Three Component Cascade Reaction of Cyclohexanones, Aryl Amines, and Benzoylmethylene Malonates: Cooperative Enamine-Brønsted Acid Approach to Tetrahydroindoles

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ABSTRACT: A three-component cascade reaction comprising cyclic ketones, arylamines, and benzoylmethylene malonates has been developed to access 4,5,6,7-tetrahydro-1\(H\)-indoles. The reaction was achieved through cooperative enamine-Brønsted catalysis in high yields with wide substrate scopes. Mechanistic studies identified the role of the Brønsted acid catalyst and revealed the formation of an imine intermediate, which was confirmed by X-ray crystallography.

1. INTRODUCTION

Nitrogen-containing heterocycles are essential components of a wide range of bioactive natural products.\(^1\) Nitrogen-based heterocycles have exhibited a wide range of biological activities including cancer, HIV, diabetes, tuberculosis, and Alzheimer’s disease.\(^2\) 4,5,6,7-Tetrahydro-1\(H\)-indoles represent an important class of structural scaffolds in the design and derivation of new pharmcophores, which can act as inhibitors for tyrosine kinase,\(^3\) anti-hepatitis C virus,\(^4\) anti-cancer and anti-oxidant agents,\(^5\) and natural products.\(^6\) 4,5,6,7-Tetrahydro-1\(H\)-indoles also serve as synthetic intermediates for natural products such as goniomitine\(^7\) and chuangxinmycin.\(^8\) Recently, 4,5,6,7-tetrahydro-1\(H\)-indoles have also been found to be present in sponge Scalarispongia species.\(^9\)

Considerable efforts have been devoted to developing synthetic methods to construct 4,5,6,7-tetrahydro-1\(H\)-indoles due to their diverse biological activity. Syntheses of N-substituted 4,5,6,7-tetrahydro-1\(H\)-indoles have been achieved through metal Lewis acid catalysis,\(^10\) Brønsted acid catalysis,\(^11\) and microwave synthesis.\(^12\) Catalyst-free conditions have also been reported.\(^13\) Benzoylmethylene malonates are effective Michael acceptors\(^14\) and have been utilized for the synthesis of heterocycles including furans, quinoxalines, imidazoles, benzo-[1,4]-thiazines, 2,4,5-trisubstituted oxazole, and pyrrolobenzo-

In 2016, Jia and coworkers reported Friedel-Crafts reactions with benzoylmethylene malonates to afford enantioselective Michael products using Cu(OTf)\(_2\) and (S)-iPr-bisoxazoline as the catalyst (Figure 1a).\(^16\) Kakiuchi et al. developed an efficient cyclization reaction with benzoylmethylene malonates and propargyl alcohols for the synthesis of hydrofurans (Figure 1b).\(^17\) Bisht and Peddinti reported a FeCl\(_3\) mediated reaction of preformed \(\beta\)-enamino ester and benzoylmethylene malonates affording pyrrolobenzoxazines (Figure 1c).\(^18\)

It has been reported that the reaction of activated alkenes\(^18,19\) or 2,3-diketoesters\(^20\) with aldehydes/ketones and amines can afford pyrroles or hydroxindoles. Most of these reactions are through the \(\beta\)-enaminone intermediate, which is derived from a 1,3-diketone and an amine. \(\beta\)-Enaminone is a common synthetic intermediate/substrate for the synthesis of pyrrole.\(^21\) In contrast, there are only three reports in the

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We started our investigation with cyclohexanone (2a), and dimethyl 2-(2-oxo-2-phenylethylidene) malonate (3a) (Table 1). Metal Lewis acids including Sc(OTf)3, Cu(OTf)2, and Y(OTf)3, were first assessed to catalyze this reaction in toluene at 50 °C. We were delighted to find out that the desired product (4a) was formed in all these reactions. However, the yields were low (18−45%, entries 1−3). The starting materials were mainly recovered after the reactions were worked up. We then tested different solvents using Y(OTf)3 as the catalyst (entries 4−9), which gave the highest yield in toluene (entry 2). Dichloromethane (DCM) turned out to be the best solvent offering 4a in 61% yield (entry 4). Interestingly, increasing the load of the catalyst by twofold did not increase the yield (entry 9). Addition of 4 Å MS enhanced the yield to 70% (entry 10). Raising the temperature to 60 °C significantly improved the efficiency of the reaction (88%, entry 11). The addition of more 4 Å MS or longer reaction time did not affect the reaction significantly (entries 12 & 13). Addition of a slight excess of 4-methoxyaniline improved the yield to 91% (entry 14).

Table 1. Optimization of Conditions

| entry | solvent | catalyst | T (°C) | additive (4 Å MS) | yield (%) |
|-------|---------|----------|--------|-------------------|----------|
| 1     | toluene | Sc(OTf)3 | 50     | -                 | 18       |
| 2     | toluene | Y(OTf)3  | 50     | -                 | 45       |
| 3     | toluene | Cu(OTf)2 | 50     | -                 | 10       |
| 4     | DCM     | Y(OTf)3  | 50     | -                 | 61       |
| 5     | THF     | Y(OTf)3  | 50     | -                 | 6        |
| 6     | EtOAc   | Y(OTf)3  | 50     | -                 | 8        |
| 7     | CH3CN   | Y(OTf)3  | 50     | -                 | 33       |
| 8     | CHCl3   | Y(OTf)3  | 50     | -                 | 46       |
| 9     | DCM     | Y(OTf)3  | 50     | -                 | 50       |
| 10    | DCM     | Y(OTf)3  | 50     | 10 mg             | 70       |
| 11    | DCM     | Y(OTf)3  | 60     | 10 mg             | 88       |
| 12    | DCM     | Y(OTf)3  | 60     | 20 mg             | 85       |
| 13    | DCM     | Y(OTf)3  | 60     | 10 mg             | 87       |
| 14    | DCM     | Y(OTf)3  | 60     | 10 mg             | 91       |
| 15    | DCM     | Yb(OTf)3 | 60     | 10 mg             | 90       |
| 16    | DCM     | (PhO)2POH | 60 | 10 mg | 93 |
| 17    | CCl4    | (PhO)2POH | 60 | 10 mg | 87 |
| 18    | DCM     | (PhO)2POH | 65 | 10 mg | 96 |

The reactions were conducted with 1.0 mmol of 1a, 0.1 mmol of 2a, and 0.1 mmol of 3a for 24 h in 1 mL of solvent. Isolated yield. a NMR yield. b 20% of Y(OTf)3 was used. c Stirred for 48 h. d 1 eq of 4-methoxyaniline was used.

Yb(OTf)3 (entry 15) showed similar activity with Y(OTf)3. A Bronsted acid, i.e., diphenyl phosphate, was also attempted and turned out to be slightly better than metal Lewis acids (entries 16 & 17). Finally, when the temperature was raised to 65 °C, an excellent yield of 96% was achieved (entry 18).

We then investigated the substrate scope of this reaction with different benzoylmethylene malonates (Table 2). Benzoylmethylene malonates with different substituents on the phenyl rings were reacted with cyclohexanone and 4-methoxyaniline under optimal conditions. Both electron-donating and electron-withdrawing groups at meta, ortho, and para positions afforded the desired 4,5,6,7-tetrahydro-1H-indoles in high yields (4b−4i, 89−99%). Disubstituted aryl groups at the meta-positions including the bulky CF3 also gave good yields (4j & 4k). However, trisubstituted aryl groups at both para and ortho positions did not give any product, indicating that steric hindrance is at play in this case (4o, 0%). We also tried different ester groups of the benzoylmethylene malonates (4l−4n, 83−96%). Larger esters such as isopropoxy esters (4m & 4n) also worked well for this reaction.

The substrate scope of arylamine and cyclic ketone were also explored (Table 3). The reaction of p-methoxyaniline and 3a worked smoothly with a 7-membered cyclic ketone, affording the desired 4,5,6,7-tetrahydro-1H-indole in 89% yield (5a). Five-membered cyclic ketone also reacted with p-methoxyaniline and 3a, albeit giving the product in lower yield (5b, 75%), likely due to the higher ring strain upon fusion with the 5-membered pyrrole ring. Six-membered heterocyclic ketones generated the desired products in good yields (5c & 5d, 87 and 83% yield, respectively). Substituted cyclohexanone also
produced the product in excellent yield (5e, 99% yield). For the scope of arylamine, electron-donating groups including methyl and methoxy groups at ortho, meta, and para positions reacted efficiently with cyclohexanone and 3a, leading to the formation of the products in good yield in 24 h (6a−6d, 93−99% yield). When electron-withdrawing bromo was present at the ortho, para, and meta positions of the arylamines, longer reaction times (48 h) were needed and the yields decreased (6e−6h, 41−67% yield). It is notable that the o-bromoaniline gave the lowest yield (41%), possibly due to the proximity of the large substituent and the NH₂ slowing down the formation of enamine with the cyclohexanone. This effect was also observed with 6i (64% yield), where a bulky t-butyl group is placed at the ortho position of the arylamine. In the case of fluoroaniline, it is interesting that the p-fluoroaniline was able to generate the product in 94% yield in 72 h. As noted above, when a bulkier group was present at the ortho position of arylamine (6f and 6i, Table 3), the reaction slowed down and the yields decreased. A similar steric effect was also observed for benzoylmethylene malonates when the ortho positions on the phenyl ring were occupied (4o, Table 1). To investigate the mechanism of this reaction, we decided to explore how steric effect affected the process of the reaction (Scheme 1). We selected 3i where a moderately bulky optimized conditions to demonstrate the functionality of this method. The desired 4,5,6,7-tetrahydro-1H-indoles were obtained in good yield for 6l (68%) and high yields for 6m and 6n (88 and 94%). The structure of 4,5,6,7-tetrahydro-1H-indoles were confirmed with ¹H and ¹³C NMR spectroscopy, mass spectrometry, and X-ray crystallography (6i, CCDC 2164186). Gram scale reaction of 1a, 2a, and 3a was also conducted (see SI), affording the product in 86% yield.

Table 2. Substrate Scope of Benzoylmethylene malonates

| Compound | Reaction Condition | Yield | Remarks |
|----------|--------------------|-------|---------|
| 5a       | 1a (1.0 mmol), 2a (0.11 mmol), 3 (0.1 mmol), 4 Å MS (10 mg), DCM (1 mL) at 65 °C for 24 h | 99% | Isolated yields |

Table 3. Substrate Scope of Ketone and Arylamine

| Compound | Reaction Condition | Yield | Remarks |
|----------|--------------------|-------|---------|
| 5a       | 1 (1.0 mmol), 2 (0.11 mmol), 3a (0.1 mmol), 4 Å MS (10 mg), DCM (1 mL) at 65 °C for 24−72 h | 99% | Isolated yields |

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Scheme 1. Mechanism Investigation: (a) Steric Effect; (b, c) Catalyst Investigation

Scheme 2. Proposed Mechanism

In summary, we have developed a novel synthetic method to access 4,5,6,7-tetrahydro-1H-indoles/pentasubstituted pyrroles, which is of high biological and pharmaceutical importance. This three-component cascade reaction involving cyclic ketones, arylamines, and benzoylmethylene malonates is concise, versatile, and efficient, affording 4,5,6,7-tetrahydro-1H-indoles in high yields with wide substrate scopes. The three-component reaction is achieved through cooperative enamine-acid (Brensted and metal Lewis acid) catalysis. Mechanistic studies indicate that the steric effect plays a crucial role in determining the output of the reaction. The formation of an imine intermediate was revealed and confirmed with X-ray crystallography. The Bronsted acid catalyst was proved to be the key to prompt the intramolecular cyclization reaction of the imine intermediate, leading to the formation of 4,5,6,7-tetrahydro-1H-indoles.

3. CONCLUSIONS

In summary, we have developed a novel synthetic method to access 4,5,6,7-tetrahydro-1H-indoles/pentasubstituted pyrroles, which is of high biological and pharmaceutical importance. This three-component cascade reaction involving cyclic ketones, arylamines, and benzoylmethylene malonates is concise, versatile, and efficient, affording 4,5,6,7-tetrahydro-1H-indoles in high yields with wide substrate scopes. The three-component reaction is achieved through cooperative enamine-acid (Brensted and metal Lewis acid) catalysis. Mechanistic studies indicate that the steric effect plays a crucial role in determining the output of the reaction. The formation of an imine intermediate was revealed and confirmed with X-ray crystallography. The Bronsted acid catalyst was proved to be the key to prompt the intramolecular cyclization reaction of the imine intermediate, leading to the formation of 4,5,6,7-tetrahydro-1H-indoles.

To gain further insight into the mechanism, we investigated the role of the acid catalyst [(PhO)₂PO₂H]. The reaction of 3i, 1a, and 2i in the absence of an acid catalyst at 65 °C resulted in 55% yield of imine 8a without observation of 9a, similar to the result with the catalyst (8a, 56% yield) (Scheme 1b). When 8a in DCM was heated to 100 °C without a catalyst, no product was observed, which is in sharp contrast with a similar reaction conducted in the presence of the acid catalyst (Scheme 1c). These data suggest that the acid catalyst, i.e., (PhO)₂PO₂H, plays a crucial role in the transformation of 8a to 9a. A mechanism of the reaction was proposed based on these experimental data (Scheme 2). Enamine A is formed in situ from cyclic ketone and arylamine, which then reacts with benzoylmethylene malonate (3) through a Michael-type addition to give 8. An equilibrium between imine 8 and enamine B can be established. The carbonyl group is then activated by (PhO)₂PO₂H to initiate an intramolecular cyclization reaction (C) to afford D, after which the loss of water provides the final 4,5,6,7-tetrahydro-1H-indole.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c05909.

Experimental procedures, 1H and 13C NMR and other characterization data, single crystal X-ray analysis, and computational methods (PDF)
Crystallographic data for the 6i complex (CIF)
Crystallographic data for 8a (CIF)

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