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Working with Hazardous Chemicals

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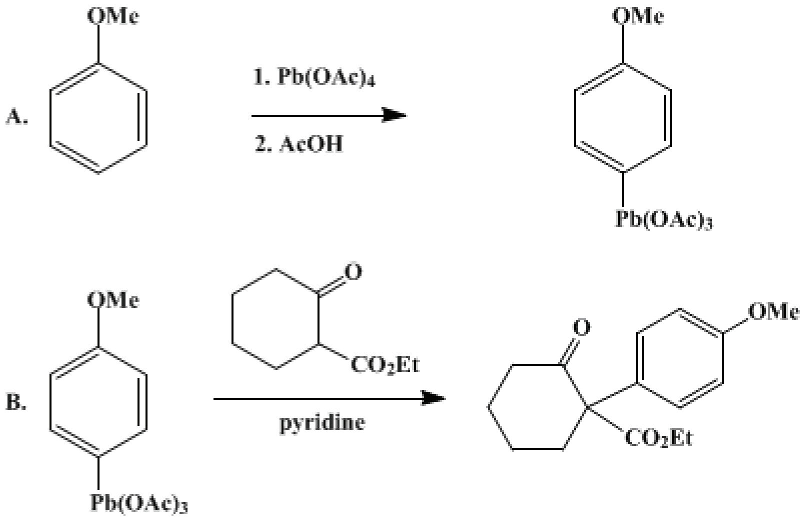
THE *C*-ARYLATION OF β-DICARBONYL COMPOUNDS: ETHYL 1-(*p*-METHOXYPHENYL)-2-OXOCYCLOHEXANECARBOXYLATE



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1. Procedure

A. *p-Methoxyphenyllead triacetate*. A 1-L Erlenmeyer flask, equipped with a magnetic stirring bar, is charged with 50 g (0.11 mol) of lead tetraacetate (Note 1), chloroform (200 mL), and 140 g (1.09 mol) of dichloroacetic acid (Note 2). To this solution is added 16 g (0.15 mol) of anisole (Note 3), and the mixture is stirred at 25°C until lead tetraacetate can no longer be detected (Note 4). The reaction mixture is washed with water (2 × 250 mL) and the chloroform solution is treated with 1.5 L of hexane (Note 5). The yellow precipitate (44 g) is collected by suction filtration and stirred with a mixture of glacial acetic acid (250 mL) and chloroform (200 mL) for 1 hr.

The chloroform solution is washed with water (2 × 250 mL) and stirred with glacial acetic acid (250 mL) for 1 hr (Note 6). The solution that results is washed with water (2 × 250 mL), and the chloroform phase is treated with 1.5 L of hexane and kept at 2°C for 48 hr. The material that precipitates is collected and dried at 0.1 mm in a desiccator (calcium chloride) for 5 hr to give *p*-methoxyphenyllead triacetate (20–22 g, 35–40%) as pale-yellow crystals, mp 138–139°C (Note 7). The product may be kept for at least 3 weeks if stored at 2°C in a sealed container.

B. *Ethyl 1-(p-methoxyphenyl)-2-oxocyclohexanecarboxylate*. A 250-mL, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 22.2 g (45 mmol) of p-methoxyphenyllead triacetate, 10.8 g (135 mmol) of pyridine (Note 8), and 70 mL of chloroform (Note 9). To this solution is added 7.0 g (41 mmol) of ethyl 2-oxocyclohexanecarboxylate (Note 10), a calcium chloride drying tube is put in place, and the mixture is stirred at 40°C (Note 11).

After 24 hr, the reaction mixture is diluted with chloroform (80 mL), and washed with water (150 mL) and 3 *M* sulfuric acid (2 × 150 mL). The water and sulfuric acid washings are each washed (Note 12) with 100 mL of chloroform. The combined chloroform extracts are washed with water (2 × 250 mL), dried with magnesium sulfate, and the solvent removed to give an orange–colored oil (10.3 g) that slowly crystallizes on standing. Crystallization from hexane (Note 5) gives 9.4 g (82%) of ethyl 1-(*p*-methoxyphenyl)-2-oxocyclohexanecarboxylate, mp 49–50°C.

2. Notes

1. Lead tetraacetate from Merck & Company, Inc. was used. Acetic acid was removed from the reagent at 0.1 mm for 24 hr, in the dark, in a desiccator containing potassium hydroxide pellets.
2. Dichloroacetic acid from Merck & Company, Inc. was used without further purification.
3. Anisole from Fluka AG was distilled before use.
4. A few drops of reaction mixture were shaken with water. A brown precipitate of PbO_2 indicates the presence of unreacted lead tetraacetate. For the quantities given, a reaction time of 1 hr at 15–20°C is adequate.
5. Hexanes, bp 60–69°C, certified by Fisher Scientific Company were used.
6. A second metathesis with glacial acetic acid is carried out to ensure complete conversion of the oligomer into the product.
7. It has been found that the yield of product is generally higher when the reaction is performed on a smaller scale. Reactions carried out on approximately one-third of the above scale have given yields of approximately 60%.
8. Pyridine from Merck & Company, Inc. was distilled and stored over potassium hydroxide pellets.
9. Chloroform was dried over calcium chloride and distilled prior to use.
10. The ethyl 2-oxocyclohexanecarboxylate used was Fluka AG practical grade and was distilled (bp 106–108°C/12 mm) before use.
11. The submitters report that after approximately 1 hr some lead(II) acetate is deposited as an orange–red gum that may temporarily restrict the motion of the stirring bar; this was not observed by the checkers. The material generally crystallizes after a short period as a white solid.
12. These washings are extracted separately in order to minimize formation of solid lead(II) sulfate.

3. Discussion

The procedure described here serves to illustrate a new, general method for effecting the α-arylation of β-dicarbonyl compounds by means of an aryllead triacetate under very mild conditions. Although the first synthesis of an aryllead triacetate was reported relatively recently, a wide range of these compounds can now be readily prepared.[2] The most direct route to these compounds is plumbation of an aromatic compound with lead tetraacetate, and in the procedure reported here *p*-methoxyphenyllead triacetate has been prepared in this way. It may also be obtained by reaction of the diarylmercury[3] or the corresponding aryltrialkylstannane[4] with lead tetraacetate; the latter provides a convenient and very general route to aryllead triacetates.

The first synthesis of *p*-methoxyphenyllead triacetate by direct plumbation was reported by Harvey and Norman,[5] who obtained the compound in 24% yield by heating anisole and lead tetraacetate in acetic acid at 80°C for 4 days. Recently it has been found[2] that a much faster reaction and higher yield of aryllead compounds can be achieved by use of a haloacetic acid in place of acetic acid, and this has allowed the synthesis of a greater range of aryllead triacetates by direct plumbation. The improved reaction rate is presumably due to an increase in electrophilicity of lead when acetate is exchanged for a more electron-withdrawing ligand. The choice of the haloacetic acid depends on the reactivity of the aromatic substrate; thus, while dichloroacetic acid has been found best for the plumbation of anisole, trichloroacetic acid is preferred in the case of toluene and biphenyl.[2]

Aryllead tricarboxylates have been shown to be intermediates in two new routes to phenols,[6], [7] and to have considerable potential as reagents for the *C*-arylation of carbon acids that are more acidic than diethyl malonate. A study of their reactions with β-diketones,[8] β-keto esters,[9] α-hydroxymethylene ketones,[10] derivatives of Meldrum's acid and barbituric acid,[11] and nitroalkanes[12] has established that such compounds, which contain only one replaceable hydrogen, undergo smooth arylation in high yield under the conditions outlined in this procedure. Compounds that contain two replaceable hydrogens are less predictable in their behavior. When a 1 : 1 ratio of substrate to aryllead compound is used, dimedone gave only diarylated product in high yield, while ethyl acetoacetate gave both mono- and diarylated products in only moderate yield.

Recently it has been shown that triphenylbismuth carbonate[13] and pentaphenyl-bismuth[14] can be used to achieve a similar arylation of β-dicarbonyl compounds. These reagents also react under very mild conditions and yields are generally high. Prior to the introduction of the organolead and organobismuth reagents, the most promising procedure for arylation of β-dicarbonyl compounds involved reaction of the enolate anion with a diaryliodonium salt, usually at 80–100°C.[15] Although only a limited range of substrates has been examined, it would appear that yields are only moderate, and in the case of dimedone a mixture of mono-, di-, and *O*-arylated products is produced. A further method, which has obvious limitations, involves the copper-catalyzed substitution of bromine in 2-bromobenzoic acids by the enolate anion of a β-dicarbonyl compound.[16]

References and Notes

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

PbO_2

haloacetic acid

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

bromine (7726-95-6)

Anisole (100-66-3)

pyridine (110-86-1)

potassium hydroxide pellets (1310-58-3)

toluene (108-88-3)

lead(II) acetate

Biphenyl (92-52-4)

Ethyl acetoacetate (141-97-9)

diethyl malonate (105-53-3)

dichloroacetic acid (79-43-6)

magnesium sulfate (7487-88-9)

Barbituric acid (67-52-7)

trichloroacetic acid (76-03-9)

dimedone (126-81-8)

ethyl 2-oxocyclohexanecarboxylate (1655-07-8)

hexane (110-54-3)

p-Methoxyphenyllead triacetate (18649-43-9)

lead(II) sulfate (7446-14-2)

triphenylbismuth carbonate

pentaphenyl-bismuth

ETHYL 1-(p-METHOXYPHENYL)-2-OXOCYCLOHEXANECARBOXYLATE (95793-86-5)

lead tetraacetate (546-67-8)