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Synthesis and antimicrobial activity of some naphthyl ether derivatives

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ABSTRACT

The main objective of this work is to synthesize naphthyl ethers in the micellar catalyzed medium, which is advantageous over the conventional method of preparation. The compounds prepared show, promising activity as therapeutic agents. In the present work, the substituted Phenacyl naphthyl ethers have been synthesized by electrophilic substitution on substituted naphtholate ion with 4-methyl phenacyl bromide or 4-chloro phenacyl bromide. The compounds have been characterized by physical data and further screened for anti-microbial activities.

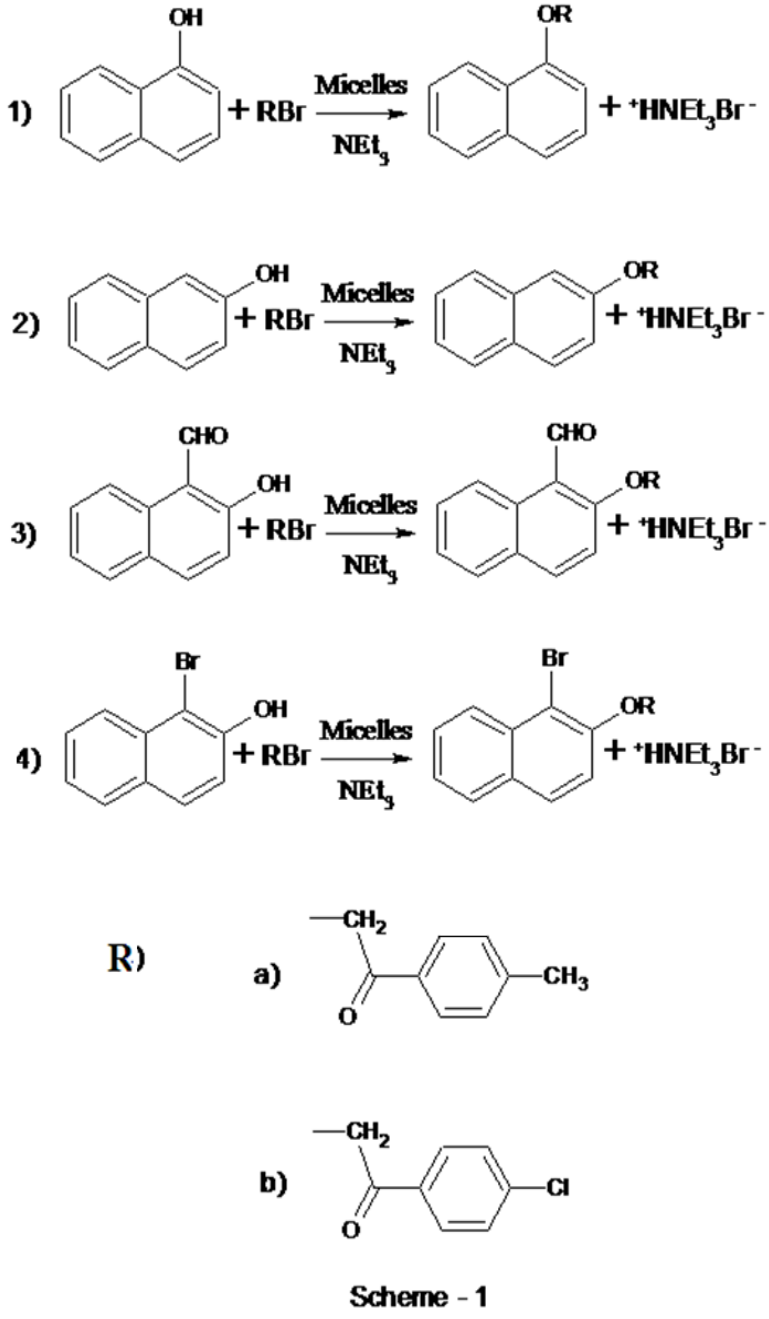
Keywords: Phenacyl naphthyl ether, Thin Layer Chromatography, FT-IR, NMR, Antimicrobial activity, Therapeutic agent.

INTRODUCTION

The aromatic ethers have been reported to show a broad spectrum of biological, agricultural and chemical engineering **[1]** applications. Notable among these are that they find application as fungicides **[2],** herbicides **[3]**, adhesives **[4]**, fire retardants **[5]**, antitumor agent **[6]** etc. Various methods have been employed to synthesize aryl ethers in that the Williamson synthesis in solvent free environments is a familiar synthesis **[7].** Recently, Nallu et. al **[8]** have reported an elegant method of synthesis of phenolic ethers using micellar medium**.** The pharmacological, agricultural and chemical engineering applications of these compounds encouraged our interest in synthesizing several new compounds and screening them for anti-microbial activity. In continuation of our earlier work **[9]**, we successfully attempted to prepare few more new naphthyl ethers and studied their antimicrobial activities.

MATERIALS AND METHODS

All the reagents and solvents used were of laboratory grade. The melting points of the compounds were determined by open capillaries on a Thomas Hoover apparatus and are uncorrected. The purity and homogeneity of compounds were checked using TLC technique. IR spectra were recorded using KBr pellets on Perkin Elmer 337 spectrophotometer, ^{1}H NMR were recorded on Bruker WH 500 spectrophotometer using $CHCl_3$ and DMSO as solvent. The Mass spectral data and C, H, analytical data were obtained from IIT, Madras. The assignment of the spectral data was made based on the literature values **[10]**.



Scheme - 1

Synthesis and Characterization of Compounds

Preparation of naphthyl ethers 1—4 (a,b)

A mixture of 1-naphthol (1.45g, 0.1mol) and triethylamine (1ml, 0.1mol) were mixed in micellar solution. 4-methyl phenacyl bromide (2.13g, 0.1mol) was dissolved in micellar solution and mixed with the solution of 1-naphthol-triethyl amine mixture. The reaction mixture was stirred for about 30^{o}C and kept overnight at room temperature. The solid product thrown out was filtered off and recrystallised using methanol. The synthetic route of mentioned compounds is shown in **Scheme-1**.

1a. 4-methylphenacyl-1-naphthyl ether: Yield- 70%**, M.P.** 78-79 ^{o}C**, R_f-** 0.43 (Ethyl acetate: methanol, 1:1); **IR (KBr) cm^{-1}** :3095 (aromatic ring –CH str), 1223 (C-O-C str), 1592 (C=C str), 2832 (aliphatic –CH), 1700 (C=O str); **^{1}H NMR** ($CDCl_3$) ppm: 8.2 (7H, m, naph), 7.2 (4H, m, -$COCH_2C_6\underline{H}_4$), 4.9(2H, s, -OCH_2), 2.3 (3H, s, CH_3)**.** **^{13}C NMR** ($CDCl_3$) ppm: 23, 70.1, 71.4, 107.2, 118.2, 124.1, 125.4, 126.2, 127.5, 128.6, 129.9, 133.8, 155.9; Mass (m/z):276 (M^+ peak).

1b. 4-chlorophenacyl-1-naphthyl ether: Yield- 68%, **M.P.** 67-68 C, **R_f:** 0.47 (Ethyl acetate: methanol, 1:1); **IR (KBr) cm^{-1}**: 3095 (aromatic ring –CH str), 1227 (C-O-C), 1592 (C=C), 2830 (aliphatic –CH str), 1700 (C=O str); **^{1}H NMR** ($CDCl_3$) ppm: 8.1 (7H, m, naph), 7.3 (4H, m,-$COCH_2C_6\underline{H}_4$), 5.2 (2H, s, -OCH_2); **^{13}C NMR** ($CDCl_3$): 70.3, 71.2, 107.2, 118.4, 124.3, 125.2, 126.2, 127.5, 128.6, 129.9, 133.8, 155.9; Mass (m/z): 296 (M^+ peak).

2a. 4-methylphenacyl-2-naphthyl ether: **Yield**: 72%, M.P. 72-75 C, **R_f**: 0.52 (Ethyl acetate :methanol, 1:1); **IR (KBr) cm^{-1}**: 3058 (aromatic ring –CH str), 1226 (-C-O-C- str), 1607 (C=C str), 1708 (C=O str), 2926 (aliphatic –CH str); **^{1}H NMR** ($CDCl_3$) ppm : 8.01 (7H, m, naph), 7.3 (4H, m, -$COCH_2C_6\underline{H}_4$), 5.2 (2H, s, - OCH_2), 2.3(3H, s, -CH_3); **^{13}C NMR** ($CDCl_3$) ppm : 23, 70.1, 71.7, 107.4,118.5, 124.2, 125.4, 126.2, 128.3, 128.6, 129.0, 133.7, 155.5; Mass (m/z): 276 (M^+ peak).

2b. 4-chlorophenacyl-2-naphthyl ether: Yield: 70%, M.P. 104-105 C, **R_f**: 0.53 (Ethyl acetate :methanol, 1:1); **IR (KBr) cm^{-1}**: 3057 (aromatic ring –CH str), 1224 (C-O-C str), 1631 (C=O str), 1584 (C=C str), 2928 (aliphatic –CH); **^{1}H NMR** ($CDCl_3$) ppm : 8.04 (7H, m, naph), 7.2 (4H, m, -$COCH_2C_6\underline{H}_4$), 5.1 (2H, s, -OCH_2); **^{13}C NMR** ($CDCl_3$) ppm : 70.3, 71.9, 107.6, 118.2, 124.2, 125.4, 127.0, 128.3, 128.6, 129.0, 133.7, 155.5; Mass (m/z): 296 (M^+ peak).

3a. 4-methylphenacyl-1-formyl -2-naphthyl ether: Yield: 69%, M.P. 142-144 C, **R_f**-0.54 (Ethyl acetate :methanol, 1:1); **IR (KBr) cm^{-1}**: 3008 (aromatic ring –CH str), 1224 (C-O-C str), 1708 (C=O str), 1607(C=C str), 2928(aliphatic –CH str); **^{1}H NMR** ($CDCl_3$) ppm : 7.99 (6H, m, naph), 7.3 (4H, m, -$COCH_2C_6\underline{H}_4$), 5.2 (2H, s, -OCH_2), 2.3 (3H, s, -CH_3), 9.2 (1H, s, -CHO); **^{13}C NMR** ($CDCl_3$) ppm : 23, 71, 122.7, 125.3, 126.1, 126.2, 126.4, 126.6, 126.8, 128.6, 132.1, 136.3, 157, 192.4; Mass (m/z) : 304 (M^+ peak)

3b. 4-chlorophenacyl-1-formyl-2- naphthyl ether: Yield: 70%, M.P. 157-155 C, **R_f**-0.51 (Ethyl acetate :methanol, 1:1); **IR (KBr) cm^{-1}**: 3057 (aromatic ring –CH str), 1230 (-C-O-C- str), 1687 (C=O str), 1584 (C=C str), 2928 (aliphatic –CH); **^{1}H NMR** ($CDCl_3$) ppm: 8.0 (6H, m, naph), 7.5 (4H, m, --$COCH_2C_6\underline{H}_4$), 4.8 (2H, s, -OCH_2), 9.2 (1H, s, -CHO); **^{13}C NMR** ($CDCl_3$)

ppm : 71, 122.6, 125.2, 126.3, 126.5, 126.6, 126.7, 126.9, 128.5, 132.2, 136.1, 157.2, 191.7; Mass (m/z) : 324 (M^+ peak).

4a. 4-methylphenacyl-1-bromo -2-naphthyl ether: Yield: 71%, M.P. 108-110, **R_f**-0.55; **IR (KBr) cm^{-1}**: 3090 (aromatic ring –CH str), 1225 (-C-O-C- str), 1700 (C=O str), 1590 (C=C str), 2973(aliphatic –CH str); **^{1}H NMR** ($CDCl_3$) ppm : 8.2 (6H, m, naph), 7.5 (4H, m, --$COCH_2C_6\underline{H}_4$), 5.4(2H, s, -OCH_2), 2.4(3H, s, CH_3); **^{13}C NMR** ($CDCl_3$) ppm; 23, 70, 122.7, 123.2, 126.0, 126.4, 126.8, 127, 128.0, 128.6, 134, 137, 157; Mass (m/z) : 375 (M^+ peak).

4b. 4-chlorophenacyl-1-bromo-2- naphthyl ether: Yield: 73%, M.P. 113-115 C, **R_f**- 0.54 (Ethyl acetate : methanol, 1:1); **IR (KBr) cm^{-1}**: 3080 (aromatic ring –CH str), 1221 (-C-O-C- str), 1698 (C=O str), 1580 (C=C str), 2986 (aliphatic –CH str); **^{1}H NMR** ($CDCl_3$) ppm : 8.2 (6H, m, naph), 7.4 (4H, m, -$COCH_2C_6\underline{H}_4$), 5.3 (2H, s, -OCH_2); **^{13}C NMR** ($CDCl_3$) ppm : 70.5, 122.6, 123.4, 126.0, 126.3, 126.7, 127.1, 128.3, 128.7,134.2, 137.1, 157.5; Mass (m/z) : 375 (M^+ peak).

RESULTS AND DISCUSSION

In the present investigation of **1 4 (a,b)** compounds have been synthesized**.**

Substituted or unsubstituted Phenacyl naphthyl ethers have been prepared in an excellent yield by electrophilic aromatic substitution on naphtholate ion by 4-chloro phenacyl bromide or 4-methyl phenacyl bromide in the presence of triethyl amine under micellar condition.

Table 1: Physical data of compound No 1 4 (a,b)

Compound No	R	Molecular formula	mp(^{o}C)	Yield (%)	R_f value
1a	-$COCH_2C_6H_4CH_3$	$C_{19}H_{16}O_2$	78	76%	0.43
1b	-$COCH_2C_6H_4Cl$	$C_{18}H_{13}O_2Cl$	67	68%	0.46
2a	-$COCH_2C_6H_4CH_3$	$C_{19}H_{16}O_2$	72	67%	0.47
2b	-$COCH_2C_6H_4Cl$	$C_{18}H_{13}O_2Cl$	104	69%	0.46
3a	-$COCH_2C_6H_4CH_3$	$C_{20}H_{16}O_3$	142	72%	0.51
3b	-$COCH_2C_6H_4Cl$	$C_{19}H_{13}O_3Cl$	157	75%	0.53
4a	-$COCH_2C_6H_4CH_3$	$C_{19}H_{15}O_2Br$	108	76%	0.54
4b	-$COCH_2C_6H_4Cl$	$C_{18}H_{12}O_2BrCl$	115	75%	0.57

Table 2: Elemental analysis of compound No. 1 4 (a,b)

Compd No	R	Molecular formula	Elemental Analysis (%)					
			Calculated			Found		
			C	H	N	C	H	N
1a	-$COCH_2C_6H_4CH_3$	$C_{19}H_{16}O_2$	82.60	5.79	-	82.58	5.80	-
1b	-$COCH_2C_6H_4Cl$	$C_{18}H_{13}O_2Cl$	72.97	4.71	-	72.99	4.68	-
2a	-$COCH_2C_6H_4CH_3$	$C_{19}H_{16}O_2$	82.60	5.79	-	82.58	5.77	-
2b	-$COCH_2C_6H_4Cl$	$C_{18}H_{13}O_2Cl$	72.97	4.71	-	72.95	4.73	-
3a	-$COCH_2C_6H_4CH_3$	$C_{20}H_{16}O_3$	78.94	5.26	-	78.96	5.28	-
3b	-$COCH_2C_6H_4Cl$	$C_{19}H_{13}O_3Cl$	70.37	4.01	-	70.39	4.03	-
4a	-$COCH_2C_6H_4CH_3$	$C_{19}H_{15}O_2Br$	64.22	4.22	-	64.20	4.18	-
4b	-$COCH_2C_6H_4Cl$	$C_{18}H_{12}O_2BrCl$	57.60	3.20	-	57.64	3.22	-

Table 3: Antimicrobial activity of compounds, zone of inhibition in mm

Compound No	*B.cereus(+)*	*S.aureus(+)*	*A.hydrophila(-)*	*A.flaves*	*A.niger*
1a	13	10	12	**16**	**18**
1b	**14**	9	13	9	12
2a	9	9	12	**27**	11
2b	13	**14**	12	8	**14**
3a	**35**	**27**	**35**	12	**32**
3b	16	16	16	**37**	**25**
4a	**20**	9	14	13	**20**
4b	8	10	13	**21**	**16**
Ampicillin	**42**	**45**	-	-	-
Miconozole	-	-	-	**48**	**40**

The purity and homogeneity of all the compounds were confirmed by sharp melting points (uncorrected) and thin-layer chromatography and the data produced in **Table-1.**

The chemical structures were confirmed by the spectral data of the compounds. The aromatic –CH stretching in IR for all the derivatives was found to be at the range of 3090 – 3000 cm^{-1}. The presence of asymmetric ether is confirmed by the absorption at 1220 – 1218 cm^{-1}. The presence of unsubstituted aldehydic group is confirmed by the band at 1700 cm^{-1}. The presence of C-Cl, C-Br linkage is confirmed by the absorption frequencies at 790 and 585 cm^{-1} respectively.

The ^{1}H NMR spectra were useful for the identification of some important protons in the compounds. For example δ 8.2 and 7.2 indicate the presence of naphthyl and phenyl ring protons respectively, the signal at δ 5.2 indicates the presence of $–OCH_2$ proton, and the peak at 2.1 ppm shows the presence of methyl linkage. The presence of aldehydic protons is indicated by the signal at the range δ 9.2. Mass spectra of the compounds gave molecular mass of compounds. The physical data of the compounds **1–4 (a,b)** are summarized in **Table-2.**

Antimicrobial activity

All the compounds (**1a, 1b, 2a, 2b, 3a, 3b, 4a** and **4b)** were screened for their antimicrobial activity against *Bacillus cerus*, *Staphylococcus aureus* and *Aeromonas hydrophila* and antifungal activity against *Aspergillus flaves* and *Aspergillus niger* at a concentration of 60 ug/ml in DMSO by Agar well-diffusion method **[11, 12]** . Standard anti-bacterial and anti-fungal drug, ampicillin and miconazole respectively were also tested under similar conditions for comparison. Zone of inhibition in mm of synthesized compounds and standard drugs are shown in **Table-3.**

CONCLUSION

A series of substituted Phenacyl naphthyl ether **1—4 (a,b)** have been newly synthesized and characterized by spectral analysis. Most of the compounds have shown anti-bacterial and anti-fungal activity to some extent. Among the compounds **3a** and **4a** show significant activity, while rest show feeble activity against *B.cerus*, However the compound **3a** shows significant activity against *A.hydrophila*, compound **3b** shows moderate activity against the same and others show feeble activities. The compounds **3a** and **3b** show significant activity, while compounds **1a, 2b**

and **4b** show moderate activity against *A.niger*. The compound **3a** shows reasonable activity against *A.flaves*.

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