Tetrahedron Letters 53 (2012) 6755–6757

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ethylene glycol as hydrogen donor for the syntheses of thymol analogues via hydrolysis of 4-methylcoumarins

Junbiao Chang *, Shuyang Wang, Zhenhua Shen, Gang Huang, Yueteng Zhang, Jing Zhao, Changwei Li, Fangfang Fan, Chuanjun Song *

College of Chemistry and Molecular Engineering, Zhengzhou University, 100 Science Avenue, Zhengzhou 450001, PR China

ARTICLE INFO

Article history:
Received 31 May 2012
Revised 20 September 2012
Accepted 26 September 2012
Available online 11 October 2012

Keywords:
Thymol
4-Methylcoumarin
Ethylene glycol
Double-bond reduction

ABSTRACT

Treatment of 4-methylcoumarins with potassium hydroxide in ethylene glycol resulted in the formation of the 'normal' 2-isopropenylphenols and/or the 'abnormal' 2-isopropylphenols depending on the nature of the substrates. The solvent ethylene glycol was believed to be the hydrogen donor for double-bonding reduction where 2-isopropylphenol was produced.

Thymol **1** (Fig. 1) is a naturally occurring phenolic terpene which showed antiseptic, antioxidant, and antibacterial activity.[1–6] Upon hydrogenation, thymol yields menthol, another important natural terpenoid with analgesic, antiseptic, and antimicrobial properties.[7–9] The most straightforward method for the synthesis of thymol is a Lewis acid catalyzed isopropylation of *m*-cresol with propylene or *iso*-propanol.[10–17] Recently, an ionic liquid catalyzed[18] or microwave-assisted[19] process has also been described. However, this approach is always associated with the production of isomer **2** where the alkylation has occurred at the position *para* to the hydroxy group, as well as the di-alkylated by-products **3** and **4**. In 2000, Rao[20] and co-workers reported that hydrolysis of 4,7-dimethylcoumarin, followed by hydrogenation of the resulting double-bond, gave thymol regioselectively in 51% overall yield. In a project searching for anti-obesity drug,[21] we need to get access to thymol and its analogues. This promoted us to re-visit Rao's route. We now disclose the full detail of our findings during the hydrolysis of 4-methylcoumarin derivatives.

As shown in Scheme 1, we first studied the hydrolysis of 4,7-dimethylcoumarin **5**, which itself was obtained by Pechmann condensation[22] between *m*-cresol and ethyl acetoacetate. The reaction was complete within 1 h by treatment of **5** with KOH in refluxing ethylene glycol. Apart from 2-isopropenyl-5-methylphenol **6** in 90% yield, a minor product was also isolated. Surprisingly, the structure was confirmed to be thymol **1** resulting from reduction of the double-bond in **6**.

Next, hydrolysis of other 4-methylcoumarins was explored and the results were collected in Table 1.

As shown in Table 1, hydrolysis of 4,6-dimethylcoumarin gave 2-isopropenyl-4-methylphenol **7a** in 87% isolated yield, together with a small amount of *p*-cresol **7b**, which probably was formed by retro-Pechmann reaction (entry 1). When an extra methyl group was introduced into the 7-position, that is, hydrolysis of 4,6,7-trimethylcoumarin resulted in the formation of a mixture of 2-isopropenyl-4,5-dimethylphenol **8a** and 4-methylthymol **8b** in a ratio of 0.56:1 according to ^{1}H NMR integration of the crude products (entry 2). **8a** and **8b** could be isolated in 20% and 34% yields, respectively, after careful chromatography. On the other hand, hydrolysis of 4,6,8-trimethylcoumarin mainly gave 2-isopropenyl-4,6-dimethylphenol **9a** (entry 3). Only a trace amount (3%) of propylphenol **9b** was obtained. Hydrolysis of other substituted 4-methylcoumarins revealed that the outcome of the products was dependent on the substrates. In particular, an electron-donating

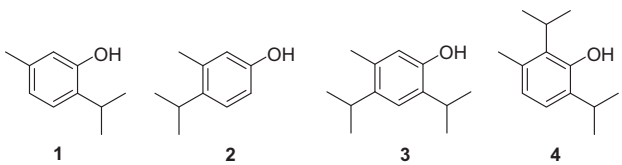
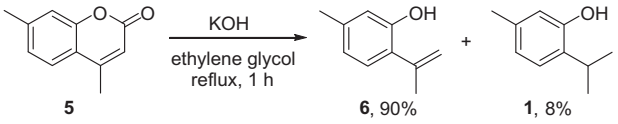


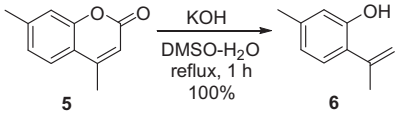
Figure 1. Possible products for the isopropylation of *m*-cresol.

* Corresponding authors.
E-mail addresses: changjunbiao@zzu.edu.cn (J. Chang), chjsong@zzu.edu.cn (C. Song).

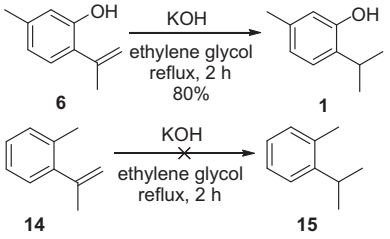
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.09.122



Scheme 1. Hydrolysis of 4,7-dimethylcoumarin.



Scheme 2.



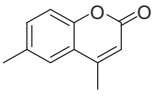
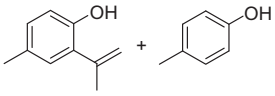
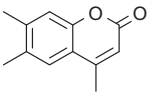
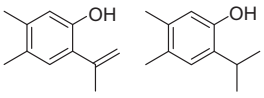
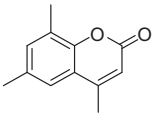
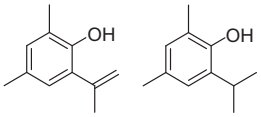
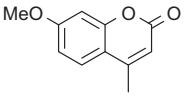
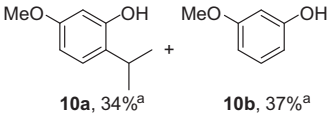
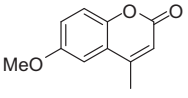
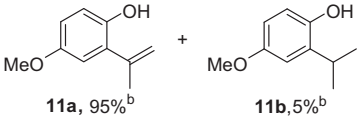
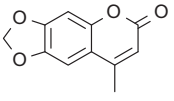
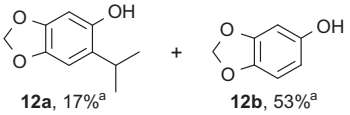
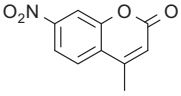
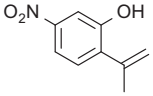
Scheme 3.

group at the 7-position of the coumarin precursor will facilitate the formation of 2-isopropylphenol derivatives. While hydrolysis of 7-methoxy-4-methylcoumarin (entry 4) and 6,7-methylenedioxy-4-methylcoumarin (entry 6) gave the corresponding 2-isopropylphenols (**10a** and **12a**), hydrolysis of 6-methoxy-4-methyl-coumarin (entry 5) resulted mainly in the formation of 2-isopropenyl-4-methoxyphenol **11a**. In the former cases, the only other products (**10b** and **12b**) were those resulting from retro-Pechmann reaction. Hydrolysis of 4-methyl-7-nitrocoumarin gave a variety of products. The ^{1}H NMR of the crude products clearly indicated the formation of 2-isopropenyl-5-nitrophenol **13** which could be isolated in low yield (10%), while no trace of 2-isopropyl-5-nitrophenol could be identified.

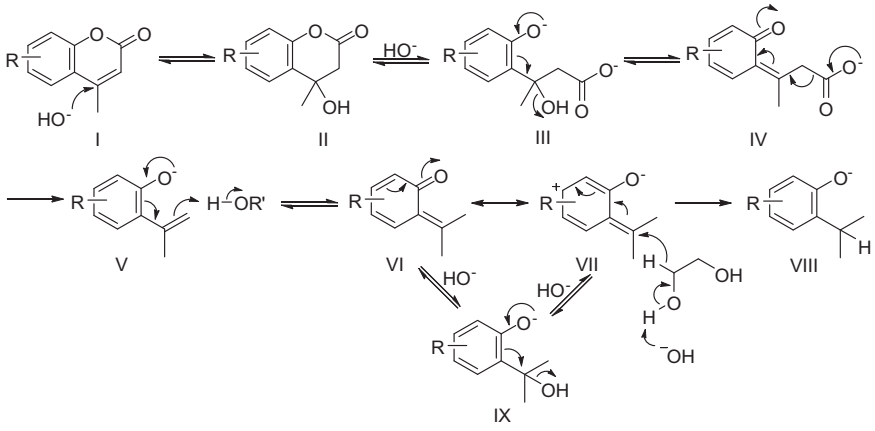
The reasons for double-bond reduction were then explored, using hydrolysis of 4,7-dimethylcoumarin as an example. The results persist running the reaction either under strict argon atmosphere or open to air, which always gave a mixture of isopropenylphenol **6** and thymol **1**. However, when a mixture of DMSO/H_2O (10:1) was used as a solvent, isopropenylphenol **6** was obtained exclusively (Scheme 2), which indicated that ethylene glycol was the hydrogen donor for double-bond reduction.

Finally, it was found that treatment of 2-isopropenylphenol **6** with KOH in refluxing ethylene glycol for 2 h also resulted in the formation of thymol **1** in 80% isolated yield (Scheme 3). However,

Table 1
Hydrolysis of 4-methylcoumarins in ethylene glycol

Entry	4-Methylcoumarins	Product(s)/Yield
1		 **7a**, 87%[a] **7b**, 8%[a]
2		 **8a**, 36%[b] **8b**, 64%[b]
3		 **9a**, 97%[b] **9b**, 3%[b]
4		 **10a**, 34%[a] **10b**, 37%[a]
5		 **11a**, 95%[b] **11b**, 5%[b]
6		 **12a**, 17%[a] **12b**, 53%[a]
7		 **13**, 10%[a]

[a]Isolated yields.
[b]Yields were determined based on integrations of the ^{1}H NMR of the crude products. No other products were evident by ^{1}H NMR.



Scheme 4. Proposed mechanism.

under identical conditions, 2-isopropyltoluene **15** could not be obtained from 2-isopropenyltoluene **14**.

Based on the results above, a plausible mechanism was proposed in Scheme 4. Michael addition of I with hydroxide anion followed by lactone-ring opening yielded III, which lost a molecule of carbon dioxide to generate isopropenylphenoxide V. V and VI were in equilibrium through enol–keto tautomerization. This equilibrium is favorable when there is an electron-donating group present at the 7-position of the initial coumarin derivative, in which case the resonance structure VII would be stabilized by having a tertiary carbenium ion. Attack of VI or VII by hydroxide generated IX. However, attack by hydride ion generated from ethylene glycol gave VIII irreversibly.

In conclusion, we have disclosed that hydrolysis of coumarin derivative will give 2-isopropenylphenol or 2-isopropylphenol depending on the nature of the substrate. The solvent ethylene glycol was believed to be the hydrogen donor where 2-isopropylphenol was produced.

Acknowledgments

We are grateful to the National Natural Science Foundation of China (Outstanding Young Scholarship to J.C., #30825043; Young Scholarship to C.S., #20902085) for the financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.122.

References and notes

1. Yanishlieva, N. V.; Marinova, E. M.; Gordon, M. H.; Raneva, V. G. *Food Chem.* **1999**, *64*, 59–66.
2. Milos, M.; Mastelic, J.; Jerkovic, I. *Food Chem.* **2000**, *71*, 79–83.
3. Mastelić, J.; Jerković, I.; Blažević, I.; Poljak-Blaži, M.; Borović, S.; Ivančić-Baće, I.; Smrečki, V.; Žarković, N.; Brčić-Kostic, K.; Vikić-Topić, D.; Müller, N. *J. Agric. Food Chem.* **2008**, *56*, 3989–3996.
4. Pearson, D. A.; Frankel, E. N.; Aeschbach, R.; German, J. B. *J. Agric. Food Chem.* **1997**, *45*, 578–582.
5. Teissedre, P. L.; Waterhous, A. L. *J. Agric. Food Chem* **2000**, *48*, 3801–3805.
6. Helander, I. M.; Alakomi, H. L.; Latva-Kala, K.; Mattila-Sandholm, T.; Pol, I.; Smid, E. J.; Gorris, L. G. M.; Wright, A. von. *J. Agric. Food Chem.* **1998**, *46*, 3590–3595.
7. Galeotti, N.; Mannelli, L. D. C.; Mazzanti, G.; Bartolini, A.; Ghelardini, C. *Neurosci. Lett.* **2002**, *322*, 145–148.
8. Allakhverdiev, A. I.; Kul'kova, N. V.; Murzin, D. Yu. *Ind. Eng. Chem. Res.* **1995**, *34*, 1539–1547.
9. Krause, E. L.; Ternes, W. *Eur. Food Res. Technol.* **1999**, *209*, 140–144.
10. Velu, S.; Sivasanker, S. *Res. Chem. Intermed.* **1998**, *24*, 657–666.
11. Grabowska, H.; Mista, W.; Trawczynski, J.; Wrzyszcz, J.; Zawadzki, M. *Appl. Catal., A* **2001**, *220*, 207–213.
12. Umamaheswari, V.; Palanichamy, M.; Murugesan, V. *J. Catal.* **2002**, *210*, 367–374.
13. Selvaraj, M.; Kawi, S. *Microporous Mesoporous Mater.* **2008**, *109*, 458–469.
14. Grabowsaka, K.; Wrzyszcz, J. *Res. Chem. Intermed.* **2001**, *27*(3), 281–285.
15. Grabowskaa, H.; Syperb, L.; Zawadzki, M. *Appl. Catal., A* **2004**, *277*, 91–97.
16. Nitta, M.; Yamaguchi, K.; Aomura, K. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2897–2898.
17. Yamanka, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2669–2673.
18. Gunaratne, H. Q. N.; Lotz, T. J.; Seddon, K. R. *New J. Chem.* **2010**, *34*, 1821–1824.
19. Ali, A. A.; Gaikar, V. G. *Ind. Eng. Chem. Res.* **2011**, *50*, 6543–6555.
20. Divakar, K. J.; Dhekne, V. V.; Kulkarni, B. D.; Joshi, P. L.; Rao, A. S. *Org. Prep. Proced. Int.* **2000**, *32*, 92–94.
21. Han, Z.; Niu, T.; Chang, J.; Lei, X.; Zhao, M.; Wang, Q.; Cheng, W.; Wang, J.; Feng, Y.; Chai, J. *Nature* **2010**, *464*, 1205–1210.
22. a) De, S. K.; Gibbs, R. A. *Synthesis* **2005**, 1231–1233; b) Khandekar, A. C.; Khandilkar, B. M. *Synlett* **2002**, 152–154.