ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS: A NOVEL SYNTHESIS OF PYRAZOLO [5,6:3',4'] PYRANO [5,4-b] ISOXAZOLES

Suzan Ibraheim Aziz, Bahia Yahia Riad, Hassan Attia Elfahham and Mohamed Hilmy Elnagdi
Chemistry Department, Faculty of Science, Minia University and Cairo University, Giza, A. R. Egypt.

Abstract: A novel synthesis of pyrano [2,3-c] isoxazoles is reported via reaction of 4-arylidene-2-isoxazolin-5-ones with malononitrile and ethyl cyanoacetate. The synthesised isoxazole derivatives were converted into derivatives of new ring system pyrazolo [5,6:3',4'] pyrano [5,4-b] isoxazole via reaction with hydrazine hydrate.

The considerable biological activities of fused azoles in the past time have stimulated considerable research in this field[1-3]. In the previous work from this laboratory we have reported several new and efficient approaches for the synthesis of fused azoles utilising active methylene nitriles and ylidene azolones as starting compounds[4]. The observation that the reaction of arylidene-azolones with malononitrile and with ethyl cyanoacetate leads to the formation of polycyclic products prompted a reinvestigation of the behaviour of 4-arylidene 3-substituted 2-isoxazolin-5-ones (1a-c) toward the same reagents. The reaction of 1a with malononitrile has been previously claimed to afford the acyclic Michael adduct 2 (R=CH_3; Ar= C_6H_5)[5].

In our laboratories it has been found that when a mixture of 1a (20 mmoles) and malononitrile (20 mmoles) is refluxed in ethanol (20 ml) in the presence of catalytic amount of piperidine (0.5 ml) followed by solvent removal, trituration with water and crystallisation of the so formed solid product, a product of melting point similar to that previously reported in literature was obtained[5]. The analytical data of the product indicated a molecular formula $C_{14}H_{11}N_3O_2$. ^1H NMR of the product revealed a pattern completly different than that expected for 2 and can only be intelligibly interpretted in terms of structure 3a. This

indicates that the product previously considered to be 2 (R=CH_3; Ar= C_6H_5) is rearlly the pyrano[2,3-c]isoxazole derivative 3a. Similar to the behaviour of 1a, compounds 1b,c reacted with malononitrile to yield the pyrano[2,3-c]isoxazole derivatives 3b,c.

Compounds 1a-c reacted with ethyl cyanoacetate in ethanol, in the presence of piperidine under the experimental conditions utilised to effect addition of 1a to malononitrile, to yield 1:1 adducts. The IR spectra of the product revealed the absence of CN absorption. ^1H NMR also showed a pyran H-4 singlet at δ 4.3 ppm. Thus, the pyrano[2,3-c]isoxazole structure 4 was suggested for these products. The formation of 3 and 4 from the reaction of 1 and malononitrile or ethyl cyanoacetate is assumed to proceed via addition of active methylene compounds to the activated double bond in 1a-c to yield the intermediate Michael adducts (2 and 5) which then cyclise under the reaction conditions into the final isolable products.

In contrast to the previously reported behaviour of 2-pyrazolin-5-one[6], 2-thiazolin-4-one[7] and 2-thiohydantoin derivatives[8] toward the action of ylidene malononitrile, 3-phenyl-2-isoxazolin-5-one (6) reacted with the cinnamonitrile derivatives 7a,b to yield only the arylidene derivative 1a. Similar products could be previously isolable as by-products during the reaction of 2-thiohydantoin derivatives with the same reagents[8]. The exact mechanism of the formation of 1a from the reaction of 6 and activated nitriles is now being under investigation.

Acyclic and cyclic β-enamino nitriles and β-enamino esters have been recently reported to react with hydrazines and amines to yield the Michael adducts which then undergo further reactions depending on the nature of the reacting enamino nitrile or ester[9,10]. The enamino nitriles 3a-c and enamino esters 4a-c reacted with hydrazine hydrate in refluxing ethanol to yield products which were formulated as the pyrazolo[5,6:3',4']pyrano[5,4-b]isoxazole derivatives 8a-c and 9a-c respectively, based on analytical and spectral data.

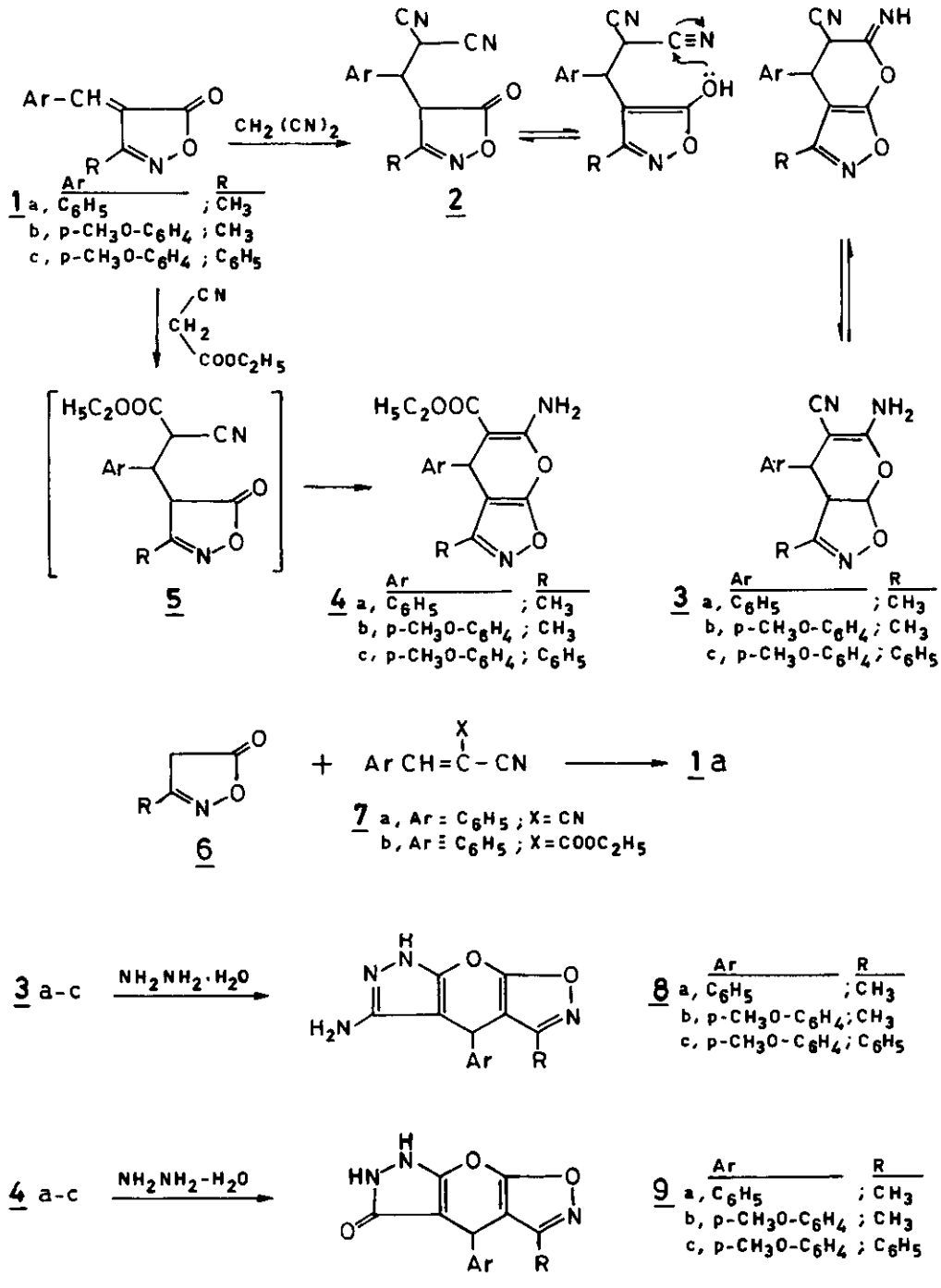
Ar-CH
CH2(CN)2
CN
CN
Ar
O
R
N
O
C≡N
OH
NH
NH2
H5C2OOC
CH2
COOC2H5
1 a, Ar = C6H5 ; R = CH3
b, Ar = p-CH3O-C6H4 ; R = CH3
c, Ar = p-CH3O-C6H4 ; R = C6H5
2
3 a, Ar = C6H5 ; R = CH3
b, Ar = p-CH3O-C6H4 ; R = CH3
c, Ar = p-CH3O-C6H4 ; R = C6H5
4 a, Ar = C6H5 ; R = CH3
b, Ar = p-CH3O-C6H4 ; R = CH3
c, Ar = p-CH3O-C6H4 ; R = C6H5
5
6
X
Ar CH=C-CN
7 a, Ar = C6H5 ; X = CN
b, Ar = C6H5 ; X = COOC2H5
3 a-c
NH2NH2·H2O
H
H2N
8 a, Ar = C6H5 ; R = CH3
b, Ar = p-CH3O-C6H4 ; R = CH3
c, Ar = p-CH3O-C6H4 ; R = C6H5
4 a-c
NH2NH2-H2O
HN
9 a, Ar = C6H5 ; R = CH3
b, Ar = p-CH3O-C6H4 ; R = CH3
c, Ar = p-CH3O-C6H4 ; R = C6H5

Table : List of the pyrano [2,3-c] isoxazole derivatives 3a-c, 4a-c and pyrazolo [5,6:3,4] pyrano [5,4-b] isoxazole derivatives 8a-c, 9a-c

Compd.*	Reac. time (h)	mp (°C)	Yield (%)	Compd.*	Reac. time (h)	mp (°C)	Yield (%)
3a	2	160	65	8a	2	285	70
3b	3	115	55	8b	2	300	70
3c	3	114	50	8c	2	170	65
4a	5	122	60	9a	2	>300	60
4b	4	78	65	9b	3	>300	65
4c	6	82	65	9c	4	>300	50

* Satisfactory elemental analyses for the newly synthesised compounds were obtained. Spectroscopic data (IR, ^{1}H NMR and MS$^+$) are in good agreement with proposed structures.

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