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An Expediuos Benzannulation reaction of Indol-3-yl-but-3-yn 2-ols to substituted 2-Iodocarbazoles via Domino 5-*endo* spirocyclization/selective vinyl shift and aromatization

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Abstract. Regioselective benzannulation reaction of indol-3-yl-but-3-yn-2-ols to functionally embellished 2-iodocarbazoles is described for the first time using iodine at room temperature in open-flask. This reaction proceeds through a cascade 5-*endo* spirocyclization, ring-rearrangement through a vinyl shift and aromatization in short time. This protocol offers direct access to uncovered 2-iodocarbazoles, with a broad substrate scope and good to moderate yields. Further, we have demonstrated the synthetic potential of these compounds using cross-coupling reactions.

Keywords: 2-iodocarbazoles; 1,2-vinyl migration; iodocyclization; benzannulation; 5-*endo*-spirocycization

Introduction

Carbazoles belong to an important class of alkaloids with high natural abundance, often found to exhibit a wide range of biological activities such as anticancer, antimicrobial, antibiotic, antipsychotic, and anti-inflammatory to name a few (Figure 1).[1-2]. Further, many molecules embedded with carbazole motifs have found applications in material science, particularly as organic light-emitting diodes (OLED), due to its wide bandgap and high luminescent properties.[3] Owing to the tremendous importance of carbazole-based structures in these fields, various synthetic strategies have been developed for the construction of functionalized carbazoles.[1-4] Despite the availability of various classical and transition metal-mediated methods to construct carbazoles, benzannulation strategy from indole has been increasingly attracted in recent years because a vast number of indoles are readily available and easily prepared. In general, alkenes,[5] alkynes,[6] dicarbonyls,[7] and other compounds[4,8] have been successfully employed as diene precursors for the construction of carbazoles from indoles through benzannulation protocol.[9] However, some of these methods suffer from limitations such as usage of precious metal catalysts (Pt, Au, Ag, Pd, etc.), harsh reaction conditions and limited functional group tolerance. Therefore it is highly desirable to develop a one-pot, transition metal-free approach for the construction of pre-functionalized carbazoles, particularly iodocarbazoles[10] because these compounds can be easily transformed into desired carbazole materials using suitable reaction conditions, such as cross-coupling reactions.

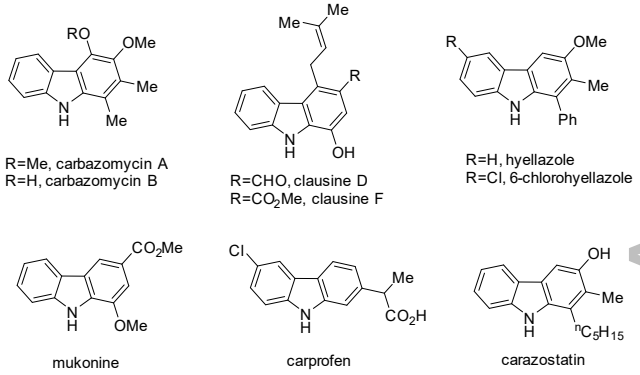

Figure 1. Representative examples of synthetic and natural carbazoles

In the past few years, iodocyclization of propargylic systems, particularly propargyl alcohols, has been emerging as one of the potential strategies for the construction of various pre-functionalized carbo and heterocyclic compounds.[11] Recently, our

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group has demonstrated a one-pot synthesis of iodo-quinolines,[11f,11h] iodochromenes,[11g] iodo-fluorenopyrans[12b] though iodocyclization of propargyl alcohols. Further, these strategic advances have led to a general, one-pot synthesis of 3-iodo-carbazoles from indole-tethered propargyl alcohols (Figure 2).[11h] To the best of our knowledge, there is no single report available to access 2-iodocarbazoles through benzannulation or iodocyclization protocol directly. Our continued investigations in the field of benzannulation reactions[12] form indole to carbazole lead us to disclose herein a highly regioselective, one-pot, transition metal-free and first approach of 2-iodocarbazole synthesis.

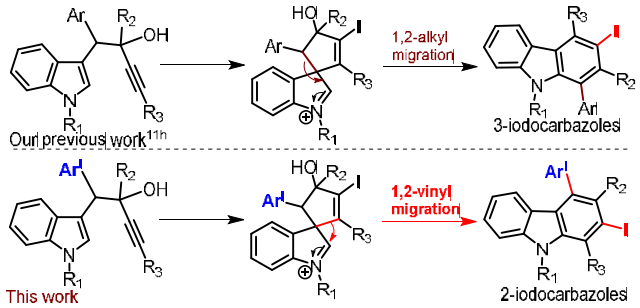


Figure 2. Our previous and current approaches of carbazoles.

Results and Discussion

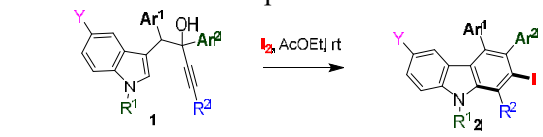
Table 1. Optimization of reaction conditions.[a]

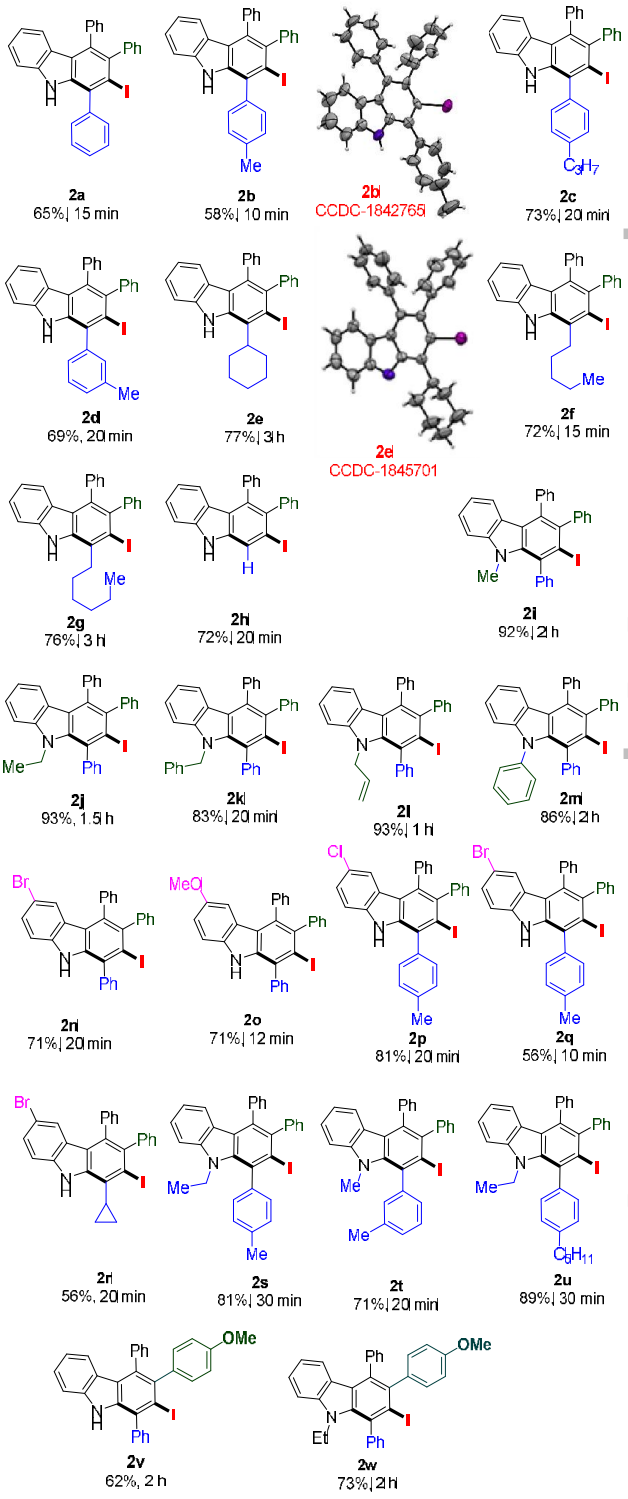
Entry	Catalyst(equiv.)	Solvent, Time	Yield(%)[b]
1	I_2 (1.2)	THF, 30 min	59
2	I_2 (1.2)	1,2-DCE, 30 min	32
3	I_2 (1.2)	Toluene, 1 h	25
4	I_2 (1.2)	CH_3CN, 30 min	53
5	I_2 (1.2)	EtOH, 1 h	nr
6[c]	**I_2 (1.2)**	**AcOEt, 15 min**	65
7	I_2 (2.0)	AcOEt, 10 min	60
8	I_2 (1.5)	AcOEt, 15 min	62
9	I_2 (1.0)	AcOEt, 1 h	58
10	I_2 (1.2) / $NaHCO_3$ (1)	AcOEt, 1 h	48

[a] All reactions were performed with 0.24 mmol of **1a** in 3 mL of solvent with Catalyst at room temperature.
[b] Isolated Yields.
[c] Optimum condition; DCE=1,2-dichloroethane, AcOEt=Ethyl acetate. nr=no reaction.

We commenced our studies by investigating the transformation of 1-(1H-indol-3-yl)-1,2,4-triphenyl but-3-yn-2-ol **1a** with molecular iodine (compound **1a** was synthesized in two steps using a known procedure).[13] The first reaction was performed by stirring 1 equiv. of **1a** and 1.2 equiv. of molecular iodine in THF at room temperature and observed the complete conversion of the starting material (**1a**) after 30 min. Despite of complete conversion, the isolated yield of anticipated 2-iodocarbazole **2a** was only 59% (Table 1, Entry 1). However, this result encouraged us to search for a better reaction condition to maximize the yield of **2a**.

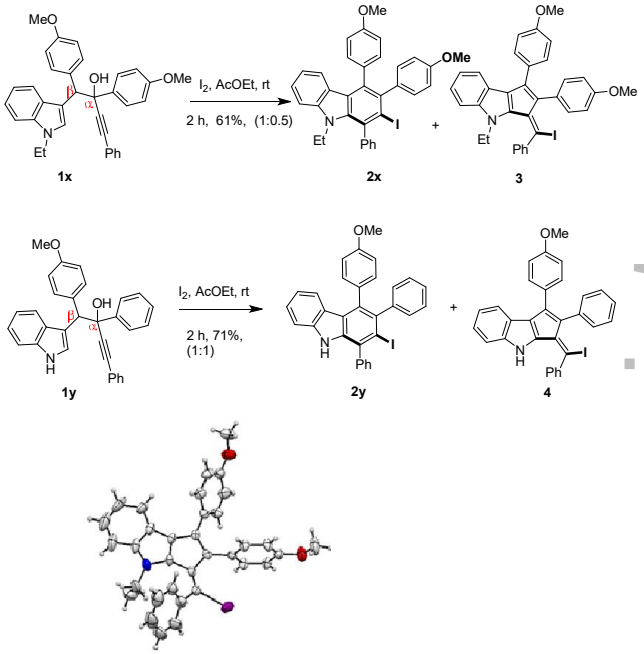
Table 2. Substrate scope.[a]





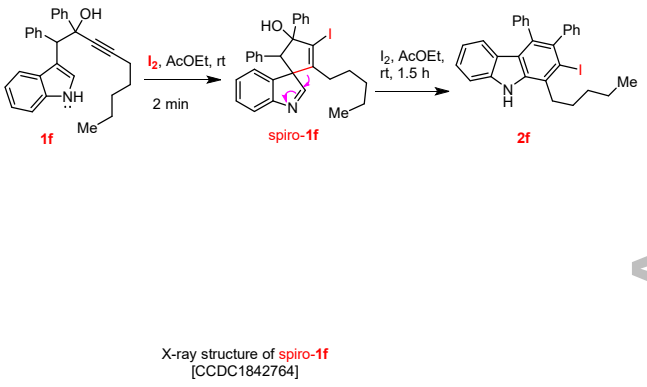
[a] General Conditions: A mixture of 1 equiv. of **1** and1.2 equiv. of iodine were stirred in 3 mL of ethyl acetate rt for a specified time.

Therefore different solvents have been introduced, and ethyl acetate was found to be the finest among 1,2-DCE, toluene and acetonitrile (Table 1, Entries 2-4). The reaction in ethanol didn't provide the desired carbazole (Table 1, Entry 5). 1.2 equivalent of iodine in EtOAc found to be furnishing the cleanest conversion into the desired 2-iodocarbazole, but the isolated yield was only 65% (Table 1, Entry 6). Alteration in iodine stoichiometry resulted in a moderate decrease in the yield of **2a** (Table 1, Entry 7-9). Addition of 1.0 equivalent of $NaHCO_3$ along with iodine restricted the complete conversion (Table 1, Entry 10) even after 1 h and yielded 48% of **2a**.[14] Therefore the reaction conditions of entry 6 have been taken as optimum for this benzannulation reaction. With the optimized condition recognized, we progressed to demonstrate the generality and scope of this iodo-cycloisomerisation process engaging diverse electronic and steric influences on indolylynol moiety by the deployment of various substitutions on indole (both *N*-1 & C-5) and alkyne terminus of ynol fragment (Table 2). Along with aromatic (**2a**-**2d**) and aliphatic substitutions (**2e**-**2g**), unsubstituted alkynol terminus (**2h**) also provided the anticipated iodo-carbazoles in good yields. Interestingly, when we switch to *N*-methylindole (**2i**), it promoted the formation of the desired carbazole in better yield (92%) than the corresponding unsubstituted one (**2a**). Subsequently, *N*-1 substitution of indoles with ethyl (**2j**), benzyl (**2k**), allyl (**2l**) and phenyl (**2m**) groups was found to be well tolerated in this reaction conditions by providing the desired carbazoles in excellent yields. Both halogen (**2n**, **2p**-**2r**) and methoxy (**2o**) substitution on the C5 position of indole ring were compatible and led to the formation of the desired carbazoles in good yields. Later, we briefly studied the effect of different electronic substitutions on the C1 and C2 phenyl rings of the 1-(1H-indol-3-yl)-1,2,4-triphenyl but-3-yn-2-ol moiety. Substitution of C2 phenyl ring with 4-methoxybenzene resulted in the formation of the desired carbazole with a 4-methoxybenzene ring in the 3rd position of the newly constructed 2-iodocarbazole ring (**2v**). N-ethyl substitution on this 4-methoxybenzene substituted indolyl-ynol moiety (**1w**) was also tolerated in this condition providing the desired carbazole **2w** in good yield. These observations indicate that the N-substituted propargyl alcohols of **1** are giving higher yields than that of NH compounds. Astonishingly, replacement of both the C1 and C2 phenyl rings with 4-methoxybenzene has introduced a deviation from the straight forward cyclomerization pathway by providing a mixture of 2-iodocarbazole **2x** and functionalized dihydrocyclopenta[b]indole **3** in 2:1 ratio via probable competitive cyclomerization & benzannulation pathway (Scheme 1).[15] The structure of **3** was unambiguously established by single-crystal X-ray diffraction (CCDC No.1922296).[16] Furthermore, the presence of a 4-methoxyphenyl group at C1 resulted in the mixture of 2-iodocarbazole (**2y**) and dihydrocyclopenta[b]indole (**4**) in 1:1 ratio. The formation of 2-iodocarbazoles **2a**-**2y** and **3**,**4** was protected through steady and complementary spectral data and single-crystal X-ray structure determination of **2b** (CCDC No. 1842765), **2e** (CCDC No. 1845701) and **3** (CCDC No. 1922296).[16]



Scheme 1. Effect of substitutions of α, β-phenyl rings of **1x**

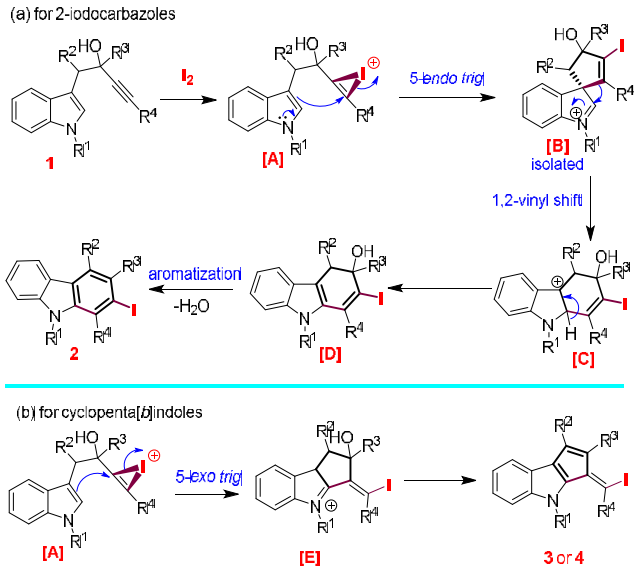
As depicted in Scheme 2, the formation of spirocyclic intermediate in this tandem iodo-cycloisomerisation process was tenable through isolation, complementary spectral data, and X-ray structure analysis of spiro-**1f**. The subjection of spiro-**1f** into the iodocyclization conditions fruitfully resulted in the corresponding 2-iodocarbazole **2f** probing the spirocyclization pathway. This helped us to propose a more accurate reaction mechanism (Scheme 4).



Scheme 2. Isolation of spirane intermediate

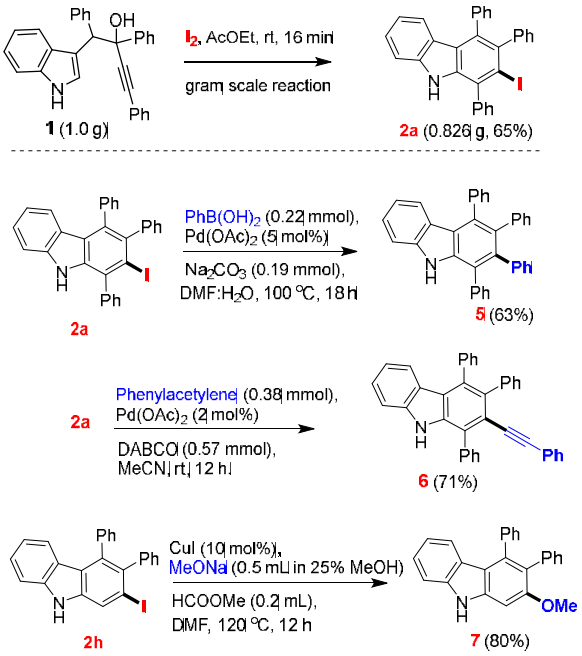
The overall study that we have conducted in this report and our previous work on a similar substrate[11h] indicate us that these reactions followed a different reaction mechanism to yield regioselective-iodo-carbazoles. In all the cases, the

basic structure of the reactant (1) is same, but (importantly) the substitution on R^2 in Scheme 3 is dictating the reaction path. When R^2 is 3-indolyl, or trimethoxyphenyl, the reaction underwent a 1,2-alkyl migration to yield 3-iodocarbazoles.[11h] In case of R^2 is phenyl group, it proceeded through the 1,2-vinyl migration to yield 2-iodocarbazoles (Table 2). When R^2 is 4-methoxy phenyl, a 5-exo trig cyclization was operated to furnish cyclopenta-fused indoles 3 and 4 (Scheme 1). Though the exact reason is not yet understood, we feel that the electronic effects of R^2 are playing a significant role in deciding the reaction path. To answer this question partly, we have performed a preliminary computational study which suggested that though the activation barrier for both migrations is quite high in magnitude 25.55 kcal/mol (1,2-alkyl migration) and 18.6 kcal/mol (1,2-vinyl migration), the final product of 1,2-vinyl is preferred minima in the potential energy surface (PES) by 9.97 kcal/mol (see the supporting information). However this needs further investigations to conclude the exact reason.



Scheme 3. Proposed reaction mechanism

Plausible reaction mechanism of formation of 2-iodocarbazoles (**2**) and cyclopenta[b]indoles (**3**-**4**) is depicted in Scheme 3. Initially, alkyne **1** is activated by the electrophilic iodine to form the cyclic iodonium intermediate [**A**], and a regioselective spirocyclization of [**A**] *via* 5-*endo* trig-cyclization yields the spirane [**B**]. Subsequent alkenyl migration affords [**C**] which upon dehydration and aromatization delivers the 2-iodocarbazoles (**2**). Even though the mechanism of dihydrocyclopenta[b]indole formation is not precise, it can be attributed to the direct annulation of indole C2 into the electrophilic cyclic iodonium intermediate [**A**] via a 5-exo trig passion to give intermediate [**E**], followed by dehydration to give **3** or **4**.



Scheme 4. Gram scale reaction and Synthetic transformations of 2-iodocarbazoles

After establishing a practicable new synthesis of 2-iodocarbazoles, the synthetic utility of these 2-iodocarbazoles has been demonstrated by transforming into various functionalized carbazole derivatives as described in Scheme 4. Pd-catalysed Suzuki coupling[17] of **2a** with $PhB(OH)_2$ resulted in the formation of 1,2,3,4-tetraphenyl carbazole (**5**) in 63% yield. Furthermore, Sonogashira coupling[18] of **2a** with phenylacetylene furnished the carbazole **6** in 71% yield. A copper-catalysed methoxy-substitution[19] of iodocarbazole **2h** was achieved to get compound **7** in 80% yield.

Conclusion

In summary, we have developed the first report of an operationally simple, iodine mediated cycloisomerization of (indole-arylyl)methane tethered propargyl alcohols to the multi-substituted 2-iodocarbazoles. This benzannulation protocol involved in a regioselective 5-*endo*-spirocyclization followed by a selective 1,2-alkenyl migration and aromatization cascade. The structure of the compounds was unambiguously confirmed with the help of single crystal X-ray data. Further, the proposed spirane intermediate was isolated and confirmed, thus affirmed the exact mechanism. This protocol offers direct access to the 2-iodocarbazoles, with a broad scope and good yields at rt in open-flask conditions. The cross-coupling reactions of these products were performed to show their synthetic viability.

Experimental Section

General Considerations

Unless otherwise indicated chemicals & solvents were purchased in high purity grade from commercial suppliers and used without further purification. Thin layer chromatography (TLC) carried out on Merck silica plates ($60F_{254}$). ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Bruker Ultra shield 500 MHz 400 MHz spectrometer and all chemical shift values refer to $CDCl_3$ (δ_H = 7.26 and δ_C = 77.16 ppm). Single crystal X-ray diffraction data were collected in Bruker D8-Quest, Rigaku Oxford and Bruker Apex-3 diffractometers. The HRMS analysis was obtained by Bruker-Maxis (ESI-TOF) mass spectrometer. Melting points were measured with a MEPA LABINDIA melting point apparatus. Column chromatographic purifications were performed on silica gel.

General Procedure for the synthesis of indole tethered propargyl alcohols (1):[13]

To a solution of phenylacetylene (0.09 g, 0.9 mmol) at 0 ºC in THF (3 mL), was added *n*-BuLi (0.479 mL of a 2 M solution in cyclohexane, 0.9 mmol). The solution was stirred at 0 ºC for 20 min, then 2-(1H-indol-3-yl)-1,2-diphenylethan-1-one (0.1 g, 0.32 mmol) in THF (1 mL) was added (2 mmol, 1.0 equiv.) at -45ºC. The resulting mixture was stirred at room temperature until the starting ketone was consumed as determined by TLC. The reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with AcOEt (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. The residue was purified by flash chromatography on silica gel using mixtures of hexane and AcOEt as eluents to obtain the 1-(1H-indol-3-yl)-1,2,4-triphenylbut-3-yn-2-ol (**1a**) in 98% (128 mg) yield.

General Procedure for Synthesis of 2-iodocarbazole (2):

Molecular iodine (95 mg, 0.37 mmol) was added to a stirred solution of 1-(1H-indol-3-yl)-1,2,4-triphenylbut-3-yn-2-ol (**1a**) (130 mg, 0.31 mmol) in AcOEt (3 mL). The resulting mixture was stirred at room temperature until **1a** was consumed as determined by TLC. The reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$ and extracted with AcOEt (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The residue was purified by flash chromatography on deactivated silica gel (60-120 mesh) using mixtures of hexane and EtOAc as eluents to obtain the corresponding products 2-iodo-1,3,4-triphenyl-9H-carbazole (**2a**) in 65% (110 mg) yield.

General Procedure for 1,2,3,4-tetraphenyl-9H-carbazole (5):[20]

$PhB(OH)_2$ (20 mg, 0.16 mmol) was added to a solution of 2-iodo-1,3,4-triphenyl-9H-carbazole (**2a**) (50 mg, 0.10 mmol) in DMF/H_2O (2:1; 3.0 mL) that contained Na_2CO_3 (11 mg,0.10 mmol), and the resulting mixture was stirred at room temperature for 5 min. $Pd(OAc)_2$ (5 mol%) was then added, and the flask was flushed with N_2 and sealed. The mixture was stirred at 100 °C for 4 h and then filtered. The filter cake was washed with diethyl ether, and the combined filtrates were extracted with diethyl ether. The combined organic layers were washed with water and brine and then dried with anhydrous Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure, and the crude residue was purified by column chromatography on silica gel to isolate pure product in 63% (56 mg) yield.

General Procedure for 1,3,4-triphenyl-2-(phenylethynyl)-9H-carbazole (6):

First $Pd(OAc)_2$ (2 mol%) was dissolved in MeCN (1mL). Then, the indicated amount of $Pd(OAc)_2$ acetonitrile solution was added to a mixture of alkyne (21 mg, 0.20 mmol) and 2-iodo-1,3,4-triphenyl-9H-carbazole (**2a**) (50 mg, 0.10 mmol), DABCO (35 mg, 0.30 mmol), and MeCN (4 mL). Then mixture was stirred under N_2 at room temperature for 12 h.The resulting mixture was filtered off, washed and extracted with diethyl ether. The combined organics were washed with water and then with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography with silica gel to give of product in 71% (33 mg) yield.

General Procedure for 2-methoxy-3,4-diphenyl-9H-carbazole (7):

-iodo-3,4-diphenyl-9H-carbazole (**1g**) (50 mg, 0.11 mmol), was added to solution of CuI (10 mol%) in DMF (2 mL) after 10 min MeONa solution (0.5 mL) of 25% MeONa in MeOH and HCO_2Me (0.2 mL) was added. The mixture was stirred at 120 °C for 12 h. The reaction was quenched with a saturated NH_4Cl aqueous solution and extracted with AcOEt (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. The residue was purified by flash chromatography on deactivated silica gel using mixtures of hexane and AcOEt as eluents to obtain the pure product in 80% (31 mg) yield.

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[14] Most of the cases, starting material, showed full conversion. However, the yields are not too high; this might be attributed to the possible decomposition.

[15] **2x** and **3** were isolated as a mixture, and the attempts were failed to separate them. The ration was determined by ^{1}H NMR data of the crude product.

[16] See supporting information for the possible route of formation, and copies of spectra and single crystal X-ray data.

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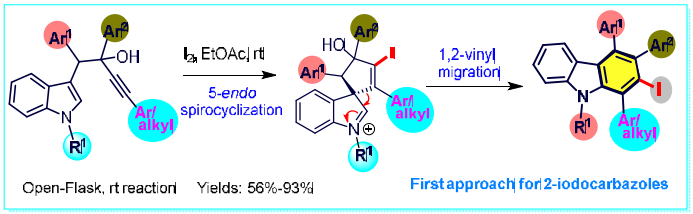

Benzannulation via iodocyclization and 1,2-vinyl migration*

Srinivasarao Yaragorla* Ravikrishna Dada and Debojyoti Bag

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An Expediuos Benzannulation reaction of Indol-3-yl-but-3-yn 2-ols to substituted 2-Iodocarbazoles via Domino 5-*endo* spirocyclization/selective vinyl shift and aromatization

First approach of 2-iodocarbazoles from benzannulation of indole-tethered propargyl alcohols is developed at room temperature in open-flask reaction using iodine.