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Regioselective cycloaddition of acetylenic esters: a one-pot synthesis of novel dihydrobenzo[*a*]carbazoles

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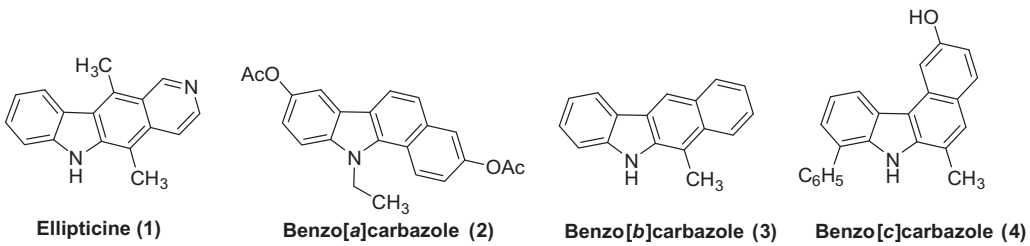
ABSTRACT

A one-pot procedure for the synthesis of highly substituted dihydrobenzo[*a*]carbazole derivatives via a regioselective cyclocondensation reaction between 2-(2,3,4,9-tetrahydro-carbazol-1-ylidene)-propanedinitrile and acetylenic esters is described.

Carbazoles and related compounds display a range of biological activities which makes them attractive compounds for both synthetic as well as medicinal chemists.[1–3] In the past two decades numerous carbazole alkaloids and synthetic analogues, many of them possessing useful pharmacological properties, have been studied. Recently, Knölker and Reddy extensively reviewed the synthesis of biologically active carbazole alkaloids.[4] Some of the most important compounds with proven chemotherapeutic value belong to the ellipticine class (**1**).[5,6] In this class of compounds a heteroaromatic ring is fused to the *b*-face of the carbazole. However, there is a growing number of carbazoles that contain aromatic or heteroaromatic rings fused to the *a*- or *c*-face of the carbazole nucleus. For example, among the various benzocarbazoles, a series of simple benzo[*a*]carbazoles and benzo[*b*]carbazoles such as (**2**) or (**3**), have been tested as candidates for the treatment of cancer as a result of their DNA intercalating properties,[7] while benzo[*c*]carbazoles such as **4** show promising profiles for intra-cyclin dependent kinase selectivity[8] (Fig. 1). Very recently, several benzocarbazole analogues have also been explored as functional building blocks in the construction of organic materials for optoelectronic devices.[9,10]

An early synthetic route towards the synthesis of substituted carbazoles focused mostly on either electrophilic additions or on ring closure methods.[11] Realisation of the potential of benzocarbazoles as both therapeutic agents as well as functional materials has sparked new efforts into finding alternative or more efficient pathways towards the preparation of these compounds. Methods that have been used are for example benzannulation,[12] Fischer



Ellipticine (1) Benzo[*a*]carbazole (2) Benzo[*b*]carbazole (3) Benzo[*c*]carbazole (4)

Figure 1. Examples of (**1**): an ellipticine; (**2**): of a benzo[*a*]carbazole; (**3**): a benzo[*b*]carbazole; (**4**) a benzo[*c*]carbazole.

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indolization,[13] modified Nenitzescu reaction,[14] cycloaddition reaction,[15] cycloaromatisation,[16]coupling reactions,[17] or radical reactions[18] and most recently annulations based on cycloaddition reactions,[19] to name just a few.

As would be expected for a family of compounds as diverse as the benzocarbazoles, synthetic results have been varied and are highly dependent on the method used and the substitution pattern of the specific target compound. Harsh reaction conditions, multistep sequences and expensive starting materials or catalysts are commonly encountered problems. The most serious drawbacks of the established methods are however a lack of flexibility and tolerance of functional groups, and regiochemical ambiguities originating from orienting effects of the substituents. There is thus still a considerable need for the development of more versatile and regioselective synthetic routes towards highly substituted benzocarbazoles, especially with respect to tolerance of a wider variety of functional groups.

As part of our ongoing studies on the development of facile methods for the synthesis of organic compounds from readily available starting materials, we would like to here describe a new versatile method designed to help address these needs, the reaction of 2-(2,3,4,9-tetrahydro-carbazol-1-ylidene)-propanedinitrile with acetylenic esters in the presence of a base, leading to highly substituted benzocarbazoles in a one-pot addition reaction.

In our initial endeavour, we investigated the reaction of 2-(6-methyl-2,3,4,9-tetrahydro-carbazol-1-ylidene)-propanedinitrile **1a** with dimethyl acetylene dicarboxylate using various base catalysts in different solvents (methanol and acetonitrile) and temperatures (Table 1). The starting material **1a** is easily prepared[20] and can be obtained by the reaction of 6-methyl-2,3,4,9-tetrahydro-carbazol-1-one **3a** with malononitrile.

Using triethyl amine, potassium carbonate or sodium methoxide as the base the target product **2a** was obtained in only low yield along with the side product **3a** (entries 1–6). With piperidine as the base a moderate yield of around 60% could be achieved (entries 7 and 8). The best yield for the reaction between **1a** and dimethyl acetylene dicarboxylate was obtained by switching to benzyltrimethylammonium hydroxide (Triton-B) as the base in refluxing acetonitrile as the solvent (Table 1). Under these conditions **2a** was isolated in nearly 80% yield, and no side products such as **3a** were observed.

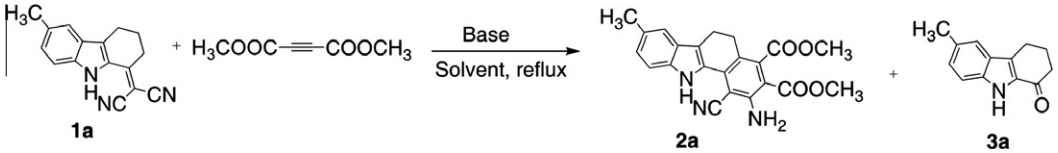
The reaction was found to be general and use of this method with various other substituted 2-(2,3,4,9-tetrahydro-carbazol-1-ylidene)-propanedinitriles **1** gave highly substituted benzo[*a*]carbazoles[21] in good yield as shown in Scheme 1 (Table 2, entries 2–5). Subsequently, we also investigated the reaction of compounds **1** with methyl propiolate instead of DMAD. Reactions proceeded smoothly and gave another series of regioselectively substituted benzo[*a*]carbazoles in excellent yields (Table 2, entries 6–10).

The structures of the products were deduced from their elemental analysis data, and from their IR, mass, ^{1}H NMR and ^{13}C NMR spectra. The structure of one of the products was also confirmed by single crystal X-ray diffraction.

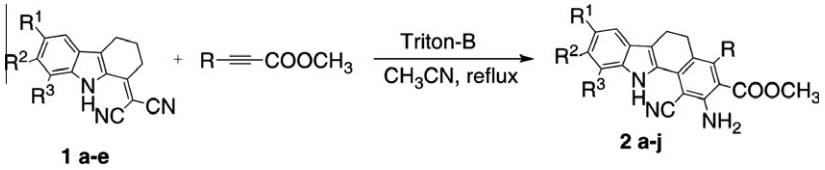
The IR spectrum of **2a**, for example, shows absorption peaks at 3438, 3375, 3342, 2211, 1733 and 1688 cm^{-1} which attest to the presence of amino, indole NH, cyano and ester groups, respectively. For compound **2f** the IR spectrum showed an unusually low frequency for the ester carbonyl group of 1688 cm^{-1}, indicating *H*-bonding between the amino group and the ester carbonyl group, confirming that the ester group must be in the C3 position. The other IR frequencies of **2f** at 3450, 3346 and 3271 cm^{-1} for the NH_2 and carbazole NH groups, and at 2207 cm^{-1} for the cyano group were again as expected. The ^{1}H NMR spectra of compounds **2a**–**i** were as expected. **2a**, for example, exhibits a series of signals in the aromatic region of the spectrum, two singlets arising from the two sets of methoxy protons (δ 3.86 and δ 3.94) and a broad singlet for the two amine protons (δ 6.57). The identities of the other compounds **2b** to **2i** were established in a similar ways with all spectroscopic data readily assignable. Finally, the structure of one of the members of the series, **2c**, was confirmed by single crystal X-ray analysis (Fig. 2).

The reaction mechanism for the formation of the substituted benzo[*a*]carbazoles **2** from the (2,3,4,9-tetrahydro-carbazol-1-ylidene)-propanedinitriles **1** by reaction with acetylenic esters is composed of several distinct steps. The reaction sequence is most likely initiated by base abstraction of a proton from **1**, followed by nucleophilic attack at the β-position of the acetylenic ester, resulting in the formation of the first intermediate with tautomeric

Table 1
Reaction of 2-(6-methyl-2,3,4,9-tetrahydro-carbazol-1-ylidene)-propanedinitrile **1a** with dimethyl acetylene dicarboxylate, under various conditions

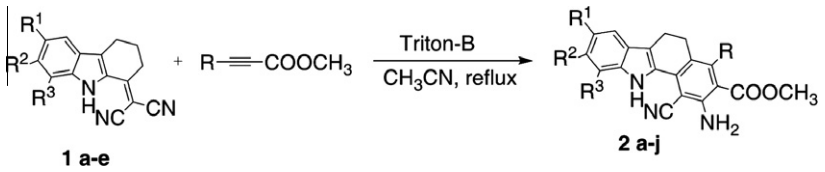


Entry	Solvent	Base	Time/h	*T* (°C)	Yield (%)	
					2a	**3a**
1	CH_3OH	Et_3N	6	60	15	38
2	CH_3CN	Et_3N	6	60	20	35
3	CH_3OH	K_2CO_3	6	80	38	40
4	CH_3CN	K_2CO_3	6	80	45	34
5	CH_3OH	CH_3ONa	6	80	22	30
6	CH_3CN	CH_3ONa	6	80	28	25
7	CH_3OH	Piperidine	6	80	56	15
8	CH_3CN	Piperidine	6	80	64	12
9	CH_3OH	Triton-B	4	80	62	0
10	CH_3CN	Triton-B	4	60	66	0
11	CH_3CN	Triton-B	4	70	70	0
12	CH_3CN	Triton-B	4	80	78	0



Scheme 1. Synthesis of 2-amino-1-cyano-5,6-dihydro-11*H*-benzo[*a*]carbazole-carboxylic ester.

Table 2
Reaction of 2-(2,3,4,9-tetrahydro-carbazol-1-ylidene)-propanedinitriles **1** with acetylene esters, in the presence of Triton-B



Entry	R^1	R^2	R^3	R	Product	Yield (%)
1	CH_3	H	H	$COOCH_3$	**2a**	78
2	H	CH_3	H	$COOCH_3$	**2b**	75
3	H	H	CH_3	$COOCH_3$	**2c**	80
4	H	H	H	$COOCH_3$	**2d**	78
5	Cl	H	H	$COOCH_3$	**2e**	70
6	CH_3	H	H	H	**2f**	82
7	H	CH_3	H	H	**2g**	77
8	H	H	CH_3	H	**2h**	85
9	H	H	H	H	**2i**	84
10	Cl	H	H	H	**2j**	74

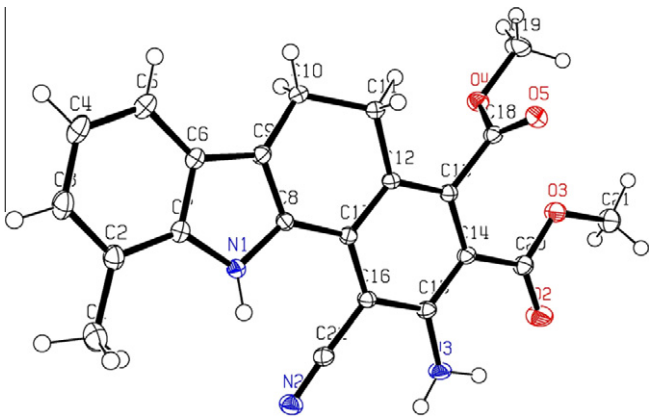
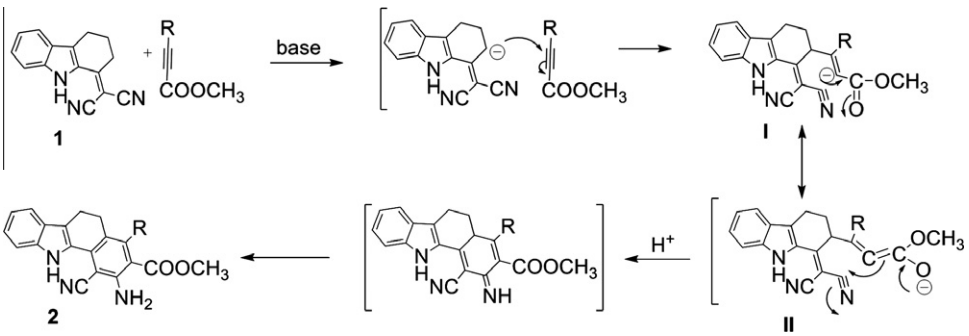


Figure 2. X-ray crystal structure of compound **2c**.

forms **I** and **II** as shown in Scheme 2. The negative charge at the α-carbon in form **I**, stabilized by the electron-withdrawing capability of the adjacent ester group, allows for an intramolecular nucleophilic ring closure to follow, and subsequent aromatisation via a tautomeric 1,5-H shift yields the final stable compound **2**. The reactions are straightforward, but yields were found to be variable depending on the base that was used. Purification was however readily accomplished by simple recrystallization for all compounds. In the case of the reaction with methyl propiolate (to yield compounds **2f–j**), the reaction was found to be highly regiospecific yielding only the product resulting from nucleophilic attack at the alkyne carbon β to the ester functionality. A possible explanation for this selectivity might be found in the greater stability of the intermediate carbanion (Scheme 2).

In conclusion, we have established a novel one-pot regioselective synthesis of dimethyl 2-amino-1-cyano-5,6-dihydro-11*H*-



Scheme 2. Mechanism for the formation of 2-amino-1cyano-5,6-dihydro-11*H*-benzo[*a*]carbazole-carboxylic esters.

benzo[*a*]carbazole-3,4-dicarboxylates and methyl 2-amino-1-cyano-5,6-dihydro-11*H*-benzo[*a*]carbazole-3-carboxylates. This new strategy allows for the synthesis of benzo[*a*]carbazoles by cycloaddition of 2-(2,3,4,9-tetrahydro-carbazol-1-ylidene)-propanedinitriles with acetylene esters in the presence of a base such as Triton-B. The one-pot procedure is straightforward and the initial results show a remarkable tolerance towards functional groups such as, for example, amines, carbonitriles or methoxycarbonyl substituents.

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Supplementary data

Supplementary data (experimental details, spectral data, and crystallographic data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.125.

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21. General procedure for the synthesis of 5,6-dihydro-11*H*-benzo[*a*]carbazoles (**2**): A mixture of 2-(2,3,4,9-tetrahydro-carbazol-1-ylidene)-propanedinitrile (**1**, 1 mmol) and acetylene esters (dimethyl acetylenedicarboxylate (or) methyl propiolate) (1 mmol) was refluxed with CH_3CN in the presence of Triton-B. After completion of the reaction as judged by TLC, the solvent was removed under reduced pressure. The product was purified by silica gel column chromatography using petroleum ether and ethyl acetate (95:5) to yield the highly substituted benzo[*a*]carbazole and crystallised using ethyl acetate. Dimethyl 2-amino-1-cyano-8-methyl-5,6-dihydro-11*H*-benzo[*a*]carbazole-3,4-dicarboxylate (**2a**):Yellow solid (0.303 g, 78%); mp: 193 °C; IR (KBr) 3438, 3375, 3342, 2211, 1733, 1688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.45 (s, 3H, CH_3), 2.79 (t, 2H, J = 8.0 Hz, 5-2H), 2.94 (t, 2H, J = 8.0 Hz, 6-2H), 3.86 (s, 3H, $COOCH_3$), 3.94 (s, 3H, $COOCH_3$), 6.57 (s, 2H, NH_2), 7.14 (d d, 1H, J_o = 8.4 Hz, J_m = 1.2 Hz, 9-H), 7.34 (d, 1H, J = 8.4 Hz, 10-H), 7.36 (d, 1H, J_m = 1.2 Hz, 7-H), 9.25 (br s, 1H, N–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 19.1 (CH_2), 20.8 (CH_3), 25.4 (CH_2), 52.3 (OCH_3), 52.3 (OCH_3), 90.1 (C), 105.0 (C), 111.4 (CH), 118. 2 (CN), 119.3 (CH), 120.1 (CH), 120.8 (C), 122.2 (C), 127.2 (C), 127.9 (C), 129.5 (C), 136.1(C), 136.2 (C), 138. 8 (C), 151.4 (C), 166.9 (C=O), 168.3 (C=O); MS, *m*/*z* (%): 389 (M^+, 100), 358 (38), 299 (86), 271 (75), 256 (35), 247 (40); Anal. Calcd for $C_{22}H_{19}N_3O_4$: C, 67.86; H, 4.88; N, 10.79%. Found: 67.81; H, 4.84; N, 10.72%.