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Brønsted Acid Mediated Nucleophilic Functionalization of Amides through Stable Amide C-N Bond Cleavage; One Step Synthesis of 2-Substituted Benzothiazoles

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Dedication ((optional))

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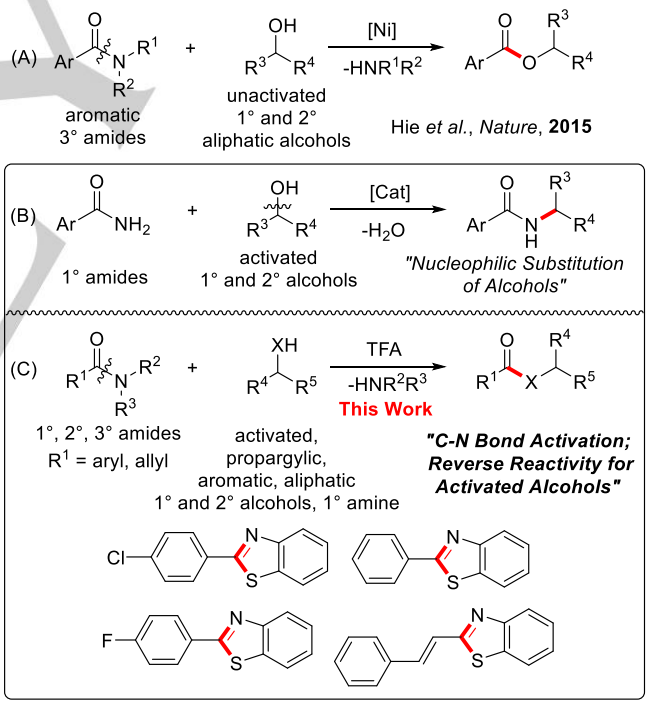
Abstract: We have developed a Brønsted acid mediated synthetic method to directly cleave stable amide C–N bonds by a variety of alcohol and amine nucleophiles. Reverse reactivity was observed and alcoholysis of amides by activated primary and secondary benzylic, and propargylic alcohols have been achieved instead of the expected nucleophilic substitution of alcohols. As an application, 2-substituted benzothiazole derivatives have been synthesized in one pot employing 2-aminothiophenol as nucleophile.

Amides are important class of organic compounds and key building block of proteins as well as several biologically active molecules.[1] These moieties are reported as thermodynamically stable enough due to conjugation of nitrogen lone pair to the carbonyl group.[2] Owing to its nucleophilic character, primary amides are widely employed as N-centered nucleophile to construct new C–N bonds during the last two decades[3,4] through catalytic direct nucleophilic substitution of the hydroxy group of activated alcohols.[4] However, the opposite reactivity, i.e., functionalization of amides through nucleophilic substitution of the amide C–N bonds are rare although Nature can easily cleave amides through the action of enzymes, such as proteases.[5] Among the chemical transformations of amide,[6] alcoholysis has drawn much interest to the chemists, as the resulting esters become much more reactive than the amide which can farther undergo a range of useful transformations.[7] In a ground breaking work, Hie and co-workers[8] reported a method of conversion of amides to esters by nickel-catalyzed activation of amide C–N bonds (Scheme 1A).[8a] Their method was found to be successful employing tertiary amide as the electrophile. A handful the alcoholysis of tertiary amide has also been reported by other groups subsequently, but they too are limited to tertiary amides.[9] Sun and co-workers reported an iron-catalyzed esterification of amides via C–N bond activation using excess HCl as additive.[10a] Corma and co-workers have recently explored the catalytic

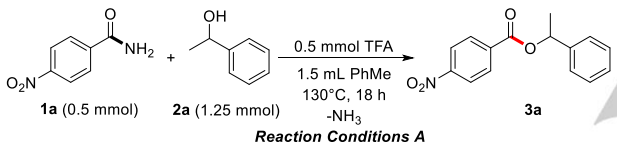


Scheme 1. Previous reports of alcoholysis of amides, nucleophilic substitution of alcohols and this work.

activity of Zr-MOF-808 for amide esterification.[10b] Importantly, activated alcohols which are susceptible to nucleophilic substitution by the amides (Scheme 1B) has rarely been reported.[11] To address these issues such as limited substrate scope, excess amounts of use of toxic additives, and use of transition metal catalysts, we herein report a simple and general protocol of Brønsted acid mediated alcoholysis and *trans*-amidation of amides through amide C–N bond functionalization. A wide range of primary as well as secondary, and tertiary

amides were successfully employed as electrophiles and primary, secondary, aromatic and activated alcohols and amines as nucleophiles. To the best of our knowledge, this is the first report of a general and single protocol under which alcoholysis of 1°, 2° and 3° amides by activated and unactivated primary, secondary, benzylic, propargylic, aliphatic and aromatic alcohols has been achieved; instead of the expected nucleophilic substitution products for activated alcohols (Scheme 1C). As an application, important heterocycles such as 2-substituted benzothiazole derivatives[12] were synthesized in one pot using 2-aminothiophenol as nucleophile. This benzothiazole forms a part of firefly luciferin and aroma constituents of tea leaves.[10] Also, the structural motif has drawn keen interest due to their wide range of biological application viz. anti-cancer,[13] anti-microbial,[14] anti-convulsant,[15] anti-viral,[16] analgesic,[17] anti-diabetic,[18] anti-inflammatory,[19] fungicidal activities.[20] It is noteworthy that, a subtle strategy was taken to make the molecules water soluble by tagging amino acid with benzothiazole molecules. It is found that amino acid levelled water soluble prodrugs known as Phortress shows anti-tumour activity against human mammary carcinoma cell lines which is comparable to doxorubicin.[21]

Table 1. Optimization of reaction parameters.

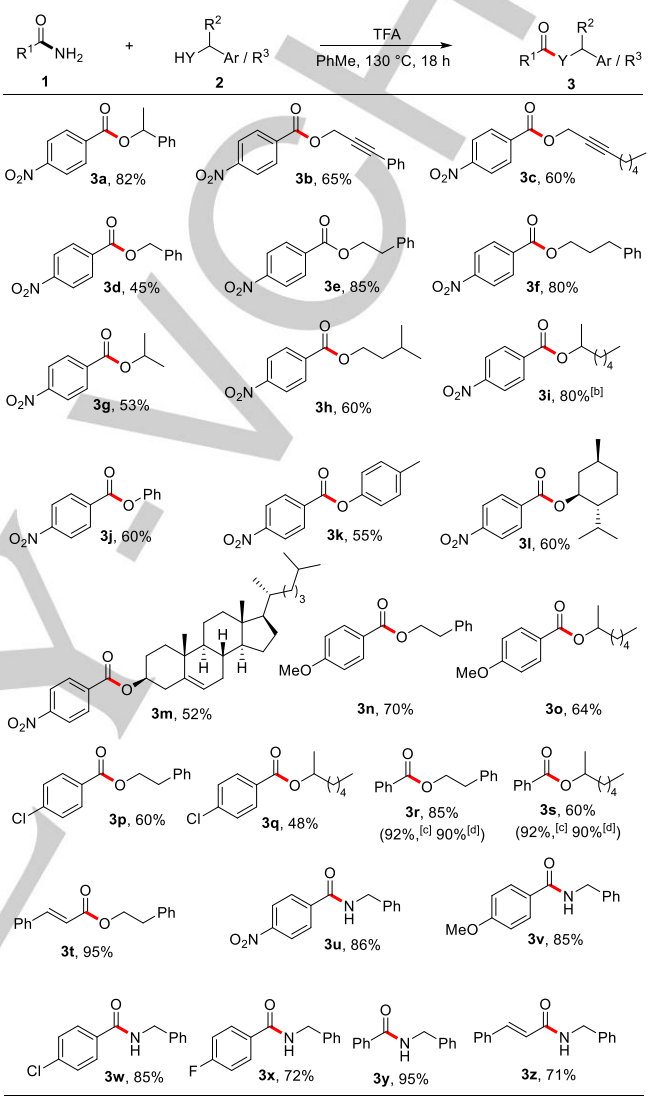


Entry	Deviation from ***Reaction Condition A***	Yield (%)[a]
1	***None***	***82***
2	110 °C	50
3	*p*-TSA·H_2O instead of TFA	12
4	TfOH instead of TFA	10
5	Trizma hydrochloride instead of TFA	0
6	$PhB(OH)_2$ instead of TFA	0
7	20 mol% TFA	16
8	1.0 mmol **2a**	76
9	1.5 mmol **2a**	80
10	1.0 mL PhMe	71
11	2.0 mL PhMe	68

[a] Yield refers to pure and isolated products.

To optimize the reaction parameters, a challenging combination of substrates 4-nitrobenzamide (**1a**) and 1-phenyl ethanol (**2a**) were chosen considering their susceptibility of direct nucleophilic substitution of **2a** (Scheme 1B). The temperature and the time were fixed at 130 °C and 18 h after an initial screening. As a continuation of our effort to develop transition metal-free Brønsted acid catalyzed protocol,[22] a variety of Brønsted acids were tested (Table 1). 1 equivalent of trifluoroacetic acid (TFA) was found to be the best to mediate the reaction between **1a** and **2a** to generate **3a**. Unfortunately, using TFA in catalytic amount generated the product, but in low yield.

Table 2. Substrate scope of alcoholysis of amides and *trans*-amidation.[a]

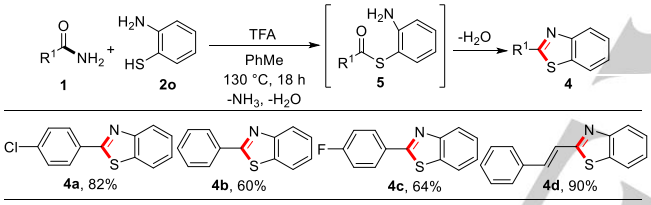


[a] Reaction conditions: **1** (0.5 mmol), **2** (1.25 mmol), TFA (0.5 mmol), in toluene solvent (1.5 mL) at 130 °C for 18 h. [b] The reaction was run for 48 h. [c] Benzanilide (**1f**) was used in place of benzamide (**1e**). [d] Weinreb amide (**1g**) was used in place of benzamide (**1e**).

The optimized reaction conditions were applied to a variety of amides and alcohols the results of which are summarized in Table 2. The protocol was found to be general with respect to primary and secondary benzylic, propargylic, aliphatic, aromatic, and natural alcohols. Secondary benzylic alcohol such as 1-phenyl ethanol (**2a**) which is susceptible to nucleophilic substitution of the hydroxyl group[4] showed reverse reactivity when subjected to react with 4-nitro benzamide (**1a**) generating the corresponding ester **3a** in 82% yields. **1a** also reacted with propargylic alcohols **2b** and **2c** to furnish the esters **3b** and **3c** in 65% and 60% yields respectively. Benzyl alcohol **2d** successfully reacted with **1a** to generate the product **3d** in 45% yield. Other types of primary and secondary alcohols, such as, 2-phenylethan-1-ol (**2e**), 3-phenylpropan-1-ol (**2f**), 2-propanol

(**2g**), 3-methylbutan-1-ol (**2h**) and heptan-2-ol (**2i**) reacted smoothly with **1a** to furnish the desired products **3e**–**3i** in good to excellent yields. Aromatic alcohols such as phenol (**2j**) and *p*-cresol (**2k**) also serve as *O*-centered nucleophile under the optimized reaction conditions to generate **3j** and **3k** in 60% and 55% yields respectively.[23] Importantly, naturally occurring alcohols such as menthol (**2l**) and cholesterol (**2m**) generated the desired ester **3l** and **3m** in 60% and 52% yield respectively when subjected to react with **1a**. The protocol was found to be general with respect to the amides. Presence of methoxy (**1b**) and chloro (**1c**) groups in the aromatic ring of the amide did not affect the outcome of the reaction. It is noteworthy to mention that secondary and tertiary amides such as benzanilide (**1f**) and Weinreb amide (**1g**) were found to be susceptible under the present reaction conditions. Along with benzamide (**1e**), **1f** and **1g** also reacted with alcohol **2e** and **2i** to generate the product in 85%, 92%, 90%; and 60%, 92%, 90% yields, respectively. Cinnamamide (**1h**) also showed excellent reactivity and generated the ester **3t** in quantitative yield when subjected to react with **2e**. The scope of the present protocol was further generalized when it was observed that benzylamine (**2n**) was also acted as *N*-centered nucleophile and reacted with all types of amides to generate the products **3u**–**3z** in good to excellent yields.

Table 3. One step synthesis of 2-substituted benzothiazole derivatives.[a]

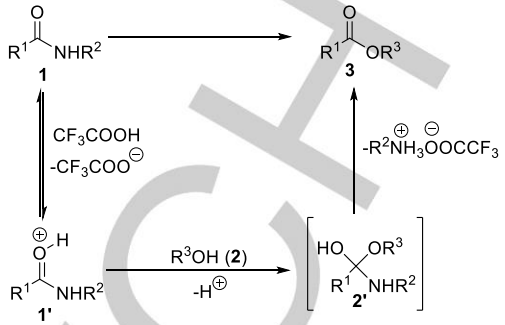


[a] Reaction conditions: **1** (0.5 mmol), **2** (1.25 mmol), TFA (0.5 mmol), in toluene solvent (1.5 mL) at 130 °C for 18 h.

As an important application, the present method was found to be useful for direct synthesis of 2-substituted benzothiazole derivatives (Table 3). 2-Aminothiophenol (**2o**) reacted with amides **1c**, **1e** and **1d** under the developed reaction conditions to generate **4a**, **4b**, **4c** respectively in 82%, 60% and 64% yields respectively. The reaction proceeded *via* sequential nucleophilic substitution of aryl C–N bonds through S-center of **2o** to generate intermediate **5** which upon intramolecular condensation produce the desired products. Amide **1h** was also successfully employed to generate 2-vinyl substituted benzoxazole derivative **4d** in 90% yields.

Based on the results and previous report,[7c] a mechanism of alcoholysis of amide has been proposed where the amide (**1**) was first protonated by the acid to generate **1'** which facilitated the nucleophilic addition of the alcohol (**2**) to generate intermediate **2'**. Finally, elimination of amine from **2'** generated the desired ester **3** (Scheme 2).[24]

In conclusion, we have developed a Brønsted acid mediated general synthetic protocol to directly cleave amide C–N bonds by a variety of alcohol and amine nucleophiles. Reverse reactivity was observed when activated primary and secondary benzylic, and propargylic alcohols were used yielding the corresponding esters instead of the expected nucleophilic substitution of alcohols. Natural alcohols such as menthol and cholesterol took



Scheme 2. Plausible mechanism of alcoholysis of amides.

part in the reaction under the present reaction conditions to generate the desired esters. Structurally important 2-substituted benzothiazole derivatives have been synthesized in one pot employing 2-aminothiophenol as nucleophile.

Experimental Section

General procedure for TFA mediated amide C–N bond activation to synthesize the products (3a–3z) (Table 2): Amide **1a**–**1h** (0.5 mmol), nucleophile (alcohol or amine) **2a**–**2n** (1.25 mmol) and freshly distilled toluene solvent (1.5 mL) were taken in a 5 mL VWR reaction vial containing a small magnet without using inert atmosphere, then TFA (40 µL, 0.5 mmol) was added. The cap of the vial was closed and the reaction mixture was stirred at r. t. for 5 min then reaction mixture was stirred at 130 °C for 18 h in an aluminum dry heating block. After completion of the reaction (by TLC, ^{1}H NMR), the crude was directly purified by silica-gel (100–200 mess) column chromatography (flash) using ethyl acetate /hexane solution to afford the desired products **3a**–**3z**.

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Keywords: Brønsted Acid • Amide • Functionalization • Benzothiazole • Amide C–N Bond Cleavage

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[24] The possibility of hydrolysis of the amide to the corresponding acid followed by *in situ* esterification of the acid was ruled out when the reaction was found to be reproducible using flame dried glass apparatus under inert atmosphere.

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Entry for the Table of Contents

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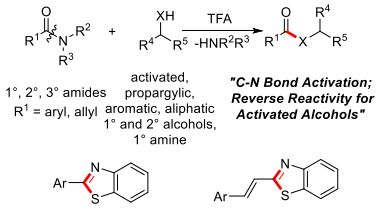

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