Scope of the Thermal Cyclization of Nonconjugated Ene–Yne–Nitrile System: A Facile Synthesis of Cyanofluorenol Derivatives

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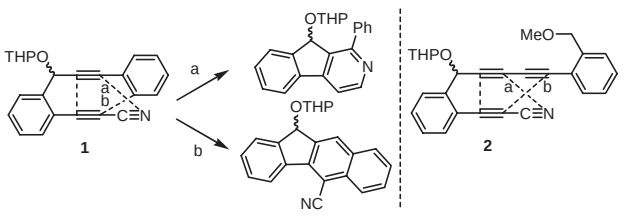
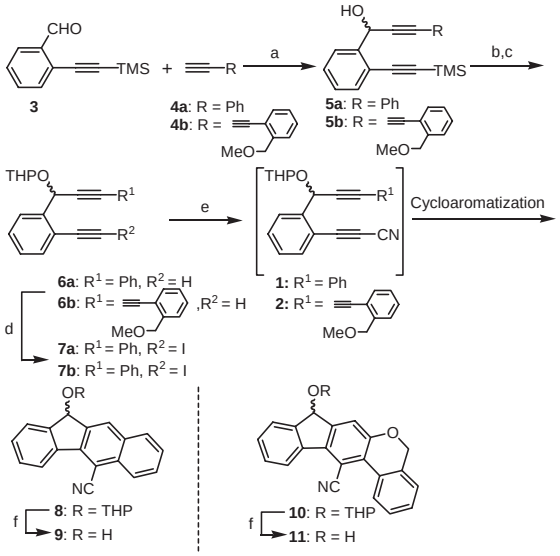
Thermal cyclizations of nonconjugated ene–diyne–nitrile **1** and ene–triyne–nitrile **2** systems were examined and proved to yield not azafluorenol, but cyanofluorenol derivatives (**9** and **11**, respectively), indicating that the cyano groups do not participate in the radical cycloaromatization but do play important roles to determine the mode of cyclization.

Conjugated ene–yne compounds have attracted much attention in the broad field of organic chemistry, since their cyclization reactions were discovered to give aromatized products by way of radical intermediates capable of DNA cleavage.[1] Although many compounds, including both natural[1a,1c,1f] and artificial products,[1b,1f,1g] have been synthesized to investigate their reactivity and to develop more potent and selective antitumor agents, modification of the conjugated ene–yne core structures has not been well studied. We reported that non-conjugated ene–ynes undergo thermal cycloaromatization (CA) reaction[2] with cleaving DNA.[3] As a new entry to the nonconjugated ene–yne compounds, we focused on ene–yne–nitrile systems (Scheme 1). The C–N triple bond (cyano group) is considered as an alternative to the C–C triple bond (alkyne), therefore, if the cyano group participates in the radical CA reaction, intriguing heterocyclic compounds, azafluorenol derivatives, whose congeners are known to be biologically active (e.g. as thrombin inhibitors,[4] and the corresponding ketones, azafluorenone derivatives act as phosphodiesterase inhibitors,[5] calcium antagonistic agents,[6] and herbicides[7]), could be formed (path a). On the other hand, if the cyano group is independent of CA (path b), the expected fluorenol products[8] whose photochemical properties[9] have attracted a broad spectrum of interest are also worthwhile. Herein, we report the synthesis and the CA reaction of ene–yne–nitriles **1** and **2**.

Synthesis of **1** commenced with a commercially available aldehyde **3** (Scheme 2). Addition of phenylethynyllithium to **3** gave alcohol **5a** (79%). Protection of **5a** as THP ether followed by the removal of the TMS group with K_2CO_3 in MeOH afforded terminal alkyne **6a** (98% for two steps), which was converted to the corresponding iodoalkyne **7a** by treatment with *N*-iodosuccinimide (NIS) and $AgNO_3$.[10] The final task was the introduction of a cyano group to the alkynyl terminus of **7a**.



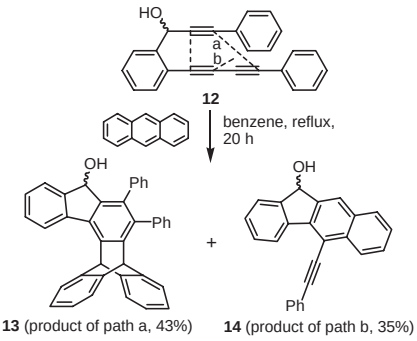
Scheme 1. Hypothetical cyclization mode of ene–diyne–nitrile **1** and ene–triyne–nitrile **2**.



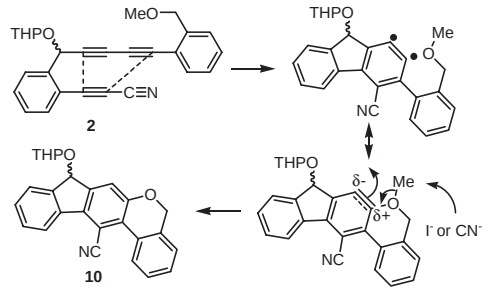
Scheme 2. Reagents and conditions: (a) **4a**, *n*-BuLi, THF, −78 °C, 1 h, then **3**, −78 °C to rt, 0.5 h, 79% (for **5a**); **4b**, MeLi–LiBr complex, THF, 0 °C, 2 h, then **3**, 0 °C to rt, 0.5 h, 63% (for **5b**); (b) DHP, PPTS, CH_2Cl_2, rt, 6 h; (c) K_2CO_3, MeOH, rt, 1 h, 98% (over 2 steps, for **6a**), 91% (over 2 steps, for **6b**); (d) NIS, $AgNO_3$, acetone, rt, 1 h; (e) CuCN, LiI, THF, reflux, 72 h; (f) PPTS, MeOH, rt, 12 h, 44% (over 3 steps, from **6a** to **9**), 11% (over 3 steps, from **6b** to **11**, with recovery of ene–triyne–nitrile (29%)).

Intriguingly, treatment of iodide **7a** with CuCN in the presence of LiI[11] in refluxing THF spontaneously furnished the cycloaromatized product **8** by way of nitrile **1**. Finally, removal of the THP group from **8** with pyridinium *p*-toluenesulfonate (PPTS) afforded **9**,[12] whose structure was determined as a cyanofluorenol derivative, in 44% yield over three steps.

We then turned our attention to the expansion of the alkynyl moiety to set ene–triyne–nitrile system **2** as a substrate for the thermal CA reaction. Synthesis of ene–triyne–nitrile **2** was initiated with aldehyde **3** and diyne **4b**[2f] instead of **4a**, and the alkynyl iodide **7b** was prepared in the sequence analogous to **7a**. As we expected, subjection of **7b** to the cyanation conditions resulted again in the formation of the cycloaromatized product **10** spontaneously. After the removal of the THP group, the structure of the resulting product was unambiguously determined by ^1H–^1H COSY and NOE experiments as fluorenol derivative **11**.[12] Contrary to the ene–yne–nitriles, the thermal cyclization of the corresponding ene–triyne **12** (carbon congener) was found to proceed through both a and b pathways (Scheme 3)[13] to give both **13** and **14**, suggesting that the cyano group is useful to determine the mode of cyclization, although it was not directly



Scheme 3. Thermal cyclization of ene–triyne **12**.



Scheme 4. Plausible mechanism of thermal cycloaromatization of **2**.

involved in the radical CA reactions,[14] probably owing to the difficulty in the homolysis of a highly polar C–N triple bond.

Although the detailed mechanism of the thermal cyclization of nonconjugated ene–yne systems is still controversial,[9a,9c] the mechanism[2f] to furnish fluorenol **10** from ene–triyne–nitrile **2** is envisaged as follows (Scheme 4): the thermal cyclization between yne and diyne moieties of **2** gives 1,2-diradical, which is a mesomeric equivalent of benzyne. Since the present benzyne is believed to be polarized by the aid of ethereal oxygen forming 6-membered cyclic transition state or intermediate, a good nucleophile (iodide or cyanide) attacks the methyl group to generate the ether-ring-fused compound **10**.

In conclusion, we have demonstrated that the thermal cyclization of nonconjugated ene–yne–nitrile systems furnishes not azafluorenol but cyanofluorenol derivatives. These findings indicate that the cyano group does not participate in the thermal radical cycloaromatization reactions directly, but is useful to determine the reaction fate to form cyanofluorenol derivatives. Furthermore, since a cyano group is facilely manipulated to a variety of functional groups, the cyanofluorenol derivatives obtained in this work can potentially be pivotal intermediates in photochemical and medicinal chemical researches. Further investigations on thermal cyclization of nonconjugated ene–ynes are in progress.

We are grateful to Dr. Tomikazu Kawano in our laboratory for discussions.

References and Notes

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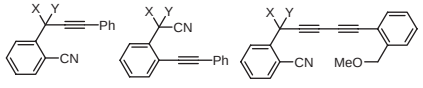
12 Spectral data of **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (1H, d, $J = 6.6$ Hz), 8.23 (1H, s), 8.19 (1H, d, $J = 8.3$ Hz), 7.89 (1H, d, $J = 8.3$ Hz), 7.73 (1H, dd, $J = 5.2$, 5.2 Hz), 7.65 (1H, ddd, $J = 7.1$, 7.1, 0.7 Hz), 7.57 (1H, dd, $J = 7.1$, 7.1 Hz), 7.50–7.46 (2H, m), 5.72 (1H, s), 2.39 (1H, s); IR ($CHCl_3$) 3416, 2217 cm^{-1}; FAB-MS (NBA) m/z 258 [$(M + H)^+$]. Spectral data of **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (1H, d, $J = 7.8$ Hz), 8.44 (1H, d, $J = 7.6$ Hz), 7.67 (1H, d, $J = 7.6$ Hz), 7.53–7.40 (4H, m), 7.52 (1H, s), 7.25 (1H, d, $J = 7.6$ Hz), 5.55 (1H, s), 5.06 (2H, s), 2.10 (1H, s); IR ($CHCl_3$) 3424, 2217 cm^{-1}; FAB-MS (NBA) m/z 311 [$(M + H)^+$].

13 Synthesis of **12** was accomplished according to the previously reported methodology: See Ref. 2a.

14 The thermal cyclization reactions of the following nonconjugated ene–yne–nitriles **15**–**20** failed even at 180 °C in refluxing 1,2-dichlorobenzene to yield only decomposed products.



15: X=OH, Y=H **16**: X=O, Y=O **17**: X=H, Y=H **18**: X=Me, Y=Me **19**: X=OH, Y=H **20**: X=O, Y=O

Published on the web (Advance View) May 24, 2008; doi:10.1246/cl.2008.662