Oxidative organocatalytic chemoselective: N-acylation of heterocycles with aromatic and conjugated aldehydes

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Citation for the original published paper (version of record):
Ta, L., Sundén, H. (2018)
Oxidative organocatalytic chemoselective: N-acylation of heterocycles with aromatic and conjugated aldehydes
Chemical Communications, 54(5): 531-534
http://dx.doi.org/10.1039/c7cc08672e

N.B. When citing this work, cite the original published paper.
Selective acylation of indoles is cumbersome often involving the need for sensitive and reactive acyl chloride derivatives or coupling reagents. Here we report a mild, functional group tolerant and highly chemoselective oxidative carbene catalyzed $N$-acylation of indoles with aldehydes. The acylation has a broad substrate scope and is compatible with substituents on both the aldehyde and the indole reaction partner. Furthermore, aza-heterocycles such as pyrrole and indazole can also be used as nucleophiles in this reaction providing the corresponding amide congeners in good yield.

The power to selectively functionalize heterocycles with multiple reactive sites is a challenging and important task. By selective functionalization, an atom efficient and protecting group free strategy can be achieved for the preparation of complex molecules. In this respect, chemoselective $N$- or $C$-functionalization of indoles has been a longstanding challenge in organic synthesis. Selective $N$-acylation of indoles is of particular importance as $N$-acylindoles are found in numerous biologically active compounds, such as, indomethacin, oxamethacin, acemetacin, L-768,242 and have also been used as imaging agents for beta amyloid plaques (Scheme 1a).

Scheme 1  (a) Bioactive acylindoles. (b) Oxidative carbene-catalyzed acylation of alcohols and amines. (c) Carbene catalyzed oxidative acylation of indoles with aldehydes. (d) Oxidative NHC catalyzed $N$-acylation of indoles.

Synthetically, $N$-acylindoles can serve as protected carboxylate derivatives, and can be set up to undergo several forms of annulation reactions with the C2-carbon.

Generally, acylation of indoles occurs at the C3-position and can for instance be selectively performed in the presence of a carboxylic acid derivative and a Lewis acid, or with the Wilsmeier–Haack reaction. Selective $N$-acylation on the other hand, is normally conducted in the presence of a reactive electrophile such as a chloride containing acylating reagent and a stoichiometric base or a carboxylic acid that needs to be activated with a coupling reagent. The use of inorganic bases and/or sensitive reagents can potentially have a negative impact on the functional group compatibility, thus restricting further development of these protocols. To overcome these concerns, Sarpong and co-workers showed that $N$-acylation of indoles could be selectively performed under mild conditions in the presence of a stoichiometric carbonylimida-zole derivative. Moreover, Scheidt and co-workers have shown that acylated indoles can be formed through a tetrapropylammonium perruthenate-catalyzed dihydrogenative coupling of alcohols.
In the field of organocatalysis, N-heterocyclic carbenes (NHCs) have received widespread attention as potent catalysts for a number of diverse reaction paths and are particularly useful in converting aldehydes into acyl donors. The key intermediate in these reactions is the acyl azolium intermediate (Scheme 1b) that can be generated either through an internal oxidation of the Breslow intermediate or in the presence of an external oxidant such as the Kharasch oxidant. The Kharasch oxidant has been used, for instance, for acylation reactions involving alcohols, azides, macrolactonizations, and amidations (Scheme 1b). With our recent interest in oxidative N-heterocyclic carbene catalysis, we wanted to investigate if the acyl azolium would generate selectivity in the acylation of densely polyfunctionalized molecules such as indoles and other heterocycles. Thus, enabling the use of available aldehydes as mild acylating reagents. Previous studies have shown that N-functionalization of indoles is indeed possible through an intramolecular reaction cascade or through an imination reaction with isocyanides. Here we report the NHC-catalyzed oxidative, chemoselective N-acetylation of indoles with aldehydes.

Our study commenced with a survey of reaction conditions where both imidazolium and triazolium salts were found to be suitable precatalysts for this reaction with being the superior one in the series (Table 1, entries 1–3). Among the bases tested DBU (entry 1) was the best alternative as compared to Cs₂CO₃ and trimethylamine (entries 4 and 5). Dichloromethane was shown to be the best solvent for the reaction compared to acetonitrile, toluene and THF (entries 6–8). The most effective combination was found to be the combination of an increased base-loading and molecular sieves (MS 4 Å) (entry 9). To conclude that the NHC has an active role as a catalyst in the reaction, a series of reactions were performed systematically excluding the NHC, base, and oxidant (entries 10 and 11). In all these cases, no product formation could be detected indicating that oxidative carbone catalysis is indeed the reaction pathway.

With our optimal reaction conditions in hand, the reaction scope was investigated (Table 2). Different α,β-unsaturated aldehydes were generally well tolerated by the reaction delivering the α,β-unsaturated acylindoles in up to 96% yield. α,β-Unsaturated acylindoles are of particular importance as they can be further functionalized in a number of metal-catalyzed reactions. Both electron donating and withdrawing substituents were compatible under our oxidative reaction conditions. For example, p-dimethylamino, o- and p-methoxy cinnamaldehyde delivers the corresponding acylindole in 70–96% yield, respectively (compounds 10, 11 and 12). Halogen substituted cinnamaldehydes are less efficient in promoting the reaction and require longer reaction times as compared to the electron rich aldehydes (compounds 13 and 14). Benzaldehydes with substituents on all positions also work as an acylating agent in this reaction delivering the benzoylated indoles in 63–97% yield (compound 16–19). Furthermore, aliphatic conjugated aldehydes are also compatible with our reaction conditions and is isolated in 73% yield.

Next the indole reaction partner was investigated (Table 3). Generally, the reactions work well for indoles incorporating a high degree of different functional groups. For instance, halogens are tolerated in positions 4, 5 and 6 and the acylated indole derivatives can be isolated in good to excellent yields (53–90% compounds 21–31). Electron donating groups such as methyl and methoxy give good reactivity and compounds 22,

### Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Precat.</th>
<th>Base</th>
<th>Additive</th>
<th>Yield</th>
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<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>7</td>
<td>DBU</td>
<td>—</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>8</td>
<td>DBU</td>
<td>—</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>DCM</td>
<td>9</td>
<td>DBU</td>
<td>—</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>DCM</td>
<td>7</td>
<td>Cs₂CO₃</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>DCM</td>
<td>7</td>
<td>Et₃N</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>7</td>
<td>DBU</td>
<td>—</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>7</td>
<td>DBU</td>
<td>—</td>
<td>36</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>7</td>
<td>DBU</td>
<td>—</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>DCM</td>
<td>7</td>
<td>DBU</td>
<td>MS 4 Å</td>
<td>81/71</td>
</tr>
<tr>
<td>10</td>
<td>DCM</td>
<td>7</td>
<td>DBU</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>DCM</td>
<td>7</td>
<td>DBU</td>
<td>—</td>
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<tr>
<td>12</td>
<td>DCM</td>
<td>7</td>
<td>DBU</td>
<td>MS 4 Å</td>
<td>0</td>
</tr>
</tbody>
</table>

* 4 (1 eq.), cinnamaldehyde (2 eq.), base (0.5 eq.), precatalyst (10 mol%), solvent (1 ml) and 2 (1 eq.). * Determined by ¹H NMR on the crude reaction mixture with durene as an internal standard. * 1.5 ml. * 0.8 ml. * 1 eq. * Isolated yield. * Without 2.

### Table 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>Isolated Yield</th>
</tr>
</thead>
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<tr>
<td>6</td>
<td>X = H, 71%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>X = o-OMe, 78%</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>X = p-OMe, 70%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>X = p-MeN, 96%</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>X = p-F, 50%</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>X = p-Cl, 42%</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Y = o-OMe, 97%</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Y = p-OMe, 92%</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Y = m-Me, 75%</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Y = p-Cl, 63%</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>73%</td>
<td></td>
</tr>
</tbody>
</table>

* All experiments were carried out by using indole (1 eq.), aldehyde (see ESI), 2 (1 eq.), NHC 7 (5 mol%), DBU (1 eq.) in DCM (0.15 M), MS (4 Å, 0.5 g) at r.t. * Isolated yields after column chromatography. * With 1.4 eq. of 2. * With 10 mol% of NHC. * With 2 eq. of 2.
tryptamine analogues incorporating functional groups such as CN and a tertiary amine are also tolerated by the reaction and compound 29 and 30 can be isolated in 56% and 75% yield, respectively. In all cases the reactions exhibited a high degree of chemoselectivity toward N-acetylation, and the C3-acylated compound was never detected. In control experiments with the N-site protected using 1-methylindole no conversion of starting materials could be observed. Other nitrogen heterocycles such as pyrrole and indazole, afforded the products in good to excellent yields (32 and 33). For instance, 6-aminoindazole can be selectively acylated in the presence of an unprotected primary amine to give 33 in 69% yield.

To improve the E-factor of the reaction, aerial oxygen was investigated as the terminal oxidant (Scheme 2). In brief, the oxidation was accomplished with a system of electron transfer mediators (FePc and 2) and oxygen and efficiently replaces the stoichiometric use of 2 providing 12 in 90% yield.21d,f,h

The acyl indoles are good synthetic building blocks and can readily undergo further transformations (Scheme 3). For example, amide 17 can be converted to yield the corresponding benzophenone 34 by a Pd-catalyzed Suzuki–Miyaura reaction, in 53% yield. This is a rare example of a Pd-catalyzed C–N bond activation of an indole-based amide and combined with our oxidative amidation offers a rapid entry to a metal catalyzed coupling of aldehydes.27

Furthermore, the C–N bond in compound 11 smoothly undergoes hydrolysis in the presence of NaOH to yield carboxylic acid 35 and indole in quantitative yields. This transformation underpins the importance of the acylindole as a prominent protecting group for both carboxylic acids and indoles.

The proposed catalytic cycle starts with base promoted formation of carbene I. Carbene I adds to the aldehyde forming Breslow intermediate II that is oxidized by 2 to form the acyl
azolium (IV). In the next step the deprotonated indole adds to
the carbonyl carbon of intermediate IV forming the acylated
indole V and regenerating catalyst I (Scheme 4).

In conclusion, a chemo- and stereo-selective synthesis of synthetically valuable N-acylated indoles has been developed using oxidative
NHC-catalyzed reaction at ambient conditions. This reaction offers acyl-
indolones in good to excellent yields with a wide substrate scope.

Electron donating and electron withdrawing substituents on
the indole are tolerated. Our oxidative
NHC-catalyzed reaction also works with other heteroaromatic
compounds and can be used in a wide variety of transformations
such as pyrrole and indazole. The oxidative acyla-
tion of N-heterocycles with aldehydes is a promising alternative
to the harsh reaction conditions that normally accompany
these types of transformations.

Funding from the Swedish Research Council (VR and
Formas) is gratefully acknowledged. Furthermore, we thank
Magnus Bergvalls stiftelse for supporting the running costs of
this project.

Conflicts of interest
There are no conflicts to declare.

Notes and references
1 (a) R. W. Hoffmann, Synthesis, 2006, 3531–3541; (b) P. S. Baran,
2 R. J. Sundberg, The chemistry of indoles, ed. R. J. Sundberg,
3 T. Y. Shen, T. B. Windholz, A. Rosegay, B. E. Witzel, A. Wilson,
J. D. Willett, W. J. Holtz, R. L. Ellis, A. R. Matzuk, S. Lucas, C. A. Winter,
F. W. Holly, L. H. Saret, E. A. Risley, G. W. Nuss and C. A. Stammer,
4 M. Gallant, C. Dufresne, Y. Gareau, D. Guay, Y. Leblanc, P. Pratit,
C. Rochette, N. Sawyher, D. M. Slipetz, N. Tremblay, K. M. Metters
5 Y. Yang, X.-H. Duan, J.-Y. Deng, B. Jin, H.-M. Jia and B.-L. Liu,
6 (a) M. J. V. de Oliveira Baptistia, A. G. M. Barrett, D. H. R. Barton,
M. Girijaavalahan, R. C. Jennings and J. J. V. Papadimitriou,
1477–1500, DOI: 10.1039/P19770001477; (b) J. H. Liu, A. Stener,
(c) A. G. M. Barrett and D. Dhanak, Tetrahedron Lett., 1987, 28,
3327–3330; (d) E. Arai, H. Tokuyama, M. S. Linsell and T. Fukuyama,
7 (a) T. A. Dwight, N. R. Rue, D. Charyk, R. Josselyn and B. DeBoef,
Org. Lett., 2007, 9, 3137–3139; (b) D. V. Patil, M. A. Cavitt and
S. France, Org. Lett., 2011, 13, 5820–5823; (c) S. R. Kandikuri,
1265–1269; (d) J. Liu, S. Zhao, W. Song, R. Li, X. Guo, K. Zhuo and
8 (a) T. Okuuchi, M. Itouama, T. Minami, T. Owa, K. Kito and
H. Yoshino, Org. Lett., 2000, 2, 1485–1487; (b) O. Ottomi, A. d. V. F.
1005–1007.
10 For selected examples of N-acylation of indoles, see: (a) W. J.
17, 544–547; (b) V. O. Ilii, Synthesis, 1979, 387–388; (c) Y. Kikugawa,
Synthesis, 1981, 460–461; (d) O. Ottoni, R. Cruz and R. Alves,
Tetrahedron, 1998, 54, 13915–13928; (e) D. S. Dhanoo, S. W. Bagley,
R. S. L. Chang, V. J. Lotti, T. B. Chen, S. D. Kivlin, G. J. Zingaro,
36, 4230–4238; (f) J. B. Bremner, S. Samosorn and J. I. Ambrus,
Synthesis, 2004, 2653–2658; (g) A. Umechara, H. Ueda and
13 (a) D. Enders, O. Niemeier and A. Henseler, Chem. Rev., 2007, 107,
3606–3653; (b) A. T. Biju, N. Kuhl and F. Glorius, Acc. Chem. Res.,
2011, 44, 1182–1195; (c) Stereoselective Organocatalysis: Bond Form-
ation Methodologies and Activation Modes, ed. R. R. Torres, John
Wiley & Sons, Inc., 2013; (d) D. M. Flanagan, F. Romanov-
Michailidis, N. A. White and T. Rovis, Chem. Rev., 2015, 115,
9307–9387.
696–707; (b) C. Zhang, J. F. Hooper and D. W. Lupton, ACS Catal.,
2017, 7, 2583–2596.

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