Spontaneous oxidation of bis(heteroaryl)methanes and bis(heteroaryl)carbinols to ketones

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Dedicated to Prof. Paolo Edgardo Todesco, on his 70th birthday
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Abstract
Oxidation reactions of bis(heteroaryl)methanes to the corresponding ketones were investigated in the absence of usual oxidation reagents and catalysts. There are strong indications that the reaction pathway involves radical species. The spontaneous oxidation of bis(heteroaryl)carbinols was also investigated by kinetic measures. Strong base catalysis, together with relevant hydrogen/deuteron isotopic effect, were observed. Both reaction pathways, from methane derivatives and from carbinols derivatives, involve the presence of a tautomeric equilibrium of the considered heterocycles.

Keywords: Oxidation, kinetics, tautomerism heterocycles

Introduction

The oxidation reaction of hydrocarbons by molecular oxygen is usually carried out by metal catalysis.1,2 Aerobic auto-oxidation of hydrocarbons was reported to be enhanced by the presence of non-ionic and cationic surfactants.3 Some hydrocarbons are oxidised in the presence of N-hydroxyphthalimide and metals or quaternary ammonium bromide.4 Potassium superoxide was reported to initiate autoxidations of some arylmethanes.5

Spontaneous oxidation of aryl methanes or of the corresponding carbinols, by atmospheric oxygen, in the absence of common oxidising reagents, is an unusual reaction.

Auto-oxidation of weakly acidic carbon atoms is known to occur in the presence of potassium t-butoxide in apolar solvents (benzene) or in poly(ethylene glycols).6 Under these experimental conditions, fluorene and diphenylmethane are oxidised to fluorenone and benzophenone, respectively. On the contrary, the oxidation of bis(heteroarylmethanes or bis(heteroaryl)carbinols such as bis(2-benzothiazolyl)methane7 (1A) or of bis(2-benzothiazolyl)carbinol (2A) to bis(2-benzothiazolyl)ketone (3A) (see Scheme 1) is a
spontaneous reaction\textsuperscript{8} in working up the solutions of 1A and 2A and it may be an undesired side reaction in all studies of 1A and 2A and of related compounds. For example, the studies of the NH/CH tautomerism\textsuperscript{8,9} on 1A (and on the related compounds) are complicated by the formation of carbinols 2 or ketones 3.

\[
\begin{array}{c}
\text{Ar}_2\text{CXH} \\
X = \text{H, 1; } \ X = \text{OH, 2} \\
\rightarrow \\
\text{Ar}_2\text{CO} \\
\end{array}
\]

\(\text{Ar} = \text{2-benzothiazolyl A 2-thiazolyl B 2-benzoazolyl C}\)

\(\text{phenyl D Ar} = \text{2-}(N\text{-methyl)-benzoimidazolyl E 2-pyridyl F}\)

Scheme 1

Previously,\textsuperscript{10} we reported the oxidation of 1A to 2,2-tetrakis(2-benzothiazolyl)ethane (4) by using a general oxidising reagent. Solutions of 4 are unstable and spontaneously give 5, as illustrated in Scheme 2

\[
\begin{array}{c}
\text{1A} \xrightarrow{\text{Ox}} (\text{BTZ})_2\text{CH} - \text{CH(BTZ)}_2 \\
\rightarrow \\
(\text{BTZ})_2\text{C} = \text{C(BTZ)}_2 \\
\end{array}
\]

BTZ = 2-benzothiazolyl

Scheme 2

Results

Oxidation of bis(heteroaryl)methanes (1) to bis(heteroaryl)ketones (3)
Firstly, we investigated the reaction of compound 1A (and of some other bis-heteroaryl methanes) by changing some experimental conditions. The main results are summarised in Table 1.
In DMSO, the oxidation of 1A to ketone 3A occurs in the presence of the oxygen. Under our experimental conditions, bases such as tertiary amines catalyse the oxidation reaction of Scheme 1: the presence of base is important as well as the presence of an oxidising species, which may be the dimethylsulfoxide. The presence of water smoothly enhances the reactivity. The reactions carried out in the presence of an acid catalyst (CH$_3$SO$_3$H) produces 3A in very low yields (less than 10%) in 3 days, while addition of an excess of H$_2$O$_2$ (see experimental section) quickly afforded 3A.

Under the same experimental condition of reaction of 1A, diphenyl methane (1D) is not converted into ketone 3D, bis(2-benzoxazolyl)methane (1C) instead, is converted into the correspondent ketone 3C by a rate considerably slower than that of 1A. Compounds 1C and 1F are reported to produce corresponding ketones 3C and 3F by oxidation with Cr$_2$O$_6$. Addition of water to the reaction mixture produces moderate increase of the reactivity.

**Table 1.** Oxidation reactions of bis(2-benzothiazolyl)methane (1A), (unless otherwise indicated) [0.1 mmol in 2 mL of solvent] to bis(2-benzothiazolyl) ketone (3A)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base$^a$</th>
<th>Reaction time$^b$ (h)</th>
<th>Yield$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMSO or CH$_3$CN</td>
<td>Et$_3$N</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>DMSO or CH$_3$CN</td>
<td>DABCO$^d$</td>
<td>8</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>CH$_3$OH/H$_2$O</td>
<td>KOH</td>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>----</td>
<td>36</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>DMSO or CH$_3$CN</td>
<td>---- (N$_2$)</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>DMSO</td>
<td>Et$_3$N (TEMPO$^e$)</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>DMSO</td>
<td>Et$_3$N (in the dark)</td>
<td>12</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>DMSO</td>
<td>Et$_3$N (H$_2$O)</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>Et$_3$N</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>THF</td>
<td>Et$_3$N (N$_2$)</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>THF</td>
<td>TEMPO$^e$</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>12$^f$</td>
<td>DMSO</td>
<td>Et$_3$N</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>13$^g$</td>
<td>DMSO</td>
<td>Et$_3$N</td>
<td>36</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ [base]= 0.05 mmol, initially added. Under aerobic conditions, unless otherwise indicated. $^b$ For reactions reaching almost quantitative conversion (entries 1, 2, 7, 9) the time is that for the disappearance of starting compound 1A, checked by TLC on silica gel, eluent dichloromethane. $^c$ Yields % of bis(2-heteroaryl) ketone, by weight; remaining percent includes mainly starting material 1A (or 1C). $^d$ DABCO: 1,4-diazabicyclo[2.2.2]octane $^e$ TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical. $^f$ bis(2-benzooxazolyl)methane (2C). $^g$ Bis(2-pyridyl)methane (1F).
As previously described,¹⁰ the oxidation reaction of 1A with the usual oxidizing reagents (KMnO₄/H₂SO₄, or Cr₂O₆/H₂SO₄) produces complicated reaction mixtures from which the coupling products 4 and 5 were isolated.

Reaction between 1A and N-bromosuccinimide (in equimolar amount), produces compound 5 in low yields, together with 50% of bromo bis(2-benzothiazolyl)methane (6).

In the presence of an excess of N-bromosuccinimide, the dibromo derivative 7 is the major product (see experimental).

No formation of 3A was observed for reactions of 1A carried out in the absence of air or in the presence of radical inhibitors, such as 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO) or thiophenol.

These facts, probably, indicate that the reaction follows a multi-step pathway with an important step involving formation of a radical species. Kinetic runs, carried out by following the appearance of 3A from 1A, were poorly reproducible and showed a curvilinear plot of log[3A] against time. We tried to obtain EPR evidence for the presence of a radical species. The only signals recorded were those related to the radical species arising from the interaction between the amine (Et₃N) and small amounts of the ketone 3A, as tested by independent spectrum of 3A and the amine.

A possible intermediate of the reaction from 1A to 3A may be the carbinol 2A. The formation of 2A as an intermediate, is justified by the fact that the oxidation reaction (under the same experimental conditions of 1A) of bis(2-benzothiazolyl)ethane (8) produces the carbinol 9 (see Scheme 3).

![Scheme 3](image)

We were not able to obtain evidence for the presence of 2A in the reaction mixtures of 1A, (by TLC analysis and by performing runs directly in the probe of the NMR spectrometer).

**Oxidation of bis(heteroaryl)carbinols (2) to bis(heteroaryl)ketones (3)**

Different procedures were tried to obtain pure carbinols 2A-C, because ketones 3 were often present in the reaction mixtures. The best way to obtain these compounds involves the reduction of the ketones 3A-C by sodium borohydride, as reported in the experimental section.

The spontaneous oxidation of 2A to ketone 3A, in DMSO, THF, CCl₄, is faster than that of 1A, and the ketone 3A is obtained in almost quantitative yield. In fact, in the reported solvents, 2A is unstable under ambient conditions, and must be stored as a solid at -25°C. The low
stability of carbinols 2 (they convert into ketones 3) necessitates their quick work up. The presence of DMSO is not essential for ketone formation from the carbinol. The key results are presented in Table 2. The behaviour in CCl₄ parallels that in THF. In this case too, addition of water (0.2 mmol, under the experimental conditions of entries 1 and 4 of Table 2) produces a small decrease in the reaction times.

In the reaction mixture of 2A we did not observe the presence of 1A. Compound 1A may be the second product (and it is oxidised to 3A at a lower rate than that of 2A) if a ‘dismutation-like’ process takes place. The oxidation reaction of carbinols 2A, 2B and 2C show a regular kinetic feature. These reactions are catalysed by bases (DABCO and Et₃N). At [DABCO]₀ = 4.9 x 10⁻² mol dm⁻³, in THF, the kₚᵣₑₛ value is not affected by the [2A]₀ values ([2]₀ means the initial concentration values of 2) in the range 3 x 10⁻⁵ to 4 x 10⁻⁴ mol dm⁻³ (kₚᵣₑₛ = 6.5±0.2) x 10⁻³ s⁻¹, error is standard deviation).

Table 2. Oxidation reaction of bis(2-benzothiazolyl)carbinol (2A) [0.1 mmol in 2 mL of solvent] to bis(2-benzothiazolyl)ketone (3A)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base a</th>
<th>Reaction time b (h)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMSO</td>
<td>---</td>
<td>0.5</td>
<td>100⁰</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>---</td>
<td>0.5</td>
<td>98⁰</td>
</tr>
<tr>
<td>3</td>
<td>DMSO</td>
<td>Et₃N</td>
<td>≤0.5</td>
<td>100⁰</td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>DABCO d</td>
<td>≤0.5</td>
<td>98⁰</td>
</tr>
<tr>
<td>5</td>
<td>DMSO</td>
<td>Et₃N (in the dark)</td>
<td>≤0.5</td>
<td>95⁰</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>---</td>
<td>5</td>
<td>96 (98)⁰</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>Et₃N</td>
<td>0.5</td>
<td>100 (100)⁰</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>---(N₂)</td>
<td>5</td>
<td>97 (96)⁰</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>---(N₂, in the dark)</td>
<td>5</td>
<td>96⁰</td>
</tr>
<tr>
<td>10</td>
<td>THF</td>
<td>Et₃N (TEMPO f)</td>
<td>0.5</td>
<td>98⁰</td>
</tr>
<tr>
<td>11</td>
<td>DMSO g</td>
<td>---</td>
<td>33 h</td>
<td>4⁰</td>
</tr>
<tr>
<td>12</td>
<td>DMSO g</td>
<td>DABCO (air)</td>
<td>33 h</td>
<td>37 i</td>
</tr>
</tbody>
</table>

a [base]= 0.1 mmol initially added, under aerobic conditions, unless otherwise indicated. b Time (hours) for disappearance of bis(2-benzothiazolyl)carbinol (2A) checked by TLC on silica gel, eluent dichloromethane/methanol: 98/2. c Yields % of bis(2-benzothiazolyl)ketone, by weight. d DABCO: 1,4-diazabicyclo[2.2.2]octane. e By spectrophotometric analysis. f TEMPO: 2,2,6,6-tetramethyl-1piperidinyloxy radical. The same results are obtained by adding 1,1-diphenylethene or thiophenol. g bis(N-methyl-2-benzoimidazolyl)carbinol (2E). h Days i The remaining percent mainly includes starting carbinol (2E), checked by ¹H NMR analysis.
The oxidation of 2A to 3A follows a first order law in the carbinol until high percent of conversion (80%) after which the reaction rate is decreased. The kinetic data obtained by initial (50%) conversion are reported in Table 3.

Table 3. Effect of the added bases on the rate of the reaction of bis(2-heteroaryl)carbinols to ketones, at 25°C

<table>
<thead>
<tr>
<th>Bis(2-benzothiazolyl)methanol (2A)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent THF</td>
<td></td>
</tr>
<tr>
<td>[DABCO] (mol dm$^{-3}$) x 10$^2$</td>
<td>0.164</td>
</tr>
<tr>
<td>$k_{obs}$ (s$^{-1}$) x 10$^3$</td>
<td>2.58</td>
</tr>
<tr>
<td>Solvent DMSO</td>
<td></td>
</tr>
<tr>
<td>[DABCO] (mol dm$^{-3}$) x 10$^2$</td>
<td>----</td>
</tr>
<tr>
<td>$k_{obs}$ (s$^{-1}$) x 10$^3$</td>
<td>0.046</td>
</tr>
<tr>
<td>Solvent THF</td>
<td></td>
</tr>
<tr>
<td>[Et$_3$N] (mol dm$^{-3}$) x 10</td>
<td>0.310</td>
</tr>
<tr>
<td>$k_{obs}$ (s$^{-1}$) x 10$^2$</td>
<td>0.470</td>
</tr>
<tr>
<td>Solvent THF$^a$</td>
<td></td>
</tr>
<tr>
<td>[DABCO] (mol dm$^{-3}$) x 10$^2$</td>
<td>0.193</td>
</tr>
<tr>
<td>$k_{obs}$ (s$^{-1}$) x 10$^3$</td>
<td>1.00</td>
</tr>
</tbody>
</table>

| Bis(2-thiazolyl)methanol (2B) |  |
| Solvent THF |  |
| [DABCO] (mol dm$^{-3}$) x 10$^2$ | 0.359 | 1.15 | 1.16 | 1.33 | 2.09 | 2.83 |
| $k_{obs}$ (s$^{-1}$) x 10$^6$ | 3.64 | 4.91 | 5.20 | 5.43 | 7.33 | 8.17 |
| Solvent DMSO |  |
| [DABCO] (mol dm$^{-3}$) x 10$^2$ | 0.286 | 0.74 | 1.09 | 1.71 | 2.06 |
| $k_{obs}$ (s$^{-1}$) x 10$^5$ | 0.654 | 1.07 | 1.27 | 1.65 | 1.81 |

| Bis(2-benzoazolyl)methanol (2C) |  |
| Solvent THF |  |
| [DABCO] (mol dm$^{-3}$) x 10$^2$ | 0.730 | 1.47 | 3.36 | 5.07 | 5.40 | 10.2 |
| $k_{obs}$ (s$^{-1}$) x 10$^5$ | 0.805 | 0.805 | 3.90 | 4.80 | 5.66 | 12.2 |

$^a$ 1-Deutero bis(2-benzothiazolyl)carbinol (10).
The decreased rate probably results from the interactions between the ketone formed during the reaction, and the starting alcohol by an equilibrium that produces an hemi-ketal, this depresses the presence of free alcohol as the ketone concentration becomes high.

Kinetic data are reported in Table 3. \( k_{\text{obs}} \) Values (in s\(^{-1}\)) linearly increase with increasing the value of [base].

Table 4 summarises data dissection using equation (1)

\[
k_{\text{obs}} = k_0 + k_B \times [\text{base}]_0
\]

where \( k_0 \) (s\(^{-1}\)) is the oxidation rate in the absence of base and \( k_B \) is the rate of the catalysed process in s\(^{-1}\) mol\(^{-1}\) dm\(^3\).

In some cases, intercept values (\( k_0 \)) show strong uncertainty, and, practically, tend to zero. The same Table 4 reports data concerning the oxidation rate of the deutero carbinol 10. In some cases, the intersection of the straight line of equation 1 agrees well with \( k_{\text{obs}} \) values independently obtained in the absence of base. The importance of base catalysis with respect to the uncatalysed oxidation is expressed by the \( k_B/k_0 \) ratios reported in Table 4.

**Table 4.** Rates of transformation of bis(heteroaryl)carbinols to ketones for spontaneous process \( (k_0, \text{ s}^{-1}) \) and base catalysed process \( k_B \) (s\(^{-1}\) mol\(^{-1}\) dm\(^3\)), at 25°C

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Solvent</th>
<th>Base(^a)</th>
<th>( k_0 )(^b)</th>
<th>( k_B )(^b)</th>
<th>( k_B/k_0 )</th>
<th>n(^c)</th>
<th>R(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2A</td>
<td>THF</td>
<td>DABCO</td>
<td>(2.2±0.3) x 10(^{-3})</td>
<td>0.54±0.03</td>
<td>245</td>
<td>7</td>
<td>0.994</td>
</tr>
<tr>
<td>2A</td>
<td>DMSO</td>
<td>DABCO</td>
<td>(1.2±1) x 10(^{-3})</td>
<td>2.2±0.1</td>
<td>1800</td>
<td>6</td>
<td>0.996</td>
</tr>
<tr>
<td>2A</td>
<td>THF</td>
<td>Et(_3)N</td>
<td>(3.4±0.4) x 10(^{-3})</td>
<td>(5.2±0.3) x 10(^{-2})</td>
<td>15</td>
<td>7</td>
<td>0.991</td>
</tr>
<tr>
<td>2A(^e)</td>
<td>THF</td>
<td>DABCO</td>
<td>(7.0±0.01) x 10(^{-4})</td>
<td>0.26±0.01</td>
<td>370</td>
<td>5</td>
<td>0.998</td>
</tr>
<tr>
<td>2B</td>
<td>THF</td>
<td>DABCO</td>
<td>(2.9±0.2) x 10(^{-6})</td>
<td>(1.9±0.1) x 10(^{-4})</td>
<td>95</td>
<td>6</td>
<td>0.990</td>
</tr>
<tr>
<td>2B</td>
<td>DMSO</td>
<td>DABCO</td>
<td>(5.4±0.6) x 10(^{-6})</td>
<td>(6.4±0.4) x 10(^{-4})</td>
<td>119</td>
<td>5</td>
<td>0.993</td>
</tr>
<tr>
<td>2C</td>
<td>THF</td>
<td>DABCO</td>
<td>(-6.4±4) x 10(^{-6})</td>
<td>(1.2±0.08) x 10(^{-3})</td>
<td>---</td>
<td>6</td>
<td>0.990</td>
</tr>
</tbody>
</table>

\(^a\) DABCO: 1,4-diazabicyclo[2.2.2]octane. \(^b\) Errors are standard deviations. \(^c\) Number of points. \(^d\) Correlation coefficient. \(^e\) 1-Deutero bis(2-benzothiazolyl)carbinol (10).

**Discussion**

**Oxidation of bis(heteroaryl)methanes (1) to bis(heteroaryl)ketones (3)**

The oxidation reaction from CH\(_2\) to CO group most likely occurs in several steps, involving carbinol species 2, but we were not able to obtain evidence for the presence of carbinols 2 in the reaction mixtures from 1A to 3A(including reactions performed directly in the NMR probe). The failure to detect the presence of carbinol 2A is a consequence of the fact that the ketone is
obtained by a reaction about $10^3$ times faster from 2A than the reaction from 1A and therefore 2A does not accumulate under the experimental conditions.

The oxidation of methane derivatives 1 requires the presence of atmospheric oxygen in the solvents (DMSO, THF, CCl₄) used. The presence of a radical scavenger did not allow the formation of ketones (entries 6, 11 of Table 1). Clearly, there is an important step involving the formation of a radical species along the oxidation reaction pathway.

We did not observe any difference between the reaction carried out in the dark and those without protection from light. In the literature¹ there are attempts to explain similar oxidation reactions of the C-H group of substituted methane derivatives to corresponding oxygenated derivatives.

Oxidation of triaryl-methanes (and of 1,1-diphenyl-ethane) in DMSO/t-butyl alcohol mixtures was studied in the presence of potassium t-butoxide.¹³ This reaction produces mainly carbinols by a radical mechanism (via peroxide derivatives) on the carbanion related to the starting methane (or ethane) derivatives.

A reasonable pathway for these reactions may be a photo-oxidation mechanism, but our evidence does not support this hypothesis.

Another possible reaction pathway involves the anionic species of 1, such as compound 11 in Scheme 4. 11 may be important in explaining the oxidation reaction in the presence of metals.

![Scheme 4](image)

Present data are hardly explained by considering the equilibrium of Scheme 4 to be important in the oxidation pathway, because the heterocyclic derivatives 1C and 1F show a reactivity significantly lower than that of 1A, but the electron-withdrawing powers of the heterocyclic moiety are very similar, as shown by heterocyclic σ values of the Hammett-like treatment (benzothiazole-2-yl $\sigma^- = 0.65$,¹⁴ benzoxazole-2-yl $\sigma^- = 0.68$,¹⁴ thiazole-2-yl, $\sigma^- = 0.63$,¹⁵ pyridine-2-yl $\sigma^- = 1.0$¹⁴).

The addition of water to the tautomeric form of 1A, may be an alternative for the formation of the carbinol (to the addition of oxygen), probably involving radical species.
Scheme 5

The inverse addition of water to the double bond should result in a ring opening reaction or return back to 1A.

The last step is an oxidative dehydrogenation: the aromatisation of 12 to 3A should be a simple elimination of hydrogen. All attempts to have evidence of formation of H₂ failed. Even if the data in Table 1 are qualitative, reaction pathway depicted in Scheme 5 (related to the benzothiazole derivative) is a reasonable picture to explain all the reported data. In particular the base is a catalyst to shift the tautomeric equilibrium¹⁶ depicted in Scheme 5. The first, produces the tautomer of 1A which is the species that reacts with water; the second produces the enol preceding the ketone 12.

The last step of Scheme 5 is an oxidative dehydrogenation: 2-benzothiazoline¹⁷ and 2-thiazoline¹⁸ are indicated to be reducing agents in mildly experimental conditions.

Under the same experimental conditions reported here, the diphenylmethane is completely unreactive. This reaction pathway agrees with the fact that when the 1,1-bis(2-benzothiazolyl)ethane (8) is prepared, the corresponding carbinol was recovered from the reaction mixtures.

Scheme 6
The pathway reported in Scheme 5, as well as that of Scheme 6, is an alternative mechanism to the usual mechanism involving anionic/radical specie.\textsuperscript{19}

Photo-oxygenation of methanes bonding isoquinoline derivatives (similar to that reported here) are indicated to start from the NH tautomer of the heterocyclic moiety.\textsuperscript{20}

**Oxidation of bis(heteroaryl)carbinols (2) to bis(heteroaryl)ketones (3)**

Our evidence supports the idea that the oxidation of carbinols 2 to ketones 3 occurs without intervention of some radical species in the rate limiting step. The presence of a radical scavenger (entry 10 of Table 2) did not affect the yields and the reaction times. Reactions carried out in dark or in sunlight, gave the same results.

With regard to changes in the heterocyclic moiety, the oxidation of 2 parallels the behaviour observed for the oxidation of the CH\textsubscript{2} group of compounds 1. The reactivity order is 2A > 2B > 2C > 2E, 2F > 2D. Also in this case the electron-withdrawing power of the heterocyclic moiety appears to be unimportant. This conclusion arises not only from data presented in Table 2, but also from kinetic data in Table 4.

The rate of both oxidation reactions of compounds 1 and 2 are enhanced by the presence of a base. This fact agrees with a proton departure in a rate limiting step (equilibrium). A possible equilibrium is represented in Scheme 7.

As expected, \( k_0 \) values are scarcely affected by the change in the amine used as catalyst, while \( k_B \) values (slopes of plots of \( k_{obs} \) versus [amine]\textsubscript{o} values) depend on the amine used: the more basic DABCO is 10 times more efficient than Et\textsubscript{3}N.

The \( k_0 \) is poorly affected by the change of the base used \([k_0(\text{THF}) \geq k_0(\text{DMSO})]\), as required by the intramolecular hydrogen shift from carbon to the nitrogen atom. The \( k_B \) depends moderately on the solvent used: for DABCO, \( k_B(\text{DMSO}) / k_B(\text{THF}) = 4 \).

Both catalysed and uncatalysed processes show a relevant isotopic effect: \( k^H_0/k^D_0 = 3.1 \) and \( k^H_B/k^D_B = 2.1 \). Clearly, the C-H bond breaking occurs in a rate limiting step for both processes. Base catalysis and isotopic effect agrees well with a reaction pathway involving the formation of the carbanionic species 13, as depicted in Scheme 7

\[
\begin{align*}
\text{ArC-} & \text{ArOH} \quad \text{BASE} \quad \text{ArC-} & \text{ArOH} + H^+ \\
& \text{13}
\end{align*}
\]

**Scheme 7**

In the case of the equilibrium depicted in Scheme 4, formation of 11 is a reasonable process. On the contrary, equilibrium of Scheme 7 affording the presence of the anionic specie 13, should compete with the equilibrium of formation of anion 14 from the dissociation of the O-H group, reasonably more acid than the C-H group.
As a consequence in the oxidation of carbinols, the pathway involving carbanions like 13, is less likely and base catalysis on the proton departure from the C-H group cannot be considered in the reaction pathway. Probably, the presence of 14 is not relevant, and, in any case it may represent a cul-de-sac. In fact, the relevant importance of a pre-equilibrium affording 14, should remove carbinols 2 from the oxidation reaction, and, consequently, the overall reaction rate should be reduced by the addition of base.

Scheme 8

A possible reaction pathway parallel to that of Scheme 5, is depicted in Scheme 8. In this scheme, tautomerism of 2 is an important step to obtain the ketone 16, via enol form 15. This statement agrees well with the fact that diphenylmethane is not reactive. In addition, six membered heterocyclic derivatives, such as pyridine derivatives, are less prone to afford N-H tautomers compared to five membered heterocycles. Thus, the oxidation of pyridine derivatives is significantly slower than the oxidation of thiazole and benzothiazole derivatives. Regarding five membered ring systems, benzothiazole derivatives are more prone to give ‘non-aromatic’ tautomeric form than the thiazole derivatives: the oxidation of benzothiazole derivatives is faster than that of thiazole derivatives. From 16, ketones 3 are easily obtained by oxidative dehydrogenation.

Conclusions

In conclusion, the oxidation of bis(heteroaryl)methanes occurs by a radical oxidation involving the NH tautomer of 1. The oxidation reactions of carbinols 2 occur via two tautomeric equilibria,
which are favored by the presence of base. In both reactions, the partially saturated compounds 12 and 16 are formed in the final step which, probably, is a fast step.

**Experimental Section**

**General Procedures.** $^1$H and $^{13}$C NMR spectra were recorded on a Varian Gemini spectrometer at 300 and 75.46 MHz, respectively. Chemical shifts are referenced to solvent. $J$ values are given in Hz. Mass spectra were recorded at an ionisation voltage of 70 eV on a VG 7070 E spectrometer. Thin-layer chromatography was performed on Merck Kieselgel 60 F$_{254}$. Melting points were measured with a Büchi apparatus and are uncorrected. THF was distilled from sodium benzophenone ketyl. Air and moisture sensitive solutions and reagents were handled in dried apparatus under an atmosphere of dry nitrogen.

**Uv/vis spectrophotometric data** were recorded with a Perkin Elmer (model Lambda 12) spectrophotometer. Under the reported experimental conditions, uv/vis spectrophotometric analysis (as well as the TLC analysis) did not show evidence for the presence of other oxidation/condensation products other than keto derivatives 3.

**Kinetic measurements** were performed by the usual procedures, by following the appearance of compounds 3, until high percent of conversion, at $\lambda_{\text{max}}$ values here reported: $3A \lambda_{\text{max}} = 343\text{nm} (\varepsilon = 2.05 \times 10^5)$; $3B \lambda_{\text{max}} = 325\text{nm} (\varepsilon = 2.20 \times 10^3)$; $3C \lambda_{\text{max}} = 335\text{nm} (\varepsilon = 1.82 \times 10^5)$

Table 3 reports $k_{\text{obs}}$ values (s$^{-1}$).

**Products**

Compounds 1D, 2D, 1F and 3F are commercially available.

**Preparation of 1,1-bis(heteroaryl)methanes 1.** 1,1-Bis(2-benzothiazolyl)methane (1A). Compound 1A was prepared by adding polyphosphoric acid (63 mL) to a mixture of 2-aminothiophenol (90 mmol) and malononitrile (45 mmol), heated at 150°C with vigorous mechanical stirring and kept at this temperature for 2h. The reaction mixture was poured in an ice/water mixture, neutralised by addition of KOH followed by NaHCO$_3$. The yellow precipitate was filtered, washed with water, dried in a desiccator in vacuo over P$_2$O$_5$, then chromatographed on silica gel column (eluant: CH$_2$Cl$_2$/CH$_3$OH 99/1). Compound 1A was obtained in 80% yield.

M.p.: 95-96 °C (Lit.,$^{22}$ 95-95.5 °C). Chemico-physical data for compound 1A are in agreement with those reported.$^{8a,9}$

1,1-Bis(2-benzooxazolyl)methane (1C). Compound 1C was obtained in 25% yield from 2-aminophenol and malononitrile in a similar procedure to obtain 1A. mp 119-120°C (Lit.,$^{23}$ 116°C). $\delta_{H}(300 \text{ MHz, CDCl}_3)$ 4.67 (2H, s, H-8), 7.33-7.38 (2H, m, H-6), 7.51-7.55 (2H, m, H-5), 7.72-7.74 (2H, m, H-7), 7.74-7.76 (2H, m, H-4); $\delta_{C}(75.56 \text{ MHz, CDCl}_3)$ 29.3, 110.7, 120.2, 124.5, 125.3, 141.1, 151.1, 159.7; MS (EI) $m/z$: 250 (M$^+$), 221, 132.
**1,1-Bis(2-benzothiazolyl)ethane (8).** Compound 8 was prepared by a condensation reaction of 2-aminothiophenol and diethyl methylmalonate in polyphosphoric acid at 250°C following the procedure described for the synthesis of 1A. The reaction mixture contains small amount (about 10%) of starting materials, and compounds 8 and 9 in the relative ratio 2:1 (calculated by $^1$H NMR analysis). Compound 8 was separated from the solution in dichloromethane, by dropwise addition of ethanol. Separated white crystals (mp 170-172 °C, Lit., 9 165 °C) show chemico-physical data in agreement with literature data,9 which states the predominance of tautomeric form 8bis in describing 8. MS (EI) $m/z$: 296 (M$^+$), 281, 297, 162, 148, 135.

Attempts to perform mono alkylation of 1A in THF (by metalation with butyllithium at -70 °C under nitrogen atmosphere followed by quenching with iodomethane) afforded 2,2-bis(2-benzothiazolyl)-2,2-propane$^{8a}$ (15) (mp 128-129 °C, Lit.,$^{8a}$ 132-134 °C) and small amount of carbinol 9 (10% of yield).

![8bis]

**Preparation of ketones 3. Bis(2-benzothiazolyl) ketone (3A).** Oxidation reaction of 1A (1.5g, 5.3 mmol) with H$_2$O$_2$ (49.4 mmol) in CH$_3$COOH (18 mL) afforded, after 24 h. at room temperature, spontaneous precipitation of 3A (yield = 60%) which was filtered, washed with water, dried in a desiccator and purified by chromatographic column (silica gel, eluent CH$_2$Cl$_2$). mp 182-183°C (Lit.,$^{24}$ 183 °C). Chemico-physical data of 3A are in agreement with those reported.$^{11}$ δ$_H$(300 MHz, CDCl$_3$) 7.49-7.57 (2H, m, H-6), 7.59-7.67 (2H, m, H-5), 7.74-7.78 (2H, m, H-7), 8.09-8.14 (2H, m, H-4); δ$_C$(75.56 MHz, CDCl$_3$) 122.1, 126.2, 127.3, 128.3, 137.8, 153.2, 162.1, 176.4.

**Bis(2-thiazolyl) ketone (3B).** A solution of thiazole (0.26 mL, 5.0 mmol) in 5.0 mL of anhydrous THF was treated with $n$-butyllithium (5.5 mmol, 1.5 M in $n$-hexane), at -70°C. After 30 min, a solution of diethyl carbonate (2.5 mmol in 5 mL of THF) was added. After 1 h, the reaction mixture was treated with 5 mL of saturated aqueous solution of NH$_4$Cl and extracted with diethyl ether. The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Compound 3B was obtained in 65% yield after purification by flash chromatography (eluent: petroleum light/ diethyl ether 4:6). mp 139-141°C (Lit.$^{25}$ 141-142 °C). Spectral data of 3B are in agreement with those reported.$^{26}$

**Bis(2-benzoxyazolyl) ketone (3C).** 3-Chloroperbenzoic acid (4.56 mmol) was added, portionwise, at 0°C, to a solution of 1C (0.800g, 3.90 mmol) in anhydrous CH$_2$Cl$_2$ (5.0 mL). After 12 h, a yellow precipitate appeared and the TLC analysis of the solution showed the presence of the compound 3C. After filtration and concentration of the solution, the residue was purified by flash chromatography (eluent: CH$_2$Cl$_2$). Compound 3C was obtained in 60% yield.
mp 174-176 °C (Lit.,11 173-175 °C. δ_H(300 MHz, CDCl_3) 7.48-7.69 (4H, m, H-5 and H-6), 7.72-7.80 (2H, m, H-7), 8.08-8.17 (2H, m, H-4); δ_C(75.56 MHz, CDCl_3) 111.9, 123.4, 126.2, 129.5, 141.0, 150.8, 155.7, 168.1; MS (EI) m/z: 264 (M^+), 236, 208, 146, 119, 102, 90.

**Bis(1-methylbenzoimidazol-2-yl) ketone (3E).** To a solution of N-methylbenzimidazole (0.88g, 6.66 mmol) in anhydrous diethyl ether (24 mL), kept at -78°C in a dried flask and under nitrogen atmosphere, a solution (2.8 mL) of n-butyl lithium (2.5 M in n-hexane) was added dropwise. After stirring for 2.5 h, a solution of 0.4 mL (3.33 mmol) of diethyl carbonate in anhydrous diethyl ether (2.0 mL) was added dropwise and the mixture was allowed to warm to room temperature overnight. The reaction mixture was acidified with 10% HCl and stirred until the precipitate formed during the reaction was dissolved. The solution was extracted with diethyl ether (3 x 10 mL) and the aqueous layer was basified with 5N NH_4OH. The white precipitate obtained was collected over a Gooch funnel and washed with water until the pH of the mother liquor was neutral. The solid was dried in a desiccator and purified by crystallization from methanol (0.58g, 60%); mp 189-191 °C (Lit.,27 190-191 °C), δ_H(300 MHz, CDCl_3) 4.15 (6H, s, CH_3), 7.30-7.52 (6H, m, H-5, H-6 and H-7), 7.95-8.03 (2H, m, H-4), δ_C(75.56 MHz, CDCl_3) 32.0, 110.2, 122.9, 123.7, 126.2, 136.8, 142.4, 146.8, 180.8; IR (CHCl_3), ν (cm⁻¹): 1654; MS (EI) m/z: 290 (M^+), 261, 159, 145, 132; HRMS: calc. for C_{17}H_{14}N_4O_1: 290.1168, found: 290.1163.

**Synthesis of carbinols 2A-C. Preparation of bis(benzothiazol-2-yl)methanol (2A): typical procedure.** A solution of sodium borohydride (0.027g, 0.71 mmol) in methanol (1.0 mL) was added, at 0 °C, in a dried flask and under nitrogen, to a solution of 3A (0.198g, 0.67 mmol) in 4.0 mL of dichloromethane. The addition of NaBH_4 produces a colour change of the solution from yellow (typical of ketone) to dark green. If the colour reverted back to yellow, additional NaBH_4 was added. When the TLC analysis (eluent: CH_2Cl_2:CH_3OH 99:1) showed complete conversion of the starting material, the reaction mixture was treated with water and extracted with CH_2Cl_2; the organic layers were washed with brine and dried over anhydrous sodium sulfate. After concentration _in vacuo_, the residue was stored at -18 °C. The yield is almost quantitative if the whole working-up is carried out in 30 min. The melting point is poorly reproducible because the carbinol is very prone to oxidation to the corresponding ketone. Carbinols may be stored in dark at -20°C for several days.

**Bis(benzothiazol-2-yl)methanol (2A).** δ_H(300 MHz, CDCl_3) 5.12-5.22 (1H, br s, OH), 6.56 (1H, s, H-8), 7.38-7.48 (2H, m, H-6), 7.48-7.58 (2H, m, H-5), 7.85-7.95 (2H, m, H-7), 8.10-8.25 (2H, m, H-4). Sometimes, a coupling between H-8 and OH (J = 4.1 Hz) was observed. δ_C(75.56 MHz, CDCl_3) 72.4, 121.9, 123.3, 125.5, 126.3, 135.4, 152.4, 171.3. All attempts to prepare 2A from the corresponding bromo derivative bis(benzothiazol-2-yl)bromomethane (6) by hydrolysis reaction failed.

**Bis(benzothiazol-2-yl)-1-deutero-methanol 2A(d).** This compound was obtained by following the typical procedure, using sodium borodeuteride: δ_H(300 MHz, CDCl_3) 5.10-5.20 (1H, br s, OH), 7.38-7.44 (2H, m, H-6), 7.48-7.54 (2H, m, H-5), 7.87-7.90 (2H, m, H-7), 8.05-8.09 (2H, m, H-4).
**Bis(thiazol-2-yl)methanol (2B).** $\delta_H(300$ MHz, CDCl$_3$) 5.7-6.2 (1H, br s, OH), 6.40 (2H, s, H-6), 7.36 (2H, d, $J = 3.3$ Hz, H-4), 7.77 (2H, d, $J = 3.3$ Hz, H-5); $\delta_C(75.56$ MHz, CDCl$_3$) 71.2, 120.3, 142.3, 171.2.

**Bis(benzooxazol-2-yl)methanol (2C).** $\delta_H(300$ MHz, CDCl$_3$) 4.55-4.65 (1H, br s, OH), 6.32-6.38 (1H, s, H-8), 7.36-7.38 (2H, m, H-5), 7.39-7.41 (2H, m, H-6), 7.53-7.56 (2H, m, H-4), 7.76-7.79 (2H, m, H-7); $\delta_C(75.56$ MHz, CDCl$_3$) 65.1, 111.1, 120.5, 124.8, 125.9, 140.2, 151.0, 162.3.

**Synthesis of bis(1-methyl-1H-benzoimidazol-2-yl)methanol (2E).** This compound was obtained as a mixture with bis (1-methylbenzimidazol-2-yl) ketone when the reaction was carried out in anhydrous THF, quenched, after 30 min., with saturated aqueous NH$_4$Cl solution and extracted with dichloromethane. After concentration of the organic layer, the F.C. of the residue (eluent: methanol) gave the carbinol (30%): white solid, mp 238-243 °C (dec.), Lit., 232-235 °C; $\delta_H(300$ MHz, DMSO-d$_6$) 4.02 (6H, s, CH$_3$), 6.60 (1H, d, $J = 5.5$ Hz, CHO), 7.02 (1H, d, $J = 5.5$ Hz, disappears after addition of D$_2$O, OH), 7.27 (2H, td, $J = 7.9$ Hz, $J = 1.2$ Hz, H-5 or H-6), 7.38 (2H, td, $J = 7.1$ Hz, $J = 1.0$ Hz, H-5 or H-6), 7.64-7.74 (4H, m, H-4 and H-7); $\delta_C(75.56$ MHz, CDCl$_3$) 31.9, 66.8, 111.4, 120.4, 124.0, 124.9, 138.1, 142.8, 153.4; MS (EI) m/z: 292 (M$^+$+), 275, 263, 161, 146, 131.

**1,1-Bis benzothiazol-2-yl-ethanol (9).** Compound 9 was also prepared by the following procedure. Butyllithium (20 mmol) was added dropwise to a solution of benzothiazole (20 mmol) in THF (50 mL) at –80°C under nitrogen and with vigorous stirring. Acetyl chloride (10 mmol) in 10 mL of THF was slowly added under vigorous stirring. After 8 hours the reaction mixture was poured into an ice-water mixture and extracted with Et$_2$O. From the Et$_2$O solution, bis(2-benzothiazole) (identified by comparison with an authentic sample) spontaneously precipitates. Carbinol 9 was separated from mother solution by addition of chloroform and slow crystallisation. Yields 30%. mp 154-155 °C, Lit., 154-156 °C. Spectral data of compound 9 are in agreement with those reported in literature.28

**Reaction of 1,1-bis(2-benzothiazolyl)methane (1A) with N-bromosuccinimide (NBS).** N-Bromosuccinimide was added, under vigorous stirring, to a solution of 1A in 10 mL of solvent, as reported in Table 5. The reaction mixture was refluxed for 4 hours, then the solvent was removed under vacuum and the residue chromatographed on silica gel column (eluent: CH$_2$Cl$_2$) in order to eliminate unreacted succinimide and to separate reaction products.

Table 5 reports some details on this reaction. Reaction products are indicated in scheme 9. Bromination reaction of 1A by molecular bromine afforded tars.

$$\text{Scheme 9}$$
Table 5. Reaction of 1A and N-bromosuccinimide (NBS)

<table>
<thead>
<tr>
<th>Molar ratio</th>
<th>Solvent and other</th>
<th>T(°C)</th>
<th>Reaction time (h)</th>
<th>Products (yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A/NBS 1:1.2</td>
<td>CH₃OH</td>
<td>25</td>
<td>2</td>
<td>5 (70)</td>
</tr>
<tr>
<td>1A/NBS 1:1</td>
<td>CH₃OH</td>
<td>25</td>
<td>2</td>
<td>5 (81)</td>
</tr>
<tr>
<td>1A/NBS 1:2</td>
<td>CCl₄</td>
<td>77</td>
<td>5</td>
<td>7 (53)</td>
</tr>
<tr>
<td>1A/NBS 1:1</td>
<td>CCl₄ and AIBN⁹</td>
<td>77</td>
<td>5</td>
<td>6 (66); 5 (7)</td>
</tr>
<tr>
<td>1A/NBS 1:1</td>
<td>CCl₄</td>
<td>77</td>
<td>2</td>
<td>6 (51)</td>
</tr>
</tbody>
</table>

⁹ Traces (0.01 mmol).

Bis(benzothiazol-2-yl)bromomethane (6). mp 228-230 °C, δ_H(300 MHz, CDCl₃) 6.90 (1H, s, H-8), 7.41-7.57 (4H, m, H-5 and H-6), 7.88-7.95 (2H, m, H-7), 8.05-8.13 (2H, m, H-4); δ_C(75.56 MHz, CDCl₃) 43.5, 121.8, 124.0, 126.1, 126.6, 136.3, 152.6, 166.6; MS (EI) m/z: 362 (M⁺ + 2), 360 (M⁺), 282, 148, 135, 82, 80.

Bis(benzothiazol-2-yl)dibromomethane (7). mp 124-126 °C, δ_H(300 MHz, CDCl₃) 7.44-7.50 (2H, m, H-6), 7.51-7.56 (2H, m, H-5), 7.87-7.90 (2H, m, H-7), 8.08-8.11 (2H, m, H-4); δ_C(75.56 MHz, CDCl₃) 51.2, 121.4, 124.4, 126.4, 126.6, 137.1, 152.4, 169.8; MS (EI) m/z: 440 (M⁺), 362, 360, 282, 268, 228, 226, 215, 213, 135, 82, 80.

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