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

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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 4π component in [4+2] cycloaddition reactions with various ketenes,1 enamines,2 isocyanates,3 oxazalones4 and dimethyl acetylenedicarboxylate.5 They have also been shown to react with isocyanides6 and Simmons-Smith reagent7 to yield imidazole derivatives and undergo electrocyclic ring closure 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 bacterial12 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, 1H NMR spectra in CDCl3 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), 13C NMR spectra were also recorded on Bruker AC-F 300 or Bruker AC-F 200 (200 MHz) spectrometer in CDCl3 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
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 (Na₂SO₄) 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 C₁₃H₁₄N₂O₂S: 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, -CH₂-N-CH₂), 3.80-3.83 (m, 4H, -CH₂-O-
CH₂), 6.78 (s, 1H, =CH-), 7.27-7.39 (m, 3H, ArH), 7.81-7.84 (m, 2H, ArH); ¹³C NMR: δ 48.5 (-CH₂-N-Ch₂), 66.2 (-CH₂-O-CH₂), 107.1 (C-4), 125.5, 128.6, 134.9 (ArC), 151.2 (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. Caled for C₂₆H₁₈N₂O₂S: C, 68.81; H, 5.60; N, 11.10. Found: C, 68.06; H, 5.12; N, 10.64. IR: 3265, 1570, 1510, 1100, 975 cm⁻¹. "H NMR: δ 5.16 (bs, 2H, -CH₂-N-), 7.12 (m, 10H, ArH), 7.70 (s, 1H, =CH-), 2.55-2.83 (m, 8H, -CH₂-CH₂-CH₂-), 2.10 (s, 3H, -CH₃), 170.7 (C=O); MS: m/z 201 (M⁺).

2-(N-Phenylamino)-4-phenyl-thiazole 4c: Yield 82%; m.p. 128-30°C. Anal. Caled for C₂₆H₁₈N₂O₂S: C, 69.31; H, 5.60; N, 11.00. Found: C, 69.27; H, 4.72; N, 11.21%. IR: 1565 (C=O), 3418 (-NH) cm⁻¹; "H NMR: δ 6.81 (s, 1H, =CH-), 7.23-7.40 (m, 8H, ArH), 7.83-7.86 (m, 2H, ArH); ¹³C NMR: δ 101.7 (C-4), 122.9, 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-phenyl-thiazole 4d: Yield 82%; m.p. 110-120°C. Anal. Caled for C₂₆H₂₁N₂O₂S: C, 72.15; H, 5.60; N, 10.52. Found: C, 72.29; H, 5.35; N, 10.56%. IR: 1560 (C=O), 3378 (-NH) cm⁻¹; "H NMR: δ 2.31 (s, 3H, -CH₃), 6.73 (s, 1H, =CH-), 7.05-7.37 (m, 7H, ArH), 7.79-7.82 (m, 2H, ArH); ¹³C NMR: δ 21.9 (-CH₃), 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-phenyl-thiazole 4e: Yield 80%; m.p. 159-60°C. Anal. Caled for C₂₆H₂₁O₂N₂S: C, 68.06; H, 5.00; N, 9.92. Found: C, 68.18; H, 4.93; N, 10.02%. IR: 1560 (C=O), 3377 (-NH) cm⁻¹; "H NMR: δ 3.79 (s, 3H, -OCH₃), 6.69 (s, 1H, =CH-), 6.82-7.36 (m, 9H, ArH); ¹³C NMR: δ 55.1 (-OCH₃), 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 2-20 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-S-ethoxycarbonylthiazole 7a: Yield 86%; m.p. 98-100°C. Anal. Caled for C₃₀H₂₁N₂O₂S: 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; "H NMR: δ 1.23 (t, J = 7.1, 3H, -CH₃), 3.16 [s, 6H, -N(CH₃)₂], 4.17 (q, J = 7.1, 2H, =CH₂), 7.33-7.38 (m, 3H, ArH), 7.69-7.74 (m, 2H, ArH); ¹³C NMR: δ 14.3 (CH₃), 39.9 [N(CH₃)₂], 60.4 (CH₄), 110.4 (C-4), 127.4, 128.8, 129.9, 155.0, 160.1 (C-5), 161.9 (C-2), 170.7 (C=O); MS: m/z 276 (M⁺).

2-Morpholin-4-phenyl-S-ethoxycarbonylthiazole 7b: Yield 81%; m.p. 102-103°C. Anal. Caled for C₃₀H₂₁N₂O₂S: C, 60.33; H, 5.72; N, 8.73%. IR: 1676, 1530, 1483 cm⁻¹; "H NMR: δ 1.24 (t, J = 7.1, 3H, -CH₃), 3.53-3.56 (m, 4H, -CH₂-N-CH₂), 3.75-3.80 (m, 4H, -CH₂-O-CH₂), 4.18 (q, J = 7.1, 2H, -CH₂), 7.32-7.35 (m, 3H, ArH), 7.66-7.71 (m, 2H, ArH); ¹³C NMR: δ 14.5 (CH₃), 48.2 (-CH₂-N-CH₂), 60.5 (CH₂), 66.1 (-CH₂-O-CH₂), 127.5, 128.9, 130.1, 160.2 (C-5), 162.1 (C-2), 170.6 (C=O); MS: m/z 318 (M⁺).

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References


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