Unexpected Products of the Reaction of Cycloalkylidene(cyano)thioacetamides with Arylmethylenemalononitriles: a Different Novel Synthetic Route to Condensed Pyridine-2(1*H*)-thiones and Condensed Carbocyclic Nitriles

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A novel synthesis of condensed 3-cyanopyridine-2(1*H*)-thiones and condensed carbocyclic nitrile derivatives utilizing arylmethylene(cyano)thioacetamides and cycloalkylidenemalononitriles or arylmethylenemalononitriles and cycloalkylidene(cyano)thioacetamides as starting components is described.

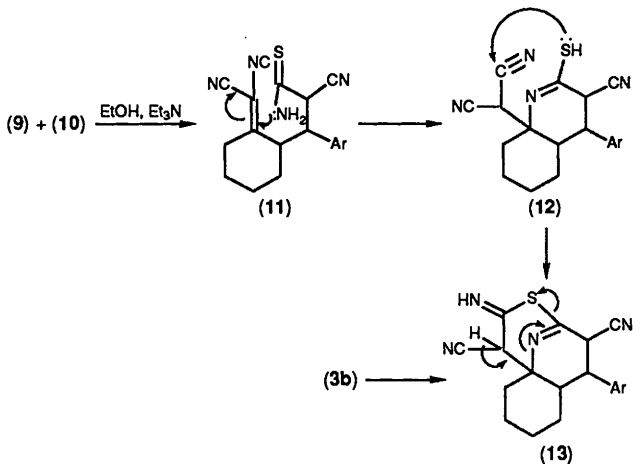
α,β-Unsaturated nitriles are potentially versatile reagents in heterocyclic synthesis.[1,2] As a part of our development of new, simple, and efficient procedures for the synthesis of fused heterocyclic compounds using a readily obtainable nitrile-containing intermediate,[3,4] we have recently reported that arylmethylene(cyano)thioacetamides can be used for the synthesis of pyridine-2(1*H*)-thiones *via* reaction with suitable active methylene reagents.[5] The present paper deals with a novel synthesis of condensed 3-cyano-pyridine-2(1*H*)-thiones and condensed carbocyclic nitrile derivatives by the reaction of arylmethylene(cyano)thioacetamides with cycloalkylidene-malononitriles, or arylmethylenemalononitriles with cycloalkylidene(cyano)thioacetamides.

Thus, it has been found that heating of cyclopentanone, cyclohexanone, or cycloheptanone with cyanothioacetamide and a catalytic amount of ammonium acetate–acetic acid in benzene for 3 h with azeotropic removal of water gave the corresponding cycloalkylidene(cyano)thioacetamides (**1**) in good yields. Compounds (**1**) react with (**2**) in refluxing ethanol containing catalytic amounts of triethylamine for 2 h to give the pyridine derivatives (**7**). The structure of compounds (**7**) was established on the basis of their elemental analysis and spectral data. Thus, structure (**7**) is supported by their mass and ^{1}H NMR spectra; the latter included a broad band near δ 13.5 assigned to the NH proton.

The formation of (**7**) from (**1**) and (**2**) is assumed to proceed *via* addition of the active methylene group of (**1**) to the double bond of (**2**) to give the intermediate (**3**). This Michael adduct then cyclizes *via* malononitrile elimination to give the intermediate dihydropyridine derivative (**5**) which is oxidized under the reaction conditions to yield (**7**).

The unexpected course of the reaction between the arylmethylenemalononitriles (**2**) and (**1**) prompted us to investigate this reaction between the cycloalkylidenemalononitriles (**9**) and the arylmethylene(cyano)thioacetamides (**10**) under the same conditions. The products (**7**) obtained were shown to be the same as those obtained from the reaction of (**1**) with (**2**) by their m.p.s and spectral data. The mechanism of the reaction of (**9**) and (**10**) is assumed to proceed through the formation of the initial adduct (**11**), which leads to the intermediate (**3**) and hence to the product (**7**) as produced by the reaction of (**1**) with (**2**).

In order to investigate the scope of this reaction further we studied the reaction of (**1**) with (**2**) under mild conditions (room temperature; 24 h). The reaction proceeded only for (**1b**). Thus, (**1b**) reacts with (**2a–c**) in ethanol containing a catalytic amount of triethylamine at room temperature to yield compounds (**6**).

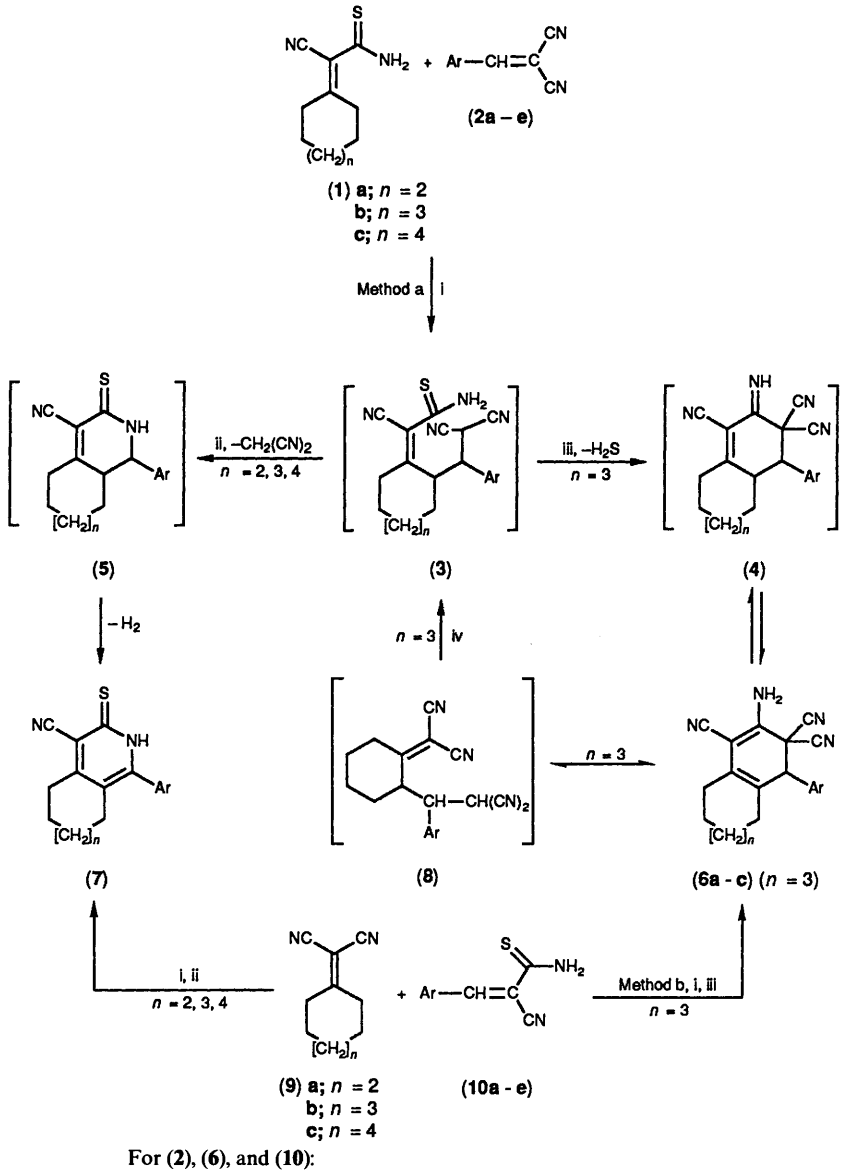


Compound (**6**) can also be prepared by the reaction of (**9b**) with (**10**) under the same conditions. The structure of (**6**) was established by mass spectroscopy and IR and ^{1}H NMR data. The IR spectra of compound (**6a**) showed two CN bands at 2 210 and 2 250 cm^{-1} and its ^{1}H NMR spectra a band at δ 6.0 (CH) and 4.83 (NH_2).

The formation of (**6**) from (**1b**) and (**2**) is assumed to proceed *via* addition of the active methylene group of (**1**) to the double bond of (**2**) to give the intermediate (**3**). This Michael adduct then cyclizes to give (**6**) *via* elimination of hydrogen sulphide. When compounds (**6**) were heated in refluxing ethanol under H_2S in the presence of catalytic amounts of triethylamine the corresponding pyridinethiones (**7**) were obtained. This can be interpreted in terms of equilibrium between (**6**) and (**4**) and also the tetracyano species (**8**). The latter would form (**7**) by addition of H_2S and loss of malononitrile, followed by cyclization and dehydrogenation.

The results indicate that cycloalkylidene(cyano)thioacetamides can add to the double bond of arylmethylenemalononitriles to give intermediate Michael adducts. However, the nature of the product depends on the nature of the cycloalkylidene ring system, and on the conditions; mild conditions give rise to products of kinetic control and severe conditions those of thermodynamic control.

We are now investigating the scope and limitation of this new reaction and its potential application for preparation of other heterocyclic compounds which are not readily accessible.



For (**2**), (**6**), and (**10**):

	Ar
a;	4-ClC_6H_4
b;	4-$MeOC_6H_4$
c;	4-MeC_6H_4
d;	2-furyl
e;	2-thienyl

	n	Ar
a;	2	4-ClC_6H_4
b;	2	4-$MeOC_6H_4$
c;	2	2-furyl
d;	2	2-thienyl
e;	3	4-ClC_6H_4
f;	3	4-$MeOC_6H_4$
g;	3	4-MeC_6H_4
h;	3	2-furyl
i;	3	2-thienyl
j;	4	4-ClC_6H_4
k;	4	4-$MeOC_6H_4$
l;	4	2-furyl
m;	4	2-thienyl

Scheme 1. *Reagents and conditions:* i, EtOH, Et_3N; ii, heat; iii, room temp.; iv, H_2S, Et_3N.

Experimental

All m.p.s points are uncorrected. IR spectra were obtained (KBr disc) on a Pye Unicam Spectra-1000 or on a Shimadzu IR 200 instrument. ^1H NMR spectra were measured on a Wilmad 270 MHz spectrometer for solutions in $(CD_3)_2SO$ using $SiMe_4$ as internal standard. Analytical data were obtained from the Microanalytical Data Centre at Cairo University.

Compounds (**2**), (**9**), and (**10**) were prepared following literature procedures.[6–8]

Cycloalkylidene(cyano)thioacetamides (**1a–c**).—To a mixture of dry benzene (200 ml), cyclopentanone, cyclohexanone, or cycloheptanone (0.01 mol), ammonium acetate (4.0 g), and glacial acetic acid (12 ml) was added cyanothioacetamide (0.01

Table 1. Characterization data for (**1a–c**), (**6a–c**), and (**7a–m**).

Compound	Recryst. solvent	M.p., *t*/°C	% Yield Method a	% Yield Method b	Mol. formula	% Found (Required) C	H	N	M^+, *m/z*
(**1a**)[a]	Benzene	108	85		$C_8H_{10}N_2S$	58.0 (57.8)	5.7 (6.1)	16.6 (16.9)	
(**1b**)[a]	EtOH	119	70		$C_9H_{12}N_2S$	60.3 (60.0)	6.4 (6.7)	15.2 (15.5)	
(**1c**)[a]	EtOH	235	60		$C_{10}H_{14}N_2S$	61.5 (61.8)	7.0 (7.3)	14.0 (14.4)	
(**6a**)[b]	Dioxane	250	66	60	$C_{19}H_{15}ClN_4$	68.0 (68.2)	4.8 (4.5)	16.3 (16.7)	334
(**6b**)[b]	Dioxane	229	76	65	$C_{20}H_{18}N_4O$	72.3 (72.7)	5.2 (5.5)	16.6 (17.0)	330
(**6c**)[b]	EtOH	278–80	55	65	$C_{20}H_{18}N_4$	76.0 (76.4)	5.5 (5.7)	17.5 (17.8)	
(**7a**)[a]	EtOH	140	55	70	$C_{15}H_{11}ClN_2S$	62.5 (62.8)	4.1 (3.8)	9.5 (9.8)	
(**7b**)[a]	EtOH–DMF[c]	248	50	55	$C_{16}H_{14}N_2SO$	67.8 (68.1)	5.2 (5.0)	9.5 (9.9)	282
(**7c**)[d]	EtOH	185	55	65	$C_{13}H_{10}N_2SO$	64.8 (64.5)	4.5 (4.1)	11.2 (11.6)	242
(**7d**)[a]	Dioxane	204	60	72	$C_{13}H_{10}N_2S_2$	60.2 (60.5)	4.2 (3.9)	10.5 (10.9)	258
(**7e**)[a]	Benzene	210	35	30	$C_{16}H_{13}ClN_2S$	63.6 (63.9)	4.5 (4.3)	9.0 (9.3)	
(**7f**)[a]	Dioxane	189	35	25	$C_{17}H_{16}N_2SO$	68.5 (68.9)	5.0 (5.4)	9.1 (9.5)	
(**7g**)[a]	EtOH	235	30	20	$C_{17}H_{16}N_2S$	72.6 (72.9)	5.5 (5.7)	9.6 (10.0)	
(**7h**)[a]	EtOH	255	65	80	$C_{14}H_{12}N_2OS$	66.0 (65.6)	5.0 (4.7)	10.5 (10.9)	256
(**7i**)[a]	MeOH–DMF	252	60	76	$C_{14}H_{12}N_2S_2$	62.0 (61.8)	4.6 (4.4)	9.9 (9.9)	
(**7j**)[e]	MeOH	140	50	66	$C_{17}H_{15}ClN_2S$	65.2 (64.9)	5.2 (4.8)	8.6 (8.9)	
(**7k**)[a]	EtOH	200	58	70	$C_{18}H_{18}N_2SO$	70.0 (69.7)	6.0 (5.8)	8.6 (9.0)	
(**7l**)[a]	MeOH	212	50	50	$C_{15}H_{14}N_2SO$	67.0 (66.7)	5.2 (5.2)	10.0 (10.4)	270
(**7m**)[a]	EtOH	220	60	74	$C_{15}H_{14}N_2S_2$	63.2 (62.9)	5.0 (4.9)	9.5 (9.8)	286

[a] Yellow. [b] Colourless. [c] DMF = dimethylformamide. [d] Brown. [e] Orange.

Table 2. IR and ^{1}H NMR data for compounds listed in Table 1.

Compound	IR, ν_{max}/cm^{-1} (selected bands)	^{1}H NMR, δ
(**1a**)	3 380, 3 300 (NH_2); 2 220 (CN)	1.82 (m, 4 H, $2CH_2$), 1.78 (m, 4 H, $2CH_2$), 9.65 (s, 2 H, NH_2)
(**1b**)	3 200–3 400 (NH_2); 2 210 (CN)	1.48–1.8 (m, 6 H, $3CH_2$), 2.28–2.60 (m, 4 H, $2CH_2$), 9.84 (s, 2 H, NH_2)
(**1c**)	3 400, 3 330 (NH_2); 2 220 (CN)	1.4–1.83 (m, 6 H, $3CH_2$), 1.9 (m, 4 H, $2CH_2$), 2.58 (m, 2 H, CH_2), 7.8 (br s, 2 H, NH_2)
(**6a**)	3 350 (NH_2); 2 210, 2 250 (CN)	1.58–3.82 (m, 8 H, $4CH_2$), 4.83 (br s, 2 H, NH_2), 6.01 (s, 1 H, CH), 7.41–7.87 (m, 4 H, C_6H_4)
(**6b**)	3 450, 3 300, 3 220 (NH_2); 2 210, 2 250 (CN)	1.22 (m, 2 H, CH_2), 1.74 (m, 2 H, CH_2), 2.23 (m, 2 H, CH_2), 3.59 (m, 2 H, CH_2), 3.9 (s, 3 H, OMe), 5.0 (br s, 2 H, NH_2, 5.8 (s, 1 H, CH), 7.1–7.7 (m, 4 H, C_6H_4)
(**6c**)	3 350 (NH_2); 2 220, 2 245 (CN)	1.3 (m, 2 H, CH_2), 1.82 (m, 2 H, CH_2), 2.23 (m, 2 H, CH_2), 2.55 (s, 3 H, CH_3), 3.5 (m, 2 H, CH_2), 5.1 (br s, 2 H, NH_2), 5.9 (s, 1 H, CH), 7.2–7.8 (m, 4 H, C_6H_4)
(**7a**)	3 450, 3 330 (NH); 2 220 (CN)	2.18 (m, 2 H, CH_2), 2.42 (m, 2 H, CH_2), 3.0 (m, 2 H, CH_2), 7.1–7.55 (m, 4 H, C_6H_4), 14.0 (br s, 1 H, NH)
(**7b**)	3 450, 3 350, 3 250 (NH); 2 210 (CN)	2.2 (m, 2 H, CH_2), 2.6 (m, 2 H, CH_2), 2.98 (m, 2 H, CH_2), 3.84 (s, 3 H, OMe), 7.0–7.5 (m, 4 H, C_6H_4), 14.2 (br s, 1 H, NH)
(**7c**)	3 300 (NH); 2 220 (CN)	1.92 (m, 2 H, CH_2), 2.7–3.1 (m, 4 H, 2 CH_2), 6.77 (m, 1 H, furan 4-H), 7.3 (d, 1 H, furan 3-H), 7.98 (d, 1 H, furan 5-H), 14.23 (br s, 1 H, NH)
(**7d**)	3 320, 3 250 (NH); 2 220 (CN)	2.18 (m, 2 H, CH_2), 2.8–3.2 (m, 4 H, $2CH_2$), 7.28 (m, 1 H, thiophen 4-H), 7.62 (d, 1 H, thiophen 3-H), 7.88 (d, 1 H, thiophen 5-H), 14.34 (br s, 1 H, NH)
(**7e**)	3 350 (NH); 2 220 (CN)	1.6 (m, 4 H, $2CH_2$), 2.60 (m, 2 H, CH_2), 2.9 (m, 2 H, CH_2), 6.9–7.5 (m, 4 H, C_6H_4), 13.9 (br s, 1 H, NH)
(**7f**)	3 400 (NH); 2 220 (CN)	1.65 (m, 4 H, $2CH_2$), 2.6 (m, 2 H, CH_2), 2.95 (m, 2 H, CH_2), 3.95 (s, 3 H, OMe), 6.95–7.6 (m, 4 H, C_6H_4), 13.9 (br s, 1 H, NH)
(**7g**)	3 450 (NH); 2 215 (CN)	1.60 (m, 4 H, $2CH_2$), 2.49 (m, 2 H, CH_2), 2.6 (s, 3 H, Me), 3.0 (m, 2 H, CH_2), 7.0–7.7 (m, 4 H, C_6H_4), 14.0 (br s, 1 H, NH)
(**7h**)	3 350 (NH); 2 225 (CN)	1.72 (m, 4 H, $2CH_2$), 2.55 (m, 2 H, CH_2), 2.8 (m, 2 H, CH_2), 6.75 (m, 1 H, furan 4-H), 7.1 (d, 1 H, furan 3-H), 7.99 (d, 1 H, furan 5-H), 13.94 (br s, 1 H, NH)
(**7i**)	3 300 (NH); 2 220 (CN)	1.54 (m, 4 H, $2CH_2$), 2.57 (m, 2 H, CH_2), 2.98 (m, 2 H, CH_2), 6.68 (m, 1 H, thiophen 4-H), 7.2 (m, 1 H, thiophen 3-H), 7.77 (d, 1 H, thiophen 5-H), 13.86 (br s, 1 H, NH)
(**7j**)	3 400 (NH); 2 220 (CN)	1.1–1.68 (m, 6 H, $3CH_2$), 2.1–2.4 (m, 2 H, CH_2), 3.0 (m, 2 H, CH_2), 7.1–7.4 (m, 4 H, C_6H_4), 14.1 (br s, 1 H, NH)
(**7k**)	3 350 (NH); 2 215 (CN)	1.12–1.8 (m, 6 H, $3CH_2$), 2.12–2.48 (m, 2 H, CH_2), 2.9 (m, 2 H, CH_2), 3.68 (s, 3 H, OMe), 6.9–7.16 (m, 4 H, C_6H_4), 13.82 (br s, 1 H, NH)
(**7l**)	3 450 (NH); 2 220 (CN)	1.28–1.90 (m, 6 H, $3CH_2$), 2.4 (m, 2 H, CH_2), 2.96 (m, 2 H, CH_2), 7.08 (m, 1 H, furan 4-H), 7.60 (m, 1 H, furan 3-H), 7.82 (m, 1 H, furan 5-H), 13.8 (br s, 1 H, NH).
(**7m**)	3 380 (NH); 2 210 (CN)	1.3–1.97 (m, 6 H, $3CH_2$), 2.44 (m, 2 H, CH_2), 3.0 (m, 2 H, CH_2), 7.12 (m, 2 H, thiophen 3,4-H), 7.75 (m, 1 H, thiophen 5-H), 13.85 (br s, 1 H, NH)

mol). The mixture was heated under reflux for 4 h in a Dean–Stark apparatus. Evaporation of most of benzene left a residue which was crystallized from the appropriate solvent.

3-Amino-5-bicyclo[4.4.0]*deca-*1,2(6)*-diene-*2,4,4*-carbonitriles* (**6a–c**).—A mixture of (**1b**) (0.01 mol) and (**2a–e**) (0.01 mol) or (**9b**) (0.01 mol) and (**10a–e**) (0.01 mol) in dry ethanol (30 ml)

containing a catalytic amount of triethylamine (1 ml) was stirred at room temperature for 24 h and then diluted with cold water. The resulting solid product was collected by filtration and crystallized from the appropriate solvent.

Cycloalkane Ring-fused 6-*Aryl*-3-*cyanopyridine*-2-(1H)-*thiones* (**7a–m**).—To a mixture of (**1a–c**) and (**2a–e**) or (**9a–c**) and (**10a–e**) (0.01 mol) in ethanol (50 ml), triethylamine (1 ml) was added. The mixture was heated under reflux for 2 h, and then set aside overnight. The resultant precipitate was filtered off and crystallized from the appropriate solvent.

For preparation of compounds (**7e–g**), to a suspension of (**6a–c**) (0.01 mol) in ethanol (50 ml), triethylamine was added. The mixture was heated under reflux under a dry stream of H_2S for 1 h, and then set aside overnight. The resultant precipitate was filtered off and crystallized from the appropriate solvent.

Acknowledgements

G. E. H. E. thanks Professor M. Hudlicky, Virginia Polytechnic Institute and State University, for the NMR and mass spectra, and IOCD for supporting this collaborative activity.

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Paper 9/02913C
Received 10*th July* 1989
Accepted 17*th October* 1989