$Rh_2(OAc)_4$-Catalyzed Regioselective Intermolecular C–H Insertion Reactions: Novel Synthesis of 2-Pyrrol-3′-yloxindoles

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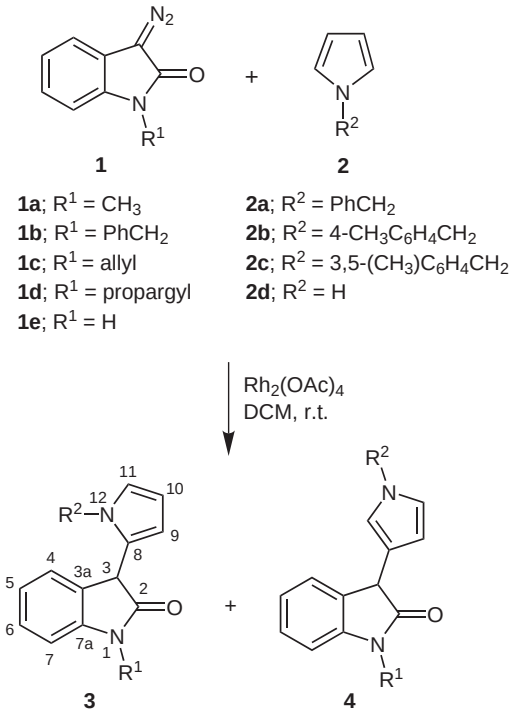
Abstract: Regioselective synthesis of 2-pyrrol-3′-yloxindoles has been achieved by the reactions of cyclic diazo carbonyl compounds **1a**–**e** with pyrrole and substituted pyrroles (**2a**–**d**) in the presence of rhodium(II) acetate catalyst via intermolecular C–H insertion reaction.

Key words: C–H insertion reaction, oxindole, pyrrole, rhodium(II) acetate

Diazo moiety has become a key component in a number of synthetic transformations since from the first recorded synthesis of α-diazo carbonyl compound by Curtius[1] in 1883. Diazo carbonyl compounds are extremely versatile and have been stupendous in many catalytic carbon-carbon bond forming reactions. There has been enormous interest in the use of rhodium(II) carboxylate catalysts, which are commercially available, air stable and functional group tolerant for many synthetic transformations of α-diazo carbonyl compounds.[2] To generate an intermediate rhodium carbenoid, the reaction of α-diazo carbonyl compounds in the presence of rhodium(II) carboxylates is a well described method, which can undergo an array of reactions such as cyclopropanation, C–H or X–H insertion and ylide formation.[3] The formation of carbon-carbon bonds using C–H insertion reaction has become a potential arsenal in synthetic organic chemistry, which can proceed either by an intermolecular or intramolecular manner.[2,4] 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.[5] Until our recent discovery on regiospecific intermolecular insertion reaction,[6] the intermolecular C–H insertion is believed to be synthetically not useful because of low selectivity and competitive intramolecular reactions.[2,4] 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.[7] The intermolecular C–H insertion reactions of cyclic metallo-carbenoids are not much developed since these intermediates always have a propensity to afford cycloadducts[8] via 1,3-dipolar cycloaddition reactions. In continuation of our interest in developing new synthetic strategies[9] employing diazo carbonyl compounds, we turned our attention to develop an efficient general approach to the synthesis of 2-pyrrol-3′-yloxindoles using cyclic metallo-carbenoids and herein we describe the preliminary results of these reactions.

The required 3-diazooxindole[10] (**1a**) and substituted pyrroles[11] **2** were assembled based on the literature procedures. The N-substituted-3-diazooxindoles **1b**–**e** were synthesized by N-alkylation of 3-diazooxindole (**1a**) using methyl iodide, benzyl bromide, allyl bromide or propargyl bromide in the presence of sodium hydride/DMF in 80% to 95% yield. Subsequently, we investigated the rhodium(II) acetate catalyzed behavior of cyclic diazo carbonyl compounds **1** with pyrroles **2** in an intermolecular fashion. The reaction[12] of *N*-methyl-3-diazooxindole (**1a**) and *N*-benzyl pyrrole (**2a**) with 1 mol% rhodium(II) acetate dimer catalyst in dry dichloromethane was stirred at room temperature under an argon atmosphere for 6 hours. The solvent was concentrated in vacuum and the chromatographic purification of the reaction mixture using flash silica gel column chromatography furnished the products **3a** and **4a** in 70% and 3% yields, respectively (Scheme 1).



Scheme 1

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The presence of amide carbonyl group in IR spectrum and a characteristic singlet at δ = 4.55 ppm for oxindolyl 3-proton in ^{1}H NMR spectrum of **3a**, confirm the C–H insertion. Further, the presence of a pyrrolyl proton in the down-field region (≈ δ = 6.70 ppm) and two pyrrolyl protons in the up-field region (≈ δ = 6.00 ppm) for compound **3a** in ^{1}H NMR spectrum, unequivocally confirm the regiochemistry of C–H insertion at 2-position of pyrrole moiety. Similarly, the regiochemistry of product **4a** was also confirmed.

Encouraged by the results obtained in these reactions, we were further interested to carry out the reactions[13] of substituted and unsubstituted 3-diazooxindoles **1a**–**e** with pyrroles **2a**–**d** (Table 1). The N-substituted 3-diazooxindoles **1a**–**d** reacts faster with N-substituted pyrroles **2a**–**c** compared to the corresponding unsubstituted analog. In all reactions, the carbenoid insertion took place regioselectively at 2-position of the pyrrole to furnish the corresponding 2-pyrrol-3′-yloxindoles **3** as the major product. The crude proton NMR-spectrum of a few reaction mixtures indicated that the presence of the minor regioisomer, which could be isolated and characterized as 3-pyrrol-3′-yloxindoles **4** (Table 1). These reactions led to facile synthesis of substituted/unsubstituted 2-pyrrol-3′-yloxindoles as a formal net C–H insertion process. It is very interesting to mention here that nearly half of the reactions, which we carried out are regiospecific. We have not obtained any other products resulting from the potential competitive intermolecular N–H insertion[14] reaction (when R^1, R^2 = H) and cyclopropanation reaction[15] (when R^1 = allyl, propargyl) of the rhodium carbenoids. Typically the quantity of the catalyst was maintained only at 1 mol% for performing the above experiments.

It is relevant to mention here that only one report exists in this line where the reactions of 2-diazo-1,3-cyclohexanedione with pyrrole have been studied by Pirrung and co-workers.[8a] However, these reactions required inert solvent such as hexaflurobenzene and reflux conditions, which resulted in the mixture of products with low yields without having any selectivity. Even with an excess amount of pyrroles (4 equiv) the cyclic diazo compounds are preferably tend to react with solvent such as fluorobenzene than pyrroles. A plausible mechanism for the reactions of cyclic diazo carbonyl compounds **1** with

Table 1 Reactions of Cyclic Diazoamides **1a**–**e** with Pyrroles **2a**–**d**

Entry	R^1	R^2	Reaction time (h)	Yield of 3 (%)[a]	Yield of 4 (%)[a]
a	CH_3	$PhCH_2$	6	70	3
b	$PhCH_2$	$PhCH_2$	6	71	4
c	allyl	$PhCH_2$	6	67	–
d	propargyl	$PhCH_2$	6	65	–
e	H	$PhCH_2$	9	65	–
f	CH_3	4-$CH_3C_6H_4CH_2$	5	72	5
g	$PhCH_2$	4-$CH_3C_6H_4CH_2$	5	75	4
h	allyl	4-$CH_3C_6H_4CH_2$	5	69	–
i	propargyl	4-$CH_3C_6H_4CH_2$	5	71	–
j	H	4-$CH_3C_6H_4CH_2$	9	58	–
k	CH_3	3,5-$(CH_3)_2C_6H_4CH_2$	5	73	4
l	$PhCH_2$	3,5-$(CH_3)_2C_6H_4CH_2$	5	75	3
m	allyl	3,5-$(CH_3)_2C_6H_4CH_2$	5	70	–
n	propargyl	3,5-$(CH_3)_2C_6H_4CH_2$	5	72	–
o	H	3,5-$(CH_3)_2C_6H_4CH_2$	9	66	–
p	CH_3	H	9	67	4
q	$PhCH_2$	H	9	74	5
r	allyl	H	9	54	–
s	propargyl	H	9	64	–

[a] Yields (unoptimized) refer to isolated and chromatographically pure compounds **3** and **4**.

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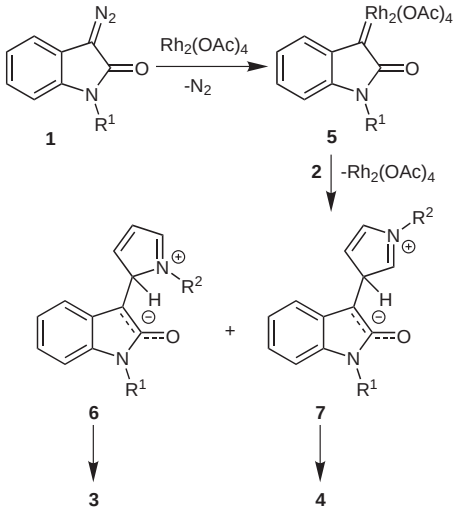
pyrroles **2** in the presence of rhodium(II) acetate may be proposed as given in Scheme 2. The initially formed transient rhodium carbenoid **5** underwent insertion to the nucleophilic 2-position with less extent to 3-position of pyrrole moiety to produce zwitterions **6** and **7**, respectively. The subsequent proton transfer of these zwitterions furnished products **3** and **4**.



Scheme 2

In conclusion, we have demonstrated the novel and mild regioselective synthesis of 2-pyrrol-3′-yloxindoles by the reactions of cyclic rhodium carbenoids generated from the cyclic diazoamides with substituted and unsubstituted pyrroles. The scope, mechanistic insights and further applications of this transformation are currently under active investigation in our laboratory and will be reported in due course.

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(12) **General Procedure for the Synthesis of 2-Pyrrol-3′-yloxindoles:** In an oven-dried flask, a solution containing 1.2 equiv of pyrrole and 1 mol% of rhodium(II) acetate dimer in 10 mL of dry dichloromethane (dried over phosphorous pentoxide) was degasified under an argon atmosphere. To this reaction mixture, a solution of 1 equiv of appropriate cyclic diazoamide in dry dichloromethane was added dropwise slowly for 1 h period under an argon atmosphere at r.t. The reaction mixture was allowed to stir and followed by TLC till the disappearance of the starting material. The solvent was removed under reduced pressure and the residue purified by flash silica gel column chromatography to afford the respective C–H insertion products.

(13) All new compounds exhibited spectral data consistent with their structures. Selected spectral data: **3-(1-Benzyl-1*H*-pyrrol-2-yl)-1-methyl-1,3-dihydro-indol-2-one (3a):** Colorless solid. Mp 115–117 °C (hexane/EtOAc). IR (KBr): 2932, 1716, 1609, 1490, 1464, 1368, 1345, 1302, 1253, 1180, 1085, 714 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.09 (s, 3 H, N-CH_3), 4.55 (s, 1 H), 5.14 (d, 1 H, *J* = 16.3 Hz), 5.51 (d, 1 H, *J* = 16.3 Hz), 5.78–5.80 (m, 1 H), 6.09 (t, 1 H, *J* = 2.5 Hz), 6.69 (t, 1 H, *J* = 2.5 Hz), 6.79 (d, 1 H, *J* = 7.7 Hz), 6.97–7.04 (m, 3 H), 7.12–7.33 (m, 5 H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 26.9 (N-CH_3) 45.1 (CH), 51.7 (N-CH_2), 108.0 (CH), 108.7 (CH), 109.3 (CH), 123.2 (CH), 124.0 (CH), 125.7 (CH), 126.1 (*quat-C*), 127.2 (CH), 127.7 (CH), 128.0 (*quat-C*), 128.1 (CH), 128.9 (CH), 129.3 (CH), 138.9 (*quat-C*), 144.9 (*quat-C*), 175.4 (*quat-C*). MS: *m/z* = 302 (38.5) [M^+], 212 (23.7), 211(100), 168 (14.3), 157 (17.6), 156 (94.5), 154(13), 91(84). Anal. Calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.26; H, 5.98; N, 9.23. **3-(1-Benzyl-1*H*-pyrrol-3-yl)-1-methyl-1,3-dihydro-indol-2- one (4a):** Colorless solid. Mp 96–98 °C (hexane/EtOAc). IR (KBr): 2928, 1718, 1627, 1469, 1463, 1368, 1355, 1309, 1263, 1187, 1066, 720 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.18 (s, 3 H, N-CH_3), 4.56 (s, 1 H), 4.99 (s, 2 H, N-CH_2), 6.11 (t, 1 H, *J* = 2.2 Hz), 6.61–6.73 (m, 2

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H), 6.93 (d, 1 H, *J* = 7.1 Hz), 7.05–7.36 (m, 8 H). MS: *m/z* = 212 [M^+]. Anal. Calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.19; H, 6.02; N, 9.29.

1-Methyl-3-[1-(4-methyl-benzyl)-1*H*-pyrrol-2-yl]-1,3-dihydro-indol-2-one (3f): Colorless oil. IR (neat): 2983, 1713, 1613, 1493, 1470, 1421, 1372, 1349, 1305, 1265, 1125, 1086, 740 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, $ArCH_3$), 3.09 (s, 3 H, N-CH_3), 4.55 (s, 1 H), 5.10 (d, 1 H, *J* = 16.1 Hz), 5.46 (d, 1 H, *J* = 16.1 Hz), 5.77 (t, 1 H, *J* = 1.7 Hz), 6.07 (t, 1 H, *J* = 2.9 Hz), 6.67 (t, 1 H, *J* = 1.7 Hz), 6.77 (d, 1 H, *J* = 7.8 Hz), 6.99–7.29 (m, 7 H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.8 (CH_3), 27.0 (CH_3,) 45.2 (CH), 51.6 (N-CH_2), 107.9 (CH), 108.7 (CH), 109.3 (CH), 123.2 (CH), 124.0 (CH), 125.7 (CH), 127.3 (CH), 128.3 (*quat-C*), 129.0 (CH), 130.0 (CH), 135.8 (*quat-C*), 137.7 (*quat-C*), 145.0 (*quat-C*), 175.4 (*quat-C*). MS: *m/z* = 316 [M^+]. Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.92; H, 6.35; N, 8.82.

1-Methyl-3-[1-(4-methyl-benzyl)-1*H*-pyrrol-3-yl]-1,3-dihydro-indol-2-one (4f): Colorless oil. IR (neat): 2965, 1715, 1612, 1486, 1467, 1451, 1363, 1347, 1320, 1280, 1116, 1085, 735 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.26 (s, 3 H, $ArCH_3$), 3.19 (s, 3 H, N-CH_3), 4.55 (s, 1 H), 4.94 (s, 2 H, N-CH_2), 6.10 (t, 1 H, *J* = 2.4 Hz), 6.59–6.64 (m, 2 H), 6.83 (d, 1 H, *J* = 7.4Hz), 7.01–7.17 (m, 5 H), 7.26–7.32 (m, 2 H). MS: *m/z* = 316 [M^+]. Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.89; H, 6.39; N, 8.87.

3-[1-(3,5-Dimethyl-benzyl)-1*H*-pyrrol-2-yl]-1-methyl-1,3-dihydro-indol-2-one (3k): Gray color solid. Mp 156–158 °C (hexane/EtOAc). IR (KBr): 2920, 1717, 1609, 1492, 1467, 1372, 1343, 1304, 1127, 1086, 843, 750 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.25 (s, 6 H, $ArCH_3$), 3.13 (s, 3 H, N-CH_3), 4.59 (s, 1 H), 5.07 (d, 1 H, *J* = 16.2 Hz), 5.45 (d, 1 H, *J* = 16.2 Hz), 5.79 (t, 1 H, *J* = 1.8 Hz), 6.09 (t, 1 H, *J* = 2.9 Hz), 6.64 (s, 2 H), 6.69 (t, 1 H, *J* = 1.8 Hz), 6.75–6.86 (m, 2 H), 7.01 (t, 1 H, *J* = 7.45 Hz), 7.14 (d, 1 H, *J* = 7.18 Hz), 7.28 (t, 1 H, *J* = 7.59 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.9 (CH_3), 26.9 (CH_3,) 45.2 (CH), 51.7 (N-CH_2), 107.8 (CH), 108.6 (CH), 109.2 (CH), 123.1 (CH), 124.0 (CH), 125.1 (CH), 125.6 (CH), 127.2 (*quat-C*), 127.3 (*quat-C*), 128.3 (*quat-C*), 129.0 (CH), 129.7 (CH), 138.7 (*quat-C*), 138.9 (*quat-C*), 144.9 (*quat-C*), 175.5 (*quat-C*). MS: *m/z* = 330 [M^+]. Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.74; H, 6.69; N, 8.51.

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