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Ultrasound-Assisted Synthesis of *N*-Acylcyanamides and *N*-Acyl-Substituted Imidazolones from Carboxylic Acids by Using Trichloroisocyanuric Acid/Triphenylphosphine

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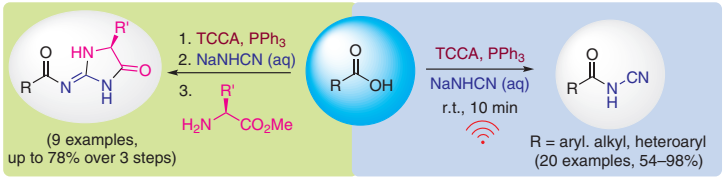

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Abstract A convenient ultrasound-assisted one-pot synthesis of *N*-acylcyanamides starting from readily available carboxylic acids and sodium cyanamide has been developed. Upon activation in the presence of trichloroisocyanuric acid (TCCA) and triphenylphosphine, a range of carboxylic acids was converted into *N*-acylcyanamides in good to excellent yields within 10 minutes at room temperature without base. Remarkably, *N*-acyl-substituted imidazolones were readily accessible through guanylation-cyclization of the in situ generated *N*-acylcyanamides.

Key words acylation, cyclization, ultrasound, trichloroisocyanuric acid, *N*-cyanocarboxamides, imidazolones

N-Acylcyanamides or *N*-cyanocarboxamides are versatile building blocks in organic synthesis. The two-nitrogen and one-carbon skeleton of the cyanamide moiety enable them to undergo numerous transformations towards a variety of interesting *N*-heterocycles such as quinazolinones,[1] benzimidazoles,[2] aminooxadiazoles,[3] N^2-acyl-2-aminoimidazoles,[4] benzothiazinones and benzothiazoles.[5] Their use in radical cascade reactions also provides access to diverse compounds including luotonin A,[6] dihydroisoquinolinones,[6d] guanidines,[7] as well as *N*-acylguanidines.[8] Moreover, the acylcyanamide unit has been incorporated into several bioactive molecules as a carboxylic acid bioisostere to enhance the membrane permeability of potential drug candidates.[9]

Because of these features, several methods have been reported for the synthesis of *N*-acylcyanamides. The classical approach is through the reaction between acid chlorides with sodium cyanamide.[10] Other methods involve a direct coupling of carboxylic acids with cyanamide by using 1,1′-carbonyldiimidazole (CDI) as the dehydrating agent,[11] deoxygenation of acylisocyanates[12] or desulfurization of acylisothiocyanates,[13] as well as palladium-catalyzed aminocarbonylation of aryl halides.[14] Nevertheless, issues associated with the methods, including the use of toxic or expensive reagents or catalysts, limited substrate scope, harsh reaction conditions, and long reaction times, remain to be addressed.

In recent years, sonochemical methodology has been applied as a powerful technique for facilitating various chemical reactions.[15] The resulting cavitation effect caused by ultrasonication can lead to an enhancement in solubility, diffusivity, penetration, and mass transportation of species in the reactions.[16] Compared to conventional stirring, ultrasonication not only shortens reaction times and minimizes the formation of side products, but also provides a greener process, lowering the cost of production with less energy consumption.

Trichloroisocyanuric acid (TCCA) is a versatile *N*-halo reagent that has been applied for chlorination and oxidation reactions.[17] Because of its low cost, ring basicity, and high chlorine content, it is considered to be an atom-economic reagent that enables reactions to be carried out in the absence of added base. As illustrated in Scheme 1, the applications of TCCA in combination with triphenylphosphine (PPh_3) as a carboxylic acid activator have recently been demonstrated in the synthesis of various derivatives.[18–21] Nonetheless, to the best of our knowledge, the reagent system has never been used in the synthesis of *N*-acylcyanamides or under ultrasonication.

Thus, in continuation of our research on the use of triphenylphosphine (PPh_3) with electrophilic additives, we decided to explore an ultrasound-assisted reaction using the combination of TCCA and PPh_3. Herein, we wish to report a convenient one-pot method for the direct conversion of carboxylic acids to *N*-acylcyanamides promoted by

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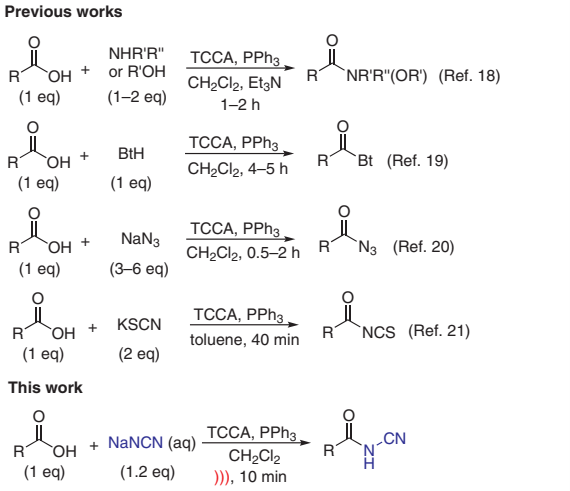


Scheme 1 Applications of the TCCA/PPh_3 system as a carboxylic acid activator

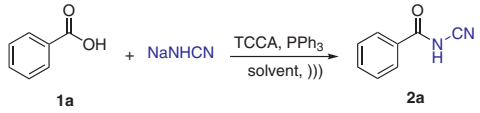
$TCCA/PPh_3$. The application of the developed protocol toward multicomponent synthesis of *N*-acyl-substituted imidazolone derivatives has also been demonstrated.

Initially, we examined the sonochemical reaction by using benzoic acid (**1a**) as a model substrate. Since sodium cyanamide (NaNHCN) is highly hydrophilic and much less soluble in organic solvents, the effect of the reaction medium was examined first. Typically, the reaction was carried out by mixing 1.0 equivalent of benzoic acid with $TCCA/PPh_3$ in 0.5:1.5 molar ratio. After brief sonication at room temperature until the starting acid was no longer observed on TLC, NaNHCN (2.0 equiv) was added to the reaction mixture, followed by sonication for a further 10 minutes.

According to Table 1, use of acetonitrile as the solvent led to *N*-cyanobenzamide (**2a**) in 65% yield (entry 1), whereas other polar solvents failed to give the product because TCCA reacts violently in these media (entries 2–4). In less polar solvent such as dichloromethane, no conversion was observed unless a few drops of water were added to assist the solubility of NaNHCN (entries 5 and 6). Further reducing the amount of the cyanamide salt or that of TCCA and PPh_3 slightly lowered the product yield (entries 7 and 8). Nevertheless, to our satisfaction, an increase in the conversion was observed when NaNHCN was pre-dissolved in water before adding it to the reaction mixture (entry 9). Notably, the rate-enhancement effect of ultrasound could be clearly observed as the reaction performed under stirring provided a lower product yield with extended reaction time (entry 10).

Having the optimal reaction conditions in hand (Table 1, entry 9), we next explored the scope and limitations of the protocol using various carboxylic acids.[22] As shown in Scheme 2, aromatic substrates having a *para* substituent (**1b**–**g**) generally provided good to excellent yields of the

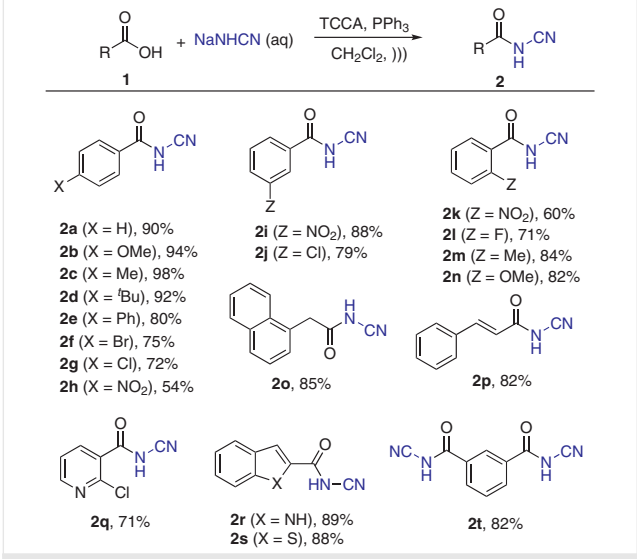
Table 1 Optimization of the Reaction Conditions[a]



Entry	TCCA (equiv)	PPh_3 (equiv)	NaNHCN (equiv)	Solvent	Yield (%)
1	0.5	1.5	2.0	CH_3CN	65
2	0.5	1.5	2.0	1,4-dioxane	trace
3	0.5	1.5	2.0	THF	n.d.
4	0.5	1.5	2.0	DMF	n.d.
5	0.5	1.5	2.0	CH_2Cl_2	n.d.
6	0.5	1.5	2.0	CH_2Cl_2	84[b]
7	0.5	1.5	1.2	CH_2Cl_2	81[b]
8	0.4	1.2	1.2	CH_2Cl_2	72[b]
9	**0.4**	**1.2**	**1.2**	**CH_2Cl_2**	**90[c]**
10	0.4	1.2	1.2	CH_2Cl_2	62[c,d]

[a] Reaction conditions: benzoic acid (0.42 mmol), solvent (1 mL), sonication for 10 min; n.d. = not detected.
[b] H_2O (2–3 drops) was added to the mixture.
[c] NaNHCN was dissolved in H_2O (0.5 mL) before adding.
[d] The reaction was stirred for 90 min.

corresponding *N*-acylcyanamides **2b**–**g**. Only *p*-nitrobenzoic acid gave product **2h** in moderate yield presumably because it decomposes easily.[14c,23] Notably, *m*-nitrobenzoic acid and *m*-chlorobenzoic acid were effectively converted into **2i** and **2j**, respectively, in high yields.



Scheme 2 Synthesis of *N*-acylcyanamides **2**

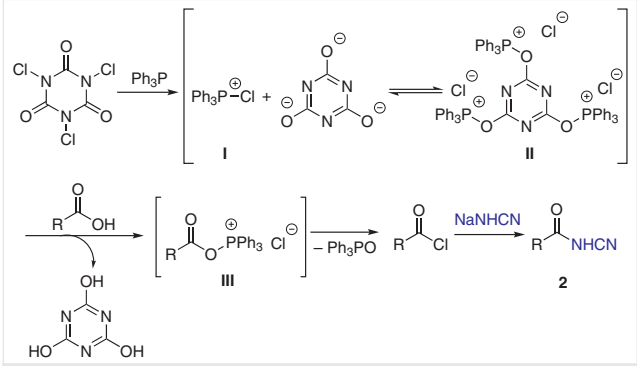
The presence of a substituent at the *ortho* position slightly lowered the yields of **2k**–**n**, which is possibly due to adverse steric effects. It should be noted that a consequence

of the mild reaction conditions was that no S_NAr side product was observed when using *o*-fluorobenzoic acid as the substrate. The reaction conditions were also applicable to carboxylic acids not conjugated with aromatic systems, as **2o** and **2p** were obtained in good yields without further optimization of the reaction conditions. Notably, cinnamic acid exclusively gave 1,2-addition product **2p** without detectable formation of any Michael addition product or double bond isomerization. Remarkably, heterocyclic acids were also viable substrates, undergoing dehydrative amidation to provide **2q–s** in good yields. Finally, a diacid substrate underwent double amidation producing *N*,*N*-dicyanoisophthalamide **2t** in 82% yield.

Imidazolones are important core structures found in a number of bioactive compounds and pharmaceuticals displaying potent inhibitory activities.[24] To demonstrate the synthetic utility of the developed protocol further, a one-pot multicomponent reaction of carboxylic acid, sodium cyanamide, and L-amino acid methyl esters to furnish *N*-acyl-substituted imidazolones was attempted.[25] The formation of the desired products could be envisaged through the addition of an in situ generated *N*-acylcyanamide with an α-amino acid methyl ester, followed by intramolecular cyclization of the intermediate guanidine. As shown in Scheme 3, the three-component reaction proceeded well with a range of α-amino esters giving the desired products **3** in satisfactory yields over three steps. The presence of electron-withdrawing substituents slightly lowered the yields of **3fc** and **3la**.

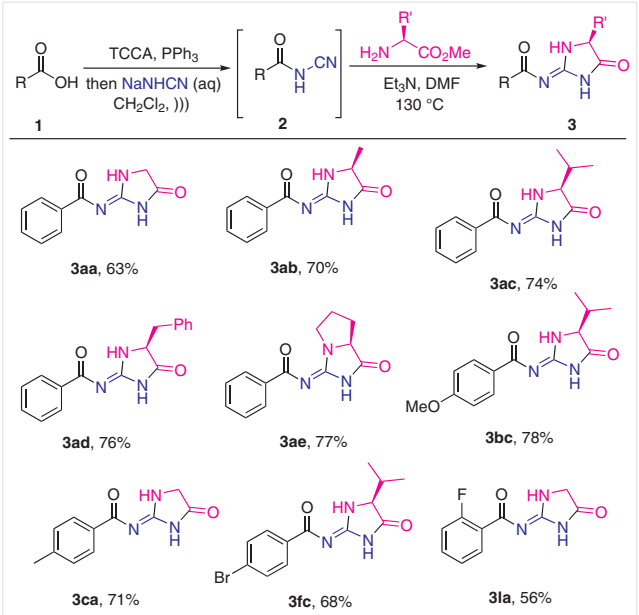
To understand the reaction mechanism better, a $^{31}P\{^1H\}$ NMR study was carried out by a real-time monitoring of the reaction between benzoic acid and NaNHCN in an NMR tube by using $CDCl_3$ as the solvent. At first, the mixture exhibited a signal at δ_p = –5.32 ppm which is due to PPh_3. This signal completely disappeared after the addition of TCCA, giving rise to a new major peak at δ_p = 64.62 ppm corresponding to triphenylphosphonium chloride.[19,26] Other lower intensity signals were also observed at δ_p = 59.62, 23.94, and 23.66 ppm that could be attributed to other oxyphosphonium species[27] (see Figure S1 in the Supporting Information). These signals disappeared upon treatment with benzoic acid, when a single peak at δ_p = 29.23 ppm corresponding to triphenylphosphine oxide appeared. These data suggest that most of the acyloxyphosphonium ion was converted rapidly to benzoyl chloride before the addition of the cyanamide salt.

Taking the above results into consideration, a mechanism of the reaction can be proposed as depicted in Scheme 4. An initial attack at the chloride atoms in TCCA by PPh_3 leads to the formation of phosphonium chloride **I** with a release of cyanuric acid. This intermediate could further react with cyanuric acid to form other phosphonium intermediates such as **II**. Phosphorylation of the carboxylic acid followed by chlorination of **III** provides an acyl chloride as the key reactive species. Final nucleophilic acyl substitution with the cyanamide salt then affords *N*-acylcyanamide **2**.



Scheme 4 Proposed mechanism for the synthesis of *N*-acylcyanamide **2**

In summary, we have developed an ultrasound-assisted synthesis of *N*-acylcyanamides from readily available and inexpensive carboxylic acids. The protocol overcomes the previous limitations of the syntheses of *N*-acylcyanamides by using the low-cost and atom-economic TCCA as reagent with short reaction times and under mild conditions. The method not only accommodates various substituents but also enables rapid access to substituted imidazolone derivatives through a three-component coupling reaction that is potentially useful for organic and medicinal chemists to develop new synthetic routes toward challenging targets where other available methods are limited or less effective.



Scheme 3 Three-component synthesis of *N*-acyl-substituted imidazolones **3**

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691583.

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(22) **Synthesis of *N*-Acylcyanamides 2; General Procedure**
To a cold solution of triphenylphosphine (0.201 g, 0.768 mmol) in CH_2Cl_2 (2 mL) was added trichloroisocyanuric acid (0.0595 g, 0.256 mmol) with continuous sonication for 5 min. The requisite carboxylic acid (0.64 mmol) was then added, and sonication was continued for 5 min. The temperature was raised to r.t. before adding an aqueous solution of sodium cyanamide (0.050 g, 0.768 mmol, 1 mL). After sonication for 10 min, the crude mixture was quenched with 1 M HCl, then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was then purified by short column chromatography by using 10% MeOH/EtOAc as the eluent.
***N*-Cyanobenzo[*b*]thiophene-2-carboxamide (2s)**
White solid; yield: 0.1139g (88%); mp 165–167 °C; R_f 0.28(20% MeOH/EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.09 (s, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 7.39 (s, 1 H), 7.30 (t, *J* = 8.0 Hz, 1 H), 7.11 (t, *J* = 8.0 Hz, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.0, 138.4, 127.7, 127.1, 125.9, 123.0, 121.1, 113.1, 109.2, 107.9..
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(25) **Synthesis of *N*-Acyl-Substituted Imidazolones 3; General Procedure**

Following the above described procedure for the synthesis of compound **2** using the requisite carboxylic acid (0.64 mmol), after complete formation of **2** as detected by TLC, the crude reaction was concentrated under reduced pressure before adding DMF (1 mL). The mixture was then transferred into a 10 mL pressure tube, followed by addition of the amino acid methyl ester hydrochloride (0.768 mmol) and NEt_3 (0.27 mL, 1.92 mmol). The pressure tube was then placed in a preset oil bath at 130 °C and the reaction mixture was stirred for 30–40 min. The mixture was then quenched with H_2O and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography by using 30–50% EtOAc/hexanes as the eluent.

***N*-(1-Oxo-5,6,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazol-3-yl)benzamide (3ae)**

Colorless oil; yield: 0.1198g (77%); R_f 0.40(40% EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.76 (s, 1 H), 8.27 (d, *J* = 7.5 Hz, 2 H), 7.52 (t, *J* = 7.5 Hz, 1 H), 7.43 (t, *J* = 7.5 Hz, 2 H), 4.14 (t, *J* = 9.0 Hz, 1 H), 3.95 (q, *J* = 9.0 Hz, 1 H), 3.47 (t, *J* = 9.0 Hz, 1 H), 2.34–2.11 (m, 3 H), 1.78 (quin, *J* = 9.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.8, 173.9, 162.0, 136.4, 132.5, 129.9, 128.1, 62.3, 46.6, 27.1, 27.0. TOF-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}N_3O_2$: 244.1086; found: 244.1081.

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