A highly regioselective C-3 benzylation reaction of indoles with alcohols catalysed by an *N*-heterocyclic carbene

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The direct C-3 alkylation of indoles with primary and secondary alcohols through the combination of KOH and an *N*-heterocyclic carbene is described. The KOH/NHC-catalysed system can give desired C-3 alkylated indoles with high selectivity in moderate to excellent yields. Moreover, this process has obvious advantages such as high atom economy and the absence of a metal source.

Keywords: *N*-heterocyclic carbene, benzylation, indole, alcohol, base, 3-benzyl indoles, 3-substituted indoles

Owing to the prevalence of the indole framework in natural products, pharmaceuticals and functional materials,[1-3] the development of efficient and environmentally benign synthetic protocols for the formation of indoles has been an important objective in organic synthesis over the years.[4,5] Among the numerous known bioactive indole derivatives, C-3 alkylated derivatives such as serotonin and melatonin (Fig.1) are of major importance.

Alkylation with alcohols directly is thought to be difficult due to the poor leaving ability of the hydroxy group in the alkylation reactions; alcohols generally require preactivation by transformation into the corresponding halides, carboxylates, esters or related compounds with good leaving groups. Nevertheless, these transformations have serious drawbacks such as poor atom economy and large quantities of unwanted byproducts.[6-9] In view of the demand for efficient and atom-economic processes, the direct alkylation of indoles with alcohols ROH is highly desirable because the only byproduct would be water (Scheme 1).

Two kinds of methodologies have been reported for the direct catalytic substitution of indoles with alcohols. One is a Lewis acid or Brønsted acid promoted Friedel–Crafts reaction.[10-18] The synthesis of C-3 alkylated indoles can be accomplished under mild reaction conditions. However, most of the synthetic approaches reported so far could only be readily accomplished with secondary alcohols. Primary alcohols are not suitable because of side reactions. Another methodology is well known as ‘a hydrogen autotransfer process. In this procedure, the alcohol is initially dehydrogenated, then undergoes a functionalisation reaction, and finally, re-hydrogenated.[19-22]Remarkable examples are the $[Cp^*IrCl_2]_2$-catalysed system,[23] the Ru-catalysed system[24] and the alumina-supported Pt nanocluster[25] catalysed system. Amongst these, the alumina-supported Pt nanocluster catalysed system is noteworthy, because this catalytic system can afford C-3 alkylated indoles with primary alcohols. However, this methodology could only be readily accomplished with primary alcohols and the preparation process of the alumina-supported Pt nanocluster catalyst needed complex handling and harsh conditions. In addition to the above two methodologies, Yus and co-workers[26] have recently reported non-catalytic C-3 alkylation by alcohol sthrough a hydrogen-autotransfer strategy with a stoichiometric amount of base. This new methodology not only readily succeeds with primary alcohols but is also successful with secondary alcohols. However, the main limitation of this strategy is that this system suffers from harsh reaction conditions (150 °C). Therefore, developing a new methodology C-3 alkylation of indoles with alcohols remains a challenge.

In recent years, *N*-heterocyclic carbenes (NHCs) have attracted considerable attention as an important type of organocatalyst.[27-29] Particularly, the inversion of the classical reactivity (umpolung) opens up new synthetic pathways. Furthermore, due to their strong basicity, some reports of aldol[30] and Michael reactions [31] catalysed by NHCs have been developed. Building on these, we became interested in exploring the organocatalytic activity of NHCs in this direct C-3 alkylation of indoles (Scheme 2) using a few commercially available *N*-heterocyclic carbene precursors **A**–**D** (Fig. 2). It was found that the NHCs exhibited significant facilitation for the C-3 alkylation of indoles.

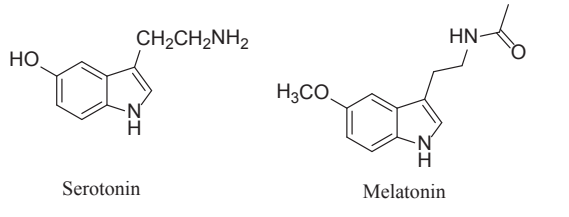
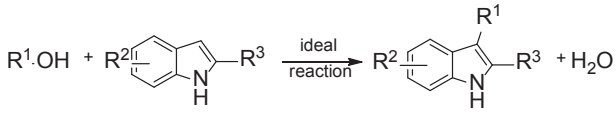
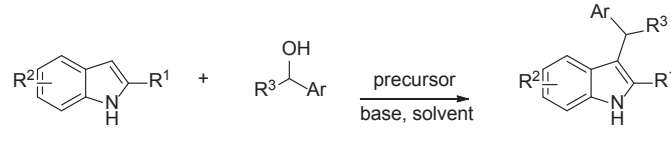


Fig. 1 Examples of biologically active indole derivatives.



Scheme 1 Ideal reaction for the direct C-3 alkylation of indoles.



Scheme 2 NHCs-mediated C-3 alkylation of indoles with alcohols.

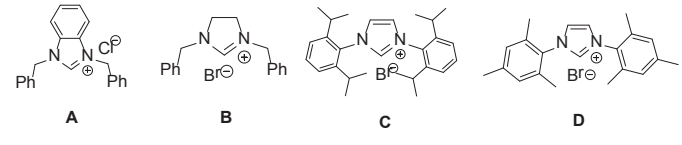


Fig. 2 *N*-heterocyclic carbene precursors used in the reaction.

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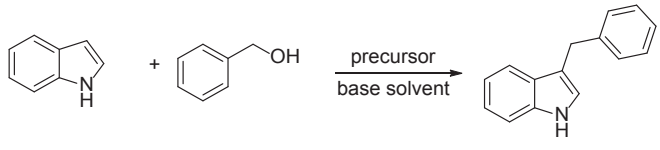
Results and discussion

For the reaction of free (N–H) indoles with alcohols, the selective formation of the C-3 alkylated products is usually a challenging task. In order to explore this process, the direct substitution between indole **1a** and benzyl alcohol **2a** was chosen as the model reaction and a brief screening of the reaction conditions was undertaken. As we expected, 3-benzyl-1*H*-indole **3a** was isolated in 74% yield when indole **1a** reacted with 2 equiv. of benzyl alcohol **2a** in the presence of NHC precatalyst **A** (5 mol%) under air in toluene at 110 °C for 24 h (Table 1, entry 1). Different types of *N*-heterocyclic carbene precursors **A–D** were tested and **D** was found to be the most effective for the preparation of **3a** under the present reaction conditions (Table 1, entries 1–4). Next, the reaction temperature was screened and it was found that the best result was obtained at 110 °C with a yield of 87% (Table 1, entries 4–6). With the amount of precatalyst **D** decreased to 2 mol%, the yield dropped to 74% and could not be improved even after prolonging the reaction time to 48 h (Table 1, entry 7). When no precatalyst **D** was used, only a low yield could be obtained (Table 1, entry 8). Optimisation of solvents for the synthesis of **3a** employing the precatalyst **D** was also undertaken and it was found that among toluene, *p*-xylene, DMF, CH_3CN and water (Table 1, entries 4 and 9–12), the best solvent in terms of yield was toluene (Table 1, entry 4). This direct C-3 alkylation of indoles was also markedly influenced by the base used (Table 1, entries 4, 13–18). Among the screened bases, KOH was found to be the most effective (Table 1, entry 4). NaOEt and NaOH were less effective, giving 3-benzyl-1*H*-indole **3a** in only 20% and 23% yields, respectively (Table 1, entries 13 and 14). When other bases including pyridine, DBU, K_2CO_3 and CH_3COONa were used, none of the desired product was observed (Table 1, entries 15–18). Finally, the optimal amount of benzyl alcohol **2a** was found to be 3 equiv. (Table 1, entry 20). **3a** was isolated in 85% yield when indole **1a** reacted with 3 equiv. of benzyl alcohol **2a** in the presence of NHC precursor **A** (5 mol%) under air in toluene at 110 °C for 24 h (Table 1, entry 21).

Having obtained the optimised reaction conditions, we turned our attention to the examination of reactant limitation of this catalytic system. The reactions of various substituted indoles with several alcohols were explored, and the results are summarised in Table 2. In order to get a high yield of the product, the reaction time is not a priority. Benzyl alcohols with electron-donating and electron-withdrawing groups at *para*-position gave excellent yields of products (**3b** and **3d**). However, steric hindrance at the *ortho*-position of a benzyl alcohol seems to have a depressing effect on yield. The *ortho*-position halogen substituted benzyl alcohols gave the desired products in a lower yield than the corresponding benzyl alcohol (**3c** and **3e**). Furthermore, indoles with electron-donating or electron-withdrawing groups all furnished the desired products **3f–l** in good to excellent yields. Note that the system also could be applied to secondary alcohols (**3m** and **3n**), albeit in moderate

Table 1 Optimisation of the reaction conditions for the synthesis of 3-benzyl-1H-indole[a]



1a **2a** **3a**

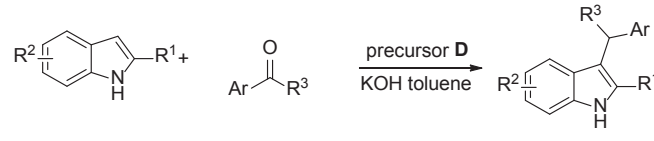
Entry	Precursor/ mol%	T/°C	**2a**/ equiv.	Base/equiv.	Solvent	Yield/%[b]
1	**A** (5)	110	2	KOH (1)	Toluene	74
2	**B** (5)	110	2	KOH (1)	Toluene	29
3	**C** (5)	110	2	KOH (1)	Toluene	45
4	**D** (5)	110	2	KOH (1)	Toluene	87
5	**D** (5)	90	2	KOH (1)	Toluene	76
6	**D** (5)	130	2	KOH (1)	Toluene	47
7[c]	**D** (2)	110	2	KOH (1)	Toluene	74
8	–	110	2	KOH (1)	Toluene	23
9	**D** (5)	110	2	KOH (1)	*p*-Xylene	83
10	**D** (5)	110	2	KOH (1)	CH_3CN	nr
11	**D** (5)	110	2	KOH (1)	DMF	nr
12	**D** (5)	110	2	KOH (1)	Water	nr
13	**D** (5)	110	2	NaOEt (1)	Toluene	20
14	**D** (5)	110	2	NaOH (1)	Toluene	23
15	**D** (5)	110	2	DBU (1)	Toluene	nr
16	**D** (5)	110	2	Pyridine (1)	Toluene	nr
17	**D** (5)	110	2	K_2CO_3 (1)	Toluene	nr
18	**D** (5)	110	2	CH_3COONa (1)	Toluene	nr
19	**D** (5)	110	1.2	KOH (1)	Toluene	57
20	**D (5)**	**110**	**3**	**KOH (1)**	**Toluene**	**95**
21	**A** (5)	110	3	KOH (1)	Toluene	85
22	**D** (5)	120	3	KOH (1)	Toluene	78
23	–	120	3	KOH (1)	Toluene	36

[a]Reaction conditions: **1a** (1.0 mmol), **2a** and precursor were mixed together in toluene (2 mL) under air and finally base was added, 24 h.

[b]Isolated yield.

[c] Reaction time is 48h.

Table 2 C-3 benzylation of indoles with alcohols catalysed by NHCsa and some realted reactions

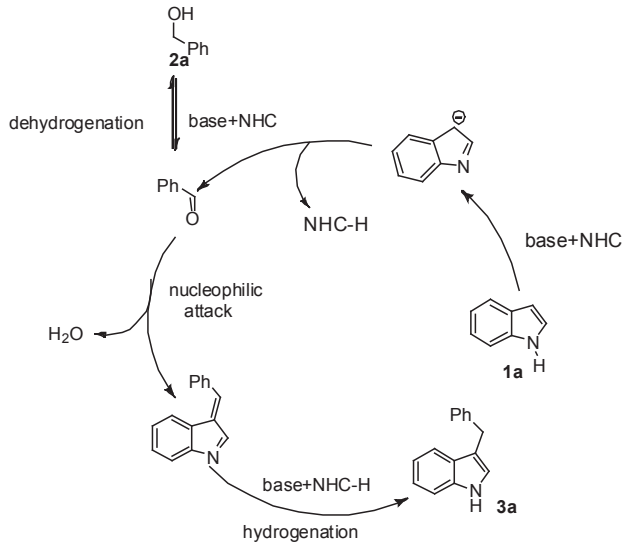


1 **2** **3**

Entry	**3**	R^1	R^2	R^3	Ar	Time/h	Isolated yield/%[b]
1	**3a**	H	H	H	Ph	24	95
2	**3b**	H	H	H	4-$CH_3OC_6H_4$	24	89
3	**3c**	H	H	H	2-BrC_6H_4	24	67
4	**3d**	H	H	H	4-BrC_6H_4	24	90
5	**3e**	H	H	H	2- ClC_6H_4	24	62
6	**3f**	H	5-Me	H	Ph	24	88
7	**3g**	H	4-MeO	H	Ph	24	90
8	**3h**	Ph	H	H	4-BrC_6H_4	24	85
9	**3i**	Me	H	H	4-BrC_6H_4	24	87
10	**3j**	H	5-F	H	Ph	24	80
11	**3k**	H	5-Cl	H	Ph	24	83
12	**3l**	H	5-Br	H	Ph	24	86
13	**3m**	H	H	Me	Ph	48	42
14	**3n**	H	H	Ph	Ph	48	67
15	**3o**	H	H	H	2-thienyl	24	88
16	**3p**	H	H	H	3-pyridyl	24	79

[a]The reaction was carried out with indole (1 mmol), alcohol (3 mmol), precursor **D** (0.05mmol), and KOH (1 equiv.) in toluene (2 mL) at 110 °C.

[b]Isolated yield.



Scheme 3 Proposed mechanism for the C-3 benzylation of indole with benzyl alcohol catalysed by KOH/NHCs.

yields. However, when indole (**1a**) and heptan-1-ol were used, no reaction occurred. The reaction also could be performed with the hydroxymethyl heteroaromatics in good yields (**3o** and **3p**). However, when simple aliphatic alcohols or ally alcohols were used instead of benzyl alcohols, no reaction occurred.

The proposed mechanism for the C-3 benzylation of indoles with benzyl alcohol catalysed by KOH/NHC is presented in Scheme 3. The base and NHC seem to play three different roles, the first one is the deprotonation of the alcohol, favouring the first dehydrogenation step, the second is the deprotonation of indole increasing the nucleophilicity at the C3-position and the third is the reduction of the C–C double bond.

Experimental

All of the reagents and solvents were commercially available and used without further purification. GC analyses were performed on an Agilent 7890A instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX 500 instrument and TMS was used as a reference. The ^{1}H NMR spectroscopic data of these precatalysts are in agreement with those reported in the literature.[29-35]

Reaction of C-3 benzylation of indoles with alcohols; general procedure

KOH (0.056 g, 1 mmol) was added to a solution of catalyst precursor D (0.05 mmol), indole (1 mmol) and alcohol (3 mmol) in toluene (2 mL), then the mixture was stirred and heated at 110 °C for an appropriate time. The mixture was then quenched by the addition of a saturated NH_4Cl solution (20 mL) and extracted with ethyl acetate (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The resulting residue was usually purified by chromatography on silica gel (hexane/ethyl acetate) to give the corresponding product.

3-Benzyl-1H-indole (**3a**): White solid; m.p. 101–102 ºC (lit.[35] 100–102 ºC).

3-(4-Methoxybenzyl)-1H-*indole* (**3b**): White solid; m.p. 82–83 ºC (lit.[35] 81–83 ºC).

3-(2-Bromobenzyl)-1H-*indole* (**3c**): Light yellow oil.[36]

3-(4-Bromobenzyl)-1H-*indole* (**3d**): Pink solid; m.p. 120–121 ºC (lit.[37] 119–120 ºC).

3-(2-Chlorobenzyl)-1H-*indole* (**3e**): Light yellow oil.[39]

3-Benzyl-5-methyl-1H-*indole* (**3f**): Yellow oil.[35]

3-Benzyl-5-fluoro-1H-*indole* (**3j**): White solid; m.p. 128-130 ºC

3-Benzyl-5-chloro-1H-*indole* (**3k**): Colourless micro-needles; m.p. 81–84 °C (lit.[38] 82–84 ºC).

3-Benzyl-5-bromo-1H-*indole* (**3l**): Yellow oil.[39]

3-*(1-Phenylethyl)-1*H-*indole* (**3m**): Pale pink solid; m.p. 69–71 ºC (lit.[25] 70–73 ºC).

3-Benzhydryl-1H-*indole* (**3n**): White solid; m.p. 122–124 ºC (lit.[26] 122–123 ºC).

3-*Thiophen-2-ylmethyl)-1*H-*indole* (**3o**): White solid; m.p. 61–64 ºC (lit.[25] 60–63 ºC).

*3-Pyridin-3-ylmethyl)-1*H-*indole* (**3p**): Colourless microneedles; m.p. 159–163 ºC (lit.[20] 159–160 ºC).

New compounds

3-Benzyl-4- methoxy-1H-*indole* (**3g**): Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.43–7.33 (m, 4H), 7.28 (t, *J* = 6.8 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 1H), 6.63 (s, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 4.38 (s, 2H), 3.92 (s, 3H);^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 141.7, 137.1, 128.1, 127.3, 124.7, 121.9, 120.3, 116.5, 115.6, 103.6, 98.7, 54.2, 32.2; MS $(M+H)^+$, 238. Anal. calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90; found: C, 80.92; H, 6.31; N, 5.84%.

3-(4-Bromobenzyl)-2-phenyl-1H-*indole* (**3h**): Colourless oil;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.57–7.48 (m, 5H), 7.48–7.42 (m, 4H), 7.36–7.30 (m, 1H), 7.23–7.15 (m, 3H), 4.30 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6, 135.1, 134.7, 131.8, 130.6, 129.1, 128.4, 128.1, 127.0, 121.6, 119.1, 118.7, 118.5, 110.1, 109.6, 29.0; MS $(M+H)^+$ 362 (^{79}Br), 364 (^{81}Br). Anal. calcd for $C_{21}H_{16}BrN$: C, 69.63; H, 4.45; N, 3.87; found: C, 69.58; H, 4.40; N, 3.81%.

3-(4-Bromobenzyl)-2-methyl-1H-*indole* (**3i**): Colourless oil;^{1}H NMR (500 MHz, DMSO) δ 10.80 (s, 1H), 7.45–7.36 (m, 2H), 7.32–7.27 (m, 1H), 7.26–7.21 (m, 1H), 7.20–7.10 (m, 2H), 7.00–6.93 (m, 1H), 6.91–6.83 (m, 1H), 4.02–3.87 (m, 2H), 2.43–2.31 (m, 3H); ^{13}C NMR (126 MHz, DMSO) δ 141.1, 134.8, 131.7, 130.5, 129.8, 127.6, 119.6, 117.9, 117.7, 117.0, 109.9, 108.2, 28.4, 10.8; MS $(M+H)^+$, 300 (^{79}Br), 302 (^{81}Br). Anal. calcd for $C_{16}H_{14}BrN$: C, 64.02; H, 4.70; N,4.67; found: C, 63.96; H, 4.65; N,4.60%.

Conclusions

NHCs belong to the most investigated reactive species in the field of organic chemistry, and are formed *in situ* by deprotonation of NHC precursors with the assistance of a base. The NHCs exhibited significant utility for the direct C-3 alkylation reaction of indoles with alcohols under suitable reaction conditions. This methodology for the generation of C-3 alkylated is indoles not only readily accomplished with primary alcohols in excellent yields, but is also accomplished with secondary alcohols in moderate yields. This methodology is of high atom economy, employing an air stable precatalyst and producing water as the only side product.

Electronic Supplementary Information

The NMR spectra of **3g**, **3h** and **3i** have been deposited in the ESI available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

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