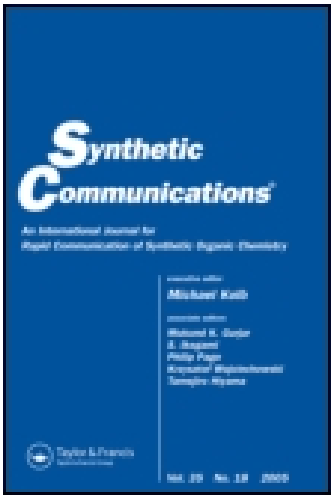

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Synthesis of Biologically Active Carvacrol Compounds using Different Solvents and Supports

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Abstract: Natural monoterpenoids have been documented for their acute toxicity and repellent, antifeedent, reproduction inhibitory, and insecticidal actions. The present work aims to derive a variety of ether and ester compounds using polymer-supported reactions from the polymer-supported carvacrol anion was reacted with alkyl halides and acid chlorides to afford carvacryl ethers and esters, respectively. Furthermore, a special study on the effect of different solvents and supports revealed that Amberlite IRA 400 (chloride form) was found to be the best polymer support and acetone among the solvents.

Keywords: carvacrol, ethers, esters, polymer-supported reactions, solvents

INTRODUCTION

The natural monoterpenoids play an important role in the enzyme system of plants and are one of the most abundant and potent groups that have biological activity against various pests. Monoterpenoids are secondary metabolites of plants that are generally considered as self-defence tactics against plant enemies. The biological activity of monoterpenoids[1–4] against insects nematodes, phytopathogenic fungi, and other pest species are believed to be related to the nature and position of specific groups or substituents.

The chemical modification of natural monoterpenoids[1–9] to various ether and ester derivatives had been reported to result in modified biological

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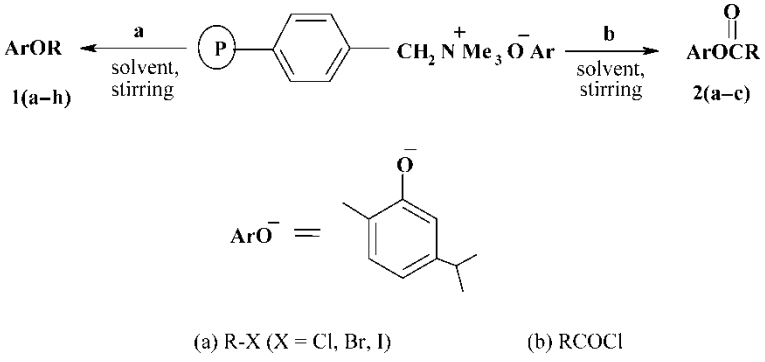
activity. The routine synthetic methods suffer from some disadvantages such as low yields, high-temperature conditions, longer reaction time, and formation of by-products in addition to tedious reaction workup.[10]

The polymer-supported methodology adopted in the work is very simple because of ease of operation and workup and also has higher yield and purity of products. Our work is more centered on the structural modification[6–9] (i.e., derivatization of natural pest-controlling compounds, which are easily degradable and less toxic and nontoxic). It is suggested that the activation of compounds are dependent upon nature and position of the functional groups rather than volatility and molecular size. Keeping in view the bioactivity of monoterpenoids, we report a simple and efficient method for the preparation of alkyl and acyl derivatives of carvacrol in higher yields and purity under mild reaction conditions.

Different polymer supports such as Amberlite IRA 400 (chloride form), Amberlyst A 26 (hydroxide form), and Indion 820 (chloride form) were used to support the carvacrol anion. The alkyl halides and acid chlorides were added to the carvacrol-supported resin in different solvents such as acetone, acetonitrile, ethanol, tetrahydrofuran, and dichloromethane. The reaction mixture was stirred until the completion of the reaction. In general, the reactions with acid chlorides were faster than alkyl halides. Isolation of pure products by simple filtration and evaporation of solvent are important features of this method (Scheme 1). The method is also inexpensive because the resin (polymer support) could be used repeatedly.

EXPERIMENTAL

All chemicals were of analytical grade, and solvents were distilled before use. Melting points and boiling points are uncorrected. Commercial Amberlite



Scheme 1. Synthesis of carvacrol ethers and esters. Solvent: acetone, acetonitrile, ethanol, tetrahydrofuran, DCM.

IRA 400 (chloride form) and Indion 820 (chloride form) were activated by treating with dil. HCl solution, and Amberlyst A26 (hydroxide form) was activated by treating with dil. NaOH.

General Procedure for Supporting Carvacrol Anion on Polymer Support

Carvacrol (15 g, 100 mmol) was dissolved in 100 ml of an aqueous solution of sodium hydroxide (4 g, 100 mmol). The activated resin (100 g) was packed in a column (2 cm in diameter and 45 cm long) and was eluted slowly dropwise (about 1.5 ml/min) with the solution of sodium salt of carvacrol. Thereafter the resin was washed with distilled water until chloride ions and excess of carvacrol anion were completely removed. It was then washed with ethanol followed by acetone and dried in vacuo at 50°C for 4 h. The exchange capacities[10] of carvacrol anion–supported resins were determined by passing a 1N NaCl (100 ml) solution through supported resin (1 g) packed in a small column. The carvacrol in the eluent was titrated against 0.01N HCl using methyl orange as an indicator. The exchange capacities of Amberlite IRA 400 (chloride form), Amberlyst A26 (hydroxide form), and Indion 820 (chloride form) were found to be 1 mmol, 1.5 mmol and 1.2 mmol anion of carvacrol per gram of dry resin, respectively.

Synthesis of Carvacryl Ethers

Carvacrol-supported Amberlite IRA 400 (10 g, 10 mmol), Amberlyst A26 (7 g, 10.50 mmol) or Indion 820 (8.5 g, 10.30 mmol) was taken separately in dry solvent (acetone, acetonitrile, tetrahydrofuran, dichloromethane, or ethanol) (25 ml), and alkyl halide (10 mmol) was added. The reaction mixture was stirred for 30–40 min depending upon reactivity of alkyl halides. The progress of reaction was monitored by silica-gel thin-layer chromatography (TLC) (hexane–pet. ether, 1:1). Then resin was filtered and washed with solvent (3 × 5 ml). The solvent, on evaporation, gave the products as listed in Tables 1–3.

1a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.19 (d, 6H, gem 2 CH_3), 2.17 (s, 3H, Ar-CH_3), 2.84 (septet, 1H, CH), 3.37 (s, 3H, -OCH_3) 6.63–6.70–7.02 (s, d, d, 3H, Ar-H);IR (neat): 744, 817, 1046, 1138, 1255, 1413, 1617, 2966, and 3009 cm^{-1}.

1g. ^{1}H NMR: δ 1.20 (d, 6H, gem 2 CH_3), 2.16 (s, 3H, Ar- CH_3), 2.78 (septet, 1H, CH), 4.02 (s, 2H, -OCH_2), 6.64–6.71–701 (s, d, d, 3H, Ar-H), 10.15 (s, 1H, -COOH); IR (neat): 766, 810, 1105, 1250, 1380, 1500, 1590, 1710, 2966, 3006, and 3450 cm^{-1}.

Table 1. Yield (%) using Amberlite IRA 400, Cl^- form, as support

Entry	R	Time (min)	Solvent					Bp [Lit. bp][2,11,12] (°C)
			Ethanol	Acetone	DCM	Acetonitrile	THF	
1a	$-CH_3$	35	82	92	78	88	74	201 [200–203]
1b	$-CH_2CH_3$	35	78	94	80	92	83	229 [228–230]
1c	$-CH_2CH_2CH_3$	30	76	78	70	93	81	231–233 [233–235]
1d	$-CH\ (CH_3)_2$	30	78	86	70	85	80	176–177 [176–178]
1e	$-CH_2CH_2CH_2CH_3$	30	80	88	73	90	82	237 [236–238]
1f	$-CH(CH_3)CH_2CH_3$	35	84	90	80	88	85	216–217 [216–218]
1g	$-CH_2COOH$	20	84	94	87	88	85	180–182 [182–183]
1h	2,4 Dinitrophenyl-	30	79	86	78	83	88	77 [77]
2a	$-COCH_3$	10	78	93	70	82	90	244 [245]
2b	$-COCH_2CH_3$	10	80	92	80	89	84	247 [247–248]
2c	$-COC_6H_5$	10	91	92	82	87	90	270 [268–270]

Table 2. Yield (%) using Amberlyst A 26, OH^- form, as support

Entry	R	Time (min)	Solvent				
			Ethanol	Acetone	DCM	Acetonitrile	THF
1a	$-CH_3$	35	78	87	76	84	80
1b	$-CH_2CH_3$	35	79	88	74	86	80
1c	$-CH_2CH_2CH_3$	30	84	92	80	88	86
1d	$-CH\ (CH_3)_2$	30	80	87	76	86	84
1e	$-CH_2CH_2CH_2CH_3$	35	80	94	84	92	89
1f	$-CH(CH_3)CH_2CH_3$	35	80	88	78	85	83
1g	$-CH_2COOH$	20	88	95	85	93	90
1h	2,4 Dinitrophenyl-	30	78	88	76	82	81
2a	$-COCH_3$	10	85	94	83	91	89
2b	$-COCH_2CH_3$	10	86	94	82	90	89
2c	$-COC_6H_5$	15	92	96	89	94	90

Table 3. Yield (%) using Indion 820, Cl^- form, as support

			Solvent				
Entry	R	Time (min)	Ethanol	Acetone	DCM	Acetonitrile	THF
1a	$-CH_3$	35	86	90	79	87	82
1b	$-CH_2CH_3$	35	88	92	80	90	84
1c	$-CH_2CH_2CH_3$	30	84	94	78	89	80
1d	$-CH\ (CH_3)_2$	35	82	90	77	86	81
1e	$-CH_2CH_2CH_2CH_3$	30	74	78	70	76	72
1f	$-CH(CH_3)CH_2CH_3$	35	78	84	70	82	74
1g	$-CH_2COOH$	20	85	92	79	88	81
1h	2,4 Dinitrophenyl-	30	84	88	76	87	80
2a	$-COCH_3$	10	87	94	78	91	83
2b	$-COCH_2CH_3$	10	85	90	79	87	81
2c	$-COC_6H_5$	15	84	93	76	90	80

Synthesis of Carvacryl Esters

Carvacryl esters (Tables 1–3) were prepared by this procedure using acid chlorides instead of alkyl halides. The acid chloride (10 mmol) was added slowly dropwise in the solution of polymer-supported carvacrol anion (10 mmol) in dry solvent (25 ml) with constant stirring at room temperature. Depending on reactivity of the acid chlorides, these reactions were completed within 10–20 min.

The yields and purity of the products were excellent compared to those obtained by conventional methods. The reactions were rapid, and the isolation of products was very simple. The resin could be used repeatedly by regeneration of activity. The synthesized compounds were characterized[11,12] by their physical constants, comparative TLC, and spectroscopic (PMR and IR) techniques with the products prepared by conventional routes.

The derivatization or structural modification through such a simple, rapid, and environmentally friendly approach in the synthesis of pesticides will be helpful to develop potent pest-management agents.

2a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22 (d, 6H, gem 2 CH_3), 2.17 (s, 3H, Ar-CH_3), 2.30 (s, 3H, $COCH_3$), 2.83 (septet, 1H, CH), 6.62–6.71–7.02 (s, d, d, 3H, Ar-H); IR (neat): 760, 800, 1100, 1233, 1500, 1600, 1750, 2990, and 3006 cm^{-1}.

2c.^{1}H NMR: δ 1.23 (d, 6H, gem 2 CH_3), 2.20 (s, 3H, Ar- CH_3), 2.85 (septet, 1H, CH), 7.00–7.62 (m, 3H and 5H, Ar-H); IR (neat): 760, 840, 1120, 1284, 1428, 1612, 1715, 2985, and 3007 cm^{-1}.

CONCLUSION

In the present investigation, Amberlite IRA 400 (chloride form) was found to be a better support, followed by Indion 820 (chloride form) and Amberlyst A26 (hydroxide form). Among the solvents, acetone was found to be the best solvent on the basis of reaction period and yield as compared to other solvents in the given order: Acetone > acetonitrile > tetrahydrofuran > ethanol > dichloromethane.

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