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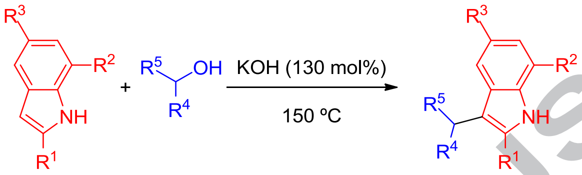

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Environmentally Friendly and Regioselective C_3-Alkylation of Indoles with Alcohols through a Hydrogen Autotransfer Strategy

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ABSTRACT

The direct alkylation of indoles using KOH and alcohols, as initial source of the electrophile, under solvent-free conditions is a safe and environmental benign strategy for selective modification of these structures at the C_3-position, without using hazardous and difficult to handle bromide or iodide derivatives or toxic and expensive transition metal catalysts. The protocol shows a broad scope, including halogenated indoles and secondary alcohols.

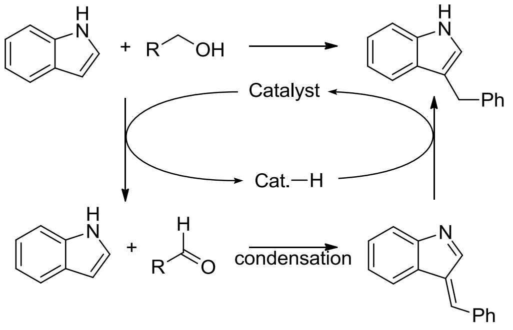
1. Introduction

The indole scaffold is one of the most industrial, agricultural and medicinal relevant cores.[1] Substituted indoles have been referred to as privileged structures since they are capable of binding to many receptors with high affinity. Therefore, their synthesis and selective modification have been the focus of active research over many years.[2] The simple alkylation of indole suffers from several fundamental problems, including the regioselectivity at *C*-3,[3] *C*-2 and *N*-1[4] positions, which have been partially solved using different strategies, conditions and catalysts. However, from the environmental, and even human hazard (due to the use of highly reactive electrophiles), point of view still there are some problems to be solved.

The standard problem of using hazard electrophilic reagents, such as alkyl bromides or iodides was solved by the use of alcohols as the source of electrophile. This alcohol strategy has been successfully used when allylic metal intermediates were involved[5] and when carbocations were generated by either acid treatment[6] or harsh conditions.[7]

The hydrogen autotransfer methodology[8] (also named borrowing hydrogen) has been also applied to the selective alkylation of indole at C_3,[9] C_2[10] and N_1[11] positions using alcohols as initial source of electrophile, just by using the appropriate transition metal catalysts (Scheme 1).

Although the presence of a metallic catalyst seems to be mandatory for the initial dehydrogenation of the alcohol and the reduction of the formed double bond, there are several examples in which this hydrogen transfer has been carried out in absence of metallic catalyst.[12] Therefore, we anticipate that, if the dehydrogenation of alcohols takes place, the most nucleophilic C_3-position of indoles could condensate to form a α,β-unsaturated imine derivative which could be reduced by the product of another dehydrogenation process.



Scheme 1. General scheme for the indole *C*-3 alkylation trough a hydrogen autotransfer.

2. Results and discussion

In our ongoing project on the use of alcohols as alkylating reagents through a hydrogen autotransfer strategy,[13] we report

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∗ Corresponding author. Tel.: +34-965903986; fax: +34-965903549; e-mail: djramon@ua.es herein the transition metal-free C_3-alkylation of indoles under solvent-free conditions.

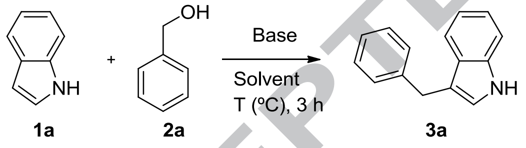
The reaction between indole (**1a**) and benzyl alcohol (**2a**) was selected as a model reaction in order to optimize the conditions (Table 1). The reaction in a mixture of xylenes using KOH (90% purity) as base at 150 ºC under an air atmosphere gave after 3 h the expected benzylated compound **3a** in an excellent yield (entry 1), as the only regioisomer.

Whereas the increase of base did not have any influence on the result, the decrease of KOH produced an important and negative effect on the chemical yield (Table 1, entries 2 and 3). The use of strict stoichiometric amount of alcohol, one equivalent to produce the electrophile and another to produce the hydrogenating source, decrease the yield meanwhile the use of a large excess did not produce any significant change in the result (entries 4 and 5). Then, the influence of solvent (entries 6-9), temperature (entry 10), and nature of base (entries 11-13) was studied, with the solvent-free conditions presented in the entry 9 of Table 1 showing a quantitative yield of product **3a**. The reaction could be scaled-up to 5 mmols without any problem.

After finding the best reaction conditions, we focused on the presence of a masked metallic catalyst on the reaction media. We repeated the reaction with a new source of KOH (99.9% purity; with less than 200 ppm of other metals) obtaining the same result (entry 14). To verify this aspect, after repeating the reaction presented in Table 1, entry 9, the ICP-MS study of the obtained mixture was performed finding that the amount of copper was only 5×10^{-3} mol% and that of palladium even lower 3×10^{-4} mol%. Although we believe that the trace impurities are not responsible for the reaction depicted in this process, it could not be completely ruled out.

Table 1

Optimization of the reaction conditions[a]



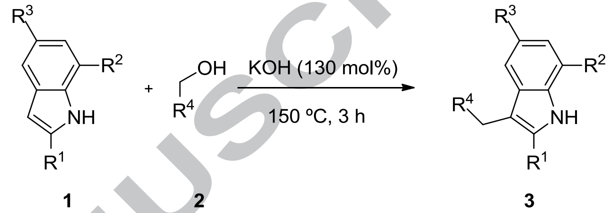
Entry	**2a** (mol%)	Base (mol%)	solvent	T (ºC)	Yield (%)[b]
1	300	KOH (130)	Xylene	150	97
2	300	KOH (50)	Xylene	150	21
3	300	KOH (250)	Xylene	150	95
4	200	KOH (130)	Xylene	150	68
5	400	KOH (130)	Xylene	150	72
6	300	KOH (130)	PhMe	150	92
7	300	KOH (130)	Dioxane	150	0
8	300	KOH (130)	H_2O	150	0
9	300	KOH (130)	-	150	99 (95)[c]
10	300	KOH (130)	-	130	5
11	300	NaOH (130)	-	150	74
12	300	*t*BuOK (130)	-	150	45
13	300	K_2CO_3 (130)	-	150	0
14	300	KOH[d] (130)	-	150	99

[a] Reaction carried out using compound **1a** (1.0 mmol). [b] Isolated yield after crystallization. [c] Reaction carried out using compound **1a** (5.0 mmol). [d] KOH used with less than 200 ppm of other metals.

The optimized protocol was applied to other substrates in order to study the scope of the reaction (Table 2). The reaction gave practically the same quantitative yields using 4-functionalised benzylic alcohols independently of the electronic nature of the functionalisation (entries 1-4). However, the possible steric hindrance of a group at the two position of aromatic ring seems to have an important effect, decreasing the yield (compare entries 1, 5 and 6). Other arylmethanol derivatives (entries 7 and 8) as well as the related heteroaryl derivatives (entries 9 and 10) gave similar results, depending on the presence of steric hindrance at the *ortho*-position of the aromatic ring of the alcohol.

Table 2

C_3-Alkylation of indoles using primary alcohols[a]



Entry	R1	R2	R3	R4	No	Yield (%)[b]
1	H	H	H	Ph	**3a**	99
2	H	H	H	4-MeOC_6H_4	**3b**	88
3	H	H	H	4-MeC_6H_4	**3c**	99
4	H	H	H	4-ClC_6H_4	**3d**	98
5	H	H	H	2-MeOC_6H_4	**3e**	76
6	H	H	H	3-MeOC_6H_4	**3f**	96
7	H	H	H	$1\text{-C}_{10}H_8$	**3g**	92
8	H	H	H	$2,3\text{-(OCH}_2\text{O)C}_6H_3$	**3h**	71[c,d]
9	H	H	H	2-Piridyl	**3i**	73
10	H	H	H	2-Thienyl	**3j**	90
11	H	H	MeO	Ph	**3k**	98[d]
12	H	H	F	Ph	**3l**	63[d]
13	H	Et	H	Ph	**3m**	76[c,d]
14	Me	H	H	Ph	**3n**	99[d]

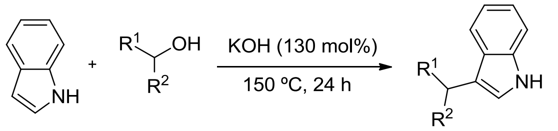
[a] Reaction carried out using compounds **1** (1.0 mmol) and **2** (3.0 mmol). [b] Isolated yield after crystallization. [c] Isolated yield after column chromatography. [d] Reaction performed during 18 h.

The presence of a substituent at the indole position had a significant influence in the reaction time, needing longer time to finish the process but keeping, in general, the previous results (entries 11-14). It should be pointed out that the reactions of indole (**1a**) with 1-butanol or with 1-heptanol failed, recovering the starting indole and the corresponding alcohol.

The optimized protocol could be applied not only to primary alcohols but also to secondary ones (Table 3). In this case, the required reaction times were increased up to one day, and the presence of several by-products arising from the auto-condensation of the in situ formed ketones (which diminished the yield of desired compound **5**) was observed. In the case of using diphenylmethanol the yield was similar to those obtained using primary alcohols thanks to the impossibility of auto-condensation of the benzophenone intermediate (entry 2 in Table 3).

Table 3

C_3-Alkylation of indole using secondary alcohols[a]



1a **4** **5**

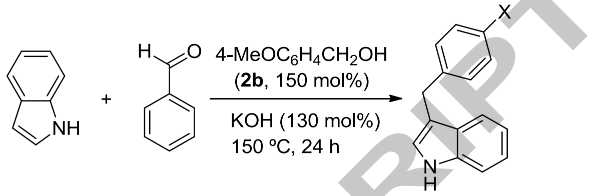
Entry	R^1	R^2	No	Yield (%)[b]
1	Ph	Me	**5a**	57
2	Ph	Ph	**5b**	91
3	-$(CH_2)_5$		**5c**	56

[a] Reaction carried out using compounds **1a** (1.0 mmol) and **4** (3.0 mmol). [b] Isolated yield after crystallization.

Finally, the possible hydrogen autotransfer mechanism was studied. The reaction of indole (**1a**) with benzyl bromide (300 mol%) and KOH in xylene at 150 ºC gave a mixture of compound **3a** (43%), 1-benzyl-1*H*-indole (35%) and 1,3-dibenzyl-1*H*-indole (18%), according to the CG and the MS spectra. The comparison with the result of entry 1 in Table 1 calls our attention to the possible difference in the mechanism, with the one followed in the reaction with benzyl bromide being close to be mediated by a cationic intermediate. Then, we repeated the reaction described in the entry 9 in Table 1 but using the alkylated 3-methyl-1*H*-indole and after 18 h the starting unchanged indole was recovered,[5f] which is another indirect proof of that the cationic benzyl intermediate is not involved. The last evidence in this direction was obtained when the reaction was performed with triphenylmethanol:[7a] after 24 h of reaction the staring indole (**1a**) was recovered unchanged.

After being quite confident that the mechanism did not involve the formation of a cationic-like intermediate from the alcohol, the role of the base was studied. The standard reaction (entry 9 in Table 1) in absence of base failed, as it was expected from the fact that a softer base than KOH had failed previously (entry 13 in Table 1). A similar reaction but using 1-methyl-1*H*-indole also failed, and only the starting material was recovered. This means that the base seems to deprotonate, at least partially, the starting indole **1**, which is in concordance with the pK_a values. Following with the possible role of the base, benzylic alcohol (**2a**) was heated in the presence of KOH at 150 ºC in a sealed tube during 18 h. We found the formation of a small amount of benzaldehyde (**6**), 15% according to GC-analysis of the crude mixture using anisol as an internal standard. However, benzaldehyde was not detected when the alcohol **2a** was heated up in absence of base. From these results, the base seems to play two different roles, the first one is the deprotonation of the alcohol, favoring the first dehydrogenation step, and the second is the deprotonation of indole increasing the nucleophilicity at the C_3-position. To corroborate the last result, indole (**1a**) and benzaldehyde (**6**) were heated at 150 ºC overnight, in the absence or presence of KOH. In the second case both starting reagents were recovered unchanged, however, in the first one benzyl alcohol (**2a**, 32%), benzoic acid, and the benzylated product **3a** (11%) appeared, together with the starting materials. These experiments highlight the central role of the base in the condensation step, as well as in the following reduction of the C-C double bond.

Finally, a competitive experiment was performed to rule out the benzyl cation intermediate and to point out the sequential condensation step followed by a reduction of the corresponding 3-alkylidene-3*H*-indole intermediate (Scheme 2). The reaction of **1a** with benzaldehyde (**6**) and (4-methoxyphenyl)methanol (**2b**) gave a mixture of compounds **3**, in which the main product **3a** was that arising from the condensation with the aldehyde followed by reduction, confirming our mechanistic hypothesis.



1a **6** (150 mol%) **3a** (X = H, 68%) and **3b** (X = OMe,13%)

Scheme 2. Competitive experiments between an aldehyde and an alcohol.

3. Conclusion

In conclusion, the direct alkylation of indoles using KOH and alcohols at 150 ºC under solvent-free conditions is a safe and environmental benign strategy for selective modification of these structures, without using hazardous and difficult to handle bromide or iodide derivatives or toxic and expensive transition metal catalysts. All these facts permit us to anticipate a good future for the process shown in this study not only in the laboratory but also in the industry.

Acknowledgments

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Supplementary data

A MOL file for representative products, detailed experimental procedures, and spectral data for all compounds associated with this article can be found in the online version, at http://dx.doi.org/

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