This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
A method for convenient synthesis of N-alkyl-2-aryl-indole-3-carbaldehyde has been described. A variety of highly valuable indolyl aldehydes have been made through this method. Electro donating groups on both aromatic rings (anilinyl and benzyl) facilitate the formation of the desired products. A benzylic C-H insertion by rhodium carbene is the key step for this transformation.

1,2,3-Trisubstituted indole moiety constitutes a large number of natural and synthetic biologically active molecules and functional materials. 3-Formyl indole is a versatile intermediate for the synthesis of indole derivatives due to the diverse transformations the aldehyde functional group could participate in. Conventionally, direct formylation of corresponding parent indole is the choice for the preparation of this class of molecule, such as Vilsmeier-Haack formylation, Reimer-Tiemann-Gattermann reaction, and recently reported protocols for direct indole formylation. On the other hand, several de novo methods for construction of 3-formyl indole from non-indole precursors have also appeared in literatures which possess some merits devoid in direct approach.

Since disclosed as a convenient 2-azavinyl carbene progenitor in 2008, 1-sulfonyl 1,2,3-triazoles have been applied with great success in a variety of efficient transformations leading to the construction of unique frameworks otherwise hardly accessible. Our interests in this research area has led to the discovery of several practical reactions, and that particularly relevant to the current report is rhodium catalyzed 3-formyl indole synthesis from triazole 1 (Scheme 1. equation a). A key event in this process is the (formal) insertion of the in situ generated metal carbene into the ortho anilinyl Csp2-H bond. Here we wish to report a complementary strategy which employed N-benzyl anilinyl triazole as starting material for a facile entry to 1-alkyl-2-aromatic-3-formyl indole (Scheme 1. equation b).

Initially, NN-bisallyl-anilinyl triazole 3a was treated with catalytic amount of Rh(OAc)₃ in heating toluene under nitrogen and tricyclic aldehyde 7a was isolated in 60% yield after hydrolysis in open flask. Efforts to expand this reaction to other close analogous have encountered unexpected difficulties as triazoles 3b and 3c, with one allyl group replaced by methyl or tosyl group respectively, delivered complex reaction mixtures. However, when substrate 3d, which carrying a N-benzyl group instead, was subjected to the identical reaction conditions, 1-allyl-2-phenyl-3-formyl indole 4d was, interestingly, isolated in 47% yield. The divergence in reaction behaviours of 3a-3d was really intriguing giving the subtle structural variations.
discrepancies among these molecules. Even though the exact reason for the substituent sensitive selectivity is not clear at present stage, it can be deduced that the azavinyl carbened 5a derived from 3a reacted with one pendent allyl double bond to give cyclopropane 6a (Scheme 2, a); while in intermediate 5d, the allyl group was out-competed by the neighbouring benzyllic C=−H for the rhodium carbene, the resulting indoline intermediate underwent in situ dehydrogenative aromatization to give 6d (Scheme 2, c). On the other hand, reactive carbenoids 5b and 5c may undergo multiple pathways leading to various products each in small quantity (Scheme 2, b).

Table 1. Preparation of 3-Formyl Indoles from Sulfonyl Triazoles

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product, Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>4a, 69%</td>
</tr>
<tr>
<td>3b</td>
<td>4b, 72%</td>
</tr>
<tr>
<td>3c</td>
<td>4c, 74%</td>
</tr>
<tr>
<td>3d</td>
<td>4d, 32%</td>
</tr>
<tr>
<td>3e</td>
<td>4e, 55%</td>
</tr>
<tr>
<td>3f</td>
<td>4f, 72%</td>
</tr>
<tr>
<td>3g</td>
<td>4g, 65%</td>
</tr>
<tr>
<td>3h</td>
<td>4h, 55%</td>
</tr>
<tr>
<td>3i</td>
<td>4i, 52%</td>
</tr>
</tbody>
</table>

Notes and references

We were interested in the C-H insertion pathway as it could serve as a complementary method for our prior de novo 3-formyl indole synthesis (Scheme 1, a). A range of N-benzyl-anilinyl sulfonyl triazoles have been made and submitted to the rhodium catalyzed reactions. The data were collected in Table 1. For the N,N-bisbenzyl series (3e-3i), the electronic impact on the reaction is prominent, evidenced by the 74% and 72% yields of 4g and 4f bearing methoxyl and methyl groups at 6-position correspondingly, and the decreased yields of chlorinated 4h (54%) and fluorinated 4i (52%). The trend that electron donating group facilitate the indole formation also held for substituent effect on the N-benzyl moiety. In N-benzyl-N-methyl series (3j-3o), the yield increased from 25% for 4-CO2Me-benzyl anilinyl triazole 3o to 55% for 4-MeO-benzyl anilinyl triazole 3l. Aromacity extended 2-naphthalenyl indole 4p was obtained from 3p in a much higher yield than corresponding 2-phenyl indole 4j from 3j (63% vs 38%).

Figure 1. Monitoring rhodium catalysed triazole decomposition via proton NMR

The trend that electron donating group facilitate the indole formation also held for substituent effect on the N-benzyl moiety. In N-benzyl-N-methyl series (3j-3o), the yield increased from 25% for 4-CO2Me-benzyl anilinyl triazole 3o to 55% for 4-MeO-benzyl anilinyl triazole 3l. Aromacity extended 2-naphthalenyl indole 4p was obtained from 3p in a much higher yield than corresponding 2-phenyl indole 4j from 3j (63% vs 38%). Moreover, he higher yields in general for the former series than for the latter ones might reflect both steric and statistical effects. Tetracyclic aldehyde 4q was easily made in 61% yield by using triazole 3q as substrate.

The authors wish to thank the Natural Science Foundation of China (21402014 and 21272077), the Natural Science Foundation of Jiangsu Province (SBK201321632), the Priority Academic Program Development of Jiangsu Higher Education Institutions (PADA), and Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology (BM2012110).
School of Pharmaceutical Engineering and Life Science, Changzhou University, Changzhou, Jiangsu Province, 213164, China. Email: meihuashen@gmail.com, huadongxu@gmail.com.

† Electronic Supplementary Information (ESI) available: The details of experiments, compound characterization and spectroscopic data. See DOI: 10.1039/c000000x/.


