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Heterocyclization of α-aminonicotinonitrile: A new approach for synthesis of triazolo[1,5-a]pyridine-8-carbonitrile

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ABSTRACT **:** ***A new series of 1,2,4-triazolo[1,5-a]pyridine and pyrido[1,2-b]triazine was synthesized. The synthesis commenced with one-pot synthesis of pyran from 4-chlorobenzaldehyde, acetyl acetone and malononitrile in the presence of piperidine. The pyran 1 undergo ring transformation to pyridine derivatives 2 and 3 via reaction with amm.acetate and hydrazine hydrate. 1-Aminopyridine intermolecular cyclized to a new triazolo[1,5-a]pyridines 4-7 via reaction with acetic anhydride, carbon disulfide, formic acid and triethyl orthoformate. The triazine 8 was synthesized via cyclization of pyridine 1 with acetyl acetone in the presence of pyridine.***

Key words: Pyran, 1-aminonicotinonitrile, intermolecular cyclization, one-pot synthesis.

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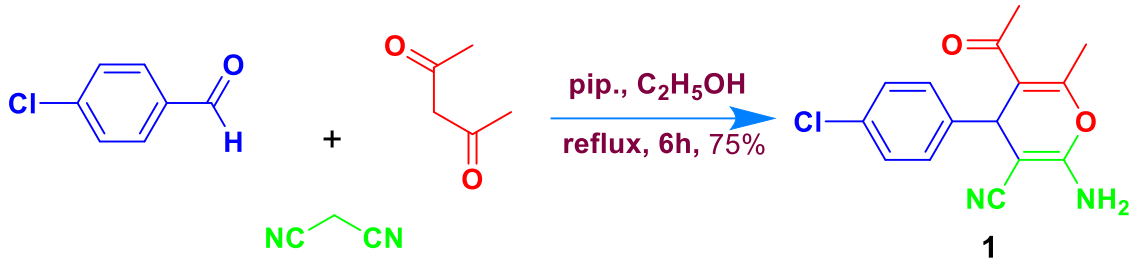
1. Introduction

Triazolo[1,5-*a*]pyridine derivatives is a one of biologically active *N*-bridged 5,6-bicyclic heterocyclic molecules that have considerable interests in the medicinal and material science .[1,2] For instance, several series of triazolo[1,5-*a*]pyridines have antidiabetic,[3,4] antibacterial,[5] anti-oxidant,[6] anti-inflammatory,[7] antidepressant[8] and antiproliferative,[9] activity. Morevere, a series of such molecules have been used as effective ligands for several transition metals[10–12] and herbicidal agents.[13] Following on with our approaches, herein we described metal-free, an effective and environmentally friendly protocol for the synthesis of a new derivatives of triazolo[1,5-*a*]pyridines utilizing 1,2-diaminopyridine as a starting molecule.

2.Results and discussion

The present work introduce a new approach for 1,2,4-triazolo[1,5-*a*]pyridine derivatives. The work commenced with one-pot condensation of 4-chlorobenzaldehyde, acetyl acetone and malononitrile in the presence of piperidine as a mild basic catalyst to afford the respective pyran derivative **1** in 75% (Scheme 1). The pyran **1** has two main bands in its IR spectrum at 2221 and 1634 for C≡N, 1634 C=O, respectively. Its ^{1}H NMR assigned four singlets at 2.10, 2.30, 4.56 and 9.10 ppm for methyl, acetyl, pyran-4-H and NH_2 protons, respectively. In addition, the aromatic protons split as two doublets at 7.41 and 7.60 ppm. The ^{13}C NMR is another evidence for formation of pyran **1** and account 13 signals at 22.10, 31.81, 51.47, 115.3, 121.8, 128.7, 128.7, 130.6, 130.6, 134.2, 156.2, 156.2, and 201.6 for sp^3, sp^2 and sp carbons.



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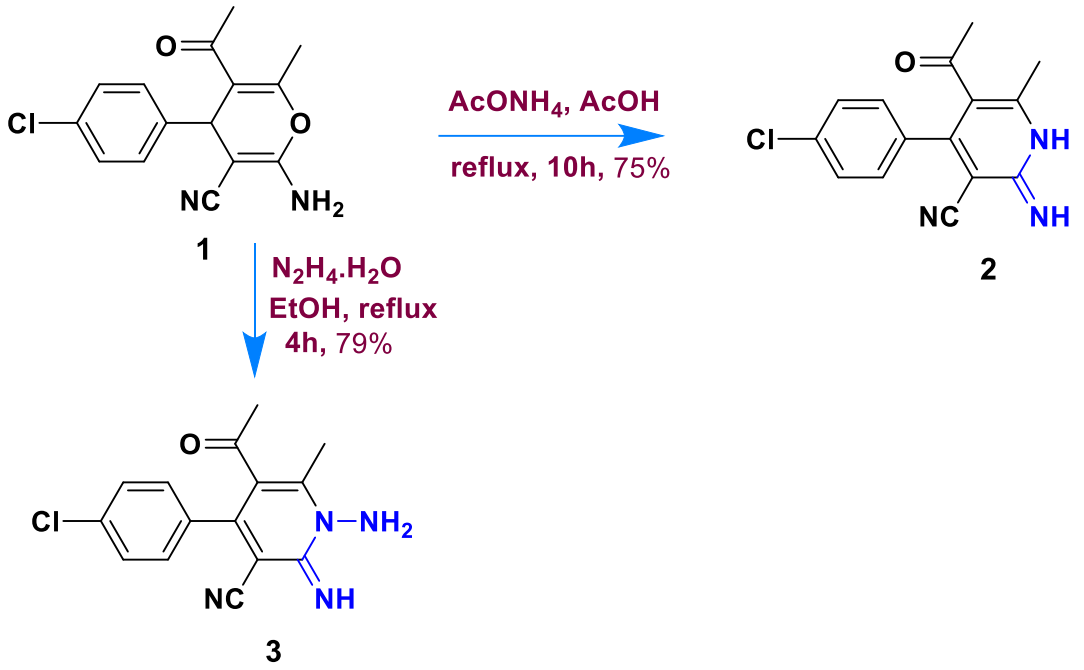
Scheme 1: Synthetic approach of pyran 1.

Pyran **1** can be underwent ring transformation to a new interested heterocyclic scaffolds. For example, reaction of compound **1** with amm. acetate in acetic acid for 10 hours afforded 2-iminopyridine 2 in 75%. At the same manner, reaction with hydrazine hydrate in ethanol afforded 1-aminonicotinonitrile **3** in 79% yield (Scheme 2). The IR spectrum of compound **2** contain three main bands at 3346, 2221, 1651 cm^{-1} for NH, C≡N and C=O functions, respectively. In addition, four singlets at 1.82, 2.23, 4.20 and 8.30 ppm for methyl, acetyl, NH and endo-cyclic NH, respectively in its ^1H NMR spectrum. The IR spectrum of compound **3** indicate the presence of NH_2, C≡N and C=O at 3322, 2230, 1643 cm^{-1}.



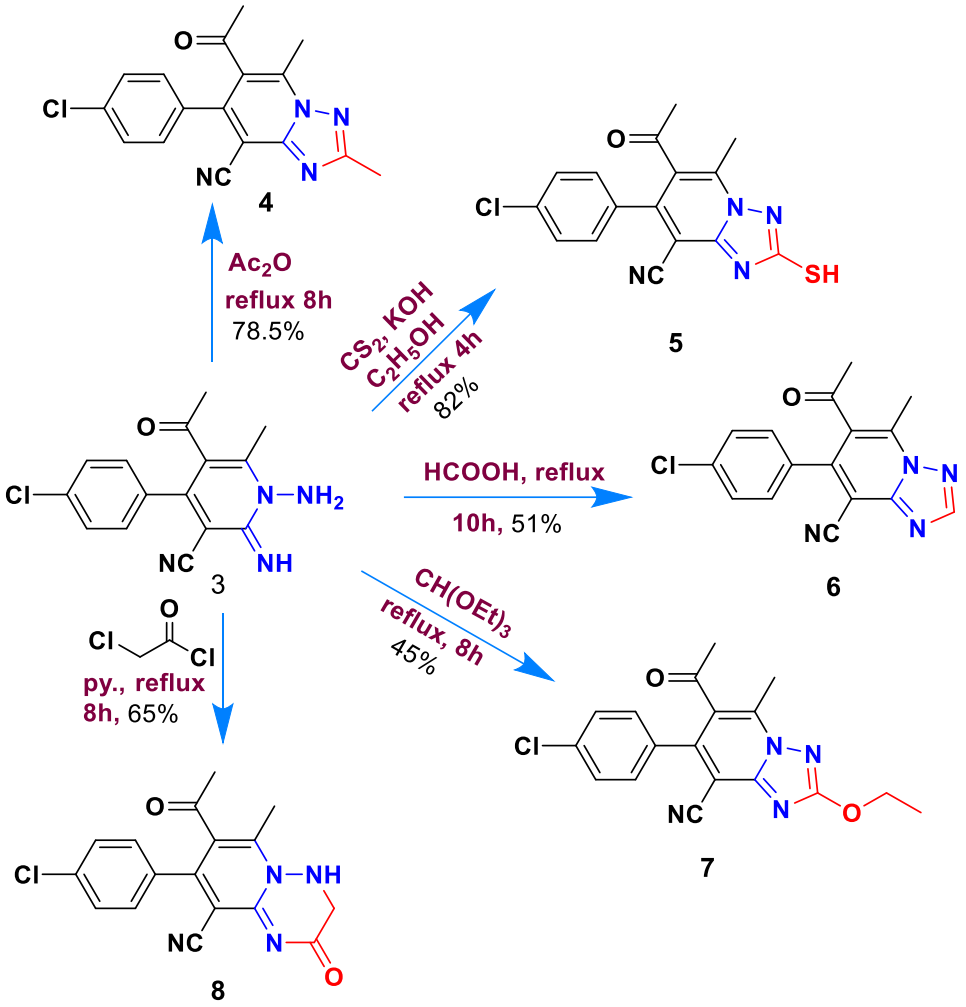
Scheme 1: Synthetic approach of pyridines 2 and 3.

Nicotinonitrile **3** contains two adjacent amino functions, that enable such compound to undergo intermolecular cyclization with electrophile-containing compounds to form more interested bicyclic pyridines such triazol[1,5-*a*]pyridine and pyrido[1,2-*b*]triazine. Thus, reflux of compound **3** with an excess of acetic anhydride, formic acid, and triethyl orthoformate afforded the desired 1,2,4-triazolo[1,5-a]pyridine derivatives 4,6 and 7, respectively in 45-78.5% yield (Scheme 3). Reaction of carbon disulfide with aminopyridine 3 in the presence of potassium hydroxide afforded 6-acetyl-7-(4-chlorophenyl)-2-mercapto-5-methyl-[1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitrile **(5)** in 82% yield.

Finally, the pyrido[1,2-*b*]triazine **8** was synthesized via intermolecular cyclization of pyridine derivative **3** with chloroacetyl chloride in the presence of pyridine (Scheme 3).

The structure of the target compounds **4-8** were confirmed from the spectral data. For exampl1e, the IR of compound **4** assigned two main bands at 2217 and 1648 cm^{-1} for C≡N and C=O functions. Its ^{1}H NMR indicate the presence of a new methyl group at 2.10 ppm for methyl at *C*-2 of the compound. The 13C NMR accounted 15 signals at 20.45, 22.51, 31.82, 100.15, 115.46, 120.62, 128.7, 128.7, 129.3, 129.3, 133.2, 135.1, 151.3, 159.7, 172.0, and 200.1 for sp^3, sp^2 and sp carbons.

Another example, is triazine **8** that has bands at 3300, 2218, 1694, and 1679 cm^{-1} for NH, C≡N, and C=O functions. The ^{1}H NMR spectrum showed the presence of cyclic methylene (CH_2) protons at 4.30 ppm as a singlet. The ^{13}C NMR assigned 15 signals at 18.04, 31.81, 53.62, 115.2, 117.12, 121.02, 128.7, 128.7, 129.9, 129.9, 130.6, 133.5, 157.13, 158.9, 165.6, 168.9, and 200.1.

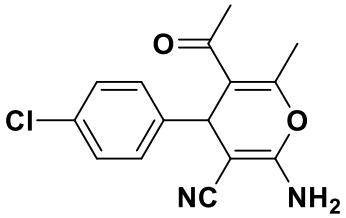


Scheme 3: Heterocyclization of 1-aminonicotinonitrile 3.

2. Experimental

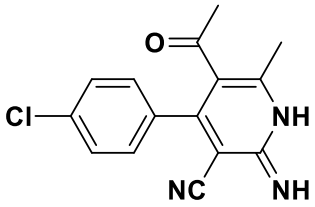
All melting points are uncorrected and were detected using an Electro-thermal IA 9100 apparatus. IR spectra (KBr) were detected on a Nexus 670 FTIR Nicolet, Fourier transform infrared spectrometer. The ^{1}H and ^{13}C NMR spectra were determined with a JEOL-JNM-LA 400 MHz spectrometer and 100 MHz for ^{13}C NMR. The chemical shifts are expressed on the δ (ppm) scale using TMS as the standard reference. TLC was carried out on Merck Silica Gel $60F_{254}$ and detected by UV light. Elemental analysis measured on a PerkinElmer 240 (microanalysis), Microanalysis Center, Cairo University Cairo, Egypt (E. Merck). The chemicals and solvents used in the synthesis of pyridine and triazolo[1,5-*a*]pyridine derivatives were obtained from Merck and Aldrich.

5-Acetyl-2-amino-4-(4-chlorophenyl)-6-methyl-4H-pyran-3-carbonitrile



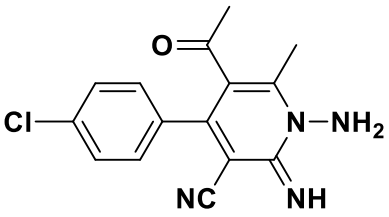
A mixture of 4-chlorobenzaldehyde (10 mml), malononitrile (10 mml) and acetyl acetone (10 mml) was heated with reflux for 6 hours in absolute ethanol and 3 drops of piperidine. The formed solid after cooling was filtered and crystallized from benzene and petroleum ether as pale yellow powder. Yield 75%, m.p = 160-162℃ .IR spectrum, υ, cm^{-1}: 2221 (C≡N), 1634 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.10 s (3H, CH_3), 2.30 s (3H, CH_3CO), 4.56 s (1H, H-4), 7.41 d (2H, J = 5.2 Hz, H_{aryl}), 7.60 d (2H, J = 10.4 Hz, H_{aryl}), 9.10 s (2H, NH_2). ^{13}C NMR spectrum, δ, ppm: 22.10, 31.81, 51.47, 115.3, 121.8, 128.7, 128.7, 130.6, 130.6, 134.2, 156.2, 156.2, 201.6. Found, %: C, 62.29; H, 4.57; N, 9.75. $C_{15}H_{13}ClN_2O_2$ (288.73). Calculated, %: C 51.58; C, 62.40; H, 4.54; N, 9.70

5-Acetyl-4-(4-chlorophenyl)-2-imino-6-methyl-1,2-dihydropyridine-3-carbonitrile



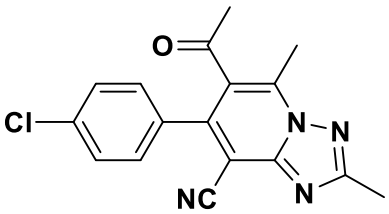
A mixture of pyran (2.88 g, 10mml) and amm.acetate (6.16 g, 10 mml) were refluxed for 12 hours in acetic acid. The formed solid after cooling was filtered off and crystallized from ethanol / petrolum ether (80:20%) as pale yellow powder. Yeild 86%, m.p = 240-242℃. IR spectrum, υ, cm^{-1}: 3346 (NH), 2221 (C≡N), 1651 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.82 s (3H, CH_3), 2.23 s (3H, CH_3CO), 4.20 s (1H, NH), 7.31 d (2H, J = 6.40 Hz, H_{aryl}), 7.72 d (2H, J = 6.80 Hz, H_{aryl}), 8.3 s (1H, $NH_{pyridine}$). Found, %: C, 63.13; H, 4.20; N, 14.77. $C_{15}H_{12}ClN_3O$ (285.73). Calculated, %: C, 63.05; H, 4.23; N, 14.71.

5-Acetyl-1-amino-4-(4-chlorophenyl)-2-imino-6-methyl-1,2-dihydropyridine-3-carbonitrile



A mixture of 2-iminopyridine (2.88 g, 10 mml) and hydrazine hydrate (0.75 mL, 15 mml) were refluxed for 4 hours in absolute ethanol. The formed solid after cooling and crystallized from benzene and petroleum ether as pale yellow powder. Yield 79%, m.p = 220-222℃. IR spectrum, υ, cm^{-1}:3322 (NH_2), 2230 (CN), 1643 (C=O). Found, %: C, 59.84; H, 4.39; N, 18.69. $C_{15}H_{13}ClN_4O$ (300.08). Calculated, %: C, 59.91; H, 4.36; N, 18.63.

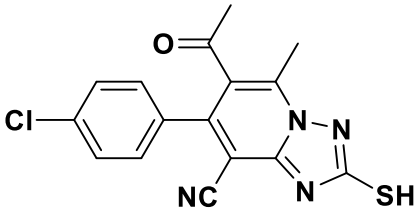
6-Acetyl-7-(4-chlorophenyl)-2,5-dimethyl-[1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitrile



A mixture of 1-aminonicotinonitrile (10 mml) and acetic anhydrite (25 mL) were heated with reflux for 8 hours. The formed solid after cooling was filtered off and crystallized from ethanol as pale yellow powder. Yield 78.5%, m.p = 142-144 ℃. IR NMR spectrum, υ, cm^{-1}: 2217 (C≡N), 1648 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.92 s (3H, CH_3), 2.10 s (3H, CH_3), 2.35 s (3H, CH_3CO), 7.40 d (2H, J = 6.8 Hz, H_{aryl}), 7.65 d (2H, J = 2.0 Hz, H_{aryl}). ^{13}C NMR spectrum, δ, ppm: 18.11, 20.45, 22.51, 31.82, 100.15, 115.46, 120.62, 128.7, 128.7, 129.3, 129.3, 133.2,

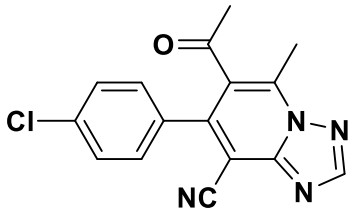
135.12, 151.38, 159.74, 172.02, 200.19 (sp^3, sp^2 and sp carbons). Found, %: C, 62.96; H, 4.00; N, 17.31. $C_{17}H_{13}ClN_4O$ (324.77). Calculated, %: C, 62.87; H, 4.03; N, 17.25.

6-Acetyl-7-(4-chlorophenyl)-2-mercapto-5-methyl-[1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitrile



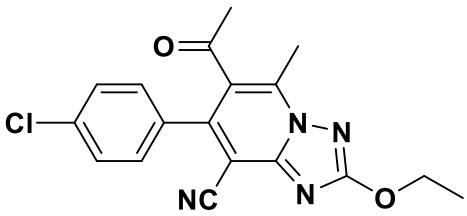
A mixture of 1-aminonicotinonitrile (10 mml) (10mml), carbon disulfide (10mml) and potassium hydroxide (10mml) were refluxed for 4 hours in absolute ethanol. The formed solid after cooling was filtered off and crystallized from benzene and petrolum ether as pale yellow powder. Yield 82%, m.p = 250-252°C. IR NMR spectrum, υ, cm^{-1}: 2919 (SH), 2222 (C≡N), 1621 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.82 s (3H, CH_3), 2.36 s (CH_3CO), 7.21 d (2H, J = 9.20 Hz, H_{aryl}), 7.52 d (2H, J = 9.2 Hz, H_{aryl}), 13.05 s (1H, SH). Found, %: C, 57.13; H, 3.27; N, 16.28. $C_{16}H_{11}ClN_4OS$ (342.80). Calculated, %: C, 56.06; H, 3.23; N, 16.34.

6-Acetyl-7-(4-chlorophenyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile



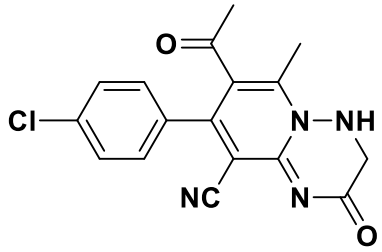
A mixture of 1-aminonicotinonitrile (10 mml) and formic acid (25 mL) were heated with reflux for 10 hours. The formed solid after cooling was filtered off and crystallized from methanol and petrolum ether as pale yellow powder. Yield 51%, m.p = 198-200°C. IR NMR spectrum, υ, cm^{-1}: 2250 (C≡N), 1699 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.92 s (3H, CH_3), 2.33 s (3H, CH_3CO), 7.46 d (2H, J = 6.80 Hz, H_{aryl}), 7.72 d (2H, J = 6.80 Hz, H_{aryl}), 8.67 s (1H, $H_{triazole}$). Found, %: C, 61.77; H, 3.60; N, 18.08. $C_{16}H_{11}ClN_4O$ (310.74). Calculated, %: C, 61.84; H, 3.57; N, 18.03.

6-Acetyl-7-(4-chlorophenyl)-2-ethoxy-5-methyl-[1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile



A mixture of 1-aminonicotinonitrile (10 mml) and triethylorthoformate (20 mL) were heated with reflux for 8 hours. The formed solid after cooling was filtered and crystallized from methanol and petrolum ether as pale yellow powder. Yield 45%, m.p = 180-182°C. IR spectrum, υ, cm^{-1}: 2222 (C≡N), 1685 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, J = 8.4 Hz, $CH_2C\underline{H}_3$), 1.96 s (3H, CH_3), 2.15 s (3H, CH_3CO), 4.45 q (2H, J = 7.2 Hz, $C\underline{H}_2CH_3$), 7.43 d (2H, J = 9.6 Hz, H_{aryl}), 7.64 d (2H, J = 8.8 Hz, H_{aryl}). Found, %: C, 60.85; H, 4.22; N, 15.84. $C_{18}H_{15}ClN_4O_2$ (354.79). Calculated, %: C, 60.94; H, 4.26; N, 15.79.

7-Acetyl-8-(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-2H-pyrido[1,2-b][1,2,4]triazine-9-carbonitrile



A mixture of 1-aminonicotinonitrile (10 mml) and chloroacetyl chloride (10 mml) were heated with reflux for 8 hours in pyridine (15 mL). The formed solid after cooling was filtered off and crystallized from methanol and petroleum ether as pale yellow powder. Yield 65%, m.p = 178-190°C. IR spectrum, υ, cm^{-1}: 3300 (NH), 1694, 1679 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.92 s (3H, CH_3), 2.31 s (3H, CH_3CO), 4.3 s (2H, CH_2), 7.35 d (2H, J = 7.80 Hz, H_{aryl}), 7.65 d (2H, J = 7.80 Hz, H_{aryl}), 10.9 s (1H, NH) ^{13}C NMR spectrum, δ, ppm: 18.04, 31.81, 53.62, 115.2, 117.12, 121.02, 128.7, 128.7, 129.9, 129.9, 130.6, 133.5, 157.13, 158.9, 165.6, 168.9, 200.1. Found, %: C, 60.01; H, 3.81; N, 16.49. $C_{17}H_{13}ClN_4O_2$ (340.77). Calculated, %: C, 59.92; H, 3.85; N, 16.44.

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