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SYNTHESIS OF HETEROCYCLES ON THE BASIS OF ANION ARYLATIED PRODUCTS OF UNSATURATED-COMPOUNDS.

PART 4*. CYCLOCONDENSATION OF 3-ARYL-2-HALO(THIOCYANATE)PROPIONITRILES

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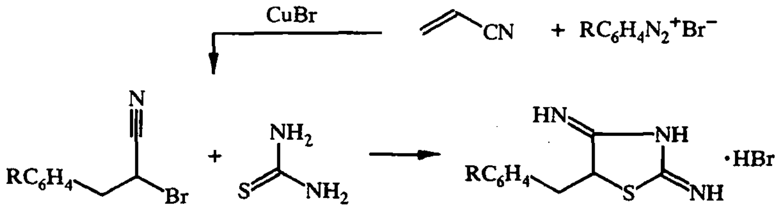
Products from the anionic arylation of acrylonitrile show ring closure on interaction with S,N-nucleophiles. The reactions of 3-aryl-2-halopropionitriles with thiourea and ammonium N-phenyldithiocarbamate give respectively 2,4-diimino-5-arylmethylthiazolidines and 4-amino-5-arylmethyl-3-phenyl-4-thiazolin-2-thiones. Hydrogen bromide reacts with 3-aryl-2-thiocyanatopropionitriles to give 4-amino-5-arylmethyl-2-bromothiazoles.

Products from the haloarylation of acrolein and acrylate esters are convenient reagents for preparation of thiazole and 4-thiazolidone derivatives [1, 2]. Here we apply a previously developed approach to methods of synthesizing heterocyclic compounds on the basis of α-functionalized nitriles made by the reaction of arene diazonium salts with acrylonitrile under conditions of copper catalysis [3]. Nitriles containing functional groups in the α position are used to make five-membered and six-membered heterocyclics, but the range of such reagents is fairly restricted [4, 5].

We have found that the bromoarylation products from the acrylonitriles Ia-c react with thiourea to give the hydrobromides of 2,4-diimino-5-arylmethylthiazolidines IIa-c (Table 1).



Ia–c

IIa–c

a R = H, b 2-Me, c 4-MeO

Iodine-substituted analogs of the nitriles Ia-c – $RC_6H_4CH_2CH(I)CN$ made by iodoarylation of acrylonitrile [6] react similarly with thiourea.

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* See [1] for Part 3.

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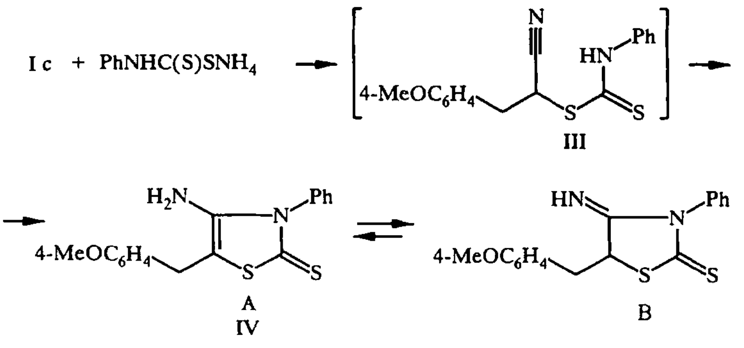
TABLE 1. Characteristics of 2,4-diimino-5-arylmethylthiazolidine Hydrobromides

Compound	Empirical formula	Found, % Calculated, % C	H	N	mp,°C
IIa	$C_{10}H_{12}BrN_3S$	41,80 44,96	4,11 4,23	14,81 14,68	246...248
IIb	$C_{11}H_{14}BrN_3S$	44,19 44,01	4,57 4,70	13,82 14,00	285...287
IIc	$C_{11}H_{14}BrN_3OS$	41,51 41,78	4,42 4,46	13,13 13,29	226...228

Compound	PMR spectrum, δ, ppm						Yield, %
	CH_2		CH (1H, dd)	$R^1C_6H_4$	NH	N^+H_2 (2H, s)	
	1H, dd	1H, dd					
IIa	3,15	3,68	5,46	7,31 (5H, m)	10,02 (1H, s); 10,08 (1H, s)	10,23	71
IIb	3,08	3,70	5,50	2,34 (3H, s, CH_3); 7,19 (4H, m)	10,01 (1H, s); 10,08 (1H, s)	10,27	60
IIc	3,09	3,58	5,41	3,74 (3H, s, CH_3O); 6,91 (2H, d); 7,20 (2H, d)	9,96 (1H, s); 10,06 (1H, s)	10,20	75

The conclusion that compounds IIa-c are in the imino form was drawn from the PMR spectra recorded in DMSO-D_6. Other likely tautomeric structures of thiazolidines IIa-c would not contain the CH_2CH fragment or would not correspond to the observed shifts and integral intensities of the NH group signals in the PMR spectra (compounds of that type have been described as 2,4-diaminothiazoles [4, 7, 8]).

The nitriles I react smoothly also with ammonium N-phenyldithiocarbamate; under the conditions used, the reaction does not stop at the stage of nucleophilic replacement of bromine by the dithiocarbamate group, but instead there is an intramolecular ring closure in the intermediate compound III:

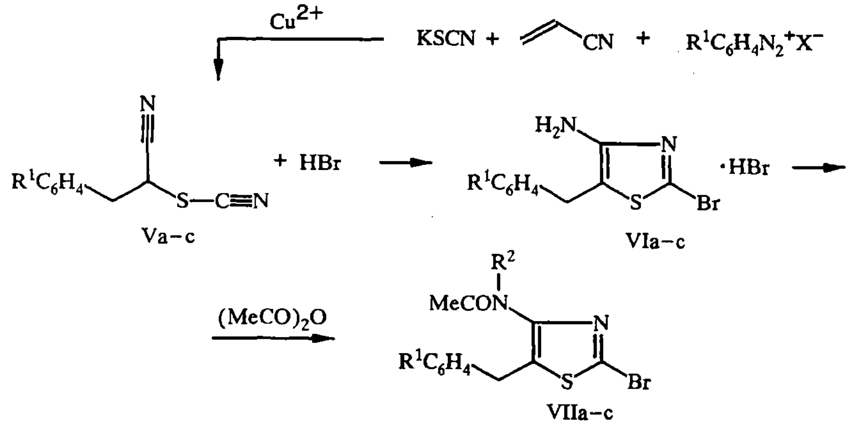


Amino-imine tautomerism is possible for compound IV as well as for imines IIa-c. Compounds of that type have been ascribed an imino form [9] or an amino form [10]. PMR spectroscopy (in DMSO-d_6) indicates that the thiazoline IV exists in the amino form.

Another type of α-substituted nitrile has been made by reacting acrylonitrile with arene diazonium tetrafluoroborates or sulfates and potassium thiocyanate. We have found that the α-thiocyanatonitriles Va-c combine with hydrogen bromide and show ring closure with the formation of the hydrobromides of the 4-amino-5-arylmethyl-2-bromothiazoles VIa-c [11]. We have isolated the aminothiazoles VIa-c as the monoacetyl or diacetyl derivatives VIIa-c.

Derivatives of 4-aminothiazole are comparatively inaccessible [12], but the proposed method gives such compounds readily, and they can be used for synthesis of complicated heterocyclic systems.

One can thus use acrylonitrile anionic arylation products for synthesizing thiazole derivatives that are impossible or difficult to synthesize by other methods.


a R^1 = 4-Me, R^2 = H; b R^1 = 2-Cl, R^2 = MeCO; c R^1 = 4-Cl, R^2 = MeCO; X = BF_4, HSO_4

EXPERIMENTAL

The PMR spectra were recorded with a Varian VXR-300 (300 MHz) in DMSO-d_6, internal standard HMDS.

The nitriles Ia-c and Va-c were obtained by methods similar to those described in [13, 14]; 3-(2-methylphenyl)-2-bromopropionitrile Ib was made with a yield of 23%, boiling point 140°C (3 mm), n_D^{20} 1.5625; 3-(4-methoxyphenyl)-2-bromopropionitrile Ic was made with a yield of 47%, bp 147-149°C (3 mm), mp 33°C (alcohol); 3-(2-chlorophenyl)-2-thiocyanatopropionitrile Vb was made with a yield of 60%, mp 67°C (CCl_4). The constants of compounds Ia, Va, and c coincide with published ones [13, 14].

5-Benzyl-2,4-diiminothiazolidine hydrobromide (IIa). To a solution of 0.76 g (10 mmole) of thiourea in 50 ml of alcohol we added 2.1 g (10 mmole) of 3-phenyl-2-bromopropionitrile Ia. The mixture was refluxed for 1 h, and the resulting precipitate was filtered off and recrystallized from alcohol. Compounds IIb, c were prepared similarly.

4-amino-5-(4-methoxyphenylmethyl)-3-phenyl-4-thiazolin-2-thione (IV). To a solution of 0.93 g (5 mmole) of ammonium N-phenyldithiocarbamate in 2 ml of DMF we added 1.2 g (5 mmole) of nitrile Ic, with stirring for 20 min at room temperature. On the addition of 50 ml of water, a precipitate of compound IV was formed, yield 94%, mp 93°C. PMR spectrum: 3.74 (3H, s, CH_3O); 3.83 (2H, s, CH_2); 4.94 (2H, s, NH_2); 6.91 (2H, d, C_6H_4); 7.18 (2H, d, C_6H_4); 7.29 (2H, m, C_6H_5); 7.54 ppm (3H, m, C_6H_5). Found, %: C 62.03; H 5.01. $C_{17}H_{15}N_2OS_2$. Calculated, %: C 62.16; H 4.91.

4-diacetylamino-2-bromo-5-(2-chlorophenylmethyl)thiazole (VIIb). To a solution of 1 g of nitrile Vb in 30 ml of anhydrous benzene we supplied HBr for 1 h; the precipitate was filtered off, 6 ml of acetic anhydride was added to it and boiled for 40 min. After cooling, the reaction mixture was poured into a 20% solution of CH_3COONa, and the resulting precipitate was filtered off and crystallized from ethyl acetate. Yield of thiazole VIIb 58%, mp 66-68°C. PMR spectrum: 2.17 (6H, s, $2COCH_3$); 4.11 (2H, s, CH_2); 7.34 (3H, m, C_6H_5); 7.47 ppm (1H, m, C_6H_5). Found, %: C 43.52; H 3.07; N 7.10. $C_{14}H_{12}BrClN_2O_2S$. Calculated, %: C 43.37; H 3.12; N 7.23.

The constants of compounds VIIa, c have been given in [11].

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