Pergamon

Tetrahedron Letters 41 (2000) 10019–10023

TETRAHEDRON LETTERS

Synthesis of enediyne model compounds producing toluene diradicals possessing a highly radical character via enyne–allene intermediates

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Received 14 July 2000; revised 4 October 2000; accepted 6 October 2000

Abstract

Development of enediyne model compounds that produce dehydrotoluene diradicals under acidic media is described. The ionic character of the diradicals is shown to be avoided by the electron-withdrawing groups in the molecules both in benzene and MeOH. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: diynes; enynes; radicals; ionization; DNA.

The neocarzinostatin chromophore (NCS-Chr) contains a diene–diyne core that undergoes a triggered rearrangement to an enyne–cumulene intermediate, which immediately produces a reactive diradical species responsible for DNA damage in vitro.[1] As a model study of the chemical reactions of NCS-Chr, we have prepared several enediyne models possessing characteristic triggering devices which initiate the generation of enyne–allene intermediates and ultimately produce dehydrotoluene diradicals.[2] Studies of the cycloaromatization of enyne–allenes (Myers–Saito reaction, **2**→**3**)[3] are of fundamental importance not only in the mechanistic study of NCS-Chr, but also toward the design of simple and bio-active NCS-Chr analogs. During our studies, we found the diradical intermediates have a polar character, and the reactions afford products arising from both dipolar (in protic solvents) and diradical (in aprotic solvents) pathways.[2] A polar diradical intermediate for the cycloaromatization process was first proposed in the pioneering studies of the Myers group,[3a,b] and was confirmed recently in the kinetic study of Finn and co-workers.[4] This cycloaromatization was proposed by Squires et al.[5] to proceed through a common intermediate best described as a linear combination of the resonance structures **3** and **4** (Scheme 1). The ionic character of the intermediate is presumed to reduce the DNA-damaging ability and other biological activities. Therefore, it is an important subject to

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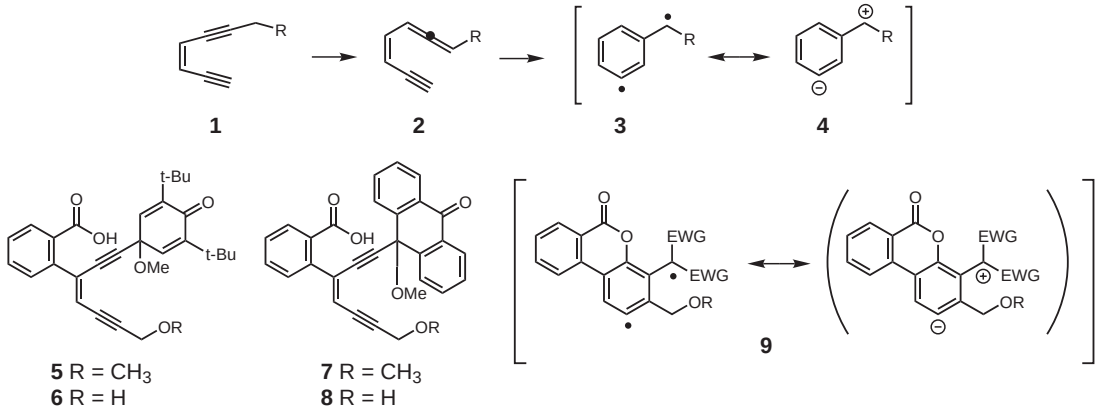
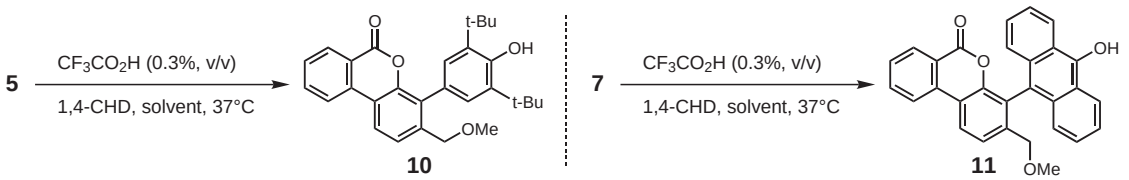
PII: S0040-4039(00)01788-3

develop a model system in which the contribution of the ionic resonance structure **4** is reduced. For this purpose, we designed novel enediyne models (**5**–**8**) having electron-withdrawing groups which are expected to avoid the ionic character of the intermediates (**9**).[6] The enediynes **5**–**8** were synthesized according to a similar procedure reported previously.



Scheme 1.

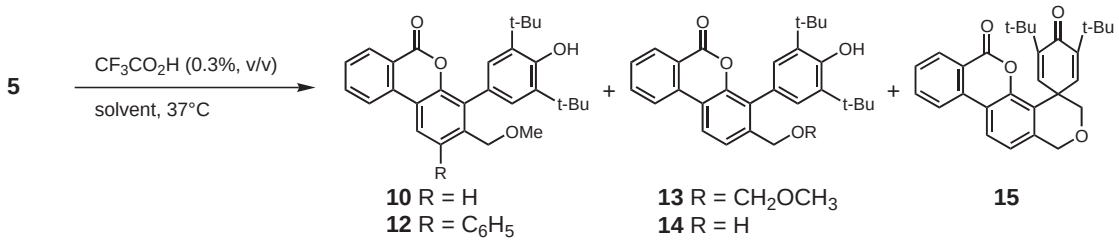
The reaction of the enediyne **5** with trifluoroacetic acid (0.3 v/v%) in the presence of 1,4-cyclohexadiene (1,4-CHD) as a hydrogen donor in benzene or MeOH at 37°C afforded the phenol **10** as the only separable product, respectively, indicating that the cycloaromatization proceeded via a diradical cyclization pathway.[7] The intermediate corresponding to enyne–allene could not be detected on TLC or by ^{1}H NMR during each reaction, therefore the relatively slow reaction rate in MeOH can be ascribed to the acid catalyzed lactone formation pathway. The reaction of **7** gave similar results and the products being formed via an ionic pathway could not be detected from either of the reaction products (Scheme 2).



Solvent	Rection time (min)		Yield (%)	
	5 →**10**	**7** →**11**	**10**	**11**
Benzene	90	5	83	87
MeOH	2880	150	53	73

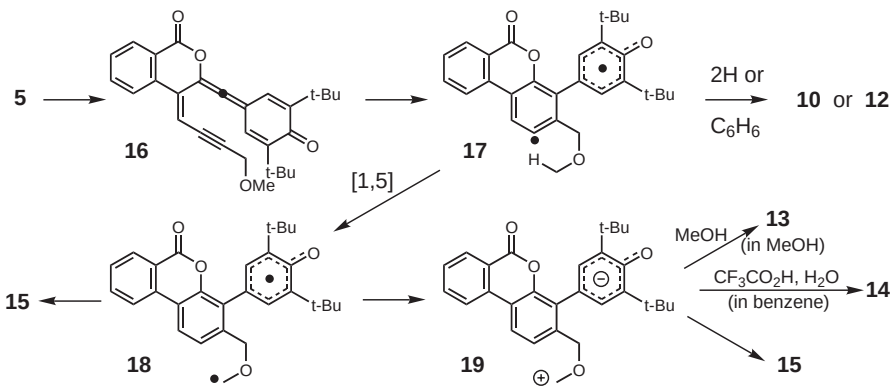
Scheme 2.

The same reaction of **5** in the absence of 1,4-CHD afforded a more intricate mixture from which **10** and **12**–**15** were isolated (Scheme 3). The reaction of **7** under the same conditions gave similar results. Mechanistically, the reaction of **5** can be rationalized as shown in Scheme 4. In the first step, enyne–allene **16** is generated under acidic conditions, which produces the toluene diradical **17** according to the Myers–Saito reaction.[2f,3] The diradical **17** abstracts hydrogens from the solvent (MeOH) to give **10** or condenses with benzene to give **12**.[8] The formation of



Solvent	Rection time (min)	Yield (%)				
		10	**12**	**13**	**14**	**15**
Benzene	90	6	28	-	15	18
MeOH	780	41	-	6	-	3

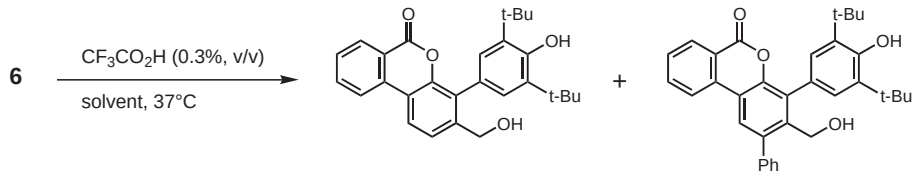
Scheme 3.



Scheme 4.

10 in a benzene solvent may be attributed to a result of the intermolecular hydrogen abstraction. The products **13** and **14** should be formed from the zwitterionic intermediate (**19**), which is assumed to be formed from the diradical **18** via a 1,5 hydrogen shift of **17**, followed by the intramolecular electron transfer. Both the diradical and ionic intermediates (**18** and **19**) have the possibility to produce **15** by recombination or ionic cyclization. To avoid the ionization described above, the alcohols **6** and **8** were prepared. As we expected, the products of cycloaromatization of these compounds are those proceeding via diradical pathways, the results being shown typically for the reaction of **6** (Scheme 5).

DNA strand cleavage by the synthesized enediynes was estimated on agarose gels by conversion of the covalently closed circular (Form I) to the open circular DNA (Form II). Table 1 shows the effect of pH on the DNA cleavage mediated by compounds **5**–**8**. In an acidic buffer solution, relatively potent DNA-cleaving activities were observed, as expected. Compounds **5** and **7**, that are expected to ionize partially in the intermediate of cycloaromatization, showed relatively low activities under any pH conditions. It is noteworthy that **6** and **8** showed weak activities under pH 8 buffer solutions. Further work will be required to clarify the mechanistic features of these activities.



14 32% (in benzene)
46% (in MeOH)

20 20% (in benzene)

Scheme 5.

Table 1
DNA cleavage by compounds **5**–**8**[a]

Compound		**5**	**6**	**7**	**8**
DNA cleavage (%)	pH 6	<5	15 ± 5	69 ± 4	97 ± 1
	pH 8	<5	15 ± 5	<5	11 ± 6

[a] Col E1 Form I DNA (12.5 μg/ml) was incubated for 12 h at 37°C with compounds (1 mM) in pH 6 and 8 phosphate buffers, and analyzed by electrophoresis (1% agarose gel, ethidium bromide staining). Results presented are mean value $\pm$ SD of three runs. A control reaction mixture without the addition of any drug was incubated and the mean value of three runs was used as the background to be subtracted from the obtained values.

In summary, this study demonstrates the development of enediyne model compounds which cycloaromatize triggered by acidic conditions via a diradical pathway predominantly. Relatively low DNA-cleaving activities of the compounds described here compared to that of naturally occurring enediyne drugs are attributable to the stable phenoxy radicals. Studies for the development of compounds having potent DNA-cleaving and cytotoxic activities according to our concept are continuing.

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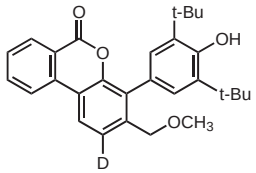
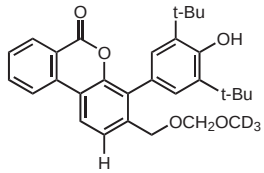
6. Recently, the synthesis of dienediyne models that undergo cycloaromatization via a diradical pathway predominantly was reported: Brückner, R.; Suffert, J. *Synlett* **1999**, 657–679.
7. The by-product of this reaction was polar and inseparable substance(s).
8. When the cycloaromatization reaction of the enediyne **5** was performed in CD_3OH, products **10d** and **13d** (extent of deuterium incorporation was ca. 59% and ca. 100%, respectively) were obtained. This result strongly suggests the existence of both diradical intermediate **17** and ionic intermediate **19**.



10d



13d