THE REACTION OF THIOGLYCOLIC ACID WITH α,β-UNSATURATED NITRILES: A NEW ROUTE FOR THE SYNTHESIS OF THIAZOLO-[3,2-*a*]PYRIDINES

Mohamed Hilmy ELNAGDI[a], Mohamed Rifat Hamza ELMOGHAYAR[a], Ahmed Hafez Hussein ELGHANDOUR[a] and Kamal Usef SADEK[b]

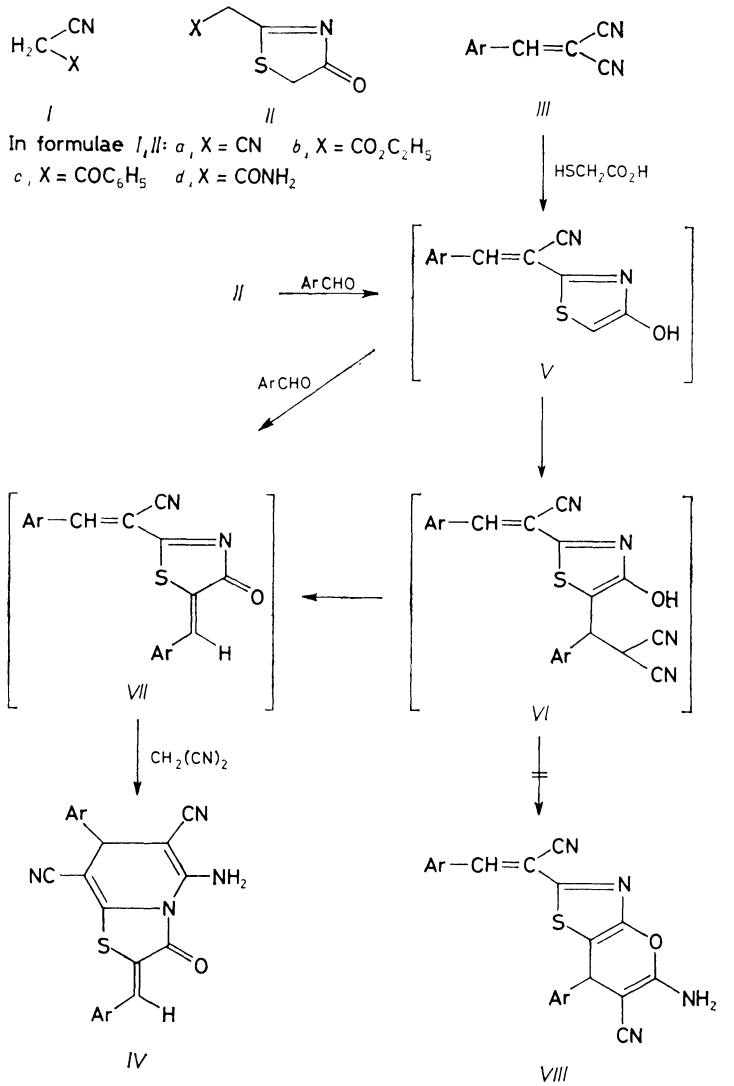
[a] *Chemistry Department, Cairo University, Giza, A.R. Egypt and*
[b] *Chemistry Department, Minia University, Minia, A.R. Egypt*

Received December 5, 1988
Accepted June 13, 1989

The reaction of cinnamonitriles with thioglycolic acid in the presence of a basic catalyst affords thiazolo[3,2-*a*]pyridine derivatives.

In the last decade we have been involved in the programme directed to the utilization of the synthetic potentialities of polyfunctionally substituted nitriles[1-3]. During this research we have reported a route for the synthesis of thiazol-4-ones[4-6] and thiazolo[3,2-*a*]pyridines[7-9] by reaction of thioglycolic acid with polyfunctional nitriles *Ia–Id* and a subsequent reaction of the thiazoles *IIa–IId* so formed with cinnamonitriles *III* to yield thiazolo[3,2-*a*]pyridines *IV*. The same synthetic approach was also reported simultaneously by another group[10]. In conjunction with this work we report here a direct one-step synthesis of *IV* by the reaction of cinnamonitriles with thioglycolic acid. Only limited synthetic approaches for thiazolo[3,2-*a*]pyridines have been presented so far[7-9]. Thus, it has been found that *IIIa–IIIf* react with thioglycolic acid to yield crystalline products in very good yields. These products were identified as *IVa–IVf*. The formation of *IVa–IVf* by the reaction of *IIIa–IIIf* and thioglycolic acid is assumed to proceed via intermediates *Va–Vf* formed by the addition of thioglycolic acid to one of the cyano functions in *IIIa–IIIf*. Compounds *Va–Vf* so formed reacted with an additional molecule of *III* to yield intermediate Michael adducts *VI*. These compounds then released malononitrile to yield *VII* which reacted with the eliminated malononitrile to yield the final thiazolo[3,2-*a*]-pyridines *IVa–IVf*. The possibility that the reaction products are pyranothiazoles *VIII* resulting from cyclization of *VI* was eliminated by means of IR spectra which revealed in each case a band at 1 700–1 730 cm^{-1} corresponding to the ring carbonyl group. This band is not expected in the IR of *VIII*.

In order to provide evidence for the proposed reaction route, the arylidenes *Va – Vf* were prepared utilizing our previously reported procedure[4] for the synthesis



of *Va*, and were converted into *VIIa – VIIf*. The treatment of *VIIa – VIIf* with malononitrile afforded *IVa – IVf*.

TABLE I

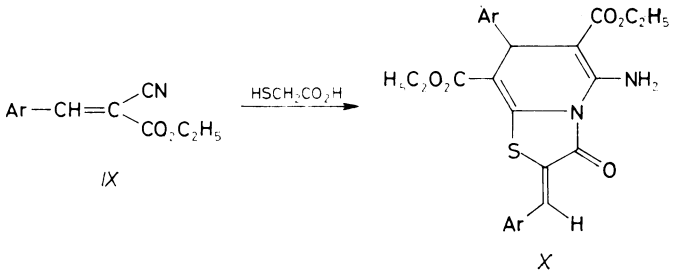
Compound	M.p., °C (Yield, %)	Formula (M.w.)	Calculated/Found			
			% C	% H	% N	% S
IVa	249–250[a,e]	$C_{22}H_{14}N_4OS$	69·1	3·7	14·7	8·4
	(88)	(382·5)	69·1	3·5	14·6	8·3
IVb	233–235[b,f]	$C_{24}H_{18}N_4O_3S$	65·1	4·1	12·7	7·2
	(85)	(442·5)	65·0	4·1	12·6	7·3
IVc	197–198[c,g]	$C_{22}H_{12}Cl_2N_4OS$	58·5	2·7	12·4	7·1
	(87)	(451·4)	58·6	2·5	12·3	7·1
IVd	266–268[d]	$C_{22}H_{12}Cl_2N_4OS$	58·5	2·7	12·4	7·1
	(82)	(451·4)	58·3	2·6	12·6	7·0
IVe	230–232[d]	$C_{18}H_{10}N_4O_3S$	59·7	2·8	15·5	8·8
	(86)	(362·4)	59·7	2·6	15·7	8·9
IVf	214–216[a]	$C_{18}H_{10}N_4OS_3$	54·8	2·6	14·2	24·4
	(83)	(394·5)	54·9	2·5	14·2	24·5
Va	198–200[c]	$C_{12}H_8N_2OS$	63·1	3·5	12·3	14·0
	(82)	(228·3)	63·3	3·4	12·0	14·0
Vb	265–266[c]	$C_{13}H_{10}N_2O_2S$	60·4	3·9	10·8	12·4
	(83)	(258·3)	60·4	3·8	11·0	12·6
Vc	169–170[c]	$C_{12}H_7ClN_2OS$	54·9	2·7	10·7	12·2
	(77)	(262·7)	55·0	2·8	10·8	12·2
Vd	206–207[d]	$C_{12}H_7ClN_2OS$	54·9	2·7	10·7	12·2
	(79)	(262·7)	55·1	2·9	10·5	12·0
Ve	224–226[d]	$C_{10}H_6N_2O_2S$	55·0	2·8	12·8	14·7
	(80)	(218·2)	55·3	2·8	13·0	14·9
Vf	245–246[d]	$C_{10}H_6N_2OS_2$	51·3	2·6	12·0	27·4
	(78)	(234·3)	51·3	2·5	12·3	27·4
VIIa	261–263[d]	$C_{19}H_{12}N_2OS$	72·1	3·8	8·9	10·1
	(79)	(316·4)	72·0	3·7	9·1	10·3
VIIb	248–249[d]	$C_{21}H_{16}N_2O_3S$	67·0	4·3	7·4	8·5
	(80)	(376·4)	67·3	4·2	7·5	8·4
VIIc	268–270[d]	$C_{19}H_{10}Cl_2N_2OS$	59·2	2·6	7·3	8·3
	(80)	(385·3)	59·2	2·7	7·0	8·4
VIId	239–240[d]	$C_{19}H_{10}Cl_2N_2OS$	59·2	2·6	7·3	8·3
	(80)	(385·3)	59·5	2·4	7·0	8·3
VIIe	257–258[d]	$C_{15}H_8N_2O_3S$	60·8	2·7	9·5	10·8
	(79)	(385·3)	60·7	2·7	9·3	10·8

TABLE I
(Continued)

Compound	M.p., °C (Yield, %)	Formula (M.w.)	Calculated/Found			
			% C	% H	% N	% S
VIIf	282–283[d] (82)	$C_{15}H_8N_2OS_3$ (328·4)	54·9 55·2	2·5 2·4	8·5 8·7	29·3 29·5
Xa	212–213[d] (85)	$C_{26}H_{24}N_2O_5S$ (476·6)	65·5 65·6	5·1 5·0	5·9 5·7	6·7 6·9
Xb	217–218[c] (87)	$C_{28}H_{28}N_2O_7S$ (536·6)	62·7 62·9	5·3 5·0	5·2 5·2	6·0 5·9
Xc	230–231[c] (88)	$C_{26}H_{22}Cl_2N_2O_5S$ (545·5)	57·3 57·5	4·1 4·0	5·1 5·0	5·9 5·8

Crystallized from: [a] DMF/ethanol; [b] DMF; [c] ethanol; [d] dioxane; [e] ref.[7] m.p. 250°C; [f] ref.[8] m.p. 235°C; [g] ref.[8] m.p. 198°C.

Similar to the behavior of *IIIa–IIIf* towards thioglycolic acid, refluxing ethylylidenecyanoacetate *IXa–IXc* and thioglycolic acid in pyridine afforded thiazolo[3,2-*a*]pyridines *Xa–Xc*. These compounds were also obtained from the reaction of *IIb* with *IXa–IXc*.



In formulae *IX*, *X*: *a*, Ar = C_6H_5 *b*, Ar = *p*-$CH_3OC_6H_4$ *c*, Ar = *p*-ClC_6H_4

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr disc) on a Shimadzu 408 spectrometer. ^{1}H NMR spectra were measured in $(CD_3)_2SO$ on an EM-390 at 90 MHz using tetramethylsilane as internal standard. Microanalytical data (C, H, N) were obtained from the Microanalytical Data Unit at Cairo University.

Reaction of *IIIa–IIIf* and *IXa–IXc* with Thioglycolic Acid

General procedure: A solution of *IIIa–IIIf* or *IXa–IXc* (0·02 mol) and thioglycolic acid (0·01 mol) in pyridine (50 ml) was heated under reflux for three hours. The solvent was then

TABLE II

Selected IR and complete ^{1}H NMR spectra for compounds listed in Table I

Compound	$\tilde{\nu}_{max}$, cm^{-1}	δ, ppm
IVa	3 420; 3 320; 3 230 (NH_2); 2 980; 2 940 (CH); 2 200 (CN); 1 730 (CO); 1 660 (NH_2)	4·5 s, 1 H (pyridine H); 6·73 br s, 2 H (NH_2); 7·3—7·6 m, 10 H (2 × C_6H_5) 7·93 s, 1 H (ylidene CH)
IVb	3 460—3 350 (NH_2); 2 980; 2 950 (CH and CH_3); 2 200 (CN); 1 720 (CO); 1 660 (NH_2)	3·8, 3·9 two singlets, 6 H (2 × OCH_3); 4·8 s, 1 H (pyridine H); 6·8—8·3 m, 11 H (aromatic, arylidene and NH_2 protons)
IVc	3 480—3 350 (NH_2); 2 220 (CN); 1 720 (CO); 1 660 (NH_2)	
IVd	3 460—3 340 (NH_2); 2 220 (CN); 1 730 (CO); 1 660 (NH_2); 1 620 (C=C)	4·8 s, 1 H (pyridine H); 7·2—7·8 m, 9 H (aromatic and arylidene protons); 8·2 br s, 2 H (NH_2)
IVe	3 400; 3 300; 3 220 (NH_2); 2 210 (CN); 1 720 (CO); 1 620 (NH_2)	
IVf	3 400; 3 280; 3 200 (NH_2); 2 200 (CN); 1 700 (CO); 1 600 (NH_2)	5·0 s, 1 H (pyridine H); 7·0—7·3 m, 2 H (thiophene 5,5′-H); 7·5—7·7 s, 2 H (thiophene 4,4′-H); 7·8—8·0 d, 2 H (thiophene 3,3′-H); 8·0—8·1 d, 1 H (arylidene CH); 8·3 s, 2 H (NH_2)
Va	1 730 (CO); 2 220 (CN)	6·0 s, 1 H (thiazol H-5); 7·3—7·8 m, 6 H (aromatic and arylidene protons); 11·3 s, 1 H (OH)
Vb	1 720 (CO); 2 220 (CN); 1 620 (C=C)	5·7 s, 1 H (thiazol H-5); 7·0—7·8 m, 5 H (aromatic and arylidene protons); 11·2 s, 1 H (OH)
Vc	1 720 (CO); 2 220 (CN); 1 630 (C=C)	
Vd	1 730 (CO); 2 220 (CN); 1 620 (C=C)	
Ve	1 720 (CO); 2 210 (CN); 1 620 (C=C)	5·8 s, 1 H (thiazol H-5); 7·8—8·0 m, 4 H (aromatic and arylidene protons); 11·3 s, 1 H
Vf	1 710 (CO); 2 220 (CN); 1 630 (C=C)	
VIIa	1 720 (CO); 2 220 (CN)	7·0—7·9 m, 11 H (aromatic and arylidene protons); 8·3 s, 1 H (arylidene CH)
VIIb	1 710 (CO); 2 210 (CN)	3·8, 4·0 two singlets (2 × OCH_3); 6·9—7·8 m, 9 H (aromatic and arylidene protons); 8·2 s, 1 H (arylidene CH)

TABLE II
(*Continued*)

Compound	$\tilde{\nu}_{max}$, cm^{-1}	δ, ppm
VIIc	1 710 (CO); 2 220 (CN)	
VIId	1 700 (CO); 2 220 (CN)	
VIIe	1 700 (CO); 2 220 (CN)	6·9—7·8 m, 7 H (aromatic and arylidene protons); 8·3 s, 1 H (arylidene CH)
VIIf	1 700 (CO); 2 220 (CN)	
Xa	3 440; 3 300 (NH_2); 3 000; 2 960; 2 940 (CH and CH_3); 1 730; 1 700 (CO bands); 1 670 (CO); 1 630 (C=C)	1·16 2 t, 6 H (2 × CH_3); 4·16 2 q, 4 H (2 × CH_2); 5·0 s, 1 H (pyridine H); 6·33 br s, 2 H (NH_2); 7·3—7·9 m, 11 H (aromatic and arylidene protons)
Xb	3 420; 3 380 (NH_2); 3 000—2 960 (CH, CH_2 and CH_3); 1 700—1 690 (ring CO); 1 720 (ester CO); 1 660 (NH_2); 1 615 (C=C)	1·2 m, 6 H (2 × CH_3); 2·98 s, 6 H (2 × OCH_3); 3·5 br 2 H (NH_2); 4·0 m, 4 H (2 × CH_2); 4·66 s, 1 H (pyridine H); 6·7—7·7 m, 8 H (aromatic protons); 8·25 s, 1 H (arylidene proton)
Xc	3 480; 3 380 (NH_2); 3 000—2 960 (CH, CH_2 and CH_3); 1 730—1 710 (ester CO); 1 690 (ring CO); 1 670 (NH_2); 1 630 (C=C)	1·25 m, 6 H (2 × CH_3); 3·9 br, 2 H (NH_2); 4·3 m, 4 H (2 × CH_2); 4·8 s, 1 H (pyridine H); 7·2—7·6 m, 8 H (aromatic protons); 8·25 s, 1 H (arylidene CH)

evaporated under reduced pressure. The remnant was triturated with water and the resulting solid was collected by filtration and crystallized from the appropriate solvent (see Tables I, II). Compounds *Xa*—*Xc* were also prepared by the reaction of *IXa*—*IXc* with *IIb*, following our previously reported procedure[8].

Synthesis of Compounds *VIIa*—*VIIf*

Ceneral procedure: Equimolecular amounts (0·01 mol) of *Va*—*Vf* and the appropriate aromatic aldehyde were heated under reflux in methanolic methoxide (50 ml containing 0·3 g dissolved sodium metal) for three hours. The solvent was then evaporated under reduced pressure. The remnant was triturated with water and neutralized with HCl. The solid product so formed was collected by filtration and crystallized from the appropriate solvent (see Tables I, II).

Reaction of *VIIa*—*VIIf* with Malononitrile

General procedure: A solution of *VIIa*—*VIIf* (0·01 mol) and malononitrile (0·01 mol) in pyridine (30 ml) was heated under reflux for two hours. The solvent was then evaporated under reduced pressure. The remnant was triturated with water and the resulting solid was collected by filtration and crystallized from the appropriate solvent (see Table I, II).

REFERENCES

1. Elnagdi M. H., Sherif S. M., Mohareb R. M.: Heterocycles *26*, 497 (1987).
2. Galil F. M. A., Elnagdi M. H.: Justus Liebigs Ann. Chem. *1987*, 477.
3. Elnagdi M. H., Abdel-Motaleb R. M., Mustafa M., Zayed M. F., Kamel E. M.: J. Heterocycl. Chem. *24*, 1677 (1987).
4. Elnagdi M. H., Elmoghayar M. R. H., Hammam A. H., Khalaf S. A.: J. Heterocycl. Chem. *16*, 1541 (1979).
5. Elnagdi M. H., Khalifa M. A., Ibraheim M. K. A., Elmoghayar M. R. H.: J. Heterocycl. Chem. *18*, 877 (1981).
6. Sadek K. U., Mourad A. E., Hafeez A. E., Elnagdi M. H.: Synthesis *1983*, 739.
7. Elmoghayar M. R. H., Ibraheim M. K. A., Elghandour A. H., Elnagdi M. H.: Synthesis *1981*, 635.
8. Sadek K. U., Hafez E. A. A., Mourad A. E., Elnagdi M. H.: Z. Naturforsch. *39B*, 824 (1984).
9. Osman S. A. M., Elgemeie G. E. H., Nawar G. A. M., Elnagdi M. H.: Monatsh. Chem. *117*, 105 (1986).
10. Kambe S., Saito K., Sakurai A., Midorikawa H.: Synthesis *1981*, 531.

Translation revised by H. P. Mašková.