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Catalytic *N*-methyl amidation of carboxylic acids under cooperative conditions†

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Amide is a fundamental group that is present in molecular structures of all domains of organic chemistry and the construction of this motif with high atom economy is the focus of the current research. Specifically, *N*-methyl amides are valuable building blocks in natural products and pharmaceutical science. Due to the volatile nature of methyl amine, the generation of *N*-methyl amides using simple acids with high atom economy is rare. Herein, we disclose an atom economic protocol to prepare this valuable motif under DABCO/Fe₃O₄ cooperative catalysis. This protocol is operationally simple and compatible with a range of aliphatic and (hetero)aromatic acids with very good yields (60–99%). Moreover, the Fe₃O₄ can be easily recovered and high efficiency is maintained for up to ten cycles.

Amide is a fundamental group that is present in molecular structures of all domains of organic chemistry.¹ It is widely distributed in natural products, synthetic drugs and functional polymers, and is also the key chemical connection in proteins.² It has been shown that amide bond formation alone accounts for 65% of all preliminary screening reactions in the pharmaceutical industry.³ This means the generation of amide bonds with high atom efficiency is of high practical importance. And not surprisingly, ‘amide formation avoiding poor atom economy reagents’ was voted as the top challenge for organic chemistry by the ACS Green Chemistry Institute in 2007.³

From synthetic point of view, the ideal way to produce amide bonds would be the direct coupling of readily available carboxylic acids and amines, but this process is thermodynamically unfavourable due to the formation of the corresponding carboxylate-ammonium salt,⁴ therefore, stoichiometric amount of coupling reagents, such as DCC, DIC, EDCI, HATU, HBTU, HCTU, SOCl₂, BOP, acid chloride *etc.*, are generally required to sidestep thermal conditions for amide bond formation.⁵ These reagents are highly successful, but the process generally suffers from poor atom economy and side products removal issue especially in the large-scale applications.⁵ To overcome these drawbacks, “nonclassical” amide bonds formation routes were investigated.⁶ In these processes,

the catalyst takes the role of a coupling reagent in generating an active ester suitable for amidation in a waste-free manner. However, these processes have not been applied in the preparation of *N*-methyl amides, probably because the methyl amine was delivered in its hydrochloride salt, alcoholic or aqueous form due to its volatile nature.

On a different note, *N*-methyl amides are extensively presented in numerous natural products and pharmaceutical molecules, as shown in Fig. 1,⁷ and the methylation of amides is a promising way to improve the pharmacological property of molecules.⁸ However, the synthesis of *N*-methyl amides compounds relies heavily on non-catalytic approaches.^{5,9} Catalytic approaches were also investigated by Hisaeda,¹⁰ Kundu,¹¹ Li,¹² Guo,¹³ Yu,¹⁴ Maruoka,¹⁵ Wang,¹⁶ Chen,¹⁷ Lamaty¹⁸ and their co-workers starting from nitriles, primary amides, aldoximes, aldehydes, lignin, carbamoylsilane and alcohols. Until recently, Thakur,¹⁹ Marce,²⁰ Sadeghzadeh²¹ and their co-workers developed elegant *N*-methyl amidation approach starting from carboxylic acids under nano-MgO, diatomite Earth@IL/ZrCl₄

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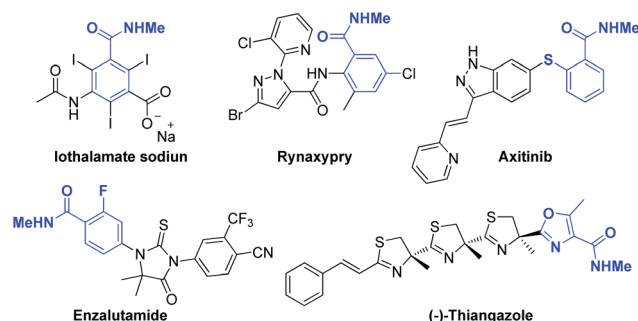


Fig. 1 Marketed drugs bearing *N*-methyl amide group.



and $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ catalysis respectively, while limitations like poor substrate scope or sophisticated tailored catalyst still persist. Mindful of all the above issues, developing an *N*-methyl amidation process of simple carboxylic acids, which is still of great challenge in synthesis, and establishing a broad (hetero) aryl scope with high atom economy from commercial available reagents and catalysts were critical considerations in this study. Moreover, the significance of *N*-methyl amides combined with our interests in the development of green synthetic approaches motivated us to explore the direct coupling of the carboxylic acids and isothiocyanates. To the best of our knowledge, this is the first successful work using isothiocyanatomethane to prepare *N*-methyl amides.

Our initial investigation begins with phenylacetic acid and isothiocyanatomethane as model substrate for condition optimization. Using acetonitrile as solvent, only trace amount of product was detected under catalyst free or *p*-toluenesulfonic acid (PTSA) catalysis conditions (Table 1, entry 1 and 2). Then, triethylamine was applied to increase the nucleophilicity of the acid and 17% yield was obtained after 48 hours (Table 1, entry 3). Consequently, different nucleophilic bases that can activate the isothiocyanate were screened and the chemical yield was increased to 65% under DABCO catalysis (Table 1, entry 3–7). Later on, in hoping of better reaction efficiency, Lewis acids that capable of lower the LUMO of the electrophile were screened. Delightfully, the chemical yield could be increased to 71% with mild Lewis acid lithium bromide and further increased to 75% with $\text{Mn}(\text{OAc})_2$ (Table 1, entry 8 and 9). Because the acetate from the $\text{Mn}(\text{OAc})_2$ may consume the isothiocyanatomethane, MnO was used to replace $\text{Mn}(\text{OAc})_2$ and better yield was achieved (Table 1, entry 10). With these encouraging results, further

endeavor were devoted to the identification of efficient metal oxides and eventually the cheap and abundant Fe_3O_4 was found to be optimal (Table 1, entry 11–13). More importantly, the benefit of Fe_3O_4 was twofold. Firstly, due to the magnetic nature of Fe_3O_4 , it could be easily recovered under magnetic conditions. Secondly, iron is not a toxic element comparing with other transition metals, therefore the trace amount of Fe_3O_4 residue will not be a problem even in the industry production. Further interrogation of reaction time and temperature reveals that shorter reaction time and lower reaction temperature was detrimental (Table 1, entry 14 and 15). Therefore, 10 mol% DABCO and 10 mol% Fe_3O_4 at 85 °C in MeCN was established as the optimal reaction conditions for substrate screening.

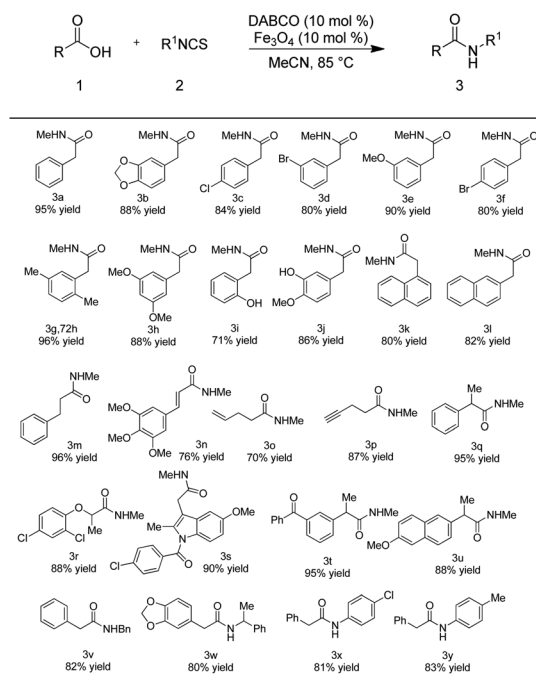
Firstly, different acids were employed to react with isothiocyanatomethane and the results were summarized in Table 2. Various aliphatic acids are compatible with our optimized reaction conditions, good to excellent yields were realized (Table 2, entry 3a–3y). Generally, electro-rich substrates give better yields compared with electro-deficient substrates (Table 2, entry 3a–3z). Moreover, functional groups like hydroxyl (3i), alkynyl (3p), alkenyl (3o), ether (3r) and amide (3s) were tolerated with our reaction conditions. Later on, steric groups were installed onto the acid and isothiocyanate partner to study the steric effect on the substrates (Table 2, entry 3q and 3w). The results reveal that the steric effect pose negligible effect on the acid so that different marketed drugs like duplosan (3r), indomethacin (3s), ketoprofen (3t) and naproxen(3u) were transformed into the corresponding methyl amide under current

Table 1 Condition optimization for the amidation reaction^a

Entry	Additive	Time (h)	Catalyst	Yield (%)
1	—	24	—	5
2	—	24	PTSA	—
3	—	48	TEA	17
4	—	48	DBU	45
5	—	48	DMAP	43
6	—	48	DBN	51
7	—	48	DABCO	65
8	LiBr	48	DABCO	71
9	$\text{Mn}(\text{OAc})_2$	48	DABCO	75
10	MnO	48	DABCO	79
11	MgO	48	DABCO	88
12	Al_2O_3	48	DABCO	85
13	Fe_3O_4	48	DABCO	98
14	Fe_3O_4	24	DABCO	75
15 ^b	Fe_3O_4	48	DABCO	80

^a Reactions were run on 1 mmol **1a** and 1.1 mmol **2a** with 10 mol% catalyst and 10 mol% additive in 1 mL of MeCN at 85 °C for 48 hours unless otherwise noted. ^b Reaction was conducted at 60 °C.

Table 2 Substrate scope for the amidation reaction^a

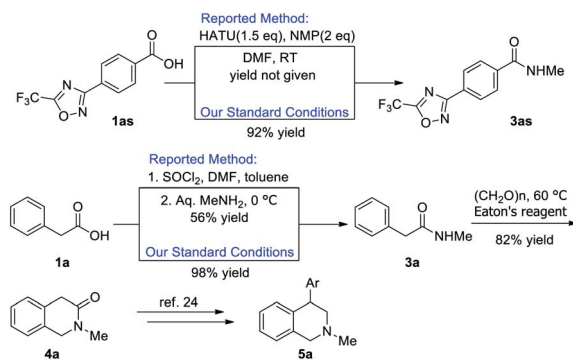


^a Reactions were run on 1 mmol **1** and 1.1 mmol **2** with 10 mol% DABCO and 10 mol% Fe_3O_4 in 1 mL of MeCN for 48 hours at 85 °C unless otherwise noted.

reaction conditions with very good yields (Table 2, entry **3r–3u**). Finally, different isothiocyanates were tested and found to be compatible with current reaction conditions, good yields were achieved for both aliphatic and aromatic isothiocyanates (Table 2, entry **3v–3y**).

Subsequently, aromatic and heteroaromatic acids were tested for their compatibility with current reaction conditions and the results were summarized in Table 3. The results reveal our reaction conditions was compatible with various aromatic and heteroaromatic acids and good to excellent yields were obtained (Table 3, entry **3aa–3ar**). Generally, electron-withdrawing groups take longer reaction time to get satisfied yield (Table 3, entry **3af** and **3ag**), while dinitro substrate give moderate yield even under prolonged reaction time (Table 3, entry **3ah**). Interestingly, when 2-mercaptobenzoic acid was used as substrate, the cyclic product **3ak** was obtained as the sole product in excellent yield. More importantly, methyl amides derived from aromatic and heteroaromatic acids are of medicinal significance. For example, compound **3aj**, **3ak** and **3ap** are key fragment of enzalutamide, axitinib and (–)-thiazogazole (as shown in Fig. 1) respectively, and all could be conveniently prepared using current procedure with excellent yields.

Furthermore, to demonstrate the synthetic utilization of our methodology, the preparation of bioactive compounds was demonstrated Scheme 1. Compound **3as** is a patent HDAC₄ inhibitor.²² Under the standard reaction conditions, **3as** could be obtained from commercially available **1as** in 92% yield. Our procedure is much more atom economy as it excluded the usage of activating reagent and excess amount of base. In a recent report, Yang group reported their pilot-scale synthesis of substituted phenylacetamides to tetrahydroisoquinoline-2-ones.²³ In their practice, corrosive thionyl chloride was applied as activating reagent and large excess amount of methyl amine was required, however, moderate yield of **3a** was obtained, while



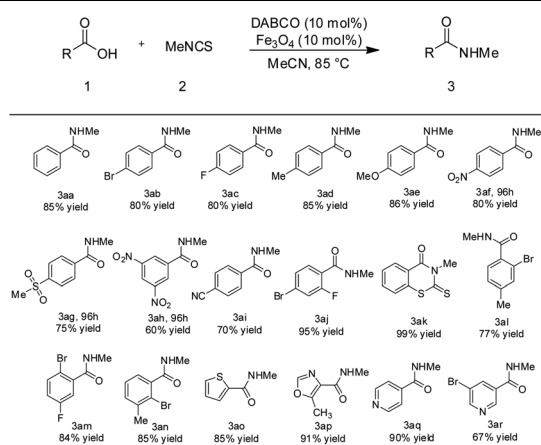
Scheme 1 Application of *N*-methyl amide.

our method can achieve better yield along with the exclusion of corrosive thionyl chloride. Following this report, tetrahydroisoquinoline-2-one **4a** could be obtained in 82% yield, which could be used in the preparation of various bioactive 4-aryl-tetrahydroisoquinolines **5a** with known procedure.²⁴

Finally, owing to the magnetic nature of Fe₃O₄, we try to recover the Fe₃O₄ from the reaction system and test its efficiency. As the Fe₃O₄ is always stuck to the magnetic stir bar, after the termination of the reaction, the reaction solution was poured out and the tub along with the magnetic stir bar was rinsed with MeCN three times, oven dried and used for the next cycle. The results shown that the Fe₃O₄ could be used 10 times and still maintained very good efficiency (Fig. 2).

Combined with the literature reports and experimental observation,²⁵ a plausible mechanism was proposed in Scheme 2. Firstly, the carboxylic acid reacts with the Fe₃O₄ to get iron (II and III) carboxylate **A**, which will coordinate to the intermediate **B** generated from DABCO and isothiocyanate to get intermediate **C**. Then, one of the carboxylate attacks intermediate **B** to release DABCO and generates intermediate **D**. Intermediate **D** goes through an intramolecular addition to generate intermediate **E**, which goes through a rearrangement reaction to get intermediate **F** with the release of carbonyl sulfide. Finally, the protonation of **F** with carboxylic acid gets the final product and regenerates the iron (II and III) carboxylate **A**.

Table 3 Substrate scope for the amidation reaction^a



^a Reactions were run on 1 mmol **1** and 1.1 mmol **2** with 10 mol% DABCO and 10 mol% Fe₃O₄ in 1 mL of MeCN for 48 hours at 85 °C unless otherwise noted.

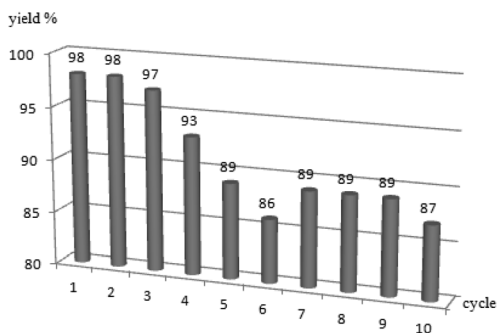
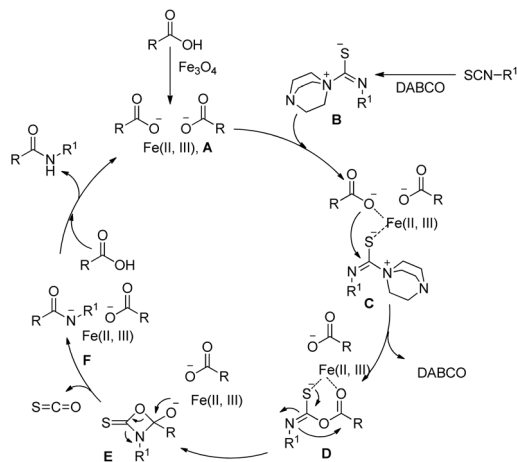


Fig. 2 The efficiency of recovered Fe₃O₄.



Scheme 2 Proposed reaction mechanism.

Conclusions

To summarize, we have developed a catalytic atom economy amidation process of simple acids with isothiocyanates using cheap and abundant DABCO and Fe_3O_4 . Our method is operational simple, exclusion of air or moisture is not required, and compatible with a range of acids and isothiocyanates. Moreover, the Fe_3O_4 could be easily recovered under magnetic conditions for up to 10 times with high efficiency. Particularly, considering the volatile nature of methyl amine, our method would be a valuable supplement of existing methyl amides preparation mythology, which will found wide application in pharmaceutical relevant compounds preparation and natural products synthesis.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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