Commun. Fac. Sci. Univ. Ank. Series B
V. 36. pp. 1–25 (1990)

UTILITY OF α-SUBSTITUTED CINNAMONITRILES IN HETEROCYCLIC SYNTHESIS

By MOHAMED KAMAL AHMED IBRAHIM

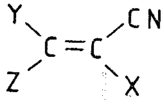
Department of Chemistry Faculty of Science, Cairo University, Giza, A.R.Egypt.

ABSTRACT

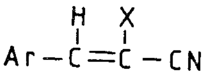
New approaches for synthesis of different mono and polyheterocyclic derivatives utilising α–substituted nitriles are surveyed. The reaction mechanism is considered as Micheael addition followed by cyclization on the cyano group of α–susbstituted cinnamonitrile or via dipolar cycloaddition reaction followed by elimination of hydrogen cyanide of the intermediate. The scope and limitation of the most important of these approachers are demonstrated.

INTRODUCTION

α, β-Unsaturated nitriles (1) are versatile reagents which have been extensively utilised in heterocyclic synthesis. In spite of enormous number of reports on the utility of these compounds in synthesis of heterocycles, up to our knowledge, the utility of α-substituted cinnamonitrile (2 a–h) in heterocyclic synthesis has never been surveyed. The utility of acrylonitrile in heterocyclic synthesis was surveyed[13] in a chapter on cynoethylation. Also, the utility of tetracyanoethylene in heterocyclic synthesis was reported previously[69] in a part of a book on chemistry of cyano group. Recently, the reactions of α,β-unsaturated nitriles in heterocyclic synthesis were reported[52,32]. The reactivities of α-substituted cinnamonitriles (2 a–h) and their use as starting material for a wide variety of reactions have been studied. Recently, in my laboratory good results have been obtained in this subject.



1



$\mathrm{Ar-\overset{H}{C}=\overset{X}{C}-CN}$

2 a - h

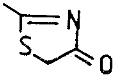
a, X = CN

b, X = $COOC_2H_5$

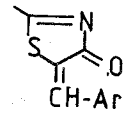
c, X = COC_6H_5

d, X = $CONHC_6H_5$

e, X =

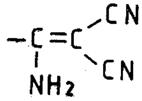


f, X =



g, X = SC_2H_5

h, X =

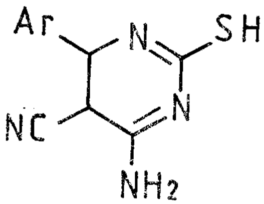


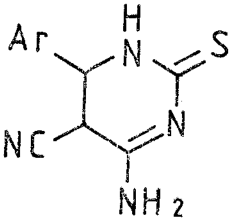
In the following, the general reactions of α-substituted cinnamonitriles (2 a–h) which have been reported are outlined.

I) Reaction with amino derivatives as:

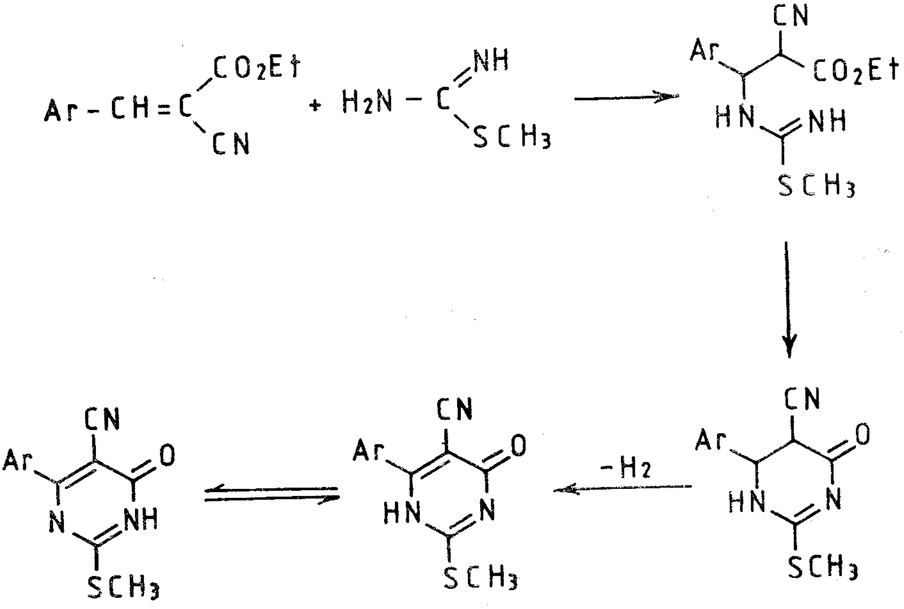
A) Thiourea and S-methylthiourea:

Thiourea reacts with α-cyanocinnamonitrile derivatives (2 a) in ethanol/piperidine to yield the corresponding pyrimidine derivative (3)[59,57]. The reaction mechanism was considered as Michael addition followed by cyclization on the cyano group of α-cyanocinnamonitrile.



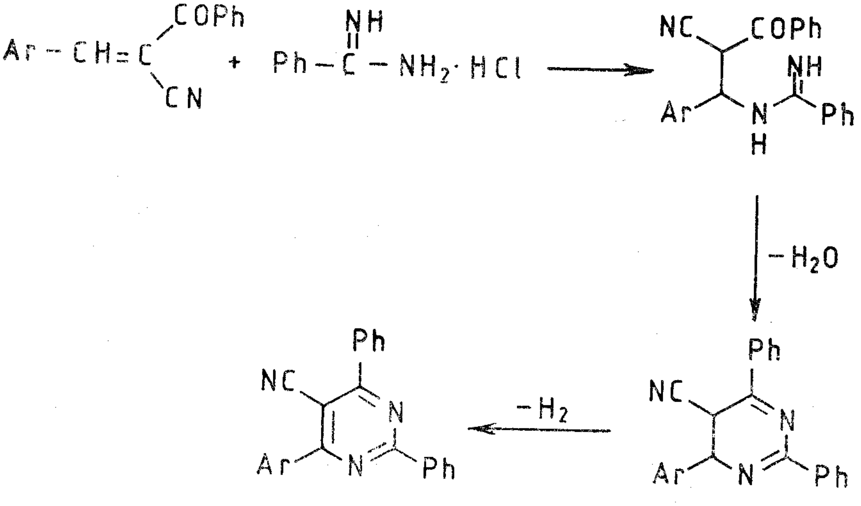


Similarly, the reaction of S-methylthiourea with α-carbethoxycinnamonitrile (2 b) in pyridine, 2-methylmercaptopyrimidinones (4) were obtained. This reaction proceeds via Michael addition then the loss of ethanol followed by autoxidation[19], as the following.



B) Benzamidine and acetamidine:

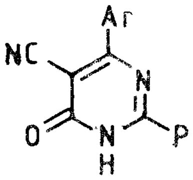
It has been shown that, benzamidine hydrochloride reacts with α-benzoylcinnamonitrile (2 c) in pyridine to give the fully aromatized arylpyrimidine derivative (5)[1], as the following.



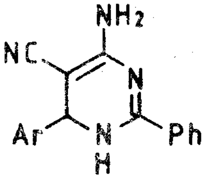
5

Similarly to the behaviour of the (2 c), α-carbethoxycinnamonitrile (2 b) reacts with benzamidine hydrochloride to give 4-aryl-5-cyano-6-oxo-2-phenyl-1,6-dihydropyrimidine derivative (6)[1].

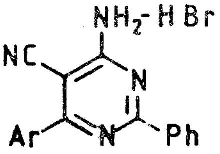
In contrast to the behaviour of (2 b, c) toward benzamidine hydrochloride, α-cyanocinnamonitrile (2 a) reacts with benzamidine hydrochloride under the same reaction conditions to give 4-amino-6-aryl-5-cyano-2-phenyl-1,6-dihydropyrimidine derivative (7)[1]. The latter could be dehydrogenated to the fully aromatized analogues (8) by treatment with bromine in acetic acid[46,10]. The reaction of guanidine with unsaturated nitrile was reported[88,4].



6



7

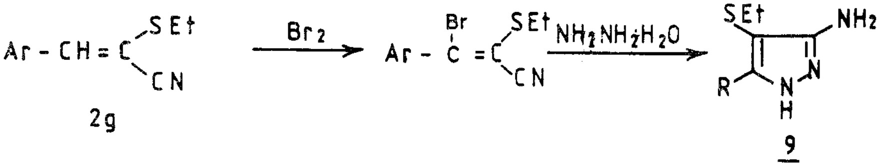


8

Several synthesis of pyrimidine derivative from the reaction of unsaturated nitriles (1–2) with acetamidine were reported[86,85]. Synthesis of vast number of heterocyclic six membered derivatives utilising unsaturated nitriles (1–2) as starting materials has been reported[5–7,11,14–16,50,64,68,71,73,79,84,85,89].

C) Hydrazine derivatives:

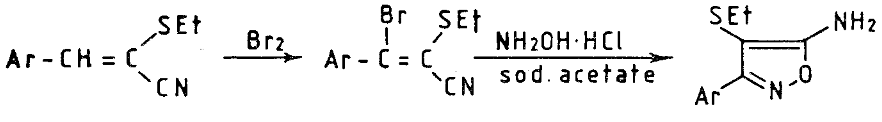
It has been shown that, α-substituted cinnamonitriles (2 a–h) reacts with hydrazine hydrate to yield the aminopyrazole derivative, such as α-ethylmercaptocinnamonitrile (2 g) afforded aminopyrazole derivative (9) via reaction with hydrazine hydrate[32] as the following.



A variety of new pyrazole derivatives have been synthesed utilising the same idea of reacting unsaturated nitriles (1–2) with hydrazine derivatives[3, 9, 12, 20–23, 29, 33, 53, 55–56, 62–63, 66–67, 72, 74–76, 80–81, 83, 87]. Also pyrazole derivatives were obtained via reaction of (1–2) with hydrazides, semicarbazides and thiosemicarbazides[20]. The formation of aminopyrazole was assumed as Michael addition of the hydrogen of hydrazine derivative to C=C group of unsaturated nitriles, followed by the addition of unsubstituted hydrazine nitrogen of the hydrazine to the cyano group of the unsaturated nitrile.

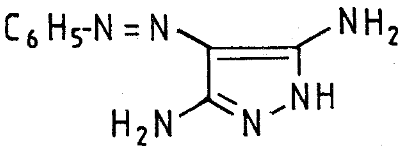
D) Hydroxylamine:

Unsaturated nitriles (1–2) have been extensively utilised for the synthesis of amino-1,2-oxazoles[34,65]. Such as, α-methylmercaptocinnamonitrile (2 g) reacts with hydroxylamine hydrochloride in sodium acetate to give amino-1,2-oxazole derivatives (10) as the following.

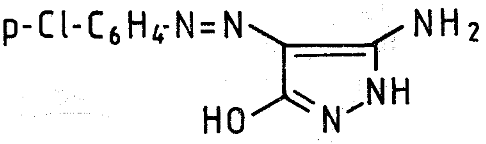


E) Amino-heterocyclic compounds:

Several syntheses of azolopyrimidine derivative from α-substituted cinnamonitriles (2 a-g) have recently been reported[57,24]. It has been found that, α-cyanocinnamonitrile (2 a) reacts with 3,5-diamino-4-penylazopyrazole (11), 3-amino-4-(p-Cl-phenylazo)5--pyrazolone (12), 2-aminobenzimidazole and 3-amino-1,2,4-triazole in ethanol/piperidine solution. The reaction products are pyrazolo-[1,5-b] pyrimidine (13), pyrazolo [1,5-b] oxazine (14), benzimidazolo-[1,2-b] pyrimidine (15) and (pyrimidino [1,2-b] triazole (16) respectively[57]. (cf. Scheme 1).

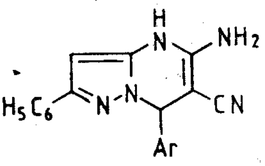


15

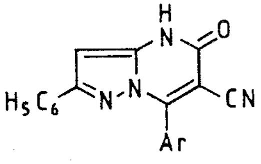


16

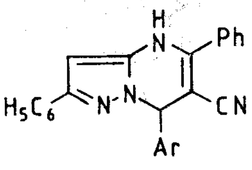
On the other hand, 5-amino-3-phenylpyrazole reacts with α-substituted cinnamonitriles (2 a-c) to give the corresponding pyrazolo [1,5-a] pyrimidine derivatives (17–19)[11] respectively.



17



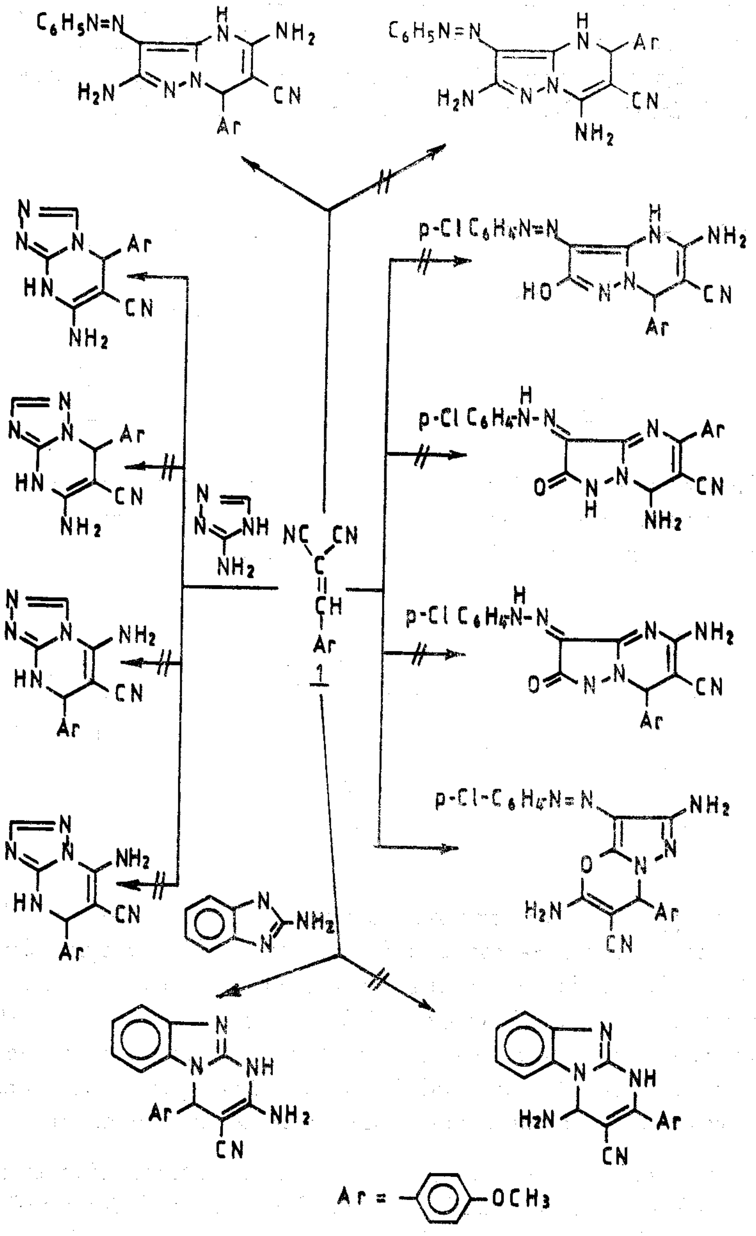
18

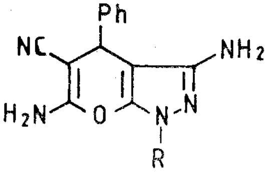


19

Aminopyrazole and aminoisoxazole derivatives have also been reported to react with α-unsaturated nitrile to yield fused pyrimidine[31, 36–40, 42–45, 48]. The formation of sufed pyrimidine is considered as the Michael addition of the hydrogen of the nitrogen ring to the C=C of α-unsaturated nitrile to give an intermediate, which readily cyclized to fused pyrimidines, through addition of the hydrogen of the amino-heterocyclic group to the cyano group of α-unsaturated nitrile.

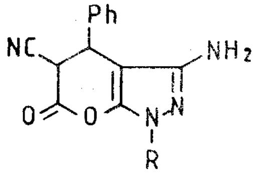
In contrast to the previous results, α-substituted cinnamonitriles (2 a-c) react with 3-amino-2-pyrazolin-5-one and 3-amino-1-phenyl-2-pyrazolin-5-one to give the corresponding pyrano [2,3-c] pyrazole derivatives (20–25)[24] respectively.


C₆H₅N=N
NH₂
H₂N
CN
Ar
p-Cl C₆H₄N=N
HO
p-Cl C₆H₄N-N
O
p-Cl-C₆H₄-N=N
NC
CN
CH
Ar
1
Ar = -C₆H₄-OCH₃



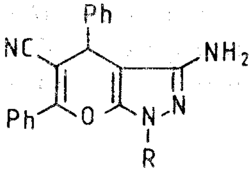
20, R = H

23, R = Ph



21, R = H

24, R = Ph



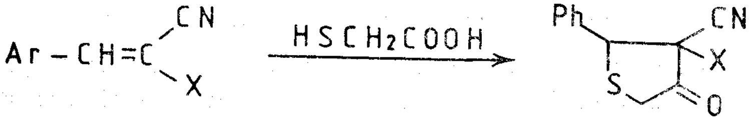
22, R = H

25, R = Ph

II) Reaction with mercaptance:

A) Thioglycollic acid:

Recently, the formation of thiophens (26) from the reaction of α-substituted cinnamonitriles (2 a-g) with thioglycollic acid has been reported[35,30]. The reaction may be thus considered as an extension of the thiophen synthesis[51].



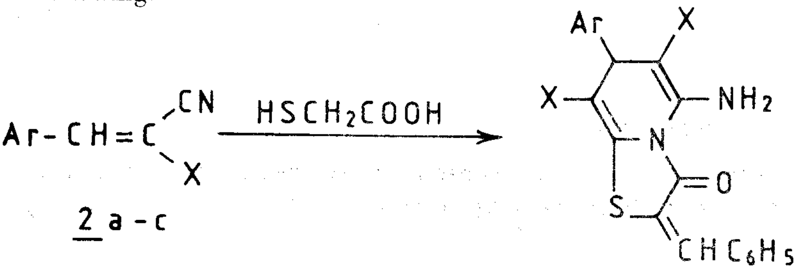
2 a-c

26, X = CN

X = COOEt

X = COPh

In contrast to the above results, it has been found that, thioglycollic acid reacts with α-substituted cinnamonitriles (2 a-c) in ethanol / piperidine solution to give thiazolo [2,3-a] pyridine derivatives (27)[27], as following.



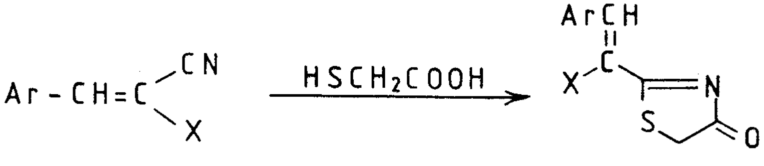
2 a-c

27, X = CN

X = COOEt

X = COPh

The same result could be obtained via reaction of α-substituted cinnamonitriles (2 a-c) with ethyl thioglycollate[61]. Also the reaction of thioglycollic acid and α-substituted cinnamonitriles (2 b,c) was reported[11] to give 2-substituted thiazolin-4-one derivative (28), as following.

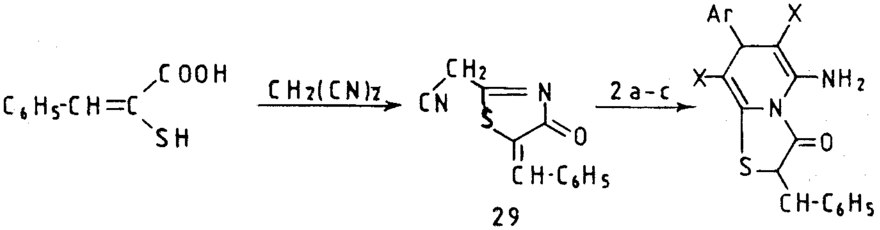


28, X = COOEt

X = COPh

The formation of thiazolo [2,3-a] pyridine derivative (27) proceeds in two steps. The first molecule of α-substituted cinnamonitrile reacts with thioglycollic acid to give 2-substituted thiazolin-4-one derivative (28). The latter reacts with second molecule of α-substituted cinnamonitrile immediately under the same reaction conditions to give (27).

Also α-mercaptocinnamic acid reacts with malononitrile to give 2-substituted thiazolin-4-one (29), then the latter reacts with α-substituted cinnamonitrile to give the corresponding thiazolo-[2,3-a]-pyridine derivative (27)[27], as following.

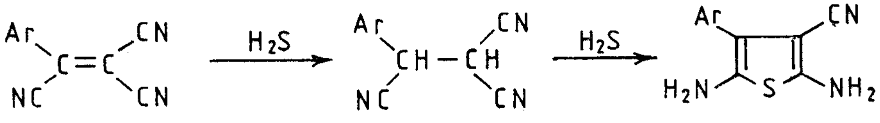


29

27

B) Hydrogen sulphide:

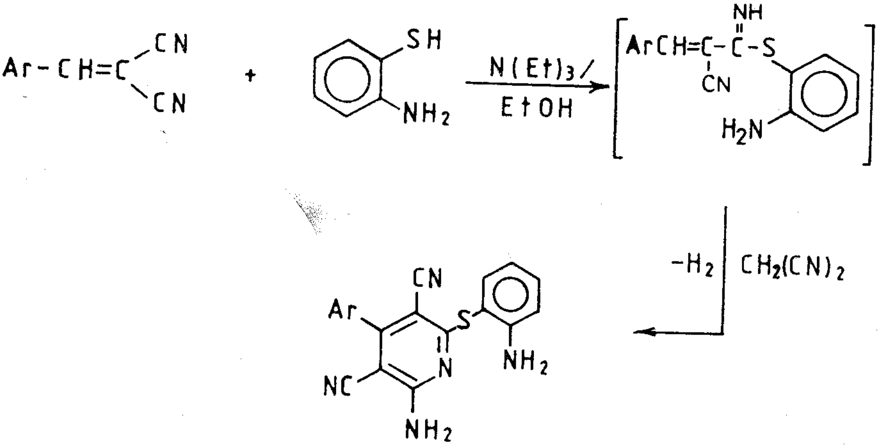
α, β-unsaturated, nitrile (1) has been reported to react with hydrogen sulphide to yield the thiophen derivative (30)[70], as following.



30

C) Aminothiophenol:

Several synthesis of pyridine derivatives from α-substituted cinnamonitriles (2 a-g) have recently been reported[61]. For example, the reaction of substituted amines as o-aminothiophenol with α-cyanocinnamonitrile (2 a) affords pyridine derivatives (31), as the following equation:



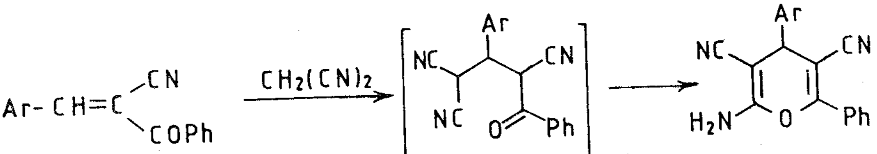
31

III) Reaction with active methylene reagents:

Several synthesis of pyran and pyridine derivatives from α-substituted cinnamonitrile and active methylene reagent as starting materials has been reported, as following:

A) Malononitrile and acetonitrile derivatives:

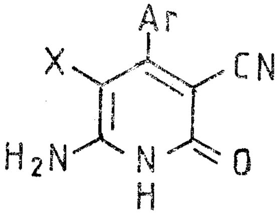
It has been found that, malononitrile reacts with α-benzoylcinnamonitrile (2 c) to give the corresponding pyran derivative (32)[34].



32

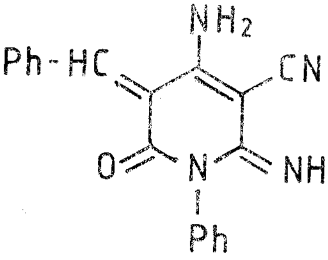
Recently, malononitrile reacts with α-phenylcarbamoylcinnamonitrile (2 d) to give pyridine derivative (33)[25].

Other interesting examples for the application of similar ideas have appeared in recent literature. For example, α-(1-amino-2,2-dicyanoethylenyl) cinnamonitrile (2 h) has been reported to react with malononitrile and ethyl cyanoacetate to yield pyridine derivatives (34 and 35)[54,49] respectively.



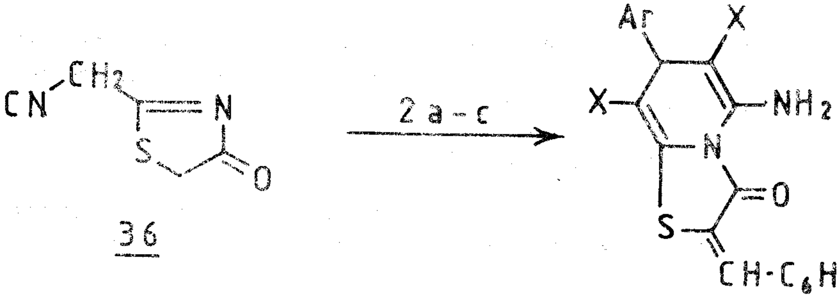
34, X = CN

35, X = COOEt



33

On the other hand, 2-(cyanomethyl) thizaolin-4-one (36) reacts with α-substituted cinnamonitrile in ethanol/piperidine solution to give the corresponding thiazolo [2,3-a] pyridine derivative (27) as following[35,27].

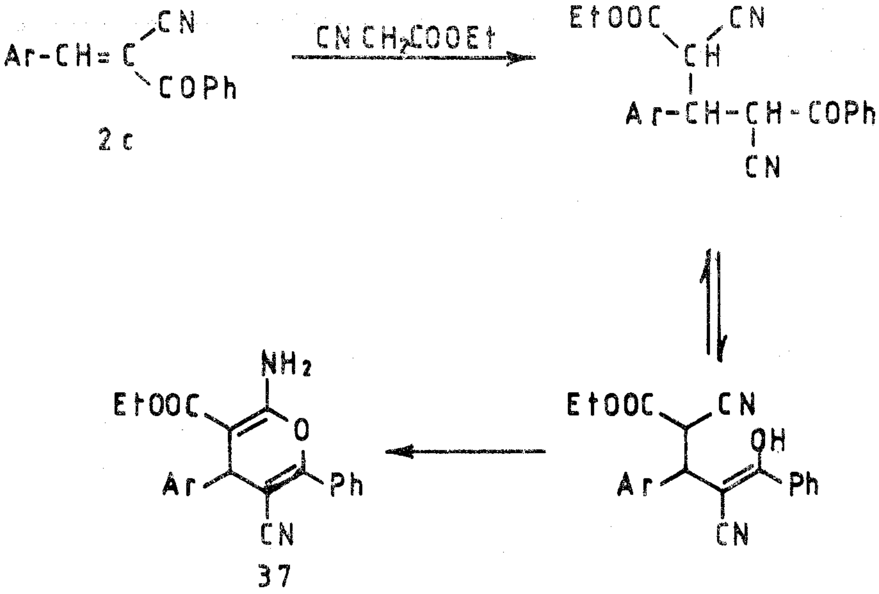


36

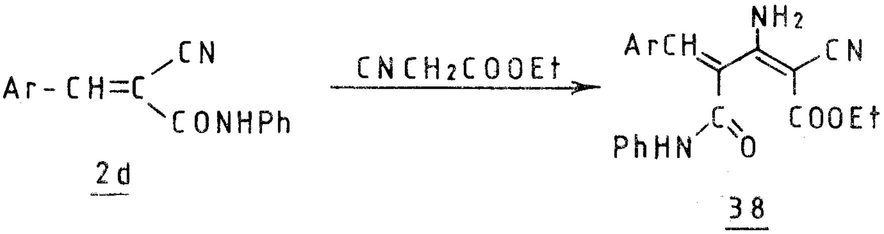
27

B) β-Cyanoesters and β-ketonitriles:

The reaction of ethyl cyanoacetate with α-benzoylcinnamonitrile (2 c) leads to the formation of pyran derivative (37) via Michael addition, as the following equation[28]:

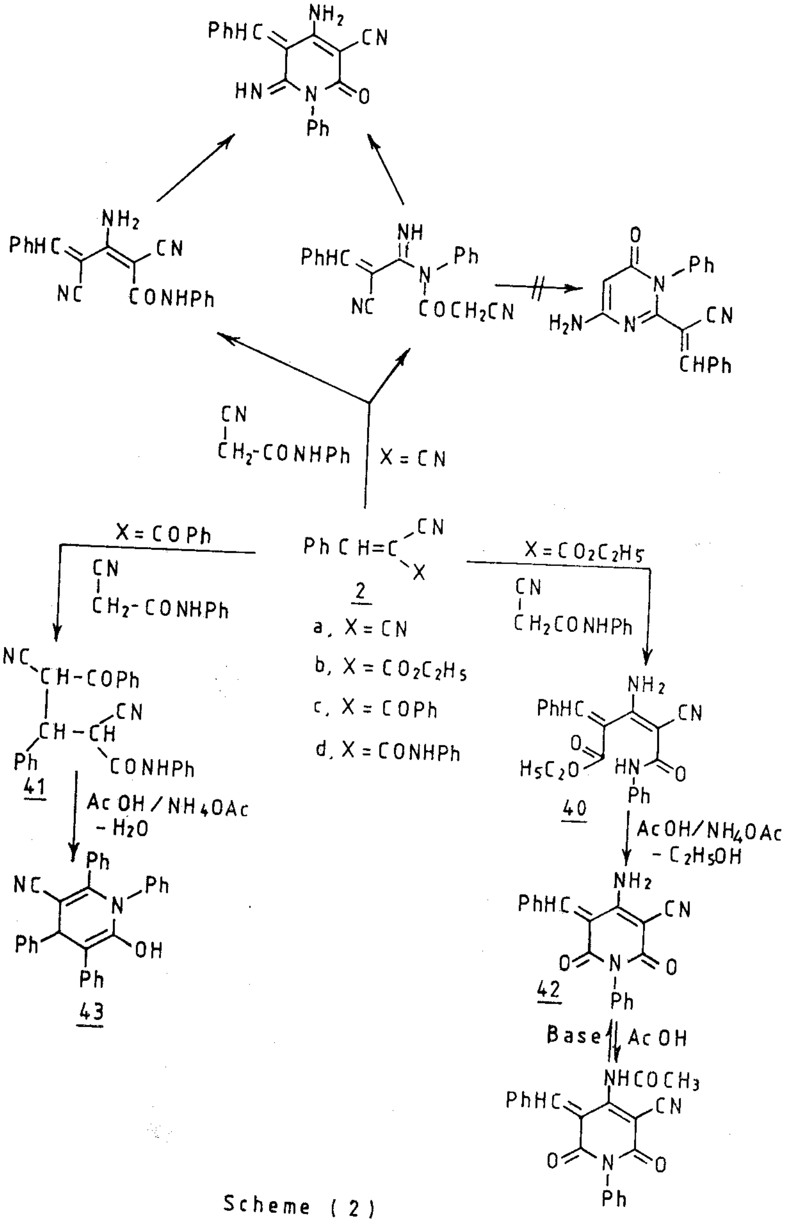


In contrast to this result, ethyl cyanoacetate reacts with α-phenylcarbamoylcinnamonitrile (2 d) to give the acyclic product (38)[25], as following.



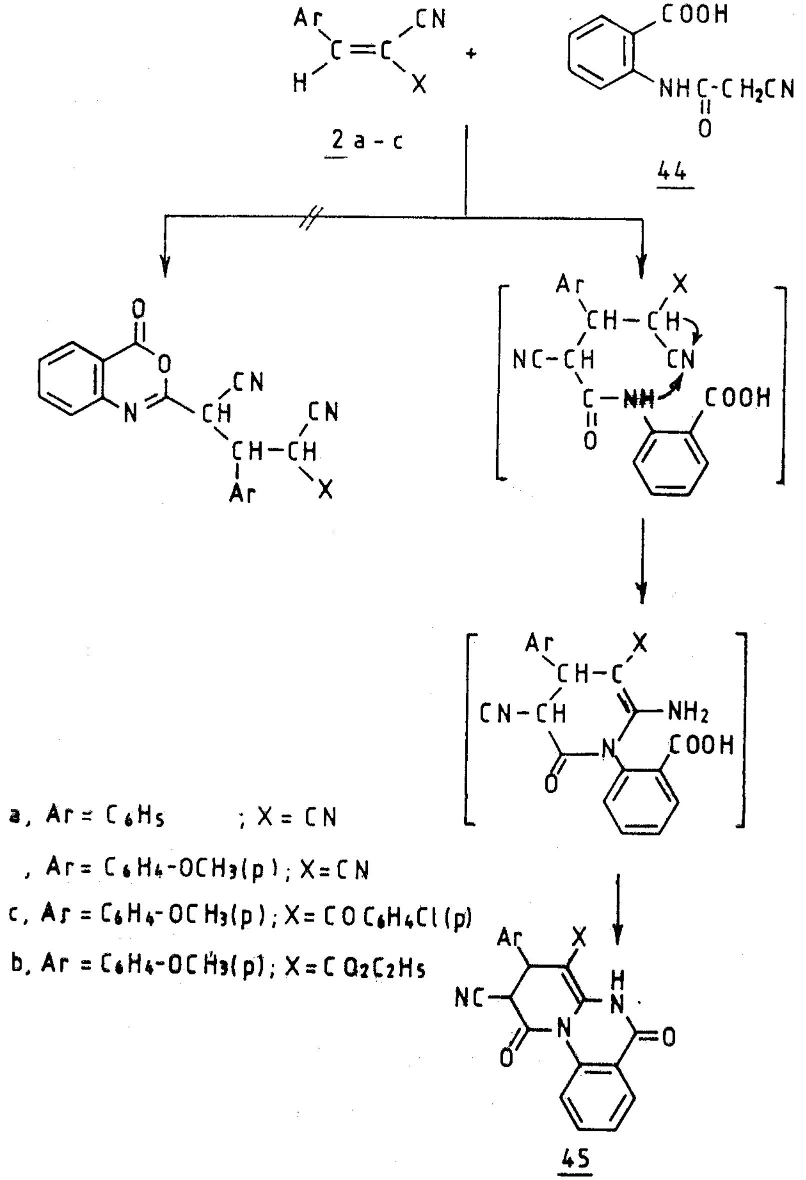
Recently, reaction of α-substituted cinnamonitriles (2 a-d) with cyanoacetanilide was reported[25]. It has been found that, α-cyanocinnamonitrile (2 a) reacts with cyanoacetanilide to give pyridine derivative (39), several other theoretically possible isomeric structures were considered. The formation of pyridine derivative (39) is asumed as two pathyway. (cf. Scheme 2).

In contrast to the above result, it was found that cyanoacetanilide reacts with α-carbethoxycinnamonitrile (2 b) and α-benzoyl-cinnamonitrile (2 c) in ethanol/triethylamine solution to give the acyclic products (40) and (41) respectively. The last two compounds were converted to pyridine derivatives (42) and (43) respectively, through refluxing in acetic acid[25]. (cf. Scheme 2).



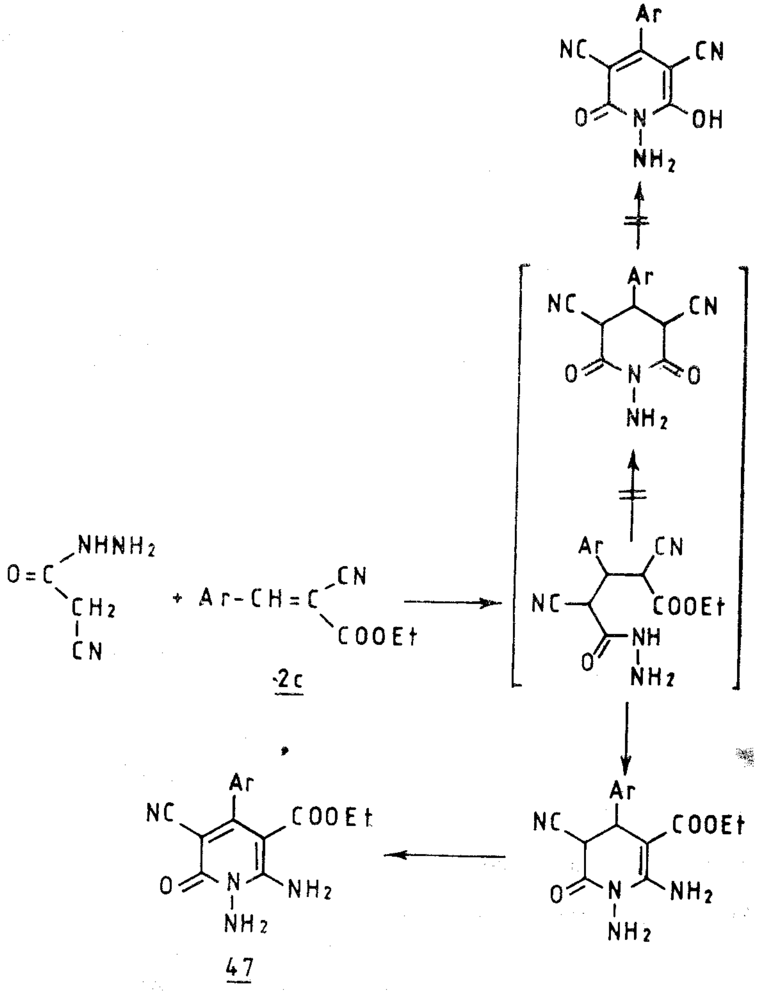
Scheme (2)

On the other hand, o-carboxycyanoacetanilide (44) reacts with α-substituted cinnamonitriles (2 a-c) to give quinoxalinopyridine derivatives (45)[90]. (cf. Scheme 3).



Scheme (3)

Similarly, it was recently reported[26] that, 2-cyanoethanioc acid hydrazide (46) reacts with α-carbethoxycinnamonitrile (2 b) to yield the corresponding 2-pyridone derivative (47). The formation of pyridone derivative (47) is assumed as the Michael addition of the active methylene group of (46) to the C=C group of the (2 b) to give the acyclic product. The latter undergos intramolecular cyclization, via the addition of the hydrogen atom of the substituted nitrogen of the acyclic intermediate to the cyano group, leads to pyridone derivative (47) under the same reaction conditions. (cf. Scheme 4)[26].



a, Ar= C_6H_5-

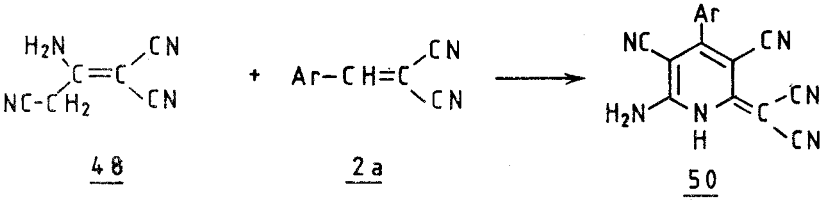
b, Ar= 4-Cl-C_6H_4-

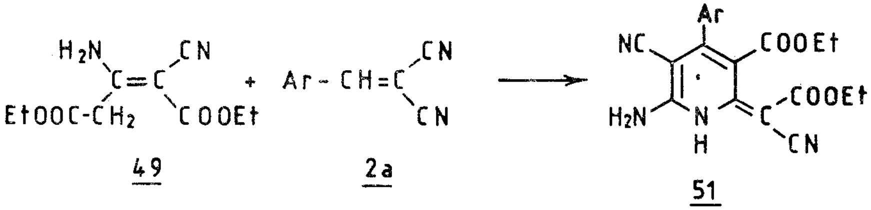
c, Ar= 4-NO_2-C_6H_4-

Scheme (4)

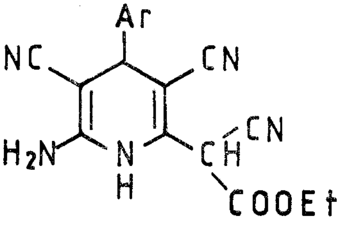
C) Active methylene enamino nitrile:

Other interesting examples for the application of similar ideas have appeared in recent literature. For example, α-substituted cinnamonitrile reacts with active methylene enamino nitriles (48–49). It has been reported that, 2-amino-1,1,3-tricyanoprop-2-ene (48) reacts with α-cyanocinnamonitrile (2 a) to yield pyridine derivative (50)[54,49]. Similarly, diethyl 3-amino-2-cyanopent-2-ene 1,5-dicarboxylate (49) was reacted with (2 a) to yield pyridine derivative (51)[49,78,47], as following.

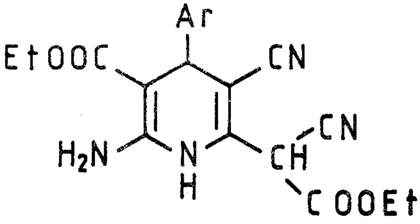




Also, ethyl 3-amino-2,4-dicyanobut-2-ene 1-carboxylate (52) reacts with α-substituted cinnamonitriles (2 a, b) to give the corresponding pyridine derivatives (53) and (54)[49] respectively.



53

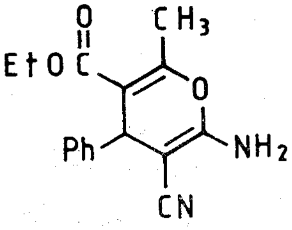


54

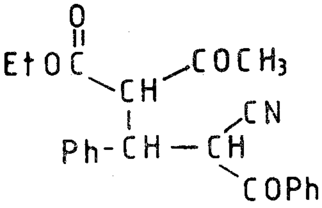
D) β Ketoester:

Recently, the reaction of α-cyanocinnamonitrile (2 a) with ethyl acetoacetate was reported[25], which leads to pyran derivative (55)[25].

In contrast the behaviour of α-cyanocinnamonitrile (2 a) with ethyl acetoacetate, α-benzoylcinnamonitrile (2 c) reacts with ethyl acetoacetate to afford the acyclic product (56)[25].



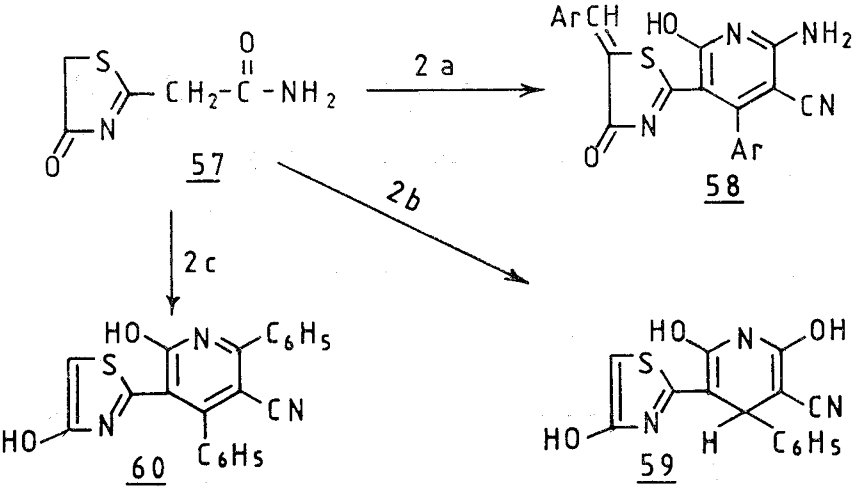
55



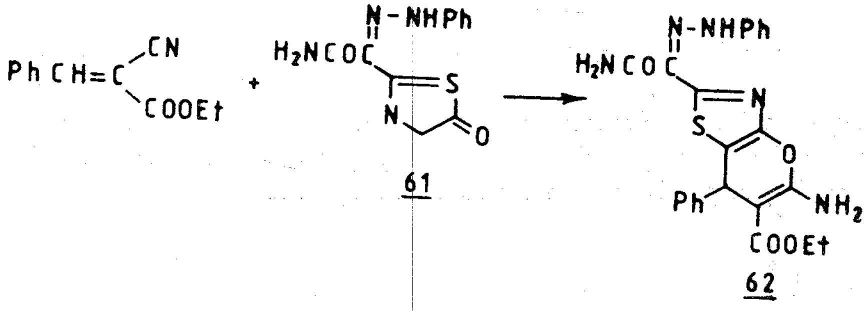
56

E) Active methylene of heterocyclic compounds:

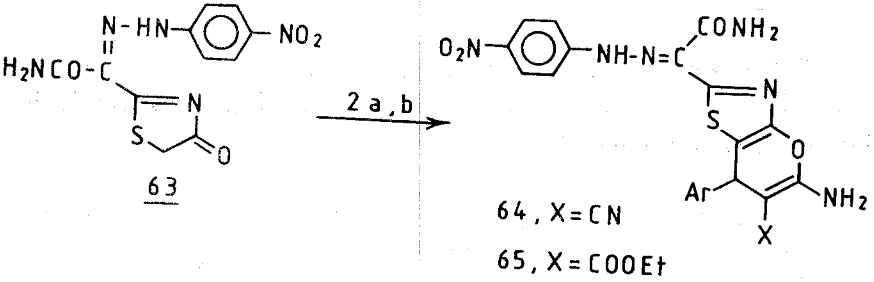
The reaction of several heterocyclic active methylene with α-substituted cinnamonitrile was reported[77]. Such as α-(2-thiazolin-4-onyl) acetamide (57) reacts with α-substituted cinnamonitriles (2 a-c) to give the corresponding 3-(-thiazolin-4-onyl) pyridine derivatives (58–60)[77] respectively.



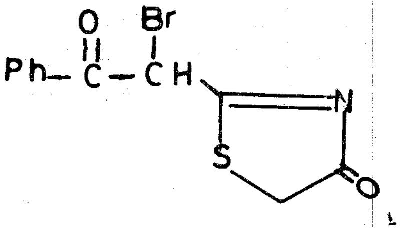
Recently, it was found that, α-carbethoxycinnamonitrile (2 b) reacts with α-(2-thiazolin-4-only)-α-phenylhydrazonoacetamide (61) to give the corresponding pyrano [2,3-d] thiazole derivative (62)[59], as following.



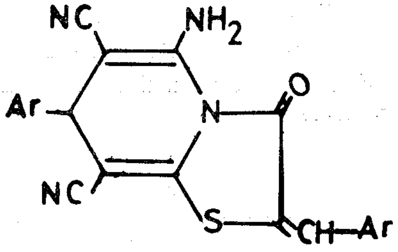
Also, α-substituted cinnamonitriles (2 a, b) react with other thiazolin-4-one derivatives (63) to give the corresponding pyrano-[2,3-d] thiazole derivatives (64) and (65) respectively[58].



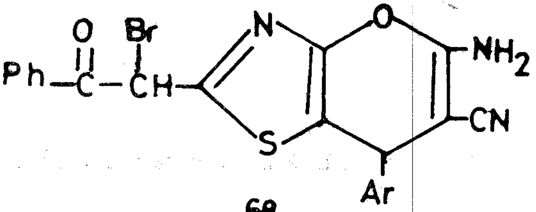
Similarly, α-cyanocinnamonitrile (2 a) reacts with (2 e) and 2-thiazolin-4-onylbenzoylbromomethane (66) to give the corresponding thiazolo [3,2-a] pyridine derivative (67) and pyrano [2,3-d] thiazole derivative (68) respectively[59], as following.



66

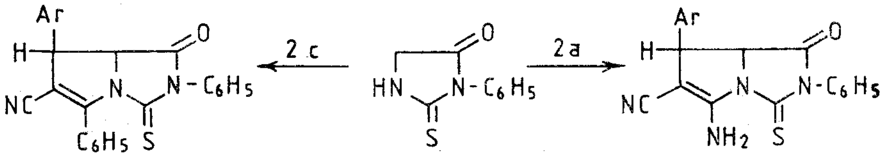


67



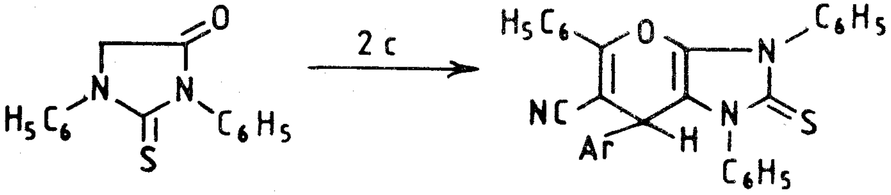
68

Recently, the reactions of α-substituted cinnamonitriles (2 a-c) with thiohydantoin derivatives were reported[18]. It was found that, 3-phenyl-2-thiohydantoin (69) reacts with α-substituted cinnamonitriles (2 a, c) to give the corresponding pyrolo [1,2-c] imidazole (70) and (71) respectively[18], as the following equation:



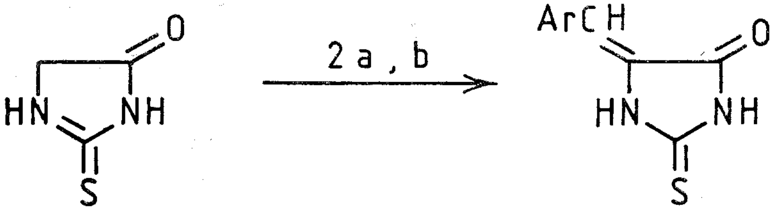
71 69 70

But 1,3-diphenylthiohydantoin (72) reacts with α-benzoylcinnamonitrile (2 c) to give the corresponding pyrano [2,3-d] imidazole derivative (73)[18], as following.



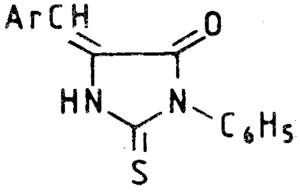
72 73

In contrast to the behaviour of thiohydantoin derivatives (69 and 72) toward α–substituted cinnamonitrile (2 c), thiohydantoin (74) reacts with α-substituted cinnamonitrile (2 a, b) to yield the 5-arylidene derivatives (75)[18].

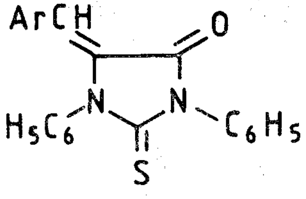


74 75

Also, compounds (69 and 72) react with (2 b) to give 5-aryl idene derivatives (76) and (77) respectively[18].

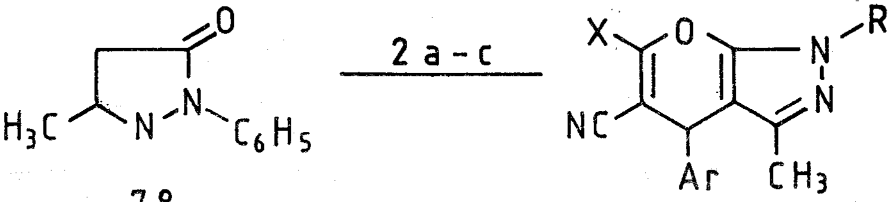


76



77

On the other hand, it was reported that, 3-methylpyrazol-5-one derivative (78) reacts with α-substituted cinnamonitrile (2 a-c) to give the corresponding pyrano [2,3-c] pyrazole derivatives (79–81) respectively[32,54,2], as following.



78

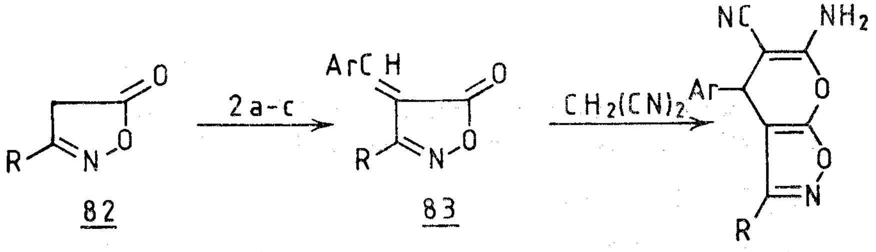
R= H , C_6H_5

79, X = NH_2

80, X = OH

81 X = C_6H_5

The reaction of 2-isoxazolin-5-one derivative (82) with α-substituted cinnamonitrile (2 a-c) was reported[8] to yield 4-arylidene-2-isoxazolin-5-one (83). The latter was reacted with malononitrile to produce pyrano [2,3-c] isoxazole derivative (84)[8], as the following equation:



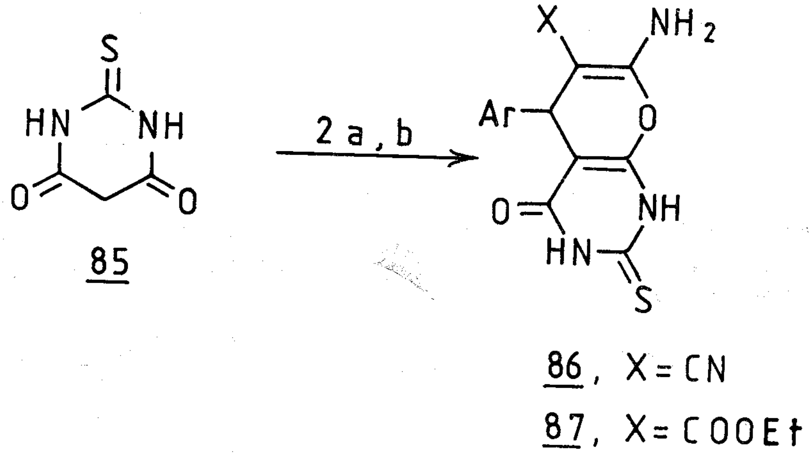
82

R CH_3, C_6H_5

83

84

Recently, it was found that, thiobarbituric acid (85) reacted with α-substituted cinnamonitriles (2, a b) to yield the corresponding pyrano [2,3-d] pyrimidine derivatives (86) and (87) respectively[59].

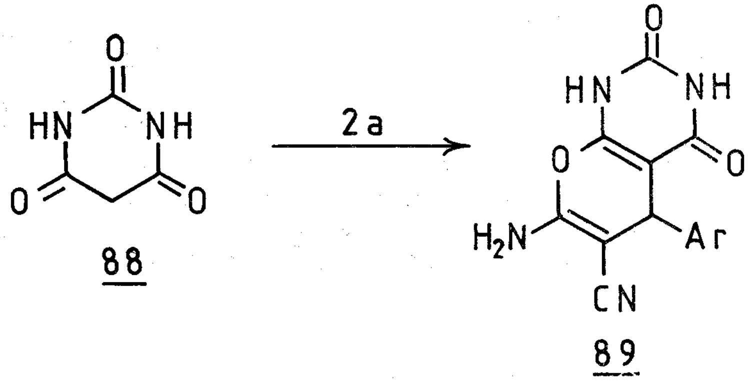


85

86, X = CN

87, X = COOEt

Similarly, it was found that, barbituric acid (88) reacted with α-cyanocinnamonitrile (2 a) to give the corresponding pyrano-[2,3-d] pyrimidine derivative (89)[59], as following.



88

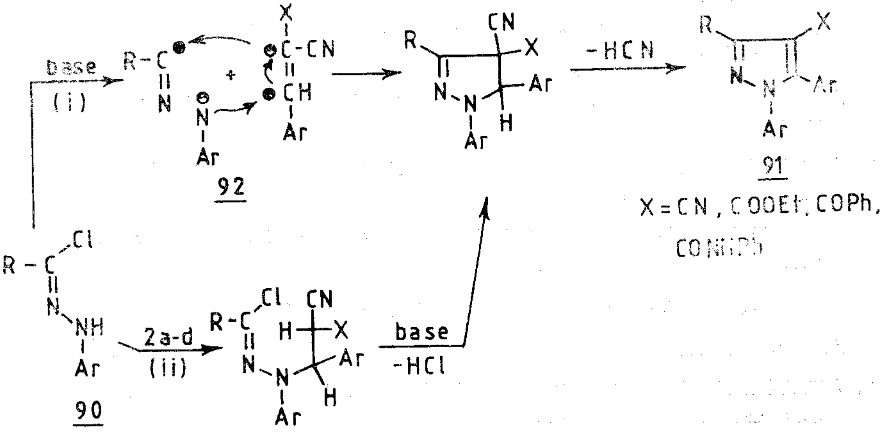
89

The reaction mechanism is considered as Michael addition followed by cyclization on the cyano group of α-substituted cinnamonitrile.

IV) Reaction with hydrazidoyl halide:

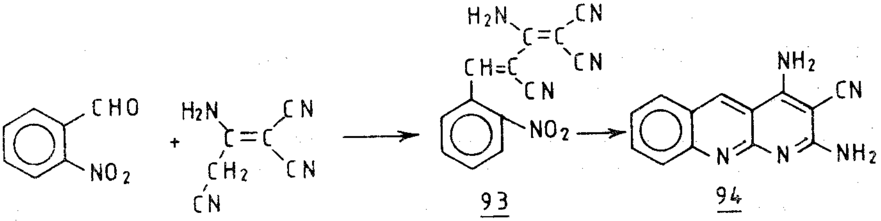
Recently, several pyrazole derivatives (91) were synthesised[60], through the reaction of α-substituted cinnamonitriles (2 a-d) with hydra-

zidoyl halides (90). The reaction mechanism is assumed as 1,3-dipolar cycloaddition of nitrile imine (92) (as shown at pathway i), or via Michael addition followed by cyclization (pathway ii)[60], as following.

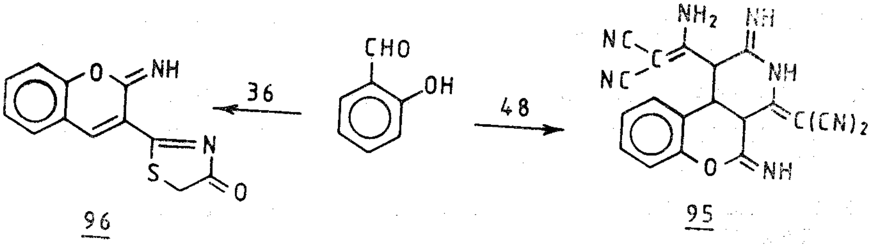


V) Intramolecular reaction:

It has been reported that, several α-substituted cinnamonitriles [bearing a nitro or hydroxyl groups in ortho position of the phenyl group] converted spontaneously after its formation, under the reaction conditions. Such as, o-nitrobenzaldehyde reacted with 2-amino-1,1,3-tricyanoprop-1-ene (48) to yield the condensation product (α-substituted cinnamonitrile derivative) (93), which readily cyclised into (94)[32] as the following equation:



Also salicylaldehyde reacts with (48) and (36) to give the benzopyrano [3,4-c] pyridine derivative (95) and iminocoumarin derivative (96) respectively[32,60], as following.



REFERENCES

1. ABD-ELFATTAH A.M. HUSSAIN S. M., EL-REERY A.M. and YOUSIF N.M., Symposium on Malononitrile and Other Reaction Malono=Synthons, Austrian Embassy at Cairo (1983) April 6 th, 14.

2. ABDOU S., FAHMY S.M., SADEK, K. U. and ELNAGDI M.H., Heterocycles (1981) 16, 2177.

3. ALCALDE E. MENDOZA J. , GARCIA MARQUINA J. M. and ALMERA, J. Heterocycl. Chem. (1974) 11 423.

4. ALEKSANDROWICZ P., BUKOWSKA M., MaACIEJEWSKI AND PREJZNER J., Can. J. Chem. (1979) 57, 2593.

5. ANTUS S., BOROSS F. and NOGRADI M., J. Chem. Soc. Chem. Commun. (1977) 333

6. ANTUS S., BOROSS F. and NOGRADI M., Justus Liebigs Ann. Chem. (1978) 107

7. AWAYA H., MASEDA C., TOMINAGA Y., NATZUKI R., MATSUDA Y. and KOBYASHI G., Chem. Pharm. Bull. (9174) 22, 1424.

8. AZIZ S. I., RIAD B.Y., ALFAHHAM H.A. and ELNAGDI M.H., Heterocycles (1982) 19, 2251.

9. BREVER H. and TREUNER U.D., Ger offen. (1974) 2, 408, 906; C.A. (1975) 832, 31354.

10. BROWN D.T., HOERGER E. and MASON S.F., J. Chem. Soc., (1955) 211.

11. BROWN D.T. and IENEGA K., Aust. J. Chem. (1975) 28, 119.

12. BURGER K., SCHICKANEDER H. and ELGUERO J., Tetrahedron lett. (1975) 33, 2911.

13. BRUSON H.A. "Organic Reaction", Ed. Adams R., Wiley J. and Sons,. New York (1949) Vol. V, P. 101.

14. CEDER O. and ANDERSSON J.E., Acta Chem. Scand. (1972) 26, 596.

15. CEDER O. and ANDERSSON J,E., Acta Chem. Scand. (1972) 26, 611.

16. CEDER O. and ROSED K., Acta Chem, Scand. (1973) 27, 2421.

17. CEDER O. and WITTE J.F., Acta Chem. Scand (1972) 26, 635.

18. DABOUN H.A.F,. Abdou S.E. HUSSEIN M.M, ELNAGDI M.H., Synthesis (1982) 502.

19. DABOUN H.A. and EL-REEDY A.M., Symposium on Malononitrile and Other Reactive Malono-Synthons, Austrian Embassy et Cairo (1983) April 7 th, 85.

20. DICKINSON C.L., WILLIAMS J.K. and MCKUSICK B.C., J. Org. Chem (1964) 29, 1915.

21. EARL R. A PUGMIRE R.J., REVANKAR G.R. and TOWNSEND L.B,. J. Org. Chem. (1975) 40, 1822.

22. EGE G. and ARNOLD P., Synthesis (1976) 52. Angew. Chem. Int. Ed. Engl. (1974) 13, 206.

24. ELFAHHAM H. A., ABDEL-GALIL F. M, IBRAHIM Y.R. and ELNAGDI M.H., J. Heterocycl. Chem. (1983) 20, 667.

25. ELGEMEIE G.E.H., ELEES S.A., ELSAKKA I. and ELNAGDI M.H., Z. Naturforsch (1983) 38b, 639.

26. ELMOGHAYER M.R.H, El-AGAMEY A.G.A., -Abel N.M. and IBRAHIM M.K.A., An Quim. (1985) 81, C, 236.

27. ELMOGHAYER M.R.H., IBRAHIM M.K.A., ELGHANDOUR A.H.H. and ELNAGDI M.H. Synthesis (1981) 635.

28. ELMOGHAYER M.R.H., Khalifa M. A. E., IBRAHIM M.K.A and ELNAGDI M.H, Monatsh. Chem. (1982) 113, 53.

29. ELNAGDI M.H., Tetrahedron (1974) 30, 2791.

30. ELNAGDI M.H., ABED N.M., ELMOGHAYER M.R.H. and FLEITA D.H, Indian J. Chem. (1976) 14b, 422.

31. ELNAGDI M.H., ALLAH S.O.A., J. Parkt. Chem. (1973) 315, 1009.

32. ELNAGDI M.H., ELFAHHAM H.A. and ELGEMEIE G.E., heterocycles (1983) 20, 519

33. ELNAGDI M.H. ELMOGHAYER M.R.H. and FLEIRA D.H., J. Prakt. Chem (1974) 316, 975.

34. ELNAGDI M.H., ELMOGHAYER M.R.H, HAFEZ E. A.A and ALMNIMA HH., J. Org.. Chem, (1975) 40, 2604.

35. ELNAGDI M.H., ELMOGHAYAR M.R.H., HAMMAM A.G. and KHALLAF S. A, J. Heterocycl. Chem. (1979) 15, 1541.

36. ELNAGDI M.H., FAHMY S. M., ELMOGHAYAR M.R.H. and ILIAS M.A.M., Z. Naturforsch. (1975) 30b, 778.

37. ELNAGDI M.H., FLEITA D.H. and ELMOGHAYAR M.R.H., Tetrahedron (1975) 31, 63.

38. ELNAGDI M. H., KANDEEL E. M and ELMOGHAYAR M.R.H., Z. Naturforsch (1977) 32 b, 307.

39. ELNAGDI M.H., KANDEEL E. M., ZAYED E.M. and KANDIL Z.E., J. Prakt. Chem. (1978) 320, 533.

40. ELNAGDI M.H., KASSAB N.A.L., FAHMY S.M. and EL-ALL F. A., J. Prakt. Chem. (1974) 316, 177.

41. ELNAGDI M. H., KHALIFA M.A.E., IBRAHIM M.K.A. and ELMOGHAYER M.R.H., J. Heterocycl. Chem. (1981) 18. 877.

42. ELNAGDI M.H., OHTA M., Bull. Chem. Soc Jpn. (1973) 46, 1830.

43. ELNAGDI M.H., OHTA M. Bull. Chem. Soc. Jpn. (1973) 46, 3813.

44. ELNAGDI M.H., SALLAM M.M.M. and ILIAS M.A.M., Helv. Chem. Acta (1975) 58, 1944

45. ELNAGDI M.H., ZAYED E. M., KAHALIFA M.A.E. and GHOZLAN S.A., Monatsh. Chem. (1981) 112, 245.

46. EVANS J. and JOHNSONS T.B., J. Am. Chem. Soc. (1930) 52, 4993.

47. FAHMY S. M., ABED N. M, MOHAREB R. M., ELNAGDI M.H., Synthesis (1982) 490.

48. FAHMY S. M. KaANDEEL E.M., EL-SAYED E.R. and ELNAGDI M.H., J. Heterocycl. Chem. (1978) 15, 1291.

49. FAHMY S. M., SADEK K. U, MOHAREB R.M and ELNAGDI M.H., "Symposium on Malononitrile and Other Reactive Malono-Synthons", Austrian Embassy at Cairo (1983) April 7 th, 55.

50. FERINI P.G., HAAS G. and ROSSİ A., Swiss Patent, (1976) 578, 535; C.A. (1977) 86, 29660.

51. FIESSELMANN AND THOMA F., Chem. Ber., (1959) 89, 1907.

52. FREEMAN F., Synthesis (1981) 925.

53. FRENCH J., PESSKE K., KRISTEN H. and BRAEUNIGER, Pharmazie (1976) 31, 851

54. FUENTES L., SOTO J.L. and VAQUERO J.J., 18th International Congress in Heterocyclic Chemistry, Graz, Austria (1981), p. 33.

55. FURUKAWA M., YUKI T. and HAYASHI S., Chem. Pharm. Bull. (1973) 21, 1845.

56. HECHT S.M., WERNAR D., TRAFICANTE D.D., SUNDARALINGGAM M., PRUSINER P. and SAKURAI T., J. Org. Chem. (1975) 40, 1815.

57. IBRAHIM M.K.A., Indian J. Chem. (1987) in press.

58. IBRAHIM M.K.A., J. Indian Chem. Soc. (1988) in press.

59. IBRAHIM M.K.A., EMOGHAYER M.R.H and SHARAF M, .Indian J. SChem (987) 26B, 216

60. IBRAHIM M.K.A., J. Pakistan Soc. of Biochemists, (1988) in press.

61. KAMBF S., SAİTO K., SAKURAI A. and MİDORIKAWA H., Synthesis (1981) 531

62. KILPPER G., Ger Offen., (1973) 2, 141, 700; C.A. (1973) 78, 136273.

63. KREUTZBERGER A. and BURGWIZ K., J. Heterocycl. Chem. (1980) 17, 265.

64. KURATA K., AWAYA H., MASEDA C., TOMINAGA Y., MATSUDA Y. and KOBAYASHİ G. Yakugaku Zasshi (1975) 95, 1431; C.A. (1976) 84, 105434.

65. MAEDA K., HOSOKAWA T., MURAHASSHI S. and MORITANI I., Tetrahedron lett. (1973) 51, 5075.

66. MARISCO J.W., JASCPH J.P. and GALDMAN L., U.S. Patent (1973) 3, 760, 084; C.A. (1974) 80, 47987.

67. MARSICO J.W., JASEPH J.P. and GALDMAN L., U.S. Patent (1972) 3, 760, 082; C.A. (1973) 79, 146518.

68. MATSUO M., AWAYS H., MASEDA C., TOMINAGA Y., NATSUKI R., MATSUDA Y. and KOBAYASHI G., Chem. Pharm. Bull. (1974) 22, 2765.

69. MEYERS A.I and SIRCAR J.C., "Additions to the Cyano Group to form Herterocycles", in the chemistry of Cyano Group, Ed. Rappopart Z., Wiley J. and Sons, New York, (1970) 341.

70. MIDDLETON W.J., ENGELHARDTV.A. and FISHER B.S., J. Am. Chem. Soc. (1958) 80, 2822.

71. NAGAHARA K., TAKAGI K. and UEDA T., Chem. Pharm. Bull. (1976) 24. 1310.

72. NAGAHARA K., TAKAGI K. and UEDA T., Chem. Pharm. Bull. (9176) 24, 2880.

73. PEDERS E.B. and CARLSEN D., TETRAHEDRON (1977) 33, 2089.

74. PESEKE K., Ger (East) Patent. (1973) 102, 382; C.A. (1974) 81, 25658.

75. PESEKE K., Pharmazie (1975) 30, 802.

76. RUDORG W.D. and AUGUSTIN M., J. Prakt. Chem. (1978) 320, 585.

77. SADEK K.U., MOURAD A.F.E., ABD-ELHAFEEZ A.E., Synthesis (1983) 739.

78. SAKLA A.B, IBRAHIM N.S. and ELNAGDI M.H., 8 th International Congress in Heterocyclic Chemistry, Graz, Austria (1981) p. 22.

79. SCHMIDT H.W. and JUNECK H., Monatsh. Chem. (1978) 109; 1075.

80. SCHMIDT R. and KLEMM K., Ger. Offen. (1975) 2, 426, 279; C.A. (1975) 82, 171367.

81. SENGA K., ROBINS R.K. and O'BRIEN D.E., J. Heterocycl. Chem. (1975) 12, 899.

82. SHAW J.T., KYLER K.S. and ANDERSON M.D., J. Heterocyccl. Chem. (1977) 14, 679.

83. SHUMAN R. F., SHEARIN W.E. and TULL R.J., J. Org. Chem. (1979) 44, 4532.

84. SOTO J.L., SEOANE C., MARTIN N. and PEREZ H., 8 th International Congress in Heterocyclic Chemistry, Graz, Austria (1981), p. 32.

85. TAYLOR E C ,"Principals of Heterocyclic Chemistry" A.C.S. Course (1978)

86. TAYLOR E.C. and MCKIPPLO, A., "The Chemistry of Cyclic Enaminonitrile and o-aminonittliles, Wiley J. and Sons, New York (1970) 306.

87. TAYLOR E.C. and PURDUM W.R., Heterocycles, (1977) 6, 1865.

88. TOKUYAMA K., Japan Kakai 74, 69, 679; C.A. (1974) 81, 13177 t.

89. PEDERSEN E.B. and CARLSEN D., Tetrahedron (1977) 33, 2089.

90. ZAYED E.M., KHALIFA M.A.E. and MOHAMED M.H., Symposium on Malononitrile and Other Reactive Malono=Synthons", Austrian Embassy at Cairo (1983) April 7 th, 79.