SYNTHESIS OF ENAMINONITRILE IMIDAZO[1. 2-a]PYRIDINE BY AN EHRlich-
SACHS TYPE REACTION ON 2-NITROSOPYRIDINE

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Abstract: An Ehrlich-Sachs type reaction on 2-nitrosopyridines with malononitrile and a few drops of triethylamine produced 3-amino-2-cyanoimidazo[1,2-a]pyridines directly. The structure of the enaminonitrile was confirmed by an independent synthesis and chemical behavior. The imidazopyridine nitroester derivative used in the synthesis was employed as a synthon in an alternative route to pyridoimidazopyrimidones.

Introduction

The imidazo[1,2-a]pyridine system is a well recognized pharmacophore which has been involved in a wide and interesting range of pharmacological activities. Numerous synthetic approaches to obtain this important heterocycle have been devised, including solid support syntheses. On the other hand, the nitroso group is a versatile functionality in organic synthesis, for example, in a recently reported preparation of pyridoimidazotropolones. In particular, the nitroso moiety in 2-nitrosopyridine has been shown to be very reactive and has been exploited in several condensation and cycloaddition reactions.

Results and Discussions

In this communication, we wish to report a very interesting transformation involving 2-nitrosopyridines in an Ehrlich-Sachs type reaction. When 2-nitrosopyridine was treated with malononitrile in an anhydrous dichloromethane solution in the presence of triethylamine, the important synthetic intermediate enaminonitrile imidazo[1,2-a]pyridine 1a was directly obtained in moderate yield. Similarly, 4-methyl and 5-methyl-2-nitrosopyridines reacted under the same experimental conditions to deliver corresponding enaminonitriles 1b and 1c (Equation 1).

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\begin{align*}
R-\text{CH (CN) /Et N} & \quad \text{CH Cl} \\
& \quad \text{R-N=CN} \\
R = H, & \quad -\text{Me}, & \quad -\text{Me} \\
\end{align*}
\]

It has been thoroughly documented that \(\alpha\)-aminonitriles can be readily cyclized to annulated heterocycles such as pyridines, pyrimidines, triazines and various other heterocyclic systems. Thus, the enaminonitrile 1a was converted into adenine derivatives 2 in good yields by an slightly modified procedure: Treatment of 1a with an excess of previously dried formamidine hydrochloride and sodium \(n\)-butoxide/butanol afforded derivative 2a in 85% yield. In a similar fashion, treatment of 1a with an excess of acetamidine afforded 2b in 76 % yield, while treatment with guanidine led to derivative 2c in 82% yield after purification (Equation 2).
An independent synthesis of 1a was carried out, not only to confirm its structure but also because a discrepancy with the reported melting point (209–211 °C) as compared to our measurement of 239-240 °C. Thus, 1a was prepared starting from ethyl 3-nitroimidazo[1,2-a]pyridine-2-carboxylate 3 (Scheme 1). Compound 3 was converted into the corresponding amide 4 by treatment with an aqueous solution of concentrated ammonium hydroxide at room temperature. The nitro-amide 4 is insoluble in most organic solvents but treatment with a large excess of phosphorus oxychloride at 110 °C for one hour gave 2-cyano-3-nitroimidazo[1,2-a]pyridine 5. Product 5 has been also prepared from 2-chloro-3-nitroimidazo[1,2-a]pyridine by treatment with potassium cyanide.

Then, compound 5 was treated with an excess of sodium dithionite in a mixture of THF/water (3:2). Workup of the reaction mixture gave a yellowish, highly fluorescent, light sensitive solid which showed spectral data similar to those obtained from the isolated product of the reaction of 2-nitrosopyridine and malononitrile. Crystallization from methanol furnished enaminonitrile 1a as yellowish needles, mp 239-240 °C.

The nitro ester derivative 3 was used in an alternative procedure to obtain guanine derivatives 7 a-c (Scheme 2). Thus, compound 3 was treated with sodium dithionite in THF/water to give the corresponding ethyl 3-aminoimidazo[1,2-a]pyridine-2-carboxylate 6. The amino ester 6 was heated with freshly distilled formamide under an inert atmosphere at 160 °C for 4 h. From the reaction mixture, derivative 7a was isolated (compound 7a has been obtained previously by treating the amino amide 8 with triethyl orthoformate). A solvent free treatment on 6 with an excess of acetamide (fusing the mixture at 90 °C and heating for 24 h), gave only traces of the desired product 7b. However, treatment of 6 with an excess of acetamide acetate in hot 2-ethoxyethanol gave compound 7b, albeit in very low yield. Compound 7c was prepared by the reaction of guanidine with a nitro ester 3. However, a similar treatment on the nitro derivative 3 with acetamide hydrochloride (using either sodium n-butoxide or sodium t-butoxide) led to the nitro amide 4, probably because of acetamide decomposition. These results show a marked chemical difference to that exhibited by the enaminonitrile array in 1a and confirm the lack of reactivity of enamino esters, such as 6, towards nucleophiles, which has been previously observed in related systems.
Product 7a was converted to adenine derivative 2a through the intermediary of a halogenated derivative 9 which, in turn, was obtained by heating 7a with phosphorus oxychloride in the presence of a catalytic amount of N,N-dimethylaniline. Compound 9 was treated with ammonia in warm 2-ethoxyethanol to give 2a. The $^1$H NMR spectrum of compound 2a shows the same signals (the characteristic two amino protons at $\delta$ 7.6 and the amidine H-3 proton at $\delta$ 8.35) as the compound obtained from 1a.

In conclusion, treatment of several 2-nitrosopyridines with malonitrile in a slightly basic medium led to the corresponding enaminoonitriles imidazo[1,2-a]pyridines. The structure of 1a was confirmed by an independent synthesis, chemical transformations and analysis of the spectroscopic data. Alternative procedures to obtain purine derivatives 7a-c from intermediate ethyl 3-nitroimidazo[1,2-a]pyridine-2-carboxylate were described.

**Experimental**

Melting points were determined in an Electrothermal melting point apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Mercury Vx 300 MHz spectrometer. Mass spectra were recorded on a MS-50 (Kratos) spectrometer.

**3-Amino-2-cyanoimidazo[1,2-a]pyridine 1a (from 2-nitrosopyridine).** 2-Nitrosopyridine 108 mg (1 mmol) was dissolved in dry CH$_2$Cl$_2$ (5 mL) under argon and the solution cooled to -60 °C. Malononitrile (0.066 g, 1 mmol), in CH$_2$Cl$_2$ (3 mL) was added followed by 5-7 drops of Et$_3$N. The reaction mixture was stirred at this temperature for 1 h. Temperature was then slowly increased to -40 °C and the mixture was stirred at this temperature for 40 min. The mixture was stirred for another 30 min at -30 °C and then allowed to reach room temperature. The yellowish green solid formed was collected by filtration and washed with Et$_2$O (2 x 5 mL). The solid was crystallized from methanol to give yellow crystals, mp 239-40 °C, 0.039g (25% yield). $^1$H NMR (DMSO-d$_6$) $\delta$ 6.61 (s, 2H), 6.80-7.50 (m, 3H), 8.1 (d, IH, J = 7Hz). $^{13}$C NMR 69.4, 111.9, 116.5, 117.3, 122.7, 124.3, 138.3, 139.9. MS m/z (rel. intensity) 158 (100), 104 (46.3), 79 (80.9). HRMS calcd for C$_8$H$_5$N$_4$: 158.05922 Found, 158.05912.
3-Amino-2-cyano-7-methylimidazo[1,2-a]pyridine 1b. Obtained in 23% yield, mp 265-266 °C dec. 1H NMR (DMSO-δ6) δ 2.3 (s, 3H), 6.52 (br s, 2H), 6.74 (d, 1H, J = 7 Hz), 7.11 (s, 1H), 8.05 (d, 1H, J = 7Hz). 13C NMR δ 20.7, 94.4, 114.9, 115.3, 116.9, 122.3, 135.1, 139.0, 139.9. MS m/z (relative intensity) 172 (100), 118 (40). HRMS calcd for C9H8N6, m/z 200.08101; found m/z 200.08161. 

3-Amino-2-cyano-5-methylimidazo[1,2-a]pyridine 1c. Obtained in 28%, mp 191-192 °C. 1H NMR (DMSO-δ6) δ 2.87 (s, 3H), 5.70 (s, 2H), 6.50 (d, 1H, J = 6.8 Hz), 7.02 (dd, 1H, J = 7.0 Hz, J = 9.0 Hz). 13C NMR δ 18.9, 100.9, 112.9, 115.8, 116.4, 125.7, 136.7, 139.9, 141.6. MS m/z (relative intensity) 172 (100), 118 (42), 93(68). HRMS calcd for C9H7N5, m/z 200.7220; Found m/z 200.7260.

2-Cyano-3-nitroimidazo[1,2-a]pyridine 5. To 2-carboxamido-3-nitroimidazo[1,2-a]pyridine 4 (1.1 g, 5.3 mmol), POCl3 (6 mL) was added under argon, and the mixture was stirred and heated to 110 °C for 1 h. Then it was allowed to cool to room temperature, and the excess of POCl3 was removed under a reduced pressure. The reaction flask was placed in an ice bath, cold water was carefully added, and the solid that separated was collected by filtration and washed with water. Crystallization from 2-ethoxyethanol (or DMSO) delivered 5 as reddish crystals; yield 0.81 g (80%), mp 167-168 °C (Lit. mp 162 °C). 1H NMR (DMSO-δ6) δ 7.6 (t, 1H, J = 6 Hz), 7.91 (t, 1H, J = 6 Hz), 8.05 (d, 1H, J = 7 Hz), 9.29 (d, 1H, J = 7 Hz). 13C NMR δ 113.54, 118.74, 119.36, 119.91, 128.70, 133.57, 135.33, 145.62. MS m/z (rel. intensity) 185 (53.9), 130 (19.2), 78 (100). HRMS calcd for C6H4N4O2: 188.0333 Found, 188.03349.

3-Amino-2-cyanoimidazo[1,2-a]pyridine 1a. 2-Cyano-3-nitroimidazo[1,2-a]pyridine 5 (0.5 g, 2.66 mmol) was dissolved in THF(10 mL) and a mixture THF/water (1:2, 15 mL) was added. The mixture was warmed to 50 °C and stirred for 4 h. Sodium dithionite (0.5 g, 2.88 mmol) was then slowly added. The solution immediately became dark and after a while, it was deep orange. After one hour another portion of sodium dithionite (0.25g, 1.4 mmol) was added. The operation was repeated until no change in color was observed. The reaction mixture was then allowed to cool to room temperature, and solvents were removed under a reduced pressure. To the residue, water (15 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The extract was dried (Na2SO4) and concentrated under a reduced pressure to leave a solid which was further crystallized from MeOH to give the title compound as yellow crystals. Yield 0.19 g, 45%, mp 239-240 °C. HRMS calcd for C9H7N5O2, m/z 158.05922; found, 158.05912.

4-Aminopyrido[1’,2’:1,2]imidazo[4,5-d]pyrimidine 2a. n-Butyl alcohol (15 mL) was carefully added to sodium (0.24 g, 10 mmol) placed in a dry flask under argon, and stirring started. When a clear solution was formed, previously dried (4 h under vacuum, at 80 °C) formamidine hydrochloride (0.8 g, 10 mmol) was added, followed by n-butyl alcohol (15 mL). After 25 min, 3-amino-2-cyanoimidazo[1,2-a]pyridine (0.27 g, 1.7 mmol) was added, followed by 5 mL of dry n-butyl alcohol. A faint yellow color developed. The mixture was heated to 80 °C for 5 h and then allowed to cool to room temperature. Solvent was removed under a reduced pressure to leave a white residue. Water (30 mL) was carefully added, the solid formed was collected by filtration and further crystallized from water to afford 0.27 g, 85.4% of 2a as a white feather like solid, mp 285-287 °C (lit. mp >260 °C). 1H NMR (DMSO-δ6) δ 7.0 (t, 1H, J = 6.8 Hz), 7.50 (t, 1H, J = 6.8 Hz), 7.60- 7.64 (m, 3H), 8.25 (s, 1H), 8.66 (d, 1H, J = 7 Hz). MS m/z (rel. intensity) 185 (100), 158 (67.4). HRMS calcd for C13H10N5: 185.07012 Found, 185.07005.

4-Amino-2-methylpyrido[1’,2’:1,2]imidazo[4,5-d]pyrimidine 2b. Acetamidine hydrochloride (0.99g, 10 mmol) was treated with 3-amino-2-cyanoimidazo[1,2a]pyridine (0.27 g, 1.7 mmol) following the above procedure to give the title compound, which was further crystallized from water to furnish white plates, mp 261-263 °C (lit. mp 238-240 °C). Yield, 0.26 g, 76%. 1H NMR (DMSO-d6) δ 2.49 (s, 3H), 6.95 (dd, 1H, J = 6Hz, J = 1Hz), 7.45- 7.56 (m, 4H), 8.61 (dd, 1H, J = 6Hz, J = 1Hz). 13C NMR δ 26.2, 112.2, 118.6, 119.7, 125.3, 130.2, 144.6, 145.1, 157.2, 168.3. MS m/z (rel. intensity), 199(100), 158(30.5). HRMS calcd for C15H10N5: 199.08577; found m/z 199.08552.

2,4-Diaminopyrido[1’,2’:1,2]imidazo[4,5-d]pyrimidine 2c. Guanidine hydrochloride (0.95 g, 10 mmol) was treated with 3-amino-2-cyanoimidazo[1,2-a]pyridine (0.27 g, 1.7 mmol) following the procedure described above to give the title compound as faint yellow plates (from water). Yield 0.28g, 82%. 1H NMR (DMSO-d6) δ 6.01 (s, 4H), 6.81(d, 1H, J = 6 Hz), 7.22 (dd, 1H, J=9Hz), 7.46 (d, 1H, J = 9 Hz), 8.26 (d, 1H, J = 6 Hz). 13C NMR δ 111.6, 116.0, 118.7, 124.5, 128.0, 143.1, 145.9, 157.9, 160.2. MS m/z (rel. intensity), 200 (100), 158 (22.7). HRMS calcd for C15H10N5, m/z 200.08101; found m/z 200.08161.
4-Hydroxy pyrido[1',2':1,2]imidazo[4,5-d]pyrimidine 7a. Ethyl 3-aminimidazo[1,2-a]pyridine-2-carboxylate 6 (0.216 g, 1.05 mmol) was placed in a flask under argon. An excess of formamide (2.0 g, 45.3 mmol) was added and heating started. At about 100 °C the mixture became homogeneous. Then, it was heated at 160 °C for 2 h. After this time the mixture was allowed to cool to room temperature and the precipitate formed was collected by filtration and washed with cold water (5 mL) and cold ethanol (5 mL). The solid was heated in a mixture ethanol/water (1/1) and then filtered to give compound 7a as a crystalline pale brown solid (0.092 g, 47 % yield) mp > 300 °C (lit. mp > 260 °C). 1H NMR (DMSO-d6) δ 7.05 (t, 1H, J = 9 Hz), 7.5 (t, 1H, J = 9 Hz), 7.70 (d, 1H, J = 9 Hz), 8.15 (s, 1H), 8.68 (d, 1H, J = 6 Hz), 12.5 (bs, 1H). 13C NMR δ 114.3, 119.4, 125.7, 127.9, 142.6, 144.9, 145.5, 158.8. MS m/z (rel. intensity) 201 (100), 160 (38.7), 159 (28.9). HRMS calcd for C_{10}H_{12}N_{4}O, m/z 186.05403; found m/z 186.05353.

4-Hydroxy pyrido[1',2':1,2]imidazo[4,5-d]pyrimidine 7b. Ethyl 3-aminimidazo[1,2-a]pyridine-2-carboxylate 6 (0.216 g, 1.05 mmol) and acetyl amine acetate (0.62 g, 5 mmol) were placed in a flask under argon. 2-Ethoxy ethanol (20 mL) was then added and heating started. The mixture was stirred and heated at 100-110 °C for 12 h, then allowed to cool to room temperature and concentrated under a reduced pressure. Water (1 mL) was added and the solid formed was collected by filtration and washed with ethanol (5 mL) and water (5 mL). The solid was treated with hot water to give 6b as a brownish solid, mp > 300 °C, 20 mg, 9.5 % yield. 1H NMR (DMSO-d6) δ 2.21 (s, 3H), 7.00 (t, 1H, J = 9 Hz), 7.51 (t, 1H, J = 9 Hz), 7.62 (d, 1H, J = 9 Hz), 8.51 (d, 1H, J = 6 Hz), 12.40 (bs, 1H). 13C NMR δ 27.19, 112.30, 118.51, 119.66, 127.82, 130.27, 144.65, 146.55, 156.12, 159.23. MS m/z (rel. intensity) 186 (100), 158 (29), 104 (64), 79 (94), 78 (94). HRMS calcd for C_{10}H_{12}N_{4}O, m/z 200.06793; found m/z 200.06693.

2-Amino-4-hydroxy pyrido[1',2':1,2]imidazo[4,5-d]pyrimidine 7c. Dry n-butanol (15 mL) was carefully added to sodium (0.14 g, 6 mmol) in a dry flask under an argon atmosphere, and the mixture was stirred until sodium was consumed. Guanidine hydrochloride (0.6 g, 6 mmol) was added (previously dried under a reduced pressure at 80 °C for at least 2 h) was then added, followed by n-butyl alcohol (10 mL). The resultant suspension was stirred at room temperature for half an hour and then 2-carboxyethoxy-3-nitro-imidazo[1,2-a]pyridine (0.2 g, 0.8 mmol) was added, followed by n-butyl alcohol (5 mL). The suspension was stirred and heated to 80 °C. After 4 h, the mixture was allowed to cool to room temperature and concentrated under a reduced pressure. The residue was treated with hot methanol, cooled, and filtered. The filtrate was concentrated to leave a pinkish solid which was further crystallized from DMSO to give the title compound as a light brown solid, 0.071 g, 41 % yield, mp > 300 °C. 1H NMR (DMSO-d6) δ 6.48 (s, 2H), 7.08 (t, 1H, J = 6 Hz), 7.57 (d, 1H, J = 6 Hz), 7.59 (d, 1H, J = 6 Hz), 8.82 (d, 1H, J = 9 Hz), 10.88 (bs, 1H). 13C NMR δ 116.4, 120.3, 126.8, 128.9, 143.7, 144.5, 156.3, 159.1. MS m/z (rel. intensity) 201(100), 160 (38.7), 159 (28.9). HRMS calcd for C_{10}H_{12}N_{4}O, m/z 201.06503; found m/z 201.06504.

4-Aminopyrido[1',2':1,2]imidazo[4,5-d]pyrimidine 2a from 9. 4-Chloropyrido[1',2':1,2]imidazo[4,5-d]pyrimidine 2a in 20 mL of a mixture ethanol/water (1/1) was added, followed by a mixture of n-butanol and cold water (5 mL). The solution was heated to 80 °C and concentrated to leave an oily residue. Water (15 mL) was added and a solid separated upon standing. The white solid was collected by filtration and washed with ethanol; yield 38 %, mp. 285-287 °C. Spectroscopic data are identical with those presented above above.

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References

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