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NEW METHOD FOR THE SYNTHESIS OF 1,2,8-TRIAZASPIRO[4.5]DECANE DERIVATIVES

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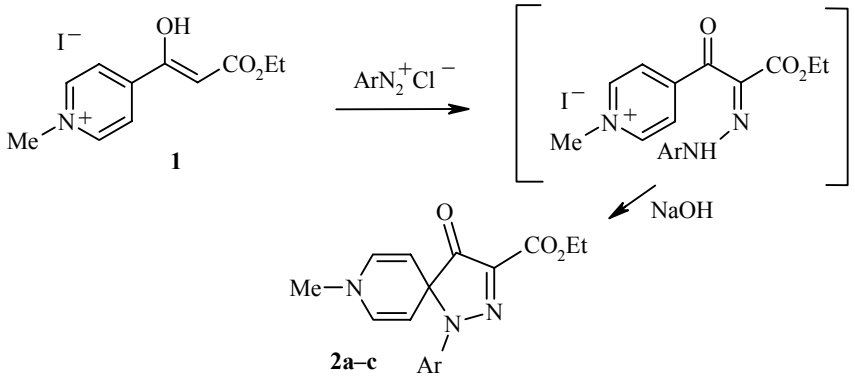
Only one method has been reported for the synthesis of 1,2,8-triazaspiro[4.5]decane derivatives based on the reaction of esters of 2-(4-piperidinylidene)acetic acid with alkylhydrazines, leading to compounds with high biological activity [1, 2]. Naito and Ninomiya [3] have reported that some N-alkylisonicotinoyl derivatives can form spirocondensed systems in the presence of bases. We have found that the reaction of 4-[(*Z*)-3-ethoxycarbonyl-1-hydroxy-1-propenyl]-1-methylpyridinium iodide (**1**) with aryldiazonium salts and subsequent treatment of the reaction mixture with base leads to ethyl 1-aryl-8-methyl-4-oxo-1,2,8-triazaspiro-[4.5]deca-2,6,9-triene-3-carboxylates **2a-c**.



a Ar = C_6H_5, **b** Ar = 4-FC_6H_4, **c** Ar = 4-ClC_6H_4

Formation of a spiro system is indicated, in particular, by the signal for the spiro atom C(5) at 76.5-76.7 ppm and the pattern for the ^{1}H NMR spectrum, which is characteristic for 1,4-dihydropyridines [3]. NOESY spectra and heteronuclear $^1H^{13}C$ correlation spectra (HMQC and HMBC), which were taken in addition to ^{1}H and ^{13}C NMR spectra, prove the structure of compound **2**. The experimental results are given in Table 1. The assignments made for the signals are shown in the scheme for compound **2a**; the HMBC and NOESY correlations, serving as the basis of these assignments, are indicated by arrows.

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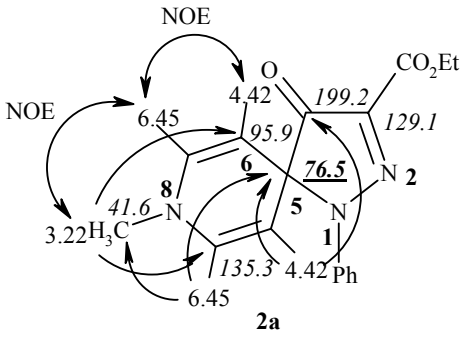

2a

TABLE 1. $^{1}H^{13}C$ Correlations for Compounds **2a** and **2b**

2a		**2b**	
Signal ^{1}H, δ, ppm	HMBC	Signal ^{1}H, δ, ppm	HMBC
7.51	140.3, 125.8, 118.6	7.47	161.9, 159.5, 136.7, 120.5
7.33	140.3, 129.1	7.03	161.9, 159.5, 136.7, 116.0
7.18	118.6	6.47	135.5, 95.7, 76.7, 41.6
6.45	135.3, 95.9, 76.5, 41.6	4.41	199.0, 161.9, 135.5, 95.7, 76.7, 14.6
4.42	199.2, 162.0, 95.9, 76.5, 14.6	3.22	135.5, 95.7
3.22	135.3, 95.9	1.40	61.3
1.41	61.3		

The IR spectra were taken on a Pye-Unicam SP3-300 spectrometer with KBr plates. The ^{1}H and ^{13}C NMR spectra were taken on a Varian Mercury 400 spectrometer at 400 and 100 MHz, respectively, in $CDCl_3$ using TMS as the internal standard. 4-[(*Z*)-3-ethoxycarbonyl-1-hydroxy-1-propenyl]-1-methylpyridinium iodide was prepared according to Bunting and Kanter [4].

Ethyl 1-Aryl-8-methyl-4-oxo-1,2,8-triazaspiro[4.5]deca-2,6,9-triene-3-carboxylates 2a-c. Aniline (3 mmol) and 21% aq. sodium nitrite (1 ml) were added with stirring to 2 N hydrochloric acid (5 ml) cooled to 0°C. The mixture was maintained for 30 min and, then, sodium acetate (1.3 g) and ethyl N-methylisonicotinoyl acetate **1** (1 g, 3 mmol) were added. The mixture was stirred for 2 h at room temperature and 10% aq. sodium hydroxide was added to bring the pH to 9. The crystalline precipitate formed was filtered off and washed with ethanol.

Ethyl Ester 2a was obtained in 54% yield (0.5 g); mp 199-201°C (ethyl acetate). IR spectrum, ν, cm^{-1}: 1735 (C=O), 1685 (C=N), 1450, 1335 (C–O), 1155 (C–O), 1098, 755, 658. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.51 (2H, d, $^{3}J = 8.0$, H-2', H-6'); 7.33 (2H, t, $^{3}J = 8.0$, H-3', H-5'); 7.18 (1H, t, $^{3}J = 8.0$, H-4'); 6.45 (2H, d, $^{3}J = 7.6$, H-7, H-9); 4.42 (4H, m, $C\underline{H}_2CH_3$, H-6, H-10); 3.22 (3H, s, N–CH_3); 1.41 (3H, t, $^{3}J = 7.0$, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 199.2 (C-4); 162.0 ($\underline{C}O_2Et$); 140.3 (C-1'); 135.3 (C-7, C-9); 129.1 (C-3, C-3', C-5'); 125.8 (C-4'); 118.6 (C-2', C-6'); 95.9 (C-6, C-10); 76.5 (C-5); 61.3 (CH_2); 41.6 (N–CH_3); 14.6 (C–$\underline{C}H_3$). Found, %: C 65.51; H 5.45; N 13.52. $C_{17}H_{17}N_3O_3$. Calculated, %: C, 65.58; H 5.50; N 13.50.

Ethyl Ester 2b was obtained in 66% yield (0.65 g); mp 215-217°C (ethanol). IR spectrum, ν, cm^{-1}: 1738 (C=O), 1685 (C=N), 1458, 1331 (C–O), 1231 (C–F), 1155 (C–O), 1098, 910, 840. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.47 (2H, m, H-2', H-6'); 7.03 (2H, m, H-3', H-5'); 6.47 (2H, d, $^{3}J = 7.6$, H-7, H-9); 4.41 (4H, m, $C\underline{H}_2Me$, H-6, H-10); 3.22 (3H, s, N–CH_3); 1.40 (3H, t, $^{3}J = 7.0$, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 199.0 (C-4); 161.9 ($\underline{C}O_2Et$); 159.5 (C-4'); 136.7 (C-1'); 135.5 (C-7, C-9); 129.3 (C-3); 120.5 (C-2', C-6'); 116.1 (C-3', C-5'); 95.7 (C-6, C-10); 76.7 (C-5); 61.3 (CH_2); 41.6 (N–CH_3); 14.6 (C–$\underline{C}H_3$). Found, %: C 61.95; H 4.83; N 12.78. $C_{17}H_{16}FN_3O_3$. Calculated, %: C 62.00; H 4.90; N 12.76.

Ethyl Ester 2c was obtained in 45% yield (0.47 g), mp 202-203°C (ethanol), IR spectrum, ν, cm^{-1}: 1740 (C=O), 1685 (C=N), 1460, 1400, 1331 (C–O), 1160 (C–O), 1098, 910, 830. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.43 (2H, d, ^3J = 8.5, H-2', H-6'); 7.30 (2H, d, ^3J = 8.5, H-3', H-5'); 6.40 (2H, d, ^3J = 7.2, H-7, H-9); 4.42 (4H, m, $C\underline{H}_2Me$); H-6, H-10); 3.23 (3H, s, $N–CH_3$); 1.40 (3H, t, ^3J = 7.2, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 199.0 (C-4); 161.9 ($\underline{C}O_2Et$); 138.9 (C-1'); 135.6 (C-7, C-9); 131.2 (C-4'); 129.8 (C-3); 129.3 (C-2', C-6'); 119.7 (C-3', C-5'); 95.7 (C-6, C-10); 76.5 (C-5); 61.5 (CH_2); 41.7 ($N–CH_3$); 14.7 ($C-\underline{C}H_3$). Found, %: Cl 10.28; N 12.16. $C_{17}H_{16}ClN_3O_3$. Calculated, %: Cl 10.25; N 12.15.

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