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Application of carbenoid N–H insertion in the synthesis of the tricyclic 1,4-dihydropyrazines

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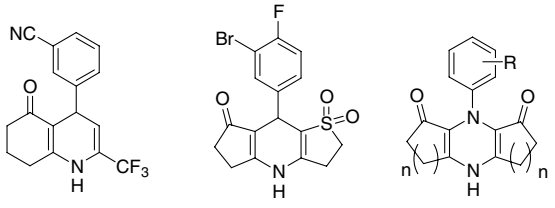
Abstract—The N–H insertion of the substituted anilines with 2-diazo-1,3-cyclohexanedione or 2-diazo-1,3-cyclopentanedione and subsequent cyclization enabled an efficient synthesis of a novel series of tricyclic 1,4-dihydropyrazines.

In the course of our medicinal chemistry effort on K_{ATP} channel openers (KCOs), we were interested in developing analogues to mimic ZD-0947 and ABT-598 structures—two leading KCOs with dihydopyridine scaffold under development by AstraZeneca and Abbott Laboratory (Fig. 1).[1] We envisaged that displacement of dihydropyridine with dihydropyrazine core would lead to a novel series of KCOs without the chiral center in ZD-0947 or ABT-598 structure. There is not much precedence on using dihydropyrazine as a surrogate of dihydropyridine in the study of biologically active compounds, probably due to the difficulty in efficient preparation of dihydropyrazine skeleton.[2] While some 1,4-dihydropyrazines are known in the literature,[3] to the best of our knowledge, the tricyclic dihydropyrazine scaffold (**I**) has not been disclosed. A search of the literatures for possible synthetic methods to 1,4-dihydropyrazine structures resulted in very few returns. One procedure drew our attention by utilization of a double carbenoid N–H insertion reaction between 2-diazo acetoacetate and anilines. This procedure was found to be very practical for the preparation of 2,6-disubstituted 1,4-dihydropyrazine system. Therefore, we applied this methodology by using either 2-diazo-1,3-cyclohexanedione or 2-diazo-1,3-cyclopentanedione (**1**) as the diazo sources for the synthesis of structures **I**. Herein, we report our preliminary study on the preparation of tricyclic 1,4-dihydropyrazines as KCOs.



ZD-0947 ABT-598 I

Figure 1.

Comparing with 2-diazo acetoacetate, 2-diazo-1,3-cyclohexanedione, and 2-diazo-1,3-cyclopentanedione (**1**) are much more reactive carbenoids that side-reactions between them and the solvents are unavoidable.[4] Formal insertion of **1** into a C-halogen or C–H bond was a major drawback to compete with the desired N–H insertion in many cases. Usually this reaction was conducted in neat condition, with one of the substrates in excess acting as solvent.[5] However, the utility of substrate as a solvent for the type of N–H insertion is not general due to the limitation on melting point, reaction temperature, and chemical stability of the substrate. To focus on obtaining the target tricyclic 1,4-dihydropyrazines, we chose benzene as the reaction solvent in our studies.

We first evaluated the carbenoid N–H reaction between 2-diazo-1,3-cyclohexanedione and 3-cyano-aniline catalyzed by rhodium acetate dimer (Scheme 1 and entries 1 and 2 in Table 1).[6] Generally the reaction afforded the mono-insertion adduct **4a** and the bis-insertion adduct **5a** through the rhodium species **2**, along with some minor side-products generated from aromatic C–H insertion between two substrates. The possible side-product from the reaction of benzene (solvent) with

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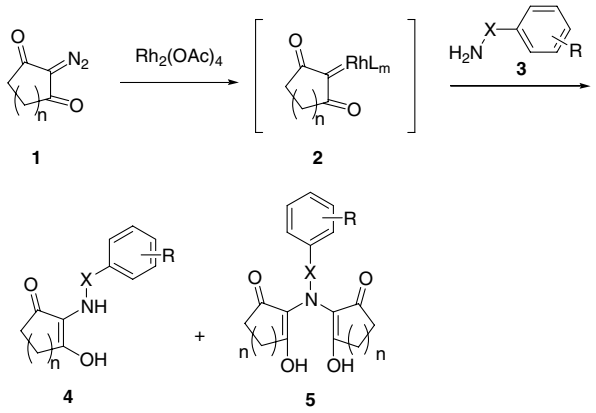

Scheme 1.

Table 1. N–H insertion of **3** with **1**[a]

Entry	*n*	X	R	**1**:**3**[b]	**4**[c] Yield (%)	**5** Yield (%)
1	2	ns[d]	3-CN	1:1	**4a** (32)	**5a** (35)
2	2	ns	3-CN	2:1	**4a** (5)	**5a** (55)
3	2	ns	3-I	2:1	**4b** (5)	**5b** (51)
4	2	ns	3.4-Di-F	2:1	**4c** (11)	**5c** (62)
5	2	ns	3-Br–4-F	2:1	**4d** (12)	**5d** (48)
6	1	ns	3-CN	2:1	**4e** (15)	**5e** (45)
7	2	C(O)	4-Cl	2:1	**4f** (41)	**5f** (5)
8	2	C(O)	4-Cl	1:1	**4f** (55)	nd[e]
9	2	C(O)	4-OMe	1:1	**4h** (52)	nd
10	2	SO_2	4-Me	1:1	**4i** (45)	**5g** (8)
11	2	CH_2	4-Cl	1:1	—[f]	—

[a] Reaction temperature: 50–70 °C; reaction time: 0.5–4 h; catalysis load: ~0.5 mmol %.
[b] Ratio of reactants **1** and **3**.
[c] Isolated yields.
[d] ns = no substitution.
[e] nd = not detected.
[f] — = no desired product.

species **2** was not detected, presumably due to the high reactivity of the primary aniline **3**. The ratio of two substrates (**1** vs. **3**) utilized significantly dictated the outcome of products **4a** and **5a**. It was found to be infeasible for obtaining **4a** as a single product after effort on optimization with the ratio of **1** and **3**, catalyst loading, temperature and time. However, when applying 2:1 ratio of 2-diazo-1,3-cyclohexanedione and the aniline, the yield of the bis-insertion adduct **5a** was greatly improved, with less than 5% of **4a** isolated. We realized that this procedure should generate synthetic utility for practical preparation of the target structure **I** via the key intermediate **5**. Analogous synthesis on various anilines **3** with either 2-diazo-1,3-cyclohexanedione or 2-diazo-1,3-cyclopentanedione (**1**) afforded the desired bis-insertion adducts **5b**–**5e** in acceptable yields, along with a small amount of mono-insertion adducts **4b**–**4e** as side products. It was interesting that mono-insertion adducts **4** were isolated as only or major products when benzamides or sulfonamides were applied as substrates for N–H insertion, as shown in entries 7–10. Adjustment of the ratio of two substrates did not drive the reaction to the bis-insertion pathway (entry 7). This result indicated that the reactivity of the N–H bond greatly affect the reaction outcome. In the cases of benzamides or sulfonamides, the N–H bond is not as reactive as that of primary anilines. Thus, the sequential N–H insertion cascade stopped at the mono-insertion stage to afford mainly **4** as products. The attempted Rh-catalyzed N–H insertion of 2-diazo-1,3-cyclohexanedione and 4-chlorobenzylamine (entry 11) failed to give either mono-insertion adduct **4** or bis-insertion adduct **5**. It is not surprising for this result since benzylamine is highly reactive toward carbonyl group in substrate **1**.

The bis-insertion adducts **5** were then treated with ammonium acetate in *t*-BuOH at 70 °C for 4–10 h to give the corresponding **6** in reasonable yields (Scheme 2). Conversion of **6** to the final tricyclic dihydropyrazines **7** was accomplished by treatment with $NaNH_2$ in refluxing THF for 6–8 h. Interestingly, direct reaction of **6** with $NaNH_2$ did not result in the cyclized adducts **7**.[7]

In summary, the carbenoid N–H insertion of anilines **3** with corresponding diazo species **1**, followed by intramolecular cyclization, provided an efficient route to a novel series of tricyclic dihydropyrazines. The biological activities will be reported elsewhere.

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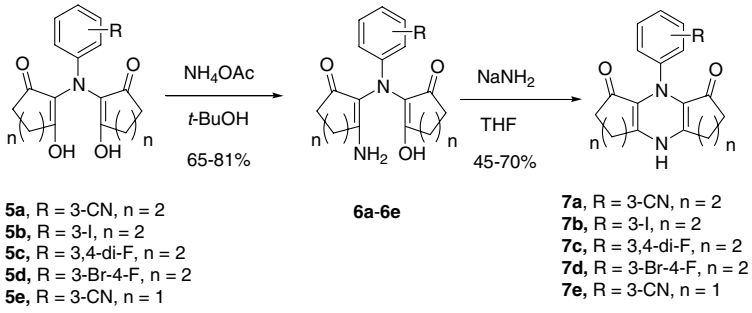

5a, R = 3-CN, n = 2
5b, R = 3-I, n = 2
5c, R = 3,4-di-F, n = 2
5d, R = 3-Br-4-F, n = 2
5e, R = 3-CN, n = 1

6a-6e

7a, R = 3-CN, n = 2
7b, R = 3-I, n = 2
7c, R = 3,4-di-F, n = 2
7d, R = 3-Br-4-F, n = 2
7e, R = 3-CN, n = 1

Scheme 2.

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6. *Typical procedure of N–H insertion reaction, synthesis of* **4a** *and* **5a**: 2-Diazo-cyclohexane-1,3-dione (470 mg, 3.40 mmol), 3-cyano-aniline (200 mg, 1.70 mmol) and rhodium acetate dimer (5 mg, 0.011 mmol) in benzene (4 mL) were heated at 70 °C for 2 h. The solid was filtered off and the filtrate was concentrated to give a yellow oil, which was purified by silica gel column chromatography to afford **4a** (19 mg, 5%) and **5a** (316 mg, 55%) as white solids. **4a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.02 (s, 1H), 7.68 (d, $J = 6.5$ Hz, 1H), 7.41 (m, 2H), 3.17 (t, $J = 8.0$ Hz, 1H), 2.45 (m, 3H), 2.15 (m, 1H), 1.90 (m, 1H). CIMS, m/z (%): 229 ($[M+1]^+$, 100). Compound **5a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.8 (br s, 2H), 7.25 (d, $J = 7.5$ Hz, 1H), 7.05 (d, $J = 7.5$ Hz, 1H), 6.76 (m, 2H), 2.75 (m, 4H), 2.55 (m, 4H), 2.11 (m, 4H). CIMS, m/z (%): 339 ($[M+1]^+$, 100). Anal. calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.35; H, 5.30; N, 8.42.
7. *Spectroscopic data for* **7a**: Yellow solid, mp 183–185 °C. ^{1}H NMR: (300 MHz, d_6-DMSO) δ 9.90 (br s, 1H), 7.28 (d, $J = 8.5$ Hz, 1H), 7.15 (d, $J = 7.5$ Hz, 1H), 6.75 (d, $J = 7.0$ Hz, 1H), 6.70 (s, 1H), 2.62 (m, 4H), 2.48 (m, 4H), 2.01 (m, 4 H). CIMS, m/z (%): 320 ($[M+1^+]$, 100). Anal. calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.48; H, 5.42; N, 13.25.