JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

Chameleonic Reactivity of Vicinal Diazonium Salt of Acetylenyl-9,10-anthraquinones: Synthetic Application toward Two Heterocyclic Targets

A. A. Stepanov,[†] L. M. Gornostaev,[‡] S. F. Vasilevsky,*[,†] E. V. Arnold,[‡] V. I. Mamatyuk,[§] D. S. Fadeev,[§] B. Gold,[⊥] and I. V. Alabugin*[,⊥]

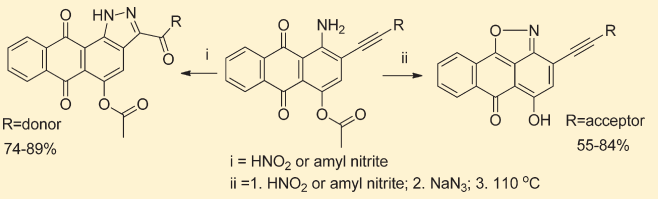
[†]Institute of Chemical Kinetics and Combustion and [§]N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, Novosibirsk 630090, Russian Federation

[‡]Department of Chemistry, Krasnoyarsk State Pedagogical University, Krasnoyarsk 660049, Russian Federation

[⊥]Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306, United States

Supporting Information

ABSTRACT: The nature of products in the diazotization of 1-amino-2-acetylenyl-9,10-anthraquinones strongly depends on the nature of substituents at both the alkyne and at the anthraquinone core. Donor substitution (NHAr, OH) at the fourth position stabilizes the diazonium salt at C1, decelerating electrophilic cyclization at the arylethynyl substituent at C2. This effect allows the replacement of the diazonium with azide group and subsequent closure into isoxazole ring with preservation of the alkyne. In contrast, electrophilic 5-*exo*-*dig* cyclizations to condensed pyrazoles is observed for the combination of donor substituents at the aryl alkyne moiety and an OAc substituent at C4. The latter process provides a new synthetic route to 3-ethynyl-[1,9-*cd*]isoxazol-6-ones that are difficult to access otherwise. DFT calculations suggest that donor substituents have only a minor effect on alkyne and diazonium polarization in the reactant but provide specific transition state stabilization by stabilizing the incipient vinyl cation. This analysis provides the first computational data on electrophilic 5-*exo*-*dig* cyclization in its parent form and the nucleophile-promoted version. This cyclization is a relatively fast but endothermic process that is rendered thermodynamically feasible by the enol-keto tautomerization with concomitant aromatization in the five-membered heteroaromatic ring. Computations suggest that the importance of nucleophilic assistance in the transition state for a relatively weak nucleophile such as water is minor because the energy gain due to the Lewis base coordination to the carbocationic center is more than compensated for by the unfavorable entropic term for the bimolecular proces.



INTRODUCTION

Synthetic transformations of plant metabolites constitute an important direction of medicinal chemistry.[1] Since hybrid molecules that combine two structural units of different nature lend themselves well to rational structural design and often possess high biological activity,[2] a number of hybrids are described in the literature such as steroid−antibiotic,[3] steroid−nucleoside,[4] triterpenoid−peptide,[5] DNA-cleaving agent−amino acid,[6] etc. In this work, we report a successful approach to bioconjugates that combine acetylenic derivatives known to have anticancer activity[7] and condensed anthraquinoid cycles, capable of intercalating DNA duplex.[8]

Earlier we have described an attempt to prepare such hybrids via cross-coupling of independently prepared 3-haloisoxazolanthrones **1a,b** either with terminal alkynes in the presence of $Pd(PPh_3)_2Cl_2$ and CuI or with copper acetylides.[9] However, these commonly used synthetic approaches proved to be inapplicable for this target: in the catalytic version the isoxazole ring opened with the formation of 4-aryl-1-amino-2-(phenylethynyl)-anthracene-9,10-diones, whereas the acetylide process led to recyclization of the amine to naphtho[2,3-*g*]indole-6,11-diones instead of the desired acetylenylisoxazoles (Scheme 1).

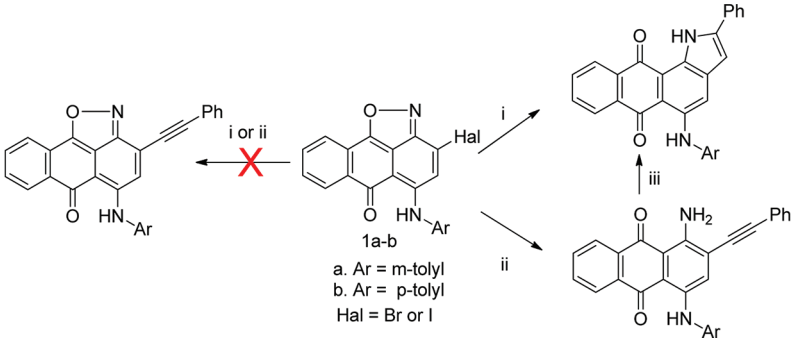
Considering these difficulties, we designed an alternative approach (Scheme 2): preparation of *vic*-acetylenylamino-9,10-anthraquinones **2a**−**d**, amine-azide transformation via the intermediate diazonium salts, and subsequent cyclizations of the *peri*-azido 2-acetylenyl-9,10-anthraquinones **3a**−**d** into the target 5-NHAr-3-R-ethynyl-6*H*-anthra[1,9-*cd*]isoxazol-6-ones **4a**−**d** (vide infra). This approach was based on the early precedent for the formation of polycyclic isoxazoles from *peri*-azido anthraquinones[10] as well as the literature report of preparation of simple aromatic azides with vicinal ethynyl moiety.[11]

However, success of the above approach has not been, a priori, guaranteed because *vic*-acetylenylanthranyl diazonium salts were also known to form either the respective condensed diazines[12] or annealed pyrazoles.[13] We supposed that the fast diazonium → azide exchange via quick addition of sodium azide to the

Received: July 8, 2011
Published: September 12, 2011

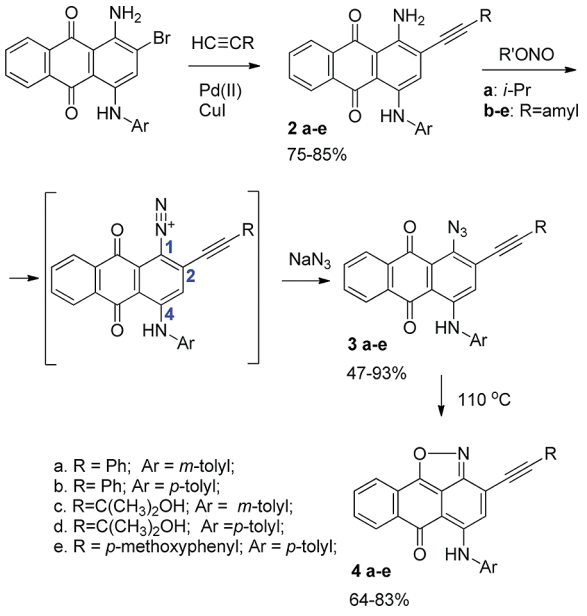
dx.doi.org/10.1021/jo2014214 | *J. Org. Chem.* 2011, 76, 8737–8748

Scheme 1. Earlier Attempts To Prepare Isoxazoles via Cross-Coupling Chemistry[a]



[a] Reagents and conditions: (i) CuC≡CPh, Py, 115° C; (ii) HC≡CPh, C_6H_6, Et_3N, $Pd(PPh_3)_2Cl_2$, PPh_3, CuI, 45-50° C; (iii) DMF, CuI, 155° C.

Scheme 2. Synthesis of 3-R-Ethynyl-6*H*-anthra[1,9-*cd*]isoxazol-6-ones 4a−e and Numeration of Substituent Positions in the Anthraquinone Moiety of Diazonium Salts



diazonium salt would allow us to minimize the probability of undesired competitive cyclizations and open access to the target 3-R-ethynyl-6*H*-anthra[1,9-*cd*]isoxazol-6-ones **4**.

RESULTS

Indeed, the Sonogashira cross-coupling of respective bromides and terminal alkynes provided 1-amino-2-alkynyl-9,10-anthraquinones **2a**−**e** in 75−85%. Diazotization of the amines was carried out with amyl nitrite in glacial acetic acid at room temperature. Addition of sodium azide to the diazonium salt solution afforded, after 1.5−2 h, 81−93% of azides **3a**−**d**.[14] The cyclizations of azides to the 3-(R-ethynyl)-6*H*-anthra[1,9-*cd*]isoxazol-6-ones **4a**−**e** was completed in 5−15 min in refluxing toluene to provide 64−83% of the target product, thus validating the new synthetic path to this class of heterocycles with preservation of the alkynyl moiety.

To test scope and limitations of this approach to acetylenylanthra[1,9-*cd*]isoxazoles, we investigated other *vic*-amino acetylenes of 9,10-anthraquinone family, in particular the derivatives containing a hydroxyl group at the fourth position of the ring. The requisite substrates are available in 64−76% via Sonogashira cross-coupling of aryl acetylenes with 1-amino-2-bromo-4-hydroxyanthracene-9,10-dione (Scheme 3).

Because diazotization of 4-hydroxy derivatives **5a**−**e** was accompanied by decomposition, we have protected the OH group via acylation. Interestingly, reaction of **5a**−**e** with acetic anhydride in pyridine proceeded selectively at the hydroxyl group, even in the presence of the amine functionality.[15]

Diazotization of acetates **6a**−**c** with nitrosylsulfuric acid (method a) with subsequent treatment of the diazonium salt solution with sodium azide yielded azides **7a**−**c** (Scheme 4). Deazotization was accompanied by deacetylation; the acyl group was absent in the products. These azides underwent smooth cyclization (20−40 min in refluxing toluene) into isoxazoles **8a**−**c** without the triple bond participation.

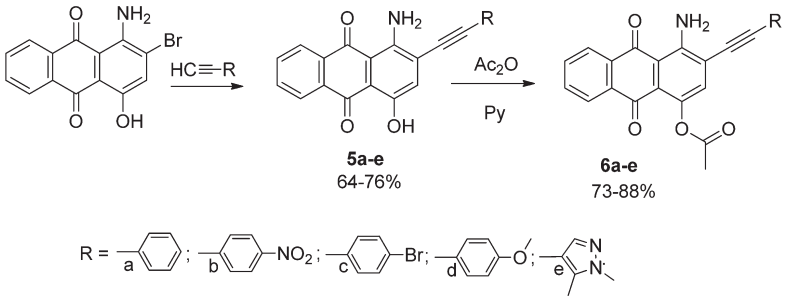
However, diazotization of the donor substrates **6d**−**e** proceeded in a drastically different manner. In particular, reaction of amines **6d**−**e** with nitrosylsulfuric acid (method a) led to the formation of cyclic products **9d**−**e**[16] via nucleophilic attack of the alkyne moiety at the terminal nitrogen of the diazonium group. Interestingly, the regiochemistry of attack is different from that observed in the classic von Richter synthesis of cinnolines.[17] Use of a milder diazotizing reagent, amyl nitrite (method b), increased the reaction time, but for neither the acceptor- nor donor-substituted substrates did it change the nature of the products. Partial deacylation was observed during diazotization of **6e** with the formation of a ∼1:1 mixture of the acylated product **9e** and the free phenol **11e**. Basic hydrolysis of this mixture led to its full conversion into the deacylated product **11e**. We have distinguished between the alternative 5-*exo*-*dig* an 6-*endo*-*dig*[18,19] product structures (compounds **9** and **10** in Scheme 5) on the basis of heteronuclear multiple bond coherence (HMBC) NMR spectra. HMBC spectra clearly favor a five-membered compound **9d** rather than a six-membered heterocycle. In particular, the C-12 carbonyl in this experiment correlates with *ortho*-protons of the anisole ring but not with the H-4 proton of the anthraqunone core. Such correlation would be impossible for the alternative six-membered structure. A more detailed discussion of the NMR experiments can be found in the Supporting Information.

DISCUSSION AND COMPUTATIONAL ANALYSIS

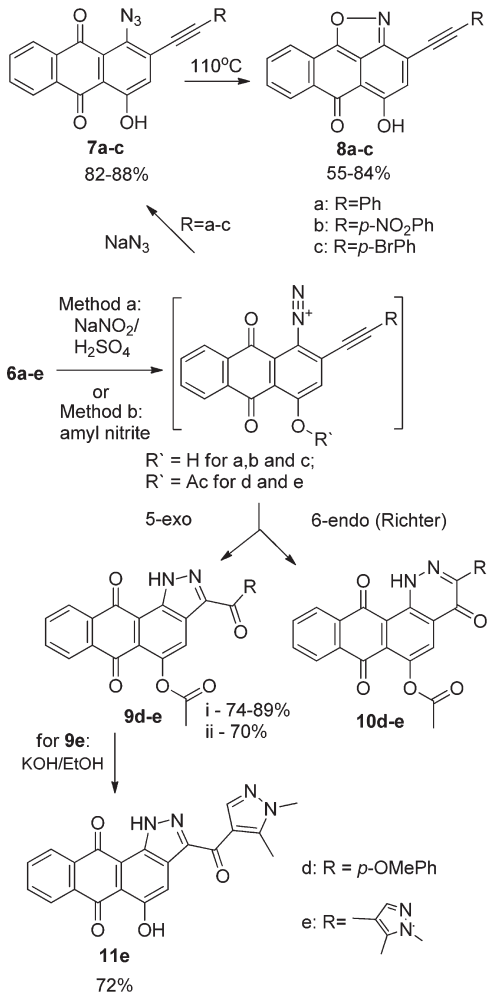
To gain further insight into reactions described in the previous section, we performed computational studies of the key

dx.doi.org/10.1021/jo2014214 |J. Org. Chem. 2011, 76, 8737–8748

Scheme 3. Preparation of Acyl-Protected Starting Alkynes



Scheme 4. Divergent Pathways Observed As a Function of Alkyne Polarization[a]

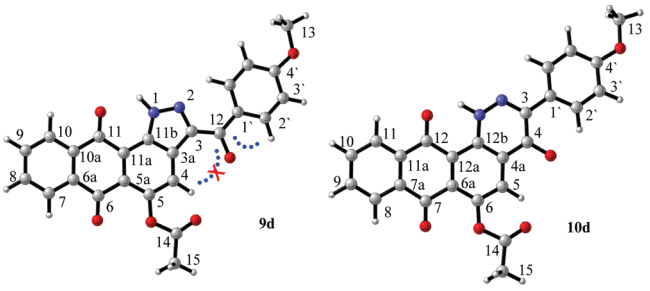


[a] Electron-donating groups led to unexpected 5-*exo-dig* products **9d**−**e**, whereas other substituents allowed preparation of the azides and their subsequent thermal cyclization into the isoxazoles **8a**−**c**.

intramolecular steps of the observed reaction cascade. All of the reactant, product, and transition-state geometries involved in the fragmentation reaction were optimized at the B3LYP/6-31G(d,p) level of theory[20] using the Gaussian 03 program.[21]

Two electronic factors are potentially important for the observed experimental effect of aromatic substituents on the

Scheme 5. Heteronuclear Multiple Bond Coherence (HMBC) Used To Distinguish between the 5-*exo* (9d) and 6-*endo* (10d) Cyclized Products[a]



[a] The carbonyl (C12) correlates with the *ortho*-protons at C2 in the anisole ring (the dashed line), but not those at C4 of the anthraquinone core, allowing the 5-*exo-dig* product **9d** to be identified.

reactivity (Scheme 6). First, the donor groups can assist the cyclization by increasing electron density at the alkyne moiety. Second, the acceptor group can facilitate hydrolysis of of the ester moiety at C4. The latter reaction transforms the acetyl moiety into a donor hydroxyl group, which provides additional stabilization to the diazonium salt and prevents the cyclization.

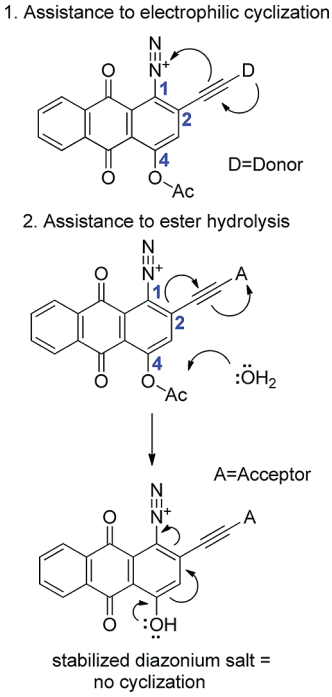
In the second scenario, the loss of acetyl group controls the reactivity: the more electron-deficient substrates **6a**−**c** do not undergo nucleophilic cyclization because hydrolysis of acetate proceeds fast. In contrast, when the OAc group remains intact in the donor substrates **6e,d**, the diazonium salts do not receive resonance stabilization from the OH group at C4 and react with the adjacent triple bond. This scenario would also explain why the diazonium salts prepared from compounds **2a**−**e** with the NHR group do not cyclize.

In the case of an accelerating effect of electron-releasing substituents on the *dig* cyclizations, one would expect the positive charge development at the vinyl carbon adjacent to the terminal electron-donor substituent. This mechanistic model is consistent with the selective formation of a five-membered ring. However, the relatively subtle substituent effect (Ph vs Ph-OMe, Scheme 7) on the observed selectivity was intriguing and prompted us to investigate polarization of reactants and the nature of transition states computationally.

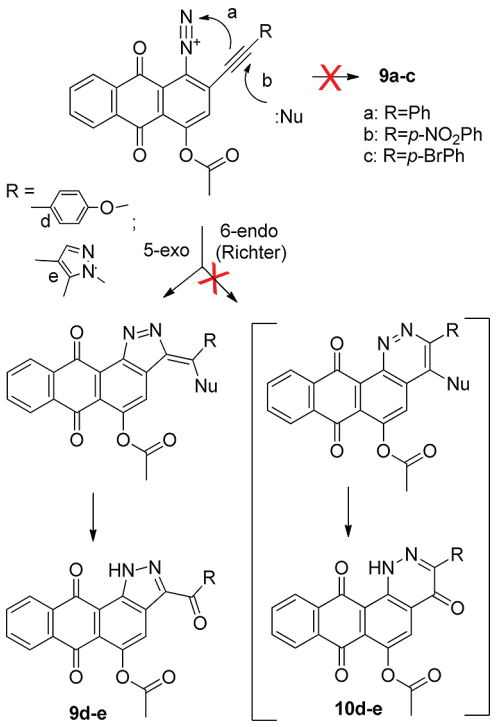
Our experiments did not provide the information whether the loss of acetyl group happens before or after the electrophilic cyclization. On one hand, it is possible that deacylation precedes the cyclization. On the other hand, we cannot exclude the possibility that hydrolysis of ester proceeds *after* the formation

dx.doi.org/10.1021/jo2014214 |*J. Org. Chem.* 2011, 76, 8737–8748

Scheme 6. Two Possible Contributions of Alkyne Substituents to the Observed Trends in Reactivity



Scheme 7. Proposed Pathway for the Formation of the 5-*exo-dig* Cyclization and the Possible 6-*endo-dig* Cyclization (Not Observed), Proceeding through a Nucleophile-Promoted Electrophilic Cyclization



of diazonium but *before* the cyclization. To address the two possibilities, our computational analysis includes substrates with the both the OH and OAc groups.

Effects of substituents at the electronic properties of the alkyne and the diazonium moieties are summarized in Table 1. The effects of terminal aryl groups are more pronounced in the alkyne moiety, especially in the π_{out} orbital directly communicating with the terminal aryl π-system. Both the in-plane and out-of-plane alkyne π-systems are polarized toward the anthraquinone moiety, and the α-carbon, which has to serve as a nucleophile in the 5-*exo-dig* cyclizations, has the greatest π-density. This effect is, as expected, the largest for the methoxy-substituted substrate. However, even the *p*-nitro group does not change the overall *direction* of alkyne polarization, which is dominated by the strongly accepting anthraquinone core. It is also potentially important that the diazonium π^*-orbital has a larger coefficient at the terminal nitrogen, which is the point of nucleophilic attack by the alkyne moiety.[22] However, the effect of substituents in these reactants is, at best, moderate. It has to manifest itself more strongly at one of the subsequent reaction stages in order to explain the observed differences in reactivity. In particular, one can expect that the terminal aryl moiety has to rotate 90° in order to provide stabilization to the developing positive charge at the alkyne β-carbon along the 5-*exo* cyclizations potential energy surface.

The effect of OAc → OH transformation on the electronic properties of alkyne is minor, which is not surprising considering the *meta* arrangement of the two groups. On the other hand, polarization of the diazonium group is moderately affected by the increased donor ability of the OH group. Interestingly, polarization of the two orthogonal π-bonds of the diazonium moiety changes in the opposite direction upon the ester hydrolysis. As the polarization of the out-of-plane π-system decreases, the polarization of the in-plane π-bond changes in the opposite direction. As the result, the overall positive charge on the diazonium nitrogens remain unchanged. The π^*_{in} coefficient at the terminal nitrogen increases, suggesting that orbital overalp leading to the bond forming π_{in}(alkyne) → $\pi^*_{in}(N_2^+)$ interaction is, somewhat cointerintuitively, enhanced by the OAc → OH transformation.

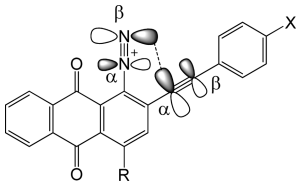
We have also analyzed the electronic interaction of alkyne substituents with the acetate moiety (Scheme 8). Due to the *meta* arrangement of the two groups, variations at the arylethynyl group has little effect at the electronic density at the carbonyl, suggesting that the rate of acetate hydrolysis should be similar for alkynes **12a,b,d**.

We have investigated the 5-*exo*/6-*endo* competition within two alternative mechanistic scenarios (vide infra) using calculations at B3LYP/6-31G(d,p) level of theory. The most straightforward mechanism includes the direct nucleophilic attack of the alkyne at the β-nitrogen of the polarized diazonium moiety, which leads to the formation of a vinyl cation.[23,24] In this mechanism, the 6-*endo* cyclization would be highly unfavorable due to the energy penalty for the inclusion of a sp-hybridized vinyl cation center in the six-membered ring. Formation of an exocyclic cation avoids the ring strain and would be more favorable, especially in the presence of cation-stabilizing substituents at the terminal carbon (Scheme 9).

Scheme 9 compares the effect of OAc versus OH substituent at C4 on the cyclization of a *p*-OMe-substituted alkyne. The 5-*exo-dig* cyclization of the acetate is predicted to have ~1.5 kcal/mol lower barrier. Acetate hydrolysis disfavors the cyclization both kinetically and thermodynamically. The 6-*endo-dig* product for the OH-substituted substrate opens to the reactant barrierlessly in silico.

dx.doi.org/10.1021/jo2014214 |*J. Org. Chem.* 2011, 76, 8737–8748

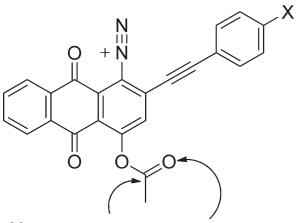
Table 1. Natural Bond Orbital (NBO) Analysis of Substituent Effects on Polarization of the Alkyne and Diazonium Moieties in Acetyl- and Arylamino-Substituted Reactants at B3LYP-6-31G(d,p)[a]



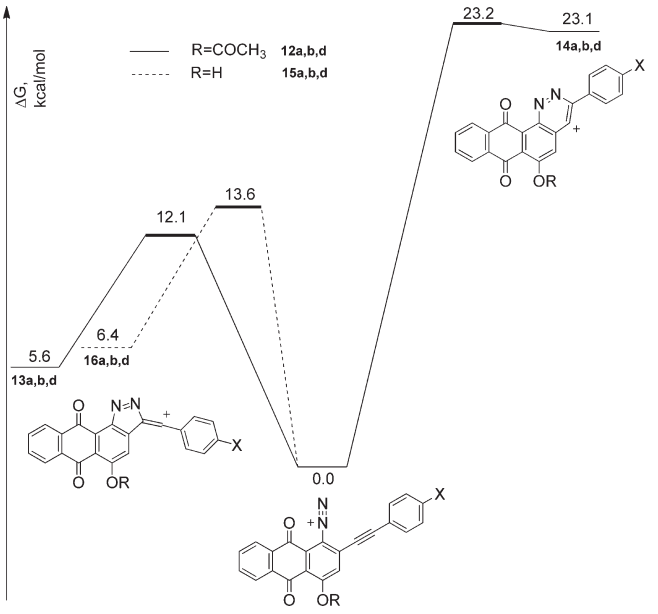
	R = OAc/OH		
	p-OMe-Ph, **12d**	Ph, **12a**	*p*-NO_2-Ph, **12b**
	Acetylene		
π_{in} polarization, % at α-carbon	52.13/52.20	52.50/52.55	52.35/52.40
π_{out} polarization, % at α-carbon	55.70/55.74	55.37/55.36	54.43/54.42
natural charge C_β, e	−0.085/−0.091	−0.084/−0.088	−0.068/−0.071
natural charge C_a, e	0.153/0.151	0.161/0.159	0.148/0.146
	Diazonium		
π^*_{in} polarization, % at β-nitrogen	59.29/59.71	59.23/59.70	59.16/59.70
π^*_{out} polarization, % at β-nitrogen	56.25/55.80	56.53/56.01	56.68/56.18
natural charge N_α, e	0.108/0.107	0.111/0.110	0.114/0.111
natural charge N_β, e	0.237/0.238	0.250/0.250	0.256/0.258

[a] Polarization of the alkyne π-orbital (the nucleophilic cyclization component) and diazonium π^*-orbital (the electrophilic cyclizations component) are shown in the table graphic (orbital lobe sizes are not to scale).

Scheme 8. Substituent Effects on Natural (NBO) Charges for the Acyl Moiety



Scheme 9. Free Energy (ΔG) Diagram of the Electrophilic 5-*exo* and 6-*endo-dig* Cyclizations of the π-Methoxy Substituted Substrate (kcal/mol) Calculated at the B3LYP/6-31G(d,p) Level with CPCM (Water) Correction[a]



[a] Energy values for the PES are relative to the reactant (the diazonium salt).

The effects of aryl substitution on the cyclization of OAc-substituted reactants are illustrated in Table 2. For R = *p*-OMe, the computations clearly predicted that the 5-*exo-dig* closure should be preferred both kinetically and thermodynamically. Although both 5-*exo* and 6-*endo* cationic cyclizations are endothermic, the energy cost for the formation of the 5-*endo* product is significantly lower and the cyclic cation resides in a deeper potential energy minimum where it can be trapped by a nucleophile with a higher probability. Interestingly, in the phenyl- and *p*-nitrophenyl-substituted cases, where 5-*exo-dig* cyclizations were not observed experimentally, the exocyclic products open back upon geometry optimization to give the acyclic starting materials. No energy minima corresponding to such products could be located computationally for both X = OAc and OH.

Although these computational results generally agree with experimental observations, we have investigated the possibility of an alternative mechanism, where the two bond formation steps (C−N (a) and C−Nu(b)) are coordinated. To account for the experimental observations, this process has to be asynchronous with the C−N bond formation proceeding ahead of the C−Nu bond formation. Interception of the incipient vinyl cation in this mechanism avoids the formation of this high energy

dx.doi.org/10.1021/jo2014214 |*J. Org. Chem.* 2011, 76, 8737–8748

Table 2. Activation Energies, Activation Free Energies, Reaction Energies, and Reaction Free Energies for the Electrophilic Cyclizations (kcal/mol) Calculated at the B3LYP/6-31G(d,p) Level

	5-*exo* **13a,b,d**		6-*endo* **14a,b,d**	
X	$\Delta E^{\ddagger}$ ($\Delta G^{\ddagger}$)	ΔE_{rxn} (ΔG_{rxn})	$\Delta E^{\ddagger}$ ($\Delta G^{\ddagger}$)	ΔE_{rxn} (ΔG_{rxn})
MeO, **12d**	12.0 (12.1)[a]	3.0 (5.6)[a]	22.3 (23.2)[a]	21.9 (23.1)[a]
H, **12a**	opens to SM		23.3 (24.5)	22.3 (24.5)
NO_2, **12b**	opens to SM		24.3 (25.5)	23.4 (25.6)

[a] CPCM (water) (radii = UA0) solvation corrections.

intermediate. This mechanistic scenario is analogous to nucleophile-promoted electrophilic cyclizations (NPEC) of alkynes and iminium ions suggested by Overman (Scheme 10).[25] In those systems, NPECs proceed *only* in the presence of a nucleophilic agent that intercepts the incipient vinyl carbocation, suggesting that this step is crucial for the cyclizations success.

Despite the significant electronic differences between our systems and the classic NPECs (e.g., different hybridization of the electrophilic part, relatively weak nucleophile (water) in our case), and much milder conditions for cyclizations described in this work than the above NPECs (~120−150 °C), we expected this mechanism to be relevant in our systems as well because in the NPEC the nucleophile intercepts the incipient vinyl cation, thus avoiding formation of this unstable intermediate

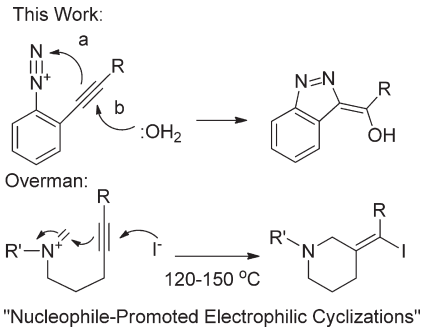
In the NPEC version, *both* 5-*exo*- and 6-*endo-dig* products correspond to shallow local energy minima. The large differences between energy and free energy barriers of activation are noteworthy. Overall, a small decrease in the $\Delta E^{\ddagger}$ due to coordination of water to the carbocationic center is minor in comparison to the unfavorable entropic contribution for this bimolecular process. At this level of theory, the NPEC pathway in the presence of a relatively weak nucleophile such as water does not offer a kinetic advantage relative to the unimolecular cyclization path. Interestingly, the energy minima corresponding to all 5-*exo-dig* products could be located in the NPEC calculations in contrast to the results reported in Table 2. Nevertheless, the 5-*exo* cyclization of a *p*-OMe-substituted substrate is still predicted to proceed much faster than the cyclizations of the two substrates lacking assistance from the donor group (Scheme 11).

Another interesting feature of the calculated energy landscape is that the 5-*exo* products reside in a deeper energy well where they can be trapped by the subsequent highly thermodynamically favorable enol-keto tautomerization. For these systems, tautomerization also leads to aromatization that provides the very large thermodynamic driving force for the overall transformation.[26] Although tautomerization of the 6-*endo* product would produce a stable aromatic product as well, the observed absence of 6-*endo* products with our experimental conditions suggests that this path remains disfavored even when the 5-*exo* path is switched off by the electronic effect of substituents.

As expected, the OAc → OH change renders nucleophile-promoted electrophilic cyclizations less favorable as well because the electron-releasing OH group provides extra stabilization to the starting material. The ~2 kcal/mol increase in the activation barriers after acetate hydrolysis suggests that 5-*exo-dig* cyclizations should be significantly decelerated.

Because this work provides the first computational analysis of a nucleophile-promoted electrophilic digonal cyclizations,

Scheme 10. Comparison of 5-*exo* Cyclization Reported in the Present Work with Nucleophile-Promoted Electrophilic Cyclization (NPEC) Reported by Overman

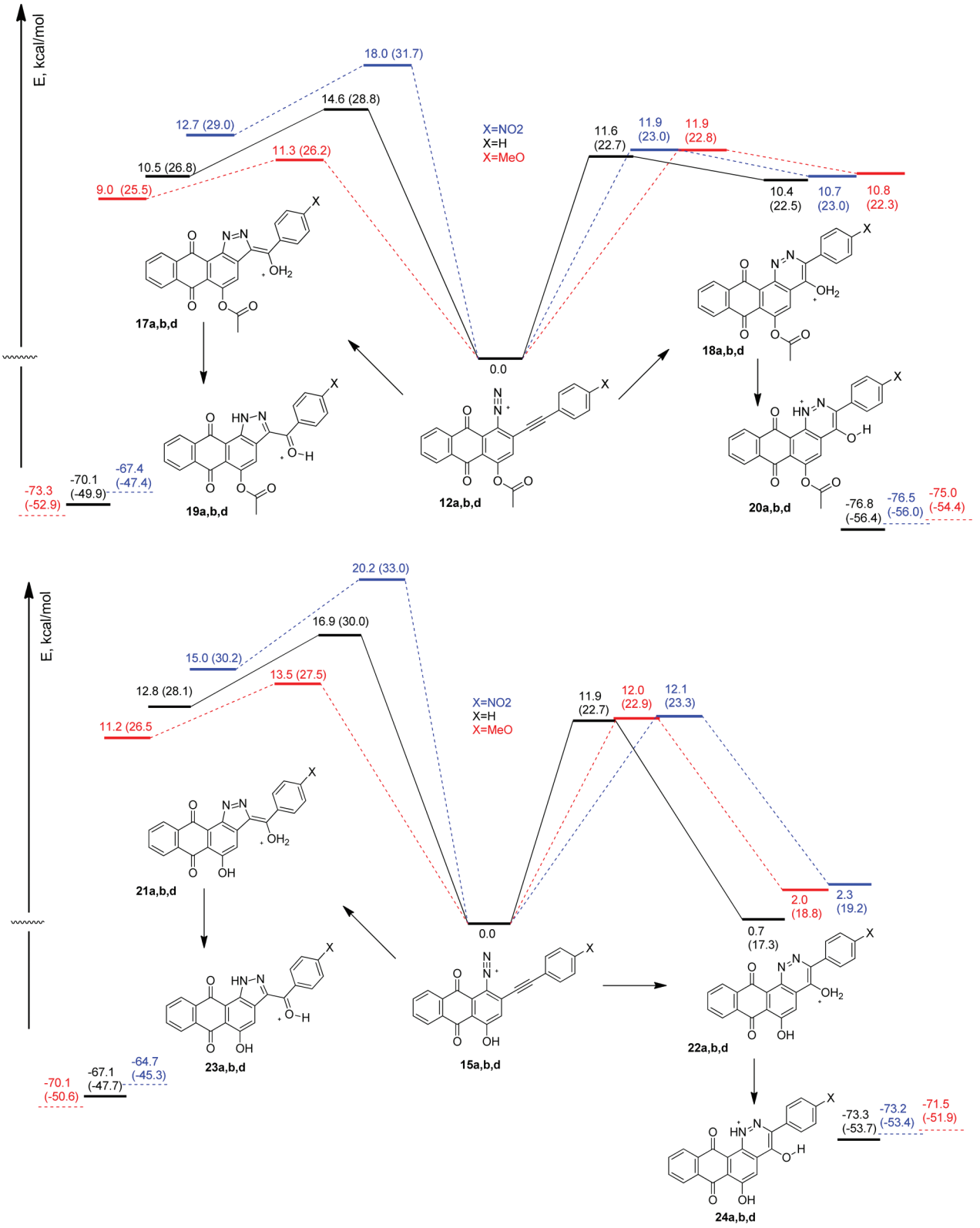


several comments are warranted regarding the nature of transition states in this process. The 5-*exo* transitions states for the two possible mechanistic scenarios are given in Scheme 12. The classic electrophilic cyclization proceeds via a much earlier transition state (TS) with the incipient C···N distance of 2.1 Å. On the other hand, in the TS for the much more endothermic NPEC process, the C···N distance is much shorter in a full agreement with the Hammond−Leffler postulate. Another interesting feature of the NPEC TS is that the formation of C−N bond is more pronounced than the formation of C−O bond, suggesting that significant carbocationic character should develop at the vinyl carbon during the cyclizations process. Rotation of the terminal aryl ring is an important motion because it aligns the aromatic π-system with the developing vinyl cation in both of the transition states. This effect, which does not manifest itself in the reactant, leads to selective TS stabilization and explains why electronic structures of reactants (Table 1) could not provide a satisfactory explanation to the observed trends in reactivity.

In summary, we have found that the nature of products in the diazotization of 1-amino-2-acetylenyl-9,10-anthraquinones strongly depends on the nature of substituents at both the alkyne and at the anthraquinone core. Donor substitution (NHAr, OH) at the fourth position stabilizes the diazonium salt and prevents electrophilic cyclization on an arylethynyl substituent at C2. This effect allows the replacement of the diazonium with azide group and subsequent closure into an isoxazole ring with preservation of the alkyne. In contrast, 5-*exo-dig* cyclization to condensed pyrazoles is observed for the combination of donor substituents at the aryl alkyne moiety and OAc substituent at C4. The latter process provides a new synthetic route to 3-ethynyl-[1,9-*cd*]isoxazol-6-ones, which are difficult to access otherwise. Computational analysis illustrates the role of alkyne polarization and selective TS stabilization via rotation of the terminal aryl group in controlling electrophilic cyclization of alkynes. This analysis provides the first computational data on electrophilic 5-*exo-dig* cyclization in its parent form and the nucleophile-promoted version. This cyclization is a relatively fast but endothermic process that is rendered thermodynamically feasible by enol-keto tautomerization with concomitant aromatization in the five-membered heteroaromatic ring. In the present computational model, the importance of nucleophilic assistance of in the transition state for such relatively weak nucleophile as water is minor because the small decrease in $\Delta E^{\ddagger}$ is more than compensated for by the unfavorable $\Delta S^{\ddagger}$ term for the bimolecular proces.

dx.doi.org/10.1021/jo2014214 |*J. Org. Chem.* 2011, 76, 8737–8748

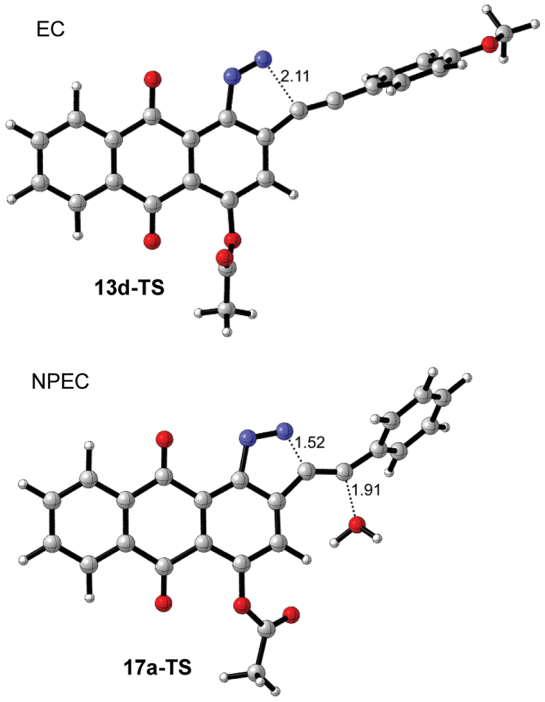
Scheme 11. Energy Diagram of the Nucleophile-Promoted Electrophilic 5-*exo* and 6-*endo-dig* Cyclizations for Acetates (Top) and Hydrolyzed Diazonium Salts (Bottom) Calculated at the B3LYP/6-31G(d,p) Level[a]



[a] Energy values for the PES are given in kcal/mol relative to the diazonium salt and water (ΔG values are given in parentheses).

dx.doi.org/10.1021/jo2014214 |*J. Org. Chem.* 2011, 76, 8737–8748

Scheme 12. Comparison of Transition State Geometries for 5-*exo-dig* Electrophilic (EC)[a] and Nucleophile-Promoted Electrophilic (NPEC) Cyclizations Calculated at the B3LYP-6-31G(d,p) Level[b]



[a] CPCM (water) (radii = UA0) solvation corrections. [b] Key incipient bond lengths are shown in Å.

EXPERIMENTAL SECTION

Materials. Column chromatography was performed on silica (0.063−0.2 mm). UV-254 plates were used for TLC analysis. The IR spectra were recorded in KBr pellets. All organic solvents were of analytical quality. Mass spectra (HRMS) were measured at 70 eV. NMR spectra were recorded at 300.13 (^{1}H) and 75.47 MHz (^{13}C) at 25 °C, 400.13 (^{1}H) and 100.61 MHz (^{13}C) at 25 °C, and 600 MHz in DMSO-d_6 at 50 °C.

Typical Procedure for the Preparation of Substituted 9,10-Anthraquinones 2a−e

4-(*p*-Toluidino)-1-amino-2-(phenylethynyl)anthracene-9,10-dione 2b. A mixture of the 4-(*p*-toluidino)-1-amino-2-bromoanthracene-9,10-dione (4.65 g, 11.42 mmol), Et_3N (5 mL), $Pd(PPh_3)_2Cl_2$ (40 mg), CuI (20 mg), and ethynylbenzene (1.34 g, 13 mmol) in 50 mL of Py was stirred under argon stream at 55 °C for 4 h until bromide was consumed (TLC control). The reaction mixture was cooled and poured into 700 mL of water. The precipitate was filtered and washed with water and ethanole. The crude product was recrystallized from dioxane to afford 4-(*p*-toluidino)-1-amino-2-(phenylethynyl)anthracene-9,10-dione **2b** (4.14 g, 85%), mp 208−209 °C (dioxane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 7.17−7.26 (dd, J = 8.3 Hz, J = 17.2 Hz, 4H), 7.35−7.40 (m, 3H), 7.52−7.55 (m, 2H), 7.65 (s, 1H), 7.70−7.72 (dd, J = 3.3 Hz, J = 5.8 Hz, 2H), 8.30−8.33 (m, 2H), 11.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 83.6, 99.1, 110.1, 111.3, 120.4, 121.5, 124.1, 126.1, 126.2, 126.6, 128.4, 129.3; 130.0, 131.6, 132.52, 132.56, 133.9, 134.3, 134.4, 136.7, 142.5, 145.4, 183.0, 183.5; HRMS found m/z 428.1522 $[M]^+$, $C_{29}H_{20}N_2O$; calcd M = 428.1519. IR (cm^{-1}) ν 1614 (C═O), 2203 (C≡C), 3063 (NH), 3456 (NH_2).

4-(*m*-Toluidino)-1-amino-2-(phenylethynyl)anthracene-9,10-dione 2a. Time of reaction 1 h, 65 °C (0.29 g, 81%), mp 177−179 °C (dioxane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 7.00 (d, J = 7.5 Hz, 1H), 7.07−7.11 (m, 2H), 7.29 (t, J = 7.6 Hz, 1H), 7.36−7.39 (m, 3H), 7.52−7.54 (m, 2H), 7.69 (s, 1H), 7.69−7.71 (dd, J = 3.3 Hz, J = 5.8 Hz, 2H), 8.29−8.32 (m, 2H), 11.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 83.6, 99.1, 110.1, 111.7, 120.4, 120.7, 121.5, 124.4, 125.3, 126.1, 126.2, 126.8, 128.4, 129.2, 129.3; 131.6, 132.5, 133.9, 134.3, 139.4, 139.5, 142.0, 145.5, 183.1, 183.5; HRMS found m/z 428.1522 $[M]^+$, $C_{29}H_{20}N_2O$; calcd M = 428.1519. IR (cm^{-1}) ν 1620 (C═O), 2203 (C≡C), 3064 (NH), 3449 (NH_2).

4-(*p*-Toluidino)-1-amino-2-(3-hydroxy-3-methylbut-1-ynyl)-anthracene-9,10-dione 2d. Time of reaction 2 h, 70 °C (0.53 g, 75%), mp 245−247 °C (dioxane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 6H), 2.36 (s, 3H), 7.11−7.21 (dd, J = 8.0 Hz, J = 28.4 Hz, 4H), 7.52 (s, 1H), 7.70−7.72 (m, 2H), 8.31−8.32 (m, 2H), 11.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 31.4, 65.8, 76.8, 77.2, 103.9, 110.2, 111.5, 120.0, 124.3, 126.3, 126.4, 127.0, 130.2, 132.73, 132.76, 134.1, 134.4, 134.6, 136.8, 142.6, 145.4, 183.3, 183.6; HRMS found m/z 410.1628 $[M]^+$, $C_{26}H_{22}N_2O_3$; calcd M = 410.1625. IR (cm^{-1}) ν 1611 (C═O), 2215 (C≡C), 3065 (NH), 3453 (NH_2).

4-(*m*-Toluidino)-1-amino-2-(3-hydroxy-3-methylbut-1-ynyl)-anthracene-9,10-dione 2c. Time of reaction 2 h, 75 °C (0.33 g, 80%), mp 182−184 °C (dioxane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 6H), 2.38 (s, 3H), 6.96−7.04 (m, 3H), 7.25 (t, J = 8 Hz, 1H), 7.54 (s, 1H), 7.68−7.70 (m, 2H), 8.28−8.29 (m, 2H), 11.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 31.2, 65.6, 76.6, 103.9, 110.1, 111.7, 119.8, 120.7, 124.5, 125.3, 126.2, 126.3, 127.0, 129.2, 132.62, 132.63, 133.9, 134.2, 139.4, 139.5, 141.9, 145.4, 183.3, 183.5; HRMS found m/z 410.1623 $[M]^+$, $C_{26}H_{22}N_2O_3$; calcd M = 410.1625. IR (cm^{-1}) ν 1619 (C═O), 2217 (C≡C), 3068 (NH), 3443 (NH_2).

4-(*p*-Toluidino)-1-amino-2-((4-methoxyphenyl)ethynyl)-anthracene-9,10-dione 2e. Time of reaction 3 h, 75 °C (0.5 g, 78%), mp 187−189 °C (toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.82 (s, 3H), 6.87 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.61 (s, 1H), 7.69−7.72 (m, 2H), 8.30−8.32 (m, 2H), 11.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 55.2, 82.6, 99.5, 110.0, 111.1, 113.5, 114.1, 121.0, 124.1, 126.1, 126.2, 130.0, 132.4, 132.5, 133.2, 134.0, 134.3, 134.4, 136.8, 142.6, 145.4, 160.3, 182.9, 183.4; HRMS found m/z 458.1623 $[M]^+$, $C_{30}H_{22}N_2O_3$; calcd M = 458.1625; IR (cm^{-1}) ν 1606 (C═O), 2200 (C≡C), 3440 (NH_2).

Typical Procedure for the Preparation of Substituted 9,10-Anthraquinones 5a−e

1-Amino-4-hydroxy-2-(phenylethynyl)anthracene-9,10-dione 5a. A mixture of the 1-amino-2-bromo-4-hydroxyanthracene-9,10-dione (1.9 g, 6 mmol), Et_3N (2 mL), $Pd(PPh_3)_2Cl_2$ (20 mg), CuI (10 mg) and alkyne-1 (0.67 g, 6.6 mmol) in 15 mL of Py was stirred under argon stream at 45 °C for 11 h until bromide is disappeared (TLC control). The reaction mixture was cooled and poured into 700 mL of ice−water. After filtration, the precipitate was washed with water and ethanol. The crude product was recrystallized from dioxane and characterized, yielding 1-amino-4-hydroxy-2-(phenylethynyl)anthracene-9,10-dione **5a** (1.47 g, 72%), mp 245−246 °C (dioxane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.43 (m, 4H), 7.57−7.60 (m, 2H), 7.73−7.82 (m, 2H), 8.31−8.34 (m, 2H), 13.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 83.2, 100.1, 108.2, 113.3, 121.1, 121.4, 125.9, 126.4, 128.2, 129.1, 129.3, 131.6, 132.3, 132.7, 134.0, 134.3, 146.2, 155.3, 182.1, 186.6; HRMS found m/z 339.0891 $[M]^+$, $C_{22}H_{13}N_1O_3$; calcd M = 339.0890. IR (cm^{-1}) ν 1624 (C═O), 2199 (C≡C), 3296 (OH), 3458 (NH_2).

1-Amino-4-hydroxy-2-[(4-nitrophenyl)ethynyl]anthracene-9,10-dione 5b. Time of reaction 3 h, 70 °C (1.18 g, 64%), mp 276−277 °C (dioxane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.74 (d, J = 8.9 Hz, 2H), 7.77 (dt, 1H, J = 7.5 Hz, J = 1.5 Hz), 7.82 (dt, 1H, J = 7.5 Hz, J = 1.5 Hz), 8.28 (d, J = 8.8, 2H), 8.32−8.37 (m, 2H),

dx.doi.org/10.1021/jo2014214 |*J. Org. Chem.* 2011, 76, 8737–8748

13.29 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 88.6, 98.2, 108.7, 113.9, 124.2, 126.4, 127.0, 128.5, 129.3, 129.4, 131.0, 132.6, 133.7, 134.0, 134.8, 135.4, 147.3, 154.9, 182.6, 187.4; HRMS found m/z 384.0735 $[M]^+$, $C_{22}H_{12}N_2O_5$; calcd M = 384.0741. IR (cm^{-1}) ν 1624 (C═O), 2203 (C≡C), 3291 (OH), 3450 (NH_2).

1-Amino-2-[(4-bromophenyl)ethynyl]-4-hydroxyanthracene-9,10-dione 5c. Time of reaction 4 h, 70 °C (0.61 g, 72%), mp 195−197 °C (dioxane). ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 7.37 (s, 1H), 7.55−7.63 (m, 4H), 7.76−7.87 (m, 2H), 8.22−8.28 (m, 2H), 13.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 84.7, 98.8, 108.0, 113.5, 120.4, 121.1, 123.3, 125.9, 126.4, 129.4, 131.5, 132.2, 132.9, 133.5, 134.3, 134.4, 146.5, 155.0, 181.9, 186.6; HRMS found m/z 416.9987 $[M]^+$, $C_{22}H_{13}N_1O_3$; calcd M = 416.9995. IR (cm^{-1}) ν 1623 (C═O), 2204 (C≡C), 3272 (OH), 3439 (NH_2).

1-Amino-4-hydroxy-2-[(4-methoxyphenyl)ethynyl]anthracene-9,10-dione 5d. Time of reaction 6 h, 75 °C (0.56 g, 76%), mp 214−216 °C (dioxane). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.82−3.83 (s, 1H), 7.06 (d, 2H, J = 8.8 Hz), 7.49 (d, 1H, J = 1.5 Hz), 7.73 (d, 2H, J = 8.8 Hz), 8.25−8.31 (m, 2H), 8.87−8.99 (m, 2H), 13.42−13.43 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.4, 82.9, 83.8, 93.4, 101.1, 113.0, 114.4, 122.1, 126.1, 126.6, 129.1, 132.2, 133.4, 133.9, 134.4, 134.8, 146.6, 155.2, 160.5, 182.0, 186.5; HRMS found m/z 369.0988 $[M]^+$, $C_{23}H_{15}N_1O_4$; calcd M = 369.0996. IR (cm^{-1}) ν 1637, 1620 (C═O), 2200 (C≡C), 3288 (OH), 3454 (NH_2).

1-Amino-2-[(1,5-dimethyl-1*H*-pyrazol-4-yl)ethynyl]-4-hydroxyanthracene-9,10-dione 5e. Time of reaction 8 h, 75 °C (0.5 g, 70%), mp 260−262 °C (dioxane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.65 (s, 3H), 7.13 (s, 1H), 7.44 (s, 1H), 7.56−7.65 (m, 2H), 8.14 (dd, 2H, J = 7.6 Hz, J = 1.2 Hz), 13.28 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 36.9, 72.8, 94.7, 100.4, 108.0, 114.5, 123.0, 126.4, 126.9, 128.7, 132.6, 133.7, 134.7, 135.1, 140.8, 143.4, 146.5, 155.7, 159.4, 182.3, 186.7; HRMS found m/z 357.1105 $[M]^+$, $C_{21}H_{15}N_3O_3$; calcd M = 357.1108. IR (cm^{-1}) ν 1635, 1623 (C═O), 2209 (C≡C), 3299 (OH), 3454 (NH_2).

Typical Procedure for the Acylation of Substituted 9,10-Anthraquinones 6a−e

1-Amino-9,10-dioxo-3-(phenylethynyl)-9,10-dihydroanthracen-1-yl Acetate 6a. To 1-amino-4-hydroxy-2-(phenylethynyl)-anthracene-9,10-dione **5a** (0.68 g, 2 mmol) in 5 mL of Py at room temperature was added acetic anhydride (1 mL, 10 mmol). After stirring for 6.5 h at 80 °C, the solution was poured into ice and filtered. The precipitate was washed with water and ethanole. The crude product was recrystallized from toluene to afford 1-amino-9,10-dioxo-3-(phenylethynyl)-9,10-dihydroanthracen-1-yl acetate **6a** (0.67 g, 88%), mp 244−245 °C (toluene). ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 2.34 (s, 3H), 7.35−7.39 (m, 4H), 7.58−7.62 (m, 2H), 7.69−7.80 (m, 2H), 8.06 (dd, J = 7.0 Hz, J = 1.8 Hz, 1H), 8.19 (dd, J = 7.3 Hz, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 21.1, 76.5, 78.7, 83.5, 100.1, 117.1, 121.7, 126.3, 126.5, 128.6, 129.5, 131.9, 133.3, 133.5, 133.6, 133.8, 134.0, 139.8, 150.0, 169.5, 184.3, 191.0; HRMS found m/z 381.0993 $[M]^+$, $C_{22}H_{13}N_1O_3$; calcd M = 381.0996. IR (cm^{-1}) ν 1634, 1661, and 1752 (C═O), 2207 (C≡C), 34043 (NH_2).

1-Amino-3-[(4-nitrophenyl)ethynyl]-9,10-dioxo-9,10-dihydroanthracen-1-yl Acetate 6b. Time of reaction 1 h, 80 °C (0.19 g, 78%), mp 235−237 °C (toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.42 (s, 1H), 7.69−7.76 (m, 4H), 8.16 (dd, J = 1.6 Hz, J = 7.3 Hz, 1H), 8.25−8.27 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 77.2, 87.9, 97.5, 113.3, 115.6, 123.8, 125.2, 126.6, 126.7, 128.4, 133.5, 133.62, 133.68, 133.9, 134.3, 140.2, 147.7, 149.8, 170.1, 182.0, 185.0; HRMS found m/z 426.0850 $[M]^+$, $C_{24}H_{14}N_2O_6$; calcd M = 426.0846. IR (cm^{-1}) ν 1635, 1662, and 1760 (C═O), 2197 (C≡C), 3456 (NH_2).

1-Amino-3-[(4-bromophenyl)ethynyl]-9,10-dioxo-9,10-dihydroanthracen-1-yl Acetate 6c. Time of reaction 1 h, 80 °C (0.14 g, 73%), mp 234−236 °C (toluene + hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.38 (s, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.70−7.78 (m, 2H), 8.16 (d, J = 7.6 Hz, 1H), 8.26 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 77.0, 84.2, 98.9, 112.8, 116.7, 120.5, 123.8, 124.3, 126.5, 126.6, 131.8, 132.9, 133.3, 133.4, 133.6, 133.7, 140.1, 149.6, 170.0, 181.9, 184.8; HRMS found m/z 459.0100 $[M]^+$, $C_{24}H_{14}N_1O_4Br_1$; calcd M = 459.0101. IR (cm^{-1}) ν 1633, 1660, and 1764 (C═O), 2201 (C≡C), 3470 (NH_2).

4-Amino-3-[(4-methoxyphenyl)ethynyl]-9,10-dioxo-9,10-dihydroanthracen-1-yl Acetate 6d. Time of reaction 1 h, 80 °C (0.09 g, 87%), mp 228−230 °C (dioxane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.83 (s, 3H), 6.90 (d, 2H, J = 8.9 Hz); 7.33 (s, 1H), 7.47 (d, J = 8.9 Hz, 2H), 7.66−7.76 (m, 2H), 8.13−8.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 55.3, 77.1, 82.1, 100.7, 112.6, 113.6, 114.2, 117.8, 123.7, 126.5, 126.6, 133.24, 133.27, 133.5, 133.6, 133.7 140.3, 149.6, 160.4, 170.0, 181.9, 184.9; HRMS found m/z 411.1103 $[M]^+$, $C_{25}H_{17}N_1O_5$; calcd M = 411.1101. IR (cm^{-1}) ν 1633, 1657, and 1761 (C═O), 2194 (C≡C), 3468 (NH_2).

4-Amino-3-[(1,5-dimethyl-1*H*-pyrazol-4-yl)ethynyl]-9,10-dioxo-9,10-dihydroanthracen-1-yl Acetate 6e. Time of reaction 1.5 h, 80 °C (0.2 g, 77%), mp 239−241 °C(toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.45 (s, 3H), 3.81 (s, 3H), 7.31 (s, 1H), 7.59 (s, 1H), 7.68−7.75 (m, 2H), 8.16 (d, J = 7.5 Hz, 1H), 8.25 (d, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2, 21.0, 36.6, 77.1, 85.4, 92.9, 101.1, 112.6, 118.0, 123.5, 126.4, 126.6, 132.9, 133.2, 133.5, 133.6, 133.7, 134.0, 140.5, 149.4, 170.0, 181.9, 184.8; HRMS found m/z 399.1210 $[M]^+$, $C_{23}H_{17}N_3O_4$; calcd M = 399.1214. IR (cm^{-1}) ν 1633, 1656, and 1760 (C═O), 2197 (C≡C), 3458 (NH_2).

Typical Procedure for the Preparation of Substituted Azides 3a−d

4-(*p*-Toluidino)-1-azido-2-(phenylethynyl)anthracene-9,10-dione 3b. To 4-(*p*-toluidino)-1-amino-2-(phenylethynyl)anthracene-9,10-dione **2b** (4.1 g, 9.58 mmol) in 70 mL of CH_3COOH at room temperature was added amyl nitrite (0.93 g, 10 mmol) during 5 min. The reaction mixture was stirred at room temperature for 45 min. The solution was poured into 250 mL of ice−water. To the stirred mixture was added a solution of sodium azide (1.5 g, 23 mmol) in 20 mL water, and the mixture was stirred at room temperature for 2.5 h. The precipitate was washed with water and dried by heating to 30 °C within 48 h. Yield **3b** 93%. IR (cm^{-1}) ν 1618 and 1675 (C═O), 2125 (N_3), 2198 (C≡C).

4-(*m*-Toluidino)-1-azido-2-(phenylethynyl)anthracene-9,10-dione 3a. Time of diazotization 0.5 h, time of reaction with sodium azide 1.5 h (0.32 g, 81%). IR (cm^{-1}) ν 1626 and 1662 (C═O), 2124 (N_3), 2210 (C≡C).

4-(*p*-Toluidino)-1-azido-2-(3-hydroxy-3-methylbut-1-ynyl)-anthracene-9,10-dione 3d. Time of diazotization 0.5 h, time of reaction with sodium azide 2 h (0.94 g, 88%). %). IR (cm^{-1}) ν 1620 and 1672 (C═O), 2127 (N_3), 2207 (C≡C).

4-(*m*-Toluidino)-1-azido-2-(3-hydroxy-3-methylbut-1-ynyl)-anthracene-9,10-dione 3c. Time of diazotization 0.5 h, time of reaction with sodium azide 2 h (0.74 g, 87%). %). IR (cm^{-1}) ν 1625 and 1668 (C═O), 2128 (N_3), 2201 (C≡C).

4-(*p*-Toluidino)-1-azido-2-((4-methoxyphenyl)ethynyl)-anthracene-9,10-dione 3e. To 4-(*p*-toluidino)-1-amino-2-((4-methoxyphenyl)ethynyl)anthracene-9,10-dione **2e** (0.155 g, 0.34 mmol) in 5 mL of CH_3COOH at room temperature was added isopropyl nitrite (0.06 g, 0.67 mmol) during 5 min. The reaction mixture was stirred at room temperature for 20 min. The solution was poured into 10 mL of ice−water. The precipitate was filtered and washed with water. Solution sodium azide (0.05 g, 0.77 mmol) in 2 mL water was added to filtrate and stirred at room temperature for 2.5 h. The precipitate was washed with water and dried by heating to 30 °C within 48 h. Yield **3e** 0.076 g, 47%. IR (cm^{-1}) ν 1626 and 1656 (C═O), 2119 (N_3), 2206 (C≡C).

Typical Procedure for the Preparation of Substituted Azides 7a−c

1-Azido-4-hydroxy-2-(phenylethynyl)anthracene-9,10-dione 7a. Solution of $NaNO_2$ (0.07 g, 1 mmol) in 1 mL H_2SO_4 was added within 5 min to solution of 1-amino-9,10-dioxo-3-(phenylethynyl)-9,10-dihydroanthracen-1-yl acetate **6a** (0.25 g, 0.65 mmol) in 5 mL of CH_3COOH at room temperature. The reaction mixture was stirred at room temperature for 30 min and poured into 1 mL of ice−water. A solution of 1 mmol of sodium azide in 1 mL of water was added with stirring. The reaction mixture was stirred at room temperature for 2.5 h. The precipitate was washed with water. Water was removed by by heating to 30 C within 48 h. Yield **7a** 0.22 g, 82%. IR (cm^{-1}) ν 1635 and 1672 (C═O), 2130 (N_3), 2211 (C≡C).

1-Azido-4-hydroxy-2-[(4-nitrophenyl)ethynyl]anthracene-9,10-dione 7b. Time of diazotization 0.5 h, time of reaction with sodium azide 2 h. (0.19 g, 84%). IR (cm^{-1}) ν 1636 and 1670 (C═O), 2129 (N_3), 2208 (C≡C).

1-Azido-2-[(4-bromophenyl)ethynyl]-4-hydroxyanthracene-9,10-dione 7c. Time of diazotization 0.5 h, time of reaction with sodium azide 2 h. (0.39 g, 88%). IR (cm^{-1}) ν 1633 and 1668 (C═O), 2128 (N_3), 2205 (C≡C).

Typical Procedure for the Preparation of Substituted Indazoles 9d−e

Method a. Solution of $NaNO_2$ (0.1 g, 1.5 mmol) in 1 mL H_2SO_4 was added to solution of 4-amino-3-[(4-methoxyphenyl)ethynyl]-9,10-dioxo-9,10-dihydroanthracen-1-yl acetate **6d** (0.41 g, 1 mmol) in 20 mL of CH_3COOH at room temperature within 5 min. The reaction mixture was stirred at room temperature for 2 h (TLC control). The solution was poured into 50 mL of ice−water. The precipitate was filtered and washed with water. Water was removed by heating to 70 °C within 2 h, yielding 3-(4-methoxybenzoyl)-6,11-dioxo-6,11-dihydro-1*H*-naphtho-[2,3-*g*]indazol-5-yl acetate **9d** (0.39 g. 89%), mp 323−324 °C (DMF). ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.46 (s, 3H), 3.90 (s, 3H), 7.14−7.16 (m, 2H, J = 8.79, 2.48, 0.09 Hz), 7.96 (m, 1H, J = 7.35, 7.34, 1.57 Hz), 7.97 (m, 1H, J = 7.43, 7.34, 1.68 Hz), 8.18 (m, 1H, J = 7.35, 1.68, 0.54 Hz), 8.24 (m, 1H, J = 7.43, 1.57, 0.54 Hz), 8.39 (m, 2H, J = 8.79, 2.35, 0.09), 8.40 (s, 1H); ^{13}C NMR (150.96 MHz, DMSO-d_6, 50 °C) δ 20.80 (C-16), 55.47 (C-14), 113.68 (C-3′), 119.23, 123.23 (C-4), 123.68, 125.91 (C-7), 126.75 (C-10), 127.12, 129.33 (C-13), 131.91, 132.49 (C-2′), 133.21, 134.35 (C-9), 134.70 (C-8), 134.90 (C-11b), 142.57 (C-3), 144.46 (C-5), 163.24 (C-4′), 169.56 (C-15), 181.70 (C-6), 182.85 (C-11), 185.48 (C-12); HRMS found m/z 440.0997 $[M]^+$, $C_{25}H_{16}N_2O_6$; calcd M = 440.1003; IR (cm^{-1}) ν 1632, 1672, and 1768 (C═O). Anal. Calcd for $C_{25}H_{16}N_2O_6$: C, 68.18; H, 3.66; N, 6.36. Found: C, 68.19; H, 3.57; N, 6.63.

3-(1,5-Dimethyl-1*H*-pyrazole-4-carbonyl)-5-hydroxy-1*H*-naphtho[2,3-g]indazole-6,11-dione 11e (Method a). Time of reaction 5 min. In this case a mixture of **9e** and **11e** (∼1/1) was obtained (0.32 g. 74%), of which 0.06 g underwent full hydrolysis by KOH in EtOH within 50 min. The solution was poured into 10 mL of water, and the mixture was neutralized by conc HCl. The precipitate was filtered and washed with water. Water was removed by heating to 70 °C within 2 h. The crude product was recrystallized from DMF to afford 3-(1,5-dimethyl-1*H*-pyrazole-4-carbonyl)-5-hydroxy-1*H*-naphtho[2,3-g]indazole-6,11-dione **11e** (0.039 g, 72%), mp >370 °C (DMF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.64 (s, 3H), 3.83 (s, 3H), 7.98−8.03 (m, 2H), 8.16−8.17 (m, 1H), 8.25−8.30 (m, 2H), 8.53 (s, 1H), 12.02 (s, 1H), 14.45 (s, 1H); ^{13}C NMR spectrum is absent due to the very low solubility of this compound (0.15 mg in 0.4 mL of DMSO at 50 °C). HRMS found m/z 428.1106 $[M]^+$, $C_{23}H_{16}N_4O_5$; calcd M = 428.1115. IR (cm^{-1}) ν 1635, 1668, and 1768 (C═O). Anal. Calcd for $C_{23}H_{16}N_4O_5$: C, 64.48; H, 3.76; N, 13.08. Found: C, 64.55; H, 3.79; N, 13.57.

3-(4-Methoxybenzoyl)-6,11-dioxo-6,11-dihydro-1*H*-naphtho[2,3-g]indazol-5-yl Acetate 9d (Method b). To 4-amino-3-[(4-methoxyphenyl)ethynyl]-9,10-dioxo-9,10-dihydroanthracen-1-yl acetate **6d** (0.082 g, 0.2 mmol) in 4 mL of CH_3COOH at room temperature was added amyl nitrite (0.035 g, 0.3 mmol) during 5 min. The reaction mixture was stirred at room temperature for 32 h (TLC control). The solution was poured into 5 mL of ice−water. The precipitate was filtered and washed with water, and water was removed by heating to 70 °C within 2 h; 0.062 g (70%) of **9d** was isolated, mp 323−324 °C (DMF).

Typical Procedure for the Preparation of Substituted Isoxazoles 4a−d and 8a−c

5-(*p*-Toluidino)-3-(phenylethynyl)-6*H*-anthra[1,9-*cd*]isoxazol-6-one 4b. Azide **3b** was boiled in 15 mL of toluene 15 min. The reaction mixture was cooled. The precipitate was filtered. The crude product was recrystallized from benzene to afford 5-(*p*-toluidino)-3-(phenylethynyl)-6*H*-anthra[1,9-*cd*]isoxazol-6-one **4b** (3.13 g, 82%), mp 229−231 °C (benzene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.28−7.36 (m, 4H), 7.37−7.42 (m, 3H), 7.61−7.68 (m, 4H), 7.79 (t, J = 7.4 Hz, 1H), 8.16 (d, J = 7.5 Hz), 8.16 (d, J = 7.5 Hz), 11.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 84.1, 100.0, 101.5, 117.0, 120.7, 121.6, 122.2, 124.4, 125.3, 126.9, 128.2, 128.3, 128.5, 129.5, 130.3, 132.0, 132.1, 132.4, 134.5, 136.7, 149.2, 151.2, 156.3, 180.1; HRMS found m/z 426,1359 $[M]^+$, $C_{29}H_{20}N_2O$; calcd M = 426,1362. IR (cm^{-1}) ν 1674 (C═O), 2203 (C≡C), 3054 (NH).

5-(*m*-Toluidino)-3-(phenylethynyl)-6*H*-anthra[1,9-*cd*]isoxazol-6-one 4a. Time of reaction 5 min (0.32 g, 81%), mp 223−225 °C (benzene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.15−7.23 (m, 3H), 7.35−7.41 (m, 4H), 7.59−7.63 (m, 4H), 7.75 (t, J = 7.2 Hz, 1H), 8.10 (d, J = 7.6 Hz, 1H), 8.50 (d, J = 7.8 Hz, 1H), 11.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 84.2, 100.0, 101.6, 117.0, 120.7, 121.5, 121.6, 122.1, 125.0, 125.2, 126.9, 127.4, 128.2, 128.3, 128.5, 129.5, 129.6, 132.0, 132.1, 132.4, 137.1, 139.9, 148.9, 151.1, 156.4, 180.1; HRMS found m/z 426.1353 $[M]^+$, $C_{29}H_{20}N_2O$; calcd M = 426.1363. IR (cm^{-1}) ν 1675 (C═O), 2198 (C≡C), 3059 (NH).

5-(*p*-Toluidino)-3-(3-hydroxy-3-methylbut-1-ynyl)-6*H*-anthra-[1,9-*cd*]isoxazol-6-one 4d. Time of reaction 5 min (0.72 g, 81%), mp 246−248 °C (benzene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (s, 6H); 2.43 (s, 3H), 7.23−7.31 (m, 4H), 7.46 (s, 1H), 7.65 (t, J = 6.9 Hz, 1H), 7.77 (t, J = 6.9 Hz,1H), 8.10 (d, J = 8 Hz, 1H), 8.53 (d, J = 8 Hz, 1H), 11.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 30.9, 65.5, 76.7, 101.4, 104.7, 116.8, 120.1, 122.1, 124.4, 125.2, 127.1, 128.2, 128.6, 130.3, 132.0, 132.4, 134.4, 136.8, 149.0, 151.0, 156.3, 180.1; HRMS found m/z 408.1459 $[M]^+$, $C_{26}H_{20}N_2O_3$; calcd M = 408.1473. IR (cm^{-1}) ν 1675 (C═O), 2220 (C≡C), 3050 (NH).

5-(*m*-Toluidino)-3-(3-hydroxy-3-methylbut-1-ynyl)-6*H*-anthra[1,9-*cd*]isoxazol-6-one 4c. Time of reaction 5 min (0.61 g, 83%), mp 235−237 °C (benzene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (s, 6H), 2.45 (s, 3H), 7.17−7.19 (m, 3H), 7.37−7.42 (m, 1H), 7.51 (s, 1H), 7.66 (t, J = 7.3 Hz, 1H), 7.78 (t, J = 8 Hz, 1H), 8.13 (d, J = 7.9 Hz, 1H), 8.55 (d, J = 7.9 Hz, 1H), 11.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 30.9, 65.4, 76.7, 101.4, 104.9, 116.7, 120.1, 121.3, 122.0, 124.9, 125.0, 126.9, 127.4, 128.1, 128.5, 129.4, 132.0, 132.3, 137.0, 139.9, 148.7, 150.9, 156.2, 180.0; HRMS found m/z 408.1451 $[M]^+$, $C_{26}H_{20}N_2O_3$; calcd M = 408.1473. IR (cm^{-1}) ν 1675 (C═O), 2209 (C≡C), 3048 (NH).

5-(*p*-Toluidino)-3-((4-methoxyphenyl)ethynyl)-6*H*-anthra-[1,9-*cd*]isoxazol-6-one 4e. Time of reaction 3 min (0.047 g, 64%), mp 236−238 °C (benzene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.85 (s, 3H), 6.9 (d, J = 8.5 Hz, 2H), 7.29−7.33 (m, 4H), 7.55 (s, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.78 (t, J = 7.8 Hz, 1H), 8.16 (d, J = 7.9 Hz, 1H), 8.57 (d, J = 7.9 Hz, 1H), 11.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 55.2, 83.5, 100.8, 101.4, 113.6, 114.0, 117.1, 121.3, 122.2, 124.5, 125.3, 126.1, 128.2, 128.5, 130.3, 132.0, 132.5,

133.9, 134.6, 136.7, 149.5, 151.3, 156.3, 160.7, 180.1; HRMS found m/z 456.1465 $[M]^+$, $C_{30}H_{20}N_2O_3$; calcd M = 456.1468. IR (cm^{-1}) ν 1674 (C═O), 2193 (C≡C), 3055 (NH).

5-Hydroxy-3-(phenylethynyl)-6*H*-anthra[1,9-*cd*]isoxazol-6-one 8a. Time of reaction 40 min (0.15 g, 70%), mp 221−223 °C (toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.39−7.45 (m, 3H), 7.67−7.69 (m, 2H), 7.75 (t, J = 7.7 Hz, 1H), 7.89 (t, J = 7.6 Hz, 1H), 8.32 (d, J = 8 Hz, 1H), 8.57 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.2, 83.4, 102.5, 104.6, 116.1, 121.4, 122.7, 124.6, 125.0, 127.1, 128.0, 128.5, 128.7, 130.1, 132.4, 135.4, 151.6, 155.7, 166.6, 178.8; HRMS found m/z 337.0745 $[M]^+$, $C_{22}H_{11}N_1O_3$; calcd M = 337.0733. IR (cm^{-1}) ν 1678 (C═O), 2200 (C≡C), 3430 (OH).

3-[(4-Nitrophenyl)ethynyl]-5-hydroxy-6*H*-anthra[1,9-*cd*]isoxazol-6-one 8b. Time of reaction 40 min (0.09 g, 55%), mp 248−250 °C (benzene). ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 6.81 (s, 1H), 7.30 (t, J = 7.4 Hz, 1H), 7.40 (d, J = 8.8 Hz, 2H), 7.45 (t, J = 7.4 Hz, 1H), 8.80−7.84 (m, 3H), 8.08 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.9, 87.0, 97.9, 104.7, 115.9, 122.2, 123.44, 123.49, 124.2, 127.1, 128.7, 132.5, 132.8, 133.2, 136.3, 147.6, 150.7, 155.7, 167.8, 174.9; HRMS found m/z 382.0583 $[M]^+$, $C_{22}H_{10}N_2O_5$; calcd M = 382.0584. IR (cm^{-1}) ν 1681 (C═O), 2206 (C≡C), 3422 (OH).

3-[(4-Bromophenyl)ethynyl]-5-hydroxy-6*H*-anthra[1,9-*cd*]isoxazol-6-one 8c. Time of reaction 20 min (0.28 g, 84%), mp 200−202 °C (benzene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.49−7.56 (m, 4H), 7.72 (t, J = 7.4 Hz, 1H), 7.86 (t, J = 7.5 Hz, 1H), 8.27 (d, J = 7.9 Hz, 1H), 8.52 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 84.0, 100.3, 104.3, 115.7, 119.9, 122.2, 123.6, 124.0, 124.3, 126.8, 127.8, 128.6, 131.6, 132.3, 133.4, 135.3, 150.9, 155.4, 166.6, 177.0; HRMS found m/z 414.9831 $[M]^+$, $C_{22}H_{10}N_1O_3$; calcd M = 414.9838. IR (cm^{-1}) ν 1682 (C═O), 2203 (C≡C), 3442 (OH).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. ^{1}H and ^{13}C NMR spectra; total energy and Cartesian coordinates for each optimized stationary point at the reaction hypersurfaces. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vasilev@kinetics.nsc.ru; alabugin@chem.fsu.edu.

■ ACKNOWLEDGMENT

This work was supported by the Interdisciplinary Grant No.93 of SB of the Russian Academy of Sciences (2009-2011), Grant RFBR No. 10-03-00257-a (2010-2012), Grant 5.9.3. of the Russian Academy of Sciences (2009−2011), and the Chemical Service Centre of SB RAS. Work at FSU has been supported by National Science Foundation (CHE-0848686).

■ REFERENCES

(1) Butler, M. S. *Nat. Prod. Rep.* **2008**, *25*, 475–516.*Cancer Drug Design and Discovery*; Neidle, S., Ed.; Elsevier: Amsterdam, 2008. *Medicinal Chemistry of Bioactive Natural Products*; Liang, X.-T., Fang, W.-S. John Wiley& Sons: New York, 2006; p 460.

(2) Hyodo, S.; Fujita, K.; Kasuyaa, O.; Takahashia, I.; Uzawab, J.; Koshino, H. *Tetrahedron* **1995**, *24*, 6717–6724. Furumi, K.; Fujioka, T.; Fujii, H.; Okabe, H.; Nakano, Y.; Matsunaga, H.; Katano, M.; Mori, M.; Mihashi, K. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 93–96.

(3) Oaksmith, J. M.; Ganem, B. *Tetrahedron Lett.* **2009**, *26*, 3497–3498.

(4) Kortylewicz, Z. P.; Nearman, J.; Baranowska-Kortylewicz, J. *J. Med. Chem.* **2009**, *16*, 5124–5143.

(5) Tolstikova, T. G.; Sorokina, I. V.; Tolstikov, G. A.; Tolstikov, A. G.; Flekhter, O. B. *Bioorg. Khim.* **2006**, *32* (3), 291–307. For other modifications of triterpenoids, see also:Vasilevsky, S. F.; Govdi, A. I.; Sorokina, I. V.; Tolstikova, T. G.; Baev, D. S.; Tolstikov, G. A.; Mamatuyk, V. I.; Alabugin, I. V. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 62–65. Vasilevsky, S. F.; Govdi, A. I.; Shults, E. E.; Shakirov, M. M.; Tolstikov, G. A.; Alabugin, I. V. *Bioorg. Med. Chem.* **2009**, *17*, 5164–5169.

(6) (a) Breiner, B.; Schlatterer, J. C.; Kovalenko, S. V.; Greenbaum, N. L.; Alabugin, I. V. *Proc. Natl. Acad. Sci.U.S.A.* **2007**, *104*, 13016. (b) Breiner, B.; Schlatterer, J. C.; Kovalenko, S. V.; Greenbaum, N. L.; Alabugin, I. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3666–3670. (c) Kovalenko, S. V.; Alabugin, I. V. *Chem. Commun.* **2005**, 1444–1446. (d) Yang, W.-Y.; Breiner, B.; Kovalenko, S. V.; Ben, C.; Singh, M.; LeGrand, S. N.; Sang, Q.-X.; Strouse, G. F.; Copland, J. A.; Alabugin, I. V. *J. Am. Chem. Soc.* **2009**, *131*, 11458–11470. (e) Yang, W.-Y.; Marrone, S. A.; Minors, N.; Zorio, D. A. R.; Alabugin, I. V. *Beilstein J. Org. Chem.* **2011**, *7*, 813–823.

(7) Dembitsky, V. M.; Levitsky, D. O. *Nat. Prod. Commun.* **2006**, *1*, 405–429. Nicolaou, K. C.; Smith, A. L.; Yue, E. W. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 5881. Liu, W.; Christenson, S. D.; Standage, S.; Shen, B. *Science* **2002**, *297*, 1170. For further use of acetylenes in the design of medicinal agents, see: Alabugin, I. V.; Kovalenko, S. V. *J. Am. Chem. Soc.* **2002**, *124*, 9052–9053. Zeidan, T.; Kovalenko, S. V.; Manoharan, M.; Clark, R. J.; Ghiviriga, I.; Alabugin, I. V. *J. Am. Chem. Soc.* **2005**, *127*, 4270–4285. Kauffman, J. F.; Turner, J. M.; Alabugin, I. V.; Breiner, B.; Kovalenko, S. V.; Badaeva, E. A.; Masunov, A.; Tretiak, S. *J. Phys. Chem. A* **2006**, *110*, 241–251. Baroudi, A.; Mauldin, J.; Alabugin, I. V. *J. Am. Chem. Soc.* **2010**, *132*, 967.

(8) Tuttle, T.; Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **2005**, *127*, 9469–9484.

(9) Vasilevsky, S.; Gornostaev, L.; Stepanov, A.; Arnold, E.; Alabugin, I. *Tetrahedron Lett.* **2007**, *48*, 1867–1870.

(10) Gornostaev, L. M.; Levdanskii, V. A.; Fokin, E. P. *Russ. J. Org. Chem.* **1979**, *15*, 1692–1698.

(11) Montevecchi, P.; Navacchia, M.; Spagnolo, P. *Eur. J. Org. Chem.* **1998**, *6*, 1219–1226.

(12) Vasilevsky, S.; Tretyakov, E. *Liebigs Ann. Chem.* **1995**, 775–779. Tretyakov, E. V.; Knight, D. W.; Vasilevsky, S. F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3721–3726.

(13) Shvartsberg, M. S.; Ivanchikova, I. D.; Fedenok, L. G. *Tet. Lett.* **1994**, 6749–6752.

(14) Diazotization of **2e** by amyl nitrite proceeded sluggishly and with the formation of byproduct. An improvement was achieved when isopropyl nitrite was used instead (reaction is complete within 50 min and 47% of **3e** was isolated after the addition of sodium azide).

(15) Sokolova, M. S.; Beresnev, V. A.; Kargina, O. I.; Gornostaev, L. M. *Russ. J. Org. Chem.* **2008**, *44*, 1631–1635.

(16) (a) See refs 12 and 13. (b) Vasilevsky, S. F.; Tretyakov, E. V. *Synth. Commun.* **1994**, *24*, 1733–1736. (c) Zolnikova, N. A.; Fedenok, L. G.; Polyakov, N. E. *Org. Prep. Proced. Int.* **2006**, *38*, 476–480. (d) Goeminne, A.; Scammells, P. J.; Devine, S. M.; Flynn, B. L. *Tetrahedron Lett.* **2010**, *51*, 6882–6885.

(17) von Richter, V. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 677–683.

(18) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.

(19) Topologicaly similar *nucleophilic* cyclizations: Vasilevsky, S. F.; Mikhailovskaya, T. F.; Mamatyuk, V. I.; Bogdanchikov, G. A.; Manoharan, M.; Alabugin, I. V. *J. Org. Chem.* **2009**, *74*, 8106–8117. See also: Vasilevsky, S. F.; Baranov, D. S.; Mamatyuk, V. I.; Gatilov, Y. V.; Alabugin, I. V. *J. Org. Chem.* **2009**, *74*, 6143–6150.

(20) (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100. (b) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (c) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627.

(21) Frisch, M. J. et al. *Gaussian 98*, Revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998. Frisch, M. J. et al. *Gaussian 03*, revision C.01;

Gaussian, Inc.: Wallingford CT, 2004 (see Supporting Information for complete references).

(22) Although we classify the cyclization as a 5-*exo-dig* electrophilic cyclization on the alkyne moiety, one could also characterize is as a nucleophilic 5-*endo-dig* closure on the diazonium. Note that the electronic structure of the diazonium moiety strongly favors nucleophilic attack at the terminal nitrogen, rendering the "*endo*" path generally dominant.

(23) Because of the low stability of vinyl cations, truly electrophilic cyclizations of alkynes are surprisingly scarce. Electrophilic closures should not be confused with the much more common electrophile-promoted nucleophilic closures (EPNC): Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937.For a general discussion of electronic effects in alkyne cyclizations, see: Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, published online ahead of print, DOI:10.1021/cr200164y. Alabugin, I.; Gilmore, K.; Manoharan, M. *J. Am. Chem. Soc.* **2011**, *133*, 32306.

(24) For representative examples of electrophilic alkyne cyclizations, see :Peterson, P. E.; Kamat, R. J. *J. Am. Chem. Soc.* **1969**, *90*, 4521. Hanack, M. *Acc. Chem. Res.* **1976**, *9*, 364. Hanack, M. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 333. Johnson, W. S.; Hughes, L. R.; Carlson, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 1281. Hanack, M.; Collins, C. J.; Stutz, H.; Benjamin, B. M. *J. Am. Chem. Soc.* **1981**, *103*, 2356. Collins., C. J.; Hanack, M.; Stutz, H.; Auchter, G.; Schoberth, W. *J. Org. Chem.* **1983**, *48*, 5260. Apeloig, Y.; Collins., J. B.; Cremer, D.; Bally, T.; Haselbach, E.; Pople, J. A.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Org. Chem.* **1980**, *45*, 3496. Franke, W.; Schwarz, H. *J. Org. Chem.* **1981**, *46*, 2806. Cunje, A.; Rodriquez, C. F.; Lien, M. H.; Hopkinson, A. C. *J. Org. Chem.* **1996**, *61*, 5212. Jin, T.; Himuro, M.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 5893. Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679. Balog, A.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 337. For a recent review on Prins-type cyclizations, see: Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413 and references therein.

(25) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612.

(26) For other H-shifts accompanied by aromatization, see: Alabugin, I. V.; Manoharan, M.; Breiner, B.; Lewis, F. *J. Am. Chem. Soc.* **2003**, *125*, 9329–9342. Alabugin, I. V.; Gilmore, K.; Patil, S.; Manoharan, M.; Kovalenko, S. V.; Clark, R. J.; Ghiviriga, I. *J. Am. Chem. Soc.* **2008**, *130*, 11535–11545.