Studies with Polyfunctionally Substituted Heteroaromatics: The Reaction of Heterocyclic Enaminonitriles with α- β-Unsaturated Nitriles

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5-Amino-4-cyano-3-phenylpyrazole (**1**) reacts with cinnamonitriles (**2**) to yield the pyrazolo[1,5-*a*]pyrimidines (**3**). Also, 5-amino-4-cyano-1-phenylpyrazole (**4**) reacts with cinnamonitriles (**2**) to yield the pyrazolo[3,4-*b*]pyridine derivatives (**5**). In contrast to this reaction, enaminothiophene (**6**) reacts with cinnamonitriles (**2**) to yield compound (**7**) not (**8**). The enaminopyrane (**9**) reacts with cinnamonitriles (**2**) to yield (**10**). Finally we have attempted to add cinnamonitriles (**2**) to thiopyrane (**13**); only rearrangement and aromatization product (**14**) was isolated.

INTRODUCTION

Polyfunctionally substituted heteroaromatics are biologically interesting molecules, and their chemistry has in the past received interest.[1-3] α,β-Unsaturated nitriles are versatile reagents that have been extensively used in heterocyclic synthesis. Recently, the reaction of α-substituted cinnamonitriles has been utilized for the synthesis of a variety of otherwise not readily accessible polyfunctionally substituted heterocycles.[4] Several new approaches for synthesis of five and six member fused heterocyclic derivatives could be achieved by using this work.[5-7] As a part of this program, the reaction of cinnamonitriles with different enaminonitriles has been reported in basic medium such as ethanol/piperidine or triethylamine and with pyridine.[8] But we used here the sodium/dioxane solution and studied the effect of this condition on the reaction of cinnamonitriles with different enaminonitriles. So, we have thus investigated the reaction of the heterocyclic enamines **1, 4, 6, 9** and **13** toward cinnamonitriles in refluxing sodium/dioxane.

DISCUSSION

The 5-amino-4-cyano-3-phenylpyrazole **1** reacted readily with arylidenemalodinitrile **2a,b** to yield pyrazolo-[1,5-*a*]pyrimidine derivatives **3a,b** which are believed to be formed via initial addition of ring nitrogen to the α,β-unsaturated system and subsequent cyclization. This reaction sequence paralleled the well established behavior of the aminopyrazole toward cinnamonitriles.[9-11]

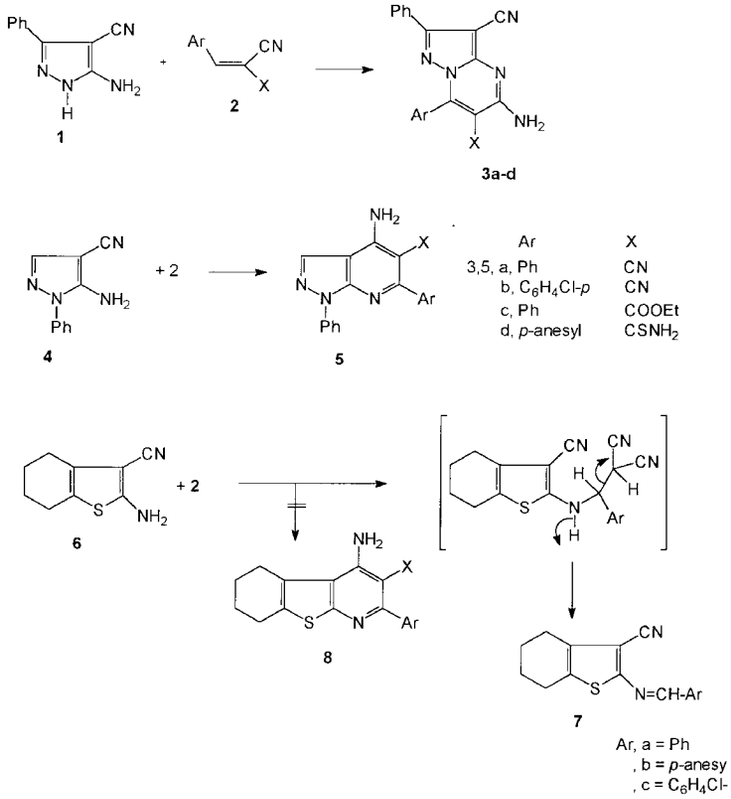
Similarly, arylideneethylcyanoacetate and arylidenecyanothio acetamide **2c** and **2d** reacted with pyrazole derivative **1** to yield the pyrazolo[1,5-*a*]pyrimidine **3c** and **3d**. Also 5-amino-4-cyano-1-phenylpyrazole **4** reacted with cinnamonitriles **2a-d** in refluxing sodium/dioxane which yielded the pyrazolo[4,5-*b*]pyridine derivatives **5a-d**. In contrast to this attempted addition of cinnamonitriles in refluxing sodium/dioxane to enaminothiophene **6**, this resulted only in the formation of Chieff base **7a-c**. Compound **7** is assumed to be formed by addition of a double bond of arylidene to NH_2 to give the Michael adduct which then spontaneously loses the malononitrile molecule to give the final product **7.**

The enaminopyrane **9** reacted with benzylidenemalononitriles to yield 1:1 adduct. This can be formulated as **10a** or **12a** or their cyclization product **11a.** ^{1}H NMR spectrum could clearly show that the product of this reaction is the adduct **10a**. It indicated disappearance of methyl signal and appearance of several aliphatic multiples that can only be integrally interpreted for this acyclic structure. Attempts to cyclize the adduct **10a** by refluxing in different conditions to yield the cyclohexanopyranes **11** failed. Also cinnamonitriles **2b-d** reacted with **9** to yield compounds **10b-d**. Finally we have attempted also adding yielidenemalonitriles to thiopyrane **13** under our experimental conditions; only rearrangement and aromatization product **14** was isolated. This product could also be produced on treatment of thiopyrane **13** with sodium/dioxane. In aqueous solutions the hydroxypyridinethione reported by Elnagdi et al[12] was isolated.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Shimadzu 470 spectrophotometer ^{1}H NMR spec-

Scheme I



Scheme II

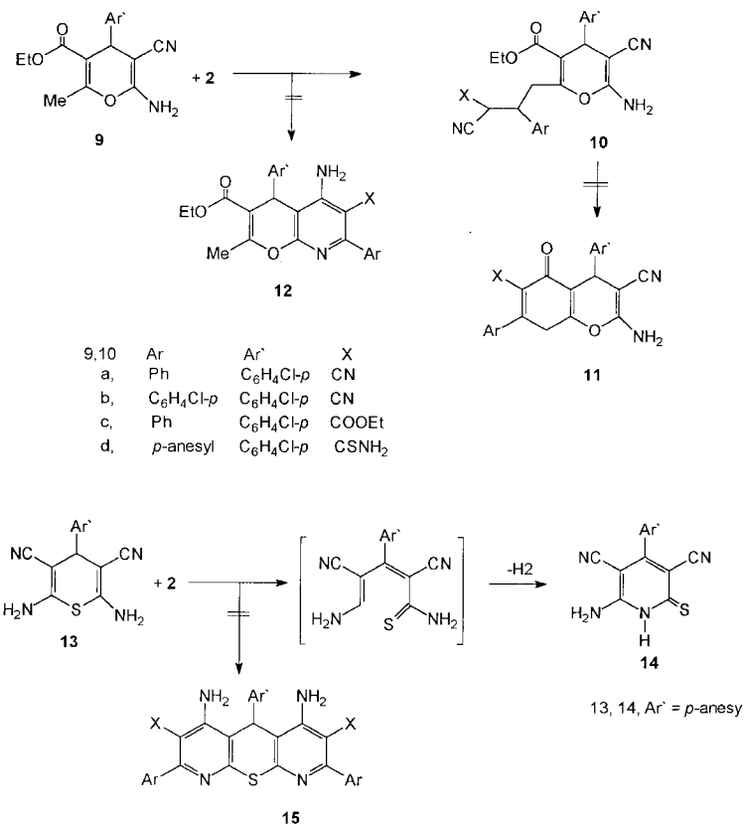


Table 1: Yields, Melting Points, and Elemental Analysis of the New Compounds

Comp. No	mp ^{0}C Solvent	yield %	Molecular formula M.weight	Calcd/(Found) C	H	N	Cl	S
3a	180 EtOH	68	$C_{20}H_{12}N_6$ (336.36)	71.40 (71.5)	3.60 (3.8)	25.0 (25.1)		
3b	177 EtOH	70	$C_{20}H_{11}N_6Cl$ (370.80)	64.78 (64.9)	2.99 (3.0)	22.66 (22.8)	9.56 (9.7)	
3c	160 EtOH	72	$C_{22}H_{17}N_5O_2$ (383.41)	68.92 (69.1)	4.47 (4.6)	18.27 (18.4)		
3d	195 EtOH	65	$C_{21}H_{16}N_6OS$ (400.46)	62.99 (63.1)	4.03 (4.2)	20.99)3.2)		8.01 (8.3)
5a	190 EtOH	81	$C_{19}H_{13}N_5$ (311.35)	73.30 (73.4)	4.21 (4.4)	22.49 (22.6)		
5b	200 EtOH	79	$C_{19}H_{12}N_5Cl$ (345.79)	66.00 (66.2)	3.50 (3.7)	20.25 (20.0)	10.25 (10.3)	
5c	150 EtOH	82	$C_{21}H_{18}N_4O_2$ (358.40)	70.38 (70.5)	5.06 (5.2)	15.63 (15.8)		
5d	180 EtOH	77	$C_{20}H_{17}N_5OS$ (375.45)	63.39 (64.2)	4.56 (4.6)	18.65 (18.8)		8.54 (8.7)
7a	240 DMF EtOH	75	$C_{16}H_{14}N_2S$ (266.36)	72.15 (72.3)	5.30 (5.5)	10.52 (10.7)		12.04 (12.2)
7b	110 EtOH/ H_2O	78	$C_{17}H_{16}N_2OS$ (296.39)	68.89 (69.0)	4.44 (4.5)	9.45 (9.6)		10.82 (11.0)
7c	100 EtOH/H_2O	80	$C_{16}H_{13}N_2SCl$ (300.81)	63.89 (64.1)	4.36 (4.6)	9.31 (9.5)	11.79 (11.9)	10.66 (10.8)
10a	165 EtOH	84	$C_{26}H_{21}N_4O_3Cl$ (472.93)	66.03 (66.2)	4.48 (4.6)	11.85 (12.0)	7.50 (7.6)	
10b	175 dioxane	81	$C_{26}H_{20}N_4O_3Cl_2$ (507.38)	61.55 (61.6)	3.97 (4.2)	11.04 (11.1)	13.98 (14.1)	
10c	180 EtOH	85	$C_{28}H_{26}N_3O_5Cl$ (519.98)	64.68 (64.8)	5.04 (5.2)	8.08 (8.1)	6.82 (6.9)	
10d	125 EtOH	77	$C_{27}H_{25}N_4O_3SCl$ (521.03)	62.24 (62.3)	4.84 (4.9)	10.75 (10.9)		6.15 (6.3)
14	260 DMF/EtOH	88	$C_{14}H_{10}N_4OS$ (282.32)	59.56 (59.8)	3.57 (3.7)	19.85 (20.1)		11.36 (11.50)

Table 2. IR , ^{1}H NMR for the New Compounds

No	IR ν cm^{-1}	^{1}H NMR (DMSO-d_6)
3a	3400-3300(NH_2); 3050 (Ar-H) , 2200 (CN).	5.5 (br, 2H, NH_2);7.0-7.8 (m,10H, Ar-H, *J* = 9 Hz).
3b	3400-3310 (NH_2); 3050 (Ar-H), 2210 (CN).	5.3 (br, 2H, NH_2); 7.1-7.6 (m, 9H, Ar-H, *J* = 9 Hz).
3c	3390-3300(NH_2); 3050 (Ar-H), 2200 (CN), 1710 (CO).	1.2 (t, 3H, CH_3, *J* = 7 Hz); 4.1 (q, 2H, CH_2, *J* = 7 Hz); 6.2 (br, 2H, NH_2) ; 7.0 - 7.7 (m,10H, Ar-H, *J* = 9 Hz).
3d	3400-3300(NH_2); 3050 (Ar-H), 2200 (CN).	(THF) 3.8 (s, 3H, OCH3), 7.2-7.5 (m, 9H, Ar-H, *J* = 9 Hz)
5a	3350-3300(NH_2); 3045 (Ar-H), 2200 (CN).	7.10-7.50 (m,11H, Ar-H and H-4 .pyrazole,) ;8.37 (br, 2H, NH_2).
5b	3380-3320(NH_2); 3050 (Ar-H), 2210 (CN).	7. 0-7.60 ,(m,10H, Ar-H and H-4.pyrazole) ;8.50 (br, 2H, NH_2).
5c	3400-3300(NH_2); 3050 (Ar-H), 1720 (CO).	1.2 (t, 3H, CH_3, *J* = 7 Hz), 4.1 (q, 2H , CH_2, *J* = 7 Hz) ; 7.1-7.5 (m,11H, Ar-H and H-4 pyrozole); 8.4 (br, 2H , NH_2).
5d	3370-3310(NH_2); 3050 (Ar-H)	3.7 (s, 3H, OCH_3); 7.0-7.50 (m,10H, Ar -H and H-4pyrozole); 8.60 (b r, 2H , NH_2).
7a	2934-2839 (aliphatic-CH), 2205 (CN).	2.8 (m, 8H, cyclohexane-H); 7.1-7.8 (m, 6H, Ar-H and CH, *J* = 9 Hz);
7b	2940-2850 (aliphatic-CH), 2200 (CN).	3.0 (m, 8H, cyclohexane-H); 3.8 (s, 3H, OCH_3), 7.0-7.6 (m, 5H, Ar-H+CH, *J* = 9 Hz)
7c	2980-2840 (aliphatic-CH), 2210 (CN).	2.8 (m, 8H,cyclohexane-H); 7.0-7.5 (m, 5H, Ar- H and CH, *J* = 9 Hz);
10a	3400-3300 (NH_2); 2998 (aliphatic-CH),2200 (CN), 1720 (CO).	0.9-1.0 (t, 3H, CH_3, *J* = 7 Hz), 3.0-3.1 (d, 2H , CH_2, *J* = 7 Hz) ; 3.5-3.6 (t, 1H, CH), 3.9- 4.0 (q, 2CH , CH_2), 5.0 (pyran-4H); 12.5 (s,1H, CH)..
10b	3390-3310 (NH_2); 2990 (aliphatic-CH),2200 (CN), 1720 (CO).	1.0 -1.1 (t, 3H, CH_3, *J* = 7 Hz), 2.9-3.1 (d, 2H , CH_2, *J* = 7 Hz) ; 3.5-3.6 (t, 1H, CH), 4.0- 4.1 (q, 2CH , CH_2), 4.9 (pyran-4H); 12.1 (s,1H, CH)..
10c	3400-3300 (NH_2); 2980 (aliphatic-CH),2210 (CN), 1720 (CO).	0.9-1.2 (t, 3H, CH_3, *J* = 7 Hz), 3.0-3.1 (d, 2H , CH_2, *J* = 7 Hz) ; 3.4-3.6 (t, 1H, CH), 3.9- 4.1 (q, 4CH , $2CH_2$), 4.8 (pyran-4H); 11.9 (s,1H, CH)..
10d	3380-3300 (NH_2); 2960 (aliphatic-CH),2200 (CN), 1710 (CO).	1.1-1.2 (t, 3H, CH_3, *J* = 7 Hz), 1.8-1.9 (d, 2H, CH_2, *J* = 7 Hz) 3.2-3.3 (t, 1H, CH), 3.7 (s, 3H, OCH_3), 3.9-4.0 (d, 2H , CH_2), 4.6 (pyran-4H); 12.0 (s,1H, CH)..
14	3300-3300 (NH_2);3100 (NH), 2200 (CN)	3.5 (s, 3H, OCH_3), 7.0-7.7 (m, 5H, Ar-CH and NH_2, *J* = 9 Hz), 12.1 (s,1H, NH).

tra were measured with a Varian EM-390 spectrometer. Microanalyses were performed by the microanalytical facility at Cairo University. Mass spectra were recorded on a mass spectrometer MS 30 MS 9 (AEI) at 70 eV.

Preparation of Compounds 3, 5, 7, 10 and 14 General Procedure

A suspension of enaminonitriles (0.01 mol) and the appropriate cinnamonitriles (0.01 mol) in sodium/dioxanee solution (30 mL) [prepared by dissolving (0.01 mol) of sodium in dioxane] was refluxed for 3 hours. The reaction mixture was poured onto ice/cold water and neutralized by dilute HCl. The solid product formed was collected by filtration and recrystallized from the proper solvents (Tables 1 and 2).

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Key Words

Pyrazolopyrimidines; Pyrazolopyridines; Enaminothiophene; Pyran; Pyridinethione derivatives.

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