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ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS: A NEW SYNTHESIS OF 3-FURAN-2-YLIDENE- AND 3-THIOPHEN-2-YLIDENE-3,6-DIHYDROPYRIDINE DERIVATIVES

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Abstract-Synthesis of 3-furan-2-ylidene- and 3-thiophen-2-ylidene-3,6-dihydropyridine derivatives via the reaction of cyanothioacetamide with furan-2-ylidene and thiophen-2-ylidene derivatives of malononitrile, ethyl cyanoacetate and benzoylacetonitrile.

As a part of a program to examine the scope and limitations of α,β-unsaturated nitriles in heterocyclic synthesis [1-4], the reactivity of cyanothioacetamide 1 toward the α,β-unsaturated nitrile derivatives 2a-f, readily obtainable via condensation of 2-furancarbaldehyde and 2-thiophencarbaldehyde with malononitrile, ethyl cyanoacetate and benzoylacetonitrile was investigated. Although it has been recently reported that 1 reacts with α-benzoylcinnamonitrile to yield 4,6-diaryl-1,2-dihydro-2-thioxo-3,5-pyridinecarbonitrile, via Michael addition of 1 to the activated double bond in the cinnamonitrile derivative, cyclisation and aromatization [5,6], we have found that the reaction of 1 with 2a-f proceeds in completely different way. Thus, 1 (0.01 mol) reacted with 2a,b (0.01 mol) when refluxed in ethanol (50 ml) containing catalytic amounts of piperidine for 2 h to yield 1:1 adducts (as revealed from Ms). Six theoretically possible structures were considered (cf. structures 3-6, chart 1). Dihydropyridine structures which might be formed via a mechanism similar to that recently proposed [6] were readly ruled out as ^{1}H nmr revealed two two proton signals at δ 2.77 and δ 2.96 ppm (D_2O exchangeable) in addition to the furanyl or thiophenyl protons and one low field singlet at δ 8.15 ppm.

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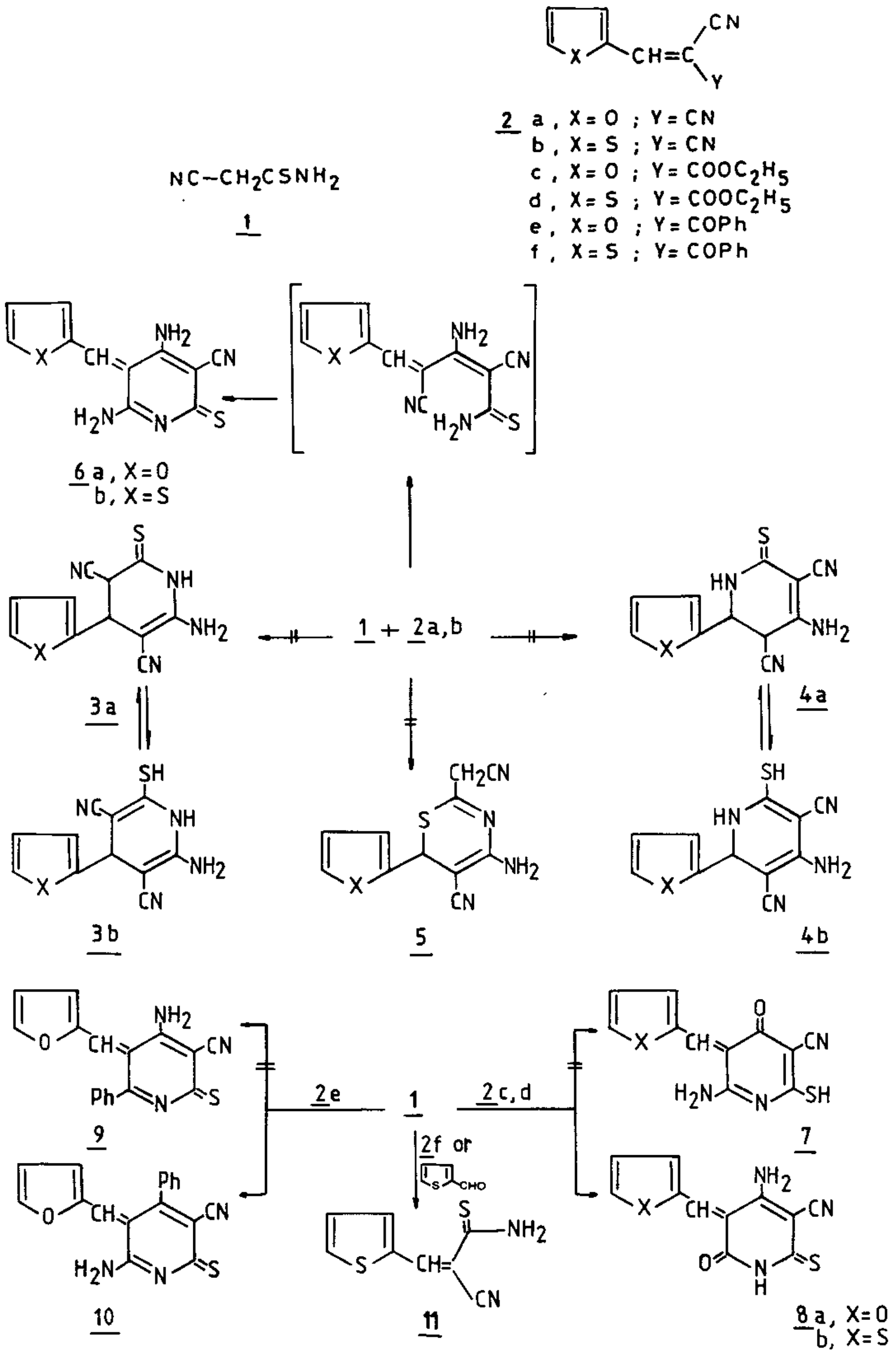

2 a, X = O ; Y = CN
b, X = S ; Y = CN
c, X = O ; Y = COOC2H5
d, X = S ; Y = COOC2H5
e, X = O ; Y = COPh
f, X = S ; Y = COPh
NC−CH2CSNH2
1
6 a, X = O
b, X = S
1 + 2a,b
3a
3b
5
4a
4b
9
10
2e
1
2c,d
2f or
11
7
8 a, X = O
b, X = S

This spectra is obviously different than expected spectra for 3a,b or 4a,b. On the same bases the thiazine structure 5 could be ruled out. In order to confirm further structure proposed for the reaction products ^{13}C nmr was inspected. ^{13}C nmr spectra revealed the absence of any sp^2 carbon and the presence of only one cyano group. Thus, structure 6 was considered for the reaction products. Compounds 6a,b are assumed to be formed via addition of 1 to the two cyano functions in 2a,b under the condition described above.

Compound 1 reacted with 2c,d under the same condition as described above to yield products of molecular formula corresponding to addition of 1 to 2c,d and ethanol elimination. Structure 7 or isomeric 8 was suggested for these products based on ^1H nmr which revealed only one down field signal for 3H which is D_2O exchangeable and thus cannot be assigned for protons linked to sp^3 carbons and a fact that excludes all other isomeric structures similar to those previously considered and excluded for the reaction product of 1 with 2a,b. Structure 8 seemed to be most likely formed as acylation of the active methylene group in 2 under reaction conditions to be highly improbable reaction.

Compound 2e reacted with 1 to yield also a 1:1 adduct. Here again ^1H nmr data were carefully inspected in order to discriminate structures similar to those proposed by Soto et al.[5,6] from the 3-ylidene structures we assigned for products of reaction of 1 and 2a-d. While ^1H nmr data clearly exclude such structures, two isomeric structures seemed, however, possible (cf. structures 9 and 10). Structure 9 was considered least likely, however, as if the product is 9 down field shift of the two ortho protons would have been expected. In contrast, 2f afforded only the thiophenylidene derivative 11 on treatment with 1 under the same reaction conditions. Compound 11 could be also directly obtained from reaction of 1 with 2-thiophencarbaldehyde. Similar ylidene group exchange has been previously reported by us in several cases and its mechanism has been discussed [7,8].

Table 1: List of compounds 6a,b; 8a,b; 10 and 11

Compound*	Solvent of cryst.	Colour	Mp (°C)	Yield (%)	Mol.formula	M^+ m/e
6a	EtOH/DMF	brown	279-81	70	$C_{11}H_8N_4OS$	244
6b	EtOH/DMF	yellow	205-06	85	$C_{11}H_8N_4S_2$	260

Compound*	Solvent of cryst.	Colour	Mp (°C)	Yield (%)	Mol.formula	M^+ m/e
8a	EtOH	yellow	254-56	80	$C_{11}H_7N_3O_2S$	245
8b	EtOH	yellow	208-10	75	$C_{11}H_7N_3OS_2$	
10	EtOH/DMF	orange	245-46	90	$C_{17}H_{11}N_3OS$	305
12	EtOH/DMF	orange	260-62	75	$C_8H_6N_2S_2$	

* Satisfactory elemental analyses for all the newly synthesised compounds were obtained.

Table 2: Spectroscopic data for compounds listed in Table 1

Compound	*IR[cm^{-1}](Selected bands)*	*^{1}H NMR δ[ppm]*
6a	3340, 3240($2NH_2$); 2220 (CN); 1620(C=N and δNH_2)	3.12(s, br, 2H, NH_2); 3.44(s, br, 2H, NH_2); 6.98(m, 1H, furan 5-H); 7.56(dd, 1H, furan 4-H); 8.15(s, 1H, furan 3-H); 8.28(s, 1H, CH)
6b*	3400($2NH_2$); 2210(CN); 1620(C=N and δNH_2)	2.72(s, br, 2H, NH_2); 2.96(s, br, 2H, NH_2); 7.34(q, 1H, thiophen 5-H); 7.77(m, 2H, thiophen 4,3-H); 8.15(s, 1H, CH)
8a	3380, 3250(NH_2 and NH); 2220(CN); 1680(CO); 1600 (δNH_2 and NH)	3.34(s, br, 3H, NH_2 and NH); 6.92(q, 1H, furan 5-H); 7.55(d, 1H, furan 4-H); 7.99(s, 1H, furan 3-H); 8.22(s, 1H, CH)
8b	3450, 3400, 3300(NH_2 and NH); 2222(CN); 1670(CO); 1600(C=N, δNH_2 and δNH)	3.01(s, br, 3H, NH_2 and NH); 7.23-7.34(m, 2H, thiophen 4,5-H); 7.88-7.98(m, 2H, thiophen 3-H and CH)
10	3400-3300, 3200(NH_2); 2200(CN); 1600-1560(δNH_2)	3.82(s, br, 2H, NH_2); 6.89 (m, 2H, furan 4,5-H); 7.44-7.88(m, 6H, furan 3-H and C_6H_5); 8.28(s, 1H, CH)
11	3500-3450(NH_2); 2220(CN); 1580(δNH_2)	2.88(d, 2H, NH_2); 7.31(q, 1H, thiophen 5-H); 7.66(dd, 1H, thiophen 4-H); 8.02(m, 2H, thiophen 3-H and CH)

* ^{13}C-nmr: 162.19 (C-2); 151.02 (C-3); 81.32 (C-4); 154.56 (C-5); 179.46 (C-6); 102.48 (C-7); 116.40 (C-8); 133.00-127.61 (aromatic carbons).

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