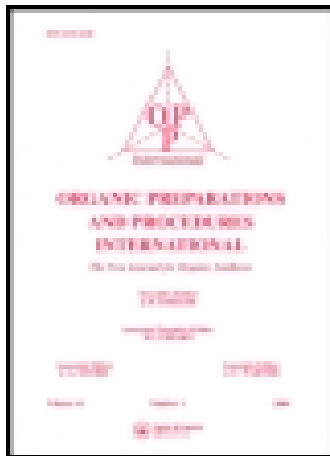


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Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/uopp20>

SYNTHESIS OF THYMYL ETHERS AND ESTERS USING POLYMER-SUPPORTED THYMOL ANION

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Published online: 11 Feb 2009.

To cite this article: P. P. Kumbhar, U. R. Kapadi, D. G. Hundiwale, S. B. Attarde, P. M. Dewang & N. S. Pawar (2009) SYNTHESIS OF THYMYL ETHERS AND ESTERS USING POLYMER-SUPPORTED THYMOL ANION, *Organic Preparations and Procedures International: The New Journal for Organic Synthesis*, 32:6, 600-603, DOI: [10.1080/00304940009355961](https://doi.org/10.1080/00304940009355961)

To link to this article: <http://dx.doi.org/10.1080/00304940009355961>

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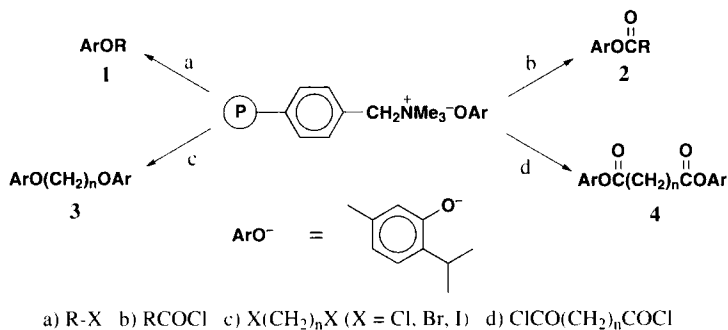
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Terpenoids play an important role in the enzyme system of plants and are one of the most abundant and potent groups of naturally occurring substances having biological activity on various pests. Monoterpenoids are natural substances and secondary metabolites of plants which are generally considered as self-defense tactics against the plant's enemies. The biological activity of monoterpenoids¹⁻⁴ against insects, nematodes, phytopathogenic fungi and other pest species is believed to be related to the nature and position of specific groups or substituents. The chemical modification⁵⁻⁹ of natural monoterpenoids to various ether and ester derivatives has been reported^{1-3, 8, 9} to result in modi-

fied biological activity. We report herein a rapid, simple and efficient method for synthesis of thymyl ethers and thymyl esters, needed for a study of the structure-activity relationships.

Amberlite IRA-400 (chloride form) resin was used to support the thymol anion. The alkyl halides and acyl chlorides were added to the thymol anion-supported resin in benzene and the mixture was stirred until the reaction was complete.¹⁰⁻¹² As expected, esters were formed more rapidly than ethers.



The yields and purity of the products are excellent compared with those obtained by conventional methods,^{2, 3, 8, 9} such as reaction of thymol with alkyl halides and acid chlorides either in aqueous alkaline medium or in dichloromethane using pyridine. The reactions are rapid and the isolation of products is very simple. The resin could be used repeatedly since its initial activity may be regenerated by treatment with HCl solution. The products were characterized by their physical constants, elemental analysis and comparative TLC with the products prepared by conventional routes.^{2, 3, 8, 9} All the products were evaluated for pesticidal activity,^{8, 9} and the ethers were found to be biologically more active than the esters.

EXPERIMENTAL SECTION

Boiling points are uncorrected. Elemental analyses were performed on a Perkin Elmer Series II CHNS/O Analyzer 2400. All chemicals were of analytical grade and solvents were freshly distilled before use. Commercial Amberlite IRA-400 (chloride form) was activated by treating it with dilute HCl solution before use. TLC was carried out on silica gel coated plates using benzene:petroleum ether (50:50) solvent mixture.

General Procedure for Supporting Thymol Anion on Amberlite IRA-400.- Thymol (15g, 100 mmoles) was dissolved in 100 mL of an aqueous solution of sodium hydroxide (4g, 100 mmoles). The activated Amberlite IRA-400 (chloride form) (100g) was packed on a column (2 cm diameter and 45 cm length) and was eluted slowly (dropwise, about 1.5 mL/min) with the above solution of sodium salt of thymol. Thereafter, the resin was washed with distilled water until complete removal of chloride ions and excess of thymol anion. It was then washed with ethanol followed by acetone and dried *in vacuo* at 50° for 6hr. The exchange capacity of thymol anion supported resin was determined by passing aqueous 1N NaCl (100 mL) through the supported resin (1 g) packed in a column. The thymol anion in the eluent was titrated against 0.01 N HCl using methyl orange as an indicator. The exchange

capacity of the resin was found to be 1.5 mmole thymol anion per gram of dry resin.

Synthesis of Thymyl Ethers (1).- A mixture of Amberlite IRA-400 thymol anion form resin (5 g, 7.5 mmoles) and alkyl halide (7.5 mmoles) in dry benzene (25 mL) was stirred for 15-30 minutes depending on the reactivity of the alkyl halide. The completion of reaction could be easily observed by change in color of the resin from grey-white to dark yellow-brown. The progress of the reaction was also monitored by TLC (benzene:petroleum ether, 50:50). Then the resin was filtered off and washed with benzene (3 x 5 mL). Removal of the solvent gave the products listed in the Table.

Synthesis of Thymyl Esters (2).- The thymyl esters were prepared by the above procedure using acid chlorides (7.5 mmoles) instead of alkyl halides. These reactions were completed within 5 to 15 minutes depending on the reactivity of the acid chlorides.

Synthesis of Dithymyl Ethers (3) and Esters (4).- The dimer type products, namely dithymyl ethers and esters, were prepared by reacting 10g (15 mmoles) of Amberlite IRA-400 thymol anion form resin with 7.5 mmoles of α,ω -dihaloalkanes $[(CH_2)_nX_2]$ and diacid chlorides $[(CH_2)_n(COX)_2]$ respectively in dry benzene (40 mL) using above procedure.

Table. Thymyl Ethers and Esters

| Cmpd | R or n | Yield (%) | bp ^a (°C) | Elemental Analysis (Found) | |
|-----------|---|-----------|------------------------|----------------------------|---------------|
| | | | | C | H |
| 1a | CH ₃ | 99 | 216 - 219 | 80.44 (80.32) | 9.81 (9.92) |
| 1b | CH ₃ CH ₂ | 98 | 222 - 226 | 80.84 (80.75) | 10.17 (10.22) |
| 1c | CH ₃ CH ₂ CH ₂ | 98 | 226 - 229 | 81.19 (80.95) | 10.48 (10.26) |
| 1d | (CH ₃) ₂ CH | 98 | 216 - 219 | 81.19 (81.26) | 10.48 (10.36) |
| 1e | CH ₃ CH ₂ CH ₂ CH ₂ | 98 | 236 - 238 | 81.49 (81.58) | 10.74 (10.62) |
| 1f | CH ₂ =CHCH ₂ | 98 | 238 - 241 | 82.05 (81.96) | 9.53 (9.52) |
| 1g | C ₆ H ₅ CH ₂ | 99 | 252 - 254 | 84.95 (84.77) | 8.38 (8.23) |
| 1h | HO ₂ CCH ₂ | 97 | 210 - 212 | 69.20 (69.21) | 7.74 (7.68) |
| 2a | CH ₃ CO | 98 | 241 - 244 | 74.96 (74.78) | 8.38 (8.12) |
| 2b | C ₆ H ₅ CO | 98 | 284 - 287 ^b | 80.28 (80.32) | 7.13 (7.15) |
| 2c | C ₆ H ₅ CH=CHCO | 98 | 220 - 223 | 81.39 (81.12) | 7.19 (7.23) |
| 3a | n = 1 | 97 | 224 - 226 | 80.72 (80.49) | 9.03 (8.76) |
| 3b | n = 2 | 98 | 227 - 229 | 80.93 (80.87) | 9.26 (9.48) |
| 4a | n = 1 | 98 | 219 - 222 | 74.97 (75.16) | 7.65 (7.91) |
| 4b | n = 2 | 98 | 235 - 236 | 75.36 (75.52) | 7.90 (7.76) |
| 4c | n = 3 | 97 | 222 - 224 | 75.72 (75.53) | 8.13 (8.16) |
| 4d | n = 4 | 97 | 235 - 238 | 76.06 (75.92) | 8.34 (8.37) |

a) Most of the bps of thymol derivatives are reported¹³ at reduced pressure (e.g. thymyl methyl ether bp₇₄₅ 211-212°, bp₁₅ 94-96°). For low melting compounds, mps (not bps) are reported in the literature. These products are liquids at our ambient room temperature (33-39°). The bps reported were determined (twice) at atmospheric pressure using a Thiele tube [open capillary end immersed in the compound (liquid) taken in a small sodium fusion tube]. b) *lit.*¹³ mp. 33-34°.

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