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AN ALDEHYDE SYNTHESIS UTILIZING THE THIAZOLE RING SYSTEM.

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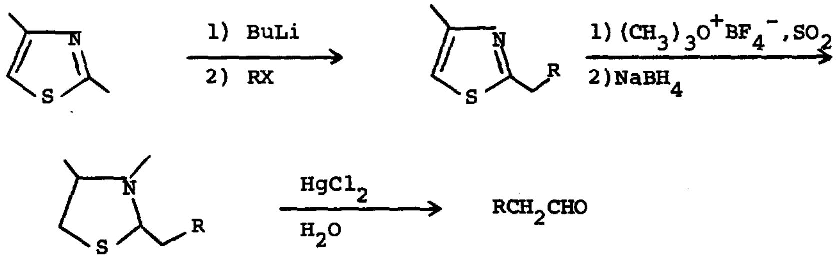
We report here an alternate aldehyde synthesis to that of Meyers.[1,2] Our synthesis is based on the hydrolysis of thiazolidines using mercuric chloride as catalyst and avoids strongly acidic conditions throughout. The synthesis is depicted below.



Overall yields of pure aldehydes from commerically available[3] 2,4-dimethylthiazole are in the range of 50-75%. Typical experimental procedures are exemplified below with the synthesis of 3-phenylpropanol.

2-(2-phenylethyl)-4-Methylthiazole. To a stirred solution of 2,4-dimethylthiazole (4.976 g, 44.1 mmole) in 35 ml dry tetrahydrofuran at -78° under nitrogen was added one equivalent of butyl lithium over 25 minutes; the resulting thick yellow suspension was stirred for an additional 20 minutes. Benzyl chloride (5.58 g, 44.1 mmole) was then added quickly, maintaining the temperature of the reaction mixture below -70°. The reaction mixture was allowed to warm to room temperature and partitioned between ether and water. The dried ether extracts yielded upon evaporation 2-(2-phenylethyl)-4-methylthiazole (8.38 g, 94% yield). The NMR spectrum (60 MHz, CCl_4) showed the following absorptions: δ 2.35 (s, 3H, vinyllic methyl); 3.08 (broad s, 4H, $N{=}C{-}\underline{CH_2}{-}\underline{CH_2}{-}$); 6.53 (s, 1H, vinyllic proton); 7.12 (s, 5H, aromatic protons).

2-(2-phenylethyl)-3,4-Dimethylthiazolidine. The crude product from the above reaction (4.409 g, 21.7 mmole) and trimethyloxonium fluoroborate (4.8 g, 32.4 mmole) were weighed into a dry flask fitted with a magnetic stirring bar and Dry-Ice -- acetone reflux condenser. Sulfur dioxide (≈ 20 ml) was distilled into the flask and the reaction mixture allowed to stir for 1.5 hours after which time the SO_2 was evaporated; the salt was then washed with several portions of petroleum ether and dried under vacuum. The salt was dissolved in 100 ml abs. ethanol and cooled to 0°. $NaBH_4$ (1.0 g) was added slowly with vigorous gas evolution and the mixture allowed to stir at room temperature for 24 hours after which an additional portion of $NaBH_4$ (1 g) was added. After an additional three hours of stirring the suspended salts were filtered and the filtrate partitioned between ether and brine. The dried (K_2CO_3) ether extracts yielded upon removal of solvent 2-(2-phenylethyl)-3,4-dimethylthiazolidine (4.39 g, 91.5% yield over two steps) as a yellow oil. The NMR spectrum (100 MHz, CCl_4) showed the following absorptions: δ 1.04 (d, J = 6, 3H, $-\overset{H}{C}-C\underline{H}_3$); δ 1.72 (m, 2H, $>CH-C\underline{H}_2-CH_2-\varphi$); δ 2.16 (s, 3H, $-\overset{|}{N}-C\underline{H}_3$); δ 2.37 (t, 2H, J = 7, $-CH_2-C\underline{H}_2-\varphi$); δ 2.50-2.92 (m, 3H, $C\underline{H}_2-S-\overset{|}{C}\underline{H}$); δ 2.95 (m, 1H, $-\overset{H}{C}-CH_3$). The IR spectrum (neat film) showed no absorbance in the 2000-2600 cm^{-1} (SH) and the 3125-3800 cm^{-1} (NH) regions. Vpc analysis (3% OV-225, 140°C) showed the presence of approximately 3% of starting thiazole as the only impurity.

3-Phenylpropanol. A solution of the crude thiazolidine (1.11 g, 5.0 mmoles) in 2 ml methanol was added to a solution of mercuric chloride (1.5 g, 5.5 mmole) in 10 ml methanol and 1 ml water. A yellow gum separated almost immediately; this gum became a fine suspension after stirring for 2.5 hours. The precipitate was removed by filtration and the filtrate partitioned betweer brine and ether. The combined ether extracts were washed with 10% HCl, water and brine and dried ($MgSO_4$). Removal of solvent gave crude 3-phenylpropanol (490 mg) which was evaporatively distilled (b.p. 100°, 0.5 mm) to yield pure 3-phenylpropanal (403 mg, 60% yield).

This method should prove useful in the synthesis of aldehydes containing acid sensitive groups. The synthetic variants developed by Meyers[4] should be applicable to this system as well.

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References

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