CHAPTER - 3

FACILE SYNTHESIS OF PHENACYL ETHERS BY USING MIXTURE OF TETRABUTYLAMMONIUM BROMIDE AND DIBENZO-[18]-CROWN-6.

ABSTRACT

Tetrabutylammonium bromide in combination with dibenzo-[18]-crown-6 is found to be highly effective in the synthesis of phenacyl ethers by reaction of phenols with phenacyl bromide.

INTRODUCTION

Preparation of ethers is an important synthetic reaction of which a wide variety of procedures have been reported in literatures in last decades. Valerius Cordus[1] described the preparation of ethyl ether from ethanol and oil of vitriol in 1544. Alexander Williamson estblished the correct formula of ethyl ether and contributed a very important method for the synthesis of ethers; the reaction of alkoxides with alkyl halides (4.1). With considerable modification, the utility of this method has become well documented by a number of workers. The formation of alkoxide coates the sodium, but by using a large excess of alcohol, the difficulty can be overcome. After the sodium has dissolved, the alkyl halide is added to form the ether[2]. Synthesis of alkyl phenyl ethers are carried out by refluxing aqueous or alcoholic solutions of alkali phenolates with alkyl halides; the yields vary with the nature of the alkyl halides (40-80%)[2,3]. The reactive halogen in benzyl halides is easily replaced by an alkoxyl groups[4,5]. The choice of a solvent is sometimes important For example, in the preparation of the alkyl ethers of

o-and p-hydroxybiphenyl from a mixture of phenol, alkyl halide and powdered potassium hydroxide; high yields are obtained using acetone as a solvent, whereas, with alcohol, only small yields are obtained[6]. Triarylmethyl chlorides reacts with alcohols directly (97%)[7]; (4.2).

Substituted diaryl ethers (ArOAr') are prepared by the reaction of alkyl phenoxides with aryl halides in the presence of copper catalyst (Ullman)[8,9]. Further studies have shown that the yield varies considerably with different copper-catalyst preparations[10,11].

By addition of alkyl halides to a hot solution of sodium in excess trimethylene glycol diluted with xylene[12,13], hydroxy ethers of the type R OCH_2CH_2OH are obtained. In a similar way the sodium phenoxide is treated with the chlorohydrin to get phenyl ethers[14,15]. The synthesis of o- and p-chlorophenyl phenyl ethers have been successfully accomplished by the Ullman procedure, whereas chlorination of diphenyl ether yields an inseparable mixture of isomers[8].

Mixed aliphatic ethers containing methyl or ethyl radicals can be synthesized from the corresponding alkyl sulphate and magnesium alcoholates[16,17], but the method is more general in the preparation of phenols[18,19]. One or both alkyl groups in the alkyl sulphate may be utilized. In the preparation of anisole, an aqueous solution of phenoxide is treated at 10°C with dimethyl sulphate. The

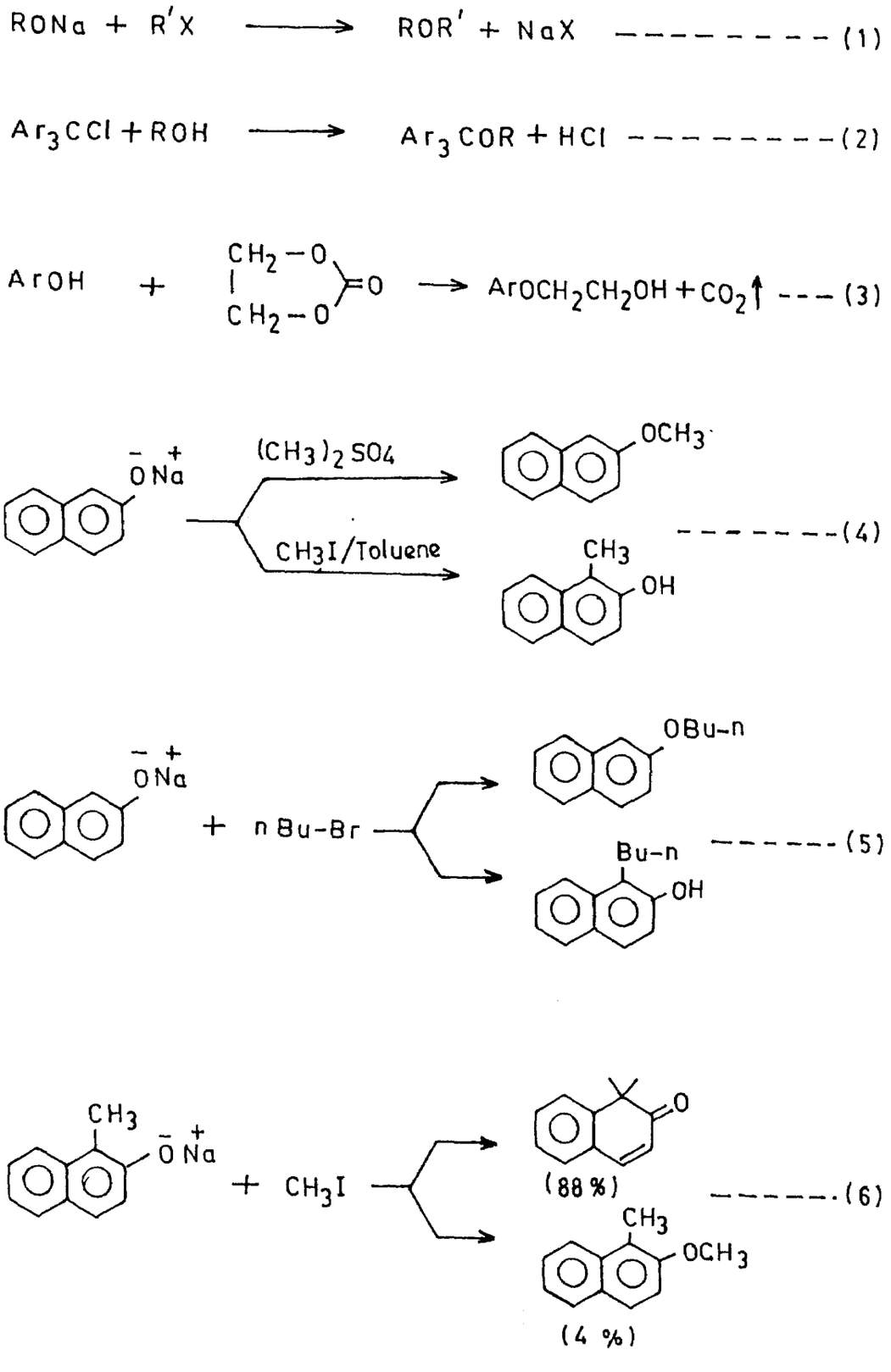
first methyl group is readily furnished but the second only under reflux. In certain phenanthrene compounds, the phenolic groups have been quantitatively methylated by adding dimethyl sulphate to a suspension of the compounds in acetone and aqueous potassium hydroxide[20].

The hydroxyethylation of phenols with ethyl sulphite or ethylene carbonate is promising reaction for the formation of hydroxyethers of $ROCH_2CH_2OH$ (4.3)[21].

The phenoxide ion is generated by treatment of the phenol with a base as sodium, sodium hydride and sodium amide in a solvent such as benzene, toluene or hexane. Then alkylation of phenoxide with the appropriate alkyl halide is then normally carried out in the same solvent. This method is again usually highly efficient, although some care must be exercised in the choice of solvent in order to avoid formation of botn C- and O-alkylated products[22,23].

The effect of solvent and alkylating agent on beta-naphthol and 1-methyl-2-naphthol have been investigated by Wenkert and co-workers[22]. Methylation of dry sodium salt of beta-naphthol with methyl sulphate gave exclusively the methyl ether while alkylation with methyl iodide in toluene led preponderantly to 1-methyl-2-naphthol (4.4). Under the latter conditions sodium beta-naphthoxide and n-butyl bromide gave both O- and C-alkyl products in a 1.4:1 ratio (4.5). Alpha-alkylation

CHART–4


RONa + R'X → ROR' + NaX ---------(1)
Ar3CCl + ROH → Ar3COR + HCl ---------(2)
ArOH + CH2–O, CH2–O, =O → ArOCH2CH2OH + CO2↑ ---(3)
ONa
(CH3)2SO4
CH3I/Toluene
OCH3
CH3
OH
-------(4)
ONa
+ n Bu-Br
OBu-n
Bu-n
OH
------(5)
CH3
ONa
+ CH3I
O
(88 %)
CH3
OCH3
(4 %)
------(6)

of already alkylated naphthols proved to be a much yielding process than alkylation of beta-naphthol itself (4.6). But the interaction of the same dry salt with n-butyl iodide gave a 59% yield of ketone and a 29% yield of ether (4.7), while treatment of dry sodium 1-(n-butyl)-naphthoxide with methyl iodide gave a similar ratio of products, 59% of ketone and 30% of ether (4.8).

Solvation as a factor in the alkylation of sodium beta-naphthoxide, in a variety of a solvents, with benzyl bromide, methyl iodide and n-propyl bromide has been studied by Kornblum and co-workers[23]. The results of these studies proved a clear demonstration of the ability of the solvent to decide the course of an ambidient anion reaction. The study of the solvent affects on the course of ambidient anion processes distinguishes between protic and aprotic solvents and which emphasized the utility of this distinction.

The preparation of highly hindered anisole is described by Cohen[24]. Sodium salt of substituted 2,4-di-tert-butyl phenols are treated with methyl iodide in toluene in a pressure bottle and heated by steam for 18 hours. The residue was extracted with petroleum ether to get corresponding anisoles.

The condensation of halogenphenols and ethyl acrylate in presence of sodium and direct hydrolysis of the mixture with cold aqueous alkali affords a number of

beta-halogenphenoxypropionic acid (4.9)[25].

Camps et.al[26] reported the synthesis of ethers from alcohols and alkyl halides in the presence of nickel bis (acetylacetonate) as catalyst (4.10).

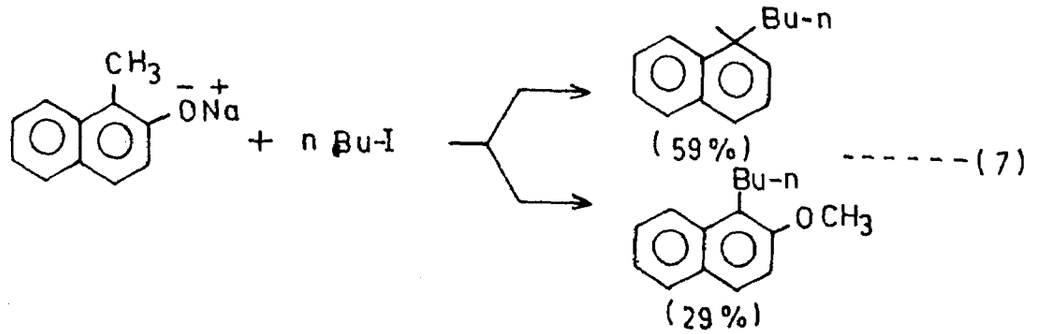
The results with nitrophenols, salicyladehyde and 1- and 2- naphthols shows O-alkylation, which is contrary to Kornblums report of C-alkylation for naphthols[23]. The exclusive O-alkylation, of this study, provides supporting evidence for kinetic data reported by Starks et.al.[27].

Bow[28] reported in 1926 that benzyl phenyl ethers were obtained when phenols were heated with benzyldimethylaniline chloride for several hours in the presence of either sodium hydroxide or sodium carbonate. This reaction has been used for preparation of methyl, ethyl, butyl and benzyl ethers, especially those of phenolic alkaloids and hydroxypyridines[29-33].

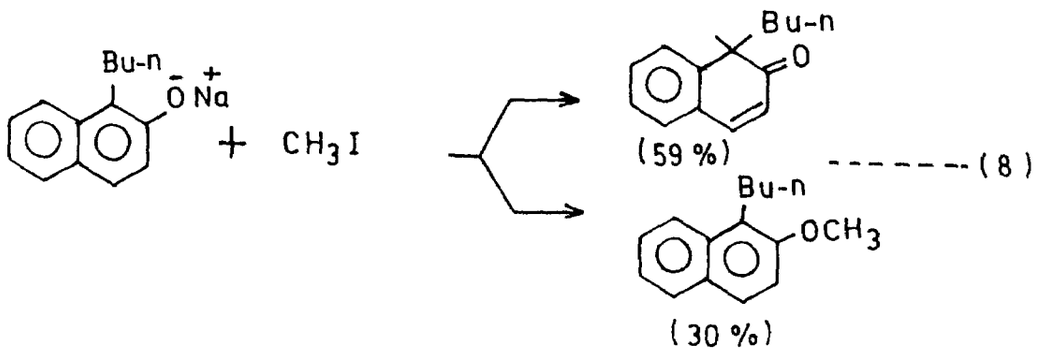
Benzyl ethers of a number of phenols have been synthesized by the use of phenolates of strongly basic anion exchange resins with an ethanol solution of benzyl chloride at room temperature[34].

The use of phase-transfer catalysis for the preparation of phenol ethers has been reported by Mckillop and co-workers[35]. Phase transfer catalysis is a technique which is of much interest in recent years and also often referred as a "ion pair partition" or "extractive

CHART-4 (contd.)

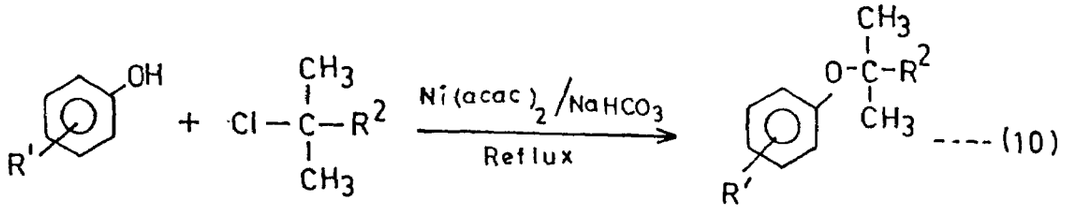


-------(7)



-------(8)

$$ArOH + CH_2{=}CH{-}COOEt \longrightarrow ArOCH_2CH_2COOEt \quad \text{-----(9)}$$



----(10)

$$\overset{+}{Q}OH + ArOH \rightleftharpoons \overset{+}{Q}ArO^{-} + H_2O \quad \text{Aqueous Phase}$$

$$\overset{+}{Q}X + ArOR \longleftarrow \overset{+}{Q}ArO^{-} + RX \quad \text{Organic Phase} \qquad \text{-----(11)}$$

$$Q^{+} = R_4N^{+}$$

$$p\text{-}MeCOC_6H_4OH + Me(CH_2)_7Br \xrightarrow[\text{Aliquat 336}]{KOH}$$

$$p\text{-}MeCOC_6H_4O(CH_2)_7Me \quad \text{----(12)}$$

alkylation". The method has a number of very useful synthetic applications and can be applied to the synthesis of aryl ethers[36]. Phenol is added to a two-phase system consisting of an aqueous solution of the quaternary ammonium hydroxide and a methylene dichloride solution of the alkylating agent. The phenol which is partitioned naturally between the two phases, is converted into the corresponding quaternary ammonium phenoxide in the aqueous phase. This latter salt has a discrete solubility in the organic phase; consequently, transport of the phenoxide ion into the methylene chloride solution is followed by rapid irreversible alkylation and formation of the phenol ether.

Ethers ROR' (R = Me, Et, Bu, Ph. R' = Me, Et, Bu, $PhCH_2$) were prepared by refluxing ROH with R'X, sodium hydroxide and PEG-400 or PEG-600 in water[37].

Aryl ethers were obtained in excellent yield under mild reaction conditions by phase transfer catalysis in absence of organic solvent[38], where the reaction of stoichiometric amount of phenol and finely powdered potassium hydroxide with alkyl bromide in presence of 2% Aliquat 336 was carried out (4.12).

Diphenyl ethers were also prepared by using ultrasonic irradiation and PTC[39]. A mixture of p-nitrochlorobenzene, phenol, tetrabutylammonium bromide and K_2CO_3 in chlorobenzene and water was stirred at 25 - 35°C

under ultrasound irradiation.

Two substituted diphenyl ethers were prepared by PTC[40]. 4- methylphenyl-4-nitro-phenyl ether and 4-chlorophenyl-4-nitrophenyl ether were prepared from corresponding phenols with 4-nitrophenyl chlorides using tetrabutylammonium bromide as PTC. The synthesis of phenyl allyl ether from phenoxide ion and allyl chloride was conducted using PEG as PTC in a two phase reaction system[41].

PRESENT WORK

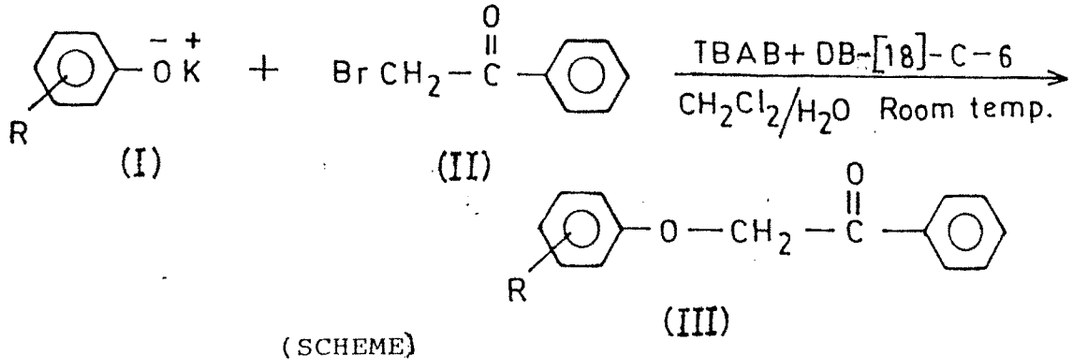
Hendrickson[42] has reported that the phenols can be protected as phenacyl ethers which have been synthesized according to traditional method and serve very well for synthetic purpose, as phenacyl ether is more readily cleaved by nucleophiles than other ether. Mohlau[43] synthesized phenacyl ethers from aqueous sodium phenoxide and phenacyl bromide or phenacyl chloride in low yield. This method has been modified by Yates and co-workers[44] to get quantitative yield of phenoxyacetophenone under reflux condition.

The use of phase transfer catalysis for the synthesis of phenacyl and 8- quinolinyl ether has been reported by Wang et.al.[45]. They have prepared number of ethers including phenacyl ethers of a range of phenols. The reaction was performed by stirring the phenolic compounds with halogen compounds in a dichloromethane or

benzene with aqueous solution of sodium hydroxide or solid sodium hydroxide in the presence of tetrabutylammonium bromide at room temperature or slightly above. In the absence of catalyst no ether was formed. However, phenacyl ether synthesized by this method requires quite longer time with lower yields.

Salunkhe et.al.[46] synthesized phenacyl ethers from polymer supported phenoxide and phenacyl bromide at room temperature. Recently Ahluwalia et. al.[47] Synthesized phenacyl ethers while studying the nature of halogens at ∝- position in carbonyl compounds.

We now report here an efficient method for synthesis of phenacyl ethers by considering their importance as protecting group and enzyme inhibition. The potassium salt of phenol (I) on treatment with phenacyl bromide (II) in two phase system (water and dichloromethane) in presence of mixture of tetrabutylammonium bromide and dibenzo-[18]-crown-6 gave correspondidng phenacyl ethers(III) in high yield within a very short time under mild reaction conditions. (SCHEME).



(SCHEME)

We have also carried out the etherification of phenol either in presence of tetrabutylammonium bromide or dibenzo-[18]-crown-6, but the reaction required more time with lower yields. Thus presence of both the catalysts plays important role during etherification because here the nucleophilicity of the alkoxyanion is enhanced and hence the reaction is completed within very short time. (Table 1).

Table-1: Effect on synthesis of phenacyl ether of phenol (0.05 mmol) using different combinations of PTC (TBAB) and dibenzo-[18]-crown-6 at room temperature.

Expt. No.	Dibenzo-[18] -crown-6 (mg)	PTC [TBAB] (mg)	Time (h)	Yield (%)
1.	0	32	4.00	88
2.	4	0	3.00	89
3.	1	32	1.5	90
4.	2	32	1.5	91
5.	3	32	1.25	92
6.	4	32	0.75	95
7.	1	48	1.5	91
8.	2	48	1.5	91
9.	3	48	1.25	93
10.	4	48	0.75	95

When the reaction was moderated by varying the amount of both catalysts (Table-1), mixture of 4 mg of

dibenzo-[18]-crown-6 and 32 mg tetrabutylammonium bromide was found to be effective in achieving rapid etherification with high yields (Expt No.6, Table-1).

The results of the syntheses of the phenacyl ethers of various phenols are given below (Table-2). The products were characterized by ^{1}H-NMR spectra (Table-4) and IR spectra. Some illustrative NMR and IR spectra of etherification are given just after the experimental part.

Table-2: Phenacyl ethers of different phenols.

Phenol	Time [min]	Yield [%]	M.P. (Lit.) [°C]
Phenol	45	95	70 (71)[48]
∝ -Naphthol	10	91	60 - 62
β -Naphthol	10	95	102 - 104 (105)[42]
o-Cresol	30	91	61 (63)[48]
p-Cresol	30	90	57 (56)[48]
o-Nitrophenol	60	88	118 (117 - 119)[49]
o-Chlorophenol	15	95	106 (107)[48]
p-Nitrophenol	60	89	146-148 (148-150)[49]
p-Chlorophenol	15	93	96 - 98 (99.5)[48]
4-Methyl,7-hydroxy coumarin	30	96	158

As expected, for the reaction with phenols containing electron withdrawing substituents, the rate was slow while for phenols containing electron donating substituents the

rate was fast (Table-2).

It was also observed that spatial co-ordination of ion and ligand cavity plays important role in using crown ethers. The etherification of potassium salt of phenol get completed in 0.75 h when dibenzo-[18]-crown-6 was used, whereas the reaction get completed in 7.5 h when [15]-crown-5 was used. Obviously the effective cavity volume of the 18 membered crown ether ring is better suited to the ion diameter of K^+ (2.66 A°). By using [15]-crown-5 the reaction was completed within 3h for sodium salt of phenol.

Solvent effect:

The formation of phenacyl ether by phase transfer catalysis proceeds in polar as well as in non polar solvents like dichloromethane, chloroform and benzene. The time required for etherification are better than non polar solvent such as benzene (Table-3).

Table-3: Solvent effect on phenacyl ether.

Compound	Solvent	Time (h)	Yield (%)
Phenol	Dichloromethane	0.75	95
	Chloroform	1.00	92
	Benzene	3.00	90

EXPERIMENTAL

General:

Potassium hydroxide (Merck), Sodium hydroxide (Qualigens), phenol (Qualigens), o-nitrophenol (SRL) p-nitrophenol (SRL), o-chlorophenol (SRL), p-chlorophenol (SRL), o-cresol (SRL), p-cresol (S.d.fine) α-naphthol (Merck) β-naphthol (Qualigens), dichloromethane (Qualigens), tetrabutylammonium bromide (Loba), dibenzo-[18]-crown-6 (Merck), [15]-crown-5 (Merck), benzene (Merck), chloroform (RL) are commercially available.

Phenacyl bromide[50] and 4-methyl -7-hydroxy coumarin[51] were prepared by the method reported in literature.

NMR: ^{1}H-NMR spectra were recorded on Brucker MSL 300 spectrometer.

IR : IR spectra were recorded on Perkin Elmer-783 spectrophotometer.

TLC: TLC was carried out using Kodak 13181 silica gel with fluorescent indicator precoated plates.

Procedure for preparation of 4-methyl-7-hydroxy Coumarin:

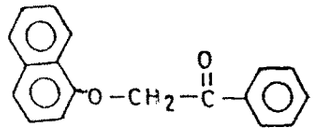
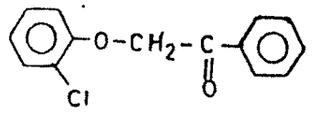
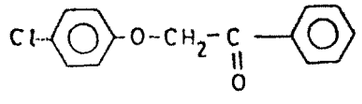
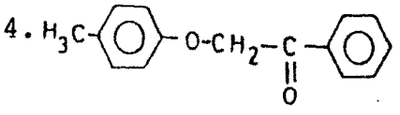
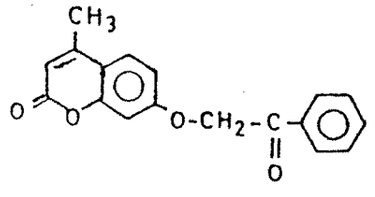
20 ml concentrated sulphuric acid was placed in a three necked flask fitted with a thermometer, mechanical stirrer and a dropping funnel. The flask was cooled in an ice bath. When the temperature falls below 10°C, a solution of 2 gms (0.018 mol) of resorcinol in 2.680 gms (2.61 ml, 0.02 mol) of redistilled ethyl acetoacetate was

added dropwise and with stirring. The temperature was maintained below 10°C by means of an ice salt during the addition. The reaction mixture was kept at room temperature for about 18 hours and then poured with vigorous stirring into a mixture of ice and water. The precipitate was collected by suction filtration and washed with cold water. The solid obtained was then dissolved in 30 ml of 5 percent sodium hydroxide solution, filtered and 2 M sulphuric acid (11 ml) was added with vigorous stirring until the solution is acidic to litmus. The crude product was filtered at the pump, washed with cold water and recrystalized from 95% ethanol.

General procedure for the synthesis of phenacyl ethers:

An aqueous solution of (2.5 ml) of I (0.05 m mol prepared by reacting stoichiometric amount of hydroxy aryl compound and aqueous potassium hydroxide) containing tetrabutylammonium bromide (32 mg) and dibenzo-[18]-crown-6 (4 mg) was added to dichloromethane (2.5 ml). The system was stirred for 10 minutes. Then phenacyl bromide II (0.05 m mol) was added and the reaction mixture was stirred at room temperature until the TLC analysis (Pet ether: EtOAc, 9:1, v/v) indicated completion of reaction. The organic layer was separated and dried over anhydrous sodium sulphate. The solvent was evaporated and the product III was purified by column chromatography. (Pet ether: EtOAc, 9:1, v/v). The products were characterized by NMR, IR and comparison with authentic samples.

Table-4 : ^{1}H-NMR Spectral data

Sr. No.	Phenacyl Ether	^{1}H-NMR ($CDCl_3$) δ(ppm)
1.		5.4 (S, 2H, $-COCH_2$) 7.4 - 8.15 (m, 12H, Ar-H)
2.		5.25 (S, 2H, $-COCH_2$) 6.78 - 7.6 (m, 7H, Ar-H) 7.8 (d, 2H, ortho to - $COCH_2$)
3.		5.24 (S, 2H, $-COCH_2$) 6.76 - 8.12 (m, 9H, Ar-H)
4.		2.24 (S, 3H, $Ar-CH_3$) 5.2 (S, 2H, $-COCH_2$) 6.72 - 8.12 (m, 9H, Ar-H)
5.		2.35 (S, 3H, $-CH_3$) 5.4 (S, 2H, $-COCH_2$) 6.15 (S, 1H, olefinic H) 6.85 (dd, 2H, Ar-H, J = 8 Hz & J = 2 Hz ortho to - OCH_2) 7.25 - 7.65 (m, 4H, Ar-H, meta to $-OCH_2$ & meta and para to CO) 7.95 (d, 2H, J = 8Hz Ar-H ortho to CO)

I.R. SPECTRA : ν max (Nujol) cm^{-1}

IR spectra of phenacyl ethers showed characteristic absorption bands at 1705 - 1690 cm^{-1} for C = O group.

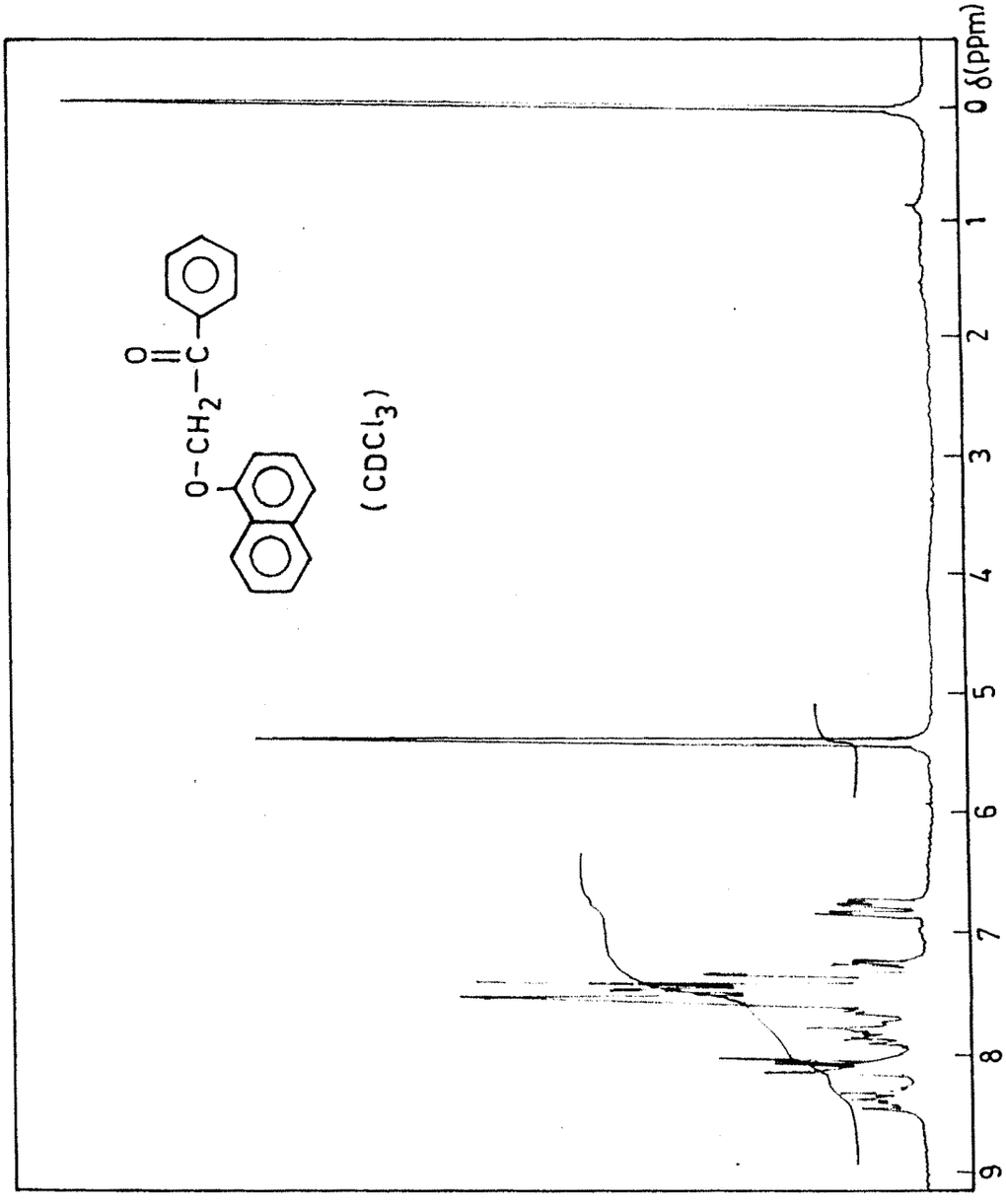


Fig. 1

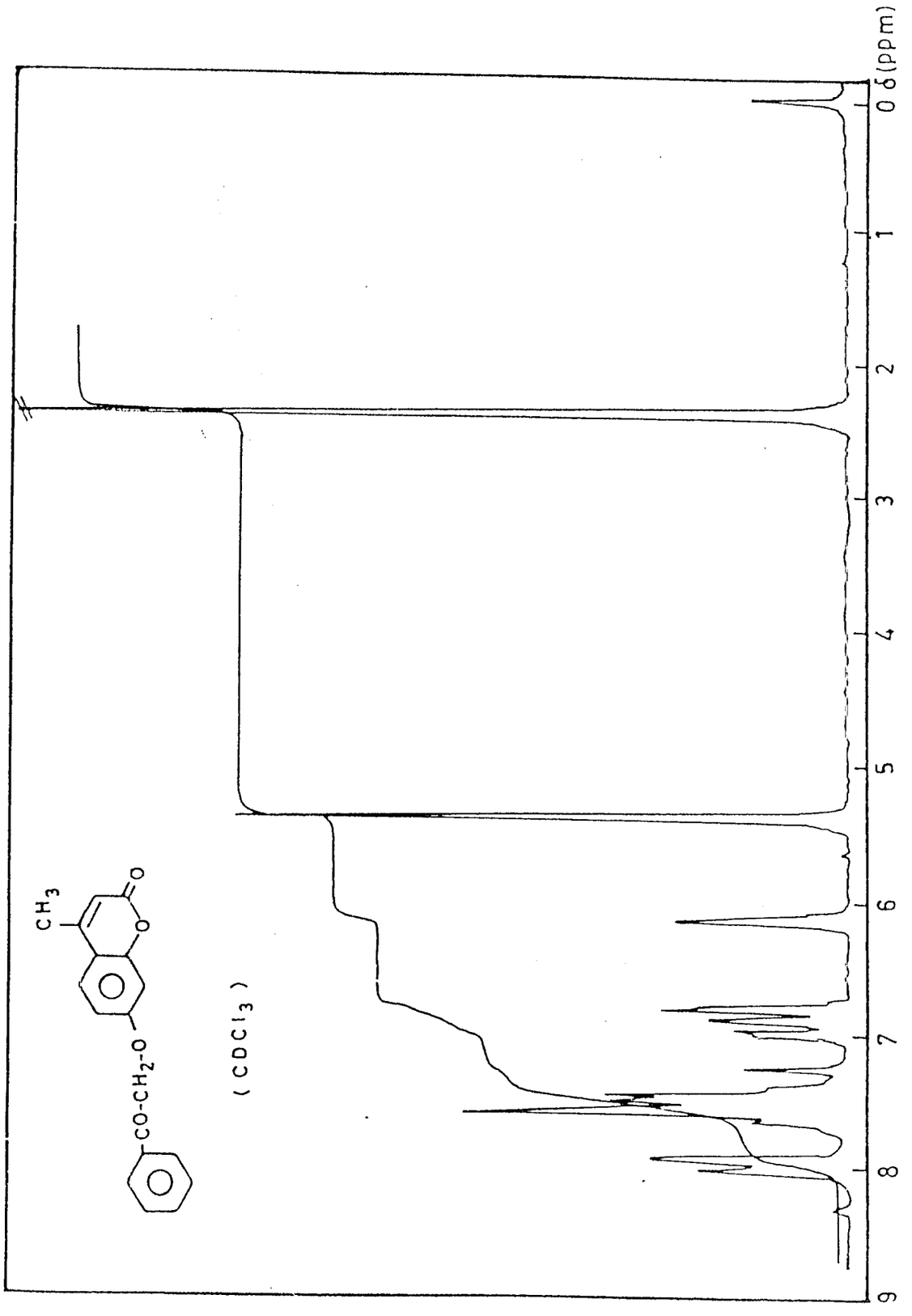


Fig. 2

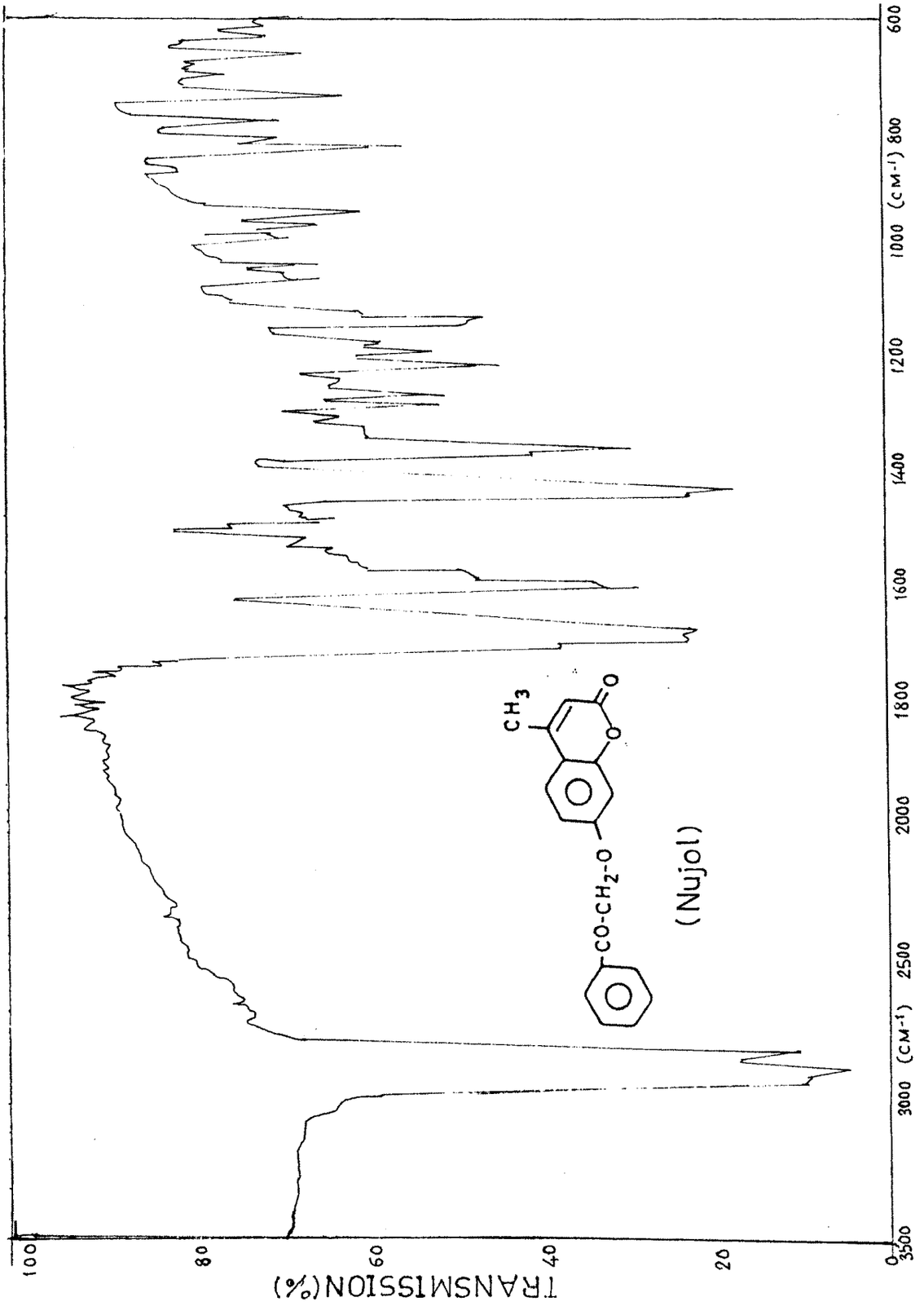

TRANSMISSION(%)
100
80
60
40
20
0
3500
3000 (CM⁻¹)
2500
2000
1800
1600
1400
1200
1000 (CM⁻¹) 800
600
WAVENUMBER
CH3
O
O
CO-CH2-O
(Nujol)

Fig. 3

REFERENCES

1. Beilstein F., Handbuch der Organischen Chemie, Vol.I, Verlag Von L. Voss, Hmburg 1833, p. 293.
2. Vogel, J. Chem. Soc., 616 (1948).
3. Olson et al., J.Am. Chem.Soc., 69, 2451 (1947).
4. Monacelli and Hennion, J.Am. Chem.Soc., 63, 1722 (1941).
5. Emerson et. al., J.Am. Chem.Soc., 69, 1905 (1947).
6. Brewster and Putman, Jr., J.Am. Chem. Soc., 61, 3083 (1939).
7. Nixon and Branch, J.Am. Chem. Soc., 58, 492 (1936).
8. Ullman and Sponagel, Ann., 350, 83 (1906).
   Suter and Green, J.Am.Chem. Soc., 59, 2578 (1937).
9. Ungnade and Orwall, Org. Syntheses, 26, 50 (1946).
10. Weston and Adkins, J.Am. Chem.Soc., 50, 859 (1928).
11. Brewster and Groening, Org. Syntheses, Coll. Vol. II, 445 (1943).
12. Smith and Sprung, J.Am. Chem.Soc., 65, 1276 (1943).
13. Bennett and Hoek, J. Chem. Soc., 472, (1927).
14. Powell, J.Am. Chem. Soc., 45, 2708 (1923).
15. Wheeler and Willson, Org. Syntheses, Coll. Vol. I, 296 (1941).
16. a) Tarbell D.S., J.Org. Chem.7, 251 (1942).
    b) Dowell Jr.A. M., Mc Cullough P.K.; Colloway J.Am. Chem.Soc., 70, 226 (1948).

c) Hurd C.D. and Perletz P. J.Am. Chem. Soc., 68, 38 (1946).

17. Weygand and Gabler, J.Prakt. Chem., 155, 332 (1940).
18. Djerassi C. and Scholz, J.Am. Chem. Soc., 69, 1688 (1947).
19. Cercherz Bull. Soc. Chim. France., 43, 762, (1928).
20. Mosettig and Stuart J.Am. Chem. Soc., 61, 1, (1939).
21. Carlson and Cretcher J.Am. Chem. Soc., 69, 1952 (1947).
22. Wenkert E., Youssefych R.D. and Lewis R.G. J.Am. Chem. Soc., 82, 4675 (1960).
23. Kornblum N., Seltzer R. and Haberfield P., J.Am. Chem Soc. 85, 1148 (1963).
24. Cohen L.A., J. Org. Chem., 22, 1333 (1957).
25. Hall R.H., and Stern E.S., J.Chem. Soc., 2035 (1949).
26. Camps F. Coll. J., Moreto J.M., Synthesis, 186 (1982).
27. Starks C.M. and Owens R.M., J.Am. Chem. Soc., 95, 3613 (1973).
28. Baw HLA,, Quart. J. Indian Chem., 3, 104 (1926); Chem Abstr., 20, 3695 (1926).
29. Merker R.L. and Scott M.J., J. Org. Chem., 26, 5180 (1961).
30. Radionov V., Bull.Soc. Chim. Fr., 39, 305, (1926).
31. Baker B.R. and McEvay F.J., J.Org. Chem., 20, 118, 136 (1955).

32. Cohen A., Haworth J.W. and Hughes E.H., J.Chem. Soc., 4374 (1952).

33. Ugelstad J., Ellingsen T. and Berge A., Act. Chem. Scand., 1593 (1966).

34. Rowe E.J., Kaufman K.L. and Piantadosi C., J.Org. Chem., 23, 1622 (1958).

35. McKillop A., Fiaud J., Hug R.P., Tetrahedron, 30, 1379 (1974).

36. Merz A., Angew, Chem., 85, 868 (1973).

37. Yu Shanxin., Huaxue Shiji, 14 (4) 246, 255 (1992).

38. Loupy, Andre, Sansoulet, Jean, Vaziri-Zand, Farchid., Bull. Soc. Chem. Fr.(6), 1027 (1987).

39. Wu Licheng., Tan Ping, Zhang Quiping., Huaxue Shiji 33 (4), 157 (1992).

40. Li Jitai, Zang, Weidong, Liu, Zhifa, Hebei Daxue Xuebao, Ziran Kereueban, 11 (3), 67 (1991).

41. Maw-Ling-Wang and Kong Rong Chang., J. of Molecular catalysis 67, 147 (1991).

42. Hendrickson J.B. and Kandall C., Tetra. Lett. 343 (1970).

43. Mohlau R., Ber. 15, 2497 (1882).

44. Yates D.G., Farnum and Stout., G.H. J.Am. Chem. Soc., 80, 197 (1958).

45. Wang C.H., Liu X-T and Chao X-H, Synthesis 858 (1982).

46. Thorat M.T., Mane R.B., Jaydale M.H., & Salunkhe M.M., J. Indian Chem. Soc., Vol. LXIV 106 (1987).

47. Ahluwalia V.K., Mehta, Bhupinder, Rawat, Manju. Synth. Commun. 22 (18) 2697 (1992).

48. Saburi Y., Yoshimoto, T., Munami K., C.A. 69, 35630 (1968).

49. Baker B.R. and Hurlburt J.A., J.Med. Chem. 10, 1129 (1967).

50. Cowper and Davidson., Organic Syntheses Coll. Vol II (480).

51. Vogel; VI, 39/40 'Text Book of Practical Organic Chemistry (Qualitative analysis).