Chemistry of Heterocyclic Compounds, Vol. 41, No. 8, 2005

CHARACTERISTICS OF THE SYNTHESIS OF SUBSTITUTED AND CONDENSED 2-METHYL-1,3-DIAZOLES

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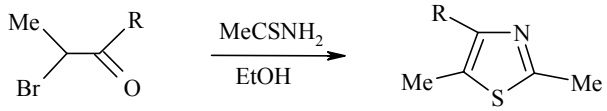
Condensation of aliphatic and carbocyclic α-bromo ketones with thioacetamide in ethanol usually leads to substituted or condensed 2-methyl-1,3-thiazoles. However in a number of cases the required compounds are only obtained in pyridine.

Keywords: α-bromo ketones, dioxane dibromide, 2-methyl-1,3-thiazoles, thioacetamide, Hantzsch condensation.

Compounds of the thiazole series are of interest on account of their high pharmacological activity. The thiazole ring is an important structural component in substances with diuretic, anthelminthic and antihistaminic properties [1], mitodepressants and mitostatics [2], antiparasitic, antipyretic, and antiviral preparations [2,3]. Thiazoles are used as antioxidants and promoters of vulcanization [2], dyestuffs [3-5] and also in the polymer industry [2-4].

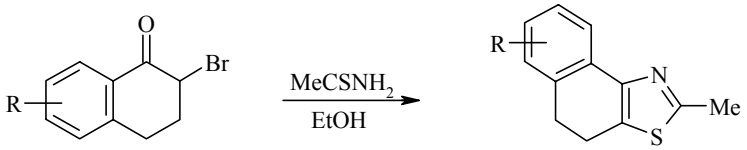
2-Methylthiazoles are used as synthons for the preparation of aldehydes and alcohols [6], while thiazolium salts may be used to obtain acyloins and benzoins [7].

The aim of the present work was to prepare 2,5-dimethyl-1,3-thiazoles containing substituents at position 4, and also condensed 2-methyl-1,3-thiazoles for subsequent functionalization at the 2-CH_3 group. All compounds were prepared by the Hanztsch method from α-bromo ketones and thioacetamide:



1a–f **2a–f**

a R = *p*-FC_6H_4; **b** R = *o*-FC_6H_4; **c** R = *m*-ClC_6H_4; **d** R = *p*-MeC_6H_4; **e** R = *p*-$MeOC_6H_4$; **f** R = 2-thienyl



3a,b **4a,b**

3 a R = 6-MeO; **b** R = 7-MeO; **4 a** R = 7-MeO; **b** R = 8-MeO

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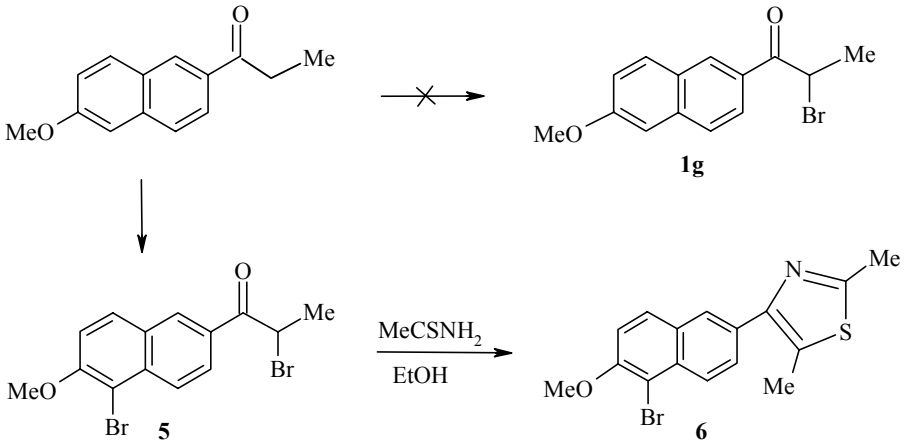
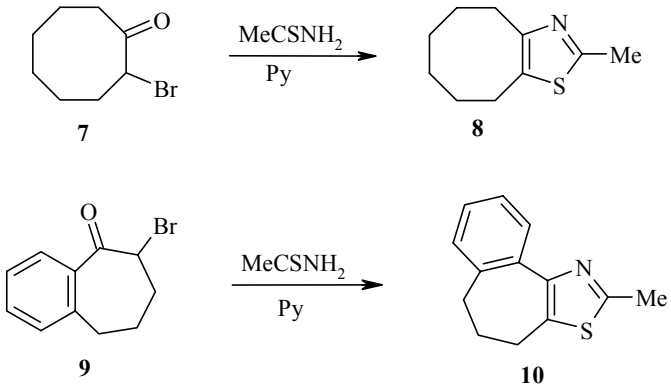
The described methods for the preparation of α-bromo ketones by radical bromination with molecular bromine or N-bromosuccinimide did not always give the desired products in high yield. In all cases we used bromination with dioxane dibromide in ether [8]. The yields of all the compounds **1a-f**, **3a,b**, **5**, **7**, and **9** were quantitative and the α-bromo ketones prepared were used without further purification for condensation with thioacetamide.

Several methods were tried to obtain 2-bromo-1-(6-methoxy-2-naphthyl)propanone (**1g**): treatment of the corresponding ketone 1) with dioxane dibromide in CH_2Cl_2; 2) with dioxane dibromide in CH_2Cl_2 in the presence of $CaCO_3$; 3) with phenyltrimethylammonium perbromide in THF. In all cases 2-bromo-1-(5-bromo-6-methoxy-2-naphthyl)propanone (**5**) was formed, despite the assertion of the authors of [9] that 2-bromo-1-(6-methoxy-2-naphthyl)propanone (**1g**) should be formed by the interaction of 1-(6-methoxy-2-naphthyl)propanone with phenyltrimethylammonium perbromide in THF.

Subsequent treatment of 2-bromo-1-(5-bromo-6-methoxy-2-naphthyl)propanone (**5**) with thioacetamide in ethanol by the standard method gave 4-(5-bromo-6-methoxy-2-naphthyl)-2,5-dimethyl-1,3-thiazole (**6**). We were unable to remove the bromine atom from the naphthalene ring in compound **6** – it did not react with metallic magnesium (synthesis of the Grignard reagent was attempted analogously to the synthesis of methoxynaphthylmagnesium bromide [10]).



Reaction of 2-bromocyclooctanone (**7**) and 2-bromobenzosuberone (**9**) with thioacetamide led to the formation of elemental sulfur and the initial ketones with bromine removed. According to GLC, the required thiazoles were formed in trace quantities. Compounds **8** and **10** were successfully synthesized in satisfactory yields by carrying out the Hanztsch synthesis in pyridine.



The ^{1}H NMR spectra of compounds **2a-f** the signals of the protons of the 2-CH_3 group occur at weak field (2.60-2.65 ppm) while those of the 5-CH_3 occur at 2.30-2.45 ppm. In some cases (for compounds **2b**, **e-f**) this signal is split (J = 3 Hz), probably as the result of interaction with a close proton of the benzene ring. The positions and multiplicities of the signals of the benzene ring correspond to the nature of the substitution.

Intense molecular ions are present in the mass spectra of the compounds synthesized. Decomposition apparently begins with loss of a molecule of acetonitrile (*m/z* 41), i.e., with immediate fission of the thiazole ring. An alternative path for decomposition of the molecular ion is the loss of a particle with mass 15 (presumably the 2-methyl group) with retention of the thiazole nucleus.

Elimination of a molecule of acetonitrile from the molecular ion was not observed in the mass spectrum of compound **10**. The intense peak with *m/z* 141 presumably corresponds to the benzotropylium cation.

Hence it has been shown that bromination of substituted aliphatic and carbocyclic ketones at the α-position proceeds quantitatively under mild conditions with dioxane dibromide in ether as the brominating agent. Bromination of 1-(6-methoxy-2-naphthyl)propanone occurs with disubstitution – in the aliphatic chain and at position 5 of the naphthalene ring – independent of the method of bromination. Subsequent condensation of the synthesized α-bromo ketones with thioacetamide in ethanol normally gave the corresponding 2-methyl-1,3-thiazoles. However in a number of cases it was necessary to use pyridine as the solvent for the condensation in place of ethanol.

EXPERIMENTAL

^{1}H NMR spectra of $CDCl_3$ solutions were recorded with a Varian UNITY INOVA (400 MHz) relative to the residual protons of the solvent. Mass spectra were obtained with a Finnegan GQ chromato-mass spectrometer equipped with a J&W Scientific DB-5MS capillary column (30 m × 0.25 mm, phase 0.25 μ 5% phenylpolysiloxane), with an ionization energy of 70 eV.

Solvents were purified and dried by known methods. Synthesis of α-bromo ketones **1a**, **d-f**, **3a-b**, **5**, **7**, and **9** was by method [8]. Their characteristics corresponded to those cited in the literature [11-19].

Synthesis of the α-Bromo Ketones 1b-c (General Method). Dioxane dibromide (3g) was added to a solution of the ketone (0.3 mol) in dry ether (150 ml) and the reaction mixture was heated until colorless. Then dioxane dibromide (74.4 g, 0.3 mol) was added over 20 min at ~20°C, the mixture was stirred for 1 h until evolution of HBr ceased, then washed with water (2 × 500 ml) and saturated NaCl solution, and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuum and the product was used without further purification.

2-Bromo-1-(2-fluorophenyl)-1-propanone (1b). Yield 100%. Oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.26-7.06 (4H, m, C_6H_4); 5.47 (1H, q, J = 9.0, CH); 2.10 (3H, d, J = 9.0, CH_3). Found, %: C 46.87; H 3.50. C_9H_8BrFO. Calculated, %: C 46.78; H 3.49.

2-Bromo-1-(2-chlorophenyl)-1-propanone (1c). Yield 100%. Oil.^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.53-7.35 (4H, m, C_6H_4); 5.65 (1H, q, J = 9.0, CH); 2.15 (3H, d, J = 9.0, CH_3). Found, %: C 43.70; H 3.35; Br 32.28; Cl 14.32. C_9H_8BrClO. Calculated, %: C 43.67; H 3.26; Br 32.28; Cl 14.32.

Preparation of Substituted 2-Methyl-1,3-thiazoles 2a-f, 6 (General Method). Thioacetamide (0.33 mmol) in ethanol (100 ml) was added to the α-bromo ketone (0.3 mmol). The reaction was exothermic after a brief heating. When the spontaneous boiling ceased the reaction mixture was boiled for a further 6-13 h, diluted with water, the ethanol was evaporated, water (50 ml) was added and the pH was adjusted to 9 with NaOH solution, the solution was extracted with ether (3 × 100 ml) or CH_2Cl_2, the extract was washed with water, saturated aqueous NaCl, and dried over Na_2SO_4. The solvent was evaporated and the residue was distilled in vacuum. Compounds **2f** and **6** were purified chromatographically (SiO_2, benzene).

Compounds 4a,b. The reaction mixture was boiled for 1 h, after which conc. HCl (25 ml) was added. The precipitate was separated, dried, suspended in water (50 ml), and solid NaOH added to pH 10. The solution produced was extracted with ethyl acetate (3 × 100 ml), and dried over Na_2SO_4. The solvent was evaporated in vacuum and the residue was chromatographed (SiO_2, $CHCl_3$) to give compounds **4a,b**.

Compounds 8 and **10** were obtained analogously to compounds **4a,b** but with pyridine as the solvent in place of ethanol.

4-(4-Fluorophenyl)-2,5-dimethyl-1,3-thiazole (2a). Yield 82%; bp 132-133°C (5 mm Hg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.56 (2H, dd, *J* = 8.6, *J* = 6.0, H_{arom}-3,5); 7.07 (2H, dd, *J* = 8.6, *J* = 8.6, H_{arom}-2,6); 2.63 (3H, s, 2-CH_3); 2.44 (3H, s, CH_3, 5-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 208 $[M+1]^+$ (13), 207 $[M]^+$(100), 206 $[M-1]^+$(23), 166 (63), 133 (23), 122 (27),107 (12). Found, %: C 63.79; H 4.87; N 6.70. $C_{11}H_{10}FNS$. Calculated, %: C 63.74; H 4.86; N 6.76.

4-(2-Fluorophenyl)-2,5-dimethyl-1,3-thiazole (2a). Yield 83%; bp 101-102°C (0.5 mm Hg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.45 (1H, t, *J* = 7.7, H_{arom}-4); 7.25 (1H, m, H_{arom}-6); 7.13 (1H, t, *J* = 7.7, H_{arom}-3); 7.05 (1H, t, *J* = 9.3, H_{arom}-5); 2.60 (3H, s, 2-CH_3); 2.27 (3H, s, 5-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 209 $[M+2]^+$ (11), 208 $[M+1]^+$ (28), 207 $[M]^+$ (100), 206 $[M-1]^+$ (27), 188 (10), 166 (80), 133 (50), 122 (54), 107 (23). Found, %: C 63.90; H 4.90; N 6.74. $C_{11}H_{10}FNS$. Calculated, %: C 63.74; H 4.86; N 6.76.

4-(2-Chlorophenyl)-2,5-dimethyl-1,3-thiazole (2c). Yield 76%; bp 130-131°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.26 (1H, dd, *J* = 3.7, *J* = 3.7, H_{arom}-2); 7.47 (1H, dd, *J* = 7.4, *J* = 3.7, H_{arom}-4); 7.30 (1H, dd, *J* = 7.4, *J* = 7.4, H_{arom}-6); 7.24-7.28 (1H, m, H_{arom}-5); 2.63 (3H, s, 2-CH_3); 2.46 (3H, s, 5-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 226 $[M+3]^+$ (5), 225 $[M+2]^+$ (39), 224 $[M+1]^+$ (30), 223 $[M]^+$ (100), 222 $[M-1]^+$ (52), 182 (56), 147 (47),13 9 (19), 102 (16). Found, %: C 59.06; H 4.50; Cl 15.95; N 6.20; S 14.41. $C_{11}H_{10}ClNS$. Calculated, %: C 59.055; H 4.51; Cl 15.85; N 6.26; S 14.33.

2,5-Dimethyl-4-(4-methylphenyl)-1,3-thiazole (2d). Yield 58%; bp 118-119°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.52 (2H, m, H_{arom}-2); 7.21 (2H, m, H_{arom}-3); 2.65 (3H, s, 2-CH_3); 2.47 (3H, d, *J* = 3.0, 5-CH_3); 2.37 (3H, s, CH_3-C_6H_5). Mass spectrum, *m/z* (I_{rel}, %): 204 $[M+1]^+$ (26), 203 $[M]^+$ (100), 202 $[M-1]^+$ (48), 162 (85), 147 (31), 128 (22), 115 (18), 91 (19). Found, %: C 70.92; H 6.55; N 6.91; S 15.60. $C_{12}H_{13}NS$. Calculated, %: C 70.89; H 6.45; N 6.89; S 15.77.

4-(4-Methoxyphenyl)-2,5-dimethyl-1,3-thiazole (2e). Yield 63%; bp 141-142°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.53 (2H, dd, *J* = 7.7, *J* = 2.7, H_{arom}-2); 6.92 (2H, dd, *J* = 7.7, *J* = 2.7, H_{arom}-3); 3.80 (3H, s, CH_3O); 2.62 (3H, s, 2-CH_3); 2.43 (3H, d, *J* = 1.0, 5-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 220 $[M+1]^+$ (35), 219 $[M]^+$ (100), 218 $[M-1]^+$ (30), 204 (19), 178 (84), 163 (99), 135 (33), 102 (16), 91 (29). Found, %: C 65.75; H 6.06; N 6.40; S 14.69. $C_{12}H_{13}NOS$. Calculated, %: C 65.72; H 5.975; N 6.39; S 14.62.

2,5-Dimethyl-4-(2-thienyl)-1,3-thiazole (2f). Yield 57%; oil, R_f 0.86 (Silufol UV-254, 10:1 benzene–acetone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.19 (1H, dd, *J* = 3.8, *J* = 1.3, H_{th}-5); 7.17 (1H, dd, *J* = 5.0, *J* = 1.0, H_{th}-3); 6.96 (1H, dd, *J* = 5.0, *J* = 3.8, H_{th}-4); 2.53 (3H, s, 2-CH_3); 2.43 (3H, s, 5-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 197 $[M+2]^+$ ((15), 196 $[M+1]^+$ (19), 195 $[M]^+$ (100), 154 (89), 153 (49), 139 (9), 121 (14), 110 (32), 95 (9). Found, %: C 55.48; H 4.72; N 7.32; S 32.95. $C_9H_9NS_2$. Calculated, %: C 55.35; H 4.64; N 7.17; S 32.84.

7-Methoxy-2-methyl-4,5-dihydronaphtho[1,2-*d*][3,1]thiazole (4a). Yield 41%; oil, R_f 0.6 (Silufol UV-254, 10:1 benzene–acetone). ^{1}H NMR spectrum, δ, ppm (*J* , Hz): 7.80 (1H, d, *J* = 8.4, H-9); 6.78 (1H, dd, *J* = 8.2, *J* = 3.0, H-8); 6.74 (1H, d, *J* = 3.0, H-6); 3.70 (3H, s, CH_3O); 2.94 (m, CH_2–CH_2); 2.70 (3H, s, 2-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 232 $[M+1]^+$ (11), 231 $[M]^+$ (100), 230 $[M-1]^+$ (28), 216 (44), 189 (9), 175 (8), 158 (6), 147 (23), 145 (11), 115 (9), 103 (9). Found %: C 67.56; H 5.65; N 6.78; S 13.67. $C_{13}H_{13}NOS$. Calculated, %: C 67.50; H 5.66; N 6.055; S 13.86.

8-Methoxy-2-methyl-4,5-dihydronaphtho[1,2-*d*][3,1]thiazole (4b). Yield 55%; oil, R_f 0.63 (Silufol UV-254, 10:1 benzene–acetone). ^{1}H NMR spectrum, δ, ppm (*J* , Hz): 7.47 (1H, d, *J* = 3.0, H-9); 7.07 (1H, d, *J* = 8.2, H-6); 6.72 (1H, dd, *J* = 8.2, *J* = 3.0, H-7); 3.65 (3H, s, CH_3O); 2.92 (m, CH_2–CH_2); 2.70 (3H, s, 2-CH_3).

Mass spectrum, *m/z* (I_{rel}, %): 232 $[M+1]^+$ (19), 231 $[M]^+$ (100), 230 $[M-1]^+$ (47), 216 (16), 200 (11),189 (13), 175 (8), 147 (14), 145 (16), 115 (11), 102 (8). Found %: C 67.51; H 5.67; N 6.00; S 13.77. $C_{13}H_{13}NOS$. Calculated, %: C 67.50; H 5.66; N 6.055; S 13.86.

4-(5-Bromo–6-methoxy-2-naphthyl)-2,5-dimethyl-1,3-thiazole (6). Yield 65%; mp 135-137°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.24 (1H, d, *J* = 8.7, H_{arom}-1); 8.02 (1H, d, *J* = 3.0, H_{arom}-4); 7.86 (1H, d, *J* = 3.0, H_{arom}-8); 7.84 (1H, d, *J* = 3.0, H_{arom}-2); 7.25 (1H, m, H_{arom}-7); 4.02 (3H, s, CH_3O); 2.65 (3H, s, 2-CH_3); 2.55 (3H, s, 5-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 349 (100), 347 (100), 334 (39), 332 (39), 306 (29), 293 (34), 291 (34), 265 (17), 263 (27), 212 (10), 184 (31), 152 (25), 134 (21), 113 (17). Found, %: C 57.42; H 4.42; N 4.12. $C_{16}H_{14}BrNOS$. Calculated, %: C 57.84; H 4.25; N 4.22.

2-Methylcycloocta[*d*][1,3]thiazole (8). Yield 53%; oil, R_f 0.44 (Silufol UV-254, 10:1 benzene–acetone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.70 (4H, dd, *J* = 13.2, *J* = 7.0, 4-,9-CH_2); 2.50 (3H, s, 2-CH_3); 1.58 (4H, m, 5-, 8-CH_2); 1.30 (4H, m, 6-, 7-CH_2). Mass spectrum, *m/z* (I_{rel}, %): 182 $[M+1]^+$ (13), 181 $[M]^+$ (100), 180 $[M-1]^+$ (3), 166 (14), 153 (95), 140 (55), 125 (54), 113 (42), 107 (55), 97 (4), 79 (41). Found, %: C 66.13; H 8.30; N 7.89; S 17.24. $C_{10}H_{15}NS$. Calculated, %: C 66.25; H 8.34; N 7.73; S 17.69.

2-Methyl-5,6-dihydro-4H-benzo[6,7]cyclohepta[1,2-*d*]3,1]thiazole (10). Yield 56%; oil, R_f 0.71 (Silufol UV-254, 10:1 benzene–acetone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.00 (1H, d, *J* = 8, H_{arom}-7); 7.29 (1H, m, H_{arom}-10); 7.18 (2H, m, H_{arom}-8,9); 2.90 (2H, t, *J* = 7.0, 4-CH_2); 2.76 (2H, m, 6-CH_2); 2.68 (2H, s, 2-CH_2); 2.60 (2H, m, 6-CH_2). Mass spectrum, *m/z* (I_{rel}, %): 216 $[M+1]^+$ (28), 215 $[M]^+$ (100), 214 $[M-1]^+$ (37), 200 (30), 182 (25), 173 (49), 141 (59), 128 (30), 115 (36). Found, %: C 72/57; H 6.12; N 6.35; S 14.45. $C_{13}H_{13}NS$. Calculated, %: C 72.52; H 6.09; N 6.51; S 14.90.

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