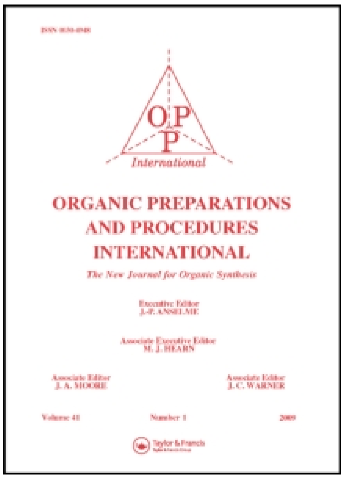

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A NEW IMPROVED SYNTHESIS OF β-PHORONE

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A NEW IMPROVED SYNTHESIS OF β-PHORONE

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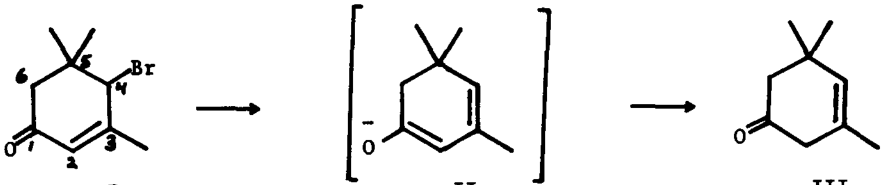
β-Phorone (III), available by the action of methylmagnesium bromide and ferric chloride on isophorone[1,2] has proved to be a valuable intermediate for the synthesis of carotenoids and related natural products,[3] since it has functionality at the difficulty-accessible 4-position. The original synthesis is difficult to duplicate. Recent improvements[2] allow III to be prepared reproducibly in 50-55% yields but at least seven other volatile products (vpc) are formed. The major contaminant is isophorone, produced either in the reaction or by subsequent isomerization of III.

We have reported[4] some chemistry of 4-bromoisophorone (I), the only other 4-substituted product readily available[5] from isophorone.[6] Although nucleophiles attack I with rearrangement,[4] we have found that reduction of I with buffered chromous acetate gives β-phorone (III) instantly as the major product. This reduction, which must proceed through the dienolate II, gives a 5:1 ratio of β-phorone and isophorone as the only products, from which β-phorone can be obtained in ca 70% yield by careful distillation. This ratio seems to represent the kinetically-controlled ratio of protonation of the enolate II at the 2- and 4-positions respectively,



I II III

since in a number of experiments under varying conditions, it was often obtained but never surpassed, either by reduction of 4-bromoisophorone by $Cr(OAc)_2$ or $CrCl_2$, or by the Grignard deconjugation of isophorone.

A number of other methods to generate III failed.[7] These included treatment of isophorone with NaH and then acid, and hydrolysis of the mixture of dienamines[6a] or dienol acetates[6b] derivable from isophorone.

The $Cr(OAc)_2$ reduction of I thus represents a marked improvement over the original synthesis of the rather unstable β-phorone since it proceeds from a stable crystalline precursor in a much cleaner reaction. For the synthesis of 4-hydroxyisophorone and related compounds,[3] the reaction mixture need not be purified until later stages, since isophorone is inert to the epoxidation reaction normally used.

After this work was complete, a new route to β-phorone appeared.[8] This involves displacement of the base-catalyzed equilibrium between β-phorone and isophorone by slow distillation of the β-phorone, and is reported to give essentially pure β-phorone. However, in our experience, much patience is required to optimize conditions to get β-phorone in reasonable purity; in addition, the yield is low, since most of the isophorone is converted into non-volatile products. Thus, for convenience and reproducibility, the present method is superior to existing syntheses of β-phorone.

EXPERIMENTAL

To a stirred suspension of 128.0 of Zn and 7.6 g of HgO in 150 ml of H_2O in a three necked flask was added 24 ml of conc. HCl. After 5 min, the amalgamated Zn was washed several times with H_2O by decanting, then the flask was fitted with two dropping funnels and a nitrogen inlet to the bottom of the flask. The system was flushed with N_2, then 64.0 g of $CrCl_3 \cdot 6H_2O$ in 250 ml of H_2O was added.[9] After 15 min, 48.0 g of NaOAc in

150 ml of H_2O was added to the bright blue solution and the mixture cooled in an ice bath. Then 20.00 g of 4-bromoisophorone (obtained in 66% yield by the method of Edgar, Harper and Kazi,[5] but using 1.1 eq of NBS) in 100 ml of acetone was added to the red mixture during 2 min, stirring was continued 1 min further, then the blue-green mixture decanted and the Zn residue washed twice with petroleum ether (40-60°). The aqueous layer was washed twice with petroleum ether, then all fractions were combined and washed twice with water and the solvent removed to give 11.12 g (90%) of a an oil showing a 5:1 ratio of β-phorone : isophorone by vpc (5% SE-30 on chromasorb G at 100°) or by nmr. No other products could be detected. Careful distillation through a vacuum-jacketed Vigreux column gave 8.91 g (70%) of β-phorone of ca. 98% purity, $bp_{0.2}$ 32-35° and 1.72 of isophorone, $bp_{0.2}$ 45-47°. Redistillation gave a sample with no detectable impurities.

In another run on a small scale, the chromous chloride was made as above, then transferred by syringe to a 10 ml Erlenmeyer flask filled with N_2 protected by a septum. A layer of petroleum ether was placed over the reagent, then an acetone solution of 4-bromoisophorone was injected into the aqueous phase by syringe, the flask immediately shaken once, the layers allowed to separate, and the organic layer withdrawn and analyzed. Contact time was estimated at not over 5-10 sec, but the ratio of β-phorone to isophorone was 5:1.

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