First example of regiospecific intermolecular C–H insertion reactions of cyclic rhodium carbenoids: novel synthesis of 3-indol-3′-yloxindoles

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Facile regiospecific intermolecular C–H insertion reactions of cyclic rhodium carbenoids have been achieved using diazo carbonyl compounds 1 and indole or *N*-substituted indoles to afford 1,3-dihydro-1′*H*-[3,3′]biindolyl-2-ones, 3a–o in an excellent yield.

Oxindole derivatives are known to possess a variety of biological activities.[1] Oxindole systems having indole 3-substituents are present in various marine microorganisms such as sponge *Hyrtios altum*.[2] Interestingly, polybromo 3,3′-biindoles are also present in the blue–green alga *rivularia firma*.[3] In continuation of our work[4] on reactions of diazo carbonyl compounds with indoles, we focused our attention on the synthesis of indolyloxindoles using cyclic rhodium carbenoids. The reaction of α-diazo carbonyl compounds with rhodium(II) carboxylates is a well described method to generate the rhodium carbenoids, which can undergo an array of reactions such as cyclopropanations, C–H or heteroatom-H insertions and ylide formations.[5] Insertion reactions of carbenes into C–H bonds have gained significant attention since the first discovery by Meerwein, Rathjen and Werner.[6] The insertion process can proceed either by an intermolecular or intramolecular pathway.[7] A number of reports are available in the chemical literature, which describe the intramolecular insertion of metal-stabilized carbenoids to the C–H bonds for the construction of five membered carbocyclic and heterocyclic systems.[8] Apparently, the intermolecular C–H insertions are believed to be synthetically not useful because of the low selectivity and competitive intramolecular reactions.[5b,7] A few literature reports are available on the intermolecular C–H insertion of metallo-carbenoids, which reveal the formation of a mixture of products without any selectivity.[9] To the best of our knowledge, there is no report in which the intermolecular C–H insertion reaction of cyclic metallo-carbenoids is achieved although these intermediates always have a propensity to afford cycloadducts[10] *via* 1,3-dipolar cycloaddition reactions. We have been extensively involved in developing new synthetic strategies[11] using diazo carbonyl compounds. Consequent to these efforts, herein we report the novel and regiospecific intermolecular C–H insertion reactions of 3-diazooxindoles with substituted/unsubstituted indoles in the presence of a Rh₂(OAc)₄ catalyst.

We investigated the rhodium(II)-catalyzed behavior of cyclic diazo carbonyl compounds† 1 with indoles 2 in an intermolecular fashion. The reaction of 3-diazooxindole (1a) and indole (2a) with 0.3 mol% rhodium(II) acetate dimer catalyst afforded biindole 3a in 81% yield (Scheme 1) with regiospecificity. The regiochemistry of the product 3a was unequivocally corroborated by single-crystal X-ray (Fig. 1) analysis.‡

Subsequently, we investigated the rhodium(II)-catalyzed reaction of cyclic diazo carbonyl compound 1a with *N*-methyl or *N*-benzylindole which furnished the C–H insertion products 3b,c respectively in very good yields (Table 1) with regiospecificity.

Encouraged by these results obtained in the above reactions, we were further interested to carry out the reactions of substituted cyclic diazo carbonyl compounds 1b–e. Surprisingly, the rhodium(II)-catalyzed reactions of diazooxindoles

1b–e with 2a–c were completed within 1 h and the chromatographic purification of the reaction mixtures resulted the respective pure products 3.§ Reactions that yielded products 3c,f,i,l,o, were followed by IR spectroscopy (disappearance of the characteristic diazo peak), due to the identical *R*f value of

1a R¹ = H
1b R¹ = CH₃
1c R¹ = CH₂Ph
1d R¹ = Allyl
1e R¹ = COPh

2a R² = H
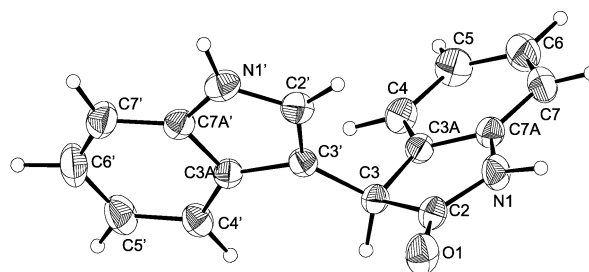**2b** R² = CH₃
2c R² = CH₂Ph
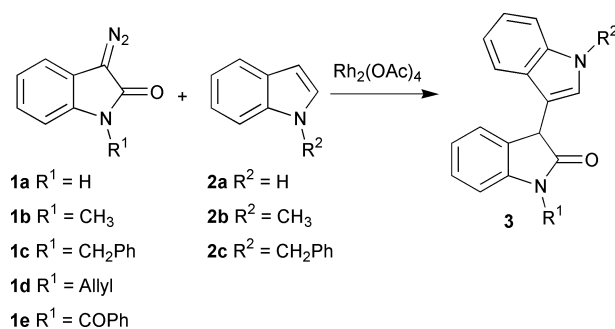
Scheme 1

Fig. 1 Crystal structure (ORTEP representation) of **3a**.

Table 1 Regiospecific C–H insertion of diazo compounds **1** with indoles **2** catalyzed by rhodium(II) acetate.*a*

Biindole 3	R¹	R²	Time	Yield*b*(%)	mp/°C
a	H	H	10 h	81	176–178
b	H	CH₃	10 h	85	180–182
c	H	CH₂Ph	10 h	87	186–188
d	CH₃	H	60 min	>99	162–164
e	CH₃	CH₃	60 min	>99	127–129
f	CH₃	CH₂Ph	60 min	>99	105–107
g	CH₂Ph	H	60 min	>99	166–168
h	CH₂Ph	CH₃	30 min	>99	95–97
i	CH₂Ph	CH₂Ph	30 min	>99	155–157
j	Allyl	H	60 min	>99	131–133
k	Allyl	CH₃	30 min	>99	119–121
l	Allyl	CH₂Ph	30 min	>99	101–103
m	COPh	H	5 min	63	147–149
n	COPh	CH₃	7 min	66	114–116
o	COPh	CH₂Ph	7 min	73	133–135

a Reactions were carried out as follows: a catalytic amount of Rh₂(OAc)₄ (0.3 mol%) was added to a stirred solution of cyclic diazo compound **1** (1 mmol) and indole **2** (1.2 mmol) in freshly prepared dry DCM at rt under an argon atmosphere. After completion of the reaction, the solvent was evaporated *in vacuo* and the residue purified by chromatography. *b* Yields (unoptimized) refer to isolated and chromatographically pure compounds of **3**.

Scheme 2
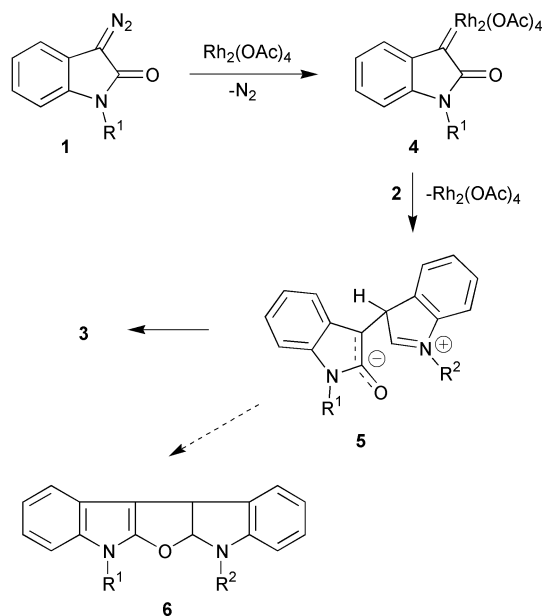
starting materials in TLC. These reactions led to the facile synthesis of substituted and unsubstituted biindoles **3** in quantitative yield evidently from many examples (Table 1). Surprisingly, the diazo carbonyl compound having an electron-withdrawing group (**1e**) underwent reaction with indoles **2a–c** in short duration, but the yield was reduced when compared with other reactions.

In all reactions, the regiospecific biindoles were obtained exclusively as a result of the C–H insertion of diazo ketones **1** to the 3-position of indoles in the presence of 0.3 mol% of $Rh_2(OAc)_4$ catalyst. We have not obtained any products resulting from the potential competitive intermolecular N–H insertion[13] reaction (where R^2 = H) of the rhodium carbenoids. A plausible mechanism for the reactions of cyclic diazo carbonyl compounds **1** with indoles **2** in the presence of rhodium(II) acetate may be proposed as given in Scheme 2. The initially formed transient rhodium carbenoid **4** underwent insertion to the nucleophilic indole 3-position to produce zwitterion **5** followed by a proton transfer to furnish product **3**. The ring closure of zwitterion **5** did not furnish any anticipated cycloadducts **6**.[10]

In summary, we have demonstrated the facile synthesis of N-substituted and unsubstituted 3-indol-3′-yloxindoles from cyclic diazo carbonyl compounds **1** and indoles **2** *via* intermolecular C–H insertion. This methodology forms the first regiospecific synthesis using an intermolecular rhodium carbenoid C–H insertion process. Further exploration of this strategy with other heterocyclic systems and approach towards the naturally existing molecules is currently in progress.

Notes and references

† The cyclic diazo carbonyl compound **1a** was obtained by the literature method.[12] The N-substituted-3-diazooxindoles (**1b–d**) were synthesized by N-alkylation of 3-diazooxindole (**1a**) with methyl iodide, benzyl bromide or allyl bromide using 10% ethanolic KOH solution. The N-benzoyl-3-diazooxindole (**1e**) was synthesized by N-benzoylation of **1a** with benzoyl chloride using n-butyllithium at −70 °C.

‡ *Crystal data for* **3a**: $C_{16}H_{12}N_2O$, M = 248.3, colorless prism $0.18 \times 0.12 \times 0.10$ mm, monoclinic, $P2_1/n$, a = 11.137(4), b = 4.6810(10), c = 23.871(6) Å, β = 95.85(2)°, V = 1238.0(6) Å^3, T = 293(2) K, Z = 4, D_c = 1.332 Mg m^{-3}, $F(000)$ = 520, μ = 0.085 mm^{-1}, λ = 0.7107 Å, 2178 reflections were collected on a CAD-4 diffractometer, 1507 were independent ($I \geqslant 2\sigma(I)$). Final R_1 = 0.0465, wR_2 = 0.1315 observed data. The largest difference peak and hole = 0.196 and −0.230 eÅ^{-3} respectively. The solid-state supramolecular arrangement of compound **3a** shows that the molecules are arranged in layers along the a-axis by alignment of the adjacent screw type molecules with three types of hydrogen bonding interactions, namely C–H⋯O, N–H⋯O and N–H⋯N. The structure was solved and refined using G. M. Sheldrick, *SHELX*97 program, University of Göttingen, Germany, 1997. CCDC 177615. See http://www.rsc.org/suppdata/cc/b2/b200412g/ for crystallographic data in cif or other electronic format.

§ All new compounds exhibited spectral data consistent with their structures.

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