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CATALYTIC HYDROGENATION OF HALOTHIAZOLES

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ABSTRACT: The hydrogenation of halothiazoles is described. The best results were obtained utilizing 10% palladium on carbon as catalyst at four atmospheres of pressure with the bromide derivatives.

Catalytic hydrogenation is a unique synthetic method for organic chemists because of its widespread application and experimental simplicity. In the case of halothiazoles, the literature contains very little with regard to hydrogenation of these interesting compounds. 2- and 5-bromothiazoles have been dehalogenated utilizing RaNi as catalyst[1,2] but we have been unsuccessful in finding any reference to the hydrogenation of thiazoles at its relatively less reactive site, the 4-position. We now wish to report herein that hydrogenation employing 10% Pd/C as catalyst, especially in the case of 4-halothiazoles, is a reliable, efficient, and simple method for achieving dehalogenation of these compounds. Furthermore, hydrogenation offers several advantages over other methods of dehalogenation of thiazoles.[3] For

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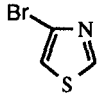
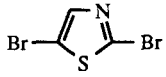
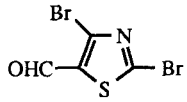
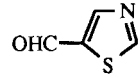
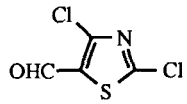
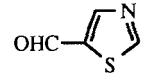
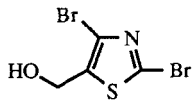
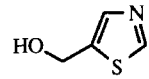
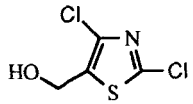
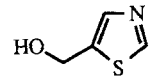
instance, there is no need for cryogenic conditions or pyrophoric reagents. The byproduct (HCl or HBr gas) is readily removed from the reaction mixture. The reaction and workup can be performed under anhydrous or aqueous conditions and the product is easily isolated, usually in high purity, by evaporation of the solvent.

Halothiazoles[4] were hydrogenated as shown in table I. We have found 10% Pd/C to be superior to RaNi, 5% Pt/C, Pd Black and 5% Rh/C as the catalyst in achieving this transformation. For instance, with respect to entry **1**, hydrogenation with 10% Pd/C gave a 91% yield of isolated product while the incorporation of the other catalysts afforded yields of less than 50%. In another example, entry **6**, the employment of 10% Pd/C resulted in a 28% yield of completely dehalogenated product whereas the utilization of the other catalysts gave yields of less than 6%. Although 1 atmosphere of pressure was sufficient to remove the bromo substituents, 4 atmospheres gave us the best results especially with regard to the chloro compounds. In addition, alternative dehalogenation procedures employing zinc and acetic acid, tin and hydrochloric acid or Grignard formation and hydrolysis gave inferior yields under varying conditions due to the water solubility of the thiazole products and/or the relative unreactiveness of the 4-halogen substituent.

Entries **1** and **2** illustrate that any position on the thiazole nucleus can be thoroughly dehalogenated under these conditions to afford the parent heterocycle. Entries **3** and **4** exhibit the dramatic difference in reactivity between chloro and bromo substituents. In contrast to the chloro compound which had to be heated to obtain a good yield, the bromo derivative was completely dehalogenated at room temperature.

Table I. Hydrogenation of Halothiazoles at 4 atm with 10% Pd/C in Methanol

Entry	Thiazole	Product [a,b]	mp/(bp) °C	Yield(%)[c]
1			(117-118)	91
2			(117-118)	92
3			(92-94 at 12 mm Hg)	91
4			(92-94 at 12 mm Hg)	72
5			(140-142 at 10 mm Hg)	94
6			(140-142 at 10 mm Hg)	28

a. Reaction conditions for entries **1**, **2**, **3** and **5** are 23°C for 12 h; for entry **4** 55°C for 15 h; and for entry **6** 60°C for 60 h.

b. All spectral and analytical data were consistent with the assigned structures.[5]

c. Isolated yields.

The product of the reaction, 5-thiazolecarboxaldehyde[6], is a key intermediate in preparing pharmaceutically useful products. Interestingly, the aldehyde functionality, under these conditions, remained generally intact probably due to poisoning of the catalyst. Further differences in reactivity with regard not only to the nature of the substituent but also to its position on the thiazole nucleus are demonstrated by entries **5** and **6**. Again, the bromothiazole was strikingly more reactive than its chloro analog (12 h at 23°C in 94% yield versus 60 h at 60°C in 28% yield) in providing 5-(hydroxymethyl)thiazole[7], a valuable synthetic precursor for preparing biologically active compounds. The major product with respect to the hydrogenation of 2,4-dichloro-5-(hydroxymethyl)thiazole was 4-chloro-5-(hydroxymethyl)thiazole (63%). In fact, by changing the reaction temperature to 23°C and monitoring by thin layer chromatography, 4-chloro-5-(hydroxymethyl)thiazole[8] was isolated in over 90% yield, thus achieving a selective dehalogenation.

General Method. To the halothiazole (10 mmol) dissolved in methanol (100 mL) containing sodium acetate trihydrate (1.1-1.5 equivalents per halogen) is added 10% palladium on carbon (10%-equal amount by weight). The mixture is shaken in a Parr hydrogenation reactor under 4 atmospheres of hydrogen at 23°C or, if needed, 60°C until the theoretical uptake of hydrogen has been consumed. The catalyst is removed by filtration and the methanol evaporated. The residue is dissolved in methylene chloride or ether, dried (Na_2SO_4), filtered and the solvent evaporated to afford the product. If necessary, the product can be further purified by distillation or chromatography.

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5. Spectral and physical data of all the compounds cited in Table I are as follows: (a) Thiazole: bp 117-118°C (lit.[4a] 117°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (s, 1H), 7.97 (d, 1H), 7.41 (m, 1H); MS (DCI/NH_3) *m/e* 86 $(M+H)^+$. (b) 5-Thiazolecarboxaldehyde: bp 92-94°C at 12 mm Hg (lit.[9] 90-94°C at 12 mm Hg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.10 (s, 1H), 9.11 (s, 1H), 8.52 (s, 1H); MS (DCI/NH_3) *m/e* 114 $(M+H)^+$. (c) 5-(Hydroxymethyl)thiazole: bp 140-142°C at 10 mm Hg (lit.[10] bp 133-140°C at 10 mm Hg), ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.80 (s, 1H), 7.80 (s, 1H), 4.92 (s, 2H), 2.12 (brs, 1H); MS (DCI/NH_3) *m/e* 116 $(M+H)^+$.

(d) 4-Bromothiazole: bp 189-190°C (lit.[4a] 189-190°C); ^{1}H NMR (300 MHz, CCl_4): δ 8.70 (s, 1H), 7.24 (s,1H); MS (DCI/NH_3) *m/e* 165 $(M+H)^+$. (e) 2,5-Dibromothiazole: mp 46-47°C (lit.[4b] 46-47°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (s, 1H); MS (DCI/NH_3) *m/e* 245 $(M+H)^+$. (f) 2,4-Dibromo-5-thiazolecarboxaldehyde: mp 80-81°C (lit.[3a] mp 80-81°C);^{1}H NMR (300 MHz, $CDCl_3$): δ 9.89 (s, 1H); MS (DCI/ NH_3) *m/e* 272 $(M+H)^+$. (g) 2,4-Dichloro-5-thiazolecarboxaldehyde: mp 48-49°C (lit.[4d] mp 48-49°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.96 (s, 1H); MS (DCI/NH_3) *m/e* 182 $(M+H)^+$. (h) 2,4-Dibromo-5-(hydroxymethyl)thiazole: mp 87-88°C (lit.[4e] mp 87-88°C);^{1}H NMR (300 MHz, $CDCl_3$): δ 4.79 (d, 2H), 2.18 (t, 1H); MS (DCI/NH_3) *m/e* 274 (M + H)$^+$. (i) 2,4-Dichloro-5-(hydroxymethyl)thiazole: mp 53-54°C (lit.[4e] mp 53-54°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.81 (d, 2H), 2.24 (t, 1H); MS (DCI/NH_3) *m/e* 184 $(M+H)^+$.

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8. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.70 (s, 1H), 4.88 (d, 2H), 2.02 (t, 1H); MS (DCI/NH_3) *m/e* 150 $(M+H)^+$. Anal. Calcd for C_4H_4ClNOS: C, 32.11; H, 2.69; N, 9.36. Found: C, 31.99; H, 2.67; N, 9.40.
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