An unusual oxidation of thiazol-2-ylmethanol in hydrolytic conditions

Maurizio D'Auria,* Giacomo Mauriello and Rocco Racioppi

Dipartimento di Chimica, Università della Basilicata, Via N. Sauro 85, 85100 Potenza, Italy

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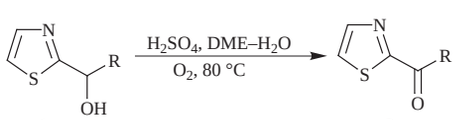
The treatment of aryl and heteroaryl thiazol-2-ylmethanols with sulfuric acid in a dimethoxyethane–water mixture at 80 °C gave the corresponding ketone as the only product in good yields. All the data are in agreement with a mechanism involving the formation of a thiazoline as intermediate. Best yields can be obtained carrying out the reaction in the presence of oxygen, showing that this reagent oxidizes the thiazoline intermediate.

Thiazoles have been used in organic synthesis as precursors of the aldehyde function by the group of Dondoni. The use of the Dondoni's procedure in the synthesis of some important natural products is well established in the literature.[1] It represents one of the most important applications of heterocycles in organic synthesis. Nevertheless, occasionally, during the preparation of thiazol-2-ylmethanols starting from 2-trimethylsilylthiazole, some ketone was obtained as the main product.[2] In particular, this type of product was obtained only when pyridine-2-carbaldehyde, thiazole-2-carbaldehyde, and thiazole-5-carbaldehyde were used as reagents, giving 27, 38, and 17% yield, respectively. Occasionally, in research devoted to the study of the conversion of 2-furylmethanols into cyclopentenones,[3] the treatment of 1,3-thiazol-2-yl(2-furyl)methanol (**1a**) with sulfuric acid in a dimethoxyethane–water mixture gave the corresponding ketone **2a**, but this reaction was not studied and was considered only an undesired side reaction.[4]

In this paper we report that the ketone can be obtained in good yield from the corresponding aryl(thiazol-2-yl)methanols when these substrates were treated with sulfuric acid in hydrolytic conditions. We decided to study this reaction considering the unusual situation of an oxidation reaction apparently in the absence of any oxidant.

Results and discussion

In order to study this reaction we have prepared some thiazolyl aryl and heteroaryl methanols. These compounds were treated with sulfuric acid in a dimethoxyethane–water mixture at 80 °C for 24 h. The results are reported in Scheme 1 and Table 1 (Procedure A).



1 **2**

a: R = 2-furyl
b: R = phenyl
c: R = 4-methoxyphenyl
d: R = 5-methyl-2-furyl
e: R = 5-bromo-2-furyl
f: R = 2-thienyl

Scheme 1

From these results we can obtain useful information about the reaction: 1, the reaction occurs with all the substrates used; 2, the reactivity does not depend on the substituents on the aryl groups.

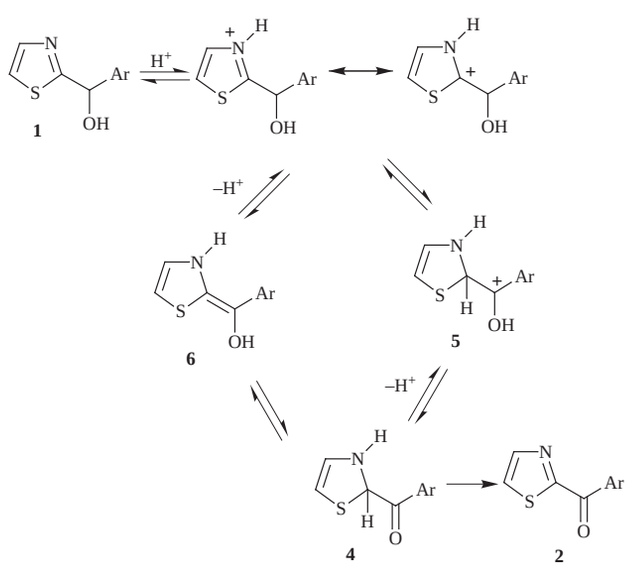
The formation of the intermediate **4** explains the observed reactivity as described in Scheme 2. It is known that 2-thiazoline derivatives can be used as reducing agents of α,β-unsaturated carbonyl compounds.[5] The need for the presence of an aryl group is due to the necessity of stabilizing the intermediate **5**.

Anyway, the mechanistic hypothesis reported in Scheme 2 needs an oxidation step. We propose that oxygen is the oxidant involved in this reaction. In order to prove this hypothesis we carried out our reaction in the presence of oxygen (Table 1,

Table 1 Oxidation of thiazol-2-ylmethanols

Substrate	R	Product	Procedure[a]	Yields (%)[b]
1a	2-Furyl	**2a**	A	50
			B	70
1b	Phenyl	**2b**	A	48
			B	72
1c	4-Methoxyphenyl	**2c**	A	49
			B	65
1d	5-Methyl-2-furyl	**2d**	A	52
			B	68
1e	5-Bromo-2-furyl	**2e**	A	45
			B	69
1f	2-Thienyl	**2f**	A	53
			B	71

[a] A = without bubbling oxygen; B = with bubbling oxygen. [b] All the yields refer to isolated chromatographically pure products.



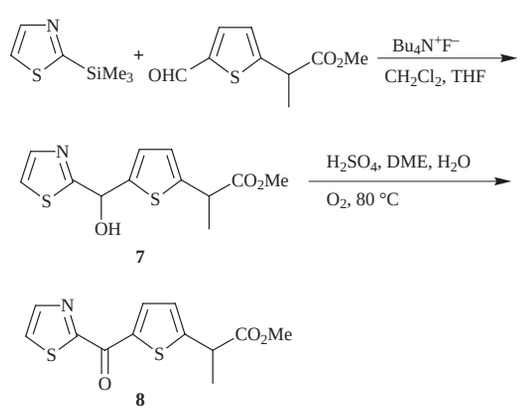
1 **6** **5** **4** **2**

Scheme 2

Procedure B). The reactions were carried out as described previously with bubbling oxygen in the solution. The results show that higher yields can be obtained, thus confirming our hypothesis. Furthermore, we carried out the reaction under argon and in this case we found that the reaction was very slow (after 64 h only 10% of the substrate **1a** was converted into the corresponding ketone).

It is noteworthy that aerial oxidation of 4-pyridyl(thiazol-2-yl)methanols has been described previously but only in basic conditions (usually sodium or potassium alcoholate).[6,7]

The reaction above described is very useful as a mild procedure for the synthesis of thiazolyl derivatives of some non-steroidal anti-inflammatory drugs, such as tolmetin, ketoprofen, and suprofen. The synthesis of the thiazolyl analogue of ketoprofen has been reported.[8] For this reason, we tested this reaction on the methanol **7**. Compound **7** can be obtained by coupling 2-trimethylsilyl-1,3-thiazole and methyl 2-(5-formyl-2-thienyl)propanoate. The latter compound can be prepared *via* a Vilsmeier–Haack reaction from methyl 2-(2-thienyl)propanoate.[9,10] The methanol **7**, thus obtained, was treated as described above giving, with a yield of 65%, the corresponding ketone **8**, a thiazolyl analogue of suprofen, which has not been reported previously (Scheme 3).



Scheme 3

In conclusion we have shown that the oxidation of thiazolyl methanol can be obtained by using a very mild method, utilizing the basic properties of the thiazole ring, and the capability of these substrates to be converted into the corresponding thiazolines. These intermediates can be oxidized by oxygen to give the final product. Finally, we have shown that this reaction can be used in the synthesis of biologically active compounds.

Experimental

Mass spectra were obtained with a Hewlett-Packard 5971 mass selective detector on a Hewlett-Packard 5890 gas chromatograph. Gas-chromatographic analyses were obtained by using an OV-1 capillary column between 70–250 °C (20 °C min^{-1}). ^1H NMR spectra were recorded with a Bruker 300 AM instrument. Elemental analyses were obtained with a Carlo Erba elemental analyser 1106. IR spectra were obtained on a Perkin-Elmer 457 spectrometer.

1,3-Thiazol-2-yl(aryl)methanol—general procedure

1,3-Thiazol-2-yl(2-furyl)methanol (1a). To furan-2-carbaldehyde (1.83 g, 19.1 mmoles) in anhydrous CH_2Cl_2 (40 ml) 2-trimethylsilyl-1,3-thiazole (3 g, 19.1 mmoles) was added at room temperature dropwise. After 4 h the mixture was diluted with THF (200 ml) and treated with tetrabutylammonium fluoride (2.14 g, 6.78 mmoles). After 1 h the solvent was partially evaporated under vacuum. The residue was treated with $NaHCO_3$ and extracted with EtOAc. The organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was chromatographed on silica gel eluting with Et_2O–*n*–hexane 2:1. 1,3-Thiazol-2-yl(2-furyl)methanol (2.8 g, 82%) was obtained. δ_H 7.75 (d, 1 H, *J* 3.1), 7.40 (m, 1 H), 7.35 (d, 1 H, *J* 3.5), 6.37 (d, 2 H, *J* 1.4), 6.12 (s, 1 H) and 4.55 (s, 1 H); ν_{max}/cm^{-1}: 3580, 3350, 2980, 1510, 1149, 1010, 890; *m*/*z* 181 (Found: C, 54.9; H, 5.5; N, 7.2. $C_9H_{11}NO_2S$ requires C, 54.80; H, 5.62; N, 7.10%).

Compounds **1b**–**1f** were synthesised according to the general procedure outlined above using the appropriate carbaldehyde.

1,3-Thiazol-2-yl(phenyl)methanol (1b). δ_H 7.70 (d, 1 H, *J* 3.5), 7.52 (m, 2 H), 7.38 (m, 3 H), 7.27 (d, 1 H, *J* 3.5), 6.09 (s, 1 H) and 4.45 (s, 1 H); *m*/*z* 193 (3%), 192 (10), 191 (80), 190 (23), 173 (8), 162 (38), 161 (47), 114 (20), 113 (10), 112 (10), 107 (19), 105 (63), 86 (57), 85 (23), 79 (52), 78 (18), 77 (100), 58 (12), 51 (30) (Found: C, 63.6; H, 6.3; N, 6.7. $C_{11}H_{13}NOS$ requires C, 63.74; H, 6.32; N, 6.76%).

1,3-Thiazol-2-yl(4-methoxyphenyl)methanol (1c). δ_H 7.59 (d, 1 H, *J* 3.5), 7.33 (m, 2 H), 7.20 (d, 1 H, *J* 3.5), 6.83 (m, 2 H), 5.96 (s, 1 H), 4.82 (s, 1 H) and 3.77 (s, 3 H); *m*/*z* 223 (5%), 222 (10), 221 (100), 220 (10), 192 (42), 177 (10), 173 (10), 160 (10), 137 (64), 136 (10), 135 (48), 121 (23), 114 (13), 113 (25), 112 (18), 109 (45), 108 (13), 94 (48), 92 (20), 86 (60), 85 (45), 78 (11), 77 (60), 66 (20), 65 (10), 64 (14), 63 (16), 59 (18), 58 (23) (Found: C, 60.8; H, 6.5; N, 5.9. $C_{12}H_{15}NO_2S$ requires C, 60.73; H, 6.37; N, 5.90%).

1,3-Thiazol-2-yl(5-methyl-2-furyl)methanol (1d). δ_H 7.67 (d, 1 H, *J* 3.5), 7.39 (d, 1 H, *J* 5), 6.13 (d, 1 H, *J* 3), 5.97 (s, 1 H), 5.8 5 (d, 1 H, *J* 3), 3.5 (s, 1 H) and 2.21 (s, 3 H); *m*/*z* 197 (5%), 196 (8), 195 (62), 178 (30), 166 (18), 152 (100), 150 (16), 136 (30), 124 (36), 123 (10), 114 (8), 113 (10), 112 (26), 111 (70), 109 (16), 95 (10), 86 (24), 85 (14), 83 (10), 82 (26), 65 (10), 59 (22), 58 (28), 57 (14), 55 (29), 53 (24), 52 (11), 51 (18), 50 (10), 43 (14) (Found: C, 57.0; H, 6.1; N, 6.5. $C_{10}H_{13}NO_2S$ requires C, 56.85; H, 6.20; N, 6.63%).

1,3-Thiazol-2-yl(5-bromo-2-furyl)methanol (1e). δ_H 7.67 (d, 1 H, *J* 3.5), 7.32 (d, 1 H, *J* 3.5), 6.20 (d, 1 H, *J* 3), 6.15 (d, 1 H, *J* 3), 6.02 (s, 1 H) and 5. 00 (s, 1 H); *m*/*z* 259 (36%), 257 (36), 231 (22), 229 (22), 203 (36), 201 (36), 175 (97), 173 (100), 150 (15), 122 (22), 119 (25), 117 (26), 112 (15), 84 (10), 62 (17), 58 (20), 57 (24), 38 (48), 37 (16) (Found: C, 39.0; H, 3.7; N, 5.2. $C_9H_{10}BrNO_2S$ requires C, 39.15; H, 3.65; N, 5.07%).

1,3-Thiazol-2-yl(2-thienyl)methanol (1f). δ_H 7.70 (d, 1 H, *J* 3.5), 7.30 (d, 1 H, *J* 3.5), 7.05 (m, 1 H), 6.75 (m, 2 H), 6.02 (s, 1 H) and 4.55 (s, 1 H); *m*/*z* 197 (40%), 180 (13), 168 (40), 136 (15), 113 (63), 112 (17), 111 (20), 97 (12), 86 (38), 85 (100), 59 (16), 58 (22), 57 (12), 39 (10) (Found: C, 50.8; H, 5.1; N, 6.5. $C_9H_{11}NOS_2$ requires C, 50.68; H, 5.20; N, 6.57%).

Oxidation of 1,3-thiazol-2-yl(aryl)methanols—general procedure

1,3-Thiazol-2-yl(2-furyl)methanol (**1a**, 500 mg) was dissolved in 2:1 DME–H_2O mixture (53 ml). Sulfuric acid (0.7 ml) was added and the mixture was stirred at 80 °C for 24 h. The mixture was poured into water and extracted with diethyl ether. The organic extracts were washed with brine and dried over anhydrous sodium sulfate. The evaporation of the solvent yielded a crude product that was chromatographed on silica gel eluting with a 2:1 diethyl ether–*n*–hexane mixture.

1,3-Thiazol-2-yl 2-furyl ketone (2a). δ_H 6.66 (m, 1 H, furyl H), 7.71 (d, 1 H, *J* 3.2, thiazolyl H), 7.80 (m, 1 H, furyl H), 8.10 (d, 1 H, *J* 3.2, thiazolyl H), and 8.21 (d, 1 H, *J* 5 H, furyl H); ν_{max}/cm^{-1} 2890, 1640, 1460, 1400, 1100, 1020; *m*/*z* 179 (Found:

C, 53.7; H, 2.7; N, 7.9; S, 18.0. $C_8H_5NO_2S$ requires C, 53.62; H, 2.81; N, 7.82; S, 17.89%).

Compounds **2b**–**2f**, **7** and **8** were synthesised according to the general procedure outlined above using the appropriate substituted methanol.

1,3-Thiazol-2-yl phenyl ketone (2b). δ_H 7.00 (m, 3 H, aromatic H), 7.67 (d, 1 H, *J* 3, thiazolyl H), 8.10 (d, 1 H, *J* 3, thiazolyl H) and 8.50 (m, 2 H, aromatic H); *m*/*z* 189 (Found: C, 63.6; H, 3.8; N, 7.3; S, 17.0. $C_{10}H_7NOS$ requires C, 63.47; H, 3.73; N, 7.40; S, 16.94%).

1,3-Thiazol-2-yl 4-methoxyphenyl ketone (2c). δ_H 3.92 (s, 3 H, OCH_3), 7.00 (m, 2 H, aromatic H), 7.70 (d, 1 H, *J* 3, thiazolyl H), 8.08 (d, 1 H, *J* 3, thiazolyl H) and 8.54 (m, 2 H, aromatic H); *m*/*z* 219 (30%), 191 (12), 190 (10), 136 (10), 135 (100), 107 (11), 92 (24), 77 (27) (Found: C, 60.4; H, 4.0; N, 6.4; S, 14.7. $C_{11}H_9NO_2S$ requires C, 60.26; H, 4.14; N, 6.39; S, 14.62%).

1,3-Thiazol-2-yl (5-methyl-2-furyl) ketone (2d). δ_H 2.50 (s, 3 H, CH_3), 6.29 (d, 1 H, *J* 3.5, furyl H), 7.68 (d, 1 H, *J* 3, thiazolyl H), 8.04 (d, 1 H, *J* 3, thiazolyl H) and 8.17 (d, 1 H, *J* 3.5, furyl H); *m*/*z* 193 (50%), 165 (40), 164 (10), 136 (22), 109 (100), 53 (45) (Found: C, 56.1; H, 3.7; N, 7.1; S, 15.5. $C_9H_7NO_2S$ requires C, 55.95; H, 3.65; N, 7.25; S, 16.59%).

1,3-Thiazol-2-yl (5-bromo-2-furyl) ketone (2e). δ_H 6.60 (d, 1 H, *J* 3.6, furyl H), 7.73 (d, 1 H, *J* 3, thiazolyl H), 8.06 (d, 1 H, *J* 3, thiazolyl H) and 8.16 (d, 1 H, *J* 3.6, furyl H); *m*/*z* 257 (34%), 255 (33) (Found: C, 37.2; H, 1.7; N, 5.5; S, 12.3. $C_8H_4BrNO_2S$ requires C, 37.23; H, 1.56; N, 5.43; S, 12.42%).

1,3-Thiazol-2-yl 2-thienyl ketone (2f). δ_H 7.23 (dd, 1 H, J_1 4.6, J_2 4, thienyl H), 7.72 (d, 1 H, *J* 3, thiazolyl H), 7.80 (dd, 1 H, J_1 4.6, J_2 1.3, thienyl H), 8.09 (d, 1 H, *J* 3, thiazolyl H) and 8.65 (dd, 1 H, J_1 4, J_2 1.3, thienyl H); *m*/*z* 195 (44%), 167 (30), 112 (8), 111 (100), 83 (11), 58 (10), 57 (12), 39 (25) (Found: C, 49.1; H, 2.5; N, 7.3; S, 32.9. $C_8H_5NOS_2$ requires C, 49.21; H, 2.58; N, 7.17; S, 32.84%).

Methyl 2-{5-[hydroxy(1,3-thiazol-2-yl)methyl]-2-thienyl} propionate (7). δ_H 7.72 (d, 1 H, *J* 3.5), 7.31 (d, 1 H, *J* 3.5), 6.72 (m, 2 H), 6.02 (s, 1 H), 4.55 (s, 1 H), 4.02 (q, 1 H, *J* 7), 3.67 (s, 3 H) and 1.55 (d, 3 H, *J* 7); *m*/*z* 283 (M^+) (Found: C, 51.0; H, 4.1; N, 5.0; S, 22.7. $C_{12}H_{13}NO_3S_2$ requires C, 50.87; H, 4.26; N, 4.94; S, 22.63%).

Methyl 2-{5-[(1,3-thiazol-2-yl)oxomethyl]} propionate (8). δ_H 1.56 (d, 3 H, *J* 7.2, CH-CH_3), 3.69 (s, 3 H, OCH_3), 4.00 (q, 1 H, *J* 7.2, C*H*-CH_3), 7.20 (d, 1 H, *J* 4 , thienyl H), 7.73 (d, 1 H, *J* 3, thiazolyl H), 7.80 (d, 1 H, *J* 4, thienyl H) and 8.10 (d, 1 H, *J* 3, thiazolyl H) (Found: C, 51.1; H, 4.1; N, 5.0; S, 22.9. $C_{12}H_{11}NO_3S_2$ requires C, 51.23; H, 3.94; N, 4.98; S, 22.79%).

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