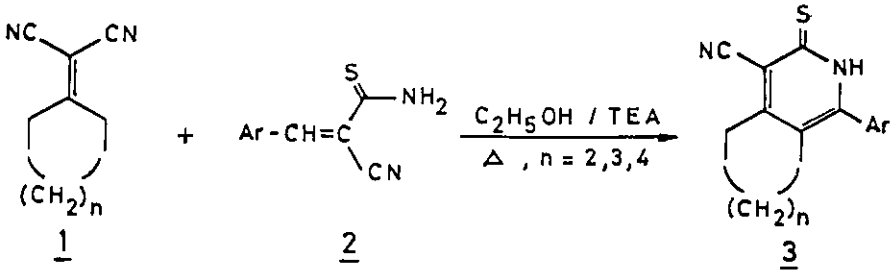
NOVEL SYNTHETIC ROUTE TO PYRIDINE-2(1H)-THIONES: UNEXPECTED PRODUCTS OF THE REACTION OF β-PHENETHYLIDENEMALONONITRILES WITH ARYLMETHYLENE-CYANOTHIOACETAMIDES

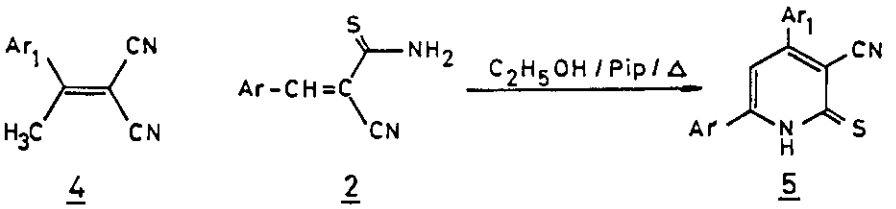
Galal Eldin Hamza Elgemeie
Chemistry Department, Faculty of Science, Bani Suef, Egypt

Abstract- A novel synthesis of 3-cyanopyridine-2(1H)-thione derivatives utilizing arylmethylenecyanothioacetamides and β-phenethylidenemalononitriles as starting components is described.

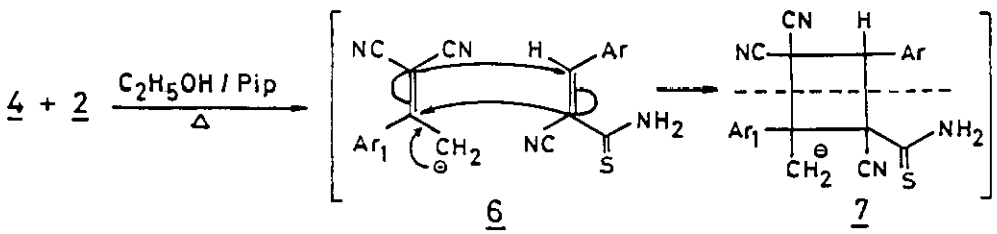
α,β-Unsaturated nitriles are versatile reagents which have been extensively utilized in heterocyclic synthesis.[1-3] Recently, we reported diverse approaches for the synthesis of pyridine-2(1H)-thiones and their condensed derivatives *via* reactions of arylmethylenecyanothioacetamides with appropriate active methylene compounds.[4,5] One of these papers have described the novel reaction of cycloalkylidenemalononitriles **1** with arylmethylenecyanothioacetamides **2** producing the condensed pyridine-2(1H)-thiones **3** of the unexpected structure.[6] We have explained the formation of **3** by a reaction sequence initiated by the exchange reaction between the cycloalkylidene group of **1** and the arylmethylene group of **2**. In order to explore the possibility that this unusual process may occur with other classes of alkylidenemalononitriles, we investigated reaction of β-phenethylidenemalononitriles **4** with arylmethylenecyanothioacetamides **2**.

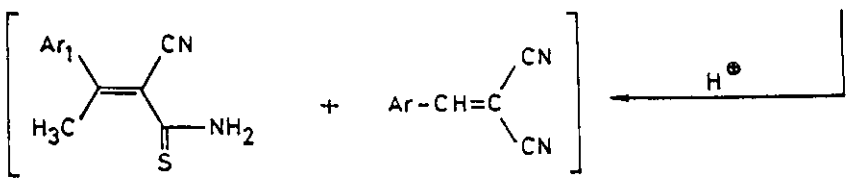
We treated β-phenethylidenemalononitriles **4** with one equivalent of arylmethylenecyanothioacetamides **2** in refluxing ethanol for 2 h and obtained the corresponding pyridine-2(1H)-thiones **5** in moderate yields (Table I). The structures of **5** were established on the basis of their elemental analyses and ms, ir and ^1H nmr spectroscopies (Table II). In accordance with the mechanism suggested for the formation of **3** from **1** and **2**,[6] the reaction may be rationalized by the following sequence. The four-membered cycloadduct **7** is initially formed from **4** and **2** *via* the transient complex **6**, and **7** consecutively collapses to arylmethylenemalononitriles **8** and β-phenethylidenecyanothioacetamides **9**. The subsequent reaction occurs between the

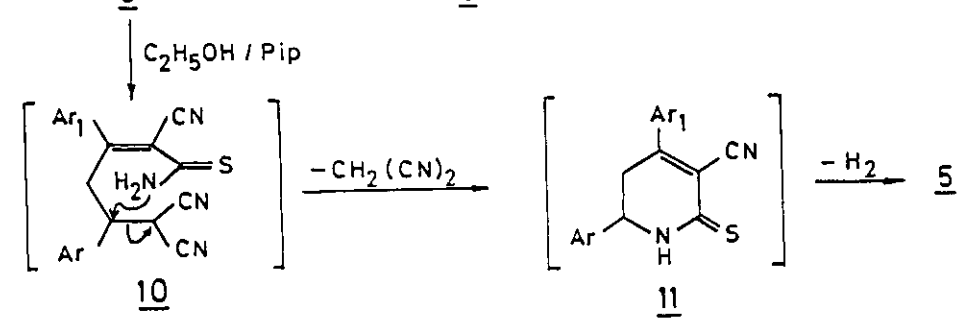




5	Ar_1	Ar
a	C_6H_5	4-Cl-C_6H_4
b	C_6H_5	4-H_3C-C_6H_4
c	C_6H_5	4-H_3CO-C_6H_4
d	C_6H_5	2-furanyl
e	C_6H_5	2-thienyl
f	4-H_3C-C_6H_4	4-Cl-C_6H_4
g	4-H_3C-C_6H_4	4-H_3C-C_6H_4
h	4-H_3C-C_6H_4	4-H_3CO-C_6H_4
i	4-H_3C-C_6H_4	2-furanyl
j	4-H_3C-C_6H_4	2-thienyl
k	4-H_3CO-C_6H_4	C_6H_5
l	4-H_3CO-C_6H_4	4-Cl-C_6H_4
m	4-H_3CO-C_6H_4	4-H_3C-C_6H_4
n	4-H_3CO-C_6H_4	4-H_3CO-C_6H_4
o	4-H_3CO-C_6H_4	2-furanyl
p	4-H_3CO-C_6H_4	2-thienyl







newly formed 8 and 9 to give the intermediate 10 via addition of the active methyl group of 9 to the activated double bond of 8. The Michael adduct 10 then cyclizes via the elimination of malononitrile to give the dihydropyridine 11 which is oxidized under the reaction conditions to yield the pyridine-2(1H)-thiones 5.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were obtained (KBr) on a Pye Unicam Spectra-1000 spectrophotometer or on a Shimadzu IR 200. ^{1}H Nmr spectra were measured on a Wilmad 270 MHz in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed as δ ppm. Mass spectra were measured on a Mass spectrometer MS 30 (AEI) at 70 ev. Analytical data were obtained from the Microanalytical Data Centre at Cairo University.

Compounds 4a-c were prepared following literature procedures.[7]

4,6-Diaryl-3-cyanopyridine-2(1H)-thiones 5a-p

To a mixture of 0.01 mol of 4 and 0.01 mol of 2 in ethanol (50 ml), piperidine (3 drops) is added. The mixture is heated under reflux for 3 h, and then allowed to stand overnight. The resulting solid is collected by filtration and crystallized from the proper solvent (cf. Table 1).

Table I: List of the Compounds 5a-p

Compound	Solvent of cryst.	mp (°C)	Yield (%)	Mol. Formula	Found / Calcd	Analysis (%)		(m/z)
					C	H	N	
5a	CH_3OH	216-218	55	$C_{18}H_{11}ClN_2S$	67.2	3.8	8.4	322
					67.0	3.4	8.7	
5b	CH_3OH	192-194	48	$C_{19}H_{14}N_2S$	75.2	4.8	8.9	302
					75.5	4.6	9.3	
5c	C_2H_5OH	224-226	55	$C_{19}H_{14}N_2OS$	71.5	4.0	8.4	318
					71.7	4.4	8.8	
5d	C_2H_5OH	210-212	50	$C_{16}H_{10}N_2OS$	68.8	4.0	9.7	
					69.1	3.6	10.1	
5e	C_2H_5OH	226-228	54	$C_{16}H_{10}N_2S_2$	64.9	3.7	9.1	
					65.3	3.4	9.5	
5f	dioxane	206-208	48	$C_{19}H_{13}ClN_2S$	67.5	3.6	8.5	
					67.8	3.9	8.5	
5g	C_2H_5OH	211	50	$C_{20}H_{16}N_2S$	75.8	4.8	8.6	316
					75.9	5.1	8.9	

Table I: Cont.

Compound	Solvent of Cryst.	mp (°C)	Yield (%)	Mol. Formula	Found / Calcd	Analysis (%)		(m/z)
					C	H	N	
5h	CH_3OH	232	40	$C_{20}H_{16}N_2OS$	71.9	5.0	8.8	332
					72.3	4.8	8.4	
5i	C_2H_5OH	196-198	40	$C_{17}H_{12}N_2OS$	70.2	4.4	9.2	
					69.9	4.1	9.6	
5j	C_2H_5OH	210-212	50	$C_{17}H_{12}N_2S_2$	66.0	3.6	8.8	308
					66.2	3.9	9.1	
5k	C_2H_5OH-DMF	220-222	60	$C_{19}H_{14}N_2OS$	71.3	4.0	8.4	318
					71.7	4.4	8.8	
5l	CH_3OH	280-282	44	$C_{19}H_{13}ClN_2OS$	64.4	3.5	8.1	352
					64.7	3.7	7.9	
5m	C_2H_5OH	234-236	46	$C_{20}H_{16}N_2OS$	72.5	5.1	8.0	
					72.5	4.8	8.4	
5n	CH_3OH-DMF	248	50	$C_{20}H_{16}N_2O_2S$	69.3	4.3	8.2	348
					69.0	4.6	8.0	
5o	CH_3OH	228-230	60	$C_{17}H_{12}N_2O_2S$	66.0	4.2	8.7	
					66.2	3.9	9.1	
5p	C_2H_5OH	234-236	64	$C_{17}H_{12}N_2OS_2$	62.9	3.5	8.3	324
					63.0	3.7	8.6	

Table II: Spectral Data for Compounds Listed in Table I

Compound	Ir (cm^{-1}) (Selected bands)	^1H Nmr (δ ppm)
5a	3320, 3200 (NH); 2225 (CN)	7.34 (s, 1H, pyridine 5-H); 7.40-8.10 (m, 9H, C_6H_5 and C_6H_4); 14.10 (br s, 1H, NH)
5b	3300, 3170 (NH); 2230 (CN)	2.5 (s, 3H, CH_3); 7.06 (s, 1H, pyridine 5-H); 7.10-8.10 (m, 9H, C_6H_5 and C_6H_4); 14.10 (br s, 1H, NH)
5c	3330, 3210 (NH); 2225 (CN)	3.92 (s, 3H, OCH_3); 7.09 (s, 1H, pyridine 5-H); 7.42-8.08 (m, 9H, C_6H_5 and C_6H_4); 14.00 (br s, 1H, NH)

Table II: Cont.

Compound	Ir (cm^{-1}) (Selected bands)	^{1}H Nmr (δ ppm)
5d	3320, 3250 (NH); 2220 (CN)	6.82 (m, 1H, furan 4-H); 7.30 (s, 1H, pyridine 5-H); 7.46-8.10 (m, 7H, C_6H_5 and furan 3,5-H); 13.90 (br s, 1H, NH)
5f	3350, 3220 (NH); 2230 (CN)	2.55 (s, 3H, CH_3); 7.08 (s, 1H, pyridine 5-H); 7.20-8.00 (m, 8H, $2C_6H_4$); 14.10 (br s, 1H, NH)
5g	3330, 3220 (NH); 2220 (CN)	2.56 (s, 3H, CH_3); 2.58 (s, 3H, CH_3); 7.10 (s, 1H, pyridine 5-H); 7.18-8.10 (m, 8H, $2C_6H_4$); 13.70 (br s, 1H, NH)
5h	3350, 3260 (NH); 2220 (CN)	2.58 (s, 3H, CH_3); 3.94 (s, 3H, OCH_3); 7.06 (s, 1H, pyridine 5-H); 7.15-8.08 (m, 8H, $2C_6H_4$); 14.00 (br s, 1H, NH)
5k	3220 (NH); 2220 (CN)	3.90 (s, 3H, OCH_3); 7.10 (s, 1H, pyridine 5-H); 7.13-8.10 (m, 9H, C_6H_5 and C_6H_4); 14.12 (br s, 1H, NH)
5l	3350 (NH); 2225 (CN)	3.85 (s, 3H, OCH_3); 7.16 (s, 1H, pyridine 5-H); 7.32-8.06 (m, 8H, $2C_6H_4$); 13.88 (br s, 1H, NH)

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