones and products of their modification

In this section, the search for effective therapeutic agents based on acetylene quinone derivatives is reported. To date, an important area of medicinal chemistry deals with the construction of so-called "hybrid" molecules via the combination of two structural units of a different nature. Acetylene derivatives of anthraquinones are promising bioconjugates known to exhibit anticancer activity. On the other hand, anthraquinoid derivatives were shown to be capable of intercalating in the DNA duplex, and many natural anthraquinones exhibited high biological activity. Therefore, it was no surprise that scientists focused their research efforts on the construction of biologically active biohybrids that combined these two pharmacophore groups into one molecule.

Using $Pd(PPh_3)_4$ as a catalyst, the reaction of 9,10- and 1,8-dibromoanthracene with ethynylferrocene in a tetrahydrofuran/triethylamine solvent mixture (THF/TEA) led to the formation of **1** and **2**. Compound **3** was prepared in a similar manner using 2,6-diiodoanthraquinone in toluene (Fig. 26).

Based on the binding energy (−10.61 kcal/mol^{-1}) and inhibition constant (16.74 nM), it was obvious that compound **2** had the best interaction with cancer-related *Aurora A* kinase protein of all the analogs in this series. Indeed, both molecular docking and cell cytotoxicity assays revealed that **2** was a more effective anticarcinogen when compared with **1** and **3** as it was capable of binding to DNA strands and triggering apoptosis [29]. Of particular interest was the antimicrobial agent Chloroquinocin 1, which was shown to be active against Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) [12]. Details on the synthesis of analogs of Chloroquinocin 1 were reported in Section 2 (Fig. 27) [12]. The route of synthesis for chloroquinone and its analogs was shown to be very effective as it provided the basis for the creation of a new series of this in-demand class of compounds.

In Section 2, the synthesis of natural pyranones using acetylene derivatives of anthraquinone was described [19]. Here, Rixson et al. were able to expand on the structure of this compound and generate a series of synthetic analogs for antitumor agent BE–26554A (Fig. 28) *via* a simple reaction route. This reaction series brought into stark focus the untapped potential of this class of pyranones as chemotherapeutic agents, especially as antibacterial and antitumor compounds that were related to BE–26554A.

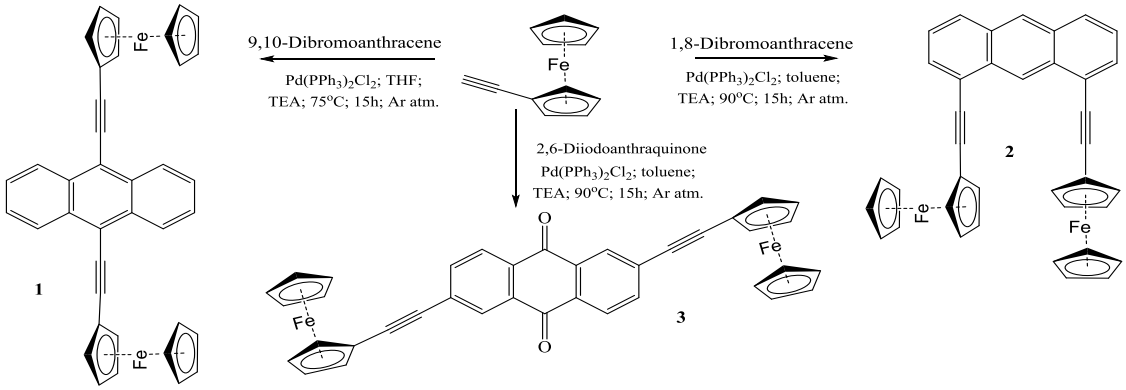


Fig. 26. Synthesis of ferrocene-substituted bis-(ethynyl)anthracene and -anthraquinone compounds

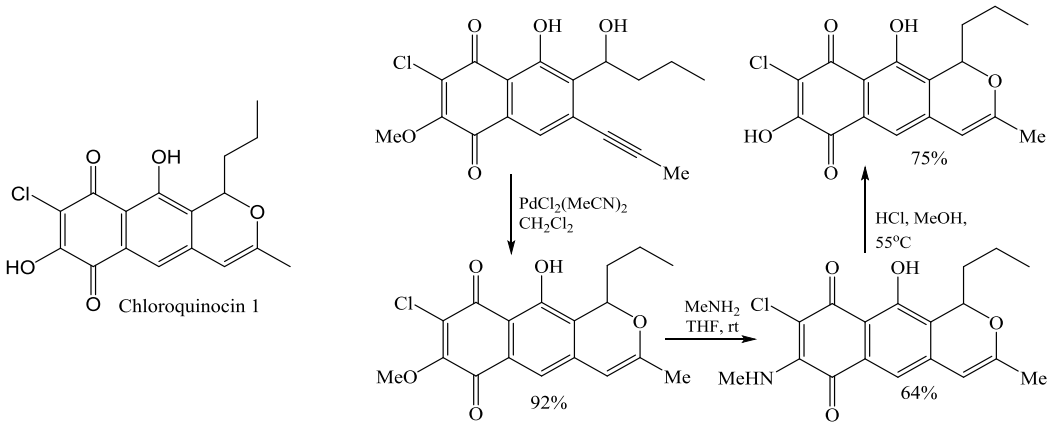


Fig. 27. Synthesis of isomeric anthrapiran-2-one analogs of the natural compound BE–26554A

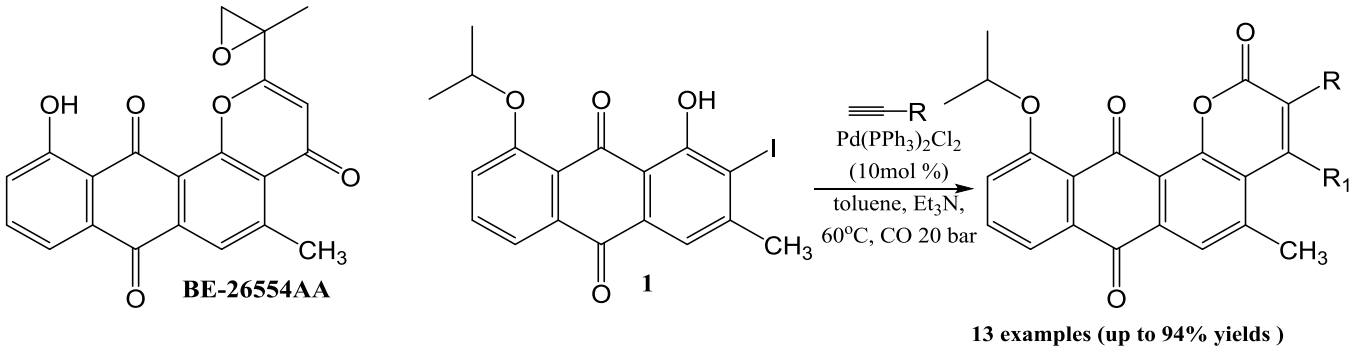


Fig. 28. Synthesis of series of analogs of natural chemotherapeutic agents BE–26554A

In the search for biologically active compounds, the annelation of *peri*-alkynyl-9,10-anthraquinones using nitrogen binucleophiles proved to be highly effective [6]. Urea, in particular, was shown to be the best nucleophile for the regioselective cyclization of alkynylanthraquinones. Unlike guanidine, the reaction between urea and 1-R-ethynyl-9,10-anthraquinones **1a**–**j** triggered the formation of a 2-R-7*H*-dibenzo [*de,h*] quinolin-7-one (**2a**–**j**) heterocyclic system (Fig. 29). Excess urea was shown to be extremely important as the reaction was more expedient when conducted in molten urea due to the reagent's poor solubility in most organic solvents, its availability, and its low cost. The absence of toxic solvents provided a green alternative to this type of reaction.

New heterocyclization of 1-R-ethynyl-9,10-anthraquinones with urea resulted in the formation of 2-R-7*H*-dibenzo [*de,h*] quinolin-7-ones which were synthetic analogs of natural alkaloids of aporphine [6]. It should be noted that the conditions of this reaction were similar to those often utilized in green chemistry processes as no aggressive reagents or solvents were used and the reaction was carried out in molten urea, a non-toxic commercially available product often used as a fertilizer in agricultural applications. Processing this reaction consisted of simply diluting the reaction mass with water and filtering the precipitated product, making this method environmentally friendly and energy-efficient. Additionally, this type of compound exhibited anticancer activities [30–32].

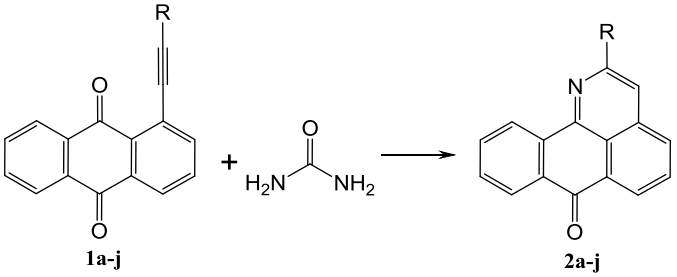


Fig. 29. Synthesis of 2-R-7*H*-dibenzo [*de,h*] quinolin-7-ones *via* green chemistry

Netzel et al. [33] described the synthesis of AQ-Ad conjugates *via* palladium coupling of *tert*-butyldiphenylsilyl (TBDPS) 5′-protected 8-ethynyl-2′-deoxyadenosine with the corresponding 2-brom-9,10-anthraquinones. The conjugates of anthraquinone–adenine (AQ-Ad) with reduction potentials were shown to be favorable for electron-transfer processes and could be used in studies on adenine oxidation in DNA (Fig. 30).

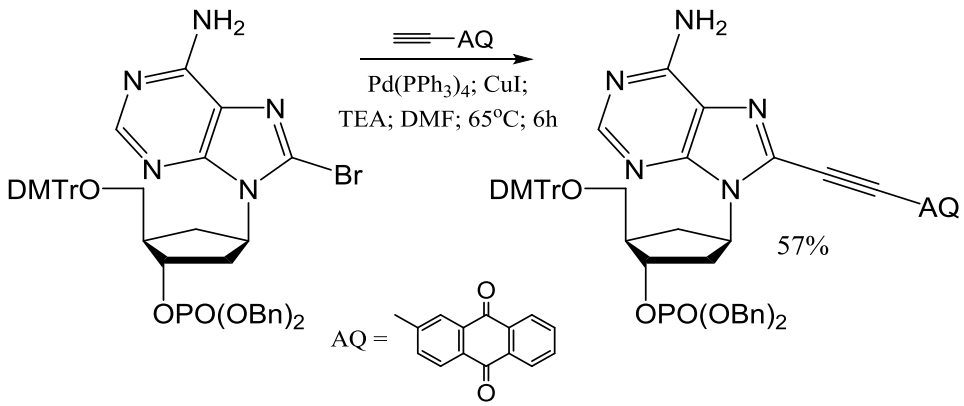


Fig. 30. Synthesis of the conjugates of anthraquinone–adenine (AQ-Ad) for studies on the oxidation of adenine in DNA

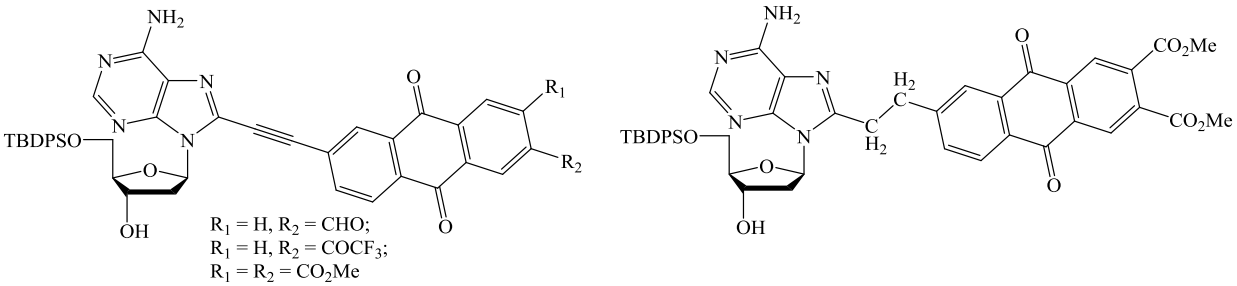


Fig. 31. Saturated and unsaturated conjugates of AQ-Ad

Attaching the AQ moiety to adenine *via* a rigid C≡C bridge facilitated regioselective control within the structure of the DNA duplex. The electrochemical potentials of these conjugates were measured in acetonitrile, and it was demonstrated that the presence of the ethynyl linkers enhanced the reduction potential of the respective compound by 125–150 mV relative to the corresponding ethyl linkers.

Conclusion

Using several examples of new and unusual transformations, this review highlights the significant synthetic potential of electron-deficient acetylenylanthraquinones and their role in expanding our understanding of the nature of the C≡C triple bond. Alkynes provide a large amount of energy which can be utilized for novel transformations. In the acetylenylquinone derivatives, the close proximity of the carbonyl groups makes the C≡C triple bond even more reactive, thus facilitating irreversible, thermodynamically advantageous chemical transformations. As a result, most of the transformations involving acetylene compounds are resource-efficient. In the search for novel medicinal agents, alkynylanthraquinones were shown to be an important class of natural alkaloids, particularly those of the aporphinoid series (aporphinoid alkaloids). The authors hope that this review will help researchers find more rational, effective routes for the synthesis of target compounds using the unique reactivity of the activated C≡C triple bond.

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