Sci. J. Fac. Sci. Monoufia Univ. Vo. VIII (1994).

SYNTHESIS OF TRIAZOLO-PYRIDINES AND HYDROXY-PYRIDINES BEARING THIOPHENE NUCLEUS.

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ABSTRACT

*Reaction of arylidene malononitrile **1** with thienylidene-cyanoacetohydrazide **2**, via Michael adduct, gave **3**. Rearrangement of **3** afforded the intermediate **4**, which aromatized to **5**, followed by dehydrogenation, to give the triazolo-pyridine derivatives **6**. While arylidene cyanoacetate **7** reacted with **2** in the same conditions via Michael adduct **8**, which eliminates ethyl alcohol to afford the intermediate **9**, which aromatized to yield the dicyano-hydroxypyridine derivatives **10**.*

INTRODUCTION

Some triazole derivatives have drawn considerable attention of the chemists because of their antiparasitic[1-4] and analgesic activities[5]. So the author synthesized some new triazolo-pyridines bearing thiophene nucleus, which may be biologically useful. In the same time, it can be used as nucleobases in the synthesis of nucleosides. Synthesis of [1,2,4]triazolo[1,5-c]pyridines was reported[6-9] by reaction of N-substituted 2-cyanoacetohydrazides with 2-cyanocinnamonitriles.

DISCUSSION

Thienylidene cyanoacetohydrazide **2** was added, through the active methylene group, to the olefinic double bond in the arylidene malononitrile **1** giving rise the Michael adduct **3**, which cyclized through rearrangement to give the intermediate **4**. Compound **4** was aromatized to **5**, which dehydrogenated to give the triazolo-pyridine derivative **6**. This route of reaction is based similarly as reported by Hadi et al.[9]

Infrared spectra[10] of **6a-f** showed absorption bands in the region of 1630 cm^{-1} for C=N (ring absorption frequency), 1650 cm^{-1} (CO-amide, cyclic), 2190-2200 cm^{-1} (CN), 3280 cm^{-1} (NH). The infrared spectra showed the presence of both CN group and NH group which indicates the formation of the triazolo-pyridine derivative **6**.

^{1}H-NMR spectrum of **6a** revealed signals at δ = 8.5 (s, 1H, NH), 7.5-7.7 (m, 5H, arom.H), 6.5-6.8 (m, 3H, thiophene protons). ^{1}H-NMR spectrum of **6b** showed δ = 8.45 (s, 1H, NH), 7.6-7.8 (m, 4H, arom.H), 6.5-6.8 (m, 3H, thiophene protons), 2.35 (s, 3H, CH_3).

When the cyanoacetohydrazide derivative **2** was added to the ethyl arylidene cyanoacetate **7**, one can expect that the reaction proceeds similarly like the arylidene malononitrile **1**, however, the dicyanohydroxy pyridine derivative **10** was obtained. When the active methylene in **2** was added to the ethylenic double bond in the arylidene **7**, it afforded the Michael adduct **8**, which cyclized by elimination of one mole of ethanol yielding **9**. Compound **9** aromatized to give the dicyano-hydroxy pyridinones **10**. This is proved by the absence of

carbonyl-ester group in the infrared spectra and ethyl ester group as multiplit in the ^{1}H-NMR.

Infrared spectra of **10a-f** showed absorption bands in the region of 1525-1575 cm^{-1} (-CH=N)[10], 1630 cm^{-1} (C=N), 1645 cm^{-1} (CO-amide), 2190-2200 cm^{-1} (CN), 3050-3450 cm^{-1} (OH). ^{1}H-NMR spectra of **10d** revealed signals at δ = 8.7 (s, 1H, OH), 6.5-6.8 (m, 3H, thiophene protons), 7.2-7.7 (m, 5H, aromatic H and -CH=N-proton). ^{1}H-NMR spectra of **10e** showed δ = 9.3 (s, 1H, OH), 6.5-7.3 (m, 7H, thiophene protons and CH=N proton).

EXPERIMENTAL

Arylidene malononitrile **1** and arylidene cyanoacetate **7** were prepared from the appropriate aldehyde by following standard procedures.[11,12]

Formation of Thienylidene-cyanoacetohydrazide 2.

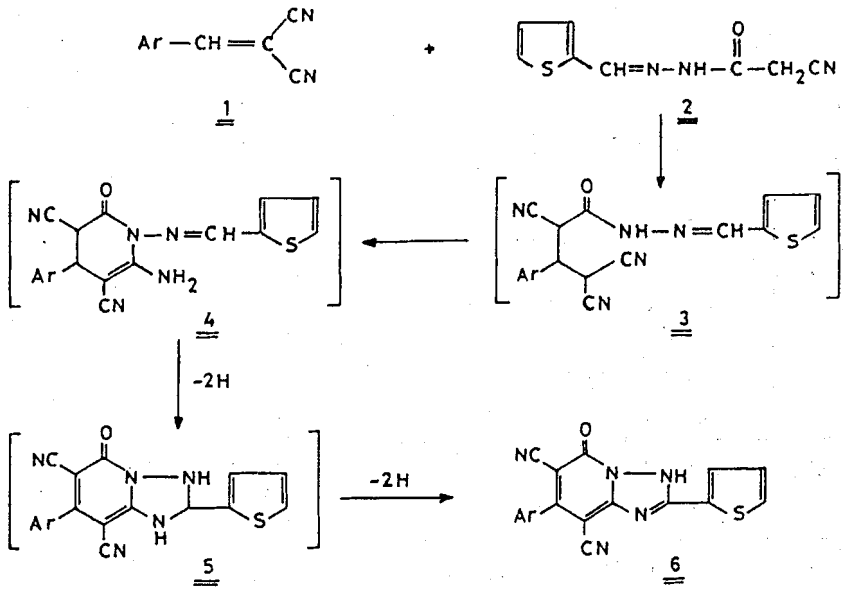
To a solution of 2-cyanoacetohydrazide (0.1 mol), in methanol (100 ml), was added thiophene-2-aldehyde (0.1 mol). The whole mixture was stirred for 1 h. A yellow precipitate was formed, filtered off, and recrystallized from methanol in yellow crystals; m.p. 190°C (Yield 85%). $C_8H_7N_3OS$ (193.2): requires C 49.7, H 3.65, N 21.74, Found C 49.39, H 3.41, N 21.35.

7-Aryl-6,8-dicyano-2-(2′-thienyl)-3H-[1,2,4]-triazolo[1,5a]pyridine-5-one 6.

General Procedure: To a suspension of 2-thienylidene-cyanoacetohydrazide **2** (0.01 mol) and the corresponding arylidene malononitrile **1** (0.01 mol) in dry ethanol (30 ml.), a few drops of piperidine were added. The reaction mixture was refluxed for a variable length of time 18-24 h until the starting material was exhausted and a solid was formed on hot. the obtained product was filtered off on hot, recrystallized from methanol (Table 1).

4-Aryl-3,5-dicyano-6-hydroxy-N-1-(2′-thienylidene)-pyridine-5-one 10.

General Procedure: To a mixture of thienylidene-cyanoacetohydrazide **2** (0.01 mol) and the appropriate ethyl arylidene-cyanoacetate **7** (0.01 mol), in dry ethanol (30 ml.), was added 3-5 drops of piperidine. The reaction mixture was refluxed for 14-24 hrs. The starting material was consumed with a precipitation of the product, the solid was filtered off, crystallized from methanol (Table 1).



6 , 10	Ar
a	C_6H_5–
b	C_6H_4·CH_3 (p-)
c	C_6H_4·OCH_3 (p-)
d	C_6H_4Cl (p-)
e	
f	

Scheme - 1

Table I Characterization Data of the Synthesized Compounds

Comp. No.	Mol. Formula (Mol. Wt.)	M.p. °C	Yield %	Analysis (Calc./Found) %		
				C	H	N
6a	$C_{18}H_9N_5OS$ (343.3)	305	31	62.96 62.43	2.64 2.97	20.39 19.78
b	$C_{19}H_{11}N_5OS$ (357.3)	312	35	63.65 63.34	3.10 2.82	19.59 19.32
c	$C_{19}H_{11}N_5O_2S$ (373.3)	296	29	61.11 60.72	2.97 3.20	18.75 18.42
d	$C_{18}H_8ClN_5OS$ (377.8)	250	36	57.22 57.75	2.13 2.42	18.53 18.35
e	$C_{16}H_7N_5OS_2$ (349.4)	245	40	55.01 54.87	2.01 2.35	20.04 20.41
f	$C_{16}H_7N_5O_2S$ (333.3)	267	35	57.65 57.52	2.11 2.39	21.01 20.85
10a	$C_{18}H_{10}N_4O_2S$ (346.3)	290	43	62.43 61.98	2.91 2.67	16.17 16.43
b	$C_{19}H_{12}N_4O_2S$ (360.4)	320	42	63.32 63.61	3.35 3.14	15.54 15.81
c	$C_{19}H_{12}N_4O_3S$ (376.4)	237	46	60.63 60.52	3.21 3.38	14.88 14.97
d	$C_{18}H_9ClN_4O_2S$ (380.8)	306	49	56.77 56.64	2.38 2.51	14.71 14.52
e	$C_{16}H_8N_4O_2S_2$ (352.4)	240	52	54.53 54.76	2.28 2.50	15.98 16.13
f	$C_{16}H_8N_4O_3S$ (336.3)	257	45	57.14 56.61	2.39 2.81	16.65 16.27

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تخليق ترايازولو-بيريدينات وهيدروكسى بيريدينات حاملة حلقة الثيوفين

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تفاعل أريليدين مالونونتريل (١) مع ثينيليدين سيانو أسيتو هيدرازيد (٢) ليعطى إضافة ميخائيل (٣) . يتعدل مركب (٣) ليعطى الوسيط (٤) حيث يتحول إلى مركب أروماتى (٥) . التركيب (٥) يفقد هيدروجين ليعطى مشتقات ترايازولو بيريدين (٦) . بينما تفاعل سيانو أسيتات الأريليدين (٧) مع (٢) فى نفس الظروف ليعطى أولا مركب الإضافة (٨) ثم يفقد جزئى كحول الإيثانول متحولقا ليعطى الوسيط (٩) ، حيث يفقد بدوره هيدروجين معطيا مركبا أروماتى : مشتق ثنائى سيانو هيدروكسى البيريدين (١٠) . وقد تم إثبات بعض المركبات الناتجة بالبروتون النووى المغناطيسى والأشعة تحت الحمراء وكذلك التحليل الدقيق للعناصر .