

## Synthesis and Photochemical Cyclization of a Novel Enyne-Carbodiimide

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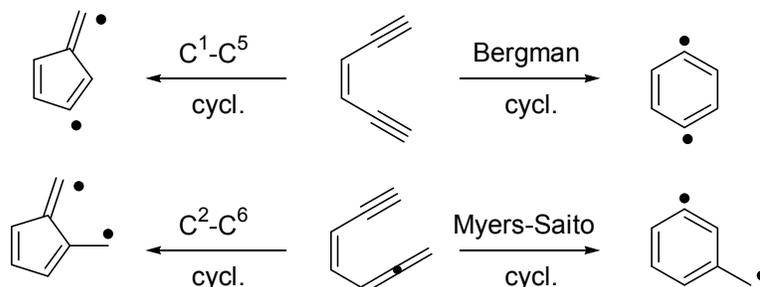
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**Abstract:** The triplet sensitized cyclization of enyne-carbodiimide **4** leads to efficient formation of indoloquinoline **5** with concomitant loss of a methyl group. The efficient loss of the methyl group was explained using AM1 semiempirical calculations.

**Keywords:** Carbodiimides; diradicals; enynes; photocyclization; triplet.

### Introduction

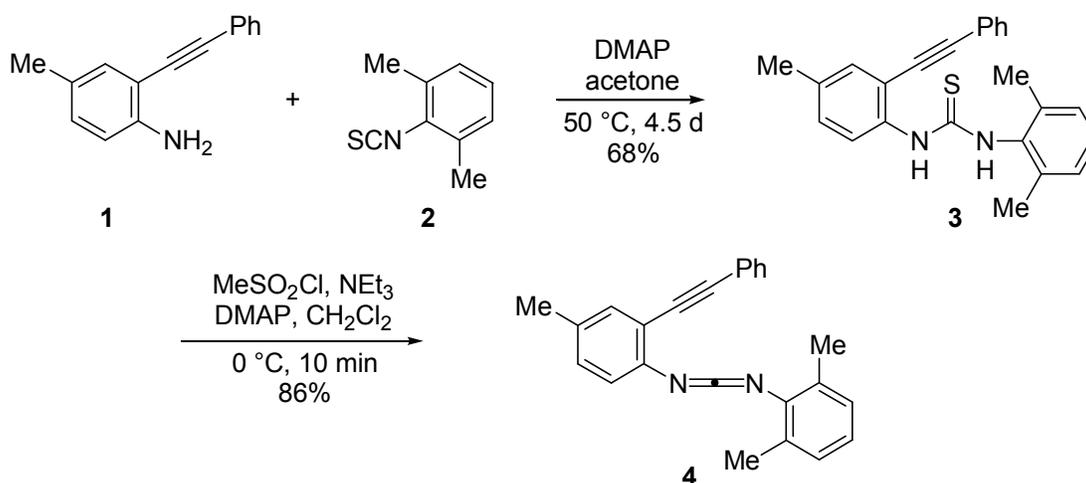
Thermal diradical cyclizations of enediynes (Bergman) [1] and enyne-allenes (Myers-Saito) [2] have attracted a lot of attention due to their key role in the mode of action of natural enediyne antitumor antibiotics [3]. Over many years, however, other cyclization pathways in these systems have been neglected, until we [4] and others [5] were able to control deliberately the regioselectivity of the thermal cyclization of enyne-allenes towards fulvene diradicals (*cf.* C<sup>2</sup>-C<sup>6</sup> cyclization).



Recently, it was demonstrated that the thermal C<sup>2</sup>-C<sup>6</sup> cyclization of enyne-carbodiimides and enyne-ketenimines [6] can be complemented by a very efficient triplet sensitized photochemical route [7]. As the latter reaction has important consequences with regards to the development of photoactive prodrugs, *e.g.* in approaches to the ellipticine family [8], we have now investigated the photocyclization of enyne-carbodiimide **4** whose *N*-phenyl terminus is sterically blocked using methyl groups. The present results indicate that the efficient photoreaction of this compound is composed of a cascade of three individual steps: diradical cyclization, ring closure on the stage of the diradical, and methyl group loss.

## Results and Discussion

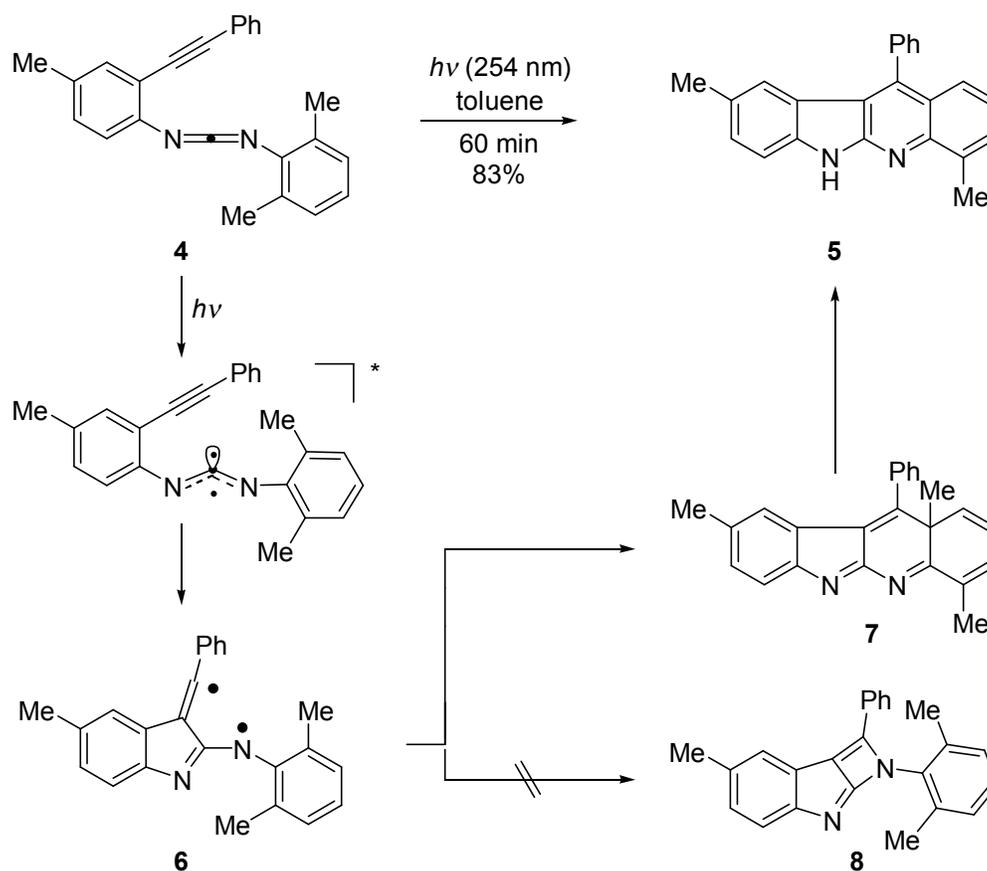
Enyne-carbodiimide **4** was synthesized as usual *via* the corresponding thiourea **3**. However, preparation of **3** was found to be much more problematic than expected. First, the reactivity of 2,6-dimethylphenyl isothiocyanate (**2**) was reduced as compared to other aryl substituted isothiocyanates, presumably because of steric hindrance caused by the *ortho*-methyl substituents, so that under usual reaction conditions (ethanol, room temperature) only small amounts of **3** were produced ( $\leq 28\%$ ) from **1** and **2**. On the other hand, at elevated temperature (*e.g.* at the boiling point of ethanol) an undesired intramolecular cyclization product resulted. Optimization of the reaction conditions and use of acetone as solvent [9] finally led to isolation of **3** in 68% yield. Carbodiimide **4** was synthesized from **3** in 86% yield according to a method described by Fell and Coppola [10] which allows for a fast and highly efficient preparation under mild conditions using methanesulfonyl chloride and triethylamine (Scheme 1).



**Scheme 1.**

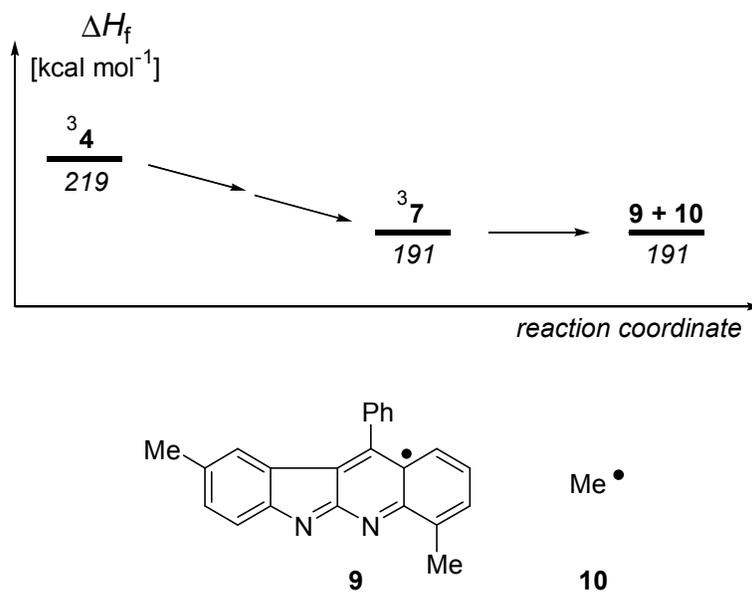
Irradiation of **4** led to formation of indoloquinoline **5** in high yield (83%) when it was carried out using triplet sensitization (toluene as triplet sensitizer at  $\lambda = 254$  nm with  $E_T = 83$  kcal mol<sup>-1</sup>) [11] for 60 min. In contrast, when **4** was irradiated without triplet sensitization (toluene,  $\lambda = 300$  nm) no reaction was observed after 90 minutes.

Previous mechanistic results [7] exclude a singlet reaction and suggest a pathway *via* the triplet excited state of the carbodiimide unit [12] which then triggers ring closure to the biradical **6**, formally by an *5-exo-dig* cyclization. **6** can be understood as a triplet analogue of the biradical that is formed in the thermal  $C^2-C^6$  cyclization of enyne-(hetero)allenes [4,6]. Direct combination of the two radical sites could lead to the strained tricycle **8** with an azet ring but this is not observed. Instead, intramolecular cyclization takes place at the 2,6-dimethylphenyl ring yielding the cross-conjugated tetracycle **7**. A concerted Diels-Alder cyclization **4**  $\rightarrow$  **7** under these conditions can be excluded both on theoretical arguments (it would violate the Woodward-Hoffmann rules [13]), and on steric grounds (the steric shielding of the methyl groups at the *N*-phenyl terminus should prevent C-C bond formation).



**Scheme 2.**

Importantly, we have not been able to detect any trace of compound **7** in the product mixture [14], which indicates that the final rearomatization step **7**  $\rightarrow$  **5** involving methyl group loss should be a very facile step in the overall reaction. To understand the mechanistic situation, we have calculated part of the energy hypersurface of the triplet reaction using the semiempirical AM1 method.[15]



**Figure 1.** Heat of formation  $\Delta H_f$  (see *italic* numbers, calculated by AM1 without *C.I.*) of the triplet excited key intermediates in the photochemical transformation  $\mathbf{4} \rightarrow \mathbf{9} + \mathbf{10}$ .

Interestingly, the calculations indicate clearly that starting from the triplet excited **7** ( $\Delta H_f = 191$  kcal mol<sup>-1</sup>) a roughly thermoneutral homolytic bond cleavage reaction to radical **9** ( $\Delta H_f = 160$  kcal mol<sup>-1</sup>) and the methyl radical (**10**) is possible ( $\Delta H_f = 31$  kcal mol<sup>-1</sup>). The energy to populate the triplet excited **7** could in principle be derived from the initial photochemical excitation of **4**, as the reaction of  $^3\mathbf{4}$  to the triplet excited  $^3\mathbf{7}$  is overall exothermic by 28 kcal mol<sup>-1</sup>. Hydrogen abstraction from toluene will then allow for the reaction  $\mathbf{9} \rightarrow \mathbf{5}$  thus completing the reaction sequence.

## Conclusions

An unusual photocyclization was presented incorporating a diradical cyclization, ring closure of the diradical and methyl loss which occurs at good yield (83%). Semiempirical calculations indicate that all steps take place on the stage of triplet excited species.

## Experimental

### General

All melting points are uncorrected. <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were obtained using a Bruker AC200 or AM250 and were recorded at 200/250 and 50/63 MHz respectively. IR spectra were recorded on a Perkin-Elmer 1605 FT-IR spectrometer. Elemental analyses were carried out on a Bruker Elemental Analyzer 1106. 4-Methyl-2-phenylethynyl aniline was synthesized according to literature procedure [16] and

characterized by comparison to literature [17]. All other reagents and chemicals were commercially available and used as received.

#### N-(2,6-Dimethylphenyl)-N'-(4-methyl-2-phenylethynyl) thiourea (**3**)

4-Methyl-2-phenylethynylaniline (500 mg, 2.41 mmol), 2,6-dimethylphenyl isothiocyanate (377 mg, 2.31 mmol) and catalytic amounts of *N,N*-dimethylamino pyridine (DMAP) were dissolved in acetone (5 mL) and stirred at 50 °C until reaction control by TLC showed complete disappearance of the isothiocyanate (4.5 d). Column chromatography on silica gel ( $R_f$  0.25, petroleum ether/CH<sub>2</sub>Cl<sub>2</sub>/ethyl acetate 20/7/2) yielded **3** as a pale yellow solid (580 mg, 1.57 mmol, 68%): m.p. 169-170 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.28 (br s, 9H, CH<sub>3</sub>), 6.87-7.25 (m, 7H), 7.29-7.38 (m, 3H), 7.59 (br s, 1H, NH), 7.97 (br s, 1H, NH), 8.41 (d, 1H, J = 9.1); most signals are broadened because of coalescence; <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ: 18.11, 20.66, 84.00, 95.07, 115.63, 122.24, 123.63 (br), 128.09, 128.70, 128.88 (br), 129.43 (br), 131.76, 132.28 (br), 132.70, 134.55, 136.82, 137.25, 179.18; several signals are broadened because of coalescence, two signals coincide; IR (neat) cm<sup>-1</sup>: 3336, 3155, 2923, 2214, 1585, 1535, 1346, 1266; elemental analysis for C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>S: Calcd C 77.80, H 5.98, N 7.56, S 8.65; Found C 77.31, H 5.92, N 7.48, S 8.44.

#### N-(2,6-Dimethylphenyl)-N'-[4-methyl-2-(phenylethynyl)phenyl] carbodiimide (**4**)

Thiourea **3** (56.8 mg, 153 μmol) was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> under an atmosphere of nitrogen and, after addition of triethylamine (70 μL, 51.1 mg, 505 μmol) and catalytic amounts of DMAP, methanesulfonyl chloride (35 μL, 51.5 mg, 356 μmol) was added dropwise via syringe under vigorous stirring and cooling in an ice bath. The mixture was stirred for 10 more minutes. Then the solvent was removed in vacuo and **4** was isolated from the crude mixture by column chromatography ( $R_f$  0.64, conditions see **3**) as a yellow oil (44.4 mg, 132 μmol, 86%) that crystallized on standing at -30 °C and that is not stable in CDCl<sub>3</sub> for longer times: m.p. 47 °C (DSC); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.34 (s, 3H, CH<sub>3</sub>), 2.36 (s, 6H, CH<sub>3</sub>), 6.88-7.00 (m, 3H), 7.05 (d, 1H, J = 8.1), 7.08-7.29 (m, 6H), 7.35 (s, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ: 19.01, 20.63, 86.20, 95.78, 118.75, 122.77, 123.85, 124.89, 127.97, 128.05, 130.18, 131.29, 132.20, 133.16, 133.55, 134.11, 134.84, 135.01, 137.46; IR (neat) cm<sup>-1</sup>: 3054, 3025, 2979, 2948, 2150 (N=C=N), 1593, 1477, 1202; elemental analysis for C<sub>24</sub>H<sub>20</sub>N<sub>2</sub>: Calcd C 85.68, H 5.99, N 8.33; Found C 85.33, H 6.08, N 8.13.

#### Photolysis

Photolysis of a degassed solution of **4** (20.0 mg, 59.4 μmol) in toluene (14 mL, *c* = 4.2 mM) was carried out in a Rayonet RPR-100 Photochemical Reactor, fitted with 16 RPR 253.7 nm lamps. The solution was placed in a quartz flask under a nitrogen atmosphere and irradiated for 60 minutes (internal water cooling to 20 ± 5 °C). When reaction control by TLC showed complete disappearance of **4** the solvent was

removed in vacuo and **5** was isolated by column chromatography on neutral alumina ( $R_f$  0.38, *n*-hexane/ethyl acetate 6/1) as a yellow solid (16.0 mg, 49.6  $\mu$ mol, 83%).

#### 4,9-Dimethyl-11-phenyl-6H-indolo[2,3-b]quinoline (**5**)

m.p. 236.5-238 °C;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.27 (s, 3H,  $\text{CH}_3$ ), 2.94 (s, 3H,  $\text{CH}_3$ ), 6.80 (s, 1H), 7.22 (d, 1H,  $J = 8.3$ ), 7.28 (d, 1H,  $J = 8.3$ ), 7.28 (dd, 1H,  $J = 8.2, 6.7$ ), 7.52-7.56 (m, 2H), 7.59-7.68 (m, 5H), 9.54 (br s, 1H, NH);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 18.88, 21.38, 110.16, 115.88, 121.38, 122.47, 123.25, 123.70, 124.55, 128.43, 128.80, 128.87, 129.08, 129.21, 129.34, 134.65, 136.91, 138.92, 142.67, 145.63, 152.33; IR (KBr)  $\text{cm}^{-1}$ : 3166, 3055, 2967, 2944, 1614, 1599, 1487, 1382, 1220; elemental analysis for  $\text{C}_{23}\text{H}_{18}\text{N}_2$ : Calcd C 85.68, H 5.63, N 8.69; Found C 85.19, H 5.97, N 8.51.

#### Calculations

Calculations were performed using the semiempirical AM1 method as implemented on a PC. The following results were obtained (without *C.I.*): **34** ( $\Delta H_f = 218.6 \text{ kcal mol}^{-1}$ ), **37** ( $\Delta H_f = 191.4 \text{ kcal mol}^{-1}$ ), **9** ( $\Delta H_f = 159.7 \text{ kcal mol}^{-1}$ ), **10** ( $\Delta H_f = 31.2 \text{ kcal mol}^{-1}$ ). Inclusion of *C.I.* (3,3) leads to similar results: **34** ( $\Delta H_f = 215.5 \text{ kcal mol}^{-1}$ ), **37** ( $\Delta H_f = 186.8 \text{ kcal mol}^{-1}$ ), **9** ( $\Delta H_f = 153.6 \text{ kcal mol}^{-1}$ ), **10** ( $\Delta H_f = 28.5 \text{ kcal mol}^{-1}$ ). The *C.I.* (3,3) results were not used as the experimental  $\Delta H_f$  (**10**) = 35  $\text{kcal mol}^{-1}$  was reproduced better without *C.I.* [18].

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*Samples Availability:* Not available.