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4-NITROPHENYL N-(1-ARYL-2,2,2-TRIFLUORO-ETHYLIDENE)URETHANES: NOVEL 1,3-ELECTROPHILIC COMPONENTS OF REACTIONS LEADING TO 6- AND 7-MEMBERED HETEROCYCLES

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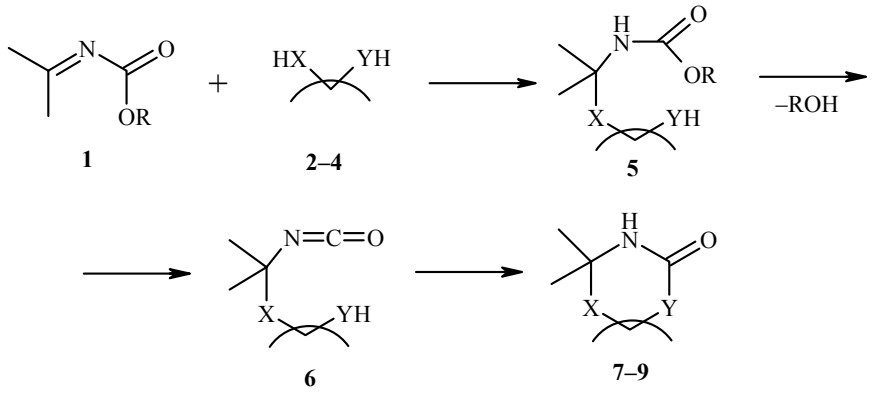
We propose an approach to synthesis of N,O,S-containing 6- and 7-membered heterocycles based on using 4-nitrophenyl N-(1-aryl-2,2,2-trifluoroethylidene)urethanes as the electrophilic components in heterocyclizations with bifunctional nucleophilic reagents.

Keywords: N-alkylideneurethanes, bifunctional nucleophiles, 5-oxoimidazo[2,3-*b*]-1,3,5-thiadiazines, 2-oxo-1,5,3-oxathiazepines, 2-oxo-1,5,3-benzoxathiazepines.

N-Alkylideneurethanes have been used as 1,2- or 1,4-components in cycloaddition reactions with electron-rich reagents [1].



1 **2–4** **5** **6** **7–9**

We have significantly expanded the synthetic possibilities of N-alkylideneurethanes by using them as 1,3-electrophilic components in heterocyclizations with bifunctional nucleophilic substrates. The proposed approach essentially involves addition of bifunctional nucleophiles **2-4** to N-alkylideneurethanes **1**, which leads to formation of acyclic products **5**, followed by generation under the reaction conditions of isocyanates of type **6** and their intramolecular cyclization to hetero systems **7-9**.

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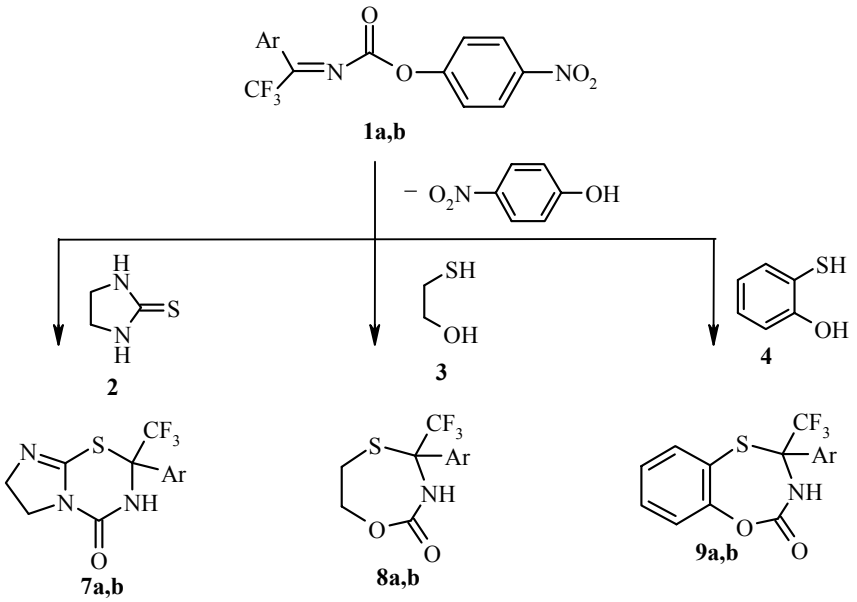

1, 7–9 a Ar = Ph, **b** Ar = 4-MeC_6H_4

The pronounced electrophilicity of the azomethine group in urethanes **1** helps the reaction occur regioselectively as a result of the formation of urethanes **5**, which cannot always be successfully achieved in cyclizations with participation of 1-chloroalkyl isocyanates [2]. A necessary condition for the heterocyclization is the ability of urethanes **5** to generate synthons **6**, which first of all depends on the nature of the substituent R. We have established that such a requirement is satisfied by 4-nitrophenyl N-alkylideneurethanes **1**, since under mild conditions (benzene, 80°C) the corresponding urethanes **5** tend to readily eliminate 4-nitrophenol with formation of isocyanates **6**, which is detected by IR spectroscopy. Such properties are lacking in 4-nitrophenyl N-alkylideneurethanes **1** (R = CH_3, $CH_2C_6H_5$), and for this reason they cannot be used as components for cyclizations, since the corresponding urethanes **5** do not undergo further conversions either at 80°C or at higher temperatures (110-140°C).

The approach considered above for synthesis of hetero systems **7-9** is illustrated by the examples of cyclocondensations of 4-nitrophenyl N-(1-aryl-2,2,2-trifluoroethylidene)urethanes **1a,b** with bifunctional nucleophiles: 2-imidazoline thione **2**, 2-mercaptoethanol **3**, and 2-mercaptophenol **4**. We have shown that when the reagents are heated in benzene, we obtain the target products in high yields: derivatives of 3-aryl-5-oxo-3-trifluoromethyl-6,7-dihydroimidazo[2,3-*b*]-1,3,5-thiadiazines **7a,b** [3], 4-aryl-2-oxo-4-trifluoromethyl-1,5,3-oxathiazepines **8a,b**, and 4-aryl-2-oxo-4-trifluoromethyl-1,5,3-benzoxathiazepines **9a,b**.

Compounds **7a,b-9a,b** (Table 1) are colorless crystalline compounds, the individual purity of which was shown by TLC while their composition was determined by elemental analysis results and their structure was proven by IR, ^1H and ^{19}F NMR spectra (Table 2). The IR spectra of compounds **7a,b** are characterized by absorption bands for the carbonyl groups of the ureide moiety in the 1660-1680 cm^{-1} region, while compounds **8a,b, 9a,b** are characterized by absorption bands for the carbonyl groups of the urethane moiety in the 1740-1770 cm^{-1} region. In the ^1H NMR spectra of all the compounds, along with signals from methyl, methylene, and aromatic protons, we see broadened singlets for the N–H protons at 7.80-8.50 ppm. The presence of the same signals in the ^{19}F NMR spectra for both the reaction mixtures and the end products is evidence for the regioselectivity of the cyclization process. The region where we see the 74-77 ppm signals indicates that the CF_3 groups are located on the sp^3-hybridized carbon atom of the S–C–N moiety, and supports a cyclic structure for the compounds obtained [4].

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (solvent for crystallization)	Yield, %
		C	H	S		
7a	$C_{12}H_{10}F_3N_3OS$	47.98 / 47.84	3.11 / 3.35	10.74 / 10.64	146-147 (hexane–benzene, 2:1)	69
7b	$C_{13}H_{12}F_3N_3OS$	50.01 / 49.52	3.91 / 3.84	10.50 / 10.17	179-180 (hexane–benzene, 1:8)	78
8a	$C_{11}H_{10}F_3NO_2S$	47.39 / 47.65	3.78 / 3.63	11.27 / 11.56	56-57 (hexane–diethyl ether, 2:1)	64
8b	$C_{12}H_{12}F_3NO_2S$	49.30 / 49.47	4.45 / 4.15	11.12 / 11.01	69-70 (hexane–diethyl ether, 2:1)	70
9a	$C_{15}H_{10}F_3NO_2S$	55.69 / 55.38	3.34 / 3.10	9.57 / 9.85	88-89 (hexane–benzene, 8:1)	57
9b	$C_{16}H_{12}F_3NO_2S$	56.68 / 56.63	3.30 / 3.56	9.56 / 9.45	77-78 (hexane–benzene, 5:1)	68

TABLE 2. Spectral Characteristics of Compounds **7-9**

Compound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectra, δ, ppm	^{19}F NMR spectra, δ, ppm
	C=O	N–H		
7a	1665	3240	3.80-3.98 (4H, m, CH_2); 7.37-7.41 (5H, m, $H_{arom.}$); 9.84 (1H, br. s, NH)	76.2
7b	1660	3220	2.29 (3H, s, CH_3); 3.78-3.95 (4H, m, CH_2); 7.15-7.54 (4H, m, C_6H_4); 9.67 (1H, br. s, NH)	76.2
8a	1750	3250 3400	2.72-2.87 (2H, m, CH_2S); 4.22-4.38 (2H, m, CH_2O); 7.42-7.61 (5H, m, C_6H_5); 8.15 (1H, br. s, NH)	74.5
8b	1745	3250 3400	2.38 (3H, s, CH_3); 2.95-3.17 (2H, m, CH_2S); 4.15-4.35 (2H, m, CH_2O); 7.18-7.47 (4H, m, C_6H_4); 8.00 (1H, br. s, NH)	75.7
9a	1750	3290 3380	7.12-7.50 (9H, m, H_{arom}); 7.80 (1H, br. s, NH)	74.1
9b	1765	3190 3360	2.28 (3H, s, CH_3); 7.16-7.41 (8H, m, H_{arom}); 8.21 (1H, br. s, NH)	74.7

EXPERIMENTAL

The IR spectra were recorded on a UR-20 in KBr disks. The ^{1}H NMR spectra were measured on a Varian Gemini spectrometer (200 MHz) in $CDCl_3$ solution, internal standard HMDS. The ^{19}F NMR spectra were obtained on a Bruker WP-200 (188 MHz) in $CDCl_3$ solution, internal standard CCl_3F. TLC was done on Silufol UV-254 plates.

4-Nitrophenyl N-(1-Aryl-2,2,2-trifluoroethylidene)urethanes (1a,b). 4-Nitrophenol (1.39 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) were added to a solution of the corresponding 1-aryl-1-chloro-2,2,2-trifluoroethyl isocyanate [5] (0.01 mol) in benzene (45 ml). The mixture was stirred at room temperature for 2 h. The triethylamine hydrochloride precipitate was filtered out, the filtrate was refluxed for 1 h, the solvent was evaporated, and the residue was recrystallized from a 1:3 hexane–benzene mixture.

Compound 1a. Yield 85%; mp 73-74°C. IR spectrum, ν, cm^{-1}: 1790 (C=O), 1720 (C=N). ^{1}H NMR spectrum, δ, ppm: 7.96-8.09 (4H, m, C_6H_4); 7.49-7.60 (5H, m, C_6H_5). ^{19}F NMR spectrum, δ, ppm: 69.23 s. Found, %: C 53.16; H 2.59; N 8.34. $C_{15}H_9F_3N_2O_4$. Calculated, %: C 53.27; H 2.68; N 8.28.

Compound 1b. Yield 86%; mp 97-98°C. IR spectrum, ν, cm^{-1}: 1800 (C=O), 1725 (C=O). ^1H NMR spectrum, δ, ppm: 7.41-8.03 (8H, m, C_6H_4); 2.29 (3H, s, CH_3). ^{19}F NMR spectrum, δ, ppm: 70.08 s. Found, %: C 54.12; H 3.25; N 8.17. $C_{16}H_{11}F_3N_2O_4$. Calculated, %: C 54.55; H 3.15; N 7.95.

3-Aryl-3-trifluoromethyl-3,4,7,8-tetrahydro-5H-imidazo[2,3-*b*]-1,3,5-thiadiazin-5-ones (7a,b), 4-Aryl-4-trifluoromethyl-3,4-dihydro-2H-1,5,3-(benzo)oxathiazepin-2-ones (8a,b, 9a,b). Triethylamine (4-5 drops) was added to a mixture of N-alkylideneurethane **1a,b** (0.005 mol) and the nucleophilic reagent **2-4** (0.005 mol) in benzene (50 ml), and the mixture was heated at the boiling point for 3 h. After the solvent was evaporated, the residue was washed with a saturated solution of Na_2CO_3 (50 ml), dried, and purified by crystallization.

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