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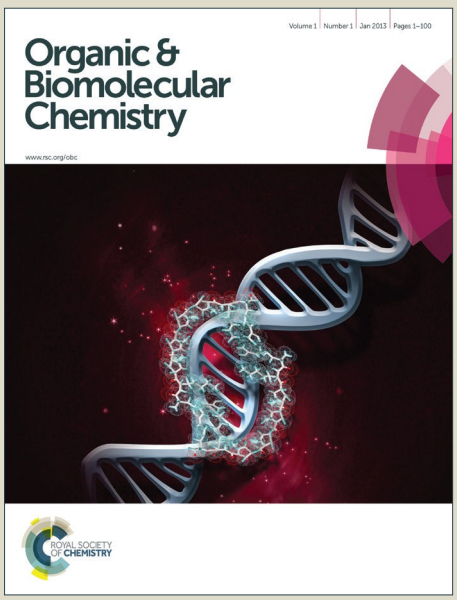

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An Efficient Approach to 1,2,3-Trisubstituted Indole Via Rhodium Catalyzed Carbene C_{sp3}-H Bond Insertion

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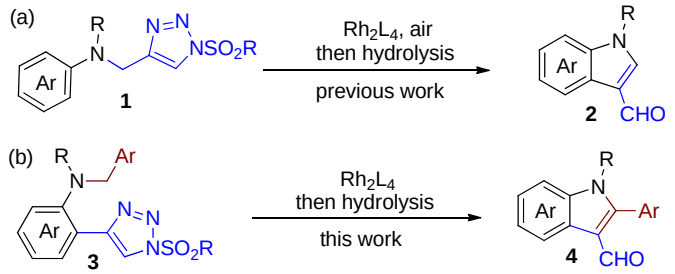
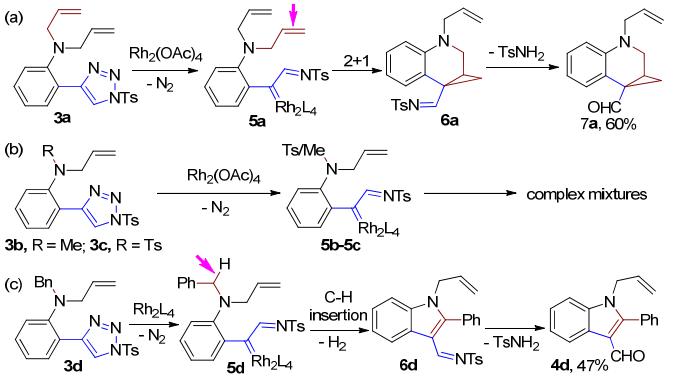
A method for convenient synthesis of N-alkyl-2-aryl-indole-3-carbaldehyde has been described. A variety of highly valuable indolyl aldehydes have been made through this method. Electro donating groups on both aromatic rings (anilinyl and benzyl) facilitate the formation of the desired products. A benzylic 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.[1] Conventionally, direct formylation of corresponding parent indole is the choice for the preparation of this class of molecule, such as Vilsmeier-Haack formylation,[2] Reimer-Tiemann-Gattermann reaction,[3] and recently reported protocols for direct indole formylation.[4] 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.[5]



Scheme 1. Complementary De Novo 3-Formyl Indole Synthesis Using Sulfonyl Triazoles

Since disclosed as a convenient 2-azavinyl carbene progenitor in 2008,[6] 1-sulfonyl 1,2,3-triazoles have been applied with great success in a variety of efficient transformations[7] leading to the construction of unique frameworks otherwise hardly accessible.[8] Our interests in this research area has led to the discovery of several practical reactions,[9] and that particularly relevant to the current report is rhodium catalyzed 3-formyl indole synthesis from triazole **1** (Scheme 1. equation a).[9a] A key event in this process is the (formal) insertion of the in situ generated metal carbene into the ortho anilinyl Csp2-H bond.[8h,l,m] Here we wish to report a complementary strategy which employed N-benzyl anilinyl triazole **3** as starting material for a facile entry to 1-alkyl-2-aromatic-3-formyl indole **4** (Scheme 1. equation b).

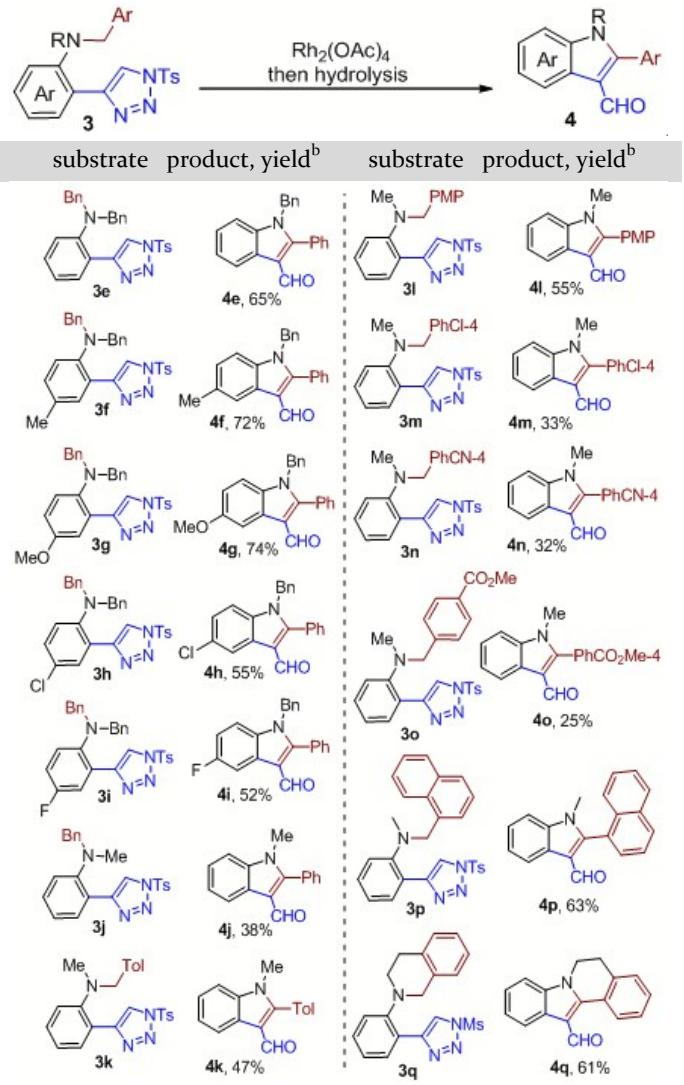


Scheme 2. The Divergent Outcomes Affected by Subtle N-Substituent Variations

Initially, N,N-bisallyl-anilinyl trizaole **3a** was treated with catalytic amount of $Rh_2(OAc)_4$ 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

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 carbenoid **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 benzylic C_{sp3}-H for the rhodium carbene,[10] 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[a]



[a]Reaction conditions: step 1) **3** (0.4 mmol), $Rh_2(OAc)_4$ (2.0 mol %), tol (4 mL), 85 °C, under N_2 for 2 h, then volatiles removed under vacuum; step 2) K_2CO_3 (1.6 mmol), MeOH (4 mL), rt, in air overnight. [b]Isolated yield.

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 trizaole **3o** to 55% for 4-MeO-benzyl anilinyl trizaole **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 reaction of triazole **3p** in $CDCl_3$ was monitored by ^1H NMR for more information (Figure 1). Peaks **a** and **b** almost disappeared when the mixture was heated at 80 °C at N_2 for 5 hours, indicating triazole **3p** decomposed completely at this point. Along the reaction course, distinct new peaks **d** and **e** emerged and grew (Figure 1. a, b, c). Flash column chromatography of this reaction mixture delivered a semi-purified product which was assigned as indolyl tosylimine **6p** based on ^1H NMR analysis (Figure 1. d). The direct observation of indole **6p** in the reaction mixture rather than its non-aromatic precursor, the corresponding indoline intermediate, suggests an instant in situ dehydrogenative aromatization after a carbene C-H insertion event.

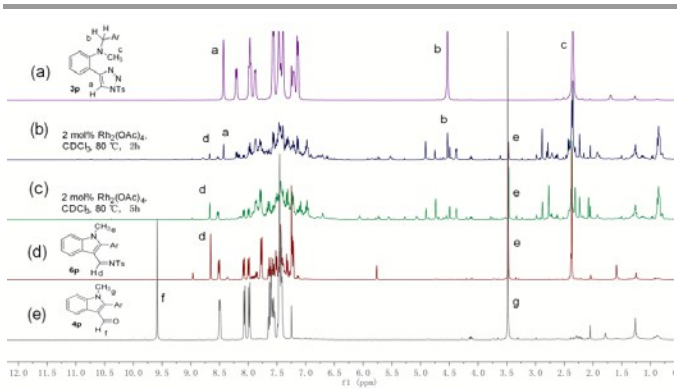


Figure 1. Monitoring rhodium catalysed triazole decomposition via proton NMR

Inclusion, 2-(N-alkyl-N-benzyl)-anilinyl triazoles have been used as facile starting materials for the synthesis of N-alkyl-2-aryl-Indole-3-Carbaldehydes. Triazoles with electro donating group on both aromatic rings usually gave higher yields than triazoles with electro withdrawing group. This method featuring a rhodium catalyzed C-H functionalization of benzyl aromatic amine and a dehydrogenative aromatization.

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Notes and references

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