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SYNTHESES AND STRUCTURE ELUCIDATION OF SOME 1- AND 2-(ARYL) SUBSTITUTED 4,5-BIS (4-METHOXYPHENYL) IMIDAZOLE DERIVATIVES

BAZI 1- VE 2-(ARİL) SÜBSTİTÜE 4,5-BİS (4-METOKSİFENİL) İMİDAZOL TÜREVLERİNİN SENTEZ VE YAPI AYDINLATMASI

ASİYE MERİÇ*, İLHAN IŞIKDAĞ

University of Anadolu, Faculty of Pharmacy, Dept. of Pharmaceutical Chemistry, 26470-Eskişehir, TURKEY

Some 1- and 2-(aryl)substituted 4,5-bis (4-methoxyphenyl) imidazole compounds and 2-(aryl) substituted 4,5-bis (4-methoxyphenyl) imidazole compounds were obtained by reacting anisil with some aldehyde derivatives in the presence of ammonium acetate. 1-Ethyl-2-(aryl) substituted 4,5-bis (4-methoxyphenyl) imidazole compounds were obtained by reacting 2-(aryl) substituted 4,5-bis (4-methoxyphenyl) imidazole derivatives with ethyl iodide in tetrahydrofuran (THF) in the presence of NaH. The structure elucidation of the compounds were achieved by using spectral data and elemental analyses results.

Bu araştırmada bir seri 1- ve 2-(aril) sübstitüe 4,5-bis (4-metoksifenil) imidazol bileşiğinin sentezi yapılmıştır. Sentezlerde, 2-(aril) sübstitüe 4,5-bis (4-metoksifenil) imidazol bileşikleri, anisil'in aldehid türevleri ile amonyum asetat varlığında reaksiyonu ile elde edilmiştir. 1-Etil-2-(aril) sübstitüe 4,5-bis (4-metoksifenil) imidazol bileşikleri ise, 2-(aril) sübstitüe 4,5-bis (4-metoksifenil) imidazol türevlerinin etil iyodür ile, NaH / THF varlığında reaksiyonu ile hazırlanmıştır. Bileşiklerin yapıları, spektral veriler ve elementel analiz sonuçları kullanılarak aydınlatılmıştır.

Keywords: *Imidazole; 2-(Aryl) substituted 4,5-bis (4-methoxyphenyl) imidazole; Anisil.*

Anahtar sözcükler: *İmidazol; 2-(Aril) sübstitüe 4,5-bis (4-metoksifenil) imidazol; Anisil.*

Introduction

Imidazole nucleus is found in a variety of compounds which possess various pharmacological effects such as, analgesic (1), antiinflammatory (2, 3), antifungal and antiprotozoal (4, 5), nematosid (6), tumor inhibitor (7, 8), sedative(9), hypolipidemic and hypocolesterolemic (10), gastric secretion inhibitor (11, 12), gastric acid neutralizer (13) and antiallergic (14) activities. Therefore, this findings prompted us to synthesize some new compounds which would be analgesic.

Materials and Methods

Melting points of the compounds were determined using Stuart Scientific Smpl melting point apparatus and were reported uncorrected. IR spectra were detected in KBr pellets using a Schimadzu-435 spectrophotometer. The ^{1}H-NMR spectra were recorded in DMSO-d_6 by Jeol-JNM-EX90A and Bruker 250 MHz spectrophotometers using tetramethylsilane as internal standard. Elemental analyses were performed by Carlo Erba 1106 Analyzer. Mass spectra were recorded on VG PLATFORM.

* Correspondence

Anisil which was used as a starting material was synthesized with novel methods (15-17).

Methods

a. General method (18-19) for synthesis of 2-(aryl) substituted 4,5-bis (4-methoxyphenyl) imidazole derivatives: 0.01 mol anisil and 0.015 mol substituted aldehyde derivatives were reacted with 0.08 mol ammonium acetate in glacial acetic acid and refluxed for 5-7 hours. At the end of the reaction, the content of the reaction vessel was poured into ice-water and neutralized with ammonia solution. The precipitate was filtered and recrystallized from ethanol.

b. General method for synthesis of 1-ethyl-2-(aryl) substituted 4,5-bis (4-methoxyphenyl) imidazole derivatives: 0.01 mol of 2-(aryl) substituted 4,5-bis (4-methoxyphenyl) imidazole compounds were stirred with 0.015 mol NaH in THF and refluxed by the addition of ethyl iodide for 1.5-2.5 hours. The content of the reaction vessel was filtered, evaporated and the residue was washed with water, dried and recrystallized from ethanol. Some characteristics of all compounds are given in Table.

1b: IR [KBr, υ_{max} ,cm^{-1}]: 3020-3000 (Ar C-H), 2950-2900 (aliph C-H), 1620-1440 (C=N and C=C), 1295 (C-N), 1240, 1175 (C-O), 840 (1,4-disubstituted benzene), 770, 750 (monosubstituted benzene). **^{1}H-NMR** [250 MHz, δ, ppm, DMSO-d_6]: 0.94 (3H, t, $-CH_2-C\underline{H}_3$), 3.70 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.88 (2H, q, $-C\underline{H}_2-CH_3$), 6.78 (2H,d,j:14.63 Hz, aromatic ring), 7.10 (2H, d, j:14.29 Hz, aromatic ring), 7.29-7.39 (4H, m, aromatic ring), 7.46-7.56 (3H, m, aromatic ring), 7.71 (2H, d, j:9.48 Hz, aromatic ring).

2b: IR [KBr, υ_{max} ,cm^{-1}]: 3132-2998 (Ar C-H), 2829 (aliph C-H), 1612-1438 (C=N and C=C), 1302 (C-N), 1242, 1171, 1030 (C-O), 838 (1,4-disubstituted benzene). **^{1}H-NMR** [90 MHz, δ, ppm, DMSO-d_6]: 0.99 (3H, t, $-CH_2-C\underline{H}_3$), 3.72 (2H, q, $-C\underline{H}_2-CH_3$), 3.89 (9H, s, OCH_3), 6.84 (2H, d, j:8.90 Hz, C_2 and C_6-H protones of 2-aryl), 7.14 (4H, d, j:8.79 Hz, C_2 and C_6-H protones of 4,5-diaryl), 7.43 (4H, d, j:8.68 Hz, C_3 and C_5-H protones of 4,5-diaryl), 7.70 (2H, d, j:8.79 Hz, C_3 and C_5-H protones of 2-aryl). **EI-MS** (m/e): 415.3(M+1, 35%), 414.3(M,100%), 399.2, 385.2, 252.2, 134.2, 133.2, 119.1, 102.9, 90.2, 76.0, 65.1

3b: IR [KBr, υ_{max} ,cm^{-1}]: 3100-3000 (Ar C-H), 2990-2900 (aliph C-H), 1615-1420 (C=N and C=C), 1322 (C-N), 1250, 1170, 1020 (C-O), 1070 (Ar C-Br), 825 (1,4-disubstituted benzene). **^{1}H-NMR** [90 MHz, δ, ppm, DMSO-d_6]: 0.93 (3H, t, $-CH_2-C\underline{H}_3$), 3.68 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.32 (2H, q, $-C\underline{H}_2-CH_3$), 6.71-7.40 (10H, m, aromatic ring), 7.68 (2H, s, C_3 and C_5-H protones of 2-aryl).

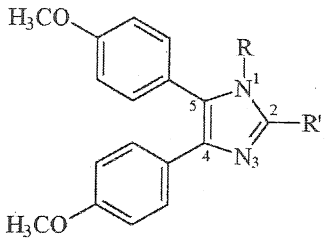
4b: IR [KBr, υ_{max} ,cm^{-1}]: 3453 (O-H), 3124 (Ar C-H), 2917 (aliph C-H), 1609-1425 (C=N and C=C), 1320 (C-N), 1245, 1142, 1027 (C-O), 872, 833 (1,2,4-trisubstituted benzene), 772 (1,4-disubstituted benzene). **^{1}H-NMR** [90 MHz, δ, ppm, DMSO-d_6]: 1.02 (3H, t, $-CH_2-C\underline{H}_3$, C_4-H protones of 2-aryl), 1.44 (3H, t, $-CH_2-C\underline{H}_3$, protones of 1-alkyl), 3.77 (3H, s, OCH_3, C_3-H protones of 2-aryl), 3.91 (6H, s, OCH_3, C_4-H protones of 4,5-diaryl), 4.12 (4H, q, $-C\underline{H}_2-CH_3$, protones of 1-alkyl and C_4-H protones of 2-aryl), 6.85 (2H, d, j: 8.79 Hz, C_2 and C_6-H protones of 2-aryl), 7.11-7.21 (4H, m, C_2 and C_6-H protones of 4,5-diaryl), 7.32-7.48 (5H, m, C_3 and C_5-H protones of 4,5-diaryl and C_5-H protone of 2-aryl).

5b: IR [KBr, υ_{max} ,cm^{-1}]: 3098-3025 (Ar C-H), 2983-2880 (aliph C-H), 1590-1450 (C=N and C=C), 1347 (C-N), 1263, 1185, 1076 (C-O), 885, 772 (1,2,4-trisubstituted benzene), 780 (1,4-disubstituted benzene). **^{1}H-NMR** [90 MHz, δ, ppm, DMSO-d_6]: 0.95 (3H, t, $-CH_2-C\underline{H}_3$), 2.67 (6H, s, CH_3), 3.84 (6H, s, OCH_3), 4.17 (2H, q, $-C\underline{H}_2-CH_3$), 6.90-7.35 (11H, m, aromatic ring).

Results and Discussion

2-(Aryl) substituted 4,5-bis (4-methoxyphenyl) imidazole compounds were obtained by the reaction of anisil with some aldehyde derivatives in the presence of ammonium acetate (18, 19). 1-Ethyl-2-(aryl) substituted 4,5-bis (p-methoxyphenyl) imidazole compounds

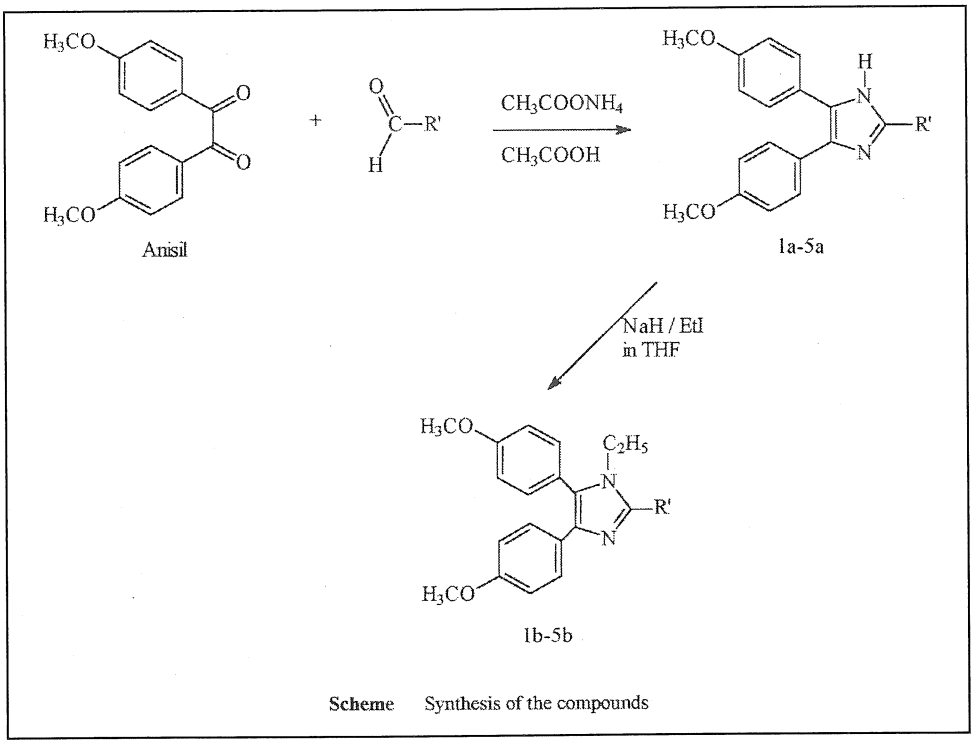
Table Some characteristics of the compounds



No	R	R'	Time (h)	Yield[a] (%)	Lit. m.p. (°C)	Exp.m.p. (°C)	Formula[b]	M. W.
1a	H	C_6H_5	5	54	99 [20]	99	$C_{23}H_{20}N_2O_2$	356.41
2a	H	C_6H_4-4-OCH_3	7	57	98 [20]	99-100	$C_{24}H_{22}N_2O_3$	386.44
3a	H	C_6H_4-4-Br	6.5	55	- [21]	102	$C_{23}H_{19}N_2O_2Br$	435.31
4a	H	C_6H_3-3-OCH_3-4-OH	5	59	139-42 [22]	139-42	$C_{24}H_{22}N_2O_4$	402.44
5a	H	C_6H_3-2,4-$(CH_3)_2$	6	68	177-9 [22]	177-9	$C_{25}H_{24}N_2O_2$	384.46
1b	C_2H_5	C_6H_5	2	68	-	197	$C_{25}H_{24}N_2O_2$	384.46
2b	C_2H_5	C_6H_4-4-OCH_3	1.5	75	-	148	$C_{26}H_{26}N_2O_3$	414.49
3b	C_2H_5	C_6H_4-4-Br	1.5	80	-	171	$C_{25}H_{23}N_2O_2Br$	463.35
4b	C_2H_5	C_6H_3-3-OCH_3-4-OC_2H_5	2	82	-	150	$C_{28}H_{30}N_2O_4$	458.54
5b	C_2H_5	C_6H_3-2,4-$(CH_3)_2$	2	71	-	58	$C_{27}H_{28}N_2O_2$	412.51

[a]No effort was made to optimize yields [b]All compounds were analyzed for C,H,N. The result had a maximum deviation of 0.4% from the theoretical value.

were obtained by the reaction of purified 2-(aryl) substituted 4,5-bis (p-methoxyphenyl) imidazole derivatives with ethyl iodide in NaH / THF (Scheme). 1-Ethyl derivatives could be synthesized also with Na^o / EtOH (NaOEt) (1), with NaOH (23), with $NaNH_2$ / THF (24) and other novel synthesis procedures (25-34) of 1-substitute imidazoles. At the syntheses which was performed with Na^o, starting material and yield were observed together with ratio of 50-50 % on TLC plate. $NaNH_2$ Was not preferred as a base since the NH_3 so formed caused the reaction to be alkaline. At the study which was done with NaOH, not only product with a yield of 40 % was obtained, but also decomposition products were observed at the chromatographic studies. This method was abandoned because minor products could not be separated from the major product. But with a pair of NaH / THF used as a base-solvent system, a good seperation was obtained. And reaction time was shorter (1-2 hours). NaH / DMF was used for this purpose at the literature related to 1-ethyl imidazole derivatives (3). THF, a solvent with very low boiling point, was eliminated easily by evaporation from reaction medium. Due to these reasons NaH / DMF method was used for synthesis of 1-ethyl 2-(aryl) substituted 4,5-bis (p-methoxyphenyl) imidazoles.



Scheme Synthesis of the compounds

Although synthesis of 4b was carried with anisil and 3-OCH_3, 4-OH benzaldehyde (vanillin), 4-OC_2H_5 derivative instead of 4-OH derivative was obtained. After further purification by recrystallization, the structure of the compounds were elucidated and confirmed by using IR and ^{1}H-NMR spectroscopic methods, elemental analyses for all compounds and MASS spectroscopy for selected compound (2b). General IR values of the compounds were: 3133-2998 cm^{-1} (ar C-H), 1620-1420 cm^{-1} (C=N and C=C), 1290-1020 cm^{-1} (C-O) stretching and 885-750 cm^{-1} (ar C-H) ring deformation bands were common for all compounds. N-H stretching band which was observed at the around of 3550-3359 cm^{-1} due to starting material was no more observed for 1b-5b. At the ^{1}H-NMR spectra of 1-ethyl imidazole derivatives, peaks around at 0.97 (3H, t, CH_2-$C\underline{H}_3$), 3.79 (3H, s, OCH_3)(for 1b, 3b and 4b) or (6H, s, OCH_3)(for 4b and 5b) or (9H, s, OCH_3)(for 2b), 3.98 ppm (2H, q, $C\underline{H}_2$-CH_3) were observed commonly. It is known that 1-ethylless imidazole derivatives would not demonstrate triplet around 0.97 ppm and quartet at 3.98 ppm. In the mass spectra of sample compound (2b), molecular ion peak and base peak were present at m/e 415.3 and 414.3, respectively. Analgesic activity study was planned as the continuation of this study.

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