Article

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# A Concise Synthetic Method for 1,3,5-Triazinane-2,4-Dithiones

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1,3,5-Triazinane-2,4-ditionas foram sintetizadas eficientemente via condensação de 2 equiv. de 1-aril-tiouréa com 1 equiv. de ácidos carboxílicos alifáticos usando cloreto férrico hexahidratado como catalisador. Este protocolo tem as vantagens de alto rendimento, condições brandas e procedimento simples.

1,3,5-Triazinane-2,4-dithiones were efficiently synthesized via condensation of 2 equiv. of 1-arylthioureas with 1 equiv. of aliphatic carboxylic acids using ferric chloride hexahydrate as a catalyst. This protocol has the advantages of high yield, mild condition and simple procedure.

**Keywords**: 1,3,5-triazinane-2,4-dithione, 1,3,5-triazinane, thiourea, carboxylic acid, synthesis

## Introduction

Heterocyclic compounds have long been known to exhibit remarkable biological and pharmacological properties.[1] Among the heterocycles, triazine derivatives have attracted much attention because they can connect with other molecules by hydrogen or coordination bond to form network supramolecular materials,[2] and they can serve as luminescent or n-type electron-carrying materials after connected with some substituents like diphenylacetylene, naphthalene and anthracene.[3] Triazine derivatives constitute well-known compounds that have been used as fungicidal,[4] antiplasmodial,[5] anti-HIV [6] and herbicidal agents,[7] and chiral discriminators,[8] hydrogen sulfide scavengers[9] and low-toxicity drug deliverers.[10] They were also applied in organic synthesis,[11] enantiodifferentiating coupling reagents,[12] catalysis,[13] molecular tectonics,[14] and polymeric materials.[15] Meanwhile, heterocycles containing a thiourea structural unit have a special place among pharmaceutically important natural and synthetic materials, showing powerful antiproliferative action,[16] antibacterial properties[17] and anticancer activity.[18] For these reasons, 1,3,5-triazinane derivatives incorporating thiourea unit may be important in many fields.

The general synthetic methods for 1,3,5-triazinane derivatives involve the reactions of *N*,*N'*-bis(aryl-methylidene)arylmethane diimines with thioureas,[19] the multi-component reactions of phosphonates, nitriles, aldehydes and isocyanates,[20] the condensation of trifluoromethanesulfonamide with formaldehyde,[21] and the reactions of thiosemicarbazones with potassium thiocyanate and benzoyl chloride.[22] However, some methods use expensive reagents, toxic organic solvents, rigorous conditions, tedious workup procedure and long reaction time. Therefore, it is necessary to develop simple and efficient synthetic methods to 1,3,5-triazinane derivatives.

In this article, we report the synthesis of 1,3,5-triazinane-2,4-dithiones by reactions of 2 equiv. of 1-arylthioureas with 1 equiv. of aliphatic carboxylic acids using ferric chloride hexahydrate as a catalyst.

## Results and Discussion

Initially, the synthesis of 1,3,5-triazinane-2,4-dithione was attempted by reaction of 1-phenylthiourea with acetic acid at room temperature under catalyst-free condition, however, no product was observed. Subsequently, the mixture of 1-phenylthiourea and acetic acid was heated at 80 °C for several hours, a new compound was isolated in low yield, which was identified to be a novel heterocyclic compound, 6-hydroxy-6-methyl-1,5-diphenyl-1,3,5-triazinane-2,4-dithione. In our further research, it was found that some Brønsted acids, such as *p*-toluenesulfonic acid (PTSA) and trichloroacetic acid (TCA), and Lewis acids, such as $AlCl_3$, $CuCl_2$, $NiCl_2$, $FeCl_3$ and $FeCl_3 \cdot 6H_2O$,

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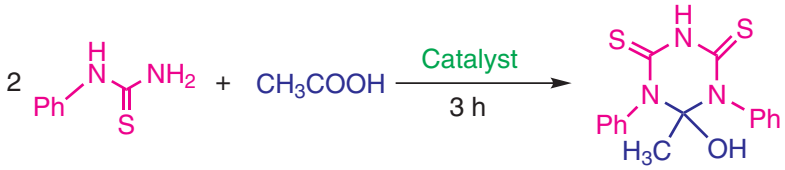
could efficiently catalyze the reaction (Table 1). Among them, $FeCl_3·6H_2O$ could give the best yield if the reaction was carried out at 80 °C using 10 mol% amount of catalyst (Table 1, entry 8). In addition, in this reaction, acetic acid was acted as a reactant and solvent.

To explore the generality and scope of the synthetic reactions, and synthesis of a series of 6-hydroxy-6-alkyl-1,5-diaryl-1,3,5-triazinane-2,4-dithiones (Scheme 1), different 1-arylthioureas and aliphatic carboxylic acids as substrates were examined under optimal conditions (Table 2). It was found that various 1-arylthioureas could efficiently react with aliphatic carboxylic acids at 80 °C in the presence of $FeCl_3·6H_2O$ to give the corresponding products in high yield. In comparison with 1-phenylthiourea, it was found that 1-arylthioureas including electron-donating groups, such as methyl and methoxyl, on the aromatic rings gave the corresponding products in higher yield and in faster rate (Table 2, entries 7-18). 1-Arylthioureas bearing electron-withdrawing substituents, such as chloro, on aromatic rings gave the corresponding product in slightly lower yield under similar conditions (Table 1, entry 19). Aliphatic carboxylic acids from $C_2$-$C_7$ were examined for the reactions, and afforded the corresponding products in high yield. In addition, aromatic carboxylic acids, such as various (un)substituted benzoic acids, were also attempted for the similar reactions, but no desired products were observed.

The resulting compounds 6-hydroxy-6-alkyl-1,5-diaryl-1,3,5-triazinane-2,4-dithiones are highly soluble in polar organic solvents including $CHC1_3$, $CH_2C1_2$, DMSO, DMF and EtOH, but insoluble in toluene, benzene, ether and *n*-hexane. The structures of all compounds were identified by infrared (IR), $^1H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectroscopies and elemental analysis. The $^1H$ NMR spectra of 6-hydroxy-6-alkyl-1,5-diaryl-1,3,5-triazinane-2,4-dithiones show the singlets of hydroxyls at 5.89-6.12 ppm and the multiplets of aromatic rings at 6.84-8.12 ppm. The IR spectra show the characteristic adsorption of hydroxyls at 3359-3450 $cm^{-1}$.

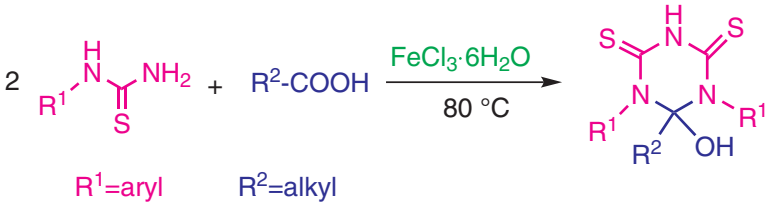
A possible mechanism for the synthesis of 1,3,5-triazinane-2,4-dithione is shown in Scheme 2.

**Table 1.** Synthesis of 6-hydroxy-6-methyl-1,5-diphenyl-1,3,5-triazinane-2,4-dithione under different conditions[a]



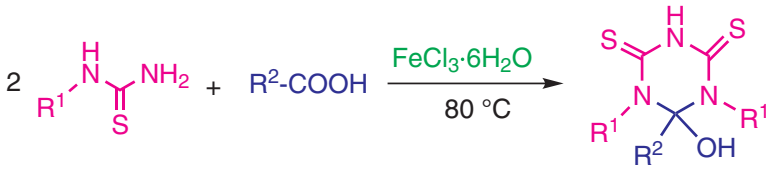

| entry | Catalyst | Amount of catalyst / (mol%) | Temperature / °C | Yield / %[b] |
|---|---|---|---|---|
| 1 | – | 0 | 80 | 10 |
| 2 | PTSA | 10 | 80 | 48 |
| 3 | TCA | 10 | 80 | 56 |
| 4 | $AlCl_3$ | 10 | 80 | 51 |
| 5 | $CuCl_2$ | 10 | 80 | 60 |
| 6 | $NiCl_2$ | 10 | 80 | 70 |
| 7 | $FeCl_3$ | 10 | 80 | 74 |
| 8 | $FeCl_3·6H_2O$ | 10 | 80 | 88 |
| 9 | $FeCl_3·6H_2O$ | 10 | 20 | 20 |
| 10 | $FeCl_3·6H_2O$ | 10 | 40 | 46 |
| 11 | $FeCl_3·6H_2O$ | 10 | 60 | 70 |
| 12 | $FeCl_3·6H_2O$ | 10 | 100 | 60 |
| 13 | $FeCl_3·6H_2O$ | 5 | 80 | 85 |
| 14 | $FeCl_3·6H_2O$ | 15 | 80 | 86 |

[a]Reaction conditions: 1-phenylthiourea (2 mmol), acetic acid (3 mmol) under different conditions; [b]isolated yields.



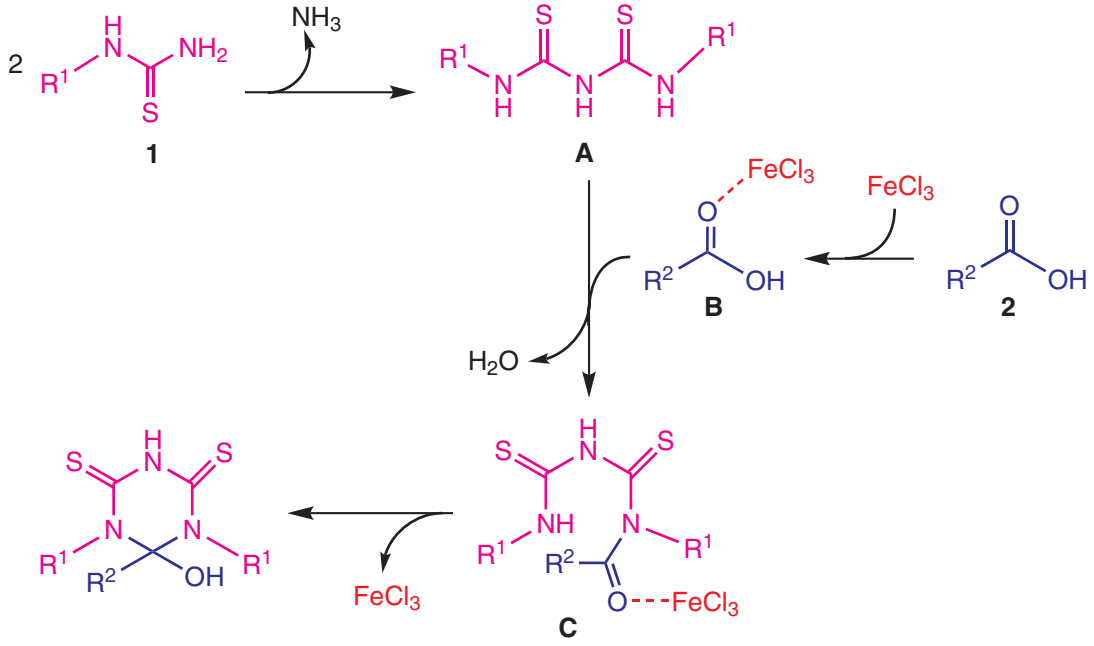

**Scheme 1.** Synthesis of 6-hydroxy-6-alkyl-1,5-diaryl-1,3,5-triazinane-2,4-dithiones.

**Table 2** Synthesis of 6-hydroxy-6-alkyl-1,5-diaryl-1,3,5-triazinane-2,4-dithiones[a]




| entry | $R^1$ | $R^2$ | time / h | mp / °C | Yield / %[b] |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | $CH_3$ | 3 | 254-256 | 87 |
| 2 | $C_6H_5$ | $C_2H_5$ | 3 | 197-198 | 85 |
| 3 | $C_6H_5$ | *n*-$C_3H_7$ | 3 | 133-135 | 84 |
| 4 | $C_6H_5$ | *n*-$C_4H_9$ | 4 | 155-157 | 80 |
| 5 | $C_6H_5$ | *n*-$C_5H_{11}$ | 4 | 124-126 | 80 |
| 6 | $C_6H_5$ | *n*-$C_6H_{13}$ | 4 | 105-106 | 79 |
| 7 | 2-$CH_3C_6H_4$ | $CH_3$ | 3 | 239-241 | 82 |
| 8 | 2-$CH_3C_6H_4$ | $C_2H_5$ | 3 | 160-162 | 88 |
| 9 | 2-$CH_3C_6H_4$ | *n*-$C_3H_7$ | 3 | 154-155 | 83 |
| 10 | 2-$CH_3C_6H_4$ | *n*-$C_4H_9$ | 4 | 123-124 | 85 |
| 11 | 4-$CH_3C_6H_4$ | $C_2H_5$ | 2 | 119-121 | 88 |
| 12 | 4-$CH_3C_6H_4$ | *n*-$C_3H_7$ | 2 | 127-129 | 90 |
| 13 | 4-$CH_3C_6H_4$ | *n*-$C_4H_9$ | 2 | 126-127 | 86 |
| 14 | 4-$CH_3C_6H_4$ | *n*-$C_5H_{11}$ | 3 | 111-113 | 80 |
| 15 | 4-$CH_3C_6H_4$ | *n*-$C_6H_{13}$ | 3 | 103-104 | 81 |
| 16 | 4-$CH_3OC_6H_4$ | $CH_3$ | 3 | 218-219 | 80 |
| 17 | 4-$CH_3OC_6H_4$ | $C_2H_5$ | 4 | 243-245 | 84 |
| 18 | 4-$CH_3OC_6H_4$ | *n*-$C_3H_7$ | 4 | 219-221 | 78 |
| 19 | 4-$ClC_6H_4$ | $CH_3$ | 4 | 208-210 | 66 |

[a]Reaction conditions: 1-arylthiourea (2 mmol), aliphatic carboxylic acid (3 mmol) and ferric chloride hexahydrate (0.2 mmol) at 80 °C; [b]isolated yields.




**Scheme 2.** The possible mechanism for the synthesis of 1,3,5-triazinane-2,4-dithiones.

Presumably, condensation of 2 equiv. of 1-arylthiourea **1** releasing a mole of ammonia first generates an intermediate **A**. One of amino groups of **A** subsequent reacts with a mole of complex **B**, which is formed from aliphatic carboxylic acid **2** and ferric chloride in the solution, to give intermediate **C** by loss of water. Subsequently the carbonyl

group of **C** undergoes the nuleophilic addition of its amino group by releasing ferric chloride to form a six-membered heterocyclic compound, 1,3,5-triazinane-2,4-dithione **3**.

## Conclusion

An efficient and concise method has been developed for the synthesis of 1,3,5-triazinane-2,4-dithiones via condensation of 2 equiv. of 1-arylthioureas with 1 equiv. of aliphatic carboxylic acids using ferric chloride hexahydrate as a catalyst. This protocol has the advantages of high yield, mild condition and simple procedure.

## Experimental

IR spectra were recorded using KBr pellets on an Alpha Centauri FTIR spectrophotometer and $^{1}H$ and $^{13}C$ NMR spectra on a Mercury-400BB instrument using $CDCl_3$ or DMSO-$d_6$ as solvents and $Me_4Si$ as internal standard. Melting points (mp) were observed in an electrothermal melting point apparatus. Flash column chromatography was carried out using 200-300 mesh silica gel at increased pressure. Aromatic thioureas were synthesized according to the literature methods.[23]

*General procedure for the preparation of 6-hydroxy-6-alkyl-1,5-diaryl-1,3,5-triazinane-2,4-dithiones*

The mixture of 1-arylthioureas (2 mmol), aliphatic carboxylic acids (3 mmol) and ferric chloride hexahydrate (0.2 mmol) was heated at 80 °C for appropriate time according to Table 2. The progress of the reactions was monitored by TLC (thin layer chromatography). After the completion of the reactions, the systems were cooled to room temperature, and the mixture was subjected to silica gel flash column chromatography (ethyl acetate, petroleum ether, 1:6) to obtain pure products.

## Supplementary Information

Full set of characterization data (IR, $^{1}H$ and $^{13}C$ NMR spectra) are available free of charge at http://jbcs.sbq.org.br as PDF file.

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