Selective Bromination of 4,5-Dimethylthiazole with *N*-Bromosuccinimide

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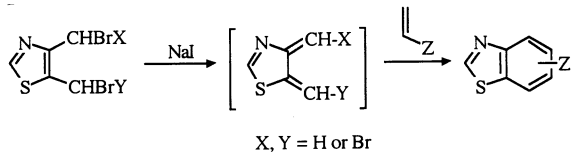
Received June 19, 1997

Keywords: Heterocycles / NBS bromination / Selective bromination / Polybrominated thiazole / Structure elucidation

Radical bromination of 4,5-dimethylthiazole (**1**) was carried out using different stoichiometries of *N*-bromosuccinimide in the presence of 2,2′-azobisisobutyronitrile. Mono-, tri- and tetrabromo compounds **2**, **5**, and **6** were obtained in good yields with regioselectivity while the dibromo derivatives **3** and **4** were formed without any selectivity. Substitution at the thiazole ring occurred in the presence of silica gel or in the perfluoro ether FC-77 ($C_8F_{16}O$), affording the 2-bromothiazole **7**. The order of reactivity observed was 5-Me > 4-Me > C-2. Structural assignment of compounds **2**−**7** was made by chemical correlations and NMR spectroscopy.

Polybrominated derivatives of 1,2-dimethylarenes or their heterocyclic analogues are useful precursors for the production of *o*-quinodimethanes (*o*-QDMs)[1][2][3]. The Diels-Alder trapping of *o*-QDMs with dienophiles is an efficient and powerful method for the building of polycyclic aromatic compounds. In order to obtain 5- or 6-functionalized benzothiazoles of biological interest, we planned to prepare selectively the dibromo-, tribromo- or tetrabromomethyl derivatives of 4,5-dimethylthiazole which would further lead to the desired substituted benzothiazole via the corresponding *o*-QDM (Scheme 1).

Scheme 1



Results and Discussion

The free-radical chlorination of 4-methylthiazole with *N*-chlorosuccinimide in the presence of benzoyl peroxide or UV radiation has been shown to afford 5-chloro-4-methylthiazole in 95% yield. When chlorination was continued, a decrease of the latter was observed while 5-chloro-4-(chloromethyl)thiazole and 2,5-dichloro-4-(chloromethyl)thiazole were formed in 72 and 24% yield, respectively[4]. The order of reactivity observed was therefore C-5 > 4-Me > C-2.

We have performed selective brominations of 4,5-dimethylthiazole (**1**) with *N*-bromosuccinimide (NBS). When the commercially available compound **1** was treated with different stoichiometries of NBS in the presence of 2,2′-azobisisobutyronitrile (AIBN) under reflux with carbon tetrachloride (method A), the brominated derivatives **2**−**6** were selectively obtained (Scheme 2 and Table 1). In contrast, the use of NBS in the presence of silica gel (method B) afforded the 2-bromo compound **7**[5] together with the monobromo derivative **2** (ratio **2**/**7** = 1:4). Carrying out the bromination with NBS in a perfluorinated solvent such as the perfluoro ether FC-77 ($C_8F_{16}O$, method C) led exclusively to 2-bromo-4,5-dimethylthiazole **7**.

Scheme 2

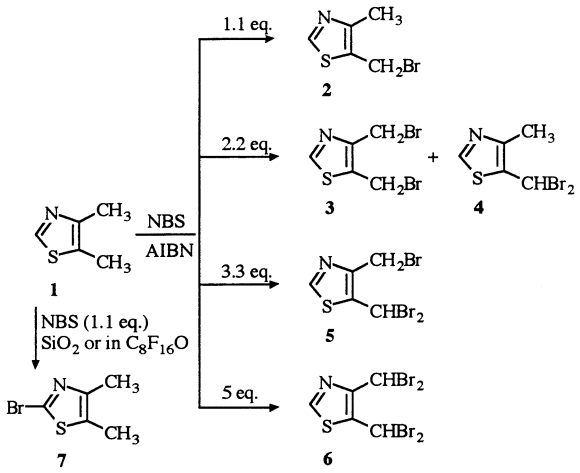


Table 1. Bromination of 4,5-dimethylthiazole (**1**) with NBS (bromo derivatives%)

NBS [equiv.]	Method	**2**	**3**	**4**	**5**	**6**	**7**	Overall yield (%)[a]
1.1	A	70	–	–	–	–	–	70
2.2	A	–	31	32	15	6	–	84
3.3	A	–	traces	traces	65	7	–	72
5.0	A	–	–	–	12	40	–	52
1.1	B	10	–	–	–	–	40	50
1.1	C	–	–	–	–	–	50	50

[a] Yields were calculated from isolated pure products.

It is apparent from Table 1 that the synthesis of the monobromo derivative **2** was regiospecifically performed with 1.1 equiv. of NBS while higher amounts gave mixtures

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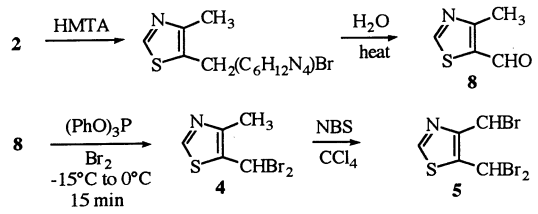
of the polybrominated compounds **3**−**6**. However, formation of the tribromo derivative **5** was found to be highly regioselective when 3.3 equiv. of NBS were employed[6]. The best yields were also observed for **2** and **5**. The 5-methyl group appeared more reactive than the 4-methyl one towards bromination under radical conditions (NBS, AIBN 10%) while C-2 remained unreactive. Substitution at this position occurred when NBS was used in the presence of silica gel or in a perfluoro ether. Compounds **2**−**7** were identified from their ^{1}H- and ^{13}C-NMR-spectral data. Assignment of the structures for the monobromo, dibromo and tribromo derivatives **2**, **4**, and **5** was made unambiguously by chemical correlations according to Scheme 3.

Scheme 3



Treatment of **2** with hexamethylenetetramine (HMTA) according to the procedure described for 3-thiophenecarboxaldehyde[7] gave after hydrolysis, 5-formyl-4-methylthiazole (**8**). The aldehyde **8** was identical with an authentic sample prepared according to a known procedure[8]. **8** was treated with bromine in the presence of triethyl phosphite to give the dibromo derivative **4** which led to **5** in the presence of NBS (1.1 eq.) and AIBN (10%) in carbon tetrachloride[6].

This work describes regioselective brominations of 4,5-dimethylthiazole with *N*-bromosuccinimide. In the presence of 2,2′-azobisisobutyronitrile, radical substitutions occurred at the methyl groups while bromination at C-2 was observed either in the presence of silica gel or when the reaction was carried out in a perfluorinated ether. This latter has never been used in such halogenation. The order of reactivity observed is 5-Me > 4-Me > C-2

Experimental Section

General: Melting points were determined in open capillary tubes with a Büchi 510 apparatus. − The ^{1}H-NMR spectra were recorded at 200 or 300 MHz in $CDCl_3$ with Bruker 200 or AM 300 spectrometers. The ^{13}C-NMR spectra were recorded at 50 or 75 MHz in $CDCl_3$. Chemical shifts are given as δ values (int. standard: TMS for ^{1}H NMR and ^{13}C NMR). The perfluorinated compound FC-77 ($C_8F_{16}O$) used in method C was purchased at ACROS.

General Procedure for Brominations of Compound **1**. − *Method A:* To a stirred solution of compound **1** (0.560 g, 5 mmol) in CCl_4 (30 ml) were added NBS (1.1 equiv.) and AIBN (0.1 g, 10%). Then, the reaction mixture was heated to reflux for 1 h. After cooling, the succinimide formed was removed by filtering. Concentration of the filtrate under vacuum and purification by column chromatography on silica gel using a mixture of diethyl ether/CH_2Cl_2/petroleum ether in a 3:3:4 ratio as the eluent afforded compound **2**. The polybromo derivatives **3**−**6** were prepared as above with NBS used in different equivalents as indicated in Table 1.

Method B: The same procedure as above was employed to obtain the 2-bromo derivative **7** except AIBN was replaced by silica gel (1 g).

Method C: To a vigorously stirred suspension of NBS (1.1 equiv.) in the perfluoro compound (15 ml) was added compound **1** (0.56 g, 5 mmol) and the reaction mixture heated to 75°C for 2.5 h. Then, the viscous fraction of the reaction mixture was washed with 4 × 20 ml of hot EtOAc and the liquid one was extracted with 3 × 30 ml of EtOAc. Evaporation of the solvent and purification of the residue as in method A afforded compound **7**.

5-Bromomethyl-4-methylthiazole (**2**): Compound **2** was obtained as a stable white solid. M.p. 217°C with decomposition. − ^{1}H NMR (300 MHz): δ = 8.61 (s, 1 H, H-2), 4.62 (s, 2 H, 5-CH_2Br), 2.37 (s, 3 H, 4-CH_3). − ^{13}C NMR (50 MHz): δ = 152.5 (C-5), 151.7 (C-2), 127.9 (C-4), 23.1 (5-*C*H_2Br), 14.9 (4-*C*H_3). − C_5H_6BrNS (190.9): calcd. C 31.27, H 3.15, N 7.29, S 16.69; found C 31.42, H 3.25, N 7.19, S 16.50.

4,5-Bis(bromomethyl)thiazole (**3**): Unstable compound, stored in CCl_4 at −18°C. − ^{1}H NMR (200 MHz): δ = 8.68 (s, 1 H, 2-H), 4.67 (s, 2 H, 5-CH_2Br), 4.57 (s, 3 H, 4-CH_2Br). − ^{13}C NMR (50 MHz): δ = 151.6 (C-2), 149.9 (C-5), 131.9 (C-4), 22.7 (5-*C*H_2Br), 19.9 (4-*C*H_2Br).

5-(Dibromomethyl)-4-methylthiazole (**4**): Unstable compound, stored in CCl_4 at −18°C. − ^{1}H NMR (200 MHz): δ = 8.90 (s, 1 H, 2-H), 6.89 (s, 1 H, 5-$CHBr_2$), 2.49 (s, 3 H, 4-CH_3). − ^{13}C NMR (50 MHz): δ = 151.6 (C-2), 147.6 (C-5), 135.0 (C-4), 27.2 (5-*C*HBr_2), 14.4 (4-*C*H_3).

4,5-Bis(dibromomethyl)thiazole (**6**): M.p. 69°C (hexane), stable in the solid state for a very short time at room temperature, may be kept at −18°C in hexane solution for several weeks. − ^{1}H NMR (300 MHz): δ = 8.78 (s, 1 H, 2-H), 7.17 (s, 1 H, 5-$CHBr_2$), 6.86 (s, 1 H, 4-$CHBr_2$). − ^{13}C NMR (75 MHz): δ = 153.0 (C-2), 149.3 (C-5), 139.0 (C-4), 29.6 (5-*C*HBr_2), 25.5 (4-*C*HBr_2).

2-Bromo-4,5-dimethylthiazole (**7**): M.p. 32°C (ref.[5] 31.5−32°C). − ^{1}H NMR (200 MHz): δ = 2.30 (s, 6 H, 4- and 5-CH_3). − ^{13}C NMR (50 MHz): δ = 148.6 (C-2), 130.6 and 130.2 (C-4 and C-5), 14.6 (4-*C*H_3), 11.2 (5-*C*H_3).

5-Formyl-4-methylthiazole (**8**): The procedure employed to prepare compound **8** was that described for 3-thiophenecarboxaldehyde[7]. The aldehyde **8** was obtained in 40% yield. − M.p. 74°C (ref.[8] 66−70°C). − ^{1}H NMR (200 MHz): δ = 10.12 (s, 1 H, CHO), 8.96 (s, 1 H, 2-H), 2.77 (s, 3 H, 4-CH_3). − ^{13}C NMR (50 MHz): δ = 182.3 (5-CHO), 161.7 (C-5), 158.7 (C-2), 132.8 (C-4), 16.1 (4-*C*H_3).

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