Brønsted Acid Catalyzed C3-Selective Propargylation and Benzylation of Indoles with Tertiary Alcohols

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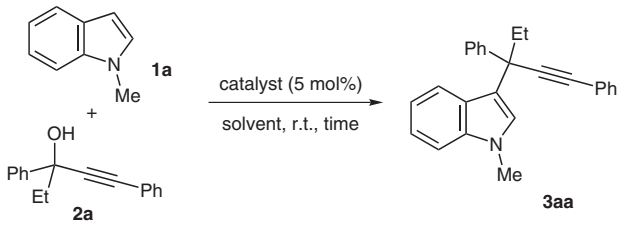
Abstract: A Brønsted acid catalyzed C3-selective *tert*-alkylation of indoles using tertiary propargylic and benzylic alcohols has been developed. New C3-propargylated indole derivatives with a quaternary carbon at the propargylic position have been efficiently synthesized. Reactions were performed in air with undried solvents, and water was the only side product of the process.

Key words: catalysis, indoles, alcohols, nucleophiles, alkylations

Facile access to substituted indoles is of general interest because they are found as building blocks in many natural products and because they have very important applications.[1] Due to the nucleophilic nature of indolyl compounds,[2] there are different ways to perform their alkylation.[3] Among them, 1,2-addition to carbonyl derivatives,[4] Michael-type reactions,[5] ring opening of epoxides and aziridines,[6] and the Pd-catalyzed allylic substitution (Tsuji–Trost reaction)[7] represent some of the most useful approaches. Also, it should be noted that few methods for the introduction of quaternary carbons at the C3-position of indoles have been reported.[8] From the synthetic point of view, the direct catalytic substitution of indoles with alcohols is an attractive reaction due to the easy availability of alcohols and due to the fact that water is the only by-product of the process. Thus recently, some transition-metal-[9] and Lewis acid catalyzed[10] methodologies for the direct substitution reaction of alcohols with indoles have been reported. However, the use of expensive, toxic and/or moisture-sensitive reagents in most of these methods limits their practical utility in large-scale synthesis. Much more appealing is the use of Brønsted acids as catalysts to perform this process.[11] In this context, the development of new methods for the alkylation of indoles with propargylic alcohols would be very interesting.[12] It should be noted that the synthesis of C3-propargylated indoles with a quaternary carbon at the propargylic position has not been reported. Moreover, no general method for the benzylation of indoles with tertiary benzylic alcohols is known.[13] Taking advantage of our experience in Brønsted acid catalysis for the nucleophilic substitution of alcohols,[14] we decided to check the possibility of performing these new reactions. Thus, in this paper we wish to report the successful alkylation of indoles at C3-position with tertiary propargylic and benzylic alcohols under Brønsted acid catalysis.

First, we investigated the model reaction of *N*-methylindole (**1a**) with tertiary alkynol **2a** using some Brønsted and Lewis acids as catalysts. Alkynol **2a** was chosen because it is an ideal substrate to test the nucleophilic substitution reaction versus the competitive elimination reaction (which gives the corresponding enyne derivative). As shown in Table 1, the use of Brønsted acids such as triflic acid (TfOH), 2,4-dinitrobenzenesulfonic acid (DNBSA), or *p*-toluenesulfonic acid (PTSA) as catalysts in MeCN at room temperature gave rise to the desired alkylated indole derivative **3aa** in good yields (entries 1–3). Several Lewis acids also catalyzed the process (entries 4–6), but the substitution reactions were significantly slower and/or less efficient. Finally, the substitution reaction did not take place in the absence of catalyst (entry 7). As expected, in the absence of the indole counterpart, and by using any of the catalysts, we observed the exclusive

Table 1 Evaluation of Brønsted or Lewis Acid Catalysts and Conditions for the Nucleophilic Substitution Reaction of **2a** with **1a**[a]



Entry	Catalyst	Solvent	Time (h)[b]	Yield (%)[c]
1	TfOH	MeCN	2	75
2	DNBSA	MeCN	3	68
3	PTSA	MeCN	2	78
4	$FeCl_3$	$MeNO_2$	24	64
5	$InBr_3$	$Cl(CH_2)_2Cl$[d]	15	70
6	I_2	MeCN	14	68
7	none	MeCN	24	0

[a] All reactions were carried out with **2a** (1.2 equiv).
[b] Time needed for complete consumption of **1a** determined by GC–MS analysis.
[c] Isolated yield of **3aa** after column chromatography.
[d] The reaction was carried out at reflux under an N_2 atmosphere.

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formation of the enyne derivative coming from an elimination process in **2a**.

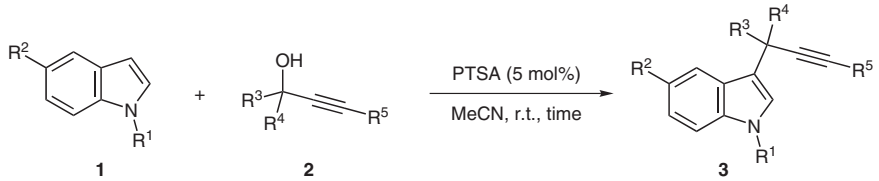
Due to the availability and easiness of handling, PTSA was selected as catalyst in the following experiments. Thus, we explored the generality of the reaction by using different indole derivatives **1a–e** and tertiary alkynols **2a–k**[15] under the best reaction conditions previously established, i.e. PTSA as catalyst and MeCN as solvent at room temperature (Table 2).

As shown in Table 2, several indoles, including those with electron-withdrawing substituents at the benzenoid moiety as well as N-unsubstituted ones, were successfully coupled. As for the alkynol counterpart, internal alkynes with either an aromatic or heteroaromatic group at the propargylic position (R^3 group),[17] or with an aromatic or alkyl group at the terminal position (R^5 group), gave good results allowing the synthesis of C3-propargylated indoles in generally high yields (Table 2). All the reactions were followed and analyzed by GC–MS and we did not observe, in the crude of the reactions, the presence of any by-product in a significant amount. So, in the cases where the yield of the isolated product was moderate, we suspect that this was due to the decomposition of the final indole derivative **3** under the reaction or purification conditions.

We were also interested in studying the reactivity of tertiary vinyl-substituted alkynols **4**.[18] Thus, their reaction with **1a**, under PTSA catalysis, regioselectively gave the corresponding C3-alkylated indole derivatives **5** in high yields (Scheme 1).[19] A S_N2'-type attack of the indole, probably favored by the conjugation of the phenyl group with the enyne moiety, accounts for the formation of these compounds.

Having successfully developed an efficient C3-propargylation of indoles with tertiary propargylic alcohols, we finally checked the possibility of applying this methodology to the synthesis of C3-benzylated indoles

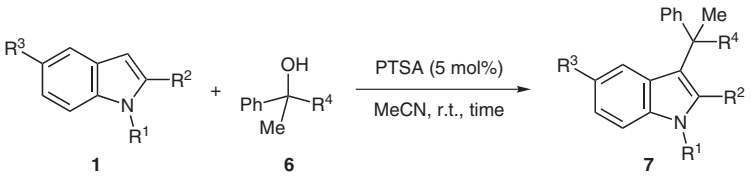
Table 2 Propargylation Reactions of Indoles **1** with Tertiary Alkynols **2**[a,16]



Entry	Indole	R^1	R^2	Alkynol	R^3	R^4	R^5	Product	Time (h)	Yield (%)[b]
1	**1a**	Me	H	**2a**	Ph	Et	Ph	**3aa**	2	78
2	**1a**	Me	H	**2b**	Ph	Me	Ph	**3ab**	2	81
3	**1a**	Me	H	**2c**	Ph	*n*-Pr	Ph	**3ac**	2	60
4	**1a**	Me	H	**2d**	Ph	*i*-Pr	Ph	**3ad**	0.5	80
5	**1a**	Me	H	**2e**	4-ClC_6H_4	Me	Ph	**3ae**	8	72
6	**1a**	Me	H	**2f**	2-Th[c]	Me	Ph	**3af**	1	85
7	**1a**	Me	H	**2g**	4-ClC_6H_4	Me	*n*-Bu	**3ag**	2	57
8	**1a**	Me	H	**2h**	Ph	*n*-Pr	*n*-Bu	**3ah**	1	80
9	**1a**	Me	H	**2i**	Ph	*i*-Pr	*n*-Bu	**3ai**	3	81
10	**1b**	H	H	**2b**	Ph	Me	Ph	**3bb**	2	70
11	**1b**	H	H	**2c**	Ph	*n*-Pr	Ph	**3bc**	6	64
12	**1b**	H	H	**2f**	2-Th[c]	Me	Ph	**3bf**	2.5	83
13	**1b**	H	H	**2g**	4-ClC_6H_4	Me	*n*-Bu	**3bg**	5	46
14	**1c**	H	NO_2	**2b**	Ph	Me	Ph	**3cb**	1	74
15	**1c**	H	NO_2	**2h**	Ph	*n*-Pr	*n*-Bu	**3ch**	1	58
16	**1d**	H	CO_2Me	**2b**	Ph	Me	Ph	**3db**	1	81
17	**1d**	H	CO_2Me	**2j**	Ph	Et	*n*-Bu	**3dj**	3	54
18	**1e**	H	Br	**2k**	Ph	Me	*n*-Bu	**3ek**	2	52

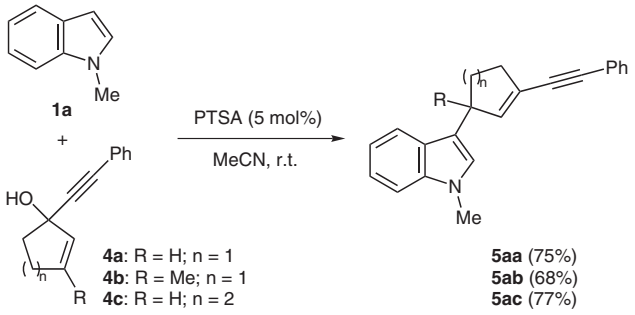
[a] Reaction conditions: **1** (2 mmol), **2** (2.4 mmol), PTSA (0.1 mmol) in MeCN (2 mL) at r.t.
[b] Isolated yield after column chromatography.
[c] 2-Thienyl.

Table 3 Benzylation Reactions of Indoles **1** with Tertiary Benzylic Alcohols **6**[a]



Entry	Indole	R^1	R^2	R^3	Alcohol	R^4	Product	Time (h)	Yield (%)[b]
1	**1a**	Me	H	H	**6a**	Me	**7aa**	36	77
2	**1a**	Me	H	H	**6b**	*n*-Bu	**7ab**	20	62
3	**1a**	Me	H	H	**6c**	Ph	**7ac**	6	83
4	**1d**	H	H	CO_2Me	**6b**	*n*-Bu	**7db**	25	60
5	**1d**	H	H	CO_2Me	**6c**	Ph	**7dc**	6[c]	71
6	**1f**	H	Me	H	**6c**	Ph	**7fc**	24	89
7	**1g**	H	Ph	H	**6a**	Me	**7ga**	2	80
8	**1g**	H	Ph	H	**6b**	*n*-Bu	**7gb**	2	72

[a] Reaction conditions: **1** (2 mmol), **6** (2.4 mmol), PTSA (0.1 mmol) in MeCN (2 mL) at r.t.
[b] Isolated yield after column chromatography.
[c] The reaction was carried out at 50 ºC.



Scheme 1 Reaction of indole **1a** with 1-propargylated 2-cycloalken-1-ols **4**

with a quaternary carbon at the benzylic position. So, the reaction of several indoles **1** with tertiary benzylic alcohols **6**,[20] under PTSA catalysis, afforded the corresponding indole derivatives **7** in high yields (Table 3). As shown in Table 3, indoles **1** with substituents at different positions were appropriate nucleophiles. Furthermore, differently substituted tertiary benzylic alcohols **6** could be coupled without any problems.

In summary, we have shown that a simple Brønsted acid, such as PTSA, is an efficient catalyst for the direct nucleophilic substitution of tertiary propargylic and benzylic alcohols with indoles. This method allows the preparation of new C3-propargylated indole derivatives with a quaternary center at the propargylic position. Although tertiary alcohols were used, the competitive elimination reaction was avoided under the optimized reaction conditions. The availability of the reagents used, the mild conditions and the fact that only water was generated as a side product, make this method an attractive and environmentally friendly process for the synthesis of C3-substituted indoles.

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(12) (a) While preparing this manuscript some works about this reaction using different Lewis acids as catalysts appeared (see ref. 10b–e). We have also reported a single example about the Brønsted acid catalyzed alkylation of indoles with propargylic alcohols: Sanz, R.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Eur. J. Org. Chem.* **2006**, 1383. (b) Remarkably, in all these reactions only secondary propargylic alcohols are used.

(13) The absence of examples where tertiary alcohols are used is probably due to their high tendency to undergo elimination processes under the acidic conditions. Only the alkylation of *N*-methylindole with 2-phenylpropan-2-ol has been reported. See ref. 10c and 11a.

(14) See ref. 12 and also: (a) Sanz, R.; Martínez, A.; Miguel, D.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Adv. Synth. Catal.* **2006**, *348*, 1841. (b) Sanz, R.; Miguel, D.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Org. Lett.* **2007**, *9*, 727. (c) Sanz, R.; Miguel, D.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Org. Lett.* **2007**, *9*, 2027. (d) Sanz, R.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Synthesis* **2007**, 3252. (e) Sanz, R.; Martínez, A.; Guilarte, V.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Eur. J. Org. Chem.* **2007**, 4642.

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(16) **Typical Procedure for the Synthesis of 3-Alkylated Indole Derivatives 3, 5, and 7; Synthesis of 3-(1,3-Diphenylpent-1-yn-3-yl)-1-methyl-1*H*-indole (3aa; Table 2, Entry 1)**: To a mixture of alcohol **2a** (0.567 g, 2.4 mmol) and *N*-methylindole (**1a**; 0.262 g, 2.0 mmol) in analytical grade MeCN (2 mL), PTSA (0.019 g, 0.1 mmol) was added. The reaction was stirred at r.t. for 2 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, 10:1) to afford **3aa** (0.545 g, 78%) as a white solid, which was recrystallized in hexane–Et_2O (2:1); mp 124–126 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.3 Hz, 3 H), 2.56 (dq, *J* = 7.2, 14.3 Hz, 1 H), 2.83 (dq, *J* = 7.2, 14.3 Hz, 1 H), 3.82 (s, 3 H), 7.16–7.24 (m, 2 H), 7.35–7.54 (m, 2 H), 7.66–7.74 (m, 2 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 7.86 (d, *J* = 7.2 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 10.1 (Me), 32.7 (Me), 34.8 (CH_2), 45.4 (C), 84.9 (C), 93.7 (C), 109.3 (CH), 118.8 (CH), 119.5 (C), 121.3 (CH), 121.6 (CH), 124.0 (C), 126.3 (C), 126.4 (CH), 126.5 (CH), 127.3 (2 × CH), 127.8 (CH), 128.1 (2 × CH), 128.3 (2 × CH), 131.7 (2 × CH), 137.7 (C), 144.6 (C). IR (KBr): 2962, 2930, 1488, 1463, 1326, 758, 741, 701 cm^{-1}. LRMS (EI): *m*/*z* = 349 (9) [M$^+$], 320 (100). HRMS: *m*/*z* calcd for $C_{26}H_{23}N$: 349.1830; found: 349.1836.

(17) A dialkyl-substituted alkynol, such as 2-methyl-4-phenyl-3-butyn-2-ol, gave a low yield (28%) of the corresponding propargylated indole when reacted with **1a**.

(18) Alkynols **4** were prepared by addition of phenylethynyllithium to the corresponding 2-cycloalken-1-one at low temperature in THF.

(19) Trace amounts of the corresponding product coming from a direct attack of the indole on the propargylic position were observed in the crude of the reactions when alcohols **4b** and **4c** were used.

(20) Alcohols **6a** and **6c** are commercially available. Alcohol **6b** was synthesized by addition of *n*-BuLi to acetophenone at low temperature in THF.