Functional Materials 12, No.3 (2005)

Diastereoselective synthesis of spirotetrahydropyridines on the basis of heterocyclic CH-acids

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Received January 19, 2005

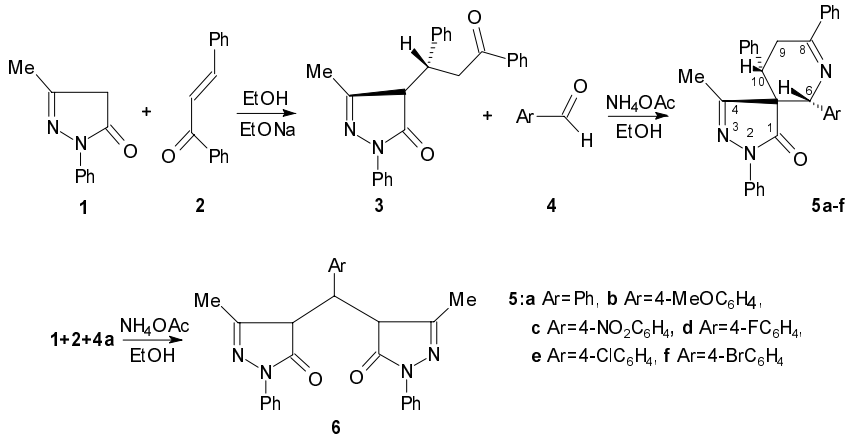
The work is devoted to the diastereoselective synthesis of 6-aryl-4-methyl-2,8,10-triphenyl-2,3,7-triazaspiro[4,5]deca-3,7-dien-1-ones and 2,4-dimethyl-7,9,11-triaryl-2,4,8-triazaspiro[5,5]undec-8-en-1,3,5-triones by reaction of 1-phenyl-3-methylpyrazolin-5-one and 1,3-dimethylbarbituric acid with chalcones and aromatic aldehydes in the presence of ammonium acetate. The stereochemistry of the compounds obtained has been determined using NOE experiment.

Работа посвящена диастереоселективному синтезу 6-арил-4-метил-2,8,10-трифенил-2,3,7-триазаспиро[4,5]дека-3,7-диен-1-онов и 2,4-диметил-7,9,11-триарил-2,4,8-триазаспиро[5,5]ундек-8-ен-1,3,5-трионов в реакциях гетероциклических CH-кислот — 1-фенил-3-метилпиразолин-5-она и 1,3-диметилбарбитуровой кислоты с халконами и ароматическими альдегидами в присутствии ацетата аммония. Стереохимия целевых продуктов определена с помощью NOE-эксперимента.

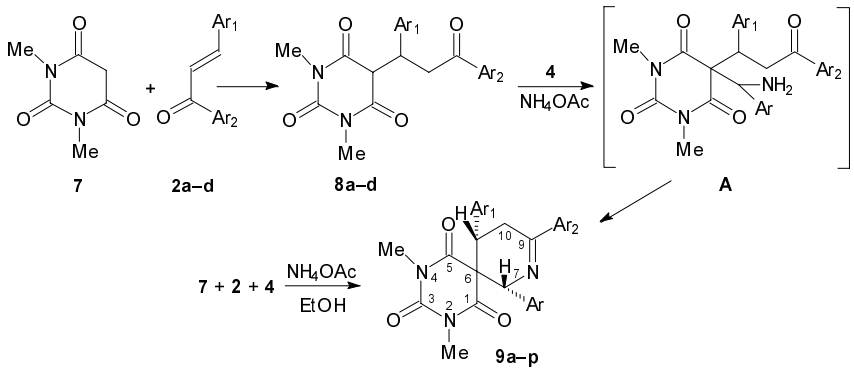
It is known that pyridine, barbituric acid and pyrazolin-5-one derivatives exhibit a high pharmacological potential. This provides a continuous attention of researchers to heterocyclic ensembles integrating these fragments. Thus, spirocompounds based on barbituric acid show a high hypnotic and sedative activity [1]. Earlier we investigated spiropyrolines obtained from 5,6-diamino-1,3-dimethyluracil and α,β-unsaturated ketones [2]. The purpose of the present work was synthesis and investigation of spirotetrahydropyridines based on such typical heterocyclic CH-acids as 1,3-dimethylbarbituric acid and 1-phenyl-3-methylpyrazolin-5-one.

The synthesis of spirotetrahydropyridines from 3-phenylisoxazolin- and 1,3-diphenylpyrazolin-5-ones, chalcones, and benzaldehyde in the presence of NH_4OAc was described before [3]. However, spirans were not obtained from substituted benzaldehydes. Authors [3] explained this fact by steric and electronic effects.

In order to decrease steric hindrances in the molecule of 1,3-diphenylpyrazolin-5-one, we have replaced phenyl radical in the position 3 of pyrazolone ring by methyl radical and reproduced the conditions of the spiran synthesis [3]. The intermediate β-adduct **3** was obtained by the well known method [3] and consequently brought in reaction with aldehydes **4** (scheme 1). As a



Scheme 1



2, 8a–d: **a** Ar_1= Ar_2=Ph; **b** Ar_1= Ph, Ar_2= 4–Cl–C_6H_4; **c** Ar_1=Ar_2= 4–MeO–C_6H_4; **d** Ar_1= 4–Me–C_6H_4, Ar_2= 4·MeO–C_6H_4.
9a–e:Ar_2= Ar_1= Ph; Ar: **a** =Ph, **b** = 4–MeO–C_6H_4, **c** = 4–NO_2–C_6H_4, **d** = 4–F–C_6H_4; **e** = 4–Br–C_6H_4; **9f–k**: Ar_1=Ph; Ar_2=4–Cl–C_6H_4; Ar: **f** = Ph, **g** = 2–MeO–C_6H_4, **h** = 4–MeO–C_6H_4, **i** = 4–NO_2–C_6H_4, **j** = 4–F–C_6H_4, **k** = 4–Br–CH_4.
9l, m: Ar_1 = Ar_2 = 4–MeO–C_6H_4; Ar: **l** 4–MeO–C_6H_4, **m** = 4–Br–C_6H_4,
9n–p: Ar_1 = 4–Me–C_6H_4; Ar_2 = 4–MeO–C_6H_4; Ar: **n** = 4–NO_2–C_6H_4, **o** = 4–Cl–C_6H_4, **p** = 4–Br–C_6H_4.

Scheme 2.

result of the interaction, 2,3,7-triazaspiro[4,5]deca-3,7-dien-1-ones **5a-5f** were isolated at rather high yields (Table 1).

The attempt of one-pot synthesis of spirans **5** was unsuccessful and led to the formation of bis-adducts **6a**. Their physicochemical and spectral characteristics are identical with the literature data [5] (Tables 1, 2).

To expand the library of spirotetrahydropyridines, we have obtained new compounds belonging to this series. 1,3-Dimethylbarbituric acid (**7**) was used as a CH-acid. The intermediate β-adducts **8a-d** were synthesized starting from chalcones **2a-d** and acid **7** in methanol in the presence of Et_3N following the literature procedures [6, 7]. A short-term refluxing (15–30 min) of intermediates **8** and aldehydes **4** with an excess of NH_4OAc in ethanol led to the formation of 2,4,8-triazaspiro[5,5]undec-8-en-1,3,5-triones **9a-9m** which typically did not require any additional purification (Scheme 2).

The presence of acceptor substitutes both in the chalcone and in the aldehyde component molecules results in an increased yield of products **9**. Using of 2-methoxybenzaldehyde decreases the yield (compound **9g**) because of steric effects. In the case of 2-nitrobenzaldehyde, the spirans **9** were not isolated at all.

It turned out that compounds **9** can be obtained in a one-pot procedure also by a short-term refluxing acid **7** with equimolar quantity of chalcones **2** and aromatic aldehydes **4** in the similar experimental conditions. The reaction duration remains essentially unchanged in this case.

Structures of the obtained compounds **5a-5f** and **9a-9p** were confirmed by spectral methods. So, the ^1H NMR spectra thereof

Table 1.Physical properties and analytical data for compounds 5a-f, 6a, 8b,c, 9a-m.

Product	Formula	M.p. (°C)	Yield, %	Elemental analysis (calculated/found)			
				C	H	N	Hal
1	2	3	4	5	6	7	8
5a	$C_{32}H_{27}N_3O$	173-174	74	81.85/ 81.83	5.80/ 5.81	8.95/ 8.98	–
5b	$C_{33}H_{29}N_3O_2$	161-162	63	79.33/ 79.30	5.85/ 5.88	8.41/ 8.38	–
5c	$C_{32}H_{26}N_4O_3$	202-203	92	74.69/ 74.68	5.09/ 5.11	10.89/ 10.89	–
5d	$C_{32}H_{26}FN_3O$	150-152	66	78.83/ 78.87	5.37/ 5.34	8.62/ 8.56	–
5e	$C_{32}H_{26}ClN_3O$	205-206	86	76.26/ 76.28	5.20/ 5.24	8.34/ 8.30	7.03/ 7.00
5f	$C_{32}H_{26}BrN_3O$	220-221	89	70.08/ 70.04	4.78/ 4.77	7.66/ 7.63	14.57/ 14.60
6a	$C_{27}H_{24}N_4O_2$	159 160 [5]	75	–	–	–	–
8b	$C_{21}H_{19}ClN_2O_4$	83	76	63.24/ 63.20	4.80/ 4.81	7.02/ 7.00	8.89/ 8.92
8c	$C_{23}H_{24}N_2O_6$	110	80	65.08/ 65.06	5.70/ 5.73	6.60/ 6.61	–
9a	$C_{28}H_{25}N_3O_3$	190-191	78	74.48/ 74.46	5.58/ 5.61	9.31/ 9.29	–
9b	$C_{29}H_{27}N_3O_4$	156-157	66	72.33/ 72.30	5.65/ 5.64	8.73/ 8.70	–
9c	$C_{28}H_{24}N_4O_5$	205-206	88	67.73/ 67.71	4.87/ 4.90	11.28/ 11.28	–
9d	$C_{28}H_{24}FN_3O_3$	203-204	56	71.63/ 71.59	5.15/ 5.17	8.95/ 8.92	

contain singlets of protons H-6 (H-7 for **9a-9p**) at 5.29–5.40 (5.58–6.02) ppm, signals of protons in the AMX (ABX) system of the CH_2(9)–CH(10) {CH_2(10)–CH(11)} fragment in the 3.14–3.79 (3.14–4.12) ppm range and multiplets of aromatic protons at 6.80–8.00 (6.74–8.16) ppm. One of the diastereotopic hydrogens of methylene group in spirans **9** is selectively exchangeable with D_2O. So, the H–D exchange is completed in around 48 h and is observed from the collapse of the ABX system into AX system for compound **9h** in the $CDCl_3$ solution with addition of D_2O. This gives an evidence of higher acidity of this proton. This considerable difference in exchange rate can reasonably be attributed to stereoelectronic control. In fact, the 3D modeling studies of **9a** show that the CH_2-C=N fragment is oriented in such a way that one C–H bond is

Table 1 (continued).

1	2	3	4	5	6	7	8
9e	$C_{28}H_{24}BrN_3O_3$	198	72 92[1]	63.40/ 63.43	4.56/ 4.52	7.92/ 7.91	15.06/ 15.09
9f	$C_{28}H_{24}ClN_3O_3$	193-194	75 80[1]	69.20/ 69.18	4.98/ 4.97	8.65/ 8.62	7.30/ 7.34
9g	$C_{29}H_{26}ClN_3O_4$	162	44	67.50/ 67.54	5.08/ 5.06	8.14/ 8.13	6.87/ 6.90
9h	$C_{29}H_{26}ClN_3O_4$	218	79	67.50/ 67.48	5.08/ 5.09	8.14/ 8.16	6.87/ 6.84
9i	$C_{28}H_{23}ClN_4O_5$	197	83	63.34/ 63.30	4.37/ 4.35	10.55/ 10.53	6.68/ 6.71
9j	$C_{28}H_{23}ClFN_3O_3$	218	84	66.73/ 66.70	4.60/ 4.63	8.34/ 8.32	7.03/ 6.99
9k	$C_{28}H_{23}BrClN_3O_3$	218	88	59.54/ 59.51	4.10/ 4.08	7.44/ 7.46	14.15/ 14.18(Br) 6.28/ 6.25 (Cl)
9l	$C_{31}H_{31}N_3O_6$	135-137	59	68.75/ 68.73	5.77/ 5.80	7.76/ 7.77	–
9m	$C_{30}H_{28}BrN_3O_5$	130	38	61.02/ 61.04	4.78/ 4.75	7.12/ 7.10	13.53/ 13.50
9n	$C_{30}H_{28}N_4O_6$	164-166	42[1]	66.66/ 66.69	5.22/ 5.20	10.36/ 10.36	–
9o	$C_{30}H_{28}ClN_3O_4$	176	34[1]	67.98/ 67.96	5.32/ 5.29	7.93/ 7.91	6.69/ 6.73
9p	$C_{30}H_{28}BrN_3O_4$	185	50[1]	62.72/ 62.70	4.91/ 4.94	7.31/ 7.29	13.91/ 13.93

[1] One-pot synthesis

adjacent to π-orbital of the imine function whereas the other C–H bond makes angle of 45° with the π-system plane. It is of interest that the same exchange process for compound **5e** goes considerably faster (about 0.5 h).

The ^{13}C NMR spectroscopy data for compounds **5d** and **9d**, **9e** do not contradict the proposed structure. The most typical signal of the carbon spiro-atom C-5 (C-6) is localized at 56–59 ppm. Thus, NMR spectroscopy data give evidence of spiroimine structure of the synthesized compounds **5a-5f**, **9a-9p**.

Mass spectra recorded for compounds **5e**, **5f** and **9e**, **9f**, **9h** also confirmed the assigned structures. Those spectra contain the molecular ion peaks of a moderate intensity. The fragmentation processes are of the same character for both types of the compounds and include successive elimination

Table 2. ^{1}H NMR and ^{13}C NMR date for compounds 5a-f, 8b,c, 9a-p

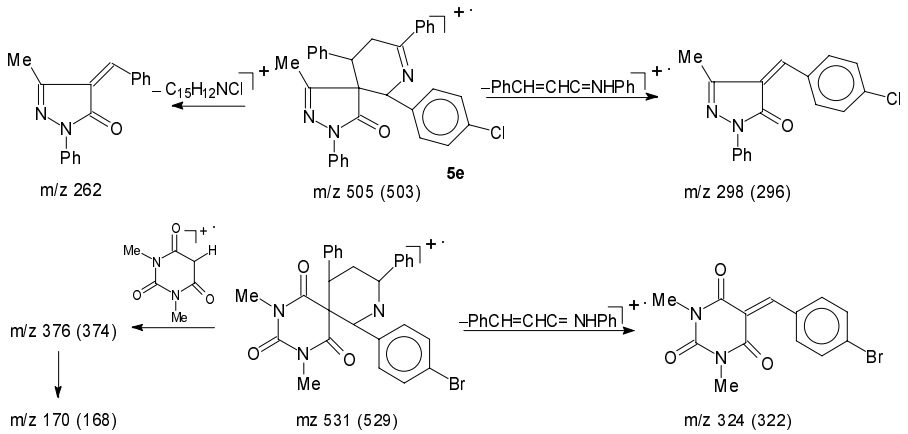
Comp.	^{1}H NMR
5a	2.26 s, 3 H (CH_3); 3.19 dd, 1 H, $^{2}J_{AM}$ = 16.4, $^{3}J_{AX}$ = 3.6 (CH_A-9); 3.61 dd, 1 H, $^{3}J_{AX}$ = 3.6, $^{3}J_{MX}$ = 12.4 (CH_X-10); 3.78 ddd, 1 H, $^{2}J_{AM}$ = 16.4, $^{3}J_{MX}$ = 12.4, ^{5}J = 3.0 (CH_M-9); 5.32 s, 1 H (CH-6); 7.07–7.43 m, 18 H (Ar); 7.97 m, 2 H (Ar).
5b	2.23 s, 3 H (CH_3); 3.19 dd, 1 H, $^{2}J_{AM}$ = 17.0, $^{3}J_{AX}$ = 3.4 (CH_A-9); 3.63 m, 5 H, $^{3}J_{AX}$ = 3.4, $^{3}J_{MX}$ = 12.6 (OCH_3+CH_X-10+CH_M-9); 5.27 s, 1 H (CH-6); 6.77 d, 2 H, J = 8.0 (Ar); 7.11–7.43 m, 15 H (Ar); 7.97 d, 2 H, J = 8.0 (Ar).
5c	2.31 s, 3 H (CH_3); 3.25 dd, 1 H, $^{2}J_{AM}$ = 16.4, $^{3}J_{AX}$ = 3.8 (CH_A-9); 3.65 dd, 1 H, $^{3}J_{AX}$ = 3.8, $^{3}J_{MX}$ = 12.2 (CH_X-10); 3.77 ddd, 1 H, $^{2}J_{AM}$ = 16.4, $^{3}J_{MX}$ = 12.2, ^{5}J = 2.8 (CH_M-9); 5.42 s, 1 H (CH-6); 7.10–7.26 m, 10 H (Ar); 7.43 m, 5 H (Ar); 7.97 d, 2 H, J = 7.6 (Ar); 8.11 d, 2 H, J = 7.6 (Ar).
5d	2.25 s, 3 H (CH_3); 3.19 dd, 1 H, $^{2}J_{AM}$ = 16.6, $^{3}J_{AX}$ = 4.4 (CH_A-9); 3.59 dd, 1 H, $^{3}J_{AX}$ = 4.4, $^{3}J_{MX}$ = 12.2 (CH_X-10); 3.70 ddd, 1 H, $^{2}J_{AM}$ = 16.6, $^{3}J_{MX}$ = 12.2, ^{5}J = 3.0 (CH_M-9); 5.30 s, 1 H (CH-6); 6.93 t, 2 H, J = 8.4; 7.09–7.44 m, 15 H (Ar); 7.94 d, 2 H, J = 7.5 (Ar).
5e	2.25 s, 3 H (CH_3); 3.19 dd, 1 H, $^{2}J_{AM}$ = 16.6, $^{3}J_{AX}$ = 4.0 (CH_A-9); 3.60 dd, 1 H, $^{3}J_{AX}$ = 4.0, $^{3}J_{MX}$ = 12.2 (CH_X-10); 3.73 ddd, 1 H, $^{2}J_{AM}$ = 16.6, $^{3}J_{MX}$ = 12.2, ^{5}J = 3.0 (CH_M-9); 5.29 s, 1 H (CH-6); 7.10–7.43 m, 17 H (Ar); 7.94 d, 2 H, J = 7.2 (Ar).
5f	2.24 s, 3 H (CH_3); 3.19 dd, 1 H, $^{2}J_{AM}$ = 16.8, $^{3}J_{AX}$ = 4.0 (CH_A-9); 3.59 dd, 1 H, $^{3}J_{AX}$ = 4.0, $^{3}J_{MX}$ = 12.2 (CH_X-10); 3.76 ddd, 1 H, $^{2}J_{AM}$ = 16.8, $^{3}J_{MX}$ = 12.2, ^{5}J = 3.0 (CH_M-9); 5.27 s, 1 H (CH-6); 7.14 d, 2 H, J = 8.0 (Ar); 7.24–7.44 m, 15 H (Ar); 7.94 d, 2 H, J = 7.8 (Ar). ^{13}C NMR: 10.0, 25.8, 38.9, 56.3, 61.5, 115.5, 117.3, 121.0, 122.0, 123.0, 123.6, 123.9, 124.0, 124.5, 125.1, 125.9, 126.5, 132.4, 133.9, 154.7, 162.6, 167.1.
8b	3.05 s, 3 H (CH_3), 3.12 s, 3 H (CH_3); 3.47 dd, 1 H, $^{2}J_{H\alpha-\alpha'}$ = 18.0, $^{3}J_{H\alpha-\beta}$ = 4.6 (CH_α); 3.96 d, 1H, $^{3}J_{H6\text{-}H\beta}$ = 3.6 (CH-6); 4.08 dd, 1H, $^{2}J_{H\alpha-\alpha'}$ = 18.0, $^{3}J_{H\alpha'-\beta}$ = 9.4 ($CH_{\alpha'}$); 4.35 m, 1 H (CH_β); 7.10 m, 2 H (Ar); 6.26 m, 3 H (Ar); 7.45 d, 2 H, J = 8.5 (Ar); 7.96 d, 2 H, J = 8.5 (Ar).
8c	3.07 s, 3 H (CH_3), 3.12 s, 3 H (CH_3); 3.42 dd, 1 H, $^{2}J_{H\alpha-\alpha'}$ = 18.0, $^{3}J_{H\alpha-\beta}$ = 5.5 (CH_α); 3.75 s, 3 H (OCH_3); 3.87 s, 3 H (OCH_3); 3.94 d, 1H, $^{3}J_{H6\text{-}H\beta}$ = 4.4 (CH-6); 4.03 dd, 1H, $^{2}J_{H\alpha-\alpha'}$ = 8.0, $^{3}J_{H\alpha'-\beta}$ = 9.0 ($CH_{\alpha'}$); 4.31 m, 1 H (CH_β); 6.77 d, 2 H, J = 8.8 (Ar); 6.91–7.03 m, 4 H (Ar); 7.99 d, 2 H, J = 8.8 (Ar).
9a	2.79 s, 3 H (CH_3); 3.02 s,3 H (CH_3); 3.21 dd,1 H, $^{2}J_{AB}$ = 18.5, $^{3}J_{AX}$ = 5.1 (CH_A-10); 3.55 ddd, 1 H, $^{2}J_{AB}$ = 18.5, $^{3}J_{BX}$ = 11.9, ^{5}J = 3 (CH_B-10); 4.11 dd, 1H, $^{3}J_{AX}$ = 5.1, $^{3}J_{BX}$ = 11.9 (CH_X-11); 5.69 s, 1 H (CH-7); 7.10–7.45 m, 13 H (Ar); 7.97–8.01 m, 2 H (Ar).
9b	2,83 s, 3 H (CH_3); 3.02 s,3 H (CH_3); 3.21 dd, 1 H, $^{2}J_{AB}$ = 18.5, $^{3}J_{AX}$ = 5.1 (CH_A-10); 3.55 ddd, 1 H, $^{2}J_{AB}$ = 18.5, $^{3}J_{BX}$ = 11.9, ^{5}J = 3 (CH_B-10); 4.11 dd, 1 H, $^{3}J_{AX}$ = 5.1, $^{3}J_{BX}$ = 11.9 (CH_X-11); 5.69 s, 1 H (CH-7); 7.10–7.45 m, 13 H (Ar); 7.97–8.01 m, 2 H (Ar).
9c	2.82 s, 3 H (CH_3); 3.02 s, 3 H (CH_3); 3.25 dd, 1 H, $^{2}J_{AB}$ = 18.3, $^{3}J_{AX}$ = 5.3 (CH_A-10); 3.46 ddd, 1 H, $^{2}J_{AB}$ = 18.3, $^{3}J_{BX}$ = 12.0, ^{5}J = 3.0 (CH_B-10); 4.03 dd, 1 H, $^{3}J_{AX}$ = 5.3, $^{3}J_{BX}$ = 12.0 (CH_X-11); 5.93 s, 1 H (CH-7); 7.12 m, 2H (Ar); 7.26–7.48 m, 8 H (Ar); 7.95–7.99 m, 2 H (Ar); 8.16 d, 2H, J = 9.0 (Ar).
9d	2.82 s, 3 H (CH_3); 3.02 s, 3 H (CH_3); 3.25 dd, 1 H, $^{2}J_{AB}$ = 18.3, $^{3}J_{AX}$ = 5.3 (CH_A-10); 3.46 ddd, 1 H, $^{2}J_{AB}$ = 18.3, $^{3}J_{BX}$ = 12.0, ^{5}J = 3.0 (CH_B-10); 4.03 dd, 1 H, $^{3}J_{AX}$ = 5.3, $^{3}J_{BX}$ = 12.0 (CH_X-11); 5.93 s, 1 H (CH-7); 7.12 m, 2H (Ar); 7.26–7.48 m, 8 H (Ar); 7.95–7.99 m, 2 H (Ar); 8.16 d, 2H, J = 9.0 (Ar).
9e	2.85 s, 3 H (CH_3); 3.01 s, 3 H (CH_3); 3.17 dd, 1 H, $^{2}J_{AB}$ = 17.7, $^{3}J_{AX}$ = 6.0 (CH_A-10); 3.48 ddd, 1 H, $^{2}J_{AB}$ = 17.7, $^{3}J_{BX}$ = 11.6, ^{5}J = 2.8 (CH_B-10); 4.04 dd, 1 H, $^{3}J_{AX}$ = 6.0, $^{3}J_{BX}$ = 11.6 (CH_X-11); 5.72 s, 1 H (CH-7); 7.03–7.46 m, 12 H (Ar); 7.95–7.99 m, 2 H (Ar). ^{13}C NMR: 28.1, 28.8, 30.6, 46.0, 58.8, 68.3, 121.5, 127.0, 128.3, 128.8, 128.9, 129.3, 130.1, 130.9, 131.7, 138.3, 138.8, 139.3, 149.8, 166.2, 167.1, 171.1.

Table 2 (continued).

Comp.	^{1}H NMR
9f	2.80 s, 3 H (CH_3); 3.02 s, 3 H (CH_3); 3.17 dd, 1 H, $^2J_{AB}$ = 18.3, $^3J_{AX}$ = 5.5 (CH_A-10); 3.52 ddd, 1 H, $^2J_{AB}$ = 18.3, $^3J_{BX}$ = 11.8, ^5J = 3.0 (CH_B-10); 4.10 dd, 1 H, $^3J_{AX}$ = 5.5, $^3J_{BX}$ = 11.8 (CH_X-11); 5.67 s, 1 H (CH-7); 7.09–7.26 m, 10 H (Ar); 7.40 d, 2 H, J = 8.2 (Ar), 7.93 d, 2 H, J = 8.2 (Ar).
9g	2.73 s, 3 H (CH_3); 3.03 s, 3 H (CH_3); 3.16 dd, 1 H, $^2J_{AB}$ = 18.8, $^3J_{AX}$ = 6.4 (CH_A-10); 3.57 dd, 1 H, $^2J_{AB}$ = 18.8, $^3J_{BX}$ = 11.8 (CH_B-10); 3.74 s, 3 H (OCH_3); 4.11 dd, 1 H, $^3J_{AX}$ = 6.4, $^3J_{BX}$ = 11.8 (CH_X-11); 6.02 s, 1 H (CH-7); 6.79 d, 1 H, J = 7.6 (Ar); 6.90–6.98 m, 3 H (Ar); 7.14–7.30 m, 5H (Ar); 7.38 d, 2 H, J = 8.0 (Ar); 7.90 d, 2 H, J = 8.0 (Ar).
9h	2.83 s, 3 H (CH_3); 3.01 s, 3 H (CH_3); 3.15 dd, 1 H, $^2J_{AB}$ = 18.6, $^3J_{AX}$ = 6.2 (CH_A-10); 3.48 ddd, 1 H, $^2J_{AB}$ = 18.6, $^3J_{BX}$ = 11.7, ^5J = 2.8 (CH_B-10); 3.76 s, 3 H (OCH_3); 4.07 dd, 1 H, $^3J_{AX}$ = 6.2, $^3J_{BX}$ = 11.7 (CH_X-11); 5.62 s, 1 H (CH-7); 6.78 d, 2 H, J = 8.2 (Ar); 7.03 d, 2 H, J = 8.2 (Ar); 7.15 m, 2 H (Ar); 7.26 m, 3H (Ar); 7.39 d, 2 H, J = 8.4 (Ar); 7.92 d, 2 H, J = 8.4 (Ar).
9i	2.84 s, 3 H (CH_3); 3.01 s, 3 H (CH_3); 3.19 dd, 1 H, $^2J_{AB}$ = 18.0, $^3J_{AX}$ = 6.0 (CH_A-10); 3.43 ddd, 1 H, $^2J_{AB}$ = 18.0, $^3J_{BX}$ = 11.4, ^5J = 3.0 (CH_B-10); 4.02 dd, 1 H, $^3J_{AX}$ = 6.0, $^3J_{BX}$ = 11.4 (CH_X-11); 5.91 s, 1 H (CH-7); 7.10 m, 2 H (Ar); 7.26–7.44 m, 7 H (Ar); 7.92 d, 2 H, J = 8.6 (Ar); 8.14 d, 2 H, J = 8.6 (Ar).
9j	2.84 s, 3 H (CH_3); 3.02 s, 3 H (CH_3); 3.16 dd, 1 H, $^2J_{AB}$ = 18.4, $^3J_{AX}$ = 6.2 (CH_A-10); 3.47 ddd, 1 H, $^2J_{AB}$ = 18.4, $^3J_{BX}$ = 11.5, ^5J = 2.8 (CH_B-10); 4.05 dd, 1 H, $^3J_{AX}$ = 6.2, $^3J_{BX}$ = 11.5 (CH_X-11); 5.69 s, 1 H (CH-7); 6.92–6.01 m, 2 H (Ar); 7.08–7.14 m, 4 H (Ar); 7.27 m, 3 H (Ar); 7.40 d, 2 H, J = 8.2 (Ar); 7.91 d, 2 H, J = 8.2 (Ar).
9k	2.85 s, 3 H (CH_3); 3.01 s, 3 H (CH_3); 3.16 dd, 1 H, $^2J_{AB}$ = 18.4, $^3J_{AX}$ = 6.2 (CH_A-10); 3.44 ddd, 1 H, $^2J_{AB}$ = 18.4, $^3J_{BX}$ = 11.9, ^5J = 2.6 (CH_B-10); 4.02 dd, 1 H, $^3J_{AX}$ = 6.2, $^3J_{BX}$ = 11.9 (CH_X-11); 5.69 s, 1 H (CH-7); 7.01 d, 2 H, J = 8.4 (Ar); 7.12 m, 2 H (Ar); 7.27 m, 5 H (Ar); 7.40 d, 2 H, J = 8.4 (Ar); 7.91 d, 2 H, J = 8.4 (Ar).
9l	2.83 s, 3 H (CH_3); 3.04 s, 3 H (CH_3); 3.16 dd, 1 H, $^2J_{AB}$ = 16.8, $^3J_{AX}$ = 5.6 (CH_A-10); 3.43 ddd, 1 H, $^2J_{AB}$ = 16.8, $^3J_{BX}$ = 11.4, ^5J = 2.2 (CH_B-10); 3.67 s, 6 H (OCH_3); 3.85 s, 3 H (OCH_3); 4.02 dd, 1 H, $^3J_{AX}$ = 5.6, $^3J_{BX}$ = 11.4 (CH_X-11); 5.58 s, 1 H (CH-7); 6.77 d, 4 H, J = 8.6 (Ar); 6.92 d, 2 H, J = 7.0 (Ar); 7.05 t, 4 H, J = 8.0 (Ar); 7.93 d, 2 H, J = 7.0 (Ar).
9m	2.84 s, 3 H (CH_3); 3.04 s, 3 H (CH_3); 3.14 dd, 1 H, $^2J_{AB}$ = 18.2, $^3J_{AX}$ = 6.0 (CH_A-10); 3.39 ddd, 1 H, $^2J_{AB}$ = 18.2, $^3J_{BX}$ = 12.0, ^5J = 3.0 (CH_B-10); 3.77 s, 3 H (OCH_3); 3.85 s, 3 H (OCH_3); 3.98 dd, 1 H, $^3J_{AX}$ = 6.0, $^3J_{BX}$ = 12.0 (CH_X-11); 5.65 s, 1 H (CH-7); 6.78 d, 2 H, J = 8.4 (Ar); 6.93 d, 2 H, J =8.4 (Ar); 7.00–7.06 m, 4 H (Ar); 7.39 d, 2 H, J = 8.2 (Ar); 7.92 d, 2 H, J = 8.2 (Ar).
9n	2.41 s, 3 H (CH_3); 2.83 s, 3 H (CH_3); 3.04 s, 3 H (CH_3); 3.18 dd, 1 H, $^2J_{AB}$ = 18.0, $^3J_{AX}$ = 5.8 (CH_A-10); 3.39 ddd, 1 H, $^2J_{AB}$ = 18.0, $^3J_{BX}$ = 11.8, ^5J = 2.6 (CH_B-10); 3.74 s, 3 H (OCH_3); 3.98 dd, 1 H, $^3J_{AX}$ = 5.8, $^3J_{BX}$ = 11.8 (CH_X-11); 5.88 s, 1 H (CH-7); 6.79 d, 2 H, J = 8.0 (Ar); 7.02 d, 2 H, J =8.0 (Ar); 7.24 d, 2 H, J = 8.0 (Ar); 7.35 d, 2 H, J = 8.0 (Ar); 7.86 d, 2 H, J = 8.0 (Ar); 8.13 d, 2 H, J = 8.0 (Ar).
9o	2.39 s, 3 H (CH_3); 2.83 s, 3 H (CH_3); 3.04 s, 3 H (CH_3); 3.15 dd, 1 H, $^2J_{AB}$ = 18.4, $^3J_{AX}$ = 6.0 (CH_A-10); 3.42 ddd, 1 H, $^2J_{AB}$ = 18.4, $^3J_{BX}$ = 12.0, ^5J = 2.7 (CH_B-10); 3.77 s, 3 H (OCH_3); 3.97 dd, 1 H, $^3J_{AX}$ = 6.0, $^3J_{BX}$ = 12.0 (CH_X-11); 5.68 s, 1 H (CH-7); 6.78 d, 2 H, J = 8.4 (Ar); 7.02–7.10 m, 4 H (Ar); 7.23 d, 4 H, J = 8.4 (Ar); 7.85 d, 2 H, J = 8.2 (Ar).
9p	2.39 s, 3 H (CH_3); 2.83 s, 3 H (CH_3); 3.04 s, 3 H (CH_3); 3.16 dd, 1 H, $^2J_{AB}$ = 18.0, $^3J_{AX}$ = 5.6 (CH_A-10); 3.41 ddd, 1 H, $^2J_{AB}$ = 18.0, $^3J_{BX}$ = 11.6, ^5J = 2.6 (CH_B-10); 3.76 s, 3 H (OCH_3); 3.98 dd, 1 H, $^3J_{AX}$ = 5.6, $^3J_{BX}$ = 11.6 (CH_X-11); 5.66 s, 1 H (CH-7); 6.78 d, 2 H, J = 8.4 (Ar); 7.00–7.06 m, 4 H (Ar); 7.23 d, 2 H, J = 8.4 (Ar); 7.38 d, 2 H, J = 8.4 (Ar); 7.85 d, 2 H, J = 8.2 (Ar).

[1] ^{13}C NMR in DMCO-d6.

[2] δ H-7 for minor diastereoisomer; contents: 9m - 20%, 9n - 10%, 9o - 5%, 9p - 10%.



Scheme 3.

Table 3. Mass spectra data for compounds 5e,f, 9e,f,h

Product	m/z, (%)
5e	505 [M$^+$] (2), 503[M$^+$] (7), 298 (20), 297 (15), 296 (55), 262 (22), 261 (10), 207 (2), 185 (84), 178 (11), 163 (10), 129 (5), 127 (14), 103 (13), 91 (21), 77 (100).
5f	549 [M$^+$] (62), 547 [M$^+$] (60), 548(23), 340 (12), 262 (43), 261 (20), 207 (2), 206 (13), 185 (29), 182 (12), 103 (17), 93 (16), 92 (13), 91 (25), 77 (100).
9e	531 [M$^+$] (41), 529[M$^+$] (37), 324 (50), 376 (6), 374 (4), 323 (100), 322 (50), 210 (20), 209 (25), 207 (16), 206 (40), 196 (16), 186 (28), 184 (16), 171 (13), 169 (9), 102 (32), 101 (67), 91 (9), 77 (36).
9f	487 [M$^+$] (3), 485 [M$^+$] (9), 332 (1), 330 (3), 245 (7), 244 (49), 243 (100), 242 (4), 240 (10), 186 (48), 130 (12), 116 (11), 104 (39), 102 (58), 89 (16), 77 (19).
9h	517 [M$^+$] (12), 515 [M$^+$] (23), 362 (2), 360 (5), 275 (14), 274 (91), 273 (100), 243 (15), 242 (4), 240 (8), 216 (30), 160 (24), 146 (17), 134 (27), 121 (9), 117 (17), 104 (10), 103 (20), 102 (20), 91 (27), 77 (36).

of hydrogen radical from M^+ and of a cation-radical of iminochalcone which results in formation of the corresponding styryl (Scheme 3).

Elimination of 1,3-dimethylbarbituric acid residue (M-155) and consequent decomposition of the daughter fragment are typical of compounds **9**. It is of interest to note that two initial fragmentation stages of compounds **5** are connected with simultaneous formation of both substituted and non-substituted styryls.

Stereochemistry of spirotetrahydropyridines **5a-5f** and **6a-6p** was determined using NOE experiment. Irradiation of H-6 (δ = 5.27) in compound **5f** resulted in NOE enhancement for H-10 (δ = 3.59), the *ortho*-protons of aryl ring at C-6 and the methyl protons at C-4 (δ = 2.24), indicating a *cis*-spatial relationship between these protons and the Me in C-4. In the light of these results, spiroimines **5a-5f** have *5R*, *6R* and *10S* configuration. A similar procedure for spiran **9f** (irradiation of H-7 (δ = 5.67) resulted in increase H-11 (δ = 4.10) and *ortho*-protons intensities on the aryl ring (at C-7) and gives an evidence of 7R, 11S configuration of the chiral centers. In addition, ^{1}H NMR spectra of compounds **9m-9p** contain an additional signal of H-7 shifted to the low field by 0.1 ppm. This signal belongs to the minor *7S*, *11S* diastereomer, its amount doing not exceed 20 % (Table 2).

Thus, the formation of spirotetrahydropyridines **5a-5f** and **9a-9p** proceeds via cascade Michael addition of CH-acids 1 or 7 to chalcones 2 resulting in compounds 3 or 8, correspondingly. Subsequent interaction of 3 or 8 with aldehydes 4 in the presence of NH_4OAc led to the intermediate A which undergoes *exo*-trigonal cyclization forming tetrahydropyridine ring.

To conclude, the synthesis method of new 6-aryl-4-methyl-2,8,10-triphenyl-2,3,7-triazaspiro[4,5]deca-3,7-dien-1-ones 5 and 2,4-dimethyl-7,9,11-triaryl-2,4,8-triazaspiro-[5,5]undec-8-en-1,3,5-triones 9 consisting in the cyclization reaction of β-adducts **3** and **8** with aromatic aldehydes and ammonia has been developed. Structures of all synthesized compounds were proved by their NMR and MS spectral characteristics. The stereochemistry of obtained spirans was determined using NOE experiment.

All melting points were determined using a Kofler apparatus and were not corrected. The ^{1}H NMR spectra were recorded in $CDCl_3$ at 200 MHz on a Varian Mercury VX-200 spectrometer. The ^{13}C NMR spectra were taken in DMSO-d6 and $CDCl_3$ on a Varian Mercury 400 (400 MHz) spectrometer. Chemical shifts are given in ppm (δ-scale), the coupling constants (*J*), in Hz. NOE experiments were made on a Varian Mercury VX-200 apparatus at 200 MHz in $CDCl_3$. Mass spectra were measured on a Varian CP-3800 spectrometer at the ionization chamber temperature 300°C, ionization voltage 70 eV, emission current 100 μA. Elemental analysis was done using a Carlo Erba 1106 instrument.

6-Aryl-2,8,10-triphenyl-4-methyl-2,3,7-triazaspiro[4,5]deca-3,7-dien-1-ones **5a-5f**. *General Procedure*. A solution of compound 3 (1 mmol), appropriate aldehyde 4 (1 mmol), NH_4OAc (15 mmol), and HOAc (0.48 mL) in ethanol (10 mL) was refluxed for 5–15 min. The crystals formed were filtered off and washed with ethanol or crystallized from ethanol (for **5a** and **5b**). The new 1,3-dimethylbarbituric acid derivatives **8b,c** were prepared by the literature procedure [6, 7] similar to those for the described adducts **8a, d.**

7,9,11-Trisubstituted-2,4-dimethyl-2,4,8-triazaspiro[5,5]undec-8ene1,3,5-triones **9a-9m**. *General Procedure*. A solution of an appropriate β-adduct 8 (1 mmol), aldehyde 4 (1 mmol), H4OAc (15 mmol), and HOAc (0.48 mL) in ethanol (10 mL) was refluxed for 15–30 min. The crystals formed were filtered off and washed with ethanol.

One-pot preparation of 7,9,11-trisubstituted-2,4-dimethyl-2,4,8-triazaspiro[5,5]undec-8-ene-1,3,5-triones **9e**, **9f**, **9n-p**. *General Procedure*. A solution of an appropriate chalcone 2 (1 mmol), acid 7 (1 mmol), aldehyde 4 (1 mmol), NH_4OAc (15 mmol), and HOAc (0.48 mL) in ethanol (10 mL) was refluxed for 0.5 h. The crystals formed were filtered off and washed with ethanol.

The work has been done according to the Contract No.F7/554-2001 dated 28.11.2001, Project #03.07/00154 "Novel ensembles of hydrogenated azoloazines", State reg. No.0102U003999, financially supported by Ukrainian Ministry for Education and Science.

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Діастереоселективний синтез спіропіридинів на основі гетероциклічних CH-кислот

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Роботу присвячено діастереоселективному синтезу 6-арил-4-метил-2,8,10-трифеніл-2,3,7-триазаспіро[4,5]дека-3,7-дієн-1-онів та 2,4-диметил-7,9,11-триарил-2,4,8-триазаспіро[5,5]ундец-8-ен-1,3,5-трионів у реакціях гетероциклічних CH-кислот–1-феніл-3-метилпіразолін-5-ону та 1,3-диметилбарбітурової кислоти з халконами та ароматичними альдегідами у присутності ацетату амонію. Стереохімію цільових продуктів визначено за допомогою NOE-експерименту.