Synthesis of 3-Allenylindoles and 3-Dienylindoles by Brønsted Acid Catalyzed Allenylation of 2-Arylindoles with Tertiary Propargylic Alcohols

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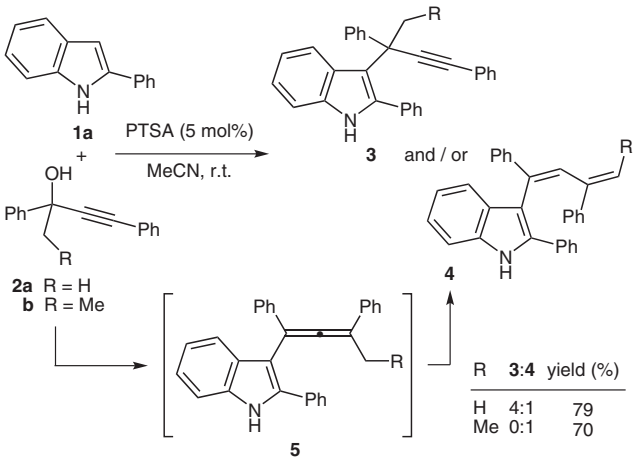
Abstract: The Brønsted acid catalyzed direct nucleophilic substitution of tertiary propargylic alcohols with 2-aryl-substituted indoles has been studied. A competitive allenylation process takes place with appropriate substituents on the alkynol moiety. Starting from 2-arylindoles, new 3-allenyl and 3-dienylindole derivatives have been easily synthesized.

Key words: catalysis, indoles, allenes, dienes, nucleophilic substitution

Indoles are building blocks of many natural products and have applications as biologically active compounds and in material science.[1] Thus, the selective functionalization of indoles has attracted considerable attention,[2] and several successful approaches for the synthesis of 3-substituted indoles have been developed based on the nucleophilic nature of the indole nucleus.[3] However, few methods are available for the introduction of quaternary carbons at the C3-position of indoles.[4] Moreover, no methods are known for the direct synthesis of C3-allenyl or C3-dienyl indole derivatives from nonfunctionalized starting indole compounds.[5] Whereas the C3-alkylation of indolyl derivatives through Friedel–Crafts processes usually requires the use of strong electrophilic reagents,[6] recently, alcohols have been reported as useful electrophiles under transition-metal[7] as well as Lewis acid catalysis.[8] The easy availability of alcohols and the fact that water would be the only byproduct of the substitution reactions make the direct catalytic nucleophilic substitution of indoles with alcohols a powerful reaction. The metal-free version of this process by using Brønsted acids as catalysts is much more appealing than the use of transition metals or typical Lewis acids.[9]

Following our interest in Brønsted acid catalyzed nucleophilic substitution reactions,[10] we have recently reported the C3-selective propargylation and benzylation of indoles with tertiary alcohols catalyzed by *p*-toluenesulfonic acid (PTSA).[11] Taking into account that in this initial study we did not evaluate the behaviour of 2-substituted indoles and due to the high synthetically usefulness of the resulting C3-alkylated indoles for subsequent transformations,[12] we further studied this type of process by using 2-arylindoles as the nucleophilic partner. Thus, in this paper we wish to report a new synthesis of 3-allenyl-2-aryl- and 2-aryl-3-dienyl-indoles from tertiary propargylic alcohols under Brønsted acid catalysis.

When we investigated the reaction of commercially available 2-phenylindole **1a** with model tertiary propargylic alcohol **2a** under our reported standard conditions,[11] that is, PTSA catalysis using acetonitrile as solvent at room temperature, the expected C3-propargylated indole **3aa** (R = H) was obtained along with a minor isomeric compound which was identified as the C3-dienyl derivative **4aa** (R = H, Scheme 1). Whereas the formation of indole **3aa** is explained through a Brønsted acid catalyzed direct nucleophilic substitution reaction,[11] the generation of the indole **4aa** could be understood by a competitive allenylation reaction leading to the allene derivative **5aa** (R = H), which undergoes further isomerization under the acidic conditions to the observed dienyl indole **4aa** (Scheme 1).



Scheme 1 Competitive propargylation/allenylation of 2-phenylindole **1a** with tertiary alkynols **2a**,**b**

At this point, we suspected that the steric hindrance of the substituents at the propargylic position of the starting alkynol could play a vital role in the regioselectivity of the alkylation reaction of 2-phenylindole derivatives.[13] To check this possibility we studied the reaction of **1a** with tertiary alkynol **2b** bearing a bulkier substituent at the propargylic position. This reaction led exclusively to the isolation of the C3-dienyl indole **4ab** (R = Me) as a single geometrical isomer (Scheme 1).[14]

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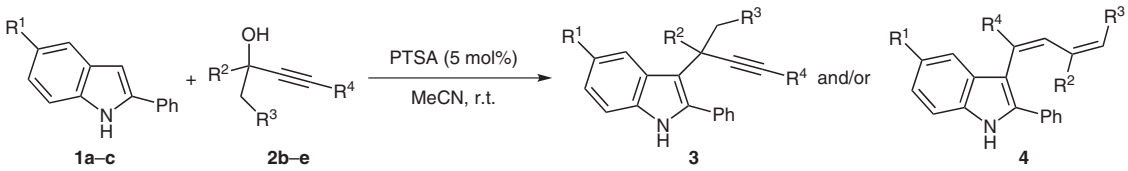
Table 1 PTSA-Catalyzed Reactions of 2-Phenylindoles **1a–c** with Alkynols **2b–e**



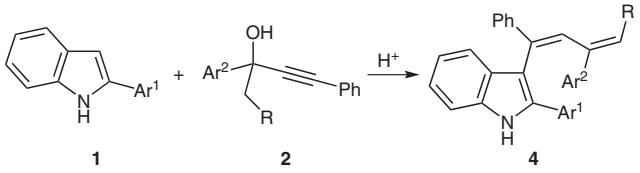
Entry	Indole	R^1	Alkynol	R^2	R^3	R^4	Product	Yield (%)[a]
1	**1a**	H	**2b**	Ph	Me	Ph	**4ab**	70
2	**1b**	Cl	**2b**	Ph	Me	Ph	**4bb**	67
3	**1c**	OMe	**2b**	Ph	Me	Ph	**4cb**	69
4	**1a**	H	**2c**	Ph	Et	*n*-Bu	**3ac** + **4ac**[b]	54[c]
5	**1a**	H	**2d**	*c*-C_3H_5	Me	Ph	**3ad**	68
6	**1a**	H	**2e**[d]	Ph	–	Ph	**3ae**	59

[a] Isolated yield after column chromatography.
[b] A 4:1 ratio of isomers was determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Yield of the isolated major isomer **3ac**.
[d] 1,3-Diphenylpropyn-2-ol.

In order to further understand the factors controlling the outcome of the process, we studied the reaction of different 2-phenylindole derivatives **1a–c**[15] with tertiary alkynols **2b–d** bearing bulky substituents at the propargylic position ($R^3 \neq H$, Table 1). First, when alkynol **2b** was tested against different indoles **1a–c**, without substituents or containing electron-withdrawing or electron-donating groups at the benzenoid moiety, the corresponding dienylindole derivatives **4** were exclusively obtained (Table 1, entries 1–3). The effect of the substituent at the terminal position of the starting alkynol (R^4) was also studied. Thus, the reaction of propargylic alcohol **2c**, bearing an alkyl group at this position, with indole **1a** mainly afforded the corresponding C3-propargylated derivative **3ac** (Table 1, entry 4). In addition, treatment of 2-phenylindole **1a** with a dialkyl-substituted tertiary alkynol such as **2d**, or with a secondary propargylic alcohol like **2e**, gave rise exclusively to the corresponding C3-propargylated indoles **3** (Table 1, entries 5 and 6).

This study allowed us to determine that formation of indoles **3** or **4** from 2-phenylindole derivatives seems to depend on the substituents present both at the propargylic and the terminal position of the triple bond in the starting alkynol. A delicate balance between the stability of the final products, the electrophilicities of the intermediate carbocations, the nucleophilicities of the different indoles,[3] and steric factors probably account for the observed regioselectivities. In any case, it seems that only tertiary propargylic alcohols such as **2b**, with aryl substituents at both the propargylic and the terminal positions (R^2 and R^4), as well as with a bulky substituent at the other propargylic position ($R^3 \neq H$), are appropriate starting materials to get the C3-dienylindole derivatives **4**.[16] However, it should be taken into account that these compounds **4** are not easily available by other strategies. So, in order to test the scope of our method, we decided to carry out a set of experiments by using different 2-arylindoles **1a**,**d–g**[15] and several phenyl-substituted tertiary benzylic alkynols **2b**,**f–j** under the standard conditions (Table 2).

Table 2 Synthesis of C3-Dienylindole Derivatives **4**[a]

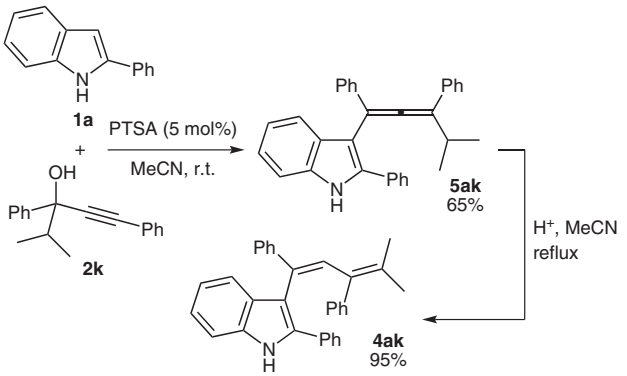


Entry	**1**	Ar^1	**2**	Ar^2	R	Product	Yield (%)[b]
1	**1d**	4-FC_6H_4	**2b**	Ph	Me	**4db**	70
2	**1e**	4-$MeOC_6H_4$	**2b**	Ph	Me	**4eb**	60
3	**1f**	2-$MeOC_6H_4$	**2b**	Ph	Me	**4fb**	65
4	**1g**	2-Th[c]	**2b**	Ph	Me	**4gb**	61
5	**1a**	Ph	**2f**	Ph	Et	**4af**	66
6	**1a**	Ph	**2g**	4-ClC_6H_4	Me	**4ag**	73
7	**1d**	4-FC_6H_4	**2g**	4-ClC_6H_4	Me	**4dg**	72
8	**1e**	4-$MeOC_6H_4$	**2g**	4-ClC_6H_4	Me	**4eg**	60
9	**1a**	Ph	**2h**	4-ClC_6H_4	Et	**4ah**	67
10	**1a**	Ph	**2i**	2-Th[c]	Me	**4ai**	54
11	**1a**	Ph	**2j**	2-Th[c]	Et	**4aj**	58

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.52 mmol), PTSA (0.025 mmol) in MeCN (2 mL) at r.t.
[b] Isolated yield after column chromatography.
[c] 2-Thienyl.

As shown in Table 2 the process seems to be general with respect to the aryl substituent at the C-2 of the indole moiety (Ar^1) as electron-withdrawing, electron-donating, and heteroaromatic groups are well tolerated. Regarding the substitution of the tertiary alkynol we found that substituted aryl or heteroaromatic groups could be present at one of the propargylic positions (Ar^2) whereas different alkyl groups could be located at the other propargylic position (CH_2R in Table 2).

Further evidence for the proposed mechanism outlined in Scheme 1 for the formation of C3-dienylindoles **4** was found when we studied the behaviour of 2-phenylindole **1a** with tertiary alkynol **2k**, bearing an isopropyl group at the propargylic position. Under standard Brønsted acid catalysis a mixture of the expected dienylindole **4ak** and the C3-allenylindole **5ak** was obtained after silica gel column chromatography. Gratifyingly, by carrying out the purification on alumina instead of silica we were able to selectively isolate the allene derivative **5ak** in 65% yield (Scheme 2). Moreover, refluxing **5ak** in acetonitrile with a catalytic amount of PTSA (5 mol%) for ca. 5 hours, allowed us to obtain the corresponding diene **4ak** in almost quantitative yield after a simple filtration through a pad of alumina (Scheme 2). These results support the competitive allenylation reaction for tertiary alkynols bearing bulky substituents at the propargylic position. The isomerization of allenes **5** to dienes **4** seems to be slowed down when the substituent at the propargylic position is branched instead of linear.



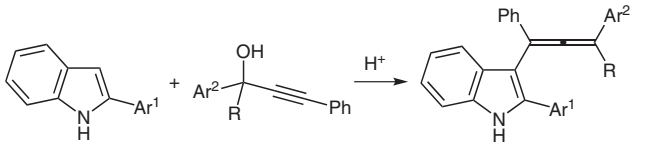
Scheme 2 Reaction of 2-phenylindole **1a** with alkynol **2k** and isolation of C3-allenylindole **5ak**

Due to the potential interest of C3-allenylindoles and to the fact that to the best of our knowledge a direct route to these compounds has not been described, we synthesized a variety of allene derivates **5** by the PTSA-catalyzed reaction of 2-arylindoles **1** with tertiary alkynols **2k–p** (Table 3). Again, different 2-arylindoles **1d–g** were initially tested with isopropyl-substituted alkynol **2k** and the corresponding allenylindoles **5** were isolated in good yields (Table 3, entries 1–3). Moreover, other alkynols **2l–p** bearing groups at the propargylic position such as cyclopropyl (Table 3, entries 4–7), cyclobutyl (Table 3, entry 8), cyclopentyl (Table 3, entries 9, 12, and 13), and cyclohexyl (Table 3, entries 10, 11, and 14) behave in the same way as **2k** leading to new and interesting C3-allenylindoles **5** in good yields. In most cases, the corresponding indole derivative **5** is easily isolated by simple filtration as it precipitates from the reaction medium. In some cases, variable small amounts of the corresponding dienes **4** remain in solution. In those cases where any of the starting compounds are not soluble in the reaction media, a larger amount (20 mol%) of PTSA had to be added in order to complete the reaction.

We have also examined the acid-catalyzed isomerization of allene derivatives **5** to the corresponding dienes **4** (see Scheme 2) with allenylindoles **5dk** and **5ek**. In these cases dienylindoles **4dk** and **4ek** could be isolated in almost quantitative yield by refluxing an acetonitrile solution of the corresponding allenyl derivative **5** in the presence of PTSA (5 mol%).

In summary, the C3-selective functionalization of 2-arylindoles by reaction with tertiary propargylic alcohols under Brønsted acid catalysis is reported. A new and straightforward synthesis of interesting 3-allenyl and

Table 3 Synthesis of C3-Allenylindole Derivatives **5**[a]



Entry	1	Ar^1	2	Ar^2	R	Prod.	Yield (%)[b]
1	**1d**	4-FC_6H_4	**2k**	Ph	*i*-Pr	**5dk**	67
2	**1e**	4-$MeOC_6H_4$	**2k**	Ph	*i*-Pr	**5ek**	82[c]
3	**1g**	2-Th[d]	**2k**	Ph	*i*-Pr	**5gk**	70[e]
4	**1a**	Ph	**2l**	Ph	*c*-C_3H_5	**5al**	55[f]
5	**1a**	Ph	**2m**	4-$MeOC_6H_4$	*c*-C_3H_5	**5am**	75[c]
6	**1e**	4-$MeOC_6H_4$	**2l**	Ph	*c*-C_3H_5	**5el**	80[c]
7	**1e**	4-$MeOC_6H_4$	**2m**	4-$MeOC_6H_4$	*c*-C_3H_5	**5em**	75[c]
8	**1a**	Ph	**2n**	Ph	*c*-C_4H_7	**5an**	69
9	**1a**	Ph	**2o**	Ph	*c*-C_5H_9	**5ao**	70
10	**1a**	Ph	**2p**	Ph	*c*-C_6H_{11}	**5ap**	81
11	**1d**	4-FC_6H_4	**2p**	Ph	*c*-C_6H_{11}	**5dp**	82
12	**1e**	4-$MeOC_6H_4$	**2o**	Ph	*c*-C_5H_9	**5eo**	65[c]
13	**1g**	2-Th[d]	**2o**	Ph	*c*-C_5H_9	**5go**	68
14	**1g**	2-Th[d]	**2p**	Ph	*c*-C_6H_{11}	**5gp**	75

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.52 mmol), PTSA (0.025 mmol) in MeCN (2 mL) at r.t.
[b] Isolated yield after column chromatography.
[c] The amount of 20 mol% of PTSA was used.
[d] 2-Thienyl.
[e] Ca. 10% of the propargylated derivative **3gk** was also formed.
[f] Ca. 20% of the propargylated derivative **3al** was also isolated.

3-dienylindoles has been developed through an environmentally friendly process with water as the only side product of the reaction.

General Procedure for the Synthesis of 3-Dienylindole Derivatives 4

Synthesis of 3-[(1*Z*,3*E*)-1,3-Diphenylpenta-1,3-dienyl]-2-phenyl-1*H*-indole (4ab)

To a mixture of alkynol **2b** (123 mg, 0.52 mmol) and 2-phenylindole (**1a**; 97 mg, 0.5 mmol) in analytical grade MeCN (2 mL) PTSA (4.8 mg, 0.025 mmol) was added. The reaction was stirred at r.t. for 0.5 h (the completion of the reaction was monitored by GC-MS and TLC). The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane–Et_2O, 7:1) to afford **4ab** (144 mg, 70%) as a white solid; mp 136–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (d, *J* = 7.1 Hz, 3 H), 5.41 (qd, *J* = 7.1, 1.0 Hz, 1 H), 6.64–6.72 (m, 3 H), 6.76–6.82 (m, 2 H), 6.88–6.94 (m, 1 H), 6.99 (d, *J* = 7.4 Hz, 1 H), 7.03–7.10 (m, 2 H), 7.11 (s, 1 H), 7.22–7.31 (m, 2 H), 7.31–7.37 (m, 4 H), 7.41–7.46 (m, 2 H), 7.60–7.66 (m, 2 H), 7.76 (s, 1 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.1 (CH_3), 110.3 (CH), 113.0 (C), 119.5 (CH), 120.8 (CH), 122.0 (CH), 125.3 (CH), 126.1 (2 × CH), 126.6 (2 × CH), 127.0 (2 × CH), 127.3 (CH), 127.4 (2 × CH), 127.5 (CH), 127.6 (CH), 128.0 (CH), 128.3 (2 × CH), 128.5 (2 × CH), 128.9 (C), 132.8 (C), 135.8 (C), 136.4 (C), 137.1 (C), 139.7 (C), 141.7 (C), 142.5 (C) ppm. LRMS (EI): *m/z* = 411 (25) [M$^+$], 382 (100), 304 (38). HRMS (EI): *m/z* calcd for $C_{31}H_{25}N$: 411.1987; found: 411.1995.

General Procedure for the Synthesis of 3-Allenylindole Derivatives 5

Synthesis of 3-(1,3-Diphenyl-4-methylpenta-1,2-dienyl)-2-(4-methoxy)-phenyl-1*H*-indole (5ek)

To a mixture of alkynol **2k** (130 mg, 0.52 mmol) and 2-(4-methoxyphenyl)indole (**1e**; 112 mg, 0.5 mmol) in analytical grade MeCN (2 mL) PTSA (19 mg, 0.1 mmol) was added. The reaction was stirred at r.t. for 1 h (the completion of the reaction was monitored by GC-MS and TLC) whereas a solid precipitated, which was filtrated to afford **5ek** (187 mg, 82%) as a whitish solid; mp 141–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.5 Hz, 3 H), 1.19 (d, *J* = 6.5 Hz, 3 H), 2.78–2.92 (m, 1 H), 3.74 (s, 3 H), 6.64 (d, *J* = 8.6 Hz, 2 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 7.08–7.28 (m, 9 H), 7.32–7.49 (m, 6 H), 8.15 (br s, 1 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 22.3 (CH_3), 22.5 (CH_3), 29.6 (CH), 55.4 (CH_3), 105.0 (C), 108.3 (C), 110.8 (CH), 114.2 (2 × CH), 115.4 (C), 120.17 (CH), 120.22 (CH), 122.2 (CH), 125.2 (C), 126.6 (2 × CH), 126.7 (CH), 126.8 (CH), 127.2 (2 × CH), 128.3 (2 × CH), 128.6 (2 × CH), 129.1 (2 × CH), 129.9 (C), 135.5 (C), 135.9 (C), 136.6 (C), 137.4 (C), 159.3 (C), 206.4 (C) ppm. LRMS (EI): *m/z* = 455 (30) [M$^+$], 412 (100), 378 (56), 291 (59), 223 (64), 115 (51), 91 (82), 77 (56). HRMS (EI): *m/z* calcd for $C_{33}H_{29}N$: 455.2249; found: 455.2262.

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(13) We have observed that the presence of an alkyl substituent at the C-2 of the indole nucleus does not give rise to significant competitive allenylation processes.

(14) The 1*Z*,3*E*-isomer was mainly formed. Variable amounts of the 1*Z*,3*Z*-isomer were detected in the crude product. After column chromatography we usually isolated the major isomer slightly contaminated with the minor one, probably due to further isomerization under the purification conditions. The stereochemistry was assessed by NOESY experiments on **4cb**, and the rest of the compounds were assigned by inference. Moreover, the structure of **4af** was confirmed by single-crystal X-ray diffraction analysis

(CCDC 729740 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif).

(15) (a) Indoles **1b**,**d**–**g** were prepared by standard Fisher indole synthesis, see: Fusco, R.; Sannicolo, F. *J. Org. Chem.* **1981**, *46*, 83. (b) On the other hand, indole **1c** was obtained by a modified Madelung synthesis, see: Houlihan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511.

(16) We have checked that the presence of alkyl or aryl groups at the nitrogen atom of the starting 2-phenylindole derivative mainly gives rise to propargylated products regardless the substituents of the alkynol.