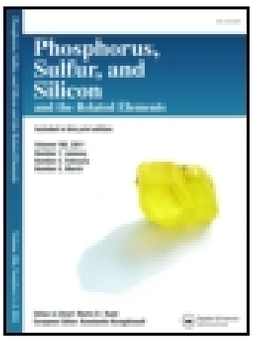

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C. Landreau , D. Deniaud , A. Reliquet & J. C. Meslin

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2-AMINO-4-DIMETHYLAMINO-1-THIA-3-AZABUTADIENES AS PRECURSORS OF THIAZOLES

C. Landreau, D. Deniaud, A. Reliquet, and J. C. Meslin
Laboratoire de Synthèse Organique, Faculté des Sciences et des Techniques, France

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The reaction of 2-amino-4-dimethylamino-1-thia-3-azabutadienes ***1*** *with α-bromoketones gave rise to 2-aminothiazoles* ***2*** *together with 2-(*N,N*-dimethylaminomethylenamino)thiazoles* ***3****. Competitive mechanisms are described. Furthermore, reaction of diene* ***1a*** *with methyl α-bromoacetate or hydroxylamine-*O*-sulfonic acid yielded respectively 2-(*N,N*-dimethylaminomethylenamino)thiazolin-4-one* ***4*** *and 5-amino-1,2,4-thiadiazole* ***5****.*

Keywords: 2,4-Diamino-1-thia-3-azabutadienes; 1,2,4-thiadiazole; thiazoles; thiazolin-4-one

INTRODUCTION

The use of 1-thia-3-azabutadienes in heterocyclic chemistry has been widely developed, particularly in our laboratory, allowing the preparation of various compounds such as *6H*-1,3-thiazines,[1–4] *2H*-1,3-thiazines,[5,6] cephems,[7–10] thiazolines[11] and thiazoles.[1,2,4] The latter are of great interest from a biological aspect. For instance, 2-guanidino-4-phenylthiazoles recently have been found to display bactericidal activities[12] while 2-amino-4-(4-chlorophenyl)-5-methylthiazole has been reported to inhibit secretion of IL-6 interleukin in osteoblastic cells.[13] Moreover such heterocyclic motifs are contained in numerous natural compounds and may consequently be involved in total syntheses.[14,21–23,26] Thus, their preparation still focuses chemists attention.[15,24,25,27]

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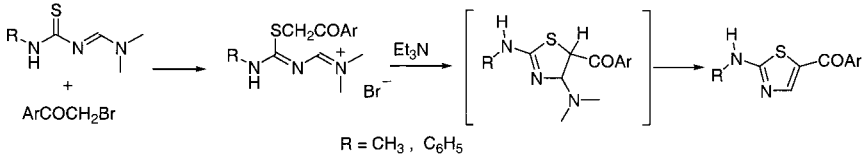
Address correspondence to D. Deniaud, Laboratoire de Synthèse Organique, UMR CNRS 66513, Nantes Cedex 44322, France. E-mail: deniaud@chimie.univ-nantes.fr

We recently have reported that 2-amino-4-dimethylamino-1-thia-3-azabutadienes, when being alkylated by methyl iodide, were convenient synthons for the preparation of various six-membered heterocycles.[16] In a view to extend this work to the preparation of five-membered ring systems, we decided to investigate the behaviour of these heteroatomic chains towards α-bromoketones, methyl α-bromoacetate and hydroxylamine-*O*-sulfonic acid.

RESULTS AND DISCUSSION

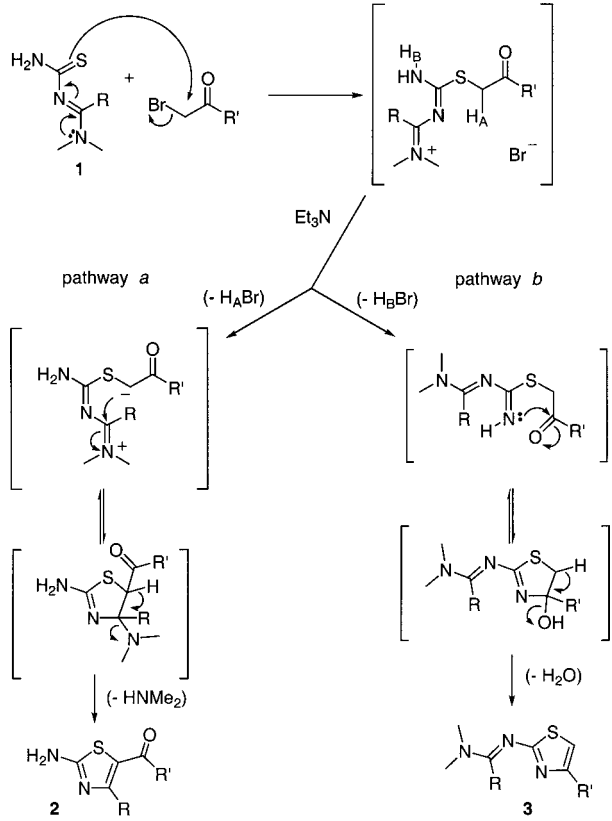
A previous study conducted in our laboratory dealt with 1-thia-3-azabutadienes bearing a monosubstituted amino group in position 2, and a good-leaving group in position 4.[4] Reaction with α-bromoketones afforded thiazoles in almost quantitative yields (Scheme 1).



SCHEME 1

As no trace of imidazole was observed, it was postulated that the reaction began by alkylation of sulfur, the intermediary salt being deprotonated by triethylamine and cyclization occurring smoothly, followed by deamination.

The extension of this procedure to similar 1-thia-3-azabutadienes **1** bearing an unsubstituted amino group in position 2 appeared more complicated, since two competitive mechanisms could take place. Indeed, the thioamide function might also be involved in a Hantzsch type synthesis.[17] This assertion was confirmed by experimental results. The first step of these reactions was common to both pathways, consisting in *S*-alkylation. The key step was the dehydrobromination of the cationic intermediate, directing the course of the reaction toward pathway *a* or *b* (Scheme 2). The expected 2-amino-5-aroylthiazoles **2** were generally obtained in good yields, as listed in Table I. The reaction proceeded by deprotonation of the *N*-alkyl amidinium bromides at the methylene group (pathway *a*), the enolate undergoing intramolecular cyclization with the iminium group, followed by loss of dimethylamine. On the other hand, competitive nucleophilic attack on the carbonyl function by the generated imine (pathway *b*) gave rise after dehydration



SCHEME 2

to 4-aryl-2-(*N*,*N*-dimethylaminomethylenamino)thiazoles **3**, in lower yields.

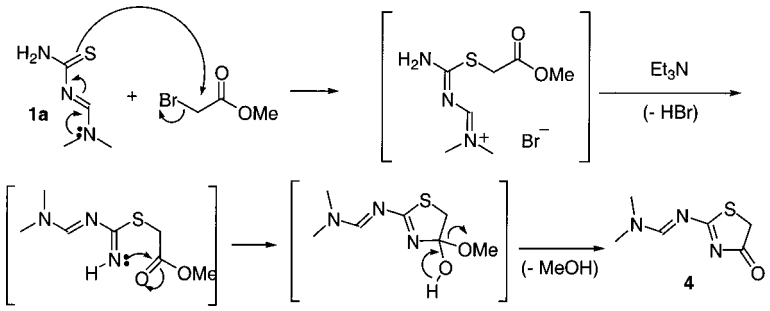
The course of the reaction was found to depend on the nature of the substituent of the bromomethyl reagent. Thus, the presence of a weaker electron-withdrawing group inhibited reaction pathway *a*, so that when thiazadiene **1a** was alkylated by methyl α-bromoacetate,

TABLE I Data for Compounds 2 and 3 Prepared

R	R′	Compounds	Yield (%)	Compounds	Yield (%)
H	*p*-BrC_6H_4	**2a**[a]	64	**3a**	29
H	*p*-ClC_6H_4	**2b**[a]	68	**3b**	17
H	*p*-$CH_3C_6H_4$	**2c**[a]	74	**3c**	22
CH_3	*p*-ClC_6H_4	**2d**	65	**3d**	21

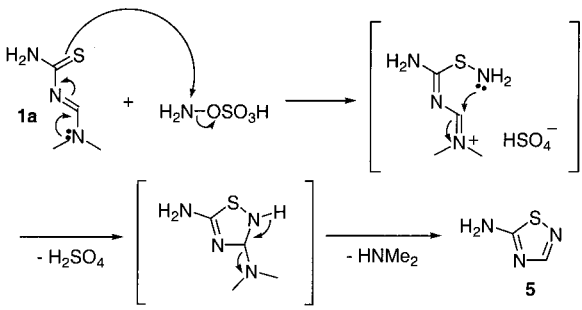
[a]See ref. 18.

then treated with triethylamine, Hantzsch synthesis took place exclusively to afford 2-(*N*,*N*-dimethylaminomethylenamino)thiazolin-4-one **4** (67%) (Scheme 3).



SCHEME 3

Furthermore, we continued our investigations by exposing thiazadiene **1a** to hydroxylamine-*O*-sulfonic acid. Amination, occurred on reflux, affording the expected 5-amino-1,2,4-thiadiazole **5**[19] (Scheme 4). This result corroborates the efficiency of this aminating agent which was first used by Lin and coworkers[20] for the synthesis of 5-aryl-1,2,4-thiadiazoles from *N*′-(thioaroyl)-*N*,*N*-dimethylamidines.



SCHEME 4

CONCLUSION

Alkylation of 4-dimethylamino-1-thia-3-azabutadienes bearing an unsubstituted amino group in position 2 occurred unambiguously at sulfur. Conversely, intermediary salts might behave ambidently in the presence of base allowing the synthesis of 2-amino-5-aroylthiazoles and

amidines derived from 4-aryl-2-aminothiazoles or 2-aminothiazolin-4-one. The reactivity of such heterocyclic amidines is currently under investigation.

EXPERIMENTAL

All reagents were purchased either from Acros Organics or Aldrich. The CNRS Analysis Laboratory (Vernaison) performed the elemental analyses. Column chromatography was conducted over silica gel 60 (40–63 μm), available from E. Merck. Thin layer chromatography was performed on 0.5 mm × 20 cm × 20 cm E. Merck silica gel plates (60 F-254). Melting points measured using a Reichert microscope are uncorrected. The ^{13}C and ^{1}H NMR spectra were recorded at room temperature using a Brucker AC 200 operating at 50 and 200 MHz respectively. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane as internal standard. Mass spectra were determined with a Hewlett Packard 5989 spectrometer. The IR spectra were obtained using a Brucker Vector 22 spectrometer. All chemicals were reagent grade and used without further purification. CH_2Cl_2 was distilled over CaH_2. All reactions were carried out under an atmosphere of nitrogen.

Preparation of Thiazadienes (1)[16]

N,*N*-dimethyl formamide dimethyl acetal (for **1a**, 13 mmol) or *N*,*N*-dimethyl acetamide dimethyl acetal (for **1b**, 13 mmol) was added to a suspension of thiourea (10 mmol) in methanol (for **1a**, 10 mL) or CH_2Cl_2 (for **1b**, 10 mL). The mixture was heated under reflux for 4 h then concentrated under vacuo. Compound **1a** was crystallized from methanol. Compound **1b** was purified by filtration through a short pad of silica gel using as eluant CH_2Cl_2/AcOEt 1/1, followed by crystallization from diethyl ether.

Preparation of Thiazoles (2) and (3)

A solution of thiazadiene **1** (4 mmol) and α-bromoketone (4 mmol) (*p*-bromophenacyl bromide for **2a** and **3a**, *p*-chlorophenacyl bromide for **2b**,**d** and **3b**,**d**, *p*-toluoylacyl bromide for **2c** and **3c**) in CH_2Cl_2 (10 mL) was stirred at room temperature for 15 min. Triethylamine (8 mmol) was then added. After further stirring for 18 h, the solvent was removed. The residue was diluted with CH_2Cl_2 and chromatographed, furnishing first thiazoles **3** (elution CH_2Cl_2/AcOEt 1/1) then thiazoles **2** (elution AcOEt). Compounds **2** and **3** were crystallized from Et_2O.

*2-Amino-5-*p*-bromobenzoylthiazole (2a)*[18]

Yellow crystals, m.p. 187°C, yield 64%. ^{1}H RMN (DMSO-d_6) δ 7.65–7.69 (m, 5H, Ar*H*, NC*H*), 8.23 (s, 2H, NH_2). ^{13}C RMN (DMSO-d_6) δ 125.4 (S*C*CO), 126.6 (Ar*C*), 130.2, 131.6 (4 × Ar*C*H), 137.2 (Ar*C*), 151.3 (N*C*H), 174.9 (S*C*N), 184.2 (*C*O). MS *m/z* (%): 284/282 (64/63, M^+), 185/183 (30/29), 157/155 (35/38), 127 (100). IR (KBr) ν cm^{-1}: 3349, 3114, 1589, 1496, 1233, 747. Anal. calcd. for $C_{10}H_7BrN_2OS$ (283.1): C, 42.42; H, 2.49; N, 9.89. Found: C, 42.38; H, 2.56; N, 9.82.

*2-Amino-5-*p*-chlorobenzoylthiazole (2b)*[18]

Yellow crystals, m.p. 220°C, yield 68%. ^{1}H RMN (DMSO-d_6) δ 7.54–7.77 (m, 4H, Ar*H*), 7.66 (s, 1H, NC*H*), 8.23 (s, 2H, NH_2). ^{13}C RMN (DMSO-d_6) δ 126.7 (S*C*CO), 128.7, 130.2 (4 × Ar*C*H), 136.5, 137.0 (2 × Ar*C*), 151.4 (N*C*H), 175.0 (S*C*N), 184.1 (*C*O). MS *m/z* (%): 240/238 (40/100, M^+), 141/139 (14/42), 127 (100), 113/111 (16/56), 99 (39). IR (KBr) ν cm^{-1}: 3443, 3081, 1604, 1478, 1255, 751. Anal. calcd. for $C_{10}H_7ClN_2OS$ (238.7): C, 50.32; H, 2.96; N, 11.74. Found: C, 50.36; H, 2.91; N, 11.68.

*2-Amino-5-*p*-toluoylthiazole (2c)*[18]

Yellow crystals, m.p. 203°C, yield 74%. ^{1}H RMN (DMSO-d_6) δ 2.37 (CH_3), 7.28–7.65 (m, 4H, Ar*H*), 7.61 (s, 1H, NC*H*), 8.12 (s, 2H, NH_2). ^{13}C RMN (DMSO-d_6) δ 21.0 (*C*H_3), 127.0 (S*C*CO), 128.3, 129.0 (4 × Ar*C*H), 135.5, 141.7 (2 × Ar*C*), 150.4 (N*C*H), 174.5 (S*C*N), 185.0 (*C*O). MS *m/z* (%): 218 (100, M^+), 203 (9), 176 (18), 119 (21), 91 (62). IR (KBr) ν cm^{-1}: 3337, 3084, 1587, 1470, 1231, 744. Anal. calcd. for $C_{11}H_{10}N_2OS$ (218.3): C, 60.53; H, 4.62; N, 12.83. Found: C, 60.52; H, 4.68; N, 12.65.

*2-Amino-5-*p*-chlorobenzoyl-4-methylthiazole (2d)*

Yellow crystals, m.p. 215°C, yield 65%. ^{1}H RMN ($CDCl_3$) δ 2.35 (s, 3H, CH_3), 5.54 (br s, 2H, NH_2), 7.40–7.70 (m, 4H, Ar*H*). ^{13}C RMN (DMSO-d_6) 18.8 (*C*H_3), 118.7 (S*C*CO), 128.6, 129.7 (4 × Ar*C*H), 136.1, 139.6 (2 × Ar*C*), 160.7 (*C*CH_3), 171.9 (S*C*N), 185.4 (*C*O). MS *m/z* (%): 253/251 (37/86, M^+), 216 (43), 141 (77), 113/111 (47/100). IR (KBr) ν cm^{-1}: 3293, 3088, 1591, 1506, 1374, 1332, 1088, 753. Anal. calcd. for $C_{11}H_9ClN_2OS$ (252.7): C, 52.28; H, 3.59; N, 11.08. Found: C, 52.03; H, 3.64; N, 11.31.

*4-*p*-Bromophenyl-2-(*N,N*-dimethylaminomethylenamino)-thiazole (3a)*

Yellow crystals, m.p. 145°C, yield 29%. ^{1}H RMN ($CDCl_3$) δ 3.11, 3.13 (2s, 6H, N(CH_3)$_2$), 6.98 (s, 1H, SC*H*), 7.45–7.75 (m, 4H, Ar*H*), 8.24 (s, 1H, NC*H*). ^{13}C RMN ($CDCl_3$) δ 34.9, 40.7 (N(*C*H_3)$_2$), 106.7 (S*C*H),

121.2 (Ar*C*), 127.5, 131.4 (4 × Ar*C*H), 133.9 (Ar*C*), 150.5 (*C*C_6H_4), 155.8 (N*C*H), 174.2 (S*C*N). MS *m/z* (%): 311/309 (100/97, M^+), 278/276 (83/80), 269/267 (11/14), 214 (13), 182/180 (19/18), 159 (16), 115 (47), 89 (54). IR (KBr) ν cm^{-1}: 3120, 2911, 1608, 1333, 1098. Anal. calcd. for $C_{12}H_{12}BrN_3S$ (310.2): C, 46.46; H, 3.90; N, 13.55. Found: C, 46.38; H, 3.99; N, 13.52.

4-p-*Chlorophenyl-2-(*N,N-*dimethylaminomethylenamino)-thiazole (3b)*

Yellow crystals, m.p. 148°C, yield 17%. ^{1}H RMN ($CDCl_3$) δ 3.11, 3.13 (2s, 6H, N(C*H*$_3$)$_2$), 6.96 (s, 1H, SC*H*), 7.30–7.81 (m, 4H, Ar*H*), 8.25 (s, 1H, NC*H*). ^{13}C RMN (DMSO-d_6) δ 34.4, 40.1 (N(*C*H$_3$)$_2$), 107.5 (S*C*H), 127.2, 128.4 (4 × Ar*C*H), 131.7, 133.6 (2 × Ar*C*), 149.2 (*C*C_6H_4), 156.1 (N*C*H), 173.9 (S*C*N). MS *m/z* (%): 267/265 (40/100, M^+), 234/232 (24/74), 170/168 (11/29), 138/136 (10/27), 115 (9), 89 (32). IR (KBr) ν cm^{-1}: 3120, 2911, 2364, 1610, 1335, 1100. Anal. calcd. for $C_{12}H_{12}ClN_3S$ (265.8): C, 54.23; H, 4.55; N, 15.81. Found: C, 54.29; H, 4.61; N, 15.73.

*2-(*N,N-*Dimethylaminomethylenamino)-4*-p-*tolylthiazole (3c)*

Yellow crystals, m.p. 123°C, yield 22%. ^{1}H RMN (DMSO-d_6) δ 2.30 (s, 3H, C*H*$_3$), 2.99, 3.12 (2s, 6H, N(C*H*$_3$)$_2$), 7.14–7.76 (m, 4H, Ar*H*), 7.33 (s, 1H, SC*H*), 8.35 (s, 1H, NC*H*). ^{13}C RMN (DMSO-d_6) δ 20.8 (*C*H$_3$), 34.5, 40.2 (N(*C*H$_3$)$_2$), 106.0 (S*C*H), 125.6, 129.0 (4 × Ar*C*H), 132.1, 136.7 (2 × Ar*C*), 150.4 (*C*C_6H_4), 156.1 (N*C*H), 173.5 (S*C*N). MS *m/z* (%): 245 (100, M^+), 212 (62), 148 (19), 147 (35), 91 (11). IR (KBr) ν cm^{-1}: 3117, 2917, 1642, 1613, 1400, 1097. Anal. calcd. for $C_{13}H_{15}N_3S$ (245.3): C, 63.64; H, 6.16; N, 17.13. Found: C, 63.71; H, 6.12; N, 17.01.

4-p-*Chlorophenyl-2-[1-(dimethylamino)ethylidenamino]-thiazole (3d)*

Yellow crystals, m.p. 90°C, yield 21%. ^{1}H RMN ($CDCl_3$) δ 2.27 (s, 3H, C*H*$_3$), 3.11 (s, 6H, N(C*H*$_3$)$_2$), 7.02 (s, 1H, SC*H*), 7.30–7.82 (m, 4H, Ar*H*). ^{13}C RMN (DMSO-d_6) δ 16.1 (C*C*H$_3$), 38.4 (N(*C*H$_3$)$_2$), 107.9 (S*C*H), 127.4, 128.7 (4 × Ar*C*H), 133.1, 133.8 (2 × Ar*C*), 150.6 (*C*C_6H_4), 161.5 (*C*CH$_3$), 173.3 (S*C*N). MS *m/z* (%):281/279 (36/98, M^+), 248/246 (34/100), 168 (18), 136 (47). IR (KBr) ν cm^{-1}: 1558, 1472, 1392, 1160, 1056, 738. Anal. calcd. for $C_{13}H_{14}ClN_3S$ (279.8): C, 55.81; H, 5.04; N, 15.02. Found: C, 55.73; H, 5.22; N, 14.94.

2-(*N,N*-Dimethylaminomethylenamino)thiazolin-4-one (4)

A solution of thiazadiene **1** (4 mmol) and methyl bromoacetate (4 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 15 min

then triethylamine (8 mmol) was added. After further stirring for 18 h, the solvent was removed. The residue, diluted with CH_2Cl_2, was chromatographed using acetone as eluant. Compound **4** was crystallized from Et_2O as yellow crystals (m.p. 131°C) in 67% yield. ^{1}H RMN ($CDCl_3$) δ 3.22, 3.23 (2s, 6H, N(CH_3)$_2$), 3.93 (s, 2H, CH_2), 8.74 (s, 1H, NC*H*). ^{13}C RMN (DMSO-d$_6$) δ 35.0, 40.9 (N(CH_3)$_2$), 39.3 (CH_2), 159.4 (N*C*H), 188.3 (*C*O), 193.4 (S*C*N). MS *m/z* (%): 171 (100, M^+), 127 (14), 103 (83), 98 (92), 70 (40). IR (KBr) ν cm^{-1}: 2968, 2928, 1688, 1621, 1492, 1242. Anal. calcd. for $C_6H_9N_3OS$ (171.2): C, 42.09; H, 5.30; N, 24.54. Found: C, 42.02; H, 5.24; N, 24.49.

5-Amino-1,2,4-thiadiazole (5)[19]

A solution of thiazadiene **1** (3 mmol) and hydroxylamine-*O*-sulfonic acid (3.3 mmol) in EtOH (10 mL) was refluxed for 8 h. After cooling to room temperature, triethylamine was added (8 mmol) and the reaction mixture was further stirred for 18 h, then concentrated. The residue, diluted with CH_2Cl_2, was chromatographed using as eluant CH_2Cl_2/AcOEt 1/1. Compound **5** was crystallized from hexane as white crystals (m.p. 115°C) in 46% yield. ^{1}H RMN (DMSO-d$_6$) δ 7.82 (s, 1H, C*H*), 7.90 (br s, 2H, NH_2). Anal. calcd. for $C_2H_3N_3S$ (101.1): C, 23.75; H, 2.99; N, 41.55. Found: C, 23.87; H, 3.05; N, 41.59.

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