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Facile chemoselective rhodium carbenoid N–H insertion reactions: synthesis of 3-arylamino- or 3-heteroarylpiperidin-2-ones

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Abstract—Rhodium(II) acetate catalyzed reactions of various substituted 3-diazopiperidin-2-ones with a range of aromatic amines, indoles, and benzotriazole yield exclusively the corresponding N–H insertion products despite competing C-H or O-H insertions. This strategy provides an example of a facile chemoselective N–H insertion reaction delivering a library of 3-arylamino and 3-heteroarylpiperidin-2-one derivatives in high yields.

Compounds that possess a 3-aminopiperidin-2-one skeleton are present in natural products and are found embedded in polycyclic frameworks, e.g. aeruginosin,[1] pseudobactin[2] and schulzeines.[3] More importantly, 3-aminopiperidin-2-ones have important biological activities. Examples are the angiotensin converting enzyme (ACE) inhibitor **1**,[4] the serine protease inhibitor **2**,[5] and thrombin inhibitors.[6] In continuation of our interest in reactions of cyclic diazoamides,[7,8] we herein delineate the chemoselective rhodium(II) acetate catalysed reaction of cyclic diazoamides with several primary and secondary amines that lead to the construction of 3-arylamino- or 3-heteroarylpiperidin-2-one derivatives via N–H insertion[9] (Fig. 1).

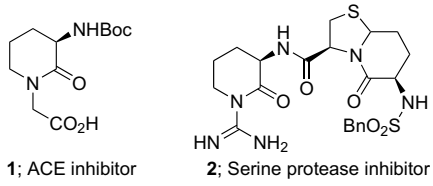
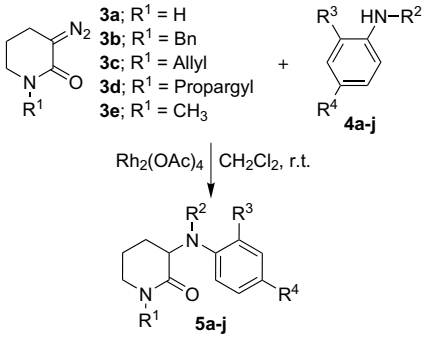


Figure 1.

Initially, we planned to study reactions of cyclic diazoamides **3** with anilines in the presence of a rhodium(II) acetate catalyst. The 3-diazopiperidin-2-one **3a** required was prepared according to the literature procedure.[10] The N-substituted 3-diazopiperidin-2-ones (**3b-e**, Scheme 1) were assembled by carrying out the appropriate N-alkylation of **3a** in the presence of sodium hydride/DMF.



Scheme 1.

The reaction of the diazoamide **3a** with aniline (**4a**) was carried out at room temperature in the presence of a catalytic amount rhodium(II) acetate for 20 min to furnish 3-phenylaminopiperidin-2-one (**5a**) in 80% yield (Scheme 2).

The product **5a** showed a characteristic double doublet at δ 3.83 in its ^{1}H-NMR, a peak at δ 54.6 in its ^{13}C NMR and DEPT-135 spectra for the NCH carbon. These characteristic data confirmed the proposed N–H

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Table 1. Synthesis of 3-arylaminopiperidin-2-ones

Entry	R^1	R^2	R^3	R^4	Time (min)	Yield (%) of **5**[a]
a	H	H	H	H	20	80
b	H	H	Cl	H	10	96
c	H	H	H	NO_2	10	97
d	H	H	H	OCH_3	120	45
e	H	H	OH	H	130	50
f	H	H	CH_3	H	25	74
g	allyl	allyl	H	H	12	76
h	H	CH_3	H	H	40	72
i	H	$CH_2CH_2CO_2Et$	H	H	30	78
j	Bn	H	Cl	H	10	96

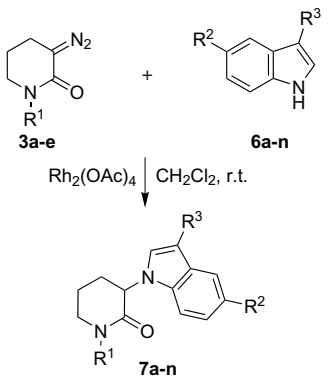
[a] Yields (unoptimized) refer to isolated pure compounds **5**.

insertion. All other data were in good agreement with the assigned structure. The reaction was repeated with various aromatic primary amines (entries **b-f**), having electron-withdrawing or -donating groups as substituents, to afford the respective 3-arylaminopiperidin-2-ones[11] **5b-f**, **5j** in moderate to good yields (Table 1).

The electronic nature of the substituents exerted a considerable effect on the yield of the reactions. Aromatic amines having electron-withdrawing substituents furnished higher yields than the amines having electron-donating groups. Interestingly, no O-H insertion product was observed in the reaction of 2-aminophenol with 3-diazopiperidin-2-one (entry **e**, Table 1).

After studying the N–H insertion reactions with primary amines, we next chose to investigate the reaction with secondary amines in order to obtain tertiary amine products. Thus, the reaction of N-substituted anilines **4g-i** with diazoamide **3** was carried out as described above to obtain the corresponding tertiary amines[11] **5g-i** in good yields *via* N–H insertion.

To advance this process further, we considered indole as a benchmark substrate. Initially, the reaction of 3-diazopiperidin-2-one (**3a**) and indole was performed in the presence of rhodium(II) acetate at room temperature for 15 min to furnish[11] *N*-(piperidin-2-on-3-yl)indole (**7a**) in 70% yield (Scheme 2). The ^{1}H-NMR spectrum of product **7a** characteristically showed a triplet at δ 4.88 for the NCH proton and the absence of an indole N–H proton. ^{13}C NMR and DEPT-135 studies revealed a characteristic peak at δ 56.6 for the NCH carbon, which clearly confirmed the formation of the N–H insertion product. The ^{1}H NMR of the crude reaction mixture was recorded and showed only the N–H insertion product formation.



Scheme 2.

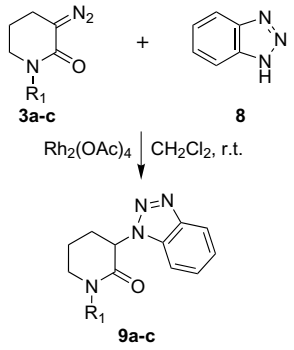
This interesting reaction with indole was generalized by performing similar reactions with various substituted indoles (Table 2) to furnish[11] the respective *N*-(piperidin-2-on-3-yl)indoles **7b-n** in very good yields. Notably, a survey of the literature revealed that the reaction of rhodium carbenoids with indoles affords only C-H insertion products via cyclopropanation followed by ring scission.[12] Our previous studies have also shown that the rhodium(II)-catalyzed reaction of diazoamides furnished exclusively C-H insertion products.[8] To our surprise, we did not observe any spectroscopically detectable indole C-H insertion products in the above reactions. Very interestingly, we observed an unusual preference for N–H insertion despite the possible competing C-H insertion reactions at the 2- or 3-position of the indole ring. The preference of N–H insertion over C-H insertion reaction for indole may be due to the less electrophilic nature of the alicyclic amide carbonyl group in **3** necessary to stabilize zwitterion formation.[8]

Encouraged by these results, we investigated the N–H insertion reaction with benzotriazole (**8**), a biologically important heterocycle.[13] Thus, the treatment of 3-diazo-

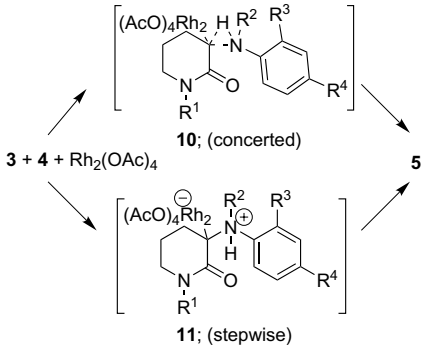
Table 2. Synthesis of N-(Piperidin-2-on-3-yl)indoles

Entry	R^1	R^2	R^3	Time (min)	Yield (%) of **7**[a]
a	H	H	H	15	70
b	H	Br	H	15	75
c	H	H	CH_3	15	60
d	H	H	CH_2CO_2Me	10	80
e	H	H	CH_2CO_2X[b]	10	75
f	H	H	CH_2CO_2Y[c]	8	74
g	CH_3	H	H	5	80
h	CH_3	Br	H	5	80
i	X[b]	H	H	2	85
j	X[b]	Br	H	5	85
k	Bn	H	H	5	82
l	Bn	Br	H	5	85
m	Y[c]	H	H	5	85
n	Y[c]	H	CH_3	4	80

[a] Yields (unoptimized) refer to isolated pure compounds **7**.
[b] X = allyl.
[c] Y = propargyl.



Scheme 3.



Scheme 4. Mechanistic pathways for N–H insertion.

Table 3. Synthesis of benzotriazoylpiperidin-2-ones

Entry	R^1	Time (min)	Yield (%) of **9**[a]
a	H	70	74
b	Bn	60	82
c	allyl	55	89

[a] Yields (unoptimized) refer to isolated and chromatographically pure compounds **9**.

piperidin-2-one **3a** with benzotriazole (**8**) in the presence of rhodium(II) acetate afforded the corresponding N–H insertion product[11] **9a** in 74% yield (Scheme 3). Similarly, the *N*-benzyl and *N*-allyl diazoamides **3b-c** afforded the respective benzotriazol-1-ylpiperidin-2-one derivatives (**9b-c**, Table 3).

In contrast to the reactions reported so far, treatment of these diazoamides with other heterocyclic substrates such as imidazole and benzimidazole was not successful. Unchanged starting materials were recovered from these reactions indicating that these heterocyclic systems might have poisoned the rhodium(II) acetate catalyst. Other metal catalysts such as copper acetate and copper acetoacetate were also tried and found to be inactive even at reflux.

Even though mechanism of rhodium carbenoid C-H insertion reactions has been elaborately described,[14] the mechanism of N–H insertion reactions is less clear. We have studied the electronic effects of substituents on the reactivity of the rhodium carbenoid N–H insertions of 3-diazopiperidin-2-one with a series of substituted anilines and the relative reactivities of the N–H bonds were analyzed (Table 1). We found that anilines with an electron-withdrawing substituent react more quickly than anilines with electron-donating substituents. Mechanistically, electron-withdrawing substituents would disfavour the formation of the ammonium ylide **11** as shown in the stepwise mechanism (Scheme 4). Electron-withdrawing substituents present in the aromatic ring tend to increase the polarity of the N–H bond and afford the insertion products in better yields. From these observations of substituent effects on the yield, the rhodium carbenoid insertion into an N–H bond is more likely to be concerted.

In conclusion, facile rhodium(II)-catalysed reactions of 3-diazopiperidin-2-ones were successfully carried out with various anilines, indoles and benzotriazole. All the reactions yielded, exclusively, the N–H insertion products rather than the competing C-H insertion products. This methodology has proved to be effective for generating libraries of 3-aminopiperidin-2-ones.

Acknowledgements

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11. All new compounds gave satisfactory spectral data consistent with their structures. Spectral data for compound **5b**: Colourless solid; mp 125 °C. IR (KBr) 3343, 3183, 2946, 1668, 1596, 1512, 1290, 1031, 741 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.29–7.09 (2H, m), 6.77 (1H, br s, NH), 6.69–6.62 (2H, m), 5.32 (1H, br s, NH), 3.90 (1H, dd, J = 10.3, 5.1 Hz), 3.41–3.34 (2H, m), 2.51–2.38 (1H, m), 2.16–1.25 (3H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 172.9 (*C*=O), 143.9 (*quat*-*C*), 130.0 (=*C*H), 128.3 (=*C*H), 124.8 (*quat*-*C*), 118.4 (=*C*H), 112.5 (=*C*H), 54.4 (N*C*H), 42.4 (N*C*H_2), 28.3 (*C*H_2), 21.5 (*C*H_2). MS (EI): *m*/*z* (%) = 226 (17) M^+ (^{37}Cl), 224 (51) M^+ (^{35}Cl), 189 (39), 179 (25), 166 (55), 153 (40), 127(31), 118 (25), 70 (100). Anal. Calcd for $C_{11}H_{13}ClN_2O$: C, 58.80; H, 5.83; N, 12.47. Found: C, 58.71; H, 5.89; N 12.45. Compound **5i**: Colourless solid; mp 108–110 °C. IR (KBr) 3203, 3076, 2952, 1727, 1666, 1598 1503, 1356, 1277, 1195, 1043, 743, 691, 501, 466 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.27–7.17 (2H, m), 6.81–6.65 (4H, m), 4.27–4.09 (3H, m), 3.75–3.56 (2H, m), 3.37–3.30 (2H, m), 2.76–2.64 (2H, m), 2.14–1.81 (4H, m), 1.29–1.22 (3H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 173.1 (*C*=O), 172.1 (*C*=O), 147.9 (*quat*-C), 129.8 (=*C*H), 118.3 (=*C*H), 115.0 (=*C*H), 62.1 (N*C*H), 61.0 (O*C*H_2), 46.4 (N*C*H_2), 42.9 (CO*C*H_2), 34.0 (*C*H_2), 26.6 (*C*H_2), 23.1 (*C*H_2), 14.8 (*C*H_3). MS (EI): *m*/*z* (%) = 290 (15) [M^+], 232 (30), 203 (33), 192 (100), 133 (22), 119 (19), 106 (79), 99 (49), 77 (33), 70 (68), 62 (27), 55 (43), 44 (40). Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.29; H, 7.60; N, 9.71. Compound **7a**: Colourless solid; mp 82 °C. IR (KBr) 3513, 3407, 3276, 1641, 1460, 1330, 1197, 743 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.61 (2H, d, J = 7.7 Hz), 7.56–7.06 (4H, m), 6.53 (1H, br s, NH), 4.88 (1H, t, J = 8.3 Hz), 3.29–2.98 (2H, m), 2.18–2.07 (2H, m), 1.82–1.48 (2H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 170.1 (*C*=O), 136.4 (*quat*-C), 129.9 (*quat*-C), 127.4 (=*C*H), 122.1 (=*C*H), 121.6 (=*C*H), 120.1 (=*C*H), 110.2 (=*C*H), 102.5 (=*C*H), 56.7 (N*C*H), 42.5 (N*C*H_2), 29.0 (*C*H_2), 21.8 (*C*H_2). MS (EI): *m*/*z* (%) = 214 (100) [M^+], 168 (24), 156 (31), 143 (22), 130 (15), 117 (53), 70 (39). Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.79; H, 6.63; N, 13.11. Compound **7i**: Brown liquid; IR(film) 3458, 3054, 2943, 2870, 1705, 1652, 1490, 1461, 1336, 1267, 1221, 928, 738 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.61 (1H, d, J = 7.5 Hz), 7.25–7.04 (3H, m), 6.51 (1H, d, J = 2.0 Hz), 5.93–5.73 (1H, m), 5.26 (2H, s), 5.2 (1H, d, J = 4 Hz), 4.98 (1H, t, J = 8.0 Hz), 4.07 (2H, d, J = 6 Hz), 3.53–3.25 (2H, m), 2.31–2.21 (2H, m), 2.03–1.85 (2H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 167.3 (*C*=O), 136.7 (*quat*-C), 133.0 (=*C*H), 129.4 (*quat*-C), 127.2 (=*C*H), 122.2 (=*C*H), 121.7 (=*C*H), 120.1 (=*C*H), 118.9 (=*C*H_2), 110.3 (=*C*H), 102.6 (=*C*H), 57.3 (N*C*H), 50.6 (N*C*H_2), 47.9 (N*C*H_2), 29.3 (*C*H_2), 21.9 (*C*H_2). MS (EI): *m*/*z* (%) = 254 (100) [M^+], 168 (38), 156 (44), 143 (32), 138 (36), 133 (26), 110 (60), 104 (18), 70 (17), 55 (19). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.09. Found: C, 75.39; H, 7.20; N, 11.12. Compound **9a**: Colourless solid; mp 135–137 °C. IR (KBr) 3213, 3089, 2954, 1662, 1492, 1327, 1219, 839, 743 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.89–7.85 (2H, m), 7.42–7.37 (3H, m), 5.57 (1H, dd, J = 9.7, 6.4 Hz), 3.53–3.39 (2H, m), 2.74–2.44 (2H, m), 2.18–1.80 (2H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 167.5 (*C*=O), 144.7 (*quat*-*C*), 137.2 (*quat*-*C*), 127.1 (*C*H), 118.5 (*C*H), 65.8 (N*C*H), 42.4 (N*C*H_2), 29.1 (*C*H_2), 21.0 (*C*H_2). MS (EI): *m*/*z* (%) = 216 (18) [M^+], 146 (12), 132 (5), 120 (28), 115 (19), 97 (83), 87 (16), 69 (64), 59 (36), 55(17), 43 (100), 28 (59). Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.28; H, 5.51; N, 25.98.
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