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NITRILES IN HETEROCYCLIC SYNTHESIS : SYNTHESIS OF SOME NEW PYRANO [3,2-d] ISOXAZOLES AND COUMARIN - 4 - YL ISOXAZOLES

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ABSTRACT

3-Methylisoxazolone (1), generated in situe from the reaction of ethyl acetoacetate with hydroxylamine hydrochloride, reacted with the cinnamonitrile derivatives (2a-f) to yield the pyranoisxaoles 5a-f- Mixtures of fomaldehyde and malononitrile or acetaldehyde and malonoitrile reacted with in situe generated isoxazolone to yield the pyranoisoxazoles 5g,h. These compounds could also be prepared via reacting 1 with the corresponding aldehyde and subsequent treatment of the fromed ylidenes 3a-h with malononitrile. The reaction of the hydroxyarylidenes 2i , j afforded the coumarin derivatives 7a, b .

DISCUSSION

Polyfunctionally substitued heteroaromatics are interesting molecules as potential pharmaceuticals and their chemistry has received considerable recent interest [1-3]. In conjunction to my work aiming to prepare new polyfunctionally substituted heterocycles as

potential biodegradable agrochemicals, samples of substituted pyranoisoxazoles were required[4-6]. Azolones are reported to react with cinnamonitriels to yield pyranoazolones[7-10]. This reaction has been conducted with pyrazolones[7] and imidazolones[9], however the reactivity of 3-methyl-2-isoxazolin-5-one toward the same reagents has not been reported. The reaction of benzylidene-2-isoazolin-5-one with malononitrile to yield pyranoisoxazoles has been reported earlier[10,11]. As 3-methyl-2-isoxazolin-5-one (1) is not readily isolable compound, I have investingated possible addition of cinnamonitriles to in situe generated 3. I have found that 1, generated in situe via raecting ethyl acetoacetate with hydroxylamine hydrochloride in pyridine solution, reacts with the cinnamonitiler 2a-h to yield 1:1 adducts. Products of reaction of 2a-h with 1 were found identical with products obtained previonusly from reaction of 3a-h with malononitrile[10,11]. These products can thus tbe assigned the acyclic Michael adduct structure **4** or isomeric pyranoisoxazole structure **5**. Although Harhash et al.[10] have assigned structure **4** for these products. Aziz et. [11] have later suggested that these compounds exist mainly as the cyclic pyrans **5**. ^{1}H NMR was thus utilized to discriminate both structures. ^{1}H NMR revealed in addition to methyl, aryl and amino signals, only one singlet for proton linked to Sp^3 carbon at 4-6 ppm. This data can only be interprettd in terms of the cyclic pyran from **5** as has been suggesed earlier by Aziz et al. [11] If the reaction product is the acyclic pyran **4** one would expect

completely different pattern in which several multiplets for protons linked to Sp^3 carbons should have appared. Compounds **5** could also be obtaind via reacting the ylidene isoxzolones **3** which was prepared in our laboratories via reacting in situe generated **1** with the corresponding aldehyde. Mixtures of malononitrile and fromaldehyde or malononitrile and acetaldeyde generated in situe the corresponding ylidene derivatives as has been suggested recently[12,13], and these reacted with **1** to yield **5g** and **5h** respectively .

The reaction of in situe generated **1** with mixture of salicylaldehyde and malononitrile or 3,5 - dibromosalicylaldehyde and malononitrile afforded the same products of reaction of malononitrile with 4-salicylidene-3-methyl-2-isoxazolin-5-one (3i) or 4-(3,5-dibromosalicyldene)-3-methyl-2- isoxazolin-5-one (3j). These were fromulated as 6a,b. fromation of these products is assumed to proceed via first condensation of the aldehyde with isoxazolone and subsequenet addition. Alternate possibility of initial condensation with malononitrile was ruled out as this compound is expected to cyclise very quickly into the coumarin deivative **7**. This latter compound could not be traced in solution. Moreover attempted addition of pyrazolone to this coumarin failed. Product **6** may be also fromulated as tautomeric **7** or isomeric **8**. Structure **7** was considered most liely based on IR speturm which revealed hydrogen bonded OH function even in dilute solution. Thus structure **6** was ruled out as it does not contain any OH. Also in compound **8**, OH group is

expected to appear as typical phenolic OH at 3500 cm^{-1} whiile in **7** intermolecular H bonds would only from stable chelates e.g. **9.**

EXPERIMENTAL

All melting points are uncorrected. IR spectra (cm-1) were recorded on a Pye Unicam SP - 1000 spectrophotometer in KBr discs. ^1H NMR spectra (ppm) were obtained in DMSO on a varian 90 MHz. Microanalytical data were obtained from the Microanalytical Center at Cairo University.

6-Amino-3-methyl-4-alkyl-pyrano[3,2-d]isoxazoles-5carbonitrile(5)

General procedure (A) :

A solution of ethyl aceatoacetate (0. 01 mol; 1.3 g) in pyridine (20 ml) was treated with hydroxylamine hydrochloride (0.01 mol; 0.7 g) .

The reaction mixture was stirred for 30 minutes then treated with the corresponding cinnamonitriles (2) , and heated under reflux 1 h in ethanol. The reaction mixture was poured onto water, the solid product , so formed, was collected by filteration and crystallised from dilute ethanol.

General procedure (B)

Equimolecular amounts (0.01 mol) of each of 4-arylidene-3-methyl-2-isoxazolin-5-ones (3) [which were prepared by the reac-

tion of solution of ethyl acetoacetate (0.01 mol) in pyridine (20 ml) and hydroxylamine hydrochloride (0.01 mol), the reaction mixture was stirred for 30 minutes then treated with the corresponding aldehyde, left overnight at room temperature] and malononitrile in 30 ml ethanol were trated with two drops of pipyridine. The reaction mixture was refluxed for 3 h After concentration, the product fromed was filtered, and crystallised from dilute ethanol. The product was found identical with speciments of compounds produced by genral procedure (A).

preparation of 5g and 5 h :

compound 1 (0.01 mol), generated in situe as has been described above was allowed to react with the appropriate aliphatic aldehyde (0.01 mol) and with malononitrile (0.01 mpl; 0.66 g) in pyridine (20 ml). The reaction mixture was heated for 30 min., then left to stand overnight. After evaporation of solvent and trituration with ethanol, it was filtered off and afforded solid product which then crystallised from dil. ethanol.

6,8 - Disubstiuted-coumarin-4yl-isoxazoles-3- carbonitrile (7a,b).

To a solution of malononoitrile (0.01 mol) in 30 ml ethanol ylidenes **3i** and **3j** (0.01 mol) were added then two drops of pipyridine. After relfux for 30 min. and evaporation of excess solvent, filteration of the solid product, it was crystallised from ethanol to obtain **7a** and **7b** respectively.

Compound No.	mp (°C)	IR
5c	150	
5d	159	
5e	240	2220-2200 cm^{-1} (CN) and
5f	220	3350 - 3200 cm^{-1} (NH2)
5g	175	
5h	182	
7b	> 300	1700-1690 cm^{-1} (CO), 2200 cm^{-1} (CN)
		3300-3200 cm^{-1} (OH).

* Statisfactory elemental analyses for the newly synthesised compounds were obtained .

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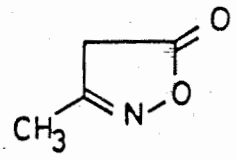

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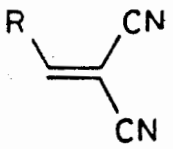

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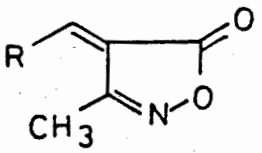

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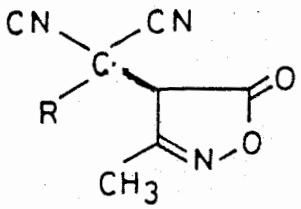

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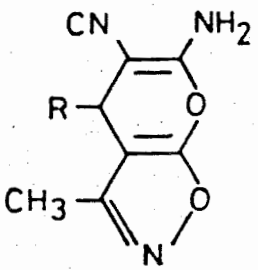


5

2 , 3 , 5 a , R = C_6H_5

b , R = C_6H_4 , OCh_3 - P

c , R = C_6H_4 , No_2 - P

d , R = C_6H_4 , $N(Ch_3)_2$ - P

e , R = C_6H_4 , Br - p

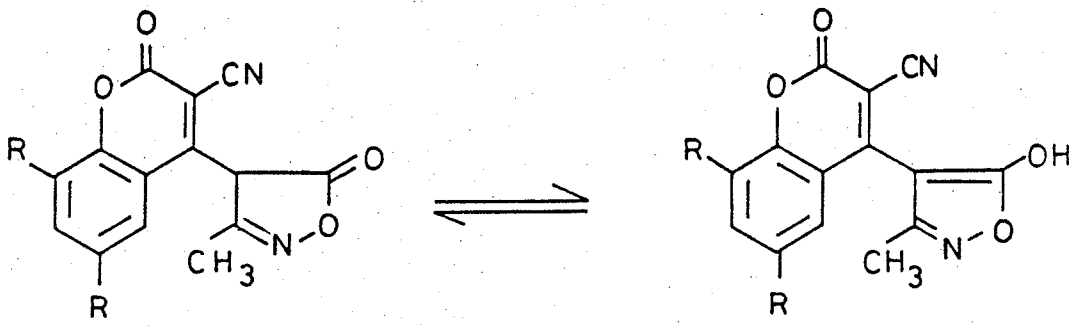
f , R = 2 - furyl

g , R = H

h , R = CH_3

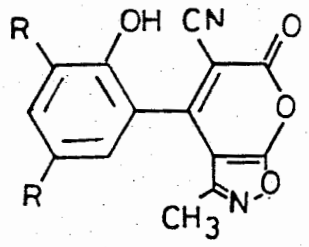
i , R = C_6H_4 , OH - o

j , R = C_6H_2 , OH - 2 ; Br_2 - 3,5



6 7

6 , 7 a , R = H ; b , R = Br



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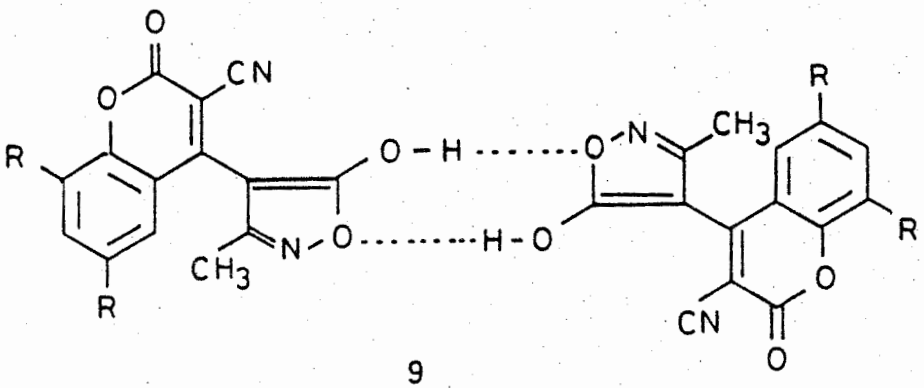

9

النيتريلات فى تخليق المركبات الحلقية غير المتجانسة: تحضير بعض مشتقات بيرانو [٣، ٢ - د] أيزوكسازول وكذلك بعض مشتقات كيومارين - ٤ - ابل ايزوكسازول

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نظرا للأهمية البيولوجية لكثير من المركبات الحلقية غير المتجانسة عديدة المجموعات الوظيفية وامتداد لهذا الاتجاه فإنه تم فى هذا البحث تحضير بعض هذه المركبات ... حيث أننى وجدت عند تفاعل ٣ - ميثيل ايزوكسازولون (1) - و الذى ينتج في الحال يتفاعل أيثيل أسيتو أسيتات مع هيدروكسيل أمين هيدروكلوريد - مع مشتقات السينامو نيتريلات (2a - f) ينتج مشتقات البيرانوايزوكسازول 5a - f .

كذلك عند تفاعل خليط من كل من الفورمالدهيد و المالونونيتريل مع المركب 1 أو خليط من الاسيتالدهيد و المالونونتيريل مع المركب 1 ينتج المركبين 5g , h على التوالى .

يمكن أيضا الحصول على بعض هذه المركبات بمفاعله بعض مشتقات البلدين للمركب 1 مع المالونونتيريل .