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New method for the synthesis of 3-chloro-2-(4-chloro-2-fluoro-5-hydroxyphenyl)-4,5,6,7-tetrahydro-2H-indazole

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Abstract : 3-Chloro-2-(4-chloro-2-fluoro-5-hydroxyphenyl)-4,5,6,7-tetrahydro-2H-indazole, which is the key intermediate of cyclic imide type compounds such as EK 5439 and S-275 series, were practically synthesized by the procedure of hydrolysis of by-products and were produced in the reaction of 2-(2-fluoro-4-chloro-5-hydroxyphenyl)-2,3a,4,5,6,7-hexahydroindazol-3-one with phosgene.(Received October 12, 2004; accepted March 23, 2005)

key word : herbicide, 3-chloro-2-(4-chloro-2-fluoro-5-hydroxyphenyl)-4,5,6,7-tetrahydro-2H-indazole, phosgene, Protox inhibitor.

We have explored the synthetic method of new cyclic imide type compounds and developed EK 5439 series which represent effective herbicidal activity (Ryu *et al.*, 2001; Ryu *et al.*, 2002). These EK 5439 compounds and S-275 series which are known as potent herbicides are carrying tetrahydroindazole moiety such as 3-chloro-2-(4-chloro-2-fluoro-5-hydroxyphenyl)-4,5,6,7-tetra hydro-2H-indazole (2) (Hirai, 1999). It was reported that compound **2** was obtained from **1** by refluxing with phosgene in low yield (26%) as shown in Scheme 1 (Nagano *et al.*, 1983).

We have found that the yield is very little or not, non reproducible, and difficult to separate by silica gel column chromatography due to the low solubility of compound **1** within common organic solvents. For the elucidation and improving of these reasons, we have separated the major by-products and certified them. They were composed of **2** and **1** as shown in scheme 2. These **3** types of coupling compounds could be decomposed by bases giving **1** and **2** (scheme 2). After trial of hydrolysis with several bases, we have found that ammonium hydroxide is the best reagent for the hydrolysis of **3**'s.

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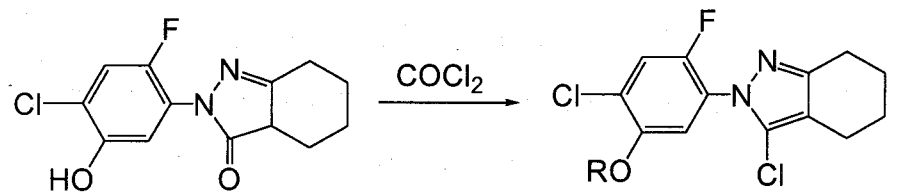
Compound **1** was reacted with phosgene in refluxing for 7 hours in toluene, and concentrated by evaporation. The crude reaction mixture was hydrolyzed with ammonium hydroxide in ethyl acetate at room temperature and acidified with diluted hydrochloride. Similar results were observed using various solvents such as methylene chloride, toluene, chloroform and THF and bases such as lithium hydroxide, sodium hydroxide, calcium hydroxide, and potassium hydroxide. According to their convenient work up by appropriate difference of solubilities to these reactants and product the best result were obtained in ethyl acetate as a solvent and ammonium hydroxide as a base. The precipitant was separated by filtration, that is composed of mostly **1** with 64% yield and can be used for the next step as reactants without further treatment. The filtrate was washed by water and brine twice following by separation through silica gel column chromatography to give **2** in 33% yield. Reactants **1** recovered from this reaction could be reused for the same procedure. After 8 times repeated this process, all of the product **2** were obtained in 91% yield.

Experimentals

Synthesis of 3-chloro-2-(4-chloro-2-fluoro-5-hydroxyphenyl)-

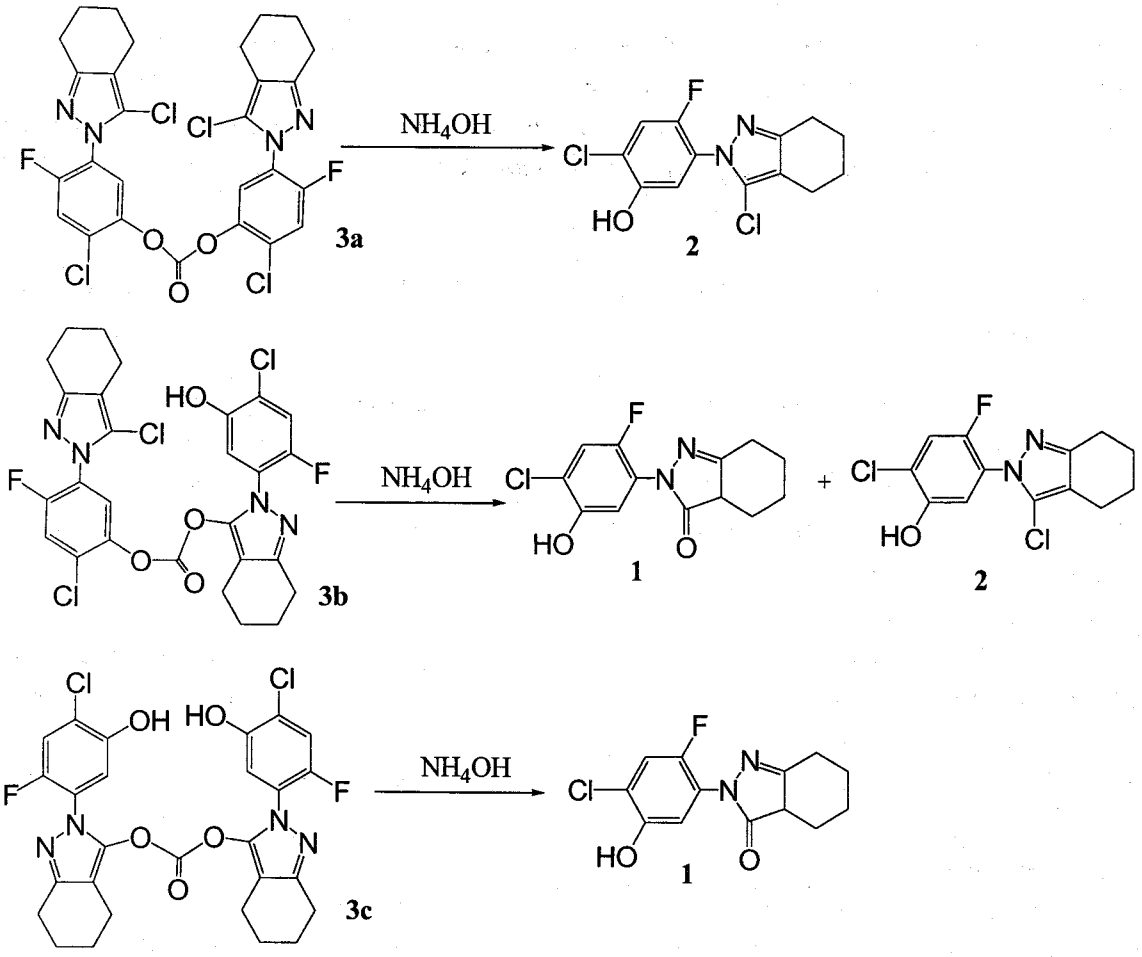


1

2, R = H

S-275, R = propargyl

Scheme 1



Scheme 2

4,5,6,7-tetrahydro-2H-indazole (2)

2-(2-fluoro-4-chloro-5-hydroxyphenyl)-2,3a,4,5,6,7-hexah ydroindazol-3-one (150 g) was added to the solution of phosgene (1,5 M, 1.4 L) and heated to reflux for 7 hrs. The reactionmixture was evaporated and added ethyl acetate(500 mL). This solution was slowly added ammonium hydroxide (28%, 300 mL) and stirred for 3 hrs at room temperature. After neutralization with concentrated hydrochloride, this solution was filtered and washed with methylene chloride and water twice, respectively. The solid was 2-(2-fluoro-4-chloro-5-hydroxyphenyl)-2,3a,4,5,6,7-hexahydroindazol-3-one, reactants almost all in 64% yield (96 g). The organic layer was evaporated and purified by silica gel column chromatography to give 3-chloro-2-(4-chloro-2-fluoro-5-hydroxyphenyl)-4,5,6,7-tetrahydro-2H-indazole in 33%

yield.

^{1}H NMR ($CDCl_3$, ppm) δ 9.20 (brs, 1H), 7.18 (d, *J*= 9.2 Hz, 1H), 7.07 (d, *J* = 6.7 Hz, 1H), 2.80~2.42 (m, 4H), 1.89~1.68 (m, 4H); MS (20 eV) m/z (real intensity) 300 (M^+, 92).

Preparation and purification of coupling compounds (3a, 3b, 3c) of 2-(2-fluoro-4-chloro-5-hydroxyphenyl)-2,3a,4,5,6,7-hexahydroindazol-3-one (1) and 3-chloro-2-(4-chloro-2-fluoro-5-hydroxyphenyl)-4,5,6,7-tetrahydro-2H-indazole (2)

2-(2-fluoro-4-chloro-5-hydroxyphenyl)-2,3a,4,5,6,7-hexahydroindazol-3-one (150 g) was added to the solution of phosgene (1,5 M, 1.4 L) and heated to reflux for 12 hrs. The reaction mixture was evaporated and purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/1) to give 3a (0.15 g), 3b (0.31 g), 3c (0.66 g).

3a. ^{1}H NMR ($CDCl_3$, ppm): 7.31 (d, *J* = 6.7 Hz, 2H), 7.27 (d, *J* = 9.2 Hz, 2H), 2.59 (m, 4H), 2.40 (m, 4H), 1.81 ~ 1.59 (m, 8H). MS (20 eV) m/z (rel intensity) 628 (M^+, 47).

3b. ^{1}H NMR ($CDCl_3$, ppm): 8.29 (brs, 1H), 7.32 (d, *J* = 6.7 Hz, 1H), 7.23 (d, *J* = 9.2 Hz, 1H), 7.03 (d, *J* = 9.2 Hz, 1H), 6.94 (d, *J* = 6.7 Hz, 1H), 2.96 ~ 2.12 (m, 8H). 1.86 ~ 1.61 (m, 8H). MS (20 eV) m/z (rel intensity) 609 (M^+, 30).

3c. ^{1}H NMR ($CDCl_3$, ppm): 8.25 (brs, 2H), 7.38 ~ 6.92 (m, 4H). 2.98 ~ 2.25 (m, 8H). 1.88 ~ 1.64 (m, 8H). MS (20 eV) m/z (rel intensity) 591 (M^+, 12).

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3-Chloro-2-(4-chloro-2-fluoro-5-hydroxyphenyl)-4,5,6,7-tetrahydro-2H-indazole의 제조방법에 관한 연구

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요약 : Protox 저해제인 cyclic imide type 화합물 중에서 EK 5439와 S-275 같은 화합물들의 필수 중간체인 3-chloro-2-(4-chloro-2-fluoro-5-hydroxyphenyl)-4,5,6,7-tetrahydro-2H-indazole은 2-(2-fluoro-4-chloro-5-hydroxyphenyl)-2,3a,4,5,6,7-hexahydroindazol-3-one을 포스겐과 반응시켜서 얻을 수 있다고 알려져 있으나, 수율이 매우 낮고 재현성이 없다. 따라서 이 반응의 부산물들을 분리 확인하여, 이 부산물들이 반응물과 목적물의 이량체임을 밝히고, 이들을 가수분해 함으로서 목적물의 합성수율을 높이고 반응물을 거의 대부분 회수할 수 있는 효과적인 방법을 개발하였다.

색인어 : 제초제, 3-클로로-2-(4-클로로-2-플루오로-5-히드록시페닐)-4,5,6,7-테트라히드로-2H-인다졸, 포스겐, 프로톡스저해제.

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