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Synthesis and Antibacterial Activity of Thymyl Ethers †

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Abstract: We have reported herein a simple and efficient synthesis method of thymyl ethers for structural modifications of natural products such as *monoterpenoids* and studies of ether derivatives of thymol in biological importance. The investigations showed that thymol reacts very smoothly with different types of substituted acetanilides. The synthesized compounds have been tested for their bacterial potency against four bacterial species. Such a structural modification will be beneficial in the field of pest management for designing the active molecules

Keywords: Thymol; Monoterpenoids; green chemistry; microwave irradiation and antibacterial activity

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1. Introduction

Thymol is an important phenolic monoterpenoid obtained from *Thymus Vulgare*. It exerts cool influenced on muscle. Like phenol it does not irritate the skin and may be taken internally. It is twenty times more antiseptic than phenol. Thymol resembles phenols in chemical properties, but its hydroxyl groups is more reactive than phenol [1,2]. Thymol is effective against gram positive, gram negative bacteria, fungi and Candida albicans yeast [3–8]. Thymus stimulates the appetite, aids in a sluggish digestion and improves liver function.

Structural modifications of phenolic monoterpenoids were obtained by reacting thymol 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 [9,10].

We report herein a rapid, simple and efficient method for synthesis of thymyl ethers that could be useful to introduce new groups of pest management agents through bio rational design of the derivatives.

2. Material and Methods

Various aromatic amines (aniline, *p*–toludine, *m*–nitro aniline, *m*–chloro aniline, *m,p*-dichloro aniline and α-napthyl amine), chloro acetyl chloride, thymol, potassium carbonate, sodium hydroxide and solvents were of analytical grade [s.d. fine chemicals, Qualigens, etc.] and distilled before use.

Melting points were determined using open capillary method in the paraffin liquid. I. R. spectra (cm^{-1}) were recorded on a Perkin Elmer RX1 FTIR spectro photometer. ^1H NMR spectra were recorded on a Bruker DRX-300 MHz: FT NMR spectrometer (chemical shift in δ, ppm). MS were recorded on a Jeol SX 102/Da mass spectrometer and elemental

analyses were performed on a Perkin-Elmer Series II CHNS analyzer 2400. A Samsung (Model No. 9 OM 9925 E) domestic Microwave oven (2450 MHz, 800 W)] was used for all experiments. The purity of compounds was checked by TLC.

3. Experimental Section

3.1. Synthesis of N-chloro Acetyl Aryl Amines (α–Chloro Acetanilides)

Add potassium carbonate (5.87 gm 0.0425 mole) in substituted anilines **3a** (4 g, 0.0425 mole) which was dissolved in 30 mL solvent, Acetone:DMF (9:1), then add drop wise chloro acetyl chloride (4.765 gm, 0.0425 mole) with constant stirring. The reaction temperature (0–5 °C) was maintained by ice-salt mixture, reflux it for 2–3 h. The progress of reaction was monitored by TLC system (Pet. Ether:$CHCl_3$, 8:2) Then, pour the reaction mixture into cold water to obtained product. The product was filtered, dried and recrystallized in ethanol solvent. Physical data of N-chloro acetyl aryl amines **3a–f** are given in a Table 1. The N-chloro acetyl aryl amines **3**$_{a–f}$ were identified by comparing their spectral data with reported values in the literature [11,14] or their melting points.

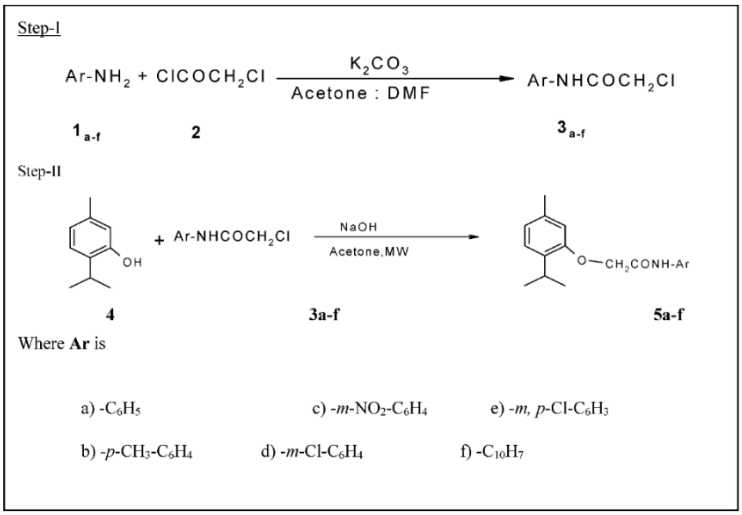
3.2. Synthesis of Thymyl Ethers Using Microwave Method

In synthesis of thymyl ethers by conventional methods,i.e., compounds **5a–f,** practical yield was less, more time was required, difficult isolation procedure and product obtained requires purification either by column chromatography or by TLC. Due to these problems, we have synthesized same compounds using micro-wave irradiation technique.

Microwave (MW) irradiation technique has opened new prospects in synthetic organic chemistry not only due to high reaction rates but also due to ease of experimental procedures and reaction selectivity and cleanliness. The use of MW techniques reduce the reaction time and improve the yield and purity of the products [15–17].

3.3. General Procedure

A mixture of thymol (2 gm, 0.013 moles), 1–2 mL 1% solution of NaOH, and 0.013 moles of α–chloro acetanilide solution **3**$_{a–f}$ in acetone (2 mL) was placed in an Erlenmeyer flask. This was subjected to microwave irradiation for sufficient interval of time using resting intervals of 1 min after every 30 s of irradiation. The progress of reaction was monitored by TLC (Pet. Ether:$CHCl_3$ 9:1). The product was extracted into ether (2 × 20 mL) and then the extract was washed with water (20 mL) and dried over sodium sulfate. After removal of the solvent needle shaped crystals of thymyl ethers were obtained, dried it and **5**$_{a–f}$.



Scheme 1. Synthesis of Thymyl ethers.

Table 1. Characterization data of the compounds **3a–f**.

Compounds	Ar	Molecular formula	M. P. (°C)	Reaction Time (h)	Yield # (%)
3a	-C_6H_5	C_8H_8NOCl	87–91	2.0	88
3b	-*p*-$CH_3C_6H_4$	$C_9H_{10}NOCl$	163–93	3.0	91
3c	-*m*-$NO_2C_6H_4$	$C_8H_7N_2O_3Cl$	90–93	2.0	82
3d	-*m*-ClC_6H_4	$C_8H_7NOCl_2$	87–92	2.5	86
3e	-*m*,*p*-ClC_6H_3	$C_8H_6NOCl_3$	97–101	2.0	84
3f	-$C_{10}H_7$	$C_{12}H_{10}NOCl$	155–157	3.0	80

Table 2. Synthesis of thymyl ethers.

Compounds [a]	Ar	Molecular Formula	M.P. (°C)	Reaction Time		Yields [b]	
				Conventional (h)	M W (min)	Conventional (%)	MW (%)
3a	-C_6H_5	$C_{18}H_{21}NO_2$	80	4.0	1.5	50	91
3b	-*p*-CH_3 C_6H_4	$C_{19}H_{23}NO_2$	77	4.5	1.0	47	90
3c	-*m*-NO_2 C_6H_4	$C_{18}H_{20}N_2O_4$	107	5.0	2.0	48	94
3d	-*m*-Cl C_6H_4	$C_{18}H_{20}NO_2Cl$	72	4.5	2.5	57	91
3e	-*m*,*p*-Cl_2 C_6H_3	$C_{18}H_{19}NO_2Cl_2$	65	5.0	1.5	60	89
3f	-$C_{10}H_7$	$C_{22}H_{23}NO_2$	115	4.5	1.5	61	91

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

3.4. Compounds and Their Spectral Data

3a: IRν_{max} (cm^{-1}): 3400 (N-H stretching), 2854 (-CH_2 stretching), 1672 (C=0 acyclic stretching, 1292, 1252 (C-N stretching of aromatic primary amine), 557, 502 (C-Cl stretching).

3b: IRν_{max} (cm^{-1}): 3237 (N-H stretching, 2923 (-CH_2- stretching), 3203, 3134 (weak extra band due to N-H stretching), 1673 (C=0 stretching of amide), 864 (*p*-di substituted aromatic). (ES/MS): *m*/*z* (297) (M^+) 298, 284, 256, 179, 163, 149 and 133.

3c: IRν_{max} (cm^{-1}): 3401 (N-H stretching), 2924, 2853 (-CH_2- stretching), 1673 (C=0 stretching of amide), 738 (*m*-di substituted aromatic). (ES/MS): *m*/*z* (317.5) (M^+) 318, 317, 289, 276, 177, 163, 149, 136, 121, 105 and 95.

3e: (ES/MS): *m*/*z* (352) (M-H) 351, 336, 310, 298, 273, 190, 174, 163, 149 and 133.

3f: IRν_{max} (cm^{-1}): 3410 (N-H stretching), 2924, 2854 (-CH_2- stretching), 1664 (C=0 stretching of amide), 1406, 1464 (1-naphthyl ring).

5a:- IRν_{max} (cm^{-1}): 3405 (-NH stretching), 2854 (Ar-H stretching), 1700 (>C=O stretching of amides), 1464 (-C-O stretching), 1463–1500 cm^{-1} (multiple bond -CH stretching). H^1 NMR spectral data ($CDCl_3$, 300 MHZ): δ 8.280 (1H, s, N-H), δ 6.679 to 7.473 (8H, m, Ar-H), δ 4.604 (2H, s, -O-CH_2), δ 3.310 to 3.376 (1H,m,-CH<), δ 2.332 (3H, s, Ar-CH_3), δ 1.295 to 1.317 (6H, d, 2-CH_3 gem.).

5b:- IRν_{max} (cm^{-1}): 3405 (-NH stretching), 2854 (Ar-H stretching), 1701 (>C=O stretching of amides), 1378–1062 (Ar-O-CH_2 stretching), 1463–1595 (multiple bond -CH stretching). H^1 NMR spectral data ($CDCl_3$,300 MHZ): δ 8.286 (1H, s, N-H), δ 6.583 to 7.473 (7H, m, Ar-H), δ 4.603 (2H, s, -O-CH_2), δ 3.310 to 3.377 (1H, m, -CH<), δ 2.332 (3H, s, Ar-CH_3), δ 1.390 (6H, d, 2-CH_3 gem.).

5c:- IRν_{max} (cm^{-1}): 3430 (-NH stretching), 2854 (Ar-H stretching), 1623 (>C=O stretching of amides), 1524 (-NO2 group), 1463–1500 (multiple bond -CH stretching). H^1 NMR spectral data ($CDCl_3$, 300 MHZ):

5d:- IRν_{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). (ES/MS): *m/z* (318) (M-H) 318, 317, 289, 276, 177, 163, 149, 136, 121, 105 and 95.

5e:- IRν_{max} (cm^{-1}): 3393 (-NH stretching), 2854 (Ar-H stretching), 1691 (>C=O stretching of amides), 1253–1378 (Ar-O-CH_2 stretching), 1463–1523 (multiple bond -CH stretching). H^1 NMR spectral data ($CDCl_3$, 300 MHZ): δ 8.340 (1H, s, N-H), δ 6.493 to 7.845 (6H, m, Ar-H), δ 4.655 (2H, s, -O-CH_2), δ 3.285 to 3.717 (1H, m, -CH<), δ 2.331 (3H, s, Ar-CH_3), δ 1.296 to 1.319 (6H, d, 2-CH_3 gem.).

5f:- IRν_{max} (cm^{-1}): 3427 (-NH stretching), 2854 (Ar-H stretching), 1707 (>C=O stretching of amides), 1251–1378 (Ar-O-CH_2 stretching), 1464–1547 (multiple bond -CH stretching). NMR spectral data ($CDCl_3$, 300 MHZ): δ 8.874 (1H, s, N-H), δ 6.772 to 8.186 (10H, m, Ar-H), δ 4.774 (2H, s, -O-CH_2), δ 3.463 to 3.529 (1H, m, -CH<), δ 2.354 (3H, s, Ar-CH_3), δ 1.254 to 1.355 (6H, d, 2-CH_3 gem.).

3.5. Antibacterial Activity

In present work, all the synthesized compounds have been tested for their bacterial potency against different bacteria (*Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris* and *Staphylococcus aureus*) species. The results are summarized in Table 3. The compounds having substituted acetanilides moiety, further coupled with thymol and their anti bacterial activity are studied.

In overall antibacterial study data, we have found that the synthesized *N*–chloro acetyl aryl amines **1a–f** reflected good antibacterial potency than the same componunds when coupled with thymol i.e., **3a–f**. Such a structural modification will be beneficial in the field of pest management for designing the active molecules.

Table 3. Antibacterial activities of compounds **3**$_{a–f}$ and **5**$_{a–f}$.

Compounds	Zone of Inhibition in mm at Concentration of 20 mg/ml			
	P. vulgaries	***S. aureus***	***E. coli***	***B. subtilis***
Aniline	----	25	----	25
3a	07	25	10	18
3b	09	28	----	12
3c	14	----	07	13
3d	18	20	----	25
3e	14	34	----	20
3f	----	23	----	20
Thymol	----	----	----	10
5a	06	----	----	----
5b	09	----	05	----
5c	14	31	----	----
5d	06	----	----	10
5e	----	----	----	06
5f	05	05	----	05

4. Results and Discussion

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

In case of *Proteus vulgaris*, the compound **3d** shows highest antibacterial potency. The parent compound aniline, thymol as well as the compound **5e,** does not shows antibacterial activity.

In comparison with aniline, N-chloro acetyl aryl amines compounds **3a–f** reflected much higher antibacterial activity, except compound **3f**. But same compound **3f** when coupled with thymol its antibacterial activity increases.

In case of *staphyloccocuus aureus* the compound **3e** reflected the highest antibacterial potency, as compared with all synthesized compounds. The compound **3c** does not possess antibacterial activity. It shows high potency when coupled with thymol moiety i.e., compound **5c**. This enhancement in activity is attributed to introduction of thymol moiety. The starting compounds thymol and the synthesized compounds **5a**, **5b**, **5d** and **5e** does not possess antibacterial activity.

In case of *Escherichia coli* all the synthesized compounds does not show remarkable antibacterial activity. Similarly the starting compound i.e., thymol and aniline does not shows antibacterial activity. The compound **3a** reflects the highest antibacterial activity against *E. coli.* and also the compounds **3c** and **5b** shows good antibacterial activity.

In case of *Bacillus subtilis* species all the compounds of the series **3a–f** show very good antibacterial activities. The parent compound aniline and **3d** compound exhibited highest antibacterial activity than other synthesized compounds. Also thymyl ether derivatives like **5d, 5e** and **5f** are remarkable one at 2% concentration. The synthesized compound **5a, 5b** and **5c** does not reflect antibacterial activity.

From overall antibacterial data, it is evident that the aniline and compounds **3a–f** shows good antibacterial potency against all test bacteria species at 2% concentration than the synthesized compounds **5a–f.** The activity order of the compounds of these series is as below.

$$\mathbf{3}_{a-f} \geq \mathbf{5}_{a-f}$$

5. Conclusions

The microwave synthesis involves prevent waste than to treat or clam up waste after it is formed that approach will require new environmentally benign synthesis catalytic methods and chemical products that are benign by design and that utilize renewable resources wherever possible [8–12].

The simple, efficient and cost effective method is described for the synthesis of thymol and carvacrol derivatives. This simple, quick and environmentally benign safe procedure is advantageous in terms of experimentation yield of product, short reaction time and avoid of toxic solvents. This is a very useful method for the synthesis and generation of potentially biological active thymol and carvacrol compounds.

6. Future Prospects

The structure-activity relationship can be established on the basis of structural modification and bioassay. MW irradiation technique has been successfully applied in synthetic organic chemistry to remove the drawbacks of conventional methodologies and reaction conditions. These are important aspects of Green Chemistry approach, because they occur more fastly, safely and environment friendly manner. Use of microwave irradiation technique without solvent or to avoid toxic solvent is beneficial to the environment. In future, the structural modification by this method will be beneficial for designing the active molecules in the pest management.

Monoterpenoids and their derivatives are completely biodegradable and do not cause environmental pollution. Extensive research are going on for the derivatization of natural products isolated from essential oils of higher plants. The monoterpenoid group is promising one of them for pest management efficacy.

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