BRØNSTED ACID–CATALYZED FRIEDEL–CRAFTS REACTION OF INDOLES TO α-KETIMINO ESTERS

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GRAPHICAL ABSTRACT

Abstract Friedel–Crafts reaction of indoles to aromatic α-ketimino esters was found to be catalyzed by camphorsulfonic acid with good yields (up to 98%) under ambient temperature. This process provides an efficient method for the synthesis of unnatural amino acid derivatives that bear quaternary carbon centers.

Keywords Bronsted acid; Friedel–Crafts reaction; indoles; α-ketimino esters

INTRODUCTION

Friedel–Crafts alkylation reaction is one of the most important C-C bond-forming reactions,[1] and provides an efficient method for the synthesis of functionalized aromatic and heteroaromatic compounds. Among the Friedel–Crafts alkylation reactions, the addition reaction of indoles to α-imino esters has attracted considerable attentions because of their wide application for the synthesis of indolyglycines, which are an important class of nonproteinogenic amino acids that possess biological and physiological activities and have frequently been used for the synthesis of the drugs macidins,[2] cephalosporin,[3] and pemedolac.[4] Compared to reactive and readily available α-aldimino ester,[5–7] the Friedel–Crafts reactions of α-ketimino esters are less studied although they are synthetically important amino acids that have

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tetrasubstituted carbon centers formed during this process. Moreover, most examples reported to date are limited to the reaction of more active N-alkoxycarbonyl or N-sulfonyl α-ketimino esters (Scheme 1), which often need harsh reaction conditions to prepare. Recently, Maruoka and coworkers reported chiral Brønsted acid–catalyzed asymmetric Friedel–Crafts reaction of indoles to α-ketimino esters (2); to overcome the poor activity of ketimines, two electron-withdrawing ester groups were employed, which limits the substrate scope of this reaction. Aromatic α-ketimino esters (3) were easy to prepare and had been used for hydrogenation reaction and radical alkylation reaction. In this context, we have been interested in the development of Friedel–Crafts reaction of indoles (5) to aromatic α-ketimino esters, which are less active and sterically more congested. Herein, we report a highly efficient addition of indoles to structurally diversified α-ketimino esters catalyzed by camphorsulfonic acid.

To promote the activity of aromatic α-ketimino ester, compound 4a was synthesized for investigation. We initially studied the addition of indole (5a) and phenyl α-ketimino ester (4a) catalyzed by various Brønsted acids (10 mol%) in dichloromethane. The representative examples are compiled in Table 1 (entries 1–7). The use of weak Brønsted acids, such as benzoic acid and acetic acid, result in prolonged reaction time and poor yields (Table 1, entries 4 and 5); whereas good yield was obtained when a strong Brønsted acid was used. For example, when trifluoroacetic acid was employed as a catalyst, the reaction was finished in 12 h with 81% isolated yield (Table 1, entry 1). The best result was obtained when camphorsulfonic acid was used with 85% yield in 12 h (Table 1, entry 3).

Having identified the best catalyst, we surveyed the influence of solvent for the Friedel–Crafts alkylation reaction (Table 1, entries 8–14). Different solvents have significant effects on the yields of the product. The reaction was sluggish in ether and 1,2-dichloroethane with yields of 43% and 58% respectively (Table 1, entries 9 and 13); however, tetrahydrofuran (THF) proved to be the ideal media for this reaction, with the yield improving to 92% in only 8 h (Table 1, entry 11).

With the optimal reaction conditions in hand, the substrate scope of the Friedel–Crafts alkylation reaction was explored, and the results are summarized in Table 2. Various substituted aromatic α-ketimino esters were examined. The electron nature of the substitute on aromatic ring has little effect on the yield of the addition products; both electron-withdrawing and electron-donating groups were tolerated, yielding the products 6 in high yield. The reaction of 2-thiophene ketimino ester (4g) led to the formation of 6g in 86% yield. Substituent on the indole C2 slightly depressed the reaction; for example, 2-methyl indole exhibits poor reactivity in this reaction with a 76% yield of 6k (Table 2, entry 11).
The substituent on the benzene motif of the indole ring has little effect on the yields of the products. An unprotected hydroxyl group on the indole ring was also tolerated; 4-hydroxyl indole (5b) reacts smoothly with 4a to generate 6h in 85% yield (Table 2, entry 8). The introduction of bulky benzyloxy group on the indole ring was also tested and the sterically more congested product 6i was isolated in 91% yield (Table 2, entry 9). Different substituents on the C5 position of indole ring were also studied and the corresponding products were obtained in 81–93% yields (Table 2, entries 10, 12, and 13). However, compound 4h without a nitro group reacted slowly with indole 5a to generate 6n in 50% yield after 48 h (Table 2, entry 14). Furthermore, only a trace amount of the corresponding product was detected on TLC when the nitro group was linked on the C5 position of the indole ring.

In summary, we have developed a novel Brønsted acid–catalyzed Friedel-Crafts alkylation reaction of indoles to less reactive aromatic α-ketimino esters. A series of indolyglycines derivatives bearing a tetrasubstituted carbon center were synthesized during this process. This reaction is efficiently catalyzed by camphorsulfonic acid with good yield (50–98%). The chiral Brønsted acid–catalyzed asymmetric Friedel–Crafts alkylation reactions are under way in this laboratory and will be reported in due course.

**General Procedure**

Camphorsulfonic acid (3.3 mg, 0.01 mmol) was added to a mixture of indole (5a, 23.4 mg, 0.2 mmol) and phenyl α-ketimino ester (4a, 26.8 mg, 0.1 mmol)
Table 2. Friedel–Crafts reaction of 4 and 5

| Entry<sup>a</sup> | 4  | 5 | 6<sup>b</sup> | Time (h) | Yield (%)<sup>c</sup> |
|-------------------|----|---|---------------|----------|----------------------|
| 1                 | 4a | 5a| 6a            | 10       | 92                   |
| 2                 | 4b | 5a| 6b            | 14       | 97                   |
| 3                 | 4c | 5a| 6c            | 14       | 98                   |
| 4                 | 4d | 5a| 6d            | 28       | 96                   |
| 5                 | 4e | 5a| 6e            | 26       | 98                   |
| 6                 | 4f | 5a| 6f            | 8        | 94                   |
| 7                 | 4g | 5a| 6g            | 24       | 86                   |
| 8                 | 4a | 5b| 6h            | 30       | 85                   |

(Continued)
in THF and stirred under room temperature until 4a disappeared, as shown by thin-layer chromatography (TLC) (about 12 h). The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 5:1) to give 6a as yellow solid (35.4 mg, 92%). 1H NMR (400 MHz, CDCl3) δ 11.21 (s, 1H), 8.84 (s, 1H), 7.95 (dd, J = 8.8, 1.8 Hz, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.45–7.41 (m, 7H), 7.15–7.11 (m, 2H), 6.99 (t, J = 7.8 Hz, 1H), 6.69 (d, J = 2.0 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 164.6, 141.3, 139.8, 139.5, 139.1, 137.8, 129.4, 127.9, 127.0, 125.7, 122.7, 122.6, 120.7, 120.2, 114.9, 114.7, 112.9, 112.7, 64.4. HRMS was calcd. for C22H16N3O4 [M+H]+: 386.1141; found: 386.1138.

Table 2. Continued

| Entry | 4 | 5 | 6 | Time (h) | Yield (%) |
|-------|---|---|---|----------|-----------|
| 9     | 4a|   |   |          | 16        | 91        |
| 10    | 4a|   |   |          | 16        | 81        |
| 11    | 4a|   |   |          | 18        | 76        |
| 12    | 4a|   |   |          | 16        | 91        |
| 13    | 4a|   |   |          | 24        | 93        |
| 14    | 4h|   | 5a|          | 48        | 50        |

*aReactions were carried out with 4a (0.1 mmol), 5a (0.2 mmol), and catalyst (0.01 mmol) in solvent (0.5 mL) under room temperature.

*bAll products were characterized by 1H NMR, 13C NMR, and HRMS.

*cIsolated yield.
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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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