Silver-Catalyzed Tandem Ammonolysis–Cyclization of 2-Alkynylbenzenamines with Tetraalkylthiuram Disulfides to 4-Methylene-4*H*-benzo[*d*][1,3]thiazin-2-amines

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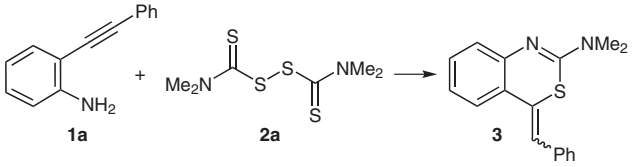
Abstract: In the presence of $AgBF_4$, the ammonolysis–cyclization tandem reactions of various 2-alkynylbenzenamines with tetraalkylthiuram disulfides afforded the corresponding 4-methylene-4*H*-benzo[*d*][1,3]thiazin-2-amines in moderate to good yields.

Key words: silver, tandem reaction, 2-alkynylbenzenamine, tetraalkylthiuram disulfide, 4-methylene-4*H*-benzo[*d*][1,3]thiazin-2-amine

The synthesis of sulfur-containing heterocycles is of continuing interest in the field of organic chemistry because of their biological and pharmacological interest.[1] Among them, benzo[*d*][1,3]thiazines, a class of privileged fragment, are found in many compounds with remarkably biological activities.[2] Therefore, a number of efficient methods for the synthesis of benzo[*d*][1,3]thiazines have been developed. The most classical method is the condensation of 2-aminobenzyl chloride with and thioamides or thioureas.[3] However, the unstable and inaccessible substrates compelled organic chemists to search for new reaction partners, particularly the sulfur sources. Recently, two alternative sulfur sources have been developed: one was the use of Lawesson's reagent,[4] the other involved isothiocyanates.[5] As a continuing interest in the construction of sulfur-containing heterocycles,[6–7] we report here a new, efficient tandem route to 4-methylene-4*H*-benzo[*d*][1,3]thiazin-2-amines from 2-alkynylbenzenamines using commercially available tetraalkylthiuram disulfides as the sulfur source (Scheme 1).[9]

Our study began with the reactions of 2-(phenylethynyl)aniline (**1a**) with tetramethylthiuram disulfide (**2a**) and AgOTf in NMP at 60 °C for 48 hours, affording the desired product **3** in 22% yield (entry 1, Table 1). Encouraged by the results, the effect of solvents was investigated (entries 1–5). While toluene, MeCN and DCE, were less effective (entries 2–4), DMSO enhanced the yield to 63% (entry 5). To our delight, good yield of **3** were achieved at either 80 or 100 °C (entries 6 and 7). However, the yield was decreased slightly at 120 °C (entry 8). A series of other catalysts, such as $AgBF_4$, $AgSbF_6$, AgOAc, $Cu(OTf)_2$, and $Pd(OAc)_2$, were evaluated, and the results revealed that $AgBF_4$ was the most effective in terms of yield (entries 9–13). It was interesting to find that the yield of **3** could be increased slightly to 91% at 80 °C after prolonged the reaction time (entry 14). Among the amounts of catalyst examined, 10 mol% of $AgBF_4$ gave the best results (entries 14 and 15). Although good yield was still achieved in the presence of stoichiometric amount of

Table 1 Screening Optimal Conditions[a]



Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	AgOTf (10)	NMP	60	48	26
2	AgOTf (10)	toluene	60	48	trace
3	AgOTf (10)	MeCN	60	48	trace
4	AgOTf (10)	DCE	60	48	trace
5	AgOTf (10)	DMSO	60	48	63
6	AgOTf (10)	DMSO	80	36	80
7	AgOTf (10)	DMSO	100	24	81
8	AgOTf (10)	DMSO	120	24	72
9	$AgBF_4$ (10)	DMSO	100	24	88
10	$AgSbF_6$ (10)	DMSO	100	24	76
11	AgOAc (10)	DMSO	100	24	78
12	$Cu(OTf)_2$ (10)	DMSO	100	24	34
13	$Pd(OAc)_2$ (10)	DMSO	100	24	trace
14	$AgBF_4$ (10)	DMSO	80	36	91 (90:10)
15	$AgBF_4$ (5)	DMSO	80	36	83
16[c]	$AgBF_4$ (10)	DMSO	80	36	76

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol) in solvent (1 mL).
[b] Isolated yield.
[c] Conditions: **2a** (0.25 mmol) was added.

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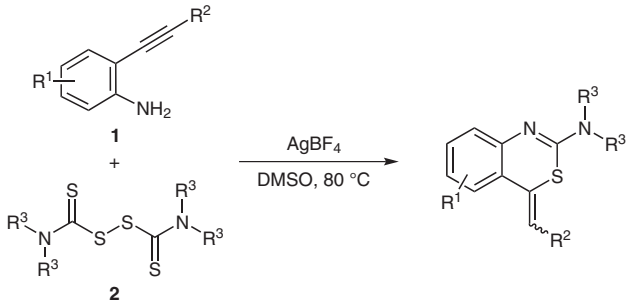
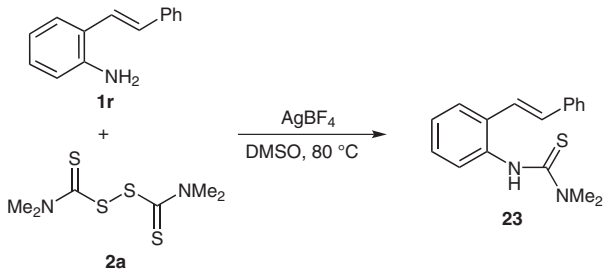
disulfide **2a** (entry 16), excess amount of disulfide **2a** could improve the reaction (entry 14). The structure of **3** was unambiguously confirmed by the X-ray single-crystal diffraction analysis (Figure 1).[10]

With the optimal reaction conditions in hand, various 2-alkynylbenamines and tetraalkylthiuram disulfides were explored for the $AgBF_4$-catalyzed tandem reaction (Table 2).[11]

Initially, treatment of substrate **1a** with two other disulfides **2b** or **2c** in the presence of $AgBF_4$ smoothly afforded the desired products **4** and **5** in 53% and 88% yields, respectively (entries 1 and 2). Subsequently, a number of substituted aryl groups at the terminal of 2-ethynylaniline were investigated, and the results demonstrated that the electronic effect of these groups affected the reaction to some extent (entries 3–9). We found that the electron-rich aryl groups, such as 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-MeC_6H_4, 2-BrC_6H_4, and 2-PhC_6H_4, provided good yields (entries 3, 4, and 6–8), whereas the electron-withdrawing acetyl- or trifluoromethyl-substituted aryl groups lowered the yields (entries 5 and 9). It was interesting to find that heteroarylalkyne **1i** was also a suitable substrate (entry 10). However, aliphatic alkynes **1j** and **1k** displayed less activity under the optimal conditions (entries 11 and 12). Finally, substituents on the aryl moiety of 2-ethynylanilines were also examined (entries 13–18). While substrates **1l–o** with a chloro group or a methyl group underwent the reaction with disulfide **2a** and $AgBF_4$ in good yields (entries 13–17), the reaction of substrate **1q**, having an electron-deficient NO_2 group, was not successful (entry 18).



Scheme 1



Scheme 2

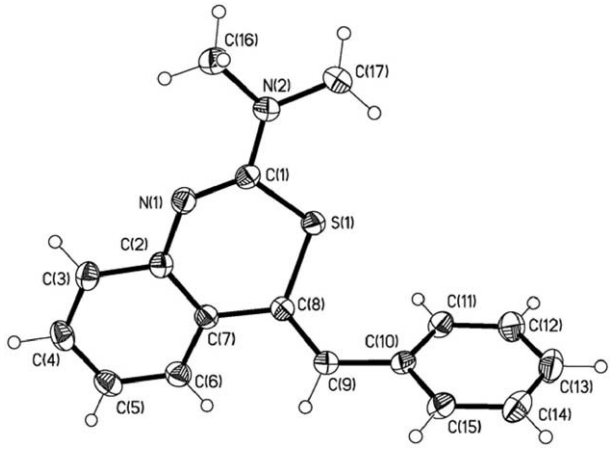
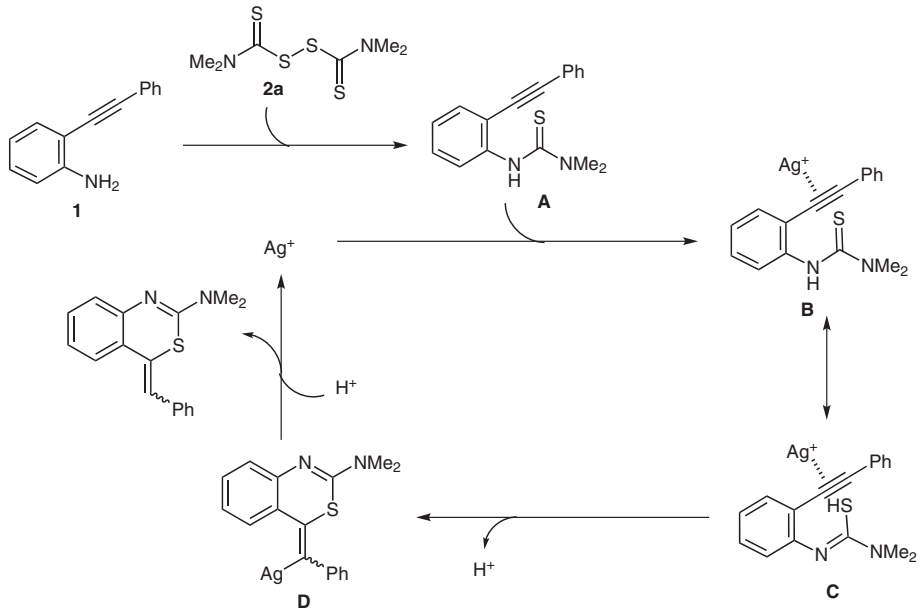


Figure 1 ORTEP diagram of the single-crystal X-ray structure of compound 3



Scheme 3 A possible mechanism

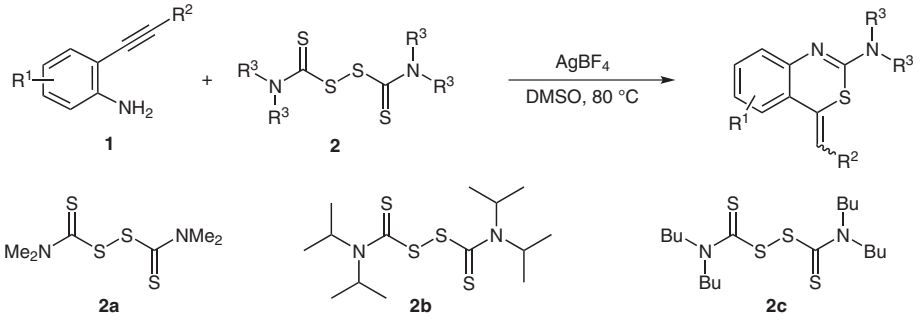
To elucidate the mechanism, a controlled reaction was carried out under the optimal conditions (Scheme 2). In the presence of $AgBF_4$, only *N*-(2-styrylbenzyl)-thiourea **23** was obtained in 30% yield from the ammonolysis reaction between 2-styrylbenzenamine **1r** and disulfide **2a**. Notably, a similar product **22** was observed using the bulky *tert*-butyl-substituted alkyne **1k** (entry 12 in Table 2).

Consequently, a possible mechanism was proposed as outlined in Scheme 3 on the basis of the present results and the previous reported mechanism.[5–7] The ammonolysis reaction of substrate **1** with disulfide **2** affords intermediate **A**, followed by its complexation with Ag^+ gives intermediate **B**. Cyclization of the intermediate **B** takes place to yield the desired product and regenerate the active Ag^+ catalyst.

In summary, we have developed a novel and efficient tandem method for the synthesis of 4-methylene-4*H*-benzo[*d*][1,3]thiazin-2-amines. In the presence of $AgBF_4$, a variety of 2-alkynylbenzenamines successfully underwent the tandem reaction with tetraalkylthiuram disulfides to selectively prepare the corresponding 4-methylene-4*H*-benzo[*d*][1,3]thiazin-2-amines in moderate to good yields. Study of the detailed mechanism and applying tetraalkylthiuram disulfides in new organic transformations for the preparation of sulfur-containing heterocycles are under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Table 2 Silver-Catalyzed Tandem Reactions of 2-Alkynylbenzenamines (**1**) with Tetraalkylthiuram Disulfides **2**[a]



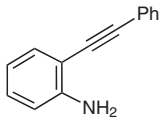
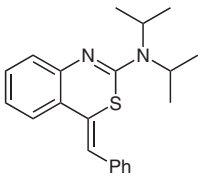
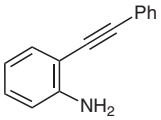
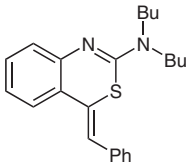
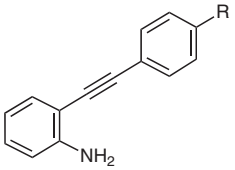
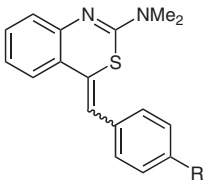
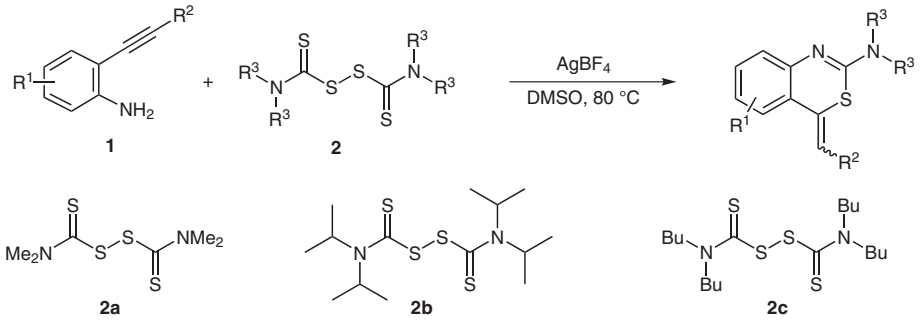
Entry	Substrate **1**	**2**	Product	Yield (%)[b]
1	 **1a**	**2b**	 **4**	53
2	 **1a**	**2c**	 **5**	88
				
3	**1b** R = Me	**2a**	**6** R = Me	85 (93:7)
4	**1c** R = MeO	**2a**	**7** R = MeO	88 (88:12)
5	**1d** R = MeCO	**2a**	**8** R = MeCO	63 (83:17)

Table 2 Silver-Catalyzed Tandem Reactions of 2-Alkynylbenzenamines (**1**) with Tetraalkylthiuram Disulfides **2**[a] (continued)



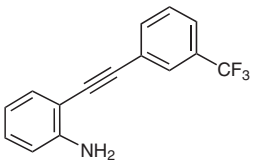
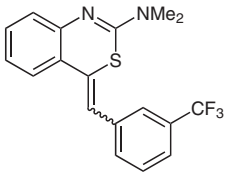
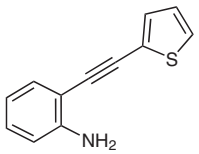
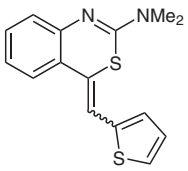
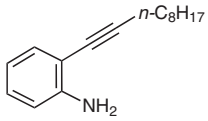
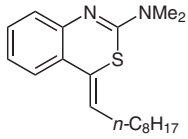
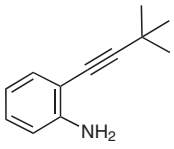
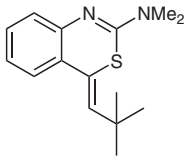
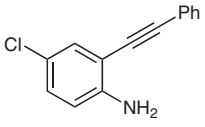
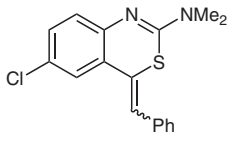
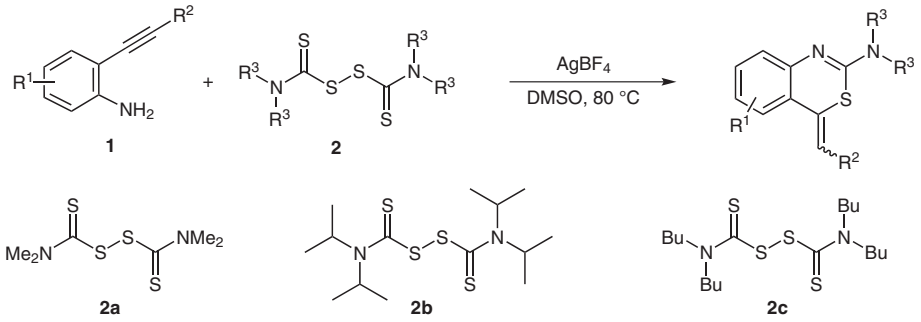
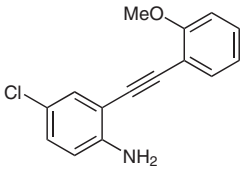
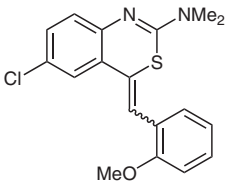
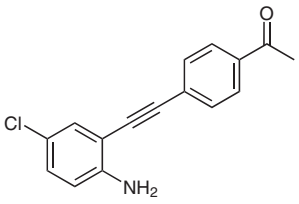
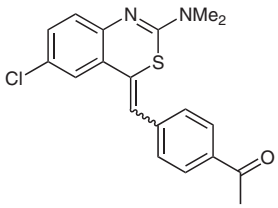
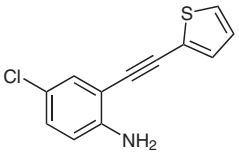
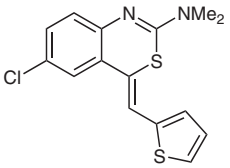
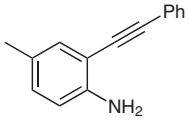
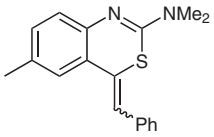
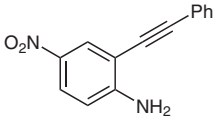
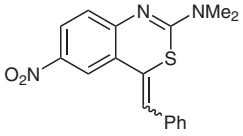
Entry	Substrate **1**	**2**	Product	Yield (%)[b]
6	**1e** R = Me	**2a**	**9** R = Me	87 (97:3)
7	**1f** R = Br	**2a**	**10** R = Br	83 (94:6)
8	**1g** R = Ph	**2a**	**11** R = Ph	77 (>99:1)
9[c]	 **1h**	**2a**	 **12**	38 (89:11)
10	 **1i**	**2a**	 **13**	86 (91:9)
11	 **1j**	**2a**	 **14**	10
12[d]	 **1k**	**2a**	 **15**	0
13	 **1l**	**2a**	 **16**	82 (90:10)

Table 2 Silver-Catalyzed Tandem Reactions of 2-Alkynylbenzenamines (**1**) with Tetraalkylthiuram Disulfides **2**[a] (continued)



Entry	Substrate **1**	**2**	Product	Yield (%)[b]
14	 **1m**	**2a**	 **17**	78 (93:7)
15	 **1n**	**2a**	 **18**	75 (81:19)
16	 **1o**	**2a**	 **19**	85
17	 **1p**	**2a**	 **20**	79 (88:12)
18	 **1q**	**2a**	 **21**	trace

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $AgBF_4$ (0.05 mmol) in DMSO (1 ml) at 80 °C for 36 h.
[b] Isolated yield. The ratio of *Z*/*E* isomers determined by ^1H NMR is given in parenthesis.
[c] At 100 °C for 5 d.
[d] Another product, 3-(2-*tert*-butylethynylphenyl)-1,1-dimethylthiourea (**22**), was isolated in 67% yield.

Acknowledgment

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(10) The crystal structure of compound **3** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 769763.

(11) **General Procedure for the Silver-Catalyzed Tandem Reaction**

A flame-dried Schlenk tube with a magnetic stirring bar was charged with 2-alkynylbenzenamine **1** (0.5 mmol), tetraalkylthiuram disulfide **2** (0.5 mmol), $AgBF_4$ (0.05 mmol), and DMSO (1 mL). The reaction mixture was stirred at 80 °C for 36 h. After the reaction was finished, the mixture was poured into EtOAc, washed with brine (3 × 10 mL), and extracted with EtOAc. The combined organic layers were dried by anhyd Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography (hexane–EtOAc) to afford the desired product.

4-Benzylidene-*N*,*N*-dimethyl-4*H*-benzo[*d*][1,3]thiazin-2-amine (3)

Z/*E* = 90:10; pale yellow solid, mp 68.9–72.6 °C (uncorrected). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.46 (m, 3 H), 7.43–7.38 (m, 2 H), 7.29–7.25 (m, 2 H), 7.21–7.17 (m, 2 H), 7.08–7.07 (m, 2 H), 3.21 (s, 0.6 H), 3.16 (s, 5.4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.3, 145.0, 136.0, 129.6, 129.4, 128.1 (2 C), 127.2, 126.0, 125.5, 124.2, 123.4, 120.0, 38.2. IR (KBr): 2924, 1560, 1187, 756 cm^{-1}. LRMS (EI, 70 eV): *m*/*z* (%) = 280 (100) [M$^+$], 236 (78). ESI-HRMS: *m*/*z* calcd for $C_{17}H_{17}N_2S$ [M + H]$^+$: 281.1107; found: 281.1104.

3-[2-(3,3-Dimethylbut-1-ynyl)phenyl]-1,1-dimethylthiourea (22)

Pale yellow solid, mp 88.1–89.3 °C (uncorrected). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.3 Hz, 1 H), 7.77 (br, 1 H), 7.37 (d, *J* = 7.7 Hz, 1 H), 7.28–7.26 (m, 1 H), 7.05–7.02 (m, 1 H), 3.41 (s, 6 H), 1.34 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.3, 140.3, 131.8, 127.8, 123.5, 121.9, 115.1, 105.7, 75.0, 41.2, 31.1, 28.3. IR (KBr): 3367, 2963, 1530, 1335, 755 cm^{-1}. LRMS (EI, 70 eV): *m*/*z* (%) = 260 (29) [M$^+$], 245 (37), 200(18), 88 (100), 88. ESI-HRMS: *m*/*z* calcd for for $C_{15}H_{21}N_2S$ [M + H]$^+$: 261.1420; found: 261.1419.

(*E*)-1,1-Dimethyl-3-(2-styrylphenyl)thiourea (23)

Pale yellow solid, mp 211.3–214.1 °C (uncorrected). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.49 (m, 1 H), 7.35 (d, *J* = 7.7 Hz, 2 H), 7.31–7.29 (m, 2 H), 7.28–7.25 (m, 4 H), 7.07–6.99 (m, 2 H), 3.30 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.3, 137.6, 137.1, 133.2, 131.5, 128.7, 128.1, 128.0, 127.3, 126.8 (2 C), 126.4, 123.7, 41.8. IR (KBr): 2924, 1524, 1332, 758 cm^{-1}. LRMS (EI, 70 eV): *m*/*z* (%) = 282 (100) [M$^+$], 249 (27), 237 (100), 204 (32), 88 (78). ESI-HRMS: *m*/*z* calcd for $C_{17}H_{19}N_2S$ [M + H]$^+$: 283.1263; found: 283.1260.