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# Ultrasound-assisted synthesis of substituted guanidines from thioureas

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## Abstract

Ultrasound-assisted synthesis of guanidine derivatives was developed using 2,4,6-trichloro-1,3,5-triazine as an inexpensive dehydrosulfurization reagent. Both 1,3-alkylaryl- and 1,3-diaryl-thioureas were rapidly converted into carbodiimides before subsequent reaction with aromatic and aliphatic amines. The method allows rapid access to highly substituted guanidines in good to excellent yields under mild conditions and with minimal use of solvent.

**Keywords** guanidine; thiourea; cyanuric chloride, triphenylphosphine; ultrasound

## Introduction

Guanidine is an important structural unit often found in many biologically and pharmaceutically related molecules.[1] Owing to its basicity and ability to form strong hydrogen-bond interactions under physiological conditions, many natural and synthetic guanidine-containing compounds have increasingly been shown to exhibit a range of biological activities including antibacterial, antifungal, antiviral, anti-inflammatory, and antitumor.[2] Moreover, various substituted guanidines have been used as key building blocks in the fields of supramolecular chemistry, synthetic receptors, recognition devices, sensors, as well as catalysis.[3]

Considering the growing demand for guanidine derivatives, a number of new methods have been developed for convenient access to this class of compounds.[4] Among the available methods, synthesis from the reaction of an amine with a substituted thiourea proceeding through an *in-situ* generated carbodiimide intermediate has been very attractive since the starting materials are relatively inexpensive and readily available. Various dehydrosulfurization reagents have been reported such as mercury(II) chloride,[5] copper(II) sulfate-silica gel,[6] copper(II) chloride,[7] 2,4,6-

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trichloro-1,3,5-triazine (TCT),[8] ethyl-3-aminopropyl carbodiimide hydrochloride (EDCI),[9,5d] and the Mukaiyama reagent.[10] Nevertheless, these protocols suffer from limitations including the use of toxic metals, expensive reagents, low yields, harsh conditions, and long reaction times.

In the recent years, sonochemical methods have proven to be a powerful technique for facilitating various chemical reactions.[11] Application of ultrasonic energy to the reaction media can lead to the formation and collapse of small bubbles of gaseous substances.[12] This cavitation effect is responsible for an enhancement in solubility, diffusivity, penetration, and mass transportation of species in certain reactions. As a consequence, the use of ultrasound in organic synthesis often shortens reaction times and minimizes the formation of undesired side products which enhances product yield and selectivity. Additionally, the method is applicable to solvent-free or low-solvent conditions leading to greener process, lowering the cost of production with less energy consumption as compared to conventional heating.[13]

2,4,6-Trichloro-1,3,5-triazine (TCT) is one of the most versatile reagents in organic synthesis due to its low cost, ready availability, and high reactivity.[14] Since all three chlorine atoms on the triazine ring are susceptible to nucleophilic displacement, TCT can be used as a scaffold for the synthesis of structurally diverse compounds[36] or it can be applied as a dehydrating agent in various functional group transformations.[15] So far, a number of methods have been developed using TCT as a coupling reagent in the synthesis of carboxylic acid derivatives. To the best of our knowledge, there is only one study reporting the use of TCT as an activating agent for the guanylation of amines.[8] In this method, TCT was applied in the presence of *N*-methylmorpholine in THF at reflux for the dehydrosulfurization of di-Boc-thiourea. However, the reaction with other substituted thiourea containing substrates was not evaluated.

In a continuation of our on-going research in developing simple and economic reactions mediated by TCT, we were interested in replacing the traditional promoters used for the dehydrosulfurization of thiourea derivatives with inexpensive and easy to handle TCT. Special attention was paid to the use of ultrasound in promoting the reaction with a limited amount of organic solvent. Thus, in this study, the ultrasound-assisted guanylation of aliphatic and aromatic amines with substituted thioureas under low solvent conditions was investigated using TCT in the presence of catalytic triphenylphosphine ($PPh_3$) as the activator.

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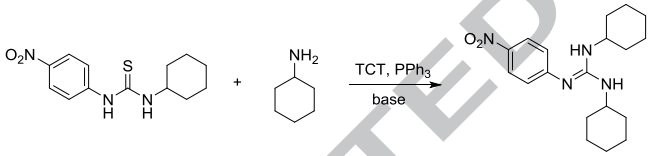
## Results and discussion

To develop the optimal reaction conditions using a minimal amount of solvent, we first investigated the guanylation reaction using 1-cyclohexyl-3-(4-nitrophenyl)thiourea and cyclohexylamine as model substrates. In our preliminary study, the sonochemical reaction was performed using equimolar amounts of TCT and thiourea in the presence of five equivalents of triethylamine in dichloromethane. The base was used in excess to facilitate the dehydrosulfurization reaction, while solvent quantity was kept at a minimum (below 250 μL which corresponded to the amount commonly applied under the solvent-drop grinding technique (< 1.5 μL/mg of solid).[16] After sonication of the mixture at room temperature for 10 min, the respective carbodiimide could be detected by TLC. Without isolation of this intermediate, cyclohexylamine (1.1 equiv) was then added, followed by sonication for a further 10 min. Unfortunately, the reaction gave a complex mixture containing alkyamino-substituted triazines as major products whereas the desired guanidine was isolated in low yield (Table 1, entry 1).

**Table 1.** Optimization of the reaction conditions[a]




| Entry | $PPh_3$ (equiv) | Base | Method | Yield (%) |
|---|---|---|---|---|
| 1 | - | $Et_3N$ | ))), rt | 30 |
| 2 | 0.1 | $Et_3N$ | ))), rt | 87 |
| 3 | 0.1 | $Cs_2CO_3$ | ))), rt | 53 |
| 4 | 0.1 | $K_2CO_3$ | ))), rt | 59 |
| 5 | 0.1 | $Na_2CO_3$ | ))), rt | 85 |
| 6 | 0.1 | $Na_2CO_3$ | stirring | 45 |
| 7 | 0.1 | $Na_2CO_3$ | grinding | 48 |
| 8 | 0.1 | $Na_2CO_3$ | ))), rt | 86[b] |

[a]Reaction conditions: 1-cyclohexyl-3-(4-nitrophenyl)thiourea (0.0757 g, 0.271 mmol), TCT (0.0500 g, 0.271 mmol), $PPh_3$, base (1.355 mmol), dichloromethane (<250 μL), 10 min, then cyclohexylamine (0.0296 g, 0.298 mmol), 10 min. [b]TCT (0.0200 g, 0.108 mmol) was used.

Based on our previous experience, we have discovered that reactions mediated by TCT could be promoted using catalytic amounts of triphenylphosphine.[17] This prompted us to further optimize the reaction conditions using $PPh_3$ as an additive, while other inorganic bases were also screened

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as a proton scavenger. According to Table 1, adding $PPh_3$ to the reaction significantly improved the product yield (entry 2) presumably due to the formation of the activated triazinylphosphonium chloride which rapidly reacted with thiourea. Upon changing the organic base to inorganic carbonate bases such as cesium carbonate and potassium carbonate, the yield of the corresponding guanidine decreased dramatically and several unidentified side-products were observed (entries 3 and 4). Nevertheless, high conversion was observed when sodium carbonate was applied as a base (entry 5). Although it is unclear why such a weak base with low solubility enabled clean conversion of the starting thiourea into the carbodiimide intermediate, it is possible that other side-reactions or decomposition of intermediates could be pronounced with more soluble carbonate bases ($Cs_2CO_3$ and $K_2CO_3$).

The effect of cavitation derived from the applied ultrasound energy was also proven to be responsible for the yield enhancement under sonochemical conditions as the same reaction carried out under stirring or grinding gave significantly lower yields (entries 6-7). Since less than a stoichiometric amount of TCT has been applied in a number of functional group transformations, the guanylation reaction was further performed using a 1:0.4 molar ratio of the thiourea and TCT. To our delight, decreasing the amount of TCT did not lead to a decrease in product yield (entry 8). Considering the benefit of using inexpensive and easy to handle sodium carbonate, we decided to use these conditions in our further investigation.

With the optimized reaction conditions in hand (Table 1, entry 8), the scope and limitation of the method were examined. A series of 1,3-disubstituted thioureas were treated with TCT/$PPh_3$ in the presence of $Na_2CO_3$ before being subjected to reaction with various amine nucleophiles under ultrasonic conditions. It was observed that the presence of an electron-withdrawing group on the aromatic ring of thioureas led to more favorable addition of the amines due to the formation of more electron deficient carbodiimide intermediates. The guanidine products were also obtained in high yields when alkylamines were used. As shown in Table 2, the reaction of 1-cyclohexyl-3-(4-nitrophenyl)thiourea with primary alkylamine, benzylamine, and secondary amines proceeded well to afford the corresponding guanidine derivatives in good yields within 10 min (entries 1-3). Guanylation with aromatic amines and heterocyclic amines gave slightly lower yields (entries 4-6). Other thiourea derivatives containing electron-withdrawing groups also reacted smoothly with the applied amines (entries 7-11). Interestingly, the reaction using

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sterically hindered diisopropylamine proceeded quickly suggesting that the use of ultrasound energy could help overcome steric effects in the reaction (entry 10).

The reaction times after amine addition to the *in-situ* generated carbodiimide were found to vary depending on the reactivity of the carbodiimide. Although 1,3-diphenylthiourea underwent rapid dehydrosulfurization to give the respective carbodiimide, subsequent reaction with amines required longer times since the carbodiimide intermediate is less activated (entries 12-13). *N,N'*-Alkylarylcarbodiimides were generally less reactive than *N,N'*-diarylcarbodiimides. Thus, 1-cyclohexyl-3-phenylthiourea underwent guanylation with cyclohexylamine with extended times (entries 14-15). It should be noted that the presence of an electron-donating substituent in the thiourea fragment gives rise to a less electrophilic carbodiimide which significantly decelerates the guanylation reaction. In accordance with the reported literature,[21] the reaction using 1-cyclohexyl-3-(*p*-tolyl)thiourea as a substrate was sluggish, however, the respective product was obtained in an acceptable yield.

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**Table 2** One-pot synthesis of *N*,*N*′,*N*″-substituted guanidines[a]

| Entry | Thiourea | Amine | Time (min) | Yield (%)[Ref] |
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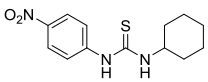
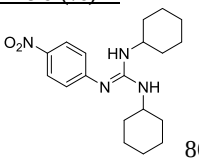
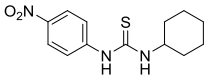
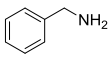
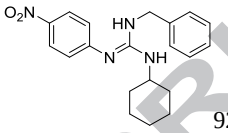
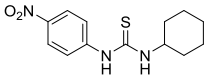
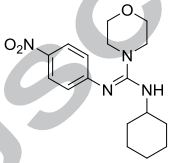
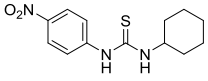
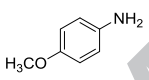
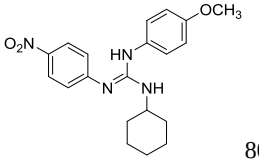
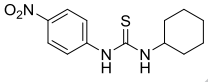
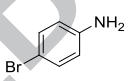
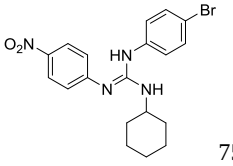
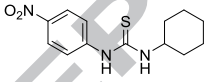
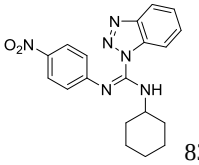
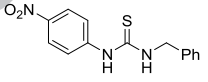
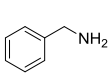
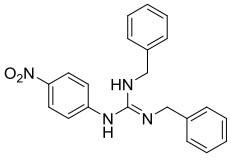
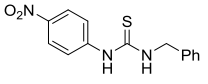
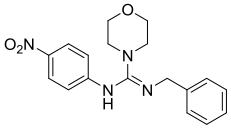
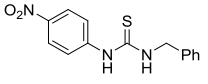
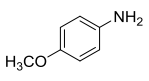
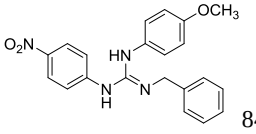
| 1 |  |  | 10 |  86[18] |
| 2 |  |  | 10 |  92 |
| 3 |  |  | 10 |  87 |
| 4 |  |  | 10 |  80 |
| 5 |  |  | 10 |  75 |
| 6 |  |  | 10 |  83 |
| 7 |  |  | 10 |  87[19] |
| 8 |  |  | 10 |  88 |
| 9 |  |  | 10 |  84 |

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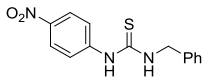
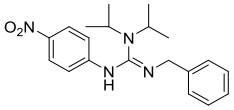
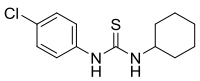
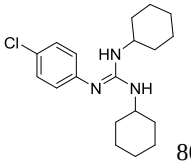
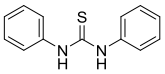
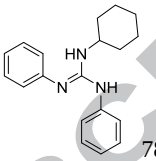
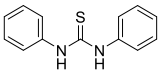
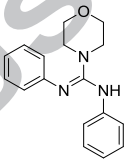
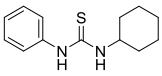
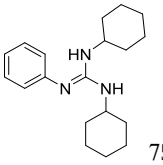
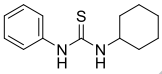
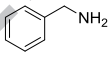
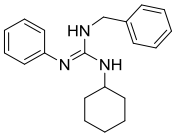
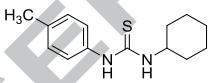
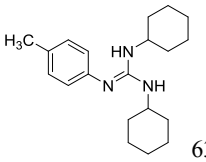
| 10 |  |  | 10 |  | 92 |
| 11 |  |  | 20 |  | 80[18] |
| 12 |  |  | 20 |  | 78[20] |
| 13 |  |  | 20 |  | 75[21] |
| 14 |  |  | 30 |  | 75[18] |
| 15 |  |  | 25 |  | 78[22] |
| 16 |  |  | 45 |  | 63[18] |

[a]Reaction conditions: thiourea (0.271 mmol), TCT (0.0200 g, 0.108 mmol), $PPh_3$ (0.007 g, 0.027 mmol), $Na_2CO_3$ (0.0861 g, 0.813 mmol) dichloromethane (250 μL), sonication, 10-15 min, then amine (0.298 mmol).

A possible mechanism for this reaction is depicted in Scheme 1. In the first step (*n* =1), TCT was activated through the formation of the corresponding triazinylphosphonium salt.[17] Displacement of the phosphonium ion with thiourea then produced intermediate **I** with concomitant release of $PPh_3$. Subsequent dehydrosulfurization of **I** gave carbodiimide along with chloro-substituted triazine thiol derivative for further reaction with thiourea in the next catalytic cycle until the

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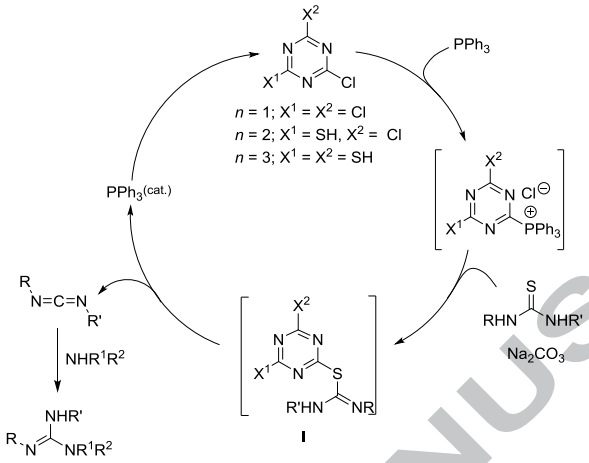
triazine-trithiol by-product was formed ($n$ = 3). Finally, nucleophilic attack of an amine on the electrophilic center of the carbodiimide led to the formation of the guanidine product.




**Scheme 1** Proposed mechanism for guanylation mediated by the TCT-$PPh_3$ system.

## Conclusion

In summary, a convenient one-pot sonochemical synthesis of highly substituted guanidines has been developed. Ultrasonic irradiation was found to complement the applied guanylation conditions where solid reactants and reagents were mixed in a low volume of solvent. Using the TCT/$PPh_3$/$Na_2CO_3$ combination, the guanylation of aliphatic and aromatic amines with 1,3-disubstituted aryl and alkyl thioureas proceeded rapidly under mild conditions. This facile, efficient, and economical method represents an excellent alternative to known procedures with simplicity in reagent handling and experimental setup and avoids an excess of organic solvent.

## Acknowledgements

Financial support from the Thailand Research Fund through the Royal Golden Jubilee Ph.D. Program to S.W. (Grant No. PHD/0206/2556) as well as the Center of Excellence for Innovation in Chemistry (PERCH-CIC), Chiang Mai University are gratefully acknowledged.

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## Supplementary data

$^{1}H$ and $^{13}C$ NMR for representative products are available. Supplementary data related to this article can be found at http://xxx.

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## Graphical Abstract

**Ultrasound-assisted synthesis of substituted guanidines from thioureas**

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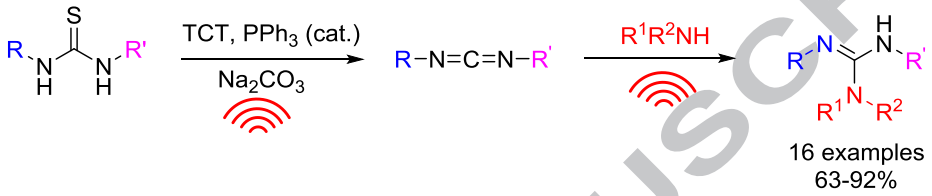
Mookda Pattarawarapan,* Subin Jaita, Sirilak Wangngae, and Wong Phakhodee

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