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Electronic Control of the Bergman Cycloaromatization: Synthesis and Chemistry of Chloroenediynes

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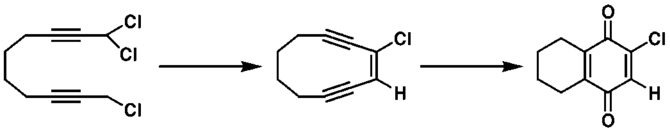
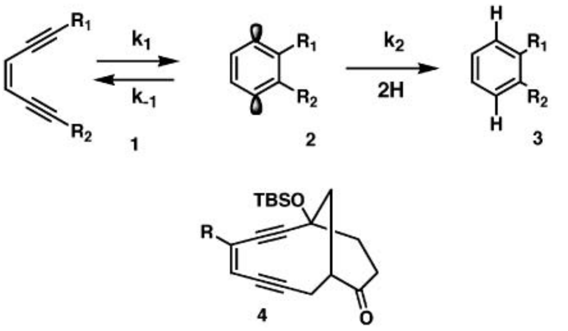
ABSTRACT



A series of cyclic mono- and dichloroenediynes have been prepared using an intramolecular carbenoid coupling reaction. The halogen atom had a retardative effect on Bergman cycloaromatization in every case examined, and atom transfer chemistry was demonstrated, resulting in formation of adducts.

The Bergman cycloaromatization reaction is a thermally allowed rearrangement of 3-ene-1,5-diynes (**1**) into the 1,4-diyl **2**, which, following atom transfer, can result in the formation of arenes **3** (Scheme 1).[1] Interest in this process has been heightened by the finding that appropriately substituted diyls **2** are capable of DNA strand scission[2] and may also be targets for proteins.[3] Though the most studied factors which influence the cycloaromatization ability of enediynes are molecular strain energy[4] and the intraacetylenic distance,[5] electronic factors are also known to play a key role.[6] Several reports on the influence of alkynyl substituents (**1**, R_1, R_2) exist, but systematic variations of the vinyl substituents of enediynes are less studied. In one key example, **4**, an electron donor group (R = $p\text{-}C_6H_5OMe$), was shown to retard cycloaromatization, possibly by stabilizing the ground state of the enediyne.[7]

Scheme 1. Electronic Control of the Bergman Cycloaromatization Reaction



Intrigued by this observation, we became interested in examining the effect of heteroatoms directly attached to the vinyl position. It could be expected that the combination of inductive and electronegativity effects may exert a unique influence on cycloaromatization, either by destabilizing the

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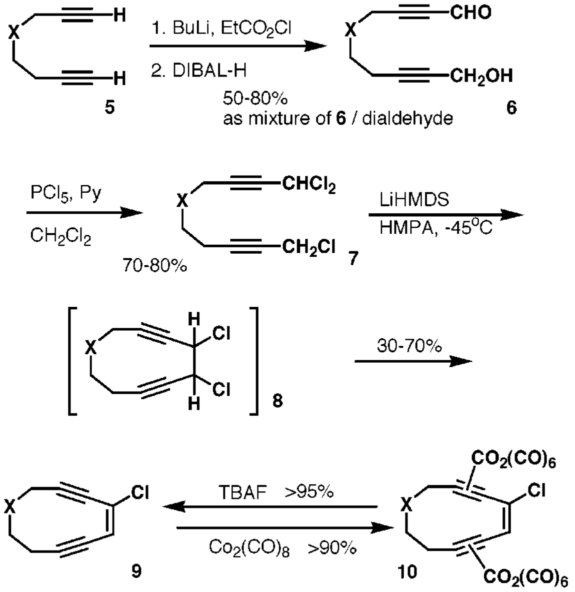
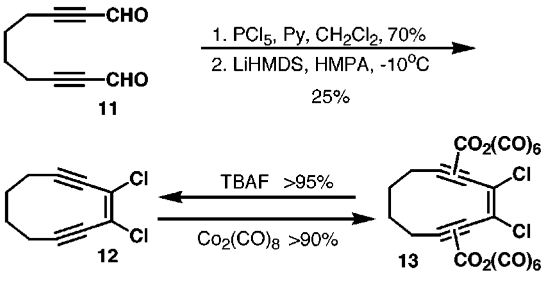
ground state or stabilizing the transition state of the process. On the basis of prior success in the preparation of cyclic enediynes using an intramolecular carbenoid coupling method,[8] we sought to provide proof-of-principal by preparing a series of halogenated enediynes.

Accordingly, using the appropriate bis-alkynes **5**, conversion to the diesters followed by selective reduction gave hydroxy aldehydes **6**, together with quantities of the dialdehydes (Scheme 2). Trichlorination gave substrates **7**,[9] which when subjected to carbenoid coupling gave enediynes **9** directly, with interception of the presumed dichlorodiyne precursors **8** proving impossible. Because of the expected thermal instability of the species, they were routinely protected as the corresponding cobalt hexacarbonyl complexes **10** and then unmasked as desired using TBAF.[10] Isolation of dialdehyde **11** in the reduction step used to prepare **6** (X = CH_2) allowed us to also investigate formation of a C-10 dichloroenediyne (Scheme 3). Accordingly, tetrachlorination followed by carbenoid coupling gave enediyne **12**, which was masked as cobalt alkyne complex **13**.

Scheme 2. Intramolecular Carbenoid Route to Chloroenediynes, X = CH_2CH_2, CH_2, −

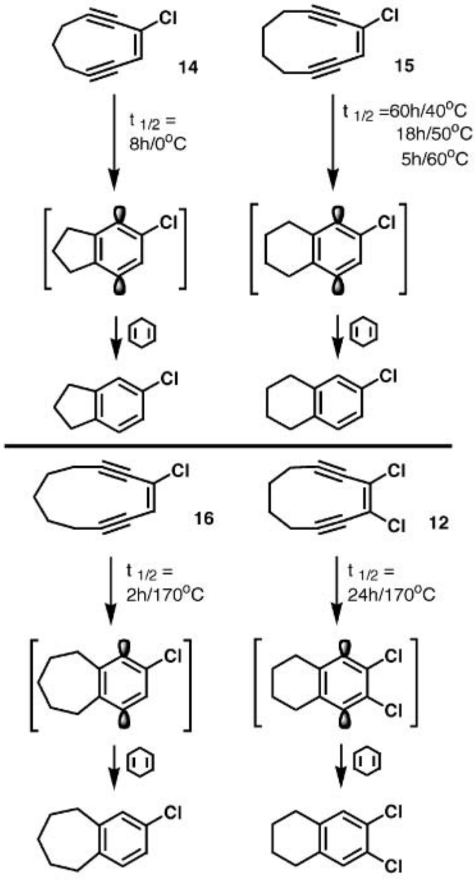


Scheme 3. Alternate Route to Dichloroenediynes



With this substrate, the carbenoid coupling required elevated temperatures and gave substantial quantities of recovered tetrachlorodiyne, pointing to the increased stability of the intermediate dihalocarbenoid intermediate. With the key enediyne substrates in hand, thermal cycloaromatization was investigated using 1,4-cyclohexadiene (neat) as hydrogen donor (Scheme 4). To our surprise, the halogen substituent had a profound effect on the half-life of the C-9 enediyne **14**, particularly when compared to the extremely labile C-9 unsubstituted enediyne whose half-life cannot be measured.[11] The half-lives of **15** and **16** are also extended compared to those of their unsubstituted analogues, and the addition of the second chlorine **12** grossly retards cycloaromatization.

Scheme 4. Thermal Bergman Cycloaromatization of Cyclic Halovinyl Enediynes



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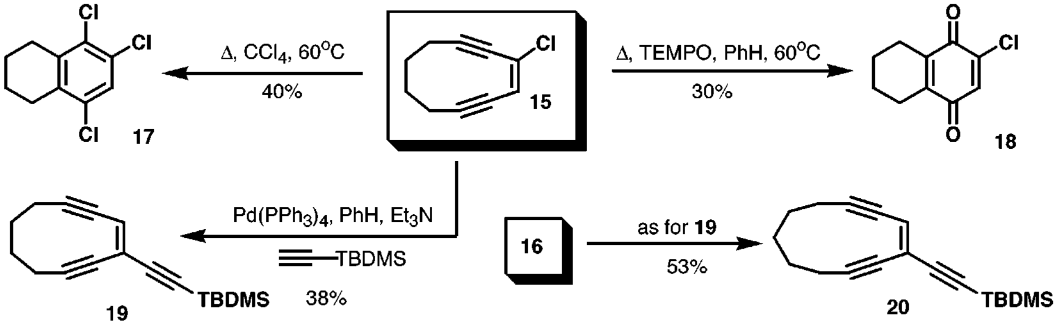
Scheme 5. Atom Transfer Chemistry of Halogenated Diyls



The origins of the stabilizing effect are presumably electronic in nature, since molecular modeling (PM3) of **12** and **15** reveals essentially no difference in intramolecular "c−d" [11] distances [3.298 and 3.297 Å, respectively, versus 3.293 Å for the C-10 unsubstituted enediyne]. This effect is most pronounced in **14** [c−d distance 2.864 Å] which would be expected to undergo spontaneous cycloaromatization in the absence of a stabilizing (electronic) effect. In addition to serving as a modulator of cycloaromatization, the presence of the halovinyl substituent offers potential in the synthesis of substituted arene products. Deliberate interception of diyls with a halogen sources is a useful approach, and in preliminary experiments, thermolysis of **15** with carbon tetrachloride gave trichloroarene **17** in good yield (Scheme 5).[12] Alternatively, oxidation using TEMPO (5 equiv) gave the interesting quinone **18**,[13] which could be a useful dienophile for preparation of anthraquinone skeletons. The thermal stability of **15** also allowed ambient Pd-mediated alkynylation to be carried out, giving **19**, which then rapidly underwent thermal decomposition. Alternatively, coupling **16** under identical conditions gave the shelf-stable enediyne **20** cleanly, even using a 1:1 ratio of alkyne.

In summary, a novel route to chloro-substituted enediynes has been demonstrated and the effect on Bergman cycloaromatization quantitated. Applications currently under investigation include preparation of analogues of otherwise thermally unstable C-9 enediynes and also C-10 enediyne mimics of the environmental toxin tetrachlorodibenzodioxin (TCDD).[14]

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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