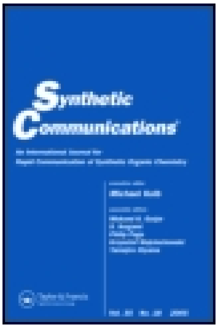

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A New Synthesis for Methyl 2-Benzyloxylphenylacetate

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A NEW SYNTHESIS FOR METHYL 2-BENZYLOXYLPHENYLACETATE

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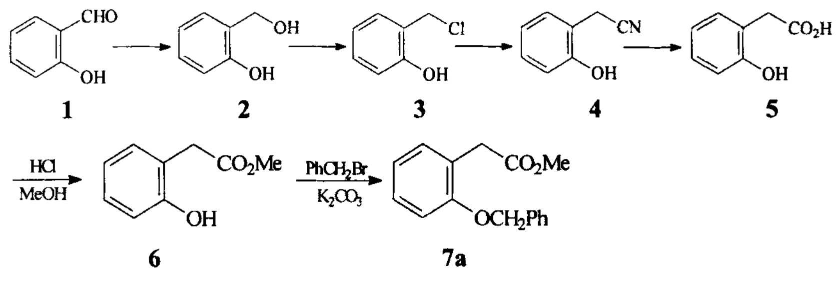
Abstract: A new synthetic method for methyl 2-benzyloxylphenylacetate, a key intermediate of a new type of fungicides, had been found, which has only 3 steps. The 80% yield of the new method is a major improvement over the 30% 6-step-process reported by the literature.

The antibiotic Strobilurin A was discovered by Anke in 1977[1], and developed to a new type of fungicides[2] with high fungicidic activities and a large antibiotic spectrum. ICIA5504 was one of these new fungicides.

In the synthesis of ICIA5504, the preparation of methyl 2-benzyloxylphenylacetate(**7a**), was critical. From salicylaldehyde (**1**), Godfrey[3] synthesized **7a** in 6 steps(scheme 1).



Scheme 1

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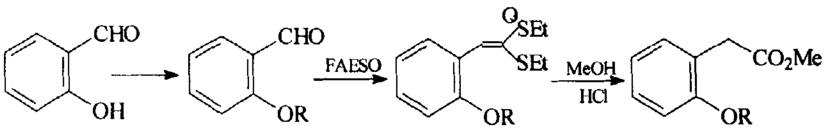
Levine[4] synthesized **6** also from salicylaldehyde in 5 steps (overall yield 59%). Barnes[5] synthesized **7a** from 2-nitrotoluene in 5 steps with an overall yield of about 1%. King[6] used 2'-hydroxylacetophenone as starting material to synthesize **7a** in 2 steps, but with a low yield. Ott[7] used the same expensive starting material to synthesize **7a** in 2 steps with a crude yield of 81%. Low yield, numbers of synthetic steps, or expensive materials, are the major disadvantages.

We used salicylaldehyde as the starting material to synthesize **7a** in only 3 steps, with a total yield of 77%. In this method, the conditions to prepare **8a** are improved also, the yield of which was increased to 91% from 63% reported by Horaguchi[8](scheme 2).



1 **8a,b** **9a,b** **7a,b**

a: R=CH_2Ph
b: R=CH_3

Scheme 2

Methyl 2-methoxylphenylacetate (**7b**) was prepared in the same method starting from anisaldehyde (**8b**: R=Me).

The reported preparations of **7b** were from 2-methoxylpheylacetic acid[9] and 2-methoxylacetophenone[10-13]. They had the same shortcomings as cited above for **7a**.

Experimental section:

All melting points were determined on a micromelting-point apparatus and were uncorrected. Elemental analysis data were obtained by use of a Yanaco CHN Corder MR-3 apparus. ^{1}H NMR spectra were recorded on a Bruker AC-P200(200MHz) Spectrometer using tetramethylsilane(TMS) as an internal standard and $CDCl_3$ as the solvent. Mass spectra were recorded on a Hewlett-packard 5988 instrument.

Preparation of compound **8a**:

A mixture of salicylaldehyde (65.0 g, 0.50 mol), benzylbromide (85.5 g, 0.50 mol), anhydrous potassium carbonate (75.0 g, 0.55 mol) and 500 mL of dry acetone was blanketed with nitrogen, stirred, and heated to reflux for 2 hours. After cooling, the mixture was filtered. After distillation of the filtrate, 96.6 g of a yellow liquid ($bp_{0.5}$: 156-158℃) was obtained, which solidified on standing (yield=91%), mp: 45-47℃ (petroleum)(literature[9]: mp: 44-46℃, yield=63%).

Preparation of compound **9a**:

The solution of FAESO[14] (38.6 g, 0.18 mol) in 50mL of dry THF was added dropwise slowly into a mixture of **8a** (23.1 g, 0.18 mol), sodium hydride (80%, 7.0 g, 0.23 mol) and 100 mL of dry THF cooled by an ice-salt bath. After the addition, the reaction mixture was stirred at room temperature overnight, and neutralized with 4N HCl to pH=2. After the addition of 100 mL of water, the mixture was extracted with ether (50 mL × 3). The combined extracts were washed with water (50 mL × 3), and dried with $MgSO_4$. After evaporation of the solvent, 59.1 g of a yellow thick liquid was obtained by flash column chromatography (petroleum/ethyl acetate=4:1), yield=95%.

Calcd. for $C_{19}H_{22}O_2S_2$: C, 65.86%; H, 6.40%;
Found: C, 65.43%; H, 6.43%
^{1}H NMR(ppm): 1.20(dt, 6H), 2.6-3.2(m, 4H), 5.12(s, 2H), 6.8-8.2(m, 10H)
MS(m/z): 302(M-44), 269, 240, 207, 91
Compound **9b** was prepared in an analogous manner, yield=90%.
Calcd. for $C_{13}H_{18}O_2S_2$: C, 57.74%; H, 6.71%
Found: C, 57.46%; H, 6.67%
^{1}H NMR(ppm): 1.1-1.3(m, 6H), 2.6-3.2(m, 4H), 3.83(s, 3H), 6.9-8.1(m, 5H)
MS(m/z): 242(M-28), 225(M-44), 194, 164, 131, 107

Preparation of compound **7a**:

Under stirring, dry HCl was vigorously bubbled into a solution of **9a** (10.0 g, 28.6 mmol) in 80 mL of anhydrous methanol. When the temperature of the reaction mixture dropped to 60℃, the mixture was poured into 300 mL ice-water and extracted with ether (100 mL × 3). The combined ether was washed with water (50 mL × 3), dried with $MgSO_4$. After evaporation of the solvent, 7.3 g of a pale yellow liquid was obtained by flash column chromatography (petroleum/ethyl acetate=10:1), yield=90%.

^{1}H NMR(ppm): 3.62(s, 3H), 3.68(s, 2H), 5.06(s, 2H), 6.8-7.5(m, 9H)
Compound **7b** was prepared in an analogous manner, yield =80%.
^{1}H NMR(ppm): 2.26(s, 3H), 3.82(s, 3H), 3.86(s, 2H), 6.76-7.44(m, 4H)
MS(m/z): 180(M^+), 149, 133, 121, 107, 91

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