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THE MICHAEL REACTION OF 2-(PHENYLTHIO)-2-PENTEN-5-OLIDE WITH SOME BENZYLIC GRIGNARD REAGENTS. SYNTHESIS OF SECOCRISPIOLIDE

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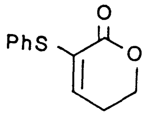
The electrophilic reactivity of 2-(phenylthio)-2-penten-5-olide toward some benzylic Grignard reagents was investigated, and 2-methylene-3-(2,6-dimethylbenzyl)-5-pentanolide (secocrispiolide) was synthesized from one of the Michael adducts.

We recently reported that 2-(phenylthio)pentenolide (**1**) was recognized as a new versatile building block for the synthesis of 3-substituted δ-lactones, because the former showed high electrophilic reactivities toward some carbon nucleophiles to give 3-substituted 2-(phenylthio)pentanolides which were convertible to a variety of 3-substituted pentanolides and pentenolides.1)

We wish to describe here a further investigation on the Michael reaction of **1** with some benzylic Grignard reagents, and the total synthesis of (±)-secocrispiolid (**2**),2) a seco-sesquiterpene lactone isolated from *Plicaria crispa* Sch. Bip., via one of the Michael adducts.



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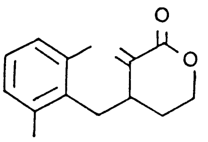

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It has long been known that condensation of Grignard reagents prepared from benzylic halides with electrophiles such as carbon dioxide and aldehydes frequently produces abnormal products resulting from the so-called allylic rearrangement of the reagents besides normal products.3)

We, therefore, were interested in the type of product in the Michael reaction of **1** with benzylic Grignard reagents and examined the reaction with benzylmagnesium or ortho-substituted benzylmagnesium bromides.

Treatment of **1** with benzyl- and 2-methylbenzylmagnesium bromides gave only normal adducts (**3a** and **3b**)[4] in high yields, respectively, whereas in the reaction with 2,6-dimethylbenzylmagnesium bromide, the product was an unstable adduct (**4c**)[5] containing the expected adduct (**3c**)[6] (Table 1). The spectral data[7] of the major product (**4c**) demonstrated that this compound was an abnormal adduct and that to our surprise, it was isolated as a cross-conjugated methylene cyclohexadiene derivative with the structure depicted.

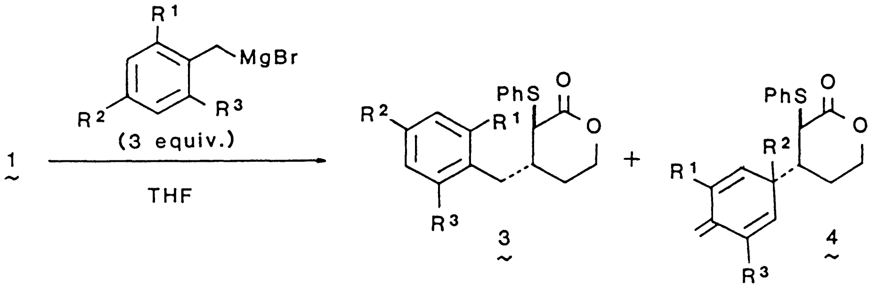


Table 1. The Michael reaction of 2-(phenylthio)pentenolide with benzylic Grignard reagents

	Grignard reagent			Reaction conditions	Product and isolated Yield / %		
	R^1	R^2	R^3		**3**[a]	**4**[a]	recovered **1**
a	H	H	H[b]	-12 °C, 20 min	82	0	16
b	Me	H	H[b]	0 °C, 1.3 h	62	0	16
c	Me	H	Me[b]	-12 °C, 20 min	34	65	0
	Me	H	Me[c]	0 °C, 1.5 h	39	45	0
d	Me	Me	Me[b]	-12 °C, 20 min	6[d]	10[d]	75

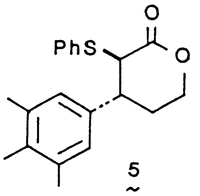
a) Although relatively small couplings (5.4-6.5 Hz, PhS-C<u>H</u>-CH-) were observed in their ^{1}H-NMR spectra, thermodynamically stable equatorial configurations were surmised for substituents on the lactone rings.

b) The Grignard reagent was prepared from magnesium ribbon and the corresponding benzyl bromide in THF by the usual procedure.

c) The Grignard reagent was prepared from active magnesium according to R. D. Rieke and S. E. Bales [J. Am. Chem. Soc., **96**, 1775 (1974)].

d) The yield was calculated from the integral ratio of the aromatic and aliphatic methyls in **3d** and **4d**, respectively, in the ^{1}H-NMR spectrum of the mixture.

The structure (**4c**) was also chemically supported by treatment of **4c** with catalytic p-toluenesulfonic acid in benzene at room temperature, 4c thereby readily aromatizing to give 3-(3,4,5-trimethylphenyl)-δ-lactone (5)[8) in nearly quantitative yield.[9)



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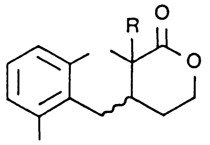
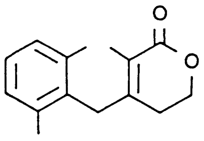
When 2,4,6-trimethylbenzylmagnesium bromide was submitted to the reaction, a mixture of normal and unstable abnormal adducts (3d and 4d)[10) was similarly obtained along with a large quantity of unreacted 1.

Having the δ-lactone (3c) in hand, the synthesis of secocrispiolide (2) was then undertaken. Treatment of the lithium enolate of 3c with methyl iodide [(i) LDA-THF, -78 °C, (ii) MeI-HMPA, -78 - -50 °C] afforded the corresponding methylated lactone (6) as an inseparable 3:1 mixture of diastereomers.[11) The lactone (6) was then oxidized with equimolar mCPBA (CH_2Cl_2, -16 °C), and the sulfoxide (7) obtained in quantitative yield was exposed to thermal elimination conditions of sulfenic acid (benzene, reflux) to give the exo-methylene lactone (2) in 23% yield along with its regioisomer (8) in 69% yield. The spectra (IR, NMR, and MS) of the former were identical with those of natural secocrispiolide.[2)



6 R=SPh
7 R=S(O)Ph



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References

1) M. Kato, A. Ouchi, and A. Yoshikoshi, Chem. Lett., 1983, 1511.

2) F. Bohlmann, K.-H. Knoll, and N. A. El-Emary, Phytochemistry, 18, 1231 (1979).

3) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York (1954), p. 1133. The terminology "normal" and "abnormal" followed the above literature, i.e., the former indicates the reaction at the benzyl position, while the latter does the reaction at the para

position of a benzyl group.

4) The NMR and IR spectra, and exact mass determinations by high resolution MS of all new compounds isolated are consistent with the proposed structures.

5) The oily **4c** gradually changed to a mixture of the aromatized **5** and some unidentified polar products on standing even at -20 °C in a refrigerater. Expeditious purification of **4c** by preparative thin-layer chromatography on silica-gel, however, gave **4c** of high purity enough for measurements of its physical constants.

6) **3c**, IR(neat) 1735 cm^{-1}; ^1H-NMR($CDCl_3$) δ 1.4-2.1 (m, 3H), 2.26(s, 6H), 2.7(d.d, J=13.3, 5.8, 1H, Ar-C$\underline{H}$aHb-), 3.18(d.d, J=13.3, 5.4, 1H, Ar-CHa$\underline{H}$b-), 3.38(d, J=6.3, 1H, S-CH-), 4.3-4.5(m, 2H, O-CH_2-), 7.02(br. s, 3H), and 7.2-7.6(m, 5H).

7) **4c**, IR(neat) 1735 cm^{-1}; ^1H-NMR($CDCl_3$) δ 1.4-1.9(m, 2H), 2.28(d, J=1, 6H), 2.1-2.4(m, 1H), 3.8[m, 1H, $(C{=}CH)_2C\underline{H}$-], 3.61(d, J=5.4, 1H, S-CH-), 4.20-4.48(m, 2H, O-CH_2-), 5.04(s, with fine splittings, 2H, =CH_2), 5.59(s, with fine splittings, 2H, =CH-), and 7.2-7.6(m, 5H); ^{13}C-NMR($CDCl_3$) δ 19.9(q), 25.2(t), 42.0 (d), 42.9(d), 49.2(d), 67.0(t), 107.7(t), 125.1(d), 126.1(s), 128.2(s), 128.7 (d), 129.2(d), 133.6(d), 135.3(s), and 169.9(s).

8) **5**, mp 107-108 °C, IR(KBr) 1735 cm^{-1}; ^1H-NMR($CDCl_3$) δ 1.8-2.2(m, 2H), 2.17(s, 3H), 2.24(s, 6H), 3.11(m, 1H, Ar-CH-), 3.97(d, J=6.3, 1H, S-CH-), 4.3-4.5(m, 2H, O-CH_2-), 6.82(br. s, 2H), and 7.2-7.6(m, 5H).

9) Attempted aromatization of **4c** with Lewis acid such as boron trifluoride etherate led to a complex mixture containing a small quantity of **5**.

10) In the ^1H-NMR spectrum of this mixture, the following signals were assignable to both products; **3d**, δ 2.28(s, 6H), 2.31(s, 3H), 6.86(br. s, 2H), and 7.2-7.5(m, 5H); **4d**, δ 1.15(s, 3H), 1.91(s, 6H), 5.11(br. s, 2H), 5.48(br, s, 2H), and 7.2-7.5(m, 5H). Methine protons on the carbon flanking phenylthio groups and methylene protons at δ-positions of the lactone rings in both compounds were observed as overlapped signals centered at 3.5 and 4.3 ppm, respectively.

11) Judging from the fact that α,β-unsaturated lactone (**8**) was obtained as the major product on thermolysis of **7** (vide post), a trans stereochemistry was surmised with respect to the phenylthio group and the β-substituent in the major product of **6**.

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