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DCC Mediated Direct Amidation of NSAID Naproxen, Ibuprofen and Ketoprofen with Secondary Amines

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Direct and atom-economical amidation of nonsteroidal anti-inflammatory drugs naproxen ibuprofen and ketoprofen with a variety of secondary amines was effected using commercially available DCC under mild and open-air conditions. These prodrug amides were obtained in good to moderate yields ranging between 30–90%.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) belong to the class of therapeutic drugs which are used for treatment of pain, fever, inflammation, and blood clotting diseases.[1] Naproxen, ibuprofen, and ketoprofen occupy an important place among the main types of NSAIDs.[2] New findings show that long-term use of these drugs decreases the rate of occurrence of certain types of cancer. This further increases the interest in this drug class.[3] Therefore, NSAID-derived drugs with better efficacy but minimized side effects are constantly being designed and synthesized.

Amides are undoubtedly one of the most fundamental functional groups in organic chemistry as they exist widely in natural products, pharmaceuticals and industrially important compounds.[4] Amide bonds are present in pesticides, peptides, and antibiotics, and occur in the structure of more than 25% of available pharmaceuticals.[5] That is why the gradual increase in their structures is unsurprising. More importantly, in biological systems, amino acids are linked to each other by amide bonds to form the protein structures. Amides can be prepared using a variety of reaction precursors and following many different reaction pathways.[6] Although oxidative amidation studies are carried out from some primary alcohols or aldehydes,[7] the most common method is condensation reactions of carboxylic acids with amines in the presence of various catalysts or activators.[8] In spite of their great importance, most of the known methods for their synthesis are often inefficient and result in hazardous wastes which have negative effects on the environment. Although the direct amidation of carboxylic acids using radio frequency heating has been carried out practically and reactive-free, the substrate scope is quite limited.[9] The use of a series of metal catalysts based on Ti, Zr, and Ta is among the alternative methods in the synthesis of amides.[8a,10] However, there are many disadvantages in these methods: many of the catalysts require multistep synthesis; the reactions must be carried out under reflux conditions using mostly aromatic solvents; non-stoichiometric acid or amine must be used; water must be removed from the reaction media by azeotropic conditions or the use of large amounts of desiccating agents. The use of boron-based catalysts in the direct amidation of carboxylic acids and amines is another effective protocol.[11] In addition to the disadvantages of metal-catalyzed amidation in this transformation; these method are often limited to active systems. Although carbodiimides, well-known as activators, are used in the direct amidation of primary amines and anilines with carboxylic acids, with best of our knowledge, we could not find any study on amidation with secondary amines.[4a,12]

Herein, we describe for the first time the synthesis of NSAID amides, derivatives of naproxen, ibuprofen, and ketoprofen with secondary amines promoted by *N*,*N*′-dicyclohexylcarbodiimide (DCC).

Results and Discussions

At the beginning of our study, we aimed to perform the amidation reaction of *N*-hydroxy-phthalimide (NHP) esters with secondary amines (Scheme 1). For this purpose, naproxen NHP ester was prepared and made to react with pyrrolidine in ACN at room temperature. In the first attempt the corresponding amide was attained in a modest yield (70%). The solvent was replaced with water in order to carry out the reaction under environmentally friendly conditions. Unfortunately, trace amount of desired product was obtained.

Since the reaction with NHP esters didn't result in excellent yields, we transitioned to work on a DCC-promoted direct amidation of carboxylic acids, the precursors of NHP esters, as a one-step atom-economic method to synthesize the amide. We determined the amidation reaction between naproxen and pyrrolidine as a model reaction and started the optimization. The obtained results are summarized in Table 1. When the reaction was carried out by adding all the reagents at the same time, no product formation was observed due to the amine deprotonated the carboxylic acid. Therefore, first, an intermediate product was formed by mixing carboxylic acid and DCC at

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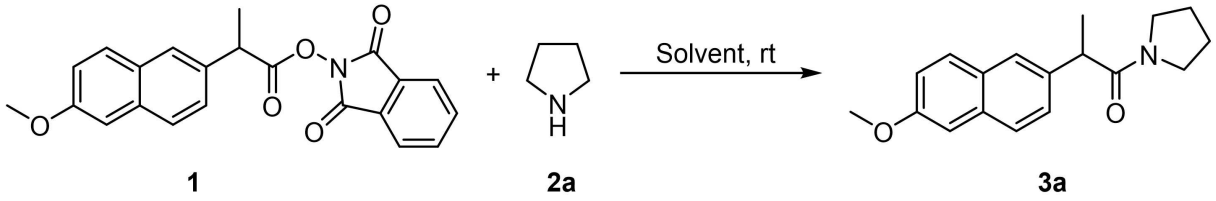
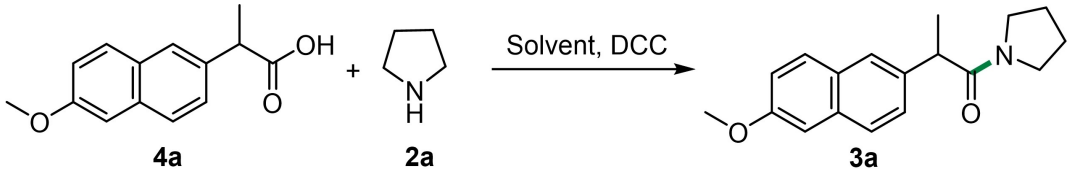


Scheme 1. Amidation reaction of *N*-hydroxyphthalimide (NHP) ester with secondary amine.

Table 1. Optimization of the Reaction Conditions.



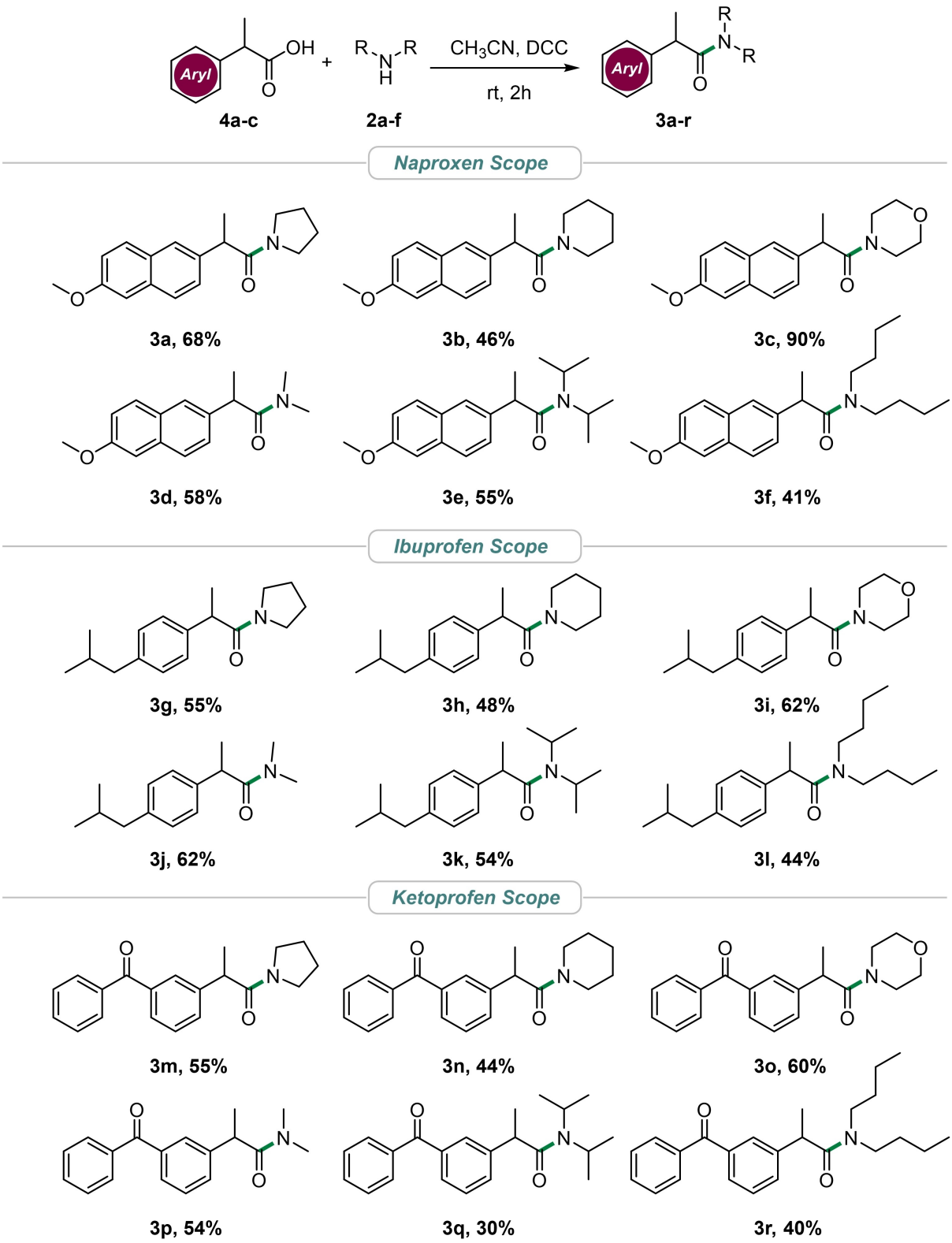
Entry	Solvent	Temperature [°C]	Yield [%][a]
1	H_2O	rt	Trace
2	DMSO	rt	25
3	DCM	rt	51
4	CH_3CN	rt	68
5	CH_3CN	rt	70[b]
6	CH_3CN	rt	69[c]
7	CH_3CN	40	59
8	CH_3CN	40	70[c]
9	CH_3CN	rt	0[d]
10	CH_3CN	rt	68[e]

The reaction was performed with **2a** (1.2 equiv), **4a** (0.2 mmol), and DCC **1** (1.2 equiv) in 3.0 mL of solvent for 2 h, [a]Isolated yields, [b]The reaction was run for 24 h, [c]2.4 equiv. **2a** was used. [d]The reaction was performed without DCC. [e]Optically active naproxen was used and enantiomeric excess (ee) of product was determined with chiral HPLC using OD-H column.

room temperature for 1 hour, and then the synthesis of the target product was carried out by adding amine. In order to choose a convenient solvent for the reaction condition a series of solvents were screened following this synthetic route. It was observed that the solvent influenced the product formation significantly. While a trace amount of product was obtained in the presence of H_2O, only 25% yield was attained in the presence of DMSO. Clearly the best result was gained in the presence of CH_3CN. No significant difference could be determined by increasing the temperature or equivalent of the amine or extending the reaction time. However, in the presence of optically pure naproxen, the more labile stereocenter in both the alpha and benzylic position underwent partial racemization, yielding the product with an enantiomeric excess of 80%. Finally, the optimal reaction conditions were found to be 1.2 equiv. DCC and 1.2 equiv. amine, in the presence of CH_3CN at ambient temperature for 2 h.

Under the established conditions, we then proceeded to determine the generality of the current DCC promoted amidation protocol and investigated the reaction scope of ketoprofen, ibuprofen and naproxen with a range of secondary amines (Scheme 2). In general, with a few exceptions, the amidation reaction resulted in moderate to good yields ranging between 30% to 90%. It was observed that the backbone of ibuprofen, ketoprofen, and naproxen had little effect on the conversion of the reaction. In regards to amine scope, higher yields were obtained while employing dimethyl amine and pyrrolidine which have less steric hindrance than the more bulky dibutyl amine and diisopropyl amine, Thus, amine steric hindrance serves to negatively affect reaction conversion. In the case of morpholine oxygen atom modulated basicity. Thus, morpholine has demonstrated higher nucleophilicity than piperidine.

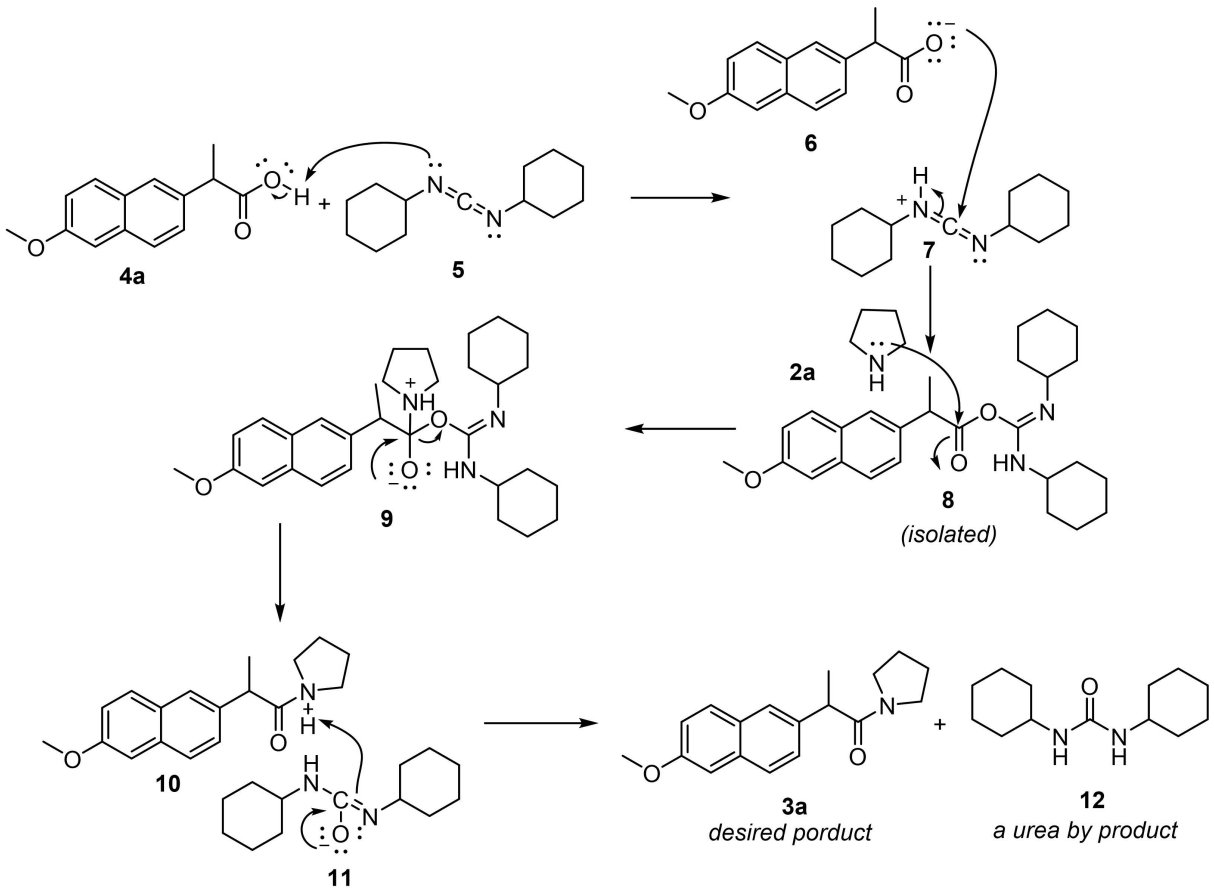
In the first step of the reaction mechanism, the lone pair of electrons from the nitrogen atom of DCC **5** attack the carboxylic acid **4a** and deprotonate it in order to form carboxylate **6**. This carboxylate **6** attacks to the electrophilic carbon center of **7** and the double bond electrons between carbon and nitrogen move onto nitrogen. In the next step, lone pair of electrons from nitrogen atom of the secondary amine nitrogen **2a** makes a nucleophilic attack on the carbonyl center of **8**, and the π bond electrons are transferred to the oxygen **9**. Afterwards, while the negative charge on the oxygen regenerates the carbonyl group **10**, *N*,*N*′-dicyclohexylcarbamimidate **11** ejects from the structure. Finally, by protonation and deprotonation the desired product amide **3a** and the byproduct urea **12** are formed (Scheme 3).



Scheme 2. Amidation of NSAID naproxen, ibuprofen and ketoprofen with secondary amines.

Conclusion

In conclusion, we have reported the direct amidation of nonsteroidal anti-inflammatory drugs naproxen ibuprofen and ketoprofen with a range of cyclic, and acyclic secondary amines in the presence of readily available and inexpensive DCC in open air under ambient conditions and reasonable reaction



Scheme 3. Plausible Mechanism.

times. The prodrug amides were obtained in good to moderate yields, and their structural characterization was carried out using NMR and mass spectroscopies.

Experimental Section

General procedure of amidation: A 5 mL vial was charged with acid (0.2 mmol) and *N*,*N*′-dicyclohexylcarbodiimide **5** (DCC, 0.24 mmol). Afterwards, 2 mL of the ACN was added. The obtained mixture was stirred for 1 h at ambient temperature. After 1 h, the amine (1.2 mmol in 1 mL of ACN) was added the mixture and the reaction performed for 1 h at ambient temperature. After that time, the ACN was removed, the desired product was obtained via column chromatography purification.

Supporting Information Summary

Supporting information includes the experimental details, spectroscopy data of the synthesized compounds.

Conflict of Interest

There are no conflicts to declare.

Keywords: Direct Amidation · NSAID · Secondary Amine · Naproxen · Ibuprofen · Ketoprofen

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