Intramolecular Dehydro Diels–Alder Reactions of Diarylacetylenes: Synthesis of 5*H*-Benzo[*j*]phenanthridine and 6*H*-Naphtho[2,3-*c*]chromene Skeletons

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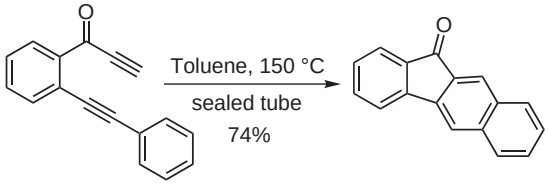
Abstract: Intramolecular dehydro Diels–Alder reactions of aniline and phenol diarylacetylene derivatives lead to the formation of 5*H*-benzo[*j*]phenanthridine and 6*H*-naphtho[2,3-*c*]chromene skeletons.

Key words: arenynes, aromatic polycycles, benzo[*j*]phenanthridines, dehydro Diels–Alder reactions, naphtho[2,3-*c*]chromenes

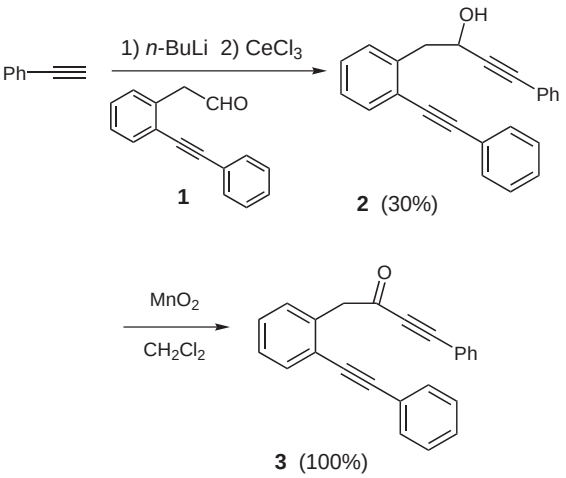
Intramolecular dehydro Diels–Alder reactions between alkynes and arenynes (or enynes) have been known since the 19th century.[1] The [4+2] cycloaddition of an alkyne unit and an arylacetylene involves the formation of a strained cyclic allene intermediate[2] that normally evolves to aromatic products by cyclohexatriene isomerization.[1b,3]

We have recently reported that the intramolecular dehydro Diels–Alder (IDDA) reaction of alkynes and diarylacetylenes provides a new route to the tetracyclic nucleus of the benzo[*b*]fluorene antibiotics (Scheme 1).[4] In that study and related work[5] the main characteristic of the starting substrates has been a three-atom tether linking the two reacting fragments.



Scheme 1

To explore the scope of the IDDA reactions of diarylacetylenes, we have now studied the thermolysis of substrates that have a four-carbon tether between the reactive units.[6] First, we prepared the propargylic alcohol **2** by addition of cerium phenylacetylide to the known aldehyde **1**,[7] and the ethynyl ketone **3** by oxidation of **2** with activated MnO_2 (Scheme 2). Alcohol **2** was very reluctant to undergo cyclization when a toluene solution of **2** was heated at 160 °C for 12 h, the starting material was recovered unaltered. Ketone **3** proved to be more reactive,[5a] but even so, heating at 160 °C afforded only relatively low yields of a mixture of products that could not be identified (although some of them had ^{1}H NMR signals suggesting that the cyclization reaction had occurred).



Scheme 2

In order to improve the above results we introduced a nitrogen atom in the connecting tether; phenylpropiolamides had behaved well in IDDA reactions,[5b] so we decided to try the cyclization reaction of a series of anilides (Scheme 3). Diarylacetylenic anilides **6** and **7** and cyclohexenyl anilides **10** and **11** were easily prepared by Sonogashira coupling of the corresponding alkynes with *o*-iodoaniline (**4**) followed by reaction of the intermediate anilines **5** and **9** with the appropriate propiolic acid. Gratifyingly, when a toluene solution of the amide **6** was heated at 160 °C, a 1.5:1 mixture of benzo[*j*]phenanthridinones **8a**[8] and **8b** resulting from the two possible cycloadditions of the phenylacetylene moieties was obtained in 64% yield as a rather insoluble white solid.[9] By contrast, amide **7** was not sufficiently activated for the cyclization[4] and only starting material was recovered after heating.

As expected, the reactions of cyclohexenyl anilides **10** and **11**, which involve no loss of aromaticity, proceeded more readily than those of the diarylacetylenic anilides **6** and **7**, affording the tetrahydrobenzo[*j*]phenanthridinones **12** and **13** as single reaction products in 64% and 41% yields, respectively.

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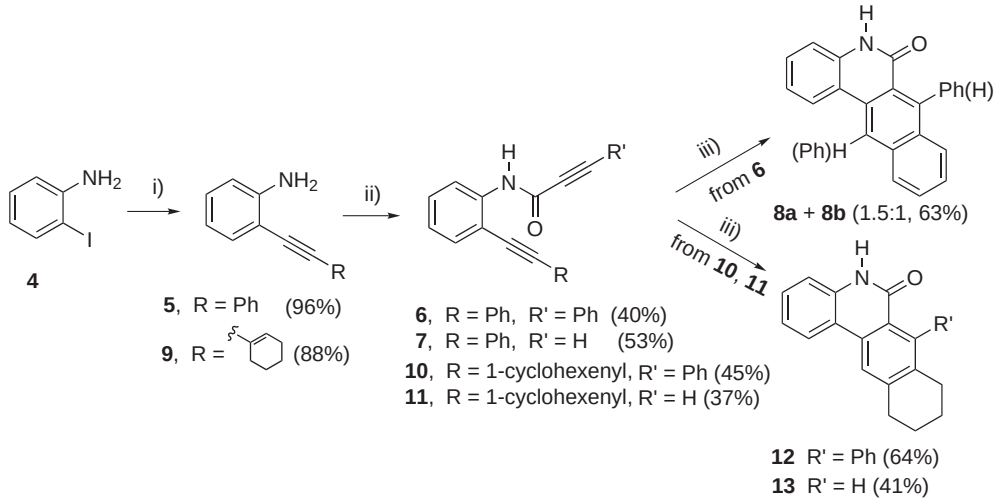

Scheme 3 *Reagents and conditions*: i) R–≡ 1.1 equiv, $PdCl_2(PPh_3)_2$ 3%, CuI 5%, THF, Et_3N, r.t.; ii) R′–≡–CO_2H 1 equiv, DCC 1.2 equiv, DMAP cat, CH_2Cl_2, 0 °C → r.t.; iii) toluene, 160 °C (0.03–0.05) M.

Interesting results were also achieved using oxygen-tethered substrates (Scheme 4). Unexpectedly, we were unable to prepare the oxygen analog of the previous substrates, the diarylacetylenic propiolate **14**, in spite of trying a variety of conditions.[10] This led us to place an electron-withdrawing group at the terminal end of the alkyne by lithiation acetylenic ether **15**[11,12] and trapping of the corresponding acetylide with acetic anhydride or ethyl chloroformate to obtain high yields of substituted acetylenes **16** and **17**, respectively. The other electron-poor substrate examined, arylacetylene **18**, was prepared by Sonogashira coupling of **15** and *p*-iodonitrobenzene in 91% yield. To our delight, **16**, **17** and **18** cyclized smoothly when heated in toluene, giving the pharmacologically interesting naphtho[2,3-*c*]chromenes **19**, **20** and **21** in 71%, 54% and 72% yield, respectively.[13,14]

In conclusion, we have shown that IDDA reactions between arylacetylenes (or enynes) and electron–deficient alkynes are useful for the synthesis of the benzo[*j*]phenanthridinone and naphtho[2,3-*c*]chromene skeletons. The method developed is atom economic and involves commercial available catalysts. Further exploration of IDDA reactions is in progress in our laboratories.

Acknowledgement

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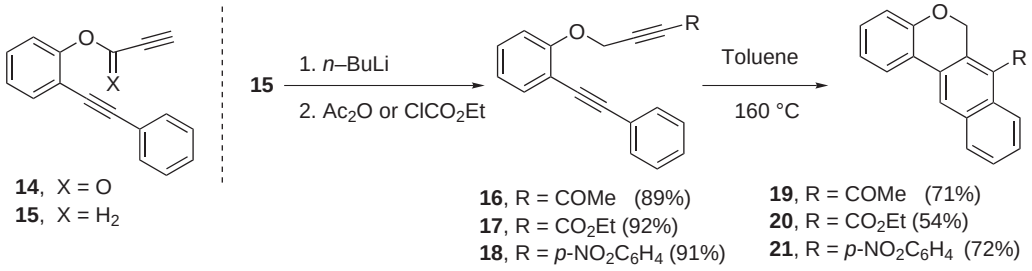

Scheme 4

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(12) Thermolysis of a mesitylene solution of **15** for 20 h at 215 °C gave a 15% yield of naphtho[2,3-*c*]chromene.

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(14) Typical experimental procedure: A solution of **16** (70 mg, 0.26 mmol) in toluene (10 mL) was heated in a sealed tube at 160 °C for 10 h. After removal of the solvent, the crude residue was purified by column chromatography on silica gel using a mixture of hexanes/EtOAc (7:1) as eluent, giving 50 mg (71%) of **19** as a pale yellow oil. ^{1}H NMR (250 MHz, CD_3Cl) δ: 8.16 (s, 1 H, Ar*H*), 7.94–7.87 (m, 2 H, Ar*H*), 7.72–7.64 (m, 1 H, Ar*H*), 7.55–7.46 (m, 2 H, Ar*H*), 7.31 (td, *J* = 7.2 Hz, 1.6 Hz, 1 H, Ar*H*), 7.13 (td, *J* = 8.5 Hz, 1.3 Hz, 1 H, Ar*H*), 7.05 (dd, *J* = 7.9 Hz, 1.3 Hz, 1 H, Ar*H*), 5.15 (s, 2 H, CH_2), 2.71 (s, 3 H, CH_3). ^{13}C NMR + DEPT (62.83 MHz, CD_3Cl) δ: 206.1 (*C*O), 155.0 (*C*), 136.1 (*C*), 133.2 (*C*), 129.9 (*C*H), 128.8 (*C*H), 128.2 (*C*), 128.0 (*C*), 127.0 (*C*H), 126.6 (*C*H), 126.2 (*C*), 124.3 (*C*H), 123.8 (*C*H), 122.5 (*C*H), 122.4 (*C*), 122.1 (*C*H), 117.6 (*C*H), 66.1 (*C*H_2), 33.1 (*C*H_3). EM *m/z* (%): 274 (M^+, 100), 273 (45), 231 (61), 202 (53). HRMS $C_{19}H_{14}O_2$: calcd 274.09938, found 274.09940.