

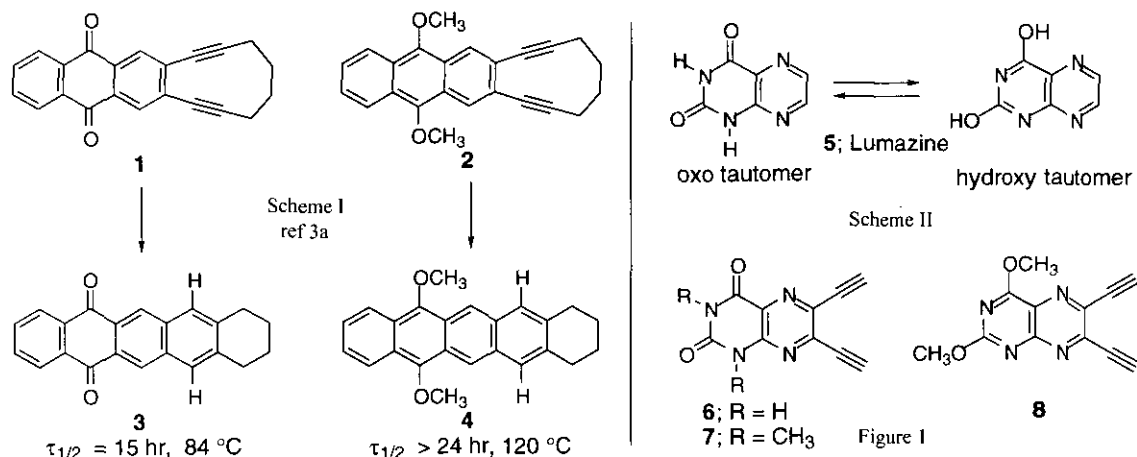
SYNTHESIS AND CYCLIZATION OF NOVEL LUMAZINE - ENEDIYNE CHIMERAS

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Abstract - Lumazine derivatives (**6** – **8**), appended with ethynyl groups in positions 7 and 8, were synthesized and examined for their ability to undergo Bergman cyclization. Oxo compound (**7**) was found to give good yields of Bergman cyclization products ($\approx 37\%$), whereas the analogues (**6**) and (**8**) did not cyclize as efficiently or gave no identifiable cyclization products.

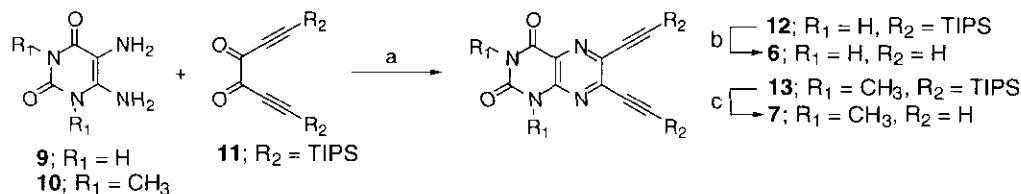
First reported in 1972, the Bergman cyclization is generally considered as the thermally allowed electronic rearrangement of a (Z)-3-ene-1,5-diyne to a 1,4-didehydrobenzene diradical which is quenched by radical sources to afford a new benzene ring.¹ In the mid 1980s studies on this reaction underwent a renaissance with the structural elucidation of a series of naturally occurring antibiotics whose cytotoxic activity was associated with a Bergman cyclization.²



Semmelhacker *et al.*^{3a} demonstrated that the cyclization of anthraquinone (**1**) underwent cyclization faster than dihydroanthraquinone derivative (**2**), suggesting a role for electron deficiency in the activation of enediynes towards Bergman cyclization (Scheme I). This idea has further been supported by other quinone / dihydroquinone pairs^{3b} and additional reports.⁴

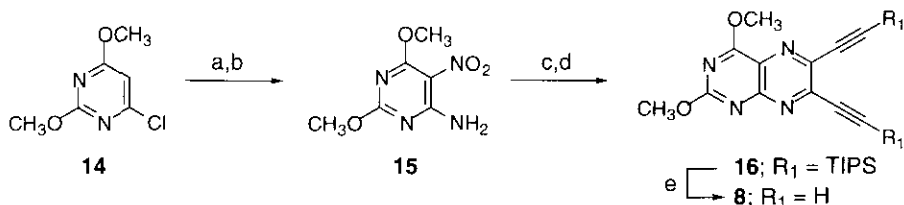
Our group has recently undertaken the examination of enediyne chimera, where the double bond of the enediyne has been incorporated into a heterocycle. Emboldened by our previous results on the activating ability of heteroarenes,⁵ we decided to begin investigations on enediyne chimeras of biologically relevant heterocycles. Our initial focus has been on lumazine analogues (**6** - **8**, Figure 1). Lumazines arise in nature from the metabolic degradation of pterins.⁶ Lumazines have been of interest recently for their fluorescent properties and their potential use as reporter groups in DNA probes.⁷ Lumazine can exist as two tautomers, but it is generally thought to exist as the oxo form in aqueous media (**5**, Scheme II). The oxo and hydroxy tautomeric forms can be considered analogous to an electron deficient quinone and aromatic dihydroquinone, respectively. Thus, it might be anticipated that the oxo tautomer would cyclize more rapidly than the hydroxy tautomer. To examine the reactivity of the tautomers, independent of equilibration, *N*-methyl derivative (**7**) and *O*-methyl derivative (**8**) were prepared to emulate the oxo and hydroxy forms, respectively. Freely equilibratable **6** was also prepared for comparison.

Compounds (**6**) and (**7**) were prepared as shown in Scheme III. Condensation of known diketone (**11**)⁸ with diamine (**9**) or (**10**) gave protected enediynes (**12**) and (**13**) in 75 % and 70 % yields, respectively. Compound (**6**)⁹ was obtained by deprotection with TBAF in 80 % yield. *N*-methyl derivative (**7**)¹⁰ was obtained from **13**, again by TBAF deprotection (80 %).



Scheme III. a) mol sieves, $\text{CH}_3\text{CO}_2\text{H}$, 2 h, rt (**12**: 75 %; **13**: 70 %); b) $(n\text{-C}_4\text{H}_9)_4\text{NF}$, THF, 0 °C, 2 h (80 %); c) $(n\text{-C}_4\text{H}_9)_4\text{NF}$, THF, -78 °C, 30 min (80 %).

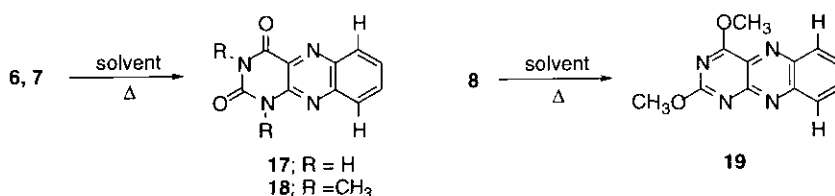
Methoxy derivative (**8**)¹¹ was prepared by the same condensation strategy (Scheme IV). Nitration of 6-chloro-2,4-dimethoxypyrimidine (**14**) followed by nucleophilic substitution afforded **15**. After catalytic hydrogenation, the crude intermediate was condensed with diketone (**11**), to give the putative enediyne (**16**). The final product (**8**) was obtained in a 48 % overall yield after deprotection.



Scheme IV. a) NaNO_3 , H_2SO_4 , 80 °C, 5 h (90 %); b) NH_4OAc , THF, reflux, 5 h (95 %); c) H_2 , 10 % Pd/C, CH_3OH , rt, 5 h; d) **11**, mol sieves, $\text{CH}_3\text{CO}_2\text{H}$, rt, 30 min (70 %, 2 steps); e) $(n\text{-C}_4\text{H}_9)_4\text{NF}$, THF -78 °C, 30 min (80 %).

Arenediynes (**6** - **8**) were examined for their ability to produce Bergman cyclization products (**17** - **19**), respectively (Scheme V, Table 1).¹² The attempted cyclization of **6** did not yield any of the cyclized product (**17**) under the conditions tested (Entries 1 and 2). The ^1H NMR spectra of the major product

from each reaction showed loss of the acetylene groups and the appearance of new vinylic hydrogens. The cyclization of **7** was much more efficient. The yield of Bergman cyclized product (**18**) was independent of solvent, concentration, and presence or absence of 1,4-cyclohexadiene (CHD; Entries 3 and 4). The yield of **18** was 36 % in neat methanol and 37 % when cyclization was performed in DMSO with CHD. Like **6**, Bergman cyclization of **8** in methanol was inefficient (Entry 6). Yet in this case trace amounts of expected product (**19**) were found. Cyclization of **8** in DMSO with 100 equiv. of CHD did not give any detectable **19** (Entry 7). However, the ^1H NMR spectra of the reaction products did show the presence of new aromatic hydrogens consistent with Bergman cyclization. The spectrum of the major isolated product also displayed two additional methyl peaks (δ 2.89, 2.81 ppm), suggesting trapping of the intermediate diradical by DMSO. To confirm that **8** does, indeed, undergo Bergman cyclization, it was heated in neat CHD to give **19** in 33 % yield (Entry 9).



Scheme V

Table 1. Bergman Cyclization of **6** - **8** (6.0 mM)

Entry	Enediyne	solvent	temp. (°C)	time (h)	$\tau_{1/2}$ (min)	Product yield (%) ^a
1	6	CH ₃ OH ^c	180	5.0		17 (0) ^d
2	6	DMSO ^b	165		5.5	17 (0) ^{d,e}
3	7	CH ₃ OH ^c	165	3.0		18 (36)
4	7	DMSO ^b	165	2.0		18 (37)
5	7	DMSO ^b	165		6.1	—
6	8	CH ₃ OH ^c	165	3.0		19 (trace) ^f
7	8	DMSO ^b	165	1.0		—
8	8	DMSO ^b	165		10.1	—
9	8	CHD	165	1.0		19 (33)

^aIsolated yield; ^b100 equiv. CHD; ^c[conc.] = 0.4 mM; ^d ^1H NMR of the crude reaction mixture shows no peaks consistent with a Bergman cyclized product; ^eobtained after kinetics experiments and heating at 165°C until **6** has completely reacted. ^f ^1H NMR of the major product is consistent with a Bergman cyclized product.

In order to compare reactivity of the oxo vs. hydroxy forms of lumazine, the kinetics of **6** - **8** were measured under identical conditions.¹³ Cyclization of **7** and **8** in DMSO (100 equiv. CHD, 165 °C) yielded half-lives of 6.1 min and 10.1 min, respectively (Table 1, Entries 5, 8). This supports, as hypothesized, that the rate of cyclization is faster for the oxo tautomer than for the fully aromatic hydroxy tautomer. The half-life for **6** under the same conditions was found to be 5.5 min (Entry 2). This half-life, however, clearly does not correspond to a Bergman cyclization.

Summary. A series of lumazine - enediyne derivatives which represent the tautomeric forms of lumazine were prepared. The *N*-methyl analogue (**7**) gave better yields of Bergman cyclized products than the

O-methyl compound (**8**) under the same conditions. Furthermore, as expected, electron deficient **7** cyclized faster than the fully aromatic species (**8**). The difference in rates between **7** and **8** suggests that tautomerization might be used as a trigger to initiate Bergman cyclization for appropriate systems. Compound (**6**) did not undergo Bergman cyclization under the conditions examined. It appears, for this series of compounds, that the relatively high temperatures necessary for cyclization result in competing reactions that lower the yield or preclude the formation of Bergman cyclized products. The synthesis of ten-membered ring analogues should circumvent such side reactions. This work is currently in progress.

ACKNOWLEDGMENT

The Donors of the Petroleum Research Fund, administered by the American Chemical Society are recognized for partial support of this project. We are also grateful for the financial assistance provided by the American Cancer Society, Florida Division, Inc. We thank Mr. X Calyptratus for technical assistance.

REFERENCES AND NOTES

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1. (a) R.R. Jones and R.G. Bergman, *J. Am. Chem. Soc.*, **1972**, *94*, 660. (b) R.G. Bergman, *Acc. Chem. Res.*, **1973**, *6*, 25.
 2. For an excellent overview of the biology and chemistry of enediynes see: *Enediyne Antibiotics as Anticancer Agents*, ed. By D.B. Borders and T.W. Doyle, Marcel Dekker, New York, 1995.
 3. (a) M.F. Semmelhack, T. Neu, and F. Foubelo, *J. Org. Chem.*, **1994**, *59*, 5038. (b) K.C. Nicolaou, A. Liu, Z. Zeng, and S. McComb, *J. Am. Chem. Soc.*, **1992**, *114*, 9279. (c) A.G. Myers and P.S. Dragovich, *J. Am. Chem. Soc.*, **1992**, *114*, 5859.
 4. (a) M. Schmittel and S. Kiau, *Chem. Lett.*, **1995**, 953. (b) M.E. Maier and B. Greiner, *Liebigs. Ann. Chem.*, **1992**, 855.
 5. C.-S. Kim and K.C. Russell, *J. Org. Chem.*, **1998**, in press
 6. H. Renbold and W.L. Gyure, *Angew. Chem., Int. Ed. Engl.*, **1972**, *11*, 1061.
 7. W. Bannwarth and F. Müller, *Helv. Chem., Acta*, **1991**, *74*, 2000.
 8. R. Faust and C. Weber, *Tetrahedron*, **1997**, *53*, 14655.
 9. Characterization Data for **6** : pale yellow solid, mp 180 °C (decomp); UV (DMSO) λ_{max} (ϵ , L mol⁻¹ cm⁻¹) 370 nm (8250), 286 nm (11500), 258 nm (8830); IR (KBr) ν_{max} 3188, 2110, 1702 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 12.18 (s, 1H), 11.83 (s, 1H), 5.18 (s, 1H), 4.85 (s, 1H); ¹³C NMR (75.4 MHz, DMSO-d₆) δ 160.0, 150.0, 147.9, 142.3, 134.4, 127.8, 90.2, 86.3, 79.7, 79.5.
 10. Characterization Data for **7** : pale yellow solid, mp 180 °C (decomp); UV (DMSO) λ_{max} (ϵ , L mol⁻¹ cm⁻¹) 372 nm (6620), 289 nm (9730); IR (CHCl₃) ν_{max} 3203, 2103, 1726, 1682, 1533 cm⁻¹; ¹H NMR (300 MHz, CD₃CN) δ 4.13 (s, 1H), 3.88 (s, 1H), 3.55 (s, 3H) and 3.37 (s, 3H); ¹³C NMR (75.4 MHz, DMSO-d₆) δ 158.6, 150.3, 146.3, 141.5, 133.9, 127.3, 90.4, 86.5, 79.52, 79.0, 29.3, 28.7.
 11. Characterization Data for **8** : pale yellow solid, mp 180 °C (decomp); UV (DMSO) λ_{max} (ϵ , L mol⁻¹ cm⁻¹) 367 nm (4860), 264 nm (8420); IR (CHCl₃) ν_{max} 3303, 2119, 1594 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.20 (s, 3H), 4.12 (s, 3H), 3.64 (s, 1H), 3.50 (s, 1H); ¹³C NMR (75.4 MHz, CDCl₃) δ 168.5, 165.1, 153.9, 146.3, 137.7, 123.7, 86.8, 84.4, 79.3, 79.0, 56.2, 56.1.
 12. The authenticity of **17** and **18** was confirmed by comparison of the products to commercial alloxazine and synthesized 1,3-dimethylalloxazine, respectively. Compound (**19**), prepared from the cyclization of **8**, showed all expected spectral characteristics.
 13. The half-lives were determined by HPLC by comparison of the absorption of the starting material vs. that of a naphthalene internal standard over time as described in reference 5.

Received, 21st September, 1998