

The reaction of 2-acetyl-4-methylphenoxyacetic acid with some bases and acid anhydrides

その他（別言語等） のタイトル	2-アセチル-4-メチルフェノキシ酢酸の反応
著者(英語)	Tsuneo Suzuki, Takaaki Horaguchi, Takahachi Shimizu
journal or publication title	Bulletin of Nippon Dental University. General education
volume	12
page range	155-163
year	1983-03-25
URL	http://doi.org/10.14983/00000243



The Reaction of 2-Acetyl-4-methylphenoxyacetic Acid with Some Bases and Acid Anhydrides

Tsuneo SUZUKI

Nippon Dental University, Niigata, 1-8 Hamaura-cho, Niigata, Japan

Takaaki HORAGUCHI and Takahachi SHIMIZU

Department of Chemistry, Faculty of Science, Niigata University, Ikarashi, Niigata

(Received November 12, 1982)

2-アセチル-4-メチルフェノキシ酢酸の反応

新潟歯学部 鈴木 常夫

新潟大学理学部 洞口 高昭

清水 隆八

前報で、5-置換 2-アセチルフェノキシ酢酸 (1) を無水酢酸中酢酸ナトリウムと反応させ、ベンゾフラン誘導体 (2) とベンゾフラン-2-カルボン酸誘導体 (3) の生成に対する置換基の効果を調べた。そして、ニトロ基は、メチル基、メトキシ基、クロロ原子に比べてベンゾフラン-2-カルボン酸 (3) の生成を増加させることがわかった。これは中間体と考えられる 3-acetoxy-2,3-dihydro-3-methyl benzofuran-2-carboxylic acid 誘導体の 2 位の水素の酸性度がニトロ基では強くなったと推察した。

さて、本報ではフラン環生成の機構解明の一環として、この反応に於る塩基、酸無水物のベンゾフラン (2) とベンゾフラン-2-カルボン酸 (3) の生成に及ぼす影響を調べ興味ある知見を得たのでここに報告する。

反応に用いた 2-アセチル-4-メチルフェノキシ酢酸 (1a) は 2-ヒドロキシ-5-メチルアセトフェノンとブrom酢酸エチルを反応させて得たフェノキシ酢酸エステルをアルカリ加水分解して得た。

1a をピリジン中無水酢酸とモル比 1:1 で反応させた時、3,5-ジメチルベンゾフラン (2a) が 41% で、又、3,5-ジメチルベンゾフラン-2-カルボン酸 (3a) が 4% の収率で得られた。更に、1a をモル比 1:5 で反応させると 2a が 56% で、又 3a が 42% の収率で得られた。この様に無水酢酸の量を増やすと 2a, 3a の総収率が増加する事がわかった。しかし、1a は無水酢酸無しでピリジン中加熱しても原料の回収に終わった。又、1a の代りに 1a のメチルエステルを反応させた所微量のベンゾフラン (2a) がガスクロマトグラフィにより検出されただけであった。これらの結果から、この反応に於て 1a は無水酢酸と反応して混合無水物になり、これが更に閉環反応、脱離反応を起こし、化合物 (2a), (3a)

を与える事が推察された。1a を種々の 酸無水物—無水トリフロオロ酢酸，無水プロピオン酸，無水イソ酪酸—と反応させた所，無水酢酸との反応と同じ様な相対収率で化合物(2)，(3)を与えた。(2a: 91-75%; 3a: 9-25%)しかし総単離収率には違いがあり無水酢酸，無水トリフロオロ酢酸，無水プロピオン酸では 2a が33~48%，3a が1~4%であったのに対し，無水イソ酪酸では 2a が83%，3a が10%であった。

次に，1a を無水酢酸中4種の塩基-酢酸ナトリウム，酢酸カリウム，トリエチルアミン，ピリジンと反応させ，2a, 3a の単離収率と相対収率を調べた。2a と 3a の相対収率は各々 81~99.7%と 19~0.3%であり，塩基の種類によってあまり違いは見られなかった。しかし総単離収率には違いが見られ，酢酸ナトリウム，酢酸カリウム，トリエチルアミンでは 2a が74~84%，3a が10~0.2%であった。しかし，ピリジンでは 2a が34%，3a が8%となり低収率であった。これはピリジンが他の塩基より塩基性が弱い為と考えられる。

The Reaction of 2-Acetyl-4-methylphenoxyacetic Acid with Some Bases and Acid Anhydrides

Synopsis. The reaction of 2-acetyl-4-methylphenoxyacetic acid with acetic anhydride in pyridine give a mixture of 3, 5-dimethylbenzofuran and 3, 5-dimethylbenzofuran-2-carboxylic acid. But in the absence of acetic anhydride the reaction did not occur. The total yields of benzofuran and benzofuran-2-carboxylic acid were increased with increasing amounts of acetic anhydride. While, methyl 2-acetyl-4-methylphenoxyacetate was treated similarly with acetic anhydride in pyridine in stead of corresponding acid. However, only trace amounts of benzofuran were obtained.

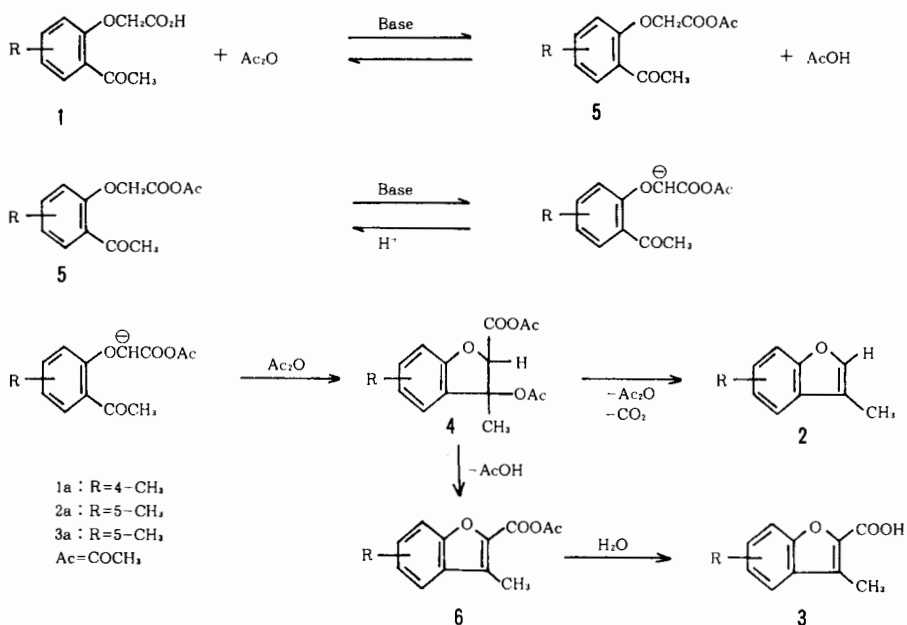
When 2-acetyl-4-methylphenoxyacetic acid was treated similarly with acetic anhydride, trifluoroacetic anhydride, propionic anhydride, or isobutyric anhydride in pyridine and with sodium acetate, potassium acetate, triethylamine, or pyridine in acetic anhydride the relative yields of benzofuran and benzofuran-2-carboxylic acid were roughly same (75-99 and 25-1%). But the total isolated yields varied according to the kinds of bases and acid anhydrides. In the case of acid anhydrides such as acetic anhydride, trifluoroacetic anhydride, and propionic anhydride benzofuran was obtained in 33-48% yields and benzofuran-2-carboxylic acid was in 4-11% yields. But in the case of isobutyric anhydride benzofuran was obtained in 83% yield and benzofuran-2-carboxylic acid was in 10% yield. In the case of bases such as sodium acetate, potassium acetate, and triethylamine benzofuran was exclusively obtained in yield above 84% and benzofuran-2-carboxylic acid was in yield below 10%. However, pyridine did not favour the production of benzofuran (34% yield) and benzofuran-2-carboxylic acid (8% yield) because of its weak basicity.

Introduction

In previous paper,¹⁾ the effects of 5-substituents was reported in the reaction of 2-acetylphenoxyacetic acid (1) with sodium acetate in acetic anhydride, and it showed that a nitro group favours the production of benzofuran-2-carboxylic acid

(3) by its strong electron-withdrawing effects. The reaction of 2-acetylphenoxyacetic acids (1) with sodium acetate in acetic anhydride are one of the intramolecular Perkin reaction and the mechanism will be similar to that of the Perkin reaction.²⁾ The conceivable mechanisms have also been shown as illustrated in Figure 1.¹⁾

The examination of the production of benzofurans (2) and benzofuran-2-carboxylic acids (3) will give a very valuable information on the mechanism for the formation of furan ring. At first of all, we examined the production of benzofuran (2) and benzofuran-2-carboxylic acid (3) in the reaction of 2-acetyl-4-methylphenoxyacetic acid (1a) with some bases and acid anhydrides.



Scheme 1. Reaction mechanisms for the formation of benzofurans and benzofuran-2-carboxylic acids

Results and Discussion

2-Acetyl-4-methylphenoxyacetic acid (1a) was prepared from the reaction of 2-hydroxy-5-methylacetophenone with ethyl bromoacetate followed by saponification. The detailed reaction conditions and physical properties of individual compounds are described in Experimental.

When 2-acetyl-4-methylphenoxyacetic acid (1a) was heated with different mole ratios of acetic anhydride in pyridine at $110 \pm 1^\circ\text{C}$ for 3 h 3, 5-dimethylbenzofuran

(**2a**) and 3, 5-dimethylbenzofuran-2-carboxylic acid (**3a**) were obtained respectively. The isolated yields of **2a** and **3a** are summarized in Table 1.

Table. 1 The reaction of 2-acetyl-4-methylphenoxyacetic acid (**1a**) or methyl ester of **1a** (**7a**) with acetic anhydride in pyridine

Compounds	Mole Ratio	Isolated	Isolated	Recovery (%)
		Yields (%)	Yields (%)	
	1a or 7a : Ac ₂ O	2a ^{a)}	3a ^{b)}	1a ^{b)} or 7a
1a	1 : 5	56	42	3
1a	1 : 1	41	4	63
1a	1 : 0	0	0	95
7a	1 : 5	≈1	0	85

a) analyzed by gas chromatography.

b) isolated as methyl ester.

In the absence of acetic anhydride the reaction did not occur and resulted in recovery of **1a**. In the case of a 1 : 1 mole ratio, the isolated yields of **2a** and **3a** were 41 and 4% respectively and 63% of **1a** was recovered. In the case of a 1 : 5 mole ratio, the isolated yields of **2a** and **3a** were 56 and 42% respectively and 3% of **1a** was recovered. The total yields of **2a** and **3a** were increased with increasing amounts of acetic anhydride. On the other hand, the reaction of methyl 2-acetyl-4-methylphenoxyacetate (**7a**) was carried out instead of **1a** under similar conditions. Only 85% of methyl ester (**7a**) was recovered and trace amounts of **2a** was detected by gas chromatography. The results suggest that a mixed anhydride (**5a**) will be formed from the reaction of **1a** and acetic anhydride by the exchange reaction²⁾ and it will give benzofuran (**2a**) and benzofuran-2-carboxylic acid (**3a**) by following cyclization and elimination reactions.

When **1a** was heated with some acid anhydrides in pyridine a mixture of **2a** and **3a** were obtained. The isolated and relative yields of **2a** and **3a** are summarized in Table 2.

The results of Table 2 show that the relative yields of **2a** and **3a** are roughly same (91-75 and 9-25%) though various acid anhydrides were used. But the total isolated yields varied. In the case of acid anhydrides such as acetic anhydride, trifluoroacetic anhydride, and propionic anhydride the isolated yields of **2a** and **3a** were 33-48 and 4-11% respectively. By use of isobutyric anhydride the isolated yields of **2a** and **3a** were 83 and 10% respectively.

Table 3 summarizes the results of the reaction of **1a** with some bases^{2a)} in acetic anhydride. The relative yields of **2a** and **3a** were almost same (81-99.7 and 19-0.3%) though various bases were used. But the total isolated yields

Table. 2 The reaction of 2-acetyl-4-methylphenoxyacetic acid (**1a**) with some acid anhydrides in a 1: 1 mole ratio in pyridine

Acid Anhydride	Isolated Yields (Relative Yields)(%)	Isolated Yields (Relative Yields)(%)	Total Yields(%)	Recovery(%)
X ₂ O	2a ^{a)}	3a ^{b)}		1a ^{b)}
X=CH ₃ CO	41 (91)	4 (9)	45 (100)	63
X=CF ₃ CO	33 (75)	11 (25)	44 (100)	62
X=CH ₃ CH ₂ CO	48 (83)	10 (17)	58 (100)	40
X=(CH ₃) ₂ CHCO ^{c)}	83 (89)	10 (11)	93 (100)	11

a) analyzed by gas chromatography.

b) separated as methyl ester.

c) in a 1: 1.5 mole ratio.

Table. 3 The reaction of 2-acetyl-4-methylphenoxyacetic acid (**1a**) with some bases in a 1: 5 mole ratio in acetic anhydride

Bases	Isolated Yields (Relative Yields)(%)	Isolated Yields (Relative Yields)(%)	Total Yields(%)	Recovery(%)
	2a ^{a)}	3a ^{b)}		1a ^{b)}
Sodium Acetate	84 (99.7)	0.2 (0.3)	84.2 (100)	0
Potassium Acetate	82 (91)	8 (9)	90 (100)	0
Triethylamine	74 (88)	10 (12)	84 (100)	13
Pyridine	34 (81)	8 (19)	42 (100)	41

a) analyzed by gas chromatography.

b) isolated as methyl ester.

varied. In the case of bases such as sodium acetate, potassium acetate, and triethylamine the isolated yields of **2a** and **3a** were 74–84 and 10–0.2% respectively. By use of pyridine **2a** and **3a** were obtained in 34 and 8% isolated yields respectively. The results of Table 3 suggest that the relative yields are not influenced by the variation of bases, and that pyridine does not favour the production of **2a** and **3a** by its weak basicity.

We wish to examine further the effects of bases and acid anhydrides in detail to elucidate the mechanism of furan ring formation.

Experimental

All the melting points are uncorrected. The infrared absorption spectra were determined with a JASCO IRA-2 diffraction grating infrared spectrophotometer and a HITACHI EPI-G grating infrared spectrophotometer. The nuclear magnetic resonance spectra were determined at 100 MHz with a JEOL Model 4H-100 NMR

spectrometer, using tetramethylsilane as the internal standard. The column chromatography was performed on silica gel (Wakogel C-200).

Preparation of 2-Acetyl-4-methylphenoxyacetic Acid (1a). A mixture of 2-hydroxy-5-methylacetophenone³⁾ (10 g), ethyl bromoacetate (16.5 g), anhydrous potassium carbonate (40 g), and acetone (200 ml) was refluxed at 70°C for 6 h. After cooling insoluble salts were removed by filtration and the filtrate was concentrated by evaporation. The residue was dissolved into ethanol (50 ml) and hydrolyzed with 3M sodium hydroxide solution (50 ml) at room temperature for 30 min. The reaction mixture was poured into cold water (100 ml) and acidified with 6M hydrochloric acid. The precipitates were filtered and washed with cold water and dried under vacuum to give 12.9 g (92%) of **1a** as crystals. Recrystallization from aqueous methanol gave colorless plates: mp 156–157°C. IR (KBr): ν_{\max} 1773 (CO₂H), 1654 cm⁻¹ (CO). NMR (CD₃COCD₃): δ 2.29 (3H, s, phCH₃), 2.67 (3H, s, COCH₃), 4.76 (2H, s, CH₂), 6.88 (1H, d, J=8.5 Hz, C₆-H), 7.28 (1H, dd, J=8.5 and 2.5 Hz, C₅-H), 7.47 (1H, d, J=2.5 Hz, C₈-H). Found: C, 63.21; H, 5.89%. Calcd. for C₁₁H₁₂O₄: C, 63.45; H, 5.81%.

Preparation of Methyl 2-Acetyl-4-methylphenoxyacetate (7a). A mixture of 2-hydroxy-5-methylacetophenone³⁾ (10 g), Methyl bromoacetate (15.3 g), anhydrous potassium carbonate (36.8 g) and 200 ml of acetone was refluxed at 70°C for 6 h. After cooling insoluble salts were filtered off by filtration and the filtrate was concentrated by rotary evaporator. The residue (9.8 g) was obtained as colorless crystals. Recrystallization from methanol gave colorless short needles: mp 54–55°C. IR (KBr): ν_{\max} 1768 (–CO₂–), 1674 (CO), 823 cm⁻¹ (two adjacent aromatic hydrogen atoms). Found: C, 65.07; H, 6.43%. Calcd. for C₁₂H₁₄O₄: C, 64.85; H, 6.34%.

Preparation of 3,5-Dimethylbenzofuran (2a). A mixture of **1a** (5.0 g), anhydrous sodium acetate (13.0 g) and acetic anhydride (85.0 ml) was heated at 110 ± 1°C for 3 h. After cooling the reaction mixture was poured into 200 ml of water and stirred for 1 h and then extracted with 300 ml of ether. The ethereal solution was washed with 3% potassium carbonate solution (40 ml × 3), with water (40 ml × 3), and dried over anhydrous sodium sulfate. The ether was removed by evaporation and the residue was distilled under reduced pressure gave 2.74 g (72%) of **2a** as colorless oil: bp 83°C at 12 Torr. IR (neat): ν_{\max} 3120, 3022, 2950, 2923, 1580, 1450, 1289, 868 (furan ring), 804 cm⁻¹ (two adjacent aromatic hydrogen atoms). Found: C, 82.03; H, 6.96%. Calcd. for C₁₀H₁₀O: C, 82.16; H, 6.89%.

The Reaction of 1a with Acetic Anhydride in a 1 : 1 Mole Ratio in Pyridine. A mixture of **1a** (70 mg, 0.336 m mole), acetic anhydride (35 mg, 0.342 m mole) and pyridine (2.7 ml) was heated at 110 ± 1°C for 3 h. After cooling 20 ml of 6M hydro-

chloric acid was added to the reaction mixture and stirred for 30 min with 80 ml of water and extracted with 300 ml of ether. The ether layer was washed with 20 ml of 6M hydrochloric acid and with 5% potassium carbonate solution and then water and dried over anhydrous sodium sulfate. The ethereal solution was concentrated until the total volume of the solution was exactly 50 ml. The quantity of 3, 5-dimethylbenzofuran (**2a**) in the ether solution was determined by gas chromatography, using hydroquinone dimethyl ether as internal standard. The yield of **2a** was 41%. The alkaline solution was acidified with 6M hydrochloric acid and extracted with 300 ml of ether. The ethereal solution was washed with water, dried over anhydrous sodium sulfate, and concentrated by rotary evaporator. Diazomethane dissolved in ether was added to the above ethereal solution until a color of solution turned yellow and maintained at room temperature for 30 min. The residue obtained by evaporation of ether was chromatographed. The first fraction eluted with benzene gave 2.7 mg (4%) of methyl 3, 5-dimethylbenzofuran-2-carboxylate (**8a**) as colorless short needles: mp 50-51 °C. IR (KBr): ν_{\max} 1713 ($-\text{CO}_2-$), 844 (furan ring), 808cm^{-1} (two adjacent aromatic hydroged atoms). Found: C, 70.45; H, 5.94%. Calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_3$: C, 70.57; H, 5.92%. The second fraction eluted with benzene-acetone gave 47mg (63%) of methyl 2-acetyl-4-methylphenoxyacetate (**7a**) as colorless short needles which was identified with the above obtained sample.

The Reaction of 1a with Acetic Anhydride in a 1: 5 Mole Ratio in Pyridine. The compound (**1a**) (70.7 mg, 0.339 m mole) was carried out with acetic anhydride (172 mg, 1.68 m mole) in pyridine (2.7 ml) and worked up similarly as described for the reaction in the 1: 1 mole ratio and the yields of **2a**, **8a**, and **7a** were 56, 42, and 3% respectively.

The Reaction of 1a without Acetic Anhydride in Pyridine. The compound (**1a**) (70 mg, 0.336 m mole) was heated at 110 ± 1 °C for 3 h in pyridine (2.7 ml) and worked up similarly as described for the 1: 1 mole ratio. **2a** and **8a** were not detected by gas chromatography and **7a** was obtained in 95% yield.

The Reaction of 7a with Acetic Anhydride in Pyridine. A mixture of **7a** (74.6 mg, 0.336 m mole), acetic anhydride (174 mg, 1.68 m mole) and pyridine (2.7 ml) was heated at 110 ± 1 °C for 3 h and worked up similarly as described for the reaction in the 1: 1 mole ratio. **2a** was obtained in below 1% yield and 85% of **7a** was recovered. **8a** was not detected by gas chromatography.

The Reaction of 1a with Trifluoroacetic Anhydride in Pyridine. The compound (**1a**) was treated with trifluoroacetic anhydride in a 1: 1 mole ratio in pyridine in stead of acetic anhydride and worked up similarly. The yields of **2a**, **8a**, and **7a** were 33, 11, and 62% respectively.

The Reaction of 1a with Propionic Anhydride in a 1:1 Mole Ratio in Pyridine. The yields of **2a**, **8a**, and **7a** were 48, 10, and 40% respectively.

The Reaction of 1a with isobutyric anhydride in a 1:1.5 Mole Ratio in pyridine. The yields of **2a**, **8a**, and **7a** were 83, 10, and 11% respectively.

The Reaction of 1a with Sodium Acetate in a 1:5 Mole Ratio in Acetic Anhydride. The compound (**1a**) (100 mg, 0.48 m mole) was treated with sodium acetate (197 mg, 2.4 m mole) in acetic anhydride (12.5 ml) and worked up similarly as described for the reaction of **1a** with acetic anhydride in the 1:1 mole ratio in pyridine. The yields of **2a**, and **8a** were 84 and 0.2% respectively.

The Reaction of 1a with potassium Acetate in a 1:5 Mole Ratio in Acetic Anhydride. The yield of **2a** and **8a** were 82 and 8% respectively.

The Reaction of 1a with Triethylamine in a 1:5 Mole Ratio in Acetic Anhydride. The yields of **2a**, **8a**, and **7a** were 74, 10, and 13% respectively.

The Reaction of 1a with Pyridine in a 1:5 Mole Ratio in Acetic Anhydride. The yields of **2a**, **8a**, and **7a** were 34, 8, and 41% respectively.

Measurement. Gas chromatograms were obtained by a Yanaco Gas Chromatograph Model G 80-FP. All gas chromatographic analyses were performed on one column which was a 1.5m, 4- ϕ , glass column packed with Silicone Gum SE-30 on Chromosorb W AW-DMCS 5% 80/100 mesh. Analytical condition: Nitrogen flow rate: 17.5 ml/min; Hydrogen pressure: 0.5 kg/cm²; Column temperature: 130 °C.

The authors wish to thank Mr. Yoshiaki Takahashi for the elemental analyses and Mr. Takao Oono for the nuclear magnetic resonance analyses.

References

- 1) T. Suzuki, T. Horaguchi, and T. Shimizu, *Bulletin of Nippon Dental University, General Education.*, **11**, 233 (1982).
- 2) a) J. R. Johnson, *Organic Reaction, Vol 1.* 210 (1942). b) B. J. Kurtev and C. G. Kratchanov, *J. Chem. Soc., (B)*, **1969**, 649.
- 3) K. W. Rosenmund and W. Schnurr, *Ann.*, **460**, 56 (1928).