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Benzene Fused Monocyclic Enediynyl Amides: Synthesis, Reactivity and DNA-Cleavage Activity in Comparison to the Corresponding Sulfonamides

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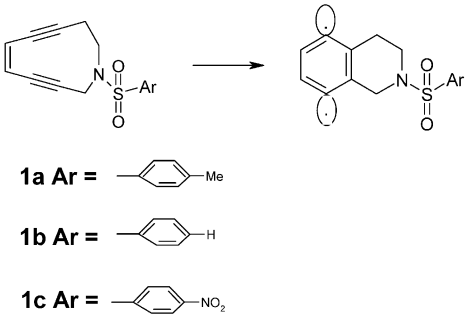
Abstract—Monocyclic enediynyl amides **2a**–**2c** have been synthesized via the corresponding free amine **5**. Kinetic studies in chloroform revealed the reactivity of these amides towards Bergman cyclization to be less than that of the corresponding sulfonamides. However, differential scanning calorimetry (DSC) measurements in the solid state and DNA-cleavage studies in aqueous buffer showed higher reactivity for the amides than the sulphonamides. © 2002 Published by Elsevier Science Ltd.

During our study with *N*-sulfonamido enediynes **1a**–**1c**, we had observed[1] a small but detectable dependence of their rates of Bergman cyclization (BC)[2–5] on the electronic nature of the aryl sulfonamide groups. The presence of electron withdrawing nitro group in **1c** made the cyclization faster (~1.5 times) as compared to the sulfonamides with electron donating methyl in **1a** or even hydrogen in **1b**. We attributed this perturbation of kinetics of BC to the greater participation of lone pair of the ring nitrogen atom in resonance with the sulfone when electron-withdrawing groups are present in the aromatic ring. Considering the fact that nitrogen atom is much more conjugated and essentially planar compared to a sulfonamido nitrogen, a rate enhancement can be expected if the sulfonamide is replaced by an amide. With this in mind, we prepared the amido enediynes **2a**–**2c** and studied their rates of BC. In this communication, we are reporting our results.



Our initial synthetic strategy is shown in Scheme 1. This was essentially similar to the reported[6] synthesis of the sulfonamido enediynes **1a**–**1c**. Only difference was the intramolecular cyclization involving the amide nitrogen and the propargylic mesylate as in **3**. Although *N*-alkylation of amides is well known,[7] the reaction failed in our system. No cyclic enediyne was obtained even in the presence of strong bases like NaH or KO^{t}Bu. Carrying out the reaction under high dilution also failed to lead to the desired product. Same thing happened during our attempt to cyclize the *N*-^{t}Boc enediynyl mesylate **3a**.

The above experience prompted us to adopt a different strategy. Since intramolecular cyclization worked well with the nucleophilic sulfonamido nitrogen, it would be better if the cyclic enediynyl sulfonamide **4a**/**4b** is first prepared and then deprotected under mild condition to the free amine **5**. The latter, in principle, can be converted to the amides as well as to other range of derivatives. Since an aromatic fused enediynyl sulfonamide has better thermal stability as compared to the non-aromatic ones,[8] we decided to implement our strategy

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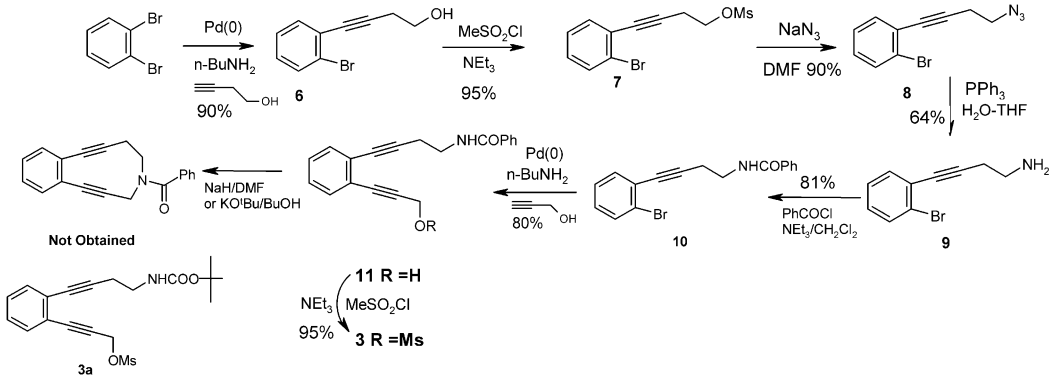
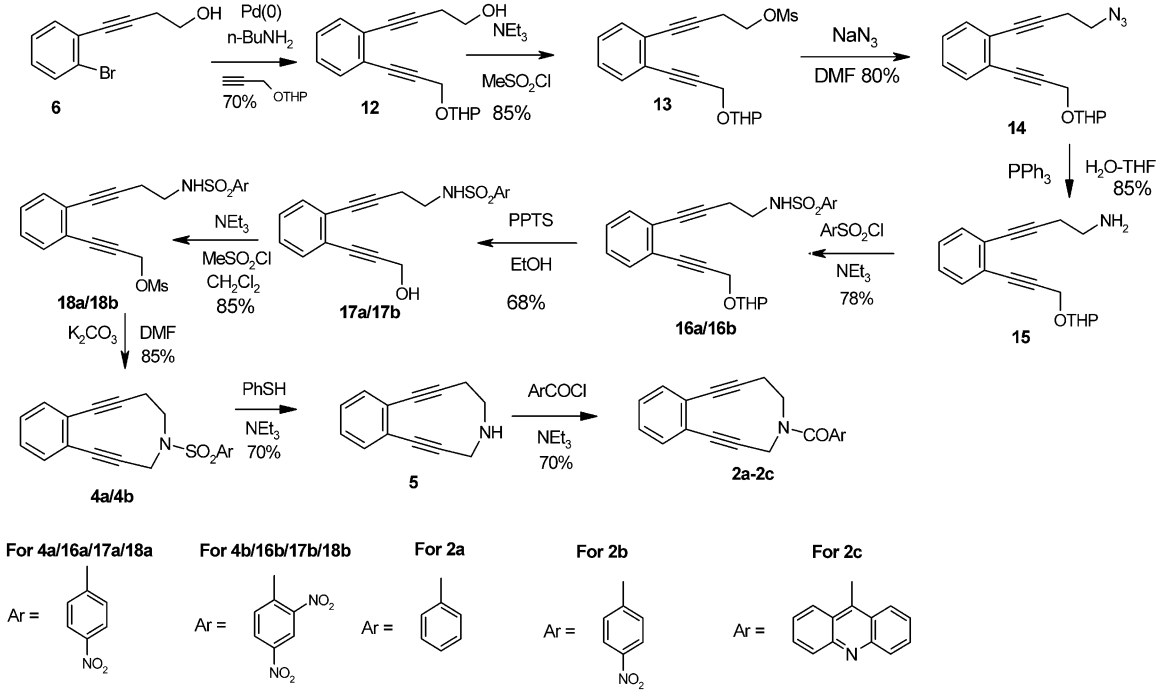
with benzene fused enediynes. Regarding the choice of protecting groups, mono or dinitro benzene sulfonamide derivatives were used, as these are reported[9] to be easily deprotected under mild conditions. However, due to the extreme lability of the nitrosulfonamido group under basic conditions, usually employed in Pd(0)-based coupling, we had to modify the previously reported method.[6] Two successive Pd(0)-catalyzed coupling[10] of dibromobenzene, first with THP-protected propargyl alcohol and then with 3-butyn-1-ol afforded the protected enediynyl alcohol **12** which was then elaborated into the 4-nitro or 2,4-dinitro benzene sulfonamide **16a**/**16b** via the azide. Removal of THP,[11] conversion to the mesylate **18a**/**18b** and treatment with K_2CO_3 in DMF generated the cyclic enediyne **4a**/**4b** in excellent yield. Both the enediynes was successfully deprotected with thiophenol and triethylamine at ambient temperature and the amine (characterized as the *p*-toluene sulfonate salt) was isolated and then converted to the various amides **2a**–**2c** by conventional procedure (acyl chloride and triethylamine) (Scheme 2).

The enediynes **2a**–**2c** appeared to be quite stable at room temperature like the sulfonamido analogues **4a**/**4b**. Single crystal X-ray analysis of the nitro amide **2b** and nitrosulfonamide **4a** revealed very little difference in the 3-D-structures of the enediynes. The major difference seems to be in the orientation of the amide or sulfonamide bearing aromatic ring. In the amide **2b**, the aromatic ring is orthogonal to the plane of the enediynes whereas in the sulfonamide **4a**, the ring is anti to the enediynes framework (Fig. 1). In solution such as in $CDCl_3$, these molecules start to cyclize only when heated to 70 °C and above. Keeping a $CDCl_3$ solution of the enediynes **2a**/**2b** in a thermostat maintained at 70 °C and by recording the ^1H NMR at different time points the precise kinetics of cyclization could be followed. The half-lives of all the enediynes that include the sulfonamides and the amides were determined and shown in Table 1 from which it was evident that the amides were cyclizing at a slower rate as compared to the sulfonamides. This was contrary to our expectations. The activation energy of the amide and the sulfonamide



Scheme 1.



Scheme 2.

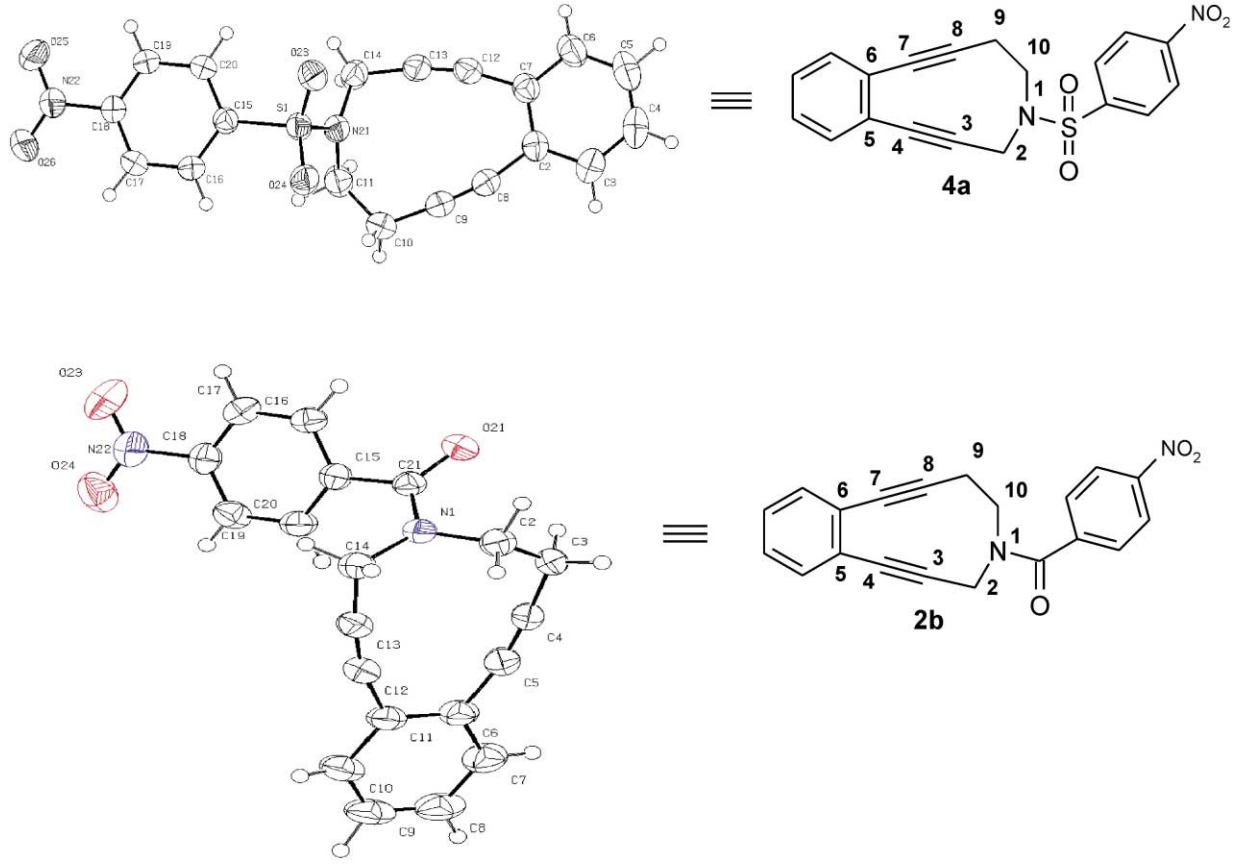


Figure 1. X-ray structure of **4a** and **2b**.

Table 1. Kinetic parameters for the cyclization of the various enediynes in $CDCl_3$

Compd	Rate constant (per h) at 70 °C	Activation energy E ♯ (*K*cal/mol)	Half life at 70 °C (h)
2a	3.7×10^{-3}	24	188
2b	5.1×10^{-3}	—	136
4a	1.43×10^{-2}	20	49
4b	2.44×10^{-2}	—	28

also followed the same trend. Thus, the amide **2a** has higher activation barrier as compared to the sulfonamide **4a**. In a particular series, amide or sulfonamide, the overall greater electron withdrawal facilitates the reaction to a certain extent.[12] The relative kinetics followed the same order even in the presence of 1,4-cyclohexadiene.

The solid-state reactivity of the amides was next studied by differential scanning calorimetry (DSC). To our surprise, it was observed that the amides showed the exothermic rise starting at a much lower temperature (~75 °C) than that for the sulfonamide for which the corresponding rise started at ~240 °C (Fig. 2). Thus the onset temperature for BC in solid state is lower for the amides. Encouraged by this observation we also checked the DNA-cleavage activity. Again to our surprise, the amides **2a**–**2c** were able to cleave the plasmid DNA at micromolar concentrations (Fig. 3). On the contrary, the sulfonamides did not show any DNA-cleavage activity even at millimolar level. Expectedly,the cleavage efficiency was highest for **2c** containing the DNA-bindind acridine moiety (Fig. 4). Thus our studies indicated that the kinetics of Bergman cyclization in organic solvents might not be good criteria for predicting the DNA-cleavage activity, which is done in aqueous buffer. In the absence of DNA, both the enediynes are stable in aqueous buffer under ambient conditions. Thus presence of DNA somehow activates the amido enediyne towards its cleavage.

In conclusion, we have synthesized the benzene fused amido enediynes from the amine as the intermediate. In organic solvents the sulfonamides showed higher reactivity whereas in the solid state and in aqueous buffer the amides showed higher reactivity towards cyclization as indicated by DSC and DNA-cleavage, respectively.

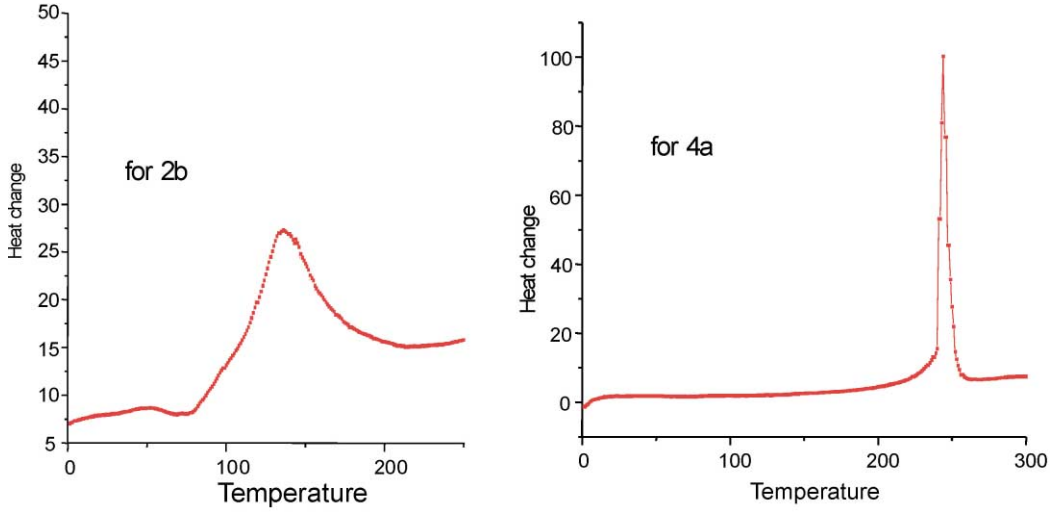


Figure 2. DSC curve of **2b** and **4a**.

Figure 3. Interaction of supercoiled DNA (in Tris–acetate buffer, pH 8.0) and various enediynes in acetonitrile; incubation was continued up to 48 h and analyzed by agarose (0.7%) gel electrophoresis using ethidium bromide stain: Lanes 1: DNA; 2: DNA + enediyne **2b** (40 μmol); 3: DNA + enediyne **2a** (40 μmol).

Figure 4. Interaction of supercoiled DNA (in Tris–acetate buffer, pH 8.0) and various enediynes in acetonitrile: Lanes 1: DNA; 2: DNA + enediyne **4a** (1 mmol); 3: DNA + enediyne **2c** (40 μmol); 4: DNA + enediyne **2b** (40 μmol).

Relevant parameters from X-ray structures:

Compd	Bond distance (Å)	Bond angle (°)		C_3–C_8 distance (Å)
2b	N–CO 1.36	C2–N–C10	118.12	3.29
	N–C2 1.47	N–C10–C9	113.2	
	N–C10 1.47	N–C2–C3	111.1	
4a	N–S 1.69	C2–N–C10	118.31	3.29
	N–C2 1.49	N–C10–C9	115.0	
	N–C10 1.47	N–C2–C3	119.8	

Selected Spectral Data

1-[4-Nitrophenylsulfonyl]-[5,6]-benz-1-aza-cyclodec-3,7-diyne (4a). White solid; mp 220 °C dec); δ_H 2.78 (2H, t, $J = 5.22$ Hz, N–CH_2–CH_2), 3.74 (2H, t, $J = 5.25$ Hz, N–CH_2–CH_2), 4.33 (2H, s, N–CH_2–CC), 7.25–7.29 (4H, m, Ar–**H**), 8.11 (2H, d, $J = 8.98$ Hz, Ar–**H**), 8.25 (2H, d, $J = 8.94$ Hz, Ar–**H**); δ_C 21.60, 43.41, 51.25, 86.49, 93.66, 98.14, 100.34, 122.92, 124.38, 127.50, 127.63, 127.81, 128.19, 128.77, 133.02, 144.0, 152.43.

1-[2,4-Dinitrophenylsulfonyl]-[5,6]-benz-1-aza-cyclodec-3,7-diyne (4b). Yellow solid; mp 160 °C (dec); δ_H 2.76 (2H, t, $J = 5.22$ Hz, N–CH_2–CH_2), 3.88 (2H, t, $J = 5.25$ Hz, N–CH_2–CH_2), 4.43 (2H, s, N–CH_2–CC), 7.30–7.38 (4H, m, Ar–**H**), 8.32 (H, dd, $J = 8.61$ Hz, $J = 2.1$ Hz, Ar–**H**), 8.50 (H, dd, $J = 8.77$ Hz, $J = 3.42$ Hz, Ar–**H**), 8.52 (H, d, $J = 8.77$, one signal is obscured); δ_C 22.32, 43.51, 52.48, 83.93, 87.82, 94.15, 98.75, 120.92, 127.54, 128.56, 128.67, 128.88, 129.28, 130.17, 133.03, 137.44, 151.31.

1-Benzoyl-[5,6]-benz-1-aza-cyclodec-3,7-diyne (2a). Brown solid; mp 78 °C; δ_H 2.96 (2H, t, $J = 5.03$ Hz, N–CH_2–CH_2), 3.92 (2H, t, $J = 5.01$, N–CH_2–CH_2), 4.21 (2H, s, N–CH_2–CC), 7.26–7.42 (7H, m, Ar–**H**), 7.61 (2H, d, $J = 2.44$ Hz, Ar–**H**); δ_C 18.76, 44.23, 50.33, 82.38, 88.04, 93.84, 98.89, 126.25, 126.85, 127.24, 127.37, 127.71, 128.05, 128.20, 128.35, 128.53, 129.06, 129.81, 130.35, 135.56, 171.60.

1-[4-Nitrobenzoyl]-[5,6]-benz-1-aza-cyclodec-3,7-diyne (2b). Pale brown solid; mp 110 °C; δ_H 2.98 (2H, t, $J = 5.29$ Hz, N–CH_2–CH_2), 3.95 (2H, t, $J = 5.24$ Hz, N–CH_2–CH_2), 4.16 (2H, s, N–CH_2–CC), 7.24–7.36 (4H, m, Ar–**H**), 7.77–7.82 (2H, m, Ar–**H**), 8.26–8.30 (2H, m, Ar–**H**); δ_C 18.56, 44.17, 50.66, 82.56, 88.91, 92.76, 98.19, 123.59, 123.90, 127.57, 127.83, 128.33, 128.51, 129.73, 131.19, 139.40, 140.84, 169.44.

1-[9-Acridinoyl]-[5,6]-benz-1-aza-cyclodec-3,7-diyne (2c). Brown solid; mp > 220 °C; δ_H 3.35 (2H, t, $J = 5.21$ Hz,

N–CH_2–C**H**$_2$), 3.97 (2H, s, N–C**H**$_2$–CC), 4.19 (2H, t, $J = 5.2$ Hz, N–C**H**$_2$–CH_2), 7.07–7.45 (6H, m, Ar–**H**), 7.75 (2H, t, $J = 7.69$ Hz, Ar–**H**), 8.03 (2H, d, $J = 8.64$ Hz, Ar–**H**), 8.29 (2H, d, $J = 8.78$ Hz, Ar–**H**); δ_C 18.55, 43.02, 50.36, 83.32, 88.13, 92.23, 97.86, 122.0, 125.34, 126.92, 127.49, 127.69, 127.96, 128.85, 129.31, 131.19, 140.54, 147.76, 168.23.

[5,6]-Benz-1-aza-cyclodec-3,7-diyne (5) 4-toluene sulfonate. δ_H 2.25 (3H, s, Ar–C**H**$_3$), 2.79 (2H, t, $J = 5.51$ Hz, N–CH_2–C**H**$_2$), 3.55 (2H, t, $J = 5.23$ Hz, N–C**H**$_2$–CH_2), 4.05 (2H, s, N–C**H**$_2$–CC), 7.00 (2H, d, $J = 7.88$ Hz, Ar–**H**), 7.60 (2H, d, $J = 8.08$ Hz, Ar–***H***), 9.77 (2H, bs, N**H**$_2$).

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