HETEROCYCLES, Vol. 71, No. 9, 2007, pp. 2049 - 2054. © The Japan Institute of Heterocyclic Chemistry
Received, 27th April, 2007, Accepted, 11th June, 2007, Published online, 12th June, 2007. COM-07-11092

SYNTHESIS OF NEW HETEROCYCLIC SYSTEM: 1(5)*H*-1,5-DIAZACYCL[3.3.2]AZINE-2,4-DIONE

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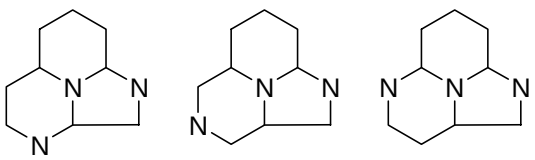
Abstract – A synthesis of hitherto unknown heterocyclic system 1(5)*H*-1,5-diazacycl[3.3.2]azine-2,4-dione (**5**) is presented. The cyclocondensation of 2,6-diaminopyridine (**1**) with maleic anhydride yielded (5-amino-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetic acid (**2**), which was converted to methyl (5-amino-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl) acetate hydrochloride (**3**). The ester (**3**) upon treatment with sodium carbonate solution underwent intramolecular cyclization to 2a,3-dihydro-1(5)*H*-1,5-diazacycl[3.3.2]azine-2,4-dione (**4**), which was oxidized in alkaline condition to provide **5**.

INTRODUCTION

Cyclazines are common subjects in theoretical and experimental studies.[1] The diazacycl[3.3.2]azines, which contain the imidazo[1,5-*a*]pyridine pharmacore, can be categorized into three types of systems (**I**-**III**) (Figure). To date only one report[2] on the synthesis of 1,3-diazacycl[3.3.2]azines (**I**) has appeared. The chemistry of 1,4-diazacycl[3.3.2]azines (**II**) has been further developed,[3] but there is no information on the 1,5-diazacycl[3.3.2]azine heterocyclic system (**III**) available.



I **II** **III**

Figure

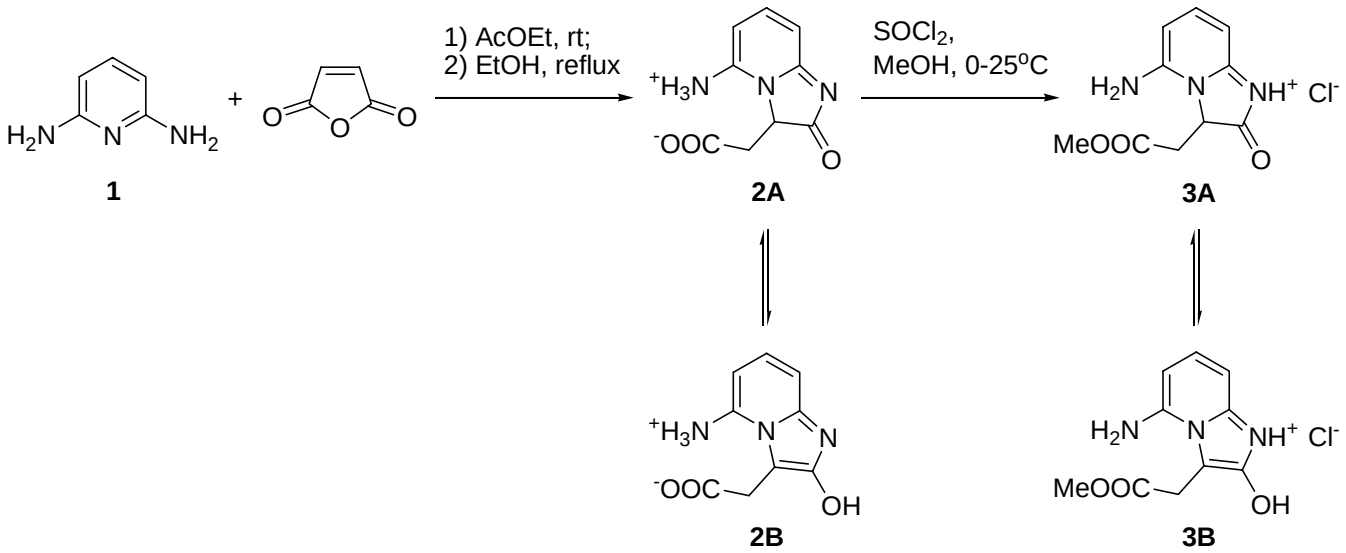
As a continuation to our program on the reactions of maleic anhydride with binucleophiles,[4] particularly in the synthesis of new heterocyclic systems,[5] we describe herein a method for the preparation of

1,5-diazacycl[3.3.2]azine system (**III**) derivative, namely 1(5)*H*-1,5-diazacycl[3.3.2]azine-2,4-dione (1,5,8b-triazaacenaphthylen-2,4-dione).

RESULTS AND DISCUSSION

The reaction of 2-aminopyridines with maleic anhydride has been shown to afford (2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetic acid.[6] Using a modification of this method we prepared amino acid (**2**) from 2,6-diaminopyridine (**1**) and maleic anhydride (Scheme 1). The tautomeric form **2A** solely was observed in the NMR spectra (DMSO-d_6 solution). However, H-3 signal in ^{1}H NMR spectrum disappeared upon addition of D_2O to DMSO-d_6 solution of **2** that indicated keto-enol tautomerism in the compound (**2**). The ^{1}H NMR spectrum of **2** in D_2O contained no H-3 signal, but the signals of the methylenic group appeared as AB system (instead of AMX system in DMSO-d_6). This type of splitting confirmed diastereotopicity of the methylenic group protons that corresponded to the form **2A**. The signal of C-3 in ^{13}C NMR spectrum appeared as an equally populated triplet at 62.6 ppm ($^2J_{CD}$ = 22.9 Hz), which was observed in D_2O solution, also supported the existence of the form **2A**.

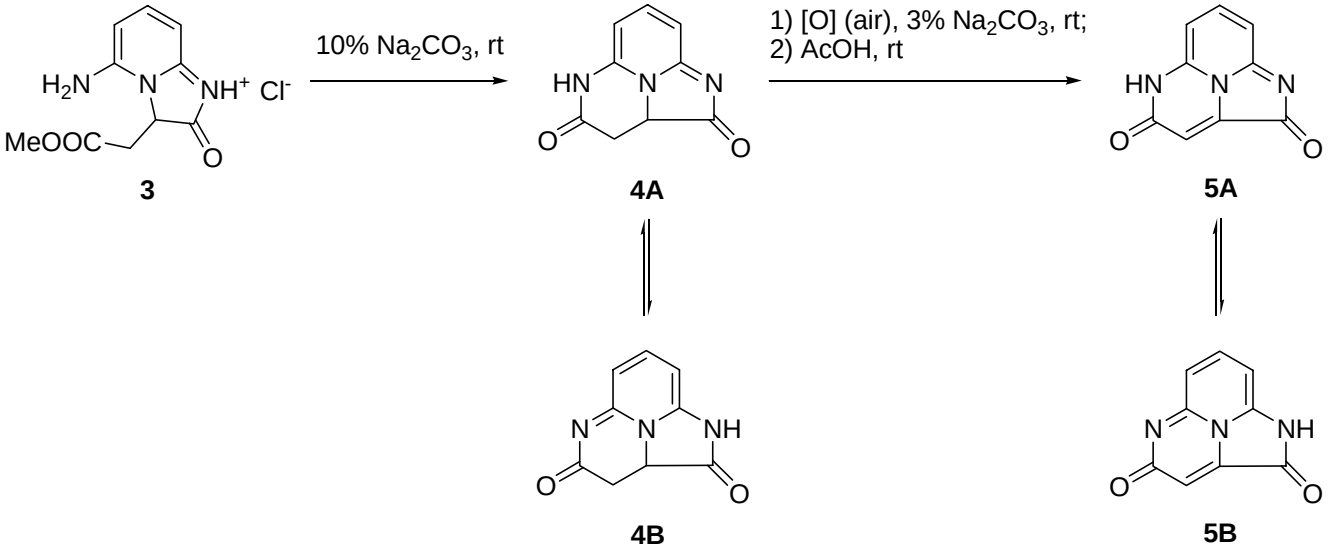
Attempts of the direct thermal intramolecular cyclization of **2** were not successful. Therefore, the acid (**2**) was treated with thionyl chloride in methanol to afford **3**. The tautomerism, similar to the compound (**2**), was observed for the ester (**3**). Interestingly, N-1 atom was found to be protonated in the compound (**3**) as indicated by cross-peaks between NH (12.89 ppm) and H-8 (6.40 ppm) signals in 2D NOESY experiment.



Scheme 1

The ester (**3**) upon treatment with sodium carbonate solution in mild condition underwent intramolecular ring closure and provided the tricyclic system 2a,3-dihydro-1(5)*H*-1,5-diazacycl[3.3.2]azine-2,4-dione (**4**) (Scheme 2). The compound (**4**) was readily enolized in alkaline condition and oxidized in aqueous solution by standing exposed to air overnight. After treatment of the resulting product with acetic acid, 1(5)*H*-1,5-diazacycl[3.3.2]azine-2,4-dione (**5**) was isolated and characterized. Annular tautomerism (forms

5A and **5B**) was found to be possible along with keto-enol tautomerism. However, we were not able to distinguish between these forms using the spectral data and X-ray crystallographic study might be required.



Scheme 2

In conclusion, an efficient and simple synthesis of new cyclazine type heterocyclic system *viz.* 1(5)*H*-1,5-diazacycl[3.3.2]azine-2,4-dione was successfully developed. Further investigation of the 1(5)*H*-1,5-diazacycl[3.3.2]azine chemistry is in the progress.

EXPERIMENTAL

General Methods. Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. IR spectra were performed on a Shimadzu IRPrestige-21 spectrophotometer in KBr discs. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer, using DMSO-d_6 or D_2O as solvents and TMS or TSP as internal references. The assignments were made using the reported data for (2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetic acids,[6] DEPT135, 2D COSY, NOESY and HMQC spectral data.

(5-Amino-2-oxo-2,3-dihydroimidazo[1,2-a]pyridin-3-yl)acetic acid (2).

The freshly recrystallized from toluene 2,6-diaminopyridine (**1**, 2.18 g, 20 mmol) was dissolved in EtOAc (40 mL) and a solution of maleic anhydride (1.96 g, 20 mmol) in EtOAc (20 mL) was slowly added with stirring at 0°C (ice bath). After stirring at 0°C for 30 min, ice bath was removed and stirring was continued for 12 h at rt. The precipitate was filtered, washed with EtOAc and refluxed in EtOH for 30 min. After cooling, the product (**2**) was filtered, washed with EtOH and recrystallized from water to give sandy crystals. Yield 2.82 g (68%); mp > 360°C (water).

IR (KBr, ν, cm^{-1}): 3550, 3466, 3369, 3102, 1727, 1682, 1634, 1591, 1551, 1407.

^{1}H NMR (300 MHz, DMSO-d_6 / TMS): δ 2.73 (1H, dd, $^3J_{AX}$ = 4.5 Hz, $^2J_{MX}$ = 17.7 Hz, H_X), 3.14 (1H, dd, $^3J_{AM}$ = 3.8 Hz, $^2J_{MX}$ = 17.7 Hz, H_M), 4.68 (1H, dd, $^2J_{AM}$ = 3.8 Hz, $^2J_{AX}$ = 4.5 Hz, H-3), 6.16 (1H, d, ^3J = 8.3 Hz, H-8), 6.19 (1H, d, ^3J = 8.3 Hz, H-6), 7.54 (1H, t, ^3J = 8.3 Hz, H-7), 8.30 (3H, br. s, NH_3^+).

^{13}C NMR (75 MHz, DMSO-d_6 / TMS): δ 34.4 (CH_2), 58.7 (C-3), 94.7 (C-8), 99.4 (C-6), 143.0 (C-7), 151.5 (C-5), 158.1 (C-8a), 171.5 (C-2), 178.4 (*C*OO$^-$).

^{1}H NMR (300 MHz, D_2O / TSP): δ 3.06 (1H, d, $^2J_{AB}$ = 17.7 Hz, H_A), 3.33 (1H, d, $^2J_{AB}$ = 17.7 Hz, H_B), 6.48 (1H, d, ^3J = 7.9 Hz, H-8), 6.63 (1H, d, ^3J = 8.7 Hz, H-6), 7.79 (1H, t, ^3J = 8.3 Hz, H-7).

^{13}C NMR (75 MHz, D_2O / TSP): δ 37.4 (CH_2), 62.6 (t, $^1J_{CD}$ = 22.9 Hz, C-3), 97.7 (C-8), 108.1 (C-6), 147.5 (C-7), 152.0 (C-5), 154.7 (C-8a), 177.6 (C-2), 178.3 (*C*OO$^-$).

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.85; H, 4.72; N, 20.28.

Methyl (5-amino-2-oxo-2,3-dihydroimidazo[1,2-a]pyridin-3-yl)acetate hydrochloride (3).

To a suspension of acid **2** (2.07 g, 10 mmol) in MeOH (30 mL), thionyl chloride (1.46 mL, 20 mmol) was added slowly with stirring at 0°C (ice bath). After stirring at 0°C for 30 min, ice bath was removed and stirring was continued for 4 h at rt. The solvent and excess of thionyl chloride were evaporated under reduced pressure and residue was recrystallized from EtOH to give sandy crystalline product (**3**). Yield 2.45 g (95%); mp > 360°C (EtOH).

IR (KBr, ν, cm^{-1}): 3372, 3075, 1757, 1730, 1675, 1646, 1586, 1410.

^{1}H NMR (300 MHz, DMSO-d_6 / TMS): δ 3.17 (1H, dd, $^3J_{AX}$ = 2.7 Hz, $^2J_{MX}$ = 18.1 Hz, H_X), 3.52 (3H, s, COO*Me*), 3.79 (1H, dd, $^3J_{AM}$ = 4.9 Hz, $^2J_{MX}$ = 18.1 Hz, H_M), 5.27 (1H, dd, $^3J_{AM}$ = 4.9 Hz, $^3J_{AX}$ = 2.7 Hz, H-3), 6.40 (1H, d, ^3J = 7.9 Hz, H-8), 6.66 (1H, d, ^3J = 8.7 Hz, H-6), 7.81 (1H, t, ^3J = 8.1 Hz, H-7), 8.82 (2H, s, NH_2), 12.89 (1H, br. s, NH).

^{13}C NMR (75 MHz, DMSO-d_6 / TMS): δ 30.1 (CH_2), 52.0 (COO*Me*), 57.7 (C-3), 92.7 (C-8), 104.7 (C-6), 144.3 (C-7), 148.5 (C-5), 151.7 (C-8a), 168.6 (*C*OOMe), 170.1 (C-2).

^{1}H NMR (300 MHz, D_2O / TSP): δ 3.37 (1H, d, $^2J_{AB}$ = 17.7 Hz, H_A), 3.63 (3H, s, COO*Me*), 3.68 (1H, d, $^2J_{AB}$ = 17.7 Hz, H_B), 6.51 (1H, d, ^3J = 7.9 Hz, H-8), 6.62 (1H, d, ^3J = 8.7 Hz, H-6), 7.81 (1H, t, ^3J = 8.3 Hz, H-7).

^{13}C NMR (75 MHz, D_2O / TSP): δ 33.2 (CH_2), 55.7 (COO*Me*), 60.9 (t, $^1J_{CD}$ = 22.6 Hz, C-3), 98.7 (C-8), 107.8 (C-6), 148.0 (C-7), 154.2, 154.8 (C-5 and C-8a), 173.6 (*C*OOMe), 178.2 (C-2).

Anal. Calcd for $C_{10}H_{12}N_3O_3Cl$: C, 46.61; H, 4.69; N, 16.31. Found: C, 46.38; H, 4.87; N, 16.09.

1(5)H-1,5-Diazacycl[3.3.2]azine-2,4-dione (5).

Salt **3** (1.29 g, 5 mmol) was dissolved in 10% aqueous Na_2CO_3 (5.5 mL) was stirred at rt. After 30 min, the precipitated bright yellow compound **4** was filtered and washed with cold water. Without further

purification, compound **4** was dissolved in 3% aqueous Na_2CO_3 (20 mL) and stirred overnight in an open flask. To the formed suspension of sodium salt of **5**, AcOH (5 mL) was added and the orange precipitate was filtered and washed with cold water. The purification of the product (**5**) can be performed using recrystallization from DMSO or, more conveniently, by reprecipitation from the solution in aqueous 10% aqueous Na_2CO_3 using AcOH. Yield 0.77 g (82%); mp > 360°C (DMSO).

IR (KBr, ν, cm^{-1}): 3448, 3059, 1735, 1699, 1667, 1617, 1605, 1485, 1456, 1393.

^{1}H NMR (300 MHz, DMSO-d_6 / TMS): δ 6.69 (1H, d, ^3J = 7.9 Hz), 6.86 (1H, d, ^3J = 8.7 Hz), 6.99 (1H, s), 7.91 (1H, t, ^3J = 8.3 Hz), 13.01 (1H, br. s. NH).

Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 57.76; H, 2.69; N, 22.45. Found: C, 57.99; H, 2.82; N, 22.78.

ACKNOWLEDGEMENTS

This work is supported by the Academic Research Fund, National University of Singapore.

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