

DIHYDROCHALCONES AS SYNTHONS FOR 2-AMINO- AND 2-MERCAPTO-4-ARYL-5-ARYLMETHYLTHIAZOLES

Vinod Kumar Ahluwalia*, Krishan Kumar Arora, and Gurvinder Kaur
Department of Chemistry, University of Delhi, Delhi-110 007,
India

Abstract - 2-Amino- and 2-mercapto-4-aryl-5-arylmethylthiazoles have been synthesised by the respective condensation of thiourea and ammonium dithiocarbamate with α -bromo- α,β -dihydrochalcones which in turn are obtained by the bromination of the corresponding dihydrochalcones.

Since nineteenth century a large number of thiazoles with different substituents have been synthesised which are known to be associated with diverse biological activities¹. But survey of the literature reveals that no thiazole having 4-aryl 5-arylmethyl substituents has ever been synthesised. Retro-synthetic analysis shows that such thiazoles can be obtained from dihydrochalcones. Earlier attempts to prepare these thiazoles from dihydrochalcones via dibromodihydrochalcones have met with failure².

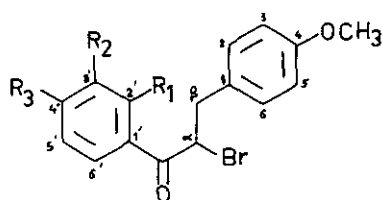
We carried out the condensation of α,β -dihydrochalcones with thiourea in presence of iodine (as per the normal procedure introduced by King et al.³ for the synthesis of thiazoles) but only starting material was recovered. The difficulty was, however, overcome by carrying out the condensation with corresponding α -bromo- α,β -dihydrochalcones.

Thus, the bromination of α,β -dihydro-4-methoxy-4'-methylchalcone with bromine in carbon tetrachloride at 30-35°C gave a product which showed carbonyl absorption at 1680 cm⁻¹ in its ir spectrum. Its nmr spectrum showed, besides other signals, a multiplet due to two protons (C _{β} -H) at δ 3.22-3.57 and a triplet due to one proton (C _{α} -H) at δ 5.28. Hence it was assigned the structure α -bromo- α,β -dihydro-4-methoxy-4'-methylchalcone (1).

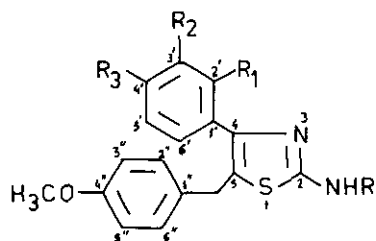
α -Bromodihydrochalcone (1) on condensation with thiourea in absolute ethanol afforded a product. Its ir spectrum showed absorptions at 3440 and 3280 cm⁻¹ (NH₂ stretching). Its nmr spectrum showed a two proton singlet at δ 4.02 (CH₂

at C_5) and a broad singlet due to two protons (exchanged with D_2O) at δ 5.30 (NH_2 at C_2). On the basis of this and elemental analysis, it was assigned the structure, 2-amino-5-(4"-methoxyphenylmethyl)-4-(4'-methylphenyl)thiazole (2). The presence of an amino group in 2 was further confirmed by the preparation of its acetyl derivative (3).

α -Bromodihydrochalcone (1) on condensation with ammonium dithiocarbamate in absolute ethanol afforded a compound as colourless shining needles. Its nmr spectrum showed besides other signals, one proton singlet (D_2O exchanged) at δ 1.71 and two protons singlet at δ 3.87 (CH_2 at C_5). Its ir spectrum showed absorption at 2510 cm^{-1} (SH stretching). On this basis it was assigned the structure, 2-mercapto-5-(4"-methoxyphenylmethyl)-4-(4'-methylphenyl) thiazole (4). The presence of mercapto group in 4 was further confirmed by the synthesis of its S-methyl derivative (5).

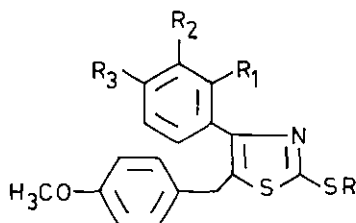


(1,6,11)



(2,7,12; R = H)

(3,8,13; R = $COCH_3$)



(4,9,14; R = H)

(5,10,15; R = CH_3)

	R_1	R_2	R_3
1-5	H	H	CH_3
6-10	OCH_3	H	OCH_3
11-15	OCH_3	CH_3	OCH_3

Similar results were obtained when reaction was extended to other dihydrochalcones. Thus, α -bromo- α,β -dihydro-2',4,4'-trimethoxychalcone (6) on condensation with thiourea and ammonium dithiocarbamate afforded 7 and 9 respectively.

Similarly α -bromo- α,β -dihydro-3'-methyl-2',4,4'-trimethoxychalcone (11) afforded 12 and 14. All these products were assigned the structures on the basis of elemental analysis, ir and nmr spectral data. Acetylation of 7 and 12 gave 8 and 13 and methylation of 9 and 14 afforded 10 and 15, respectively. Table 1 summarises the yield, mp and spectral data of all these compounds.

All the thiazole derivatives synthesised have shown 30-60% fungal inhibition against *Aspergillus fumigatus* and *Aspergillus niger* and marginal antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.

Table 1.

Compound ^a	Yield [%]	mp ^b [°C]	ir [$\nu_{\text{max}}^{\text{KBr cm}^{-1}}$]	nmr (CDCl ₃ /TMS) [δ (ppm)]
<u>1</u>	95.4	oil	1680	2.35(3H,s, CH ₃); 3.22-3.57(2H,m, C ₃ -H) 3.80(3H,s, OCH ₃); 5.28(1H, t, $\underline{J}$ 7Hz, C ₄ -H); 6.81(2H,d, $\underline{J}$ 9Hz, C ₃ -H and C ₅ -H) 7.19 and 7.24(each 2H, each d, $\underline{J}$ 9Hz, C ₂ -H, C ₆ -H, C ₃ '-H and C ₅ '-H) and 7.86(2H,d, $\underline{J}$ 9Hz, C ₂ '-H and C ₆ '-H).
<u>2</u>	88.0	176-177	3440 and 3280	2.37(3H,s, CH ₃); 3.78(3H,s, OCH ₃); 4.02 (2H,s, CH ₂); 5.30(2H, br s, exchanged with D ₂ O, NH ₂); 6.84(2H,d, $\underline{J}$ 9Hz, C ₃ "-H and C ₅ "-H); 7.12 and 7.23(each 2H, each d, $\underline{J}$ 9Hz, C ₃ '-H, C ₅ '-H, C ₂ "-H and C ₆ "-H) and 7.44(2H,d, $\underline{J}$ 9Hz, C ₂ '-H and C ₆ '-H).
<u>3</u>	86.9	142-143	3180 and 1650	1.63(3H,s, COCH ₃); 2.40(3H,s, CH ₃); 3.49 (1H, br s, exchanged with D ₂ O, NH); 3.80 3H,s, OCH ₃); 4.14(2H,s, CH ₂); 6.84(2H, d, $\underline{J}$ 9Hz, C ₃ "-H and C ₅ "-H); 7.13 and 7.23(each 2H, each d, $\underline{J}$ 9Hz, C ₃ '-H, C ₅ '-H C ₂ "-H and C ₆ "-H) and 7.44(2H,d, $\underline{J}$ 9Hz, C ₂ '-H and C ₆ '-H).
<u>4</u>	85.7	184-185	2510	1.71(1H, br s, exchanged with D ₂ O); 2.40 (3H,s, CH ₃); 3.77(3H,s, OCH ₃); 3.87(2H, s, CH ₂); 6.85(2H,d, $\underline{J}$ 9Hz, C ₃ "-H and

				$C_{5''}-H$; 7.08(2H,d, $\underline{J}$ 9Hz, $C_{2''}-H$ and $C_{6''}-H$) and 7.28(4H,s, $C_{2'}-H$, $C_{3'}-H$, $C_{5'}-H$ and $C_{6'}-H$).
<u>5</u>	85.7	oil	-	2.35(3H,s, CH_3); 2.58(3H,s, SCH_3); 3.67(3H,s, OCH_3); 4.02(2H,s, CH_2); 6.85(2H,d, $\underline{J}$ 9Hz, $C_{3''}-H$ and $C_{5''}-H$); 7.16 and 7.31(each 2H, each d, $\underline{J}$ 9Hz, $C_{3'}-H$, $C_{5'}-H$ and $C_{2''}-H$, $C_{6''}-H$).
<u>6</u>	90.5	oil	1655	2.89-3.62(2H,m, $C_{\beta}-H$); 3.63, 3.70 and 3.74(each 3H, each s, $3 \times OCH_3$); 5.40(1H,t, $\underline{J}$ 7Hz, $C_{\alpha}-H$); 6.32(1H,d, $\underline{J}$ 2.5Hz, $C_{3'}-H$); 6.43(1H,dd, $\underline{J}$ 9Hz and 2.5Hz, $C_{5'}-H$); 6.73(2H,d, $\underline{J}$ 9Hz, $C_{3''}-H$ and $C_{5''}-H$); 7.12(2H,d, $\underline{J}$ 9Hz, $C_{2''}-H$ and $C_{6''}-H$) and 7.70(1H, d, $\underline{J}$ 9Hz, $C_{6'}-H$).
<u>7</u>	79.8	174-175	3450 and 3280	3.73, 3.75 and 3.77(each 3H, each s, $3 \times OCH_3$); 3.81(2H,s, CH_2); 5.05(2H,br s, exchanged with D_2O , NH_2); 6.50(1H,d, $\underline{J}$ 2.5Hz, $C_{3'}-H$); 6.53(1H,dd, $\underline{J}$ 9Hz and 2.5Hz, $C_{5'}-H$); 6.78(2H,d, $\underline{J}$ 9Hz, $C_{3''}-H$ and $C_{5''}-H$); 7.10(2H,d, $\underline{J}$ 9Hz, $C_{2''}-H$ and $C_{6''}-H$) and 7.25(1H,d, $\underline{J}$ 9Hz, $C_{6'}-H$).
<u>8</u>	90.9	170-171	3180 and 1655	1.65(3H,s, $COCH_3$); 3.72, 3.78 and 3.84(each 3H, each s, $3 \times OCH_3$); 3.89(2H,s, CH_2); 6.53(2H,m, $C_{3'}-H$ and $C_{5'}-H$); 6.79(2H,d, $\underline{J}$ 9Hz, $C_{3''}-H$ and $C_{5''}-H$); 7.07(2H,d, $\underline{J}$ 9Hz, $C_{2''}-H$ and $C_{6''}-H$) and 7.26(1H,d, $\underline{J}$ 9Hz, $C_{6'}-H$).
<u>9</u>	89.8	169-170	2520	1.72(1H,s,exchanged with D_2O); 3.79(6H,s, $2 \times OCH_3$); 3.81(3H,s, OCH_3); 3.83(2H,s, CH_2); 6.51(2H,m, $C_{3'}-H$ and $C_{5'}-H$); 6.82(2H,d, $\underline{J}$ 9Hz, $C_{3''}-H$ and $C_{5''}-H$); 7.06(2H,d, $\underline{J}$ 9Hz, $C_{2''}-H$ and $C_{6''}-H$) and

				7.17(1H,d, $\underline{J}$ 9Hz, C ₆ ,-H).
<u>10</u>	95.2	Oil	-	2.57(3H,s, CH ₃); 3.75(6H,s,2xOCH ₃); 3.82(3H,s,OCH ₃); 3.91(2H,s,CH ₂); 6.45 (2H,m,C ₃ , -H and C ₅ , -H); 6.76(2H,d, $\underline{J}$ 9Hz, C ₃ "-H and C ₅ "-H); 7.08(2H,d, $\underline{J}$ 9Hz, C ₂ "-H and C ₆ "-H) and 7.22(1H, d, $\underline{J}$ 9Hz, C ₆ , -H).
<u>11</u>	89.6	Oil	1650	2.08(3H,s,CH ₃); 2.98-3.69(2H,m,C ₆ -H); 3.34,3.72 and 3.84(each 3H,each s, 3xOCH ₃); 5.58(1H,t, $\underline{J}$ 7Hz,C ₄ -H); 6.57 (1H,d, $\underline{J}$ 9Hz, C ₅ , -H); 6.71(2H,d, $\underline{J}$ 9Hz, C ₃ -H and C ₅ -H); 7.14(2H,d, $\underline{J}$ 9Hz,C ₂ -H and C ₆ -H) and 7.39(1H,d, $\underline{J}$ 9Hz,C ₆ , -H).
<u>12</u>	79.8	181-182	3435 and 3270	2.14(3H,s,CH ₃); 3.50,3.73 and 3.80 (each 3H, each s, 3xOCH ₃); 3.82(2H,s, CH ₂); 4.94(2H, br s, exchanged with D ₂ O, NH ₂); 6.61(1H,d, $\underline{J}$ 9Hz, C ₅ , -H); 6.75(2H,d, $\underline{J}$ 9Hz,C ₃ "-H and C ₅ "-H); 7.05(2H,d, $\underline{J}$ 9Hz,C ₂ "-H and C ₆ "-H) and 7.27(1H,d, $\underline{J}$ 9Hz and C ₆ , -H).
<u>13</u>	90.9	140-141	3170 and 1650	1.64(3H,s,COCH ₃); 2.18(3H,s,CH ₃); 3.34,3.66 and 3.77(each 3H, each s, 3xOCH ₃); 3.83(2H,s,CH ₂); 6.65(1H,d, $\underline{J}$ 9Hz, C ₅ , -H); 6.75(2H,d, $\underline{J}$ 9Hz,C ₃ "-H and C ₅ "-H); 7.06(2H,d, $\underline{J}$ 9Hz, C ₂ "-H and C ₆ "-H) and 7.26(1H,d, $\underline{J}$ 9Hz,C ₆ , -H).
<u>14</u>	92.8	185-186	2510	1.71(1H,s,exchanged with D ₂ O); 2.11 (3H,s,CH ₃); 3.50,3.70 and 3.74(each 3H,each s,3xOCH ₃); 3.77(2H,s,CH ₂); 6.59(1H,d, $\underline{J}$ 9Hz,C ₅ , -H); 6.73(2H,d, $\underline{J}$ 9Hz,C ₃ "-H and C ₅ "-H); 6.96(2H,d, $\underline{J}$ 9Hz,C ₂ "-H and C ₆ "-H) and 7.05(1H, d, $\underline{J}$ 9Hz, C ₆ , -H).

15 85.0 Oil - 2.13(3H,s,CH₃); 2.56(3H,s, SCH₃); 3.44,
 3.63 and 3.76(each 3H, each s, 3xOCH₃);
 3.81(2H,s,CH₂); 6.54(1H,d,J 9Hz,C₅,-H);
 6.61(2H,d,J 9Hz,C₃"-H and C₅"-H); 6.93
 (2H,d,J 9Hz,C₂"-H and C₆"-H) and 7.05
 (1H,d,J 9Hz,C₆,-H).

a. Satisfactory microanalysis obtained for all the products.

b. Not corrected

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