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NUCLEOPHILIC SUBSTITUTION IN A SERIES OF 2-METHYLSULFONYL-5-CHLOROPYRIMIDINE-4-CARBOXYLIC ACID DERIVATIVES

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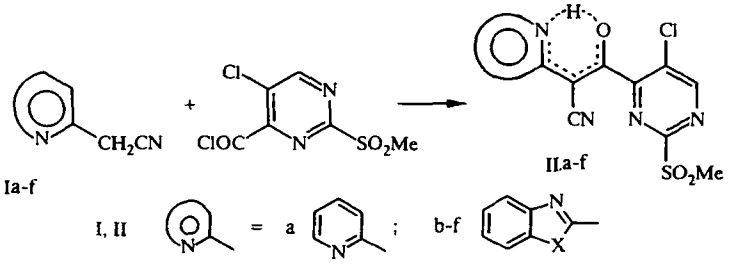
α-(2-Methylsulfonyl-5-chloropyrimidinoyl-4)-2-azahetarylacetonitriles were prepared by the reaction of 2-methylsulfonyl-5-chloropyrimidine-4-carboxylic acid chloride with 2-cyanomethylazaheterocycles.

The reaction of 2-halogen-substituted aromatic and heterocyclic carboxylic acids with 2-cyanomethylazaheterocycles I was investigated previously [1-3]. The C-acyl derivatives obtained, containing a mobile halogen atom, then underwent intramolecular nucleophilic hetarylation with the formation of condensed heterocycles.

The reactivity of C-acyl derivatives II containing two departing groups of different mobility with respect to nucleophilic agents was investigated in the present study. α-(2-Methylsulfonyl-5-chloropyrimidinoyl-4)-2-azahetarylacetonitriles IIa-f were obtained by the reaction of 2-azahetarylacetonitriles I with 2-methylsulfonyl-5-chloropyrimidine-4-carboxylic acid chloride in the presence of pyridine.



b X = NH; c X = NMe; d X = NCH_2Ph; e X = S; f X = CH=CH-

The spectral characteristics of compounds II are in good agreement with the data reported previously in [1-4]. Intense absorption bands of stretching vibrations of a sulfonyl group in the 1130-1120 and 1315-1300 region, a characteristic absorption band of a conjugated nitrile group at 2205-2195, and absorption at 3400-3100 cm^{-1} corresponding to an intramolecular hydrogen bond are observed in the IR spectra. A signal of an exchangeable proton in the 13.25-15.16 ppm region whose chemical shift is not a function of the concentration of the solution is observed in the PMR spectra (DMSO-D_6), and this confirms the formation of an intramolecular hydrogen bond. Signals of a pyrimidine ring proton at 9.41-9.47 and methylsulfonyl group protons in the 3.46-3.49 ppm region are also characteristic.

The pyrimidine nucleus of C-acyl derivatives IIa-f contains two departing groups. The halogen atom in position 5 of the pyrimidine ring is substituted by nucleophilic agents with difficulty [5], but in the given case, it is activated by methylsulfonyl and carbonyl groups. For this reason, intramolecular attack of the heterocycle by the nitrogen atom could be expected, as observed for less mobile halogens [1-3]. It was found that the methylsulfonyl group is regioselectively substituted under the effect of primary and secondary aliphatic amines and mercaptans.

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TABLE 1. Characteristics of Compounds IIa-f and III-X

Compound	Empirical formula	Found, % / Calculated, %			mp, °C,* solvent	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm (DMSO-D_6)	Yield, %
		Cl	N	S				
1	2	3	4	5	6	7	8	9
IIa	$C_{13}H_9ClN_4O_3S$	10,68 / 10,53	16,76 / 16,64	9,50 / 9,52	229...232 dioxane	1310, 1130 (SO_2) 2192 (CN)	15,16 (H, s, H*[2]); 9,42 (H, s, H dioxane); 8,49, 8,25, 7,46 (4H, m, pyridine H); 3,47 (3H, s, SO_2CH_3)	91
IIb	$C_{15}H_{10}ClN_5O_3S$	9,37 / 9,43	18,64 / 18,64	8,50 / 8,53	282...284 dioxane	1310, 1125 (SO_2) 2195 (CN)	13,36 (2H, s, NH and H*[2]); 9,41 (H, s, pyrimid. H); 7,5 (4H, symmetr. m, benzimidazole H.); 3,48 (3H,s, SO_2CH_3)	89
IIc	$C_{16}H_{12}ClN_5O_3S$	9,21 / 9,09	17,95 / 17,97	8,17 / 8,22	257...259 dioxane	1310, 1130 (SO_2) 2195 (CN)	13,49 (H, s, H*[2]); 9,42 (H, s, pyrimid. H); 7,77, 7,40 (4H, m, benzimidazole H); 4,02 (3H, s, N–CH_3); 3,48 (3H, s, SO_2CH_3)	94
IId	$C_{22}H_{16}ClN_5O_3S$	7,73 / 7,61	15,22 / 15,03	6,91 / 6,88	241...243 DMF	1305, 1130 (SO_2) 2190 (CN)	13,70 (H, s, H*[2]); 9,40 (H, s, pyrimid. H); 7,1...7,9 (9H, m, arom. H.); 5,87 (2H, s, CH_2); 3,46 (3H, s, SO_2CH_3)	93
IIe	$C_{15}H_9ClN_4O_3S_2$	8,94 / 9,02	14,19 / 14,26	16,40 / 16,32	256...259 DMF	1315, 1128 (SO_2) 2200 (CN)	14,50 (H, s, H*[2]); 9,44 (H, s, pyrimid. H); 7,3...8,2 (4H, m, benzothiazole H; 3,48 (3H, s, SO_2CH_3)	90
IIf	$C_{17}H_{11}ClN_4O_3S$	9,25 / 9,16	14,54 / 14,48	8,18 / 8,29	255...257 dioxane	1305, 1130 (SO_2) 2190 (CN)	15,03 (H, s, H*[2]); 9,47 (H, s, pyrimid. H); 8,68, 7,5...8,25 (6H, m, quinoline H); 3,49 (3H, c, SO_2CH_3)	91
III	$C_{15}H_{11}ClN_6O$	10,96 / 10,85	26,88 / 25,72		275...277 DMF	3300 (NH_2) 2195 (CN)	13,25 (H, s, H*[2]); 8,4 (H, s, pyrimid. H); 7,72...7,28 (4H, m, benzothiazole H); 6,95 (2H, s, NH_2); 3,97 (3H, s, N–CH_3)	85

TABLE 1 (continued)

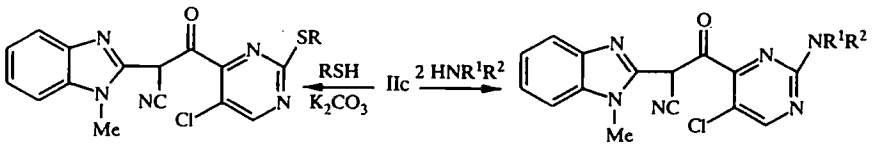
1	2	3	4	5	6	7	8	9
IV	$C_{15}H_{12}ClN_7O$	10,20 / 10,37	28,80 / 28,69		255 DMF	3280 ($NHNH_2$) 2190 (CN)	12,8 (3H, br.s, NH_2 and H^{*2}); 10,08 (H, s, NH); 8,57 (H, s, pyrimid. H.); 7,72, 7,39 (4H, m, benzimidazole H); 3,98 (3H, s, N–CH_3)	82
V	$C_{22}H_{17}ClN_6O$	8,77 / 8,50	20,02 / 20,16		226...227 (without decomp.) dioxane	2200 (CN)	13,39 (H, s, H^{*2}); 8,44 (H, s, pyrimid. H); 8,18 (H, t, NH); 7,7, 7,3 (9H, m, arom. H); 4,51 (2H, d, CH_2); 3,98 (3H, s, N–CH_3)	94
VI	$C_{25}H_{23}ClN_6O_3$	7,35 / 7,22	17,16 / 17,12		222...223 (without decomp.) dioxane	2195 (CN)	13,4 (H, s, H^{*2}); 8,48 (H, s, pyrimid. H); 7,7, 7,4 (5H, m, NH and benzimidazole H); 6,8 (3H, m, arom. H); 3,99 (3H, s, N–CH_3); 3,70 (6H, s, –3,4($CH_3O)_2$); 3,34, 2,80 (4H, m, –HN$\underline{CH_2}\underline{CH_2}$–Ar)	91
VII	$C_{20}H_{19}ClN_6O$	8,91 / 8,98	21,38 / 21,28		282...284 DMF	2195 (CN)	13,41 (H, s, H^{*2}); 8,46 (H, s, pyrimid. H); 7,72, 7,37 (4H, m, benzimidazole H); 4,00 (3H, s, N–CH_3); 3,74, 3,42, 1,58 (10H, pyridine CH_2)	95
VIII	$C_{19}H_{17}ClN_6O_2$	9,05 / 8,93	21,36 / 21,18		268...270 dioxane	2195 (CN)	13,41 (H, s, H^{*2}); 8,56 (H, s, pyrimid. H); 7,73, 7,37 (4H, m, benzimidazole H); 3,98 (3H, s, N–CH_3); 3,69 (8H, m, CH_2 morpholine CH_2	96
IX*[3]	$C_{19}H_{16}ClN_5O_3S$	8,44 / 8,25	16,33 / 16,29	7,55 / 7,46	208...209 (without decomp.) *n*-butanol	2200 (CN) 1725 (CO)	13,47 (H, s, H^{*2}); 8,56 (H, s, pyrimid. H); 7,43 (4H, m, benzimidazole H); 4,22 (2H, q, $\underline{CH_2}CH_3$); 4,10 (2H, s, SCH_2); 3,98 (3H, s, N–CH_3); 1,24 (3H, t, $CH_2\underline{CH_3}$)	78
X	$C_{17}H_{14}ClN_5O_2S$	9,14 / 9,14	17,96 / 18,05	8,23 / 8,26	218...220 ethanol	2195 (CN)	13,41 (H, s, H^{*2}); 8,88 (H, s, pirimid. H); 7,75...7,4 (4H, m, benzimidazole H); 5,00 (H, t, OH); 4,00 (3H, s, N–CH_3); 3,69 (2H, m, –$\underline{CH_2}$OH); 3,25 (2H, t, SCH_2)	73

*The synthesized compounds melt with decomposition.

*[2]Signal of proton contained in a chelate ring.

*[3]Spectrum recorded in $CDCl_3$

The reaction was conducted in boiling dioxane with an excess of amine; starting compound IIc gradually dissolved, and the reaction was concluded after 3-5 h with close to quantitative yields. Potash was used as the base for generation of thiolates in the case of SH-nucleophiles.



IX, X

IX R = CH_2CO_2Et;
X R = CH_2CH_2OH

III–VIII

III R^1, R^2 = H, H; IV R^1, R^2 = H, NH_2;
V R^1, R^2 = H, CH_2Ph;
VI R^1, R^2 = H, 3,4-$(CH_3O)_2C_6H_3CH_2$–;
VII R^1, R^2 = $-(CH_2)_5-$;
VIII R^1, R^2 = $-(CH_2)_2-O-(CH_2)-$

Weaker nucleophiles (arylamines and arylhydrazines) did not react with compound IIc even on prolonged boiling in dioxane.

Compounds III-X obtained are high-melting, crystalline substances which are stable during storage. The spectral characteristics and data from elemental analysis confirm their structure. All substances obtained contain chlorine. There is no signal of a methylsulfonyl group in the PMR spectra of compounds III-X (DMSO-D_6). A pyrimidine ring proton signal is observed at 8.44-8.57 ppm; its shift by almost 1 ppm to the strong field is due to the electron-donor properties of the incorporated substituent. The signal of NH protons which disappear when D_2O is added to the sample is observed for compounds III-VI. Substitution of the methylsulfonyl group in compound IIc does not significantly affect the spectral characteristics of the remaining fragment of the molecule. The absorption band of the nitrile group in the IR spectra of compounds IV-X is located in the region of 2205-2195 cm^{-1}. The corresponding signals in the PMR spectra of these compounds are in agreement with those for compound IIc.

EXPERIMENTAL

The evolution of the reactions and purity of the synthesized compounds were monitored chromatographically on Silufol UV-254 plates; the eluent was chloroform—methanol mixture, 9:1. The IR spectra were recorded on a Pye Unikam Sp-300 in KBr pellets. The PMR spectra of the synthesized compounds were recorded in DMSO-D_6 or in $CDCl_3$ on a Bruker WP-100 with TMS as internal standard. The chemical shifts were measured with a precision of up to 0.01 ppm.

2-Methylsulfonyl-5-chloropyrimidine-4-carboxylic acid chlorides were obtained by heating 0.01 mole of the corresponding acid [6] and 5 ml of thionyl chloride in 30 ml of benzene for 7 h. After drying by vacuum evaporation, the residue was treated with a new portion of benzene with subsequent evaporation. The acid chloride obtained was used without further purification.

α-(2-Methylsulfonyl-5-chloropyrimidinoyl-4)-2-azahetarylacetonitriles (IIa-f). Here 0.01 mole of pyridine and 0.01 mole of 2-methylsulfonyl-5-chloropyrimidine-4-carboxylic acid II were added to a solution of 0.01 mole of the corresponding 2-cyanomethylazaheterocycle Ia-f in 25 ml of dioxane. The reaction mixture was heated in a water bath for 2-3 h; the solvent was then evaporated in a vacuum. The residue was treated with water, filtered, dried, and recrystallized from the corresponding solvent.

α-(2-Amino-5-chloropyrimidinoyl-4)-1-methyl-2-benzimidazolylacetonitrile (III). A suspension of 0.6 g (1.54 mmole) of α-(2-methylsulfonyl-5-chloropyrimidinoyl-4)-1-methyl-2-benzimidazolylacetonitrile (IIc) in 20 ml of dioxane was heated to 60-80°C and a 25% aqueous solution of ammonia was added by drops while stirring until starting compound IIc disappeared. The solution obtained was evaporated, and the residue was washed with water, filtered, dried and recrystallized from DMF.

α-(2-Hydrazino-5-chloropyrimidinoyl-4)-1-methyl-2-benzimidazolylacetonitrile (IV). Here 2.2 mmole of hydrazine hydrate was added to a suspension of 0.6 g (1.54 mmole) of α-(2-methylsulfonyl-5-chloropyrimidinoyl-4)-1-methyl-2-benzimidazolylacetonitrile (IIc) in 25 ml of dioxane. The mixture was boiled for 3-3.5 h, and the starting compound gradually dissolved. The solvent was evaporated, and the residue was treated with water, filtered, dried, and recrystallized from DMF.

α-(2-Alkylmercapto-5-chloropyrimidinoyl-4)-1-methyl-2-benzimidazolylacetonitriles (V-VIII) were prepared similar to compound IV.

α-(2-Alkylmercapto-5-chloropyrimidinoyl-4)-1-methyl-2-benzimidazolylacetonitriles (IX, X). Here a quantity of 0.44 g (3 mmole) of potash was added to a mixture of 0.6 g (1.54 mmole) of α-2-methylsulfonyl-5-chloropyrimidinoyl-4)-1-methyl-2-benzimidazolylacetonitrile and 1.6 mmole of the corresponding mercaptan in 20 ml of dioxane and the mixture was boiled for 2 h. The solvent was evaporated in a vacuum. Then 80 ml of water was added to the residue and it was neutralized with acetic acid to pH 7. The residue was filtered off, dried, and recrystallized from an appropriate solvent.

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