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Rapid access to 3-acyl indoles using ethyl acetate/triflic acid couple as the acylium donor and Cu(OAc)$_2$ catalysed aerial oxidation of indole benzoins†‡

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Esters are potential acyl donors but are relatively unexplored for that purpose. A facile installation of acyl groups at the C-3 position of indoles under triflic acid catalysed conditions with easily available and cheap esters as new acylating agents is described herein. Furthermore, heterocycles like *N*-protected pyrrole, furan and thiophene were also suitable substrates for similar C-2 acylation. Analogous C-3 benzoylated products of indole were obtained, albeit in lower yields, by using methyl benzoate as a benzoyl donor. The benzoylated products were synthesised in much better yields *via* a copper(II) catalysed aerial oxidation of indole containing benzoins.

Esters are underused electrophiles in acylation reactions when compared to other acylating agents, mostly following biocatalytic routes.[1,2] A reason for this is that the low reactivity of esters does not easily allow formation of the corresponding acylium cation intermediates required for acylation of aromatic rings under general acid-mediated reaction conditions (mimicking $A_{Ac}1$) and thus, there is a requirement to cast new light on this long and unsolved problem.

On the other hand, 3-acyl indoles can be prepared from indole and other acylating agents, such as expensive and highly air/moisture sensitive reagents/catalysts,[3] esters with the aid of Lewis acids,[4] or by other methods.[5] 3-Acyl indoles are useful compounds that are used as building blocks in synthetic chemistry,[6] and are well-known antibacterial[7] and antimalarial[8] agents (Fig. 1). They are useful against other diseases caused by parasites as well.[9] Such molecules are also used as 5-HT$_6$ receptor antagonists,[10] antimitotic or anti-tubulin polymerisation agents,[11] and to combat HIV,[12] diabetes[13] or even cancer.[14]

However, these simple compounds (3-acyl or 3-benzoyl indoles) are strikingly expensive commodities (>100–300 $ per g) when obtained from commercial sources.[15] Therefore the use of cheap materials to synthesise those compounds under a metal-free strategy would be highly desirable.

In a recent report, the efficiency of ethyl acetate acting as an acyl donor under acidic conditions was investigated by Williams.[16] Additionally, the 3-acylation of indoles has already been studied using different yet related reagents like ketones,[3a] acids,[3d,17] anhydrides,[18] acetyl chlorides[3e,19] or amides.[20] Transition metal catalysis with nitriles,[21] α-oxocarboxylic acids[22] and ethyl arylacetates[23] has also been used. Encouraged by the above results, the author hereby reports the use of economically friendly and laboratory abundant ethyl acetate as a new indole 3-acylating agent under the influence of catalytic triflic acid in a metal-free technique.

When *N*-methyl indole (**1a**) was subjected to acylation in refluxing ethyl acetate (**2a**) with 0.4 equivalents of TfOH, the 3-acyl product **3a** was isolated in 71% yield within 3 hours of reaction time (first entry, Table 1). The corresponding triflic anhydride reagent afforded 60% product (entry 2), whereas when using p-TsOH only the decomposed substrate was

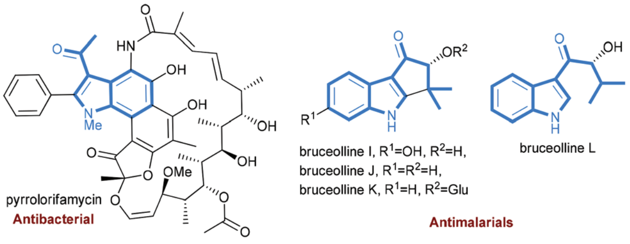

Fig. 1 The importance of 3-acyl indole substructures.[7,8]

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† Dedicated to Professor Ramanathan Gurunath on the occasion of his 55th birthday.

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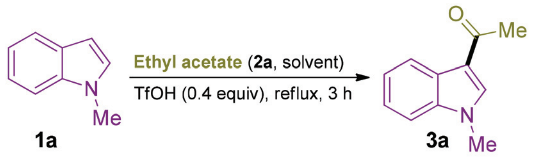
Table 1 Optimization of the yield of 3-acyl indole (**3a**)[a]

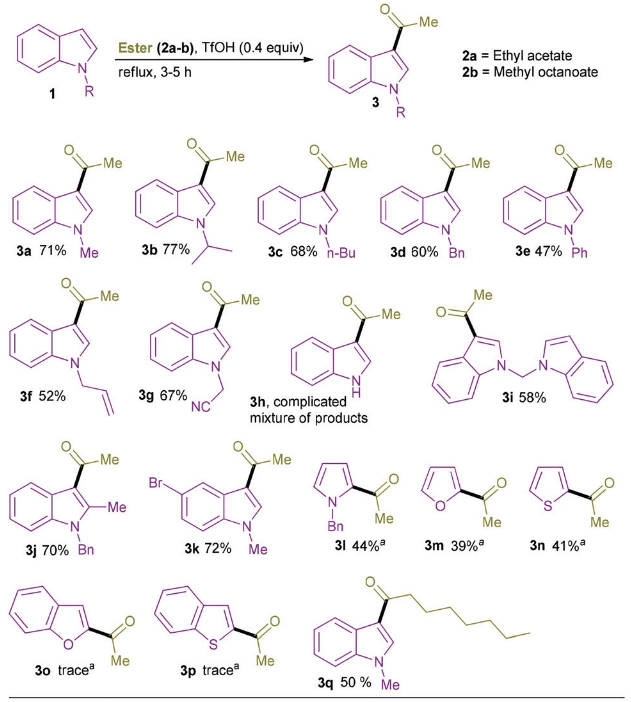


Entry	Deviation from the optimized conditions (2.0 mL EtOAc used per mmol of **1a**)	Time (h)	Yield[b] (%)
1	None	3	71
2	0.4 Equiv. Tf_2O used	1.5	60
3	0.4 Equiv. p-TsOH used	2	Decomposition
4	0.4 Equiv. 12 N HCl used	0.5	Decomposition
5	0.4 Equiv. $SnCl_4$ used	48	33
6	0.4 Equiv. H_3PO_4 used	48	16
7	0.4 Equiv. $BF_3{\cdot}Et_2O$ used	48	No reaction
8	0.4 Equiv. $(CF_3CO)_2O$ used	48	No reaction
9	0.4 Equiv. DABCO used	48	29
10	0.4 Equiv. DBU used	48	40
11	0.4 Equiv. DMAP used	48	15
12	0.2 Equiv. TfOH used	8	48
13	0.6 Equiv. TfOH used	3	69
14	1.0 Equiv. TfOH used	2	61
15	Reaction carried out at RT	48	25

[a] Red text signifies acidic conditions, blue text signifies basic conditions. [b] All yields are isolated yields.

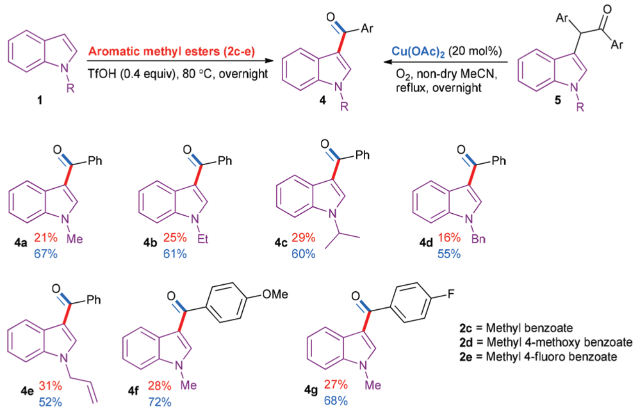
observed (entry 3). Similar decomposition took place when 12 N HCl was utilized as the catalyst (entry 4). Catalytic $SnCl_4$ or H_3PO_4 gave low yields of **3a** (entries 5 and 6). The use of $BF_3{\cdot}Et_2O$ or $(CF_3CO)_2O$ turned the reactions bleak (entries 7 and 8). Some catalytic basic reagents were also tried in this reaction (entries 9–11), among which, only DBU gave a respectable yield of 3-acyl indole (entry 10). Therefore, the ability of DBN-type bases to catalyse indole 3-acylations, in addition to 3-benzoylations, was also proved.[24] The stoichiometry of TfOH was examined and the product yield was 48% with 20 mol% of TfOH, which turned to 69% with 60 mol% TfOH, and then decreased to 61% with stoichiometric use of the acid (entries 12–14, respectively). Lastly, when the reaction was carried out with a catalytic amount of TfOH but at ambient temperature, only 25% yield of **3a** was found after prolonged stirring (entry 15).

After obtaining the best condition, an examination of the substrate scope was carried out by using different *N*-substituted indoles (Scheme 1). Moderate yields were obtained with isopropyl (**3b**) or *n*-butyl (**3c**) *N*-protected indoles. *N*-Benzyl (**3d**) and *N*-phenyl (**3e**) protected indoles acted as suitable substrates and gave fair yields. Other unsaturated *N*-protecting groups (**3f** and **3g**) offered similar yields. Unprotected indole only afforded a complex mixture of products (**3h**) and no isolation of the desired compound was possible whatsoever. Interestingly, diindolylmethane gave 58% of the mono acyl product **3i** only with no detected di-acylated product. *N*-Benzyl indole with a C-2 methyl substituent gave 70% of the required product (**3j**). The 5-bromo substituted substrate displayed similar reactivity under these conditions to give 72% of the product (**3k**). Further investigations on monocyclic heteroaryl substrates, *viz*. *N*-benzyl pyrrole, furan and thiophene, gave the 2-acylation products albeit in lower yields (**3l–3n**, respectively). This was achieved using 0.6 equivalents of the Brønsted acid,[24] although further increase in the quantity of acid deteriorated the reaction yields. Thus, this is a very important procedure for the functionalization of other non-indole heterocycles as well as being of synthetic interest. Unfortunately, benzofuran and benzothiophene furnished only trace yields of the desired products. Using an ester with a long carbon chain (*n* = 8, **2b**) acid with **1a** furnished ketone **3q** in 50% yield.



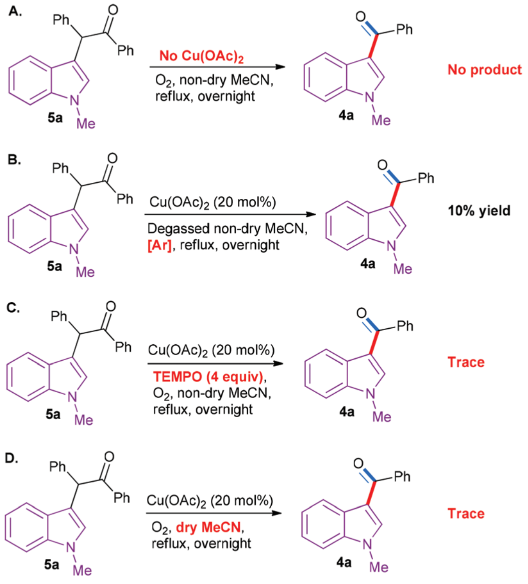
a0.6 Equiv TfOH was used

Scheme 1 Substrate scope of the acylation reaction.



Scheme 2 Synthesis of 3-benzoyl indoles.

A similar strategy for the 3-benzoylation of the substrates[25] was developed using methyl benzoate (**2c**) to afford product class **4**. *N*-Protecting primary (**4a** and **4b**) or secondary alkyl groups (**4c**) were used, with subtle increments in the yields observed along the series (red yields, Scheme 2). Benzyl (**4d**) or unsaturated *N*-protected indoles (**4e**) gave 16% and 31% yields, respectively. The overall yields were significantly less when compared to the acylation (Scheme 2, given in red). A parallel process for the syntheses of **4** by aerial oxidation of indole substituted benzoins (**5**),[26] catalysed by a copper(II) salt in non-dry acetonitrile solvent was studied and gave relatively improved product yields (blue yields, Scheme 2). Interestingly, it did not require any other reagents except the transition metal salt in a catalytic amount.[26b] To the best of the author's knowledge there is only one other copper(II)-mediated method available to afford these indole analogues of benzophenone and this proceeds *via* a complicated decarboxylation of α-oxocarboxylic acids.[27]

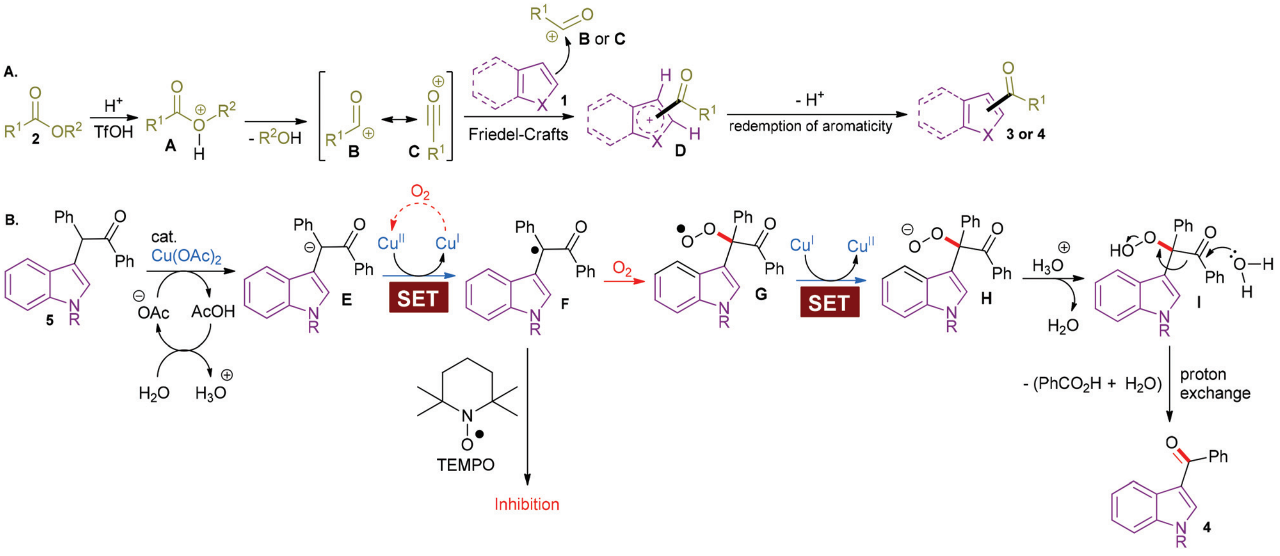


Scheme 3 Control experiments.

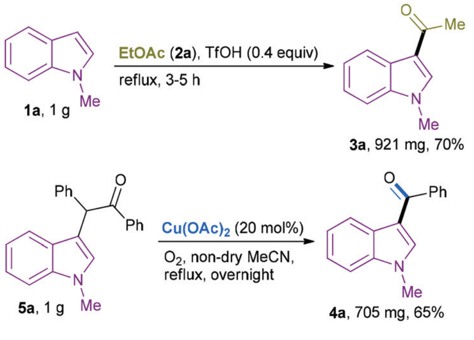
When substituted aromatic methyl esters **2d** and **2e** were used under the first protocol (0.4 equiv. TfOH) ketones **4f** and **4g** were afforded. These compounds were also synthesised in satisfactory yields using the $Cu(OAc)_2/O_2$ oxidation method (Scheme 2). The importance of all these products has already been discussed in the introductory section.

To elucidate a mechanistic path of the $Cu(OAc)_2/O_2$ mediated oxidation, some control experiments were performed using **5a** as the substrate. The reactions were designed to prove the necessity of $Cu(OAc)_2$, oxygen, radical intermediates and moisture in this protocol. The absence of catalytic oxidant $Cu(OAc)_2$ did not furnish any reaction (Scheme 3A). Performing the reaction in the absence of oxygen (Scheme 3B) provided only a 10% yield of **4a**. In the presence of the radical scavenger TEMPO only a trace amount of **4a** was detected, which confirmed that a radical mechanism is involved (Scheme 3C). A similar scenario was observed when moisture free solvent was used, proving the requirement of water in the reaction (Scheme 3D).

The general Scheme 4A describes a regular Brønsted acid-catalysed Friedel–Crafts type acylation of an electron-rich heterocycle (**1**) with an ester (**2**). Nucleophilic attack of the arene π-electrons at the carbonyl centre of the acylium ion **B** or alkylidyne oxonium ion **C** followed by aromatization of adduct **D** gives product **3** or **4**. Based on the control experiments described in Scheme 3, Scheme 4B is shown as a probable mechanistic route for the aerial oxidative transformation to give 3-benzoyl indoles (**4**). The process is started by formation



Scheme 4 Probable mechanisms of the acid catalysed 3-acylation of heterocycles by esters ($A_{Ac}1$) and the aerial oxidation of substituted benzoins **5** in presence of $Cu(OAc)_2$.



Scheme 5 Gram-scale syntheses of **3a** and **4a**.

of **E** by deprotonation of the indole benzyl proton α- to the carbonyl group of **5** by acetate (which is regenerated by protonating a water molecule). This is followed by a single electron transfer oxidation to give radical **F** as part of the Cu^{II}/Cu^{I} catalytic cycle.[28] Radical **F** traps an oxygen molecule affording the peroxy radical **G**,[29] which in turn gives peroxide anion **H** *via* the single electron reduction by Cu^{I}.[30] Peroxide **I** is then formed by proton exchange with the hydronium ion and receives an attack from a water molecule furnishing the ketone product **4**, leaving benzoic acid behind (detected by HRMS).

To achieve the industrial applicability of this process, the synthesis of **3a** and **4a** were repeated at gram-scale. The outcomes were pleasing, as the percentage yields observed at smaller scales were almost completely reproduced (Scheme 5).

Conclusions

In all, this project describes a simple yet synthetically important installation of acyl/benzoyl groups at the C-3 position of indoles using esters as new acyl donors. The relatively unexplored acyl-donating ability of esters is thought to be under the catalytic influence of triflic acid. Interestingly, *N*-protected pyrrole, furan and thiophene also afforded the corresponding 2-acyl products albeit in low yields. The process does not require a transition metal. As an alternate route, 3-benzoyl indoles are prepared with better yields by the Cu(ɪɪ)-catalysed aerial oxidative degradation of indole substituted benzoins. This report shall be a very good addition to the other available general synthetic procedures for the 3-acylation/benzoylation of indoles.

Conflicts of interest

There are no conflicts to declare.

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