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Communications to the Editor

One-Step Synthesis of 5-(4-Fluorobenzyl)-2-furyl Methyl Ketone: A Key Intermediate of HIV-Integrase Inhibitor S-1360

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Abstract:

Practical one-step synthesis of 5-(4-fluorobenzyl)-2-furyl methyl ketone was accomplished by Friedel–Crafts benzylation of 2-furyl methyl ketone with 4-fluorobenzyl chloride in the presence of $ZnCl_2$. Two reaction conditions and their work-up procedures are reported. The first utilizes an anhydrous condition in dichloromethane, providing a convenient procedure for the isolation of the product. The second involves an aqueous condition, which offers a large-scale ecological and safe manufacturing process.

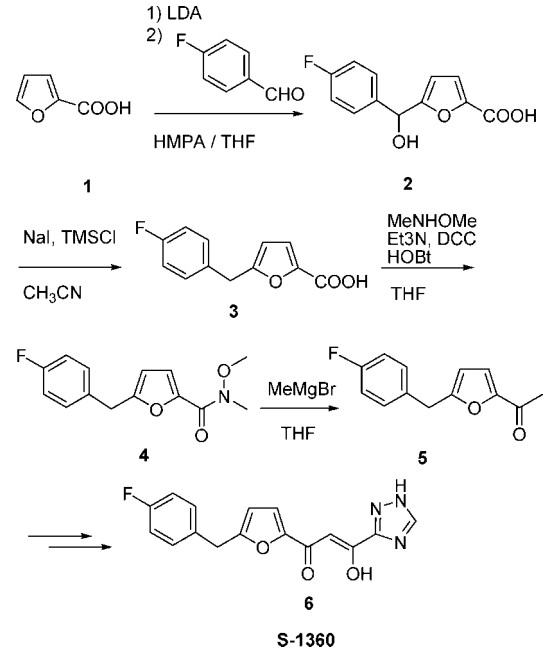
Introduction

5-(4-Fluorobenzyl)-2-furyl methyl ketone (**5**) is a key intermediate in the synthesis of HIV-integrase inhibitor S-1360, which was found in the Discovery Research Laboratory of Shionogi & Co., Ltd.[1] The HIV integrase has been considered an attractive therapeutic target, since HIV cannot replicate without integration in a host chromosome.[2] To develop S-1360, we needed a low-cost and reliable synthetic method by which S-1360 could be prepared on a large scale.[3] Here we report two procedures for the one-step synthesis of **5** via Friedel–Crafts benzylation.

Results and Discussion

The medicinal chemistry route of S-1360 is shown in Scheme 1. A few kilograms of ketone **5** were synthesized by this route for nonclinical use. 2-Furoic acid (**1**) was lithiated with 2 molar equiv of LDA in the presence of HMPA, and the obtained dilithio derivative reacted with 4-fluorobenzaldehyde to give an alcohol **2**. This alcohol was reduced by TMSCl/NaI[4] to afford 5-(4-fluorobenzyl)-2-furoic acid (**3**), which can be purified by crystallization. The acid **3** was converted into the corresponding Weinreb's amide[5] **4** and allowed to react with methylmagnesium chloride to give ketone **5**.

Scheme 1. **Medicinal chemistry route of S-1360**



This chemistry presented the following problems for industrial manufacturing of **5**. (1) Toxic HMPA is needed to dissolve the generated dilithio derivatives. (2) Iodine has to be recovered in order to protect the environment. (3) LDA, MeNHOMe·HCl, HOBt and MeMgCl are expensive. To eliminate these scale-up issues, we investigated other synthetic methods. Friedel–Crafts-type reactions of electron-rich furans[6] and electron-deficient furans[7] are well known,[8] but there are few examples of furyl ketones. The exception is the Friedel–Crafts alkylation of 2-furyl methyl ketone (**7**),[9] which led us to examine the Friedel–Crafts benzylation of **7**.

Method A. We developed an excellent synthetic method of **5**, which involves Friedel–Crafts reaction of **7** with

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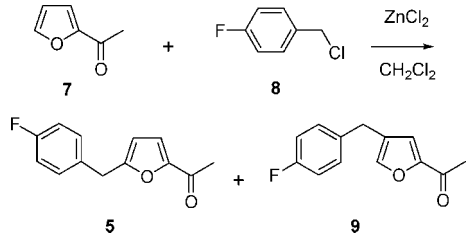
Scheme 2. **Method A**



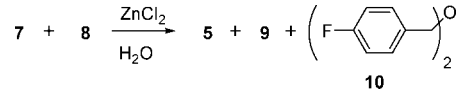
p-fluorobenzylchloride (**8**) in the presence of anhydrous $ZnCl_2$ in dichloromethane to afford **5** in 53%[10] yield accompanied by 1%[10] of 4-(4-fluorobenzyl)-2-furyl methyl ketone (**9**) (Scheme 2). This one-step synthesis presents the following advantages. The starting materials **7** and **8** are inexpensive, and the isolation procedure of **5** is convenient. Namely, a mixture of **7**, 2 molar equiv of **8**, 1.5 molar equiv of anhydrous $ZnCl_2$ powder and dichloromethane was stirred at 45 °C. As the reaction proceeded, a complex with **5** and $ZnCl_2$ precipitated in dichloromethane. The precipitates were collected by filtration to remove **9** and other impurities and then washed with water to obtain free **5** in 42% yield.[10] The obtained **5** could be used without further purification.

Although a few kilograms of **5** were synthesized by this procedure for nonclinical use, the issue remains that this procedure needs dichloromethane, which can be harmful to the environment, as a reaction solvent. We therefore searched for another procedure for the Friedel–Crafts reaction.

At first, we tried it in the absence of a solvent. Friedel–Crafts reaction of **7** with benzylchloride **8** without solvent also gave ketone **5** but posed two problems. (1) The reaction mixture easily solidified and was not suitable for large-scale synthesis. (2) On a 20-L scale, the three materials **7**, **8** and $ZnCl_2$ were stirred and heated to start the reaction, but we were not able to control it. A reaction calorimeter study of this reaction revealed a large heat evolution of 327 kJ/mol and an adiabatic temperature rise of 355 °C. In order to control the reaction, **7** was added gradually into a mixture of **8** and $ZnCl_2$, but this procedure gave **5** in poor yield.

Method B. We investigated other solvents to replace dichloromethane and found H_2O to be the best (Scheme 3). The Friedel–Crafts reaction in the presence of H_2O is a two-

Scheme 3. **Method B**



layer system, which contains a layer of organic compounds and aqueous $ZnCl_2$ solution. Namely, the mixture of **7**, 2 molar equiv of **8**, and 1.05 molar equiv of $ZnCl_2$ in 2 vol of water was stirred at 85 °C for 6 h. The Friedel–Crafts reaction gave 70%[10] of **5** accompanyied by 5%[10] of ketone **9** and 5%[10] of di-4-fluorobenzyl ether (**10**). In order to remove the isomer **9** and the ether **10**, the isolation procedure of **5** needed distillation under reduced pressure and then crystallization under −10 °C from mixed solvents of isopropyl alcohol and *n*-hexane. The desired ketone **5** was isolated in 43% yield from **7**. The calorimeter study revealed the total energy given off during this reaction with H_2O to be 23.7 kJ/mol, which corresponded to an adiabatic temperature rise of 14 °C. This condition was adopted for large-scale synthesis and we were able to obtain ca. 500 kg/lot of ketone **5** successfully.

Conclusion

We have developed a convenient and economical one-step synthesis of **5** starting from the easily available compounds **7** and **8**. This procedure includes two different conditions. For small-scale synthesis in a laboratory, the reaction by anhydrous $ZnCl_2$ in dichloromethane can be recommended. On the other hand, for large-scale synthesis, the reaction with water should be adopted to protect the environment and reduce the safety risk. Modification of our procedures should be useful for synthesizing 5-substituted-2-furyl ketones.

Experimental Section

General. Melting point was determined on Büchi apparatus and is uncorrected. The ^{1}H NMR spectra was measured on a Varian Gemini 300 MHz FT NMR spectrometer.

5-(4-Fluorobenzyl)-2-furyl Methyl Ketone (5). Method A. To a solution of **7** (19.71 g, 0.18 mol) in dichloromethane (120 mL) were added **8** (42.9 mL, 0.36 mol) and $ZnCl_2$ (36.6 g, 0.27 mol), and the mixture was allowed to reflux with stirring. After 12 h the precipitated complexes with **5** and zinc chloride were collected and washed with dichloromethane. Water was added to the complexes, the mixture was extracted with ethyl acetate, and the organic layer was washed with water and aqueous $NaHCO_3$ and then dried over anhydrous Na_2SO_4. The solvent was removed in vacuo. *n*-Hexane was added to the residue, and the precipitates were collected by filtration and dried to give **5** (16.4 g, 42%). Mp 28 °C. ^{1}H NMR δ ($CDCl_3$): 2.43 (s, 3H), 4.01 (s, 2H), 6.09 (d, J = 3.5 Hz, 1H), 6.96–7.26 (m, 5H).

5-(4-Fluorobenzyl)-2-furyl Methyl Ketone (5). Method B. A mixture of **7** (187.2 g, 1.7 mol), **8** (491.6 g, 3.4 mol), aqueous 50% $ZnCl_2$ (486.6 g, 1.785 mol) and water (131 mL) was vigorously stirred at 85 °C. After 6 h ethyl acetate (1498 mL)

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(10) The reaction mixture was quenched with H_2O and extracted with dichloromethane or ethyl acetate extract. The yield was estimated by HPLC analysis of the extract.

was added to the reaction mixture, and the organic layer was washed with 3.65% aqueous HCl (936 mL × 3), 5% aqueous $NaHCO_3$ (936 mL) and water (936 mL). Each aqueous layer was back-extracted with ethyl acetate (374 mL). The combined organic layer was condensed in vacuo and then distilled under reduced pressure at 115–144 °C (370–210 Pa). A mixture of the distillate and isopropyl alcohol (144.4 mL) was allowed to cool at 0 °C with stirring, and then seed crystals were added. After 0.5 h *n*-hexane (288.7 mL) was added, and then the mixture was allowed to cool at –10 °C with stirring. After 2 h the obtained crystals were filtered, washed with chilled *n*-hexane, and dried to give **5** (161.2 g, 43%).

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