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A convenient one-pot synthesis of trisubstituted 1,3,5-triazines through intermediary amidinothioureas

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ABSTRACT

A thiophile-promoted one-pot synthesis of trisubstituted 1,3,5-triazines starting from isothiocyanates, *N*,*N*-diethylamidines, and carbamidines has been studied. The reaction proceeds through the formation of intermediary amidinothioureas, which react with carbamidines in the presence of mercury(II) chloride to generate the desired 1,3,5-triazines in good to moderate yields (40–70%).

1,3,5-Triazines are one of the oldest classes of organic compounds that continue to be of interest due to their interesting pharmacological properties. Members of this class have been found to possess anti-tumor,[1] corticotrophin-releasing factor-1 receptor antagonist,[2] leukotriene C_4 (LTC_4) antagonist,[3] inosine monophosphate dehydrogenase (IMPDH) inhibitory,[4] erm methyltransferase inhibitory,[5] and reticuloendothelial hyperfunction depressive activities.[6] Despite the biological importance of 1,3,5-triazines, synthetic methods for the preparation of analogs containing different substituents at each carbon are limited.

Cyanuric chloride has been used widely for the preparation of trisubstituted triazines, but stepwise replacement of the three chlorines with Grignard reagents, ammonia, and amines is often unreliable and leads to mixtures of compounds.[4,7] The synthesis of triazines with alkyl substituents can be problematic using this methodology due to the highly reactive nature of the Grignard reagents. More general routes to these compounds involve the reaction of substituted biguanides with acid chlorides,[8] anhydrides,[9] or carboxylates.[5,6] However, the preparation of substituted biguanides requires harsh conditions and isolation of the products are difficult due to their high water solubility. The cyclizations of acylamidines with amidines or guanidines gave s-triazines with different substitutents.[10] This is a convenient synthetic route to trisubstituted 1,3,5-triazines, but it allows only two variations at position 4 of the triazine ring. The recently published procedure involves the treatment of isothiocyanates with sodium hydrogencyanamide, followed by amidines in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) hydrochloride.[11] This protocol appears to be general with isothiocyanates (both aromatic and aliphatic) and aromatic carbamidines, while less hindered aliphatic carbamidines lead to undesired *N*-cyanoguanidines. Therefore, it is still of continued interest and great importance to explore novel and efficient synthetic approaches for such heterocycles. Herein, we report a convenient, one-pot procedure for the preparation of trisubstituted 1,3,5-triazines through intermediary amidinothioureas which is applicable for the wide range of substituents at each carbon of the triazine ring.

During the course of our recent studies on amidinothioureas for the synthesis of biologically interesting heterocycles, we reported the synthesis of various amidinoguanides from amidinothioureas using mercury(II) chloride as a thiophile.[12] It was envisaged that this methodology could be extended to the preparation of trisubstituted 1,3,5-triazine by replacing anilines with binucleophilic carbamidines. Thus, 4-chlorophenyl isothiocyanate **1** ($R^1 = 4\text{-}ClC_6H_4$) was reacted with readily available *N*,*N*-diethyl acetamidine **2** ($R^2 = CH_3$) in THF to provide the corresponding intermediary amidinothiourea **3** (Scheme 1). Without isolation of intermediary amidinothiourea, it was treated with benzamidine hydrochloride **4** ($R^3 = C_6H_5$) at room temperature in the presence of triethylamine and mercury(II) chloride. The desulfurization of the amidinothiourea was monitored visually based on the formation of the black precipitate of HgS. The formation of 1,3,5-triazine was observed as a new spot at the uppermost part of the TLC. The reaction mixture was kept under stirring for another 4 h and after column chromatographic purification, it was identified as the desired triazine **5** by LC, MS, and ^1H NMR (Table 1, entry 1).

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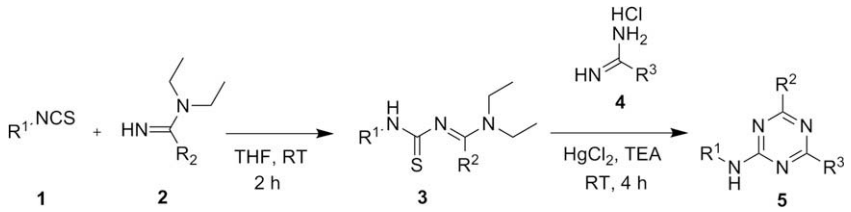

Scheme 1.

Table 1
Synthesis of trisubstituted 1,3,5-triazines

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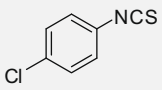
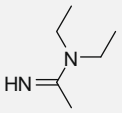
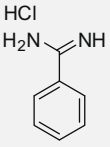
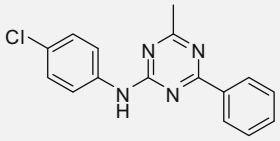
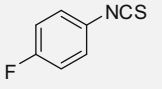
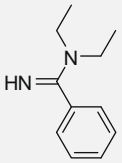
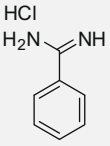
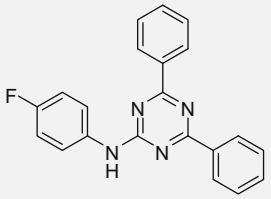
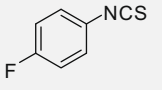
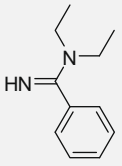
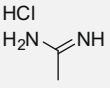
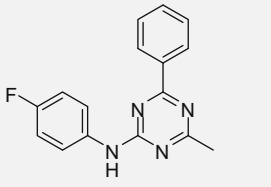
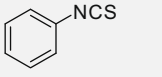
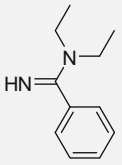
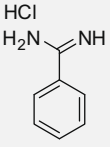
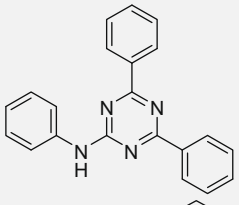
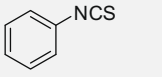
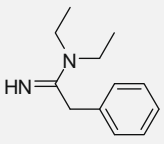
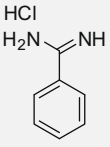
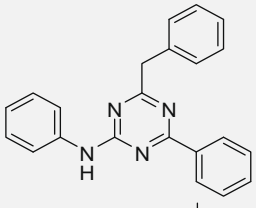
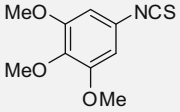
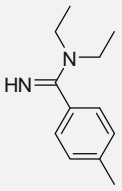
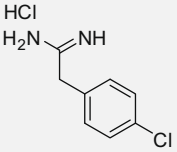
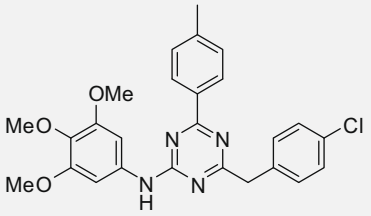
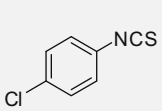
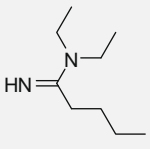
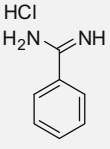
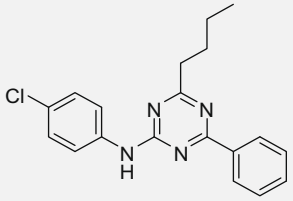
1					70
2					67
3					40
4					65
5					45
6					40
7					65

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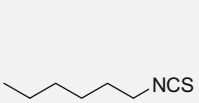
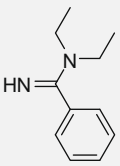
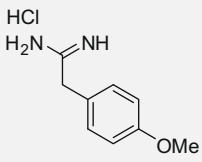
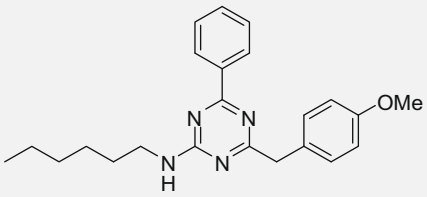
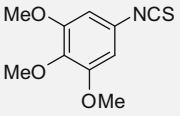
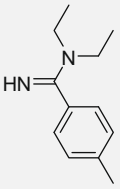
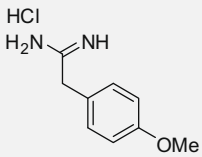
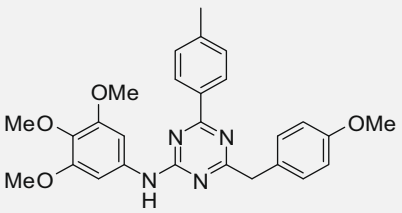
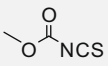
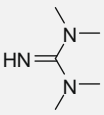
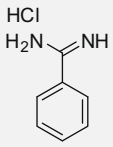
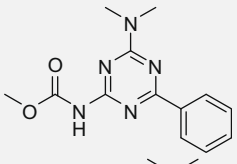
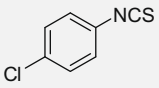
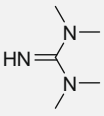
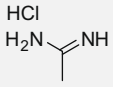
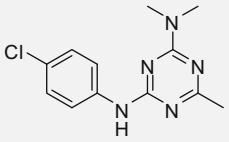
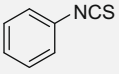
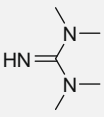
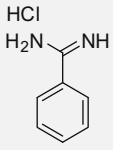
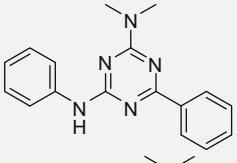
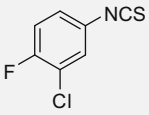
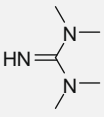
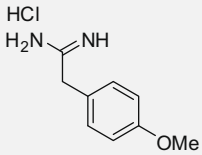
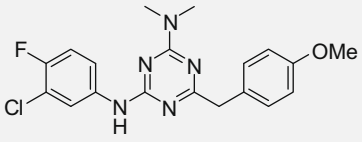
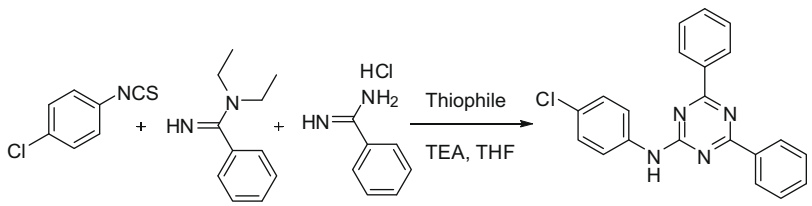
Table 1 (*continued*)

Entry	Isothiocyanates **1**	*N*,*N*-Diethylamidines or tetramethylguanidine **2**	Carbamidines **4**	Products **5**	Yield[a] (%)
8					45
9					50
10					62
11					50
12					80
13					55

[a] Isolated yield.

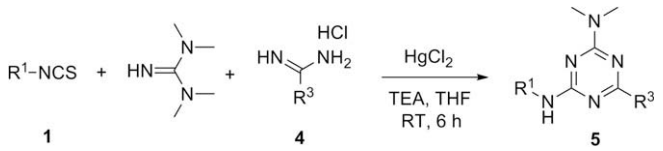
Copper sulfate–Silica Gel,[13] lac sulfur on alumina-triethanolamine[14] and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) hydrochloride[15] have been used as thiophiles for the guanylation of amines by thioureas. We reasoned that these reagents can be studied to identify the most suitable reagent for this reaction in one-pot without the isolation of intermediates. We chose to compare these reagents as our thiophiles (Table 2) and monitored the formation of (4-chlorophenyl)-(4, 6-diphenyl-[1,3,5]triazin-2-yl)-

Table 2
Reaction of 4-chlorophenyl isothiocyanate, *N*,*N*-diethyl benzamidine, and benzamidine hydrochloride to generate 4-chlorophenyl-(4,6-diphenyl-[1,3,5] triazin-2-yl)-amine mediated by a thiophile



	Thiophile	Reaction time	Yield[a] (%)
a	$HgCl_2$	6 h	75
b	$Hg(OAc)_2$	12 h	No reaction
c	$CuSO_4{\cdot}SiO_2$	12 h	10
d	Lac sulfur:Alumina	12 h	No reaction
e	EDC hydrochloride	12 h	55

[a] Isolated yield.



Scheme 2.

amine in a model reaction. On the basis of the product yield it was clear that EDC hydrochloride and $HgCl_2$ were the optimal reagents for this reaction. We studied the generality of both the thiophiles for the synthesis of desired triazines. EDC hydrochloride failed to yield triazines when acetamidine hydrochloride was used as a binucleophile, but $HgCl_2$ gave the desired product. Therefore, $HgCl_2$ was selected as a general thiophile for all other reactions.

All the reactions between isothiocyanates, *N*,*N*-diethylamidines, and carbamidines with systematic variations of R^1, R^2, and R^3 proceeded smoothly to afford the corresponding 1,3,5-triazines in good to moderate yields (Scheme 1). The generality of this new synthetic method for the efficient construction of 1,3,5-triazines was investigated by employing $HgCl_2$ as a thiophile using THF as a solvent at room temperature.[16] The results are summarized in Table 1. The generality of this method for the synthesis of 2,5-diamino-1,3,5-triazines was also studied by reacting isothiocyanates with tetramethylguanidine followed by condensation with carbamidines in the presence of $HgCl_2$ (Scheme 2, Table 1, entries 10–13).

In conclusion, we have reported a convenient one-pot synthesis of biologically important trisubstituted 1,3,5-triazine derivatives from readily available starting materials under mild conditions. The reaction is applicable to a wide range of substituted isothiocyanates, *N*,*N*-diethylamidines, and carbamidines.

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Supplementary data

Supplementary data (general experimental procedure and spectral data for representative compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.034.

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16. *General experimental procedure for the preparation of trisubstituted 1,3,5-triazines*: To a stirred solution of isothiocyanate **1** (1 mmol) in THF (5 mL), *N*,*N*-diethylamidine **2** (1 mmol) was added at room temperature and allowed to stir for 2 h. To the stirred reaction mixture triethylamine (15 mmol) and carbamidine hydrochloride **4** (1.2 mmol) were added at room temperature. Mercury(II) chloride (1 mmol) was added slowly to the reaction mixture (slight exothermic) and the mixture was allowed to stir for another 4 h at room temperature. Initiation of the desulfurization was observed by the formation of black HgS precipitate. Progress of the reaction was monitored by TLC using ethyl acetate/hexane (3:7) as a mobile phase. After the completion of the reaction, the reaction mixture was diluted with THF (5 mL) and filtered through a Celite bed to remove the black precipitate of HgS. The filtrate was concentrated in vacuum and purified by silica gel (60–120 mesh) column chromatography using 12% ethyl acetate in hexane as a mobile phase to give triazines **5**. The same experimental protocol was followed for the preparation of 2,5-diamino-1,3,5-triazines (Scheme 2, Table 1, entries 10–13) using tetramethylguanidine instead of *N*,*N*-diethylamidines.