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Synthesis of new dimeric carvacrol compounds

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Abstract: The polymer supported carvacrol anion was reacted with 1,2-dibromoethane, 1,4-dibromoethane, oxalyl dichloride, malonyl dichloride, succinyl dichloride, glutaroyl dichloride, and adipoyl dichloride to afford the corresponding dimeric carvacryl ethers or esters.

Keywords: Dimeric carvacrol ethers; dimeric carvacrol esters; polymer supported reactions

1. Introduction

The natural monoterpenoids play an important role in the enzyme system of plants and are one of the most abundant and potent groups having 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[1-10] to various ether and ester derivatives had been reported to result in modified biological activity. The routine synthetic methods suffer from some disadvantages like low yields, high temperature conditions, longer reaction time and formation of byproducts in addition to tedious reaction workup.[11] In our previous studies[12-14], we used polymer-supported methodologies to synthesize phenol and carvacrol derivatives. As a part of ongoing studies, we adopted the methodology to synthesize dimeric ether or ester derivatives of carvacrol in the present paper.

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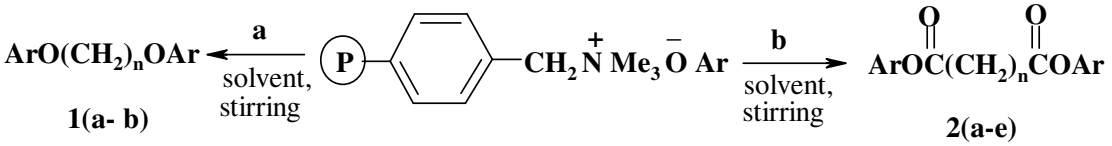
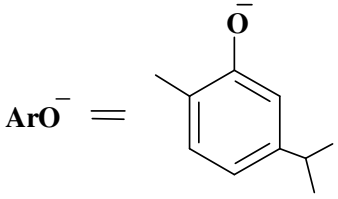
2. Results and Discussion

Different polymer supports such as Amberlite IRA 400 (chloride form), Amberlyst A 26 (hydroxide form) and Indion 820 (chloride form) were used to support carvacrol anion. Amongst Amberlite IRA 400 (chloride form) was found to be better support followed by Indion 820 (chloride form) and Amberlyst A26 (hydroxide form). The alkyl dihalides and acid dichlorides were added to the carvacrol supported resin in different solvents such as acetone, acetonitrile, ethanol, tetrahydrofuran and dichloromethane (Scheme 1). 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





(a) Br-$(CH_2)_n$-Br
n = 2, 4

(b)ClC(O)$(CH_2)_n$C(O)Cl
n = 0, 1, 2, 3, 4

Solvent: acetone, acetonitrile, ethanol, tetrahydrofuran, DCM

Scheme 1: Synthesis of dimeric carvacrol ethers and esters

The reaction mixture was stirred until the completion of reaction. In general, the reactions with acid dichlorides were faster than alkyl dihalides. The yields and purity of the products (Table 1-3) were excellent compared to those obtained by conventional methods. The reactions were rapid and the isolation of products was very simple.

The synthesized compounds were characterized by spectroscopic (^{1}HNMR and IR) techniques in comparison with the products prepared by conventional routes.

Isolation of pure products by simple filtration and evaporation of solvent is an important feature of this method. The method is also inexpensive as the resin (polymer support) could be used repeatedly by regeneration of activity.

dimeric carvacrol compounds

Table 1. Amberlite IRA 400, (chloride form).

Entry	Time (min)	Solvent, Yield (%)					bp(^{o}C) [Lit. bp (^{o}C)][13]
		Ethanol	Acetone	DCM	Acetonitrile	THF	
1a	35	78	92	81	87	90	182-184 [184]
1b	40	82	90	85	88	90	132-133 [132]
2a	10	83	91	82	92	88	190 [190]
2b	15	80	93	78	91	87	199-200
2c	15	88	93	85	90	83	210-212
2d	10	91	94	88	92	87	250-252
2e	20	82	88	79	87	85	203-204 [203]

Table 2. Amberlyst A 26 (hydroxide form)

Entry	Time (min)	Solvent, Yield (%)				
		Ethanol	Acetone	DCM	Acetonitrile	THF
1a	35	85	93	83	90	88
1b	30	84	92	80	89	84
2a	10	90	92	88	89	86
2b	15	78	90	77	89	85
2c	15	86	89	84	88	87
2d	10	80	87	79	85	83
2e	20	84	90	81	87	85

Table 3. Indion 820 (chloride form)

Entry	Time (min)	Solvent, Yield (%)				
		Ethanol	Acetone	DCM	Acetonitrile	THF
1a	40	82	90	72	86	76
1b	30	83	90	78	88	82
2a	10	85	92	74	89	80
2b	15	84	88	78	86	82
2c	15	89	93	83	91	88
2d	10	90	94	84	93	87
2e	20	89	92	82	90	86

3. Conclusion

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

4. Experimental

All chemicals were of analytical grade and solvents were distilled before use. Melting points and boiling points are uncorrected. Commercial Amberlite 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. The ^{1}HNMR spectra were scanned on Brucker 300 MHz instrument.

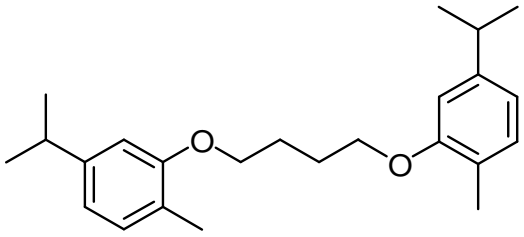
4.1. General procedure for supporting carvacrol anion on polymer support

It was prepared as described in our previous procedure.[13]

4.2. General procedure for synthesis of dimeric carvacryl ethers

Carvacrol supported Amberlite IRA 400 (20 g, 20 mmol), Amberlyst A26 (14 g, 20 mmol) or Indion 820 (17 g, 20 mmol) was taken separately in dry solvent (acetone, acetonitrile, tetrahydrofuran, dichloromethane or ethanol) (50ml) and α, ω dibromoalkane (10 mmol) was added and the reaction mixture was stirred for 30-40 min. depending upon reactivity of α, ω dibromoalkane. The progress of reaction was monitored by silica gel TLC (hexane: pet. ether, 1:1). Then resin was filtered and washed with solvent (3X5 ml). The solvent on evaporation gave the products 1a,b.

Ethyl-1,2-bis[2-methyl-5-(1-methylethyl)phenyl] ether (1a). [Formula: $C_{22}H_{30}O_2$], yellow liquid, (bp 182-184 ^{0}C): ^{1}H NMR (δ, ppm): 1.22 (d, 12H, gem 4 CH_3, J= 6.8 Hz), 2.30 (s, 6H, 2 Ar- CH_3), 3.05 (septet, 2H, 2CH, J= 5.0 Hz), 5.39 (s, 4H,-CH_2-CH_2-) 6.62 –7.02 (m, 6H, Ar-H); IR(neat, cm^{-1}): 3005, 2992, 1615, 1587, 1275, 1245, 1150 and 752.

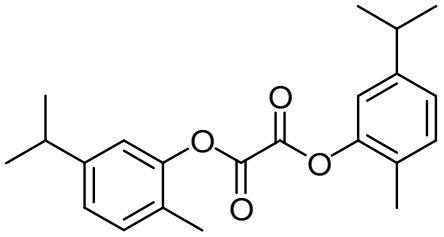


Butyl-1,2-bis[2-methyl-5-(1-methylethyl)phenyl] ether (1b). [Formula: $C_{24}H_{34}O_2$], pale yellow liquid, (bp 132-133 ^{0}C): ^{1}H NMR (δ, ppm): 1.21 (d, 12H, gem 4 CH_3, J= 6.0 Hz), 2.02 (m, 4H, -CH_2-CH_2-), 2.18 (s, 6H,Ar- CH_3), 2.80 (septet, 2H, 2 CH, J= 5.0 Hz), 3.41 (m, 4H, $(OCH_2)_2$), 6.63 –7.02 (m, 6H, Ar-H); IR (neat, cm^{-1}): 3007, 2986, 1618, 1588, 1275, 1246, 1148 and 752.

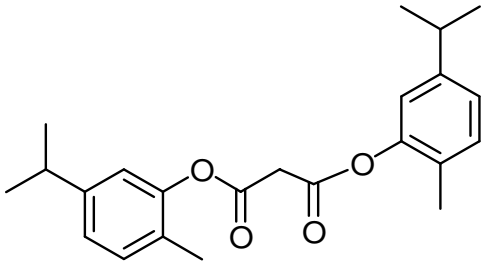
dimeric carvacrol compounds

4.3. General procedure for synthesis of dimeric carvacryl esters

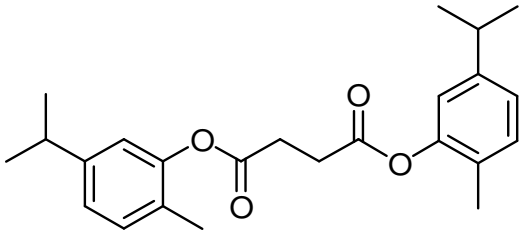
Dimeric carvacryl esters (Table 1-3) were prepared by the above procedure using acid dichlorides instead of alkyl dihalides. The acid dichloride (10 mmol) was added slowly dropwise in the solution of polymer supported carvacrol anion (20 mmol) in dry solvent (50 ml) with constant stirring at room temperature. Depending on reactivity of the acid dichlorides, these reactions were completed within 10 - 20 min.



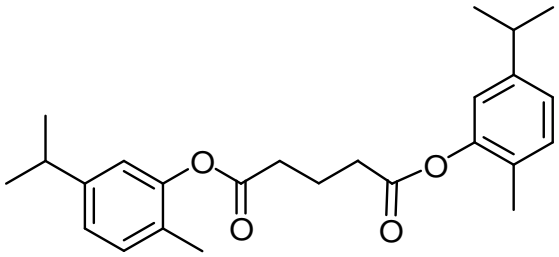
Ethanedioic acid-1,2-bis[2-methyl-5-(1-methylethyl)phenyl] ester (2a). [Formula: $C_{22}H_{26}O_4$], pale yellow liquid, (bp 190 ^{0}C): ^{1}H NMR (δ, ppm): 1.17 (d, 12H, 4 gem –CH_3, J=6.2 Hz), 2.18 (s, 6H, 2 Ar-CH_3), 2.73 (septet, 2H, 2CH, J=5.8 Hz), 6.63-6.99 (m, 6H, Ar-H); IR (neat, cm^{-1}): 2990, 1745, 1617, 1500, 1400, 1250, 1100, 800 and 750.



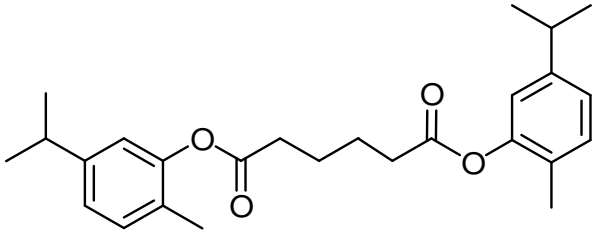
Propanedioic acid-1,2-bis[2-methyl-5-(1-methylethyl)phenyl] ester (2b). [Formula: $C_{23}H_{28}O_4$], yellow liquid, (bp 199-200 ^{0}C): ^{1}H NMR (δ, ppm): 1.18 (d, 12H, 4 gem –CH_3, J= 6.8 Hz), 2.19 (s, 6H, 2 Ar-CH_3), 2.79 (septet, 2H, 2CH, J= 5.0 Hz), 2.86 (s, 2H,-CH_2-) 6.62-7.01(m, 6H, Ar-H); IR (neat,cm^{-1}): 2985, 1742, 1618, 1589, 1270, 1215 and 752.



Butanedioic acid-1,2-bis[2-methyl-5-(1-methylethyl)phenyl] ester (2c). [Formula: $C_{24}H_{30}O_4$], yellow liquid, (bp 210-212 ^{0}C): ^{1}H NMR (δ, ppm): 1.20 (d, 12H, 4 gem –CH_3, J= 6.5 Hz), 2.19 (s, 6H, 2 Ar-CH_3), 2.62 (s, 4H, - CH_2CH_2-) 2.80 (septet, 2H, 2CH, J= 5.8 Hz), 6.65-7.13 (m, 6H, Ar-H); IR (neat, cm^{-1}): 2990, 1740, 1616, 1272, 1216 and 755.



Pentanedioic acid-1,2-bis[2-methyl-5-(1-methylethyl)phenyl] ester (2d). [Formula: $C_{25}H_{32}O_4$], yellow liquid, (bp 250-252 ^{0}C): ^{1}H NMR (δ, ppm): 1.18 (d, 12H, 4 gem –CH_3, J= 6.1 Hz), 2.22 (s, 6H, 2 Ar-CH_3), 2.68 (m, 2H, middle –CH_2-), 2.70 (t, 4H, -CH_2-) 2.80 (septet, 2H, 2CH, J= 4.2 Hz), 6.62-7.20 (m, 6H, Ar-H); IR (neat, cm^{-1}): 2992, 1740, 1615, 1592, 1270, 1215 and 760.



Hexanedioic acid-1,2-bis[2-methyl-5-(1-methylethyl)phenyl] ester (2e). [Formula: $C_{26}H_{34}O_4$], pale yellow liquid, (bp 203-204 ^{0}C): ^{1}H NMR (δ, ppm): 1.21(d, 12H, 4 gem –CH_3, J= 6.5 Hz), 2.12 (t, 4H, middle -CH_2CH_2-, J= 4.5 Hz) 2.20 (s, 6H, 2 Ar-CH_3), 2.63 (t, 4H, 2-$COCH_2$-, J= 6.2 Hz) 2.82 (septet, 2H, 2CH, J= 5.3 Hz), 6.65-7.25 (m, 6H, Ar-H); IR (neat, cm^{-1}): 2995, 1740, 1615, 1590, 1272, 1215, 1061 and 756.

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