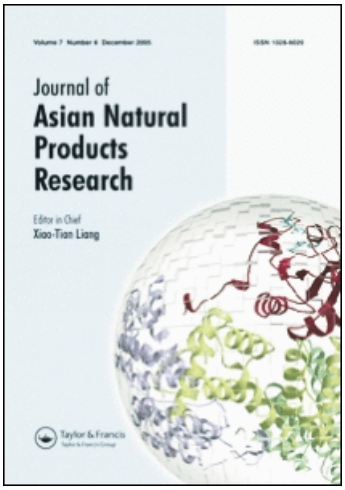

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ORIGINAL ARTICLE

Synthesis and antibacterial activity of carvacryl ethers

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Structural modifications of phenolic monoterpenoid obtained by reacting carvacrol with various substituted α-chloro acetanilides, to improve biological activities which give the product with better yield and higher purity under mild reaction conditions with the help of microwave irradiation techniques.

Keywords: carvacrol; monoterpenoids; microwave irradiation; antibacterial activity; structure–activity relationships

1. Introduction

Carvacrol is an important phenolic monoterpenoid obtained from the essential oils. It resembles phenols in their chemical properties, but their hydroxyl groups are more reactive [1,2]. Carvacrol is an antiseptic, carminative, disinfectant, and escharotic; combined, it forms an efficient gargle in inflammatory conditions. It is not employed internally. In dental practice, carvacrol has been used as a substitute for creasote, carbolic acid, and glycerole of thymol in the treatment of odontalgia, sensitive dentine, alveolar abscess, and as an antiseptic in the pulp canals of teeth [3,4].

The pesticidal efficiency of substituted acetanilides and carvacrol promoted us to undertake the synthesis of the derivatives of natural monoterpenoids. The structural modifications of phenolic monoterpenoids were obtained by reacting carvacrol with various substituted α-chloro acetanilides, to improve biological activities which give the product with better yield and higher purity under mild reaction conditions with the help of microwave (MW) irradiation techniques [5,6].

We report herein a rapid, simple, and efficient method for the synthesis of carvacryl ethers needed for the study of structure–activity relationships.

2. Results and discussion

Considering that MW irradiation using commercial domestic oven has been used to accelerate organic reactions, the high heating efficiency gives remarkable rate enhancement and dramatic reduction in reaction times and better yields. It appears interesting to introduce a substituted acetanilide moiety into carvacrol under MW irradiation. The synthesis of ether compounds by conden-

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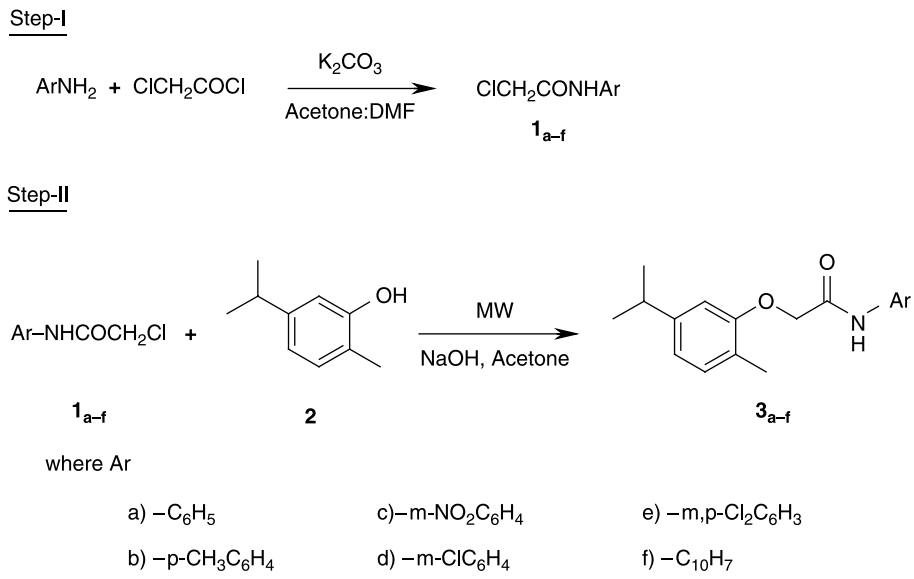

Scheme 1. Synthesis of carvacryl ethers.

sation of carvacrol (**2**) with various substituted α-chloro acetanilides ($\mathbf{1_{a-f}}$) (Scheme 1) under MW irradiation technique in short time is reported (Table 1). The investigations showed that carvacrol reacts very smoothly with different types of substituted acetanilides. The yield of carvacryl ethers was found to be moderate. In order to determine the optimum conditions for the synthesis of ether derivatives of carvacrol in faster and efficient ways, the effect of variation in the molar ratios of reagent and the irradiation time and power level of MW setup was investigated. After some experimentation, it was found that setup conditions generally provide carvacryl ethers in moderate yields. The optimum conditions employed are as follows: the molar ratio of α-chloro acetanilides and carvacrol is 1:1.1 and the irradiation time (2–3 min and 300 W power level) of MW setup is for 30 s time intervals. The compounds were obtained in optimum yield by MW irradiation technique with the aim to increase the yield. The synthesized compounds were identified on the basis of IR, ^{1}H NMR, MS, and CHNS analyzer. The data of all the synthesized compounds are given in Section 3.

In the present work, all the synthesized compounds are tested for their bacterial potency against four bacterial species, viz. *Proteus vulgaris*, *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis* species.

3. Experimental

3.1 General experimental procedures

Various aromatic amines (aniline, *p*-toluidine, *m*-nitro aniline, *m*-chloro aniline, *m,p*-dichloro aniline, and α-naphthyl amine), chloro acetyl chloride, carvacrol, sodium hydroxide, pyridine, and solvents were synthetic grade commercial products (SD Fine Chemicals, Mumbai, India and Qualigens Ltd, Mumbai, India) and were distilled before use.

Melting points were determined using the open capillary method in the paraffin liquid and are uncorrected. IR spectra (cm^{-1}) were recorded on a Perkin-Elmer RX1 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker DRX-300 MHz FT-NMR spectrometer (chemical shifts in ppm). FAB-MS were recorded on a Jeol SX 102/Da-600 mass spectrometer

Table 1. MW synthesis of carvacryl ethers.

Entry[a]	Ar	Molecular formula	MP (°C)	Reaction time		Yield[b]	
				Conventional (h)	MW (min)	Conventional (%)	MW (%)
3a	—C_6H_5	$C_{18}H_{21}NO_2$	55–60	4.0	1.5	50	91
3b	—*p*-$CH_3C_6H_4$	$C_{19}H_{23}NO_2$	75	4.5	3.0	48	92
3c	—*m*-$NO_2C_6H_4$	$C_{18}H_{20}N_2O_4$	60–62	5.0	3.0	47	90
3d	—*m*-ClC_6H_4	$C_{18}H_{20}NO_2Cl$	Semi-solid	4.5	2.5	55	92
3e	—*m,p*-$Cl_2C_6H_3$	$C_{18}H_{19}NO_2Cl_2$	105	5.0	2.5	62	94
3f	—$C_{10}H_7$	$C_{22}H_{23}NO_2$	107–110	4.5	1.0	60	93

Notes: [a]All products were identified using comparison of their physical and spectral data (IR, NMR, MS, and CHNS analyzer).
[b]Isolated yields.

and elemental analyses were performed on a Perkin-Elmer Series II CHNS Analyzer 2400. A Samsung (Model No. OM 9925 E) microwave oven (2450 MHz, 800 W) was used for all experiments. The purity of compounds was checked by TLC.

3.2 Synthesis of N-chloro acetyl aryl amines (α-chloro acetanilides)

The *N*-chloro acetyl aryl amines $\mathbf{1_{a-f}}$ were synthesized and identified by comparing their spectral data with reported values in the literature [7,8] or their melting points.

3.3 Synthesis of carvacryl ethers using MW method

For the synthesis of carvacryl ethers by the conventional method, i.e. compounds $\mathbf{3_{a-f}}$, practical yield was less, more time was required, isolation procedure became difficult, and also the product obtained required purification either by column chromatography or by preparative TLC. Due to these problems, we synthesized the same compounds using MW irradiation technique.

MW irradiation technique has opened new prospects in synthetic organic chemistry not only from the view point of high reaction rates and ease of experimental procedures but also due to high yields of products, their purity and reaction selectivity, and cleanliness. The use of MW techniques considerably reduced the reaction time and improved the yield and purity of products [9–13].

3.4 General procedure

A mixture of carvacrol (2.9 g, 0.013), 1–2 ml of 1% solution of NaOH and 0.013 moles of α-chloro acetanilide $\mathbf{1_{a-f}}$ solution in acetone (2 ml) was placed in an Erlenmeyer flask. This was subjected to MW irradiation for sufficient interval of time using resting intervals of 1 min, and after every 30 s of irradiation, the progress of the reaction was monitored by TLC (9:1). The product was extracted with ether (2× 20 ml) and the extract was washed with water and dried over sodium sulfate. Removal of the solvent afforded carvacryl ethers, needle-shaped crystals, which were dried and recrystallized in ethanol to obtain a pure form of products listed in Table 1.

3.4.1 Compound *3a*

IR ν_{max} (cm^{-1}): 3268 (—NH stretching), 2956–2854 (Ar-H stretching), 1598 (>C═O stretching of amides), 1464 (—C—O stretching), 1253–1378 (Ar-O—CH_2 stretching); ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 8.28 (1H, s, N—H), 6.67–7.47 (8H, m, Ar-H), 4.60 (2H, s, —O—CH_2), 3.31–3.37 (1H, m, —CH<), 2.33 (3H, s, Ar-CH_3), 1.29–1.31

(6H, d, $J = 6.6$ Hz, 2-CH_3 *gem*). Elemental analysis: C, 76.29%, H, 7.47%, N, 4.94%; calcd for $C_{18}H_{21}NO_2$: C, 75.99%, H, 7.41%, N, 4.91%.

3.4.2 Compound **3b**

IR ν_{max} (cm^{-1}): 3400 (NH stretching), 2854 (Ar-H stretching), 1708 (>C═O stretching of amides), 1463 (—C—O stretching), 1255–1378 (Ar-O—CH_2 stretching); ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 8.30 (1H, s, N—H), 6.66–7.47 (7H, m, Ar-H), 4.61 (2H, s, —O—CH_2), 2.85–2.91 (1H, m, —CH<), 2.32–2.33 (3H, s, Ar-CH_3), 1.22–1.24 (6H, d, $J = 6.6$ Hz, 2-CH_3 *gem*). ESI-MS: *m/z* 297 $[M]^+$, 298, 297, 284, 283, 256, 253, 179, 163, 149, 133. Elemental analysis: C, 76.73%, H, 7.80%, N, 4.71%; calcd for $C_{19}H_{23}NO_2$: C, 76.62%, H, 7.71%, N, 4.67%.

3.4.3 Compound **3c**

IR ν_{max} (cm^{-1}): 3366 (—NH stretching), 2854 (Ar-H stretching), 1594 (>C═O stretching of amides), 1464 (—C—O stretching), 1253–1378 (Ar-O—CH_2 stretching), 1523 (—NO_2 group); ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 8.00 (1H, s, N—H), 6.66–7.98 (7H, m, Ar-H), 4.66 (2H, s, —O—CH_2), 2.79–2.92 (1H, m, —CH<), 2.34 (3H, s, Ar-CH_3), 1.22–1.25 (6H, d, $J = 6.9$ Hz, 2-CH_3 *gem*). Elemental analysis: C, 65.84%, H, 6.14%, N, 8.53%; calcd for $C_{18}H_{20}N_2O_4$: C, 65.72%, H, 5.95%, N, 8.24%.

3.4.4 Compound **3d**

IR ν_{max} (cm^{-1}): 3411 (—NH stretching), 2854 (Ar-H stretching), 1595 (>C═O stretching of amides), 1254–1378 (Ar-O—CH_2 stretching), 1459–1523 (multiple bond —CH stretching); ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 8.12 (1H, s, N—H), 6.68–7.88 (7H, m, Ar-H), 4.62 (2H, s, —O—CH_2), 2.78–2.90 (1H, m, —CH<), 2.33 (3H, s, Ar-CH_3), 1.22–1.25 (6H, d, $J = 6.9$ Hz, 2-CH_3 *gem*); ESI-MS: *m/z* 317.5 $[M]^+$, 318, 289, 177, 149, 136, 121, 105, 95. Elemental analysis: C, 68.03%, H, 6.34%, N, 4.41%; calcd for $C_{18}H_{20}NO_2Cl$: C, 67.94%, H, 6.25%, N, 4.19%.

3.4.5 Compound **3e**

IR ν_{max} (cm^{-1}): 3264 (—NH stretching), 2854 (Ar-H stretching), 1748 (>C═O stretching of amides), 1462 (—C—O stretching), 1291–1378 (Ar-O—CH_2 stretching), 868–812 (—Cl group); ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 8.34 (1H, s, N—H), 6.49–7.84 (6H, m, Ar-H), 4.65 (2H, s, —O—CH_2), 3.28–3.71 (1H, m, —CH<), 2.33 (3H, s, Ar-CH_3), 1.29–1.31 (6H, d, $J = 6.9$ Hz, 2-CH_3 *gem*); ESI-MS: *m/z* 352 $[M-H]^-$, 351, 336, 310, 298, 289, 273, 190, 174, 163, 149, 133. Elemental analysis: C, 61.37%, H, 5.44%, N, 3.98%; calcd for $C_{18}H_{19}NO_2Cl_2$: C, 62.21%, H, 5.35%, N, 3.77%.

3.4.6 Compound **3f**

IR ν_{max} (cm^{-1}): 3420 (—NH stretching), 2854 (Ar-H stretching), 1696 (>C═O stretching of amides), 1463 (—C—O stretching), 1377–1246 (Ar-O—CH_2 stretching); ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 8.87 (1H, s, N—H), 6.77–8.18 (10H, m, Ar-H), 4.77 (2H, s, —O—CH_2), 3.46–3.52 (1H, m, —CH<), 2.35 (3H, s, Ar-CH_3), 1.25–1.35 (6H, d, $J = 6.6$ Hz, 2-CH_3 *gem*). Elemental analysis: C, 79.25%, H, 6.95%, N, 4.20%; calcd for $C_{22}H_{23}NO_2$: C, 78.98%, H, 6.77%, N, 4.03%.

Thus, neat reactants subjected to MW irradiation gave the required products more quickly and with better yield in comparison to the traditional methodologies [14].

3.5 Antibacterial activity

In the present work, all the synthesized compounds are tested for their bacterial potency against different bacteria species (*B. subtilis*, *E. coli*, *P. vulgaris*, and

Table 2. Antibacterial activities of compounds $\mathbf{1_{a-f}}$ and $\mathbf{3_{a-f}}$.

Compounds	Zone of inhibition in mm at a concentration of 20 mg ml^{-1}			
	P. vulgaris	*S. aureus*	*E. coli*	*B. subtilis*
Aniline	–	25	–	25
1a	07	25	10	18
1b	09	28	–	12
1c	14	–	07	13
1d	18	20	–	25
1e	14	34	–	20
1f	–	23	–	20
Carvacrol	07	–	–	13
3a	–	–	–	08
3b	–	–	–	–
3c	–	–	05	–
3d	16	17	–	21
3e	10	20	–	18
3f	07	–	–	06

S. aureus). The results are summarized in Table 2. It was assumed to synthesize various derivatives of the natural monoterpenoid and compare the respective bioactivities with their parent compound; carvacrol, to initiate structure–activity relationships; to consider the mode of action of these compounds. Such a structural bioactivity relationship data will be beneficial in the field of pest management for designing the active molecules.

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