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Letter

Nanocellulose as a Reaction Media and Stoichiometric Reagent for $FeCl_3$-Mediated Reductive Functionalization of Nitro Compounds

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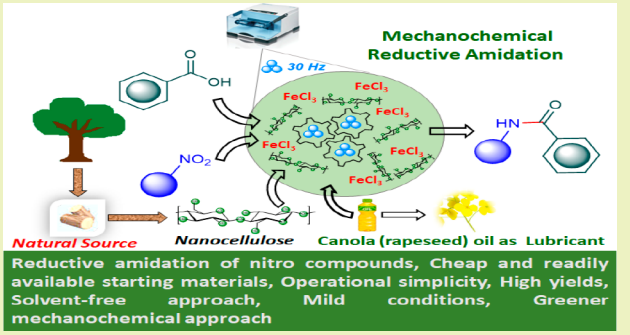
ABSTRACT: Among a wide array of synthetic amides, N-aryl/alkyl amides are an important class of structural motifs having significant importance in pharmaceutical and agrochemical industries. In this regard, a rapid, low-cost, and environmentally friendly synthesis of N-aryl/alkyl amides still remains in a high demand. Herein, we report a convenient route for the mechanochemical synthesis of N-aryl/alkyl amides via $FeCl_3$-catalyzed reductive amidation of nitro compounds, as well as acylation of aliphatic/aromatic amines with carboxylic acids using nanocellulose as the reaction media/stoichiometric reducing agent. The protocol was found to be simple, efficient, and environmentally benign to obtain a diverse array of the respective amides with good to excellent yields. Furthermore, the use of nitro compounds, amines, and carboxylic acids as cheap and readily available starting materials, $FeCl_3$ as a nontoxic catalyst, and nanocellulose as the biodegradable reaction media as well as the stoichiometric reducing agent makes this protocol in the category of a green chemical transformation.



KEYWORDS: *Mechanochemistry, Nanocellulose, N-Aryl/alkyl amides, Reductive amidation, Solvent-free green conditions, Catalysis, Sustainability*

INTRODUCTION

Amide functionality is one of the most prevalent structural units comprising the backbone of naturally occurring peptides and a vast number of natural products and biomolecules, as well as many pharmaceutical products. In particular, N-aryl/alkyl amides are the ubiquitous structural motifs known for their wide range applications in pharma- and agrochemical industries for the synthesis of various drug intermediates, surfactants, pesticides, dye precursors, medicines, and other functional materials.[1−7] As a consequence, the synthesis of N-aryl/alkyl amide and its derivatives is considered as one of the most important transformations in synthetic organic chemistry and attracted much attention from synthetic organic and process chemists.

Known methods to synthesize N-aryl/alkyl amides include coupling (acylation/benzoylation) of amines with carboxylic acids in the presence of activating reagents including acid chlorides, anhydrides, carbodiimides, or aryl boronic acids.[8−12] Nevertheless, these methods are associated with one or other drawbacks, such as the use of a stoichiometric amount of the aforementioned activating reagents that are generally toxic, hazardous, and expensive, and the process may require an additional activation step which can lead to the formation of undesired side products which makes these protocols a multistep-complicated task and censure their applicability in context to the Green Chemistry principles.[13]

To address these problems, considerable attention has been devoted to develop a convenient synthesis of N-aryl/alkyl amides via transition-metal-catalyzed direct transformation of readily available nitro derivatives. For instance, the groups of Beller,[14] Driver,[15] and Wu[16] independently reported the synthesis of various amides via the Pd-catalyzed aminocarbonylation of arenes or olefins with nitroarenes, whereas the groups of Hu[17−19] and Zeng[20] described the Ni-, Cr-, or Mn-catalyzed reductive amidation of nitroarenes with carboxylic acid esters, Boc-protected secondary amides, or tertiary amides (Scheme 1a). Of note, the latter strategies utilized Zn, Mn, and Mg metals as the reducing agents for nitroarenes to derive more reactive nitrogen-containing intermediates. Wang and co-workers developed a novel approach to synthesize amides via activation of an aromatic acid with triphenylphosphine and iodine followed by treatment with a nitroarene using Mn powder.[21] Two more approaches to access N-aryl amides have also been developed through the reductive amidation[22] and decarboxylative/oxidative amidation of aryl α-ketocarbox-

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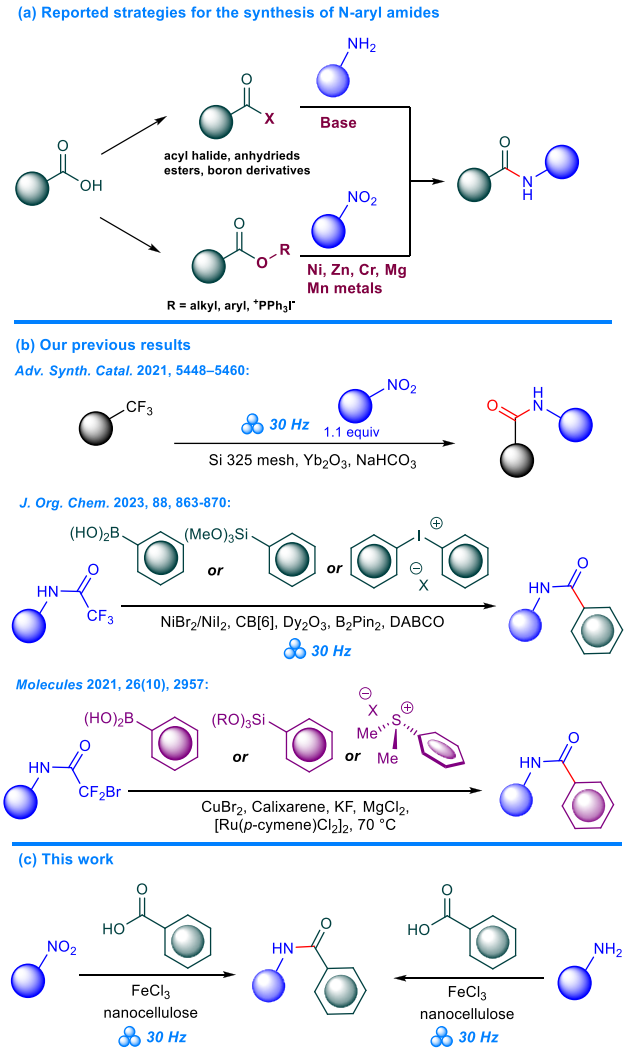
Scheme 1. (a) Reported Strategies, (b) Our Previous Results, and (c) the Present Concept for the Synthesis of N-Aryl/alkyl Amides



ylic acids with nitroarenes.[23] Our group has also developed three diverse strategies for the synthesis of N-aryl/alkyl amides via defluorinative arylation of trifluoroacetamides[24] or bromodifluoroacetamides[25] and via reductive amidation of nitro compounds with CF_3-contaning substrates[26] (Scheme 1b). Nevertheless, these methods still have limited pharmaceutical relevance as they use expensive transition metals, toxic activating reagents, shock sensitivity, poor atom economy, high reaction temperatures, and prolonged reaction times along with complex purification procedures. Thus, there is an urgent need to develop an environmentally benign and cost-effective synthetic strategy to access N-aryl/alkyl amides using readily available starting materials and nontoxic catalysts. Furthermore, with the growing emphasis on the environmental impact, mechanochemically induced transformations have gained substantial interest in the development of solvent-free and energy efficient synthetic procedures.[27−29]

It is well-known that iron is the fourth most abundant element (6.3%) in the Earth's crust and first in the category by weight. It is one of the most essential elements of living organisms and present many biologically active systems such as heme, ferritin, and rubredoxin.[30] As a cheap and nontoxic commercially available iron salt, $FeCl_3$ has attracted chemists toward the development of various iron-catalyzed reactions under mild reaction conditions. Because of the ease of operational simplicity, $FeCl_3$ can be handled easily during the course of reaction and workup procedures. Therefore, $FeCl_3$ has been considered as a catalyst of choice over other transition metals in many organic transformations such as cross-couplings, cyclization, oxidation, reduction, Friedel−Crafts reactions, Pechmann reaction, metathesis, and direct C−H functionalization reactions.[30]

Derived from renewable bioresources, nanocellulose has received considerable attention in synthetic chemistry due to its unique physical and chemical properties including high specific surface area, high crystallinity and mechanical strength, and controllable surface phenomena.[31] In addition to biodegradability, nanocellulose possesses many hydroxyl groups and ether linkages exhibiting strong water absorption/scavenging properties.[32] Because of the large surface area, high reactivity, and specific morphology, nanocellulose has shown potential to form stable suspensions in a wide range of reaction media. Among the many applications, nanocellulose has been used as the catalyst in numerous organic transformations[33] and also been used as an additive as well as the support for the metal nanoparticles or catalysts with improved stability and catalytic activity.[34]

Utilizing the aforementioned characteristic features of nanocellulose, $FeCl_3$ and in continuation of our long-standing interest dedicated for the development of novel, efficient, and sustainable transformations,[35−39] herein we report two diverse routes for the mechanochemical synthesis of N-aryl/alkyl amides via $FeCl_3$-catalyzed (i) reductive amidation of nitro compounds and (ii) acylation of aliphatic/aromatic amines with carboxylic acids using nanocellulose as the convenient reaction media and stoichiometric reagent. Furthermore, the use of nitro compounds, amines, and carboxylic acids as cheap and readily available starting materials, $FeCl_3$ as a nontoxic catalyst, and nanocellulose as the biodegradable reaction media makes this protocol in the category of a green chemical transformation.

RESULTS AND DISCUSSION

Our starting point was the identification of appropriate reaction parameters for the synthetic protocols proposed here. Inspired from our recently developed approach on $FeCl_3$ nanocellulose-mediated mechanochemical of synthesis of 3-acylchromones via dehydrative coupling of *ortho*-hydroxyarylenaminones and carboxylic acids[40] and continuing this research, we embarked to screen the similar conditions for other synthetic scenarios, particularly for amide bond formation. Deliberately, two sets of model reactions have been designed for the convenient synthesis of N-aryl/alkyl amide: (i) acylation of amines with carboxylic acids and (ii) reductive amidation of nitro compounds with carboxylic acids. Initially, we started our investigation carrying out the solid phase reaction between 3-(trifluoromethyl)aniline **2a** (1 equiv) with 4-(*tert*-butyl)benzoic acid **3a** (1.4 equiv) as the model substrates in the presence of various acylation catalysts, oligo-/polysaccharides (0.5 g/mmol) as reaction media, and toluene (0.4 mL) as a lubricant by using a molecular ball mill with a working frequency of 30 Hz, for 60 min, at room temperature (Scheme 2). It is obvious that $AlCl_3$ is one of the widely used catalysts in a variety of acylation reactions. Thus, we initiated the catalyst screening on the model reaction starting from

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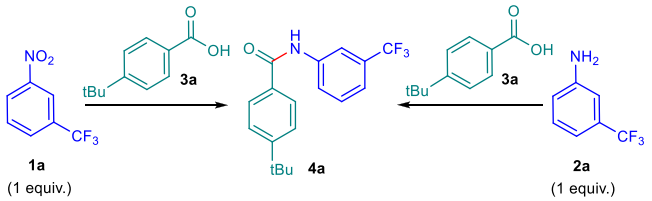
Scheme 2. Model Reaction to Set the Optimization Conditions



$AlCl_3$ (2.2 equiv) in the presence of starch and β- and γ-cyclodextrin or nanocellulose as the reaction media (Table 1, entries 1−4). Except for the reaction in starch (Table 1, entry 1), all the above acylation reactions proceeded smoothly providing the targeted amide **4a** with moderate to good yields. These results indicated that nanocellulose could be the convenient reaction media for the proposed acylation reaction, forming the desired product **4a** with 74% yield (Table 1, entry 2) while **4a** was obtained with the respective yield of 67% and 65% in β- and γ-cyclodextrin (Table 1, entries 3−4). These results prompted us to perform the model reaction in nanocellulose as the optimum reaction media.

A variety of *p*-block salts such as $AlBr_3$, $GaBr_3$, $GeCl_4$, and $InBr_3$ have also been screened as the acylation catalysts to test their ability to catalyze the model reaction in nanocellulose (Table 1, entries 5−8). Among the bromide salts used, $AlBr_3$ has shown superiority over others yielding the targeted product **4a** in 69% yield (Table 1, entry 5) while 34% and 30% yields of **4a** were detected the respective bromides of Ga and In (Table 1, entries 6 and 8). Similarly, only 31% yield of **4a** has been observed in the presence of $GeCl_4$ (Table 1, entry 7). Apart from these *p*-block catalysts, we switched our intention to test the transition metal salts including $CoCl_3$, $NiCl_2$, and $FeCl_3$ (Table 1, entries 9−11). To our delight, $FeCl_3$ showed potential yielding the desired product **4a** with 84% isolated yield (Table 1, entry 11); however, the reaction failed with $NiCl_2$ (Table 1, entry 10), while only traces of **4a** were detected using $CoCl_3$ (Table 1, entry 9). The choice of $FeCl_3$ could be great over the traditionally used $AlCl_3$ catalyst in terms of it is low cost, nontoxicity, and ease of operational simplicity during the course of reaction and workup procedures.

With these results and understanding, we choose $FeCl_3$ as the optimum catalyst, but the major concern was in the use of toluene as a lubricant as the aromatic solvents are carcinogenic in nature. Alternatively, we tested cheap, nontoxic, and naturally derived canola oil (rapeseed oil) as a lubricant replacing the toluene along with the decreased equivalents of $FeCl_3$ (i.e., 0.5 equiv). Diminution in the equivalents of $FeCl_3$ with the use of canola oil (0.15 mL) as a lubricant in the model reaction did not show a significant change in the yield of **4a** which was isolated with 82% yield (Table 1, entry 12). A sudden drop (up to the half) in the yield of **4a** was noted in absence of any added lubricants which suggests the crucial role of the lubricant during mechanical grinding (Table 1, entry 13).

In the search of a better reaction media, the model reaction has also been carried out in starch and β- and γ-cyclodextrin using $FeCl_3$ as the catalyst and canola oil as the lubricant (Table 1, entries 14−16). The reaction failed to deliver the

Table 1. Optimization Table for the Amidation of Amine 2a

Entry	Reaction components	Milling frequency/time	Yield (%) **4a**
	Reactions in solid phase		
1	**3a** (1.4 equiv), $AlCl_3$ (2.2 equiv), starch (0.5 g/mmol), toluene (0.2 mL)	30 Hz/90 min	trace
2	**3a** (1.4 equiv), $AlCl_3$ (2.2 equiv), nanocellulose (0.5 g/mmol), toluene (0.3 mL)	30 Hz/90 min	74
3	**3a** (1.4 equiv), $AlCl_3$ (2.2 equiv), β-cyclodextrin (0.5 g/mmol), toluene (0.3 mL)	30 Hz/90 min	67
4	**3a** (1.4 equiv), $AlCl_3$ (2.2 equiv), γ-cyclodextrin (0.5 g/mmol), toluene (0.3 mL)	30 Hz/90 min	65
5	**3a** (1.4 equiv), $AlBr_3$ (2.2 equiv), nanocellulose (0.5 g/mmol), toluene (0.3 mL)	30 Hz/90 min	69
6	**3a** (1.4 equiv), $GaBr_3$ (2.2 equiv), nanocellulose (0.5 g/mmol), toluene (0.3 mL)	30 Hz/90 min	34
7	**3a** (1.4 equiv), $GeCl_4$ (2.2 equiv), nanocellulose (0.5 g/mmol), toluene (0.3 mL)	30 Hz/90 min	31
8	**3a** (1.4 equiv), $InBr_3$ (2.2 equiv), nanocellulose (0.5 g/mmol), toluene (0.3 mL)	30 Hz/90 min	30
9	**3a** (1.4 equiv), $CoCl_3$ (2.2 equiv), nanocellulose (0.5 g/mmol), toluene (0.3 mL)	30 Hz/90 min	trace
10	**3a** (1.4 equiv), $NiCl_2$ (2.2 equiv), nanocellulose (0.5 g/mmol), toluene (0.3 mL)	30 Hz/90 min	0
11	**3a** (1.4 equiv), $FeCl_3$ (2.2 equiv), nanocellulose (0.5 g/mmol), toluene (0.3 mL)	30 Hz/90 min	84
12	**3a (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.5 g/mmol)**,canola oil (0.15 mL)	**30 Hz/90 min**	**82**
13	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.5 g/mmol)	30 Hz/90 min	40
14	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), starch (0.5 g/mmol), canola oil (0.15 mL)	30 Hz/90 min	0
15	**3a** (1.4 equiv), $FeCl_3$ (2.2 equiv), β-cyclodextrin (0.5 g/mmol), canola oil (0.15 mL)	30 Hz/90 min	77
16	**3a** (1.4 equiv), $FeCl_3$ (2.2 equiv), γ-cyclodextrin (0.5 g/mmol), canola oil (0.15 mL)	30 Hz/90 min	68
17	**3a** (1.4 equiv), $FeCl_3$ (0.4 equiv), nanocellulose (0.4 g/mmol), canola oil (0.15 mL)	30 Hz/90 min	65
18	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.3 g/mmol), canola oil (0.15 mL)	30 Hz/90 min	29
19	**3a** (1.4 equiv), $FeCl_3$ (2.2 equiv), nanocellulose (0.2 g/mmol), canola oil (0.15 mL)	30 Hz/90 min	10
20	**3a** (1.4 equiv), $FeCl_3$ (2.2 equiv), nanocellulose (0.1 g/mmol), canola oil (0.15 mL)	30 Hz/90 min	0
21	**3a** (1.4 equiv), $FeCl_3$ (2.2 equiv), nanocellulose (0 g/mmol), canola oil (0.15 mL)	30 Hz/90 min	0
	Reactions in solution		
22	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.5 g/mmol), toluene (20 mL), reflux	−/24 h	0
23	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.5 g/mmol), EtOH (20 mL), reflux	−/24 h	0
24	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.5 g/mmol), MeOH (20 mL), reflux	−/24 h	0
25	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.5 g/mmol), Isopropanol (20 mL), reflux	−/24 h	0
26	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.5 g/mmol), 1,4-dioxane (20 mL), reflux	−/24 h	0

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Table 2. Optimization Table for the Reductive Amidation of Nitro Compound 1a

Entry	Reaction components	Milling frequency/time	Yield (%) **4a**
	Reactions in solid phase		
1	**3a** (1.4 equiv), $AlCl_3$ (2.2 equiv), starch (1.5 g/mmol), toluene (0.4 mL)	30 Hz/90 min	trace
2	3a (1.4 equiv), $AlCl_3$ (2.2 equiv), nanocellulose (1.5 g/mmol), toluene (0.4 mL)	30 Hz/90 min	0
3	**3a** (1.4 equiv), $AlCl_3$ (2.2 equiv), α-cyclodextrin (1.5 g/mmol), toluene (0.4 mL)	30 Hz/90 min	0
4	**3a** (1.4 equiv), $AlCl_3$ (2.2 equiv), β-cyclodextrin (1.5 g/mmol), toluene (0.4 mL)	30 Hz/90 min	0
5	**3a** (1.4 equiv), $AlCl_3$ (2.2 equiv), γ-cyclodextrin (1.5 g/mmol), toluene (0.4 mL)	30 Hz/90 min	0
6	**3a** (1.4 equiv), $AlBr_3$ (2.2 equiv), nanocellulose (1.5 g/mmol), toluene (0.4 mL)	30 Hz/90 min	0
7	**3a** (1.4 equiv), $GaBr_3$ (2.2 equiv), nanocellulose (1.5 g/mmol), toluene (0.4 mL)	30 Hz/90 min	0
8	**3a** (1.4 equiv), $GeCl_4$ (2.2 equiv), nanocellulose (1.5 g/mmol), toluene (0.4 mL)	30 Hz/90 min	0
9	**3a** (1.4 equiv), $InBr_3$ (2.2 equiv), nanocellulose (1.5 g/mmol), toluene (0.4 mL)	30 Hz/90 min	0
10	**3a** (1.4 equiv), $CoCl_3$ (2.2 equiv), nanocellulose (1.5 g/mmol), toluene (0.4 mL)	30 Hz/90 min	trace
11	**3a** (1.4 equiv), $NiCl_2$ (2.2 equiv), nanocellulose (1.5 g/mmol), toluene (0.4 mL)	30 Hz/90 min	0
12	**3a** (1.4 equiv), $FeCl_3$ (2.2 equiv), nanocellulose (1.5 g/mmol), toluene (0.4 mL)	30 Hz/90 min	78
13	**3a (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (1.5 g/mmol),**canola oil (0.3 mL)	30 Hz/90 min	**79**
14	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (1.5 g/mmol)	30 Hz/90 min	29
15	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), starch (1.5 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	0
16	**3a** (1.4 equiv), $FeCl_3$ (2.2 equiv), α-cyclodextrin (1.5 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	60
17	**3a** (1.4 equiv), $FeCl_3$ (2.2 equiv), β-cyclodextrin (1.5 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	71
18	**3a** (1.4 equiv), $FeCl_3$ (2.2 equiv), γ-cyclodextrin (1.5 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	70
19	**3a** (1.4 equiv), Fe_2O_3 (0.5 equiv), nanocellulose (1.5 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	0
20	**3a** (1.4 equiv), Fe_3O_4 (0.5 equiv), nanocellulose (1.5 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	0
21	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (1.2 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	61
22	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.9 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	37
23	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.6 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	0
24	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.3 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	0
25	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	0
	Reactions in solution		
26	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (1.5 g/mmol), toluene (20 mL), reflux	−/24 h	0[a]
27	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (1.5 g/mmol), EtOH (20 mL), reflux	−/24 h	0[a]
28	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (1.5 g/mmol), MeOH (20 mL), reflux	−/24 h	0[a]
29	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (1.5 g/mmol), Isopropanol (20 mL), reflux	−/24h	0[a]
30	**3a** (1.4 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (1.5 g/mmol), 1,4-dioxane (20 mL), reflux	−/24 h	0[a]

[a]3-(Trifluoromethyl)aniline was detected as main product.

desired product **4a** in starch (Table 1, entry 14); however, 77% and 68% yields of **4a** were observed in β- and γ-cyclodextrin, respectively (Table 1, entries 15−16). With these results, the first set of optimization conditions for the acylation of amines is set as 50 mol % of $FeCl_3$ as the catalyst with nanocellulose as reaction media and canola oil as the lubricant (Table 1, entry 12). To confirm the individual role of $FeCl_3$ and nanocellulose in this transformation, the optimization studies have further been carried out using different combinations of the catalytic system (Table 1, entries 17−21). The results revealed that the yields of compound **4a** were observed to be decreased gradually, or the reaction failed with the decreased amount of nanocellulose (0.5 to 0.1 g/mmol) along with increased equivalents of $FeCl_3$ (Table 1, entries 17−20). Notably, the reaction failed in the absence of the reaction media, i.e., nanocellulose (Table 1, entry 21). From these observations, it is clear that both $FeCl_3$ and nanocellulose have a significant role in this transformation.

To validate the demand for the present mechanochemical approach, the model reaction has also been performed in a variety of organic media such as toluene, ethanol, methanol, isopropanol, and 1,4-dioxane under the conventional heating conditions. Nevertheless, all of these of solvent-dependent reactions failed to deliver the targeted amide **4a** under these optimized conditions (Table 1, entries 22−26).

Inspired from the above success, we then directed our efforts optimizing the reaction conditions for our second proposed route for synthesis of N-aryl/alkyl amides via reductive amidation of nitro compounds (Scheme 2, Table 2). The reaction of 1-nitro-3-(trifluoromethyl)benzene **1a** (1 equiv) with 4-(*tert*-butyl)benzoic acid **3a** (1.4 equiv) has been nominated as the model reaction (Scheme 2). We embarked on testing the above optimal conditions [mechanomilling, $FeCl_3$ (0.5 equiv), nanocellulose (1.5 g/mmol), canola oil (0.3 mL)]. Delightfully, the targeted amide **4a** was produced with 79% yield just in 90 min (Table 2, entry 13), which means the previously optimized conditions for the acylation of **2a** (Table 1, entry 2) were also compatible for the reductive amidation of nitro compound **1a** with a good consistency. Nevertheless, in a search of the improved yield, we have tested all the previous optimal conditions for the proposed reductive amidation of **1a** with respect to various catalysts, reaction media, and lubricants. (Table 2). However, all of the catalyst−reaction media combinations in the model reaction failed to deliver the expected amide **4a** (Table 2, entries 1−11). For example, in the case of 3-(trifluoromethyl)aniline **2a**, $AlCl_3$ exhibited one of the best results for acylation (Table 1, entry 2) while the reductive amidation of **1a** failed under the same optimization conditions (Table 2, entry 2). Among the catalysts used, only $FeCl_3$ was found to be compatible in the proposed reductive amidation reaction, and as such, it was the catalyst of the

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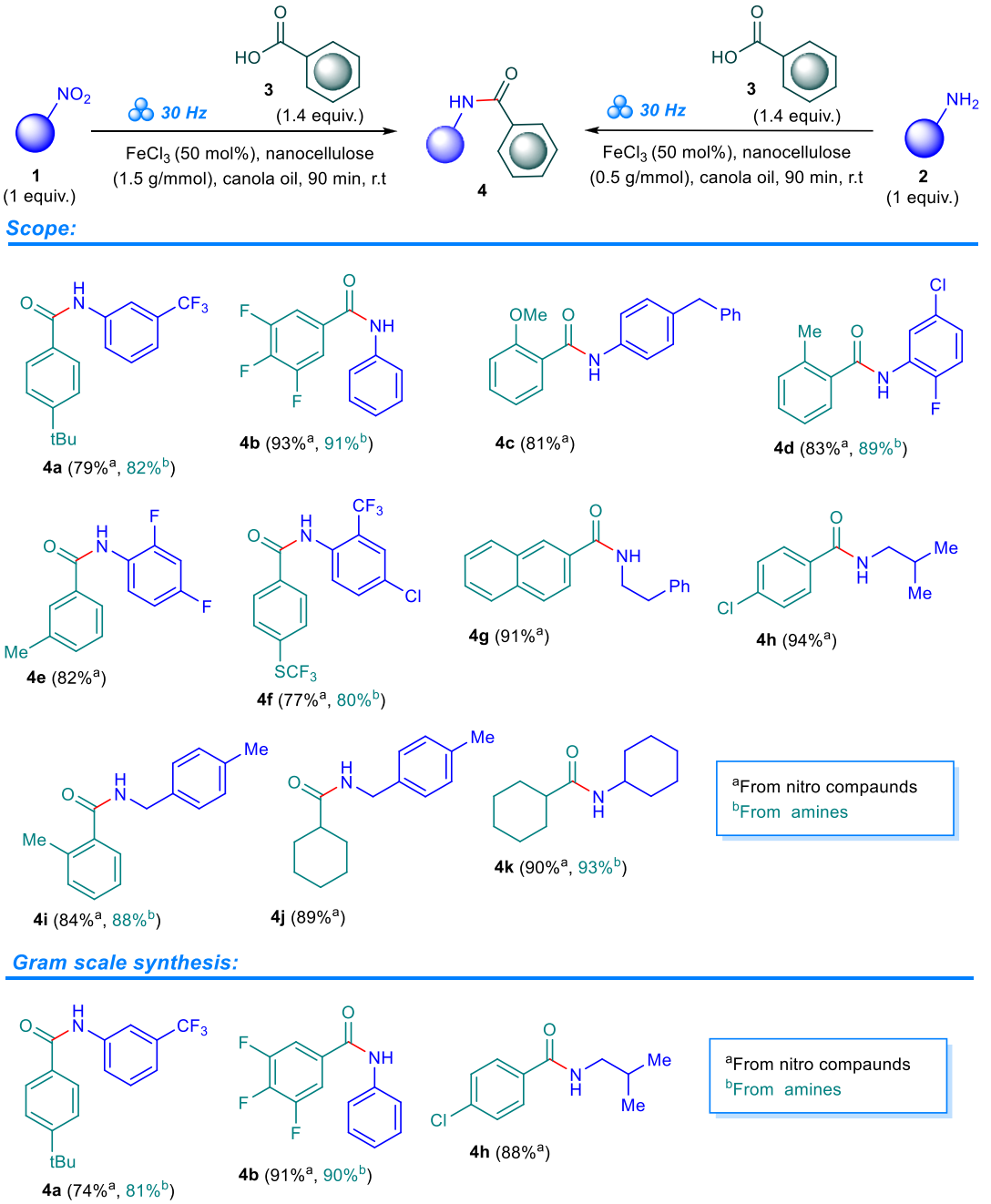
Scheme 3. Scope of Substrates for the Synthesis of Amides 4a−k



optimum choice (Table 2, entry 13). The absence of canola oil led to the formation of **4a** but with only 29% yield (Table 2, entry 14). The effectiveness of the model reaction has also been tested by performing the reaction in different reaction media, including starch and α-, β-, and γ-cyclodextrins using $FeCl_3$ as the catalyst and canola oil (0.3 mL) as the lubricant (Table 2, entries 15−18). Notably, the reaction failed in starch (Table 2, entry 15) while the product **4a** was observed in good yields (60%−71%) in cyclodextrins as the reaction media (Table 2, entries 16−18). These results might be attributed due to the fact that cyclodextrins are cyclic oligosaccharides that belong to a group of structurally related natural materials, formed during bacterial digestion of cellulose and also have been recognized as potential kinetic surrogates for cellulose.[41] In order to improve the yield, other iron sources, such as hematite (Fe_2O_3) and magnetite (Fe_3O_4), have also been tested. However, the formation of the desired product **4a** was not observed (Table 2, entries 19−20) citing the importance of $FeCl_3$ over the other Fe salts. The solid phase optimization reactions have also been screened with a decreased amount (1.2 to 0 g/mmol) of nanocellulose (Table 2, entries 21−25). A gradual decrease in the yields of **4a** has been observed (Table 2, entries 21−22), and eventually, the reaction failed to deliver the targeted product **4a** in 0.6 and 0.3 g/mmol or in absence of nanocellulose (Table 2, entries 23−25). These results revealed that the role of nanocellulose is crucial in this transformation. It has acted as a convenient reaction medium as well as a stoichiometric reagent for the reductive amidation of compound **1a**.

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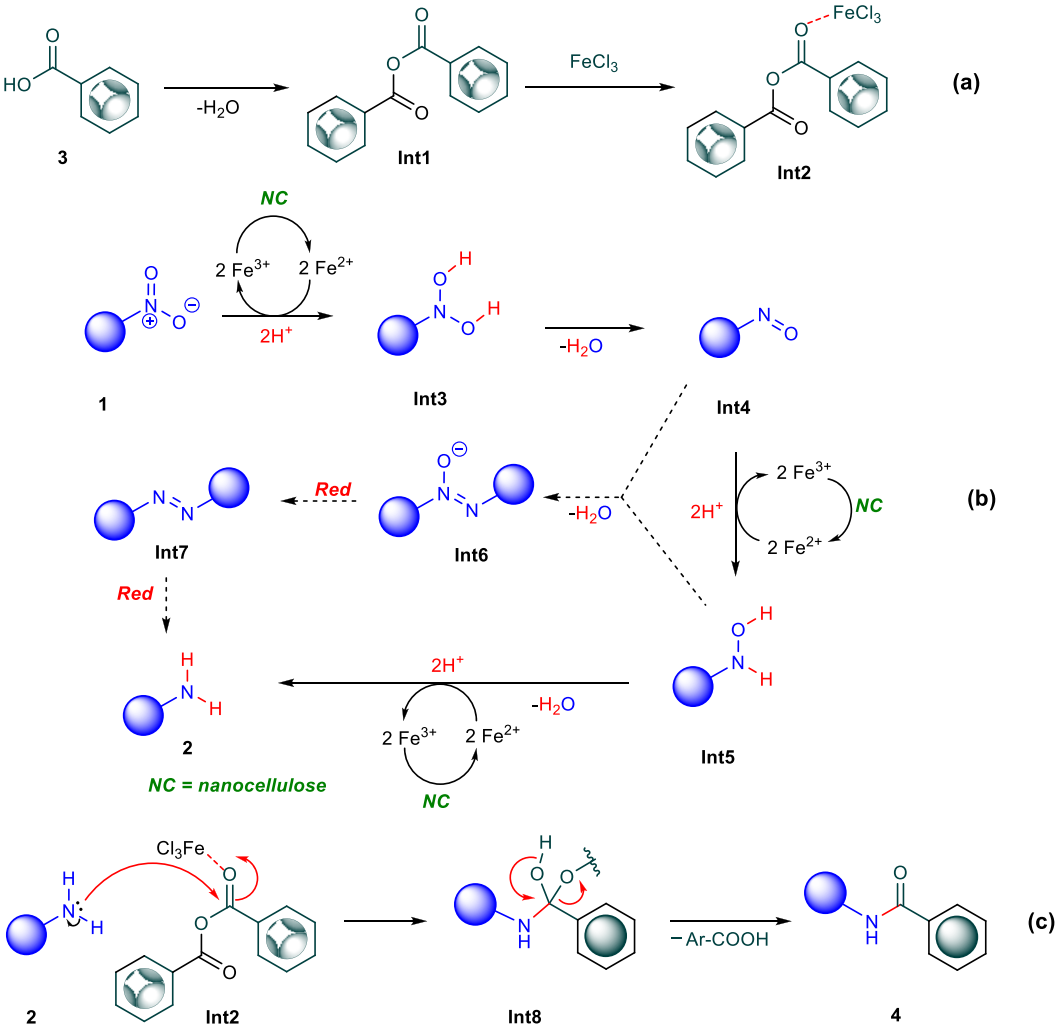
Scheme 4. Plausible Mechanism for Reductive Amidation of Nitro Compounds: (a) Formation anhydride intermediate, (b) Reduction of Nitro Compound, and (c) Amidation of Anhydride Intermediate



Additionally, the reductive amidation reaction of **1a** has been tested in the solution phase utilizing different organic solvents under reflux conditions, but all the reactions failed (Table 2, entries 26−30) showing the superiority of mechanical grinding over the conventional heating methods in the present protocol.

With these optimized conditions in hand, we sought to study the scope and generality for the proposed amidation protocols. As shown in Scheme 3, a variety of the aliphatic/aromatic nitro compounds **1** or amines **2** reacted with aromatic acids to yield the desired amides **4** in good to excellent yields. Initially, the reactivities of different classes of nitro or amino compounds were explored. For the nitroarenes or anilines bearing electron-rich and electron-deficient substituents in the aromatic ring, amides **4a−f** were produced in 77%−93% yields. Aromatic acid with a fused benzene ring (i.e., 2-naphthoic acid, **3g**) also tolerated well toward the proposed amidation reaction. Moreover, the aliphatic carboxylic acid such as cyclohexyl carboxylic acid (**3i**) has also been screened to check the generality of the present amidation protocol for the utilization of the aliphatic acids. Two such cyclohexyl amides **4j** and **4k** have been synthesized with 89% and 90% yields, respectively. In addition, a series of amides bearing N-alkyl (**4g−h**), N-benzyl (**4i−j**), and N-cyclohexyl substituents (**4k**) have been prepared smoothly from the respective nitro or amine precursors. Analyzing the scope and generality of the present amidation strategy, a range of amides bearing not only the aromatic rests (**4a−f**) but also aliphatic (**4g−i**) and alicyclic substituents (**4j−k**) can be easily synthesized under the proposed optimized reactions. The proposed synthetic protocols not only showed a good compatibility toward a broad range of substrates but also were found to be scalable up to 10 mmol quantities with respect to the starting amino/nitro compounds enabling the preparation of three representatives (**4a**, **4b**, and **4h**) in gram scale quantities (Scheme 3).

Based on the reported literature and our observations, a plausible mechanism for the reductive amidation of nitro compounds has been proposed (Scheme 4).[42−44] It has been assumed that the mechanism involved three simultaneous reactions, namely, (a) self-condensation of aromatic acids, (b) reduction of nitro compounds to corresponding amines, and (c) acylation of amines. Both the nanocellulose and $FeCl_3$ have crucial roles in all above reactions. In the first step, the carboxylic acid precursor **3** undergoes self-condensation in the presence of nanocellulose to form the anhydride intermediate **Int1** (Scheme 4a). Nanocellulose may also act as the scavenger of the water molecule produced during the condensation step. The carbonyl oxygen of **Int1** coordinates with $FeCl_3$ to form a

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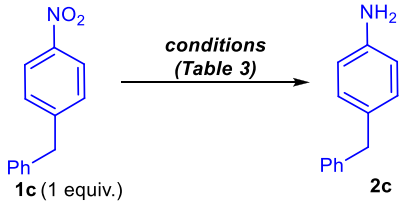
coordination intermediate **Int2** where Fe(III) enhances electrophilicity of the benzoyl ester. Meanwhile, the reduction of a nitro compound has been initiated by a nanocellulose–$FeCl_3$ catalytic system (Scheme 4b). It has been assumed that initially nanocellulose reduces Fe^{3+} to Fe^{2+},[45] and then, Fe^{2+} embarks on the reduction of nitro compound **1** to N,N-dihydroxyamino intermediate **Int3** which further undergoes dehydration to yield nitroso intermediate **Int4**. The nitroso intermediate **Int4** further reduced to the respective hydroxyl amine species **Int5** which undergoes the sequential protonation, dehydration, and reduction to form the respective amine **2**. Apart from this direct reduction route, the formation of amine **2** can also be possible through the condensation route (shown by dashed arrow, Scheme 4b). The condensation of **Int4** and **Int5** leads to the formation of the N-oxide intermediate **Int6**. The intermediate species **Int6** reduced to the diazo intermediate **Int7** which upon the influence of $FeCl_3$ nanocellulose further reduced to generate the expected amine **2**. In the final step, the carbonyl functionality of **Int2** undergoes a nucleophilic attack by the N atom of the amine **2** to form **Int8** which upon decarboxylation delivers the targeted amide **4** (Scheme 4c).

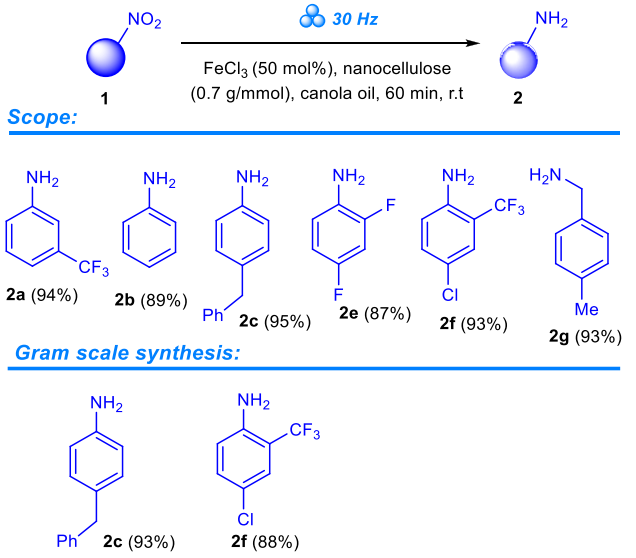
From the mechanistic perspective, we believe that the reductive amidation of nitro compounds proceeds through the formation of an amine in the intermediate step via a synergy of $FeCl_3$ nanocellulose and then undergoes acylation with carboxylic acids to yield the corresponding amide. Furthermore, nanocellulose has played a dual role in this transformation. It has not only acted as reaction media but also served as a stoichiometric reagent for the reduction of nitro compounds. To test this hypothesis, we screened the similar optimization conditions (0.5 equiv $FeCl_3$ and 0.7 g/mmol nanocellulose) for the reduction of nitro compound **1c** to obtain the respective amine **2c**. (Scheme 5, Table 3, entry 1).

Scheme 5. Model Reaction for Reduction of Nitro Compound 1c



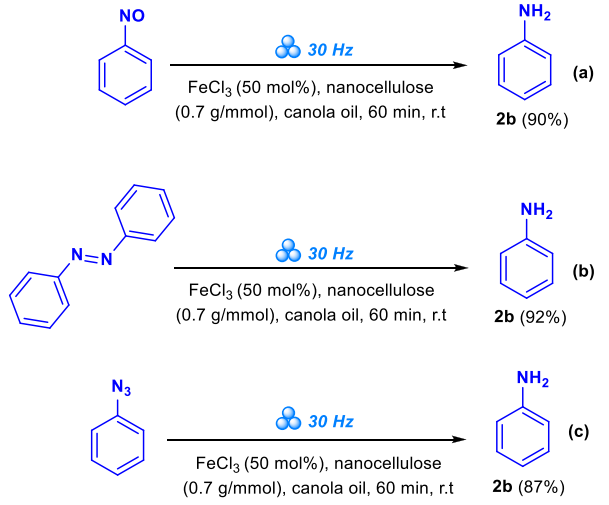
Expectedly, the reaction proceeded smoothly to deliver the amine **2c** with 95% yield in 1 h (Table 3, entry 1). A similar trend of decrease in yields of **2c** has been observed with the decreased amount of nanocellulose (Table 3, entries 2–4). Likewise, the reduction did not work in the absence of nanocellulose (Table 3, entry 5). As shown in Scheme 6, six such amine derivatives **2a–g** have been synthesized with

Scheme 6. Scope of Redaction of Nitro Compounds



excellent yields following the above optimized conditions. Furthermore, three control experiments have been conducted in order to understand the participation of azocompounds and other related structures as the possible intermediates (Scheme 7a–c). In all cases, the optimized conditions (Table 3, entry 1)

Scheme 7. Reduction of Possible Intermediates: (a) Nitrosobenzene, (b) Azobenzene, and (c) Azidobenzene



were found to be compatible to reduce all the tested intermediates delivering the amine **2b** in good yields which also confirmed the crucial role of nanocellulose as a stoichiometric reducing agent. In addition, to validate the

Table 3. Optimization Table for the Reduction of Nitro Compound 1c

Entry	Reaction components	Milling frequency/time	Yield (%) 2c
	Reactions in solid phase		
1	**1c (1 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.7 g/mmol), canola oil (0.3 mL)**	30 Hz/90 min	**95**
2	**1c** (1 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.6 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	79
3	**1c** (1 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.4 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	52
4	**1c** (1 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0.2 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	11
5	**1c** (1 equiv), $FeCl_3$ (0.5 equiv), nanocellulose (0 g/mmol), canola oil (0.3 mL)	30 Hz/90 min	0

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greenness of the present protocol, the Green Chemistry matrix such as reaction mass intensity (RMI) score and atom economy has been calculated for the model reactions (see SI).

Very recently, we have developed a solvent-free strategy for the mechanochemical synthesis of 3-acylchromones $FeCl_3$ nanocellulose-mediated dehydrative coupling of *ortho*-hydroxyarylenaminones and carboxylic acids.[40] The optimization studies of this acylation approach revealed that the utilization of 50 mol % of $FeCl_3$ as a catalyst with nanocellulose as reaction media and canola oil as lubricant led to the formation of 3-acylchromones with excellent yields. Then, on top of that, we decided to screen the similar conditions for other synthetic scenarios, particularly for the amide bond formation via reductive amidation of nitro compounds. As an outcome, we are disclosing the astonishing results of $FeCl_3$ nanocellulose-mediated reductive amidation of nitro compounds, as well as acylation of aliphatic/aromatic amines with carboxylic acids in the present protocol.

CONCLUSIONS

The construction of an amide bond is one of the key transformations in synthetic organic chemistry to derive natural products and biomolecules with endowed biological activities. Among the plethora of synthetic amides, N-aryl/alkyl amides are ubiquitous structural motifs finding significant relevance in the pharmaceutical and agrochemical industries. In search of a better alternative, herein, we disclose a rapid, cost-efficient, and environmentally benign route for the mechanochemical synthesis of N-aryl/alkyl amides via $FeCl_3$-catalyzed acylation of amines with carboxylic acids, as well as reductive amidation of nitro compounds using nanocellulose as the convenient reaction media and stoichiometric reducing agent. The utilization of nitro compounds, amines, and carboxylic acids as cheap and readily available starting materials, $FeCl_3$ as a nontoxic catalyst, and nanocellulose as the biocompatible reaction media/stoichiometric reagent makes this protocol much more interesting from the perspective of green chemical synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.3c04372.

General information, synthetic procedures, spectral data, and copies of ^1H and $^{13}C\{1H\}$ NMR (PDF)

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Notes

The authors declare no competing financial interest.

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