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Divergent Cyclizations of 1-R-Ethynyl-9,10-anthraquinones: Use of Thiourea as a "S^{2-}" Equivalent in an "Anchor-Relay" Addition Mediated by Formal C−H Activation

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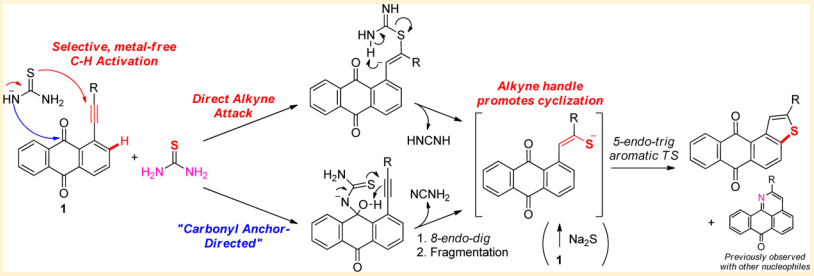
Supporting Information



ABSTRACT: The EtONa-mediated reaction of *peri*-R-ethynyl-9,10-anthraquinones with thiourea yields 2-R-7*H*-dibenzo[*de*,*h*]-quinolin-7-ones and 2-R-anthra[2,1-*b*]thiophene-6,11-diones. Although 2-R-7*H*-dibenzo[*de*,*h*]quinolin-7-ones were observed previously in reactions with other N-centered nucleophiles (hydrazine, guanidine, and urea), the formation of 2-R-anthra[2,1-*b*]thiophene-6,11-diones is a new reactivity path. DFT computations analyzed factors responsible for the switch in reactivity and the relative importance of two possible pathways: (1) the "anchor-relay" mechanism mediated by nucleophilic attack at the carbonyl and (2) direct attack at the alkyne. The two pathways converge on a vinyl sulfur anion, set up for a 5-endo-trig cyclization at the *ortho*-position. Subsequent rearomatization/oxidation provides the fused thiophene product via formal C−H activation. The calculations suggest that the latter pathway, the direct attack at the alkyne, is more likely, due to the relatively high barrier for the 8-endo-dig cyclization (pathway 1). Computational insights led to a more selective synthesis of fused thiophenes, based on the reaction of acetylenic anthraquinones with sodium sulfide. This reaction does not require prefunctionalization at the *ortho*-position since direct C−H activation is efficient. The absence of fused five-membered heterocycles in earlier work was investigated computationally. The other N-centered nucleophiles form stronger anion−π complexes with the electron-deficient quinone core, promoting carbonyl attack over direct alkyne attack.

INTRODUCTION

The high reactivity and unique features of acetylenic compounds account for their diverse applications in many areas of organic synthesis, chemical biology,[1] and medicinal chemistry.[2] Due to its electrophilicity and favorable spatial location relative to the carbonyl group of the quinoid core, the alkyne moiety of *peri*-R-ethynyl-9,10-anthraquinone serves as a particularly convenient model for investigation of factors which control the regioselectivity of alkyne cyclizations.[3]

Previously, we have shown that the reaction route in *peri*-R-ethynyl-9,10-anthraquinones is, to a large extent, defined by the nature of nucleophile. For example, the reaction of 1-R-ethynyl-9,10-anthraquinones with hydrazine leads to the formation of heterocycles I and II,[4] with guanidine I, III, and IV,[5] whereas interaction with urea leads to the formation of only I.[6] All products arise from nucleophilic attack at C-9 (the carbonyl), initiating the cascade (Figure 1).

Considering the diversity of the above transformations, as well as the structural relation of the heterocycles I, III, and IV to alkaloids of the *Aporphinoid* family,[7] we investigated the direction of cyclizations of 1-R-ethynyl-9,10-anthraquinones with thiourea—another multifunctional nucleophile related to urea and guanidine. In this manuscript, we discuss the new directions of reactivity originating from the presence of a sulfur atom in this reagent.

These transformations allow for the metal-free functionalization at a nonactivated position of a phenyl ring via formal C−H activation. The alkyne serves as a functional handle for direct formation of fused thiophenes after oxidative rearomatization.

RESULTS

The starting 1-R-ethynyl-9,10-anthraquinones **1a−g** were prepared via the standard Sonogashira[8] and Castro[9] reactions

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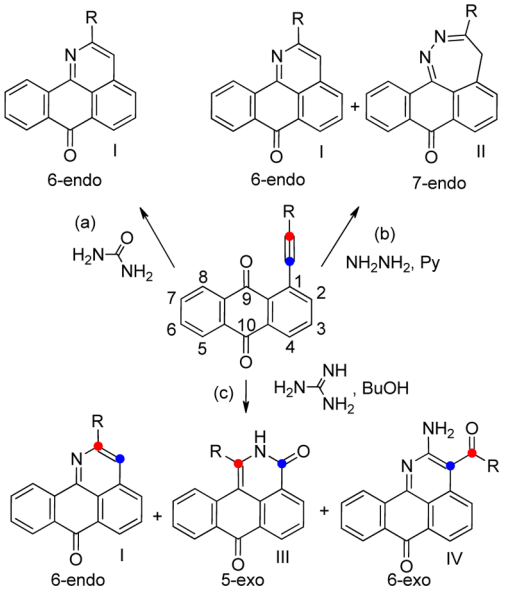


Figure 1. Diverging reactivity of acetylenic quinones toward multifunctional nucleophiles: urea (a), hydrazine (b), and guanidine (c).

as described earlier.[5,6] Reaction with excess thiourea was carried out in polar solvents in the presence of sodium ethoxide. For substrates **1a,e**, this procedure leads to the formation of two heterocyclic products: 2-R-7*H*-dibenzo[*de*,*h*]quinolin-7-ones **2** and 2-R-anthra[2,1-*b*]thiophene-6,11-diones **3**. In the case of alkynes **1f,g**, only 2-R-7*H*-dibenzo[*de*,*h*]quinolin-7-ones **2** were observed.

In our initial experiments, the reaction was accompanied by the formation of side products that were difficult to separate. This difficulty led to lower yields of the final products **2** and **3**. Considering that the side processes are likely to be associated with the reactions of the starting alkynes with the decomposition products of thiourea,[10] we have searched for solvents which can overcome the low solubility of thiourea and stabilize the anionic reaction intermediates. Optimization of the reaction conditions indicated that pyridine is the most suitable reaction media, much superior to alcohols, where thiourea is also soluble. Yields of the products are summarized in Table 1.

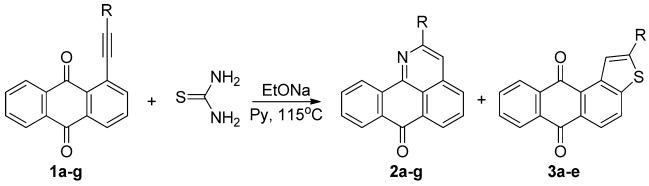
The high nucleophlicity of the reactive media prevented us from using *peri*-R-ethynyl-9,10-anthraquinones **1** with an activating substituent at the triple bond. Due to the formation of complex inseparable mixtures in the reaction of thiourea with alkynes **1i,j** where R is electron withdrawing we could not expand our study of electronic effects favoring the formation of 2-R-anthra[2,1-*b*]thiophene-6,11-diones **3** to such substrates.

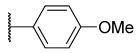
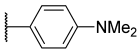
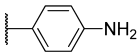
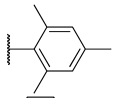
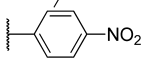
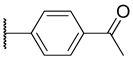
On the other, the observed lack of reactivity of 1-mesitylethynyl-9,10-anthraquinone **1h** illustrates the importance of steric factors. The analogous effect has been observed in the reaction of 1-mesitylethynyl-9,10-anthraquinone with urea[6] and guanidine.[5]

COMPUTATIONAL DETAILS

Calculations were performed using Gaussian 03 software[11] with geometries and energies obtained at the B3LYP/6-31G(d,p) level of theory. Reactants, products, and intermediates were confirmed as minima and the transition state structures were confirmed as saddle points with a single imaginary frequency through frequency calculations. Coordinates, total energies, and imaginary frequencies (for transition state structures) can be found in the Supporting Information.

Table 1. Reaction Time and Yields of Heterocycle 2a−g and 3a−e in the Reaction of Thiourea with Alkynes 1a−g in Pyridine



Alkyne	R	Product	Yields, %	Reaction time, h
1a	Ph	**2a**	20	26
		3a	23	-
1b		**2b**	10	18
		3b	67	-
1c		**2c**	36	8
		3c	25	-
1d	Bu	**2d**	26	12
		3d	38	-
1e	C_5H_{11}	**2e**	16	9
		3e	45	-
1f		**2f**	40	9
1g		**2g**	56	36
1h		No reaction		
1i		Inseparable mixture		
1j		Inseparable mixture		

DISCUSSION

Mechanistic Considerations. The formation of 2-R-7*H*-dibenzo[*de*,*h*]quinolin-7-ones **2** was observed in every case. Generally, their yield varied but, in several cases (e.g., for alkynes **1f,g**), these heterocycles were the only isolated products.

The formation of dibenzo[*de*,*h*]quinolines proceeds via nucleophilic attack at the carbonyl, leading to the formation of the hemiaminal intermediate, analogous to the reactions of 1-R-ethynyl-9,10-anthraquinones with hydrazine, guanidine and urea. Deprotonation of the resulting hemiaminal at nitrogen would give the delocalized anion (**5a**, Figure 2), which can undergo a 6-endo nucleophilic closure with a subsequent (or concomitant) elimination of HNCS and water. The addition/cyclization/fragmentation cascades proceeds similarly to the reactions of 1-R-ethynyl-9,10-anthraquinones with guanidine[5] and urea.[6] Calculations suggest this occurs as an electrophile-promoted nucleophilic closure, with the proton of the hydroxyl group coordinating at the alkyne and providing electrophilic assistance to the nucleophilic attack.

The presence of a S-atom slightly decreases the nucleophilicity of the key "pre-cyclization" intermediate **5** and increases the 6-endo-dig cyclization barrier (26.0 kcal/mol) in comparison to the analogous barriers for urea- and guanidine-mediated cyclizations (24.0 and 22.2 kcal/mol, respectively). The higher barrier for this process, coupled with the greater nucleophilicity

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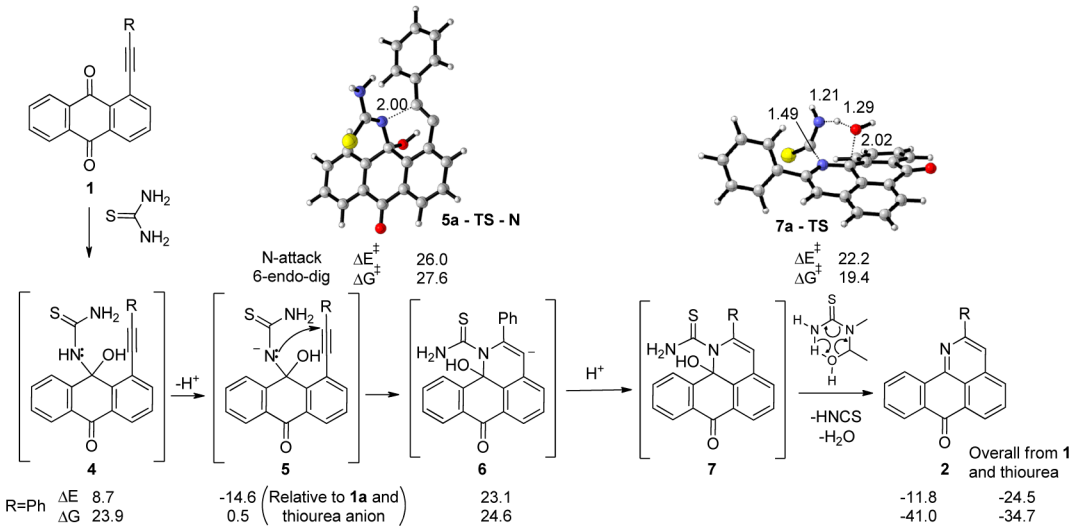

Figure 2. Proposed mechanism and calculated energies (R═Ph) for the formation of 2-R-7*H*-dibenzo[*de*,*h*]quinolin-7-ones **2**. Calculations performed at the B3LYP/6-31G(d,p) level of theory. Energies are given in kcal/mol relative to the previous stationary point unless otherwise noted. Bond lengths are in Ångstroms.

of sulfur (relative to oxygen and nitrogen), allows alternate reaction pathways to take place.

In contrast, the formation of 2-R-anthra[2,1-*b*]thiophene-6,11-diones **3** has no analogues in the reactions with other nucleophiles. A priori, one can suggest that formation of the annealed heterocycle could proceed in two different ways (Figure 3).

In the first scenario, which we will refer to as the "carbonyl anchor-directed" process, the formation of 2-R-anthra[2,1-*b*]thiophene-6,11-dione **3** starts from the same hemiaminal intermediate formed via the attack at the ninth (the carbonyl) carbon of the anthraquinone core that is responsible for the formation of 2-R-7*H*-dibenzo[*de*,*h*]quinolin-7-one **2** (outlined above in Figure 2). Since this anion is an ambident nucleophile, it can also attack the alkyne moiety not only via the nitrogen but also via the sulfur atom.

Analogously, to the 6-endo-dig cyclizations of the N-nucleophilic center, the 8-endo-dig attack by the sulfur atom can also be promoted by the electrophilic assistance of an intramolecular H-bond to the developing carbanionic center. Further evolution of this interaction leads to the full intramolecular proton transfer from the hydroxyl moiety to the carbanion, effectively trapping the cyclic intermediate (**9**, Figure 3). Subsequent fragmentation reforms the carbonyl and expels $NCNH_2$ to give the sulfur-centered anion **11**. The latter is set up for a 5-endo-trig cyclization at the *ortho* position, providing enolate **12**.

An alternative pathway comes from direct attack of thiourea at the alkyne. Protonation of the resulting vinyl anion is followed by a fragmentation which expels HNCNH and gives the same sulfur-centered anion **11** as in the "carbonyl anchor-directed" pathway.

Rearomatization and oxidation irreversibly trap the relatively unstable enolate **12**, yielding 2-R-anthra[2,1-*b*]thiophene-6,11-dione, **3**. This process is analogous to the long known, S_NH, nucleophilic substitution in quinones (Figure 9, top), which will subsequently be discussed in more detail.

The "carbonyl anchor-directed" is more complex but appealing from two perspectives. First, it shares a common origin with the known directions of reactivity originating from

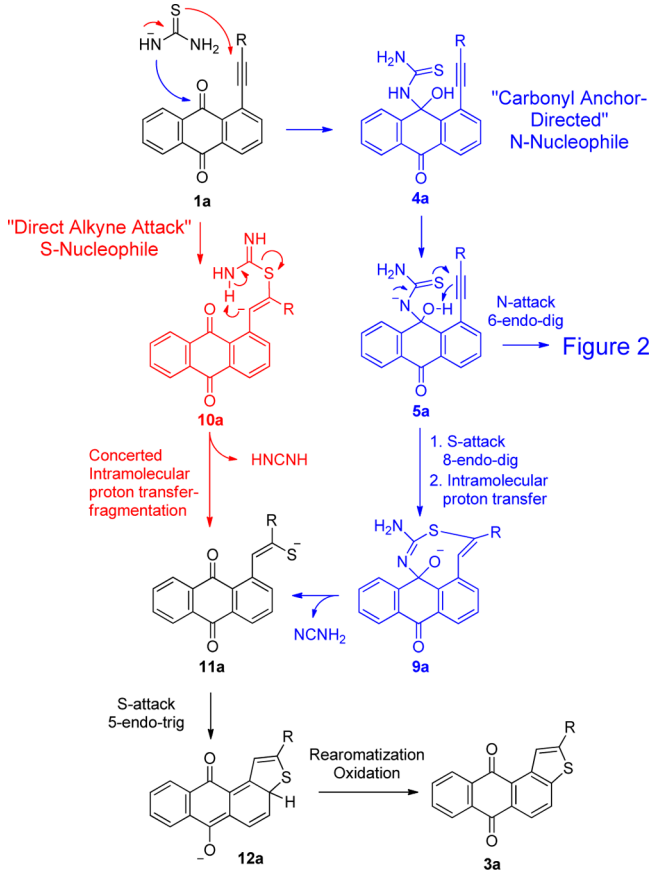

Figure 3. Possible mechanisms for the formation of 2-R-anthra[2,1-*b*]thiophene-6,11-diones, **3**, converging on the S-centered anion, **11**. The B3LYP/6-31G(d,p) optimized geometries and energies for the transformation of alkyne **1a** to **3a** (R═Ph) are given in Figure 4.

the attack at the carbonyl. Additionally, the change from a N- to the S-attack by the N,S-ambident nucleophile is consistent with the greater nucleophilicity of sulfur relative to nitrogen and oxygen. Second, if this mechanism can operate in such a system, this finding may have larger implications. It illustrates

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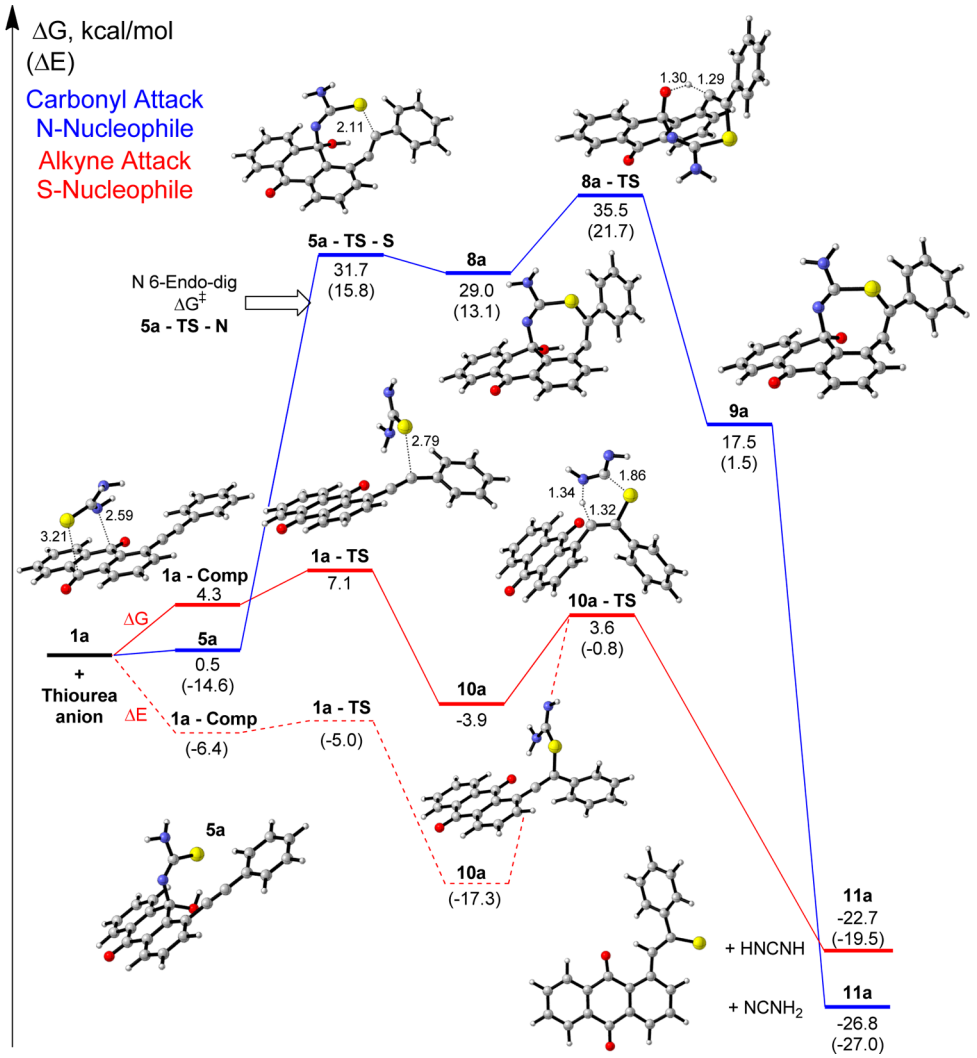

Figure 4. Proposed pathways and reaction/activation free energies for the formation of S-anion intermediate **11a** calculated at the B3LYP/6-31G(d,p) level of theory. Reaction/activation energies are also shown (in parentheses) to illustrate the entropic effects. The blue depicts the "carbonyl anchor-directed" pathway, while the red depicts direct alkyne attack. Dotted red lines illustrate the enthalpically favorable precomplexation of reactants (ΔE). All energies are given relative to the isolate reactant and anion (in kcal/mol). Bond lengths given in Ångstroms.

how attack of a multifunctional nucleophile at a more reactive center of a multifunctional electrophile can be used as a general directing principle in controlling selectivity of nucleophilic processes. In this scenario, the initial attack "anchors" the bifunctional reagent reversibly at a "relay" position as a hemiaminal. The intramolecular constraints at the anchor point then direct the second attack of the remaining "unbound" part of the reagent at the target. This "anchor/relay" strategy can be used to control chemo-, regio- and stereoselectivity of nucleophilic additions in a way similar to "relay metathesis,"[12] "chiral relay auxillaries,"[13] "anion relay chemistry,"[14] and related processes.

In contrast, the "direct alkyne attack" is straightforward. However, it is not clear why it would not occur for the other bifunctional nucleophiles related to thiourea. In addition, despite polarizing the alkyne to help facilitate attack at the desired carbon, donor substituents should deactivate the nucleophilic attack at this target overall. Finally, if the key fragmentation releasing the vinyl thiolate intermediate **11** is concerted with proton transfer, then it should involve the less stable E-isomer of carbanion **10.** Formation of this anion should carry an additional thermodynamic penalty.

As both pathways converge on intermediate **11**, and the subsequent rearomatization/oxidation steps are undoubtedly thermodynamically favorable, the computational analysis of the latter steps of the cascade was unnecessary. However, the competition between the two pathways to the vinyl intermediate **11** required computational mapping of the respective potential energy surfaces.

Computational Analysis of the Diverging Pathways. The direct attack of thiourea at the alkyne is predicted to be the more energetically favorable pathway (for **1a**, R = Ph). The barrier relative to the isolated reactants was calculated to be negative, unless entropy is considered, providing a positive free energy of activation (Figure 4, red dotted, ΔE, and solid lines, ΔG). This prompted our investigation of the possibility of precomplexation prior to bond formation. Although the complex formed between the electron-rich anion of thiourea and the electron-deficient anthraquinone core was found to be favorable enthalpically, the entropic penalty cancels this stabilization (**1a**−**Comp**, Figure 4). Notably, the complexes formed between the anions of guanidine/urea and the anthraquinone starting material were found to be favorable, even when the entropic penalty is included.[15] Enthalpically, the

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barrier is only positive when calculated relative to this anion-π complex.[16] Both analyses are depicted in Figure 4, providing a positive barrier for the initial addition step, either relative to the anion-π complex (ΔE, red dotted lines) or by considering free energies of activation/reaction (ΔG, red solid lines). Quick trapping of the resulting vinyl anion, followed by a fragmentation, expels HNCNH and gives the sulfur-centered anion **11a**. From here, the formation of 2-phenylanthra[2,1-*b*]thiophene-6,11-dione **3a** follows the previously discussed pathway (Figure 3), where the S-anion undergoes a 5-endo-trig cyclization (this reaction has recently been shown to benefit from aromatic stabilization in the transition state despite being *nonpericyclic*)[17] at the *ortho* position, followed by subsequent rearomatization and oxidation (Figure 8).

While nucleophilic attack, at both the carbonyl (N-nucleophile) and the alkyne (S-nucleophile) is facile (Figure 5), the formation of 2-phenylanthra[2,1-*b*]thiophene-6,11-dione **3a** most likely proceeds through direct attack at the alkyne. While attack at the carbonyl still readily occurs (leading to the formation of 2-phenyl-7*H*-dibenzo[*de*,*h*]quinolin-7-one **2a**) the relatively high barrier for the 8-endo-dig cyclization (Figure 6) deems this pathway less likely as a route to afford 2-phenylanthra[2,1-*b*]thiophene-6,11-dione **3a**. Attack at the alkyne in the rate limiting step is also consistent with the observation that the two examples where the formation of 2-(4-aminophenyl)anthra[2,1-*b*]thiophene-6,11-dione **3f** was not observed, correspond to the two electron rich substrates **1g** (R = di-Me-pyrazolyl) and **1f** (R = *p*-NH_2Ph). On the other hand, the surprisingly high yield for the thiophene from **1b** (R = *p*-MeOPh) suggests that the role of alkyne polarization is likely to be quite complex.

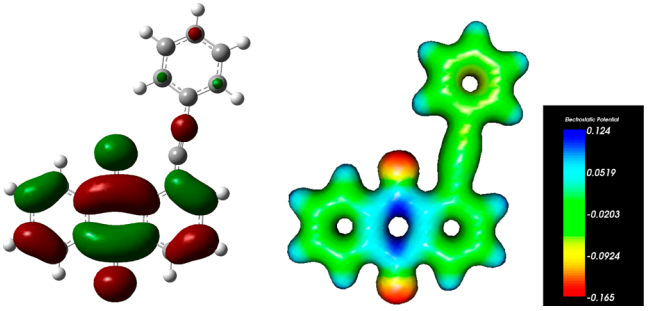

Figure 5. LUMO (left) and electrostatic potential map (right) of the alkynyl anthraquinone. Note that there is no preferred site for the nucleophile attack. Calculated at the B3LYP/6-31G(d,p) level of theory.

The key structural features of the 8-endo-dig cyclization TS are shown in Figure 6. Although activation energy needed to reach this structure is relatively low (15.8 kcal/mol), the unfavorable entropy contribution renders the free energy of activation much higher (31.7 kcal/mol). The origin of these differences is in a highly preorganized TS where two processes occur simultaneously: (a) the nucleophilic attack of the S-nucleophile at the in-plane alkyne π-system and (b) proton coordination at the out-of-plane π-system at the positions where negative charge increases due to the above nucleophilic attack. Since the two reactions involve orthogonal π-systems of the alkyne moiety, they are not synchronized perfectly. Nevertheless, the unique features of this reaction display intriguing similarity to a pseudopericyclic reaction.[18]

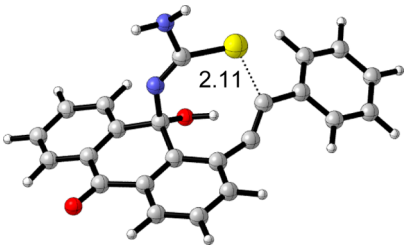

Figure 6. Optimized geometry of the 8-endo-dig cyclization (**5a-TS-S**) of the S-anion attacking the alkyne in the "carbonyl anchor-directed" pathway. The hydroxyl proton facilitates the process via simiultaneous coordination at the out-of-plane alkyne π-system. Calculated at the B3LYP/6-31G(d,p) level of theory. Incipient bond length given in Å.

It must be noted that the product of nucleophilic attack by nitrogen at the carbonyl was only a minimum when the resulting O-anion was trapped via protonation, making direct comparison of barriers for alkyne versus carbonyl attack impossible. The addition step was predicted to be uphill (**4a**, Figure 7) unless the energy is calculated for the addition/proton transfer (**5a**), relative to the starting alkyne (**1a**) and the thiourea anion. Even then, the free energy for the addition step is predicted to be essentially zero. While this pathway results in the formation of 2-R-7*H*-dibenzo[*de*,*h*]quinolin-7-ones **2**, the relatively unfavorable nucleophilic attack at the carbonyl allows alternate pathways to begin to compete.

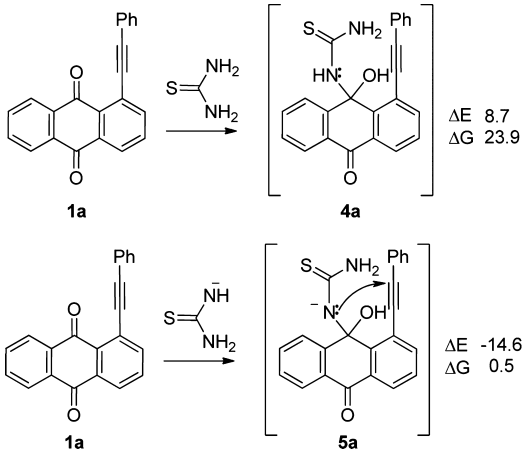

Figure 7. Calculated energies (in kcal/mol) for thiourea (top) and thiourea anion (bottom) addition to the carbonyl of 1-phenylethynyl-9,10-anthraquinone **1a**. Optimized at the B3LYP/6-31G(d,p) level of theory.

The absence of products resulting from direct attack at the alkyne by other nucleophiles was an initially surprising observation. Carbonyl addition is less favorable for thiourea than for previous nucleophiles, giving the possibility of alternate pathways. This can also be explained by the anion–π complexes formed between the deprotonated forms of urea/guanidine and the starting alkyne.[15] It was found that complex formation increased in favorability from thiourea→urea→guanidine, and only showed a negative free energy for complex formation for the latter two nucleophiles. The activation barrier for alkyne attack relative to this complex followed the reverse trend, as would be expected for the reactivity trends associated with unproductive reactant stabilization. Since these complexes are centered above the plane of the anthraquinone core, the

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stronger complexes facilitate attack at the carbonyl (for urea and guanidine).

One has to note the important role of base (EtONa) in the reactions. In the absence of base, we observed a significant increase in the formation of side products and lower yields for the heterocycles **2** and **3**. The possible roles of EtONa involve the deprotonation of thiourea, stabilization of other anionic intermediates involved in this cascade transformation, and assisting in aromatization.[19]

Computational analysis provides some insights into the possible role of the base. For example, **4a** (Figure 7) was only a minimum when the O-anion was protonated. Additionally, the transformation from intermediate **6a** to **7a** (Figure 2) may occur via intramolecular proton transfer (as is seen in **8a-TS** (Figure 4)) but in the absence of a counterion to stabilize the resulting O-anion, the carbonyl is reformed, breaking the C−N bond. Intermolecular trapping of the vinyl anion provides **7a** as a stable precursor in route to the formation of 2-phenyl-7*H*-dibenzo[*de*,*h*]quinolin-7-one **2a**.

The regioselectivity of the reaction seems to follow a more complex trend than in the reaction of alkynes **1** with both guanidine,[5] where the ratio of products was controlled by the nature of substituent R, and urea,[6] where a single product was observed. It seems that strong electron donor substituents (R = *p*-MeOPh) further polarize the alkyne (in a push−pull mechanism with the help of the electron withdrawing quinone core), but due to the aforementioned complications arising from strongly activating substituents (toward nucleophilic attack by solvent, R = *p*-NO_2Ph or *p*-AcPh), further studies of electronic perturbation of product formation could not be conducted.

Formal C−H Activation via Nucleophilic Substitution. In both suggested pathways for the formation of **3** (Figure 3), the transformation of **11** to **3** proceeds via a 5-endo-trig cyclization at C-2 of the anthraquinone core, followed by subsequent oxidation and rearomatization (**12** to **3**, Figure 8). The S_NH nucleophilic substitution of hydrogen (hydride) is generally

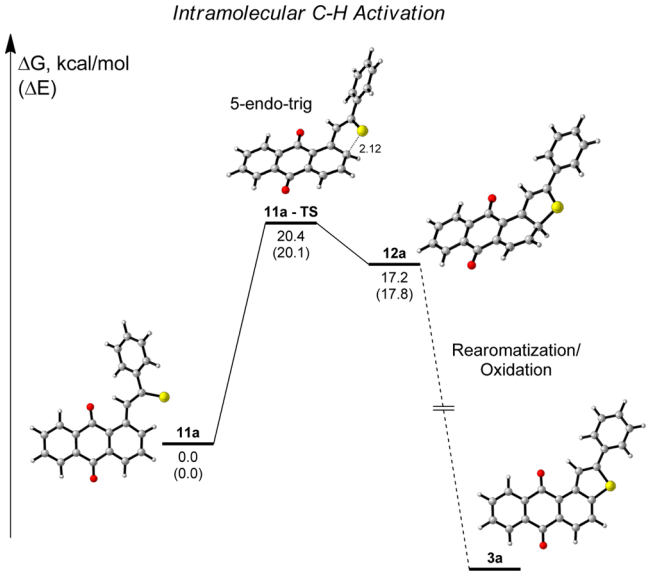

Figure 8. Reaction and activation energies for the transformation of S-anion intermediate **11a** into 2-phenylanthra[2,1-*b*]thiophene-6,11-dione **3a** calculated at the B3LYP/6-31G(d,p) level of theory. All energies are given in kcal/mol. Bond lengths given in Ångstroms.

difficult and requires harsh conditions. This type of reaction is usually limited to the highly electrophilic substrates such as nitroarenes, cationic complexes of hetarenes, 1,4-benzo- and 1,4-naphthoquinones. It is less common for 9,10-anthraquinones because nucleophilic substitution cannot proceed directly at the quinone ring but has to involve the adjacent ring which is only moderately activated by the acceptor.[20]

The S_NH nucleophilic substitution in quinones is generally considered a redox process which proceeds via nucleophilic addition, forming a hydroquinone (Figure 9, top). In the next step, the hydroquinone is oxidized to the final product either by oxygen from the air or by another molecule of the starting quinone.[20] The final steps in Figures 3 and 8 are analogous but occur through an adjacent ring (Figure 9, bottom). An interesting possibility, specific to the fragmentation-mediated reactions of thiourea, is that the oxidant required for the transformation of **12** to **3** is the methanediimine side-product expelled upon fragmentation of either **9** or **10**. Deprotonation of one of the enols could help facilitate delivery of a hydride to the methanediimide, forming formimidamide. Calculations suggest that the more likely oxidant is the starting quinone **1a** (Figure 9, bottom), due to the aromatic stabilization gained in both the fused thiophene **3a** and the resulting hydroquinone anion.

Formation of 2-R-anthra[2,1-*b*]thiophene-6,11-diones **3** have been reported previously, but required activation in the anthraquinone substrate. The formation of this family of heterocycles from related quinones was only observed for the reaction of 2-chloro-substituted 1-alkynyl-9,10-anthraquinones with sodium sulfide, where C-2 has been activated by the presence of a halogen (Figure 10).[21] This work has been extended to the synthesis of benzo[*b*]thiophenes and selenophenes, benzo[1,2-*b*:4,5-*b*′]dithiophenes and diselenophenes, and benzo[1,2-*b*:3,4-*b*′:5,6-*b*″]trithiophenes and triselenophenes from *o*-halo-alkynylbenzene precursors.[22] The scope and yields of benzo[*b*]thiophenes have been improved upon through the use of a copper catalyst.[23] In these cases an anionic 5-endo-dig cyclization[3,17,24] of the thiolate (following nucleophilic aromatic substitution at the *ortho*-halogen) forms the thiophene ring.

Encouraged by these results with thiourea, we have investigated the direct reaction of alkynes **1** with sodium sulfide and found a clean reaction leading to the formation of annealed thiophenes **3** in moderate yields (Table 2). The significant synthetic advantage of our approach is that it does not require introduction of halogen to activate C-2 for the nucleophilic substitution (Figure 9, bottom).

This finding opens access to polycyclic aromatic quinones, 2-R-anthra[2,1-*b*]thiophene-6,11-diones **3** without the need for activation at the *ortho*-position via introduction of a halogen atom and/or use of metal catalysts. Instead, the alkyne moiety acts as a functional handle, putting the thiolate in close proximity to the anthraquinone. This allows for intramolecular attack at the unactivated *ortho*-position through a 5-endo-trig cyclization (Figure 8). The nucleophilic aromatic substitution of a hydride (rather than a halogen) is possible due to the role of the alkyne, directing attack at C-2.

■ CONCLUSIONS

The newly observed 2-R-anthra[2,1-*b*]thiophene-6,11-diones **3** form through a cascade initiated by nucleophilic attack by thiourea at the alkyne, followed by facile trapping of the vinyl anion, then fragmentation with loss of methanediimide,

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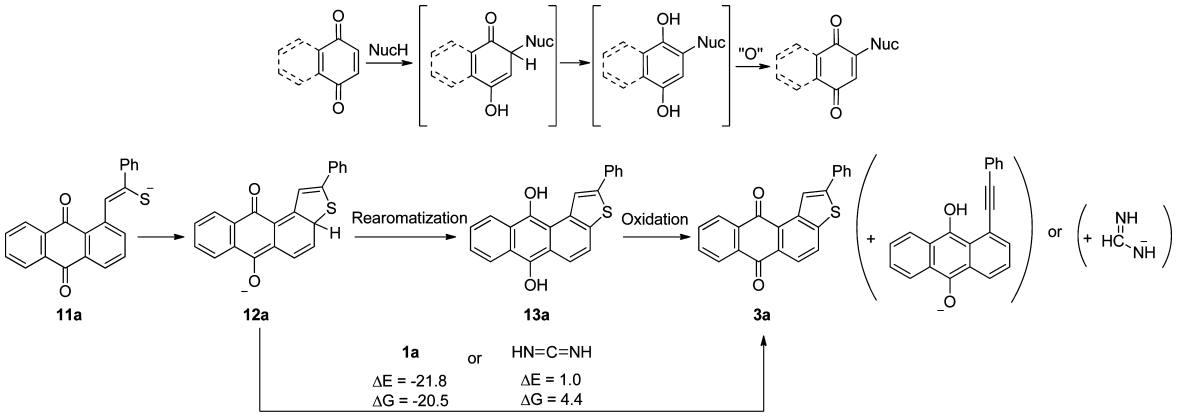

Figure 9. S_NH nucleophilic substitution in quinones (top) and the analogous S_NH nucleophilic substitution in anthraquinones (bottom) proceeding through an adjacent ring. Reaction energies (B3LYP/6-31G(d,p)) for the oxidations of enolate **12a** considered are given below (using either methanediimine or the starting quinone **1a** as the oxidant).

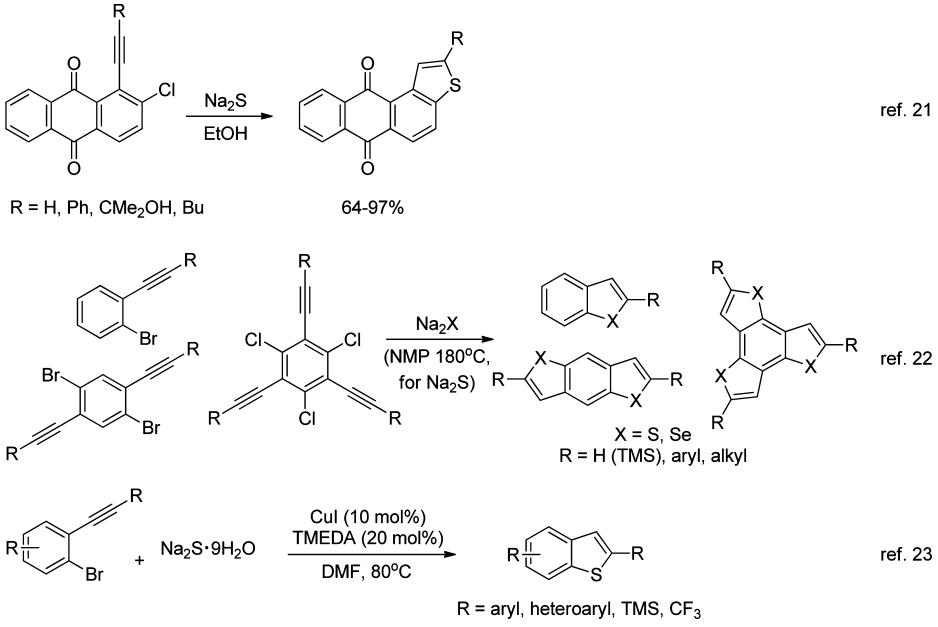

Figure 10. Literature examples of the formation of 2-R-anthra[2,1-*b*]thiophene-6,11-diones **3** from 2-chloro-1-alkynyl-9,10-anthraquinones and related benzothiophenes/selenophenes from *o*-halo-alkynylbenzene precursors.

providing the S-anion. This step anchors the sulfur anion to the anthraquinone core, where a 5-endo-trig cyclization is the only viable pathway that can be trapped irreversibly. This reaction has recently been shown to benefit from aromatic stabilization in the transition state (despite being nonpericyclic).[17] The fused thiophene ring in the product (after subsequent aromatization/oxidation) is the product of formal C−H activation at C-2 without the need for a metal catalyst.

The computational analysis of the proposed pathways leading to the 2-R-anthra[2,1-*b*]thiophene-6,11-diones **3** provide insights into the "anchor-relay" type mechanistic approach. This strategy can potentially be used for greater control of nucleophilic additions to dictate the chemo-, regio-, and stereoselectivity in the product. The design of substrates with various electrophilic centers to react, in a controlled fashion, with multifunctional nucleophiles will open the door for the discovery of many unique new transformations.

The mechanistic studies led us to a more selective synthesis of the fused thiophene products. Through our method, the previous requirement of prefunctionalization at the ortho-aromatic carbon relative to the alkyne is no longer necessary.

While observed before, the structures of 2-R-7*H*-dibenzo-[*de*,*h*]quinolin-7-ones prepared in this work are analogous to natural alkaloids of the *Aporphinoid* family.[25] These compounds show promise in the search for anticancer agents[26] and display enhanced acetylcholine esterase suppression properties.[27] On the other hand, 2-R-anthra[2,1-*b*]thiophene-6,11-diones are related to anthra[2,3-*b*]thiophene-5,10-diones, which displayed high cytotoxicity toward several cancer cell lines.[28]

EXPERIMENTAL SECTION

The IR-spectra were recorded in KBr pellets. Combustion analysis was performed with CHN-analyzer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400.13 and 100.61 MHz, respectively at 25 °C. Chemical shifts are reported in parts per million (ppm). The mass spectra were obtained on a DFS (Double Focusing Sector) High Resolution GC/MS by the direct injection method (the temperature of the ionization chamber was 220−270 °C and the ionization voltage was 70 eV).

Reaction of 1-(*R*-Ethynyl)-9,10-anthraquinones with Thiourea. A mixture of 1-(R-ethynyl)-9,10-anthraquinone (2 mmol),

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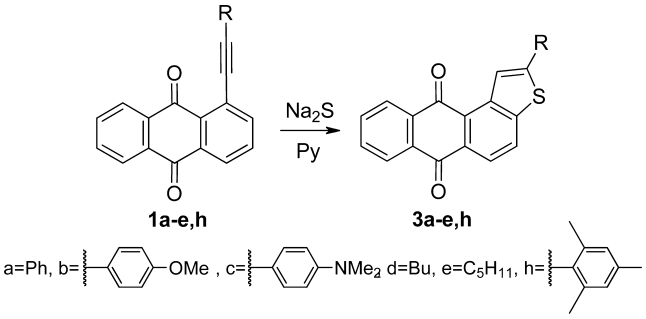
Table 2. Reaction Time and Yields of Heterocycles 3a−e,h in the Reaction of Sodium Sulfide with Alkynes 1a−e,h



alkyne	yield (%)	reaction time (h)
1a	62	1.5
1b	56	1.5
1c	70	2
1d	45	1.5
1e	43	1.5
1h	61	16

thiourea 1 g (13 mmol) and EtONa 0.14 g (2 mmol) in 25 mL of pyridine was boiled for 9−36 h (Table 1). Then a mixture CH_2Cl_2 (200 mL) and water (200 mL) was added, the organic layer was separated, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The products are separated by column chromatography on Al_2O_3 in (elution with toluene). Subsequent recrystallization gave pure compounds.

*2-Phenylanthra[2,1-b]thiophene-6,11-dione (**3a**).* The yield is 156 mg (23%), mp 245−246 °C (from benzene), lit. mp 246.5−247.5 °C.[21]

*2-Phenyl-7H-dibenzo[de,h]quinolin-7-one (**2a**).* The yield is 123 mg (20%), mp 204−205 °C (from toluene-hexane), lit. mp 207−208 °C.[4]

*2-(4-Methoxyphenyl)anthra[2,1-b]thiophene-6,11-dione (**3b**).* The yield is 496 mg (67%), mp 248−249 °C (from toluene − ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (3H, s), 7.00 (2H, ddd, J = 2.2, 2.9, 9.0 Hz), 7.76−7.84 (4H, m), 8.16 (1H, d, J = 8.3 Hz), 8.26 (1H, d, J = 8.3 Hz), 8.29−8.34 (2H, m), 8.95 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 114.7, 120.0, 122.3, 126.4, 127.1, 127.1, 127.2, 128.0, 128.4, 133.2, 133.9, 134.3, 134.4, 139.2, 146.9, 150.5, 160.8, 183.8, 184.6. Anal. Calcd for $C_{23}H_{14}O_3S$: C, 74.58; H, 3.81; S, 8.66. Found: C, 74.60; H, 3.89; S, 8.70. IR (KBr): 1662 (C═O) cm^{-1}.

*2-(4-Methoxyphenyl)-7H-dibenzo[de,h]quinolin-7-one (**2b**).* The yield is 67 mg (10%), mp 206−207 °C (from toluene), lit. mp 206−207 °C.[6]

*2-(4-Dimethylaminophenyl)anthra[2,1-b]thiophene-6,11-dione (**3c**).* The yield is 192 mg (25%), mp 254−255 °C (from 1,4-dioxane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (6H, s), 6.76 (2H, d, J = 8.8 Hz), 7.72 (2H, d, J = 8.8 Hz), 7.74−7.84 (2H, m), 8.11 (1H, d, J = 8.3 Hz), 8.21 (1H, d, J = 8.3 Hz), 8.26−8.36 (2H, m), 8.89 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.4, 112.3, 118.2, 121.5, 121.8, 126.6, 127.0, 127.1, 127.8, 128.1, 131.9, 133.3, 133.7, 134.2, 134.4, 139.7, 146.8, 151.2, 151.8, 183.9, 184.6. Anal. calcd for $C_{24}H_{17}NO_2S$: C, 75.17; H, 4.47; N, 3.65; S, 8.36. Found: C, 75.28; H, 4.42; N, 3.73; S, 8.80. IR (KBr): 1657 (C═O) cm^{-1}.

*2-(4-Dimethylaminophenyl)-7H-dibenzo[de,h]quinolin-7-one (**2c**).* The yield is 252 mg (36%), mp 242−243 °C (from toluene − ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (6H, s), 6.89 (2H, ddd, J = 2.2, 2.9, 9.0 Hz), 7.65 (1H, m), 7.84 (2H, m), 8.03 (1H, s), 8.13 (1H, dd, J = 1.2, 7.3 Hz), 8.22 (2H, ddd, J = 2.2, 2.9, 9.0 Hz), 8.43 (1H, dd, J = 1.2, 7.8 Hz), 8.55 (1H, dd, J = 1.2, 7.3 Hz), 9.11 (1H, dd, J = 1.2, 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.6, 112.5, 114.4, 121.4, 125.7, 127.1, 127.6, 128.1, 128.7, 129.3, 130.2, 130.5, 132.7, 133.7, 133.9, 136.6, 137.3, 148.0, 151.3, 152.4, 183.9 (C═O). Anal. calcd for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 7.99. Found: C, 82.23; H, 4.95; N, 7.93. IR (KBr): 1655 (C═O) cm^{-1}.

*2-Butylanthra[2,1-b]thiophene-6,11-dione (**3d**).* The yield is 243 mg (38%), mp 80−82 °C (from toluene-hexane), lit. mp 83.5−84.5 °C.[21]

*2-Butyl-7H-dibenzo[de,h]quinolin-7-one (**2d**).* The yield is 149 mg (26%), mp 94−95 °C (from hexane), lit. mp 97−98 °C.[4]

*2-Pentylanthra[2,1-b]thiophene-6,11-dione (**3e**).* The yield is 300 mg (45%), mp 95.5−97 °C (from benzene-hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.0 Hz), 1.40 (4H, m), 1.80 (2H, p, J = 7.2, 15.0 Hz), 2.97 (2H, t, J = 7.5 Hz), 7.71−7.80 (2H, m), 8.05 (1H, d, J = 8.3 Hz), 8.16 (1H, d, J = 8.3 Hz), 8.21−8.30 (2H, m), 8.43 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.5, 30.8, 31.4, 31.5, 121.7, 122.6, 126.8, 126.9, 127.1, 127.9, 131.5, 133.1, 133.7, 134.1, 134.2, 138.3, 147.1, 153.7, 183.7, 184.4. Anal. calcd for $C_{21}H_{18}O_2S$: C, 75.42; H, 5.43; S, 9.59. Found: C, 75.80; H, 5.55; S, 9.57. IR (KBr): 1664 (C═O); 2854, 2928, 2955 (Alk).

*2-Pentyl-7H-dibenzo[de,h]quinolin-7-one (**2e**).* The yield is 96 mg (16%), mp 90−91 °C (from hexane), lit. mp 90−91 °C.[6]

*2-(4-Aminophenyl)-7H-dibenzo[de,h]quinolin-7-one (**2f**).* The yield is 258 mg (40%), mp 256−257 °C (from 1,4-dioxane-ethanole). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (2H, br.s), 6.87 (2H, ddd, J = 1.9, 2.7, 8.6 Hz), 7.66 (1H, m, J = 1.3, 7.5 Hz), 7.82−7.89 (2H, m), 8.05 (1H, s), 8.14−8.19 (3H, m), 8.44 (1H, dd, J = 1.3, 7.5 Hz), 8.58 (1H, dd, J = 1.1, 7.2 Hz), 9.10 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.8, 115.4, 121.6, 125.7, 127.6, 128.4, 129.0, 129.3, 129.6, 130.3, 130.6, 132.7, 133.7, 134.0, 136.5, 137.3, 147.7, 148.2, 152.2, 183.9. HRMS m/z calcd for $C_{22}H_{14}N_2O$ 322.1101, found 322.1095. IR (KBr): 1653 (C═O); 3344, 3421 (NH_2) cm^{-1}.

*2-(1,5-Dimethylpyrazol-4-yl)-7H-dibenzo[de,h]quinolin-7-one (**2g**).* The yield is 364 mg (56%), mp 237−238 °C (from toluene), lit. mp 238−239 °C.[6]

Reaction of 1-(*R*-Ethynyl)-9,10-anthraquinones with Na_2S. A mixture of 1-(*R*-ethynyl)-9,10-anthraquinone (0.65 mmol), $Na_2S{\cdot}9H_2O$ 470 mg (1.95 mmol) in 6 mL of pyridine was boiled 2−16 h (Table 2). Then mixture CH_2Cl_2 (50 mL) and water (100 mL) was added, the organic layer was separated, washed with aq HCl (18%; 100 mL), dried (Na_2SO_4) and evaporated in vacuo. The resulting residue was purified by chromatography (silica gel or Al_2O_3; toluene) and crystallized.

*2-Phenylanthra[2,1-b]thiophene-6,11-dione (**3a**).* The yield is 137 mg (62%), mp 245−246 °C (from toluene), lit. mp 246.5−247.5 °C.[21]

*2-(4-Methoxyphenyl)anthra[2,1-b]thiophene-6,11-dione (**3b**).* The yield is 135 mg (56%), mp 247−248 °C (from toluene − ethyl acetate).

*2-(4-Dimethylaminophenyl)anthra[2,1-b]thiophene-6,11-dione (**3c**).* The yield is 174 mg (70%), mp 254−255 °C (from 1,4-dioxane).

*2-Butylanthra[2,1-b]thiophene-6,11-dione (**3d**).* The yield is 94 mg (45%), mp 80−82 °C (from toluene-hexane).[21]

*2-Pentylanthra[2,1-b]thiophene-6,11-dione (**3e**).* The yield is 93 mg (43%), mp 95.5−97 °C (from benzene-hexane).

*2-(2,4,6-Trimethylphenyl)anthra[2,1-b]thiophene-6,11-dione (**3h**).* The yield is 150 mg (61%), mp 187−188 °C (from toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (6H, s), 2.36 (3H, s), 6.99 (2H, s), 7.75−7.82 (2H, m), 8.22 (1H, dd, J = 0.8, 8.3 Hz), 8.28−8.35 (3H, m), 8.58 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$,) δ 20.8, 21.3, 122.2, 125.5, 127.0, 127.3, 127.7, 128.1, 128.5, 130.4, 131.8, 133.2, 133.9, 134.2, 137.7, 138.4, 138.8, 148.4, 149.0, 184.5, 183.9. HRMS m/z calcd for $C_{25}H_{18}O_2S$ 382.1022, found 382.1019. IR (KBr): 1668 (C═O) cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra for new compounds, additional computational analysis, and geometries and energies of for all reactants, intermediates, transition states, and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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