FACILE SYNTHESIS OF ARYL-SUBSTITUTED 1,2,5,6-TETRAHYDROPYRIMIDINES AND THEIR STEREOCHEMICAL INVESTIGATION

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The present work is devoted to the investigation of 2,4,6-triaryl-1,2,5,6-tetrahydropyrimidine derivatives. A new facile approach to their synthesis based on the reaction of α,β-unsaturated ketones, carbonyl compounds and ammonia was developed. Some stereochemical features of the compounds obtained were fixed on the base of NMR data (including COSY and NOESY experiments).

Keywords: Nitrogen heterocycles; 1,2,5,6-Tetrahydropyrimidines; Multicomponent reactions; Synthetic methods; Structure elucidation; NMR spectroscopy; Chalcones; Pyrimidines; Heterocyclizations.

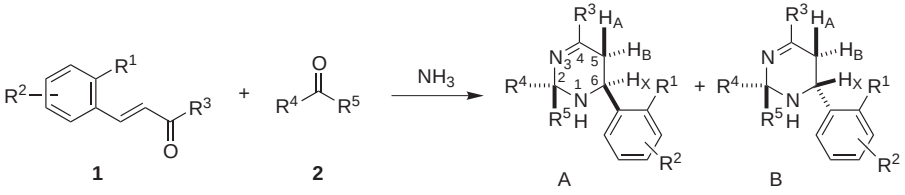
2,4,6-Triaryl-1,2,5,6-tetrahydropyrimidines are little studied due to the absence of convenient methods of their synthesis. Compounds of this class show a wide spectrum of physiological activity[1,2] and, moreover, include several fragments (–NH–, –C=N–, aryl substituents) suitable for subsequent chemical modification, which allows to synthesize large libraries of new heterocycles. On the other hand, these substances are appropriate objects for studying fundamental problems concerning stereochemistry and electron structure of organic compounds.

To the present date, only one two-step method of synthesis of such type of tetrahydropyrimidines is described in the literature[3]. The first step is a reaction of aromatic aldehydes and ammonia with formation of *N*,*N*′-bis(arylmethylidene)arylmethanediamines. Their reaction with ketones containing active hydrogen in α-position is the second step. This method has several serious weak points. First of all, it does not allow to introduce two aryls into position 2 or two different substituents into positions 2 and 6 of the pyrim-

idine moiety. Second, according to the literature data[3] the direction of the second stage of the reaction depends on the nature of ketone.

We have developed a method of synthesis of 2,4,6-triaryl-substituted 1,2,5,6-tetrahydropyrimidines **3** consisting in the reaction of chalcones **1**, carbonyl compounds **2** and ammonia. A similar approach has been described for preparation of some alkyl-substituted 1,2,5,6-tetrahydropyrimidines[4]. Authors of this work described reaction of some α,β-unsaturated ketones (propan-2-one, 4-methylpent-3-en-2-one, 2-acetyl-3-phenylacrylic acid ethyl ester) with aliphatic and aromatic aldehydes and ketones in aqueous ammonia. The aim of our work was to extend this method for aromatic unsaturated ketones.

In the course of the investigation, a series of 1,2,5,6-tetrahydropyrimidines **3a**–**3o** was synthesized (Scheme 1). Better yields of the target compounds and shorter reaction time were observed in the case of formation of 2-hydroxy derivatives (compounds **3a**–**3m**). This could be associated with the hydrogen bond between the hydroxy group of chalcone and ammonia,



3	R^1	R^2	R^3	R^4	R^5
a	OH	H	3-BrC_6H_4	4-ClC_6H_4	H
b	OH	H	4-MeC_6H_4	3,5-$Cl_2C_6H_3$	H
c	OH	H	4-$MeOC_6H_4$	2-$EtOC_6H_4$	H
d	OH	H	4-$MeOC_6H_4$	4-ClC_6H_4	H
e	OH	H	4-EtC_6H_4	2-MeO-5-BrC_6H_3	H
f	OH	H	4-$EtOC_6H_4$	4-ClC_6H_4	H
g	OH	H	4-MeC_6H_4	4-BrC_6H_4	H
h	OH	3-MeO	4-ClC_6H_4	3-FC_6H_4	H
i	OH	3-MeO	4-ClC_6H_4	3-$MeOC_6H_4$	H
j	OH	3-EtO	4-ClC_6H_4	2-FC_6H_4	H
k	OH	3-EtO	3-$MeOC_6H_4$	4-FC_6H_4	H
l	OH	5-Cl	4-EtC_6H_4	4-BrC_6H_4	H
m	OH	H	4-MeC_6H_4	CH_3	CH_3
n	H	H	Ph	Ph	H
o	H	4-OH	4-$MeOC_6H_4$	4-ClC_6H_4	H

SCHEME 1

which facilitates the addition of ammonia to the double bond of α,β-unsaturated ketone. An indirect confirmation of this assumption is the fact that in the case of 4-hydroxychalcone (compound **3o**) an increase in the yield and reaction rate was not observed.

Starting 2-hydroxychalcones were synthesized by a literature method[5,6] from salicylic aldehydes and corresponding acetophenones. The synthesis of chalcones and 4-hydroxychalcones was carried out by the known way[7]. Subsequent reaction of the α,β-unsaturated ketones **1** with carbonyl compounds **2** and ammonia gave 1,2,5,6-tetrahydropyrimidines **3a**–**3o**.

Structures of compounds **3a**–**3o** were proved by ^{1}H and ^{13}C NMR spectrometry using hydrogen-deuterium exchange between the obtained tetrahydropyrimidines and CH_3OD to establish positions of the signals NH and OH groups.

^{1}H NMR spectra of tetrahydropyrimidines **3a**–**3o** contain all necessary signals – multiplet of methyl protons at 2.60–3.10 ppm, broad singlets of protons in positions 2 and 6 of the heterocycle (4–6 ppm) and multiplets of aromatic protons at 6.5–9 ppm. Signals of protons of amino, hydroxy and all other functional groups are also present in the spectra. Data of ^{13}C NMR spectroscopy are not in contradiction with structures of **3a**–**3o**.

Mass spectra recorded for compounds **3c** and **3e** also confirmed the assigned structures: **3c**: *m/z* 402 (100%) $[M]^+$, **3e**: *m/z* 466 (100%) $[M]^+$.

Thus, in the reaction of chalcones **1** with aromatic aldehydes **2** and ammonia, 2,4,6-triaryl-1,2,5,6-tetrahydropyrimidines **3a**–**3o** were obtained. According to the ^{1}H and ^{13}C NMR spectral data (chemical shifts and multiplicity), alternative structures, for example 3,4,5,6- or 1,2,3,6-terahydropyrimidines, were excluded.

In most cases the target tetrahydropyrimidines **3** were obtained as mixtures of diastereomers. This conclusion was made on the basis of detailed analysis of doublets of the signals in ^{1}H NMR spectra. The existence of diastereomers is explained by the presence of two chiral centers in all compounds **3** with the exception of **3m**. The amount of minor diastereomer could vary in quite a wide range. Expectedly, when R^3 is equal to R^4 (compound **3m**) the doublets of signals in the spectra were not observed.

It is also necessary to note a multiplet character of ^{1}H NMR signals of protons in positions 4 and 6 of the pyrimidine ring. By proton spin-spin decoupling, the interaction of proton in position 2 with CH_2 group was proved in compounds **3a**–**3l**, **3n**, **3m** (^5J is about 1 Hz). Suppression of the signal of proton in position 2 of the heterocycle led to simplification of the CH_2 signals. This allowed to establish coupling constants in the ABX sys-

tem: for major diastereomers A the $^3J_{AX}$ are 10–11 Hz, the $^3J_{BX}$ are 4–5 Hz and $^2J_{AB}$ are about –17 Hz. The COSY spectrum of compound **3g** contains cross-peaks between the CH_2 signals and the proton in position 2 in pyrimidine ring. It also demonstrates the long-range interaction in compounds **3a–3l**, **3n**, **3m**.

With regard to magnitudes of spin-spin coupling constants (Table I), some stereochemical features of spatial structure of major diastereomers A of compounds **3** were fixed: the aryl substituent in position 6 is equatorial, therefore H_X is axial. Correspondingly, H_A is axial (trans to H_X) and H_B is equatorial. To establish a spatial location of R^3 and R^4, a NOESY experiment for compound **3g** was made. The presence of cross-peaks between signals of $C_{(2)}H$ and $C_{(6)}H$ allows to assume that in the major diastereomer A, R^4 = H is axial and R^3 is equatorial. Between signals of the minor diastereomer B,

TABLE I
Spin-spin coupling constants (in Hz) obtained by decoupling experiment for compounds **3a–3o**

Compound	$^2J_{AB}$		$^3J_{AX}$		$^2J_{BX}$	
	A	B	A	B	A	B
3a	–17.2	–16.5	10.1	4.2	4.5	4.4
3b	–17.0	–16.3	10.2	4.5	4.4	4.2
3c	–16.9	–16.1	10.4	4.0	4.3	4.8
3d	–17.5	–	10.2	–	4.9	–
3e	–17.7	–16.7	10.4	4.8	4.4	4.4
3f	–17.1	–	10.5	–	4.2	–
3g	–17.0	–16.2	10.1	5.1	4.6	4.1
3h	–16.8	–16.1	10.6	4.8	4.4	4.3
3i	–17.2	–16.5	10.5	4.4	4.3	4.3
3j	–17.0	–16.2	10.8	4.2	4.1	4.4
3k	–16.9	–16.1	11.0	4.8	4.3	4.2
3l	–17.4	–	10.4	–	4.5	–
3m	–17.2		10.1		4.4	
3n	–16.5	–16.0	10.0	4.9	4.7	4.3
3o	–17.2	–16.5	10.2	4.4	4.0	4.0

such cross-peaks are not present. Analysis of spin-spin coupling constants for minor diastereomers B obtained in the frame of decoupling experiment showed the absence of axial-axial constants in the ABX fragment of molecule. Hence in the diastereomers B, H_X is equatorial.

Thus, a new facile method of synthesis of 2,4,6-triaryl-1,2,5,6-tetrahydropyrimidines **3** consisting in reaction of α,β-unsaturated ketones **1**, carbonyl compounds **2** and ammonia was developed. The structures of all synthesized compounds were proved by their NMR and MS spectral characteristics. Some stereochemical features of the obtained tetrahydropyrimidines were established.

EXPERIMENTAL

Melting points for mixture of diastereomers were determined with a Kofler apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 200 MHz (50 MHz for ^{13}C) on a Varian Mercury VX-200 spectrometer and analysed with ADVASP™ Analyzer program (Umatek International Inc.). Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. COSY and NOESY experiments were made on a Bruker AC250 apparatus at 250 MHz in $CDCl_3$. Mass spectra were measured on a Varian MAT-CH-6 spectrometer; temperature of ionization chamber was 300 °C, ionization voltage 70 eV, emission current 100 μA. Elemental analysis was made on a Carlo Erba 1106 instrument.

2,4,6-Trisubstituted-1,2,5,6-tetrahydropyrimidins **3**. General Procedure

To a solution of of appropriate phenylprop-2-en-1-one **1** (2 mmol) in methanol saturated with ammonia, carbonyl compound **2** (2 mmol) was added and the mixture was stirred at room temperature for 48 h. The crystals formed were filtered off and crystallized from propan-2-ol. The ratio of diastereoisomers A/B of compounds **3** was determined from their ^{1}H NMR spectra.

4-(3-Bromophenyl)-2-(4-chlorophenyl)-6-(2-hydroxyphenyl)-1,2,5,6-tetrahydropyrimidine (**3a**). Yield 54%; A 90%, B 10%. M.p. 187–189 °C. For $C_{22}H_{18}BrClN_2O$ (441.8) calculated: 59.82% C, 4.11% H, 18.09% Br, 8.03% Cl, 6.34% N; found: 59.80% C, 4.15% H, 18.07% Br, 8.05% Cl, 6.30% N. ^{1}H NMR, A (B): 2.63 (3.08) m, 2 H (CH_2); 3.20 (3.42) bs, 1 H (NH); 4.39 (3.96) bs, 1 H (CH-6); 5.68 (5.89) bs, 1 H (CH-5); 6.6–8.3 m, 12 H (Ar); 10.12 bs, 1 H (OH). ^{13}C NMR: 35.7 (CH_2-5); 53.2 (CH-6); 75.3 (CH-2); 116.4, 117.9, 126.6, 127.9, 128.1, 128.9, 129.8, 130.1, 131.3, 132.2 (CH_{Ar}); 121.9, 124.8, 134.3, 138.8, 157.6 (C_{Ar}); 167.7 (C-4).

2-(3,5-Dichlorophenyl)-6-(2-hydroxyphenyl)-4-(4-methylphenyl)-1,2,5,6-tetrahydropyrimidine (**3b**). Yield 55%; A 89%, B 11%. M.p. 185–186 °C. For $C_{23}H_{20}Cl_2N_2O$ (411.3) calculated: 67.16% C, 4.90% H, 17.24% Cl, 6.81% N; found: 67.12% C, 4.92% H, 17.27% Cl, 6.82% N. ^{1}H NMR, A (B): 2.33 s, 3 H (CH_3); 2.69 (3.14) m, 2 H (CH_2); 3.20 (3.63) bs, 1 H (NH); 4.42 (4.07) bs, 1 H (CH-6); 5.90 (6.00) bs, 1 H (CH-2); 5.6–8.3 m, 11 H (Ar); 10.26 bs, 1 H (OH). ^{13}C NMR, A (B): 21.2 (CH_3); 36.7 (36.2) (CH_2-5); 53.4 (46.2) (CH-6); 80.1 (77.2) (CH-2); 116.4 (115.9), 117.9 (117.5), 127.2, 127.3, 127.5, 128.1, 128.3 (128.2), 130.1 (130.0) (CH_{Ar}); 124.8 (124.2), 135.2 (135.3), 136.4 (136.2), 138.4 (138.1), 140.0 (139.5), 157.6 (157.4) (C_{Ar}); 168.2 (167.7) (C-4).

2-(2-Ethoxyphenyl)-6-(2-hydroxyphenyl)-4-(4-methoxyphenyl)-1,2,5,6-tetrahydropyrimidine (**3c**). Yield 57%; A 67%, B 23%. M.p. 175–177 °C. For $C_{25}H_{26}N_2O_3$ (402.5) calculated: 74.60% C, 6.51% H, 6.96% N; found: 74.63% C, 6.53% H, 7.01% N. ^{1}H NMR, A (B): 1.34 t, 3 H, *J* = 7.0 ($OCH_2C\mathbf{H}_3$); 2.73 (3.11) m, 2 H (CH_2); 3.21 (3.36) bs, 1 H (NH); 3.80 s, 3 H (OCH_3); 4.08 q, 2 H, *J* = 7.0 ($OC\mathbf{H}_2CH_3$); 4.34 (4.10) bs, 1 H (CH-6); 5.87 (5.97) bs, 1 H (CH-2); 6.6–8.1 m, 12 H (Ar); 10.70 bs, 1 H (OH). ^{13}C NMR, A (B): 15.0 ($OCH_2\mathbf{C}H_3$); 35.7 (34.3) (CH_2-5); 53.4 (47.8) (CH-6); 55.1 (OCH_3); 64.6 ($O\mathbf{C}H_2CH_3$); 69.1 (65.5) (CH-2); 110.2 (109.8), 112.4 (112.2), 116.4 (16.0), 117.9 (117.7), 119.0 (18.9), 126.2 (126.0), 128.1 (127.8), 129.4 (129.1), 129.9 (129.8), 131.1 (131.0) (CH_{Ar}); 124.8 (124.7), 133.6 (133.4), 157.8 (157.6), 159.0 (158.8), 160.2 (160.1) (C_{Ar}); 167.8 (167.0) (C-4).

2-(4-Chlorophenyl)-6-(2-hydroxyphenyl)-4-(4-methoxyphenyl)-1,2,5,6-tetrahydropyrimidine (**3d**). Yield 52%; A 92%, B 8%. M.p. 187–188 °C. For $C_{23}H_{21}ClN_2O_2$ (392.9) calculated: 70.31% C, 5.39% H, 9.02% Cl, 7.13% N; found: 70.35% C, 5.40% H, 9.00% Cl, 7.20% N. ^{1}H NMR, A (B): 2.60 (3.08) m, 2 H (CH_2); 3.21 (3.41) bs, 1 H (NH); 3.79 s, 3 H (OCH_3); 4.37 (3.98) bs, 1 H (CH-6); 5.64 (5.83) bs, 1 H (CH-2); 6.6–8.1 m, 12 H (Ar); 10.18 bs, 1 H (OH). ^{13}C NMR: 36.7 (CH_2-5); 54.4 (CH-6); 55.1 (OCH_3); 76.8 (CH-2); 112.3, 115.4, 117.9, 126.2, 128.0, 128.1, 129.8, 131.2 (CH_{Ar}); 124.9, 130.2, 132.8, 134.2, 159.3, 160.8 (C_{Ar}); 171.1 (C-4).

2-(5-Bromo-2-methoxyphenyl)-4-(4-ethylphenyl)-6-(2-hydroxyphenyl)-1,2,5,6-tetrahydropyrimidine (**3e**). Yield 54%; A 70%, B 30%. M.p. 193–195 °C. For $C_{25}H_{25}BrN_2O_2$ (465.4) calculated: 64.52% C, 5.41% H, 17.17% Br, 6.02% N; found: 64.55% C, 5.36% H, 17.20% Br, 6.08% N. ^{1}H NMR, A (B): 1.19 t, 3 H, *J* = 7.5 ($CH_2C\mathbf{H}_3$); 2.65 q, *J* = 7.5, 2 H ($C\mathbf{H}_2CH_3$); 2.75 (3.12) m, 2 H (CH_2); 3.20 (3.55) bs, 1 H (NH); 3.85 s, 3 H (OCH_3); 4.38 (4.10) bs, 1 H (CH-6); 5.87 (5.97) bs, 1 H (CH-2); 6.6–8.1 m, 11 H (Ar); 10.53 bs, 1 H (OH). ^{13}C NMR, A (B): 17.1 ($CH_2\mathbf{C}H_3$); 29.8 (29.7) ($\mathbf{C}H_2CH_3$); 36.9 (35.3) (CH_2-5); 54.4 (49.8) (CH-6); 56.2 (OCH_3); 68.6 (62.5) (CH-2); 114.3 (114.0), 116.4 (115.9), 117.9 (117.7), 127.4 (127.0), 127.5, 127.9 (127.8), 129.0 (128.9), 130.1 (130.0), 133.3 (133.1), 135.0 (134.7) (CH_{Ar}); 100.3 (99.7), 124.8 (124.6), 137.7 (137.5), 148.1 (148.0), 155.9 (155.7), 157.8 (157.7) (C_{Ar}); 167.6 (167.1) (C-4).

2-(4-Chlorophenyl)-4-(4-ethoxyphenyl)-6-(2-hydroxyphenyl)-1,2,5,6-tetrahydropyrimidine (**3f**). Yield 60%; A 92%, B 8%. M.p. 185–188 °C. For $C_{24}H_{23}ClN_2O_2$ (406.9) calculated: 70.84% C, 5.70% H, 8.71% Cl, 6.88% N; found: 70.81% C, 5.72% H, 8.75% Cl, 6.91% N. ^{1}H NMR, A (B): 1.32 t, *J* = 6.7, 3 H ($OCH_2C\mathbf{H}_3$); 2.58 (3.08) m, 2 H (CH_2); 3.21 (3.39) bs, 1 H (NH); 4.05 q, *J* = 6.7, 2 H ($OC\mathbf{H}_2CH_3$); 4.37 (4.06) bs, 1 H (CH-6); 5.64 (5.82) bs, 1 H (CH-2); 6.7–7.9 m, 12 H (Ar); 10.22 bs, 1 H (OH). ^{13}C NMR: 15.2 ($OCH_2\mathbf{C}H_3$); 32.7 (CH_2-5); 53.5 (CH-6); 64.1 ($O\mathbf{C}H_2CH_3$); 75.8 (CH-2); 112.1, 114.7, 116.4, 117.9, 125.8, 128.1, 129.4, 129.8 (CH_{Ar}); 124.9, 128.7, 132.8, 157.9, 161.1, 161.8 (C_{Ar}); 168.8 (C-4).

2-(4-Bromophenyl)-6-(2-hydroxyphenyl)-4-(4-methylphenyl)-1,2,5,6-tetrahydropyrimidine (**3g**). Yield 65%; A 91%, B 9%. M.p. 193–195 °C. For $C_{23}H_{21}BrN_2O$ (421.3) calculated: 65.57% C, 5.02% H, 18.96% Br, 6.65% N; found: 65.60% C, 5.05% H, 18.91% Br, 6.70% N. ^{1}H NMR, A (B): 2.32 s, 3 H (CH_3); 2.61 (3.07) m, 2 H (CH_2); 3.21 (3.62) bs, 1 H (NH); 4.37 (3.93) bs, 1 H (CH-6); 5.63 (5.83) bs, 1 H (CH-2); 6.6–7.9 m, 12 H (Ar); 10.21 bs, 1 H (OH). ^{13}C NMR: 21.2 (CH_3); 35.7 (CH_2-5); 53.4 (CH-6); 75.8 (CH-2); 116.4, 117.9, 127.2, 127.3, 128.4, 128.7, 129.1, 132.2 (CH_{Ar}); 122.4, 124.9, 136.0, 137.4, 138.8, 157.7 (C_{Ar}); 167.9 (C-4).

4-(4-Chlorophenyl)-2-(3-fluorophenyl)-6-(2-hydroxy-3-methoxyphenyl)-1,2,5,6-tetrahydropyrimidine (**3h**). Yield 53%; A 85%, B 15%. M.p. 167–169 °C. For $C_{23}H_{20}ClFN_2O_2$ (410.9) calculated: 67.23% C, 4.91% H, 8.63% Cl, 4.62% F, 6.82% N; found: 67.20% C, 4.95% H, 8.64% Cl, 4.59% F, 6.80% N. ^{1}H NMR, A (B): 2.63 (3.03) m, 2 H (CH_2); 3.20 (3.59) bs, 1 H (NH); 3.75 s, 3 H (OCH_3); 4.40 (4.00) bs, 1 H (CH-6); 5.67 (5.87) bs, 1 H (CH-2); 6.6–8.1 m, 11 H (Ar);

9.49 bs, 1 H (OH). ^{13}C NMR, A (B): 35.9 (34.5) (CH_2-5); 56.0 (48.2) (CH-6); 58.1 (OCH_3); 73.3 (72.0) (CH-2); 114.7 (114.6), 114.9 (114.8), 115.3 (115.2), 121.0 (120.8), 121.9 (121.7), 124.4 (124.1), 127.2 (126.9), 128.0 (127.7), 130.1 (130.0) (CH_{Ar}); 125.0 (124.9), 135.1 (135.0), 138.0 (137.6), 138.6 (138.2), 143.0 (142.8), 146.7 (146.6), 164.4 (164.3) (C_{Ar}); 167.5 (166.9) (C-4).

4-(4-Chlorophenyl)-6-(2-hydroxy-3-methoxyphenyl)-2-(3-methoxyphenyl)-1,2,5,6-tetrahydropyrimidine (**3i**). Yield 56%; A 55%, B 45%. M.p. 161–163 °C. For $C_{24}H_{23}ClN_2O_3$ (422.9) calculated: 68.16% C, 5.48% H, 8.38% Cl, 6.62% N; found: 68.20% C, 5.51% H, 8.32% Cl, 6.61% N. ^{1}H NMR, A (B): 2.65 (3.03) m, 2 H (CH_2); 3.59 (3.19) bs, 1 H (NH); 3.72 s, 3 H (OCH_3); 3.74 s, 3 H (OCH_3); 4.06 (4.38) bs, 1 H (CH-6); 5.84 (5.63) bs, 1 H (CH-2); 6.6–8.1 m, 11 H (Ar); 9.65 bs, 1 H (OH). ^{13}C NMR, A (B): 35.5 (33.9) (CH_2-5); 55.1 (49.4) (CH-6); 56.1 (OCH_3); 60.92 (OCH_3); 76.1 (73.2) (CH-2); 114.0 (113.8), 114.6 (114.4), 114.9 (114.8), 121.0 (120.7), 121.1, 122.3 (122.1), 127.2 (126.9), 127.9 (127.6), 130.1 (130.0) (CH_{Ar}); 125.1 (125.0), 135.0 (134.9), 138.1 (138.0), 138.6 (138.4), 142.0 (142.2), 146.6 (146.3), 160.1 (160.0) (C_{Ar}); 168.1 (167.3) (C-4).

4-(4-Chlorophenyl)-2-(2-fluorophenyl)-6-(3-ethoxy-2-hydroxyphenyl)-1,2,5,6-tetrahydropyrimidine (**3j**). Yield 51%; A 80%, B 20%. M.p. 180–182 °C. For $C_{24}H_{22}ClFN_2O_2$ (424.9) calculated: 67.84% C, 5.22% H, 8.34% Cl, 4.47% F, 6.59% N; found: 67.80% C, 5.25% H, 8.32% Cl, 4.50% F, 6.61% N. ^{1}H NMR, A (B): 1.32 t, J = 6.9, 3 H ($OCH_2C\mathbf{H}_3$); 2.70 (3.10) m, 2 H (CH_2); 3.24 (3.65) bs, 1 H (NH); 4.01 q, J = 6.9, 2 H ($OC\mathbf{H}_2CH_3$); 4.43 (4.16) bs, 1 H (CH-6); 5.92 (6.09) bs, 1 H (CH-5); 6.6–8.8 m, 11 H (Ar); 9.64 bs, 1 H (OH). ^{13}C NMR, A (B): 14.5 ($OCH_2\mathbf{C}H_3$); 35.8 (33.4) (CH_2-5); 54.8 (49.7) (CH-6); 64.7 ($O\mathbf{C}H_2CH_3$); 76.0 (73.0) (CH-2); 114.3 (114.0), 120.5 (120.4), 120.7 (120.6), 121.8 (121.5), 123.5 (123.0), 127.2 (127.0), 127.9 (127.5), 128.5 (128.4), 130.1 (130.0) (CH_{Ar}); 124.9 (124.5), 129.7 (129.4), 134.9 (134.8), 139.0, 143.2 (143.0), 148.2 (148.1), 163.1 (163.0) (C_{Ar}); 168.5 (167.8) (C-4).

6-(3-Ethoxy-2-hydroxyphenyl)-2-(4-fluorophenyl)-4-(4-methoxyphenyl)-1,2,5,6-tetrahydropyrimidine (**3k**). Yield 55%; A 70%, B 30%. M.p. 158–160 °C. For $C_{25}H_{25}FN_2O_3$ (420.5) calculated: 71.41% C, 5.99% H, 4.52% F, 6.66% N; found: 71.43% C, 6.02% H, 4.50% F, 6.70% N. ^{1}H NMR, A (B): 1.31 t, J = 7.3, 3 H ($OCH_2C\mathbf{H}_3$); 2.66 (3.05) m, 2 H (CH_2); 3.25 (3.64) bs, 1 H (NH); 3.52 s, 3 H (OCH_3); 3.99 q, J = 7.3, 2 H ($OC\mathbf{H}_2CH_3$); 4.38 (4.02) bs, 1 H (CH-6); 5.66 (5.86) bs, 1 H (CH-2); 6.6–7.7 m, 11 H (Ar); 9.54 bs, 1 H (OH). ^{13}C NMR, A (B): 14.3 ($OCH_2\mathbf{C}H_3$); 35.7 (33.0) (CH_2-5); 55.1 (49.9) (CH-6); 55.76 (OCH_3); 64.6 ($O\mathbf{C}H_2CH_3$); 76.2 (73.5) (CH-2); 110.9 (110.7), 114.8 (114.54), 118.0 (117.9), 120.5 (120.1), 120.7 (120.6), 122.0 (121.8), 123.8 (123.5), 128.4 (128.3), 131.1 (130.7) (CH_{Ar}); 124.7 (124.2), 128.8 (128.7), 140.1 (139.8), 143.2 (143.0), 150.1 (150.0), 158.4 (158.2), 161.7 (161.6) (C_{Ar}); 166.5 (165.1) (C-4).

2-(4-Bromophenyl)-4-(4-ethylphenyl)-6-(2-hydroxy-5-chlorophenyl)-1,2,5,6-tetrahydropyrimidine (**3l**). Yield 60%; A 99%, B 1%. M.p. 178–179 °C. For $C_{24}H_{22}BrClN_2O$ (469.8) calculated: 61.36% C, 4.72% H, 17.01% Br, 7.55% Cl, 5.96% N; found: 61.34% C, 4.75% H, 16.98% Br, 7.52% Cl, 6.01% N. ^{1}H NMR, A (B): 1.17 t, J = 7.5, 3 H ($CH_2C\mathbf{H}_3$); 2.63 q, J = 7.5, 2 H ($C\mathbf{H}_2CH_3$); 2.60 (3.09) m, 2 H (CH_2); 3.20 bs, 1 H (NH); 4.37 (3.88) bs, 1 H (CH-6); 5.64 (5.88) bs, 1 H (CH-2); 6.7–8.0 m, 11 H (Ar); 10.26 bs, 1 H (OH). ^{13}C NMR: 16.0 ($CH_2\mathbf{C}H_3$); 28.9 ($\mathbf{C}H_2CH_3$); 35.7 (CH_2-5); 55.7 (CH-6); 75.4 (CH-2); 115.9, 123.0, 127.5, 127.5, 127.7, 128.8, 130.0, 130.8 (CH_{Ar}); 122.4, 126.0, 135.9, 137.5, 148.2, 156.3 (C_{Ar}); 167.0 (C-4).

2,2-Dimethyl-6-(2-hydroxyphenyl)-4-(4-methylphenyl)-1,2,5,6-tetrahydropyrimidine (**3m**). Yield 58%. M.p. 168–171 °C. For $C_{19}H_{22}N_2O$ (294.4) calculated: 77.52% C, 7.53% H, 9.52% N; found: 77.50% C, 7.56% H, 9.50% N. ^{1}H NMR, A (B): 1.41 s, 3 H (CH_3); 1.42 s, 3 H (CH_3);

2.32 s, 3 H (CH_3); 2.48 (2.98) dd, $^2J_{AB}$ = –17.2, $^3J_{AX}$ = 10.1, $^3J_{BX}$ = 4.4, 2 H (CH_2); 3.20 bs, 1 H (NH); 4.29 dd, $^3J_{AX}$ = 10.1, $^3J_{BX}$ = 4.4, 1 H (CH-6); 6.7–7.9 m, 8 H (Ar); 10.50 bs, 1 H (OH). ^{13}C NMR: 20.1 (CH_3); 31.44 (CH_3); 31.46 (CH_3); 39.1 (CH_2-5); 50.5 (CH-6); 80.3 (C-2); 117.2, 118.4, 126.5, 126.6, 127.5, 128.0, 130.5 (CH_{Ar}); 124.4, 138.1, 138.9, 156.6 (C_{Ar}); 156.0 (C-4).

2,4,6-Triphenyl-1,2,5,6-tetrahydropyrimidine (**3n**). Yield 20%; A 80%, B 20%. Separated as an oil and purified by flash chromatography (silica gel, ethyl acetate–hexane 1:3). M.p. 69–70 °C. For $C_{22}H_{20}N_2$ (312.4) calculated: 84.58% C, 6.45% H, 8.97% N; found: 84.60% C, 6.42% H, 9.01% N. ^{1}H NMR, A (B): 2.58 (2.76) m, 2 H (CH_2); 3.02 (3.12) bs, 1 H (NH); 3.90 (4.19) bs, 1 H (CH-6); 5.60 (5.80) bs, 1 H (CH-2); 6.7–8.1 m, 15 H (Ar). ^{13}C NMR, A (B): 36.7 (33.2) (CH_2-5); 63.0 (60.9) (CH-6); 75.2 (73.0) (CH-2); 126.1 (125.9), 126.7 (126.5), 127.2 (127.1), 127.6 (127.4), 127.9 (127.8), 128.3 (128.0), 128.5 (128.4), 129.0 (128.9), 132.1 (132.0) (CH_{Ar}); 136.9 (136.7), 139.0 (138.9), 144.5 (144.1) (C_{Ar}); 166.0 (C-4).

2-(4-Chlorophenyl)-6-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,2,5,6-tetrahydropyrimidine (**3o**). Yield 25%; A 60%, B 40%. M.p. 170–171 °C. For $C_{23}H_{21}ClN_2O_2$ (392.9) calculated: 70.31% C, 5.39% H, 9.02% Cl, 7.13% N; found: 70.35% C, 5.34% H, 9.00% Cl, 7.11% N. ^{1}H NMR 3.04 bs, 1 H (NH); 3.70 s, 3 H (OCH_3); 4.06 m, 2 H (CH_2); 4.48 bs, 1 H (CH-6); 5.12 bs, 1 H (CH-2); 6.5–8.2 m, 12 H (Ar); 9.5 bs, 1 H (OH). ^{13}C NMR, A (B): 36.2 (33.1) (CH_2-5); 55.5 (OCH_3); 62.0 (59.8) (CH-6); 76.1 (73.2) (CH-2); 112.3 (112.1), 115.4 (115.0), 126.4 (126.2), 127.9 (127.6), 128.4 (128.1), 130.0 (129.7) (CH_{Ar}); 129.6 (129.4), 133.2 (133.0), 135.1 (135.0), 135.9 (135.7), 156.2 (156.1), 160.2 (160.1) (C_{Ar}); 167.8 (167.5) (C-4).

REFERENCES

1. Huang Z., Ma Q., Bobbitt J. M.: *J. Org. Chem.* **1993**, *18*, 4837.
2. Vicente J., Chicote M. T., Guerrero R., de Arellano M. C. R.: *Chem. Commun.* **1999**, *16*, 1541.
3. Takajo T., Kambe S., Sato K.: *Synthesis* **1977**, 647.
4. Asinger F., Thiel M., Baltz H.: *Monatsh. Chem.* **1957**, *88*, 464.
5. Le Fevre: *J. Chem. Soc.* **1929**, 2773.
6. Pathak V. N., Pathak R., Gupta R., Oza C. K.: *Synth. Commun.* **1997**, *10*, 1811.
7. Dhar D. N. in: *The Chemistry of Chalcones and Related Compounds* (D. Barton, Ed.), p. 8. Wiley Interscience, New York 1981.