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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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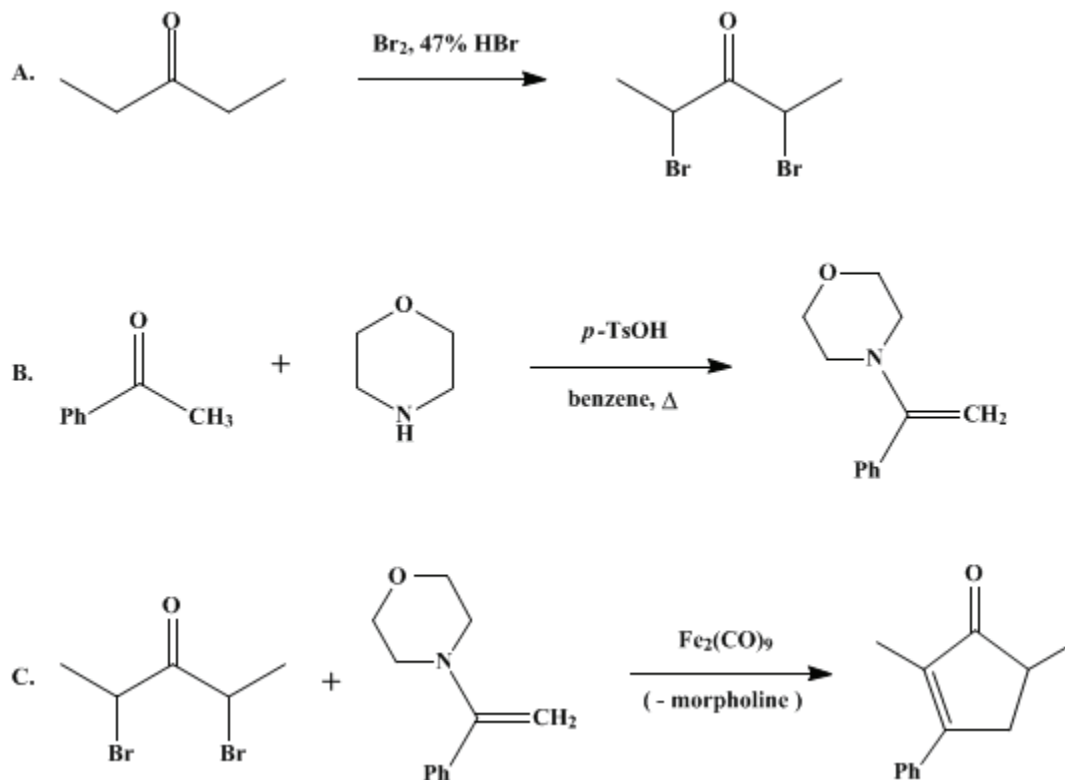
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.520 (1988); Vol. 58, p.56 (1978).

CYCLOPENTENONES FROM α,α' -DIBROMOKETONES AND ENAMINES: 2,5-DIMETHYL-3-PHENYL-2-CYCLOPENTEN-1-ONE

[2-Cyclopenten-1-one, 2,5-dimethyl-3-phenyl-]



Submitted by R. Noyori¹, K. Yokoyama, and Y. Hayakawa.

Checked by Michael J. Haire and William A. Sheppard.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required. The reaction in Part C should be carried out in a well-ventilated hood because iron carbonyls are highly toxic.

A. *2,4-Dibromo-3-pentanone* (**1**). A 300-ml., three-necked, round-bottomed flask equipped with a magnetic stirrer, a thermometer, and a 125-ml., pressure-equalizing dropping funnel, connected to a trap for absorbing hydrogen bromide evolved during the reaction (Note 1), is charged with 43.0 g. (0.500 mole) of diethyl ketone and 100 ml. of 47% hydrobromic acid. The dropping funnel is charged with 160 g. (1.00 mole) of bromine, which is added with stirring over a 1-hour period, causing the temperature of the reaction mixture to increase to 50–60°. After addition is complete, stirring is continued for an additional 10 minutes, before 100 ml. of water is added to the reaction mixture. The separated heavy organic layer is washed with 30 ml. of saturated aqueous sodium bisulfite. The brownish organic solution is dried over calcium chloride and distilled under reduced pressure through a 15-cm. vacuum-jacketed Vigreux column, yielding 85.2–92.5 g. (70–76%) of 2,4-dibromo-3-pentanone (**1**) (Note 2), b.p. 51–57° (3 mm.), as a slightly yellow liquid.

B. *α -Morpholinostyrene* (**2**). A mixture of 75.0 g. (0.625 mole) of acetophenone, 81.0 g. (0.930

mole) of [morpholine](#) (Note 3), 200 mg. of [p-toluenesulfonic acid](#), and 250 ml. of [benzene](#) is placed in a 500-ml., round-bottomed flask equipped with a water separator (Note 4), under a reflux condenser protected by a calcium chloride drying tube. Separation of water begins with reflux and is complete after 180 hours. After the mixture is cooled to room temperature, 200 mg. of [sodium ethoxide](#) is added to remove [p-toluenesulfonic acid](#), and the mixture is concentrated with a vacuum rotary evaporator (50°, 80–100 mm.). The crude oily product is distilled under reduced pressure through a 15-cm. vacuum-jacketed Vigreux column. After 40–50 ml. of a mixture of [morpholine](#) and [acetophenone](#) is recovered as a forerun at 40–90° (20 mm.), 67.5–75.4 g. (57–64%) of [α-morpholinostyrene](#) is collected as a pale yellow liquid, b.p. 85–90° (0.03 mm.) (Note 5).

C. [2,5-Dimethyl-3-phenyl-2-cyclopenten-1-one](#) (3). A 1-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a rubber septum, and a bubbler filled with liquid paraffin is charged with 40.0 g. (0.110 mole) of diiron nonacarbonyl (Note 6) and 250 ml. of dry [benzene](#) (Note 7). The system is flushed with [nitrogen](#), and 56.8 g. (0.300 mole) of [α-morpholinostyrene](#) (Note 8) and 24.4 g. (0.100 mole) of [2,4-dibromo-3-pentanone](#) (1) are injected by syringe through the rubber septum. The flask is immersed in a 32° bath, and the reaction mixture is stirred under a [nitrogen](#) atmosphere (Note 9). After 20 hours 230 g. of silica gel (Note 10) and 100 ml. of [benzene](#) are added. The resulting slurry is stirred at 32° for an additional 2.5 hours (Note 11). The whole mixture is poured onto a silica gel pad (Note 10) and (Note 12) with the aid of 200 ml. of [diethyl ether](#), and the pad is washed with 1 l. of [ether](#) (Note 13) and (Note 14). The combined organic solutions are concentrated on a vacuum rotary evaporator (Note 13), giving 35–45 g. of the desired cyclopentenone 3, a brown oil contaminated by [acetophenone](#) formed by decomposition of the excess enamine. The oil is distilled under reduced pressure with a short-path distillation apparatus (Note 15). The forerun of 20–25 g., b.p. 35–50° (0.1 mm.), is recovered [acetophenone](#). At 100–105° (0.02 mm.), 12.0–12.4 g. [64–67% yield (Note 14)] of cyclopentenone 3 is obtained as a pale yellow oil, which crystallizes on cooling with ice water. Recrystallization from [hexane](#) gives an analytical sample as colorless needles, m.p. 57–59° (Note 16).

2. Notes

1. See [Figure 7](#) in *Org. Synth.*, **Coll. Vol. 1**, 95 (1941).
2. The submitter reported a yield of 116 g. (95%). Care should be taken to prevent the dibromoketone from coming into contact with the skin; allergic reactions have been observed in several cases. Also, the checkers found the crude product to have lachrymatory properties. Immediate use after distillation is recommended if high yield is to be obtained in the next step.
3. An excess of [morpholine](#) is required because a considerable amount is lost with the water that separates during the reaction.
4. See [Figure 12](#) in *Org. Synth.*, **Coll. Vol. 3**, 381 (1955).
5. The distilled product is 97% pure and contaminated with 3% [acetophenone](#) (NMR analysis). Since the enamine is easily hydrolyzed and deteriorates on long standing, use of a freshly-distilled material is recommended. The checkers found that [α-morpholinostyrene](#) contaminated with 20% [acetophenone](#) could be used for the next step without any significant reduction in yield.
6. Diiron nonacarbonyl is available from Alpha Inorganics, Inc., or Strem Chemicals, Inc. The submitters made the complex through photolysis of [iron pentacarbonyl](#) by the method of King.² Procedures for preparation are also given by Braye and Hübel,³ who use the name diiron enneacarbonyl.
7. The submitters used [benzene](#) distilled from [lithium aluminum hydride](#), but the checkers used ACS-grade [benzene](#) as well as [benzene](#) distilled from [lithium aluminum hydride](#), with no significant change in yield.
8. The submitters obtained a markedly lower yield of product when an excess of the enamine was not used.
9. Evolution of [carbon monoxide](#) begins a few minutes after mixing the starting materials, continuing for *ca.* 3 hours. Cessation of gas evolution does not necessarily mean completion of the cyclocoupling reaction.
10. The submitters used Merck Kieselgel 60 (70–230 mesh ASTM).
11. This procedure is for elimination of [morpholine](#) from the labile primary product, [2,5-dimethyl-3-morpholino-3-phenylcyclopentanone](#).
12. The 150 g. of silica gel is packed in a 13 (diameter) × 12-cm. (length) glass filter.
13. The filter cake and the distillate must be treated with [nitric acid](#) to decompose the contaminants of

iron carbonyl complexes. This treatment should be done very carefully in a well-ventilated hood, because carbon monoxide is evolved vigorously.

14. The submitters reported a yield of 14.8–15.6 g. (80–84%) based on the starting dibromide. The submitters report that the cyclopentenone product seems to absorb on silica gel, and 1 l. of ether is required to attain complete extraction. A smaller quantity of ether wash was used by the checkers. ¹H NMR analysis of the crude mixture before distillation indicated the formation of the cyclopentenone **3** in 83–87% yield.

15. See Figure 2 in *Org. Synth., Coll. Vol. 6*, 436 (1988).

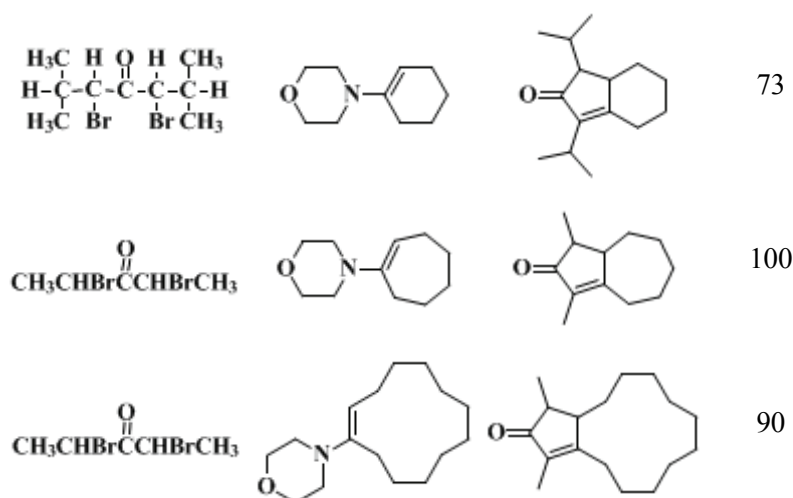
16. The spectral properties of pure product are as follows: IR (CCl₄) cm⁻¹: 1696 (conjugated C=O) and 1626 (conjugated C=C); UV (C₂H₅OH) nm. max. (ε): 220 (5220) and 279 (11,200); ¹H NMR (CCl₄), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.22 (d, *J* = 7.0, 3H, CHCH₃), 1.91 (t, *J* = 2.0, 3H, vinyl CH₃), 2.1–2.7 (m, 2H, CHCH₃ and a methylene *H cis* to CH₃), 3.14 (d of d of q, *J* = 18, 7.5, and 2.0, 1H, methylene *H trans* to CH₃), and 7.38 (m, 5H, C₆H₅).

3. Discussion

The starting materials, 2,4-dibromo-3-pentanone⁴ and α-morpholinostyrene,⁵ have been prepared in satisfactory yields by modifying known procedures. The procedure for the 3 + 2 → 5 cyclocoupling reaction is essentially that described originally by the submitters.⁶ The main advantages of this procedure are the directness, the availability of starting materials, and the wide generality for preparation of 2,5-dialkyl-2-cyclopenten-1-ones, as shown in Table I. Enamines derived from aldehydes, open-chain ketones, and cyclic ketones can be employed. The method has been extended to the synthesis of spiro[4.*n*]alkenones and certain azulene derivatives.⁶ A reaction mechanism for the cyclocoupling reaction has been advanced.⁷ The reactive oxyallyl intermediates generated from dibromoketones and iron carbonyls can be trapped efficiently by enamines,⁶ aromatic olefins,⁸ 1,3-dienes,^{9,10} furans,^{10,11} carboxamides,¹² and alkyl 1*H*-pyrrole-1-carboxylates.¹³ Intramolecular trapping of the reactive species by olefin or furan has also been achieved.¹⁴ At present, dibromides of methyl ketones cannot be used as starting materials except in intramolecular cyclocoupling reactions. However, polybromoketones, including α,α,α',α'-tetrabromoacetone, serve as a precursors of the reactive species in certain cases, and the coupling reactions have been applied to various naturally occurring products.^{14,15,16,17,18,19}

TABLE I
IRON CARBONYL-PROMOTED CYCLOPENTENONE SYNTHESIS^a

Dibromide	Enamine	Product ^b	Yield (%) ^c
$\text{CH}_3\text{CHBrC(=O)CHBrCH}_3$			79
$\begin{array}{ccccccc} \text{H}_3\text{C} & \text{H} & \text{O} & \text{H} & \text{CH}_3 & & \\ & & & & & & \\ \text{H}-\text{C}-\text{C}-\text{C}-\text{C}-\text{C}-\text{H} & & & & & & \\ & & & & & & \\ \text{H}_3\text{C} & \text{Br} & & \text{Br} & \text{CH}_3 & & \end{array}$			72
$\text{CH}_3\text{CHBrC(=O)CHBrCH}_3$			74
$\text{CH}_3\text{CHBrC(=O)CHBrCH}_3$			100



^aReference ⁶.

^bA mixture of epimers, when possible, is obtained.

^cIsolated yield based on starting dibromide.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

silica gel

Diiron nonacarbonyl

$\alpha,\alpha,\alpha',\alpha'$ -tetrabromoacetone

calcium chloride (10043-52-4)

Benzene (71-43-2)

ether,
diethyl ether (60-29-7)

carbon monoxide (630-08-0)

nitric acid (7697-37-2)

HYDROBROMIC ACID,
hydrogen bromide (10035-10-6)

bromine (7726-95-6)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

Acetophenone (98-86-2)

sodium ethoxide (141-52-6)

Furan (110-00-9)

diethyl ketone (96-22-0)

lithium aluminum hydride (16853-85-3)

morpholine (110-91-8)

hexane (110-54-3)

iron pentacarbonyl

p-toluenesulfonic acid (104-15-4)

2,5-Dimethyl-3-phenyl-2-cyclopenten-1-one,

2-Cyclopenten-1-one, 2,5-dimethyl-3-phenyl- (36461-43-5)

2,4-Dibromo-3-pentanone (815-60-1)

α -morpholinostyrene (7196-01-2)

2,5-dimethyl-3-morpholino-3-phenylcyclopentanone

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