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A PRACTICAL SYNTHESIS OF 6-ACETYLSALICYLIC ACID METHYL ESTER

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ABSTRACT: A new and efficient synthesis of the title compound is reported. The method includes a regioselective ortho-lithiation step in none polar solvents at an ambient temperature and the overall yield for 5 steps is more than 70% from a commercially available 3-hydroxyacetophenone.

In the course of our research programme on the development of new herbicide **1** (KIH-6127),[1] large quantities of methyl 2-hydroxy-6-[(N-methoxyimino)ethyl]-benzoate (**2**), which holds a pivotal position as a key intermediate for **1**, has been required. Although **2** seems to be prepared from methyl 1-hydroxy-6-acetylbenzoate (**3**) with O-methylhydroxylamine hydrochloride ($MeONH_2 \cdot HCl$) or sulfate, an efficient synthetic method for **3** has been less studied. A previous

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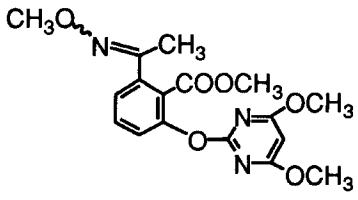
investigation aimed at the synthesis of **3** from 3-nitrophthalic anhydride has been undergone in an unacceptable yield.[2] Lithiation of (arene)chromium tricarbonyl complexes, followed by carbonylation with methyl chloroformate, gave a mixture of 2- and 4-methoxycarbonylated products.[3]

Although we have recently developed a novel route to **2**,[4] we have subsequently discovered a new, extremely concise and efficient route which affords pure **3** excluded cyclic byproduct (vide infra), the details of which are reported here. The method described in this article is operationally simple and gives excellent yield of **3**, and is applicable to an industrial scale synthesis (more than hundreds kilogram scales) without use of column chromatography.



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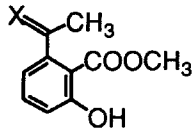


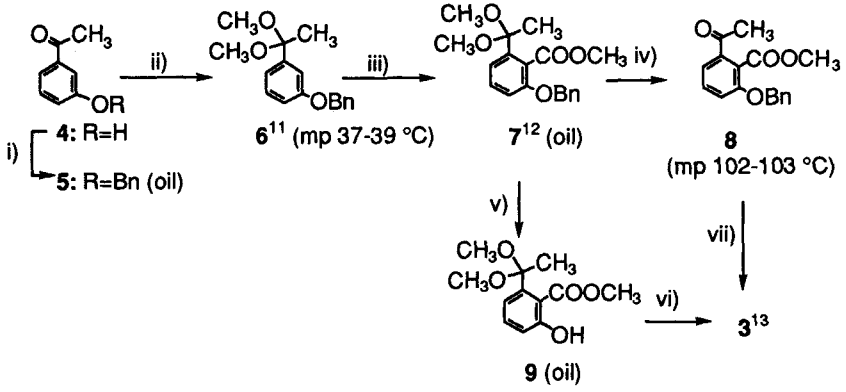
2: X=N-OCH_3

3: X=O

Our synthetic approach toward **3** is derived, conceptually,[5] from the regioselective ortho-lithiation of protected 3-hydroxyacetophenone (**6**) as a key step. Though the ortho-lithiation of **6** should be highly anticipated to afford **7** selectively, the prime concern was to avoid *cryogenic reaction* and use of *etherial solvents* from an industrial viewpoint.

The explored synthetic scheme commences with protection of the hydroxy group of 3-hydroxyacetophenone (**4**). Thus, benzylation of commercially available

4 using solid-liquid phase-transfer technique[6] gave the benzyl ether **5** in an almost quantitative yield. The chlorobenzene solution of **5**, without separation, was treated with trimethoxymethane (1.2 equiv) in the presence of methanesulfonic acid (0.01 equiv) plus anhydrous sodium sulfate (0.01 equiv) and methanol (6 equiv) in toluene,[7] giving the dimethylacetal derivative **6** in high yield. (>95%)



i) NaOH (1.1 equiv), Bu_4NBr (0.05 equiv) in C_6H_5Cl, 75 °C, 3h; then BnCl (1.05 equiv), 2 h.
ii) CH_3OH (6 equiv), CH_3SO_3H (0.01 equiv), Na_2SO_4 (0.01 equiv), $CH(OCH_3)_3$ (1.2 equiv) in toluene, rt, 3h.
iii) 20% BuLi in c-Hexane (1.1 equiv), rt, 3 h; then $ClCOOCH_3$ (1.1 equiv) was slow added at 10 °C for 3 h.
iv) HCl (0.005 equiv) in CH_3OH, 30 °C, 4 h.
v) 1 atm H_2 in toluene, Pd/C, rt, 5 h.
vi) HCl (0.03 equiv) in CH_3OH, rt, 2 h.
vii) 1 atm H_2 in EtOAc, Pd/C, rt, 20 h.

With a large quantity of **6** in hand, we next attempted directed ortho-lithiation of **6**, followed by carbonylation, to give 2-carbomethoxy product **7**. In ether, the lithium salt of **6** seems to be quite unstable at an ambient temperature, in which case very poor yield of **7** was obtained. After several unsuccessful attempts, it was finally found that the reaction of **7** with n-butyllithium at *room temperature* in *none*

polar solvents such as toluene, hexane, and cyclohexane affords the promising results.[8] Among them, a reaction at room temperature in cyclohexane gave the most satisfactory result to give the desired **7**. Thus, the reaction of **6** with 20% cyclohexane solution of n-butyllithium (1.1 equiv) in cyclohexane (rt, 3 h) afforded the lithium salt of **6**. Without isolation, the lithium salt was treated with methyl chloroformate (1.1 equiv) at 10 ℃, to give **7** in 83% yield (GC) after quenching with water. This was selectively deacetallized under very mild acid condition[9] (0.5% HCl, 0.005 equiv in methanol, 30 ℃, 4 h) to give the corresponding ketone **8** as a sole product, mp 102-103 ℃, in 71.3% overall yield from **4**.[10] The results for the ortho-lithiation step were summarized in Table. No formation of the regioisomer of **7** was definitely ascertained by GC-MS analysis of the crude product. Debenzylation of **8** (H_2, Pd/C) afforded the title compound **3** in 95% yield, mp 97-98 ℃ (lit.,[2] mp 96-97 ℃).

Table. Lithiation of **6** in various solvent systems[a)]

Solvent	n-BuLi	GC Composition **6** : **7**
Hexane	15% hexane soln	24 : 60
Toluene	15% hexane soln	16 : 73
cyclohexane	15% hexane soln	6 : 83
cyclohexane	20% cyclohexane soln	3 : 86
cyclohexane	20% cyclohexane soln[b)]	35 : 13[c)]
ether	15% hexane soln	15 : 2[d)]

a) **6**: n-BuLi: $ClCOOCH_3$ = 1: 1.1: 1.1. b) TMEDA (1.1 equiv) was added. c) 3-Benzyloxyphenylacetylene was obtained in 34% yield. d) The remainder was a complex mixture.

An alternative route from **7** to **3** *via* **9** was also succeeded. The resulting **3**, mp 96-99 ℃, was completely identical by the comparison of the NMR and IR spectrum with the above sample.

In conclusion, we have succeeded in disclosing a new synthetic route to **3**, which has made feasible a practical synthesis of **1**. Taking into account high regioselectivity observed for the formation of **7** and use of commercially available inexpensive starting material, overall process may hold promise as one of the practical method for preparing **3**.

EXPERIMENTAL

A typical procedure for the preparation of **8** is as follows. A mixture of **4** (162 g, 1.2 mol), 50% Bu_4NBr (38.7 g, 0.06 mol), and NaOH (52.5 g, 1.32 mol) in C_6H_5Cl (720 ml) was stirred at 75 ℃ for 3 h. To the resulting mixture was added benzyl chloride (160 g, 1.26 mol) during 20 min, then the whole mixture was stirred for 2 h and washed with water (720 ml, 2x360 ml). The chlorobenzene solution of **5** was dehydrated by azeotropically distilling the liberated water for 2 h using Dean-Stark apparatus. After cooling to room tempertature, CH_3OH (1.70 g, 0.012 mol) was added to the mixture. To the resulting mixture was added $CH(OCH_3)_3$ (153 g, 1.8 mol) at 15 ℃. After stirring at 20 ℃ for 3 h, the mixture was quenched with 1%NaOH (240 g), and washed with water (2x240 ml). Removal of the solvent gave the crude **6** (323 g, purity 94.1% by GC). To a cyclohaxane (475 ml) solution of the crude **6** (323 g) was added 20% BuLi cyclohexane solution (418 g, 1.3 mol) at 10 ℃, and then the mixture was stirred at

room temperature for 3 h. To the resulting solution cooled again to below 10 ℃, was added methyl chloroformate (124 g, 1.3 mol) at 10 ℃ during 3 h. Then, the reaction mixture was washed with water (475 ml, 2x240 ml) and concentrated to give yellow oil (386.5 g). The GC analysis of the oil revealed that the mixture was consist of 86% of **7** and 3% of **6**. Without purification, a methanol (586 ml) solution of the yellow oil containing **7** (386.5 g) was treaterd with 0.5% HCl (42.6 g, 5.85 mmol) at 30 ℃ for 4 h. After neutrallization with 6% NaOH, the solution was cooled to 5 ℃ to precipitate light yellow crystals of **8**. Yield was 243 g (71.3% yields for 4 steps from **4**), mp 102-103 ℃. Mass: *m/z* 284 (M^+). ^{1}H-NMR ($CDCl_3$): δ 2.56 (s 3H), 3.93 (s, 3H), 5.15 (s, 2H), 7.0-7.6 (m, 8H). IR (KBr): 1730, 1690, 1470, 1275, 1080, 1030, 760 cm^{-1}.

Methyl 1-hydroxy-6-acetylbenzoate (**3**). A mixture of **8** (14.2 g, 50 mmol) and 5% Pd/C (0.71 g) in ethyl acetate (150 ml) was stirred for 20 h under 1 atm of H_2. Filtration and concentration gave **3** (9.11 g, 94%), which was recrystallized from toluene (30 ml) to give the pure **3** (5.44 g) having a mp 97.3-98.2 ℃ (lit.[2] mp 96-97 ℃) (100% purity by GLC). Mass: *m/z* 194 (M^+). ^{1}H-NMR ($CDCl_3$): δ 2.47 (s 3H), 3.93 (s, 3H), 6.69-7.60 (m, 3H), 10.2-11.3 (brs, 1H). IR (KBr): 3200, 1700, 1590, 1470, 1370, 1300, 1280, 1190, 1120, 1070, 910, 790, 760 cm^{-1}.

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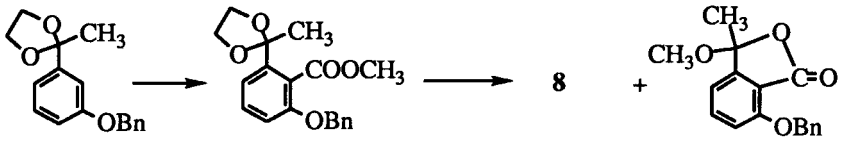
7. The transformation from **5** to **6** in methanol was certainly succeeded. At first, the chlorobenzene solution of **5** was reacted with $CH(OCH_3)_3$ (1.2 equiv) in the presence of p-TsOH·H_2O (0.05 equiv) plus anhydrous Na_2SO_4 (0.05 equiv) in methanol, giving **6** in an almost quantitative yield. The acetal **6** was so fairly unstable that it was decomposed during recovery of methanol. Therefore, the resulting mixture was poured into water to be extracted with ethylacetate, giving **6** in 97% isolated yield. However, a drawback of the method is that large quantities of methanol should be thrown away in waste water in the work-up process, which is never negligible problem in an industrial scale preparation. Accordingly, we explored the revised procedure in the text, which minimized the amount of disposal of methanol.

8. Directing ortho-lithiation in benzene or Et_2O-TMEDA has recently reported: Paquette, L.A. and Schulze, M.M., *Tetrahedron Lett.*, **1993**, *34*, 3235.

9. In the first place, we used ethylene ketal as a protection for the acetyl function of **4**. Regioselective ortho-lithiation and methoxycarbonylation of **10** in toluene underwent to produce **11** in good yield. However, the removal of the ethylene ketal of **11** under acidic conditions (10% HCl in CH_3OH, 0.4 equiv)

tends to a sizable cyclic byproduct **12**[14]. Accordingly, pure **8** could not be isolated without use of column chromatography in this case.



10 **11** **12**

10. In a large scale synthesis (113 Kg of **4**), 79.1% overall yield for 4 steps was performed.
11. IR (KBr): 3000, 2950,1600, 1490, 1430, 1270, 1230, 1050, 1020, 880, 800 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.52 (s, 3H), 3.17 (s, 6H), 5.06 (s, 2H), 6.7-7.6 (m, 9H).
12. IR (neat): 2950, 1740, 1580, 1455, 1270, 1050, 880, 740 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.59 (s, 3H), 3.18 (s, 6H), 3.84 (s, 3H), 5.07 (s, 2H), 6.7-7.6 (m, 8H).
13. IR (KBr): 3200, 1695, 1680, 1580, 1460, 1300, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.54 (s,3H), 4.00 (s, 3H), 6.7-7.6 (m, 3H), 10.75 (s, 1H).
14. Mp 124-126 ℃. IR (KBr): 2930, 1760, 1610, 1480, 1300, 1270, 1190, 1070, 1010, 900, 820, 760, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.78 (s, 3H), 3.07 (s, 3H), 5.32 (s, 2H), 6.94-7.68 (m, 3H).

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