Facile Synthesis of 5-Aryl-1-[(arylamino)methyl]-1,3,5-triazinane-2-thiones

Zhenfeng Zhang,* Siqian Wang, and Guisheng Zhang*

College of Chemistry and Environmental Science, Henan Normal University, Xinxiang 453007, People's Republic of China
*E-mail: zzf5188@sohu.com

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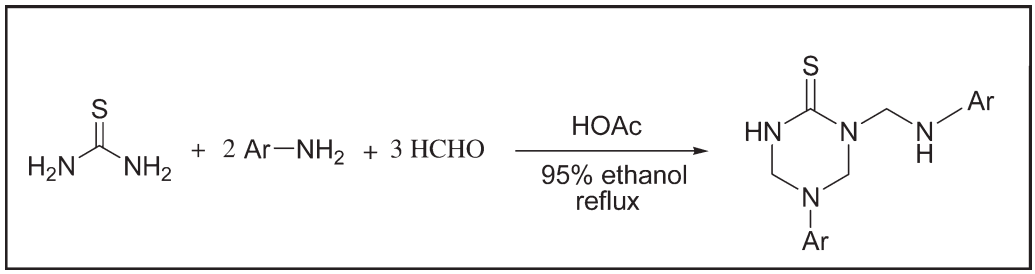

A series of 5-aryl-1-arylaminomethyl-1,3,5-triazinane-2-thiones has been prepared in a one-step procedure from condensation of readily available aromatic amines with thiourea and formaldehyde. A mechanism is presented to account for the formation of the products. The overall sequence provides a simple and efficient route to prepare in good to excellent yields and in a short experimental time.

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INTRODUCTION

Heterocyclic compounds containing thiourea structural unit have found some powerful bioactivities, such as powerful ectoparasiticidal action [1], potent antidiabetic properties [2], and anti-HIV activity [3,4]. In addition, some such compounds can serve as calcium channel blockers, antihypertensive agents, and α-1a-antagonists [5]. Therefore, it is not surprising that searching for new methods to synthesize heterocyclic compounds starting from thiourea has received special attention. Burke and Petersen have early reported the synthetic studies of 5-alkyl or 4,6-dialkyl substituted 1,3,5-triazinane-2-thiones [6a,b]. However, for 5-aryl-1-arylaminomethyl-1,3,5-triazinane-2-thiones, only 5-phenyl-1-[(phenylamino)-methyl]-1,3,5-triazinane-2-thione (**4a**, Fig. 1) was reported as an abnormal product [7]. The facile and effective approaches to a series of the titled compounds, and their bioactivities have not been reported so far. In our efforts to find bioactive 1,3,5-triazinane-2-thione compounds, we designed a series of diversely substituted 5-aryl-1-arylaminomethyl-1,3,5-triazinane-2-thiones (Fig. 1) and tried to prepare them following the literature procedure [7]; however, we did not obtained such compounds except for **4a**. In this article, we describe a method whereby a wide variety of 5-aryl-1-arylaminomethyl-1,3,5-triazinane-2-thiones can be prepared rapidly and in excellent yields by a one-step synthesis from readily available materials and their antitumor activities.

RESULTS AND DISCUSSION

Initially, we attempted to prepare 1,5-disubstituted 1,3,5-triazinane-2-thiones (**4a–h**) following the literature procedure [7] for **4a**, using a three-component condensation of thiourea with arylamines and aqueous formaldehyde in a one-pot manner at 1:2:2 ratio in ethanol at room temperature. However, the desired compounds were not obtained except for **4a**. It was noted that white precipitates appeared from the reaction mixtures when the reactions were performed for **4b–h**. The precipitate was *N*-methylenearylamine or its trimer, 1,3,5-triaryl-1,3,5-triazacyclohexane, in terms of its ^{1}H-NMR spectrum. The formation of the precipitate cumbered the further aminomethylation of thiourea to produce **4b–h**. When the reaction mixture was refluxed with a catalytic amount of acetic acid, the precipitate smoothly underwent the aminomethylation of thiourea to afford the desired compounds. Taking into account the structural characteristic of these compounds and the above unexpected finding, the ratio of reactants was adjusted to thiourea:anilines:formaldehyde = 1:2:3, and the reaction temperature was elevated to explore a better route to 1,5-disubstituted 1,3,5-triazinane-2-thiones. It turned out that this one-pot three-component procedure worked very well under the optimized conditions (Scheme 1). Accordingly, thiourea **1**, 4-toluidine **2d**, and aqueous formaldehyde **3** were mixed in ethanol (95%), after the addition of a catalytic amount of acetic acid (5 mol %), the mixture was refluxed with

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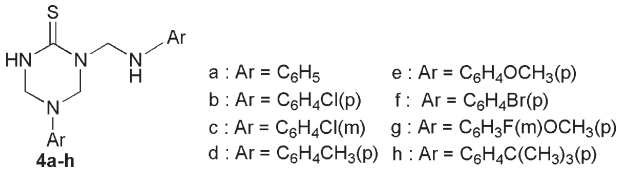


Figure 1. 5-Aryl-1-arylaminomethyl-1,3,5-triazinane-2-thiones.

stirring for about 10 min. Finally, the product **4d** was isolated in high yields.

Encouraged by our initial observation, we further explored the substrate scope and limitation of this reaction. Various aromatic primary amines with different substituents were reacted with thiourea and formaldehyde under the same reaction conditions (Scheme 1). As shown in Table 1, all reactions proceeded smoothly to afford the corresponding 1,5-disubstituted 1,3,5-triazinane-2-thiones **4** in high yields. However, the reactions of aromatic amines carrying strongly electron-withdrawing substituent(s), such as 3- or 4-nitrobenzenamine, were not occurred. In addition, we also explored the reaction of urea, in place of thiourea, with aromatic amine and formaldehyde under the same conditions; unfortunately, the corresponding 1,3,5-triazinane-2-ones were not obtained.

The structures of the products **4a–h** were characterized on the basis of their elemental analysis, ^{1}H-NMR and ^{13}C-NMR spectra. Meanwhile, structures of compounds **4a**, **4b**, and **4g** were further confirmed by X-ray crystal structure analysis [8,9].

Compounds **4a** and **4c–f** were evaluated for their antitumor activities by cell-culture bioassay. They showed inhibitory activity toward dual-specificity phosphatase Cdc25A by 12.99, 46.23, 13.20, 3.06, 0.67%, respectively, at a concentration of 20 μg/mL [10].

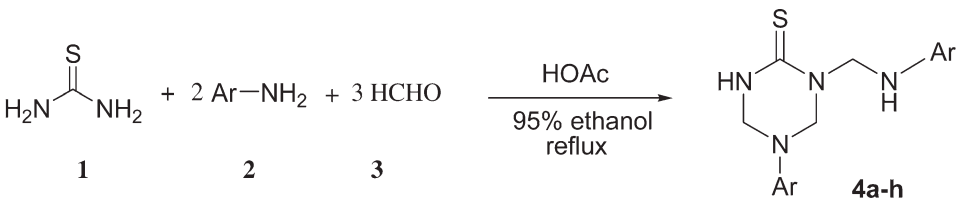
Asymmetrically structural feature of these target molecules suggests an interesting reactive mechanism, which is different from that for the similar reaction of urea (thiourea), formaldehyde, and primary aliphatic amines [6]. Although no definitely accessible mechanistic pathway can be delineated at present time, the following mechanistic concept may be advanced to account for the formation of the products **4** (Scheme 2). Although this is likely to be an equilibrium nucleophilic addition of anilines **2** to formaldehyde **3** leads to *N*-hydroxymethylanilines reaction, addition compounds **5** are expected to undergo rapid dehydration in the presence of acid to a highly reactive carbenium ion which may be formulated as a resonance-stabilized *N*-phenyliminium species, i.e., **6**. In the presence of the thiourea, each two iminium ions **7** are intercepted by one thiourea molecule to furnish intermediate **7**. It was then reacted with the third formaldehyde molecule, to give addition product **8**. Finally, the cyclization and dehydration of **9** under generally acetic acid-catalyzed reaction conditions produced 1,3,5-triazinane-2-thione derivatives **4**. This mechanism is also supported by the fact that reaction with aryl amines, carrying electron-withdrawing groups, did not occur. In this situation, the intermediate **6** could not be stabilized by delocalization to the benzene ring, and the transformation from intermediate **5–6** does not seem to happen.

In summary, we have shown that the condensation reaction of aromatic amines, thiourea, and formaldehyde occurs efficiently in boiling in 95% ethanol as a solvent, providing a convenient and rapid synthesis of a series of 5-aryl-1-arylaminomethyl-1,3,5-triazinane-2-thiones in high yield, by a simple procedure and short experimental time. Compound **4c** showed inhibitory activity toward dual-specificity phosphatase Cdc25A (cell division cycle 25A) at a concentration of 20 μg/mL *in vitro*.

EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra were recorded on Avance 400/DPX (Bruker) (400 MHz and 100 MHz, respectively) from DMSO-d_6 solutions using the residual solvent signal as reference. Elemental analysis was carried out on a Heraeus VarioEL-III C, H, and N analyzer. All reagents and solvents were commercially available and used without further purification. Chemical shifts are reported in parts per million. All chemical

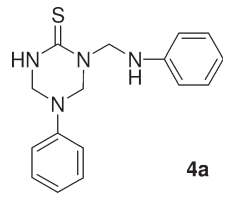
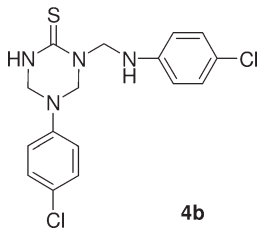
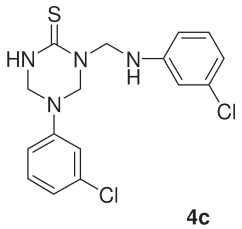
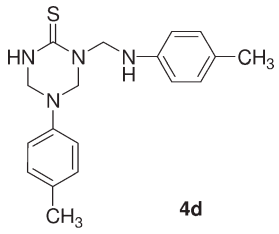
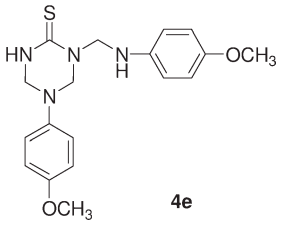
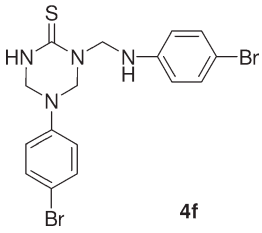
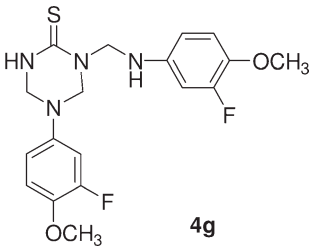
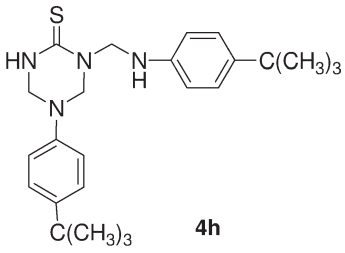
Scheme 1. The one-pot synthesis of the 5-aryl-1-arylaminomethyl-1,3,5-triazinane-2-thiones.



	a	b	c	d	e	f	g	h
Ar:	C_6H_5	$C_6H_4Cl(p)$	$C_6H_4Cl(m)$	$C_6H_4CH_3(p)$	$C_6H_4OCH_3(p)$	$C_6H_4Br(p)$	$C_6H_3F(m)OCH_3(p)$	$C_6H_4C(CH_3)_3(p)$

Table 1

One-pot preparation of 1,5-disubstituted 1,3,5-triazinane-2-thiones.

Entry	Product	Yield (%)[a,b]	Entry	Product	Yield (%)[a,b]
1	 **4a**	**77**	**5**	 **4b**	**91**
2	 **4c**	**82**	**6**	 **4d**	**80**
3	 **4e**	**73**	**7**	 **4f**	**85**
4	 **4g**	**85**	**8**	 **4h**	**74**

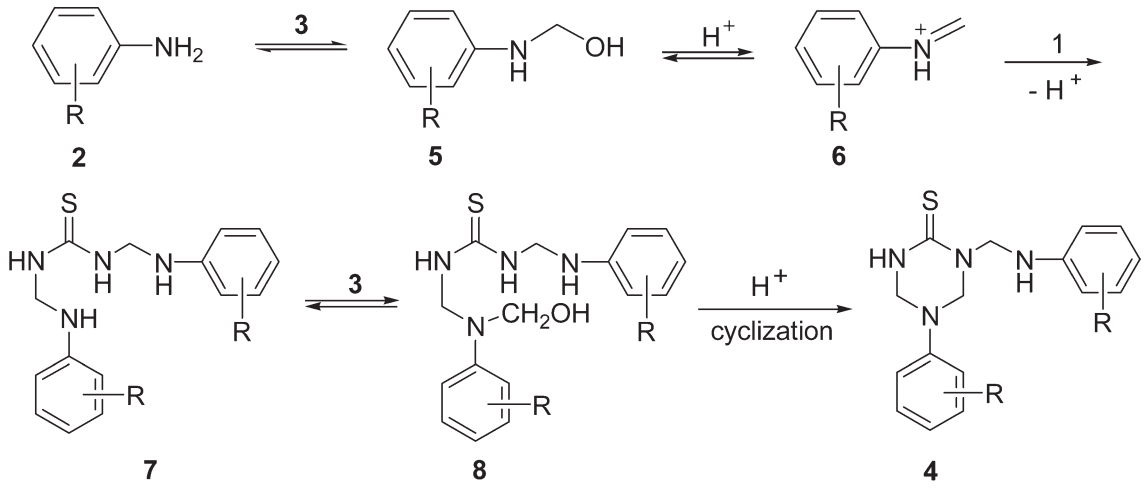
[a] Isolated yields.
[b] Reaction time is within 10 min.

shift values are quoted in ppm and coupling constants quoted in Hz.

General procedure for the preparation of 4a–h. To a mixture of thiourea (0.1 mol) and aniline (0.2 mol) in ethanol (95%), aqueous formaldehyde (0.3 mol) and a catalytic amount of acetic acid (5 mol %) were added. The resulted mixture was refluxed with stirring for about 10 min, then allowed to stand overnight at room temperature to precipitate the product completely. The precipitate was filtered off, washed with ethanol (95%), dried, and recrystallized to give the pure product **4**.

5-Phenyl-1-[(phenylamino)methyl]-1,3,5-triazinane-2-thione (4a). The pure compound **4a** was obtained as a white solid by recrystallization from acetonitrile (77% yield), mp 160–162°C; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 7.10–6.58 (m, 10H), 6.45 (t, J = 7.2 Hz, 1H), 5.23 (d, J = 6.8 Hz, 2H), 4.79 (s, 2H), 4.57 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 176.0, 146.2, 145.7, 128.2, 128.1, 120.7, 117.2, 116.4, 112.4, 60.7, 59.2, 57.4; m/z = 297.6, 194.5. Anal. Calcd. for $C_{16}H_{18}N_4S$: C, 64.40; H, 6.08; N, 18.78. Found: C, 64.34; H, 6.22; N, 18.73.

Scheme 2. Possible mechanism for the formation of products **4a–h.**



5-(4-Chlorophenyl)-1-{[(4-chlorophenyl)amino]methyl}-1,3,5-triazinane-2-thione (4b) The compound was recrystallized from DMSO (slight dark), mp 166–168°C; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.37 (s, 1H), 6.80–7.08 (m, 8H), 6.59 (t, J = 6.8 Hz, 1H), 5.20–5.19 (d, J = 6.8 Hz, 2H), 4.78 (s, 2H), 4.57 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 176.9, 145.8, 145.3, 128.7, 128.6, 125.6, 120.7, 119.8, 114.8, 61.6, 59.8, 57.7; m/z = 365.5, 367.5, 228.4. Anal. Calcd. for $C_{16}H_{16}Cl_2N_4S$: C, 52.32; H, 4.39; N, 15.25. Found: C, 52.28; H, 4.46; N, 15.16.

5-(3-Chlorophenyl)-1-{[(3-chlorophenyl)amino]methyl}-1,3,5-triazinane-2-thione (4c) The compound was recrystallized from 95% ethanol (colorless), mp 149–151°C; ^{1}H-NMR (400 MHz), DMSO-d_6): 8.41 (s, 1H), 7.08–6.56 (m, 8H), 6.71–6.61 (t, J = 6.4, 1H), 5.22–5.25 (d, J = 6.4, 2H), 4.81 (s, 2H), 4.62 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 177.1, 148.7, 148.1, 134.0, 130.6, 130.5, 128.8, 121.6, 117.8, 116.9, 116.7, 112.8, 112.1, 61.5, 59.7, 57.7; m/z = 367.6, 228.5. Anal. Calcd. for $C_{16}H_{16}C_{l2}N_4S$: C, 52.32; H, 4.39; N, 15.25. Found: C, 52.24; H, 4.46; N, 15.21.

5-(4-Methylphenyl)-1-{[(4-methylphenyl)amino]methyl}-1,3,5-triazinane-2-thione (4d) The precipitate was recrystallized from ethyl acetate (white), mp 170–172°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 6.91–6.71 (m, 8H), 6.18 (t, J = 7.2 Hz, 1H), 5.17–5.15 (d, J = 7.2 Hz, 2H), 4.71 (s, 2H), 4.50 (s, 2H), 2.14 (s, 3H), 2.13 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 177.6, 145.7, 145.1, 131.5, 130.5, 130.4, 126.6, 119.2, 114.4, 63.1, 61.1, 59.5, 21.2, 21.1; m/z = 326.6. Anal. Calcd. for $C_{18}H_{22}N_4S$: C, 66.22; H, 6.79; N, 17.16. Found: C, 66.00; H, 6.99; N, 17.01.

5-(4-Methoxyphenyl)-1-{[(4-methoxyphenyl)amino]methyl}-1,3,5-triazinane-2-thione (4e) The compound was recrystallized from ethyl acetate (white), mp 150–152°C; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.24 (s, 1H), 6.85–6.63 (m, 8H), 6.06 (t, J = 6.8 Hz, 1H), 5.16–5.14 (d, J = 6.8 Hz, 2H), 4.67 (s, 2H), 4.45 (s, 2H), 3.62 (s, 3H), 3.61 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 176.9, 154.6, 151.8, 140.8, 140.4, 120.1, 114.8, 114.6, 114.4, 62.8, 60.8, 59.0, 55.4, 55.3; m/z = 358.7, 208.5. Anal. Calcd. for $C_{18}H_{22}N_4O_2S$: C, 60.31; H, 6.19; N, 15.63. Found: C, 60.23; H, 6.28; N, 15.46.

5-(4-Bromophenyl)-1-{[(4-bromophenyl)amino]methyl}-1,3,5-triazinane-2-thione (4f) The compound was recrystallized from anhydrous ethanol (colorless), mp 167–169°C; ^{1}H-NMR: (400 MHz, DMSO-d_6) δ: 8.42 (s, 1H), 7.23–6.78 (m, 8H), 6.66 (t, J = 6.8 Hz, 1H), 5.22–5.20 (d, J = 6.8, 2H), 4.80 (s, 2H), 4.59 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 177.0, 146.4, 145.8, 131.8, 131.6, 120.8, 120.3, 115.5, 113.6, 61.6, 59.7, 57.8; m/z = 302.7, 274.4, 272.4, 186.4. Anal. Calcd. for $C_{16}H_{16}Br_2N_4S$: C, 42.12; H, 3.54; N, 12.28. Found: C, 42.05; H, 3.69; N, 12.20.

5-(3-Fluoro-4-methoxyphenyl)-1-{[(3-fluoro-4-methoxyphenyl) amino]methyl}-1,3,5-triazinane-2-thione (4g) The compound was recrystallized from ethyl acetate (brown), mp 166–168°C; ^{1}H-NMR: (400 MHz, DMSO-d_6) δ: 8.36 (s, 1H), 6.52–6.87 (m, 6H), 6.34 (t, J = 6.8 Hz, 1H), 5.16–5.17 (d, J = 6.8, 2H), 4.75 (s, 2H), 4.54 (s, 2H), 3.72 (s, 3H), 3.71 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 177.1, 154.0, 153.1, 151.6, 150.7, 142.4, 141.3, 139.0, 115.9, 114.4, 109.1, 107.7, 102.0, 62.6, 60.3, 58.3, 57.0, 56.4; m/z = 395.8, 394.8, 242.6. Anal. Calcd. for $C_{18}H_{20}F_2N_4O_2S$: C, 54.81; H, 5.11; N, 14.20. Found: C, 54.92; H, 5.28; N, 14.08.

5-(4-Tert-butylphenyl)-1-{[(4-tert-butylphenyl)amino]methyl}-1,3,5-triazinane-2-thione (4h) The compound was recrystallized from ethanol (white), mp 187–189°C; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.26 (s, 1H), 7.31–6.82 (m, 8H), 6.35 (t, J = 6.8 Hz, 1H), 5.26 (d, J = 6.8, 1H), 4.79 (s, 2H), 4.60 (s, 2H), 4.56 (s, 1H), 1.26 (s, 9H), 1.20 (s, 9H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 176.7, 144.4, 139.7, 126.1, 125.9, 118.7, 118.4, 117.1, 113.4, 61.6, 60.1, 58.5, 34.2, 34.1, 31.9, 31.6; m/z = 411.7, 409.7, 250.5. Anal. Calcd. for $C_{24}H_{34}N_4S$: C, 70.20; H, 8.35; N, 13.64. Found: C, 70.55; H, 8.57; N, 13.49.

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[10] The cdc 25A protein were produced as GST fusion from *E. coli* cultures and purified by affinity chromatography on glutathione-Sepharose resin. Phosphatase activity of Cdc25A was assayed in 100 L of buffer containing 10 m*M* HEPES (pH 8.0), 50 m*M* NaCl, and 1 m*M* dithiothreitol (DDT), with 40*M* *O*-methylfluorescein monophosphate as a substrate, using 96-well microtiter plates.