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Palladium-catalysed decarboxylative nitrile insertion via C-H activation or self-coupling of indole-2-carboxylic acids: A new route to indolocarbolines and triindoles

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The best conditions for the reaction of 1a with 2b (see ESI, Table S1) were: 10 mol % of Pd(OAc)$_2$ as catalyst, Ag$_2$CO$_3$ (2.0 equiv) as oxidant at 80 °C for 12 h (65% yield; entry 4). The scope of this decarboxylative [Pd]-catalysed reaction was then examined with respect to both indole-2-carboxylic acids 1 and nitriles 2 (Table 1). Gratifyingly, this protocol was general to a wide range of indole carboxylic acids and nitriles (48-65 %) except in the case of 3aa where formation of triindoles was significant (vide infra). Compounds of type 4-5 were not obtained in other cases (viz. entries 2-22). The yield of the isolated product was moderate probably because of the formation of insoluble silver carboxylate salt (X-ray powder diffraction). A variety of substrates including cinnamyl nitrile afforded the expected products 3ab-3jd in good yield. Nitrile attached to heterocyclic moiety or a functional group like CHO attached to phenyl moiety of nitrile were perfectly tolerated (products 3aj-3ak). X-ray structures of compounds 3aa (Figure S3) and 3ac (Figure S4) have been determined. The new carbolines exhibit fairly strong fluorescence emission spectra in the visible region (see ESI).

Table 1. Formation of indole fused α-carbolines 3*
The intermediate palladium(II) carboxylate species I (Scheme 1) is formed first. This proposal is consistent with the fact that 1a reacts with Pd(OAc)$_2$ (1:1 stoichiometry) even at room temperature (25 °C) within 15 min with the complete consumption of 1a. Species I undergoes carbo-palladation at the 3-position affording the key palladacycle intermediate II. Decarboxylation of II results in the metallated species III. Meanwhile, 1a undergoes decarboxylation in the presence of silver carbonate affording the arylic metal species IV, which on transmetalation with the Pd$_0$ species III gives the biaryl Pd$_0$ species V. Intermediate V gives the biindolyl VI (also see Scheme 2 below) and Pd$_0$ by reductive elimination. This Pd$_0$ species may be oxidized in the presence of Ag$_2$O salt to regenerate active Pd$_0$ species. The in situ produced biindolyl VI undergoes palladation to give VII. This species has been proposed earlier by Liang et al. Species VII upon nitrile insertion produces VIII. Upon intramolecular C-H activation, VIII leads to the palladacycle IX that by reductive elimination affords indole fused α-carboline 3ab. Again, Pd$_0$ is reoxidized to Pd$_0$ via Ag$_2$O, thus closing the catalytic cycle.

As mentioned above, the pathway for the formation of indole fused α-carboline (e.g., 3ab) is assumed to take place via biindolyl intermediate by dual C-H activation. To confirm this, we performed a reaction between biindolyl VI and benzonitrile. Satisfyingly, this reaction afforded α-carboline 3ab in 52% yield (Scheme 2) vindicating our proposal. Formation of 3ab from VI is not a simple [4+2] cycloaddition, since in the absence of the catalyst, the reaction did not take place. Also, dimethylacetylene dicarboxylate (DMAD) did not undergo [4+2] cycloaddition with VI. These results are also consistent with the involvement of palladium catalyst in the final steps.

Scheme 1 Plausible pathway for decarboxylative coupling of 1a and nitrile 2b.

The reaction of 1-methyl-indole-2-carboxylic acid 1a with benzonitrile 2b using of Pd(OAc)$_2$ [10 mol %]/Ag$_2$CO$_3$ [2 equiv] in DMF at 80-90 °C afforded three products. One was indole fused α-carboline (3ab; ~10 %); the other two were the heptacyclic triindoles (diindolocarbazoles). After careful chromatography, both symmetrical and unsymmetrical triindoles (overall yield 35%) were isolated thus revealing a new type of reaction in indole chemistry. Such products must have been formed in several reactions of indole substrates (albeit in small quantities) where Pd(OAc)$_2$/Ag$_2$CO$_3$ system is utilized, but to our knowledge, are not reported thus far.

In the above reaction, benzonitrile is not required for the formation of triindoles. Even a blank reaction of 1a with Pd(OAc)$_2$/Ag$_2$CO$_3$ in DMF led to the symmetrical and unsymmetrical triindoles in an overall yield of 48% (Table S2, entry 4). Inspired by this, we synthesized triindoles 4a, 5a, and 5a using the protocol: Pd(OAc)$_2$ (10 mol %)/
Ag2CO3 (2.0 equiv) in DMF at 80 °C for 10 h (48% overall yield; Table S2, entry 4). Because of the closeness in the Rf values of the symmetrical and unsymmetrical triindoles, we were able to separate both the isomers only in selected cases. Overall, four symmetrical triindoles (4a, 4i, 4k, and 4l) and five unsymmetrical triindoles (5a-b, 5h, 5i, and 5l) have been obtained in a pure state.2 Quite pleasingly, the yield (after isolation) and selectivity of 5a was dramatically increased to 50% by keeping the reaction for 12 h at 30 °C and then slowly raising the temperature to 50 °C during 12 h (Table 2, entry 2). This observation may be related to kinetic/steric parameters. Inspired by this, we prepared compound 5b also in 42% yield (entry 5). In other cases, both the isomers were formed under these conditions. The structures of 5b and 4k were confirmed by single crystal X-ray analysis (Figures S5 and S6).14 fluorescence spectra for selected compounds are provided as ESI.

Table 2. Synthesis of triindoles (dindolocarbazoles) 4 and 5

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>R1, R2</th>
<th>triindolea</th>
<th>overall yield [%]</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>sym</td>
<td>unsym</td>
</tr>
<tr>
<td>1</td>
<td>1a</td>
<td>H, Me</td>
<td>4a (20%)</td>
<td>5a (28%) 48</td>
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<tr>
<td>2c</td>
<td>1a</td>
<td>H, Me</td>
<td>-</td>
<td>5a (50%) 50</td>
</tr>
<tr>
<td>3d</td>
<td>1b</td>
<td>OMe, Me</td>
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<td>5b (30%) 45</td>
</tr>
<tr>
<td>4d</td>
<td>1h</td>
<td>H, Bn</td>
<td>Not isolated</td>
<td>5h (32%) 43</td>
</tr>
<tr>
<td>5c</td>
<td>1h</td>
<td>H, Bn</td>
<td>-</td>
<td>5h (42%) 42</td>
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<tr>
<td>6</td>
<td>1i</td>
<td>H, EOM</td>
<td>4i (21%)</td>
<td>5i (31%) 52</td>
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<tr>
<td>7d</td>
<td>1k</td>
<td>OMe, Bn</td>
<td>Not isolated</td>
<td>4k (35%) 44</td>
</tr>
<tr>
<td>8</td>
<td>1l</td>
<td>H, Bu</td>
<td>4l (20%)</td>
<td>5l (30%) 50</td>
</tr>
</tbody>
</table>

Reactions were performed at rt for 12 h and then heated to 50 °C (oil bath) for 12 h. In these cases, only one isomer was isolated in a pure state. The other isomer was eluted along with the first one (very close Rf values); this was obtained only as the isomeric mixture. The combined weight (isomeric mixture + pure isomer) corresponds to the total yield.

In summary, a new [Pd]-catalysed cyclization reaction of indole carboxylic acids with a nitrile (e.g., acetonitrile or benzonitrile) involving nitrile insertion and leading to fluorescence active indolocarbazoles, is discovered. This result is significant because acetonitrile or benzonitrile is often used as a solvent in [Pd]-catalysed reactions involving indoles. In the absence of the nitrile, triindoles are obtained. This observation acts as a caveat while using the common [Pd]-catalyst/Ag2CO3 system in similar reactions. To our knowledge, there is no such previously recorded report.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental details including Tables S1-S4, structures showing the importance of α-carboline/ triindoles (Figures S1-S2), Structures of 3aa, 3ac, 4b, 4k and A (Figure S3-S7), fluorescence spectra (Figures S8-S22), CIF file and 1H-13C NMR spectra. See DOI:10.1039/c0c000000x


13 We observed a small quantity of such triinolides in the reaction between allenes and indole carboxylic acids, but could not identify them earlier. An indolocaraboline, though, was identified. See: R. Rama Suresh, K. C. Kumara Swamy, J. Org. Chem., 2012, 77, 6959.

14 a) Crystallographic data for the structures 3aa, 3ac, 5b, 4k and A have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1029448-1029452.


19 Coordination by (terminal) nitrile nitrogen may also be relevant, because compound 1a did not react with benzaldehyde, κ-buty1 isocyanate or phenylisothiocyanate.
