Radical Reactions

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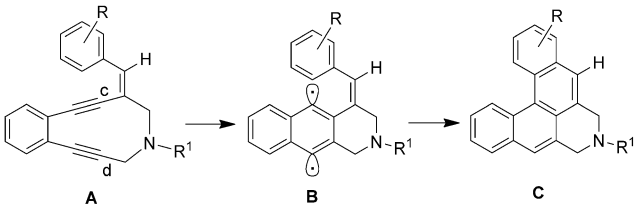
Synthesis of Angularly Fused Aromatic Compounds from Alkenyl Enediynes by a Tandem Radical Cyclization Process**

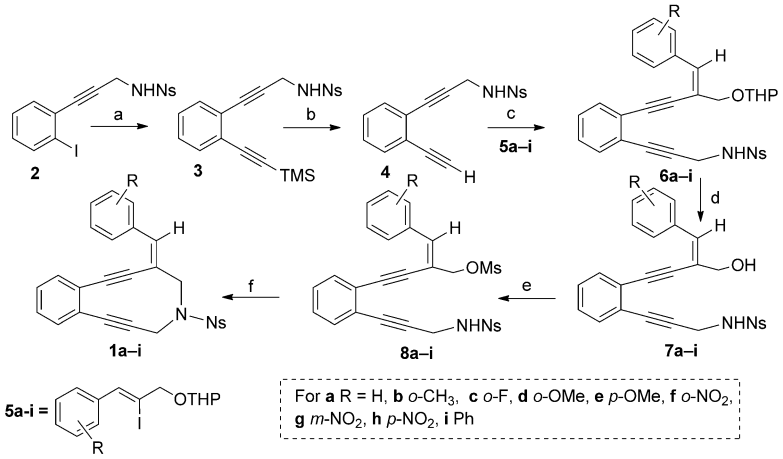
*Snigdha Roy, Anakuthil Anoop, Kumar Biradha, and Amit Basak**

The synthetic potential of the Bergman cyclization (BC)[1] has not been greatly explored despite remarkable progress in the understanding of the reaction mechanism[2] and the mode of biological action of enediynes.[3] The radicals within the 1,4-diradical generated during the BC are distally oriented, thus preventing self-quenching, which can lead to a highly strained bicyclo system, and are spin-paired by an external quencher.[4] The 1,4-diradical can undergo polymerization,[5] which causes the usual low yield of cyclized products. BC and related reactions involve the formation of benzenoid frameworks and, hence, are attractive for the synthesis of polyaromatic and benzannulated compounds. John and Tour[6] reported the formation of polyphenylenes using BC, while Grissom and Calkins[7] demonstrated the tandem radical cyclization of enediynes with diverse alkenyl acceptors. Diradicals generated in a porphyrin network have been trapped with a neighboring aromatic ring (Smith and co-workers,[8a] and Zaleski and co-workers[8b]). Taking a cue from these results and the *ortho* effect reported by Alabugin and co-workers,[9] we studied the reactivity of aryl exomethylene N-substituted cyclic enediynes of type **A** (Scheme 1). The initial intention was to explore the effect the π cloud of an aromatic ring[10] positioned above one of the alkynes of an enediyne framework would have on the BC. We did observe some interesting variations in reactivity depending on the R substituent present on the aromatic ring. However, the more important aspect is the synthesis of the angularly fused polyaromatic compounds [4]helicenes (**C**)[11] in high yields. The process, which involves the BC as the key step of an unprecedented tandem radical reaction, offers a general route to these compounds and also expands the synthetic potential of the BC.



Scheme 1. Synthesis of [4]helicenes.

The aryl enediynes **1** required for our study were prepared from *o*-iodo propargyl amine **2**[12] by using a six-step protocol. A Sonogashira coupling[13] with trimethylsilyl acetylene followed by a desilylation produced the enediyne **4**. Another coupling reaction with the *Z*-iodo alkene (obtained by a halo-Wittig reaction)[14] followed by THP removal furnished the acyclic enediyne **7**. This was converted into the mesylate **8**, which on treatment with K_2CO_3 in anhydrous DMF[15] produced the cyclic enediyne **1** (Scheme 2). NOESY spectra (see the Supporting Information) confirmed the positioning of the aryl ring to be above the enediyne alkyne.



Scheme 2. Synthesis of target enediynes **1a–i**. Reagents and conditions: a) TMS-acetylene, Pd(0), CuI, Et_3N, THF, RT, 8 h, 75%; b) KF, CH_3OH, RT, 1 h, 80%; c) **5**, Pd(0), CuI, Et_3N, THF, 12 h, 45–56%; d) PPTs, EtOH, RT, 6 h, 82–85%; e) MsCl, Et_3N, CH_2Cl_2, 0°C, 5 min, 55–62%; f) K_2CO_3, DMF, RT, 4 h, 54–70%. DMF = *N*,*N*′-dimethylformamide, Ms = methanesulfonyl, Ns = 4-nitrobenzenesulfonyl, PPTs = pyridinium *p*-toluenesulfonate, THF = tetrahydrofuran, THP = tetrahydropyranyl, TMS = trimethylsilyl.

As a test study, enediyne **1** was dissolved in [D_6]DMSO and kept at 90°C (Scheme 3). The reaction was monitored by recording the ^{1}H NMR spectra at different times. There was a gradual decrease in the signals for the substrate accompanied

[*] Dr. S. Roy, Prof. A. Anoop, Prof. K. Biradha, Prof. A. Basak
Department of Chemistry, Indian Institute of Technology
Kharagpur 721 302 (India)
E-mail: absk@chem.iitkgp.ernet.in

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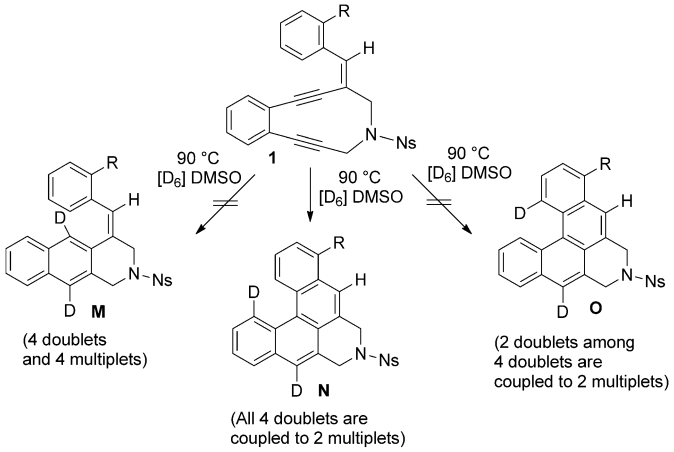


Scheme 3. Possible BC products. DMSO = dimethylsulfoxide.

by the appearance of new signals corresponding to product. The reaction conversion was mostly free from unwanted side reactions (see the NMR studies in the Supporting Information) and the products were isolated and purified by column chromatography on silica gel. The ^{1}H NMR spectrum showed two sets of doublets, one for H1 and H3 each coupled to H2, which gave a multiplet at δ 7.71, and the other for H9 and H11 each coupled to H10, which gave a multiplet at δ 7.69 (Figure 1 a). This finding indicated the presence of two 1,2,3-trisubstituted benzene rings as shown in structure **N** and thus ruled out the normal BC product **M** as well as the alternate structure **O** (Scheme 3). The mass spectra also supported the presence of two deuterium atoms in the product. Carrying out the reaction in DMSO furnished the fully protiated product, from which two new signals appeared in the ^{1}H NMR spectrum, one at δ 7.72 (s, H8) and the other (H12) obscured in the region δ 7.64–7.72; the combined integration for this region amounted to six protons (Figure 1 b). Final confirmation of the structure came from single-crystal X-ray analysis[16] of the product **9a** (Figure 2). The reaction was found to be very general, and a large array of differently substituted [4]helicenes were obtained (Scheme 4). Considering the concurrent triple annulation, the yields can be considered to be impressive.

Regarding the mechanism, we propose the following. The tandem cyclization was initiated by the BC of **1** to furnish two new rings, B and C (Scheme 5). The second step involved addition of the aryl radical **10a** to the proximally placed aromatic ring E resulting in the simultaneous formation of ring D and a new radical on ring E.[17] This radical, upon hydrogen abstraction from ring A,[18] furnished another new radical intermediate **10c**. Abstraction of deuterium (hydrogen in the case of nondeuteriated DMSO) with a subsequent oxidation produced the helicenes. The diradical **10a** is possibly quite shielded by the molecular framework, thus making it almost inaccessible for polymerization or external quenching.

NMR-based kinetic studies were performed with substrates **1a–i** at 90 °C in [D$_6$]DMSO to determine the effect of the substituents on the rate of the annulations. A considerable rate perturbation was observed upon variation of the

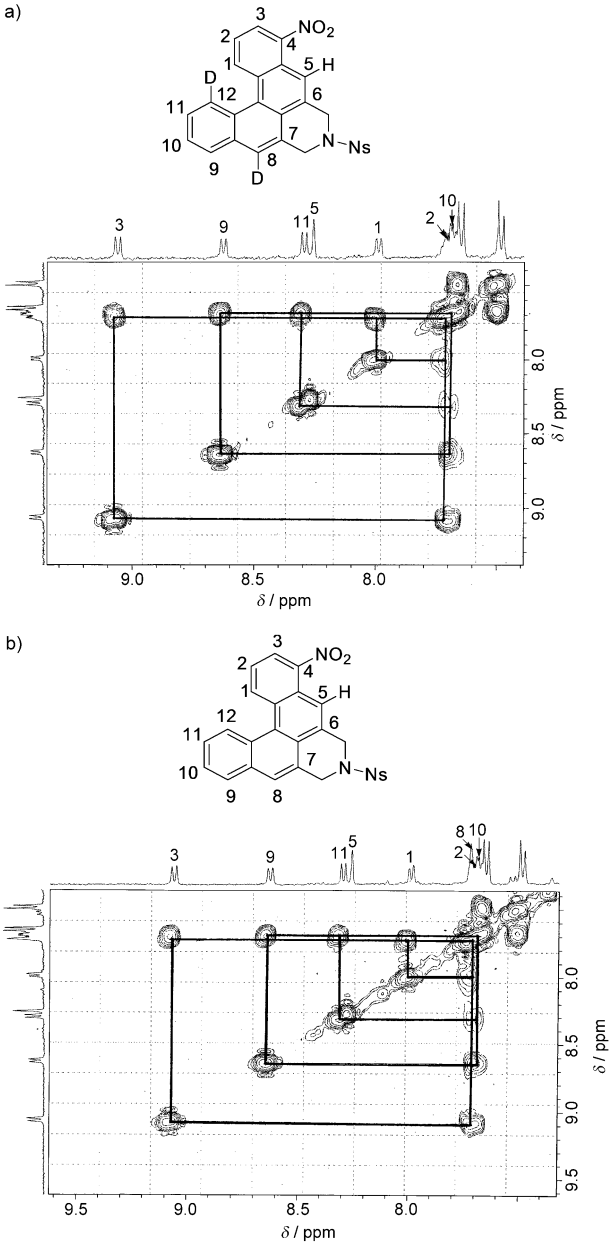


Figure 1. COSY spectra of **9f** performed in: a) deuteriated DMSO, b) nondeuteriated DMSO.

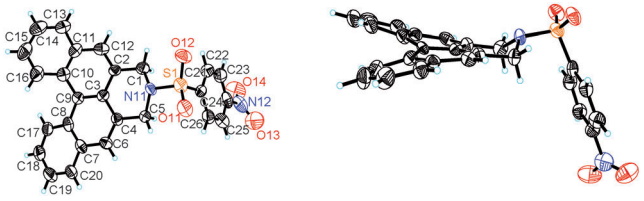
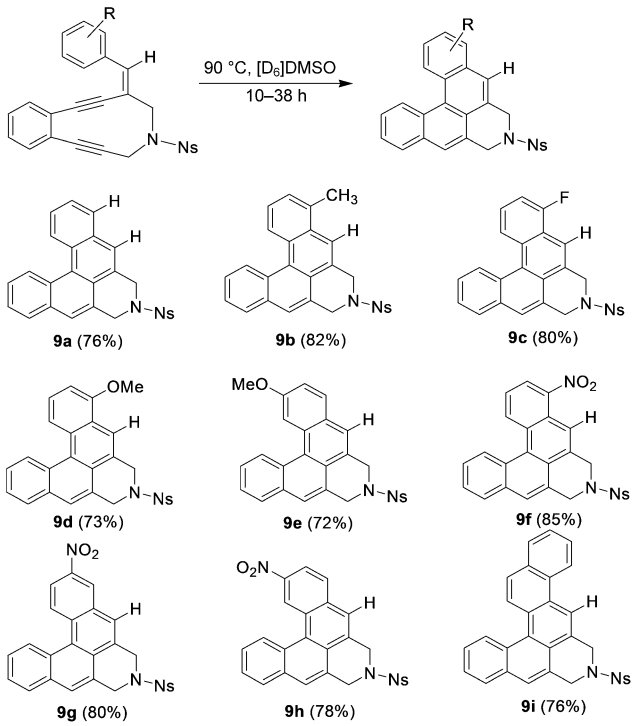
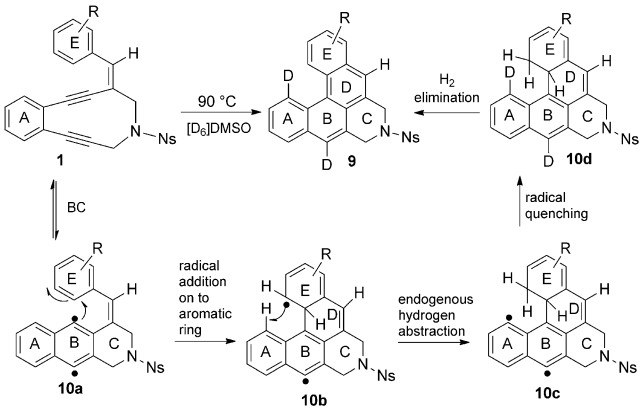


Figure 2. ORTEP diagram of **9a** with the thermal elipsoids shown at 30% probability.

substituents on ring E as well as their orientations (Table 1). For different *ortho* substituents on ring E, the measured rate constants varied in the range of 6×10^{-6} to 29×10^{-6} s^{-1}. The cyclization rates of compounds with nitro substituents at *o*, *m*, and *p* positions follow a decreasing trend (**1f–h**). To assess the



Scheme 4. Synthesized [4]helicenes.

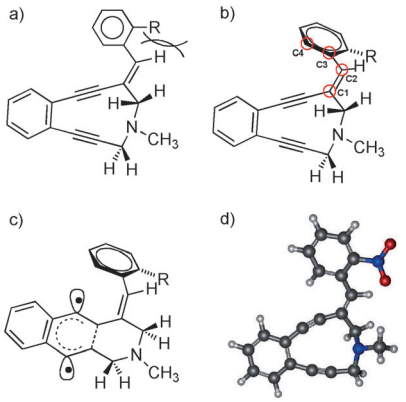


Scheme 5. Mechanism of tandem cyclization.

Table 1: Calculated and experimental results. Φ represents the tilting of the substituted phenyl ring (Scheme 6b) measured as the torsion angle made of C1-C2-C3-C4.

Enediyne	BP86		B3LYP [kcal mol^{-1}]		Φ [°]	Experimental rate constant [$\times 10^6$ sec^{-1}]
	ΔE^{act}	ΔG^{act}	ΔE^{act}	ΔG^{act}		
1a	24.03	23.69	34.40	34.06	5.02	7.83
1b	23.26	22.97	33.43	33.14	15.43	17.58
1c	23.84	23.32	34.15	33.63	6.75	10.61
1d	23.51	23.29	33.75	33.52	9.27	6.86
1f	22.99	22.41	33.33	32.75	23.88	29.17
1g	24.10	23.85	34.45	34.20	4.80	6.06
1h	23.95	24.23	34.47	34.75	4.53	5.89

role of the substituents on ring E (electronic or steric), the activation energy for the BC step was computed using density functional theory (for computational details see the Supporting Information). The simple phenyl-sustituted enediyne **1a** was taken as the reference. The activation free energy for the BC step for **1a** was calculated to be 34.06 kcal mol^{-1}. The phenyl group in **1a** is involved in through-bond conjugation of the π system extended over alkene and alkyne carbon atoms, all of which lie nearly in the same plane. Substitution at the *ortho* position forces the aryl ring to be tilted out of this plane (Scheme 6), thus causing reduced conjugation and destabili-



Scheme 6. a) Schematic drawing showing the steric interaction between R and H for the structure with the phenyl ring in plane with the olefinic and acetylenic carbon atoms, b) and c) G.S and T.S. structures in which steric repulsion is avoided by having the phenyl ring tilted, d) optimized geometry of **1f** in which the phenyl ring is tilted as shown in (b).

zation of the system. In the transition-state geometries for all the cases studied (**1**‡**a–d** and **1**‡**f–h**), the phenyl group is also tilted (Scheme 6c) and therefore the destabilization resulting from the bulky substituent is relatively less in the transtition state compared to that in the adducts. This greater destabilization of **1f** as compared to **1a**, is expected to reduce the relative activation energy, thus causing a rate enhancement.[19]

Experimentally, a fivefold increase in the reaction rate was observed when there was a nitro substituent in the *ortho* position, thus giving a predicted difference in energy barrier of about 1 kcal mol^{-1}. The activation energy difference from B3LYP calculation (1.31 kcal mol^{-1}) is in reasonable agreement with the experimental results. Thus, it can be concluded that increasing the steric bulk of R will create more tilting of the aryl ring and will thus cause a greater destabilization of the starting enediyne and hence greater reactivity. The calculated order, *o*-NO_2 (**1f**) > *o*-Me (**1b**) > *o*-OMe (**1d**) > *o*-F (**1c**) > H (**1a**) > *m*-NO_2 (**1g**) > *p*-NO_2 (**1h**) roughly follows the steric bulk of R (Table 1).[20] The extent of tilting (Φ, Table 1) also follows the same order. Except for the methoxy-substituted phenyl (**1d**), which reacted at the slowest rate, the predicted order is in agreement with the experimental observation. Because of the rotational flexibility,[21] it is difficult to rank the methoxy group according to its steric bulk. Changing the position of the nitro substitution on the phenyl group increases the activation free energy in the order

ortho > *meta* > *para*. Thus, the steric effects are more pronounced for the nitro group, because the electronic effect on the *ortho* and *para* substitution is similar but there is a difference in the energy barrier of 1.45 kcal mol^{-1}. This comes from a larger energy difference between the *para*- and *ortho*-enediyne substrates (**1g** is more stable than **1f** by 4.46 kcal mol^{-1}) than from their corresponding transition state (3.01 kcal mol^{-1}). Substitution at the *meta* and *para* positions does not have any steric influence and therefore has similar activation barriers (difference of ca. 0.5 kcal mol^{-1}). This small difference may be due to the electronic effects coming from the *meta* and *para* positions. A similar trend of reactivity was also obtained in BP86-based calculations.

In conclusion we have been successful in developing a BC-mediated tandem radical route to [4]helicenes. The proposed mechanism is well supported by the results in deuteriated and nondeuteriated solvents. Presently we are working on extending the method to the synthesis of chiral helicenes.

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