A Novel Synthetic Approach to 6,7-Dihydro-5H-imidazo[1,5-a]-pyrazin-8-ones

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Supporting Information

Experimental Section

5-Acetyl-2,2-dimethyl-[1,3]dioxane-4,6-dione (5): A solution of 2,2-dimethyl-[1,3]dioxane-4,6-dione **3** (5.8 g , 40 mmol) and pyridine (6.5 g, 82mmol) in 75 mL of methylene chloride was cooled to 0 °C under nitrogen atmosphere. Then a solution of acetyl chloride **4** (3.4 mL, 48 mmol) in 25 mL of methylene chloride was slowly added over 1 hour period. The reaction mixture was stirred at 0 °C for another hour and warmed up to room temperature and kept stirring over night. The reaction mixture was diluted by adding 50 mL of methylene chloride. The organic solution was washed with 3x 75 mL of 10% hydrogen chloride aqueous solution and 100 mL of water. The collected organic layer was dried over sodium sulfate and concentrated to give a dark brown solid. The solid was poured into 250 mL of hot ether, filtered to remove the insoluble stuff and collected filtrate. The filtrate was concentrated to give 5-acetyl-2, 2-dimethyl- [1,3] dioxane-4, 6-dione **5** as an orange color solid (6.4g, 86%yield).

¹HNMR(CDCl₃) δ 2.68 (s, 3H), 1.74 (s, 6H)

HPLC: Rt = 0.8 min. MS [M-H] (m/z) 185

2-(3-Oxo-butyrylamino)-3-phenylpropionic acid methyl ester (7): L-phenylalanine methyl ester **6** (1.8g, 10 mmol) and 5-acetyl-2,2-dimethyl-[1,3]dioxane-4,6-dione **5** (1.9g, 10 mmol) was dissolved in 40 mL anhydrous dioxane. The reaction mixture was refluxed for 4 hours and concentrated. The residue was dissolved in 200 mL of EtOAc and the organic layer was washed with 100 mL 2N HCl and 100 mL of brine. The collected organic layer was dried over sodium sulfate and concentrated. The residue was purified by flash chromatography to give 2-(3-oxo-butyrylamino)-3-phenylpropionic acid methyl ester **7** (2.3g, 86% yield).

¹HNMR(CDCl₃) δ 7.30 (m, 4H), 7.19 (m, 1H), 4.85 (dd, 1H), 3.73 (s, 3H), 3.38 (s, 2H), 3.10 (m, 2H), 2.21 (s, 3H) ¹³CNMR(CDCl₃) δ 203, 171.7, 165.2, 135.7, 129.2, 128.6, 127.2, 53.4, 52.4, 49.5, 37.9, 30.9

LC/MS : Rt = 1.65 min. MS [M-H] (m/z) 262

2-(2-Hydroxyimino-3-oxo-butyrylamino)-3-phenylpropionic acid methyl ester (8): A solution of 2-(3-oxo-butyrylamino)-3-phenyl-propionic acid methyl ester **7** (1.1g, 4.3mmol) in 7 mL of acetic acid was cool to 0 °C. Then sodium nitrite (0.90g, 13 mmol) in 2.6 mL of water was slowly added to the reaction. The reaction mixture was stirred at 0 °C for 15 minutes and diluted with 130 mL of water. The aqueous layer was extracted with 3x170 mL of EtOAc. The combined organic layers were dried over sodium sulfate and concentrated to give 2-(2-hydroxyimino-3-oxo-butyrylamino)-3-phenylpropionic acid methyl ester **8** (1.3g, 100% yield).

LC/MS : Rt = 1.85 min. MS [M+H] (m/z) 293, MS [M-H] (m/z) 291

[[2-(4-Methoxyphenyl)-5-methyl-3H-imidazole-4-carbonyl]-amino]-phenylacetic acid methyl ester (10):

To 2-(2-hydroxyimino-3-oxo-butyrylamino)-3-phenylpropionic acid methyl ester **8** (1.30g, 4.4 mmol) in 10 mL of was added 4-methoxybenzylamine **9** (0.68g, 4.9 mmol) and triethyl amine (0.92 mL, 6.6 mmol). The reaction mixture was heated at 80 °C for 1.5 hours and concentrated. The residue was diluted with 50 mL of EtOAc and the organic layer was washed with 50 mL of brine. The collected organic layer was dried over sodium sulfate and concentrated. [[2-(4-Methoxyphenyl)-5-methyl-3H-imidazole-4-carbonyl]-amino]-phenylacetic acid methyl ester **10** (2.50g, 63%yield) was obtained after flash chromatography purification.

¹HNMR(CDCl₃) δ 8.05 (d, 1H), 7.72 (d, 2H), 7.27 (m, 5H), 6.72 (d, 2H), 4.94 (m, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.71 (s, 1H), 3.33 (m, 1H), 3.11 (m, 1H), 2.23 (s, 3H)

LC/MS : Rt = 2.51 min. MS [M+H] (m/z) 394, MS [M-H] (m/z) 392

2-(4-Methoxy-phenyl)-5-methyl-3H-imidazole-4-carboxylic acid (1-hydroxymethyl-2-phenylethyl)-amide (11): To Lithium aluminum hydride (110mg, 3.9 mmol) in 5 mL of anhydrous THF was added a solution of {[2-(4-methoxyphenyl)-5-methyl-3H-imidazole-4-carbonyl]-amino}-phenylacetic acid methyl ester **10** (150mg, 0.38mmol) in 5 mL anhydrous THF. The reaction mixture was stirred at room temperature for one hour then a Fisher work up procedure was used. The filtrate was dissolved in 50 mL EtOAc and the organic layer was washed with brine. The organic layer was washed with 50 mL of brine. The collected organic layer was dried over sodium sulfate and concentrated to give 2-(4-methoxyphenyl)-5-methyl-3H-imidazole-4-carboxylic acid (1-hydroxymethyl-2-phenyl-ethyl)-amide **11** (102mg, 100%yield).

¹HNMR(CD₃OD) δ 7.82 (d, 2H), 7.32 (m, 4H), 7.19 (m, 1H), 7.03 (d, 2H), 4.28 (m, 1H), 3.86 (s, 3H), 3.62 (d, 2H), 2.96 (m, 2H), 2.53 (s, 3H)

LC/MS : Rt = 2.00 min. MS [M+H] (m/z) 366, MS [M-H] (m/z) 364

6-Benzyl-3-(4-methoxy-phenyl)-1-methyl-6,7-dihydro-5H-imidazo[1,5-a]pyrazin-8-one (12): To 2-(4-methoxyphenyl)-5-methyl-3H-imidazole-4-carboxylic acid (1-hydroxymethyl-2-phenylethyl)amide **11** (190mg, 0.54 mmol) in 2 mL of methylene chloride was added N-bromosuccinimide (135mg, 0.76 mmol), triphenyl phosphine (200 mg, 0.76mmol) and triethyl amine (0.50 mL, 3.5 mmol). The reaction mixture was stirred at room temperature for one hour then concentrated. 6-Benzyl-3-(4-methoxyphenyl)-1-methyl-6,7-dihydro-5H-imidazo[1,5-a]pyrazin-8-one **12** (160mg, 85% yield) was obtained after reverse phase chromatography.

¹HNMR(DMSO-d₆) δ 7.91 (d, 2H), 7.33 (m, 4H), 7.26 (m, 1H), 7.09 (d, 2H), 4.93 (m, 1H), 4.80 (m, 1H), 4.71 (m, 1H), 3.83 (s, 3H), 3.81 (s, 1H), 3.11 (m, 1H), 3.00 (m, 1H), 2.52 (s, 3H)

LC/MS : Rt = 2.49 min. MS [M+H] (m/z) 348, MS [M-H] (m/z) 346

7-Allyl-6-benzyl-3-(4-methoxyphenyl)-1-methyl-6,7-dihydro-5H-imidazo[1,5-a]pyrazin-8-one (1): To 6-benzyl-3-(4-methoxyphenyl)-1-methyl-6,7-dihydro-5H-imidazo[1,5-a]pyrazin-8-one **12** (17mg, 0.049 mmol) in 1 mL of anhydrous THF was added sodium hydride [60% in mineral oil (4mg, 0.10mmol)]. The reaction mixture was stirred at room temperature for 10 minutes, then allyl bromide (7.1mg, 0.059 mmol) was added to the reaction. Then the reaction mixture was continued stirring at room temperature over night and then was concentrated. 7-Allyl-6-benzyl-3-(4-methoxyphenyl)-1-methyl-6,7-dihydro-5H-imidazo[1,5-a]pyrazin-8-one **1** (14 mg, 72% yield) was obtained after reverse phase chromatography.

¹HNMR(CDCl₃) δ 7.75 (d, 2H), 7.27 (m, 5H), 6.92 (d, 2H), 5.97 (m, 1H), 5.31 (d, 1H), 4.95 (d, 1H), 4.56 (m, 2H), 4.30 (t, 1H), 4.11 (t, 1H), 3.83 (s, 3H), 3.27 (dd, 1H), 2.78 (dd, 1H), 2.56 (s, 3H)

LC/MS : Rt = 2.03 min. MS [M+H] (m/z) 388.

Characterization of 6,7-Dihydro-5H-imidazo[1,5-a]pyrazin-8-ones Derivatives 1

R ₁	R ₂	R ₃	R ₄	HPLC (Min) MS (M+H)
Me	Bn	4-Methoxyphenyl	Me	1.92 362
Me	Bn	4-Methoxyphenyl	Bn	2.34 438
Me	Bn	4-Methoxyphenyl	Allyl	2.03 388
Me	Bn	4-Chlorophenyl	Me	2.02 366, 368
Me	Bn	4-Chlorophenyl	Bn	2.53 442, 444
Me	Bn	4-Chlorophenyl	Allyl	2.24 392, 394
Me	Bn	4-Methylphenyl	Me	1.93 346
Me	Bn	4-Methylphenyl	Bn	2.44 422
Me	Bn	4-Methylphenyl	Allyl	2.11 372
Et	Bn	4-Methoxyphenyl	Me	2.02 376
Et	Bn	4-Methoxyphenyl	Bn	2.44 452

Et	Bn	4-Methoxyphenyl	Allyl	2.20 402
Et	Bn	4-Chlorophenyl	Me	2.26 380, 382
Et	Bn	4-Chlorophenyl	Bn	2.63 456, 458
Et	Bn	4-Chlorophenyl	Allyl	2.40 406, 408
Et	Bn	4-Methylphenyl	Me	2.11 360
Et	Bn	4-Methylphenyl	Bn	2.53 436
Et	Bn	4-Methylphenyl	Allyl	2.29 386
Ph	Bn	4-Methoxyphenyl	Me	2.35 424
Ph	Bn	4-Methoxyphenyl	Bn	2.69 500
Ph	Bn	4-Methoxyphenyl	Allyl	2.43 450
Ph	Bn	4-Chlorophenyl	Me	2.52 428, 430
Ph	Bn	4-Chlorophenyl	Bn	2.87 504, 506
Ph	Bn	4-Chlorophenyl	All	2.67 454, 456
Ph	Bn	4-Methylphenyl	Allyl	2.63 434
Me	Isopropyl	4-Methoxyphenyl	Allyl	1.80 340
Me	Me	4-Methoxyphenyl	Allyl	1.63 312
Me	Me	4-Chlorophenyl	Allyl	1.66 316, 318
Me	H	4-Methylphenyl	Allyl	1.47 282