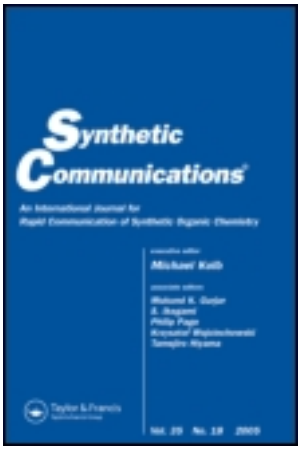

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A Facile Synthetic Method of Herbicidal 2,3-Dihydro-3-methylene-2-substituted-phenyl-1H-isoindol-1-one Derivatives

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A FACILE SYNTHETIC METHOD OF HERBICIDAL 2,3-DIHYDRO-3-METHYLENE-2-SUBSTITUTED- PHENYL-1*H*-ISOINDOL-1-ONE DERIVATIVES

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ABSTRACT : Herbicidal 2,3-dihydro-3-methylene-2-substitutedphenyl-1 *H*-isoindol-1-one derivatives **7** have been synthesized. They were prepared from the easily available phenol derivatives 1 in 5 steps in moderate yields.

3,4-Disubstituted-5-methylene pyrrolidinone derivatives were known as selective herbicides and plant growth regulators.[1-4] The substituents at the position of 3 and 4 were limited to hydrogen and alkyl groups. In the course of our synthetic efforts to prepare preemergent herbicides for the control of weeds in the fields of corn, we attempted to prepare 2,3-dihydro-3-methylene-2-substitutedphenyl-1 *H*-isoindol-1-one derivatives. In this paper, we wish to describe on the short and efficient synthetic methods for the described compounds. The synthesis is straightforward as shown in **Scheme** 1.

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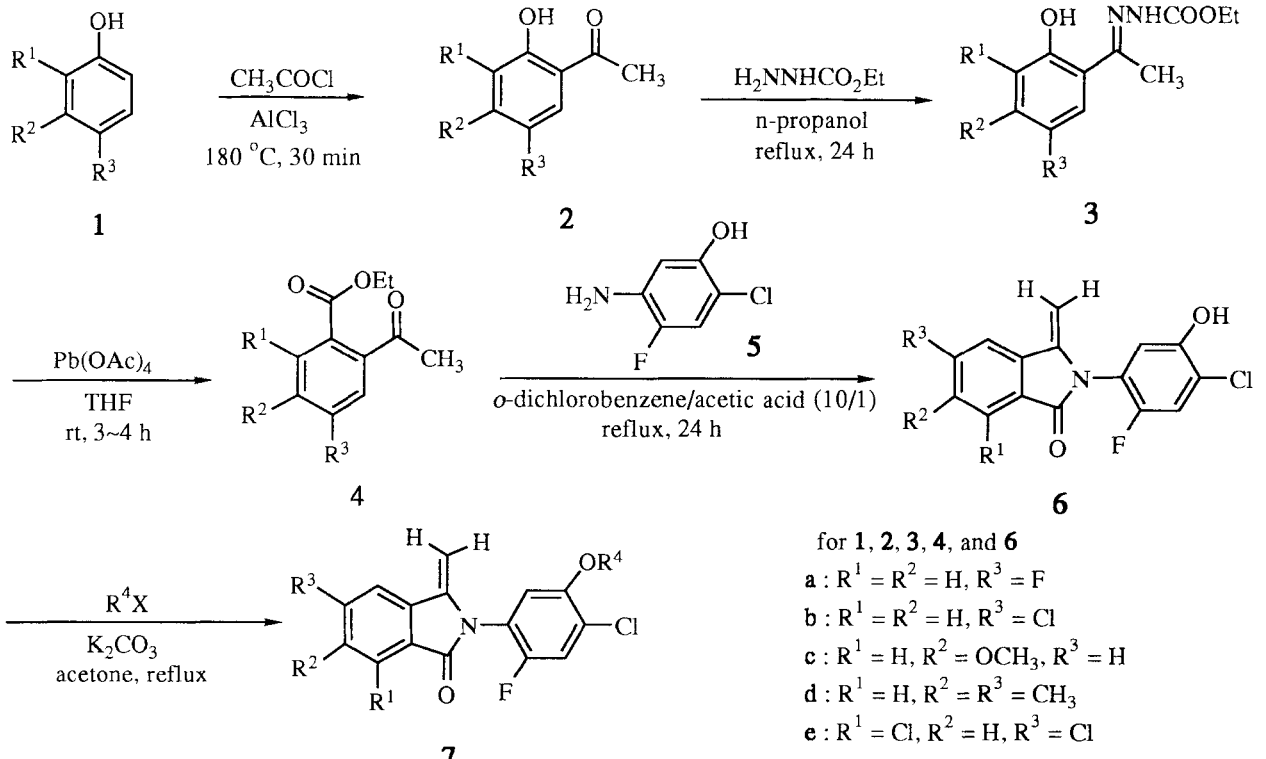

Scheme 1

Thus, appropriately substituted phenol derivatives **1** were treated with acetyl chloride in the presence of anhydrous aluminium chloride and the reaction mixture was heated to 180 °C for 30 min. After Fries rearrangement 2-acetylphenol derivatives **2** were obtained in good yields (65-98%). The required *o*-acetylaryl carboxylate derivatives **4** were prepared according to the reported procedure from **2**.[5-6] The reaction of **2** with ethyl carbazate in n-propanol afforded the hydrazone derivatives **3** in good yields (70-92%). Lead tetraacetate mediated oxidative cleavage reaction of **3** in tetrahydrofuran at room temperature gave the *o*-acetylaryl carboxylate derivatives **4** in 40-72% yields. With five *o*-acetylaryl carboxylates in hand, we attempted the reaction with 4-chloro-2-fluoro--5-hydroxyaniline (**5**)[7] in various reaction conditions to obtain the desired 3-methylene isoindolone derivatives **6**. However, the results were not so good.[8] Best results were obtained by refluxing the reaction mixture of **4** and **5** in *o*-dichlorobenzene and acetic acid (10/1). The representative results were summarized in **Table 1**. Column purified **6** was converted to the herbicidal *O*-alkylation product **7** by the conventional method in acetone in the presence of potassium carbonate. Propargyl bromide, ethyl iodide, and 2-chloropropionitrile were used as the representative alkylating reagent and the results were summarized in **Table 2**. Compounds **7** have some herbicidal activity, especially the compound **7a** with propargyl substituent (R^4 = propargyl) showed good herbicidal activity against various weed species. Further studies on the optimization of the herbicidal activity and selectivity by changing the structure of **7** are under progress. In summary, in this paper we described on the facile synthetic method of 2,3-dihydro-3-methylene-2-substitutedphenyl-1*H*-isoindol-1-one system.

Table 1. Yields and ^{1}H NMR Data of **2**, **3** , **4**, and **6**

Compound[a]	^{1}H NMR (DMSO-d_6, δ)	Yield (%)[b]
2a	2.60 (s, 3H), 7.40 (dd, 1H), 7.60 (td, 1H), 7.65 (dd, 1H), 11.5 (brs, 1H)	65
2b	2.72 (s, 3H), 7.07 (d, 1H), 7.64 (dd, 1H), 7.97 (d, 1H), 11.85 (brs, 1H)	70
2d	2.22 (two s, 6H), 2.60 (s, 3H), 6.80 (s, 1H), 7.65 (s, 1H), 11.95 (brs, 1H)	98
2e	2.72 (s, 3H), 7.92 (d, 1H), 8.02 (dd, 1H), 11.8 (brs, 1H)	98
3a	1.32 (t, 3H), 2.35 (s, 3H), 4.25 (q, 2H), 6.95 (q, 1H), 7.15 (t, 1H), 7.22 (dd, 1H), 10.95 (brs, 1H), 12.75 (brs, 1H)	82
3b	1.30 (t, 3H), 2.32 (s, 3H), 4.20 (q, 2H), 6.90 (d, 1H), 7.30 (dd, 1H), 7.59 (d, 1H), 10.88 (brs, 1H), 13.0 (brs, 1H)	70
3c	1.28 (t, 3H), 2.30 (s, 3H), 3.75 (s, 3H), 4.25 (q, 2H), 6.42 (s, 1H), 6.45 (dd, 1H), 7.45 (d, 1H), 10.62 (brs, 1H), 12.2 (brs, 1H)	85
3d	1.26 (t, 3H), 2.20-2.30 (three s, 9H), 4.22 (q, 2H), 6.68 (s, 1H), 7.28 (s, 1H), 10.62 (brs, 1H), 12.64 (brs, 1H)	84
3e	1.30 (t, 3H), 2.33 (s, 3H), 4.25 (q, 2H), 7.60 (t, 2H), 10.9 (brs, 1H), 12.7 (brs, 1H)	92

Table 1. Continued

Compound[a]	^{1}H NMR (DMSO-d_6, δ)	Yield (%)[b]
4a	1.33 (t, 3H), 2.52 (s, 3H), 4.35 (q, 2H), 7.02 (d, 1H), 7.15 (td, 1H), 7.95 (d, 1H)	72
4b	1.38 (t, 3H), 2.55 (s, 3H), 4.35 (q, 2H), 7.33 (d, 1H), 7.45 (dd, 1H), 7.86 (d, 1H)	68
4c	1.35 (t, 3H), 2.52 (s, 3H), 3.86 (s, 3H), 4.35 (q, 2H), 7.00 (d, 1H), 7.15 (d, 1H), 7.55 (d, 1H)	48
4d	1.35 (t, 3H), 2.32 (two s, 6H), 2.51 (s, 3H), 4.35 (q, 2H), 7.15 (s, 1H), 7.60 (s, 1H)	44
4e	1.40 (t, 3H), 2.57 (s, 3H), 4.45 (q, 2H), 7.62 (d, 1H), 7.71 (d, 1H)	40
6a	4.8 (d, 1H), 5.65 (t, 1H), 7.0-8.1 (m, 5H), 10.65 (brs, 1H),	30
6b	4.8 (d, 1H), 5.7 (t, 1H), 7.0-8.35 (m, 5H), 10.63 (brs, 1H)	32
6c	3.90 (s, 3H), 4.62 (d, 1H), 5.42 (t, 1H), 7.03-8.00 (m, 5H), 10.6 (brs, 1H)	43
6d	2.30 (s, 3H), 2.50 (s, 3H), 4.62 (d, 1H), 5.43 (t, 1H), 7.02-7.86 (m, 4H), 10.50 (brs, 1H)	45
6e	4.88 (t, 1H), 5.82 (d, 1H), 7.1-9.0 (m, 4H), 10.68 (brs, 1H)	30

[a]Compound **2c** was commercially available. [b]Isolated yields.

Table 2. Synthesis of 3-Methylene Isoindolone Derivatives **7**

Product (7)	mp (°C)	Yield (%)[a]
6a + propargyl bromide	123-124	91
6b + propargyl bromide	159-160	99
6c + propargyl bromide	149-150	95
6d + propargyl bromide	141-143	99
6e + propargyl bromide	179-181	98
6c + ethyl iodide	117-118	99
6d + ethyl iodide	123-124	88
6e + ethyl iodide	143-145	95
6a + 2-chloropropionitrile	182-184	96
6c + 2-chloropropionitrile	128-130	96
6d + 2-chloropropionitrile	123-124	94

[a]Yields are isloated, and the products were confirmed by ^{1}H NMR and mass spectra.

EXPERIMENTAL

General Procedure for the Preparation of **2a-e**.

To the phenol derivatives **1** (30 mmol) was added acetyl chloride (2.5 g, 32 mmol) with stirring at room temperature. The reaction mixture was slowly warmed until the evolution of gas had practically ceased. To the reaction mixture anhydrous aluminium chloride (4.0 g, 30 mmol) was added portionwise and the dark solution was slowly heated to 180 °C for 30 min and then cooled to room temperature. To this hard cake was slowly added c-HCl/H_2O (25 mL/100 mL) and stirred overnight. The white crystalline solid was collected by filtration and washed with water. The solid was dried over calcium chloride in a vacuum desiccator to afford **2a-e**.

General Procedure for the Preparation of **3a-e**

2a-e (10 mmol) and ethyl carbazate (1.15 g, 11 mmol) were dissolved in n-propanol (50 mL) and refluxed for 24 h. The precipitated solid was collected by filtration to give the pure hydrazone derivatives **3a-e**. The filtrates were concentrated in vacuo and the residue was purified by column chromatograpy on silica gel (chloroform) to give additional **3a-e**.

General Procedure for the Preparation of **4a-e**

Hydrazone derivatives **3a-e** (10 mmol) were dissolved in tetrahydrofuran (100 mL) and lead tetraacetate (4.45 g, 10 mmol) was gradually added. The reaction mixture was stirred at room temperature for 3-4 h. Filtering off the solid material and removing the solvent by evaporation afforded an oil which was subjected to column chromatograpy on silica gel (toluene) to give the *o*-acetylaryl carboxylate derivatives **4a-e**.

General Procedure for the Preparation of **6a-e**

Ethyl *o*-acetylaryl carboxylates **4a-e** (5 mmol) and 4-chloro-2-fluoro-5-hydroxyaniline (**5**, 810 mg, 5 mmol) were dissolved in *o*-dichlorobenzene (50 mL) and acetic acid (5 mL) and heated to reflux for 24 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with water (2 x 100 mL). The organic layers were dried over sodium sulfate and evaporated to afford crude products. Further purification was achieved by column chromatograpy on silica gel (toluene/ethyl acetate, 10/1).

General Procedure for the Preparation of **7**

6a-e (1 mmol), potasium carbonate (140 mg, 1 mmol), and R^4X (2.5 mmol) were mixed in dry acetone (70 mL) and heated to reflux for 24 h. After

cooling to room temperature, the solid material was filtered off. The filtrates were concentrated and the residue was purified by column chromatograpy on silica gel (toluene/ethyl acetate, 10/1) to give the desired products.

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7. 4-Chloro-2-fluoro-5-hydroxyaniline (**5**) was prepared from 4-fluorophenol in 5 steps in 31 % overall yield .
8. For example, the reaction of **4a** and **5** in acetic acid (reflux, 24 h) gave only 15% of **6a**.

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