One Step Synthesis of 3-Cyano-4-(5-nitrobenzothienyl)pyridines and 3-Cyano-4-(5-nitrobenzothienyl)pyridin-2-ones for Biological Evaluation

S. M. A. D. Zayed and A. Attia

Laboratory of Applied Organic Chemistry, National Research Centre, Dokki, Cairo, Eygpt

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A new one-vessel reaction has been developed for the synthesis of substituted aminocyanopyridines **2** and cyanopyridin-2-ones **3**. Compounds **2a-c** and **3a-c** were readily obtained by heating molar amounts of 5-nitrobenzothiophene-2-carboxaldehyde **1**, the appropriate acetyl derivative and the active methylene compound (malononitrile or ethyl cyanoacetate) in presence of ammonium acetate. The new method had the advantage of being quick, economic and of general application. A possible mechanism for the reaction, has been suggested.

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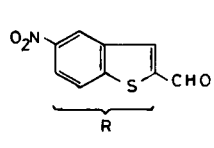
Cyanopyridines of type **2** and **3** were found to possess a pronounced antimicrobial activity (1,2). They are normally prepared by reaction of active methylene compounds with the corresponding propenone derivatives in the presence of ammonium acetate (1-7). This procedure is time consuming and experiences some difficulties especially with propenones bearing pyridine moieties (1,2). Nevertheless, the yield was reported to be not exceeding 10-30%.

In the present work, a method for one-step synthesis of some new cyanopyridines is reported. Furthermore, the method displays distinct advantages: it is quick and easy to perform, it uses almost readily available starting materials and gives the products in a good yield.

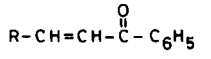
Thus, heating a mixture of equimolecular amounts of 5-nitrobenzothiophene-2-carboxaldehyde (**1**) (8), the acetyl derivative and malononitrile in the presence of excess of ammonium acetate in absolute alcohol, afforded within a period of 3-5 minutes, the corresponding 2-amino-3-cyano-4,6-disubstituted pryidines **2** in good yield, Table 1.

In the same manner, the reaction of **1** with ethyl cyanoacetate gave the corresponding 3-cyano-4,6-disubstituted pyridin-2-ones **3**, Table 1.

The infrared spectra and elemental analysis of compounds **2** and **3** are in accordance with the assigned structures. They show ir absorption bands corresponding for ν (NH), ν (C≡N), Ar-NO_2 and ν (C=O). The spectra supported also the presence of compounds **2** in the amino form (2A) and compounds **3** in the keto form structure (3A) in accordance with previous reports (1,9,10).



1



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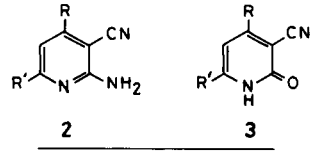


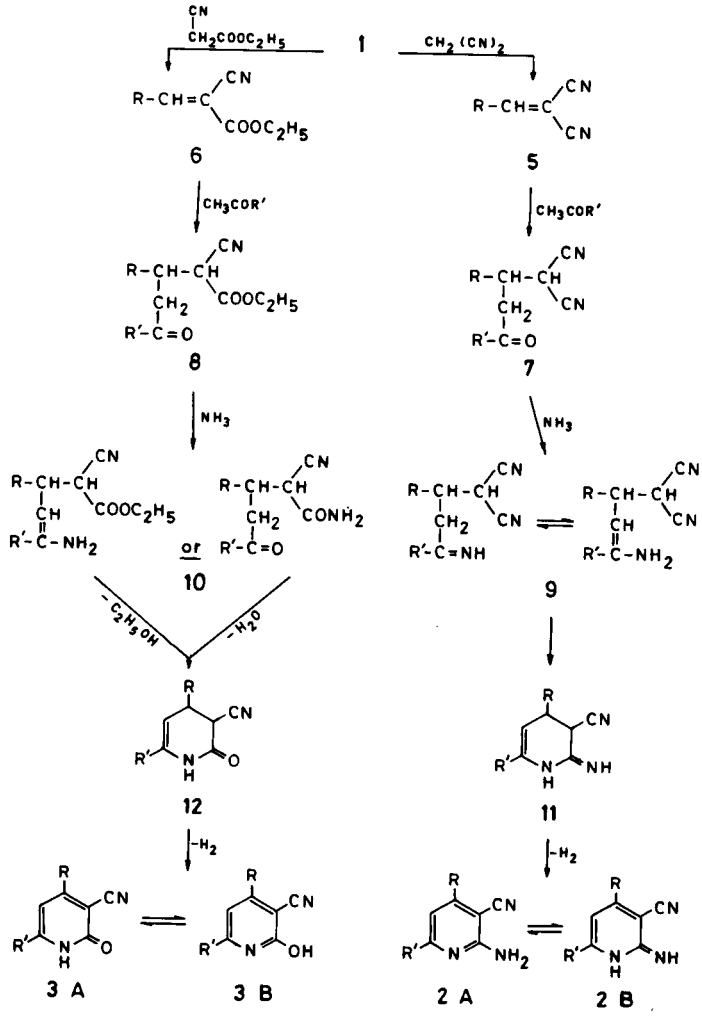
2 3

a, R' = phenyl
b, R' = p-chlorophenyl
c, R' = 4-pyridyl

Table 1

Physical and Spectral data of Compounds **2** and **3**.

Compound	Yield %	mp °C solvent	Molecular formula (mol. wt.)	Analysis, Found/Calcd. C	H	N	IR (Potassium bromide), cm^{-1} ν (NH)	ν (C=N)	Ar-NO_2	ν (C=O)
2a	65	>230 DMF/H_2O	$C_{20}H_{12}N_4O_2S$ (372.38)	64.72 64.50	3.10 3.24	14.21 15.04	3375-3480	2225	1570, 1345	—
2b	65	>315 DMF	$C_{20}H_{11}N_4O_2SCl$ (406.84)	59.96 59.04	3.36 2.73	13.47 13.77	3370-3430	2225	1570, 1350	—
2c	55	>300 DMF	$C_{19}H_{11}N_5O_2S$ (373.37)	61.28 61.12	3.61 2.96	18.92 18.76	3370-3400	2225	1570, 1350	—
3a	65	>350 DMF	$C_{20}H_{11}N_3O_3S$ (373)	64.57 64.34	3.07 2.95	11.21 11.26	3100-3200	2225	1575, 1345	1660
3b	60	>300 DMF	$C_{20}H_{10}N_3O_3SCl$ (407.82)	58.97 58.89	3.11 2.45	10.37 10.31	3100-3200	2225	1575, 1340	1660
3c	60	>340 DMF	$C_{19}H_{10}N_4O_3S$ (374.36)	60.90 60.95	2.87 2.69	15.03 14.97	3100-3200	2225	1570, 1340	1660



Scheme 1

The chemical structure of compounds **2** and **3** has been proven by comparison of their chromatographic behaviour with those of compounds prepared by the conventional method from the appropriate propenone derivative **4** and the active methylene compound.

The one-vessel reaction is believed to proceed *via* an initial attack of the active methylene compound on the aldehyde group of **1** to give the 1,1-dicyano-2-substituted ethylene **5** or ethyl-1-cyano-2-substituted acrylate **6**. This condenses with the acetyl derivative to give the Michael adduct **7** or **8** which in turn is converted to the imino derivatives **9** or **10**, respectively. The tautomeric amino form of the latter compounds cyclize under the reaction conditions affording the dihydropyridines **11** or **12**, followed by dehydrogenation to give finally the cyanopyridines **2** or **3**, respectively, Scheme 1.

The above explanation is supported by isolation of the Michael adducts **5** and **6** from the reaction of **1** with malononitrile and/or ethyl cyanoacetate in presence of catalytic amounts of ammonium acetate or piperidine. Heating the Michael adducts **5** and **6** with acetyl derivatives yielded the corresponding cyanopyridines **2** and **3**, respectively. Furthermore, condensation of the propenone derivative **4** with malononitrile or with ethyl cyanoacetate in the presence of excess of ammonium acetate afforded the formation of **2** and **3**, respectively.

The biological activity of the newly synthesized compounds is being evaluated.

EXPERIMENTAL

Melting points are uncorrected. Microanalysis were performed by the Central Services Laboratory, NRC, Cairo. The ir spectra (potassium bromide, ν max in cm^{-1}) were recorded on a Beckman IR spectrophotometer Model Acculab 8.

Preparation of 5-Nitrobenzo[*b*]thiophene-2-carboxoyl Chloride.

A mixture of (24.5 g) of 5-nitrothianaphthene-2-carboxylic acid (11)

(sodium salt) was mixed with anhydrous sodium carbonate (13.3 g), 60 ml of thionyl chloride in 60 ml dry toluene was heated, filtered while hot, concentrated and cooled. The solid formed was filtered off and crystallized from benzene to give (14.9 g) of the acid chloride, mp 161°.

Preparation of 5-Nitrobenzo[*b*]thiophene-2-carboxaldehyde.

To a stirred suspension of sodium borohydride (2 g) in dry dioxane (30 ml), (2.3 g) of the acid chloride was added. The reaction mixture was refluxed for 5 minutes, allowed to stand for one hour at room temperature and decomposed with water. The yellow solid separated was filtered off, washed with water, 2*N* hydrochloric acid and again with water, and crystallized from ethanol to give (1.98 g) of 5-nitro-2-hydroxymethylthionaphthene, mp 125° [lit 125-126° (8)].

To a stirred suspension of the obtained alcohol (0.54 g) in 10 ml of *t*-butyl alcohol, a freshly prepared solution of *t*-butyl chromate (12) in *t*-butyl alcohol was added in portions until the solid was dissolved. Addition of water to the reaction mixture gave the carboxaldehyde derivative **1**, mp 201° (acetic acid) in 96% yield, [lit mp 201-204° (8)].

Preparation of Cyanopyridine **2** and **3**. General Procedure.

Equimolecular amounts of **1**, the acetyl derivative, malononitrile and/or ethyl cyanoacetate (0.0025 mole) and (0.02 mole) of ammonium acetate in 10 ml of absolute alcohol was heated on water-bath. After a period of 3-5 minutes, a yellow solid formed, filtered off, washed with hot alcohol and crystallized to give the corresponding cyanopyridine derivatives **2** and **3**, respectively, Table 1.

Preparation of 1,1-Dicyano-2-substituted Ethylene **5** or Ethyl-1-cyano-2-substituted Acrylate **6**.

A mixture of **1** and molononitrile and/or ethyl cyanoacetate (0.0025 mole) and (0.002 mole) of ammonium acetate (or 3 drops of piperidine) in 10 ml of absolute alcohol, was refluxed on water-bath. A solid formed after 5 minutes. The reaction mixture was refluxed for one hour more, and filtered while hot. The solid was crystallized to give: the ethylene derivative **5**, mp 310° dec (dimethylformamide/water), (98%); ir (potassium bromide): 2220 cm^{-1} (C≡N).

Anal. Calcd. for $C_{12}H_5N_3O_2S$ (255.24): C, 56.41; H, 1.97; N, 16.46. Found: C, 56.63; H, 2.04; N, 16.70.

Also obtained with the acrylate derivative **6** which had mp 270° (acetic acid), (96%); ir (potassium bromide): 2220 cm^{-1} (C≡N) and 1700 cm^{-1} (C=O).

Anal. Calcd. for $C_{14}H_{10}N_2O_4S$ (302.29): C, 55.62; H, 3.33; N, 9.26. Found: C, 55.48; H, 3.26; N, 9.31.

Reaction of **5** or **6** with Acetyl Derivatives.

Equimolecular amounts of **5** or **6** and the acetyl derivative (0.0025 mole) and (0.02 mole) of ammonium acetate in 10 ml of absolute alcohol were refluxed for one hour. The product obtained was worked up to give **2** or **3**, respectively (60-68%).

Preparation of Propenone Derivative **4**.

To a mixture of **1** (0.01 mole) in 30 ml of alcohol, and 10 ml of 10% alcoholic sodium hydroxide solution, acetophenone (0.015 mole) was dropwise added while stirring. The reaction mixture was stirred for one hour, allowed to stand over night and poured into ice-water. The solid formed was filtered off, washed with cold water, dried and crystallized from benzene giving (75%) of **4**, mp 220°; ir (potassium bromide): 1655 cm^{-1} (C=O) and 1585 cm^{-1} (C=C); uv: (methanol) λ max (ε) 250 nm (10800) and 335 nm (19000).

Anal. Calcd. for $C_{17}H_{11}NO_3S$ (309.35): C, 65.99; H, 3.58; N, 4.53. Found: C, 65.90; H, 3.70; N, 4.32.

Reaction of **4** with Malononitrile.

Equimolecular amounts of **4** and malononitrile (0.001 mole) and (0.008 mole) of ammonium acetate in 10 ml of absolute alcohol were heated on water bath for 3 hours. The solid formed was separated, washed with water then with alcohol and crystallized to give (35%) of **2a**.

Reaction of **4** with Ethyl Cyanoacetate.

In the same manner mentioned above, reaction of **4** with ethyl cyanoacetate afforded (38%) of **3a**.

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