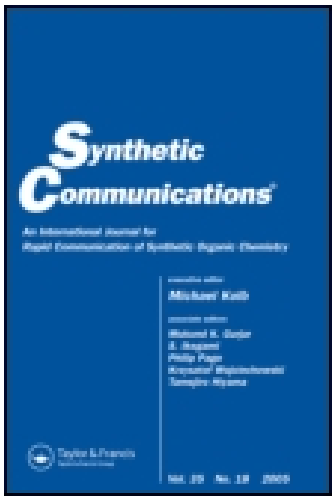

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The Synthesis of Aminobenzothiazoles from 2,3-Biaryl-5-anilino-Δ^3-1,2,4-thiadiazolines

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ABSTRACT

2-Amidinobenzothiazoles **4** can be prepared in high yields by a thermally-promoted rearrangement of thiadiazolium salts **1** or thiadiazolines **2**. Addition of base to the rearrangement of the thiadiazolium salts can improve the yields by the prior conversion of the thiadiazolium salts to the corresponding thiadiazoline free bases. The rearrangement of the thiadiazolines may go through an electrophilic aromatic substitution or free radical pathway.

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5-Amino-1,2,4-thiadiazoles, either in the form of salts (thiadiazolium salts **1**) or free bases (thiadiazolines **2**), can be synthesized from readily accessible amidinothioureas **3** using a variety of oxidizing agents such as elemental halogens,[2] *N*-chlorosuccinimide (NCS),[3] or diethyl azodicarboxylate (DEAD).[4] As shown in Sch. 1, when bromine[3,5] or *N*-bromosuccinimide (NBS)[3] were used as the oxidizing agents, 2-amidinobenzothiazoles **4** could be obtained at yields as high as 85%. Kurzer and Sanderson had reported the isomerization of 2-aryl-5-arylamino-3-arylimino-Δ^3-1,2,4-thiadiazolines**5** to 2-guanidinobenzothiazoles **6**.[6] We hereby report our studies investigating the rearrangement of 2,3-biaryl-5-anilino-Δ^3-1,2,4-thiadiazolium bromides **1** or thiadiazolines **2** to 2-amidinobenzothiazoles **4** to demonstrate that this method is a viable means of preparing compounds of type **4**.

Thiadiazolium bromides **1** were incubated in dimethyl sulfoxide at 65°C for 16 h at a concentration of 1.0 mg/mL (Method A).[7] The crude reactions were analyzed by LC/MS, and the results were compared to the LC retention times of the starting materials. Compounds **1a** to **1g** all generated products **4** (Table 1). In the cases of **1a**, **1e**, and **1g**, there were no thiadiazolium bromides which remained after this period of time, whereas **1b**–**d**, and **1f** still had some thiadiazolium bromide starting material. **1h** and **1i** did not show any reaction because the 2- and 6-positions of the aniline ring were blocked. The stability of **1j** and **1k** suggested that the rearrangement reaction require both a proton and an aryl ring on the 5-amino nitrogen. The free base of **1f** was prepared by treating the corresponding thiourea with *N*-chlorosuccinimide and followed by the extraction from saturated $NaHCO_3$ aqueous solution, and was then converted to other acid addition salts. The resulting thiadiazolium salts were subjected to the incubation condition (Method A), and the extent of formation of **4f** was found to be dependent on the strength of the acids (Fig. 1). The free base thiadiazoline **2f** and the salts of the weaker acids, such as succinic and phosphoric acids, were completely transformed to **4f**. The strong acid salts, such as those from sulfuric acid, HCl, and HBr, displayed partial conversion of between 55% to 65% under the same reaction conditions. When 3.0 mol-equiv. of triethylamine was added to the reaction in dimethyl sulfoxide at 65°C for 16 h (Method B),[8] **4a**–**g** were synthesized in good to excellent yields (60–97%).

Based on the above observations, we suggest that the rearrangement might start from the thiadiazolines **2**, as shown in Sch. 2. The stability of **1j** might be due to the *N*-methyl group blocking the

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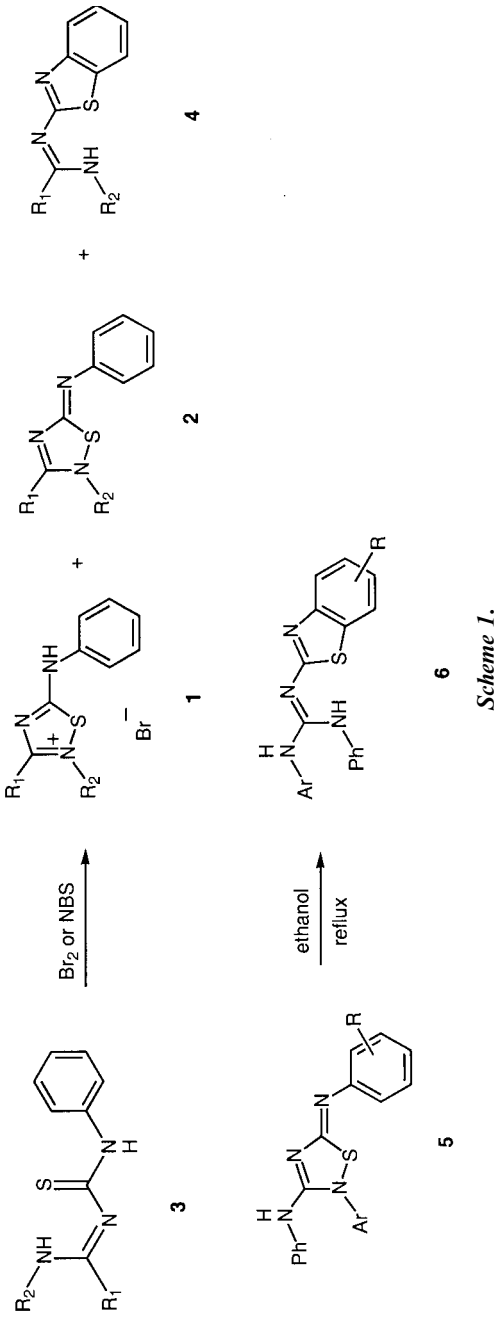
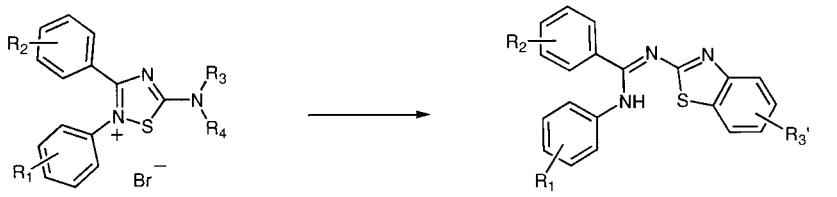


Scheme 1.

Table 1. Rearrangement of thiadiazolium salts **1a**–**1h** in DMSO at 65°C with methods A and B to generate 4-amidinobenzothiazoles **4**.



1 **4**

No.	R_1	R_2	$R_3(R_3')$[a]	R_4	Method A purity[b] of **4** (% of remaining **1**)	Method B isolated yield[c]
1a	H	H	Ph	H	61% (0)	56%
1b	H	H	2-OMePh	H	46% (27%)	80%
1c	H	H	2-ClPh	H	71% (3%)	61%
1d	2-MeO	H	Ph	H	42% (11%)	89%
1e	2-Cl	H	Ph	H	76% (0)	78%
1f	2-OMe	2-OMe	Ph	H	56% (28%)	95%[d]
1g	2-OMe	2-OMe	3,5-F-Ph	H	100% (0)	97%[d]
1h	2-OMe	2-OMe	2,6-F-Ph	H	0 (100%)	0
1i	2-OMe	2-OMe	2-Cl-6-Me-Ph	H	0 (100%)	0
1j	2-Me	H	4-OMePh	Me	0 (100%)	—
1k	H	H	Bn	H	0 (100%)	—

[a]R_3' were the substitutions on the phenyl rings.
[b]The percentages were calculated based to the peak area integration of analytical HPLC traces.
[c]The yields were calculated after the purification from semi-preparative HPLC.
[d]No purification is needed.

formation of thiadiazoline **2j** from thiadiazolium bromide **1j**. The results in Fig. **1** also support the relative importance of thiazolines **2** in the reaction pathway because the weak acid salts can equilibrate to **2f** more readily, and hence **4f** could be generated quantitatively. We reasoned that addition of a base to the reaction mixture might increase the rate of the rearrangement. Rearrangement of **1f** became significantly slower in ethanol or water, or at low temperatures and pH.

The mechanism of the isomerization of **5** to **6** was proposed to proceed via aqueous hydrolysis by addition of water to the 2-N and

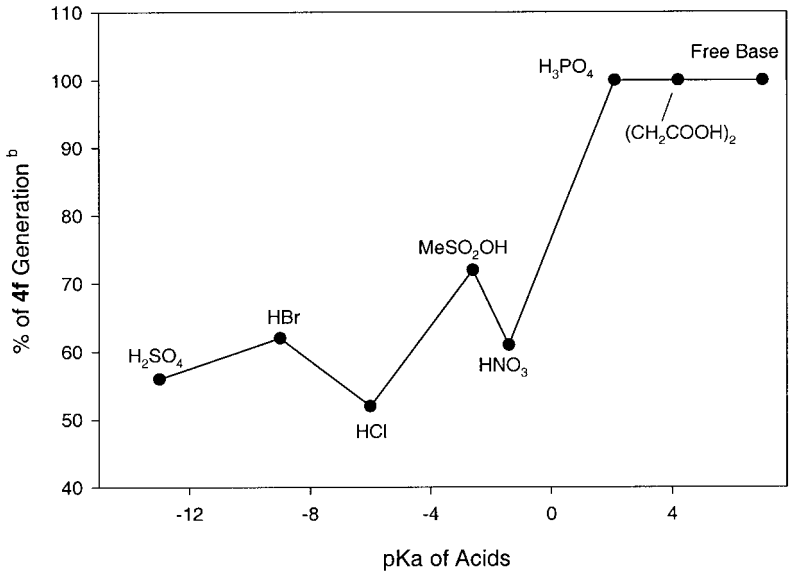
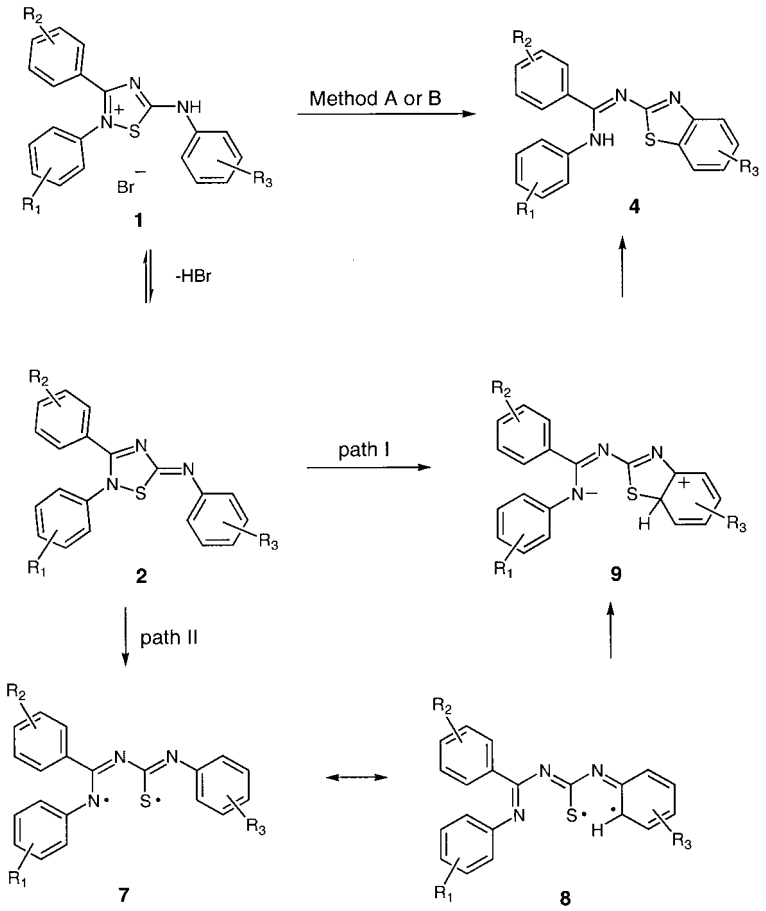


Figure 1. Generation of **4f** from **1f** in various acid salt forms; (a) Incubation at 1.0 mg/mL in DMSO at 65°C for 16 h; (b) The percentages were calculated from the integration of peak area on HPLC analysis compared with **1f** prepared independently; (c) The pKa values were obtained from Ref.[9]

1-S atoms, followed by elimination of water from the hydroxyl group on sulfur and the ortho-hydrogen from the 5-anilino phenyl ring which provided the observed benzothiazole products.[6] Since there is no water present in the reactions we studied, this mechanism can be excluded. As shown in Sch. 1, we propose two possible pathways for the conversion of thiadiazolines **2** to the products **4**. Pathway I involves an electrophilic aromatic ring substitution, whereas pathway II starts from the breakdown of the labile N-S bond in **2** and proceeds by a radical mechanism. Pathway I can be used to explain the stability of **1k** because, after forming thiadiazoline **2k**, methylene substitution on the phenyl ring is not as activating as amino substitution, and therefore electrophilic aromatic substitution does not occur. Pathway II can still occur in this case since the methylene group prevents the delocalization of the radical on the nitrogen to the 5-aminobenzyl ring, although the resulting product would be a six-member ring.

In summary, we have discovered the rearrangement of 2,3-biaryl-5-anilino-Δ^3-1,2,4-thiadiazolium bromides or thiadiazolines to 2-



Scheme 2.

amidinobenzothiazoles. The mechanism of the reaction may go through an electrophilic aromatic ring substitution or a free radical pathway. We have shown that 2-amidinobenzothiazoles **4** can be synthesized in good yields by adding base to the thiadiazolium salts **1** in dimethyl sulfoxide at an elevated temperature or directly from thiadiazolines **2**. The amidinobenzothiazoles that are prepared in this manner would be expected to have useful pharmaceutical or other biological properties if screened broadly against a variety of suitable protein targets.

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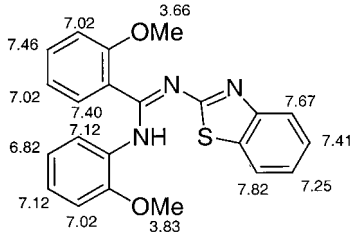
REFERENCES

1. Author's current address: Shanghai Hutchison Pharmaceuticals, Suite 1107, Hua Sheng Building, 399 Jiu Jiang Road, Shanghai, China, P.R., Postal Code: 200001.
2. Goerdeler, J.; Löbach, W. Reaction of 5-imino-Δ^3-1,2,4-thiadiazolines with heterocumulenes. Chem. Ber. **1979**, *112*, 517–531.
3. Chetia, J.P.; Mazumder, S.N.; Mahahan, M.P. One-pot synthesis of 2-aryl-3-phenyl(benzyl)-5-phenylimino-Δ^4-1,2,4-thiadiazolines using *N*-Chlorosuccinimide. Synthesis **1985**, 83–84.
4. Kihara, Y.; Kabashima, S.; Uno, K.; Okawara, T.; Yamasaki, T.; Furukawa, M. Oxidative heterocyclization using diethyl azodiacarboxylate. Synthesis **1990**, 1020–1023.
5. Bohrisch, J.; Patzel, M.; Grubert, L.; Liebscher, J. Synthesis of *S,N*-heterocycles from *N*-thioacyllactamimines. Phos. Sulfur Silicon **1993**, *84*, 253–256.
6. Kurzer, F.; Sanderson, P.M. Thiadiazoles. Part X. The synthesis and isomerisation of 2-aryl-5-arylamino-3-arylmino-Δ^4-1,2,4-thiadiazolines. J. Chem. Soc. **1960**, 3240–3249.
7. Experimental procedure for the synthesis of **4f** (Method A): **1f** (0.500 g, 1.06 mmol) was dissolved in 60 mL of DMSO. The solution was heated at 65°C for 16 h. DMSO was removed by GeneVac (Model: HT-12). The resulting crude was purified by semi-preparative HPLC column. 235 mg of **4f** was isolated as a TFA salt at a yield of 43.9%. Compound **4f** had the same molecular ions as the thiadiazolium cations **1f** on the ESI-MS spectroscopy except that **4f** had fragment of the benzothiazole. ^{1}H NMR of **6f** in acetone-d_6 at r.t. showed a typical rotameric splitting of the two *ortho*-methoxy protons into four peaks and the complexity of the aromatic protons. Upon heating, the ^{1}H NMR of **3f** in DMSO-d_6 (80°C) showed the collapse of the four methoxy proton peaks into two peaks and the simplification of peaks in the aromatic area. ^{1}H TOCSY NMR in DMSO-d_6 at 80°C showed that one of the *ortho*-protons on the anilinophenyl ring disappeared, indicating ring closure at the *ortho*-position. ^{13}C-^{1}HMBC, HETCOR, and COSY NMR

spectroscopy obtained in DMSO-d_6 (80°C) were used to assign the ^{1}H NMR peaks as followed (chemical shifts in ppm):



4f

8. Experimental procedure of the synthesis for **4f** (Method B): **1f** (0.500 g, 1.06 mmol) was dissolved in 10 mL of TEA (0.444 mL, 3.19 mmol) in DMSO. The solution was heated at 65°C for 16 h. DMSO was removed by GeneVac. The resulting yellow crystalline solid was dissolved in 20 mL of saturated aqueous $NaHCO_3$, and was extracted with EtOAc. The organic layers were dried over Na_2SO_4, and 418 mg (95% yield) of pure **4f** was obtained without purification. Anal. calcd: C, 67.84; H, 4.92; N, 10.79; S, 8.23. Found: C, 67.59; H, 4.99; N, 10.60; S, 7.87.
9. (1) Gordon, A.J.; Ford, R.A. *The Chemist's Companion*: *A Handbook of Practical Data*, *Techniques*, *and References*; Wiley: New York, 1972; 58 pp; (2) Dean, J.A. *Lange's Handbook of Chemistry*, 13th Ed.; McGraw-Hill: New York, 1985; 5 pp.

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