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SYNTHESIS OF 2-CYANOMETHYLAZAHETEROCYCLES

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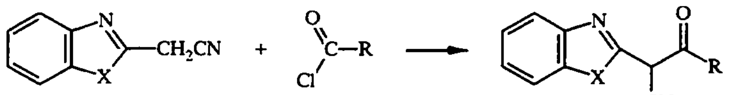
2-(α-Aryloxyacetyl)cyanomethyl-, 2-(α-1-adamantylacetyl)cyanomethyl-, 2-(α-adamantoyl)cyanometyl-, and 2-(α-1-naphthylacetyl)cyanomethylazaheterocycles have been synthesized by treating 2-cyanomethylazaheterocycles with carboxylic acid chlorides. The 2-cyanomethylbenzimidazoles exist in the enaminoketone form. The biological activity of the synthesized compounds was studied and substances possessing fungicidal activity discovered.

We have previously reported the reaction of 2-cyanomethylazaheterocycles I-IV with anhydrides and with aliphatic, aromatic, and heterocyclic acid chlorides [1-3]. However, acyl derivatives containing aryloxymethylene and adamantyl groups in the acyl residue have not previously been prepared.

It is known that aryloxyacetic acids are used as powerful pesticides [4], hence it might be expected that the compounds synthesized by us are potentially biologically active.

Reaction of compounds I-IV with the acid chlorides of aryloxyacetic, 1-adamantylcarboxy, 1-adamantylacetic, and 1-naphthylacetic acid Va-i in the presence of base give 2-(α-RCO)cyanomethylazaheterocycles VIa-i, VIIa-e, g-i, VIIIa-i, and IXa-e, g, h.

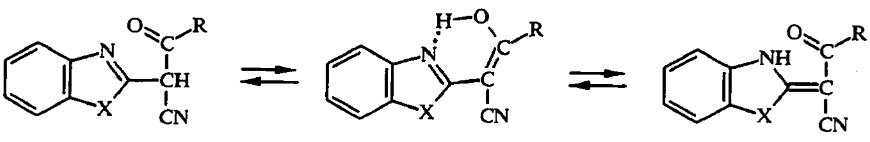


I-IV Va-i Via-i; VIIa-e, g-i; VIIIa-i; IXa-e, g, h

I, VII a-i , X = CH=CH—; II, VII a-e , g-i X = NH; III, VIII a-i X = NCH_3; IV, IX a-e, g, h X = S;
V—IX a R = $C_6H_5OCH_2$; b R = 4-$CH_3C_6H_4OCH_2$; c R = 4-$C_2H_5C_6H_4OCH_2$; d R = 4-$ClC_6H_4OCH_2$;
e R = 2,4-$Cl_2C_6H_3OCH_2$; f R = 2,4,5-$Cl_3C_6H_2OCH_2$; g R = 1-naphtylmethylene
h R = 1-adamantylmethylene ; i R = 1-adamantyl

In all of the examples studied by us only the C-acyl derivatives were obtained (see Table 1).

The compounds prepared can exist in three tautomeric forms: A, B, and C.



A B C

In the PMR spectra of acyl derivatives VIa-i, VIIIa-i, and IXa-e, g, h recorded in DMSO-D_6 there is observed a singlet at 13.2-16.0 ppm for a proton contained in a chelated ring, the signal disappearing on shaking the sample with D_2O.

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TABLE 1. Parameters for 2-(α-R)Cyanomethylazaheterocycles VIa-i, Va-e, g-i, VIIIa-i, IXa-e, g, h

Compound	Empirical formula	mp, °C	Found, %			Calculated, %		
			N	Cl	S	N	Cl	S
VIa	$C_{19}H_{14}N_2O_2$	187,5	9,27			9,27		
VIb	$C_{20}H_{16}N_2O_2$	168	8,95			8,86		
VIc	$C_{21}H_{18}N_2O_2$	156...157	8,70			8,48		
VId	$C_{19}H_{13}ClN_2O_2$	208,5	8,34	10,70		8,32	10,53	
VIe	$C_{19}H_{12}Cl_2N_2O_2$	218	7,55	18,96		7,55	19,10	
VIf	$C_{19}H_{11}Cl_3N_2O_2$	215*	7,08	26,30		6,91	26,22	
VIg	$C_{23}H_{16}N_2O$	150	8,38			8,33		
VIh	$C_{23}H_{24}N_2O$	229...230	8,35			8,37		
VIi	$C_{22}H_{22}N_2O$	205*	8,54			8,48		
VIIa	$C_{17}H_{13}N_3O_2$	300*	14,55			14,43		
VIIb	$C_{18}H_{15}N_3O_2$	>300*	13,85			13,76		
VIIc	$C_{19}H_{17}N_3O_2$	298*	13,28			13,16		
VIId	$C_{17}H_{12}ClN_3O_2$	302*	12,88	10,75		12,89	10,88	
VIIe	$C_{17}H_{11}Cl_2N_3O_2$	>300*	11,72	19,57		11,66	19,68	
VIIg	$C_{21}H_{15}N_3O$	297...298	12,77			12,91		
VIIh	$C_{21}H_{23}N_3O$	>300*	12,70			12,60		
VIIi	$C_{20}H_{21}N_3O$	270...271	13,08			13,16		
VIIIa	$C_{18}H_{15}N_3O_2$	204...206	13,86			13,76		
VIIIb	$C_{19}H_{17}N_3O_2$	208...209	13,09			13,16		
VIIIc	$C_{20}H_{19}N_3O_2$	200...201	12,75			12,61		
VIIId	$C_{18}H_{14}ClN_3O_2$	216...217	12,48	10,51		12,37	10,43	
VIIIe	$C_{18}H_{13}Cl_2N_3O$	223...224	11,69	19,72		11,73	19,79	
VIIIf	$C_{18}H_{12}Cl_3N_3O_2$	243...244	10,35	25,98		10,28	26,08	
VIIIg	$C_{22}H_{17}N_3O$	234...235	12,38			12,38		
VIIIh	$C_{22}H_{25}N_3O$	202	12,21			12,09		
VIIIi	$C_{21}H_{23}N_3O$	212	12,56			12,60		
IXa	$C_{17}H_{12}N_2O_2S$	235...237	9,02		10,47	9,09		10,40
IXb	$C_{18}H_{14}N_2O_2S$	237...238	8,61		10,08	8,69		9,95
IXc	$C_{19}H_{16}N_2O_2S$	219	8,30		9,65	8,33		9,53
IXd	$C_{17}H_{11}ClN_2O_2S$	253	8,28	10,42	9,46	8,17	10,34	9,35
IXe	$C_{17}H_{10}Cl_2N_2O_2S$	246...247	7,55	18,92	8,45	7,40	18,80	8,49
IXg	$C_{21}H_{14}N_2OS$	256...257	8,30		9,54	8,18		9,36
IXh	$C_{21}H_{22}N_2OS$	232...233	8,12		9,20	8,01		9,15

*Melts with decomposition.

The existence of tautomers B and C is supported by the presence of an absorption band at 2800-2600 cm^{-1} in the IR spectrum corresponding to a chelate type intramolecular hydrogen bond. The absorption band for the nitrile group is seen at 2205-2195 cm^{-1}. The shift to long wave when compared to its usual position in the IR spectra can be explained by the existence of the acyl derivatives in forms B and C in the solid state also. Hence neither in the solid nor the solution state is the ketone form observed.

From their PMR spectra it appears that VIIa-e, g-i exist in the enamino ketone form C.

The spectra recorded in DMSO-D_6 show both the symmetrical multiplet for the phenylene protons of the benzimidazole at 6.8-7.6 ppm and a narrow two proton singlet at 12.5-13.2 ppm, disappearing on addition of D_2O.

The compounds prepared are crystalline materials stable on storage. However, on heating to their melting point many of them decompose.

Biological testing has shown that compounds IXe, VIi, and VIIIg are active against *Phytophthora infestans*, VIIIe against *Erisyphe graminis*, and VIIId against *Septoria nodorum*.

EXPERIMENTAL

Monitoring of the course of the reaction and the purity of the compounds synthesized was performed chromatographically using Silufol UV-254 plates. IR Spectra were taken on a Pye Unicam SP-300 instrument for KBr tables.

PMR Spectra were recorded in DMSO-D_6 and CF_3COOD using a Bruker WP-100 instrument (100 MHz) and TMS internal standard. Chemical shift values were measured with an accuracy of 0.01 ppm.

2-(α-Aryloxyacetyl)cyanomethylazaheterocycles VIa-f, VIIa-e, VIIIa-f, IXa-e. Pyridine (0.81 ml, 0.01 mole) and the acid chloride Va-i (0.01 mole) were added to the 2-cyanomethylazaheterocycle I-IV (0.01 mole) in dioxane. The reaction mixture was heated on a water bath for 2 h and the solvent evaporated *in vacuo*. The residue was washed with water, filtered, dried, and recrystalled from dioxane or isopropanol to give the product in 90-96% yield.

2-(α-1-Adamantylacetyl)cyanomethylazaheterocycles VIe-IXh, 2-(α-1-adamantoyl)cyanomethylazaheterocycles VIi-VIIIi, and 2-(α-1-naphthylacetyl)cyanomethylazaheterocycles VIg-IXg were obtained similarly to the method reported above in 91-95% yields.

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