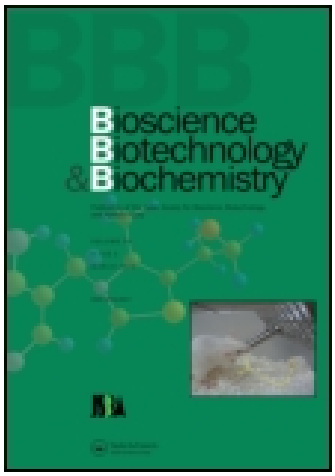

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Facile Synthesis of 2-Hydroxy-6-methylbenzaldehyde, an Alarm and Sex Pheromone Component of Astigmatid Mites†

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2-Hydroxy-6-methylbenzaldehyde (5) is a component of astigmatid mites, functioning as the alarm and sex pheromones, and the establishment of its convenient synthesis is prerequisite and of vital importance to develop applications of these pheromones for practical use.

The target compound (5) was effectively synthesized from *m*-cresol (1) by the following four steps in a 44% overall yield: protection of the hydroxyl group by a tetrahydropyranyl group, blocking the active site (6-position of 1) by a trimethylsilyl group *via* lithiation and subsequent silylation, formylation *via* lithiation and successive quenching by dimethylformamide, and deprotection by a trifluoroacetic acid treatment.

Key words: 2-hydroxy-6-methylbenzaldehyde; alarm pheromone; sex pheromone; Astigmata; Acaridae

The compound, 2-hydroxy-6-methylbenzaldehyde (**5**), is widely distributed among astigmatid mites, not only as the alarm pheromone of *Tyrophagus perniciosus* (Acarina: Acaridae)[1] and as the sex pheromone in the brown-legged mite *Aleuroglyphus ovatus* (Troupeau) (Acarina: Acaridae)[2] and in *Acarus immobilis*,[3] but also as an opisthonotal gland component of unknown functions in the following four species of mites: the grain mite *Acarus siro* (Acarina: Acaridae),[4] the house dust mite *Dermatophagoides farinae* (Astigmata: Pyroglyphidae),[5] the mold mite *Tyrophagus putrescentiae*,[6] and the wet grain mite *Caloglyphus rodriguezi*.[7]

Although compound **5** is obtainable from *m*-cresol (**1**) by Fries rearrangement of *m*-cresol formate as a key reaction,[1,4] it is formed as a minor by-product, while the major product is 2-hydroxy-4-methylbenzaldehyde, possibly because of steric hindrance. All attempts to separate both isomers by silica gel column chromatography have failed, and only a tedious procedure by preparative GLC resulted in successful separation,[1,4] although the method was not practical for preparing a substantial amount of **5**.

An alternative method to obtain **5** in an isomer-free condition have been reported, starting from 2-methyl-5-nitro-benzoic acid *via* four steps.[8] but the starting benzoic acid is not commercially available at present.

It was therefore worth trying to establish a convenient synthetic method for **5**, not only for studying its function among each species of mites, but also for developing new strategies for controlling these astigmatid mites by pheromones, because they are known as noxious agricultural pests that attack crops in the field and in the greenhouse, as well as stored products.

The hydroxyl group of **1** was protected by a tetrahydropyranyl group to give **2**. Introduction of the formyl group at the 2-position of **2** may have been achieved by lithiation with *n*-butyllithium (*n*-BuLi) and subsequent quenching with dimethylformamide; however, the reaction also tended to give undesirable 2-hydroxy-4-methylbenzaldehyde as the major product, like the case of the Fries rearrangement.[1,4] Another route was therefore devised to synthesize isomer-free **5**, as summarized in Fig. In order to prevent formylation at the 6-position of **2**, the position was tentatively blocked by a trimethylsilyl group *via* lithiation[9,10] and subsequent silylation to give **3** in a 74% yield. The silylated compound (**3**) was then subjected to formylation *via* lithiation and subsequent quenching with dimethylformamide according to the reported method,[11] to successfully give **4**. The trimethylsilyl group was then removed by treating with trifluoroacetic acid by following the reported method[12] to give **5**. The idea to block the active site of phenol during formylation was successfully demonstrated to give a 44% overall yield.

The yield of **4** from **3** was heavily dependent on the solvent as summarized in Table, possibly because of the cluster size of *n*-BuLi in the solvent. A satisfactory result

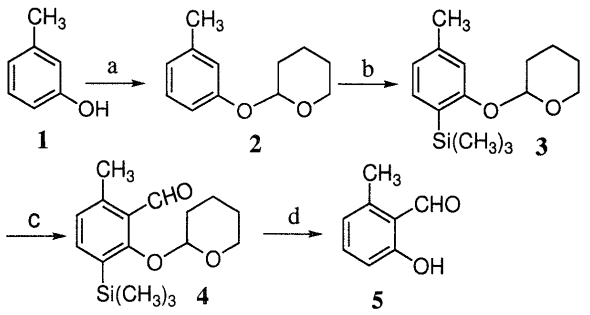

Fig. Synthetic Route to 2-Hydroxy-6-methylbenzaldehyde.

a) dihydropyran/HCl; b) *n*-butyllithium/ether and hexane, then trimethylsilylchloride/xylene; c) *n*-butyllithium/hexane and tetramethylethylenediamine, then dimethylformamide; d) trifluoroacetic acid/CCl_4.

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Table Solvent Conditions and Yields of Formylation Product **4**

Exp. No.	Comp. **3** (mmol)	Solvents (ml)				Yield of comp. **4**
		THF	Et_2O	Hexane	TMEDA	
1	7.95	20	10			22.7
2	7.95	20	10		2	32.7
3	7.95		30			8.6
4	3.79		15		1	74.9
5	3.79			15	1	83.1
6	16.30			66	4.3	71.8

THF, tetrahydrofurane; TMEDA, tetramethylethylenediamine.

was attained by lithiation in a mixture of hexane and tetramethylethylenediamine, and by subsequent quenching with dimethylformamide. When *n*-BuLi was present in the monomeric form,[13] the reaction might have proceeded even at the highly hindered site (the 2-position of **3**), while in ether, *n*-BuLi was present in the tetrameric form and the reaction gave a poor yield.

Thus, the target compound (2-hydroxy-6-methylbenzaldehyde, **5**) was successfully synthesized by lithiation of **3** as the key step. The method is applicable to prepare a substantial amount of **5** in four steps for developing devices to manipulate pheromone communications among astigmatid mites in future.

Experimental

The ^{1}H-NMR spectrum was measured with a Bruker A300 NMR spectrometer, using tetramethylsilane as an internal standard and $CDCl_3$ as the solvent. GLC analyses were performed with Hewlett Packard 5890 Plus apparatus equipped with an HP-5 capillary column. Chromatograms were processed with a Hewlett Packard model 3390A Integrator. GC/MS spectra were recorded on an HP-5989B mass spectrometer operated at 70 eV, using the same GLC column and operating conditions as those just stated. Column chromatography was carried out in columns packed with Wakogel C-200 (Wako Pure Chem. Ind. Co.). TLC was performed on silica gel precoated plates (Merck 60 HF_{254}), using each indicated solvent, and was visualized by iodine vapor.

Preparation of 3-methylphenyl tetrahydropyranyl ether (**2**). *m*-Cresol (**1**, 10.7 g, 99 mmol) was dissolved in dihydropyran (12.1 g, 144 mmol), and two drops of conc. hydrochloric acid were added to the solution while vigorously stirring under ice-cooling. After 30 min, the mixture was allowed to warm to r.t. and kept for an additional 90 min while stirring. To the mixture was added water, and the product was extracted with ether. The extract was successively washed with 2 N NaOH twice and with satd. NaCl twice, dried over Na_2SO_4 overnight, and evaporated under reduced pressure. The oily residue (18.6 g) gave a new spot [R_f 0.69, different from *m*-cresol (R_f 0.14)] by TLC (benzene as the developing solvent), and was purified in a silica gel column (186 g) to give **2** (18.1 g, 96% yield). GC-MS *m/z*: 108 (M^+ and the base ion), 107 (38%), 85 (62%), 84 (58%), and 55 (31%). ^{1}H-NMR ($CDCl_3$) δ 7.14 (1H, t, J=7.8 Hz, Ar-H), 6.87 (1H, s, Ar-H), 6.82 (1H, d, J=7.3 Hz, Ar-H), 6.78 (1H, d, J=7.3 Hz, Ar-H), 5.39 (1H, t-like, –OCHO–), 3.91 (1H, ddd, $OC\underline{H}_aH_b$–), 3.58 (1H, m, $-OCH_a\underline{H}_b$–), 2.31 (3H, s, Ar-CH_3), 1.96–2.02 (1H, m), 1.81–1.86 (2H, m), and 1.56–1.69 (3H, m).

Preparation of 3-methyl-6-trimethylsilylphenyl tetrahydropyranyl ether (**3**). To a dry ethereal (50 ml) solution of **2** (10 g, 52 mmol), a 1.6 M hexane solution of *n*-BuLi (36.5 ml, 57.3 mmol) was added dropwise while ice-cooling under an N_2 atmosphere, and the mixture was stirred for 1 h and then kept at r.t. for 18 h. To the resulting mixture, a dry xylene (50 ml) solution of trimethylsilylchloride (6.25 g, 57.6 mmol) was added dropwise while stirring, before the mixture was refluxed for 2 h. To the mixture, water was added dropwise, and the product was extracted with ether twice. The combined extracts were successively washed with 2 N NaOH twice and saturated NaCl twice, dried over Na_2SO_4 overnight, and evaporated under reduced pressure. The oily residue (50.5 g) gave a new spot (R_f 0.37) by TLC developed with 20% benzene in hexane, and was chromatographed in a silica gel (750 g) column to give **3** (10.2 g, 38.5 mmol, 74% yield). ^{1}H-NMR ($CDCl_3$) δ: 7.27 (1H, d, J=7.3 Hz, Ar-H), 6.94 (1H, s, Ar-H), 6.80 (1H, d, J=7.5 Hz, Ar-H), 5.47 (1H, t-like, –OCHO–), 3.90 (1H, ddd, $OC\underline{H}_aH_b$–), 3.64 (1H, m, $-OCH_a\underline{H}_b$–), 2.33 (3H, s, Ar-CH_3), 1.99–2.03 (1H, m), 1.85–1.90 (2H, m), 1.56–1.74 (3H, m), and 0.29 (9H, s, $-Si(CH_3)_3$–).

Preparation of 2-formyl-3-methyl-6-trimethylsilylphenyl tetrahydropyranyl ether (**4**) *by formylation*. To a hexane (43 ml) solution of **3** (4.3 g, 16.3 mmol), tetramethylethylenediamine (4.3 ml) and an *n*-BuLi solution (1.6 M in hexane, 11.2 ml) were successively added at −80°C under an N_2 atmosphere. The mixture was kept for 15 min at −80°C, and then kept at r.t. for 2.75 h. To the mixture, a hexane (22 ml) solution of dimethylformamide (3.5 g, 50 mmol) was added dropwise. After 3 h of stirring, water was added dropwise, and the mixture was extracted twice with ether. The combined extract was successively washed with 2 N NaOH twice and saturated NaCl twice, dried over Na_2SO_4 overnight, and evaporated under reduced pressure.

The oily residue (4.9 g) gave a spot (R_f 0.18) by TLC (developed with 50% benzene in hexane), and the spot was purified by silica gel (100 g) to give **4** (3.43 g, 11.7 mmol, 71.8% yield).

^{1}H-NMR ($CDCl_3$) δ: 10.42 (1H, s, –CHO), 7.52 (1H, d, J=7.5 Hz, Ar-H), 7.02 (1H, d, J=7.6 Hz, Ar-H), 4.67 (1H, dd, J=8.6 Hz and 2.3 Hz, –OCHO–), 3.92 (1H, ddd, $OC\underline{H}_aH_b$–), 3.30 (1H, m, $-OCH_a\underline{H}_b$–), 2.57 (3H, s, Ar-CH_3), 2.07–2.12 (1H, m), 1.92–1.94 (1H, m), 1.74–1.78 (1H, m), 1.45–1.59 (3H, m), and 0.33 (9H, s, $-Si(CH_3)_3$).

Synthesis of 2-hydroxy-6-methylbenzaldehyde (**5**). To a CCl_4 (1 ml) solution of **4** (0.491 g, 1.68 mmol), trifluoroacetic acid (1 ml) was added dropwise, and the mixture was stirred for 18 h at r.t. To the mixture, water was added and the product was extracted twice with ether. The combined extract was successively washed with 2 N NaOH twice and saturated NaCl twice, dried over Na_2SO_4 overnight, and evaporated under reduced pressure. The oily residue (0.645 g) gave a new spot (R_f 0.34) by TLC (developed with 50% benzene in hexane), and was chromatographed in a silica gel (13 g) column to give **5** (0.198 g, 1.46 mmol, 86.9% yield). GC-MS *m/z*: 136 (M^+, 92%), 135 (100%), 118 (7.7%), 107 (11%), 90 (18.6%), and 77 (19.9%). ^{1}H-NMR ($CDCl_3$) δ: 11.90 (1H, s, –CHO), 10.3 (1H, s, Ar-OH), 7.37 (1H, t, J=7.6 Hz, Ar-H), 6.81 (1H, d, J=8.5 Hz, Ar-H), 6.71 (1H, d, J=7.4 Hz, Ar-H), and 2.61 (3H, s, Ar-CH_3).

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