One-pot synthesis of 3-amino-4-aryl- and 3-amino-4-hetarylfurazans*

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A "one-pot" method for the synthesis of 3-amino-4-aryl- and 3-amino-4-hetarylfurazans from β-aryl- and 4-β-hetaryl-β-oxo acid esters was developed.

Key words: arylfurazans, hetarylfurazans, aminofurazans, nitrosation, cyclization.

Earlier,[1] we obtained 3-alkyl-4-aminofurazans from ethyl β-alkyl-β-oxopropionates without isolating intermediate products. It was interesting to study whether this reaction could be applied to the synthesis of aminofurazans (AF) containing an aryl or hetaryl substituent. Note that no general methods for the synthesis of both alkyl and aryl AF derivatives have been available hitherto.[2,3]

It turned out that our methodology is also efficient for the synthesis of AF with aromatic substituents. For instance, the one-pot process involving hydrolysis of the corresponding ester of a β-aryl- or β-hetaryl-β-oxo acid, nitrosation at the activated methylene group, and treatment of the resulting intermediate with an alkaline solution of hydroxylamine in the presence of urea afforded the target AF (Table 1). The occurring processes are shown in Scheme 1. The starting esters of β-aryl- and β-hetaryl-β-oxo acids are commercially accessible or easily prepared.[4]

* Dedicated to Corresponding Member of the Russian Academy of Sciences E. P. Serebryakov on the occasion of his 70th birthday.

Table 1. Yields, melting points, and mass spectra of the AF obtained

Ar	Yield (%)	M.p./°C		Molecular formula	Molecular mass	MS, m/z (I_{rel} (%))
		Our data	Literature data			
Ph	75	100—101	99[5]	$C_8H_7N_3O$	161.16	161 $[M]^+$, 131 $[M - NO]^+$
2-FC_6H_4	45	115—116	114—116[6]	$C_8H_6FN_3O$	179.15	179 $[M]^+$, 149 $[M - NO]^+$
4-FC_6H_4	67	134—135	—	$C_8H_6FN_3O$	179.15	179 $[M]^+$, 149 $[M - NO]^+$
2-ClC_6H_4	58	54—55	53—55[6]	$C_8H_6ClN_3O$	195.61	196, 194 $[M]^+$, 166, 164 $[M - NO]^+$
4-ClC_6H_4	70	138—139	137—139[7]	$C_8H_6ClN_3O$	195.61	196, 194 $[M]^+$, 166, 164 $[M - NO]^+$
4-BrC_6H_4	48	146—147	138—141[7]	$C_8H_6BrN_3O$	240.06	241, 239 $[M]^+$, 211, 209 $[M - NO]^+$
2-MeC_6H_4	46	88—90	86—88[8]	$C_9H_9N_3O$	175.19	175 $[M]^+$, 145 $[M - NO]^+$
3-MeC_6H_4	75	78—79	76—77[8]	$C_9H_9N_3O$	175.19	175 $[M]^+$, 145 $[M - NO]^+$
4-MeC_6H_4	72	143—144	142[9]	$C_9H_9N_3O$	175.19	175 $[M]^+$, 145 $[M - NO]^+$
3,4-$Me_2C_6H_3$	51	112—113	111—113[8]	$C_{10}H_{11}N_3O$	189.22	189 $[M]^+$, 159 $[M - NO]^+$
2-$MeOC_6H_4$	47	113—115	112—114[6]	$C_9H_9N_3O_2$	191.19	191 $[M]^+$, 161 $[M - NO]^+$
4-$MeOC_6H_4$	63	104—105	101—102[7]	$C_9H_9N_3O_2$	191.19	191 $[M]^+$, 161 $[M - NO]^+$
3,4,5-$(MeO)_3C_6H_2$	48	177—178	174—175[10]	$C_{11}H_{13}N_3O_4$	251.24	251 $[M]^+$, 221 $[M - NO]^+$
4-$MeSC_6H_4$	66	126—128	126—127[11]	$C_9H_9N_3OS$	207.25	207 $[M]^+$, 177 $[M - NO]^+$
2-$CF_3C_6H_4$	50	70—72	68—70[6]	$C_9H_6F_3N_3O$	229.16	229 $[M]^+$, 199 $[M - NO]^+$
3-$CF_3C_6H_4$	73	89—90	88—89[10]	$C_9H_6F_3N_3O$	229.16	229 $[M]^+$, 199 $[M - NO]^+$
2-Thienyl	51	114—115	114—115[12]	$C_6H_5N_3OS$	167.19	167 $[M]^+$, 137 $[M - NO]^+$
3-Pyridyl	57	156—157	149—151[13]	$C_7H_6N_4O$	162.15	162 $[M]^+$, 132 $[M - NO]^+$

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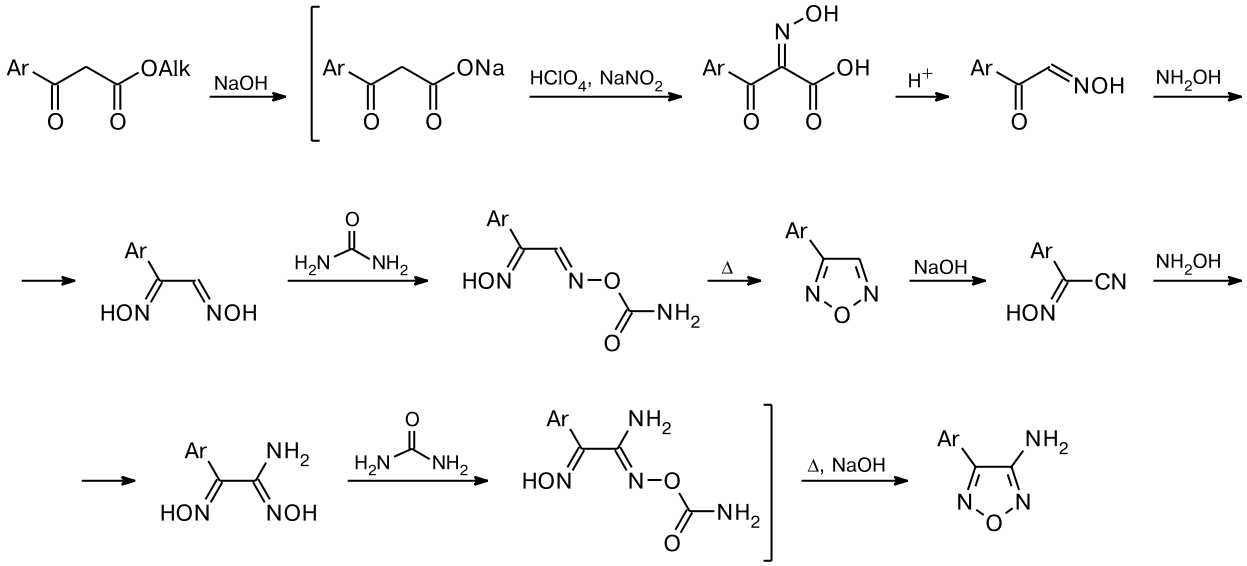
Scheme 1



As can be seen in Table 1, hetaryl-AF derivatives were obtained by this method in satisfactory to high yields. Note also that the yields of all earlier known compounds increased.

Thus, we developed a simple general one-pot method for the synthesis of 3-amino-4-aryl- and 3-amino-4-hetarylfurazans from alkyl β-aryl- and β-hetaryl-β-oxopropionates, which involves cascade heterocyclization.

Experimental

Melting points were determined with a Gallenkamp unit (Sanyo Co.). Natural-isotope ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 and 75.7 MHz, respectively). Chemical shifts are given in the δ scale with a solvent as the internal standard. Mass spectra were recorded on Finnigan MAT INCOS-50 and Varian MAT CH-111 instruments (EI, 70 eV). IR spectra were recorded on a Perkin—Elmer Model 577 spectrometer (in pellets with KBr). The course of the reaction was monitored and the purity of the products was checked by TLC on Silufol UV-254 plates; spots were visualized with UV irradiation.

Synthesis of 3-amino-4-(4-fluorophenyl)furazan (general procedure). Methyl 4-fluorobenzoylacetate (19.6 g, 0.1 mol) was added at 0 °C to a solution of NaOH (4.4 g, 0.11 mol) in water (50 mL) and the resulting mixture was stirred for 12 h. Sodium nitrite (8.3 g, 0.12 mol) was added and then 20% $HClO_4$ (0.23 mol) was slowly added dropwise at $T \leq 10$ °C. After the acid was added completely, the reaction mixture was warmed to room temperature and left for ~14 h. Then a solution of $NH_2OH \cdot HCl$ (27.8 g, 0.4 mol) in water (50 mL) was added dropwise with vigorous stirring. After half the solution of hydroxylamine was added, a solution of NaOH (18 g, 0.45 mol) in water (40 mL) was simultaneously added dropwise from a second dropping funnel at a temperature no higher than 30 °C. Then a mixture was heated to 95 °C over 1.5 to 2 h and urea (6 g, 0.1 mol) was added in one portion. The resulting mixture was refluxed for 3 h and cooled. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from $CHCl_3$—light petroleum (1 : 1). Found (%): C, 53.66; H, 3.43; N, 23.41. $C_8H_6FN_3O$. M = 179.15. Calculated (%): C, 53.63; H, 3.38; N, 23.45. IR (KBr), ν/cm^{-1}: 3448, 3324, 3248, 1632, 1612, 1576, 1536, 1488, 1396, 1312, 1248, 1164, 1104, 1056, 984, 884, 848. ^1H NMR (DMSO-d_6), δ: 6.22 (br.s, 2 H, NH_2); 7.37 (t, 2 H, CH=CF, J = 8.7 Hz); 7.82 (dd, 2 H, CH—C—Het, J = 5.5 Hz). ^{13}C NMR (DMSO-d_6), δ: 116.2 (d, CH=CF, J = 21.6 Hz); 122.1 (d, C_i, J = 2.6 Hz); 130.2 (d, CH—C—Het, J = 8.6 Hz); 146.2 (C—Ar); 155.3 (C—NH_2); 163.3 (d, C—F, J = 246.7 Hz). ^{19}F NMR (DMSO-d_6), δ: −109.5.

Other AF given in Table 1 were obtained analogously. Their spectral characteristics were identical with those of authentic samples. The mass spectra of all the products contain an intense molecular ion peak and a signal for the fragment $[M - NO]^+$ characteristic of furazan derivatives.

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