Short Paper

One-pot Fries rearrangement to synthesize hydroxyaryl ketone from phenol and carboxylic acid

—— *in situ* activation of carboxylic acid by Tf_2O/TfOH system ——

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Fries rearrangement reaction is a rearrangement of phenolic esters for preparing hydroxyaryl ketones, but the starting phenolic esters and their precursors acyl halides are sometime unstable to isolate. As a preliminary study to apply several carboxylic acid or amino acid to Fries rearrangement, a one-pot synthesis of hydroxyaryl ketones from a simple carboxylic acid was investigated. The process is envisioned in which carboxylic acid is converted *in situ* to mixed acid anhydride (RCO-OTf), then to phenolic esters and finally rearranged to the hydroxyaryl ketones. A one-pot reaction using benzoic acid as the carboxylic acid in the 3:7-Tf_2O/TfOH system afforded the para-product of the Fries rearrangement, 4-hydroxybenzophenone, in high yield. One hour after initiation of the reaction, phenyl benzoate was detected and then disappeared, supporting rearrangement *via* the phenolic ester.

Keywords: Fries rearrangement, Hydroxyaryl ketone, *In situ* activation

1. Introduction

Hydroxyaryl ketones are one of the important intermediates for pharmaceuticals and agrochemicals, and Fries rearrangement reaction is of industrial importance for their preparation. This reaction is a rearrangement of phenolic esters catalyzed by Lewis or Bronsted acids. Hashimoto and co-works reported that trifluoromethanesulfonic acid (TfOH) is effective as a catalyst for the Fries rearrangement and as a solvent[(1)].

Attempting to introduce an aminoacyl skeleton from an amino acid into a hydroxyaryl ketone requires a multi-step process of protecting the amino group and activating the carboxyl group, and there are also concerns about the instability of the carboxyl halide. As a preliminary study to introduce several carboxylic acid or amino acid, a one-pot synthesis of hydroxyaryl ketones from a simple carboxylic acid was investigated. We hypothesized that a TfOH/Tf_2O mixture could activate the carboxylic acid to facilitate formation of ester with phenol followed by acyl migration, and developed a one-pot rearrangement process from a carboxylic acid and phenol to the hydroxyphenyl ketone (Fig. 1). The process is envisioned in which the carboxylic acid is converted to the mixed acid anhydride (RCO-OTf) *in situ*, then to the phenol ester and finally rearranged to the hydroxyaryl ketone.

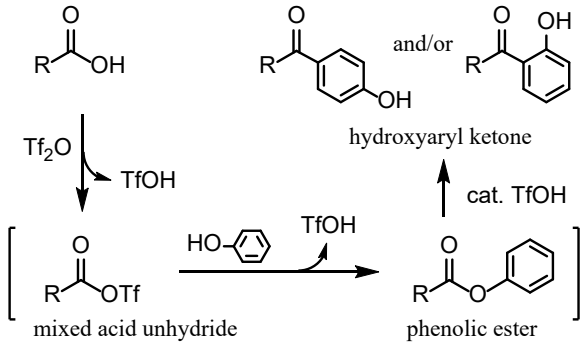

Fig. 1 Design of one-pot Fries rearrangement based on *in situ* activation of carboxylic acid by Tf_2O.

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2. Experimental

2.1 Apparatus

Reaction progress was monitored with Agilent Technologies 7890 GC system equipped with 5975 mass selective detector, and the reaction products were referred with NIST08 library.

2.2 Fries rearrangement of phenolic ester in TfOH

The procedure is mostly based on the literature[(1)]. Phenyl benzoate 56.6 mg (0.29 mmol) was dissolved in 0.5 mL of TfOH at 0°C under N_2 atmosphere. The reaction mixture was warmed to room temperature and stirred for 2 h, and the mixture was quenched with cold water and ethyl acetate. The organic layer was washed with water and saturated $NaHCO_3$, then analyzed by GC/MS with 20.8 mg of biphenyl as an internal standard.

2.3 Reaction of Benzoic acid and Phenol in Tf_2O

Benzoic acid 34.5 mg (0.28 mmol), phenol 26.2 mg (0.28 mmol), and Tf_2O 1.5 mL were added to the reaction tube and stirred at room temperature (17-22 °C). At several interval, parts of the reaction mixture were withdrawn and extracted with cyclopentyl methyl ether (CPME)/ saturated $NaHCO_3$. The organic layers were analyzed by GC/MS.

2.4 Reaction of Benzoic acid and Phenol in Tf_2O/TfOH

Benzoic acid 34.2 mg (0.28 mmol), phenol 26.4 mg (0.28 mmol), Tf_2O 0.30 mL (1.8 mmol) and TfOH 0.70 mL (8.0 mmol) were added to the reaction tube under N_2 atmosphere and stirred for 1-48 h at room temperature (17-22 °C). At the prescribed period, each reaction pot was quenched in a mixture of 30 mL-CPME / 100 mL-saturated $NaHCO_3$. The organic layers were added 4-hydroxy-2-methylacetophenone as an internal standard, and analyzed by GC/MS to quantify the products.

3. Results and Discussion

3.1 Fries rearrangement of phenolic ester in TfOH

Phenyl benzoate was rearranged to 4-hydroxybenzophenone catalyzed by TfOH in 90% analytical yield, consistent with the literature[(1)].

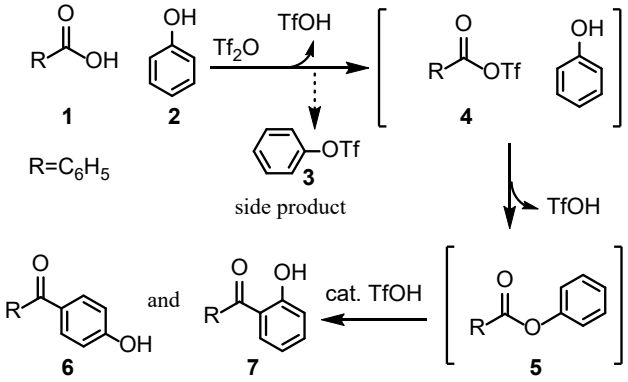

Fig. 2 Proposed reaction pathway for the reaction of benzoic acid and phenol in 3:7-Tf_2O/TfOH system

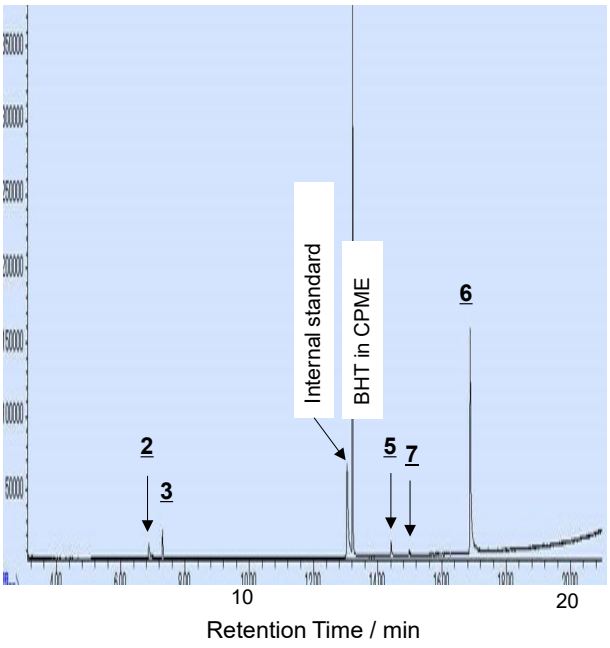

Fig. 3 Chromatogram for the reaction mixture of benzoic acid and phenol in 3:7-Tf_2O/TfOH at 1 h past

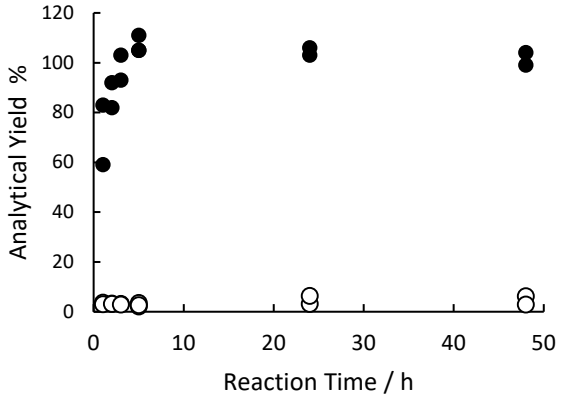

Fig. 4 Time course the one-pot Fries rearrangement.
●: 4-hydroxybenzophenone ○: phenyl triflate

3.2 Reaction of Benzoic acid and Phenol in Tf_2O

The reaction of benzoic acid and phenol in Tf_2O gave a stable phenyl triflate in the first 2 hours and the desired Fries rearrangement products, 4- or 2-hydroxybenzophenones, was not detected over the 48 hours.

3.3 Reaction of Benzoic acid and Phenol in Tf_2O/TfOH

A reaction in 3:7-Tf_2O/TfOH afforded 4-hydroxybenzophenone **6**, 2-hydroxybenzophenone **7**, and side product phenyl triflate **3**. A reaction intermediate, phenyl benzoate **5**, was detected in the first hour as shown in Fig. 3 and then disappeared, supporting the formation of the ketone by rearrangement through the phenolic ester **5** (Fig. 2).

Fig. 4 shows the changes over time products. The para-product **6** was the major product and was afforded in good yield. The rearrangement reaction was complete after 5 hours. Also, the yield of the ortho product **7** was less than 1%. The unintended reaction to phenyl triflate **3** could be suppressed to 3-4% yield.

4. Conclusion

A facile one-pot synthesis of hydroxyaryl ketones from carboxylic acids was developed. In a reaction using benzoic acid as carboxylic acid, the para-product of Fries rearrangement, 4-hydroxybenzophenone, was obtained in high yield. We are further considering the extension to one-pot reactions from amino acids, including protection of amino groups.

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References

(1) Ryo Murashige, Yuka Hayashi, Syo Ohmori, Ayuko Torii, Yoko Aizu, Yasuyuki Muto, Yuta Murai, Yuji Oda, Makoto Hashimotol: "Comparisons of O-acylation and Friedel-Crafts acylation of phenols and acyl chlorides and Fries rearrangement of phenyl esters in trifluoromethanesulfonic acid: effective synthesis of optically active homotyrosines" *Tetrahedron*, **Vol.67**, pp.641-649 (2011).