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ALKYLTHIO DERIVATIVES OF THE AMINOKETENE S,N-ACETALS OF HETEROCYCLIC β-DICARBONYL COMPOUNDS: ONE STAGE SYNTHESIS AND PROPERTIES

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Treatment of phenyl isothiocyanate with heterocyclic β-dicarbonyl compounds gave novel aminoketene S,N-acetals, whose alkylation using haloalkanes has been studied.

Keywords: 1,3-dimethyl-2,4,6-(1H,3H,5H)-pyrimidinetrione, haloalkanes, isothiocyanates, N-methylmorpholine, tetrahydrofuran-2,4-dione.

Aminoketene S,N-acetals, obtained from derivatives of cyanoacetic and other CH-acids with isothiocyanates, have found widespread use in the synthesis of functionalized heterocycles [1-6], including those with antitumor activity [7].

In a continuation of our work studying the synthetic potential of heterocyclic β-dicarbonyl compounds as synthons for preparing biologically active molecules [8, 9] we have investigated the nucleophilic addition of 1,3-dimethyl-2,4,6-(1H,3H,5H)-pyrimidinetrione (**1**) and tetrahydrofuran-2,4-dione (**2**) to phenyl isothiocyanate (**3**) in the presence of an organic base in DMF at 25°C. This reaction occurs *via* a stage of formation of betaine intermediates **4**, **5**. The regioselective alkylation of the latter by the haloalkanes **6a-g** leads to the formation of alkylation products exclusively at the sulfur atom (**7a-g**, **8**) in high yields (see Table 1).

The ^{1}H NMR spectra of compounds **7a-g** show signals for the SCH_2 and NH group protons at 2.95-3.82 and 11.89-13.82 ppm, as well as signals for the protons of the aryl substituents. The signals for the NH group protons are strongly shifted and this is likely due to the formation of a stable, intramolecular hydrogen bond between the NH and C=O groups in the compounds **7a-g, 8** (characteristic of a betaine type structure [10, 11]). Thus in the case of compound **8** we have separated a stable *Z*-isomer because of the unsymmetrical structure of the molecule **5**. Oxidation of compound **7b** in chloroform using *m*-chloroperbenzoic acid (**9**) gives the sulfone **10** which has been characterized by us from the presence of sulfone absorption bands at 1330 and 1150 cm^{-1} in the IR spectrum. An X-ray structural study of derivatives of this class of compound will be additionally published.

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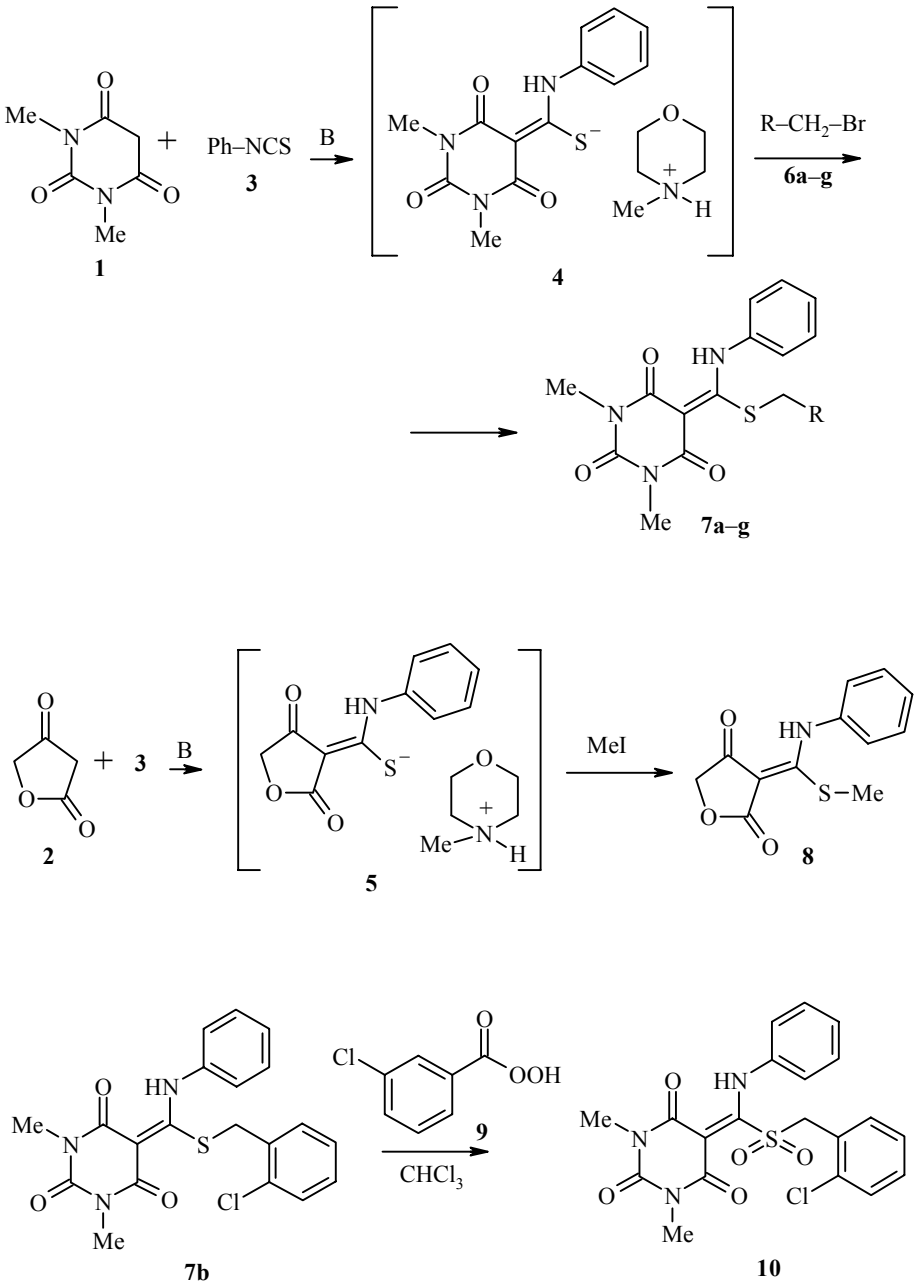
TABLE 1. Characteristics of the Synthesized Compounds **7** and **8**

Compound	Empirical formula	Found, % / Calculated, %					mp, °C*	IR spectrum,*[2] $\nu_{C=O}$, cm^{-1}	Chemical shift, δ, ppm				Yield, %
		C	H	Cl	N	S			$2CH_3$–N (s, 6H)	S–CH_2– (s, 2H)	Ar (m)	–NH (br. s, 1H)	
7a	$C_{14}H_{15}N_3O_3S$	55.00 / 55.07	4.90 / 4.95		13.40 / 13.76	10.70 / 10.50	153-154	1630, 1710	3.25	2.95	7.31-7.40 (5H)	13.82	93
7b	$C_{20}H_{18}ClN_3O_3S$	57.70 / 57.76	4.36 / 4.32	8.58 / 8.52	10.30 / 10.10	7.80 / 7.71	202-203	1628, 1700	3.18	3.80	7.44-7.53 (9H)	13.63	90
7c	$C_{20}H_{19}N_3O_3S$	63.03 / 62.98	5.25 / 5.02		10.10 / 11.02	8.51 / 8.40	195-196	1630, 1700	3.17	3.74	7.26-7.43 (10H)	13.55	87
7d	$C_{20}H_{18}ClN_3O_3S$	57.70 / 57.76	4.36 / 4.32	8.59 / 8.52	10.26 / 10.10	7.77 / 7.71	197-199	1625, 1700	3.18	3.78	7.20-7.34 (9H)	13.51	89
7f	$C_{20}H_{18}ClN_3O_3S$	58.66 / 57.76	4.72 / 4.32	8.61 / 8.52	10.14 / 10.10	7.91 / 7.71	203-204	1610, 1710	3.18	3.76	7.17-7.33 (9H)	13.50	92
7g	$C_{20}H_{17}Cl_2N_3O_3S$	53.57 / 53.34	3.74 / 3.80	15.53 / 15.75	9.41 / 9.33	7.20 / 7.12	229-230	1605, 1700	3.18	3.82	7.37-7.54 (8H)	13.41	96
8*[3]	$C_{12}H_{11}NO_3S$	57.71 / 57.82	4.36 / 4.45		5.54 / 5.62	12.67 / 12.86	162-163	1710, 1755	–	2.34	7.56-7.62 (5H)	11.89	56

* Solvent for crystallization: acetonitrile (**7a-g**) and methanol (**8**).

*[2] The absorption for the NH group did not appear due to the formation of the intramolecular bond.

*[3] Chemical shift of the CH_2 ring fragment (s, 2H) δ = 4.43 ppm.



B = N-methylmorpholine, **6**, **7 a** R = H, **b** R = 2-Cl–C_6H_4, **c** R= Ph, **d** R = 3-Cl–C_6H_4, **f** R = 4-Cl–C_6H_4, **g** R = 3,4-Cl_2–C_6H_3

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer for KBr tablets. ^{1}H NMR Spectra were taken on a Bruker VXR-300 (300 MHz) instrument for solutions in DMSO-d_6 with TMS as internal standard. Monitoring of the course of the reaction and the purity of the materials was carried out using TLC on Silufol UV-254 plates (eluent acetone–hexane, 3:5).

The parameters for the synthesized compounds **7a-g**, **8** are given in Table 1.

5-[1-Alkylthio-1-(phenylamino)methylidene]-1,3-dimethylhexahydro-2,4,6-pyrimidinetrione (7a-g) (General Method). Mixture of compound **1** (1.56 g, 10 mmol), phenyl isothiocyanate **3** (1.35 g, 10 mmol), and N-methylmorpholine (1.01 g, 10 mmol) in DMF (20 ml) was stirred for 2 h at 25°C and a precipitate of compound **4** was formed The haloalkane **6a-g** (10 mmol) was added to the reaction mass and it was stirred until full solution of the precipitated compound **4** occurred. The product was then allowed to stand for 40 min at 25°C, diluted with water (25 ml), and the precipitated material was filtered off and washed with methanol.

3-[(Z)-1-Methylthio-1-(phenylamino)methylidene]tetrahydro-2,4-furandione (8). A mixture of compound **2** (1.00 g, 10 mmol), phenyl isothiocyanate (1.35 g, 10 mmol), and N-methylmorpholine (1.01 g, 10 mmol) in DMF (10 ml) was stirred for 24 h at 25°C. Methyl iodide (1.41 g, 10 mmol) was added to the solution obtained and the product was stirred for 40 min at 25°C, after which it was diluted with water (20 ml) and the precipitate formed was filtered off.

5-[1-(2-Chlorobenzylsulfonyl)-1-phenylaminomethylidene]-1,3-dimethylhexahydro-2,4,6-pyrimidine-trione (10). Acid **9** (0.45 g, 0.24 mmol) was added to a suspension of compound **7b** (1.0 g, 0.24 mmol) in chloroform (15 ml) which was cooled to 10°C. The mixture was left to stand at room temperature for 8 h. The chloroform solution was evaporated on a water bath to give the product which was recrystallized from methanol. Yield 0.61 g (56.6%); mp 124-125°C. IR spectrum, ν, cm^{-1}: 1330, 1150, 1710, 1630, 1650. ^1H NMR spectrum, δ, ppm: 3.16 (6H, s, $2CH_3$–N); 3.56 (2H, s, CH_2); 7.40-7.53 (9H, m, aromatic protons); 13.71 (1H, br. s, NH). Found, %: C 53.52; H 3.89; Cl 7.86; N 9.27: S 7.07. $C_{20}H_{18}ClN_3O_5S$. Calculated, %: C 53.63; H 4.05; Cl 7.92; N 9.38; S 7.16.

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