Mechanochemical synthesis of primary amides from carboxylic acids using TCT/NH_4SCN

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Mechanochemical synthesis of primary amides from carboxylic acids using TCT/NH_4SCN

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Abstract

A facile and effective approach toward the synthesis of primary amides from carboxylic acids has been developed. In the presence of 2,4,6-trichloro-1,3,5-triazine, a combination of ammonium thiocyanate and potassium carbonate led to the rapid conversion of carboxylic acids into the corresponding amides within five minutes grinding at room temperature. The use of ammonium thiocyanate as the amine source is unprecedented and exclusive formation of primary amides is observed only under the liquid-assisted grinding conditions.

Keywords: Carboxylic acid; Cyanuric chloride; Amide; Ammonium thiocyanate; Mechanosynthesis

Introduction

Primary amides are prevalent in natural products, pharmaceuticals, and bioactive molecules.[1] Moreover, they are versatile precursors and intermediates in the synthesis of various valuable products.[2] Although a number of nonclassical routes toward primary amides have been developed starting from carboxylic acid derivatives,[3] nitriles,[4] aldoximes,[5] aldehydes,[6] alkynes,[7] alcohols,[8] amines,[9] or aryl iodides,[10] these methods generally require expensive catalysts, harsh reaction conditions, long reaction times, and have limited substrate scope.

While several problems remain to be overcome, the classical condensation of ammonia with acyl chlorides or with carboxylic acids in the presence of an activator appears to be the most straightforward route for primary amide synthesis. This could be due to advantages such as readily available and less expensive materials, mild reaction conditions, and a broad range of functional group compatibility.[11]

Nevertheless, due to its weak basicity, gaseous nature, and low solubility in organic solvents, the direct use of ammonia is not ideal and often requires high-pressure reactors. To minimize the safety hazard, volatile ammonia could be replaced with easier to handle, less toxic, and inexpensive ammonium salts. Whereas the application of ammonium salts such as NH_4Cl,[12] NH_4OAc,[13] NH_4HCO_3[14] have been reported in amide bond formation, the use of ammonium thiocyanate (NH_4SCN) has never been explored, possibly due to the potential for side-reactions such as thiocyanation and the formation of acyl isothiocyanates.[15]

Although waste management has become a major issue in modern industry, the majority of available organic reactions still rely mainly on solution-phase chemistry involving the use of a large excess of volatile organic solvent and highly toxic chemicals. Thus, it is desirable to develop more environmentally friendly processes using safer reagents, requiring fewer synthetic steps, with minimal use of organic solvents.[16] In this regard, mechanochemical synthesis, especially those carried out with the addition of a small amount of solvent (so called liquid-assisted grinding (LAG) or solvent drop grinding) has been increasingly adopted as an alternative greener protocol.[17] This technique offers several benefits in terms of energy efficiency, selectivity, ease of operation, and solvent reduction.

In continuation of our studies on the use of 2,4,6-trichloro-1,3,5-triazine (TCT) as an activator of carboxylic acids, various LAG conditions using less toxic and easy to handle inorganic bases have been investigated.[18] Herein, we report a simple, rapid, and high yielding TCT-mediated mechanochemical synthesis of primary amides from carboxylic acid using NH_4SCN as an ammonia source.

Results and Discussion

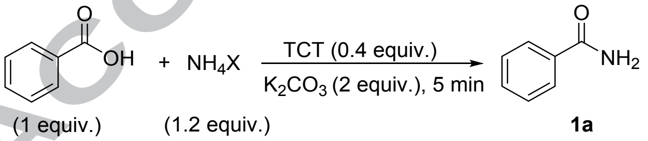
Initially, benzoic acid was chosen as the model substrate to optimize the reaction conditions including the type of ammonium salts as the source of ammonia, solvents, and energy input method (Table 1). The reaction under LAG conditions was typically carried out by mixing benzoic acid and TCT which were ground together using a mortar and pestle in the presence of potassium carbonate (2 equiv.) and a few drops of THF (calculated to be less than 1 μL/mg of solids). After one minute, the time at which the starting acid was completely consumed, the ammonium salt (1.2 equiv.) was added, followed by grinding for five minutes.

The reaction of benzoic acid with NH_4I or NH_4Br gave benzamide **1a** in good yields (Entries 1-2). However, other ammonium salts were less effective (Entries 3-5). Interestingly, the best result was obtained with NH_4SCN leading to the exclusive formation of **1a** in high yield without detectable side-products from thiocyanation (Entry 6).

Considering the weak nucleophilicity of ammonia compared to the thiocyanate or isothiocyanate ion, the obtained result is unexpected, especially since aroylthiocyanates can be derived from carboxylic acids using the TCT/Et_3N/NH_4SCN combination.[15f] Therefore, a further experiment was carried out using KSCN instead of NH_4SCN. Only benzoic anhydride and some remaining starting material were detected without formation of the corresponding acyl isothiocyanate. This led us to postulate that under the grinding conditions where the inorganic base and the ammonium salt are not entirely soluble, the anion (SCN^-) could be protonated and exist in the form of thiocyanic acid (HSCN) or mainly as its tautomer, isothiocyanic acid (HNCS), which did not react with the formed activated triazine ester. The decomposition of ammonium thiocyanate to H_2S is highly unlikely as the formation of ammonia, hydrogen sulfide, and carbon disulfide proceeds upon prolong heating at high temperature. However, heat generated from friction may cause the thiocyanate to isomerize into thiourea which makes the reagent ineffective as a thiocyanating agent.[19]

The effect of the solvent added during grinding was further compared. According to entries 6-10, the reaction in THF was more efficient than those using other solvents. When the reaction conditions in entry 6 was applied under conventional stirring or under sonication in an ultrasonic bath, the reaction was incomplete and benzoic anhydride was obtained as a major product along with benzamide in much lower yields (Entries 11-12). This data indicates that the grinding process plays an essential role in altering the reaction path and product selectivity, possibly through efficient mixing with an increased contact surface area between the solid reagent and the reactants.[20]

Table 1. Optimization of the reaction conditions[a]



Entry	NH_4X	Solvent	Method	Yield (%)
1	NH_4I	THF	grinding	75
2	NH_4Br	THF	grinding	90
3	NH_4Cl	THF	grinding	38
4	$(NH_4)_2SO_4$	THF	grinding	21
5	$(NH_4)_2CO_3$	THF	grinding	66
6	NH_4SCN	THF	grinding	95
7	NH_4SCN	EtOH	grinding	NR
8	NH_4SCN	acetone	grinding	85
9	NH_4SCN	CH_2Cl_2	grinding	20
10	NH_4SCN	toluene	grinding	18
11	NH_4SCN	THF	stirring	23
12	NH_4SCN	THF	sonication	35

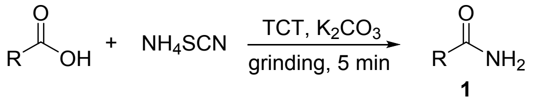
[a]Reagents and conditions: benzoic acid (0.066 g, 0.542 mmol), TCT (0.040 g, 0.216 mmol), K_2CO_3 (1.084 mmol), NH_4X (0.650 mmol).

With the optimized reaction conditions in hand (Table 1, entry 6), we then turned our attention to evaluating the scope and limitations of the protocol using a variety of carboxylic acids. The reaction time was constant for all substrates so that the product yields would reflect the reactivity of the substrates under the applied conditions.

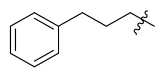
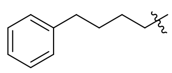
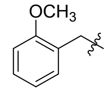
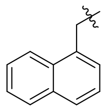
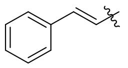
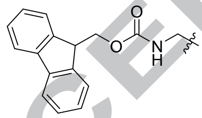
According to Table 2, electron-rich substrates tend to give the amide products in higher yields when compared with substrates containing electron-withdrawing groups (Entries 1-10). Additionally, naphthanoic acids and aliphatic carboxylic acids were smoothly converted into the corresponding primary amides with satisfying results (Entries 11-16). In the reaction with an α,β-unsaturated acid such as cinnamic acid (Entry 17), only the amide was isolated without formation of the Michael addition product. These conditions are also compatible with the Fmoc protecting group which is sensitive to aminolysis (Entry 18). Moreover, the reaction took place within five minutes at room temperature instead of several hours using other solution-based stirring conditions.[21] Interestingly, in all experiments, the amide products were exclusively obtained without detectable formation of other potential side-products such as anhydrides, acyl isothiocyanates, or those derived from thiocyanation of the benzene ring.

It should be noted that although the synthesis of primary amides from carboxylic acids has previously been carried out under solvent-free conditions, such as those using silica-supported ammonium chlorides/TsCl/Et_3N[12d] or NH_4Cl/SiO_2-TCT/Et_3N,[12c] our protocol is more straightforward and does not involve supported reagents which require extra preparation steps nor the excess use of a toxic organic base.

Table 2. TCT-mediated synthesis of primary amides



Entry	R-	Amide **1**	Yield (%)
1	C_6H_5-	**1a**	95

2	4-$MeOC_6H_4$-	**1b**	99
3	4-MeC_6H_4-	**1c**	94
4	4-ClC_6H_4-	**1d**	89
5	4-BrC_6H_4-	**1e**	85
6	4-$NO_2C_6H_4$-	**1f**	69
7	2-$MeOC_6H_4$-	**1g**	98
8	2-MeC_6H_4-	**1h**	98
9	2-ClC_6H_4-	**1i**	91
10	2-$NO_2C_6H_4$-	**1j**	71
11	1-naphthyl	**1k**	90
12	2-naphthyl	**1l**	97
13		**1m**	95
14		**1n**	78
15		**1o**	88
16		**1p**	98
17		**1q**	90
18		**1r**	86

[a]Reagents and conditions: carboxylic acid (0.542 mmol), TCT (0.040 g, 0.216 mmol), K_2CO_3 (0.150 g, 1.084 mmol), THF (< 1 μL/mg solids), 1 min, then NH_4SCN (0.045 g, 0.650 mmol), 5 min.

Conclusion

In summary, a rapid, facile, and efficient method for the preparation of primary amides directly from carboxylic acids has been developed. This procedure represents the first example utilizing ammonium thiocyanate for the *in situ*–generation of ammonia in an amidation reaction. Such a reagent can be used as an alternative ammonia source, especially when the reaction is ineffective using other ammonium salts. The exclusive formation of primary amides without other side reactions under mechanochemical synthesis is also noteworthy and further investigation on this type of reaction is underway.

Acknowledgements

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Supplementary data

Experimental details and ^{1}H NMR spectra for all products are available. Supplementary data related to this article can be found at http://xxx.

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Highlights

- Direct synthesis of primary amides from carboxylic acids is reported.
- The reaction proceeded rapidly using TCT/NH_4SCN under grinding.
- Amides were afforded in high yields with functional group tolerant.

22.

Graphical Abstract

Mechanochemical synthesis of primary amides from carboxylic acids using TCT/NH_4SCN

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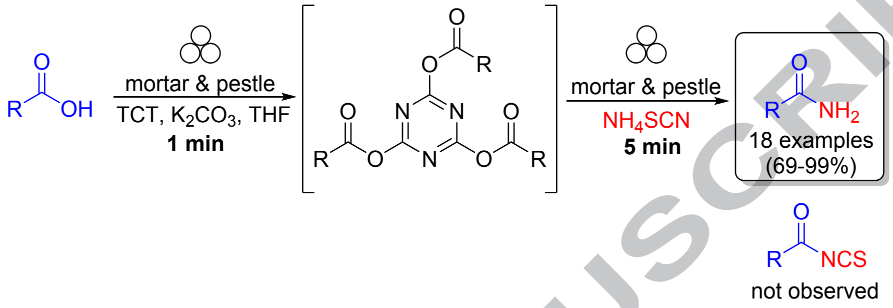

23.