Indian Journal of Chemistry
Vol. 41B, June 2002, pp. 1286-1289

## Note

# Facile one-pot synthesis of 2-aminothiazoles from 1,3-diazabuta-4-methylthio-1,3-dienes

Paramita D Dey, Arun K Sharma, Jayakumar S & Mohinder P Mahajan*

Department of Pharmaceutical Sciences,
Guru Nanak Dev University, Amritsar 143005, India.

e-mail: mohinderpmahajan@angelfire.com

*Received 26 December 2000; accepted (revised) 18 September 2001*

Convenient one pot synthesis of 2-aminothiazole derivatives involving reactions of 1,3-diazabuta-1,3-dienes with thioglycolic acid, ethyl bromoacetate are reported.

In recent years the 1,3-diazabuta-1,3-dienes have been reported to effectively participate as $4\pi$ component in [4+2] cycloaddition reactions with various ketenes,[1] enamines,[2] isocyanates,[3] oxazalones[4] and dimethyl acetylenedicarboxylate.[5] They have also been shown to react with isocyanides[6] and Simmons-Smith reagent[7] to yield imidazole derivatives and undergo electrocyclic ringclosure to quinazoline derivatives.[8] However, these diazadienes, apparently having more than one electrophilic and nucleophilic sites, have not been exploited in their reactions with suitable electrophilic and nucleophilic reagents. Also, the compounds containing a thiazole ring are widely distributed in nature and are reported to display significant biological activity.[9] Further, the heterocycles possessing a 2-amino-thiazole structural moiety have shown wide range of applications in drug development,[10] against inflammation,[11] bacterial[12] and HIV infections.[13] We report herein the reactions of 4-methylthio-1,3- diazabuta-1,3- dienes with thioglycolic acid and ethyl bromoacetate resulting in a convenient route to the synthesis of thiazole derivatives.

The reactions of 4-methylthio-1,3-diazabuta-1,3-dienes **1** with equimolar amount of thioglycolic acid, in refluxing benzene, resulted in good yields of 2-amino-5-phenylthiazoles **4**. The formation of thiazoles **4** was also observed, albeit slowly, when the same reaction was carried out at room temperature. The formation of thiazoles **4** in these reactions may be explained through the sequence of reaction intermediates shown in **Scheme I**. In this Scheme, it is assumed that the initial nucleophilic displacement of methylthio group of **1** by thioglycolic acid yields an intermediate **2**, which on intramolecular proton abstraction followed by cyclisation leads to another intermediate **3**. The decarboxylative deamination of this intermediate finally yields the desired thiazole **4**. The facile decarboxylative deamination of intermediate **3** under mild reaction conditions in the absence of any base is interesting, since, to our knowledge all known reactions of this type either involve high reaction temperature and/or the presence of an external base.

The treatment of **1** with ethyl bromoacetate in refluxing benzene, either in the presence of DBU or few drops of DMF just to dissolve the initially formed sulfonium salt **5**, resulted in the formation of 2-secondaryamino-4-phenyl-5-ethoxycarbonyl thiazoles **7**. The thiazoles **7** formed in these reactions are probably the result of an intramolecular proton abstraction, bromide ion induced demethylation of the sulfonium salt **5**, cyclisation to intermediate **6** followed by deamination (**Scheme II**). The structures **4** and **7** for these thiazoles were confirmed on the basis of analytical data and spectral evidences.[14]

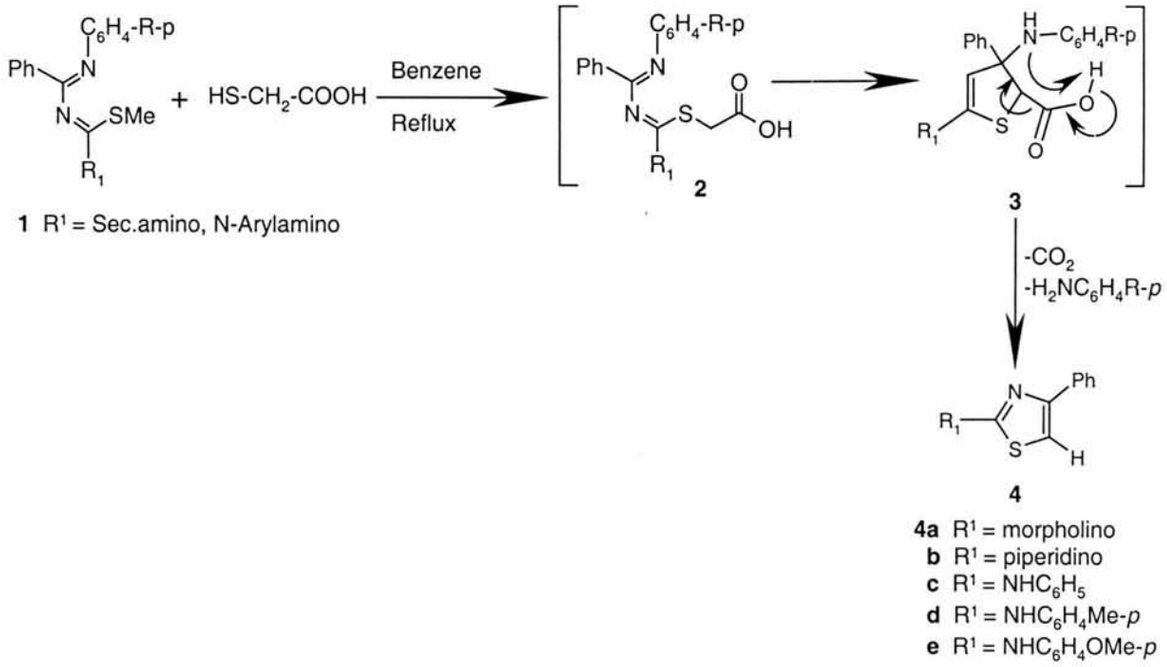
## Experimental Section

Melting points were determined with a Toshniwal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 983 Infrared spectrophotometer using KBr disc, $^1$H NMR spectra in $CDCl_3$ with Varian 390 (90 MHz), Bruker AC-F 300 (300 MHz) and Bruker AC-F 200 (200 MHz) spectrometers using TMS as internal standard ($J$ values are in Hz), $^{13}$C NMR spectra were also recorded on Bruker AC-F 300 or Bruker AC-F 200 (200 MHz) spectrometer in $CDCl_3$ using TMS as internal standard and Mass spectra by electron impact at 70 eV on Shimadzu GCMS-QP-2000 Spectrometer.

**Starting materials**: All 1,3-Diazabuta-1,3-dienes were prepared according to the reported procedures.[14]

### Reactions of 1,3-diazabuta-1,3-dienes with thioglycolic acid

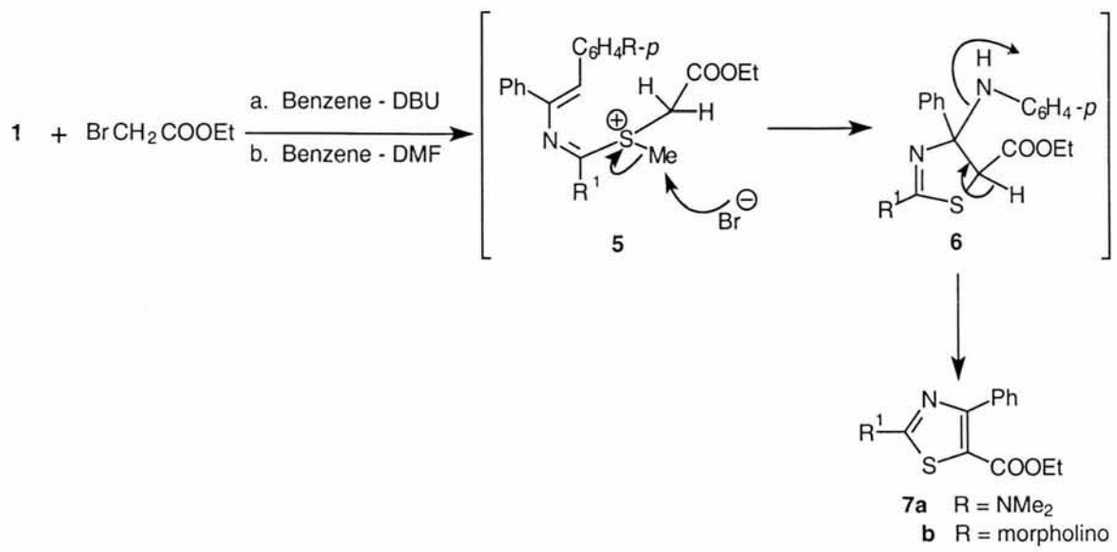
**General procedure for 4**. A solution of 1,3-diazabuta-1,3-dienes (10 mmole) and thioglycolic acid (12 mmole) in dry benzene (25 mL) was stirred under reflux for 1.5-2 hr or stirred at room




**1** $R^1$ = Sec.amino, N-Arylamino

**4a** $R^1$ = morpholino
**b** $R^1$ = piperidino
**c** $R^1$ = $NHC_6H_5$
**d** $R^1$ = $NHC_6H_4Me$-*p*
**e** $R^1$ = $NHC_6H_4OMe$-*p*

**Scheme I**




**7a** R = $NMe_2$
**b** R = morpholino

**Scheme II**

temperature for 8-10 hr. The reaction mixture was washed with sodium bicarbonate solution (20mL). The organic layer was washed further with water (2 x 25 mL), dried ($Na_2SO_4$) and evaporated under reduced pressure to give an oily liquid, which was column chromatographed on silica gel using a mixture (1:5) of ethyl acetate and hexane as eluent to yield **4**. This was recrystallised from a mixture (1:10) of ethyl acetate and hexane.

**2-Morpholino-4-phenyl-thiazole 4a**: Yield 80%; m.p. 69-70°C. Anal. Calcd for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37. Found: C, 63.54; H, 5.69; N, 11.41%. IR: 1531 (C=N)$cm^{-1}$; $^1H$ NMR: δ 3.39-3.43 (m, 4H, $-CH_2-N-CH_2-$), 3.80-3.83 (m, 4H, $-CH_2-O-$

$CH_2$-), 6.78 (s, 1H, =CH-), 7.27-7.39 (m, 3H, ArH), 7.81-7.84 (m, 2H, ArH); $^{13}$C NMR: δ 48.5 (-$CH_2$-N-$CH_2$-), 66.2 (-$CH_2$-O-$CH_2$-), 101.7 (C-4), 126.0, 127.6, 128.5, 134.9 (ArC), 151.8 (C-5), 171.2 (C-2); MS: *m/z* 246 ($M^+$).

**2-Piperidino-4-phenyl-thiazole 4b**: Yield 83%; m.p. 66-67°C. Anal. Calcd for $C_{14}H_{16}N_2S$: C, 68.81; H, 6.60; N, 11.46. Found: C, 68.69; H, 6.66; N, 11.53 %. IR: 1538 (C=N) $cm^{-1}$; $^1$H NMR: δ 2.55-2.83 (m, 6H, -$CH_2$-$CH_2$-$CH_2$-), 3.45-3.81 (m, 4H, -$CH_2$-N-$CH_2$-), 6.83 (s, 1H, =CH-), 7.40-7.63 (m, 3H, ArH), 7.96-8.13 (m, 2H, ArH); $^{13}$C NMR: δ 25.1 (-$CH_2$-$CH_2$-$CH_2$-), 49.4 (-$CH_2$-N-$CH_2$-), 100.6 (C-4), 125.9, 127.3, 128.3, 135.1 (ArC), 151.7 (C-5), 171.0 (C-2); MS: *m/z* 244 ($M^+$).

**2-(N-Phenylamino)-4-phenyl-thiazole 4c**: Yield 82%; m.p. 128-30°C. Anal. Calcd for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.10. Found: C, 71.29; H, 4.72; N, 11.21%. IR: 1565 (C=N), 3418 (-NH) $cm^{-1}$; $^1$H NMR: δ 6.81 (s, 1H, =CH-), 7.23-7.40 (m, 8H, ArH), 7.83-7.86 (m, 2H, ArH); $^{13}$C NMR: δ 101.7 (C-4), 122.9, 126.1, 127.9, 128.6, 129.4, 134.5 (ArC), 151.2 (C-5), 164.8 (C-2); MS: *m/z* 252 ($M^+$).

**2-[N-(*p*-Methylphenylamino)]-4-phenylthiazole 4d**: Yield 82%; m.p. 110-12 °C. Anal. Calcd for $C_{16}H_{14}N_2S$: C, 72.15; H, 5.30; N, 10.52. Found: C, 72.29; H, 5.35; N, 10.56 %; IR: 1560 (C=N), 3378 (-NH) $cm^{-1}$; $^1$H NMR: δ 2.31 (s, 3H, -$CH_3$), 6.73 (s, 1H, =CH-), 7.05-7.37 (m,7H, ArH), 7.79-7.82 (m, 2H, ArH); $^{13}$C NMR: δ 21.9 (-$CH_3$), 101.8 (C-4), 120.3, 127.0, 128.8, 129.0, 130.1, 133.3, 134.6 (ArH), 151.3 (C-5), 164.1 (C-2); MS: *m/z* 266 ($M^+$).

**2-[N-(*p*-Methoxyphenylamino)]-4-phenylthiazole 4e**: Yield 80%; m.p. 159-60°C. Anal. Calcd for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92. Found: C, 68.18; H, 4.93; N, 10.02%. IR: 1560 (C=N), 3377 (-NH) $cm^{-1}$; $^1$H NMR: δ 3.79 (-s, 3H, -$OCH_3$), 6.69 (s, 1H, =CH-), 6.82-7.36 (m, 9H, ArH); $\delta_C$: 55.1 (-$OCH_3$), 100.1 (C-4), 121.7, 125.9, 127.5, 128.3, 133.4 (ArH), 151.3 (C-5), 164.9 (C-2); MS: *m/z* 282 ($M^+$).

### Reactions of 1,3-diazabuta-1,3-dienes with ethyl bromoacetate

**General procedure for 7** (A). To a solution of 1,3-diazabuta-1,3-diene **1** (10 mmole) in dry benzene (25 mL) was added ethyl bromoacetate (10 mmole) in dry benzene (10 mL) and stirred at room temperature for 4-6 hr (TLC). DBU (12 mmole) was added and the reaction mixtre refluxed for 5-6 hr (monitored by TLC), cooled to room temperature, poured in water (50 mL), extracted with ethyl acetate (2×20 mL), washed with water (2×20 mL), dried ($Na_2SO_4$) and evaporated under reduced pressure to yield crude product, which was chromatographed on silica gel using a mixture (1:6) of ethyl acetate and hexane as eluent.

(B). To a solution of 1,3-diazabuta-1,3-diene **1** (10 mmole) in dry benzene (20 mL) was added a solution of ethyl bromoacetate (10 mmole) in dry benzene (10 mL) and stirred at room temperature for 4-6 hr. Few drops of DMF were added to dissolve the salt formed and the reaction mixture heated at 100°C for 3-4 hr (monitored by TLC) and worked up as described in procedure A.

**2-Dimethylamino-4-phenyl-5-ethoxycarbonylthiazole 7a**: Yield 86%; m.p. 98-100°C. Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C,60.85; H, 5.84;N,10.14; Found: C,60.90; H, 5.82,N,10.16 %. IR: 1699, 1570, 1481 $cm^{-1}$; $^1$H NMR: δ 1.23 (t, *J* = 7.1, 3H, -$CH_3$), 3.16 [s, 6H, -$N(CH_3)_2$], 4.17 (q, *J* = 7.1, 2H, -$CH_2$-), 7.33-7.38 (m, 3H, ArH), 7.69-7.74 (m, 2H, ArH); $^{13}$C NMR: δ 14.3 ($CH_3$), 39.9 [$N(CH_3)_2$], 60.4 ($CH_2$), 110.4 (C-4), 127.4, 128.8, 129.9, 135.0, 160.1 (C-5), 161.9 (C-2), 170.7 (C=O); MS: *m/z* 276 ($M^+$).

**2-Morpholino-4-phenyl-5-ethoxycarbonylthiazole 7b**: Yield 81%, m.p. 102-103°C. Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H,5.70; N,8.80. Found: C, 60.33; H,5.72; N,8.73%. IR: 1676, 1530, 1483 $cm^{-1}$; $^1$H NMR: δ 1.24 (t, *J*=7.1, 3H, -$CH_3$), 3.53-3.56 (m, 4H, -$CH_2$-N-$CH_2$-), 3.75-3.80 (m,4H, -$CH_2$-O-$CH_2$-), 4.18 (q, *J*=7.1, 2H, -$CH_2$-), 7.32-7.35 (m, 3H, ArH), 7.66-7.71 (m, 2H, ArH); $^{13}$C NMR: δ 14.5 ($CH_3$), 48.2 (-$CH_2$-N-$CH_2$-), 60.5 ($CH_2$), 66.1 (-$CH_2$-O-$CH_2$-), 127.5, 128.9, 130.1, 160.2 (C-5), 162.1 (C-2), 170.6 (C=O); MS: *m/z* 318($M^+$).

### Acknowledgement

Authors (A K S and S J) are grateful to CSIR, New Delhi for Research Associate Fellowship and Senior Research Fellowship, respectively and the financial support by CSIR, New Delhi, under grant No: 01(1590/99/EMR-11) is gratefully acknowledged.

### References

1 (a) Sharma A K & Mahajan M P, *Tetrahedron*, 53, **1997**, 13841. and references therein; (b) Rossi E, Abbiati G & Pini E, *Tetrahedron*, 53, **1997**, 14107. and references therein.

2 (a) Barluenga J, Tomas M, Ballesteros A & Lopez A, *Tetrahedron Lett*, 30, **1989**, 4573. (b) Rossi E, Stradi R & Visentin P, *Tetrahedron*, 46, **1990**, 3581.

3 Barluenga J, Tomas M, Ballesteros A & Lopez A, *Synthesis*, **1989**, 228.

4 Sain B, Singh S P & Sandhu J S, *Tetrahedron Lett*, 32, 1991, 5151;*Tetrahedron*, 48, **1992**, 4567.

5 (a) Guzman A, Romero M, Talamas F X, Villena R, Greenhouse R & Muchowski M, *J Org Chem*, 61, **1996**, 2470. (b) Ibnusaud I, Malar E J P & Sundaram N, *Tetrahedron Lett*, 31, **1990**, 7357.

6 Morel G, Marchand E, Foucaud, A & Toupet L, *J Org Chem*, 54, **1989**, 1185.

7 Jayakumar S, Ishar M P S & Mahajan M P, *Tetrahedron Lett*, 39, **1998**, 6557.

8 Rossi E, Calabrese D & Farma, F, *Tetrahedron*, 47, **1991**, 5819.

9 (a) Erlenmeyer H & Schmidt P *Hel. Chim Acta*, 29, **1946**, 1957.
(b) Erlenmeyer H & Degan K, *Helv Chim Acta*, 30, **1947**, 592.
(c) Gregory H & Wiggins L F, *J Chem Soc*, **1947**, 1400.
(d) Paetzel M, Schulz A, Liebscher J, Richter W & Richter M, *J Het Chem*, 29, **1992**, 1209 (Eng).
(e) Cocco M T & Onnis V, *Synthesis*, **1993**, 199.
(f) Patil A S & Bagavant G, *J Indian Chem Soc*, 71, **1994**, 205.(g) Arulmoli T & Khadsi B G, *Indian J Pharm Sci*, 56, **1994**, 192.
(h) Shah N M & Joshi, V, *Ind J Het Chem*, 4, **1994**, 59.

10 Patt W C, Hamilton H W, Taylor M D, Ryan M.J, Taylor (Jr). D G, Connolly C J C, Doherty A M, Klutchko S R, Sircar I, Steinbaugh B A, Batley B L, Painchaud C A, Rapundalo S T, Minchniewicz B M & Olson S C J, *J Med Chem*, 35, **1992**, 2562.

11 (a) Haviv F, Ratajczyk J D, DeNet R W, Kerdesky F A, Walters, R L, Schmidt S P, Holms J H, Yong P R, Carter G W, *J Med Chem*, 31, **1988**. 1719.
(b) Clemence F, Martret O L, Delevallee F, Benzoni J, Jouanen A, Jouquey S, Mouren M & Deraedt, R, *J Med Chem*, 31, **1988**, 1453.

12 Tsuji K & Ishikawa H, *Bioorg. Med. Chem Lett*, 4, **1994**, 1601.

13 Bell F W, Cantrell A S, Hoberg M, Jaskunas S R, Jahanson N G, Jordon C L, Kinnick M D, Lind P, Morin (Jr) J M., Noreen R, Oberg B, Palkowitz J A, Parrish C A, Pranc J, Zhang H & Zhou X-X, *J Med Chem*, 38, **1995**, 4929.

14 (a) Mazumdar, S N & Mahajan M P, *Synthesis*, **1990**, 417.
(b) Dey P D, Sharma A K, Mahajan M P, *Tetrahedron*, 51, **1995**, 7459.