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Synthesis of Carbazoles from Ynamides by Intramolecular Dehydro Diels−Alder Reactions†

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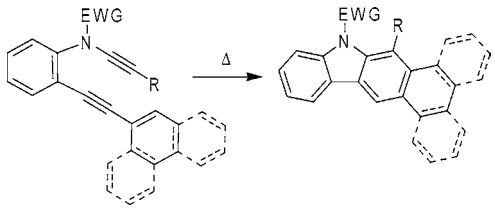
ABSTRACT



A new approach to carbazoles and benzannulated carbazoles by means of intramolecular dehydro Diels−Alder reactions of ynamides is reported. By using this approach, carbazoles and benzo[*b*]-, tetrahydrobenzo[*b*]-, naphtho[1,2-*b*]-, naphtho[2,1-*b*]-, and dibenzo[*a,c*]carbazoles have been prepared in moderate-to-good yields.

Carbazoles constitute an important and growing class of alkaloids displaying a wide variety of biological activities.[1] Carbazole derivatives are also widely used as building blocks for potential organic semiconductors,[2] organic light-emitting diodes,[3] electroluminiscent materials,[4] and polymers with other useful electrical properties.[5] Accordingly, syntheses of carbazoles and modified carbazoles have been extensively studied.[6,7] We recently described the preparation of substituted benzo[*b*]- and benzo[*c*]fluorenes, the carboanalogues of benzannulated carbazoles, by means of intramolecular dehydro Diels−Alder (IDDA) reactions of substituted diarylacetylene systems (arenynes).[8] We now report a new adaptation of this strategy using substituted ynamides **1**[9−11]

† Dedicated with best wishes to Prof. Rafael Suau on the occasion of his 60th birthday.

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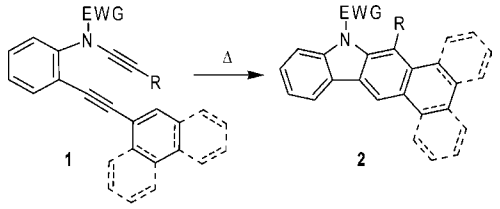
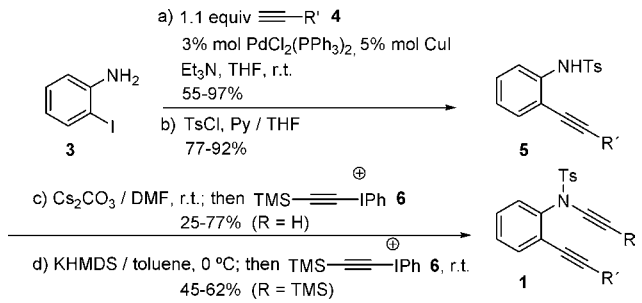
to synthesize carbazoles and benzannulated carbazoles **2**[12] (Scheme 1).

Scheme 1. Strategy for Synthesis of Carbazoles and Benzannulated Carbazoles by Intramolecular Dehydro Diels−Alder Reaction of Ynamides



Ynamides **1** were prepared in three steps starting from commercially available *o*-iodoaniline (**3**). Sonogashira reactions between **3** and terminal alkynes **4**, followed by N-tosylation, gave alkynes **5** (which were also obtained by Sonogashira reactions of tosylated **3** with **4**) and N-ethynylation of alkynes **5** with (trimethylsilyl)ethynyliodonium salt **6**, then gave the desired ynamides **1** in good overall yields (Scheme 2, Table 1).[13] Using Cs_2CO_3 as the base in

Scheme 2



the last step afforded desilylated **1** (R = H); using KHMDS retained the TMS group.[7a,13]

Initially, IDDA reactions were carried out by simply heating ynamides **1** in toluene at 150 °C (Table 1, conditions A).[8] Not unexpectedly, in most cases, much better results were obtained at the same temperature in a mixture of toluene and Et_3N (Table 1, conditions B).[8b,d] For example, for ynamide **1a**, the change of medium raised the yield of 2-methylcarbazole **2a** from a poor 16% yield to an acceptable 40% (Table 1, entries 1 and 2). Remarkably, however, access to the interesting tetrahydro-5*H*-benzo[*b*]carbazole nucleus **2b** was achieved in 55% yield using toluene alone (entry 3),[14] and yields that were almost as good were obtained when the nitrogen was protected as a carbamate (entries 4 and 5). To our delight, our metal-free IDDA approach to carbazoles nicely complements the efficient intermolecular Rh(I)-catalyzed [2 + 2 + 2] cycloaddition of ynamides with alkynes.[7a]

Benzannulated carbazole ring systems are found only rarely in nature but are of considerable interest because of their potential antitumoral[15] and other pharmacological properties,[16] and as building blocks for organic materials.[2−5] Several synthetic approaches to benzo[*b*]carbazoles (2-deazaellipticines) have been developed over the past half-century,[6] including benzannulation of indoles,[17] Fischer indolization of phenylhydrazones,[18] Diels−Alder reactions of pyrano[3,4-*b*]indol-3-ones,[19] 4*H*-furo[3,4-*b*]indoles[20] and 2,4-dihydropyrrolo[3,4-*b*]indoles,[21] and cycloaromatization of *N*-[2-(1-alkynyl)phenyl]keteneimines;[12b] yields have varied between 22% and 98%. The main failing of these methods is their lack of flexibility, since they allow almost exclusively the synthesis of the parent benzo[*b*]carbazole nucleus but not that of benz[*b*]annulated analogues. In this work, we first approached the parent benzo[*b*]carbazole **2c** by heating **1c** in toluene (conditions A), which gave **2c** in a moderate 30%

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(13) See Supporting Information.

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Table 1. Results of Intramolecular Dehydro Diels−Alder Reactions of Ynamides **1**

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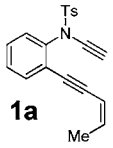
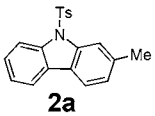
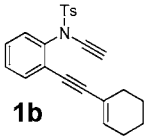
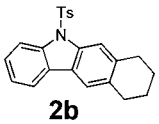
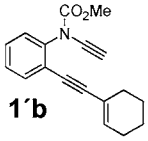
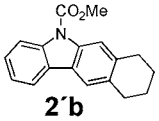
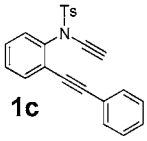
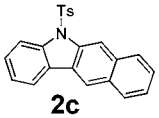
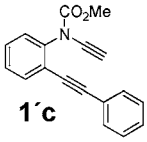
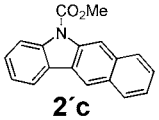
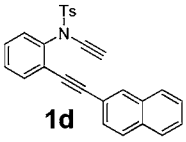
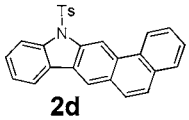
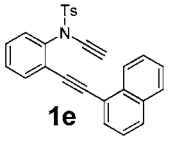
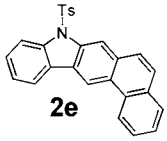
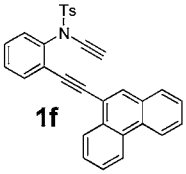
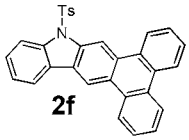
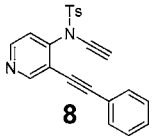
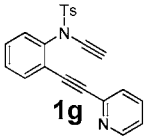
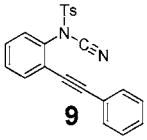
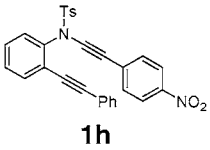
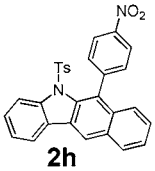
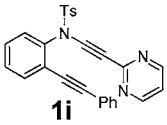
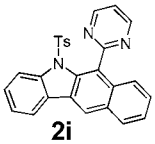
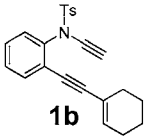
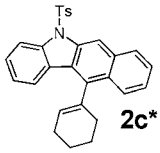
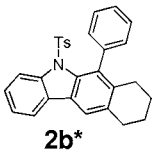
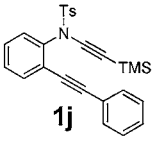
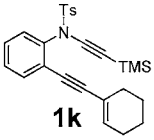
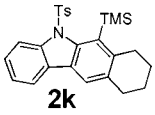
1	 **1a**	A	 **2a**	16
2	**1a**	B	**2a**	40
3	 **1b**	A	 **2b**	55
4	 **1´b**	A	 **2´b**	35
5	**1´b**	B	**2´b**	43
6	 **1c**	A	 **2c**	30
7	**1c**	B	**2c**	12
8	**1c**	C	**2c**	15
9	 **1´c**	A	 **2´c**	42
10	**1´c**	B	**2´c**	50
11	 **1d**	A	 **2d**	21
12	**1d**	B	**2d**[c]	90
13	 **1e**	A	 **2e**	10
14	**1e**	B	**2e**	30
15	 **1f**	A	 **2f**	27
16	**1f**	B	**2f**	58
17	 **8**	A	Dec.	

entry	ynamide	ex.[a]	product	%
18	 **1g**	A	Dec.	
19	**1g**	D	**7g**	85
20	 **9**	A	Starting material	
21	**9**	B	idem	
22	**9**	C	idem	
23	 **1h**	A	 **2h**	16
24	 **1i**	A	 **2i**	10
25[b]	 **1b**		 **2c***  **2b***	**2c*** (8) + **2b*** (16)
26	 **1j**	A	Dec.	
27	**1j**	C	Dec.	
28	 **1k**	B	 **2k**	72
29	**1k**	C	**2k**	85

[a] Experimental conditions. A: **1** (0.01M), toluene (typically, 6 mL), 150 °C, sealed tube. B: conditions A plus 0.5 mL of Et_3N. C: conditions A plus 0.5 mL of MeOH or ^{i}PrOH. D: conditions A plus 1 eq of AcOH. [b] Reagents and conditions: **1b** (1 eq), PhI (1.1 eq), 5% $Pd(PPh_3)_4$, 2% CuI, 2:1 Et_3N/toluene, 60 °C. [c] Refluxing **2d** with TBAF gave detosylated **2d*** in 95% yield.[13]

yield (entry 6). Surprisingly, lower yields (12−15%) were obtained in basic or protic media (conditions B and C, respectively; entries 7 and 8),[8] and when a mixture of toluene and AcOH was used, hydrolysis of the ynamide group occurred giving **7c** in 68% yield (Figure 1).[13] However,

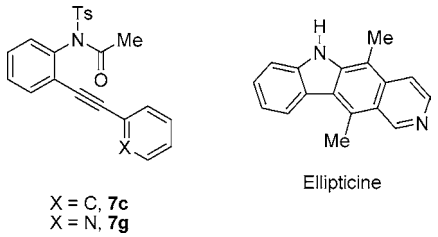


Figure 1.

protecting the nitrogen as a carbamate gave more satisfactory yields (42% and 50%; entries 9 and 10). More importantly, unlike the methods mentioned above, the ynamide IDDA approach allowed the uneventful preparation of benz[*b*]-annulated carbazoles with additional benzene rings: heating ynamides **1d**−**f** in conditions B gave the known naphtho-[1,2-*b*]carbazole[17d] **2d** (90% yield, entry 12), and the hitherto unknowns naphtho[2,1-*b*]carbazole **2e** (30% yield, entry 14) and dibenzo[*a*,*c*]carbazole **2f** (58% yield, entry 16). The parent 12*H*-naphtho[1,2-*b*]carbazole **2d*** was obtained from **2d** in 95% yield by refluxing with TBAF in THF to remove the protecting group.[7a]

Our next goal was the synthesis of isomers of the skeleton of the interesting antitumoral agent ellipticine (Figure 1),[6] but all attempts to prepare pyrido[4,3-*b*]benzo[*f*]indole, pyrido[3,2-*b*]carbazoles, or indolo[2,3-*b*]quinolines met with failure. Heating **8**[22] or **1g** in toluene at 150 °C led to their decomposition, giving at best traces of the desired cyclized products (entries 17 and 18), heating **1g** in the presence of AcOH gave exclusively the hydrolysis product **7g** (Figure 1), albeit in very good yield (entry 19), and heating cyanamide **9**[23] had no effect (entries 20−22), a result that contrasts with the exceptionally easy photocyclizations of the related aryldiimides.[24]

We next examined the regioselectivity of the dehydro Diels−Alder reaction by installing a second aryl ring in the starting ynamide **1** (R = Ar). Substrates in which the extra ring was electron-deficient (**1h** and **1i**)[25] gave the 6-aryl-benzo[*b*]carbazoles **2h** and **2i** regioselectively, though in rather poor yields (entries 23 and 24), indicating that the cycloaddition occurred selectively on the more electron-rich phenyl.[26] Interestingly, when the cyclohexenylynamide **1b** was subjected to Sonogashira conditions in the presence of iodobenzene, two carbazoles were isolated, 11-cyclohex-enylbenzo[*b*]carbazole **2c*** in 8% yield and 6-phenyltetrahy-drobenzo[*b*]carbazole **2b*** in 18% yield,[13] suggesting that after initial phenylation of **1b**[25] the two possible cycloadditions had occurred in roughly a 1:2 ratio (entry 25).

Finally, we investigated whether benzo[*c*]carbazoles might be prepared through rearrangement of the cyclic allene intermediate that would be formed in the course of the IDDA reaction of phenylsilylynamide **1j**.[27] Unfortunately, all attempts at IDDA reaction of **1j** led to its decomposition (entry 26), even when we tried to trap the putative initial cyclic allene in the presence of MeOH (entry 27). By contrast, cyclohexenylsilylynamide **1k** smoothly cyclized in very good yields to the 6-(trimethylsilyl)tetrahydrobenzo[*b*]carbazole **2k** (entries 28 and 29).

In conclusion, we have shown that IDDA reactions of ynamides allow the synthesis of both carbazoles and benz-annulated carbazoles in relatively good yields. These results open new perspectives for the application of ynamides in the field of polycyclic aromatic chemistry.

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Supporting Information Available: Experimental procedures and spectral data for **1a**,**c**,**e**,**f**,**h**,**k**, **2a**,**c**,**e**,**f**,**h**,**k, 2b***, **2c***, **7c,** and **8**; and ^{1}H and ^{13}C/DEPT spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Obtained following the same procedure as for **1** (Scheme 2) but starting with 4-amino-3-bromopyridine.

(23) Prepared in 51% yield by treatment of **5c** with BrCN in the presence of KH.

(24) Schmittel, M.; Rodríguez, D.; Steffen, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2152.

(25) Prepared by Sonogashira cross-coupling reactions of **1** (R′ = H) with the corresponding aryl iodides. Tracey, M. R.; Zhang, Y.; Frederick, M. O.; Mulder, J. A.; Hsung, R. P. *Org. Lett.* **2004**, *6*, 2209.

(26) In fact, electron-rich substrates, gave complex mixtures showing that, most likely, the cycloaddition is not regioselective.

(27) TMS-substituted cyclic allenes of the benzo[*b*]- series could isomerize to the more stable benzo[*c*]- form, see (a) Rodríguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Am. Chem. Soc.* **2001**, *123*, 9178. (b) Rodríguez, D.; Castedo, L.; Domínguez, D.; Saá, C. *Synthesis* **2004**, 761.