



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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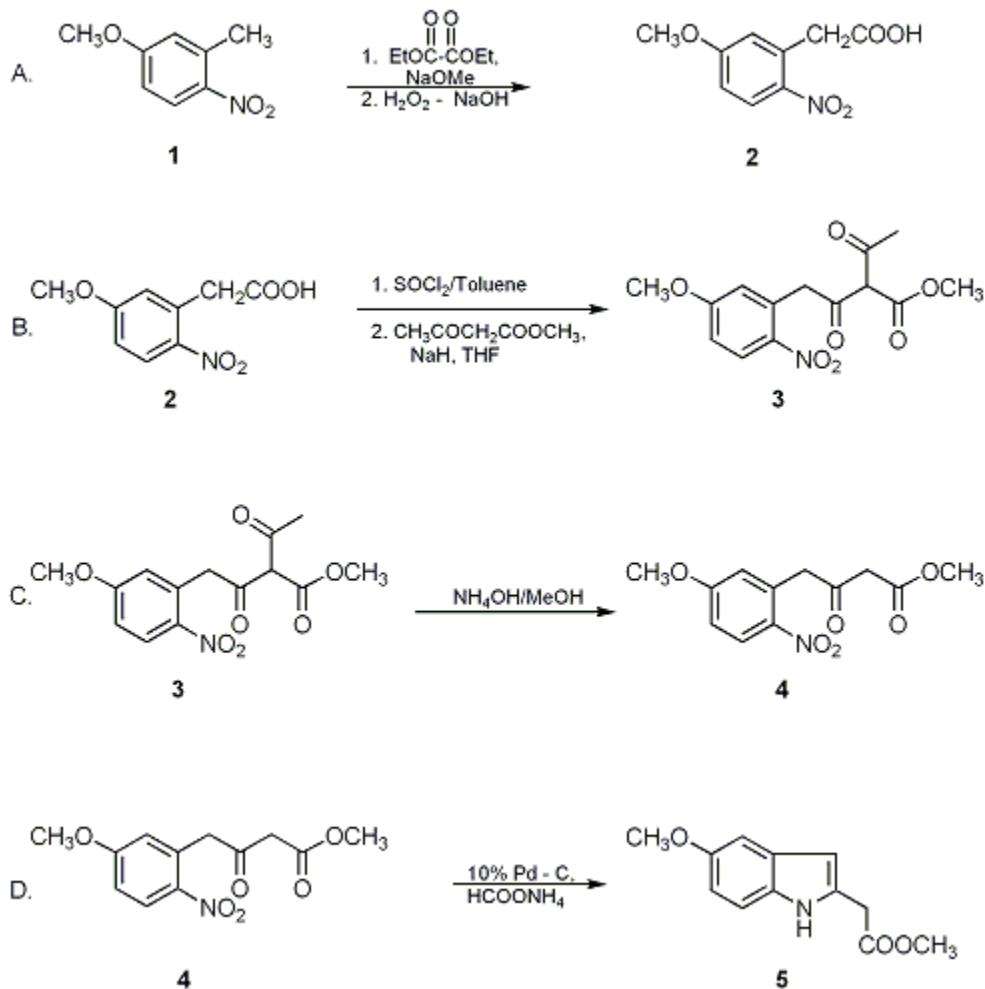
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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INDOLE-2-ACETIC ACID METHYL ESTERS: METHYL 5-METHOXYINDOLE-2-ACETATE

[1H-Indole-2-acetic acid, 5-methoxy-, methyl ester]



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1. Procedure

A. *5-Methoxy-2-nitrophenylacetic acid*, **2**.^{3,4} A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, 50-mL addition funnel, and a reflux condenser fitted with an inert gas (argon) inlet tube that is attached to a mineral oil bubbler. The system is flushed with argon, flame dried, cooled to room temperature, and maintained under a positive pressure of argon. The reaction flask is charged with 18.8 g (0.34 mol) of anhydrous powdered sodium methoxide (Note 1) in 60 mL of anhydrous diethyl ether (Note 2). The flask is cooled in an ice bath and 47.5 mL (0.35 mol) of diethyl oxalate (Note 1) is added over 5 min from the addition funnel. The ice bath is removed and the resulting mixture is stirred at room temperature for 15 min. At the end of this time a pale yellow, thick suspension results, to which 50 g (0.3 mol) of anhydrous powdered 3-methyl-4-nitroanisole, **1**, (Note 1) is added, followed by 75 mL of anhydrous ether (Note 2). The orange-red mixture is heated to reflux for 4 hr. After the flask is cooled to room temperature approximately 1 L of water is added to dissolve the resulting thick orange precipitate (Note 3). The red solution is transferred to a 4-L beaker and kept cold

using an ice-water mixture. Alternate portions of 30% hydrogen peroxide (Note 1) and 10 N sodium hydroxide (Note 4) are added to the cold red solution. Addition of hydrogen peroxide bleaches the solution and addition of sodium hydroxide restores the red color. This procedure is repeated 3 to 4 times until further addition of 10 N sodium hydroxide solution does not result in a color change (Note 5). The yellow brown solid is collected by filtration; it is impure starting material (wt 6–10 g) (Note 6). The filtrate is poured into a 4-L beaker, cooled to 0°C, and acidified with concentrated hydrochloric acid (Note 2) to precipitate 5-methoxy-2-nitrophenylacetic acid. The solid is collected on a Büchner funnel, washed with cold water until the filtrate is neutral, and then dried to give 45.3–48.5 g (70–75%) of an almost colorless product, mp 172–176°C (Note 7). Two recrystallizations in methanol give colorless product, mp 175–176°C (Note 8).

B. *Methyl (5-methoxy-2-nitrophenylacetyl)acetoacetate*, **3** (CAUTION, see (Note 13)). A 2-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, inert gas inlet, and two stoppers is flame dried and cooled to room temperature under an atmosphere of argon. The flask is charged with 42.5 g (0.20 mol) of **2** in 480 mL of anhydrous toluene (Note 2). To the resulting suspension is added 15.3 mL (0.21 mol) of thionyl chloride (Note 9) followed by 2 mL of anhydrous N,N-dimethylformamide (DMF) (Note 2). As soon as the DMF is added the color of the mixture turns light red. The mixture is stirred at room temperature overnight (Note 10). A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, 250-mL pressure-equalizing funnel, and an inert gas inlet is flame dried and allowed to cool to room temperature under argon. The flask is charged with 10.1 g (0.49 mol) of 97% sodium hydride (Note 1) in 280 mL of dry tetrahydrofuran (THF) (Note 11) and then cooled to 0°C in an ice bath. A solution of 45.3 mL (0.42 mol) of methyl acetoacetate (Note 1) in 160 mL of dry THF (Note 11) is placed in the addition funnel and added dropwise to the reaction flask over a period of 45–50 min. After the addition is complete the light gray-colored solution is quickly transferred to a dried, 500-mL addition funnel (Note 12). The funnel is mounted on the flask containing the acid chloride solution. The solution of methyl acetoacetate anion is added to the crude acid chloride solution (Note 13) over 5 min and the resulting mixture is stirred overnight at room temperature. Water (350 mL) is added to the reaction mixture and the mixture is stirred for 15 min before being poured into a 2-L separatory funnel. The layers are separated and the aqueous layer is extracted with ether (2 × 150 mL). The combined organic layers are washed with brine and dried over sodium sulfate (Note 1). The filtered organic layer is concentrated under reduced pressure and the residue is dissolved in 100 mL of methanol. After cooling in the freezer overnight, the yellow crystals that separate are collected and dried to give 34.8–37.3 g (56–60%) of **3** (Note 14), (Note 15), suitable for use in the next step.

C. *Methyl 4-(5-methoxy-2-nitrophenyl)-3-oxobutyrate*, **4**. A 1-L, three-necked flask equipped with a magnetic stirring bar, an inert gas inlet, and a stopper is charged with 25.2 g (0.08 mol) of **3** in 200 mL of reagent grade methanol (Note 2) followed by 20 mL of ammonium hydroxide (Note 2). The beige suspension turns red as soon as ammonium hydroxide is added. After about 15 min a white solid precipitates (Note 16). The mixture is stirred at room temperature for 30 min, filtered and the solid is washed with 10–15 mL of cold methanol. The filtrate is concentrated under reduced pressure and the residue is collected on a filter. This procedure is repeated once more (Note 17). After three filtrations the combined solid weighs 16.3–17.4 g (75–80%), which is suitable for use in the next step. Recrystallization from methanol gives a colorless product (Note 18).

D. *Methyl 5-methoxyindole-2-acetate*, **5**. A flame dried, 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a condenser under argon is charged with 19.6 g (0.07 mol) of **4** followed by 450 mL of anhydrous methanol (Note 2). A slurry of 1.9 g of 10% palladium over activated carbon (Note 1) in 20 mL of anhydrous methanol is added to the flask (Note 19) followed by 53.5 g (0.8 mol) of ammonium formate (Note 1), (Note 20). The reaction mixture is stirred at room temperature for 1 hr (Note 21) and then filtered through a bed of Celite. The Celite is washed with 100 mL of anhydrous methanol and the solvents are removed under reduced pressure to give a beige solid. The residue is triturated with 350 mL of cold water and the insoluble material (Note 22) is filtered and then dried to give 13.5–14.3 g (84–89%) of **5** (Note 23).

2. Notes

1. Sodium methoxide, 3-methyl-4-nitroanisole, diethyl oxalate, 30% hydrogen peroxide, 97% sodium hydride, methyl acetoacetate, sodium sulfate, 10% palladium on activated carbon, ammonium formate, and 5-methoxy-2-nitrophenylacetic acid were purchased from Aldrich Chemical Company, Inc., and were used without further purification.
2. Anhydrous solvents such as diethyl ether, N,N-dimethylformamide, toluene, and methanol were purchased from Mallinckrodt Inc. and were used without further drying. Concentrated hydrochloric acid and ammonium hydroxide were also purchased from Mallinckrodt Inc.
3. Water was added in portions of 300–400 mL each to the reaction flask. The mixture was stirred for 5–10 min and the red solution was decanted into a separate flask. This procedure was repeated until all the solid went into solution.
4. Sodium hydroxide was purchased from Fischer Scientific Company.
5. The total amounts of 30% hydrogen peroxide and 10 N sodium hydroxide used were 60–70 mL and 20–25 mL, respectively.
6. The melting point of the crude compound is 50–60°C; the NMR and IR correspond to starting material.
7. The physical properties are as follows: m.p. 175–176°C (lit value:³ 174–176°C); IR (KBr) cm^{-1} : 3140–2740, 2660, 1715, 1620, 1580, 1510, 1410, 1340, 1320, 1290, 1260, 1200, 1175, 1090, 1040, 955, 850, 830, 760, 710, 630; NMR (DMSO- d_6) δ : 3.86 (s, 3 H, OCH₃), 3.97 (s, 2 H, CH₂), 7.04–7.10 (m, 2 H, H₄, H₆), 8.13 (d, 1 H, J = 8.8, H₃); MS m/e 212 (M+1).
8. It is essential to have compound **2** as a colorless product; otherwise the yield in the next step is poor.
9. Thionyl chloride was purchased from Aldrich Chemical Company, Inc., and distilled prior to use.
10. If a clear solution did not result at the end of 16–18 hr, the mixture was warmed at 35–40°C for 1 hr or until a clear solution resulted; then it was cooled to room temperature.
11. Reagent grade tetrahydrofuran was purchased from Mallinckrodt Inc. and freshly distilled from sodium metal and benzophenone.
12. A 500-mL, pressure-equalizing funnel was oven-dried and then cooled under argon.
13. 5-Methoxy-2-nitrophenylacetyl chloride was never isolated from the reaction mixture. It is known^{5,6} that 2-nitrophenylacetyl chloride is a potentially explosive material, but it is not documented that the 5-methoxy derivative is also hazardous. 5-Methoxy-2-nitrophenylacetyl chloride was also prepared as described by Rosenmund and his co-workers,⁷ and was used in the crude form.
14. Depending on the purity of the starting material, the yield of **3** has been as high as 80%.
15. The analytical sample melted at 78–79°C after crystallization from methanol. The spectra are as follows: IR (KBr) cm^{-1} : 2960, 2850, 1710, 1620–1390, 1350–1250, 1190, 1090, 1035, 950, 910, 890, 840, 760, 730, 630; NMR (CDCl₃) δ : 2.40 (s, 3 H, COCH₃), 3.84 (s, 3 H, COOCH₃), 3.99 (s, 3 H, OCH₃), 4.50 (s, 2 H, CH₂), 6.77 (d, 1 H, J = 2.6, H₆), 6.90 (dd, 1 H, J = 2.8, 9.0, H₄), 8.19 (d, 1 H, J = 9.0, H₃); MS m/e 310 (M+1).
16. If there is no precipitate, a few crystals of starting material **3** are added to the reaction flask to initiate crystallization.
17. After a total of three filtrations, the filtrate contained 5-methoxy-2-nitrophenyl-acetamide and 4-(5-methoxy-2-nitrophenyl)-4-oxobutyramide as the by-products in varying amounts.
18. The physical properties are as follows: mp 85–87°C; IR (KBr) cm^{-1} : 3470, 3130, 2980, 2850, 1710, 1590, 1500, 1440, 1400, 1200, 1065, 1010, 865, 850, 760, 750, 700, 630, 620; NMR (CDCl₃) δ : 3.66 (s, 2 H, CH₂), 3.77 (s, 3 H, COOCH₃), 3.87 (s, 3 H, OCH₃), 4.20 (s, 2 H, ArCH₂), 6.73 (d, 1H, J=2.8, H₆), 6.89 (dd, 1 H, J = 2.8, 9.2, H₄), 8.19 (d, 1 H, J = 9.2, H₃); MS m/e 268 (M+1).
19. Excess ammonium formate was necessary for completion of the reaction.
20. The slurry was prepared by adding ice-cold methanol to 10% palladium on activated charcoal. The slurry was transferred to the reaction flask with a pipet.
21. The reaction was monitored by TLC, using silica gel plates and 2:1 ethyl acetate–hexane.
22. If an oil resulted, it was taken up in ethyl acetate (150 mL) and the two layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL); the organic layers were combined, dried (Na₂SO₄) and concentrated under reduced pressure at 35–40°C to give 12.7–13.5 g (80–85%) of product **5** as an oil that solidifies on cooling in the freezer.
23. The physical properties are as follows: mp 96–98°C; IR (KBr) cm^{-1} : 3370, 3020, 2970, 2840, 1720, 1595, 1485, 1445, 1395, 1330, 1205, 1120, 1035, 1010, 980, 950, 845, 810, 770, 735, 695, 625⁻¹; NMR (CDCl₃) δ : 3.74 (s, 3 H, COOCH₃), 3.82 (s, 2 H, CH₂), 3.83 (s, 3 H, CH₃), 6.27 (d, 1 H, J = 1.0, H₃), 6.81 (dd, 1 H, J = 2.4, 8.8, H₆), 7.01 (d, 1 H, J = 2.4, H₄), 7.23 (d, 1 H, J = 8.8, H₇), 8.53 (s, 1 H, NH);

MS m/e 220 (M+1). The product must be stored in the freezer; on the bench top it turns red.

24. The physical properties for [methyl \(2-nitrophenylacetyl\)acetoacetate](#) are as follows: mp 82–83°C; IR (KBr) cm^{-1} : 2960, 1705, 1515, 1400, 1335, 1080, 860, 790, 720 cm^{-1} ; NMR (CDCl_3) δ : 2.41 (s, 3 H, COCH_3), 3.85 (s, 3 H, COOCH_3), 4.20 (s, 2 H, CH_2), 4.50 (s, 2 H, CH_2), 7.36–7.65 (m, 3 H), 8.16 (t, 1 H).

25. The physical properties for [methyl 4-\(2-nitrophenyl\)-3-oxobutylate](#) are as follows: mp 50–51°C; IR (KBr) cm^{-1} : 2960, 1750, 1715, 1610, 1575, 1520, 1440, 1340, 1265, 1200, 1070, 1010, 795, 730, 705 cm^{-1} ; NMR (CDCl_3) δ : 3.66 (2 H, $\text{COCH}_2\text{COOMe}$), 3.76 (s, 3 H, COOCH_3), 4.25 (s, 2 H, Ar- CH_2), 7.30 (d, 1 H, $J = 7.2$), 7.50 (t, 1 H), 7.6 (t, 1 H), 8.10 (d, 1 H, $J = 6.8$).

26. The physical properties for [methyl indole-2-acetate](#) are as follows: mp 71–74°C; IR (KBr) cm^{-1} : 3430, 3405, 3320, 3220, 1740, 1720, 1660, 1620, 1565, 1525, 1430, 1340, 1300, 1280, 1190, 1170, 1030, 860, 820, 790, 780, 730, 700 cm^{-1} ; NMR (CDCl_3) δ : 3.61 (s, 3 H, COOCH_3), 3.71 (s, 2 H, CH_2), 7.42–7.58 (m, 4 H), 7.93 (m, 1 H), 7.97 (d, 1 H, $J = 1.8$).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Compound **5** and its 5-H-analog can be prepared in one to two steps from the known intermediates [5-methoxyindole-2-acetonitrile](#) and [indole-2-acetic acid](#), respectively. [5-Methoxyindole-2-acetonitrile](#) is obtained in very poor overall yield when the patented procedure is followed.⁸ [Indole-2-acetic acid](#) is prepared from [indole-2-carboxylic acid](#)^{9,10} in five steps or from [indole](#)^{11,12} in three steps. The first method involves six steps for the one carbon homologation and the overall yield is 23%. The second method involves protection and deprotection of the [indole nitrogen](#). In addition the reaction conditions for the lithiation step require a very low (-78°C) temperature and for the Wolff-Kishner step a very high (180°C) temperature. The procedure described here illustrates a general synthetic method for the preparation in three steps of substituted [indole-2-acetic acid methyl esters](#) from [o-nitrophenylacetic acid](#) and its derivatives. The overall yields are 30–40% and the reactions can be carried out on a large scale. The purity of the intermediates and the products is greater than 90% as determined by NMR. One of the intermediates, [o-nitrophenylacetyl chloride](#), is considered to be a potentially explosive material; therefore it is never isolated, but is used in its crude form. Although it is not known whether [5-methoxy-2-nitrophenylacetyl chloride](#) is an explosive material, it is also prepared and used in its crude form.

Compound **5** and its 5-H-analog are useful intermediates in preparing a number of 5-substituted 6H-pyrido[4,3-b]carbazoles.^{9,10,13} These pyridocarbazoles are potential antitumor agents.

The corresponding 5-H analogs of the title compound are prepared using the procedure described for compounds **3**, **4**, and **5** in 55–61%, 65–70%, and 80–86% yield, respectively.

References and Notes

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

palladium over activated carbon

palladium on activated carbon, ammonium formate

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

sodium sulfate (7757-82-6)

sodium methoxide (124-41-4)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

palladium on activated charcoal (7440-05-3)

hydrogen peroxide (7722-84-1)

ammonium hydroxide (1336-21-6)

ammonium formate (540-69-2)

Tetrahydrofuran (109-99-9)

N,N-dimethylformamide (68-12-2)

sodium hydride (7646-69-7)

Indole (120-72-9)

indole nitrogen

indole-2-carboxylic acid (1477-50-5)

hexane (110-54-3)

Methyl acetoacetate (105-45-3)

diethyl oxalate (95-92-1)

argon (7440-37-1)

INDOLE-2-ACETIC ACID METHYL ESTERS,
methyl indole-2-acetate,
indole-2-acetic acid methyl ester

Methyl 5-methoxyindole-2-acetate,
1H-Indole-2-acetic acid, 5-methoxy-, methyl ester (27798-66-9)

5-Methoxy-2-nitrophenylacetic acid (20876-29-3)

3-methyl-4-nitroanisole (5367-32-8)

Methyl (5-methoxy-2-nitrophenylacetyl)acetoacetate (130916-40-4)

methyl acetoacetate anion

Methyl 4-(5-methoxy-2-nitrophenyl)-3-oxobutyrate (130916-41-5)

5-Methoxy-2-nitrophenylacetyl chloride

2-nitrophenylacetyl chloride,
o-nitrophenylacetyl chloride (22751-23-1)

5-methoxy-2-nitrophenyl-acetamide

4-(5-methoxy-2-nitrophenyl)-4-oxobutyramide

methyl (2-nitrophenylacetyl)acetoacetate (160206-92-8)

methyl 4-(2-nitrophenyl)-3-oxobutyrate (119209-56-2)

5-methoxyindole-2-acetonitrile

indole-2-acetic acid

o-nitrophenylacetic acid (3740-52-1)