

Michael Addition between Isatin and Acrylate Derivatives

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Abstract: A simple and efficient Michael addition of isatin to acrylate in the presence of KOH was described. Methyl β -(2,3-dioxoindolin-1-yl) propanoate was synthesized firstly by the addition of isatin to methyl acrylate in a feasible approach using 10% KOH as catalyst in DMF with the highest yield of 72.5% under the optimized conditions. A series of β -(2,3-dioxoindolin-1-yl) propanoate derivatives was synthesized according to this approach and gave moderate to relative high yields. The directive distinct color changes in this reaction were illuminated by the reaction mechanism analysis.

Keywords: Acrylate, β -(2,3-dioxoindolin-1-yl) propanoate, isatin, Michael addition.

INTRODUCTION

β -N-substituted carbonyl compounds, the essential components of many drugs and bioactive compounds, such as β -peptides [1], vitamin B₃ [2], emeriamine [3], cryptophycin [4] and TAN-1057 A [5], are commonly prepared by Michael addition of amino or β -amido to α,β -unsaturated carbonyl compound. In contrast to the assorted Michael addition methods for various nucleophiles, there are only a few works about the *N*-conjugate addition of amides and their derivatives. NaOH in THF [6], *t*-BuOK in PhCl [7], K₂CO₃ in DMF [8], TBSOTf-NEt₃ [9], Si(OEt)₄-CsF [10], Pd(PhCN)₂Cl₂ [11] and ethyl orthoformate-camphorsulfonic acid [12] have been used in the Michael addition of thiolactams, lactams and aliphatic amides to α,β -unsaturated compounds. However, to the best of our knowledge, only limited Michael addition of aromatic amides to α,β -unsaturated esters has been reported [13, 14].

As a special aromatic amide, isatin (indole-2,3-dione), is an important versatile nature product found in plants of the genus *Isatis* [15], *Calanthe discolor* LINDL. [16], *Couroupita guianensis* Aubl. [17] and even in mammalian tissues. Its function as a modulator of biochemical processes has been the subject of several discussions [18]. Besides, isatin is well-known as versatile building blocks, which can be used for the synthesis of a large variety of heterocyclic compounds, such as indoles and quinolines, and as a raw material for drug synthesis [19]. Therefore, to extend of our studies on isatin, in this paper, we will report the Michael addition between isatin and acrylate derivatives under mild condition.

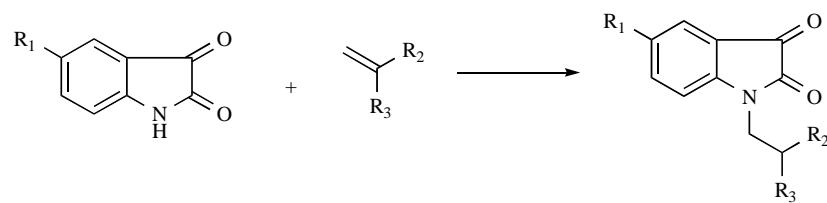
RESULTS AND DISCUSSION

The first feasibility of the approach was investigated by the reaction of isatin with methyl acrylate under different bases and solvents (Scheme 1; R₁, R₂ = H, R₃ = COOCH₃). A reaction mixture of isatin (1.0 mmol), methyl acrylate (1.2 mmol) and base (0.1 mmol) in 20 mL solvent was stirred at a certain temperature, and the target compound (methyl β -(2,3-dioxoindolin-1-yl) propanoate, compound 1) was separated by column chromatography after the reaction. The results are shown in Table 1.

From the table, it can be seen that the base and the solvent affect the yield deeply. Only the homogeneous strong bases, NaOH and KOH, catalyze this reaction effectively, either weak base (Na₂CO₃, K₂CO₃, NH(C₂H₅)₂, N(C₂H₅)₃) or the heterogeneous strong base (CaO) can hardly impulse this reaction in kinds of solvent. On the other hand, the solvent is also an important factor affecting the yield. For NaOH and KOH catalyzed reactions, DMF is a favorable solvent giving relative high yields. Besides, THF is an optional solvent with a moderate yield. But the reactions can hardly undergo in other solvents even under high temperature. So in the following reactions, KOH and DMF were selected as the catalyst and solvent. Then, the proper load of KOH in this reaction was screened, and the results were shown in Fig. (1). From the results, it can be found that less load of KOH gave low yield, 10% (molar ratio) was the optimal load with the highest yield of 72.5%. However, increasing the load of KOH was not helpful to the yield for the possible reason of the saponification of ester in the presence of KOH.

To understand the scope of this Michael addition reaction, a series of acrylate derivatives was investigated under the optimal reaction condition, and the results were shown in Table 2. All acrylate derivatives were transformed to their corresponding β -(2,3-dioxoindolin-1-yl) propanoate

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Scheme 1. The Michael addition between isatin and methyl acrylate derivatives. $R_1 = H, CH_3, Cl$; $R_2 = H, CH_3$; $R_3 = COOCH_3, COOC_2H_5, CONH_2, CN$.

Table 1. Screening of Base and Solvent for the Michael Addition Between Isatin and Methyl Acrylate

| No. | Base | Solvent | Temperature (°C) | Time (h) | Yield (%) |
|-----|---|--------------------|------------------|----------|-----------|
| 1 | NaOH | DMF | 25 | 8 | 68.8 |
| 2 | NaOH | MeOH | 65 | 8 | trace |
| 3 | NaOH | CH ₃ CN | 81 | 8 | trace |
| 4 | NaOH | THF | 25 | 48 | 52.4 |
| 5 | KOH | DMF | 25 | 12 | 72.5 |
| 6 | KOH | MeOH | 65 | 24 | 8.0 |
| 7 | KOH | CH ₃ CN | 81 | 8 | trace |
| 8 | KOH | THF | 25 | 48 | 54.7 |
| 9 | Na ₂ CO ₃ | DMF | 25 | 12 | 0 |
| 10 | K ₂ CO ₃ | DMF | 25 | 12 | trace |
| 11 | CaO | DMF | 25 | 12 | 0 |
| 12 | NH(C ₂ H ₅) ₂ | DMF | 25 | 12 | 0 |
| 13 | N(C ₂ H ₅) ₃ | DMF | 25 | 12 | 8.2 |
| 14 | — | Pyridine | 25 | 12 | * |

*The result is complex and there is no target product.

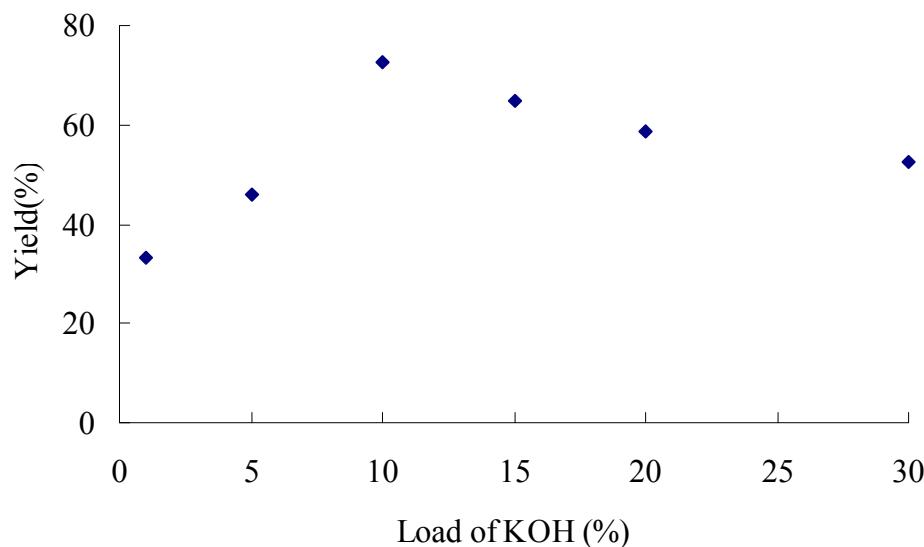


Fig. (1). The effect of the load of KOH on the yield of compound **1**.

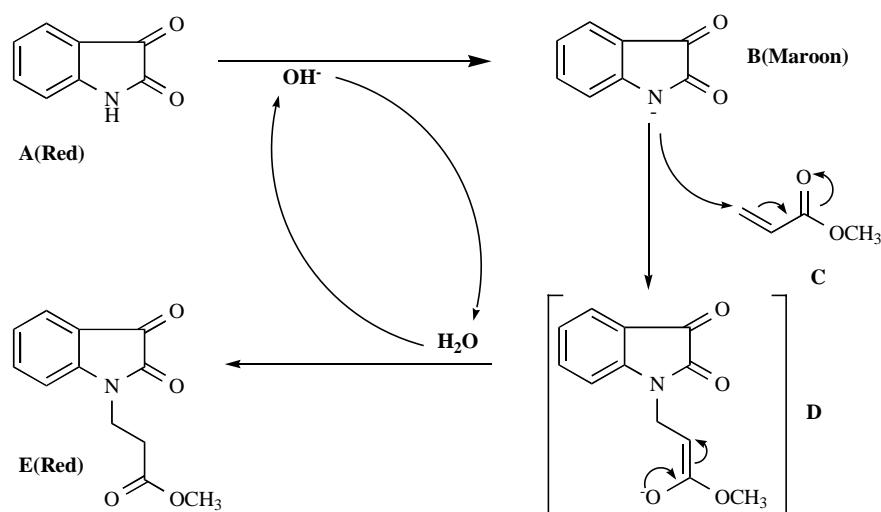
with moderate to high yields. The highest yield was obtained in the reaction of isatin with acrylonitrile, and a reasonable poor yield was found in the reaction of isatin with acrylamide for the existing of the acidic protons of amido. The α -methyl of acrylate restrains the reaction for the proper

reason of steric hindrance, and the substitute of isatin affects the reaction weakly.

The process of this Michael reaction between isatin and methyl acrylate can be described as Scheme 2. The amino proton of isatin (**A**) can be captured by the added base, while

Table 2. The Michael Addition Between Isatin and Acrylate Derivatives

| Compound | R ₁ | R ₂ | R ₃ | Yield (%) |
|----------|-----------------|-----------------|------------------------------------|-----------|
| 1 | H | H | COOCH ₃ | 72.5 |
| 2 | H | H | COOCH ₂ CH ₃ | 70.1 |
| 3 | H | CH ₃ | COOCH ₃ | 63.8 |
| 4 | H | H | CN | 81.8 |
| 5 | H | H | CONH ₂ | 23.6 |
| 6 | CH ₃ | H | COOCH ₃ | 75.0 |
| 7 | Cl | H | COOCH ₃ | 77.4 |
| 8 | CH ₃ | H | CN | 83.5 |

**Scheme 2.** The process of base catalyzed Michael addition between isatin and methyl acrylate.

the red solution of **A** turns to maroon solution (**B**). Followed by a typical anion addition to α,β -unsaturated ester, the target compound (**E**) is formed, at the same time, OH⁻ is regenerated and turns into the next catalysis cycle. As anion **B** is consumed, the color of the solution turned to red gradually indicating the end of this reaction.

EXPERIMENTAL

All starting materials and solvents (A.R. grade) were commercially available and were used without further purification. NMR spectra were recorded in the stated solutions using a Bruker Drx-400 spectrometer operating at 400 MHz for 1H. The chemical shifts are reported in ppm (δ) values and the coupling constants (J) are reported in hertz. Mass spectra were recorded on a Micromass Platform spectrometer using the direct-inlet system operating in the electron impact (EI) mode at 75 eV. Elemental analyses used a Carlo Erba 1106 element analysis instrument.

General Experimental Procedure

To a stirred solution of isatin (1.0 mmol) with methyl acrylate (1.2 mmol) in 20 ml of DMF, KOH (0.1 mmol) was added. The reaction mixture was stirred under room temperature for 8 h. The mixture was poured into 50 ml

water and washed by ethyl acetate (30 ml×3) and 10% NaCl (20 ml×3) sequentially. The organic layer was dried by anhydrous Na₂SO₄ over night. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (silica gel, gradient of 20:1 petroleum ether/ethyl acetate) to give the target products, compound **1** (yield, 72.5%). ¹H-NMR (CDCl₃, 400 MHz), δ : 7.51(1H, d, J = 7.6 Hz), 7.46(1H, t, J = 7.6 Hz), 7.09(1H, t, J = 7.6 Hz), 6.97(1H, d, J = 7.6 Hz), 4.01(2H, t, J = 8.0 Hz), 3.66(3H, s), 2.74(2H, t, J = 8.0 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ : 182.4, 171.3, 158.1, 150.5, 138.5, 125.4, 123.8, 117.6, 110.4, 52.1, 36.2, 31.8; MS m/z : 233 (M⁺).

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