Chemistry of Heterocyclic Compounds, Vol. 44, No. 7, 2008

SYNTHESIS AND ALKYLATION OF $N_{(3)}$-ARYL-$N_{(5)}$-PHENYL-6-AMINO-4-ARYL(2-FURYL)-2-THIOXO-1,2,3,4-TETRAHYDROPYRIDINE-3,5-DICARBOXAMIDE

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$N_{(3)}$-Aryl-$N_{(5)}$-phenyl-6-amino-4-aryl(2-furyl)-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxamides have been obtained by the interaction of N-phenyl-3-aryl(2-furyl)-2-cyanoacrylamides with 3-amino-3-thioxopropananilides under the conditions of the Michael reaction. $N_{(3)}$-Aryl-$N_{(5)}$-phenyl-2-alkylthio-6-amino-4-aryl(2-furyl)-3,4-dihydropyridine-3,5-dicarboxamides and $N_{(3)}$,$N_{(5)}$-diphenyl-6-benzylthio-4-(2-furyl)-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxamides were synthesized by alkylation of the products.

Keywords: dihydropyridines, tetrahydropyridines, alkylation, heterocyclization, Michael reaction.

Derivatives of 3,5-dicarbamoyl-substituted partially hydrogenated pyridines attract the attention of investigators in connection with the discovery of a series of biologically active compounds among them, in particular, calcium channel antagonists [1-5].

Previously we obtained for the first time 3-carbamoyl-6-methyl-5-phenyl-2-thioxocarbamoyl-1,2,3,4-tetrahydropyridine-4-spirocyclohexane [6] by the Michael reaction and 6-amino-2-mercaptopyridine-3,5-dicarboxamides by the $S_N$vin reaction [7].

In the present work the interaction has been investigated of N-phenyl-3-aryl(2-furyl)-2-cyanoacrylamides **1a-d** with 3-amino-3-thioxopropanilides **2a-b** in absolute ethanol at 20°C in the presence of sodium ethylate. It was shown that this reaction leads to the formation of $N_{(3)}$-aryl-$N_{(5)}$-phenyl-6-amino-4-aryl(2-furyl)-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxamides **3a-e** (Table 1). The pathway for this process probably includes the formation of the appropriate Michael adducts **4**, readily converting under the conditions of the reaction by intramolecular chemoselective heterocyclization into the substituted partially hydrogenated pyridines **3a-e**.

The corresponding $N_{(3)}$-aryl-$N_{(5)}$-phenyl-2-alkylthio-6-amino-4-aryl(2-furyl)-3,4-dihydropyridine-3,5-dicarboxamides **6a-c** were synthesized on interacting compounds **3** with alkyl halides **5a,b** in ethanol in the presence of sodium ethylate. Replacement of sodium ethylate in this reaction by aqueous KOH solution and heating the reaction mixture to 50°C is accompanied not only by the formation of the corresponding organic sulfide but also by hydrolysis of the amino group. $N_{(3)}$,$N_{(5)}$-Diphenyl-6-benzylthio-4-(2-furyl)-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxamide (**7**) was obtained in this way.

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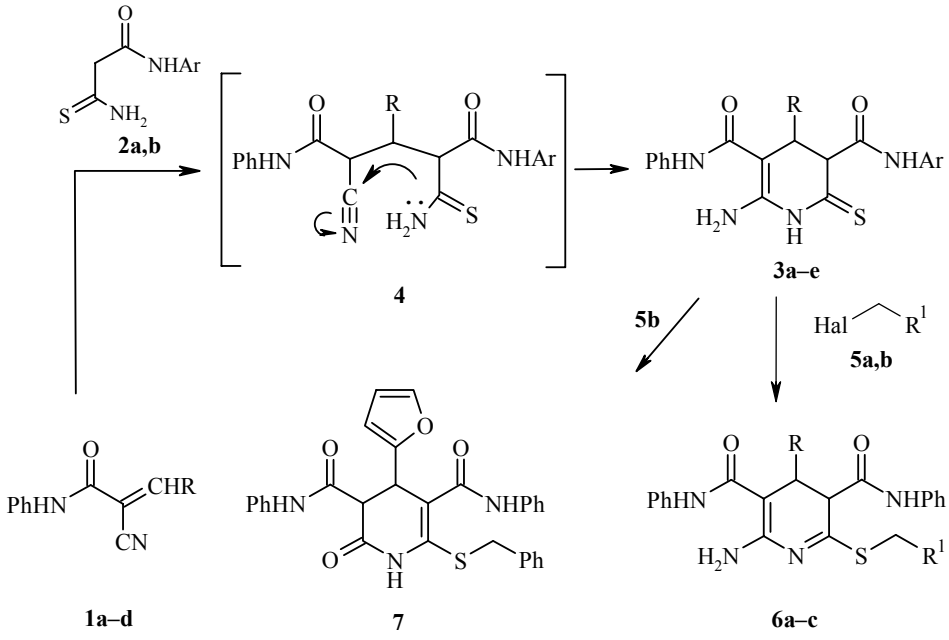
A characteristic of the ^{1}H NMR spectra of compounds **3a-e** is the presence of all the proton signals of the substituents of the tetrahydropyridine nucleus in the appropriate regions (Table 2), and also of signals of the H-3 and H-4 protons as singlets at 4.07-4.25 and 5.01-5.09 ppm respectively. The absence of splitting of these signals into the expected doublets may be explained by the formation of a conformation of the tetrahydropyridine ring in which the dihedral angle of the H–$C_{(3)}$–$C_{(4)}$–H fragment, described by the Karplus equation, approaches 90° [8].



1 a R = 2-furyl, **b** R = Ph, **c** R = 4-MeC_6H_4, **d** R = 4-ClC_6H_4; **2 a** Ar = Ph, **b** Ar = 3-MeC_6H_4; **3 a–d** Ar = Ph; **a** R = 2- furyl, **b** R = Ph, **c** R = 4-MeC_6H_4, **d** R = 4-ClC_6H_4, **e** Ar = 3-MeC_6H_4, R = 4-ClC_6H_4; **5 a** Hal = I, R^1 = H, **b** Hal = Cl, R^1 = Ph; **6 a** R = 2-furyl, R^1 = H, **b** R = R^1 = Ph, **c** R = 4-MeC_6H_4, R^1 = Ph

TABLE 1. Characteristics and Data of Elemental Analysis of Compounds **3a-e, 6a-c, 7**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3a	$C_{23}H_{20}N_4O_3S$	63.79 / 63.87	4.72 / 4.66	12.78 / 12.95	230-233	72
3b	$C_{25}H_{22}N_4O_2S$	67.70 / 67.85	5.12 / 5.01	12.50 / 12.66	195-197	86
3c	$C_{26}H_{24}N_4O_2S$	68.18 / 68.40	5.12 / 5.30	12.09 / 12.27	208-210	82
3d	$C_{25}H_{21}ClN_4O_2S$	62.76 / 62.95	4.29 / 4.44	11.58 / 11.75	190-192	85
3e	$C_{26}H_{23}ClN_4O_2S$	63.42 / 63.60	4.52 / 4.72	11.29 / 11.41	193-195	79
6a	$C_{24}H_{22}N_4O_3S$	64.63 / 64.56	4.81 / 4.97	12.35 / 12.55	204-206	70
6b	$C_{32}H_{28}N_4O_2S$	72.13 / 72.16	5.28 / 5.30	10.41 / 10.52	207-209	77
6c	$C_{33}H_{30}N_4O_2S$	72.39 / 72.50	5.32 / 5.53	10.08 / 10.25	173-175	79
7	$C_{30}H_{25}N_3O_4S$	68.68 / 68.82	4.76 / 4.81	8.18 / 8.03	224-226	58

TABLE 2. ^{1}H NMR Spectrum of Compounds **3a-e, 6a-c,** and **7**

Compound	Chemical shifts, δ, ppm, *J* (Hz)
3a	4.24 (1H, s, H-3); 5.09 (1H, s, H-4); 5.99 (1H, d, *J* = 2.6, H-3 furan); 6.34 (1H, dd, *J* = 2.6, *J* = 1.6, H-4 furan); 6.90 (1H, t, *J* = 7.2, H_{arom}); 7.05 (1H, t, *J* = 7.4, H_{arom}); 7.20-7.54 (9H, m, H-5 furan and H_{arom}); 8.25 and 9.57 (both 1H, both br. s, NH_2); 10.52 and 10.57 (both 1H, both br. s, 2NHCO); 13.18 (1H, br. s, $N_{(1)}H$)
3b	4.11 (1H, s, H-3); 5.06 (1H, s, H-4); 6.90 (1H, t, *J* = 7.0, H_{arom}); 7.07 (1H, t, *J* = 7.0, H_{arom}); 7.20 (4H, m, H_{arom}); 7.31-7.38 (5H, m, H_{arom}); 7.54 (2H, d, *J* = 7.5, H_{arom}); 7.58 (2H, d, *J* = 7.5, H_{arom}); 8.17 and 9.41 (both 1H, both br. s, NH_2); 10.52 and 10.54 (both 1H, both br. s, 2NHCO); 13.33 (1H, br. s, $N_{(1)}H$)
3c	2.25 (3H, s, CH_3); 4.07 (1H, s, H-3); 5.01 (1H, s, H-4); 6.90 (1H, t, *J* = 6.7, H_{arom}); 7.07 (1H, t, *J* = 6.7, H_{arom}); 7.12 (2H, d, *J* = 6.9, H_{arom}); 7.20 (2H, t, *J* = 7.0, H_{arom}); 7.24 (2H, d, *J* = 6.9, H_{arom}); 7.32 (2H, t, *J* = 6.6, H_{arom}); 7.53 (2H, d, *J* = 7.8, H_{arom}); 7.58 (2H, d, *J* = 7.8, H_{arom}); 8.13 and 9.38 (both 1H, both br. s, NH_2); 10.49 and 10.51 (both 1H, both br. s, 2NHCO); 13.32 (1H, br. s, $N_{(1)}H$)
3d	4,25 (1H, s, H-3); 5.02 (1H, s, H-4); 6.89 (1H, t, *J* = 7.1, H_{arom}); 7.05 (1H, t, *J* = 7.2, H_{arom}); 7.19 (2H, t, *J* = 7.7, H_{arom}); 7.30 (2H, t, *J* = 7.7, H_{arom}); 7.38 (2H, d, *J* = 8.3, H_{arom}); 7.47 (2H, d, *J* = 8.3, H_{arom}); 7.53 (2H, d, *J* = 8.0, H_{arom}); 7.65 (2H, d, *J* = 8.1, H_{arom}); 8.92 and 9.91 (both 1H, both br. s, NH_2); 10.52 and 10.96 (both 1H, both br. s, 2CONH); 13.35 (1H, br. s, $N_{(1)}H$)
3e	2.21 (3H, s, CH_3); 4.25 (1H, s, H-3); 5.01 (1H, s, H-4); 6.72 (1H, d, *J* = 6.8, H_{arom}); 7.03-7.10 (2H, m, H_{arom}); 7.28-7.48 (8H, m, H_{arom}); 7.65 (2H, d, *J* = 8.4, H_{arom}); 8.88 and 9.88 (both 1H, both br. s, NH_2); 10.52 and 10.95 (both 1H, both br. s, 2NHCO); 13.30 (1H, br. s, $N_{(1)}H$)
6a	2.43 (3H, s, CH_3); 3.96 (1H, c, H-3); 4.74 (1H, s, H-4); 6.11 (1H, d, *J* = 2.0, H-3 furan); 6.34 (1H, dd, *J* = 2.0, *J* = 1.5, H-4 furan); 6.92 (1H, t, *J* = 7.3, H_{arom}); 7.05 (1H, t, *J* = 7.3, H_{arom}); 7.19 (2H, t, *J* = 7.8, H_{arom}); 7.30 (2H, t, *J* = 7.8, H_{arom}); 7.52 (2H, d, *J* = 7.7, H_{arom}); 7.56-7.60 (3H, m, H_{arom} and H-5 furan); 7.78 (2H, br. s, NH_2); 8.40 and 10.25 (both 1H, both br. s, 2NHCO)
6b	3.60 (1H, s, H-3); 4.23 and 4.37 (both 1H, both d, ^2J = 13.1, CH_2); 4.66 (1H, s, H-4); 6.92 (1H, t, *J* = 7.2, H_{arom}); 7.08 (1H, t, *J* = 7.2, H_{arom}); 7.14–7.35 (12H, m, H_{arom}); 7.39 (2H, d, *J* = 8.0, H_{arom}); 7.44 (2H, d, *J* = 8.1, H_{arom}); 7.56 (2H, br. s, NH_2); 7.61 (2H, d, *J* = 8.0, H_{arom}); 8.89 and 9.91 (both 1H, both br. s, 2NHCO)
6c	2.25 (3H, s, CH_3); 3.57 (1H, s, H-3); 4.24 and 4.37 (both 1H, both d, ^2J = 13.2, CH_2); 4.62 (1H, s, H-4); 6.93 (1H, t, *J* = 6.5, H_{arom}); 7.06–7.50 (16H, m, H_{arom}); 7.56 (2H, br. s, NH_2); 7.61 (2H, d, *J* = 7.5, H_{arom}); 8.84 and 9.88 (both 1H, both br. s, 2NHCO)
7	3.90 (1H, d, *J* = 5.3, H-3); 4.12 and 4.24 (both 1H, both d, ^2J = 12.1, CH_2); 4.70 (1H, d, *J* = 5.3, H-4); 6.20 (1H, d, *J* = 3.0, H-3 furan); 6.35 (1H, dd, *J* = 3.0, *J* = 1.9, H-4 furan); 7.00 (1H, t, *J* = 7.3, H_{arom}); 7.07 (1H, t, *J* = 7.3, H_{arom}); 7.20-7.35 (10H, m, H_{arom}); 7.44 (1H, d, *J* = 7.9, H_{arom}); 7.56-7.60 (3H, m, H-5 furan and H_{arom}); 9.58 (1H, br. s, $N_{(1)}H$); 10.30 and 10.32 (both 1H, both br. s, NHCO)

We also noted the presence of signals of the amino group protons displayed as two broadened singlets at 8.31-8.92 and 9.38-9.91 ppm respectively. These data show the nonequivalence of the NH_2 group protons, caused probably by intramolecular hydrogen bonds. Previously, according to X-ray structural data, we detected the presence of an extremely strong intramolecular hydrogen bond, closing a six-membered ring between a hydrogen atom of the amino group and the oxygen atom of an amide fragment in pyridine, in which the amino group and the arylcarbamoyl fragment are disposed vicinally [9].

The mass spectra of the substituted tetrahydropyridine-2-thiones **3a-e** are characterized by the presence of a peak for the molecular ion at an even number, which corresponds to the "nitrogen rule" [10], and also by the presence of an $[M+2]^+$ ion which may indicate the content in the molecule of one sulfur atom [11] (Table 3).

A special feature of the ^{1}H NMR spectra of substituted 3,4-dihydropyridines **6a,b** and tetrahydropyridin-2-one **7** is the splitting of the SCH_2Ph methylene group proton signals into two doublets, which indicates their nonequivalence, caused by the absence of rotation of the alkyl substituent around the S–CH_2Ph bond. This fact, known in a series of partially hydrogenated 2-alkylthiopyridines [12, 13], enables ^2J be recorded for the SCH_2Ph group, which is within the limits 12.1-13.2 Hz (Table 2).

TABLE 3. IR and Mass Spectra of Compounds **3a-e, 6a-c**, and **7**

Compound	IR spectrum, ν, cm^{-1}		Mass spectrum, *m/z* (I_{rel}, %)
	NH_2, NH	CONH, δ_{NH_2}	
3a	3380, 3296, 3161	1684, 1656	434 (14) $[M+2]^+$, 432 $[M]^+$ (62), 430 $[M-2]^+$ (100), 356 (19), 312 (14), 218 (9), 193 (7), 124 (6), 84 (5)
3b	3302, 3268 2965	1684, 1654	444 $[M+2]^+$ (9), 442 [M] (49), 440 $[M-2]^+$ (100), 366 (12), 322 (10), 280 (6), 188 (15), 154 (7), 106 (9), 85 (16)
3c	3359, 3177, 2963	1687, 1622	458 $[M+2]^+$ (11), 456 $[M]^+$ (65), 454 $[M-2]^+$ (100), 428 (6), 380 (8), 352 (12), 188 (15), 159 (13), 122 (10), 84 (17)
3d	3350, 3294, 3134	1696, 1662	479 $[M+2]^+$ (48); 477 $[M]^+$ (100), 384 (18), 356 (9), 239 (11), 186 (5), 94 (16)
3e	3318, 3296, 2956	1686, 1631	492 $[M+1]^+$ (61), 491 (100) $[M]^+$, 459 (10), 398 (14), 296 (5), 220 (19), 180 (11), 83 (10)
6a	3342, 3218, 2995	1698, 1653	448 $[M+2]^+$ (37), 447 $[M+1]^+$ (100), 428 (5), 354 (10), 260 (8), 157 (50), 99 (11)
6b	3365, 3300, 3115	1684, 1637	534 $[M+2]^+$ (50), 533 $[M+1]^+$ (100), 440 (12), 295 (16), 157 (48), 94 (22)
6c	3352, 3205, 3199	1683, 1653	546 $[M]^+$ (48), 544 $[M-2]^+$ (100), 388 (11), 261 (9), 136 (15), 106 (4), 84 (7)
7	3310, 3214, 2965	1685, 1647	524 $[M+1]^+$ (100), 432 (15), 157 (14), 94 (12)

EXPERIMENTAL

The IR spectra of the synthesized compounds were recorded on a IKS-40 instrument in nujol. The ^1H NMR spectra were recorded on a Varian Mercury 400 (400 MHz) instrument in DMSO-d_6 solution, internal standard was TMS. The mass spectra were obtained on a Chrommass GC/MS instrument Hewlett-Packard 5890/5972, on a HP-5 column MS (70 eV) in methylene chloride solution. Melting points were determined on a Kofler block. A check on the progress of reactions and the purity of the substances obtained was effected by TLC on Silufol UV-254 plates, eluent was an acetone–hexane mixture, 3:5, visualization with iodine vapor and UV light.

$N_{(3)}$,$N_{(5)}$-Diphenyl-6-amino-4-(2-furyl)-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxamide (3a), $N_{(3)}$,$N_{(5)}$,4-Triphenyl-6-amino-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-carboxamide (3b), $N_{(3)}$,$N_{(5)}$-Diphenyl-6-amino-2-thioxo-4-(4-tolyl)-1,2,3,4-tetrahydropyridine-3,5-dicarboxamide (3c), $N_{(3)}$,$N_{(5)}$-Diphenyl-6-amino-4-(4-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxamide (3d), and $N_{(3)}$-(3-Tolyl)-$N_{(5)}$-phenyl-6-amino-4-(4-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxamide (3e). The CH-acid **2a,b** (5 mmol) was added at 20°C to a stirred solution of metallic sodium (0.115 g, 5 mmol) in absolute ethanol (30 ml) and stirred for 10 min to form a homogeneous phase. The appropriate acrylamide **1a-d** (5 mmol) was then added, the mixture stirred for 2 h, after which the mixture was diluted with 10% hydrochloric acid to pH 6, and left at room temperature. After 1 day the solid which formed was filtered off, washed with ethanol and with hexane, and recrystallized from ethanol (Tables 1-3).

$N_{(3)}$,$N_{(5)}$-Diphenyl-6-amino-4-(2-furyl)-2-methylthio-3,4-dihydropyridine-3,5-dicarboxamide (6a), $N_{(3)}$,$N_{(5)}$,4-Triphenyl-6-amino-2-benzylthio-3,4-dihydropyridine-3,5-dicarboxamide (6b), and $N_{(3)}$,$N_{(5)}$-

6-amino-2-benzylthio-4-(4-tolyl)-3,4-dihydropyridine-3,5-dicarboxamide (6c). A solution of metallic sodium (0.115 g, 5 mmol) in absolute ethanol (15 ml) was added to a stirred suspension of compound **3a-c** (5 mmol) in absolute ethanol (15 ml) at 20°C, and stirred for 10 min to obtain a homogeneous phase. Alkyl halide **5a,b** (5 mmol) was added to the reaction mixture, which was stirred for 1 h, and then left for 2 days at room temperature. The solid formed was filtered off, washed with ethanol, and with hexane, and recrystallized from ethanol (Tables 1-3).

$N_{(3)}$,$N_{(5)}$-Diphenyl-6-benzylthio-4-(2-furyl)-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxamide (7). A 10% aqueous solution of KOH (1.68 ml, 3 mmol) was added to a stirred suspension of compound **3a** (1.30 g, 3 mmol) in ethanol (30 ml), and the mixture was stirred at 50°C until complete solution. Benzyl chloride **5b** (0.35 ml, 3 mmol) was added to the obtained solution, and the mixture was left for 2 days. The resulting solid was filtered off, washed with ethanol, and with hexane, and recrystallized from ethanol (Tables 1-3).

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