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Single-Flask Synthesis of *N*-Acylated Indoles by Catalytic Dehydrogenative Coupling with Primary Alcohols

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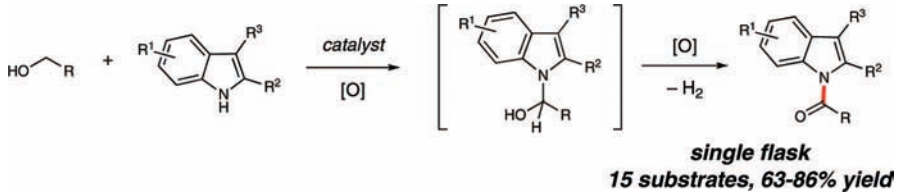
ABSTRACT



Indoles and alcohols can be coupled in a dehydrogenative process catalyzed by tetrapropylammonium perruthenate. This efficient approach to indolylamides proceeds in a single flask under mild conditions. By employing substituted indoles and alkyl, branched, or benzylic alcohols, a variety of indolylamides can be formed. Aryl indolylamides can be functionalized through an additional dehydrogenative coupling to furnish elaborated polycyclic heterocycles similar to biologically active structures previously reported.

Amides are important, abundant, compounds that are utilized in a broad range of chemical disciplines.[1] Given the ubiquity of this stable functional group and its central place in proteins and polymers, amide formation remains a fundamental transformation in organic synthesis.[2] The formation of amides by the oxidation of the acyl C−H of aldehydes is an attractive, direct method[3] that circumvents the need for coupling agents and prerequisite oxidation. Of particular interest is the potential application of this method toward the synthesis of indolylamides. In addition to their function as protected carboxylate derivatives,[4] indolylamides are desirable synthetic targets. *N*-Acyl indoles are present in numerous biologically active molecules (Figure 1) such as the nonsteroid anti-inflammatory agent indomethacin (**1**),[5]

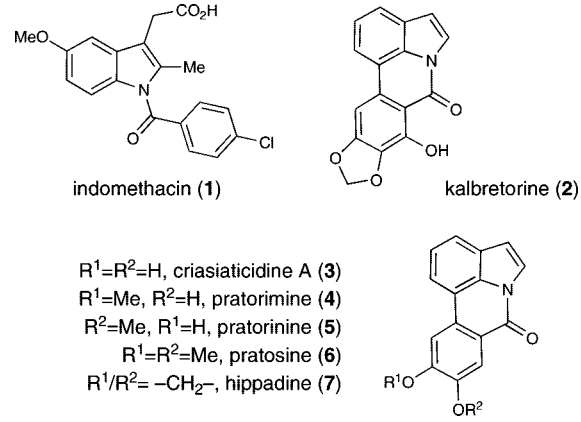


Figure 1. Bioactive indolylamides.

members of the pyrrolophenanthridone class of natural products[6] isolated from the Amaryllidaceae family (**2**−**7**),[7] and 6*H*-isoindolo[2,1-*a*]indol-6-ones (vide infra).

The dehydrogenative coupling of indoles and alcohols[8] (Figure 2) is an efficient approach to these synthetically

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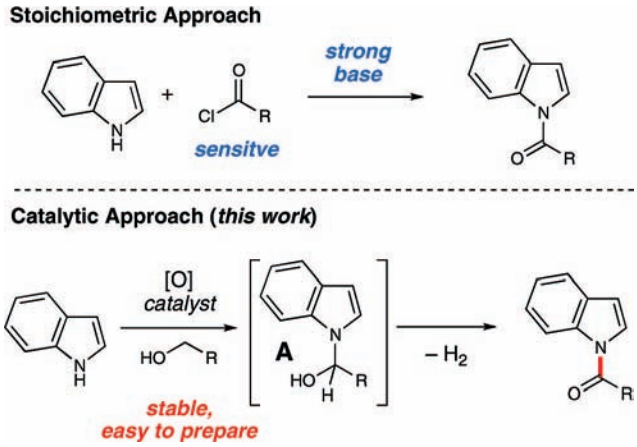
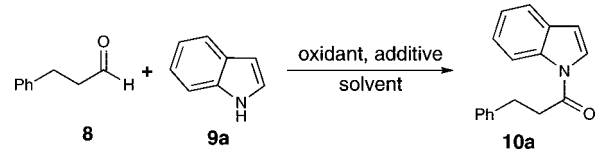


Figure 2. Dehydrogenative coupling of indoles and alcohols.

useful *N*-acylated indole structures. Furthermore, a strategy that accesses higher oxidation states in a single operation (i.e., alcohol to amide) simultaneously exploits the advantages of tandem processes and facilitates the functionalization of challenging substrates. Indoles and pyrroles were attractive targets for this process due to the stability of the aminal intermediate (**A**).[9,10] Herein we report the dehydrogenative coupling of indoles and alcohols, which does not require the use of strong hydride or alkyllithium bases and also obviates the need for sensitive or less accessible acid chloride or anhydride acylating agents.[11] In addition, this process utilizes starting materials in the readily available alcohol oxidation state. To the best of our knowledge this transformation represents the first intermolecular dehydrogenative coupling of aromatic amines and alcohols.

Our previous work, utilizing nucleophilic *N*-heterocyclic carbene (NHC) catalysts in tandem oxidation reactions,[12] led us to investigate the acylation potential of that process with respect to amines.[13] With indole as the nucleophile, we were pleased to observe the formation of the *N*-acylated product **10a** under reaction conditions employing various azolium salts and oxidants (results not shown). The reaction was found to also proceed in the absence of the nucleophilic catalyst (Table 1, entry 1), presumably due to the formation

Table 1. N-Acylation of Indole with Hydrocinnamaldehyde



8 9a 10a

entry	oxidant	additive	**9a**:**8**	solvent[a]	yield (%)[b]
1	MnO_2	none	10:1	toluene[c]	12
2	PCC	none	10:1	toluene[c]	16
3	TPAP/NMO	4 Å mol sieves	10:1	CH_2Cl_2	4
4	TPAP/NMO	4 Å mol sieves	10:1	CH_3CN	15
5	TPAP/NMO	4 Å mol sieves	5:1	CH_3CN	36
6	TPAP/NMO	4 Å mol sieves	1:1	CH_3CN	18
7	TPAP/NMO	4 Å mol sieves	1:1	CH_3CN[d]	81 (74)

[a] At 25 °C with **8** at 0.33 M. [b] Yields calculated by GC (isolated yield in parentheses). [c] At 100 °C. [d] **8** at 0.6 M.

and oxidation of an aminal intermediate, similar to **A**, which results from indole acting as a nucleophile and attacking the aldehyde in place of the heterocyclic catalyst.[14] This reaction occurs specifically at the nitrogen atom of indole. Previous reports indicating nucleophilicity at the C3 position of the heterocycle generally require activation through Lewis acid[15] or other catalyst.[16] The divergence of the reactivity in this system is a particularly interesting observation and further mechanistic investigations are being carried out to elucidate the causes for this reactivity. A screen of oxidants and

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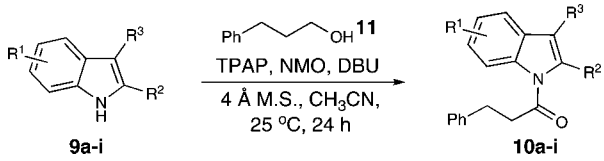
(14) Although the possibility exists for coupling of the indole with a substrate in the carboxylic acid oxidation state,[11] significant amounts of the carboxylic acid were not observed with prolonged exposure of 3-phenyl-1-propanol or hydrocinnamaldehyde to oxidation conditions in the absence of indole.

solvents (entries 1−4) revealed that the catalytic (5 mol %) oxidant tetrapropylammonium perruthenate (TPAP) in combination with 4-methylmorpholine-*N*-oxide (NMO)[17] allowed this oxidation to take place at ambient temperature,[18] albeit in similarly poor yields. Acetonitrile was found to be a more optimal solvent for this transformation than dichloromethane.

The concentration of the nucleophilic indole **9a** had a significant effect on the results of this oxidation (entries 4−7). When the concentration was greater than 1.5 M (entries 4 and 5), lower yields were observed, while concentrations in the range of 0.5−1.5 M provided the highest yields (entry 7). Further dilution (entry 6) had a negative effect on the yield of the *N*-acylated heterocycle.

Because TPAP is known to oxidize alcohols to aldehydes, we explored the use of 3-phenyl-1-propanol (**11**) as a coupling partner. After initial oxidation to an aldehyde, formation of the aminal via nucleophilic addition of the indole derivative allowed further oxidation to the *N*-acyl heterocycle (Table 2, entry 1). This oxidative process is

Table 2. Dehydrogenative Coupling of Indoles[a]



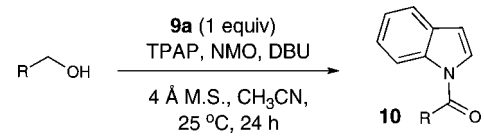
entry	indole	R^1	R^2	R^3	yield (%)[b]
1	**9a**	H	H	H	81
2	**9b**	5-OMe	H	H	86
3	**9c**	5-Br	H	H	76
4	**9d**	5-CO_2Me	H	H	73
5	**9e**	4-Br	H	H	74
6	**9f**	H	H	CO_2Me	70
7	**9g**	H	H	Me	63
8	**9h**	7-Me	H	H	0
9	**9i**	H	Me	H	0

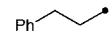
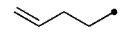
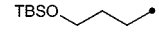
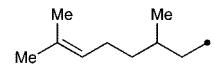
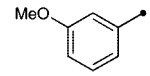
[a] See Supporting Information for full experimental details. [b] Isolated yield.

viable using a variety of indole derivatives. 5-Substituted indoles (Table 2, entries 2−4) were suitable substrates. The more nucleophilic **9b** gave the highest yield, while an electron-withdrawing group at this position decreased the yield (entry 4). 3-Substituted indoles (entries 6 and 7) yielded acylated product, but the more encumbered aminal resulting from the combination of 2-substituted or 7-substituted indoles and the alcohol were not capable of undergoing this oxidation (entries 8 and 9), most likely due to the bulky nature of the oxidizing agent. Indoles were found to be superior to pyrrole, indazole, and 7-aza-indole, all of which resulted in no acylation. Carbazole was also investigated and gave poor results (<40% yield of acylated product).

Variation of the acylating alcohol shows steric interactions influencing the oxidation of the aminal intermediate. Unbranched alkyl alcohols (Table 3, entries 1−4) gave the best

Table 3. Dehydrogenative Coupling with Alcohols[a]



entry	R	product	yield (%)[b]
1		**10a**	81
2		**10j**	77
3		**10k**	71
4		**10l**	64
5		**10m**	73
6		**10n**	65
7		**10o**	69
8		**10p**	34
9		**10q**	83

[a] See Supporting Information for full experimental details. [b] Isolated yield.

results, while increased substitution at the α-position decreased the yield (entries 6 and 7). This process tolerates the presence of silyl ethers (entry 4) and olefins (entries 3 and 5). The sterically demanding substrate derived from 2,2-dimethyl-1-propanol was afforded in low yield (entry 8). The use of a benzylic alcohol provided the *N*-acyl product as well (entry 9).

A modification of the procedure using TPAP and molecular oxygen as the oxidative system[19] gave the product in comparable yields (Scheme 1). This green oxidative coupling[20] of alcohols and indole derivatives allows for the

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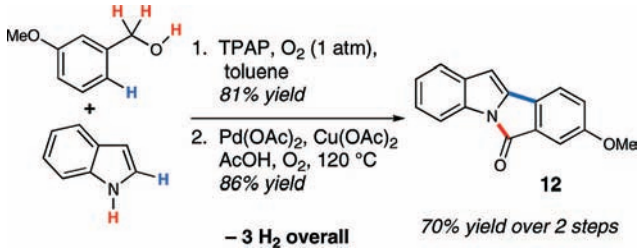
Scheme 1. Synthesis of Bioactive Tetracycles



further elaboration of substrates such as **10q**. This process was also effective for other alcohols, as **10a** and **10m** were successfully obtained in 72% and 66% yields, respectively, using molecular oxygen as the oxidant.[21]

The direct acylation of indole using a benzaldehyde derivative yields acylated indole **10q**, which when treated with palladium(II) acetate (employing the conditions of DeBoef[22]), cyclizes to form tetracyclic compound **12** from the sequential dehydrogenation of indole and a simple benzyl alcohol (Scheme 1). 6*H*-Isoindolo[2,1-*a*]indol-6-ones of this type have been shown to mimic melatonin[23] and batracyclin.[24] These compounds possess several modes of biological activity,[25] including binding to MT_3 melatonin receptors, topisomerase inhibition, cytotoxicity, and antiproliferative activity against L1210 leukemia cells.

N-Acylated heterocycles can be synthesized from aromatic amines and alcohols or aldehydes. A variety of indole derivatives and acylating agents, restricted by steric interactions about the resultant aminal, can be used in this process. The oxidation is carried out with a catalytic oxidant (TPAP), which can be used in low catalyst loadings (<5 mol %) to efficiently provide these useful substrates from readily available starting materials in an environmentally friendly manner. This method has been applied to the preparation of potentially bioactive 6*H*-isoindolo[2,1-*a*]indol-6-one frameworks. Further investigations of the mechanism and new applications of this dehydrogenative coupling process are underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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