

Note

An Improved Process for the Synthesis of Piperitenone from Mesityloxiide and Methyl Vinyl Ketone*

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Piperitenone (**1**) is a minor component in the essential oil obtained from *Mentha pulegium* var. *Villona* Benth. This monoterpenoid is of interest because it can be converted asymmetrically into a variety of important compounds such as pulegone, piperitone, menthone and menthol.¹⁾

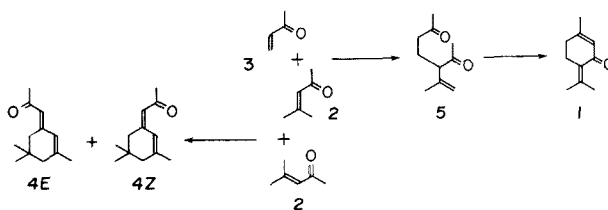
Besides being available from natural sources, **1** can be synthesized by several methods.²⁾ Bergmann and Bracha³⁾ have reported a synthetic procedure for **1** involving the condensation of mesityloxiide (**2**) with methyl vinyl ketone (**3**) using sodium *tert*-butoxide as condensing agent in toluene. This procedure appeared attractive especially from the standpoint of the facility of preparation. However, Naves and Conia⁴⁾ have refuted this work and they claimed that the process of Bergmann and Bracha mainly yields isoxylitones, the self-condensation product of **2**, and only less than 8% of **1**. Subsequently, numerous investigations⁵⁾ have been attempted to attain a high yield of **1** suppressing simultaneously formation of isoxylitones.

One of the authors has prepared **1** successfully with a 51% yield by the condensation of **2** with **3** or 4-diethylamino-2-butanone using Triton B in ether followed by removal of isoxylitones by the formation of their

semicarbazones.⁶⁾ We have also confirmed the structures of isoxylitone-A and B, the main components of isoxylitones, to be **4E** and **4Z**.⁷⁾ In these investigations, we have found that when alkali metal alkoxide was used as condensing agent the self-condensation of **2** occurred in an aprotic solvent (e.g., *n*-hexane, benzene), but little or no reaction occurred if the solvent was replaced by a protic solvent [e.g., ethanol], tetrahydrofuran (THF) or a hydrous aprotic solvent. This finding could be applied to the preparation of **1**, free of codistilling isoxylitones, with excellent results.

Our experimental data are summarized in Table I. Expts. 1 and 2 were carried out according to the procedure of the BASF group,^{5d)} in which a large excess of **2** was required as both substrate and solvent, but the products obtained in our experiment were only **4E** and **4Z**. Expts. 3, 5 and 6 were the same procedures as those reported by Beereboom,^{5b)} and he was successful in obtaining a 54% yield of **1** by adopting the reaction conditions of Expt. 3. As shown in Expt. 4, when a potassium hydroxide pellet was used instead of the powder, the reaction stopped before reaching completion and the intermediate, 3-isopropenyl-2,6-heptadione (**5**), was obtained predominantly. The best yield of **1** was gained with the process of Expt. 7. To a solution of **2** (0.12 mol 12.0 g) in THF (300 ml) was added simultaneously a solution of **3** (0.04 mol, 3.0 g) in THF (60 ml) and a solution of Triton-B (40% MeOH soln., 0.6 g) over 90 min from two dropping funnels. After all the solutions had been added at room temperature, the mixture was refluxed for 80 min. The gas chromatogram of the reaction mixture showed that the product consisted of **1** alone. The reaction mixture was worked up as usual to afford **1** with a 77.8% yield. Its properties agreed in all respects with those reported previously.⁶⁾ The yield of **1** exceeded any of those described earlier.

In Expt. 9, when benzyltriethylammonium chloride was used as the phase transfer catalyst in an aqueous THF solution containing sodium hydroxide, the self-condensation of **2** was suppressed completely and **1** was obtained with a 31.1% yield.



* Syntheses of Terpenes by the Condensation of Aliphatic Compounds. Part VI. For Part V, see O. Nakanishi, I. Ichimoto and H. Ueda, *Nippon Nôgeikagaku Kaishi*, **54**, 105 (1980).

TABLE I. PREPARATION OF PIPERITENONE (1), 3-ISOPROPENYL-2,3-HEPTADIONE (5) AND ISOXYLITONE (4) BY THE CONDENSATION OF MESITYLOXIDE (2) WITH METHYL VINYL KETONE (3) UNDER VARIOUS CONDITIONS

Expt. No.	Substrate (g)		Condensing agent (g)	Conditions and solvent	Product and yield
	2	3			
1 ^a	45.0	1.0	25% KOH aq. soln. 10	azeo. rfx. PhH (50 ml)	4 5.1 g
2 ^a	45.0	1.0 ^b	25% KOH aq. soln. 10	azeo. rfx. PhH (50 ml)	4 5.0 g
3 ^a	8.7	1.7	KOH (powder) 0.4	rfx. 30 min THF (100 ml)	1 1.2 g (46.7%)
4	8.7	1.7	KOH (pellet) 0.4	rfx. 30 min THF (100 ml)	5 2.2 g (53.9%)
5 ^a	6.3	1.2	NaH 0.15	rfx. 30 min THF (50 ml)	4 3.5 g
6 ^a	9.8	2.3	<i>t</i> -BuOK 0.3	0~10°C THF (25 ml)	1 1.0 g (20.3%)
7	12.0	3.0	Triton-B 40% MeOH 0.6	rfx. 80 min THF (420 ml)	1 5.0 g (77.8%)
8	5.0	2.0	KOH 0.2 ^c	rfx. 120 min THF (100 ml)	1 0.5 g (11.7%)
9	12.0	3.0	50% KOH aq. ^d soln. 2.0	rfx. 180 min THF (20 ml)	1 2.0 g (31.1%)

azeo. rfx = azeotropic reflux.

^a Expts. 1, 2 and 3, 5, 6 were carried out according to the procedures reported by BASF^{5d)} and Beereboom,^{5b)} respectively.

^b 3-Ketobutanol was used instead of 3.

^c Dibenzo-18-crown-6-polyether (0.3 g) in benzene (10 ml) was added.

^d Benzyltriethylammonium chloride (0.6 g) was used as phase transfer catalyst.

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