A Rapid Assembly of Furo[3,4-*b*]- and Pyrrolo[3,4-*b*]carbazolones by Domino Wittig Diels–Alder Reaction

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Dedicated to Prof. R. S. Mali on his 70th birthday

Abstract: Regioisomeric hexahydrofuro[3,4-*b*]carbazol-1-ones, hexahydropyrrolo[3,4-*b*]carbazol-1-ones, hexahydrofuro[3,4-*b*]carbazol-3-ones and hexahydropyrrolo[3,4-*b*]carbazol-3-ones were synthesized in 59% to 62% yields by domino Wittig Diels–Alder reactions from indole-3-carboxaldehyde and indole-2-carboxaldehyde and Wittig reagents. Further the corresponding carbazolelactones and carbazolelactams were obtained by oxidation with DDQ.

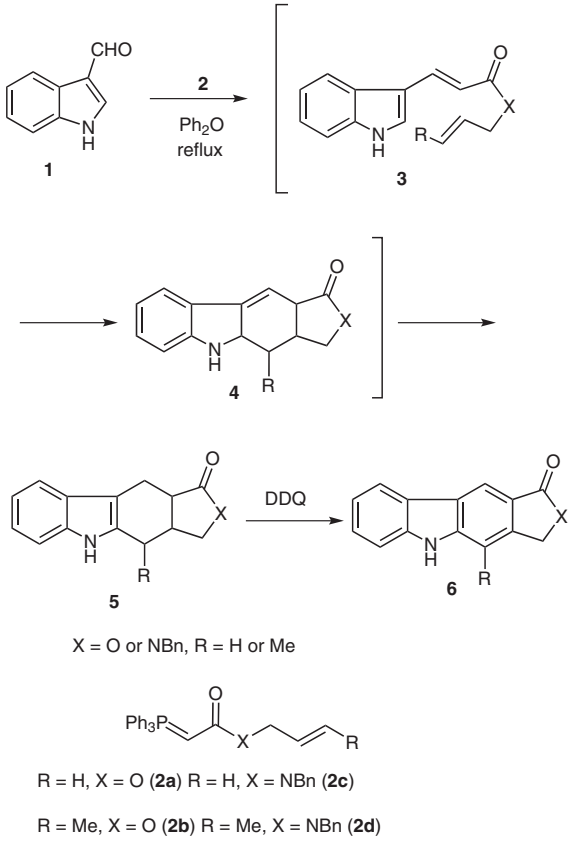
Key words: domino Wittig, Diels–Alder, furocarbazoles, pyrrolocarbazoles

A large number of substituted carbazole alkaloids have been isolated[1] from plants in last few decades. Both, natural and synthetic carbazoles display a wide range of biological activities which includes inhibition of CDK-5, antitumor, psychotropic, anti-inflammatory, antimicrobial, antihistamine, antibiotic, and antioxidative activities.[2] Application of carbazoles in material science is also well documented.[3] Consequently, the development of regioselective synthesis[4] of functionalized tetrahydrocarbazole and carbazole scaffolds has gained paramount interest. A plethora of reviews[5] is available on the synthesis of carbazole alkaloids.

The ubiquitous presence of a lactone and a lactam unit in many polycyclic antineoplastic agents[6] prompted us to undertake the synthesis of carbazolelactones and carbazolelactams. Further impetus was provided by the cytotoxicity exhibited by the recently isolated γ-lactone carbazole against human leukemia cell line.[6a]

Domino reactions[7] are of current interest for the synthesis of complex molecules. In continuation of our endeavors in domino methodologies,[8] we report herein a facile synthesis of furo[3,4-*b*]carbazolones and pyrrolo[3,4-*b*]carbazolones using domino Wittig–Diels–Alder reaction sequence.[9]

Thus, when indole-3-carboxaldehyde (**1**), was subjected to domino Wittig Diels–Alder reaction protocol[8e,10] with phosphorane **2a** a mixture of two diastereomers, *cis*- and *trans*-3,3a,4,5,10,10a-hexahydro-1*H*-furo[3,4-*b*]carbazol-1-one (**5a**) was obtained in 1:1 ratio (HPLC) in 60% yield.



Scheme 1 Synthesis of carbazolones using indole-3-carboxaldehyde

In this one-pot reaction first the Wittig reaction takes place to form *E* unsaturated ester **3a**, which under the reaction conditions undergoes intramolecular Diels–Alder reaction to form **4a**, which then rapidly isomerizes to **5a** (Scheme 1).

The *cis* diastereomer was assumed to have arisen from the *syn* transition state while the *trans* from the *anti* transition state (Scheme 2). The formation of both the diastereomers in equal proportion suggests that the energy barrier between the two transition states is negligible. Interestingly, no dimeric product due to intermolecular Diels–Alder reaction was observed though the conjugated double bond in **3** can also behave as a dienophile. Compound **5a** was then easily oxidized with DDQ to the required furo[3,4-*b*]carbazol-1-one. The success of this reaction prompted us to condense phosphorane **2b** with **1** to obtain a mixture

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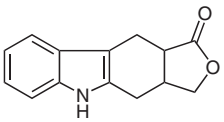
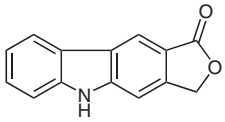
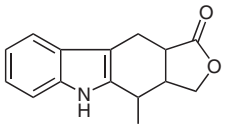
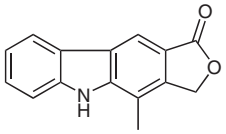
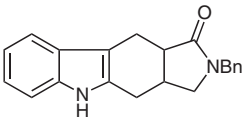
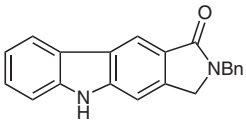
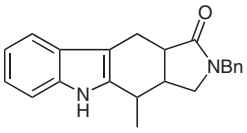
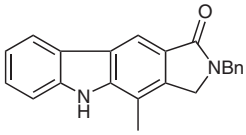
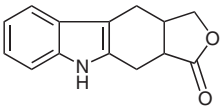
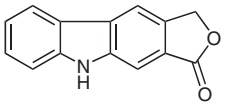
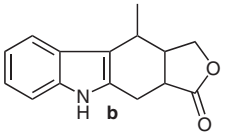
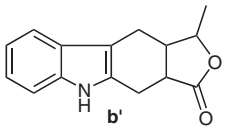
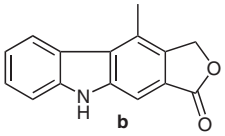
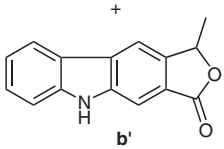
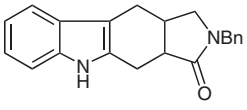
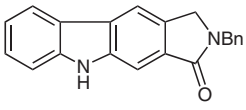
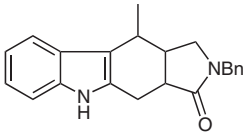
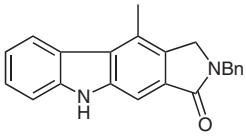
of diastereomers of **5b** which were directly converted into **6b**.

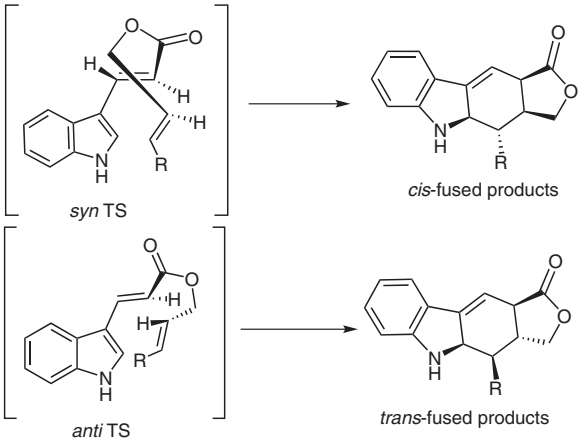
Having synthesized the furocarbazolones **6a**,**b**, our next aim was to prepare the corresponding pyrrolocarbazolones, for which **1** was reacted with the phosphorane **2c** under similar reaction conditions. As expected a mixture of *cis* and *trans* fused 2-benzyl-2,3,3a,4,10,10a-hexahydropyrrolo[3,4-*b*]carbazol-1(5*H*)-one (**5c**) was formed which on oxidation gave **6c**. With phosphorane **2d**, a mixture of diastereomers of **5d** was obtained, which on aromatization gave the carbazolone **6d** (Table 1).

We next undertook the synthesis of carbazole lactones and lactams regioisomeric to **6a–d** using indole-2-carboxaldehyde **7**. Thus, when **7** was subjected to similar reaction conditions with **2a**, a mixture of *cis*- and *trans*-3a,4,10,10a-tetrahydro-1*H*-furo[3,4-*b*]carbazol-3(5*H*)-one (**10a**) was obtained in 60% yield. Compound **10a** was then easily oxidized to **11a** using DDQ (Scheme 3). The reaction of **7** with phosphorane **2b**, however, yielded an isomeric product **11b′** in major amount. The formation of **11b′** could be accounted from an allylic ester rearrangement of the Wittig product intermediate prior to the Diels–Alder reaction (as shown in Scheme 4).

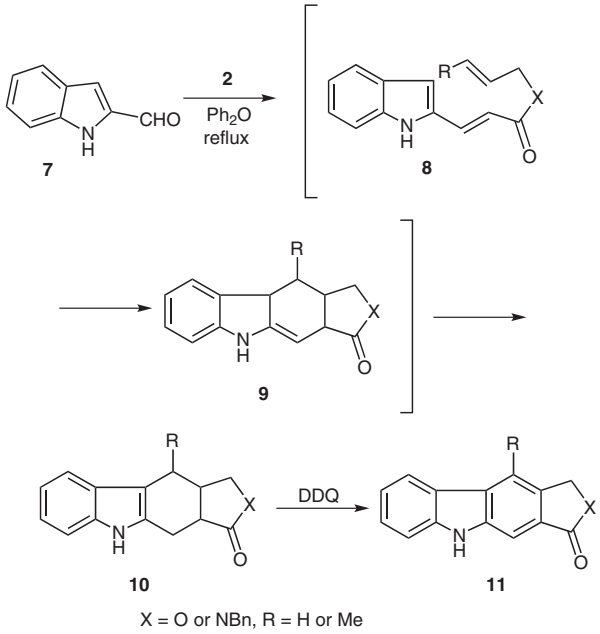
Table 1 Product of Domino Wittig–Diels–Alder Reaction and Oxidation

Entry	Aldehyde	Phosphorane	Product **5/10**		Yield (%)[a]	Product **6/11**		Yield (%)[a]
1	**1**	**2a**	**5a**		60	**6a**		62
2	**1**	**2b**	**5b**		61	**6b**		59
3	**1**	**2c**	**5c**		62	**6c**		15
4	**1**	**2d**	**5d**		61	**6d**		11
5	**7**	**2a**	**10a**		61	**11a**		59
6	**7**	**2b**	**10b**	 + 	57	**11b**	 + 	58[b]
7	**7**	**2c**	**10c**		62	**11c**		28
8	**7**	**2d**	**10d**		61	**11d**		34

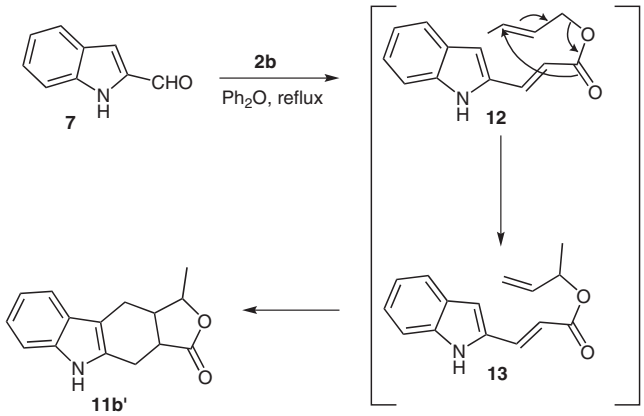
[a] Isolated yield.
[b] The ratio of **11b/11b′** (0.2:1.0) was determined by ^{1}H NMR.



Scheme 2 Transition states involved in Diels–Alder reaction.



Scheme 3 Synthesis of carbazolones using indole-2-carboxaldehyde



Scheme 4 Probable mechanism for the formation of **11b′**

For obtaining hexahydropyrrolo[3,4-*b*]carbazol-3-ones, **7** was treated with phosphorane **2c**,**d**. With phosphorane **2c**, a mixture of diastereomers (*cis*- and *trans*-fused) of 2-benzyl-1,2,3a,4,10,10a-hexahydropyrrolo[3,4-*b*]carbazol-3(5*H*)-one (**10c**) was formed. Phosphorane **2d** provided the corresponding 2-benzyl-4-methyl-1,2,3a,4,10,10a-hexahydropyrrolo[3,4-*b*]carbazol-3(5*H*)-one (**10d**). The compounds **10c** and **10d** were aromatized to obtain **11c** and **11d**, respectively.

In conclusion we have demonstrated that the functionalized tetrahydrocabazoles can be rapidly assembled using domino Wittig and Diels–Alder reaction protocol. During this sequence, Wittig reaction, intramolecular Diels–Alder reaction and isomerization take place in a domino fashion.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) **General Procedure for the Tandem Wittig–Diels–Alder Reaction for Preparation of Tetrahydrocarbazole Lactones (5a,b/10a,b) and Tetrahydrocarbazole Lactams (5c,d/10c,d)**: A solution of indole carboxaldehyde **1/7** (1 mmol) and phosphorane **2a–d** (1.5 mmol) in diphenyl ether (10 mL) was refluxed under nitrogen atmosphere for 2–8 h. The crude mixture was subjected to column chromatography over silica gel and diphenyl ether was removed using hexanes as eluent. Further elution with 30–40% EtOAc and hexanes afforded the corresponding γ-lactones **5a**,**b/10a**,**b** and γ-lactams **5c**,**d/10c**,**d**.
General Procedure for Aromatization Using DDQ: A mixture of tetrahydrocarbazoles **5a–d/10a–d** (1 mmol) and DDQ (3 mmol) in dioxane (10 mL) was refluxed for 8 h. The reaction mixture was allowed to cool to ambient temperature and filtered. The filtrate was then concentrated under reduced pressure. The resulting residue was dissolved in EtOAc (20 mL) and washed with 2 N NaOH (20 mL) and H_2O (20 mL). The organic phase was dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The resulting residue on purification using flash chromatography with hexanes–EtOAc (70:30) gave the oxidized products **6a–d/11a–d**.
3,5-Dihydro-1*H*-furo[3,4-*b*]carbazol-1-one (6a): ^{1}H NMR (300 MHz, DMSO): δ = 5.46 (s, 2 H), 7.21 (t, *J* = 7.8 Hz, 1 H), 7.49 (t, *J* = 7.8 Hz, 1 H), 7.53 (d, *J* = 8.1 Hz, 1 H), 7.62 (s, 1 H), 8.30 (d, *J* = 7.8 Hz, 1 H), 8.66 (s, 1 H), 11.78 (s, 1 H). ^{13}C NMR (300 MHz, DMSO): δ = 69.85, 104.29, 111.83, 116.03, 118.12, 120.10, 121.47, 122.56, 124.50, 127.28, 141.27, 144.40, 144.85, 171.69. HRMS: *m/z* [M + Na] calcd for $C_{14}H_9O_2N$: 246.0531; found: 246.0524.