Synthesis of 2-amino-5-aryl-1,3,4-thiadiazoles and their condensed analogs with the use of aromatic nitriles

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Aromatic nitriles are found to readily react with thiosemicarbazide and 4-amino-3-methyl-1,2,4-triazol-5-thione in a solution of polyphosphoric acid to give corresponding 2-amino-5-aryl-1,3,4-thiadiazoles.

Key words: aromatic nitriles, polyphosphoric acid, thiosemicarbazide, ethyl acetoacetate, 4-amino-3-methyl-1,2,4-triazol-5-thione, cyclodehydratation, 2-amino-5-aryl-1,3,4-thiadiazoles, 2-aryl-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-a]pyrimidines, 2-aryl-5-methyl-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazoles.

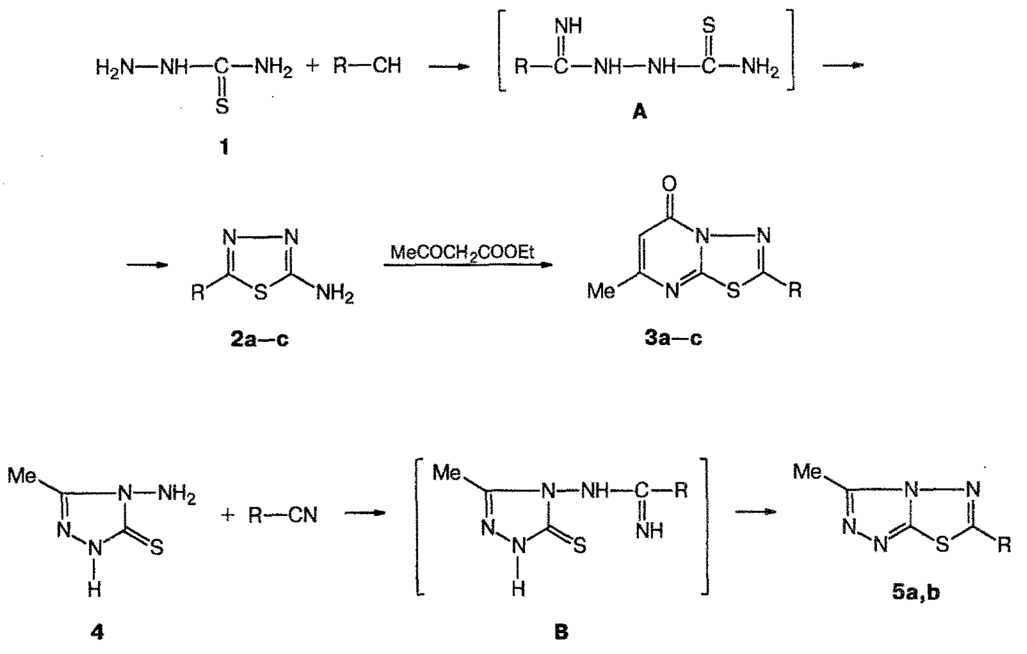
Aromatic nitriles have previously been found[1,2] to react with thiosemicarbazide (**1**) in boiling trifluoroacetic acid to give 2-amino-5-aryl-1,3,4-thiadiazoles (**2**). Low yield (~50 %) of **2** and the long duration of the reaction (60 h) are essential disadvantages of the method.

Our studies[3,4] showed the reaction of **1** and 4-amino-3-methyl-1,2,4-triazol-5-thione (**4**) with ethyl cyanoacetate in polyphosphoric acid (PPhA) solution to be an effective method of synthesis of condensed 1,3,4-thiadiazoles.

In this work, the reaction of aromatic nitriles with **1** and **4** in PPhA (95—100 °C, 5—6 h) is found to give **2a—c** thiadiazoles and 2-aryl-5-methyl-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazoles (**5a—b**), respectively, with nearly quantitative yield (Scheme 1).

The reaction of **1** with aromatic nitriles in the presence of ethyl acetoacetate leads in one step to 2-aryl-7-methyl-5-oxo-5*H*-1,3,4-thiadiozolo[3,2-*a*]- pyrimidines (**3a—c**). Compound **3a** was obtained previously[7] by the reaction of **1**, benzoic acid, and ethyl acetoacetate in

Scheme 1



R = Ph (**a**), *p*-$MeOC_6H_4$ (**b**), *m*-$O_2NC_6H_4$ (**c**)

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Table 1. Yields and melting points of synthesized compounds **2**, **3**, and **5**

Compound	Yield (%)	M.p./°C	
		found	references
2a	98	225—228	225[6]
2b	92	186—189	188[6]
2c	88	227—229	230[6]
3a	73	199—202	201[7]
3b	92	244—247	246[7]
3c	81	233—235	234[7]
5a	80	177—179	177[8]
5b	94	163—167	—

methanosulfonic acid containing phosphorus anhydride. Satisfactory yields of **3b,c** were achieved[7] when aromatic acids reacted with 3-amino-6-methyl-2-thiouracyl.

The nitriles in PPhA seem to be easily transformed into imine esters of polyphosphoric acid[5] which turn to amidrazones (**A**, **B**) by the action of hydrazine group of **1** or **4** and form further compounds **2** or **5** after elimination of ammonia molecule.

Experiment

General synthetic approach to 2-amino-5-aryl-1,3,4-thiadiazoles (2a—c), 2-aryl-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines (3a—c), and 2-aryl-5-methyl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles (5a,b). A mixture of 0.01 mol of aromatic nitrile, 0.01 mol of thiosemicarbazide **1** or triazolthione **4**, and 10—15 g of PPhA was heated for 5—6 h on a boiling water bath (in the case of **3**, 0.0105 mol of ethyl acetoacetate was added, and the mixture was heated an additional 4—5 h). It was then diluted with a four- to fivefold excess of H_2O and neutralized with a 40 % solution of NaOH to pH 7—8. The crystals were transferred to a filter, washed with water, dried in air, and recrystallized from aqueous dioxane. The yields and melting points of synthesized compounds **2**, **3**, and **5** are given in Table 1. PMR spectrum of **5b** (DMSO-d_6), δ: 2.25 (s, 3 H, Me); 4.70 (s, 3 H, MeO); 6.93 (d, 2 H, Ph); 7.69 (d, 2 H, Ph). Found (%): C, 53.12; H, 3.94. $C_{11}H_{10}N_4OS$. Calculated (%): C, 53.64; H, 4.09.

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