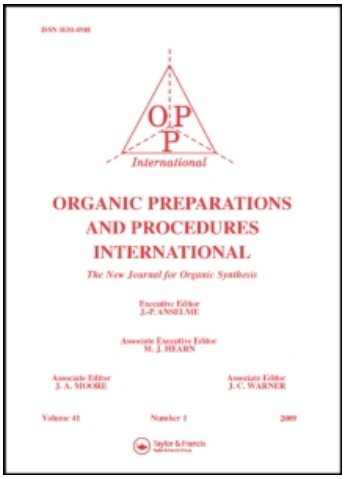

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A NOVEL ROUTE TO THYMOL FROM *m*-CRESOL

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To cite this Article Divakar, K. J. , Dhekne, V. V. , Kulkami, B. D. , Joshi, P. L. and Rao, A. S.(2000) 'A NOVEL ROUTE TO THYMOL FROM *m*-CRESOL', Organic Preparations and Procedures International, 32: 1, 92 — 94
To link to this Article: DOI: 10.1080/00304940009356753
URL: http://dx.doi.org/10.1080/00304940009356753

A NOVEL ROUTE TO THYMOL FROM *m*-CRESOL†

Submitted by (10/04/99)

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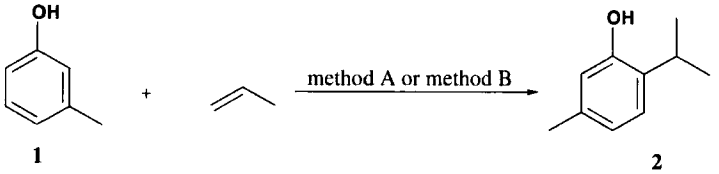
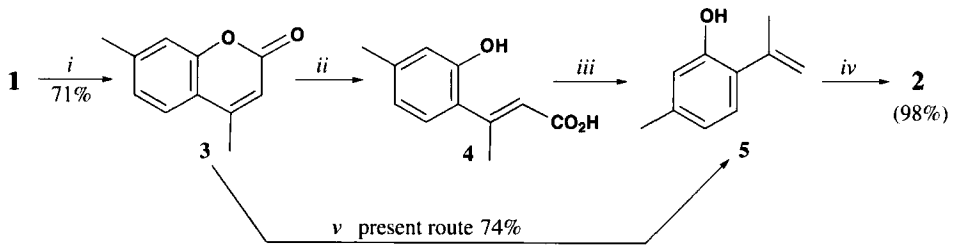
Thymol **2**, a naturally occurring phenolic terpene used as an antiseptic,[1] has been prepared by alkylation of *m*-cresol **1**, with propylene in the presence of alumina (method A)[2] or aluminium 3-



1 **2**

methylphenoxide (method B).[3] With alumina, **2** is formed in 63% yield (7 % of 4-isopropyl-3-methylphenol as by-product) while method B gives **2** in 75% yield (13% of 2,6-diisopropyl-3-methylphenol as by-product); however, both procedures require a purification step.



i) ethylacetoacetate, acidify, heat; *ii*) NaOH, heat / acidify; *iii*) heat; *iv*) H_2, Raney Ni; *v*) NaOH, ethanediol, heat / acidify

We now report an improved procedure which passes through compound **5** which itself may be valuable for the preparation of naturally occurring compounds related to thymol.[4,5]

4,7-Dimethylcoumarin (**3**) is a crystalline compound which may be obtained in good yield (71%) and high purity (>99%) from the Pechmann reaction with m-cresol. Fries and Fickewirth[6] had prepared the unsaturated acid **4** by heating **3** with alkali followed by acidification and showed that on heating, acid **4** readily loses CO_2 to give phenol **5**. It has been observed during the present study that heating the coumarin **3** with alkali at a high temperature (~190°) provides the phenol **5** (after acidification); evidently, the acid **4** underwent decarboxylation in alkaline medium. The hydroxyl group, situated *ortho* to the acid side-chain, is essential to facilitate decarboxylation since cinnamic acid itself and other substituted cinnamic acids do not undergo decarboxylation when heated with alkali at 190°.[7] Hydrogenation of the phenol **5** furnished thymol **2** which is free from regioisomers; thus, the overall yield of **2**, free from regioisomers, is 51% starting from **1**.

EXPERIMENTAL SECTION

All mps and bps are uncorrected. IR spectra were recorded as liquid film or Nujol mull on Perkin-Elmer model 137B or 599B spectrophotometer. ^{1}H-NMR. spectra were recorded on Varian T-60 or WH-90 spectrometers. Microanalysis was carried out in the microanalytical section of our laboratory. GC was determined on Carlo-Erba: Fractovap No. 2450, Integrator: 3390A Hewlett Packard and Detector: F. I. D.

2-(2-Hydroxy-4-methylphenyl)-1-propene (5).- A mixture of 4,7-dimethylcoumarin **3** (87.0g, 0.5 mmol),[6,8] NaOH (80.0g, 2.0 mmol) and 1,2-ethanediol (500mL) was heated under reflux under N_2 for 2 hrs, cooled, diluted with water (1.0L) and covered with ether (300mL). Dilute HCl (0.5N) was added with stirring till the pH was 2. The organic layer was separated and aqueous layer extracted with ether (200mL ×2). The combined ethereal extracts were washed with water and dried (Na_2SO_4). After removal of solvent, the residue was distilled *in vacuo* to yield 55g (74%) of **5** as a colorless liquid, bp. 130-135°/ 40mm; NMR (CCl_4): δ, 6.87-6.52 (m, 3H, ArH), 5.38 (s, 1H, OH), 5.27 (m, 1H, vinyl H), 5.05 (m, 1H, vinyl H), 2.27 (s, 3H, $ArCH_3$), 2.08 (m,3H, CH_3-C=C).

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.86; H, 8.28

Thymol (2).- A mixture of phenol **5** (50.0g,), ethanol (500mL) and Raney nickel (10g) was stirred under hydrogen in an autoclave at 3-5 atmospheres at room temperature (30°) till hydrogen absorption ceased. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. Distillation of the residue furnished 50.0g. (98%) of **2** as a colorless liquid, bp. 135-140°/50mm; the IR and ^{1}H-NMR spectra were identical with those of an authentic sample. 1H-NMR and GLC studies show that thymol thus prepared contains less than detectable amounts (1%) of regioisomers of thymol. The distillate solidified on standing at room temperature. A sample recrystallized from ether/pet ether mixture showed mp. 50-51°, lit.[6] mp. 51°.

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† This work is covered by Indian Patent No. 146327; *Chem. Abstr.*, **92**, P58436n (1980).

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SYNTHESIS OF 4,6-DINITROINDOLE

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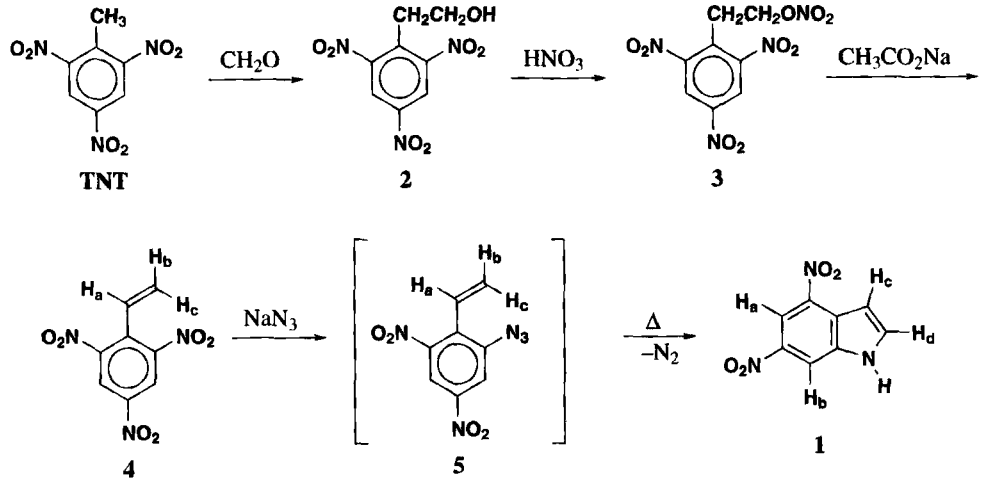
Nitroindoles represent an attractive synthetic target for the preparation of physiologically active compounds.[1,2] To our surprise, 4,6-dinitroindole is not a known compound. The present paper describes the synthesis of **1** from 2,4,6-trinitrotoluene (TNT) according to the following scheme.



Although compounds **2**, **3** and **4** have been described previously,[6,7] they were not characterized by NMR spectroscopy. The assignment of protons H_a, H_b and H_c in 2,4,6-trinitrostyrene (**4**) has been made on the basis of the following NMR criteria: ${}^3J_{trans} > {}^3J_{cis} >> {}^2J_{gem}$.[8] The *ortho*-nitro group is substituted selectively upon interaction of styrene **4** with sodium azide in DMF at 20°. 2-Azido-4,6-dinitrostyrene (**5**) is a labile compound which is converted to **1** even during crystallization from Pr^{i}OH. The structure of **1** was unambiguously determined by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and microanalysis.