OXIDATION OF 2-MERCAPTOBENZO HETERAZOLES BY DIMETYLDIOXIRANE. A NEW METHOD FOR A SYNTHESIS OF C-2 SUBSTITUTED BENZIMIDAZOLE, BENZOXAZOLE, AND BENZOTHIAZOLE DERIVATIVES

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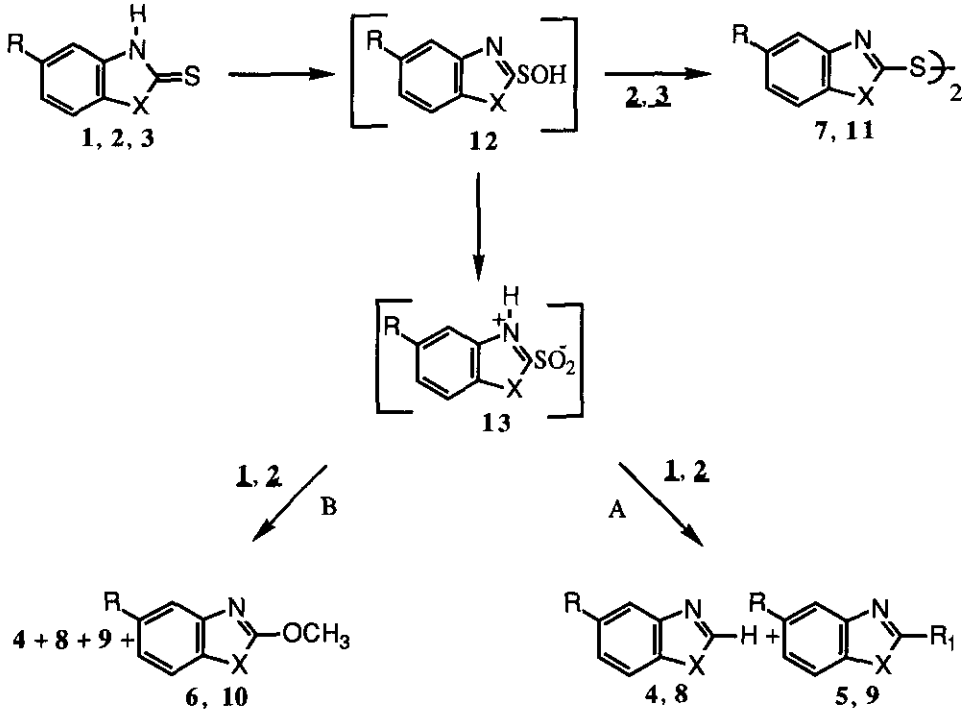
Abstract-New and efficient reactions in which 2-mercapto-benzoheterazoles are selectively converted by dimethyldioxirane, under mild experimental conditions, to several C-2 substituted benzoimidazole, benzoxazole, and benzothiazole derivatives are reported.

C-2 Substituted benzimidazole, benzoxazole and benzothiazole derivatives have interesting antiviral, antibacterial, and herbicidal activities.[1] Several synthetic methods are known for the synthesis of these derivatives, mainly consisting in use of nucleophilic substitution on 2-halogeno-heterazole derivatives,[2] metallation,[3] or heterocyclization of suitable precursors.[4] However, the different synthetic methods used for these syntheses show varying degree of success as well as limitations due to side reactions.
Recently, we have employed dimethyldioxirane, a new and selective oxidant,[5] for the oxidation of thioamide moiety present in substituted thiouracils,[6] thiopyrimidine and thiopurine nucleosides[7] in the presence of alcohol to afford site-specific introduction of an alkoxymoieties at C-2(C-4) and C-6 of the uracil and guanine residues, respectively. By these first results we have observed that the behaviour of thioamide moiety towards dimethyldioxirane is multifarious, depending on the nature of the substrate

as well as on the actual reaction conditions. In this report we have established that this methodology is a useful and general tool for new and efficient reactions in which 2-mercapto-heterazoles are selectively converted by dimethyldioxirane (as acetone solution[8]), under mild experimental conditions, to several C-2 substituted benzimidazole, benzoxazole, and benzothiazole derivatives.

Dimethyldioxirane reacts with 2-mercapto-5-methylbenzimidazole (**1**), 2-mercaptobenzoxazole (**2**), and 2-mercaptobenzothiazole (**3**) to afford different products depending on reaction conditions. The oxidation of **1** performed in CH_2Cl_2 at 25°C (method A) yielded a mixture of two easily chromatographically separable products, 5-methylbenzimidazole (**4**) as a main product and 2-hydroxy-5-methylbenzimidazole (**5**) as a by-product (Scheme 1, Table 1, Entry 1).



1, **4**, **6**: R=CH_3, X=NH; **2**, **7**, **8**, **10**: R=H, X=O; **3**, **11**: R=H, X=S; **5**: R=CH_3, R_1=OH, X=NH; **9**: R=H, R_1=CH_2COCH_3, X=O

Method A: Dimethyldioxirane (1.5 eq/mol, 0.05 N acetone solution), CH_2Cl_2, 25 °C. Method B: Dimethyldioxirane (1.5 eq/mol, 0.05 N acetone solution), CH_3OH, 25 °C.

Scheme 1

In the formation of compound (**5**) the moisture present in the distilled dioxirane-acetone solution was an essential ingredient; in fact, only traces of **5** were detected when the dioxirane-acetone solution was dried over $MgSO_4$ before use, even if it is known that $MgSO_4$ catalyzed some decomposition of the dioxirane.[9] Under these experimental conditions compound (**4**) was isolated in 75% yield.

Table 1: Oxidation of 2-mercaptoheterazoles (**1**, **2**,**3**,**17** and **18**)

Entry	Substrate	Method[a]	Product(s)	Yield(%)
1	1	A	4	55 (75)[b]
			5	18
2	1	B	6	74
			4	20
3	2	A	7	42
			8	18
			9	37
4	2	B	10	72
			8	11
			9	13
5	3	A	11	95
6	3	B	11	88
7	1	C	14a	75
			14b	62 (21)[c]
			14c	54 (29)[c]
			14d	57 (35)[c]
8	2	C	8	20
			15	68
9	3	C	16	79
10	17	B	19	81
11	18	B	20	53
			21	15

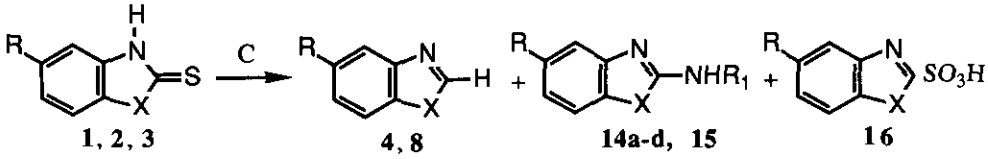
All oxidations were carried out using 2 mmol of substrate and a freshly prepared solution of dimethyldioxirane (0.05 N acetone solution). [a] Method A:dioxirane, CH_2Cl_2, 25 °C. Method B: dioxirane, CH_3OH, 25 °C. Method C: dioxirane, amine (3 eq/mol), CH_2Cl_2, 25 °C. [b] Yield refers to the reaction performed in the presence of $MgSO_4$. [c] Yield of compound **4** as a by-product.

When the reaction was carried out in CH_3OH at 25 °C (method B), 2-methoxy-5-methylbenzimidazole (**6**) was obtained in good yield, togheter with **4** (Table 1, Entry 2). The oxidation of **2** in CH_2Cl_2 at 25 °C afforded the

disulfide (**7**) as the main product, benzoxazole (**8**),[10] and the unexpected 2-acetonylderivative (**9**) (Table 1, Entry 3). Moreover, the same reaction carried out in CH_3OH gave a separable mixture of 2-methoxybenzoxazole (**10**), **8**, and **9** (Table 1, Entry 4). The oxidation of **3** yielded both in CH_2Cl_2 and in CH_3OH the disulfide (**11**) in good yield (Table 1, Entries 5 and 6) while we did not detect the expected benzothiazole or its 2-alkoxyderivative.

On the basis of the known reactivity of the thioamide moiety with oxidants,[11] it is resonable to suggest that the oxidation of compounds (**1**, **2**, and **3**), which exist predominantly in the ketoform,[12] proceeds through initial formation of the thioamide *S*-oxide[13] which can tautomerise to heterazole-2-sulphenic acid (**12**).[14] This "transient" species, that we did not detect in our reaction mixtures, can react with another molecule of substrate to give disulfide,[15] or it may be oxidized to heterazole-2-sulphinic acid (**13**); this intermediate, in accord with previous reports,[17a] might yield a C-2 ion derivative (not shown), sulphur dioxide, and a proton through heterolytic cleavage of the C-S bond. The latter ion will then capture a proton to give compounds (**4**) and (**8**). Furthermore, the nucleophilic displacement of the whole sulphur-containing group of (**13**) is possible in presence of nucleophiles to afford C-2 substituted derivatives.[17b] In the latter case, the formation of 2-acetonylderivative (**9**), obtained in the oxidation of compound (**2**), may be due to condensation between the reactive sulphinic acid intermediate and the acetone present in the dioxirane solution. Furthermore, it is interesting to note that the behaviour of 2-mercaptobenzothiazole (**3**) towards dimethyldioxirane is very different from that of 2-mercaptobenzimidazole (**1**) (compound (**2**) showing an intermediate behaviour), probably because of the different stability of the corresponding sulphenic acid intermediates. Although it is known that stable sulphenic acids are characterized by the presence of either polar groups, or bulky groups, or both, adjacent to the sulphenic acid moiety,[18] to the best of our knownledge there are no reports about the influence exerted by the nature of the heteroatom adjacent to thioamide moiety on the oxidation pathway. In view of the successful application of this procedure for site-specific introduction of nitrogen nucleophiles on C-2 position of the heterazole ring, the oxidation of 2-mercaptoheterazoles (**1**, **2**, and **3**) with dioxirane in the presence of amines was further examined. The oxidation of **1** performed in CH_2Cl_2 at 25 °C in the presence of several amines (ammonia, ethylamine, n-propylamine and n-butylamine; 3 eq/mol) as nucleophiles (Method C) gave 5-methyl-2-aminobenzimidazole (**14a**) and 5-methyl-2-(alkylamino)benzimidazole derivatives (**14b-d**) in moderate yields as main products and 5-

methylbenzimidazole (**4**) as a by-product (Scheme 2, Table 1, Entry 7). Similarly, the oxidation of **2** performed in CH_2Cl_2 at 25 °C in the presence of ammonia (3 eq/mol; 2.0 N methanol solution) gave 2-aminobenzoxazole (**15**) as a principal product and **8** as a by-product (Scheme 2, Table 1, Entry 8).



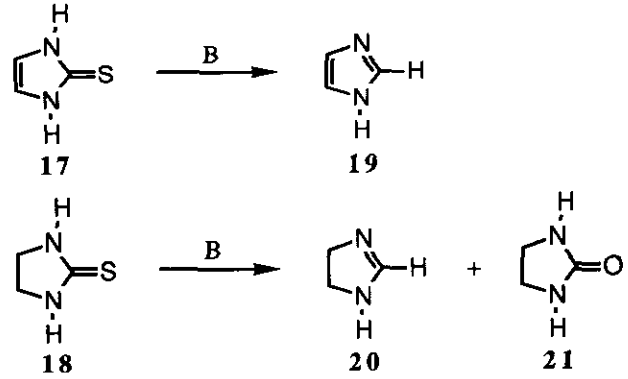
a: R_1=H; **b**: R_1=C_2H_5; **c**: R_1=C_3H_7; **d**: R_1=C_4H_9

1, 4, 14a-d: R=CH_3, X=NH; **2, 8, 15**: R=H, X=O; **3, 16**: R=H, X=S.

Method C: Dimethyldioxirane (1.5 eq/mol, 0.05 N acetone solution), amine (3 eq:mol), CH_2Cl_2, 25 °C.

Scheme 2

On the other hand, oxidation of **3** under the previously described experimental conditions gave benzothiazole-2-sulphonic acid (**16**) as an only isolable product (Scheme 2, Table 1, Entry 9). No sulphenic acid derivatives were detected under these experimental conditions in spite of described[19] formation of benzothiazole-2-sulphenamides during the cooxidation of **3** and amines with NOCl.



Method B: Dimethyldioxirane (1.5 eq/mol, 0.05 N acetone solution),CH_3OH (5 ml), CH_2Cl_2, 25 °C.

Scheme 3

Finally, in order to establish the generality of this procedure, we studied the oxidation with dimethyldioxirane of 2-mercaptoimidazole (**17**) and 2-

mercaptoimidazolidine (**18**). The reaction of **17** with dimethyldioxirane in CH_3OH at 25 °C (Method B) yielded imidazole (**19**)[10] as an only isolated product, in good yield (Scheme 3, Table 1, Entry 10). Similarly, oxidation of **18**, under the previously described experimental conditions, gave 2-imidazoline (**20**) as a main product, and 2-imidazolidone (**21**) as a by-product (Scheme 3, Table 1, Entry 11). On the basis of the above results, it was conceived that the nature of the heteroatom adjacent to thioamide moiety might be an important factor to direct the reaction of compounds (**1**), (**2**), and (**3**) with dimethyldioxirane, and that the oxidation of thiourea moiety, present in compounds (**17**) and (**18**), did not afford disulfides in accord with the behaviour of 2-mercaptobenzimidazole (**1**) and with the results reported by Wolfgang[20] on the oxidation of acyclic N,N-disubstituted thiourea derivatives. Furthermore, since in the latter oxidations we have not detected the presence of C-2 methoxy-substituted products, the isolation of compound (**21**) as a by-product in the oxidation of 2-mercaptoimidazolidine (**18**) may be due to hydrolysis of the corresponding *S*-oxide derivative.[20]

EXPERIMENTAL

Nmr spectra were recorded on a Varian Gemini (200 MHz) spectrometer and chemical shift are reported in δ values. Ir spectra were recorded on a Perkin Elmer 298 spectrophotometer using NaCl plates. Microanalyses were performed by C. Erba 1106 analyzer. Mass spectra were recorded on a Kratos MS80 spectrometer. Melting points were obtained on a Reichert Kofler apparatus and are uncorrected. All solvents were ACS reagent grade and were redistilled and dried according to standard procedure. Chromatographic purifications were performed on columns packed with Merck silica gel 60, 230-400 mesh for flash technique. Thinlayer chromatography was carried out using Merck plates Kieselgel 60 F_{254}.

Starting compounds

Commercially available 2-mercapto-5-methylbenzimidazole (**1**), 2-mercapto-benzoxazole (**2**), 2-mercaptobenzothiazole (**3**), 2-mercaptoimidazole (**17**) and 2-mercaptoimidazolidine (**18**) (Aldrich, Co.) were used without further purification.

Oxidation of compounds (1, 2, 3, 17, and 18) with dimethyldioxirane. General procedure.

A dimethyldioxirane solution was prepared using the procedure reported by Adam and co-workers,[8] and the dioxirane content (*ca.* 0.07 N) was assayed with methylphenylsulfide, yielding the corresponding sulfoxide; the latter being determined by ^{1}H-nmr. The reactions were carried out by adding the freshly prepared solution of dioxirane to solutions of the desired substrate (2 mmol) in 5 ml of the appropriate solvent (Methods A and C: CH_2Cl_2; Method B: CH_3OH) and when necessary in the presence of amines (3 eq/mol) as nucleophiles (Method C), at 25 °C, until the substrate disappeared (tlc eluent chloroform:methanol=8.0:2.0). The resulting solution was transferred to a round bottomed flask and concentrated. The residue was purified by flashchromatography using chloroform:methanol=9.5:0.5 as the eluent.

5-Methylbenzimidazole (4)- (198 mg, 75%), oil; Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.59; H, 6.08; N, 21.31; ν_{max} ($CHCl_3$) 3500 (NH) and 1600 (C=N) cm^{-1}; δH (200 MHz; $CDCl_3$) 2.47 (3H, s, CH_3), 7.10-7.55 (3H, m, Ph-H), 7.93 (1H, s, CH); *m/z* 132 (M^+, 38%).

5-Methyl-2-hydroxybenzimidazole (5)- (51 mg, 18%), mp 292-294 °C (from EtOH) [lit.,[21] mp 293-295 °C].

5-Methyl-2-methoxybenzimidazole (6)- (169 mg, 74%), oil; Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.54; H, 6.18; N, 17.40; ν_{max} ($CHCl_3$) 3500 (NH) cm^{-1}; δH (200 MHz; DMSO-d_6) 2.32 (3H, s, CH_3), 3.34 (3H, s, OCH_3), 6.80-7.10 (3H, m, Ph-H), 12.40 (1H, bs, NH); *m/z* 164 (M^+, 51%).

2,2'-Bisbenzoxazoledisulfide (7)- (252 mg, 42%), mp 111-113 °C (from EtOH/H_2O) [lit.,[22] mp 112-113 °C].

2-Acetonylbenzoxazole (9)- (93 mg, 37%), oil; Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.0. Found: C, 68.65; H, 5.21; N, 7.92; ν_{max} ($CHCl_3$) 2850 (CH) and 1760 (CO) cm^{-1}; δH (200 MHz; DMSO-d_6) 2.30 (3H, s, CH_3), 4.50 (2H, s, CH_2), 7.20-7.40 (4H, m, Ph-H); m/z 175 (M^+, 72%).

2-Methoxybenzoxazole (10)- (215 mg, 72%), mp 211-213 °C (from EtOH); Anal. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 19.91. Found: C, 64.68; H,

5.41; N, 19.95; ν_{max} ($CHCl_3$) 2890 (CH) cm^{-1}; δH (200 MHz; DMSO-d_6) 3.80 (3H, s, OCH_3), 6.80-7.40 (4H, m, Ph-H); m/z 149 (M^+, 25%).

2,2'-Bisbenzothiazoledisulfide (11)- (612 mg, 95%), mp 179-181 °C (from $EtOH/H_2O$) [lit.,[23] mp 181 °C].

5-Methyl-2-aminobenzimidazole (14a)- (205 mg, 75%), mp 202-204 °C (from $EtOH/H_2O$) [lit.,[24] mp 203-204 °C].

5-Methyl-2-(ethylamino)benzimidazole (14b)-(155 mg, 62%), oil; Anal. Calcd for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.81; H, 7.99; N, 22.37; ν_{max} ($CHCl_3$) 3500 (NH) cm^{-1}; δH (200 MHz; $CDCl_3$) 0.74 (3H, t, *J*=7 Hz, CH_3), 1.89 (3H, s, CH_3), 2.41 (2H, q, *J*=7 Hz, NCH_2), 6.49-6.97 (3H, m, Ph-H); *m/z* 175 (M^+, 33%).

5-Methyl-2-(propylamino)benzimidazole (14c)- (204 mg, 54%), oil; Anal. Calcd for $C_{11}H_{15}N_3$: C, 69.81; H, 7.99; N, 22.20. Found: C, 69.68; H, 7.93; N, 22.37; ν_{max} ($CHCl_3$) 3450 (NH) cm^{-1}; δH (200 MHz; $CDCl_3$) 0.80 (3H, t, *J*=6.5 Hz, CH_3), 1.93 (2H, m, CH_2), 2.16 (3H, s, CH_3), 3.10 (2H, m, NCH_2), 6.95-7.25 (3H, m, Ph-H); *m/z* 189 (M^+, 41%).

5-Methyl-2-(butylamino)benzimidazole (14d)- (231 mg, 57%), oil; Anal. Calcd for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67. Found: C, 70.78; H, 8.50; N, 20.88; ν_{max} ($CHCl_3$) 3450 (NH) cm^{-1}; δH (200 MHz; $CDCl_3$) 0.89 (3H, t, *J*=6.5 Hz, CH_3), 1.45 (2H, m, CH_2), 1.65 (2H, m, CH_2), 2.14 (3H, s, CH_3), 2.91 (2H, m, NCH_2), 7.05-7.55 (3H, m, Ph-H); *m/z* 203 (M^+, 38%).

2-Aminobenzoxazole (15)- (223 mg, 68%), mp 127-129 °C (from H_2O) [lit.,[25] mp 128-129 °C].

Benzothiazole-2-sulphonic acid (16)- (340 mg, 79%), mp> 258 °C [lit.,[26] mp>260 °C].

2-Imidazoline (20)- (113 mg, 81%), mp 45-46 °C [lit.,[27] mp 45 °C].

2-Imidazolidone (21)- (91 mg, 53%), mp 134-136 °C [lit.,[28] mp 133-135 °C].

ACKNOWLEDGEMENTS

We are grateful to Dr. R. Ciafrino and Dr. M.L. Barcherini for the preparation of some samples; financial support from Italian *MURST* is acknowledged.

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Received, 18th July, 1994